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Novartis Research and Development

ACZ885

Clinical Trial Protocol CACZ885V2301 / NCT03626545

A randomized, double-blind, placebo-controlled, phase III study evaluating the efficacy and safety of canakinumab in combination with docetaxel versus placebo in combination with docetaxel in subjects with non-small cell lung cancer (NSCLC) previously treated with PD-(L)1 inhibitors and platinum-based chemotherapy (CANOPY-2)

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List of abbreviations

ADA	Anti-Drug Antibodies
AE	adverse event
AESI	adverse event of special interest
AIC	Akaike information criterion
ALK	Anaplastic Lymphoma Kinase
ALP	alkaline phosphatase
alpha-FP	Alpha-Fetoprotein
ALT	alanine aminotransferase
ANA	Antinuclear Antibody
ANC	Absolute Neutrophil Count
ASMA	Anti-Smooth Muscle Antibody
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AUCi	Area Under the Curve with respect to increase
b.i.d.	twice a day
Beta-hCG	Beta-Human Chorionic Gonadotropin
BLRM	Bayesian Logistic Regression Model
BOR	Best Overall Response
BUN	blood urea nitrogen
BVN	Bivariate normal
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcomes Study
CAPS	Cryopyrin Associated Periodic Syndromes
CD-transferrin	Carbohydrate Deficient-transferrin
CFR	Code of Federal Regulation
CHF	Congestive Heart Failure
CI	Confidence Interval
Cmax	Concentration maximum
Cmin	Concentration minimum
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CO	Country Organization
COA	Clinical Outcome Assessments
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CRS	Case Retrieval Strategy

[redacted]

CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CTT	Clinical Trial Team
CV	Coefficient of variation
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DDI	Drug-drug Interaction
DDS	Dose-Determining Set
DILI	Drug-Induced Liver Injury
DL1	Dose Level 1
DLRT	Dose Level Review Team
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration Of Response
EBV	Epstein-Barr Virus
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-linked immunoabsorbent assay
EMA	European Medicines Agency
EOI	End of Infusion
EORTC	European Organization for Research and Treatment of Cancer
EOT	End Of Treatment
ePRO	Electronic Patient Reported Outcome
ERCP	Endoscopic Retrograde Cholangiopancreatography
EU	European Union
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fludeoxyglucose-Positron emission tomography
FFPE	Formalin-Fixed Paraffin Embedded
FMF	Familial Mediterranean Fever
FPFV	First Patient First Visit

[redacted]

G-CSF	Granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyltransferase
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
HSV	Herpes Simplex Virus
i.v.	intravenous
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG1	Immunoglobulin G 1
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL	Interleukin
IL-1β	Interleukin-1β
IN	Investigator Notification
INN	International Nonproprietary Names
INR	International Normalized Ratio
IQR	InterQuartile Range
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Insulin Tolerance Tests
IUD	Intrauterine device
IUS	Intrauterine system
LDH	lactate dehydrogenase
LFT	Liver function test

[redacted]

LLN	lower limit of normal
LLOQ	Lower Limit Of Quantification
LLQ	lower limit of quantification
LPLV	Last Patient Last Visit
MACE	Major Adverse Cardiovascular Events
MAP	Meta-Analytic-Predictive
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial Infarction
MKD	Mevalonate Kinase Deficiency
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
MSD	Meso Scale Discovery
NASH	Nonalcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse events
NSCLC	Non-small cell lung cancer
o.d.	once a day
OLE	Open Label Extension
ORR	Overall Response Rate
OS	Overall Survival
p.o.	Oral
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamic(s) Progressive Disease
PD-(L)1	Programmed death-ligand 1
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PK	pharmacokinetic(s)
PR	Partial Response
PRO	Patient Reported Outcome
PS	Performance Status
PT	Prothrombin time
QLQ	Quality of Life Questionnaire
QMS	Quality Management System
QoL	Quality of Life
QxW	Every x weeks
R value	ALT/ALP in multiples of ULN
RBC	Red blood cell(s)
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic Acid
RoW	Rest of the World

[redacted]

RP3R	Recommended Phase 3 Regimen
s.c.	subcutaneous
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Steering Committee
sCR	serum creatinine
SD	Stable Disease
SOP	Standard Operating Procedure
SUSARs	Suspected Unexpected Serious Adverse Reactions
T1/2	Terminal Half-Life
T1D	Type 1 Diabetes
T3	Triiodothyronine
T4	Thyroxine
TB	Tuberculosis
TBIL	Total Bilirubin
TNF	Tumor Necrosis Factors
TRAPS	Tumor Necrosis Factor Receptor Associated Periodic Syndrome
TSH	Thyroid-Stimulating Hormone
TTP	Time To Progression
TTR	Time To Response
ULN	Upper limit of normal
ULOQ	Upper Limit Of Quantification
UNK	Unknown
US	United States Ultrasound
USPI	US-Package Insert
VAS	Visual Analogue Scale
VATS	Video-Assisted Thoracic Surgery
vs.	versus
WBC	White blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.

[redacted]

Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 2 (10-Jun-2020)

Amendment rationale

The CACZ885V2301 study, initiated in Jan-2019, completed enrollment on 30-Mar-2020, with a total number of 8 subjects enrolled in the safety run-in part, followed by 237 subjects in the randomized phase III part. The Recommended Phase III Regimen (RP3R) of Canakinumab 200 mg, s.c combined with docetaxel 75mg/m2 i.v. Q3W was confirmed as part of the conduct of the safety run-in part in Apr-2019. As of release of this amendment, 10-Jun-2020, all 8 subjects from the safety run-in part have discontinued study treatment, while 63 in the randomized part are still being treated on study.

[redacted]

Changes to the protocol

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

The following sections, tables and figures were changed:

- Protocol summary: [redacted]
- Section 3 and Figure 3-2: addition of Open Label Extension design specification; in addition, rectification on criteria met to discontinue efficacy follow-up
- Table 4-1: rationale on introducing an Open Label Extension in randomized part has been inserted
- Section 6.1.3: description of subject study treatment plan in OLE inserted
- Section 6.1.5: stated that the treatment discontinuation criteria in OLE is the same as that in safety run-in and blinded randomized part
- Section 6.3.2: added information related to treatment assignment in OLE
- Section 6.4: insertion of treatment unblinding prior to opening of OLE
- Section 6.5.4.2: clarifications made in reporting and managing potential DILI cases to align with Novartis Liver Safety Guidance
- Section 6.7.2: correction of typo on subcutaneous injection angle from 90 to 45-degree to align with Instruction for Use (reference document used for canakinumab dose administration)

[redacted]

- Table 8-1: allowable time window specific to OLE cycle visits inserted
- Table 8-2 and Table 8-3: the start point of safety follow-up period rectified to align with the wording used in protocol text
- Table 8-3: added possibility for randomized subjects to enter into OLE
- Table 8-4: separate Visit Evaluation Schedule created for OLE
- Section 8.3.2 and Table 8-5: imaging assessment schedule plan added for OLE; central imaging assessments collection and quality check to be discontinued in OLE
- Section 8.4.1, Table 8-6, Section 8.4.4, Section 8.4.5 and Section 8.5.2.1: wording related to OLE assessments added
- Section 8.5.1: clarification added on ePRO collection procedure and reduced ePRO collection in OLE
- Section 8.5.3.1: clarifying that tumor block collected at disease progression should be submitted as preferred than slides
- Section 8.5.2.2 and Table 16-17: clarification on approximate number of subjects per arm in PK docetaxel subset
- Section 9.2: end of study definition revised to more specifically cover the cases of positive or negative study readouts
- Section 10.1.1.1: AESI DILI name was updated to abnormal liver parameters to reflect MedDRA search more accurately
- Section 10.1.2: clarification added on malignant neoplasm not considered as a disease progression of the study indication; guidance provided on confirmed COVID-19 infection to be considered as medically significant and therefore to be reported as SAE
- Section 10.1.4: details inserted on actions to be taken for pregnancy occurring on study treatment as well as the duration of follow-up with new born
- Section 11.2: revision made on data captured in Interactive Response Technology (IRT) system
- Section 12: data scope enlarged to include those to be collected post cut-off date for the primary OS analysis
- Section 12.7: wording revised on the primary intent of the interim analysis

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]

Amendment 00-CN.01 (08-Jul-2019)

Amendment rationale

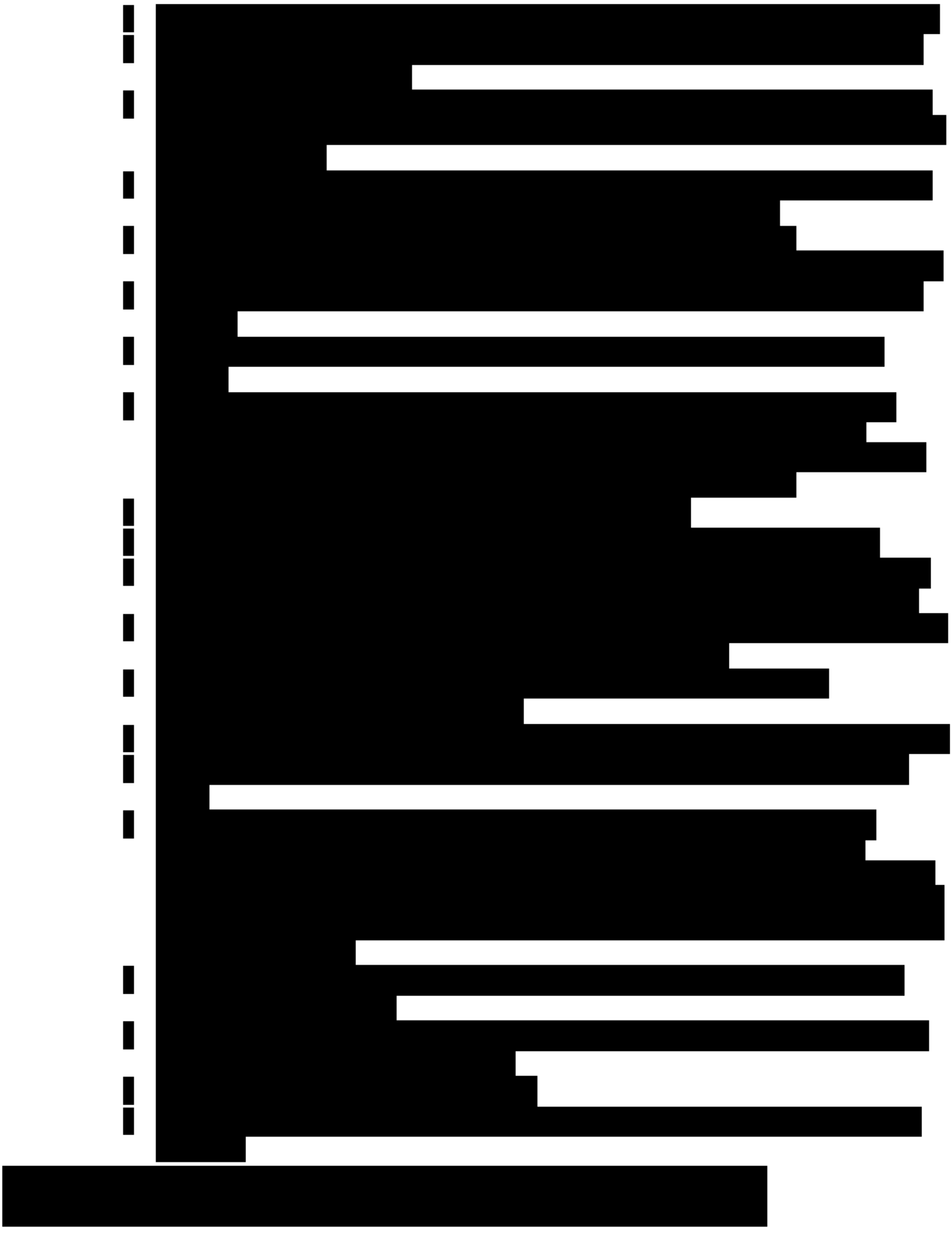
[redacted]

Editorial revisions and text corrections were made throughout the protocol for clarification, where required.

Changes to the protocol

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

[redacted]



In addition, as part of this amendment, minor editorial changes (e.g. typographical mistakes, grammatical changes, rewording) to improve flow and consistency, and correction of spelling errors or typographical errors have been made throughout the protocol.

IRB Section

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Protocol summary

Protocol number	ACZ885V2301
Full Title	A randomized, double-blind, placebo-controlled, phase III study evaluating the efficacy and safety of canakinumab in combination with docetaxel versus placebo in combination with docetaxel in subjects with non-small cell lung cancer (NSCLC) previously treated with PD-(L)1 inhibitors and platinum-based chemotherapy (CANOPY-2)
Brief title	Study of efficacy and safety of canakinumab in combination with docetaxel in subjects with non-small cell lung cancers as a second or third line therapy.
Sponsor and Clinical Phase	Novartis, Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This phase III study is designed to evaluate the role of IL-1β inhibition in combination with docetaxel in subjects with advanced NSCLC previously treated with PD-(L)1 inhibitors and platinum-based chemotherapy.
Primary Objective(s)	**Part 1: Safety run-in** • To confirm the Recommended Phase 3 Regimen (RP3R) of the combination of canakinumab and docetaxel. **Part 2: Double-blind, randomized, placebo-controlled part** • To compare the overall survival (OS) in the docetaxel plus canakinumab arm versus docetaxel plus placebo arm.
Secondary Objectives	**Part 1: Safety run-in** • To characterize the safety and tolerability of the combination of canakinumab and docetaxel. • To assess the preliminary clinical anti-tumor activity of canakinumab and docetaxel combination. • To characterize the pharmacokinetics (PK) of canakinumab and docetaxel when given in combination. **Part 2: Double-blind, randomized, placebo-controlled part** • To evaluate the 2 treatment arms with regards to progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), time to response (TTR) and duration of response (DOR) based on local investigator assessment per RECIST1.1. • To characterize the safety profile of the combination of docetaxel and canakinumab. • To assess the effect of docetaxel plus canakinumab vs docetaxel plus placebo on PROs (EORTC QLQ-C30, lung specific module QLQ-LC13 and EQ-5D-5L) including lung cancer symptoms, health-related quality of life and health status. • To characterize the pharmacokinetics of canakinumab when given in combination. • To characterize the immunogenicity (anti-drug antibodies (ADA)) of canakinumab. • To assess the effect of docetaxel plus placebo vs. docetaxel plus canakinumab arms on ECOG performance status.

[redacted]

Study design	This study has been designed as a Phase III trial and consists of 2 parts: **Part 1 - safety run-in** (open label) will confirm the Recommended Phase 3 Regimen (RP3R) of the combination of canakinumab and docetaxel. **Part 2 – randomized** (double blind, placebo-controlled) will evaluate the efficacy and safety of canakinumab in combination with docetaxel versus placebo in combination with docetaxel. [redacted]
Population	The study population will include adult subjects with locally advanced or metastatic NSCLC, who have progressed on platinum-based chemotherapy and PD-(L)1-inhibitor. Subjects must be docetaxel naive. Subjects with targetable oncogenic drivers Epidermal Growth Factor Receptor (EGFR) or Anaplastic Lymphoma Kinase (ALK) will be excluded. **Part 1 - Safety run-in**: Approximately 9 subjects will be enrolled in order to have at least 6 evaluable subjects. Male or female ≥ 18 years of age. **Part 2 - Randomized part**: Approximately 226 subjects will be randomized in a 1:1 ratio. Male or female ≥ 18 years of age.
Key Inclusion criteria	• Histologically confirmed locally advanced or metastatic (stage IIIB-stage IV) NSCLC. • Subject has received one prior platinum-based chemotherapy and one prior PD-(L)1 inhibitor therapy for locally advanced or metastatic disease. • Subject with ECOG performance status (PS) of 0 or 1. • Subject with at least 1 evaluable (measurable or non-measurable) lesion by RECIST 1.1 in solid tumors criteria. For the full eligibility criteria, please refer to Section 5.
Key Exclusion criteria	• Subject who previously received docetaxel, canakinumab (or another IL-1β inhibitor), or any other systemic therapy for their locally advanced or metastatic NSCLC other than one platinum-based chemotherapy and one prior PD-(L)1 inhibitor. • Subject with EGFR-sensitizing mutation or ALK rearrangement by local testing. • History of severe hypersensitivity reaction to monoclonal antibodies, taxanes or any known excipients of these drugs (i.e. Polysorbate-80-containing infusions, mannitol, histidine).
Study treatment	Canakinumab or placebo in combination with docetaxel.
Efficacy assessments	• Survival assessment. • Tumor assessment by RECIST 1.1, measured every 6 weeks during the first 12 months, and every 12 weeks thereafter.

[redacted]

	• Note for Open Label Extension: tumor assessment to be performed every 12 weeks until 36 months since randomization, and every 6 months thereafter.
Key safety assessments	• Physical examination. • ECOG Performance status (PS). • Weight and vital signs. • Adverse Events (AEs). • Laboratory abnormalities. • Note for Open Label Extension: lab assessments to be performed every 2 cycles.
Other assessments	• Patient Reported Outcomes: EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-5L. • Pharmacokinetics (PK)/immunogenicity (IG) samplings [redacted] • Note for Open Label Extension: reduced ePRO data collection [redacted] PK/IG [redacted] collection will stop. [redacted]
Data analysis	All analysis sets are defined in Section 12.1. **Primary endpoint:** **Part 1- Safety run-in part** The determination of RP3R will be guided by a Bayesian analysis of Dose Limiting Toxicity (DLT) data for the first 42 days that subjects receive the combination of canakinumab and docetaxel. Section 16.2. The dose limiting toxicity (DLT) relationship of canakinumab in combination with docetaxel will be modeled by a 5-parameter Bayesian Logistic Regression Model (BLRM) for each dose regimen that comprises single agent toxicity parts and interaction part. Single agent toxicity is modeled using logistic regression for the probability of a subject experiencing a DLT against log-dose. The odds of a DLT for each dose regimen are then calculated under no interaction for the two single agent toxicities, and interaction is accounted for by adjusting these odds with additional model parameters (odds multipliers). Dosing regimen decisions are guided by the escalation with overdose control (EWOC) principle (Rogatko et al. 2007). [redacted] **Part 2- Randomized phase III part** Assuming proportional hazards model for OS, the null hypothesis will be tested at one-sided 2.5% level of significance.

[redacted]

	The primary efficacy analysis to test this hypothesis and compare the two treatment groups will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance in favor of the docetaxel plus canakinumab arm. The stratification factors are line of therapy and histology. The primary efficacy variable, OS, will be analyzed at the interim analysis and final analysis of a group sequential design, using a Lan-DeMets (O'Brien-Fleming) α-spending function. Analyses will be based on the Full Analysis Set (FAS) population according to the randomized treatment group and strata assigned at randomization. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, median and associated 95% confidence intervals will be presented for each treatment group. The Hazard Ratio (HR) for OS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test. **Secondary endpoints:** **In Safety run-in part**, ORR, DCR, and DOR will be summarized in FAS by dose cohort. **In Randomized part**, the PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, using a stratified Cox model. ORR, DCR and their 95% confidence interval will be presented by treatment group. The distribution functions of TTR and DOR will be estimated using the Kaplan-Meier method. The median TTR and DOR along with their 95% CIs will be presented by treatment arm.
Keywords	ACZ885, canakinumab, docetaxel, NSCLC, IL-1β, PD-(L)1, CANOPY

[redacted]

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1.1 Background on non-small cell lung cancer and use of immunotherapy

An estimated 1.8 million people were diagnosed globally with lung cancer in 2012 and there were 1.6 million deaths from this disease. The number of new lung cancer cases is expected to grow by about 70% over the next 2 decades (Globocan 2012). Non-small cell lung cancer (NSCLC) accounts for 85% of the lung cancer diagnoses (Jemal et al 2011). The majority of patients present with advanced disease.

The standard first-line therapy for treatment of patients with stage IIIB to IV NSCLC with no targetable oncogenic mutations is platinum-based chemotherapy. The median overall survival of advanced NSCLC subjects treated with platinum doublets is 8-10 months, with approximately 50-70% of subjects having disease stabilization or shrinkage in response to first-line chemotherapy (Schiller et al 2002, Scagliotti et al 2002, Scagliotti et al 2008). Following the progression on platinum-based chemotherapy, single-agent docetaxel is the standard of care based on efficacy and safety data from the randomized studies demonstrating benefits of docetaxel 75 mg/m^2 over vinorelbine or ifosfamide (Fossella et al 2000) or versus best supportive care.

Immunotherapy has further shaped the treatment landscape of advanced NSCLC in patients who progressed on platinum-based chemotherapy. Three monoclonal antibodies targeting PD-1 and PD-L1 (nivolumab, pembrolizumab, and atezolizumab) have each proven superiority over single agent docetaxel in pretreated NSCLC patients and have been recently approved by the Health Authorities in this setting. The clinical benefit was apparent across squamous and non-squamous histologies (Herzberg et al 2017).

Table 1-1 Overall survival benefit of immunotherapy for treatment of advanced Non-Small Cell Lung Cancer

PD-(L)1 inhibitor	Reference	NSCLC histology	Median OS in months in PD-(L)1 inhibitor arm (95% CI)	Median OS in months in docetaxel arm (95% CI)	HR [95% CI] and p value
Nivolumab	Borghaei et al 2015	Non-squamous	12.2 [9.7-15.0]	9.4 [8.1-10.7]	HR 0.73 [0.59 - 0.89] p = 0.002
Nivolumab	Brahmer et al 2015	Squamous	9.2 [7.3-13.3]	6.0 [5.1-7.3]	HR 0.59 [0.44 - 0.79] p < 0.001
Pembrolizumab	Herbst et al 20 16	Squamous and non-squamous	12.7 [10.0-17.3]	8.5 [7.5-9.8]	HR 0.61 [0.49–0.75] p<0.0001
Atezolizumab	Rittmeyer et al 2017	Squamous and non-squamous	13.8 [11.8-15.7]	9.6 [8.6-11.2]	HR 0.73 [0.62–0.87] p=0.0003

More recently, pembrolizumab was evaluated in combination with platinum-based chemotherapy in the randomized Phase 3 studies KEYNOTE-189 in first line patients with non-squamous NSCLC (Gandhi et al 2018) and KEYNOTE-407 in first line patients with squamous

[redacted]

NSCLC (Paz-Ares et al 2018). The pembrolizumab arm compared to chemotherapy alone significantly prolonged OS in both studies. In KEYNOTE-189 median OS: not reached vs. 11.3 months, HR=0.49 [95% CI: 0.38-0.64] and in KEYNOTE-407, median OS: 15.9 vs. 11.3 months, HR=0.64 [95% CI: 0.49-0.85].

Despite the progress offered by the PD-(L)1 inhibitors in combination with platinum-based chemotherapy in first line, or after progression on platinum-based therapy in second line, the median overall survival is still short. In four randomized studies leading to regulatory approvals of three different PD-(L)1 inhibitors, the median overall survival ranged from 9.2 to 13.8 months. [redacted]

1.1.1.2 Role of IL-1β and resistance mechanisms to PD-(L)1 inhibitors

Chronic inflammation plays an important role in the development of non-small cell lung cancer (NSCLC). Key etiological risk factors such as smoking, 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 (O'Callaghan et al 2010, Krysan et al 2008). 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. Polymorphisms in the promoter region of the IL-1 gene result in altered levels of IL-1β expression and are associated with an increase in lung cancer risk (Li and Wang 2013). Extensive preclinical data to supports the role of IL -1β in several distinct steps in carcinogenesis including tumor initiation, promotion, angiogenesis, and metastasis (Dalgleish and O'Byrne 2006, Mantovani et al 2008, O'Byrne et al 2000).

Mechanisms of resistance to PD-(L)1 inhibitors are not yet clearly established (Martini et al 2017). Activation of inflammation and elevated baseline CRP levels are associated with lower response/resistance to immunotherapies. In a study of 99 subjects with NSCLC treated with first line platinum-doublet therapy followed by nivolumab, baseline CRP > 50mg/L was associated with inferior OS (Naqash et al 2017). In a separate study including 24 subjects with squamous cell lung cancer treated with nivolumab, subjects with baseline CRP below median (64 mg/L) had substantially longer median time to treatment failure than when CRP was above median (Brustugun et al 2017). These data support investigating the role IL1-β inhibitors in the treatment of patients with NSCLC and measuring CRP at baseline and during treatment.

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

1.1.2.1 Overview of canakinumab

Canakinumab is a high-affinity human anti-interleukin-1β (IL-1β) monoclonal antibody that belongs to the IgG1/κ isotype subclass. Canakinumab is manufactured in a murine SP2/0 cell line. Canakinumab is marketed under the brand name ILARIS®. It is approved for the treatment of several diseases: 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), Still's disease and gouty arthritis.

[redacted]

Novartis has investigated canakinumab use in the secondary prevention of major adverse cardiovascular events (MACE) in the **C**anakinumab **AN**ti-inflammatory **T**hrombosis **O**utcomes **S**tudy (CANTOS) study. In this randomized, placebo controlled study for patients with a history of prior myocardial infarction and inflammatory atherosclerosis and elevated hs-CRP at baseline, 10,061 subjects were enrolled and were treated with either placebo or 50, 150 to 300 mg s.c. every three months. The administration of canakinumab demonstrated a clinically and statistically significant effect in reducing the risk of MACE.

Since treatment with immune suppression in transplant medicine and in rheumatic disorders has been found to cause cancers (Geissler 2015, Turesson and Matteson 2013), a pre-specified safety analysis in CANTOS was included to evaluate the development of cancer as an adverse event. This analysis showed that canakinumab reduced the occurrence of lung cancer and lung cancer mortality compared to placebo in a dose-dependent manner. Lung cancer mortality was significantly reduced in subjects treated with the highest canakinumab dose (HR=0.23 [95% CI 0.10-0.54]) and in the pooled canakinumab subjects (p=0.0002 for trend across all active-treated patients) (Ridker et al 2017a). The median hs-CRP at baseline for subjects who were subsequently diagnosed with cancer was 6.0 mg/L. Canakinumab treatment resulted in dose-dependent decrease in hs-CRP of 26-41% and IL-6 decrease of 25-43% (Ridker et al 2017a).

Circulating tumor DNA was detected at baseline in 66% (44/67) of lung cancer subjects from CANTOS, suggesting that these subjects may have had pre-existing cancer at baseline. One hypothesis to explain the lower lung cancer incidence and lower lung cancer mortality is that canakinumab reduced the rate of progression, invasiveness and metastatic spread of already existing tumors, which were too small to be detected at study entry (Ridker et al 2017a). This data along with the preclinical information that IL-1β supports tumorigenic inflammation provides a rationale to investigate the therapeutic role of canakinumab.

[redacted]

Table 1-2 Canakinumab characteristics

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

[redacted]

1.1.2.2 Docetaxel

Docetaxel is a microtubule inhibitor which is approved for a variety of indications, including monotherapy for locally advanced or metastatic NSCLC after platinum therapy failure. Neutropenia is the main dose limiting toxicity. It is dose dependent and reversible with median time to ANC nadir is 7 days and median duration of severe neutropenia (<500 cells/mm^3) of 7 days. Febrile neutropenia and infections grade can occur with increased frequency in patients

[redacted]

with elevated bilirubin or concomitant elevations of alkaline phosphatase (ALP) with AST/ALT (USPI).

Docetaxel is metabolized by the CYP3A4 enzyme: In vivo studies showed that the exposure of docetaxel increased 2.2-fold and its clearance diminished by 49% when it was co-administered with ketoconazole, a potent inhibitor of CYP3A4.

Docetaxel at the dose of 75mg/m^2 is the standard chemotherapy used in NSCLC patients after failure to a prior platinum-based chemotherapy regimen and served as the control arms for several studies exploring the role of PD-(L)1 inhibitors in this setting (Borghaei et al 2015, Brahmer et al 2015, Herbst et al 2016, Rittmeyer et al 2017) described also in the background Section 1.1.1.1.

1.1.3 Potential for drug-drug interactions

Canakinumab is not anticipated to be directly eliminated through hepatic/renal metabolism and excretion to compete with the elimination of docetaxel. Therefore, the risk of drug-drug interaction (DDI) between canakinumab and docetaxel is anticipated to be low. Docetaxel is a CYP3A4 substrate. Therefore, concomitant use of docetaxel and drugs that inhibit CYP3A may increase the exposure to docetaxel and should be avoided. Similarly, concomitant use of docetaxel and drugs that induce CYP3A may reduce the exposure to docetaxel and should be used with caution (Section 6.2).

1.2 Purpose

This phase III study is designed to evaluate canakinumab in combination with docetaxel and the role of IL-1β inhibition in subjects with advanced NSCLC previously treated with PD-(L)1 inhibitors and platinum-based chemotherapy. The randomized III part will be preceded by a safety run-in part in which the recommended dose of the combination of canakinumab and docetaxel will be confirmed.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Safety run-in part**: To confirm the Recommended Phase 3 Regimen (RP3R) of the combination of canakinumab and docetaxel	• Incidence rate of dose limiting toxicities (DLTs) in the first 42 days associated with the administration of canakinumab in combination with docetaxel.
• **Randomized part**: To compare the overall survival (OS) in the docetaxel plus canakinumab arm versus docetaxel plus placebo arm	• OS
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Safety run-in part**: To assess the preliminary clinical anti-tumor activity of canakinumab and docetaxel combination	• ORR, DOR and DCR by investigator's assessment according to RECIST 1.1

[redacted]

Objective(s)	Endpoint(s)
• **Safety run-in part**: To characterize the safety and tolerability of the combination of canakinumab and docetaxel	• Type, frequency and severity of adverse events, changes in laboratory values, vital signs, ECGs
• **Safety run-in part**: To characterize the pharmacokinetics (PK) of canakinumab and docetaxel when given in combination	• Concentration of canakinumab/docetaxel and PK parameters
• **Randomized part**: To evaluate the 2 treatment arms with regards to progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), Time to response (TTR) and duration of response (DOR) based on local investigator assessment per RECIST1.1	• PFS, ORR, DCR, TTR and DOR based on local investigator assessment per RECIST 1.1
• **Randomized part**: To characterize the safety profile of the combination of docetaxel and canakinumab	• AEs ([redacted] ECGs, vital signs and laboratory abnormalities
• **Randomized part**: To assess the effect of docetaxel plus canakinumab vs. docetaxel plus placebo arms on PROs (EORTC QLQ-C30, lung specific module QLQ-LC13 and EQ-5D-5L) including lung cancer symptoms, health-related quality of life and health status	• Time to definitive 10 point deterioration symptom scores of chest pain, cough and dyspnea per QLQ-LC13 questionnaire are primary PRO variables of interest. Time to definitive deterioration in global health status/QoL, shortness of breath and pain per QLQ-C30 are secondary PRO variables of interest. Change from baseline in EORTC-QLQ C30 and LC13, EQ-5D-5L
• **Randomized part**: To characterize the pharmacokinetics of canakinumab when given in combination	• Concentration of canakinumab/docetaxel and PK parameters
• **Randomized part**: To characterize the immunogenicity (anti-drug antibodies, ADA) of canakinumab	• Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment
• **Randomization part:** To assess the effect of docetaxel plus placebo vs. docetaxel plus canakinumab arms on ECOG performance status	• Time to definitive deterioration of the ECOG performance status of the score from baseline.
[redacted]	

3 Study design

This is a multicenter phase III study evaluating the efficacy and safety of canakinumab in combination with docetaxel versus placebo in combination with docetaxel, as second or third line treatment, in adult subjects with advanced NSCLC who have progressed after prior PD-

[redacted]

(L)1 inhibitor. Subjects must have been pre-treated with platinum-based chemotherapy (either given together with the PD-(L)1 inhibitor or sequentially).

This is a 2-part study:

Part 1: Safety run-in ([redacted])

Prior to the randomized part of the study, a safety run-in to confirm the Recommended Phase 3 Regimen (RP3R) of the combination of canakinumab and docetaxel will be conducted.

Approximately 9 subjects will be enrolled in order to have a minimum of 6 evaluable subjects, who will be treated with full doses of docetaxel and canakinumab dose level 1 (DL1): canakinumab 200 mg s.c. + docetaxel 75mg/m^2 i.v. on Day 1 of each 21-day cycle.

Subjects will be assessed for at least 2 complete cycles of treatment (21 days per cycle; a total of 42 days) for safety evaluation (DLT-Dose Limiting Toxicities) to define RP3R. Once this dose and schedule are confirmed, the randomized part of the study will begin.

All subjects will be followed for efficacy and safety evaluations as outlined in detail in Section 8 and continue being treated until reasons for discontinuation of study treatment are met (Section 9.1.1).

[redacted] If judged necessary, additional subjects might be enrolled in the Dose Level 1 (DL1) cohort, or a de-escalation to Dose level minus 1 (DL-1) might also be considered. There will be no dose de-escalation beyond DL-1. Please refer to Section 6.5.1.2 for more details on the determination of the RP3R.

[redacted]

Part 2: Double-blind, randomized, placebo controlled part (including the option to transition to the Open Label Extension) [redacted]

Once the RP3R for the combination of canakinumab with docetaxel has been confirmed in part 1, the randomized, double blind, placebo controlled part of the study will open.

Approximately 226 subjects will be randomized in a 1:1 ratio to either docetaxel with canakinumab or docetaxel with placebo after the subject has met all entry criteria:

- Arm A:canakinumab s.c at RP3R + docetaxel 75mg/m^2 i.v. Q3W

[redacted]

- Arm B:placebo s.c. at RP3R + docetaxel 75mg/m^2 i.v. Q3W

Screening phase and enrollment/randomization

Subjects must sign an informed consent form (ICF) prior to any study specific screening evaluations and as early as 28 days prior to the enrollment (safety run-in) / randomization.

Following completion of all required screening procedures (refer to Section 8) and verifying subject eligibility, the subject will be enrolled (safety run-in part) or randomized via the Interactive Response Technology (IRT) system to one of the 2 treatment arms described above. The randomization will be stratified based on number of prior lines of therapy in the advanced setting (1 prior line of therapy versus 2 prior lines of therapy) and histology (squamous vs. non-squamous).

Treatment phase:

Study treatment will begin on Cycle 1 Day 1 with the first administration of study treatment. Subjects will continue treatment until reasons for discontinuation of study treatment are met (Section 9.1.1).

[redacted]

Subjects will be evaluated radiologically at baseline then every 6 weeks during the first 12 months, and every 12 weeks thereafter to assess treatment response until PD by RECIST 1.1 as assessed by investigators.

An end of treatment visit will be performed when subjects permanently discontinue study treatment.

No crossover treatment from placebo to canakinumab is allowed.

Post treatment safety and efficacy follow-up

After treatment discontinuation, all subjects will be followed for safety evaluations as outlined in detail in Section 8 during the safety follow up period.

Due to the long half-life of canakinumab (26 days), subjects will be followed for safety up to 130 days (5 times the half-life) after the last dose of canakinumab/placebo. In case new anti-neoplastic therapy is initiated, safety follow-up will focus on events suspected to be related to study treatment only.

In addition to the 130 days safety follow up, subjects who discontinue study treatment without prior documented PD, will continue efficacy assessments in the efficacy follow up phase, irrespective of the start of new anti-neoplastic therapy, and until documented PD as per investigator, subject withdrawal of consent, physician's decision, pregnancy, lost to follow up, death or study is terminated by the sponsor as outlined in Section 8.

Survival follow-up

[redacted]

After study treatment discontinuation, the subject's survival status will be collected every 12 weeks as part of the survival follow up.

Overall Survival being the primary endpoint in this trial, every effort should be made to comply with the survival follow up schedule and ensure the collection of patient survival data.

[redacted]

If statistical significance is not reached at the final OS analysis, the study will end after all subjects have discontinued study treatment (Section 9.2).

[redacted]

4 Rationale

4.1 Rationale for study design

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

Table 4-1 Rationale for study design

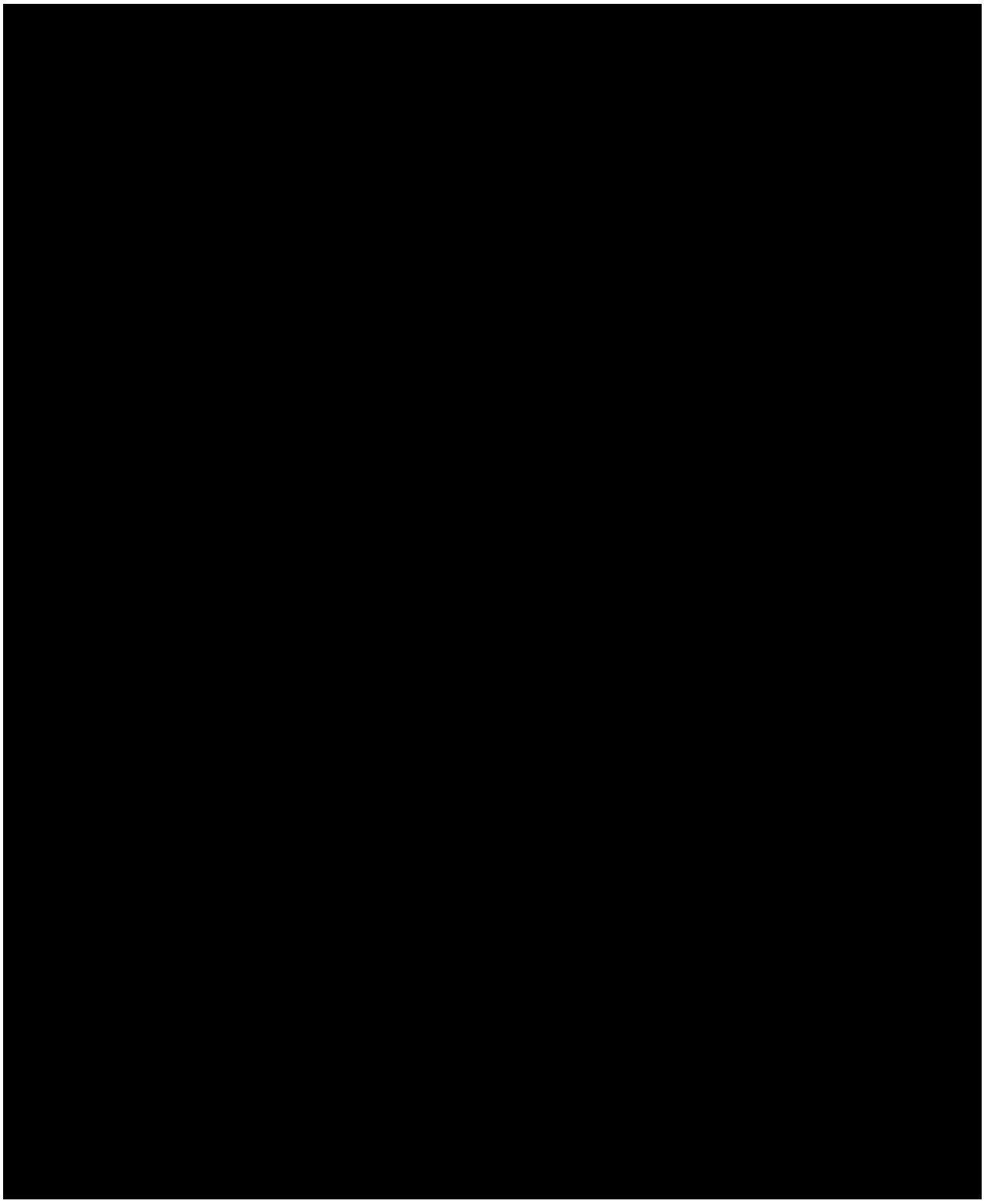
Study Design Aspect	Rationale
Subject population	The study will enroll subjects who are docetaxel naive, and candidates for therapy with docetaxel, that will be used as the combination partner and comparator. Subjects with targeted oncogenic drivers (EGFR or ALK) will be excluded (Section 5).
Two-parts study including a Safety run-in	The randomized phase III will be preceded by a safety run-in in order to confirm the dose of the combination of canakinumab and docetaxel [redacted]
Randomization stratification factors: • number of prior lines of therapy in the advanced setting (1 prior line of therapy vs. 2 prior lines of therapy) • histology (squamous vs. Non-squamous).	The stratification factors have been selected to balance prognostic factors between the two arms • Subgroup analyses of overall survival in recently published non-squamous NSCLC study showed difference in treatment effect by line of therapy (Borghaei et al. 2015). • Median overall survival in subjects with squamous NSCLC is expected to be shorter than in subjects with non-squamous NSCLC histology regardless of treatment (Brahmer et al. 2015; Borghaei et al. 2015).
Placebo control and Double blinding	This is to reduce bias in investigator assessment of efficacy, safety and PRO outcomes.
No treatment cross-over from placebo to canakinumab arm after disease progression as per RECIST 1.1 will be allowed.	This is to reduce confounding in OS outcome

4.1.1 Rationale for choice of background therapy

No treatment is approved after failure to a PD-(L)1 inhibitor and platinum based chemotherapy; commonly, docetaxel is used as a standard of care. Observations from studies investigating docetaxel in subjects with NSCLC of all histologies who have failed a platinum based chemotherapy, indicate that docetaxel monotherapy results in a median PFS of 2.8 to 4.2 months and median OS of 8.5 to 9.6 months (Brahmer et al 2015, Borghaei et al 2015, Herbst et al 2016, Rittmeyer et al 2017). No data however are available assessing the efficacy of docetaxel after failure to PD-(L)1 inhibitors beyond anecdotal case reports (Park et al 2018, Schvartsman et al 2017). Therefore, based on these data, and given the different mechanism of action of docetaxel and PD-(L)1 inhibitors, it is expected that efficacy with docetaxel after PD-(L)1 inhibitor therapy would be similar to the one observed with docetaxel in PD-(L)1 inhibitor naive subjects. Docetaxel will thus be used as backbone chemotherapy. It also has a well-established safety profile and no overlapping toxicities or major DDI are expected when combined with canakinumab (Section 4.2).

[redacted]

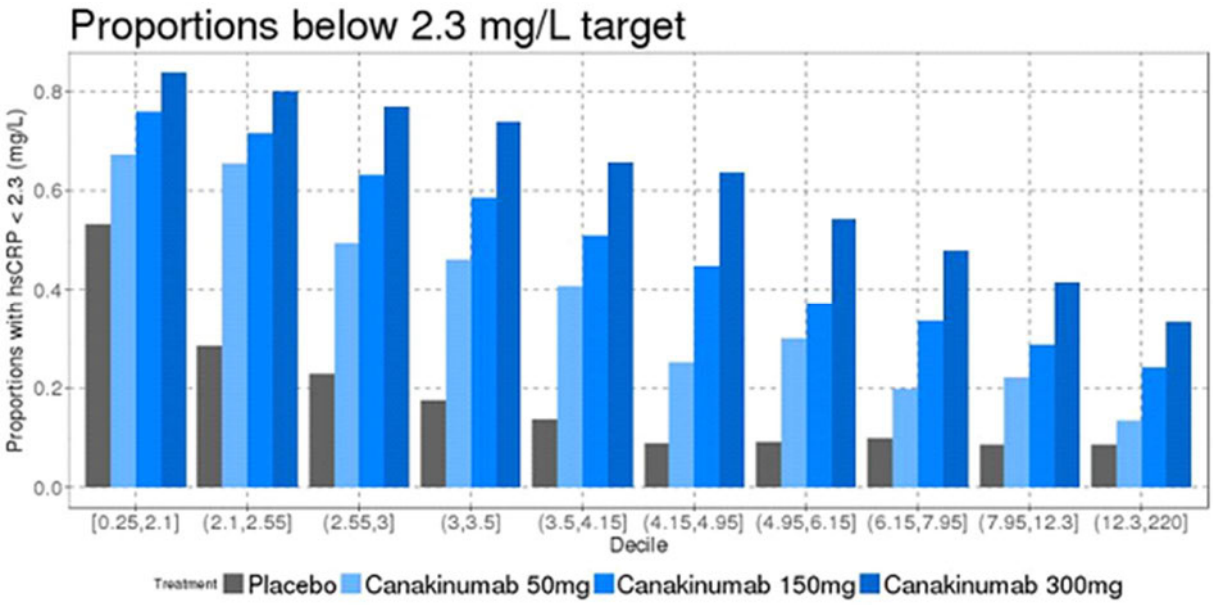
4.2 Rationale for dose/regimen and duration of treatment



4.2.2 Efficacy and pharmacodynamics (PD) considerations

The different median baseline hs-CRP levels among canakinumab-treated subjects in CANTOS who were subsequently diagnosed with cancer compared to those who were not (median 6.0 mg/L [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 2017b) 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. Studies examining hs-CRP levels in Stage I through Stage III NSCLC subjects show that higher hs-CRP levels is correlated with higher stage and poor prognosis (Alifano et al 2011, Hara et al 2010, Vaguliené et al 2011).

Figure 4-2 Proportions of subjects with hs-CRP < 2.3 mg/L by baseline hs-CRP deciles 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 consideration

Refer to Section 1.1.2 and the current canakinumab Investigator's Brochure. The canakinumab dose and schedule being explored in this phase III study is similar in terms of pharmacokinetics to the already approved in non-oncology indications 300mg Q4W regimen (Section 4.2.1). Several canakinumab trials are ongoing in oncology: in particular, canakinumab is being evaluated in subjects with advanced NSCLC in an ongoing phase 1b study, [CPDR001X2103]. This study is examining the safety and tolerability of PDR001, a PD-1 inhibitor from Novartis, in combination with various targeted therapies or immunotherapies, including canakinumab. It has shown that canakinumab at 600 mg s.c. Q8W is safe to be combined with PDR001 administered at 400 mg i.v. Q4W (RP2D). Based on preliminary population PK simulation, 600

mg s.c. Q8W generates steady-state Cmax greater than that attained at the selected NSCLC dose of 200 mg s.c. Q3W. Therefore, no unexpected safety issues are expected with the administration of canakinumab at the doses of 200 mg Q3W in NSCLC subjects.

4.2.4 Consideration for combination with docetaxel

There are no data available defining the recommended doses of docetaxel and canakinumab when given in combination. These will be confirmed in the first part of this study (safety run in). At least 6 subjects will receive the two drugs and be followed for 42 days to confirm the starting dose of the combination. Once this dose is confirmed, the randomized part of the study will begin.

Full dose of docetaxel (75mg/m^2 Q3W) and canakinumab (200 mg Q3W) will be given as starting dose for the combination in the safety run-in:

- The risk of DDI between canakinumab and docetaxel is anticipated to be low as described in Section 1.1.3. The PK of docetaxel and canakinumab will be characterized in this study, so that DDI, if any, between these two agents, can be explored.
- There are two key toxicities overlapping between canakinumab and docetaxel:
  - Neutropenia:
    - When docetaxel is given at the dose of 75mg/m^2 Q3W in pre-treated NSCLC subjects (Borghaei et al 2015, Brahmer et al 2015, Rittmeyer et al 2017), neutropenia (reported as treatment related adverse event) range between 14-33% all grades, and 12-30% grade 3-4; with febrile neutropenia rates between 10 and 11%.
    - In the CANTOS study, all-grade neutropenia was reported in 2.0% vs. 0.9% in subjects treated with canakinumab 300 mg vs. placebo, respectively. However, the rate of severed neutropenia (grade 3) was below 1% and similar to placebo. There was no grade 4 neutropenia in subjects treated with any canakinumab dose.
  - Infections:
    - In docetaxel arms of recent clinical studies, no infection was reported at a rate above 5% (Brahmer et al 2015, Rittmeyer et al 2017) or 10% (Borghaei et al 2015). However, cases of death due to febrile neutropenia (1 subject out of 268; Borghaei et al 2015); to respiratory infection (1 out of 578 subjects; Rittmeyer et al 2017) and to sepsis (1 out of 129 subjects; Brahmer et al 2015) were reported in these studies.
    - In the CANTOS study, infections were one of the most frequently reported adverse events. In the 300 mg dose, the rate of viral upper respiratory tract infection was 12.5-13.9% (range of frequency across 50 to 300 mg doses) of canakinumab-treated subjects versus 12.3% in the placebo group.

Elevated bilirubin, AST, ALT and alkaline phosphatase are uncommonly observed with either drug. However, during treatment with docetaxel, subjects with elevation of bilirubin or abnormalities of transaminases concurrent with alkaline phosphatase are at increased risk of developing grade 4 neutropenia, febrile neutropenia, infections and other toxicities. Monitoring of bilirubin and liver function tests will be required during the course of this study as per assessment schedule in Table 8-2 and Table 8-3.

[redacted]

4.2.5 Conclusion for dose regimen selection

Every 3 weeks dosing schedule of canakinumab is feasible based on its half-life of 26 days, and its ability to suppress CRP for at least 1 month as previously demonstrated in two single-dose phase 2 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. 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. Lastly there is a high likelihood that the full dose of docetaxel and canakinumab can be combined together given the limited risk of overlapping safety profile and low risk of DDI. The protocol includes appropriate safety assessment to monitor and manage these risks (please refer to Section 6.5 for further details).

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

Following progression after platinum based chemotherapy, docetaxel monotherapy is considered a standard of care. Given the different mechanism of action of docetaxel and PD-(L)1 inhibitors, one can assume that docetaxel efficacy outcomes post PD-(L)1 inhibitor therapy should remain similar to the one observed with docetaxel in PD-(L)1 inhibitor naive subjects. Docetaxel will thus be used as comparator therapy.

4.4 Purpose and timing of interim analyses/design adaptations

The purpose and timing of the OS interim analysis is detailed in Section 12.7.

4.5 Risks and benefits

The intended study population is non-small cell lung cancer (NSCLC) subjects previously treated with platinum-based chemotherapy and PD-(L)1 inhibitors. In this patient population, safety and efficacy of docetaxel has been well-established since its approval in 1996. Canakinumab or a matching placebo will be administered on the same treatment day as docetaxel. The use of placebo is necessary to minimize bias when assessing efficacy and safety of the combination treatment.

Because of different mechanisms of action and different metabolism, there is no expected significant drug-drug interaction. As a result, adding canakinumab is not likely to change the established safety profile of docetaxel with a potential exception of neutropenia and infections (overlapping toxicities). Treatment with the combination could potentially result in a higher rate and/or grade of neutropenia and infections. The incidence and severity of all adverse events, but in particular: neutropenia, infections and pre-defined dose-limiting toxicities will be assessed in a safety run-in part before the start of randomization. During the study, the risks associated with neutropenia and infections will be minimized by following the monitoring procedures prior to each docetaxel and canakinumab/ placebo administration and by modifying

[redacted]

the dose as stated in the protocol. Docetaxel has genotoxic effects and may alter male fertility. Therefore, men being treated with docetaxel are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

Canakinumab is approved for pediatric indications in subjects 2 years and older. In animal embryo-fetal development studies with canakinumab, there was no evidence of embryotoxicity or fetal malformations. However, docetaxel can cause fetal harm when administered to a pregnant woman. This study will exclude pediatric subjects, women who are pregnant, could become pregnant or are currently nursing. Women of childbearing potential and sexually active males will be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

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

In the CANTOS study, the incidence of lung cancer was lower among subjects treated with canakinumab vs. placebo (see Section 1.1.2.1 for details about CANTOS study). Through the same mechanisms, canakinumab may potentially improve outcomes (overall survival, progression-free survival and objective response) while maintaining the overall quality of life in the intended population of this study.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol. The risk to subjects in this study may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Given a potential overall survival benefit and a manageable risk of potential infections, canakinumab in combination with docetaxel has a favorable risk-benefit ratio in the defined study population.

5 Population

The study population will include adult subjects with locally advanced or metastatic (stage IIIB-IV) non-small cell lung cancer, who have been previously treated with and progressed on platinum-based chemotherapy and PD-(L)1-inhibitor (either in combination or sequentially). Subjects must be docetaxel naive. Prior neo-adjuvant or adjuvant systemic therapy may be allowed if relapse has occurred more than 12 months from the end of the therapy as outlined below.

Subjects with targetable oncogenic drivers (EGFR-sensitizing / ALK rearrangement) will be excluded.

[redacted]

5.1 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures
2. Subject is an adult male/female ≥ 18 years of age at the time of informed consent
3. Histologically confirmed locally advanced/metastatic (stage IIIB-IV) NSCLC
4. Subject has received one prior platinum-based chemotherapy and one prior PD-(L)1 inhibitor therapy for locally advanced or metastatic disease:
   - Subject may have received the platinum based chemotherapy for advanced or metastatic disease and the PD-(L)1 inhibitor either together (in the same line of treatment) or sequentially (two different lines of treatment) and then progressed
   - Subject who received the PD-(L)1-inhibitor as maintenance (no progression on platinum-doublet chemotherapy) and progressed on PD-(L)1 are eligible
   - Subjects who received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and a PD-(L)1 inhibitor and developed recurrent or metastatic disease while on or within 12 months of completing therapy are eligible
   - Subjects with recurrent disease > 12 months after adjuvant or neoadjuvant platinum based chemotherapy, who also subsequently progressed during or after a platinum doublet regimen and a PD-(L)1 inhibitor (given either together or sequentially to treat the recurrence), are eligible
5. Subject with ECOG performance status (PS) of 0 or 1
6. Subject with at least 1 evaluable (measurable or non-measurable) lesion by RECIST 1.1 in solid tumors criteria.
7. Subject must have recovered from all toxicities related to prior systemic therapy to grade ≤ 1 [redacted]. Exception to this criterion: subjects with any grade of alopecia
8. Subjects must have adequate organ function including the following laboratory values at the screening visit:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (without growth factor support)
   - Platelets ≥ 100 x 10^9/L (without growth factor support)
   - Hemoglobin (Hgb) > 9 g/dL (4 weeks without transfusions or erythropoietin)
   - Aspartate transaminase (AST) ≤ 3 x ULN
   - Alanine transaminase (ALT) ≤ 3 x ULN
   - Total bilirubin ≤ ULN
   - Serum amylase ≤2 x ULN or pancreatic amylase ≤ 1.5 x ULN
   - Serum lipase ≤ 1.5 x ULN
   - Creatinine clearance ≥ 60 mL/min by calculation using Cockcroft-Gault formula
9. Subject must be able to communicate with the investigator and comply with the requirements of the study procedures.

5.2 Exclusion criteria

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

[redacted]

1. Patient who previously received docetaxel, canakinumab (or another IL-1β inhibitor), or any other systemic therapy for their locally advanced or metastatic NSCLC other than one platinum-based chemotherapy and one prior PD-(L)1 inhibitor.
2. Subject with EGFR-sensitizing mutation and/or ALK rearrangement by local laboratory testing
   - Note: Subjects with NSCLC of pure squamous cell histology can initiate treatment without EGFR or ALK testing or result, however, subjects with pure squamous cell histology that are known to have EGFR/ALK sensitizing mutations are excluded.
   - Subjects with known BRAF V600 mutation or ROS-1 rearrangement will be excluded, if required by local guidelines
3. History of severe hypersensitivity reaction to monoclonal antibodies, taxanes or any known excipients of these drugs (i.e. Polysorbate-80-containing infusions, mannitol, histidine).
4. Previously untreated or symptomatic central nervous system (CNS) metastases or lepto-meningeal disease.

   Note: subjects with treated CNS metastases with radiotherapy and/or surgery, without evidence of CNS disease progression ≥4 weeks after treatment completion and off corticosteroid therapy for ≥ 2 weeks prior to treatment start are eligible.
5. Presence or history of a malignant disease, other than the resected NSCLC, 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
6. Subject with suspected or proven immunocompromised state or infections, including:
   - Evidence of active or latent tuberculosis (TB) as determined by locally approved screening methods. If the screening results require treatment as per local guidelines or clinical practice, then the patient is not eligible.
   - Chronic or active hepatitis B or C.
   - Known history of testing positive for Human Immunodeficiency Virus (HIV) infections. For countries where HIV testing is mandatory: testing positive for HIV during screening using a local test.
   - Any other medical condition (such as active infection, treated or untreated), which in the opinion of the investigator places the patient at an unacceptable risk for participation in immunomodulatory therapy.
     - Note: Subjects with localized condition unlikely to lead to a systemic infection e.g. chronic nail fungal infection are eligible.
   - Allogeneic bone marrow or solid organ transplant
   - Treatment with any immune modulating agent in doses with systemic effects e.g.:
     - Prednisone >20 mg (or equivalent) oral or intravenous daily for > 14 days;
     - Prednisone >5 mg and ≤20 mg (or equivalent) daily for > 30 days;
     - Equivalent dose of methotrexate > 15 mg weekly
     - Subject receiving any biologic drugs targeting the immune system (for example, TNFa blockers, anakinra, rituximab, abatacept, or tocilizumab).

[redacted]

- Note: Daily glucocorticoid-replacement for conditions such as adrenal or pituitary insufficiency is allowed.
- Note: Topical, inhaled or local steroid use in doses that are not considered to cause systemic effects are permitted.
- Note: Steroids for pre-medication related to chemotherapy as per local standard of care are permitted.

7. Subject has received live vaccination within 3 months prior to first dose of study drug.
8. Subject has had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to starting study drug or has not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and subject can be enrolled in the study ≥1 week after the procedure.
9. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or subjects who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment is allowed.
10. Grade ≥2 motor or sensory neuropathy symptoms
11. Clinically significant, uncontrolled cardiac disease and/or recent cardiac event (within 6 months), such as:
    - Unstable angina or myocardial infarction within 6 month prior to screening
    - Symptomatic congestive heart failure (defined as New York Heart Association Grade II or greater)
    - Documented cardiomyopathy
    - Clinical significant cardiac arrhythmias
    - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, unless controlled prior to screening
12. History of interstitial lung disease or pneumonitis grade ≥ 2
13. Uncontrolled diabetes as defined by the investigator.
14. Known active or recurrent hepatic disorder including cirrhosis.
15. Subject has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment cause unacceptable safety risks, contra-indicate patient participation in the clinical study or compromise compliance with the protocol (e.g. chronic pancreatitis)
16. Subject is currently receiving treatment with drugs known to be strong inhibitors or strong inducers of isoenzyme CYP3A. The patient must have discontinued strong inhibitors or strong inducers before the treatment is initiated. Switching to a different medication prior to randomization is allowed. Please refer to the Table 16-12 for a list of strong inhibitors or strong inducers of CYP3A4
17. Patient is concurrently using other anti-cancer therapy

[redacted]

18. Participation in a prior investigational study within 30 days prior to enrollment or within 5 half-lives of the investigational product (other than chemotherapy or checkpoint inhibitors), whichever is longer or those who are expected to receive any other investigational drug or device during the conduct of the study.
19. Pregnant or breast-feeding (lactating) women or women who plan to become pregnant or breast-feed during the study. Pregnant or nursing women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
20. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during the study and 6 months after chemotherapy discontinuation. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or 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 subjects 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 childbearing 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 six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.
21. Sexually active males unless they use a condom during intercourse while taking drug and during 6 months after chemotherapy discontinuation and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

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

[redacted]

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

For this study, the term "investigational or study drug" refers to Novartis study drug canakinumab.

The other drug to be used in this study is docetaxel. "Study treatment" refers to the combination of canakinumab (or matching placebo) and docetaxel.

Canakinumab or matching placebo will be supplied by Novartis in the form of solution for injection as ready-to-use pre-filled syringes. Two strengths and respective corresponding matching placebos will be supplied (refer to Table 6-1).

Docetaxel will be procured locally as it is commercially available in each participating country .

Table 6-1 Investigational / control drugs / placebo

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	150mg/1mL AND 50mg/0.5mL	200 mg	Q3W or Q6W[a]
Placebo		0mg/1mL AND 0mg/0.5mL	0 mg	
Docetaxel	Concentrated solution for i.v. preparation	strength varies from suppliers	75 mg/m^2	Q3W

[a] Depending on RP3R (recommended phase 3 regimen) defined during safety run-in part (Part 1)

The study drug, canakinumab/placebo will be given as subcutaneous injections. All injections (one syringe of 1 mL and one syringe of 0.5 mL) will be administered at study sites by trained site staff.

Storage conditions are described in the medication label. Medication labels will comply with the legal requirements of each country and be printed in the local language.

The Recommended phase 3 Regimen (RP3R) of canakinumab in combination with docetaxel will be confirmed during the safety run-in part of the study (please refer to Section 6.5.1 for more details).

Docetaxel will be given as an intravenous infusion (75 mg/m^2) on Day 1 of each 21 days cycles, as per product label and local practice.

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

6.1.1.1 Supply and administration of study treatment

Supply of study treatment

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

[redacted]

Docetaxel will be provided locally by the study site, subsidiary or designee as commercially available, in each participating country according to local clinical practices and local regulations.

Administration of study treatment

Canakinumab or placebo (one syringe of 1 mL and one syringe of 0.5 mL) will be administered by study site personnel via subcutaneous injections once every 3 weeks or 6 weeks as determined in part 1 (safety run-in part). Subjects should be provided instructions to notify the study site personnel if symptoms of injection reaction occur after any canakinumab injection.

The administration and infusion durations of docetaxel should follow the locally approved label and local practice.

6.1.2 Additional study treatments

All subjects should be premedicated with oral corticosteroids per local practice, such as for example dexamethasone 16 mg per day (e.g., 8 mg b.i.d.) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Alternative premedication dosing or schedule may be administered as per local label or clinical practice.

6.1.3 Treatment arms/group

Part 1: Safety run-in

In the safety run-in part of the study, subjects will be treated with docetaxel in combination with canakinumab as described below:

- canakinumab 200 mg, s.c + docetaxel 75mg/m^2 i.v. on Day 1 of each 21-day cycle

Note: dose level minus 1 (DL-1), i.e., canakinumab 200 mg, s.c. Q6W + docetaxel 75 mg/m^2, i.v. Q3W, may be investigated after review of the data collected for the canakinumab 200 mg, s.c. Q3W regimen (Section 6.5.1.1).

Part 2: Double-blind, randomized, placebo controlled

In the randomized part of the study, subjects will be assigned at Cycle 1 Day 1 to one of the following 2 treatment arms/groups in a ratio of 1:1

- Arm A: canakinumab at RP3R + docetaxel 75mg/m^2 i.v. every 21 days
- Arm B: placebo at RP3R + docetaxel 75mg/m^2 i.v. every 21 days

[redacted]

6.1.4 Guidelines for continuation of treatment

Subject should continue to receive the study treatment until one or more criteria for treatment discontinuation described in Section 9.1.1 are met.

[redacted]

In case docetaxel is permanently discontinued because of unacceptable toxicities, the investigator can continue canakinumab/ placebo treatment until disease progression as long as:

- There is no clinical or radiologic evidence of disease progression;
- The patient is continuing to benefit from study drug treatment as assessed by the Investigator;
- The patient clearly understands the risks associated with continuing treatment with canakinumab/ placebo.

6.1.5 Treatment duration

Subjects will continue to receive study treatment until reasons for discontinuation of study treatment are met (Section 9.1.1). No crossover treatment from placebo to canakinumab is allowed in the blinded randomized part. [redacted]

6.1.5.1 Treatment beyond disease progression

Not applicable

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In general, the use of any concomitant medication/therapy deemed necessary for the care of the subject (e.g. such as Granulocyte colony-stimulating factor (G-CSF), anti-emetics, anti-diarrhea) is permitted except when specifically prohibited (see Section 6.2.2).

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

Prior treatment for tuberculosis infection should be listed on the eCRF. Influenza vaccines administered two years prior to study start and pneumococcal vaccines administered five years prior to study start should be recorded on the eCRF. Vaccinations taken during the trial should also be reported on the eCRF. Subjects must be discontinued from the trial if administered any live vaccine during the course of the study (see Section 6.2.2).

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). Caution should be exercised when administering small molecule drugs with narrow therapeutic index, such as warfarin (Table 16-13) concomitantly with canakinumab.

[redacted]

Given the potential DDI via cytokine modulation by canakinumab, subjects who are on warfarin or warfarin like treatment with narrow therapeutic index should have their international normalized ratio (INR) measured locally and warfarin or warfarin like treatment dose adjusted accordingly within one month from starting study treatment. No PK DDI is expected between warfarin and docetaxel as these two drugs are eliminated by different CYP-mediated enzymes (warfarin by CYP2C9, docetaxel by CYP3A) and are not inhibitor/inducer of each other's metabolism.

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

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. 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 enrolled, 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 Palliative radiotherapy

Palliative radiation is permitted. It should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow (see Section 16.1).

If palliative radiotherapy is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out.

No dose modification of study drug (canakinumab/placebo) is needed during palliative radiotherapy.

6.2.2 Prohibited medication

6.2.2.1 Prohibited medications for canakinumab/placebo

Use of any treatments below is 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 study treatment.

- Any anti retro-virals and / or any biologic drugs targeting the immune system (e.g., TNFa blockers, anakinra, rituximab, abatacept, tocilizumab)
- Treatment with any immune modulating agent in doses with systemic effects e.g.:
  - Prednisone >20 mg (or equivalent) oral or intravenous daily for > 14 days;
  - Prednisone >5 mg and ≤20 mg (or equivalent) daily for > 30 days;
  - Equivalent dose of methotrexate > 15 mg weekly
  - Topical, inhaled or local steroid use in doses that are not considered to cause systemic effects are permitted
  - Washout period is not mandated, but the steroid half-life and tapering schedule need to be considered in patients treated with chronic high dose steroids

[redacted]

- Steroids for pre-medication related to chemotherapy as per local standard of care are permitted

- Live and attenuated vaccines within 3 months of study treatment and after initiation of study drug. Subjects must be discontinued from the trial if administered any live vaccine during the course of the study

Any additional investigational drugs, devices, chemotherapy, or any antineoplastic therapies that may be active against cancer are NOT allowed after the start of study treatment and until the end of study treatment

6.2.2.2 Prohibited medications for docetaxel

Increased docetaxel toxicity has been observed when concomitant administration of strong CYP3A4 inhibitors (antifungals, ritonavir, macrolides). The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided (see Section 16.3). If the concomitant use of a strong CYP3A4 inhibitor cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of docetaxel may be suitable during the treatment with the strong CYP3A4 inhibitor. Please follow local guidelines as per standard of care and product labels. In patients treated with strong CYP3A4 inhibitors, the washout period is not mandated, but the strong inhibitor's half-life needs to be considered.

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.

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

The investigator or designated staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT.

Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed. If the subject fails to be enrolled (safety run-in) or randomized or start treatment for any reason, the reason will be entered into the appropriate eCRF.

6.3.2 Treatment assignment, randomization

Prior to dosing, for all subjects who fulfill all inclusion/exclusion criteria, the investigator or his/her delegate will log on to the IRT system and confirm that the subject fulfills all the inclusion/exclusion criteria by completing the key eligibility criteria checklist embedded in the system.

Part 1: Safety run-in

[redacted]

During the safety run-in part, approximately 9 subjects will be enrolled in order to have at least 6 evaluable subjects. They will be enrolled via IRT to treatment with canakinumab in combination with docetaxel.

Part 2: Randomized

During the randomized part, approximately 226 subjects will be randomized via IRT to one of two treatment arms (canakinumab in combination with docetaxel or placebo in combination with docetaxel) in a 1:1 ratio.

During the randomized part, 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 number will not be communicated to the caller. 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. Random permuted blocks scheme will be used for this study. The randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

A separate medication randomization list will be produced by or under the responsibility of Novartis Global Clinical Supplies (GCS) using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study treatments.

Randomization will be stratified during screening by the number of prior lines of therapy received and histology (squamous vs. non-squamous). Please refer to Section 16.4 for the eligibility algorithm.

During Part 1 and Part 2 of the study, the study treatment phase begins on Cycle 1, Day 1 with the first administration of study treatment. Cycle 1 Day 1 should occur no later than 3 days after registration into IRT system.

[redacted]

6.4 Treatment blinding

Part 1: Safety run-in part

Not applicable.

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

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

OS interim analysis will be performed by an independent statistician and reviewed by a data monitoring committee (DMC). Unblinded results from the Interim Analysis (IA) for OS will not be communicated to the Sponsor's clinical team or to any party involved in the study conduct (apart from the independent statistician and DMC members) until the DMC has determined that

[redacted]

either: (i) interim OS analyses has crossed the pre-specified boundary for efficacy or (ii) the study needs to be terminated due to any cause including safety reasons. Investigators and subjects will remain blinded to study treatment until OS is statistically significant at the interim or final analyses.

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

[redacted]

6.5 Dose escalation and dose modification

6.5.1 Dose confirmation guidelines

6.5.1.1 Starting dose

The starting dose is 75mg/m^2 Q3W for docetaxel and 200 mg s.c. Q3W for canakinumab. Should the regimen not be feasible, an alternative schedule will be implemented with increasing the interval of canakinumab administration from Q3W to Q6W while maintaining the dose of canakinumab and maintaining the dose and schedule of docetaxel. Please refer to Table 6-2.

The recommended regimen to be used for the randomized part of the study will be the one determined at the end of the safety run-in part.

Table 6-2 Dose levels

Dose level	Dosing and schedule	Change from previous regimen
Dose level 1 (DL1)	Canakinumab 200 mg, s.c., Q3W + Docetaxel 75mg/m^2, i.v., Q3W	Starting dose
Dose level minus 1 (DL-1)*	Canakinumab 200 mg, s.c., Q6W + Docetaxel 75mg/m^2, i.v., Q3W	Change in canakinumab frequency of administration
* it is possible for additional and/or intermediate regimen/dose levels to be added during the course of the study based on emerging data.		

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

For the purposes of confirming the recommended dosing regimen for canakinumab in combination with docetaxel to be used in the randomized part of the study, each cohort will consist of a minimum of 6 newly enrolled subjects who will be treated at the specified dose level.

[redacted]

The first cohort of 6 subjects will be treated with the starting Dose Level 1. Each subject will be considered evaluable for dose decision if he/ she has completed 42 days of treatment with minimum drug exposure ≥50% or experienced a Dose Limiting Toxicity (DLT- refer to Section 6.5.2) during the first 42 days of treatment.

Dose regimen decision will be made by Dose Level Review Team (DLRT) consisting of the Novartis team including at least one clinician, drug safety representative, biostatistician and at least one investigator participating in the study who has enrolled subjects into the safety run-in part of the study. Decision will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, (DLTs), all CTCAE [redacted] Grade ≥ 2 toxicity, and PK data during the first 42 days of combination treatment from evaluable subjects.

[redacted]

If the first 2 subjects in a cohort experience a DLT, further enrollment to that cohort will stop. The BLRM will be updated with this new information and re-evaluation of the available safety, PK, and PD data will occur. By incorporating information gained at the preceding dose levels, additional subjects may be enrolled into the current dose level only if the combination still meets the EWOC criteria. Alternatively, if recruitment to the same dose level may not resume, a new cohort of subjects may be recruited to a dose level-1 (Section 6.5.1.1) as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk that this lower dose exceeds toxicity remains below 25% (EWOC). Re-escalation may then occur if data in subsequent cohorts supports this (EWOC criteria are satisfied) and Investigators and Novartis personnel agree.

The recommended dose regimen is confirmed when the following conditions are met:

1. At least 6 evaluable subjects have been treated at this dose and observed for 42 days
2. This dose satisfies the EWOC criteria
3. The selected regimen is recommended either per the model or by review of all clinical data by the members of the Dose Level Review Team (DLRT).

If the Dose Level Review Team (DLRT) cannot confirm the Dose Level 1 based on the available data, the team will make a recommendation to either expand the cohort for additional subjects in Dose Level 1 or enroll a minimum of 6 subjects in Dose Level -1.

6.5.1.3 Implementation of dose regimen decisions

To implement dose regimen decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. Drug administration at another next lower dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is the recommended regimen to proceed with.

[redacted]

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

6.5.1.4 Implementation of dose escalation decisions

Not applicable

6.5.1.5 Intra-Subject dose escalation

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

6.5.2 Definitions of dose limiting toxicities (DLTs)

Dose-limiting toxicities will be collected and used in the safety run-in part of the study. A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to the underlying disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 42 days of treatment with docetaxel and canakinumab and meets any of the criteria included in Table 6-3 . The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) [redacted] will be used for all grading. In addition to DLTs, the decision about the recommended Phase 3 dose will be based on a synthesis of all relevant data available including all CTCAE [redacted] Grade ≥ 2 and PK data during the first 42 days of combination treatment from evaluable subjects.

The investigator must notify the sponsor immediately of any DLT.

Table 6-3 Criteria for defining dose-limiting toxicities

TOXICITY	**DLT CRITERIA** (NCI CTCAE v5.0 will be used for grading)
Hematological	• Grade 4 neutropenia lasting more than 14 days • Grade 4 febrile neutropenia • Grade 4 anemia • Grade 3 thrombocytopenia with clinically significant bleeding (i.e. life threatening and invasive intervention indicated) regardless of duration or requirement for transfusion • Grade 4 thrombocytopenia
Infection	• Drug-related Grade 4
Cutaneous reactions	• ≥ Grade 3
Peripheral neuropathy	• ≥ Grade 3

Hepato-biliary	• Grade 4 bilirubin elevation
	• For subjects with normal baseline AST and ALT values:
	  • AST or ALT > 8.0 × ULN
	• For subjects with normal baseline AST and ALT and normal baseline bilirubin value:
	  • AST or ALT > 3.0 × ULN combined with total bilirubin > 2.0 × ULN without evidence of cholestasis
	• For subjects with abnormal baseline AST or ALT or abnormal baseline bilirubin value:
	  • [AST or ALT > 2 × baseline AND > 3.0 × ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 × baseline AND > 2.0 × ULN] without evidence of cholestasis

[redacted]

TOXICITY	DLT CRITERIA (NCI CTCAE [redacted] will be used for grading)
Pneumonitis	• Grade 2 pneumonitis if it persists > 7 days despite treatment with corticosteroids. • ≥ Grade 3 pneumonitis of any duration
Gastrointestinal	• Nausea and vomiting ≥ Grade 3 for > 3 days despite optimal anti-emetic therapy. • ≥ Grade 3 diarrhea for > 5 days despite optimal antidiarrheal treatment (which could include steroids).
Pancreas	• Symptomatic serum amylase or lipase elevation, medical intervention required (Pancreatitis Grade 3 or higher)
Hypertension	• ≥ Grade 3 hypertension related to the study medication if it persists > 7 days despite optimal anti-hypertensive treatment • Grade 4 hypertension of any duration
Cardiac	• ≥ Grade 3 cardiac event that is symptomatic or requires medical intervention
Other Adverse Events	Other clinically significant adverse events: • ≥ Grade 3 adverse event that has not been previously identified for docetaxel and/or canakinumab. • ≥ Grade 3 AEs that are known to occur with docetaxel and/or canakinumab, but cannot be controlled using the recommended product-specific management guidelines or leads to <50% of planned exposure of study medications • Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 12 weeks should be considered to be DLTs by the Investigators and Novartis, even if not Grade 3 or higher.
Events which will NOT be considered as DLT for the purpose of this protocol: Clinically insignificant laboratory values ≤ Grade 2. For laboratory values ≥ Grade 3, the maximum allowable time limit for correction of electrolyte abnormalities to ≤ Grade 1 is 72 hr. Events secondary to disease progression and concomitant medications should not be considered DLTs. Decision about RP3R will be made by Dose Level Review Team (DLRT) based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs , all CTCAE [redacted] Grade ≥ 2 toxicity, and PK data during the first 42 days of combination treatment from evaluable subjects.	

6.5.3 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule, dose interruptions are permitted as described below, in order to allow the subject to continue the study treatment:

- Docetaxel dose modifications will follow the investigator's best judgment, locally approved docetaxel label and local clinical practice.
- Canakinumab dose reductions are not permitted, only increase in the dosing interval is allowed (from Q3W to Q6W; from Q6W to Q9W). The longest dosing interval allowed is Q9W. Once the dosing interval is increased (i.e. from Q3W to Q6W; from Q6W to Q9W) due to toxicity, the dosing interval cannot be reverted to the previous dosing interval. Refer to Table 6-4.

For docetaxel and canakinumab/placebo administered as a combination:

- Docetaxel and canakinumab/ placebo should be administered on the same day. If docetaxel needs to be interrupted due to toxicity, then canakinumab/ placebo must also be interrupted. If canakinumab/ placebo needs to be interrupted due to related toxicity, then docetaxel may also be interrupted.

[redacted]

- Docetaxel and canakinumab/ placebo administration can be delayed up to 42 days until criteria to resume treatment are met. If the criteria to resume treatment are not met after 42 days, consider permanently discontinue docetaxel and continue canakinumab alone. If docetaxel is permanently discontinued due to toxicities, the Investigator can continue canakinumab/ placebo alone until RECIST 1.1 disease progression (Section 6.1.5).

After permanent docetaxel discontinuation:

- If canakinumab/ placebo alone is interrupted for >12 weeks or if the subject misses >2 doses of canakinumab/ placebo due to canakinumab/ placebo-related toxicities (whichever is longer), canakinumab/ placebo must be permanently discontinued.

These changes must be recorded on the appropriate eCRF page.

6.5.3.1 Guidelines for mandatory dose modifications for canakinumab/placebo

Mandatory dose interruption or discontinuation of canakinumab/placebo in the management of study drug related adverse reactions are summarized in Table 6-4. Clinical judgment of the treating physician should guide the management plan of each subject based on individual benefit/risk assessment. However, for events requiring discontinuation in Table 6-4, treatment must be discontinued.

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

Table 6-4 Criteria for mandatory dose interruption and re-initiation for canakinumab/ placebo for adverse drug reactions

Worst toxicity (CTCAE [redacted] during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab/ placebo**
General guidance for adverse events considered to be related to canakinumab (to be followed whenever no other specific guidance is described in this table)	
Grade 1/ Grade 2	Maintain dose level
Grade 3	Interrupt dose until resolved to ≤ Grade 2, then increase dosing interval[a]
Grade 4	Permanently discontinue investigational drug treatment
Exceptions to the above general guidance	
Neutropenia (ANC)	
Grade 2 (ANC < 1500 - 1000/mm^3)	Interrupt until CTC grade 1 or less then maintain dose.
Grade 3 (ANC < 1000 - 500/mm^3)/ Grade 4 (ANC < 500/mm^3) for <7 consecutive days	Interrupt until resolved to ≤ Grade 1, then: • For subjects receiving docetaxel, maintain canakinumab/ placebo at the same dosing interval • After permanent discontinuation of docetaxel, increase canakinumab/ placebo dosing interval.[a]
Grade 4 (ANC < 500/mm^3) for >7 consecutive days.	Permanently discontinue investigational drug treatment.
Grade 4 Febrile neutropenia	Permanently discontinue investigational drug treatment

[redacted]

Worst toxicity (CTCAE [redacted]) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab/ placebo**
Thrombocytopenia	
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Interrupt dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7, permanently discontinue investigational drug treatment
Serum creatinine	
Grade 3	Interrupt dose until resolved to ≤ Grade 2 or baseline, then re-start at the same dose • If not resolved within 14 days, then permanently discontinue subject from investigational drug treatment
Isolated bilirubin elevation[b]	
Any elevation > ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation (e.g. disease progression [imaging]). Treat alternative causes according to local institutional guidelines
Grade 2 > 1.5 - 3.0 x ULN	Maintain dose. 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[c]	Interrupt dose. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline. • If resolved in ≤ 14 days, maintain dosing intervals • If resolved in > 14 days, then increase canakinumab/matching-placebo dosing intervals[a].
Grade 4 > 10.0 x ULN[c]	See footnote[f] - otherwise permanently discontinue investigational drug treatment
Isolated AST or ALT elevation[b]	
With normal baseline AST/ALT:	
Grade 1 > ULN - 3.0 x ULN	Maintain dose level
Grade 2 > 3.0 - 5.0 x ULN	Maintain dose level. Repeat LFTs within 48-72 hours; if still abnormal then monitor LFTs at least weekly, until resolved to ≤ 3.0 x ULN[d, e]
Grade 3: AST or ALT > 5.0 - 10.0 x ULN	Interrupt dose. Repeat LFTs within 48-72 hours; monitor LFTs at least weekly, until resolved to ≤ 3.0 x ULN or to baseline. Then: • If resolved in ≤ 14 days, maintain dose level • If resolved in > 14 days, then increase dosing intervals[a]
Grade 3: AST or ALT > 10.0 - 20.0 x ULN	Discontinue subject from investigational drug treatment. Repeat LFTs within 48-72 hours; monitor LFTs at least weekly until resolved to ≤ baseline, then increase canakinumab/matching-placebo dosing intervals [a].
Grade 4: AST or ALT > 20.0 x ULN	Permanently discontinue subject from investigational drug. Repeat LFTs within 48-72 hours; 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 dose. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to baseline. • If resolved in ≤ 14 days, maintain dose level; • If resolved in > 14 days, increase the dosing interval[a].

[redacted]

Worst toxicity (CTCAE [redacted]) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab/ placebo**
ALT/AST > 3.0 x baseline AND >10 x ULN	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor weekly until resolved to baseline, then increase the dosing interval[a].
AST or ALT (>20 x ULN)	Permanently discontinue study treatment
AST/ALT increase associated with concomitant total bilirubin increase[b]	
With normal baseline LFTs	
AST or ALT (>3.0xULN) associated with concomitant total bilirubin >2.0 x ULN without evidence of cholestasis[d] (unless Gilbert's syndrome)	Interrupt dose. Assess if case is true DILI[f]. **If DILI confirmed** - Permanently discontinue **If Not DILI** – interrupt treatment. Treat the identified cause according to institutional guidelines. Repeat LFTs within 48-72 hours, then monitor weekly, till enzyme levels resolve to ≤Grade 1 or Baseline. Refer to Section 6.5.4.2 for additional follow-up of potential drug induced liver injury cases as applicable.

[redacted]

Worst toxicity (CTCAE [redacted]) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab/ placebo**
With abnormal baseline LFTs	
ALT or AST > 3 x baseline, OR ALT or AST >8 x ULN (whichever is lower) combined with total bilirubin >2.0x ULN	After recovery, re-administration of study treatment could be considered only if Investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study drug/s and dose regimen, should be discussed with the Novartis medical and safety team. Refer to Section 6.5.4.2 for additional follow-up of potential drug induced liver injury cases evaluations as applicable
Pancreatitis	
Grade 3	Interrupt canakinumab until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then discontinue subject from investigational drug treatment
Hypertension	
Grade 3	Interrupt dose until resolved ≤ Grade 1, then maintain dose level
Diarrhea	Institute appropriate anti-diarrheal treatment and follow general guidelines
Rash/photosensitivity	Initiate/institute appropriate skin toxicity therapy (such as antihistamines and/or topical corticosteroids) and follow general guidelines
Steven Johnson Syndrome, Toxic epidermal necrolysis	Permanently discontinue investigational drug treatment
Tuberculosis or reactivation of hepatitis infection	Permanently discontinue investigational drug treatment
Asymptomatic laboratory abnormalities	Provide supportive care and replacement therapy • If clinically significant, follow general guidelines

LFTs- Liver function Tests

[a] Canakinumab/ placebo dosing interval can be increased from Q3W to Q6W and from Q6W to Q9W.

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

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

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

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

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

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

[redacted]

6.5.4 Follow-up for toxicities

6.5.4.1 Follow up for infections

Infections are the most common adverse event observed with canakinumab administration and may be related to canakinumab treatment. Subjects should be followed closely for any signs or symptoms of infection and receive prompt appropriate treatment for and suspected infection. Subjects will have a urinalysis performed at every study visit (screening and throughout the study treatment).

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

DILI Diagnosis

Subjects with transaminase increase combined with total bilirubin (TBIL) increase may be indicative of potentially severe DILI, 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 (See Table 6-4 in Section 6.5.3.1). Subjects meeting any of the following criteria will require further follow-up and assessments as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 3 x baseline] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

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

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

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

Perform relevant examinations (Ultrasound or MRI, Endoscopic Retrograde Cholangiopancreatography (ERCP)) as appropriate, to rule out if increases in liver parameters 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).

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 ($R \leq 2$), or hepatocellular ($R \geq 5$) or mixed ($R > 2$ and < 5) type injury.

[redacted]

Table 6-5 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 6-5 Guidance on specific clinical and diagnostic assessments

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

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

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

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

DILI Management

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

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

- Repeating liver enzyme and serum bilirubin tests **two or three times weekly**. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.

[redacted]

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

These assessments should be done in addition to the assessments of immunological markers 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 Serious Adverse Event (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 appropriate eCRF.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time the study treatment is to be administered, IRT needs to be accessed for the medication (kit) number. The date and time of all study treatment injections administered during the study and any deviations from the protocol treatment schedule will be captured by the investigator staff or by field monitor on the appropriate study treatment dispensing form.

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

6.6.2 Emergency breaking of assigned treatment code

Part 1: Safety run-in

Since this part is open-label, there is no need for treatment unblinding instructions.

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

[redacted]

Emergency code breaks must only be undertaken when it is required to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

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

- protocol number
- study drug name (if available)
- subject number

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

Study treatment must be discontinued once emergency unblinding has occurred.

6.7 Preparation and dispensation

For canakinumab/placebo:

Each study site will be supplied by Novartis with study drug in packaging of identical appearance per product volume.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label, which corresponds to one of the four formulations provided (two active and two corresponding placebo forms). For more details, please refer to Section 6.1. For further information on canakinumab/placebo injection, please refer to the "Instructions for use canakinumab/placebo".

Investigator staff will identify the study treatment packages for the subject at each dispensing visit by contacting the IRT and obtaining the medication numbers. Immediately before administering the study treatment, the investigator staff will detach the outer parts of the labels from the packaging and affix them to the source document (Drug Label Form) for that subject's unique subject number.

Appropriate documentation of the subject specific dispensing process must be maintained.

For docetaxel:

Docetaxel will be supplied locally as commercially available and labeled accordingly to comply with legal requirements of each country. Preparation and dispensation should follow local guidelines as per standard practice and product label.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Investigational drug 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 drug must be stored according to the instructions specified on the canakinumab/placebo labels and in the Investigator's Brochure and the docetaxel supplier's label. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels of canakinumab/placebo 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.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

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

6.7.1.2 Handling of additional treatment

Not applicable

6.7.2 Instruction for prescribing and taking study treatment

Subjects will receive docetaxel 75mg/m^2 and canakinumab/placebo at the RP3R as confirmed during the safety run-in part of the study (Please refer to Section 3 for more details on the study design, and Section 6.5.1 for more details of confirmation of RP3R).

Canakinumab injection will be administered first followed by a 30-minute observation. Docetaxel infusion will be administered second.

For canakinumab/placebo:

Study drug will be administered as a subcutaneous injection by appropriately trained study center personnel.

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

All injections must be administered by the site staff only.

1. Choose an injection site on the upper arm, upper thigh, abdomen or buttocks. Do not use an area that has a rash or broken skin, or is bruised or lumpy. Avoid injecting into scar-tissue as this may lead to insufficient exposure to canakinumab. Avoid injecting into a vein.
2. Clean the injection site with a new alcohol swab. Allow the area to dry. Uncap the injection needle.

[redacted]

3. Gently pinch the skin up at the injection site. Hold the syringe at an approximately 45-degree- angle and in a single, smooth motion, push the needle straight down completely into the skin.
4. Keep the needle all the way in the skin while slowly pushing the syringe plunger down until the barrel is empty. Release the pinched skin and pull the needle straight out. Dispose of the needle and syringe in the sharps container without recapping or removing the needle.
5. After the injection: Do not rub the injection area. If bleeding occurs, apply a clean, dry cotton swab over the area, and press gently for 1 to 2 minutes, or until bleeding stops. Then apply an adhesive bandage.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

For docetaxel:

Docetaxel administration should follow local guidelines as per standard of care and product labels, including steroids pre-medication. See Section 6.1.2.

7 Informed consent procedures

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

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

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

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

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

Women of childbearing potential and female partners of male participants must be informed that them or their partner 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.

[redacted]

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

[redacted]

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

8 Visit schedule and assessments

The Assessment schedules (Table 8-2, Table 8-3 and Table 8-4) list all of the assessments and indicate with an "X and S", the visits when they are performed. Treatment cycles are intended to be 3 weeks (21 days), but the treatment can be delayed in order to manage toxicities according to the dose modification criteria in Section 6.5.3. Imaging will be performed every 6 weeks from C1D1 regardless of any treatment delays. Patient reported outcome questionnaires will be completed prior to any assessments, treatments, or receipt of results

Please refer to Table 8-1 for allowable visits window.

Table 8-1 Allowable window for subject assessments

Visit name	Window
Screening	-28 days from the 1st dose of study drug
Cycle 1: Day 1	within 3 days after enrollment (safety run-in part 1) or randomization (randomized part 2)
Cycle 2 onward	± 3 days
[redacted]	[redacted]
Imaging evaluations	± 7 days
EOT	≤ 7 days after stopping study treatment

Every effort must be made to follow the schedule of assessments within the windows outlined in the protocol. If an off-schedule imaging assessment is performed, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Missed or rescheduled visits should not lead to automatic discontinuation.

Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the appropriate eCRF.

All data obtained from these assessments must be supported in the subject's source documentation.

[redacted]

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

Period	Screening	Treatment										Follow up	
Visit Name		Cycle 1					Cycle 2		Cycle 3 etc	EOT	Safety follow up (130 days after last study treatment)	Efficacy follow up	Survival follow up (every 12 weeks)
Days	-28 to -1	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 15	Day 1	-	-	-	-
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												
Prior/concomitant medications	From 28 days prior to starting study treatment until 130 day after EOT or start of new antineoplastic medications, whichever is sooner. After starting a new antineoplastic med., only report concomitant medications for AEs/ SAEs suspected to be related to study treatment.												
Non-drug therapies and procedures	From 28 days prior to starting study treatment until 130 day after EOT or start of new antineoplastic medications, whichever is sooner. After starting a new antineoplastic med., only report non-drug therapies for AEs/ SAEs suspected to be related to study treatment.												
Prior anti-neoplastic therapies (medications, surgery, radiotherapy)	X												
IRT Enrollment		X											
Physical Examination	S	S					S		S	S	S		

[redacted]

Period	Screening	Treatment										Follow up	
Visit Name		Cycle 1					Cycle 2		Cycle 3 etc	EOT	Safety follow up (130 days after last study treatment)	Efficacy follow up	Survival follow up (every 12 weeks)
Days	-28 to -1	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 15	Day 1	-	-	-	-
ECOG performance status	X	X					X		X	X	X	X	
Vital Signs	X	X					X		X	X	X		
Body Height	X												
Body Weight	X	X					X		X	X	X	X	
Determination of tuberculosis status	S												
HIV screen where locally required	S												
Hepatitis screen	X	As clinically indicated											
Hematology	X	X			X	X	X	X	X	X	X		
Blood Chemistry	X	X			X	X	X	X	X	X	X		
Coagulation	X	As clinically indicated											
Urinalysis	X	X					X		X	X	X		
Serum pregnancy test	X									X			
Urine pregnancy test[1]		S					S		S		S		
CT or MRI of chest and abdomen	X	Every 6 weeks for the first 12 months and every 12 weeks after the first 12 months of treatment until disease progression										X	
CT or MRI of brain	X	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen										If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	

[redacted]

Period	Screening	Treatment										Follow up	
Visit Name		Cycle 1					Cycle 2		Cycle 3 etc	EOT	Safety follow up (130 days after last study treatment)	Efficacy follow up	Survival follow up (every 12 weeks)
Days	-28 to -1	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 15	Day 1	-	-	-	-
Whole body bone scan	X	If clinically indicated										If clinically indicated	
CT scan or MRI of other metastatic sites	If clinically indicated	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen										If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	
Localized bone CT, MRI or X-Ray	If clinically indicated	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen										If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	
Photography (for any skin lesions)	If clinically indicated	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen										If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	
Electrocardiogram (ECG)[2]		X[3]							C6D1[3]				
Drug administration (docetaxel/ canakinumab)		Day 1 of each cycle											
IRT drug discontinuation										X			

[redacted]

Period	**Screening**	**Treatment**										**Follow up**	
Visit Name		**Cycle 1**					**Cycle 2**		**Cycle 3 etc**	**EOT**	**Safety follow up (130 days after last study treatment)**	**Efficacy follow up**	**Survival follow up (every 12 weeks)**
Days	**-28 to -1**	**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**-**	**-**	**-**	**-**
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.												SAEs related to study treatment
Canakinumab PK sampling[4]		X[5]					X[3]		(C4D1, C6D1)[3]	X[6]			
Canakinumab Immunogenicity sampling[4]		X[3]							(C4D1, C6D1)[3]	X[6]			
Docetaxel PK sampling[4]		X[3,7]					X[3,7]		(C3D1, C4D1)[3]				
Antineoplastic therapies since discontinuation of study treatment											X	X	X
Disposition assessment	X									X	X		
Survival follow-up													X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] For women of childbearing potential only
[2] For further details please refer to Section 8.4.4 Electrocardiogram (ECG)
[3] Pre-dose
[4] Also to be collected as unscheduled as clinically indicated
[5] Pre-dose on C1D1 / Post-dose on C1D2, C1D3, C1D8 and C1D15
[6] Post-dose
[7] EOI (within 5 mins), then 2, 4, 6 and 8 hr post start of infusion on Cycle 1 Day 1 and Cycle 2 Day 1

[redacted]

Table 8-3 Assessment Schedule, Randomized part

Period	Screening	Treatment							Follow up	
Visit Name		Cycle 1		Cycle 2		Cycle 3 etc / or until entering in OLE[16]	EOT	Safety follow up (130 days after last study treatment)	Efficacy follow up	Survival follow up (every 12 weeks)
Days	-28 to -1	Day 1	Day 15	Day 1	Day 15	Day 1	-	-	-	-
Informed consent	X									
Optional pharmacogenetic 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									
Optional Archival or Newly obtained tumor sample[15]	X									
Prior/concomitant medications	From 28 days prior to starting study treatment until 130 day after EOT or start of new antineoplastic medications, whichever is sooner. After starting a new antineoplastic med., only report concomitant medications for AEs/ SAEs suspected to be related to study treatment.									
Non-drug therapies and procedures	From 28 days prior to starting study treatment until 130 day after EOT or start of new antineoplastic medications, whichever is sooner. After starting a new antineoplastic med., only report non-drug therapies for AEs/ SAEs suspected to be related to study treatment.									
Prior anti-neoplastic therapies (medications, surgery, radiotherapy)	X									
IRT randomization		X								

[redacted]

Period	Screening	Treatment							Follow up	
Visit Name		Cycle 1		Cycle 2		Cycle 3 etc [redacted]	EOT	Safety follow up (130 days after last study treatment)	Efficacy follow up	Survival follow up (every 12 weeks)
Days	-28 to -1	Day 1	Day 15	Day 1	Day 15	Day 1	-	-	-	-
Physical Examination	S	S		S		S	S	S		
ECOG performance status	X	X		X		X	X	X	X	
Body Height	X									
Body Weight	X	X		X		X	X	X	X	
Vital Signs	X	X		X		X	X	X		
HIV screen where locally required	S									
Determination of tuberculosis status	S									
Hepatitis screen	X	As clinically indicated								
Hematology	X	X	X	X	X	X	X	X		
Blood Chemistry	X	X	X	X	X	X	X	X		
Coagulation	X	As clinically indicated								
Urinalysis	X	X		X		X	X	X		
Serum pregnancy test	X						X			
Urine pregnancy test[1]		S		S		S		S		
Electronic Patient Reported Outcomes (ePROs)[2]				Day 1 of each cycle regardless of study treatment dosing and prior to any assessments, treatment or receipt of results				at the EOT and (within 7 and 28 days of progression)[3]	at the same timepoints as the imaging collection until progression then within 7 and 28 days of the progression.[4]	
CT or MRI of chest and abdomen	X	Every 6 weeks for the first 12 months and every 12 weeks after the first 12 months of treatment until disease progression							X	

[redacted]

Period	Screening	Treatment							Follow up	
Visit Name		Cycle 1		Cycle 2		Cycle 3 etc [redacted]	EOT	Safety follow up (130 days after last study treatment)	Efficacy follow up	Survival follow up (every 12 weeks)
Days	-28 to -1	Day 1	Day 15	Day 1	Day 15	Day 1	-	-	-	-
CT or MRI of brain	X	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen							If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	
Whole body bone scan	X	If clinically indicated							If clinically indicated	
CT scan or MRI of other metastatic sites	If clinically indicated	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen							If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	
Localized bone CT scan, MRI or X-Ray	If clinically indicated	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen							If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	
Photography (for any skin lesions)	If clinically indicated	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen							If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	
Electrocardiogram (ECG)[5]		X[6]				C6D1[6]				
Drug administration (docetaxel/canakinumab or docetaxel/placebo)		Day 1 of each cycle								
IRT drug discontinuation							X			
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.									

[redacted]

Period	Screening	Treatment							Follow up	
Visit Name		Cycle 1		Cycle 2		Cycle 3 etc / or until entering in OLE[16]	EOT	Safety follow up (130 days after last study treatment)	Efficacy follow up	Survival follow up (every 12 weeks)
Days	-28 to -1	Day 1	Day 15	Day 1	Day 15	Day 1	-	-	-	-
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.									SAEs related to study treatment

[redacted]

Period	Screening	Treatment							Follow up	
Visit Name		Cycle 1		Cycle 2		Cycle 3 etc / [redacted]	EOT	Safety follow up (130 days after last study treatment)	Efficacy follow up	Survival follow up (every 12 weeks)
Days	-28 to -1	Day 1	Day 15	Day 1	Day 15	Day 1	-	-	-	-
[redacted]										
Antineoplastic therapies since discontinuation of study treatment								X	X	X
Disposition assessment							X	X		
Survival follow-up										X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] For women of childbearing potential
[2] Prior to administration of investigational product or any other procedure
[3] For subjects discontinuing study treatment due to RECIST 1.1 progression and entering the safety follow up period
[4] For subjects discontinuing study treatment without prior documented RECIST 1.1 progression
[5] For further details please refer to Section 8.4.4 Electrocardiogram (ECG)
[6] Pre-dose
[7] Also to be drawn unscheduled at the time of disease progression, prior to the start of new antineoplastic therapy
[redacted]
[12] Post-dose
[redacted]
[14] EOI (within 5 mins), then 2, 4 and 6 hr post start of infusion on Cycle 1 Day 1 and Cycle 4 Day 1
[redacted]

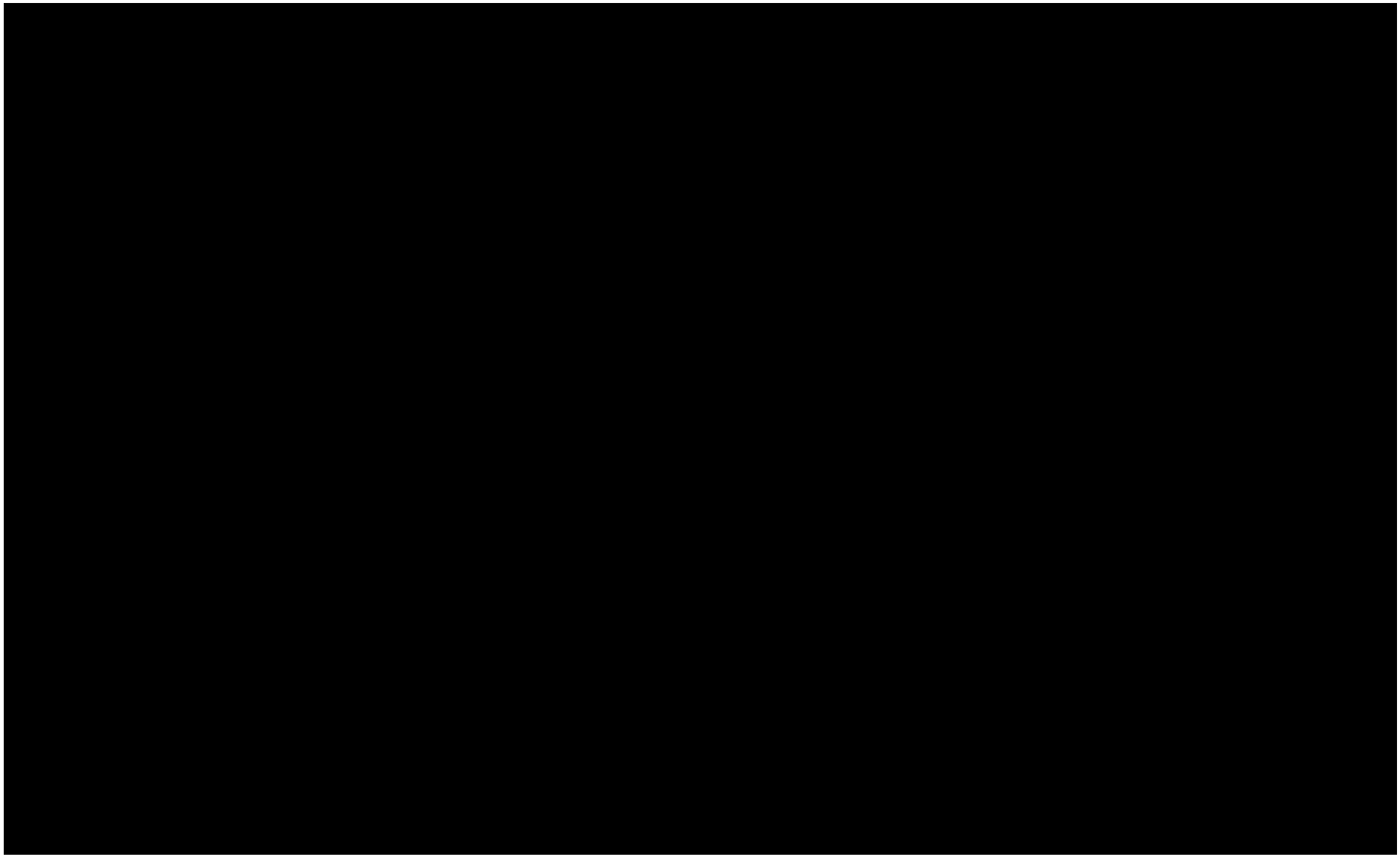
[redacted]

Period	Screening	Treatment							Follow up	
Visit Name		Cycle 1		Cycle 2		Cycle 3 etc / [redacted]	EOT	Safety follow up (130 days after last study treatment)	Efficacy follow up	Survival follow up (every 12 weeks)
Days	-28 to -1	Day 1	Day 15	Day 1	Day 15	Day 1	-	-	-	-
[redacted]										

[redacted]

[redacted]

[redacted]



[redacted]

[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 the enrollment (safety run-in) / randomization (see Table 8-2 and Table 8-3 for list of assessments to be performed). Laboratory parameters may be retested within the 28-day screening period for an individual subject if such parameters meet an exclusion criterion when initially tested. Laboratory assessments performed as part of the screening evaluations will not be required to be repeated prior to dosing (except complete blood count if not done within 7 days prior to treatment start) unless deemed clinically necessary by investigator and/or required as per local institutional policies.

Imaging assessments will be performed at screening between Day -28 and Day -1. 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 as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images.

A new ICF will need to be signed if the investigator chooses to re-screen the subject after a subject has screen failed. In case of re-screening, a new subject ID will be generated, however, site has to provide original subject ID in respective eCRF to link the two subjects for reporting and validation. All required screening activities must be performed when the subject is re-screened for participation in the study. An individual subject may only be re-screened once for the study. Once the number of subjects screened and enrolled is likely to ensure target enrollment, the Sponsor may close the study to further screening. In this case, the subjects who screen failed will not be permitted to re-screen.

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

8.1.1 Eligibility screening

When all screening procedures are completed and once the subject's eligibility has been checked and confirmed (i.e., all inclusion/exclusion criteria have been verified), the key eligibility criteria checklist will be completed prior to the first dose of study drug in the IRT system by the investigator or designee. The eligibility check will be embedded in the IRT system. For the randomized part of the study, allocation to one of the two study arms will also be registered via IRT.

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

8.1.2 Information to be collected on screening failures

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

[redacted]

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

8.2 Subject demographics/other baseline characteristics

Data to be collected on subject characteristics at screening include:

- Demographic information (age, gender, race and ethnicity as allowed by local regulations)
- Other background or relevant medical history (including smoking history)
- Any additional treatment received after the PD-(L)1 inhibitor and enrollment in the current study and response to the received additional treatment.
- Cancer characteristics including diagnosis, history, extent of cancer, prior antineoplastic therapies (medications, radiation, surgeries), date of progression prior to study entry
- Other assessments will be completed for the purpose of determining eligibility for inclusion in the study (i.e., ECOG Performance Status, complete physical examination, vital signs, hematology, blood chemistry, coagulation studies, urinalysis, serum pregnancy test for all female subjects).
- Prior and current concomitant medications and surgical and medical procedures
- Tumor imaging assessments - Refer to Table 8-5 .

Data to be collected on C1D1 pre-dose include:

- Patient Reported Outcomes (PROs)
- 12-Lead ECG
- PK [redacted] G

8.3 Efficacy

8.3.1 Survival assessment

All subjects will be followed for survival status every 3 months regardless of treatment discontinuation reason until death, lost to follow-up, or withdrawal of consent for survival follow-up. Additional survival assessments may be performed outside the 3 months follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs. Survival information can be obtained via phone, and information will be documented in the source documents and relevant CRFs. Information on the therapies received for NSCLC, if any, after treatment with study medication has been completed will be collected (including start date, stop date).

8.3.2 Tumor assessments

Tumor response will be assessed locally based on RECIST 1.1 (Eisenhauer et al 2009). The imaging assessment collection plan is presented in Table 8-2, Table 8-3, Table 8-4 and Table 8-5.

[redacted]

All imaging assessments will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. Central review of the imaging assessments may be performed if deemed necessary. Please refer to the site imaging operations manual for additional information on image acquisition and data collection by the imaging CRO. Central collection and quality check of imaging assessments will be discontinued in OLE.

Imaging assessments should be scheduled using the C1D1 date as the reference and should be respected regardless of whether treatment with study treatment is temporarily withheld or unscheduled assessments are performed.

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 imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent.

Combined Positron Emission Tomography (PET)/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of IV contrast media. At the discretion of the Investigators, Fluorodeoxyglucose (FDG)-PET scans may be performed to document progressive disease per RECIST 1.1 (Section 16.1).

Table 8-5 Imaging Assessment Collection Plan

Procedure	Screening / Baseline	Post baseline (during Treatment)	Efficacy follow up
CT or MRI of Chest and Abdomen (with intravenous contrast enhancement)	Mandated	Mandated every 6 weeks during the first 12 months, and every 12 weeks thereafter until progression of disease (PD) as per RECIST 1.1 or subject withdrawal End of Treatment (EOT): done for all subjects without prior documented RECIST 1.1 PD and who do not enter the efficacy follow-up phase provided the last scan was not conducted within 30 days prior to the end of study treatment For OLE only: Every 12 weeks until 36 months since randomization, then every 6 months thereafter until progressive disease (PD) as per RECIST 1.1	Efficacy Follow-up for progression: continue tumor assessments using the same schedule until RECIST 1.1 PD (regardless of start of new anti-neoplastic therapy).
Brain CT or MRI	Mandated	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated or positive at baseline, follow same schedule as CT/MRI of chest and abdomen
Whole body bone scan	Mandated	If clinically indicated	If clinically indicated
CT scan or MRI of other metastatic sites (e.g., neck, pelvis, etc.)	Only if clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen

[redacted]

Procedure	Screening / Baseline	Post baseline (during Treatment)	Efficacy follow up
Localized bone CT scan, MRI or x-ray (for any skeletal lesions identified on the whole body bone scan that are not visible on the chest/abdomen and pelvis, if applicable, CT or MRI)	Only if clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen
Photography (for any skin lesions)	Only if clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen

Baseline imaging assessments: Imaging assessments will be performed at screening/baseline within 28 days of start of treatment .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 as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images. Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

Post-baseline imaging assessments: Imaging assessments should be performed using the same imaging modality used at baseline, irrespective of study treatment interruption or actual dosing. Imaging assessments for response evaluation will be performed every 6 weeks for the first 12 months and every 12 weeks thereafter until disease progression per RECIST 1.1 by investigator assessment, subject withdrawal of consent, pregnancy, lost to follow-up or death.

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

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

[redacted]

8.3.3 Appropriateness of efficacy assessments

Tumor assessments every 6 weeks of chemotherapy are consistent with the standard clinical practice. National Comprehensive Cancer Network (NCCN) guidelines for NSCLC recommend response assessment every 6-12 weeks. In subjects with NSCLC previously treated with platinum-based chemotherapy, the median PFS is approximately 4 months or 16 weeks.

[redacted]

Conducting tumor evaluations more than 6 weeks apart may expose a subject to an unnecessary treatment if the disease progression event takes place between the infrequent assessments.

8.4 Safety

During treatment

Safety will be monitored by assessing physical examination, Eastern Cooperative Oncology Group (ECOG) Performance Status, vital signs, body weight, ECG, Patient Reported Outcomes, laboratory assessments including hematology, chemistry, coagulation, and urinalysis, as well as collecting adverse events at every visit. For details on AE collection and reporting, refer to Section 10. All safety assessments should be completed as per Table 8-2 Table 8-3 and Table 8-4.

Post treatment discontinuation

All safety assessments should be completed as per Table 8-2, Table 8-3 and Table 8-4. However, if the subject begins post treatment antineoplastic medication before the completion of the 130-Day safety follow-up visit, the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected AEs and suspected SAEs will continue to be collected up to Day 130.

8.4.1 Laboratory evaluations

Central laboratories will be used for the analysis of scheduled hematology, biochemistry and other blood specimens collected as part of safety monitoring (as detailed in Table 8-2, Table 8-3, and Table 8-6). Local laboratories will be used for safety monitoring (as detailed in Table 8-4 and Table 8-6) in the OLE. Additional timepoints should be added as deemed necessary per the investigator's best judgment to make sure toxicity profile is sufficiently characterized (e.g. DLT assessment in the safety run-in) and dose adjustments performed to safeguard the safety of the patient.

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). Laboratory values obtained during the Screening phase from the central laboratory will be used to assess subject's eligibility. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 8).

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) and in those cases locally unscheduled testing may be performed and used for eligibility assessments.

Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the Central Laboratory Manual/Flowchart.

If at any time a subject has laboratory parameters obtained from a different (outside) laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory. The investigator is responsible for reviewing all laboratory reports for subjects in the study and evaluating any abnormalities for clinical significance.

[redacted]

The results of the local laboratory will be recorded in the appropriate eCRF if any the following criteria are met:

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

Table 8-6 Clinical laboratory parameters collection plan

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

8.4.1.1 Laboratory testings

Hematology, chemistry, coagulation, urinalysis and infectious disease markers tests are to be performed according to the Visit Schedules outlined in Table 8-2, Table 8-3 and Table 8-4.

Laboratory assessment done ≤ 7 days of first dose of study treatment are permitted to be used as Cycle 1 Day 1 labs and do not need to be repeated.

More frequent laboratory testing may also be performed as medically necessary, and for accurate DLT determination in the safety run-in. Additional results from unscheduled hematology lab evaluations should be recorded in the appropriate Unscheduled Visit eCRF.

Estimate of Glomerular Filtration Rate (via estimated creatinine clearance rate) will be done centrally using Cockcroft-Gault formula:

[redacted]

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

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

When serum creatinine is measured in µmol/L:

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

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

8.4.2 Determination of tuberculosis status

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

8.4.3 Performance status

The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale as specified in Table 8-7 (Oken et al 1982) following the schedule given in Table 8-2, Table 8-3 and Table 8-4.

Table 8-7 ECOG Performance Status

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

8.4.4 Electrocardiogram (ECG)

Local single 12-lead ECGs should be recorded prior to the dose administration, after the subject has been resting for 5-10 min prior to the time point indicated in Table 8-2 and Table 8-3. ECGs should be performed within 20 minutes prior to the collection of PK sample where applicable. Local ECGs should be performed as clinically indicated in OLE as recommended in Table 8-4.

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.

[redacted]

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 C1D1 should be reported on the appropriate eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the appropriate eCRF page.

8.4.5 Pregnancy and assessments of fertility

During screening, a serum pregnancy test will be completed for all female subjects. On Cycle 1 Day 1 prior to dosing, at subsequent cycles and during safety follow-up, a urinary pregnancy test (dipstick) will be performed. A serum pregnancy test will also be completed at EOT of safety run-in part and EOT of double-blind randomized part. The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. Refer to Table 8-2 and Table 8-3. Urine pregnancy test will be performed at each visit for women with childbearing potential in OLE as indicated in Table 8-4. If local requirements dictate otherwise, local regulations should be followed.

Women who are determined not to be of childbearing potential before the study will only be tested at screening. When non-childbearing 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 childbearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential (such testing is not covered as part of the study assessments). If local requirements dictate otherwise, additional local regulations should be followed.

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

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

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

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

[redacted]

biasing the subject's perspective. In this study, the completion of the ePRO questionnaires by a third party is not allowed. If subject belongs to vulnerable populations (i.e. illiterate, blind) and is not able to complete ePRO alone, hence no ePRO will be collected, this would not be a protocol deviation.

In the blinded randomized part the ePROs questionnaires must be completed on Day 1 of each cycle regardless of study treatment dosing. If study treatment is delayed, ePROs questionnaires will not be completed again on the actual dosing day of the same cycle, ePROs questionnaires will be completed again at the end of treatment visit and then:

- For subjects discontinuing treatment due to RECIST 1.1 progression and entering the safety follow up period, PROs will be collected within 7 days of the reported progression (potentially at the time of the end of treatment visit) and then again within 28 days of the progression.
- For subjects discontinuing study treatment without prior documented RECIST 1.1 progression, PROs will be collected, during the efficacy follow up period, at the same timepoints as the imaging collection until progression. Following progression, PROs will then be collected within 7 days and 28 days (-7/ +14 days) of the progression.

The ePRO data will only be collected at the C1D1 of OLE and at the disease progression in the OLE as indicated in Table 8-4.

Subjects should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, the electronic tablet device will alert subjects of any missing responses, subjects should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all subjects, including from those who discontinue prior to the study evaluation completion visit, however, if subjects refuse to complete questionnaires, this should be documented in study source records. Subject's refusal to complete study questionnaires are not protocol deviations.

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

8.5.2 Pharmacokinetics

8.5.2.1 Blood collection (serum) for canakinumab pharmacokinetics (PK), [redacted] and immunogenicity (IG) during Safety Run-in Part and Randomized part

Time points of blood sample collection for canakinumab/placebo PK, IG [redacted] are outlined in Table 16-14 (safety run-in part) and Table 16-15 (randomized part)- Appendix 5. Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein.

If dose level -1 (DL-1) of canakinumab/placebo 200 mg Q6W is explored as an alternative schedule (see Section 6.5.1.1), the canakinumab PK, [redacted] and IG sampling schemes in Section 16.7 will be followed.

On days and time points where blood IG and PK samples are to be drawn, the PK sample must be drawn first. If subjects experience a SAE or an AE leading to the discontinuation of the study

[redacted]

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 IG samples (at the time of the event and 8 weeks later) need to be taken.

If subjects experience an AE or SAE leading to a canakinumab dosing interval increase to Q6W or Q9W (Section 6.5.3), do not collect canakinumab PK, [redacted] and/or IG samples on a visit cycle if canakinumab is not administered. Collect PK, [redacted] and/or IG samples if canakinumab is administered on a visit cycle in which samples are already scheduled as stated in Table 16-14 (safety run-in) and Table 16-15 (randomized).

The date and time of the last dose and the time of PK and IG blood draw should be recorded on appropriate eCRF. All samples will be given a unique sample number and a dose reference ID.

Refer to central laboratory manual and flowchart for detailed PK, IG [redacted] collection.

No PK, IG [redacted] samples will be collected in the OLE.

8.5.2.2 Blood collection (plasma) for docetaxel pharmacokinetic during the Safety Run-in part and Randomized part

Time points of blood sample collection for docetaxel PK are outlined in Table 16-16 (safety run-in part) and Table 16-17 (randomized part). Only a subset of patients (50 subjects, i.e. approximately 25 subjects per arm) in randomized part will have docetaxel PK taken. Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein opposite to the arm used for infusion. If study treatment was administered via a central venous catheter, sample collection for PK should be from a different site.

Refer to central laboratory manual and flowchart for detailed PK collection.

If subjects experience a SAE or an AE leading to the discontinuation of the study treatment, an unscheduled PK blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded.

8.5.2.3 Analytical method

Bioanalysis for PK, IG [redacted] assessment will employ the validated assays. The detailed method description to assess canakinumab (PK, [redacted] and IG) and docetaxel concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).

- Canakinumab will be quantified in serum using a validated competitive ELISA method, with an anticipated lower limit of quantification (LLOQ) of 100 ng/mL.
- The IG against canakinumab will be assessed in serum using a validated Meso Scale Discovery (MSD) electrochemiluminescence assay.

[redacted]

[redacted]

[redacted]

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 permanently stopped, 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.

An end of treatment visit will be performed when subjects permanently discontinue the study treatment. This visit should take place ≤ 7 days after the last dose of study treatment, if possible and the disposition 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.

Study treatment must be discontinued under the following circumstances

- Subject/guardian decision
- Physician decision
- Disease progression by RECIST 1.1
- Pregnancy
- Any situation in which study participation might result in a safety risk to the subject
- Subject lost to follow up
- Study terminated by the 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 also contact the IRT to register the subject's discontinuation from study treatment. If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of assigned treatment code section (Section 6.6.2).

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (Section 9.1.2). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

[redacted]

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.

After study treatment discontinuation, all randomized and/or treated subjects should have a safety follow-up visit conducted 130 days after last administration of study treatment. 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.

For subjects who discontinue treatment **without** prior documented disease progression by RECIST 1.1 will continue tumor assessments until documented disease progression by RECIST 1.1 as per investigator assessment, withdrawal of consent, pregnancy, lost to follow-up or death irrespective of start of new anti-neoplastic therapy.

9.1.1.1 Replacement policy

Safety run-in part:

Subjects will not be replaced on study. However, if a subject is considered as non-evaluable for the Dose-Determining Set (DDS), enrollment of a new subject to the current cohort will be considered if there is less than the required number of evaluable subjects. Enrollment of new subjects may be considered until at least the minimum number 6 of evaluable subjects is achieved within the cohort. Minimum numbers of evaluable subjects per cohort are defined in Section 6.5.1.2.

Randomization part:

During the randomization part, no replacement is needed.

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 allow further collection of personal data

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

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

Further attempts to contact the 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 8-2, Table 8-3 and Table 8-4.

[redacted]

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

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

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

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 diligence has been completed.

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 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. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

[redacted] At the time of the primary analysis, a primary clinical study report (CSR) will be produced.

[redacted]

[redacted]

At the end of the study, every effort will be made to continue provision of investigational drug outside this study through an alternative setting to subjects who in the opinion of the Investigator are still deriving clinical benefit.

[redacted]

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any 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 adverse events.

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

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

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

1. The Common Toxicity Criteria (CTC) AE grade (version 5.0). Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) [redacted]
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.

[redacted]

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 adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/withdrawn
6. its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal or unknown).

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

Adverse events that begin or worsen after informed consent should be recorded in the AE eCRF. Conditions that were already present at the time of informed consent should be recorded in the medical history eCRF. Adverse event monitoring should be continued for at least 130 days following the last dose of study treatment. If a new antineoplastic therapy is initiated during the 130-day safety follow-up period, only AEs suspected to be related to study treatment will be collected in Adverse Events eCRF. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, loss of response, progression to accelerated phase or blast crisis), should not be reported as a serious adverse event, except if the investigator considers that the progression of malignancy is related to study treatment.

Adverse events 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 [Canakinumab Investigator Brochure].

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

- they induce clinical signs or symptoms
- they are considered clinically significant

[redacted]

- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

10.1.1.1 Adverse events of special interest

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

Adverse events of special interest are defined on the basis of an ongoing review of the safety data and include:

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

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening

Note: Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

[redacted]

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines). Confirmed COVID-19 infection should be considered as medically significant, therefore should be reported as SAE.

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

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

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

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has provided informed consent and until at least 130 days after the subject has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. If a new antineoplastic therapy is initiated during the 130-day safety follow-up period, only SAEs suspected to be related to study treatment will be collected in Adverse Events eCRF. Note: Any SAEs experienced after the 130-day safety follow-up period and prior to start of new post study treatment antineoplastic medication should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

The following SAE reporting timeframes apply:

[redacted]

- 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.
- 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 Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO&PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same 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 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 subject becomes pregnant, the study treatment should be stopped, and the trial subject must be asked to read and sign pregnancy consent form to allow the Study Investigator 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. If a pregnancy occurs while on study treatment, the new born will be followed for up to 12 months. Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported. Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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.

[redacted]

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate eCRF 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 Dose Administration eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

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

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first subject. The DMC will review at defined intervals the safety data as well as the efficacy and safety data from the final OS analysis and interim OS analyses of the double-blind, randomized, placebo-controlled part of the study. The DMC meeting will be held approximately every six months. Additional DMC reviews may be performed if considered appropriate by DMC. DMC will recommend to the sponsor whether to continue, modify or terminate a trial. Additional details on the conduct of final OS and interim OS analyses can be found in Section 12.7.

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

10.2.2 Steering Committee

A steering committee will be established comprising of investigators participating in the trial, i.e. not being members of the 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.

[redacted]

11 Data Collection and Database management

11.1 Data collection

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

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

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

Data collected by third parties (hematology, biochemistry, [redacted] PK and PROs) will be sent electronically to Novartis.

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

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

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

[redacted]

[redacted]

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. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis 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, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

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

12 Data analysis and statistical methods

Part 1- Safety run-in part

The analysis to determine the Recommended Phase 3 Regimen (RP3R) will be conducted when at least 6 evaluable subjects in the treatment cohort have been observed for dose limiting toxicity (DLT) for the first 42 days (2 cycles) at the starting dose level to establish the RP3R.

The final analysis of study data for safety run-in part will be established at the time of the primary analysis for the randomized part, when approximately 137 OS events are expected to have occurred or when OS is declared statistically significant at the efficacy interim OS analysis (approximately 96 deaths are expected at the efficacy interim OS analysis). At this time, all follow-up data for all subjects from safety run-in part will be included and will be analyzed by dose cohorts: DL1 and DL-1.

[redacted]

Part 2- Randomized phase III part

[redacted]

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

12.1 Analysis sets

12.1.1 Full Analysis Set

Part 1- Safety run-in part

The full analysis set (FAS) and safety set are defined in the same way and comprise all subjects to whom study treatment has been assigned and who received at least one dose of any study treatment (i.e. at least one dose of any component of canakinumab or docetaxel (including incomplete infusion)). Subjects will be analyzed according to the dose regimen they have been assigned to.

Part 2- Randomized phase III part

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

12.1.2 Safety set

Part 1- Safety run-in part

See definition of FAS.

Part 2- Randomized phase III part

The Safety Set includes all subjects who received at least one dose of study drug. Subjects will be analyzed according to the study treatment they received, either docetaxel plus canakinumab or docetaxel plus placebo. The 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 Dose-determining set

Part 1- Safety run-in part

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

[redacted]

A subject meets the minimum exposure criterion if the subject receives at least one dose of canakinumab and one dose of docetaxel within first 42 days, or if the subject didn't receive the planned number of doses due to dose limiting toxicity. Subjects who do not experience a DLT during the first 42 days are considered to have sufficient safety evaluations if they have been observed for ≥ 42 days following the first dose.

Subjects will be analyzed according to the study treatment received as defined for the safety set.

Part 2- Randomized phase III part

Not applicable.

12.1.4 Pharmacokinetic analysis set

Part 1- Safety run-in part

The Pharmacokinetic Analysis Set (PAS) consists of all subjects who received at least one dose of study drug and have at least one evaluable pharmacokinetic (PK) sample. The definition of an evaluable PK blood sample will be further specified in the Statistical Analysis Plan (SAP). PAS will be defined for canakinumab and docetaxel separately.

Part 2- Randomized phase III part

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

12.1.5 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 dose cohort for the FAS in the safety run-in part and by treatment arm for the FAS and safety set in the randomized phase III part. Relevant medical histories and current medical condition at baseline will be summarized separately by system organ class and preferred term, by dose cohort for the FAS in the safety run-in part and by treatment arm for the FAS and safety set in the randomized phase III part.

12.3 Treatments

The Safety set will be used for the analyses below.

The exposure related analyses will be presented by treatment cohort and canakinumab dose regimen for the safety run-in part and by treatment group for the randomized Phase III part.

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

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

[redacted]

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

12.4 Analysis of the primary endpoint(s)

Part 1- Safety run-in part

The primary objective is to determine the Recommended Phase 3 Regimen (RP3R) of the combination of canakinumab and docetaxel for the randomized part.

Part 2- Randomized phase III part

The primary objective is to compare the overall survival (OS) in the docetaxel plus canakinumab arm versus docetaxel plus placebo arm.

12.4.1 Definition of primary endpoint(s)

Part 1- Safety run-in part

The primary endpoint is the incidence of dose limiting toxicities in the first 42 days of dosing associated with administration of canakinumab in combination with docetaxel.

Part 2- Randomized phase III part

The primary endpoint is OS, defined as the time from the date of randomization to the date of death due to any cause. Censoring conventions are provided below in Section 12.4.3.

12.4.2 Statistical model, hypothesis, and method of analysis

Part 1- Safety run-in part

Identification of recommended regimen

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

Bayesian adaptive approach

The determination of RP3R will be guided by a Bayesian analysis of DLT data for the first 42 days during which subjects receive the combination of canakinumab and docetaxel (Section 16.2).

The dose-toxicity relationship of canakinumab in combination with docetaxel will be modeled by a 5-parameter BLRM for each dose regimen that comprises single agent toxicity parts and interaction part. Single agent toxicity is modelled using logistic regression for the probability of a subject experiencing a DLT against log-dose. The odds of a DLT for each dose regimen are then calculated under no interaction for the two single agent toxicities, and interaction is accounted for by adjusting these odds with additional model parameters (odds multipliers).

Dose recommendation

[redacted]

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

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

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

Starting dose

The starting dosing regimen is 200 mg sc Q3W canakinumab and 75 mg/m^2 i.v. Q3W docetaxel (Section 6.5.1.1). For this starting dose level of canakinumab (i.e. 200 mg Q3W), the prior risk of excessive toxicity is 15.7%, which satisfies the EWOC criterion.

Listing of DLTs

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

Part 2- Randomized phase III part

Assuming proportional hazards model for OS, the null hypothesis will be tested at one-sided 2.5% level of significance:

H_{01} (null hypotheses): $\Theta_1 \geq 0$ vs. H_{a1} (alternative hypotheses): $\Theta_1 < 0$

Where Θ_1 is the log hazard ratio of OS in the docetaxel plus canakinumab (investigational) arm vs. docetaxel plus placebo (control) arm.

The primary efficacy analysis to test this hypothesis and compare the two treatment groups will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance in favor of the docetaxel plus canakinumab arm. The stratification will be based on following randomization stratification factors (line of therapy: 1 prior line of therapy vs. 2 prior lines of therapy; and histology: squamous vs. non-squamous). The primary efficacy variable, OS, will be analyzed at the interim analysis and final analysis of a group sequential design, using a Lan-DeMets (O'Brien-Fleming) α-spending function.

Analyses will be based on the FAS population according to the randomized treatment group and strata assigned at randomization. The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, median and associated 95% confidence intervals will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test.

[redacted]

12.4.3 Handling of missing values/censoring/discontinuations

Part 1- Safety run-in part

Subjects who are ineligible for the DDS will be excluded from the primary analysis (incidence of DLT during first 42 days of canakinumab in combination with docetaxel), although their data will be used for all remaining analyses.

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

Part 2- Randomized Phase III part

If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date).

12.4.4 Sensitivity and Supportive analyses

Part 1- Safety run-in part

Not applicable.

Part 2- Randomized phase III part Sensitivity analyses will be performed for OS in the FAS. Hazard ratio and 95% confidence interval for OS will be obtained from:

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

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

If the primary analysis is statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed for the following subgroups:

- Gender (male vs. female)
- Age (<65 vs., ≥65 years)
- ECOG performance status (0 vs. 1)
- Smoking history (Former/Current vs. Never)
- Prior line of therapy (1 vs. 2)
- [redacted]
- [redacted]

Additional subgroup analyses with different thresholds or variables (e.g. hs-CRP on treatment) may be conducted for OS. Details will be specified in the SAP.

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

12.5 Analysis of secondary endpoints

Part 1- Safety run-in part

[redacted]

The secondary objectives in this part of the study are to characterize the safety and tolerability, the pharmacokinetics and to assess preliminary anti-tumor activity of canakinumab in combination with docetaxel. The incidence and severity of adverse events (AEs) and serious adverse events (SAEs), as well as changes in laboratory values, ECOG PS, vital signs, weight, physical examination, and cardiac parameters will be summarized. For all safety and tolerability descriptive analyses, the safety set will be used. All listings and tables will be presented by dose cohort. Refer to Section 12.5.2 for more details.

Refer to Section 12.5.3 for details on the analysis of secondary PK objectives.

Part 2- Randomized phase III part

The secondary objectives in this part of the study are to compare the two treatment groups with respect to PFS, tumor related efficacy variables (ORR, DCR, TTR and DOR based on RECIST 1.1), safety and tolerability, quality of life, pharmacokinetics, and immunogenicity.

12.5.1 Efficacy endpoints

Part 1- Safety run-in part

In order to assess preliminary anti-tumor activity, ORR, DCR and DOR will be summarized in FAS by dose cohort, using the local investigator assessment per RECIST1.1. For definitions of these endpoints, refer to Section 12.4 and Section 12.5.1 for the randomized part of the study.

Part 2- Randomized phase III part

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

PFS is defined as the time from the date of randomization to the date of the first documented disease progression based on local investigator assessment per RECIST1.1 or death due to any cause. PFS will be assessed via local review according to RECIST 1.1. PFS will be censored if no PFS event is observed before the analysis cut-off date. The censoring date will be the date of the last adequate tumor assessment prior to cut-off. PFS will be analyzed in the FAS population according to the randomized treatment group and strata assigned at randomization. The PFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

Overall response rate (ORR) is defined as the proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR) as per local review that is subsequently confirmed. ORR will be evaluated according to RECIST 1.1 (see Section 16.1). ORR based on RECIST1.1 will be calculated based on the FAS and according to the intent-to-treat (ITT) principle. ORR and its 95% confidence interval will be presented by treatment group. BOR for each subject is determined from the sequence of overall (lesion) responses according to the following rules:

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

[redacted]

- SD = at least one SD assessment (or better) > 5 weeks after randomization (and not qualifying for CR or PR).
- Non-CR/Non-PD = at least one non-CR/non-PD assessment (or better) > 5 weeks after randomization (and not qualifying for CR or PR).
- PD = progression ≤ 13 weeks after randomization (and not qualifying for CR, PR or SD).

Complete and partial responses must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.Disease control rate (DCR) is defined as the proportion of subjects with BOR of CR, PR, or SD or Non-CR/Non-PD.

DCR will be evaluated according to RECIST 1.1(see Section 16.1 for details).DCR based on RECIST1.1 will be calculated based on the FAS and according to the ITT principle. DCR and its 95% confidence interval will be presented by treatment group.

Time to response (TTR) is defined as duration of time between the date of randomization and the date of first documented response of either CR or PR, which must be subsequently confirmed (although date of initial response is used, not date of confirmation).

TTR will be evaluated according to RECIST 1.1(see Section 16.1 for details).

All subjects in the FAS will be included in TTR calculations. Subjects without a confirmed CR or PR will be censored at the study-maximum follow-up time (i.e., LPLV-FPFV) for subjects with a PFS event (i.e., disease progression or death due to any cause), or at the date of the last adequate tumor assessment for subjects without a PFS event. TTR will be listed and summarized by treatment group based on RECIST1.1. The distribution function of TTR will be estimated using the Kaplan-Meier method. The median TTR along with 95% CIs will be presented by treatment arm.

Duration of response (DOR) is defined as the duration of time between the date of first documented response (CR or PR) and the date of first documented progression or death due to any cause.

Duration of response (DOR) only applies to subjects whose best overall response is complete response (CR) or partial response (PR) based on tumor response data per local review. If a subject has not had an event, DOR is censored at the date of last adequate tumor assessment. Subjects who never achieved a BOR of CR or PR will be excluded from the analysis. The distribution function of DOR will be estimated using the Kaplan-Meier method. The median DOR along with 95% CIs will be presented by treatment arm.

12.5.2 Safety endpoints

12.5.2.1 Analysis set and grouping for the analyses

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

For the safety run-in part cohort, summary tables and listings will be presented by dose cohort. For the randomized part, summaries and listing will be presented by treatment group.

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

[redacted]

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 treatment up to 130 days after last dose of study treatment
3. post-treatment period: starting at day 131 after last dose of study treatment.

12.5.2.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs with onset date during the on-treatment period, the treatment-emergent AEs.

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

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

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

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

12.5.2.3 Laboratory abnormalities

Grading of laboratory values will be assigned programmatically as per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) [redacted] The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE [redacted], results will be categorized as low/normal/high based on laboratory normal ranges. If required, for certain laboratory parameter, values lower than lower limit of normal (LLN) or higher than upper limit of normal (ULN) may further be summarized into categories based on multiples of LLN or ULN respectively.

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

- Listing of all laboratory data with values flagged to show the corresponding CTCAE [redacted] grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE [redacted]

- 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 [redacted] grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE [redacted]

- 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 analyses if needed, for example figures plotting time course of raw or change in laboratory tests over time or box plots may be specified in the analysis plan.

12.5.2.4 Other safety data

ECG

Notable ECG abnormalities will be summarized. In addition, a listing of these subjects will be produced by treatment arm.

Vital signs

Data on vital signs will be tabulated and listed, notable values will be flagged.

12.5.2.5 Immunogenicity

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

[redacted]

12.5.3 Pharmacokinetics

PAS will be used in the pharmacokinetic data analysis in both safety run-in and randomized part of the study. 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 docetaxel concentrations will be presented at each scheduled timepoint for both safety run-in and randomized part of the study.

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

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

12.5.3.1 Population pharmacokinetic analysis

If there is adequate amount of data, a mixed-effects model may be applied to the serum canakinumab concentration-time data from this study along with other studies to generate post-hoc estimates of pharmacokinetic parameters using Non Linear Mixed Effects Modeling (NONMEM) to characterize canakinumab exposure and to determine the effects of intrinsic (i.e. demographic factors) and extrinsic covariates (e.g. concomitant medications) 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

[redacted]

reported in a separate population pharmacokinetic report. Similarly, population PK analysis may also be applied to docetaxel to determine the effects of canakinumab on docetaxel.

12.5.4 Patient reported outcomes

Three patient-reported outcomes (PRO) questionnaires will be assessed: EORTC QLQ-C30 with QLQ-LC13 incorporated and the EQ-5D-5L. QLQ-C30 and QLQ-LC13 will be considered as the primary scale. Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide for each respective subject questionnaire (Fayers et al 2001, Van Reenen et al 2015). No imputation procedures will be applied for missing items or missing assessments.

The FAS will be used for analyzing PRO data. Time to definitive 10 point deterioration symptom scores of chest pain, cough and dyspnea per QLQ-LC13 questionnaire are primary PRO variables of interest.

Utilities derived from EQ-5D-5L together with time to definitive deterioration in global health status/QoL, shortness of breath and pain per QLQ-C30 are secondary PRO variables of interest. The time to definitive 10 point deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10 points absolute increase from baseline (worsening) of the corresponding scale score, with no later change below this threshold i.e. < 10 points was observed or if this increase was observed at the last assessment for the subject, or death due to any cause. If a subject has not had an event, time to definitive deterioration will be censored at the date of the last adequate assessment. The distribution will be presented descriptively using Kaplan-Meier curves. Summary statistics from Kaplan-Meier distributions will be determined, including the median time to definitive 10 point deterioration along with two-sided 95% confidence interval. Additionally, time to definitive deterioration with different definition for deterioration may be specified in the SAP as deemed appropriate. A stratified Cox regression will be used to estimate the hazard ratio (HR), along with two-sided 95% confidence interval.

Descriptive statistics will be used to summarize the original scores, as well as change from baseline, of the QLQC30/ QLQ-LC13 and EQ-5D-5L at each scheduled assessment time point for each treatment group. Additionally, change from baseline in the scale and subscale values at the time of each assessment will be summarized. Subjects with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

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

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

ECOG Performance Status

[redacted]

ECOG performance status as described in Section 8.4.3 will be used to assess physical health of subjects. An analysis of the time to definitive deterioration of the ECOG PS by one category of the score from baseline will be performed using Kaplan-Meier and Cox regression method. A deterioration is considered definitive if no improvements in the ECOG PS status is observed at a subsequent time of measurement during the treatment period following the time point where the deterioration is observed.

[redacted]

12.7 Interim analyses

Part 1- Safety run-in part

The decision for RP3R in the safety run-in will be based on analyses performed after each cohort. More precisely, after each cohort of subjects the next dose will be chosen depending on the observed data (based on safety, PK, tolerability data, guided by the recommendations from the BLRM of DLT using EWOC, and recommendations from

[redacted]

participating investigators). Details of this procedure and the process for communication with Investigators are provided in Section 6.5.2.

Part 2- Randomized phase III part

One interim analysis is planned after approximately 96 of the approximately 137 targeted OS events (i.e., at approximately 70% information fraction) have been observed. This interim analysis is expected to occur around 20 months from the date of first subject randomized in the study. The primary intent of this interim analysis is to claim superior efficacy. There is no intent to assess futility at this interim analysis. The interim analysis will only be carried out after all subjects have been randomized and (if not withdrawn early) should have at least one post baseline assessment.

An α-spending function according to a two-look (Lan-DeMets) group sequential design with (O'Brien-Fleming) type stopping boundary (as implemented in East 6.4) will be used to construct the efficacy stopping boundaries (Lan and DeMets 1983). Based on the choice of α-spending function described above and if the interim analysis is performed exactly after 96 OS events, the efficacy boundary in terms of p-value scale (or equivalently Z-statistic scale) at the interim is calculated as p = 0.0074 (or Z = 2.436). The observed (i.e. nominal) p-value has to be smaller than 0.0074 (or equivalently the observed Z-statistic has to be > Z-statistic scale boundary = 2.436) to conclude superior efficacy at the interim analysis.

Since the observed number of events at the interim analysis may not be exactly equal to the planned 96 OS events, the efficacy boundary will need to be recalculated using the pre-specified α-spending function and based on the actual number of observed events at interim and the total number of targeted events to calculate the exact information fraction. The observed p-value (or Z-test statistic) at the interim analysis will then be compared against the re-calculated efficacy boundary.

If the study continues to the final OS analysis, the final OS analysis will be performed when approximately 137 OS events have been observed. In practice, the final analysis will be based on the actual number of OS events observed at the cut-off date for the final OS analysis and α already spent at the interim analyses. The boundary for the final analysis will be derived accordingly from the pre-specified α-spending function such that the overall significance level across all analyses is maintained at 0.025.

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

Table 12-1 Simulated probabilities to stop for efficacy at the interim or final OS analysis

Scenario	Look	# OS events	Simulated cumulative probabilities (%)	Simulated incremental probabilities (%)
Under H_0 (HR=1)	Interim	96	0.8	0.8
	Final	137	2.4	1.6
Under H_a (HR=0.57)	Interim	96	61.2	61.2
	Final	137	89.7	28.5
Under HR=0.67	Interim	96	32.6	32.6
	Final	137	65.0	32.4

[redacted]

Note: Simulation is performed in East 6.4 with number of simulations = 10,000 and randomization seed =1234.

Any unblinding that can occur following interim/final OS analyses are described in Section 6.4.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Safety run-in part

No formal statistical power calculations to determine sample size were performed for this part of the study. In the case that the starting dose (canakinumab 200 mg sc Q3W with the fixed dose combination of docetaxel 75 mg/m^2 i.v. Q3W) is confirmed to be safe and tolerated, the safety run-in part is expected to enroll approximately 9 subjects in a cohort in order to have at least 6 evaluable subjects (i.e. who met the minimum exposure criterion and had sufficient safety evaluations during the first 6 weeks of canakinumab in combination with docetaxel dosing). Otherwise, up to 18 additional subjects are foreseen to be enrolled to assess additional cohorts.

Randomized phase III part

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

Based on available data (Herbst et al 2016, Rittmeyer et al 2017), the median OS in the docetaxel plus placebo arm is expected to be around 8 months. It is expected that treatment with docetaxel plus canakinumab will result in a 43% reduction in the hazard rate for OS, i.e., an expected hazard ratio of 0.57 (which corresponds to an increase in median OS to 14 months under the exponential model assumption).

Then in order to ensure 90% power to test the null hypothesis: OS hazard ratio = 1, versus the specific alternative hypothesis: OS hazard ratio = 0.57, it is calculated that a total of 137 deaths need to be observed. This calculation assumes analysis by a one-sided log-rank test at the overall 2.5% level of significance, subjects randomized to the two treatment arms in a 1:1 ratio, and a 2-look group sequential design with a Lan-DeMets (O'Brien-Fleming) alpha spending function using an information fraction of 70%. If the final analysis is performed when the targeted 137 OS events are observed after exactly 96 OS events have been observed at IA, the observed hazard ratio will have to be < 0.711 to declare statistical significance. Assuming that enrolment will continue for 18 months with an accrual rate of approximately 5 subjects/month in the first 3 months, and approximately 10 subjects/month for the next 3 months, and approximately 15 subjects/months till the completion of enrollment, along with an assumed 5% dropout rate/year for OS, a total of 226 subjects will need to be randomized to observe the targeted 137 death events at about 8 months after the randomization date of the last subject, i.e., 26 months after the randomization date of the first subject. These calculations were made using the software package East 6.4.

[redacted]

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

13.4 Quality Control and Quality Assurance

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

[redacted]

14 Protocol adherence

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

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

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

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

[redacted]

15 References

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16 Appendices

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

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Glossary

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

[redacted]

TTP	Time to progression
UNK	Unknown

16.1.1 Introduction

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

The efficacy assessments described in Section 16.1.2 and the definition of best response in Section 16.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.1.3.2 is summarizing the "time to event" variables, rules, which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 16.1.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.1.2 Efficacy assessments

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

16.1.2.1 Definitions

16.1.2.1.1 Disease measurability

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

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

For patients without measurable disease see Section 16.1.3.2.8.

Measurable lesions (both nodal and non-nodal)

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

[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 patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with >= 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

16.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Information on how patients with non-measurable disease at baseline will be evaluated for response and how this data will be handled in the statistical analyses is described in Section 16.1.3.2.8.

16.1.2.2 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v.) contrast. The following considerations are to be made when evaluating the tumor:

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

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

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a 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 patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

16.1.2.3 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 16.1.2.1.1.
- **Nodal target**: See Section 16.1.2.1.1. A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.
- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target

lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 16-1) and non-target lesions (Table 16-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-3) as well as the presence or absence of new lesions.

16.1.2.4.1 Follow-up and recording of lesions

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

Non-nodal lesions

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

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

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

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

Nodal lesions

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

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

[redacted]

16.1.2.4.2 Determination of target lesion response

Table 16-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm [2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]
[1] SOD for CR may not be zero when nodal lesions are part of target lesions [2] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR [3] In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.1.2.2).	

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of all measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- Missing measurements: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is

[redacted]

100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.

- Nodal lesion decrease to normal size: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- Lesions split: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- Lesions coalesced: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
- Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
- Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
- Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.1.2.4.3 Determination of non-target lesion response

Table 16-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK):	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline[2].

1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer does prevail..
2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. >= 10 mm) the response can only be '**Non-CR/Non-PD**' unless there is unequivocal progression of the non-target lesions (in which case response is **PD**) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 16.1.2.4.2for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

[redacted]

16.1.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 16.1.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to >= 10 mm for the first time in the study plus 5 mm absolute increase.

FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 16.1.2.2.

16.1.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 16-3.

Table 16-3 Overall lesion response at each assessment

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

[1] This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2] Once confirmed PR was achieved, all these assessments are considered PR.
[3] As defined in Section 16.1.2.4.

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

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

[redacted]

16.1.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 16.1.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

16.1.3.1 Best overall response

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

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 130 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

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

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

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

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 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).

[redacted]

- 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 patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

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

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

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

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

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

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

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

[redacted]

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

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

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize patients 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 patients 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 patients with progressive disease within 8 weeks of the start of treatment.

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

16.1.3.2 Time to event variables

16.1.3.2.1 Progression-free survival

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

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

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.

[redacted]

16.1.3.2.2 Overall survival

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

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

16.1.3.2.3 Time to progression

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

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

16.1.3.2.4 PFS2

A recent EMA guidance (EMA 2012) recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues with regards to censoring foreseen.

16.1.3.2.5 Time to treatment failure

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

[redacted]

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

16.1.3.2.6 Duration of response

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

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

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

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

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

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

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

[redacted]

16.1.3.2.7 Time to response

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

Although an analysis on the full population is preferred, a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 16.1.3.2.6. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

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

Assessment date

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

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

Start dates

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

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

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

[redacted]

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 backdating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 16.1.3.2.8).

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

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

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

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

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with non-measurable disease is derived slightly differently according to Table 16-4.

[redacted]

Table 16-4 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD
[1] As defined in Section 16.1.2.4.		

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

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

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

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

16.1.3.2.10 Sensitivity analyses

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

Based on definitions outlined in Section 16.1.3.2.7, and using the (FDA Guidelines 2007) on endpoints as a reference, the following analyses can be considered:

[redacted]

Table 16-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
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	Ignore the new anticancer therapy and follow situations above (ITT approach) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1] Definitions can be found in Section 16.1.3.2.7.

[2] After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.1.3.2.7.

[3] The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

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

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

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

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

[redacted]

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

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DOR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DOR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the patient is switched to a new cancer therapy.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

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

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

[redacted]

16.1.4 Data handling and programming rules

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

16.1.4.1 Study/project specific decisions

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

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

16.1.4.2 End of treatment phase completion

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

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

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

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- 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 patient from trial.

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

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations.

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

- Adverse event

[redacted]

- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor

16.1.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

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

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

16.1.4.5 Programming rules

The following should be used for programming of efficacy results:

16.1.4.5.1 Calculation of 'time to event' variables

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

[redacted]

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

16.1.4.5.2 Incomplete assessment dates

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

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 16.1.3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

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

16.1.4.5.3 Incomplete dates for last known date patient alive or death

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

16.1.4.5.4 Non-target lesion response

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

16.1.4.5.5 Study/project specific programming

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

16.1.4.5.6 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 16-5)

[redacted]

- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 16.1.3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

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

16.1.5 References (available upon request)

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

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[redacted]

16.2 Appendix 2: Statistical Details for Safety Run-in Part: Bayesian logistic regression model (BLRM): prior and design properties for hypothetical data scenarios

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

16.2.1 Statistical Models

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

16.2.1.1 Single agent part

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

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

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

where d_1^*= 75 mg/m^2 Q3W and d_2^*= 200 mg Q3W (reference doses) are used to scale the doses of Docetaxel and Canakinumab, respectively. Hence, $\alpha 1$ and $\alpha 2$ (>0) are the single-agent odds of a DLT at d_1^* and d_2^*, respectively; and β_1 and β_2 (>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

16.2.1.2 Interaction

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

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

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

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

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

16.2.1.3 Prior specifications

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

[redacted]

Prior distribution for the logistic parameters

A MAP approach was used to incorporate the dose-DLT data from historical studies for Canakinumab. To make the prior more robust, an additional mixture component corresponding to high toxicity was introduced.

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

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

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s (s=1,…,S). The corresponding probability of a DLT is π_{ds}. α_s is the single-agent odd of a DLT at d^* and β_s is the increase in the log-odds of a DLT by a unit increase in log-dose.

The model specifications for the derivation of the MAP prior are as follows:

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

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

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

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

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

normal priors for μ_1 and μ_2,

log-normal priors for τ_1 and τ_2, and

a uniform prior for ρ.

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

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

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

Single agent Docetaxel

Single dose 75 mg/m^2 Q3W is studied in this study. A weakly prior will be assumed according to a DLT rate of 13%. The median for the prior distribution of $\log(\beta_1)$ is set to 0 to correspond to a doubling of dose leading to a doubling of the odds of DLT. The standard deviation for $\log(\alpha_1)$ is derived assuming that there is 90% probability that the DLT rate is lower than 25%

[redacted]

for the model.The standard deviation for $\log(\beta_1)$ is 1. The correlation between the two standard deviations is 0.

Single agent Canakinumab

For Canakinumab, this study uses a mixture prior consisting of four components. Component 1, 2 and 3 are derived based on dose-DLT data from Canakinumab oncology study [CACZ885I2202] by MAP approach. The assigned total weight for Component 1, 2 and 3 is 90%. Component 4 allows for a higher toxicity case. The assigned weight for Component 4 is 10%.

Component 1, 2 and 3

For the MAP model for Canakinumab, reference dose d_2^*=200 mg Q3W is used, and data from S=1 historical study is available.

Canakinumab dose levels in Q3W and Q6W dosing schedule are converted to Q4W by finding out the dose level in Q4W which provides equivalent area under the curve (AUC0-6 weeks) for dose levels in Q3W and Q6W. The simulated PK profiles of canakinumab at 200 mg Q3W and 300 mg Q4W are comparable PK for Canakinumab. Hence, 200 mg on Q3W regimen is equivalent to 300 mg on Q4W regimen and 200 mg on Q6W is equivalent to 150 mg on Q4W regimen.

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

The prior distributions for the model used for deriving the MAP priors are specified in Table 16-6

Table 16-6 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent Canakinumab model parameters

Parameter	Prior distribution
μ_1	N(mean = logit(0.10), sd = 2)
μ_2	N(mean = 0, sd=1)
τ_1	log-normal(mean = 0.250, sd = log(2)/1.96)
τ_2	log-normal(mean = 0.125, sd = log(2)/1.96)
ρ	uniform(-1,1)

Historical data is presented in Table 16-7

[redacted]

Table 16-7 Historical data from [CACZ885I2202]

Canakinumab Q4W dose level (mg)	Converted to dose level in Q8W (mg)	Number of patients completed 4 months	Number of patients with AEs leading to permanent treatment discontinuation in first 4 months	Number of patients in total
5	10	87	0	87
15	30	93	1	94
50	100	84	0	84
150	300	90	1	91

Component 4:

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

- For the intercept parameter $\log(\alpha_2)$, the prior mean of -1.099 is derived based on the a-priori median of an assumed 25% DLT rate at the reference dose d_2*= 200 mg Q3W. By setting the standard deviation =2, the respective 95% a-priori interval for probability of DLT at dose 200 mg Q3W is wide (0.7%, 94.4%), which represents weak prior information.
- For the log-slope parameter $\log(\beta_2)$, the prior mean of 0 and prior standard deviation of 1 allow for very flat to very steep slopes. Therefore, it is a weakly informative prior. The interpretation is as follows: when tripling the dose, the odds of having a DLT are multiplied by a factor of 3^{β_2}.
- The Component 4 is set to be (-1.099, 0, 2, 1, 0)

Interaction parameter: weakly prior distribution

Based on the available information, the interaction is centered at a 0% increase in odds of DLT docetaxel and under each canakinumab dosing regimen. However, in all cases, considerable uncertainty remains as to the true interaction, and normal priors are used that allow for both synergistic and antagonistic toxicity. The following assumptions will be used for interaction parameter for the model:

- η_{12} is normally distributed and centered at 0, i.e. 0% increase in odds of DLT over independence at the combination starting dose
- 97.5th percentile is log(3), i.e. 3-fold increase in odds of DLT over independence at the combination starting dose

All the information to derive the prior distributions for the model parameters is provided in Table 16-8 .

16.2.2 Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 16-8.

The prior summaries for DLT rates for are summarized in Table 16-9.

[redacted]

Table 16-8 Prior distribution for the model parameters

Parameter	Mean	Standard deviations	correlation	weight
Single agent Docetaxel prior				
BVN Mixture ($\log(\alpha_1)$, β_1)				
Weakly informative prior	(-1.901 , 0)	(0.626, 1.000)	0	1.000
Single agent Canakinumab prior				
BVN Mixture ($\log(\alpha_2)$, β_2)				
Component 1 (MAP prior)	(-3.847 , -0.475)	(0.651, 0.493)	0.176	0.427
Component 2 (MAP prior)	(-3.128 , 0.018)	(0.732, 0.425)	0.463	0.246
Component 3 (MAP prior)	(-4.736 , -1.105)	(0.737, 0.696)	0.004	0.227
Component 4 (high toxicity)	(-1.099 , 0)	(2, 1)	0	0.100
Interaction parameter				
Normal				
η_{12}	0	0.561	N/A	N/A

Table 16-9 Summary of prior distribution of DLT rates

Docetaxel dose (mg Q3W)	Prior probabilities that P(DLT) is in the interval :			Mean	SD	Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]			2.5%	50%	97.5%
	In combination with Canakinumab 100 mg Q3W							
75	0.535	0.380	**0.085**	0.181	0.187	0.048	0.152	0.502
	In combination with Canakinumab 200 mg Q3W							
75	0.475	0.368	**0.157**	0.183	0.209	0.039	0.167	0.668
Note: The P(DLT) on the excessive toxicity interval is highlighted bold.								

16.2.3 Hypothetical on-study scenarios

To illustrate the performance of the Bayesian model used to guide dose de-escalation, hypothetical dose de-escalations scenarios following the provisional dose levels specified: Docetaxel 75mg/m^2, i.v., Q3W+ Canakinumab 200 mg, s.c., Q3W or Docetaxel 75mg/m^2, i.v., Q3W+ Canakinumab 200 mg, s.c., Q6W. In each case, the dose that can be used in the next cohort of patients is shown. This dose is determined using the model based assessment of the risk of DLT in future patients and the dose de-escalation rules.

Table 16-10 shows on-study dosing recommendations for some hypothetical data scenarios.

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

[redacted]

Table 16-10 Dose decisions recommended by BLRM under EWOC

Scenario	Docetaxel 75 mg/m^2 + Canakinumab	Number of		Next dose level			
		patients	DLTs	Docetaxel 75 mg/m^2 + Canakinumab	P(Target toxicity)	P(excessive toxicity)	Median P(DLT)
1	200 mg Q3W	6	0	200 mg Q3W	0.233	0.016	0.108
2	200 mg Q3W	6	1	200 mg Q3W	0.426	0.068	0.159
3	200 mg Q3W	6	2	200 mg Q3W	0.537	0.200	0.223
4	200 mg Q3W	6	3	200 mg Q6W	0.471	0.431	0.305
5	200 mg Q3W	6	3				
	200 mg Q6W	6	0	200 mg Q6W	0.584	0.050	0.183
6	200 mg Q3W	6	3				
	200 mg Q6W	6	1	200 mg Q6W	0.68	0.119	0.220
7	200 mg Q3W	6	3				
	200 mg Q6W	6	2	200 mg Q6W	0.661	0.248	0.263
8	200 mg Q3W	6	3				
	200 mg Q6W	6	3	Stop	0.537	0.429	0.311

Note that the overdose criterion is defined as P(excessive toxicity) < 0.25. *Additional dose levels may be added if allowed by the BLRM.

[redacted]

16.3 Appendix 3: List of prohibited concomitant medications and concomitant medications requiring caution

Table 16-11 List of medications to be used with caution for docetaxel

Moderate CYP3A4/5 inhibitors			
netupitant	darunavir	grapefruit juice	crizotinib
atazanavir/ritonavir	darunavir/ritonavir	aprepitant	tofisopam
amprenavir	diltiazem	casopitant	lomitapide
atazanavir	verapamil	cimetidine	
	imatinib	nilotinib	
Moderate CYP3A4/5 inducers			
bosentan	efavirenz	etravirine	modafinil
nafcillin	lersivirine	talviraline	tipranavir
	lopinavir		
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: April 2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. The lists provided may not be exhaustive.			

Table 16-12 Drugs to be avoided while on study

Strong CYP3A4/5 inhibitors			
Macrolide antibiotics:	**Antivirals:**	**Antifungals:**	**Others:**
clarithromycin	indinavir	itraconazole	conivaptan
telithromycin	lopinavir	ketoconazole	elvitegravir
troleandomycin	nelfinavir	posaconazole	mibefradil
	ritonavir	voriconazole	nefazodone
	saquinavir		
	tipranavir		
Strong CYP3A4/5 inducers			
avasimibe	carbamazepine	phenobarbital	phenytoin
rifabutin	rifampin	st. John's wort	
Source: Adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: April 2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. The lists provided may not be exhaustive.			

Table 16-13 CYP3A substrates with narrow therapeutic index, or sensitive CYP2C9 substrates with narrow therapeutic index** to be used with caution when administering concomitantly with canakinumab

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

[redacted]

* Compounds known to increase the corrected QT (QTc) interval that are also primarily metabolized by CYP3A4/5.

For an updated list of CYP2C9 substrates, CYP3A substrates, inhibitors and inducers, please reference the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database.

**Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

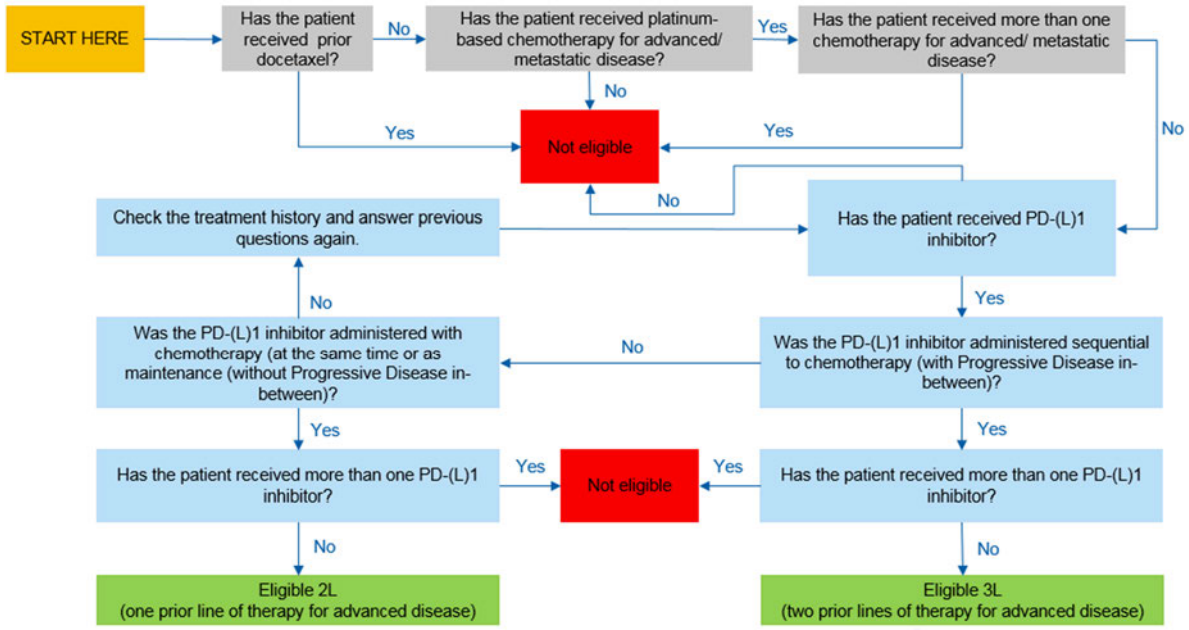
16.4 Appendix 4: Eligibility algorithm

Treatment, which counts as chemotherapy for advanced/ metastatic disease:

- Platinum-based chemotherapy for stage IIIb/IV
- Adjuvant/ neoadjuvant platinum-based chemotherapy and progressed within 12 months of end of therapy

Treatment, which doesn't count as chemotherapy for advanced/ metastatic disease:

- Adjuvant/ neoadjuvant platinum-based chemotherapy and progressed > 12 months of end of therapy



[redacted]

16.5 Appendix 5: Schedule of blood collection (serum) for canakinumab pharmacokinetics (PK) and immunogenicity (IG) during Safety Run-in Part and Randomized part for dose level 1 with canakinumab/placebo 200mg s.c. Q3W regimen

Table 16-14 Blood collection (serum) for canakinumab pharmacokinetics (PK) and immunogenicity (IG) during Safety Run-in part

Dose Reference Identification (ID)		PK sample number	IG sample number[b]	Scheduled time points			
Dose ID following sampling	Dose ID prior to sampling*			Cycle	Day	Scheduled time (hours)	Description
1		101	201	1	1	0 hr[a]	Pre-dose
1		102		1	2	24 hr (±2h)	Post-dose
1		103		1	3	48 hr (±8h)	Post-dose
		104		1	8	168 hr (±12h)	Post-dose
1		105		1	15	336 hr (±24h)	Post-dose
2	1	106		2	1	0 hr[a]	Pre-dose
3	20	107	202	4	1	0 hr[a]	Pre-dose
4	21	108	203	6	1	0 hr[a]	Pre-dose
		109	204	EOT	NA	Anytime	Post-dose
NA	NA	1001+[c]	2001+ [d]	NA	NA	Unscheduled	

* These dose reference IDs refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK and IG samples.

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

[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 1001.

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

Table 16-15 Blood collection (serum) for canakinumab pharmacokinetics (PK), immunogenicity (IG) [redacted] during Randomized part

Dose Reference Identification (ID)		PK sample number	IG sample number[b]	[redacted]	Scheduled time points (hours)			
Dose ID following sampling	Dose ID prior to sampling*				Cycle	Day	Scheduled time (hours)	Description
11		301	401		1	1	0 hr[a]	Pre-dose
11		302			1	15	336 hr (±24h)	Post-dose
12	31	303	402		4	1	0 hr[a]	Pre-dose
13	32	304	403		6	1	0 hr[a]	Pre-dose
14	33	305	404		12	1	0 hr[a]	Pre-dose
15	34	306			18	1	0 hr[a]	Pre-dose
		307	405		EOT	NA	Anytime	Post-dose
		308	406		safety follow-up	NA	130 days after EOT	

[redacted]

NA	NA	3001+[c]	4001+ [d]	[redacted]	NA	NA	Unscheduled and at the time of progression or AE	

* These dose reference IDs refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK, IG [redacted] samples.

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

[b] IG [redacted] 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 3001.

[d] IG sample numbers for any unscheduled IG collection will start with 4001.

16.6 Appendix 6: Schedule of blood collection (plasma) for docetaxel pharmacokinetic during the Safety Run-in part and Randomized part

Table 16-16 Blood collection (plasma) for docetaxel (1 hr IV infusion) pharmacokinetics (PK) during Safety Run-in part

Dose Reference Identification (ID)		PK sample number	Scheduled time points for PK sampling		
Dose ID following sampling	**Dose ID prior to sampling**		**Cycle**	**Day**	**Scheduled time (hours)**
51		601	1	1	Pre-infusion[a]
51		602	1	1	EOI (within 5 mins)
51		603	1	1	2 hr (±10 minutes)[b]
51		604	1	1	4 hr (±15 minutes)[b]
51		605	1	1	6 hr (±30 minutes)[b]
51		606	1	1	8 hr (±30 minutes)[b]
52	51	607	2	1	Pre-infusion[a]
52		608	2	1	EOI (within 5 mins)
52		609	2	1	2 hr (±10 minutes)[b]
52		610	2	1	4 hr (±15 minutes)[b]
52		611	2	1	6 hr (±30 minutes)[b]
		612	2	1	8 hr (±30 minutes)[b]
53	52	613	3	1	Pre-infusion[a]
54	53	614	4	1	Pre-infusion[a]
NA	NA	6001+[c]	NA	NA	Unscheduled

EOI = end of infusion

* These dose reference IDs refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample

[a] Take PK samples within 30 min before the infusion begins

[b] Time relative to beginning of infusion

[c] Sample numbers for any unscheduled blood collection will start with 6001.

Note:

- PK blood samples are collected from the arm opposite from infusion site.
- Plasma samples are collected for PK assessment

[redacted]

Table 16-17 Blood collection (plasma) for docetaxel (1 hr infusion) pharmacokinetics (PK) during Randomized part (subset of 50 subjects, i.e. approximately 25 subjects per arm)

Dose Reference Identification (ID)		PK sample number	Scheduled time points for PK sampling		
Dose ID following sampling	**Dose ID prior to sampling**		**Cycle**	**Day**	**Scheduled time (hours)**
61		701	1	1	Pre-infusion[a]
61		702	1	1	EOI (within 5 mins)
61		703	1	1	2 hr (±10 minutes)[b]
61		704	1	1	4 hr (±15 minutes)[b]
61		705	1	1	6 hr (±30 minutes)[b]
62	61	706	2	1	Pre-infusion[a]
63	621	707	4	1	Pre-infusion[a]
63		708	4	1	EOI (within 5 mins)
63		709	4	1	2 hr (±10 minutes)[b]
63		710	4	1	4 hr (±15 minutes)[b]
63		711	4	1	6 hr (±30 minutes)[b]
NA	NA	7001+ [c]	NA	NA	Unscheduled

EOI = end of infusion

* These dose reference IDs refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample

[a] Take PK samples within 30 min before the infusion begins

[b] Time relative to beginning of infusion

[c] Sample numbers for any unscheduled blood collection will start with 7001.

Note:

- PK blood samples are collected from the arm opposite from infusion site.
- Plasma samples are collected for PK assessment

[redacted]

16.7 Appendix 7: Schedule of blood collection for canakinumab pharmacokinetics (PK) and immunogenicity (IG) for dose level -1 with canakinumab/placebo 200 mg s.c. Q6W regimen

Table 16-18 Blood collection (serum) for canakinumab pharmacokinetics (PK) and immunogenicity (IG) during the safety run-in part for dose level-1 (DL-1)

Dose Reference Identification (ID)		PK sample number	IG sample number[b]	Scheduled time points (hours)			
Dose ID following sampling	Dose ID prior to sampling*			Cycle	Day	Scheduled time (hours)	Description
41		651	751	1	1	0 hr[a]	Pre-dose
41		652		1	2	24 hr (±2h)	Post-dose
41		653		1	3	48 hr (±8h)	Post-dose
41		654		1	8	168 hr (±12h)	Post-dose
41		655		1	15	336 hr (±24h)	Post-dose
41		656		2	1	504 hr (±48h) post-C1D1 dose)	Post-dose
42	41	657	752	3	1	0 hr[a] (or 1008 hr post-C1D1 dose)	Pre-dose
42		658	753	4	1	504 hr (±48h) post-C3D1 dose)	Post-dose
43	42	659	754	5	1	0 hr[a] (or 1008 hr post-C3D1 dose)	Pre-dose
		660	755				EOT, Post-dose
		6501+[c]	7501+ [d]				Unscheduled

* These dose reference IDs refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK and IG samples.

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

[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 6501.

[d] IG sample numbers for any unscheduled IG collection will start with 7501.

Table 16-19 Blood collection (serum) for canakinumab pharmacokinetics (PK) and immunogenicity (IG) [redacted] during the randomized part for dose level-1 (DL-1)

Dose Reference Identification (ID)		PK sample number	IG sample number[b]	[redacted]	Scheduled time points			
Dose ID following sampling	Dose ID prior to sampling*				Cycle	Day	Scheduled time (hours)	Description
81		801	901		1	1	0 hr[a]	Pre-dose
81		802			1	15	336 hr (±24h)	Post-dose
82	81	803	902		3	1	0 hr[a] (or 1008 hr post-C1D1 dose)	Pre-dose

[redacted]

Dose Reference Identification (ID)		PK sample number	IG sample number[b]	[redacted]	Scheduled time points			
Dose ID following sampling	Dose ID prior to sampling*				Cycle	Day	Scheduled time (hours)	Description
82		804	903		4	1	504 hr (±48h) post-C3D1 dose)	Post-dose
83	82	805	904		5	1	0 hr[a] (or 1008 hr post-C3D1 dose)	Pre-dose
84	91	806			11	1	0 hr[a] (or 1008 hr post-C9D1 dose)	Pre-dose
85	92	807	905		17	1	0 hr[a] (or 1008 hr post-C15D1 dose)	Pre-dose
		808	906					EOT, Post-dose
		809	907					safety follow-up, 130 days after EOT
		8001+[c]	9001+ [d]					Unscheduled and at the time of progression or AE

* These dose reference IDs refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK, IG [redacted] samples.

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

[b] IG [redacted] 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 8001.

[d] IG sample numbers for any unscheduled IG collection will start with 9001.

[redacted]