NOVARTIS

Clinical Development

ACZ885

CACZ885V2201C / NCT03968419

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

Statistical Analysis Plan (SAP) Amendment 2

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Template Document History – Changes compared to previous version

Date	Version number	Summary of changes
15-Oct-2019	1.0	N/A
28-Apr-2020	2.0	The main rationale for SAP Amendment 1 is: • To implement the request from the Health Authority to modify the target population for both the primary and secondary endpoint of Major Pathological Response (MPR)in all three treatment arms from "evaluable subjects" to "randomized subjects" as implemented in the protocol amendment V01. • The statistical assumptions for the target MPR rate for the combination arm was updated to 45% which is a 25% absolute improvement to account for the change of analysis population from evaluable subjects to randomized subjects. • [redacted] • Specify the analyses to assess the relationship between key blood or tissue based biomarkers and MPR
20-June-2022	3.0	The main changes in SAP Amendment 2 are: • Added wordings in Section 1 to document recuitment halt • Included estimand language in Section 1.2 as per new SAP template • Updated the definition of date of last exposure to study drug/treatment to take into account the patients' withdrawal of consent in Section 2.1.3.6 • Updated the definition of on-treatment period and post-treatment period in Section 2.1.3.10 • Implemented the summaries about COVID-19 related protocol deviations in Section 2.3 • Removed the wording "antineoplastic surgery will be coded using MedDRA" in Section 2.4.2 • In Section 2.5.2 added "or has the surgery performed but with unevaluable MPR result" in the primary variable of primary estimand. Clarified that posterior distribution will be based on data from subjects in the

Date	Version number	Summary of changes
		FAS. Provided more details about the analysis supporting primary endpoint • Updated the prior distribution in Section 2.5.2, 2.6.1 and 5.4.1, to reflect the change of the MPR rate in the canakinumab in combination with pembrolizumab arm, from "50% in the evaluable patients" to "45% in the randomized patients". • [redacted] • Removed listings of all biomarker data in Section 2.10 • Updated the true MPR rate in Table 3-2 • In Section 5.4.1 removed SAS code and added explanation about how confidence interval for MPR and MPR difference will be obtained in SAS. Updated true MPR value. Removed "evaluable"

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List of abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
BOR	Best Overall Response
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dose Administration Record
DI	Dose Intensity
DRL	Drug Reference Listing
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
i.v.	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MPR	Major Pathological Response
NCI	National Cancer Institute
ORR	Overall Response Rate
PAS	Pharmacokinetic Analysis Set
PDI	Planned Dose Intensity
PK	Pharmacokinetics
Q3W	Every 3 Week
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization
WHO-DD	World Health Organization-Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) describes the planned analyses for the primary clinical study report (CSR) of study CACZ885V2201C, a randomized, open-label, phase II study of canakinumab or pembrolizumab as monotherapy or in combination as neoadjuvant therapy in subjects with resectable non-small cell lung cancer.

As specified in the Section 3 of study protocol, the primary analysis will be performed after all subjects have had surgical resection or have discontinued study treatment earlier due to any reason. At this time, the CSR for primary analysis will be produced. On Feb. 1, 2022, Novartis decided to halt the recruitment into the study given the number of subjects already randomized to the study and the challenges with recruitment.

No change was made to the statistical assumptions and the impact on the probability of declaring proof of efficacy (power) and the probability of missing proof of efficacy (type I error rate) will be limited. The primary analysis will be conducted as planned according to the protocol.

The content of this SAP is based on protocol CACZ885V2201C version 01 (dated 07-Apr-2020). All decisions regarding the primary analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

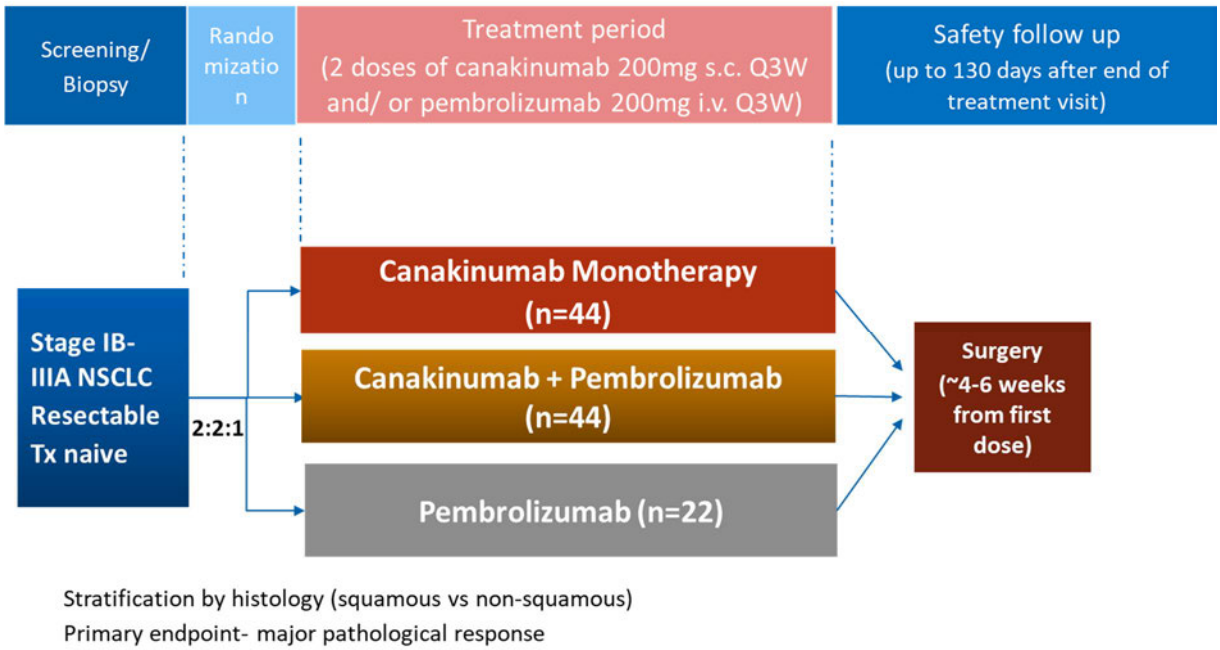
This is a phase II, randomized, open-label study evaluating efficacy and safety of canakinumab or pembrolizumab monotherapy or in combination as neoadjuvant treatment.

Approximately 110 subjects were planned to be randomized in a 2:2:1 ratio to one of the treatment arms (Canakinumab alone, Cankinumab in combination with Pembrolizumab and Pembrolizumab alone) . Subjects randomized will receive two doses of canakinumab (200mg s.c. Q3W) alone or in combination with pembrolizumab or two doses of pembrolizumab as single agent (200mg i.v. Q3W) (Figure 1-1). Randomization will be stratified by histology (squamous vs non-squamous). Subjects with adenosquamous histology can be stratified as squamous or non-squamous based on the predominant histology.

The primary endpoint is the MPR rate as assessed by the percentage of subjects with ≤ 10% residual viable cancer cells based on central review. Primary analysis will be performed after all subjects have had surgical resection or have discontinued study treatment earlier due to any reason.

No formal interim efficacy analysis is planned in this study.

Figure 1-1 Study Design



1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

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

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

1.2.1 Primary estimands

The primary estimand will be described by the following five attributes:

1. The **target population** is defined as all randomized patients who are histologically confirmed NSCLC stage IB-IIIA (per AJCC 8th edition), deemed suitable for primary resection by treating surgeon, except for N2 and T4 tumors.
2. The **primary variable** is the percentage of subjects with a major pathological response (defined as ≤ 10% residual viable cancer cells per central review). Any patient who has >10% residual viable cancer cells, or starts new antineoplastic therapy prior to surgery, or does not have the surgery performed, or have the surgery performed but with unevaluable MPR results, is considered as a non-responder.
3. The **study treatment** is canakinumab as monotherapy or in combination with pembrolizumab.

4. The **intercurrent events** of interest in this study are: start of new antineoplastic therapy prior to surgery and discontinuation of study treatment prior to surgery. These intercurrent events will be addressed as follows:
    a. **Start of new antineoplastic therapy prior to surgery**: subject will be considered as non-responder (composite strategy)
    b. **Discontinuation of study treatment prior to surgery:** subject will be included in the analysis regardless of this intercurrent event (treatment-policy strategy).
5. The **summary measure** is MPR rate with its corresponding two-sided exact binomial 95% confidence interval (Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.) in canakinumab alone arm and canakinumab in combination with pembrolizumab arm.

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis statistics and programming team. SAS version 9.4 or later will be used to perform all data analyses and to generate tables, figures and listings.

2.1.1 Data included in the analysis

Data from all participants who signed main informed consent in centers that participate in this study will be used in the analysis. Data collected after patients' withdrawal of informed consent for further participation in the study will not be reported (except for death date, if it is obtained from public records).

The analysis cut-off date for the primary analysis of study data will be established after all subjects have had surgical resection or have discontinued study treatment earlier due to any reason. All statistical analyses will be performed using all data collected in the database up to the data cutoff date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

2.1.2 General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of subjects enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables by treatment arm; a missing category will be included as applicable. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.
Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, percentiles, minimum, and maximum) by treatment arm.

2.1.3 General definitions

2.1.3.1 Study drug and study treatment

The study drug refers to canakinumab and pembrolizumab. The study treatment refers to canakinumab monotherapy, canakinumab in combination with pembrolizumab, and pembrolizumab monotherpay.

2.1.3.2 Date of first administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug is administered and recorded on the Dosage Administration Record (DAR) (e)CRF. The date of first administration of study drug will also be referred as ***start date of study drug***.

Note : Dates from "DAR – PK sampling" (e)CRF will not be used for this derivation.

2.1.3.3 Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug is administered and recorded on DAR (e)CRF. The date of last administration of investigational drug will also be referred as ***end date of study drug***.

Note 1: Dates from "DAR – PK sampling" (e)CRF will not be used for this derivation.

Note 2: Last date of study drug exposure may not be the same as the last date of study drug (See Section 2.1.3.6)

2.1.3.4 Date of first administration of study treatment

The date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment (canakinumab, pembrolizumab) was administered as per the DAR (e)CRF.

For the sake of simplicity, the date of first administration of study treatment will also be referred as ***start date of study treatment***.

For canakinumab monotherapy and pembrolizumab monotherapy arms, the date of first administration of study treatment is the same as the date of first administration of study drug.

For canakinumab and pembrolizumab combination arm, the date of first administration of study treatment is derived as the first date when a nonzero dose of any component of study treatment was administered as per the DAR (e)CRF. For example: if 1st dose of canakinumab is

administered on 03-Jan-2019, and 1st dose of pembrolizumab is administered on 05-Jan-2019, then the date of first administration of study treatment is on 03-Jan-2019.

2.1.3.5 Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a nonzero dose of study treatment (canakinumab, pembrolizumab) was administered as per DAR (e)CRF.

For canakinumab monotherapy and pembrolizumab monotherapy arms, the date of last administration of study treatment is the same as the date of last administration of study drug.

For canakinumab and pembrolizumab combination arm, the date of last administration of study treatment is derived as the last date when a nonzero dose of any component of study treatment was administered as per Dose Administration (e)CRF. For example: if the last canakinumab dose is administered on 15-Apr-2019, and the last dose of pembrolizumab is administered on 17-Apr-2019, then the date of last administration of study treatment is on 17-Apr-2019.

2.1.3.6 Last date of exposure to study drug/treatment

The study treatment schedule is organized in cycles of 21 days. The last date of exposure to study drug (canakinumab, pembrolizumab) will be derived as follows:

- Min ((last date of administration of study drug + (length of cycle duration - 1), i.e. [last date of study drug administration + 20]), date of death, last contact date in case subject is lost to follow-up, withdrawal of consent date)

The last date of exposure to canakinumab+pembrolizumab study treatment is derived to be the latest date among the last date of exposure to canakinumab and pembrolizumab. If the derived last date of exposure to study drug/study treatment goes beyond the data cutoff date, it should be truncated to the date of data cutoff. 'Date of last administration of study drug' and 'Date of last contact' are defined in Section 2.1.3.3 and Section 2.1.3.12 respectively.

2.1.3.7 Study day

The study day, describes the day of the event or assessment date, relative to the reference start date (randomization date or start date of study treatment).

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

The reference start date for safety assessments (e.g. adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption, PK and etc.) is the start date of study treatment.

The reference start date for all other non-safety assessments (e.g., MPR assessment, tumor response, and ECOG performance status) is the date of randomization.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

2.1.3.8 Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

2.1.3.9 Baseline

For efficacy evaluations, the last non-missing assessment, including unscheduled assessments on or before the date of randomization is taken as "baseline" value or "baseline" assessment. In the context of baseline definition, the efficacy evaluations also include ECOG performance status. For biomarker, the last available data collected before the first dose of study treatment will be defined as "baseline".

For safety evaluations, the last available assessment on or before the date of start of study treatment is taken as "baseline" assessment.

If subjects have no value as defined above, the baseline result will be missing.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected, then the worst value should be considered as baseline.

2.1.3.10 On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of subject's informed consent to the day before first administration of study treatment
2. ***on-treatment period***: from date of first administration of study treatment to 130 days (approximately five terminal half-lives of canakinumab/pembrolizumab) after the date of last administration of study treatment
3. ***post-treatment period***: starting at day 131 after the date of last administration of study treatment

Safety summaries (tables, figures) and summaries of on-treatment death include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).
An ***on-treatment assessment*** is defined as any assessment performed after the date of first administration of study treatment i.e. assessments performed in the following time interval (including the lower and upper limits): from date of first administration of study treatment +1 up to 130 days after the date of last administration of study treatment.

In case at time of the analysis, the date of last administration of study treatment is missing, on-treatment adverse event/assessment include any adverse event/assessment recorded in the database which occur after the start date of the study treatment.

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

2.1.3.11 Windows for multiple assessments

Time windows will be defined for descriptive summary of ECOG performace status data by visit and longitudinal data analysis. If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered.

Table 2-1 Time windows for ECOG performance status

Time Window	Planned Visit Timing	Time Window Definition
Treatment phase		
Baseline	On or before Study Day 1*	≤ Study Day 1
Week 3	Study Day 22	Study Days 2 to end of treatment visit date^ + 7 "Note: EOT visit data will be included if obtained within 7 days after EOT visit"
Safety follow-up		
Safety follow-up 1	26 days from EOT	[end of treatment visit date + 8; end of treatment visit date + 52]
Safety follow-up 3	78 days from EOT	[end of treatment visit date + 53; end of treatment visit + 104]
Safety follow-up 5	130 days from EOT	[end of treatment visit date + 105; end of treatment visit + 156]

* Study Day 1 = randomization date
^ Use end of treatment disposition date if EOT visit date is not available

2.1.3.12 Last contact date

The last contact date will be derived for subjects not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-2 Last contact date data sources

Source data	Conditions
Date of Randomization	No condition
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed.

Source data	Conditions
End of treatment date from end of treatment page	No condition
Safety follow-up visit date	If the visit is completed and the patient doesn't die before the visit
Surgery date from surgery page	"Was a Surgery Performed?" marked as 'Yes'
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term
Imaging assessment date	Imaging marked as done

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the subject was seen or contacted on that date. No date post cut-off date will be used. Imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date.

2.2 Analysis sets

Full Analysis Set (FAS)

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

Safety Set

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

Pharmacokinetic analysis set (PAS)

The PAS consists of all subjects who received at least one dose of study drug and have at least one evaluable PK sample. The PAS will be defined for canakinumab and pembrolizumab separately.

The canakinumab pharmacokinetic analysis set (**PAS-canakinumab**) includes all subjects who provide at least one evaluable canakinumab PK concentration. For a concentration to be evaluable, subjects are required to:

- Receive at least one dose of canakinumab prior to sampling except C1D1 pre-dose sample

- Have pre-dose samples drawn prior to the 2nd dose of canakinumab
- Receive 200 mg of canakinumab prior to post-dose PK sampling
- It is collected (except for cycle 1 day 1) between 16 days (384 hours) and 26 days (624 hours) after the last 200 mg canakinumab dose administration

The pembrolizumab pharmacokinetic analysis set (**PAS-pembrolizumab**) includes all subjects who provide at least one evaluable pembrolizumab PK concentration. For a concentration to be evaluable, subjects are required to:

For pre-dose sample:

- It is collected before the next dose administration
- It is collected (except for cycle 1 day 1) between 16 days (384 hours) and 26 days (624 hours) after the last 200 mg pembrolizumab dose administration

For post-dose sample:

- Received 200 mg of pembrolizumab prior to post-dose PK sampling
- For end-of-infusion samples, have the sample collected within 2 hours post end of infusion

Subject Classification:

Subjects may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules defined in Table 2-3.

Table 2-3 Subject classification based on protocol deviations and non-PD criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent	Not applicable
Safety Set	No written informed consent	No dose of any component of study treatment
PAS-canakinumab	No written informed consent	See definition of PAS-canakinumab
PAS-pembrolizumab	No written informed consent	See definition of PAS-pembrolizumab

Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a subject withdraws full consent is recorded in the eCRF.

Additional data for which there is a separate informed consent, e.g. PK, biomarker etc., collected in the clinical database without having obtained that consent will not be included in the analysis. These data will be excluded by the presence of the appropriate protocol deviation criterion.

2.2.1 Subgroup of interest

Due to small sample size for each arm, no formal subgroup analyses is planned. [redacted] More details can be found in Section 2.10 and Section 2.11.

2.3 Subject disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) and Safety Set will be used for all baseline and demographic summaries and listings unless otherwise specified. Summaries will be reported by treatment arm. In addition, listings will be reported by treatment arm. No inferential statistics will be provided.

Enrollment status

The following summaries will be provided for the FAS in each of the three treatment arms:

1. Number (%) of subjects who were randomized
2. Number (%) of subjects who received at least one dose of study treatment after randomization

Number (%) of subjects screened will be summarized by country and center. In addition, the number (%) of subjects randomized will be summarized by country, center and treatment group.

For subjects who are screen failures, the reasons for not completing screening will be summarized based on "Screening Phase Disposition" eCRF.

Basic demographic and background data

Demographic and other baseline data including disease characteristics will be summarized and listed by treatment arm. Categorical data (e.g. gender, age groups: <65 and ≥ 65 years, race, ethnicity, WHO performance status, smoking history) will be summarized by frequency counts and percentages; the number and percentage of subjects with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index) will be summarized by descriptive statistics (e.g., N, mean, median, standard deviation, percentiles, minimum and maximum).

BMI (kg/m^2) will be calculated as weight[kg] / (height[m]^2) using weight and height at baseline.

Baseline stratification factors

The number (%) of subjects in each randomization stratum based on data obtained from the IRT system will be summarized overall and by treatment arm for the FAS. Discordances between the stratum recorded in IRT at the time of randomization and the actual stratum recorded in the clinical database through the data collected on eCRF will be cross-tabulated and listed.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: primary site of cancer, predominant histology/cytology, additional histology/cytology, stage at initial diagnosis, time since initial diagnosis, stage at time of study entry and other relevant information if collected.

Medical history

Relevant medical histories and current medical conditions at baseline will be summarized and listed by treatment arm. The summaries will be presented by primary system organ class (SOC), preferred term (PT) and treatment arm. Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

All data collected at baseline (e.g., other informed consent than main study informed consent) will be listed.

Subject disposition

The number (%) of randomized subjects included in the FAS will be presented by treatment arm. The number (%) of screened and not-randomized subjects and the reasons for screening failure will also be displayed. The number (%) of subjects in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented overall and by treatment arm.

The following summaries will be provided (with % based on the total number of FAS subjects):

- Number (%) of subjects who were randomized (based on data from IRT system)
- Number (%) of subjects who were randomized but not treated (based on 'DAR' eCRF page not completed for any study treatment component)
- Primary reason for not being treated (based on "Treatment disposition" eCRF page)
- Number (%) of subjects who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered*)*
- Number (%) of subjects who are still on-treatment (based on the 'Treatment disposition' page not completed);
- Number (%) of subjects who discontinued the study treatment phase (based on the 'Treatment disposition' page)
- Primary reason for study treatment phase discontinuation (based on the 'Treatment disposition' page)
- Number (%) of patients who are still in the safety follow-up phase (based on presence of the 'Treatment disposition' page and absence of the' Study disposition' page)

- Number (%) of patients who discontinued from safety follow-up phase (based on completion of 'Study disposition' page)
- Primary reasons for discontinuation from safety follow-up phase (based on discontinuation reasons entered under 'Subject Status' in the 'Study discontinuation' page).

Protocol deviations

The number (%) of subjects in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the edit-check specification) overall and by treatment arm for the FAS. All protocol deviations will be listed.

In addition to the pre-defined standard PD terms, Novartis has also defined 6 new protocol deviations and the corresponding relationship (health status related vs. site lockdown, patient concerns, etc.) to the COVID-19 pandemic in line with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (March 2020) and "Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic" (April 2020) from EMA as listed below. Two additional study specific PDs are also defined to capture treatment delay/interruption and MPR Assessment missed due to COVID-19. The following deviations related to the COVID-19 pandemic will be summarized.

- Missing visits
- Changes in procedures and assessments
- Planned visits not done at sites
- Changes in drug supply method
- Treatment not given
- Patient discontinuation due to COVID-19 situation
- Treatment delayed/interrupted
- MPR Assessment missed due to COVID-19

A cross-tabulation of COVID-19 related PD vs. corresponding relationship will also be produced by treatment arm.

Analysis sets

The number (%) of subjects in each analysis set will be summarized by treatment arm and randomization stratum. Reasons for exclusion of patients from analysis sets will be tabulated separately overall and by treatment arm.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure, cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by treatment arm. The number (%) of subjects with interruptions, discontinuation and the corrresponding reasons, will be summarized and listed.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study drug

Duration of exposure to study drug (canakinumab and pembrolizumab) is defined as

Duration of exposure (days) = (last date of exposure to study drug) – (date of first administration of study drug) + 1

Duration of exposure to study treatment

Duration of exposure to study treatment is the same as the duration of exposure to study drug for Canakinumab only and Pembrolizumab only treatment arms. For Canakinumab+Pembrolizumab arm, duration of exposure to study treatment is derived by taking into account the duration of exposure to each study drug:

Duration of exposure (days) = (last date of exposure to study treatment) – (date of first administration of study treatment) + 1

The duration includes the periods of temporary interruption except for the last one, a dose interruption occurring after the last date of exposure to study drug won't be considered. 'Date of first administration of study drug/treatment' and 'last date of exposure to study drug/treatment' are defined in Section 2.1.3.

Duration of exposure to study drug/treatment will be summarized using descriptive statistics (mean, standard deviation etc).

Cumulative dose

Cumulative dose for any component of study treatment is defined as the total dose of the medication given during the study treatment exposure.

Cumulative dose will be summarized using descriptive statistics by treatment arm for each component of study treatment. For subjects who do not receive any drug the cumulative dose will be set to zero.

The cumulative dose is defined according to the type of dosing schedule and is calculated from the DAR eCRF.

The cumulative dose for canakinumab and pembrolizumab is defined based on the days when the subject is assumed to have taken a non-zero dose during dosing periods.

Dose intensity and relative dose intensity

Dose intensity (DI) for subjects with non-zero duration of exposure is defined as follows:

DI (dosing unit / cycle) = Actual Cumulative dose (dosing unit) / (last dose date-first dose date+dose interval) *21 (days/cycle).

For canakinumab, dose interval is 21 days. For pembrolizumab, dose interval is 21 days.

For subjects who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

- for canakinumab, PDI is 200mg/cycle;

- for pembrolizumab, PDI is 200mg/cycle.

Relative dose intensity (RDI) is defined as follows:

RDI = DI (dosing unit / cycle) / PDI (dosing unit / cycle) * 100%.

For canakinumab and pemborolizumab, the dosing unit is mg. DI and RDI will be summarized for each of the study drug (canakinumab and pembrolizumab) by treatment arm using descriptive summaries. In addition, categorical summary of RDI for each study drug will be presented. The number of administrations of each study drug component of the study treatment will be summarized.

Dose interruptions or permanent discontinuations

The number of subjects who have dose interruptions and permanent discontinuations and the corresponding reasons, will be summarized separately for each of the study treatment components. The duration of the interruption will also be summarized by descriptive statistics.

'Dose interrupted', and 'Dose permanently discontinued' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose interruptions, and permanent discontinuations, respectively. The corresponding fields 'Reason for dose interrupted' and 'Reason for permanent discontinuation' will be used to summarize the reasons.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

2.4.2 Prior, concomitant and post treatment therapies

Post treatment anti-cancer therapy

Given neoadjuvant setting, no prior antineoplastic therapies are allowed.

Antineoplastic medications since discontinuation of study treatment will be summarized by Anatomical Therapeutic Chemical (ATC) class, preferred term and treatment arm.

Separate listings will be produced for anti-neoplastic medications, radiotherapy, and surgery since discontinuation of study treatment.
Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD). Details regarding WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the FAS.

Concomitant therapy

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO ATC classification system and summarized by lowest ATC class, preferred term and treatment arm using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC, preferred term and treatment arm. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 130 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 130 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

2.5 Analysis of the primary objective

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

2.5.1 Primary endpoint

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

2.5.2 Statistical hypothesis, model, and method of analysis

The primary estimand will be described by the following five attributes:

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

5. The **summary measure** is MPR rate with its corresponding two-sided exact binomial 95% confidence interval (Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.) in canakinumab alone arm and canakinumab in combination with pembrolizumab arm.

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

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

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

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

The posterior distribution of MPR will be derived from the prior distribution and all available data from the subjects in the FAS. A minimally informative unimodal Beta prior (Neuenschwander et al 2008) Beta(3/7, 1) and Beta(9/11, 1) will be used for canakinumab monotherapy and canakinumab in combination with pembrolizumab, respectively. Please refer to Section 5.4.1 for details of prior distribution. The posterior mean of MPR will be calculated and the MPR rate with its corresponding two-sided exact binomial 95% confidence interval (Clopper CJ and Pearson ES (1934)) will be estimated in both the canakinumab monotherapy arm and canakinumab in combination with pembrolizumab arm. The posterior probability that MPR>= 20% and the posterior probability that MPR>= 30% will be calculated for canakinumab monotherapy arm and canakinumab in combination with pembrolizumab arm, respectively. Waterfall plot for percentage of residual viable tumor based on central review in canakinumab monotherapy arm and canakinumab in combination with pembrolizumab arm will be generated.

2.5.3 Handling of missing values/censoring/discontinuations

Refer to Section 2.5.2 for details on handling of intercurrent events. Subjects who have an unknown MPR status due to surgery not being performed (including lost to follow-up or withdrawal of study consent before surgery) or due to unevaluable MPR results will be considered as non-responders when estimating MPR rate.

2.5.4 Supportive analyses

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

The target population, study treatment, the primary variable and the summary measure will be the same as for the primary estimand except for handling of the intercurrent event of starting new antineoplastic therapy prior to surgery. Subjects will be included in the analysis for MPR

regardless of this intercurrent event (treatment-policy strategy). Same analyses will be done as for the primary estimand.

2.6 Analysis of secondary efficacy objective(s)

The secondary efficacy objectives are to:

- To assess the MPR rate at the time of surgery
  a) in the randomized pembrolizumab monotherapy arm based on central review
  b) in all three randomized treatment arms based on local review
  c) to estimate the difference in MPR and posterior probability that the difference in MPR is ≥ 10% between the randomized canakinumab + pembrolizumab combination arm and randomized pembrolizumab monotherapy arm based on central review
- To assess overall response rate in randomized subjects treated with canakinumab or pembrolizumab as monotherapy and in combination based on local review on the EOT visit
- To assess surgical feasibility rate in each treatment arm based on randomized subjects

2.6.1 MPR rate

MPR rate (1) based on local review in all 3 treatment arms and (2) based on central review in pembrolizumab monotherapy arm will be assessed in the same patient population as the primary estimand. The intercurrent events and the strategy for handling intercurrent events will be the same as primary estimand.

MPR rate for all the above specified analyses will be summarized by treatment arm along with the two-sided exact binomial 95% confidence interval (Clopper and Pearson 1934). Waterfall plot for percentage of residual viable tumor based on central review in pembrolizumab arm will be generated.

The difference in MPR rate between canakinumab in combination with pembrolizumab and pembrolizumab single agent arm along with the two-sided exact 95% confidence interval based on Chan and Zhang (1999) will be summarized based on central review using the same patient population used in the primary analysis, including the strategy for handling intercurrent events. The posterior probability that the difference is 10% or greater in MPR rate will also calculated in the following way: first, sampling from posterior distribution of MPR rate for each arm; then, calculating the sampling differences and probability that the difference is 10% or greater between the two arms. The minimal informative Beta prior Beta(9/11, 1) and Beta(3/7, 1) will be used for canakinumab in combination with pembrolizumab arm and pembrolizumab single agent arm, respectively.

2.6.2 Overall response rate (ORR)

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

The BOR will be determined from response assessments undertaken while on treatment. In addition, only tumor assessments performed before the start of any further anti-neoplastic therapies will be considered in the assessment of BOR. A new anticancer therapy is defined as any secondary anticancer therapy (either systemic treatments, radiotherapy or surgery) received during or post study treatment.

2.6.3 Surgical Feasibility Rate

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

2.7 Secondary objective: safety analyses

All safety analyses will be performed based on the Safety Set and will be presented by treatment arm unless specified otherwise.

2.7.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study treatment, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding by treatment arm. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades (version 5.0) for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the canakinumab monotherapy arm.

The following adverse event summaries will be produced by treatment arm:

- Overview of adverse events and deaths
- AEs by SOC and PT (all AEs and AEs related to at least one study drug component)

- AEs by PT (all AEs and AEs related to at least one study drug component) and maximum CTC grade
- AEs leading to permanent discontinuation of one of the study drug component, AEs leading to canakinumab permanent discontinuation
- AEs leading to dose interruption
- AEs requiring additional therapy
- SAEs (all SAEs and SAEs related to at least one study drug component) and SAEs leading to fatal outcome.
- Summary of SAEs and non-SAEs with number of occurrences (an occurrence is defined as >1 day between start and prior end date of record of same preferred term).

2.7.1.1 Adverse events of special interest / grouping of AEs

Data analysis of AESIs

An adverse event of special interest (AESI) is a grouping of adverse events that are of scientific and medical concern specific to compound canakinumab. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. The groups are defined according to the MedDRA terms defined in the program Case Retrieval Strategy (CRS) document and will be summarized. The latest version of the CRS document available at the time of the analyses will be used. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided by treatment arm, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose interruption, hospitalization, death etc.).

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

AESI groupings are specified in the electronic Case Retrieval Strategy (eCRS). The latest version of the eCRS available at the time of the analysis will be used

2.7.2 Deaths

Separate summaries for on-treatment and all deaths will be produced by treatment arm, system organ class and preferred term.

All deaths will be listed, and post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.7.3 Laboratory data

When analyzing laboratory related date, all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the laboratory parameters collected no later then 130 days after the last study treatment administration date (see Section

2.1.3). Grading of laboratory values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). Each subject will be counted only for the worst grade observed post-baseline.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value (hypo and hyper worst grade will be summarized separately if applicable)
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- If there are multiple assessments as baseline candidate, the central lab assessment will be defined as "baseline". If there are multiple assessments from the central lab or the local lab, the worst assessment will be defined as "baseline."

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized by treatment arm:

The following summaries will be produced:

- ALT > 3xULN
- ALT > 5xULN
- ALT > 10xULN
- ALT > 20xULN
- AST > 3xULN
- AST > 5xULN
- AST > 10xULN
- AST > 20xULN
- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN

- ALT or AST > 20xULN
- Total bilirubin (BILI) > 2xULN
- Total bilirubin (BILI) > 3xULN

AST and ALT =< ULN at baseline

- ALT or AST > 3xULN & BILI > 2xULN
- ALT or AST > 3xULN & BILI > 2xULN & ALP ≥ 2xULN
- ALT or AST > 3xULN & BILI > 2xULN & ALP < 2xULN

AST and ALT > ULN at baseline

- Elevated ALT or AST > 3xULN & BILI (>2x Bsl or 2x ULN)
- Elevated ALT or AST > 3xULN & BILI (>2x Bsl or 2x ULN) & ALP ≥ 2xULN
- Elevated ALT or AST > 3xULN & BILI (>2x Bsl or 2x ULN) & ALP < 2xULN

Elevated AST or ALT defined as: >3x ULN if =< ULN at baseline, or (>3x Bsl or 8x ULN) if > ULN at baseline.

In addition, a listing of all BILI, ALT, AST and ALP values for subjects with a post-baseline BILI > 2xULN, ALT> 3xULN or AST > 3xULN will be provided.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

A listing of all ECG assessments will be produced by treatment arm.

2.7.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), respiratory rate (breaths per minute), pulse rate (beats per minute), supine systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-4 below.

Table 2-4 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=180 with increase from baseline of >=20	<=90 with decrease from baseline of >=20
Diastolic blood pressure (mmHg)	>=105 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Respiratory rate (bpm)	< 12	> 25
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	-

The number and percentage of subjects with notable vital sign values (high/low) will be presented by treatment arm.

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged.

2.7.4.3 ECOG performance status

The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) performance status scale, ranging from 0 to 5, as specified in Table 2-5 below.

Table 2-5 ECOG Performance Scale

Score	Description
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

Time window for ECOG PS are defined in Table 2-1 . If the closest assessment to the target date has two or more ECOG filled out on the same date, then the worst ECOG PS value will be used.

Time windows are applicable for descriptive summary of ECOG data by visit only.

Frequency counts and percentages of patients in each score category will be provided by treatment arm and time point.

2.7.4.4 Other safety data

Other safety data (e.g. data relating to liver events) will be listed in the safety set.

Data from other tests will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

All assessments collected later than 130 days after the last treatment date will be flagged in the listings.

Any statistical tests performed to explore the data will be used only to identify any interesting comparisons that may warrant further consideration.

2.8 Secondary objective: Pharmacokinetic endpoints

Pharmacokinetic data analyses will be performed for canakinumab and pembrolizumab concentrations. The following analyses are for canakinumab concentrations. They are also applicable and will be repeated for pembrolizumab concentrations.

PAS-canakinumab and PAS-pembrolizumab will be used in the pharmacokinetic data analysis for canakinumab and pembrolizumab concentrations, respectively.

PK concentrations

Descriptive statistics (n, m (number of non-zero concentrations), arithmetic mean, CV% mean, SD, median, geometric mean, CV% geo-mean, minimum and maximum) for canakinumab concentration will be presented at each scheduled time point for the PAS-canakinumab.

Individual concentration-time profiles for canakinumab evaluable concentrations with median will be displayed graphically for PAS-canakinumab on the semi-log view. In addition, the mean (+/- SD) and geometric mean concentration-time profiles for canakinumab over time will be displayed graphically for PAS-canakinumab on the linear and semi-log view.

All individual plasma canakinumab concentration data will be listed by treatment using the FAS.

Handling of PK data below LLOQ or missing

All concentration values below the lower limit of quantitation (LLOQ) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. LLOQ values will be treated as zero in any calculations of summary statistics, and treated as missing for the calculation of the geometric means and their CV%. The number of non-zero concentrations will also be reported in the summary statistics.

Missing values for any PK data will not be imputed and will be treated as missing.

Population pharmacokinetic analysis

If there is adequate amount of data, a mixed-effects model may be applied to the serum canakinumab concentration-time data from this study along with other studies to generate post-hoc estimates of pharmacokinetic parameters using NONMEM to characterize canakinumab

exposure and to determine the effects of intrinsic (i.e. demographic factors) and extrinsic covariates (e.g. concomitant medications, formulation) on canakinumab exposure. If there is sufficient data for analysis, the details of the population pharmacokinetic analyses may be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report.

2.9 Secondary objective: Immunogenicity

Immunogenicity data will be summarized using the safety set. Immunogenicity will be characterized descriptively by tabulating anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment. A shift table of subjects with positive or negative anti-canakinumab and anti-pembrolizumab antibodies overall and by visit will be produced ("positive" corresponds to "worst"). A listing will be provided by subject with supporting information (i.e. ADA sample status at each timepoint (including titer for positive samples) and subject ADA status). In addition, a listing will also be provided for subjects with neutralizing antibodies (NAB) testing results. Dependng on the incidence of immunogenicity, additional analysis of the effect of ADA status on PK, efficacy or safety may be performed.

2.10 Secondary objective: Biomarkers

As a project standard, only biomarkers collected in the clinical database will be analyzed. [redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

The FAS will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

Biomarker objectives

The secondary objective related to biomarker is to assess the relationship between key blood or tissue based biomarkers and MPR.

List of biomarkers evaluated and the collection time points

The biomarkers evaluated in the study are listed in Table 2-6 below.

Table 2-6 Scheduled sample biomarker summary table for secondary [redacted] objectives

Biomarker	Time point	Sample
Key IHC (e.g., PD-L1, CD8) and other tissue immune markers	Baseline biopsy and resection	Tissue
[redacted]		
hs-CRP	Cycle 1 Day 1 (pre-dose) Cycle 2 Day 1 (pre-dose) EOT Safety follow-up 1 Safety follow-up 3 Safety follow-up 5	Blood (serum)
Cytokine panel testing, including hs-IL-6	Cycle 1 Day 1 (pre-dose) Cycle 2 Day 1 (pre-dose) EOT Safety follow-up 1 Safety follow-up 3 (only hs-IL-6) Safety follow-up 5 (only hs-IL-6)	Blood (plasma)
[redacted]		

Relationship between key blood/tissue based biomarker and MPR

The relationship between key IHC markers (PD-L1, CD8), key cytokines (hs-CRP and hs-IL-6) assessed at baseline, and MPR will be explored. MPR based on the following pre-defined baseline biomarker subgroups will be explored. The estimated and its 95% confidence interval of MPR in each subgroup, will be summarized and plotted.

- PD-L1 level (<1% vs. 1%-49% vs. ≥50%)
- hsCRP level (<2mg/L vs. ≥2mg/L)
- hsCRP level (<10mg/L vs. ≥10mg/L)
- hsCRP level (<50 mg/L vs. ≥50 mg/L)
- hsCRP level (<Q1 vs. ≥Q1 and <Q2 vs. ≥Q2 and<Q3 vs. ≥Q3)
- hs-IL-6 level (<Q1 vs. ≥Q1 and <Q2 vs. ≥Q2 and <Q3 vs. ≥Q3)
- CD8 level (<median vs. ≥median)
- CD8 level (<3% vs. >= 3%)

Quartile of the biomarker concentration is defined as:

- <Q1: <25th percentile

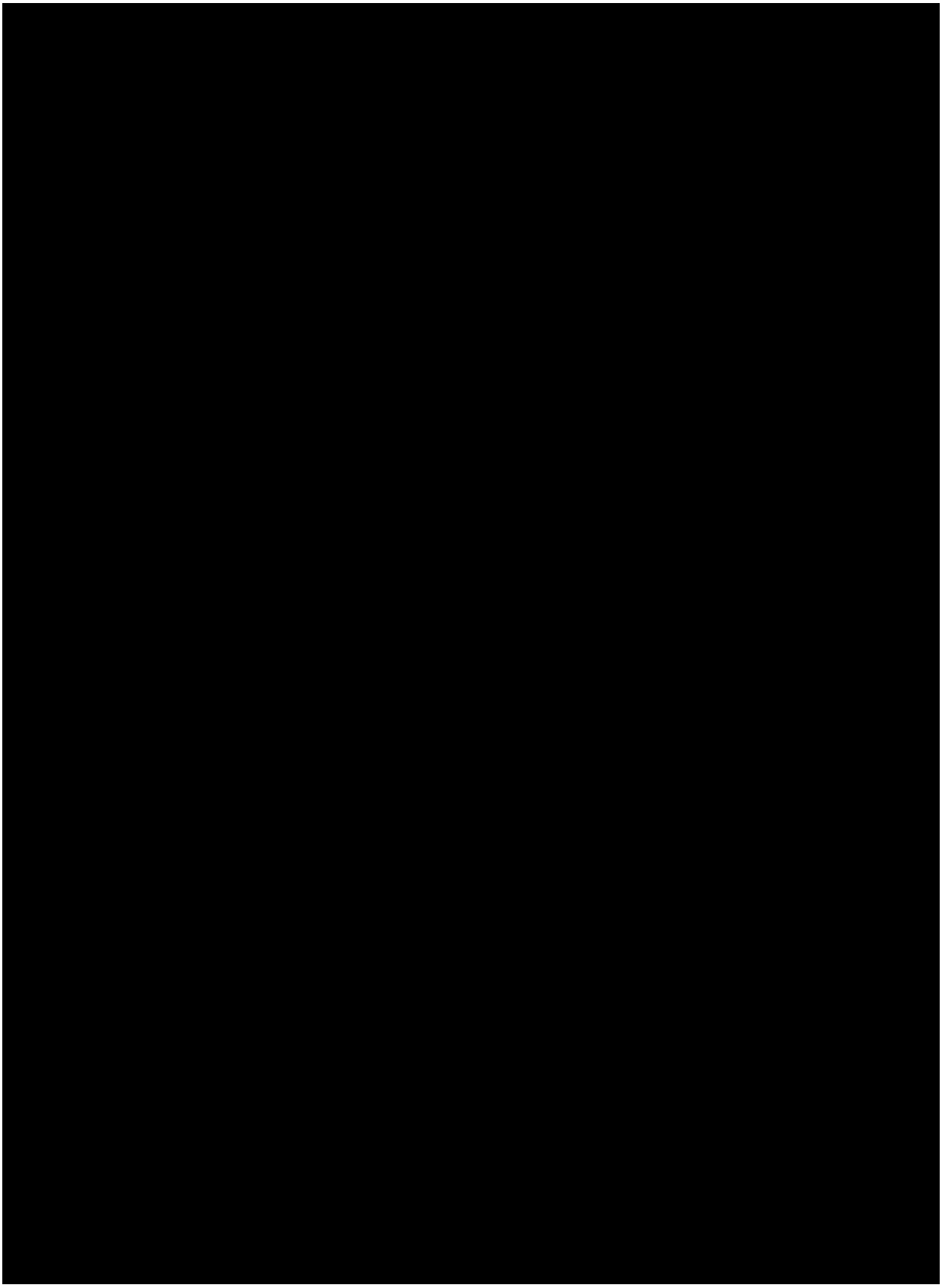
- ≥Q1 to <Q2: ≥25th percentile and <50 percentile
- ≥Q2 to <Q3: ≥50th percentile and <75th percentile
- ≥Q3: ≥75th percentile

Additional cutoff might be explored if clinically indicated.

MPR will be summarized by treatment arm and subgroup along with the two-sided exact binomial 95% confidence interval (Clopper and Pearson 1934).

In addition, baseline and changes from baseline for the IHC markers and cytokines (absolute change, percent change and fold change) at each time point will be summarized by MPR status and for all subjects in tables that include sample size, mean, standard deviation, CV%, median, minimum and maximum. For fold change from baseline, geometric mean and geometric CV% will also be included.

In addition, association between MPR and time profiles of key IHC markers (PD-L1, CD8) and key cytokines (hs-CRP and hs-IL-6) will be displayed graphically by the MPR status and for all subjects.



2.12 Interim analysis

Not applicable

3 Sample size calculation

3.1 Primary analysis

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

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

Among the 44 subjects randomized to canakinumab single agent treatment, at least 14 responders are needed to meet the proof of efficacy criteria. When the true MPR rate is $\leq 20\%$, the probability of erroneously declaring proof of efficacy is at most 4.4%, while the probability of declaring proof of efficacy is at least 89.8% for MPR $\geq 40\%$ (Table 3-1).

Among the 44 subjects randomized to the canakinumab and pembrolizumab combination treatment, at least 20 responders are required to meet the proof of efficacy criteria. When the true MPR rate is $\leq 30\%$, the probability of erroneously declaring proof of efficacy is at most 2.1% while the probability of declaring proof of efficacy is at least 92.2% for MPR $\geq 55\%$ (Table 3-2). Assuming an enrollment rate of 6 subjects per month, the enrollment will be completed at approximately 18 months and MPR assessment for the last patient randomized will occur at approximately 20 months from the date of first subject randomized in the study.

Table 3-1 Operating characteristics with 44 subjects randomized to canakinumab treatment arm

True MPR	Probability of declaring proof of efficacy (12 or more responders)	Probability of missing proof of efficacy (11 or less responders)
20%	4.4%	95.6%
30%	45.2%	54.8%

True MPR	Probability of declaring proof of efficacy (12 or more responders)	Probability of missing proof of efficacy (11 or less responders)
40%	89.8%	10.2%
50%	99.5%	0.5%

Table 3-2 Operating characteristics with 44 subjects randomized to the canakinumab + pembrolizumab combination treatment arm

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

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation of the start date of infusion/injection or end date for infusion will be applied. Complete dates are required as per eCRF.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Missing Element	Rule
day	• If available month and year = month and year of study treatment start date then o If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY. o Else set start date = study treatment start date. • If available month and year > month and year of study treatment start date then 01MONYYYY • If available month and year < month year of study treatment start date then 15MONYYYY

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.2.1 Other imputations

Not applicable

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 5.0 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE version 5.0, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. For laboratory tests that are graded for both low and high values, summaries will be done

separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

5.4 Statistical models

5.4.1 Primary analysis

The estimate of the response rates (e.g., MPR, ORR, surgical feasibility rate) will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper and Pearson 1934).

SAS procedure FREQ will be used to estimate the proportion of responders, along with the associated 95% two-sided exact binomial CI. The difference in MPR rate along with the two-sided exact 95% confidence interval based on Chan and Zhang (1999) can be obtained by using "exact" statement.

Calculation of posterior probability

The criteria for proof of efficacy are:

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

for canakinumab single agent arm and

- the mean of the posterior distribution of MPR is at least 45% and

- the posterior probability that the MPR is ≥ 30% is at least 90%

for canakinumab and pembrolizumab combination arm.

Let p_1 denote the MPR rate for canakinumab single agent and follow a beta prior distribution Beta(a_1,b_1), where a_1>0, b_1>0. Let y_1 out of n_1 patients reach MPR in canakinumab single agent arm. Then the posterior distribution of p_1 is Beta(a_1+ y_1, b_1+ n_1-y_1) (Spiegelhalter et al. 2004). Similarly, for canakinumkab and pembrolizumab combination arm, the posterior distribtuion of p_2 is Beta(a_2+ y_2, b_2+ n_2-y_2).

A minimally informative unimodal Beta prior (Neuenschwander et al. 2008) will be used. For canakinumab single agent arm, the parameters will be chosen so that the mean of the prior distribution is equal to 0.3, which corresponds to Beta(3/7, 1). For canakinumab in combination with pembrolizumab arm, the parameters will be chosen so that the median of the prior distribution is equal to 0.45, which corresponds to Beta(9/11, 1).

The efficacy criteria will be assessed based on the actual number of patients enrolled. For example, if the total number of patients in canakinumab is *44*, the first efficacy criterion requires that at least *14* patients who are MPR responders. In that case, the posterior distribution is Beta(*3/7+14, 1+44-14*) and the posterior probability P(MPR rate ≥ *0.2*) = *96.5%*.

6 Reference

1. Chan IS, Zhang Z. (1999) Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics, 55(4), 1202-1209.
2. Clopper CJ and Pearson ES (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrical, 26, 404-413.
3. Neuenschwander B, Branson M and Gsponer T (2008). Critical aspects of the Bayesian approach to Phase I cancer trials. Statistics in Medicine, 27, 2420-2439.
4. Pataer A, Kalhor N, Correa AM, et al (2012) Histopathologic response criteria predict survival of patients with resected lung cancer after neoadjuvant chemotherapy. J Thorac Oncol p. 825-32.
5. Spiegelhalter DJ, Abrams KR and Myles JP (2004). Bayesian Approaches to Clinical Trials and Health-care Evaluation. Chichester, Wiley.