SAMSUNG BIOEPIS

Statistical Analysis Plan

A Phase III, Randomised, Double-blind, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB8 (proposed bevacizumab biosimilar) and Avastin® in Subjects with Meta static or Recurrent Non-squamous Non-small Cell Lung Cancer

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MODIFICATION HISTORY

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			overall response and no central imaging data will not considered as non-responder in PPS." 2. Added a subgroup analysis by ADA status for primary endpoint and secondary endpoints 3. Added analyses of Nab and overall ADA 4. Added the definition of the overall ADA 5. Following Changes are made to appendix 6. TOC of results for CSR: Figure deleted (i.e., Figure 14.2-3.1~14.2-4.2, Figure 14.2-6.1~14.2-6.2); Table added (i.e. Table 14.3-3.1~14.3-3.3; Table14.2-3.3.1~14.2-3.5.2; Table 14.3.1-1.15)
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List of Abbreviations

ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemistry
BLQ	Below the Lower limit of Quantification
BSA	Body Surface Area
CCr	Creatinine Clearance
CR	Complete Response
CSR	Clinical Study Report
DOB	Date of Birth
DOR	Duration of Response
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal Growth Factor Receptor
ENR	Enrolled Set
EOT	End of Treatment
FAS	Full Analysis Set
IP	Investigational Product
NAb	Neutralising Antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PDs	Protocol Deviations
PD	Progressive Disease
PFS	Progression Free Survival
PK population	Pharmacokinetic population
PPS	Per-Protocol Set
PR	Partial Response
PT	Preferred Term
RAN	Randomised Set
RDI	Relative Dose Intensity
SAE	Serious Adverse Event
SAF	Safety Set

SAP	Statistical analysis plan
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
ULQ	Upper limit of quantification

1. INTRODUCTION

This document describes the planned analyses as well as the rules and conventions to be used in the presentation and analyses of efficacy, safety, pharmacokinetics and immunogenicity data for the first database lock for reporting the 24-week clinical study report (CSR) and final database lock for reporting the 52-week CSR. This statistical analysis plan (SAP) has been based upon the Clinical Study Protocol SB8-G31-NSCLC Amendment 2 (Aug. 18, 2016) and the electronic Case Report Form (eCRF), Version 6.0 (Mar. 17, 2017).

The following analyses will be performed for this study.

- **Interim safety analysis for the 1st Data and Safety Monitoring Board (DSMB) meeting:**
  The SAP for the 1st DSMB meeting describing the methodology and presentation of results will be prepared as a separate document and included in the DSMB Charter. The statistical analyses will be performed by an independent statistical reporting team and the results will be communicated with the DSMB board by an unblinded statistician.
- **Main analysis for 24-week CSR:**
  The primary analysis for the 24-week CSR data will take place when at least 24 weeks has elapsed since the last subject is randomised. The results will be provided based on the unblinded treatment groups for reporting purpose.
- **Final analysis for 52-week CSR:**
  The final analysis for the 52-week CSR will take place when the last subject completes the study or after the corresponding visit. All efficacy, safety, pharmacokinetics and immunogenicity data will be analysed and reported for the 52-week CSR and submitted again to health authority in terms of complements.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to demonstrate the equivalence of SB8 to Avastin®, in terms of the best overall response rate (ORR) during induction treatment period by 24 weeks of chemotherapy in subjects with metastatic or recurrent non-squamous non-small cell lung cancer (NSCLC).

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the efficacy of SB8 compared to Avastin® by
  - Progression free survival (PFS)
  - Overall survival (OS)

- Duration of response (DOR)

- To evaluate the safety and tolerability of SB8 compared to Avastin®
- To evaluate the pharmacokinetics of SB8 compared to Avastin®
- To evaluate the immunogenicity of SB8 compared to Avastin®

2.3. Exploratory Objective

The exploratory objective is:

- To evaluate the best ORR during induction treatment period by 11 and 17 weeks

3. STATISTICAL METHODS

3.1. Analysis Sets

Enrolled Set [ENR]: The Enrolled Set will consist of all subjects who provide informed consent for this study.

Randomised Set [RAN]: The Randomised Set will consist of all subjects who receive a randomisation number at the Randomisation. For analyses and displays based on RAN, subjects will be classified according to the treatment they are assigned at randomisation.

Full Analysis Set [FAS]: The Full Analysis Set will consist of all randomised subjects. The subjects will be analysed based on the treatment they were randomised to by intention-to-treat principle. However, subjects who do not qualify for randomisation and are inadvertently randomised into the study will be excluded from FAS, provided these subjects do not receive any investigational product (IP) during the study.

Per-protocol set [PPS]: The Per-Protocol Set will consist of all FAS subjects who complete at least first two cycles of combination chemotherapy with a tumour assessment and do not have any major protocol deviations that impact the primary efficacy assessment. Major protocol deviations that will lead to the exclusion from the PPS will be pre-specified, and the PPS will be determined prior to unblinding treatment codes.

Safety Set [SAF]: The Safety Set will consist of all subjects who received the study drug at least once. This analysis set will be used for the safety analyses. The subjects will be analysed based on the treatment they received.

Pharmacokinetic population [PK population]: This set will consist of subjects allocated to PK sub-study who have at least one measured serum concentration of bevacizumab.

The number of subjects in the analysis sets will be summarised by treatment group and overall for the RAN. A by-subject listing of analysis population details will be provided for the RAN by treatment group and will include: country, centre, subject, age, sex, race, inclusion/exclusion flag for each population, and reason for exclusion from PPS.

3.2. Protocol Deviations

All Protocol Deviations (PDs) will be defined, classified and reported per a separate Protocol Deviation Specification document. PDs will be classified as major and minor. PDs will not lead to subject withdrawal unless they indicate a significant risk to the subject's safety.

PDs and analysis sets will be reviewed and confirmed through the blind data review meeting to decide which subjects and/or subject data will be excluded from certain analyses prior to database lock. Decisions regarding the exclusion of subjects and/or subject data from the specific analysis set (see 3.1) will be made prior to treatment code unblinding and will be documented and approved.

A summary of the number and percentage of subjects with PDs by PDs severity (major and minor), PDs classification will be presented by treatment group and overall. Percentages will be based on the number of subjects randomised.

A by-subject listing of major and minor PDs will be provided including subject identifier, PDs classification, PDs description, PDs severity and exclusion from specific analysis sets.

4. GENERAL CONSIDERATIONS

4.1. Study Day

Study Day (in days) will be calculated from date of randomisation and it will be used to show start and stop day of assessments or events.

For visit (or event) prior to randomisation,
Study day = Date of assessment (or event) – (Date of randomisation).

For visit (or event) at or after randomisation,
Study day = Date of assessment (or event) – (Date of randomisation) + 1.

In case that the event date is partial or missing, the date will appear partial or missing in the listings. And study day will be calculated after proper imputation has been carried out as described in APPENDIX 1.

4.2. Baseline

The Baseline value will be defined as the last available measurement value prior to or on the date of first IP administration.

4.3. Retests, Unscheduled Visits and Early Termination Data

In general, unscheduled and retest safety measurements will not be included in the by-visit summaries, but will contribute to the incidence of abnormalities and across visit summary. Measurement at the end of treatment (EOT) visit will be mapped to the next scheduled visit since last IP administration, such as anti-drug antibodies (ADA), vital signs, and weight, etc.

Listings will include all scheduled, unscheduled, retest and early discontinuation data with the nominal visit originally recorded on the eCRF.

4.4. Common Calculations

For quantitative measurements, changes from baseline at Visit (as defined in APPENDIX 4) will be calculated as:

Change at Visit = Measurement value at Visit – Baseline Value (Baseline)

Changes from baseline in categorical data will be summarised using shift tables, where appropriate.

Duration is calculated as (excluding treatment duration):

Duration (days) = (End Date – Start Date + 1)
Duration (weeks) = (End Date – Start Date + 1) / 7
Duration (months) = (End Date – Start Date + 1) / 30.44
Duration (years) = (End Date – Start Date + 1) / 365.24

Duration of treatment is defined in Section 10.

4.5. Software Version

All analyses will be conducted using SAS version 9.2 or a higher version.

5. STATISTICAL CONSIDERATIONS

5.1. Missing Data

In the primary efficacy analysis for FAS, the response of the subjects without any post-baseline tumour assessment will be imputed as following:

- Missing data from subjects who withdrew from the study due to Progressive Disease (PD), lack of efficacy and adverse events (AEs) without any tumour assessment will be considered as non-responder. The PD (i.e., lack of efficacy) and AE were collected as "Disease Progression (Non-fatal)" and "Adverse Event", respectively, from the item "primary reason for treatment discontinuation" on the Discontinuation of Treatment page of the eCRF.
- Missing data from subjects who withdrew from the study with reasons other than PD, lack of efficacy and AEs without any tumour assessment will be imputed using multiple imputation method.
- Missing data from subjects who remained in the study but do not have any valid tumour assessment will be imputed using multiple imputation method.

In the primary efficacy analysis for the PPS, missing data will not be imputed.

All safety analysis and descriptive summaries will be based on the observed data. Missing safety data will not be imputed.

5.2. Multiple Comparisons/Multiplicity

No adjustments for multiplicity are required.

6. DISPOSITION AND WITHDRAWALS

A clear accounting of the disposition of all subjects who enter the study will be provided, from enrolment to study completion. The subject disposition summaries include the following:

- The number of subjects enrolled, the number and percentage of screen failures and reasons for screen failure, using the ENR.
- Subjects completed induction treatment period, ongoing maintenance treatment period, subjects discontinued from induction/maintenance treatment period, the reasons of discontinuation of treatment period will be summarised by treatment group, using the ENR.

- A by-subject listing of subject disposition will be generated using the ENR, including start/end date of induction/maintenance treatment period, primary reasons of withdrawal or screening failure.

The similar summary statistics for subject disposition will be performed by centre and treatment group, using the RAN.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject demographics and baseline characteristics will be summarised by treatment group for the RAN and PK population. The following demographics and baseline characteristics will be summarised:

Demographics Characteristics

- Age (years) – calculated relative to date of randomisation.
  Compute the difference in years between date of birth (DOB) and date of randomisation.
  If the month of randomisation is earlier than the month of DOB or if the month is the same but the day of randomisation is earlier than the day of DOB, then subtract 1 year from the calculated age.
  If DOB is partial date (missing day and month), age will be derived as (year of randomisation) – (year of birth) – 1, to apply conservative age for unknown day and month cases.
- Age group (< 65 and ≥ 65, < 70 and ≥ 70)
- Gender – Male, Female
- Race – White, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other
- Ethnicity– Hispanic or Latino, Chinese, Indian (Indian subcontinent), Japanese, Mixed Ethnicity, Other
- Country
- Region (EU vs. non-EU)
- Weight (kg) at baseline
- Height (cm) at baseline
- BMI (kg/m^2) – derived as $\frac{weight(kg)}{height(m)^2}$
- BSA(m^2) – derive as $\sqrt{\frac{(height(cm)\times weight(kg))}{3600}}$

Other Baseline Characteristics

- Epidermal growth factor receptor (EGFR) gene status
- ALK gene status
- Cancer type (dominant histological classification)
- Stage of disease, based on TNM classification
- Duration of disease (months, from first NSCLC diagnosis date to study day 1)
- Eastern cooperative oncology group (ECOG) performance status (0, 1, ≥ 2)
- Smoking status (never smoked, former smoker, and current smoker)

8. MEDICAL AND SURGICAL HISTORY

Medical and surgical history excluding NSCLC will be summarised by treatment group for the RAN. Frequency table will be provided by System Organ Class (SOC) and Preferred Term (PT), coded by the latest version of Medical Dictionary for Regulatory Activities (MedDRA version 20.0). NSCLC medical and surgical history will be summarised similarly.

A by-subject listing of medical and surgical history excluding NSCLC will include SOC, PT, verbatim term, start date, end date and current status. The by-subject listing of NSCLC medical and surgical history will include first NSCLC pathologic diagnosed date, SOC, PT, verbatim term, start date, end date, anatomical location (if surgery) and current status.

9. MEDICATIONS AND PROCEDURES

Prior and Concomitant Medications

Prior medication will be defined as medication which started and ended prior to the first dose of the IP. Concomitant medication will be defined as medications which ended on or after the first dose of IP or are on-going at the end of the study. Imputation of partial dates for prior/concomitant medication is described in APPENDIX 1. Prior and concomitant medications will be summarised by treatment group for the SAF. Frequency table will be provided by anatomical therapeutic chemistry (ATC) term, PT by World Health Organization-Drug Dictionary Enhanced (WHO-DDE version 01 March, 2015).

Prohibited Medications

Prohibited medications will be summarised similarly by treatment group for the SAF. Prohibited medications with MedDRA codes or ATC codes and prohibited duration are defined in APPENDIX 3.

Prior and Concomitant Radiotherapy for NSCLC

Prior radiotherapy for NSCLC will be defined as radiotherapy which started and ended prior to the first dose of the IP. Concomitant radiotherapy will be defined as radiotherapy which ended on or after the first dose of IP or are on-going at the end of the study. Imputation of partial dates for prior/concomitant radiotherapy is described in APPENDIX 1. Prior and concomitant radiotherapy for NSCLC will be summarised by treatment group, respectively, for the SAF. Frequency table will be provided by site and reason for use for the SAF.

By subject listings of prior and concomitant medications, prohibited medications, prior and concomitant radiotherapy for NSCLC will be provided for the SAF.

Significant Non-Drug Therapy

The significant non-drug therapies include any of followings:

- Prior or Concomitant Radiotherapy for NSCLC and reason for use is primary lesion control
- Prior systemic anti-cancer therapy for NSCLC

Significant non-drug therapies will be summarised by treatment group, respectively, for the SAF.

By subject listing of prior systemic anti-cancer therapy for NSCLC will be provided for the SAF.

10. STUDY MEDICATION EXPOSURE

Investigational product (IP) refers to SB8 (proposed bevacizumab biosimilar) or EU sourced Avastin®. Non-Investigation product (non-IP) refers to Paclitaxel and Carboplatin. Exposure to study medication will be provided for IP and non-IP, respectively, using the SAF. Exposure summary will be based on the actual dose administered (mg) collecting in the eCRF.

If IP and non-IP is discontinued or completed at least 21 days prior to the cut-off date,
Duration of exposure (weeks) = (Last administration date – First administration date + 21)/7

If study medication is continued at cut-off date,
Duration of exposure (weeks) = (Cut-off date – First administration date + 1)/7

The summaries of study medication will be presented for IP and non-IP, respectively. The summaries of study medication exposure include following analysis:

- Duration of exposure to study medication using descriptive statistics.
- Number of subjects received infusion by cycle.
- Number of infusion (cycle) received per subject by treatment period (induction, maintenance, overall).
- Dose modification (delay, interruption, reduction) and reason for modification by treatment period (induction, maintenance, overall).
- Cumulative actual dose by treatment period (induction, maintenance, overall).
- Cumulative planned dose by treatment period (induction, maintenance, overall).
- Relative Dose Intensity (RDI) will be presented by treatment period (induction, maintenance, overall). RDI is based on the cumulative actual dose and the cumulative planned dose and will be calculated as follows:

$$\text{RDI (\%)} = \frac{\text{Cumulative actual dose}}{\text{Cumulative plannded dose}} \times 100$$

- Cumulative planned dose of IP (mg) = Sum of (actual body weight (kg) at every cycle × 15 mg/kg)

- Cumulative planned dose of Paclitaxel (mg) = Sum of (actual Body Surface Area (BSA) at every cycle × 200 mg/m^2)
- Cumulative planned dose of Carboplatin (mg) = Sum of ([AUC 6] × (CCr at every visit + 25))
- Carboplatin will be administered by Calvert formula (AUC 6) every 3 weeks during the induction treatment period. Creatinine clearance (CCr) must be calculated prior to every dosage of carboplatin using below the formula (Cockcroft-Gault equation) and it should NOT exceed 125 ml/min:
  Male:
  $$\text{CCr} = \frac{(140 - \text{Age [y]}) \times \text{body weight [kg]}}{72 \times \text{serum creatinine [mg/dL]}}$$
  Female:
  $$\text{CCr} = \frac{(140 - \text{Age [y]}) \times \text{body weight [kg]}}{72 \times \text{serum creatinine [mg/dL]}} \times 0.85$$

The actual body weight is subject's body weight measured and documented at baseline and at every cycle. Actual body weights should be used in calculating BSA at each cycle.

Listing of IP administration will be provided, including infusion start date/time, end date/time, medication kit ID, actual administration dose, dose delay, reason of delay, infusion interruption, reason of interruption, not done, reason of not done and infusion related reaction. Listing of non-IPs administration will include infusion start date/time, end date/time, actual administration dose, dose reduction, reason of reduction, not done, reason of not done and infusion related reaction.

11. EFFICACY OUTCOMES

11.1. Primary Efficacy Analysis

The primary efficacy endpoint is the best ORR during induction treatment period by 24 weeks of chemotherapy. The best ORR is defined as the proportion of subjects whose best overall response is either complete response (CR) or partial response (PR) according to RECIST v1.1 during the induction treatment period. The mathematical formula is

$$\text{Best ORR} = \frac{\text{\# of subjects with best overall response of CR or PR during induction treatment period by 24 weeks}}{\text{\# of subjects in the analysis set}}$$

If a subject has either CR or PR at least once during induction treatment period by 24 weeks the subject will be considered as the responder. The primary efficacy analysis will be based on the data from the independent central review.

The overall response will be summarised using descriptive statistics (N, %) by treatment group and cycle in FAS based on the data from the independent central review and investigator review.

In addition, the best overall response during induction treatment period by 24 weeks will be summarised using descriptive statistics (N, %) by treatment group in FAS based on the data from the independent central review and investigator review.

The subject without any post-baseline tumour assessment based on the data from the independent central review will be categorized as 'NE' in the overall response and best overall responses summaries. These subjects based on the data from the investigator review will be categorised in a similar manner.

The overall response of 'Non-CR/Non-PD' based on the data from the independent central review will be categorized as 'NE' in the overall response and best overall responses summaries.

Hypothesis, statistical model, and method of analysis

The null hypothesis tested for the primary efficacy analysis will be either (1) SB8 is inferior to Avastin® or (2) SB8 is superior to Avastin® based on a pre-defined equivalence margin.

For US Food and Drug Administration or other regulatory agency submissions for those who are in favour of risk ratio, the primary efficacy analysis will be performed in the FAS for the ratio of best ORR (best ORR of SB8/best ORR of Avastin®) by 24 weeks, and the equivalence will be declared if the 90% confidence interval (CI) of the best ORR ratio is contained within the pre-defined equivalence margin of [0.737, 1.357].

The primary efficacy analysis for the ratio will be performed using the log binomial model (implemented via SAS procedure GENMOD) with treatment as an explanatory variable and best ORR as a response. The response is assumed to be Binomial distributed with the log link function ($f(x) = \log(x)$). This link can be used with any distribution.

In the primary efficacy analysis for the FAS, response of the patients without any post-baseline tumour assessment will be imputed. The method of imputation is defined in 5.1.

For EMA, MFDS or other regulatory agency submissions for those who are in favour of risk difference, the primary efficacy analysis will be performed in the PPS for the difference of the best ORR (best ORR of SB8 – best ORR of Avastin®) by 24 weeks, and the equivalence between the two treatment groups will be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [-12.5%, 12.5%].

The primary efficacy analysis for the difference of the best ORR will be performed using the binomial model (implemented via SAS procedure GENMOD) with treatment as an explanatory variable and best ORR as a response. The response is assumed to be Binomial distributed with the link function ($f(x) = x$). This link can be used with any distribution. The dependent variable is not transformed.

In the primary efficacy analysis for the PPS, missing data will not be imputed.

The SAS syntaxes of the log binomial model and the binomial model for primary endpoint analyses are specified in APPENDIX 5.

In addition, the best ORR will be summarised using descriptive statistics (N, %) by SB8 and Avastin® along with two-sided exact binomial 95% CIs.

Sensitive Analysis of Primary Efficacy Endpoint
The following sensitivity analysis will be performed to explore the robustness of the primary efficacy result.

1. The primary efficacy analysis for the ratio and the difference of the best ORR, respectively, will be performed for the PPS and FAS.

2. The sensitivity analysis will be performed using the log binomial model and binomial model with the covariates of age (< 70, ≥ 70 years), sex (Male, Female), region (EU, non-EU) and treatment.

The SAS syntaxes of the log binomial model and the binomial model for sensitivity analyse of primary endpoint are specified in APPENDIX 5.

Subgroup analysis
The above analyses will also be carried out in the subgroup categories:

- Age group (<65 years vs. ≥ 65 years and <70 years vs. ≥ 70 years)
- Gender (Male vs. Female)
- Race (White vs. Other)
- Country(Russia vs. Ukraine vs. Georgia, Hungary, Spain, Germany vs. Belarus, Romania, Serbia, Poland vs. Korea, Thailand, Taiwan)
- Region (EU vs. non-EU)
- ECOG Performance Status (0 vs.1)
- Smoking Status (Never smoked vs. Former smoker vs. Current smoker)
- Cancer type (Adenocarcinoma vs. Other)

11.2. Secondary Efficacy analyses

The secondary efficacy endpoints of PFS, OS and DOR will be analysed for PPS and FAS.

11.2.1. Progression Free Survival (PFS)

Progression free survival (PFS) is defined as the time in month from the date of randomisation to the date of PD or death regardless of the cause of death. Subjects who are not progressed at the time of analysis will be censored at the last tumour assessment date.

The mathematical formula is

$$\text{PFS (months)} = \frac{(\text{date of PD or death} - \text{date of randomisation} + 1)}{365.24} \times 12$$

The distribution of PFS will be estimated using the Kaplan-Meier method. PFS will be analysed using Kaplan-Meier method and will be summarised as follows:

- Number and percentage of patients with PFS events (i.e., deaths or PD)
- Number and percentage of censored patients
- Kaplan-Meier estimates of 2, 4, 6, 8, 10, 12 months PFS rate, including the corresponding 95% CIs
- Kaplan-Meier estimates of median including corresponding 95% CI, 25th and 75th percentile, minimum and maximum

The sensitivity analysis will be performed in FAS and PPS, using the Cox proportional hazard model with the covariates of age (< 70, ≥ 70 years), sex (Male, Female), region (EU, non-EU), and treatment to explore the robustness of the PFS analysis results.

PFS analysis will be based on the FAS and PPS, with tumour response assessed by independent central review.

The SAS syntaxes of the Cox proportional hazard model for PFS analyses are specified in APPENDIX 5.

Handling of censoring

If a patient has no PD or is not known to have died at the date of analysis cut-off, PFS will be censored at the date of the last radiological tumour assessment before data cut-off or patient withdrawal from the study. The date of the last radiological tumour assessment is the date of the last tumour assessment with overall lesion response of CR, PR or Stable Disease before an event or a censoring reason occurred. If there is no available post-baseline tumour assessments are available (before an event or a censoring reason occurred) then the date of randomisation will be used as a censoring point.

In particular, PFS will be censored at the date of the last radiological tumour assessment if one of the following occurs: No PD; the event (PD or death) occurring after more than one missing assessments; treatment discontinuation for undocumented PD, toxicity or other reason. Refer to Table 11-1 for censoring and event date options and outcomes for PFS.

Table 11-1 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline tumour assessment	Date of randomisation	Censored
PD or death at or before next scheduled assessment	Date of the last radiological tumour assessment demonstrating PD, or date of death	Progressed
New anticancer treatment started without documented PD	Date of last radiological tumour assessment prior to initiation of new therapy	Censored
PD or death after more than one missing assessments	Date of the last radiological tumour assessment	Censored
No PD	Date of the last radiological tumour assessment	Censored
Treatment discontinuation for undocumented PD (i.e. clinical PD based on investigator claim)	Date of the last radiological tumour assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of the last radiological tumour assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed

A listing of PFS will be provided, including date of randomisation, date of event, endpoint description for PFS and PFS.

11.2.2. Overall Survival (OS)

Overall survival (OS) is defined as the time from date of randomisation to date of death due to any cause. A cut-off date will be established for each analysis of OS. All deaths occurring on or before the cut-off date in the FAS and PPS will be used in the OS analysis.

The mathematical formula is

$$\text{OS (months)} = \frac{(\text{date of death} - \text{date of randomisation} + 1)}{365.24} \times 12$$

The distribution of OS will be estimated using the Kaplan-Meier method. OS will be analysed using Kaplan-Meier method and will be summarised as follows:

- Number and percentage of patients with event
- Number and percentage of censored patients
- Kaplan-Meier estimates of 2, 4, 6, 8, 10, 12 months OS rate, including the corresponding 95% CIs
- Kaplan-Meier estimates of median including corresponding 95% CI, 25^{th} and 75^{th} percentile, minimum and maximum

The sensitivity analysis will be performed in FAS and PPS, using the Cox proportional hazard model with the covariates of age (< 70, ≥ 70 years), sex (Male, Female), region (EU, non-EU), and treatment to explore the robustness of the PFS analysis results.
OS analysis will be based on the FAS and PPS.

Handling of censoring
If a patient is not known to have died at the time of analysis cut-off, OS will be censored at the date of last contact.

A listing of OS will be provided, including date of randomisation, date of event, endpoint description for OS and OS.

11.2.3. Duration of Response (DOR)

Duration of response (DOR) only applies to the subjects who achieve an initial tumour response. The start date is the date of first documented response of CR or PR and the end date is defined as the date of the first documented PD or death. Subjects continuing without PD or death due to underlying cancer will be censored at the date of their last adequate tumour assessment using the censoring rule described for PFS analysis.

The mathematical formula is $\text{DOR (months)} =$

$$\frac{(\text{date of the first PD or death} - \text{date of first response of CR or PR} + 1)}{365.24} \times 12$$

DOR will be analysed based on the FAS and PPS, with tumour response assessed by independent central review.

DOR will be summarised using descriptive statistics by treatment group. A listing of DOR will be provided, including date of first documented response, date of event, endpoint description for DOR and DOR.

11.2.4. Best ORR, PFS and DOR evaluated by Investigator

The following analyses of best ORR, PFS and DOR results evaluated by Investigators will be performed:

- The ratio of best ORR (best ORR of SB8/best ORR of Avastin®) during induction treatment period by 24 weeks will be analysed in FAS and PPS using the log binomial model with treatment.
- The ratio of best ORR (best ORR of SB8/best ORR of Avastin®) during induction treatment period by 24 weeks will be analysed in FAS and PPS using the log binomial model with covariates of age (< 70, ≥ 70 years), sex (Male, Female), region (EU, non-EU), and treatment.
- The difference of best ORR (best ORR of SB8-best ORR of Avastin®) during induction treatment period by 24 weeks will be analysed in FAS and PPS using the binomial model with treatment.
- The difference of best ORR (best ORR of SB8-best ORR of Avastin®) during induction treatment period by 24 weeks will be analysed in FAS and PPS using the binomial model with covariates of age (< 70, ≥ 70 years), sex (Male, Female), region (EU, non-EU), and treatment.
- The PFS will be analysed in FAS and PPS using Kaplan-Meier method.
- The sensitivity analysis of PFS will be performed in FAS and PPS, using the Cox proportional hazard model with the covariates of age (< 70, ≥ 70 years), sex (Male, Female), region (EU, non-EU), and treatment.
- A listing of PFS evaluated by Investigators will be provided, including date of randomisation, date of event, endpoint description for PFS and PFS.
- DOR will be summarised using descriptive statistics in both FAS and PPS by treatment group.
- A listing of DOR will be provided, including date of first documented response, date of event, endpoint for DOR and DOR.

In addition, a concordance summary of best overall response during induction treatment period by 24 week (Response vs. No response) to assess the level of agreement between independent central review and investigator review will be produced.

A by-subject listing of tumour response (i.e., response of target lesions, non-target lesions, new lesions, and overall response) will be provided.

11.3. Efficacy analysis by overall ADA result

The following analyses of best ORR, PFS, OS and DOR results by overall ADA result up to Cycle 7 (Positive, Negative, Inconclusive) and PFS and OS results by overall ADA result up to EOT (Positive, Negative, Inconclusive) will be performed for exploratory purpose. The best ORR, PFS and DOR analysis will be based on the FAS and PPS, with tumour response assessed by independent central review. The OS analysis will be based on the FAS and PPS:

- The ratio of best ORR (best ORR of SB8/best ORR of Avastin®) during induction treatment period by 24 weeks by overall ADA result up to Cycle 7 will be analysed in FAS and PPS by using the log binomial model with treatment.

- The difference of best ORR (best ORR of SB8-best ORR of Avastin®) during induction treatment period by 24 weeks by overall ADA result up to Cycle 7 will be analysed in FAS and PPS using the binomial model with treatment.

- The PFS by overall ADA result up to Cycle 7 and EOT will be analysed in FAS and PPS using Kaplan-Meier method.

- The OS by overall ADA result up to Cycle 7 and EOT will be analysed in FAS and PPS using Kaplan-Meier method.

- DOR by overall ADA result up to Cycle 7 will be summarised using descriptive statistics in both FAS and PPS by treatment group

11.4. Exploratory Efficacy analysis

The exploratory efficacy endpoint is the best ORR during the induction treatment period by 11 and 17 weeks and will be analysed in a similar manner to the primary endpoint analysis.

12. SAFETY OUTCOMES

All safety analyses will be performed using the SAF.

12.1. Adverse Events

All reported terms for AEs will be coded using the latest version of MedDRA version 20.0. National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE version 4.03) will be used by investigator to assess the severity grade of all AEs. For all AE tables, subjects will be counted once for each PT and each SOC. Unless specified otherwise, AEs will be summarised in the alphabetical order of SOC and then decreasing frequency of PT within the SOC for the treatment group. If the frequency of PT within the SOC is tied, PT will be sorted alphabetically.

All AEs

All pre-treatment AEs and treatment-emergent adverse events (TEAEs) will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events.

A Pre-treatment AE will be defined as any AE with an onset date before the date of first administration of IP.

A TEAE will be defined as any AE with an onset date on or after the date of the first administration of IP. AEs which are already present before the first IP and increase in severity after the first IP will be considered as TEAEs. Pre-existing AEs before the first IP with no increase in severity after the first IP will not be considered as TEAEs.

An overview of AEs by treatment group will be provided, including number of subjects experiencing TEAEs, drug related TEAEs, serious TEAEs, serious drug related TEAE, TEAEs leading to discontinuation of study medication, drug related TEAE leading to discontinuation of study medication, and deaths.

Imputation of partial dates of AE record is described in APPENDIX 1.

Listing of all AEs will be provided by treatment group and will include AE term (SOC, PT, and Verbatim term), start date/time and corresponding study day, end date/time and corresponding study day, severity, infusion related reaction, relationship, action taken, outcome, flag of adverse events of special interest (AESI), seriousness including criteria of serious adverse event (SAE).

Pre-treatment AE

Pre-treatment AEs will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events.

Treatment-emergent Adverse Event

TEAEs will be summarised by SOC and PT and by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events, separately. TEAEs with incidence by PT > 5% will be additionally summarised by SOC, PT and CTCAE grade.

Other Adverse Events

An Other AEs will be defined as all AE excluding SAEs. Other AEs with incidence by PT > 5% will be additionally summarised by SOC, PT and CTCAE grade.

Severity

TEAEs with Grade 3 - 5 will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events. If same event occurred more than once in the same subject, the highest severity grade will be used for the analysis.

Relationship (Causality)

Drug related TEAE will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events. Relationship to IP and non-IPs will be tabulated respectively. If a subject reports the same TEAE more than once within that SOC and PT, the TEAE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

Infusion Related Reaction Assessment

Infusion related reactions of AEs will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events. Listing of Infusion related reactions will be provided, including both AEs and non-AEs.

Outcome

TEAE outcome will be summarised into "Recovered/Resolved", "Recovered/Resolved with sequelae", "Not recovered/Not resolved (Ongoing)", "Fatal", and "Unknown" categories for number of events by treatment group. TEAE with outcome of "Recovering/Resolving" will be considered as "Not recovered/Not resolved (Ongoing)". A similar summary of Serious TEAE outcome will be presented.

TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to discontinuation of study medication will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events. TEAEs leading to discontinuation of IP and non-IPs will be tabulated separately. TEAEs leading to dose reduction will be summarised similarly.

Listing of TEAEs leading to discontinuation of study medication will be provided.

TEAEs Leading to Dose Modification

TEAEs leading to dose Modification will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events. Listing of TEAEs leading to dose modification will be provided.

TEAEs Leading to Death

AEs leading to death will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events. Listing of AEs leading to death will be provided. Drug related AEs leading to death will be summarised similarly.

Serious Adverse Events

SAEs will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events. Listing of SAEs will be provided. IP and non-IPs related SAE will be summarised similarly, respectively.

Adverse Events of Special Interest

The following AEs will be classified as AESIs in this study:

- Hypertension NCI-CTCAE v4.03 grade ≥ 3
- Proteinuria ≥ 2+ proteinuria on urine dipstick (or other ways of urinalysis) and 24 hours urine protein excretion ≥ 1 g or protein/creatinine ratio in spot urine ≥ 1 g/g creatinine (or ≥ 226.0 mg/mmol creatinine)

AESI will be summarised by SOC, PT and CTCAE grade, including the number and percentage of subjects experiencing events. Listing of AESI will be provided.

Deaths

Death and primary cause of death will be summarised by the number and percentage of subjects experiencing events. Listing of death will be provided.

TEAEs by overall ADA result

All TEAE based on categories of overall ADA result up to EOT (Positive, Negative, Inconclusive) will be summarised by SOC, PT, including the number and percentage of subjects experiencing events.

12.2. Laboratory Evaluations

Clinical laboratory assessments will include haematology, biochemistry, coagulation, serology, urine protein and pregnancy test. A list of laboratory assessments to be included in the outputs is referred to APPENDIX 2. Lab value will be converted to standard unit, as reference in the NCI-CTCAE.

Quantitative laboratory measurements reported as '< X', i.e. below the lower limit of quantification (BLQ), or '> X', i.e. above the upper limit of quantification (ULQ), will be

converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as '< X' or '> X' in the listings.

The following summaries will be provided for laboratory data:

- Summary Statistics for Haematology Parameters
- Summary Statistics for Biochemistry Parameters
- Summary Statistics for Coagulation
- Summary Statistics for Urine Protein
- Number and percentage of subjects experiencing abnormal laboratory AEs by CTCAE grade

A by-subject listing of all laboratory data will be provided by treatment group, with indicator of CTCAE grade if applicable. A list of laboratory assessments will be provided by treatment group.

Retest results will be reported in the listings as well as the original results, even if performed at a different laboratory or by a different method. The original lab values will be used in the summaries.

CTCAE Grading of Laboratory Data

Laboratory measurements will be graded using the NCI-CTCAE v4.03 (see APPENDIX 2). In case of overlapped range between local normal range and abnormal criteria in CTCAE grading, local normal range will be considered preferentially.

Laboratory Reference Ranges

Abnormal values will be graded in Grade 1 to 5 according the CTCAE criteria in APPENDIX 2 and normal values will be presented as Grade 0.

12.3. Vital Signs

Vital signs will include blood pressure, pulse rate, and body temperature. Both raw values and changes from baseline will be analysed using descriptive statistics at each scheduled time point.

Vital Signs Clinically Significant Abnormal Criteria

Clinically significant abnormal quantitative vital signs measurements will be identified in accordance with the following predefined clinically significant abnormal criteria:

Table 12-2 Clinically Significant Abnormal Criteria of Vital Signs

Vital Sign	Unit	Category	Criterion[a]
Systolic Blood Pressure	mmHg	Low	≤ 90 mmHg AND change from baseline ≤ - 20 mmHg
		High	≥ 150 mmHg AND change from baseline ≥ 20 mmHg
Diastolic Blood Pressure	mmHg	Low	≤ 50 mmHg AND change from ≤ - 15 mmHg
		High	≥ 100 mmHg AND change from ≥ 15 mmHg
Pulse Rate	beats/min	Low	≤ 50 beats/min AND change from baseline ≤ - 15 beats/min
		High	≥ 120 beats/min AND change from baseline ≥ 15 beats/min
Body Temperature	˚C	Low	≤ 35˚C AND change from baseline ≤- 1.1˚C
		High	≥ 38.3 ˚C AND change from baseline ≥ 1.1 ˚C

[a] For the baseline time point, only the criterion on absolute values is applicable

The number and percentage of subjects experiencing clinically significant abnormal vital signs will be summarised by treatment group at each scheduled time point.

12.4. Other Observations Related to Safety

Physical Examination

Actual Body Weight will be summarised by treatment group at each scheduled time point using descriptive statistics. A by-subject listing will be provided as well.

ECOG Performance Status

Change from the baseline ECOG performance status to each scheduled endpoint ECOG performance status will be summarised by a shift table with categories 0, 1, ≥2. A by-subject listing of ECOG performance status will be provided.

12-Lead Electrocardiogram (ECG)

Change from the baseline 12-Lead Electrocardiogram result to each scheduled endpoint ECG result will be summarised by a shift table. The number of subjects with or without clinically significant ECG abnormalities at baseline and at EOT will be tabulated.

12.5. Immunogenicity

The immunogenicity analyses will be performed using the SAF.

The number and percentage of subjects with ADA results (i.e., Positive, Negative and Inconclusive) will be presented by treatment groups in each cycle (i.e., pre-dose of Cycle 1, 3, 5, 7, and the EOT visit).

The number and percentage of subjects with neutralising antibodies (NAbs) results (i.e., Positive, Negative, Inconclusive) will be presented by treatment groups in each cycle (i.e., pre-dose of Cycle 1, 3, 5, 7, and the EOT visit).

In addition, the number of percent of subject with ADA positive will be summarised by titre and treatment in each cycle.

The incidence of overall ADA results (i.e., Positive, Negative, Inconclusive) will be presented by treatment group at Cycle 7 and EOT. Overall ADA result is defined as below:

- "Positive" for a subject with treatment-induced or treatment-boosted ADA, where treatment-induced ADA indicates at least one positive result after pre-dose of Cycle 1 for subjects with negative ADA at pre-dose of Cycle 1, and treatment-boosted ADA indicates at least one positive result with higher titre level compared to pre-dose of Cycle 1 after pre-dose of Cycle 1 for subjects with positive ADA at pre-dose of Cycle 1.

- "Negative" for a subject without positive ADA until Cycle 7 and EOT.

- "Inconclusive" for a subject with positive ADA at Cycle 1 and without positive result with higher titre level observed after pre-dose of Cycle 1 up to Cycle 7 and EOT.

Overall ADA result up to Cycle 7 will summary for subjects with at least one ADA result up to Cycle 7 and EOT if the subject withdrawal prior to Cycle 7. Overall ADA result up to EOT will summary for subjects with at least one ADA result up to EOT. Subjects with no ADA result after pre-dose of Cycle 1 or missing baseline result will be excluded.

For exploratory purposes, the summary for immunogenicity results will be provided by cycle with the following statistics:

- The association between ADA result and treatment will be assessed using Chi-square test or Fisher's exact test

A by-subject listing of immunogenicity assessment at pre-dose of Cycle 1, 3, 5, 7, and at the EOT visit (at least 21 days after last IP administration and prior to subsequent therapy) will be provided.

13. PHARMACOKINETICS

The pharmacokinetic analysis will be performed for the PK population.

The PK parameters (pre-dose, C_{trough} and post-dose, C_{max}) of pre-dose of Cycle 1, 3, 5, and 7 will be summarised descriptive statistics by treatment group and cycle, such as n (number of subjects with non-missing values or without PDs for PK blood sampling at the cycle), arithmetic mean, standard deviation (SD), coefficient variation (CV%), geometric mean, geometric SD, geometric CV%, median, minimum, and maximum. And, n' (number of subjects contributing to the calculation of geometric statistics) will be also presented. Below the lower limit of quantitation (BLQ) concentrations at pre-dose will be set to zero for the computation of descriptive statistics, except for geometric mean, geometric standard deviation, and geometric CV%, for which they will be excluded. BLQ concentrations at post-dose and quantifiable concentrations at pre-dose of Cycle 1 will be excluded for summary of descriptive statistics. Those samples will be documented in the CSR. "Not reportable" (N/R) or "Quantity Not Sufficient" samples will be treated as missing and excluded for summary of descriptive statistics.

In addition, individual serum concentration (C_{trough} and C_{max}) and PK blood sampling time will be listed.

The arithmetic mean (±SD) serum concentration-time profiles will be plotted by treatment group (overlaid in the same graph) on a linear scale, where BLQ concentrations at post-dose and quantifiable concentration at pre-dose of Cycle 1 is treated in the same way as summary of descriptive statistics mentioned above. "Not reportable" (N/R) or "Quantity Not Sufficient" samples are also treated in the same way as summary of descriptive statistics mentioned above.

Individual serum concentration-time profiles will be presented by treatment group on linear scale, where actual concentration will be presented. All BLQ concentrations will be set to zero for individual concentration-time profile regardless of BLQ at post-dose and quantifiable concentrations at pre-dose of Cycle 1 will be presented as it is. "Not reportable" (N/R) or "Quantity Not Sufficient" samples will be treated as missing and excluded from individual concentration-time profile.

PK parameters by overall ADA result

The PK parameters (pre-dose, C_{trough} and post-dose, C_{max}) of pre-dose of Cycle 1, 3, 5, and 7 based on categories of overall ADA result up to Cycle 7 (Positive, Negative, Inconclusive) will be summarised descriptive statistics by treatment group and cycle.

14. DETERMINATION OF SAMPLE SIZE

Regarding the calculation of the equivalence margin for the ratio of the best ORR by 24 weeks, a meta-analysis published by Botrel et al. using all of the four published comparative trials that evaluated bevacizumab in combination with chemotherapy (i.e. E4599 [Sandler, 2006], AVAiL (BO17704)[Reck, 2009], AVF0757 [Johnson, 2004], JO19907 [Niho , 2012] was considered. The ORR for Avastin® was reported as 34.9% (133 of 381 patients), 34.7% (114 of 329 patients), 32.4% (11 of 34 patients) and 56.2% (68 of 121 patients) compared to the ORR of 15.1% (59 of 392 patients), 21.7% (71 of 327 patients), 18.8% (6 of 32 patients) and 33.9% (20 of 59 patients) for chemotherapy, in E4599, AVAiL, AVF0757 and JO19907 respectively.

The overall ratio of the best ORR and the 70% CI from above four studies are calculated to be CCI using the fixed effect method from meta-analysis. Retaining the CCI % of the effect of Avastin® over the placebo in the lower margin, the equivalence margin of [0.737, 1.357] will be used for the primary analysis with the ratio of the best ORR by 24 weeks.

For the primary analysis with the difference of the best ORR by 24 weeks, the equivalence margin of [-12.5%, 12.5%] will be used due to the similar derivation.

For the calculation of the equivalence margin for the difference of the best ORR by 24 weeks, E4599 [Sandler, 2006] and AVAiL [Reck, 2009] studies were considered. The ORR for Avastin® was reported as 34.9% (133 of 381 patients) and 37.8% (130 of 344 patients), compared to the ORR of 15.1% (59 of 392 patients) and 21.6% (75 of 347 patients) for chemotherapy, in E4599 and AVAiL, respectively.

The overall difference in the best ORR and its 95% CI from these two studies are calculated to be CCI % [CCI %, CCI %] using the fixed-effect method from meta-analysis, or for 80% CI to be [CCI %, CCI %]. The equivalence margin of [-12.5%, 12.5%] will ensure the superiority of SB8 over placebo with a small safety margin retaining CCI % for 95% CI and CCI % for 80% CI of the effect over the placebo in the difference of best ORR.

With 305 completers in each treatment group, the two-sided 90% CI of the best ORR ratio is expected to lie within [0.737, 1.357] with approximately 80% power, and the two-sided 95% CI of the best ORR difference between Avastin® and SB8 is expected to lie within [-12.5%, 12.5%] with 80% power when the expected best ORR is assumed to be 35%. Assuming a 10% drop-out rate, a total of 678 subjects (339 subjects per treatment group) will be randomised.

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9. Sandler AB, Gray R, Michael C. et al. Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer. *N Engl J Med.* 2006; 355: 2542-2550.

APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings. However, in general, when calculating relative days, partial dates with missing day only will be assumed to be 15th of the month, and partial dates with both missing day and month will be assumed to be June 30. Otherwise, the following rules in the given table will be applied for each case.

Algorithm for Treatment-Emergent Adverse Events:

Start/ Increase Severity Date	Stop Date	Action
Known	Known	If start date < first dose of IP date, then not TEAE, If start date ≥ first dose of IP date, then TEAE.
	Partial	If start date < first dose of IP date, then not TEAE, If start date ≥ first dose of IP date, then TEAE. The last day of the month and the last month (i.e. December) will be used if the stop day/month is missing.
	Missing	If start date < first dose of IP date, then not TEAE, If start date ≥ first dose of IP date, then TEAE.
Partial, but known components show that it cannot be on or after first IP taken date	Known	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
	Partial	Not a TEAE. The first day of the month and January will be used if the start day/month is missing. The last day of the month and the last month (i.e. December) will be used if the stop day/month is missing.
	Missing	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.

Start/ Increase Severity Date	Stop Date	Action
Partial, could be on or after first IP taken date	Known	If stop date ≥ first dose of IP date, then TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date. If stop date < first dose of IP date, then not TEAE. The first day of the month and January will be used if the start day/month is missing.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If the imputed stop date < first dose of IP date, then not TEAE, If the imputed stop date ≥ first dose of IP date, then TEAE.
	Missing	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date.
Missing	Known	If stop date < first dose of IP date, then not TEAE, If stop date ≥ first dose of IP date, then TEAE.
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: - If the imputed stop date < first dose of IP date, then not TEAE, - If the imputed stop date ≥ first dose of IP date, then TEAE.
	Missing	Considered as a TEAE.

Algorithm for Prior/Concomitant Medication and Radiotherapy:

Start Date	Stop Date	Action
Known	Known	If stop date < first dose of IP date, considered as prior, If stop date ≥ first dose of IP date and start date ≤ EOT date, considered as concomitant.
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If the imputed stop date < first dose of IP date, considered as prior, If the imputed stop date ≥ first dose of IP date and start date ≤ EOT date, considered as concomitant.
	Missing	Considered as concomitant.
Partial	Known	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < first dose of IP date, considered as prior, If stop date ≥ first dose of IP date and the imputed start date ≤ EOT date, considered as concomitant.
	Partial	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If the imputed stop date < first dose of IP date, considered as prior, If the imputed stop date ≥ first dose of IP date and the imputed start date ≤ EOT date, considered as concomitant.
	Missing	Impute start date as earliest possible date (i.e., first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be considered as prior medication, If the imputed start date ≤ EOT date, considered as concomitant.
Missing	Known	If stop date < first dose of IP date, considered as prior, If stop date ≥ first dose of IP date, considered as concomitant.

Start Date	Stop Date	Action
	Partial	Impute stop date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If the imputed stop date < first dose of IP date, considred as prior, If the imputed stop date ≥ first dose of IP date, considered as concomitant.
	Missing	Considered as concomitant.

Algorithm for Age:

Date of Assessment	Date of Birth (DOB)	Action
Known	Known	1) Month and day information of [Date of assessment] is equal to OR later than month and day information of [DOB], Age derived as Year of (Date of assessment) – Year of (DOB) 2) Month and day information of [Date of assessment] is prior to month and day information of [DOB], Age derived as Year of (Date of assessment) – Year of (DOB) – 1
	Partial	If day and month of DOB is missing, Age derived as Year of (Date of assessment) – Year of (DOB) – 1

APPENDIX 2. CTCAE GRADING FOR LABORATORY PARAMETERS

Laboratory measurements will be graded using the NCI-CTCAE v4.03.

			Grade				
Analytic	**Direction**	**Unit**	**1**	**2**	**3**	**4**	**5 (Death)**
Haemotology							
Haemoglobin	Hypo	g/L	100 =< Value < LLC	80 =< Value < 100	Value < 80		
	Hypo	g/dL	10 =< Value < LLC	8 =< Value < 10	Value < 8		
	Hypo	mmol/L	6.2 =< Value < LLC	4.9 =< Value < 6.2	Value < 4.9		
WBC	Hypo	10^9/L	3 =< Value < LLC	2 =< Value < 3	1 =< Value < 2	Value < 1	
	Hypo	/mm3	3000 =< Value < LLC	2000 =< Value < 3000	1000 =< Value < 2000	Value < 1000	
Neutrophils	Hypo	10^9/L	1.5 =< Value < LLC	1 =< Value < 1.5	0.5 =< Value < 1	Value < 0.5	
	Hypo	/mm3	1500 =< Value < LLC	1000 =< Value < 1500	500 =< Value < 1000	Value < 500	
Lymphocytes	Hypo	10^9/L	0.8 =< Value < LLC	0.5 =< Value < 0.8	0.2 =< Value < 0.5	Value < 0.2	
	Hypo	/mm3	800 =< Value < LLC	500 =< Value < 800	200 =< Value < 500	Value < 200	
	Hyper	10^9/L		4 < Value =< 20	20 < Value		

			Grade				
Analytic	**Direction**	**Unit**	**1**	**2**	**3**	**4**	**5 (Death)**
	Hyper	/mm3		4000 < Value =< 20,000	20,000 < Value		
Monocytes	NA						
Eosinophils	NA						
Basophils	NA						
Platelet count	Hypo	10^9/L	75 =< Value < LLC	50 =< Value < 75	25 =< Value < 50	Value < 25	
	Hypo	/mm3	75,000 =< Value < LLC	50,000 =< Value < 75,000	25,000 =< Value < 50,000	Value < 25,000	
Biochemistry							
Serum creatinine	Hyper	umol/L	ULC < Value =< 1.5 × ULC	1.5 × ULC< Value =< 3 × ULC	3 × ULC< Value =< 6 × ULC	6 × ULC< Value	
	Hyper	umol/L	BL < Value =< 1.5 × BL	1.5 × BL < Value =< 3 × BL	3 × BL < Value		
BUN							
Alanine aminotransferase (ALT)	Hyper	U/L	ULC < Value =< 3 × ULC	3 × ULC< Value =< 5 × ULC	5 × ULC< Value =< 20 × ULC	20 × ULC< Value	
Aspartate aminotransferase (AST)	Hyper	U/L	ULC < Value =< 3 × ULC	3 × ULC< Value =< 5 × ULC	5 × ULC< Value =< 20 × ULC	20 × ULC< Value	
Alkaline phosphatase (ALP)	Hyper	U/L	ULC < Value =< 2.5 × ULC	2.5 × ULC< Value =< 5 × ULC	5 × ULC< Value =< 20 × ULC	20 × ULC< Value	
Total bilirubin	Hyper	umol/L	ULC < Value	1.5 × ULC< Value	3 × ULC< Value =<	10 × ULC< Value	

			Grade				
Analytic	**Direction**	**Unit**	**1**	**2**	**3**	**4**	**5 (Death)**
			=< 1.5 × ULC	=< 3 × ULC	10 × ULC		
Albumin	Hypo	g/L	30 =< Value < LLC	20 =< Value < 30	Value < 20		
	Hypo	g/dL	3 =< Value < LLC	2 =< Value < 3	Value < 2		
Sodium	Hypo	mmol/L	130 =< Value < LLC		120 =< Value < 130	Value < 120	
	Hyper	mmol/L	ULC < Value =< 150	150 < Value =< 155	155 < Value =< 160	160 < Value	
Potassium	Hypo	mmol/L		3 =< Value < LLC	2.5 =< Value < 3	Value < 2.5	
	Hyper	mmol/L	ULC < Value =< 5.5	5.5 < Value =< 6	6 < Value =< 7	7 < Value	
Chloride	NA						
Coagulation							
INR	Hyper	ratio	ULC < Value =< 1.5 × ULC	1.5 × ULC< Value =< 2.5 × ULC	2.5 × ULC< Value		
Serology							
HBV	NA						
HCV	NA						
Urinalysis							
Urine protein	Hyper		1+	2+			
	Hyper	g/24hrs	Value < 1	1 =< Value =< 3.4	3.5= < Value		
Pregnancy test							
Pregnancy test	NA						

APPENDIX 3. PROHIBITED MEDICATIONS AND THERAPIES OF NSCLC

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
Anticoagulants or thrombolytic agent:		
Regular use of aspirin	Preferred Term: ACETYLSALICYLIC ACID PT Code: 00002701 ATC 4 Code/Text: B01AC/ PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	Prior to Randomisation
Aspirin (≥325 mg daily)[a] **After randomisation, low dose aspirin (< 325mg daily) is allowed if medically indicated at the discretion of Investigator.*	Preferred Term: ACETYLSALICYLIC ACID PT Code: 00002701 ATC 4 Code/Text: B01AC/ PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	From Randomisation to EOT
Antiplatelet agents such as Clopidogrel (≥ 75 mg/day), dipyridamole, ticlopidine and/or cilostazol[b]	Preferred Term: CLOPIDOGREL PT Code: 01220701 ATC 4 Code/Text: B01AC/ PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN Preferred Term: DIPYRIDAMOLE PT Code: 00042901 ATC 4 Code/Text: B01AC/ PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN Preferred Term: TICLOPIDINE	Within 10 days prior to Randomisation to EOT

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
	PT Code: 00543201 ATC 4 Code/Text: B01AC/ PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN Preferred Term: CILOSTAZOL PT Code: 00958901 ATC 4 Code/Text: B01AC/ PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN ATC 4 Code/Text: B01AC/ PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN *ATC 3 Code/Text: M01A/ ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS *ATC 3 Code/Text: M01B/ ANTIINFLAMMATORY/ANTIRHEUMATIC AGENTS IN COMBINATION * Event will be extracted from the merged PD listing prior to database lock.	

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
Warfarin, intravenous heparin, low molecular weight heparin, factor Xa inhibitors, thrombin inhibitors, thrombolytic agents including tissue plasminogen activator, anistreplase, streptokinase, urokinase[c] **After randomisation, anticoagulation is allowed if medically indicated*	ATC 4 Code/Text: B01AA/ VITAMIN K ANTAGONISTS ATC 4 Code/Text: B01AB/ HEPARIN GROUP ATC 4 Code/Text: B01AD/ ENZYMES ATC 4 Code/Text: B01AE/ DIRECT THROMBIN INHIBITORS ATC 4 Code/Text: B01AF/ DIRECT FACTOR XA INHIBITORS ATC 4 Code/Text: B01AX/ OTHER ANTITHROMBOTIC AGENTS	Within 28 days prior to Randomisation to EOT
Any drugs (include herbal medications) that has not received regulatory approval for any indications	* Event will be extracted from the merged PD listing prior to database lock.	From Randomisation to EOT
Anticancer systemic therapy other than paclitaxel/carboplatin/Avastin®/SB8[d]	Preferred Term: CISPLATIN PT Code: 00412101 ATC4 Code/Text: L01XA/ PLATINUM COMPOUNDS Preferred Term: DOCETAXEL PT Code: 01256101 ATC4 Code/Text: L01CD/ TAXANES Preferred Term: VINORELBINE PT Code: 00988501 ATC4 Code/Text: L01CA/ VINCA ALKALOIDS AND ANALOGUES	From Randomisation to EOT

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
	Preferred Term: GEMCITABINE PT Code: 01215701 ATC4 Code/Text: L01BC/ PYRIMIDINE ANALOGUES Preferred Term: ETOPOSIDE PT Code: 00511901 ATC4 Code/Text: L01CB/ PODOPHYLLOTOXIN DERIVATIVES Preferred Term: IRINOTECAN PT Code: 01280201 ATC4 Code/Text: L01XX/ OTHER ANTINEOPLASTIC AGENTS Preferred Term: VINBLASTINE SULFATE PT Code: 00115802 ATC4 Code/Text: L01CA/ VINCA ALKALOIDS AND ANALOGUES Preferred Term: MITOMYCIN PT Code: 00315201 ATC4 Code/Text: L01DC/ OTHER CYTOTOXIC ANTIBIOTICS	

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
	Preferred Term: PEMETREXED PT Code: 01493901 ATC4 Code/Text: L01BA/ FOLIC ACID ANALOGUES Preferred Term: RAMUCIRUMAB PT Code: 06331501 ATC4 Code/Text: L01XC/ MONOCLONAL ANTIBODIES Preferred Term: CRIZOTINIB PT Code: 07210501 ATC4 Code/Text: L01XE/ PROTEIN KINASE INHIBITORS Preferred Term: AFATINIB PT Code: 06508201 ATC4 Code/ Text: L01XE/ PROTEIN KINASE INHIBITORS Preferred Term: CERITINIB PT Code: 08340901 ATC4 Code/Text: L01XE/ PROTEIN KINASE INHIBITORS	

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
	Preferred Term: ERLOTINIB PT Code: 01611401 ATC4 Code/Text: L01XE/ PROTEIN KINASE INHIBITORS Preferred Term: GEFITINIB PT Code: 01560101 ATC4 Code/Text: L01XE/ PROTEIN KINASE INHIBITORS Preferred Term: ALECTINIB PT Code: 08021201 ATC4 Code/Text: L01XE/ PROTEIN KINASE INHIBITORS Preferred Term: NIVOLUMAB PT Code: 07872901 ATC4 Code/Text: L01XC/ MONOCLONAL ANTIBODIES Preferred Term: PEMBROLIZUMAB PT Code: 08342801 ATC4 Code/Text: L01XC/ MONOCLONAL	

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
	ANTIBODIES Preferred Term: NECITUMUMAB PT Code: 06332601 ATC4 Code/Text: L01XC/ MONOCLONAL ANTIBODIES Preferred Term: CETUXIMAB PT Code: 01490501 ATC4 Code/Text: L01XC/ MONOCLONAL ANTIBODIES Preferred Term: IFOSFAMIDE PT Code: 00310701 ATC4 Code/Text: L01AA/ NITROGEN MUSTARD ANALOGUES Preferred Term: PACLITAXEL PT Code: 01116001 ATC4 Code/Text: L01CD/ TAXANES Preferred Term: PACLITAXEL ALBUMIN PT Code: 01116004 ATC4 Code/Text: L01CD/ TAXANES	

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
Major surgical procedure (include open lung biopsy)[e] *If a major surgical procedure is indicated after randomisation, treatment needs to be held for at least 28 days after surgery and subject needs to completely recover from surgery. The maximum allowed delay is 6 weeks from the last IP infusion.	* Codes will be identified before database lock, based on the medical review of all procedure coding result.	Within 28 days prior to Randomisation
Minor surgical procedure[f] *If a minor surgical procedure is indicated after randomisation, treatment needs to be held for at least 7 days after surgery and subject needs to completely recover from surgery. The maximum allowed delay is 6 weeks from the last IP infusion.	* Codes will be identified before database lock, based on the medical review of all procedure coding result.	Within 7 days prior to Randomisation
Live/attenuated vaccine	ATC4 Code/Text: J07BJ/ RUBELLA VACCINES Preferred Term: SMALLPOX VACCINE PT Code: 00049301 ATC4 Code/Text: J07BX/ OTHER VIRAL VACCINES Preferred Term: DENGUE FEVER VACCINE PT Code: 09008301 ATC4 Code/Text: J07BX/ OTHER VIRAL VACCINES Preferred Term: VARICELLA ZOSTER VACCINE	Within 12 weeks prior to Randomisation to Cycle 7 Day 1

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
	PT Code: 06643101 ATC4 Code/Text: J07BK/ VARICELLA ZOSTER VACCINES Preferred Term: BCG VACCINE PT Code: 00002001 ATC4 Code/Text: J07AN/ TUBERCULOSIS VACCINES Preferred Term: POLIO VACCINE PT Code: 06439201 ATC4 Code/Text: J07BF/ POLIOMYELITIS VACCINES Preferred Term: MEASLES MUMPS & RUBELLA LIVE ATTENUATED PT Code: 06439501 ATC4 Code/Text: J07BD/ MEASLES VACCINES Preferred Term: ROTAVIRUS VACCINE PT Code: 01456401001 ATC4 Code/Text: J07BH/ ROTA VIRUS DIARRHEA VACCINES Preferred Term: YELLOW FEVER VACCINE PT Code: 00102101	

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
	ATC4 Code/Text: J07BF/ POLIOMYELITIS VACCINES Preferred Term: INFLUENZA VACCINE PT Code: 01389801 ATC4 Code/Text: J07BB/ INFLUENZA VACCINES Preferred Term: RABIES VACCINE PT Code: 00141201 ATC4 Code/Text: J07BG/ RABIES VACCINES Preferred Term: TYPHOID VACCINE Preferred Code: 00167001 ATC4 Code/Text: J07AP/ TYPHOID VACCINES	
Intravenous bisphosphonates and/or invasive dental procedure *Allowed after randomisation if determined by investigator as clinically necessary (ex. Bone metastases related to NSCLC or tooth abscess requiring extraction, etc.)	Preferred Term: BISPHOSPHONATES PT Code: 90049001 ATC 4 Code/Text: M05BA/ BISPHOSPHONATES Preferred Term - DENTAL OPERATION PT Code – 10061812 HLT: DENTAL AND GINGIVAL THERAPEUTIC PROCEDURES HLT Code: 0012317 HLGT: HEAD AND NECK THERAPEUTIC	Within 28 days prior to Randomisation

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
	PROCEDURES HLGT Code:10019190 SOC SURGICAL AND MEDICAL PROCEDURES SOC Code:10042613	
Radiotherapy[g]	Preferred Term: NON-SMALL CELL LUNG CANCER PT Code:10061873 HLT: NON-SMALL CELL NEOPLASMS MALIGNANT OF THE RESPIRATORY TRACT CELL TYPE SPECIFIED HLT Code: 10029664 HLGT: RESPIRATORY AND MEDIASTINAL NEOPLASMS MALIGNANT AND UNSPECIFIED HLGT Code: 10038666 SOC: NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) SOC Code:10029104 Preferred Term: RADIOTHERAPY PT Code: 10037794 HLT: RADIOTHERAPIES SITE UNSPECIFIED HLT Code: 10037796 HLGT: THERAPEUTIC PROCEDURES AND SUPPORTIVE CARE NEC	Within 14 days prior to Randomisation to EOT

Medication or Therapies	MedDRA Codes or ATC Codes	Time to be prohibited
	HLGT Code: 10043413 SOC: SURGICAL AND MEDICAL PROCEDURES SOC Code: 10042613	

EOT = end of treatment; NSAIDs = non-steroidal anti-inflammatory drugs
Local anaesthesia is defined as anaesthesia of a small part of the body such as a tooth or an area of skin.
[a] After randomisation, low dose aspirin < 325mg daily is allowed if medically indicated (cardiac prophylaxis, etc.) and there is no bleeding diathesis that would increase the risk of therapy at the discretion of Investigator.
[b] Non-chronic use of NSAIDS (not including aspirin) for symptom management is permitted if there is no bleeding diathesis that would increase the risk of therapy at the discretion of Investigator.
[c] After randomisation, therapeutic anticoagulation (heparin, warfarin, etc.) is allowed if medically indicated in case of new thromboembolic events (i.e., deep venous thrombosis) at the discretion of Investigator. Refer to Section 6.4.2 Table 4 for specific guidelines. Non-systemic use of anticoagulants (ex. heparin flush) to maintain patency of intravenous injection devices is allowed.
[d] Nab-paclitaxel or other formulation of paclitaxel is not allowed in this study.
[e] Requiring more extensive procedure than local anaesthesia (involving general anaesthesia or respiratory assistance or regional anaesthesia) or open lung biopsy.
[f] Requiring local anaesthesia or following procedures; mediastinoscopy, percutaneous needle aspiration, core biopsy, placement of vascular access device, endobronchoscopy ultra sono & transbronchial needle aspiration (EBUS & TBNA), pleural biopsy, thoracentesis, pleurodesis, catheter insertion/removal, tooth extraction, superficial incision.
[g] Radiotherapy of palliative purpose to non-progressive non-target lesions is allowed during the treatment period. If target lesions are included in irradiated field, then those lesions should not be evaluated as measurable thereafter. It is strongly recommended that the Investigator consult to the Sponsor at the timing of planning radiotherapy. IP and non-IPs should be suspended during radiotherapy and may be resumed at the discretion of the Investigator.

APPENDIX 4. VISIT NAME

Time Point	Visit Long Name
Screening	Screening
Induction Treatment Period	Cycle 1
	Cycle 2 *
	Cycle 3 *
	Cycle 4 *
	Cycle 5 *
	Cycle 6 *
Maintenance Treatment Period	Cycle 7
	Cycle 8
	Cycle 9
	Cycle 10
	Cycle 11
	…
	Unscheduled
	End of Treatment
	End of Study
	Follow-up

*In case of toxicities, non-IPs may be discontinued before Cycle 6. The cycles afterwards may continue IP as monotherapy at the discretion of Investigator. Cycles with monotherapy of IP will be mapped to the maintenance treatment period.

APPENDIX 5. STATISTICAL MODEL AND SAS SYNTAX

Analysis of ratio for response rates of two treatments

Risk ratio analysis will be performed using the log binomial model (implemented via SAS procedure GENMOD) with treatment as an explanatory variable and best ORR as a response. The response (i.e., best ORR) is assumed to be Binomial distributed with the log link function. The risk ratio will be presented with 90% Wald confidence limits.

The SAS syntax is specified as follows:

```
PROC GENMOD DATA = <input_dataset>;
  CLASS <treat_var>(REF=<Avastin>)/PARAM=ref;
  MODEL <response> = <treat  var>      /DIST = bin
                                        LINK = log
                                        TYPE3
                                        ;
  ESTIMATE 'SB8 vs. Avastin' <treat_var> 1 / EXP ALPHA = 0.1;
RUN; QUIT;
```

where treat_var = treatment group
response = 1 for response, 2 for non-response

The sensitivity analysis of the risk ratio will be performed using the log binomial model with age group (< 70, ≥ 70 years), sex (Male, Female), region (EU, non-EU), and treatment as explanatory variables and best ORR as a response. The response (i.e., best ORR) is assumed to be Binomial distributed with the log link function. The risk ratio will be presented with 90% Wald confidence limits.

The SAS syntax is specified as follows:

```
PROC GENMOD DATA = <input_dataset>;
  CLASS <treat_var>(REF=<Avastin>) <agegrp_var> <sex_var> <reg_var> /PARAM=ref;
  MODEL <response> = <treat_var> <agegrp_var> <sex_var> <reg_var>
                                                  /DIST = bin
                                                   LINK = log
                                                   TYPE3
                                                   ;
  ESTIMATE 'SB8 vs. Avastin' <treat_var> 1 / EXP ALPHA = 0.1;
RUN;QUIT;
```

where treat_var = treatment group
response = 1 for response, 2 for non-response
agegrp_var = age group (< 70, ≥ 70 years)
sex_var = sex (Male, Female)
reg_var = region (EU, non-EU)

Analysis of the difference for response rates of two treatments

Analysis of the difference will be performed using the binomial model (implemented via SAS procedure GENMOD) with treatment as an explanatory variable and best ORR as a response. The response (i.e., best ORR) is assumed to be Binomial distributed. The difference will be presented with 95% Wald confidence limits.

The SAS syntax is specified as follows:

```
PROC GENMOD DATA = <input_dataset>;
  CLASS <treat_var>(REF=<Avastin>)/PARAM=ref;
  MODEL <response> = <treat_var> /DIST = bin
                                 LINK = ID
                                 TYPE3
                                 ;
  ESTIMATE 'SB8 vs. Avastin' <treat_var> 1 -1/ ALPHA = 0.05;
RUN; QUIT;
```

where treat_var = treatment group
response = 1 for response, 2 for non-response

The sensitivity analysis of the difference of response rates will be performed using the binomial model with age group (< 70, ≥ 70 years), sex (Male, Female), region (EU, non-EU), and treatment as explanatory variables and best ORR as a response. The response (i.e., best ORR) is assumed to be Binomial distributed. The difference of response rates will be presented with 95% Wald confidence limits.

The SAS syntax is specified as follows:

```
PROC GENMOD DATA = <input  dataset> ;
  CLASS <treat_var>(REF=<Avastin>) <agegrp_var> <sex_var> <reg_var>
        /PARAM=ref;
  MODEL <response> = <treat_var> <agegrp_var> <sex_var> <reg_var>
                                 /DIST = bin
                                 LINK = ID
                                 TYPE3
                                 ;
  ESTIMATE 'SB8 vs. Avastin' <treat_var> 1 -1/ ALPHA = 0.05;
RUN;QUIT;
```

where treat_var = treatment group
response = 1 for response, 2 for non-response
agegrp_var = age group (< 70, ≥ 70 years)
sex_var = sex (Male, Female)
reg_var = region (EU, non-EU)

Confidence interval for response rate

Response rate is defined as the percentage of subjects who have a specific event (e.g., Best ORR). The 100(1 − α)% confidence interval of a response rate will be estimated by using

exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934].

The SAS syntax is specified as follows:

```
PROC FREQ DATA = <input_dataset>;
  BY <treat_var>;
  TABLES <response>/BINOMIAL(EXACT);
RUN;
```

where treat_var = treatment group
response = response (e.g., best ORR)

Analysis the association between ADA result and treatment response rate

The association between ADA result and treatment will be assessed using Chi-square test or Fisher's exact test as implemented in PROC FREQ with option CHISQ.

The SAS syntax is specified as follows:

```
PROC FREQ DATA = <input  dataset>;
  TABLES <treat_var>*<ada_var>/CHISQ;
RUN;
```

where treat_var = treatment group
ada_var = ADA results

Analysis of time to events data

- ***Kaplan-Meier Method***

An estimate of the survival function in each treatment group will be constructed using Kaplan-Meier (product-limit) method as implemented in PROC LIFETEST with METHOD=KM option. The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG.

25th, 50th, and 75th percentile survivals for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarised. The STRATA statement in LIFETEST procedure will be used to analyse time to event data with ties.

The SAS syntax is specified as follows:

```
ODS GRAPHICS ON;
PROC LIFETEST DATA = <input_dataset> METHOD=KM CONFTYPE=LOGLOG
                                     PLOTS =SURVIVAL (ATRISK=0 to
                                     12 by 2);
  TIME    <sur_time_var>*<censor_var>(<list>);
  STRATA <treat_var>;
RUN;
ODS GRAPHICS OFF;
```

where treat_var = treatment group
sur_time_var = survival time

censor_var = censoring variable
list = a list of values of censor_var which were indicated as a censor

- ***Cox proportional hazards model***

The Cox proportional hazards model using SAS procedure PHREG (with TIES=EXACT option in the MODEL statement). A Cox proportional hazard model will be, i.e. the MODEL statement will include the treatment group variable, age group(< 70, ≥ 70 years), sex group (Male, Female), and region group (EU, non-EU) as covariates. Survival probability with 95% confidence interval at specific time points will be performed by using BASELINE statement. Hazard ratio with two-sided 95% confidence interval will be based on Wald test.

The SAS syntax is specified as follows:

```
ODS GRAPHICS ON;
PROC PHREG DATA = <input_dataset>   PLOTS = SURVIVAL;
  CLASS <treat_var (ref='x')> <agegrp_var (ref='x')> <sex_var(ref='x')>
                                                    <reg_var(ref='x')>;
  MODEL <sur_time_var>*<censor_var>(<list>)= <treat_var> <agegrp_var> <sex_var>
                        <reg_var>/ TIES=EXACT;

  BASELINE   <OUT=output_dataset> <SURVIVAL=_ALL_> ;
  HAZRDRATIO   <treat_var> / CL=wald;
RUN;
ODS GRAPHICS OFF;
```

where treat_var = treatment group
sur_time_var = survival time
censor_var = censoring variable
list = a list of values of censor_var which were indicated as a censor
agegrp_var = age group(< 70, ≥ 70 years)
sex_var = sex (Male, Female)
reg_var = region (EU, non-EU)

APPENDIX 6. TOC OF RESULTS FOR CSR

14.1 Demographic Data

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		during induction treatment period by 24 weeks (RECIST 1.1) - Central Review (Full Analysis Set)
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Table	14.2-2.7.1	Analysis of Overall Survival (Full Analysis Set)
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Table	14.2-2.8.1	Sensitivity Analysis of Overall Survival (Full Analysis Set)
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Table	14.2-2.9.1	Analysis of Duration of Response - Central Review (Full Analysis Set)
Table	14.2-2.9.2	Analysis of Duration of Response - Central Review (Per-Protocol Set)
Table	14.2-3.1.1	Subgroup Analysis of Ratio in Best Overall Response Rate during induction treatment period by 24 weeks (RECIST 1.1) - Central Review (Full Analysis Set)
Table	14.2-3.1.2	Subgroup Analysis of Ratio in Best Overall Response Rate during induction treatment period by 24 weeks (RECIST 1.1) - Central Review (Per-Protocol Set)
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