Statistical Analysis Plan

1302.5 INVICTAN®-2

A multicenter, randomized, double-blind Phase III trial to evaluate efficacy and safety of BI 695502 plus chemotherapy versus Avastin® plus chemotherapy in subjects with advanced nonsquamous Non-Small Cell Lung Cancer

Author:

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Statistical Analysis Plan Signature Page

Statistical Analysis Plan V5.0 (Dated 13NOV2018) for Protocol 1302.5 INVICTAN®-2.

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Output Templates Signature Page

Please refer to Output Templates V4.0 (Dated 08JUN2018) for Protocol 1302.5 INVICTAN®-2.

Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	22DEC2016		Not Applicable – First Version
2.0	24MAY2017		Updated based on Sponsor comments received on dry run 1 and DSMB members comments received on DSMB 3.
3.0	08AUG2017		Updated based on Sponsor comments received on dry run 1 follow-up and dry run 2, implementation of additional requests.
4.0	08JUN2018		Update based on Protocol amendment v8.0 - switch of all subjects on trial medication to Avastin®. Update to Appendix 8 based on review by medical advisor. Inclusion of Changes to Planned Analyses and Note to File (Primary Analyses). Removal of outputs for Japanese subgroup for Final Analyses.

V5.0	13NOV2018		Sub-group Analyses (+10 additonal sub-groups) and additional tables for consistency with Primary CTR Update for listings in the post-switch period.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BLQ	Below the lower limit of quantification
BIcMQ	Boehringer Ingelheim-customized MedDRA query
BP	Blood Pressure
BSA	Body Surface Area
CI	Confidence Interval
CR	Complete Response
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of Variation
DBL	Data Base Lock
DOR	Duration of Response
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EOT	End of Treatment
FAS	Full Analysis Set

GFR	Glomerular filtration rate
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
IPV	Important Protocol Violation
IXRS	Interactive Voice Telephone and Web Response System
LLN	Lower Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
N	Population size (N for sample size, n for available data)
NCI-CTC	National Cancer Institute Common Terminology Criteria
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
(ns)NSCLC	(Nonsquamous) non-small cell lung cancer
NE	Not Evaluable
NA	Not analyzed
NTP	Non-Treatment Period
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PPS	Per Protocol Set
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors

REP	Residual Effect Period
RND	Randomized Set
RR	Risk Ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Screened Set
SD	Stable Disease
SFU	Safety Follow-up
SI	System International
SMQ	Standardized MedDRA Query
SOC	System Organ Class
Std Dev	Standard Deviation
SWS	Switched Set
TB	Tuberculosis
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TOST	Two One-sided Tests
TS	Treated Set
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
US	United States of America
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, data for Protocol 1302.5 **INVICTAN®-2**.
It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
The document pertains to the primary analysis and the final analysis at the end of the study.
This trial statistical analysis plan (TSAP) is based on protocol amendment 7 version 8.0, dated 17 January 2018, following the recommendation of the sponsor on 21 Dec 2017 that all subjects should be switched from BI 695502/US-licensed Avastin® to the reference product bevacizumab (commercially available Avastin®) as soon as it was available at the respective clinical site. The analysis of the primary efficacy endpoint is not impacted by the switch in the trial medication as all subjects had already completed the Week 18 assessments at the time of the transition. The secondary efficacy endpoints will be censored at the point of switch for all switched subjects. Limited safety data (adverse events, will be analyzed for the post-switch period.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this trial is to establish statistical equivalence in terms of efficacy (best overall response rate [ORR], proportion of subjects with complete response [CR] plus partial response [PR]) until 18 weeks of first-line treatment with BI 695502 plus chemotherapy versus US-licensed Avastin® plus chemotherapy followed by maintenance monotherapy with either BI 695502 or US-licensed Avastin®.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the trial are to evaluate further efficacy parameters (progression-free survival [PFS], overall survival [OS] and duration of response [DOR]) and the safety and tolerability of BI 695502 versus US-licensed Avastin®.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase III, randomized, double-blind, multicenter, active comparator, parallel two-arm trial. Approximately 660 subjects (330 subjects per arm) with advanced nonsquamous non-small cell lung cancer (nsNSCLC) will be randomized in a 1:1 ratio to receive either BI 695502 (Arm B) or US-licensed Avastin® (Arm A) in combination with Paclitaxel and Carboplatin.
The randomization will be stratified by the following variables:

- Sex (male versus female)
- Smoking status (never smoked versus current/past smoker)
- NSCLC stage (recurrent versus Stage IV).
- Ethnicity stratification factor (East Asian origin versus non-East Asian)

Subjects will receive treatment with 15 mg/kg of BI 695502 or US-licensed Avastin® followed by standard combination chemotherapy consisting of Paclitaxel 200 mg/m^2 followed by Carboplatin target area under the curve (AUC) 6 mg/mL·min (30- to 60-minute infusion) with adequate pre- and concomitant medication every 3 weeks (each cycle) for up to 6 cycles (induction cycles).
After Cycle 4 to 6, if the subject has CR, PR or stable disease (SD), i.e., responding or stabilized subjects, maintenance treatment with BI 695502/ US-licensed Avastin® monotherapy can be started per the original randomization. Subjects will then receive BI 695502 or US-licensed Avastin® as a single agent until disease progression (according to Response Evaluation Criteria in Solid Tumors 1.1 [RECIST 1.1] [2]), death, withdrawal of consent, or unacceptable toxicity, whichever occurs earlier.

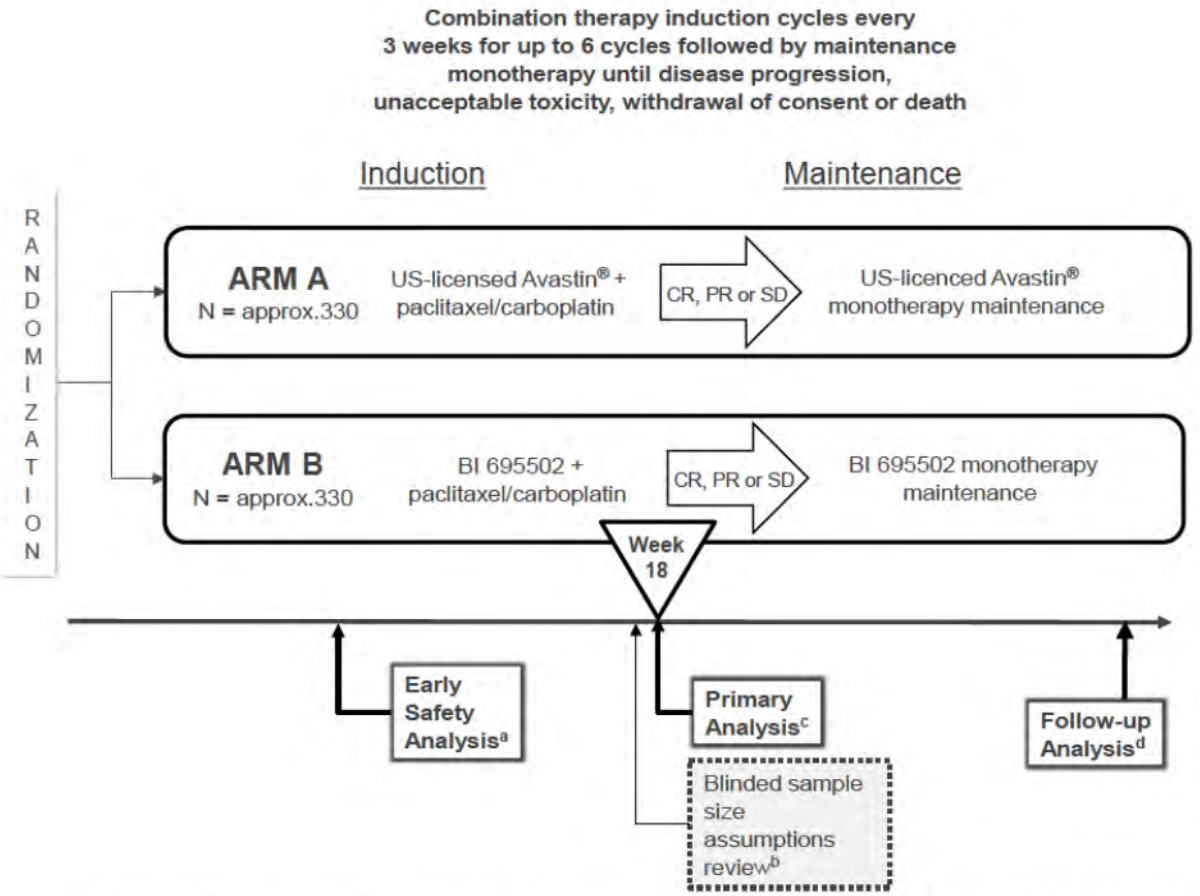
Starting as of 21 December 2017, the sponsor recommended that all subjects should be switched from BI 695502/ US-licensed Avastin® to the reference product bevacizumab (commercially available [open label Avastin®[1]]), as soon as it was available at the respective clinical site. If Avastin® was not immediately available, the investigators were temporarily

[1] Both hereafter referred to as Avastin®

allowed the continuation of trial medication. The Switch Visit is defined in Section 6.5. To maintain blinding, all subjects still under treatment at the time of the switch partook of the Switch Visit regardless of randomization group.

Further details of the trial design can be found in the protocol Section 3.1. An overview of the trial design is shown in Figure A.

Figure A: Overview of trial design



a An early safety analysis will be reviewed after approximately 20 subjects per arm have been treated for 3 cycles (40 subjects).

b. Blinded sample size assumptions review to start when approximately 200 subjects (100 subjects per arm) have had tumor response assessments performed until Week 18.

c. The primary analysis will be performed after all subjects in the primary analysis population have had tumor response assessments performed until Week 18.

d. A follow-up (final) analysis will be conducted at a later time point.
NB: As from 21st December 2017 – all subjects were to be switched to Avastin®.

3.2. SCHEDULE OF EVENTS

The flow chart of events can be found in the 'Flow Chart" section of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

The protocol, Section 7.3.1.1 defines that overall response rate will be evaluated from the date of randomization. The starting point of all analyses for overall response rate will be the date of first administration of trial medication. This change is in line with the RECIST 1.1 guideline, Section 4.4. Also, the purpose of this trial is to compare BI 695502 treatment to treatment with Avastin®. It is not expected that the change in starting point will lead to differences in analysis since there are no planned tumor assessments between randomization and start of therapy.

And the following additional decisions were taken:

- Section 15.1.4.3: According to the protocol, Section 7.4.1, for the primary endpoint, in order to preserve any observed difference between treatment groups, best ORR will be assumed to be missing at random. Robustness of the primary conclusion to the missing at random assumption will be evaluated by sensitivity analyses that will take account of the reason for discontinuation.
- For clarification, missing or non-evaluable response assessments will not be imputed in the primary analysis. Subjects with no documented CR or PR according to RECIST 1.1 are always classified as non-responders. However, the reason for discontinuation will be evaluated and a sensitivity analysis based on multiple imputation will be performed.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Analyses for Data Safety Monitoring Board (DSMB) meetings
- Blinded evaluation of sample size assumption

- Primary Analysis (documented in Primary Analysis Clinical Trial Report [CTR])
- Final Analysis (documented in the Final CTR)

This document will provide details for Primary Analysis and Final Analysis.
The analyses for DSMB meetings are described in a separate SAP. Specifications for the blinded evaluation of the sample size assumptions are provided in a separate document.

The Primary and Final analyses described in this SAP will be performed by Biostatistics following Sponsor Authorization of this SAP, Sponsor Authorization of Analysis Sets and after Data Snapshot/Database Lock has taken place.

4.1. PRIMARY ANALYSIS

The Primary Analysis CTR will include the analyses of the primary efficacy as well as all available secondary and other efficacy endpoints and safety, data. The analysis of efficacy will be based on the full analysis set (FAS) and in addition, the per protocol set (PPS) will be used for the primary efficacy analysis. The analysis of safety will be based on the treated set (TS),

The primary analysis will take place when all primary efficacy endpoint data are available, i.e., after for all subjects all Week 18 tumor response assessments have undergone central imaging review, or earlier if no more subjects are expected to complete the Week 18 visit due to progression, treatment stop for unacceptable toxicity or death.

To facilitate this, a cut-off date will be defined as the last tumor assessment date among all subjects within 18 weeks +14 days after the start of treatment or earlier if no more subjects are expected to complete the Week 18 visit due to progression, treatment stop for unacceptable toxicity or death (APPENDIX 5).
After the data cut-off date all data until cut-off date will be cleaned and evaluated.

The data will be unblinded at the time point of the primary analysis for the team members involved in the analysis (including the sponsor and its designees). The study will continue in a blinded manner and anyone involved in the primary analysis at Week 18 will no longer be involved in further study conduct. Other team members will remain blinded. The logistical details ensuring the integrity of study conduct in order to protect the validity of the final analysis will be described in a separate logistic plan prior to primary analysis unblinding.

The results will be summarized in a Primary Analysis CTR (primary analysis of efficacy safety,

4.2. FINAL ANALYSIS

A further analysis will be conducted at the end of the study. In this final analysis, all analyses performed at the primary analysis time point will be repeated with the updated data set, in particular with respect to safety and the endpoints collected. The results of this analysis will be summarized in a separate Final CTR.

The final analysis will include reporting of the switch from the trial medication (BI 695502 or US-licensed Avastin®) to Avastin®. For efficacy endpoints, data for switched subjects will be considered censored at the Switch Visit. There will be no analysis of efficacy or laboratory data for the post-switch period. Limited safety, data will be analyzed for the post-switch period (See Section 16).
Post-switch data will only be tabulated where specified in the relevant sections below. All availabe post-switch data will be listed.
For definition of the Switch Visit, see Section 6.5. For definitions of the pre-switch and post-switch time periods, see Section 6.7.

5. ANALYSIS SETS

Agreement and authorization of subjects included / excluded from each analysis set will be conducted prior to the unblinding of the study. A blinded data review meeting will be set up to decide on the final allocation rules to assign single subjects to the analysis sets.

Prior to the final analyses, the analysis set allocation made at the time of primary analyses, will be reviewed to take account of any additional information pertaining to randomization or up

until 18 weeks tumor assessment, that has been received post interim database lock. The data will be re-reviewed following the same procedures and guidelines in place at the time of the primary analyses. Any changes to analysis set allocation post-interim database lock will be documented in the Final CTR.

For the primary analysis selected data will be presented for both the Full Analysis Set (FAS) and Treated Set (TS). For the final analysis, due to one to one subject matching between the TS and FAS the following rules will apply: Demographic and Baseline characteristics (FAS), Surgical and Medical History (TS), Medications (TS), Exposure (TS), Efficacy (FAS), Safety (TS).

5.1. SCREENED SET [SCR]

The screened (SCR) set will contain all subjects who provided informed consent for this study.

5.2. RANDOMIZED SET [RND]

The randomized (RND) set will contain all subjects in the SCR who were randomized.

5.3. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will consist of all randomized subjects who received at least one dose of trial medication and had a baseline tumor assessment. Subjects will be assigned to the treatment to which they were randomized. The primary analysis will be based on the FAS.

5.4. PER PROTOCOL SET [PPS]

The per protocol set (PPS) will contain all subjects in the FAS who did not experience any important clinical trial protocol (CTP) violation affecting efficacy analysis. The decisions regarding important protocol violations (IPVs), and the definition of the analysis population, will be finalized prior to database lock or snapshot and prior to unblinding. Only IPVs considered to potentially have a major distorting influence on the primary endpoint will result in subjects being excluded from the PPS. For the definition of these important protocol violations, see APPENDIX 7.

Subjects will be assigned to the treatment to which they were randomized.

5.5. TREATED SET [TS]

The treated set (TS) will contain all subjects who signed informed consent and who received at least one dose of trial medication.

Subjects will be assigned according to actual treatment received. If there is any doubt whether a subject was treated or not, they will be assumed treated for the purposes of analysis. In case of any inadvertent change between randomized treatment groups in the pre-switch period (i.e. by error and not associated with the Switch Visit)

5.7. SWITCHED SET [SWS]

The 'Switched Set' will contain all subjects who provided informed consent to switch to commercial Avastin® and who received at least one dose of Avastin® post-switch.

The SWS is applicable for the post-switch period (Section 6.7). For the pre-switch period, the SWS retain their allocation to sets 5.1-5.5.

Subjects who had completed treatment, or were no longer in the study at the time of the switch will not perform a Switch Visit. To distinguish from the Switched Set, this group are referred to as 'non-switched' subjects. Data for 'non-switched' subjects will be analyzed to the extent available and corresponds to the pre-switch period only (Section 6.7).

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.
For the pre-switch period, the reference start date (Study Day1) is defined as the day of the first dose of trial medication. For subjects randomized but not treated, it is the day of randomization. This will be applied for all endpoints except for PFS and OS where the randomization date will be used as reference start date and DOR where the first documented CR or PR date will be used as reference start date.

Reference start date or study day will appear in every listing where an assessment date or event date appears.

- If the start date of the event is on or after the reference start date then:

Study Day = (start date of event – reference start date) + 1.

- If the start date of the event is prior to the reference start date then:

Study Day = (start date of event – reference start date).

In the situation where the event date is partial or missing, Study Day and any corresponding durations will appear missing in the listings. For tables, the imputation rules from APPENDIX 2 will be used.

The reference start day for the post-switch period is defined in Section 6.5.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). If the last non-missing measurement (data and time, whenever time is recorded) and the reference start date/time coincide, then that measurement will be considered as baseline. Adverse events (AEs) and medications commencing on the reference start date will be considered as happening on treatment.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit table summaries and by-visit graphs but will be present in the listings, individual data graphs and Hepatic Injury / Hy's Law by visit tables. Unscheduled tumor assessments will be used for all efficacy endpoint analyses and for by-visit table summaries of target, non-target and new lesions.
In the case of a retest (recorded as unscheduled visits), the latest available measurement within 3 days after the planned assessment will be used for by-visit summaries.
Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

This section describes the windows used for the statistical analysis of tumor assessments in this trial.
For the assessment of the primary efficacy endpoint best ORR at Week 18, a time window of ±14 days will be applied, meaning that every imaging up to Week 18 + 14 days will be included.

For the analysis of PFS, DOR and ORR by timepoint, the following windows will be considered:

Tumor assessment 1 (Cycle 3)	from day 1* to day 63
Tumor assessment 2 (Cycle 5)	from day 64 to day 105
Tumor assessment 3 (Cycle 7)	from day 106 to day 147
Tumor assessment 4 (Cycle 10)	from day 148 to day 207
...	...

From Cycle 10 onwards, the tumor assessments should be performed every 3 cycles (meaning every 63 days).
*Randomization date (as defined in Section 9) for analysis of PFS, DOR; and Treatment start date for analysis of ORR by timepoint. These windowing conventions will apply for reporting in the pre-switch period (Section 6.7). PFS, DOR, or ORR will not be presented for the post-switch period.

6.5. SWITCH VISIT

The Switch Visit is defined as the visit on which commercial Avastin® was administered for the first time. The assessments to be performed at the Switch Visit (prior to Avastin® administration) are specified in the Protocol (Flow Chart 1.2).

6.6. SAFETY FOLLOW UP VISIT

All subjects are required to return for a Safety Follow Up (SFU) Visit 18 weeks after their last administration of trial medication. For the SWS, the 18 week period will commence from the last administration of trial medication in the pre-switch period.

If a switched subject continues to receive treatment with Avastin® beyond 18 weeks after the last dose of trial medication in the pre-switch period, then no SFU will be performed. In all cases, an End of Treatment (EOT) Visit will be performed 21 days after the last dose of Avastin®. The Protocol (Section 5.3.2) advises that ADA/nADA samples are taken at the SFU Visit, or at 18 weeks after the last administration of trial medication in the pre-switch period.

A diagrammatic overview of the EOT and SFU Visits in the post-switch period are shown in APPENDIX 10.

After the SFU Visit or discontinuation of Avastin® (whichever occurs later) subjects will be monitored for survival every 3 months until death or end of trial, whichever is earlier.

The last survival information is retrieved from the eCRF page "Survival Information" for the last visit performed in the Survival period.

6.7. DEFINITION OF PRE-SWITCH AND POST-SWITCH TIME PERIODS

The pre-switch period is defined as the period up until the Switch Visit. For non-switched subjects this period corresponds to the whole trial, up until the end of the study.

The post-switch period is defined as the period at and after the Switch Visit until the end of the study. The post-switch time period is applicable to the Switched Set only (Section 5.7)

For the post-switch period tables and listings, subjects will be defined as either 'BI 695502 to Avastin' or 'Avastin to Avastin' in accordance with their initial treatment group.

6.8. STATISTICAL TESTS

The statistical tests and significance levels used for efficacy endpoints are described in detail in Section 15.1.3.

6.9. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value.

For quantitative measurements, percentage of change from baseline will be calculated as:

$$\left(\frac{\textbf{Test Value at Visit x} - \textbf{ Baseline Value}}{\textbf{Baseline Value}}\right)\textbf{X 100}$$

6.10. SOFTWARE VERSION

All analyses will be conducted using SAS® version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors will be used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Treatment groups:
  - Treatment (BI 695502 versus US-licensed Avastin®)
- Stratification factors (eCRF):
  - Sex (male, female) as recorded on eCRF page "Demographics"
  - Smoking status (never smoked, current/past smoker) as recorded on eCRF page "Smoking Habits"
  - NSCLC stage (recurrent, Stage IV) as recorded on eCRF page "Diagnosis and extent of cancer – NSCLC" – "Stage of cancer at screening"
  - Ethnicity (East Asian origin versus non-East Asian). The derivation is based on race as recorded on eCRF page "Demographics"
    - ➔ East Asian origin, if "East Asian" is ticked
    - ➔ Non-East Asian origin, if "American Indian or Alaska Native", "Non-East Asian", "Black or African American", "Native Hawaiian or Other Pacific Islander", "White" or "Other" are ticked.

  The above stratification factors were also recorded by the IXRS for use in the randomization process.
- Other covariates:
  - Number of cycles (see Section 15.1.4.4)
  - Region (definition of regions are described in Section 7.5)

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally (approximately 250 clinical sites). Few subjects are expected to be recruited per site.

7.3. MISSING DATA

Missing safety data will not be imputed, unless otherwise specified in Section 16.

Missing efficacy data will be handled as described in Sections 15.1.2 and 15.2.2 of this analysis plan for the primary analysis.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No multiplicity-adjustment will be performed.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.
The shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.
The number of subjects included in each analysis set will be summarized by treatment group.
The subject disposition and withdrawals will be presented for the SCR. Relevant dispositions and withdrawals in the post-switch period will also be presented (as denoted by #):

The subject disposition and withdrawals will be presented for the SCR per site:

The Residual Effect Period (REP) is defined as the last date of trial medication + 16 weeks (112 days) inclusive. This definition applies to the pre-switch period only. For handling of the REP in the post-switch period, see Section 16.

Important protocol violations, as defined in APPENDIX 7, will be presented for the RND.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

For the primary analysis, demographic data and other baseline characteristics will be presented for the FAS and TS. For the final analysis data will be presented for the FAS.

The baseline disease characteristics will be reported:

Accountability for missing data will be displayed in case of any missing entries.

10.1. DERIVATIONS

- Age (years) = (date of consent– date of birth)/365.25

In the case where the date of birth is partial (only year is available), the corresponding age will

be presented based on the imputations specified in APPENDIX 2.

- Grading of hypertension (The grade with the worst case (highest grade) will be used in the corresponding summaries):
  - Grade 0: systolic blood pressure (BP) < 120 mm Hg and diastolic BP < 80 mm Hg
  - Grade 1: systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg
  - Grade 2: systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg
  - Grade 3: systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg

In the case where the date of event is partial (only year is available), the corresponding date will be presented based on the imputations specified in APPENDIX 2.

11. SURGICAL AND MEDICAL HISTORY

Surgical and Medical History information will be presented for the FAS and TS (primary analysis) and TS (final analysis).
Medical History and Surgeries/Procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or higher if available at the time of the data cut-off.

11.1. MEDICAL HISTORY AND PREVIOUS SURGICAL PROCEDURES

Medical History and Previous Surgical Procedures as well as Active Medical History and Concomitant Surgical procedures will be presented by SOC (System Organ Class) and PT (Preferred Term).
The system organ classes will be sorted by internationally agreed EMA SOC order (refer to APPENDIX 4), PTs will be sorted by decreasing frequency within SOCs based on total count.

11.2. PRIOR AND CONCOMITANT RADIOTHERAPY

Prior and concomitant radiotherapy, as reported in the eCRF, will be presented by anatomic site (some anatomic sites will be grouped, see APPENDIX 9) by decreasing frequency based on total count

12. MEDICATIONS

Medications will be presented for the FAS and TS (primary analysis) and TS (final analysis).

Medications will be coded using WHO Drug Dictionary version MAR2016 or higher if available at the time of the data cut-off. No Anatomical Therapeutic Chemical (ATC) class coding will be performed. The medical terms will be summarized by WHO-DD Preferred Name.
The WHO-DD Preferred Names will be sorted by decreasing frequency based on total count.

12.1. PRIOR ANTI-CANCER DRUG THERAPIES

Prior anti-cancer drug therapies, as reported in the eCRF, will be presented using WHO-DD preferred names.

12.2. PREVIOUS, CONCOMITANT AND POST-TRIAL MEDICATION THERAPY

See APPENDIX 2 for handling of partial dates for medications. In the case where it will not be possible to define a medication as prior, concomitant or post, the medication will be classified by the worst case; i.e. concomitant. Concomitant medications will also be reported separately for the post-switch period .

12.3. CONCOMITANT ANTIHYPERTENSIVE MEDICATION

The additional information on anti-hypertensive medications will be reported for the pre-switch period:

Identification of these anti-hypertensive medications will be based on pre-specified WHO-DD preferred names according to medical input. The following process will be used by the medical advisor:

12.4. HEMATOPOIETIC GROWTH FACTOR MEDICATIONS

Hematopoietic growth factors will be presented for the TS for the pre-switch period.
Identification of these hematopoietic growth factors will be based on pre-specified WHO Drug terms according to medical input.

13. TRIAL MEDICATION EXPOSURE

Trial medication is defined as BI 695502 or US-licensed Avastin®. For the post-switch period, trial medication is defined as Avastin®.
For the pre-switch period, exposure to trial medication will be presented for the FAS, PPS and TS (primary analysis) and for the TS and PPS (final analysis). For the post-switch period, exposure to trial medication will be presented and listed separately for the SWS.

13.1. INFUSION PRE-MEDICATION

Pre-medication is defined as dexamethasone, diphenhydramine and/or cimetidine/ranitidine (or any equivalent within these groups of medications).
Pre-medication will be presented for Cycle 1- Cycle 6 using WHO-DD preferred names and will be sorted by decreasing frequency in BI 695502 treatment arm.

13.2. TRIAL MEDICATION AND CHEMOTHERAPY

The frequency and percentage of subjects treated compared to the number of subjects expected to be treated at each cycle will be presented for trial medication, Paclitaxel and Carboplatin.

14. DOSE INTENSITY AND RELATIVE DOSE INTENSITY

The dose intensity and the relative dose intensity for the trial medication and chemotherapy will be calculated.

14.1. DERIVATIONS

Dose Intensity
The dose intensity is defined as the total dose of trial medication or chemotherapy given in a fixed time period.

Relative Dose Intensity

The relative dose intensity (%) is defined as the dose intensity (in <UNIT>/week) divided by the protocol planned dose (in <UNIT>/week) x 100.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

The primary endpoint will be analyzed with primary analysis according to the following outline.

Primary endpoint: Best ORR (CR/PR, vs not CR/PR) within 18 weeks, central assessment	Population	Equivalence margin, CI for analysis
primary analysis (global CTP)	FAS	(0.736, 1.359), 90%*
primary analysis (local protocol amendment Japan): 95% CI and comparing to original margin	FAS	95% CI compared to margins (0.736, 1.359)
sensitivity analysis - PPS	PPS	(0.736, 1.359), 90%*

* 95% CI will be displayed as well

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is the best ORR, defined as the proportion of subjects with unconfirmed CR or PR as assessed by central imaging review until 18 weeks after the start of treatment. Best ORR will be evaluated from date of first administration of trial medication until either progression, treatment stop for unacceptable toxicity, death or up to 18 weeks, whichever happens earlier.

More specifically, this means that the best ORR will be evaluated for each subject separately from the date of first administration of trial medication (i.e. Study Day 1) until either:

- Progression according to RECIST 1.1 based on independent central review,
- Unacceptable toxicity defined by end of treatment due to adverse event as reported in the eCRF,
- Death as reported in the eCRF,
- Up to 18 weeks (i.e. study day 141 inclusive=18 weeks * 7 days +1 +14 days),

whichever happens earlier.

Subjects who start subsequent anticancer therapy will typically have progressed or stopped treatment due to unacceptable toxicity. In case a subject starts subsequent anti-cancer therapy but the ORR evaluation period of that subject is still ongoing, the subject's best ORR will be evaluated only until start of subsequent anti-cancer therapy.

Unscheduled assessments recorded during the evaluation period for best ORR will be taken into account for determination of best ORR. Tumor assessments started on study day 141 but not completed on study day 141 will be fully included in the evaluation of best ORR.

Subjects who stop the treatment for any other reason than adverse event, death or progression according to RECIST 1.1 and have not started a second line treatment by Week 18, will be included in the best ORR evaluation.

The imaging charter describes the central imaging assessment. RECIST 1.1 is the basis for the central imaging review.

The ratio in best ORR between BI 695502 versus US-licensed Avastin® will be used for analysis of the primary endpoint.

More specifically, the **best Overall Response Rate (ORR)** refers to the proportion of subjects with any CR or PR during the evaluation period. This is the proportion of subjects with "objective response (CR+PR)" according to RECIST 1.1 (Section 4.8).
In contrast, the wording **best response** will be used to refer to the best individual response category (in the order CR, PR, SD, PD, non-evaluable and missing) during the evaluation period.

Throughout the rest of this document, these terminologies will be used.

For a subject who discontinued treatment due to an AE, the subject's date of 'End of Treatment' corresponds to the date of the subject's last infusion. However, in cases where the start date of the adverse event leading to the study drug discontinuation is after the subject's last infusion date, the end of treatment is imputed as the date of the AE with the earliest start date after the subject's last infusion date.

15.1.2. Missing Data Methods for Primary Efficacy Variable(s)

For the purposes of the primary endpoint primary analysis, subjects who do not have documented CR or PR at a specific time point will be considered as non-responders at this time point. Missing or non-evaluable response assessments will not be imputed and will be considered as non-responder.
The imaging charter (Section 6.2.2, criterion 13.D) details the criteria needed to handle missing assessments in the central independent review.
For the subjects who withdraw consent, or who are lost to follow-up before Week 18, no data will be imputed. Only the assessments available will be used. However if there is no post-baseline assessment at all then the subject will be imputed as a non-responder.

15.1.3. Primary Analysis of Primary Efficacy Variable(s)

The primary test for equivalence will be performed with respect to BI 695502 versus US-licensed Avastin®. The primary hypothesis is based on the ratio in best ORR between the two treatments:

H0: Ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) ≤0.736 or ≥1.359.

H1: Ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) within the interval (0.736, 1.359).

For the calculation and justification of the equivalence margin please refer to Protocol Section 10.6.1. Tables 15.1.3:1 and 15.1.3:2 further illustrate what differences between the ORR by Week 18 in both treatment arms would lead to CIs of ORR ratios within the pre-specified margin based on the 90% and 95% CIs of ORR ratio, respectively.

Avastin® arm	BI 695502 arm	
ORR	Minimal ORR to declare equivalence (difference to ORR control group)	Maximal ORR to declare equivalence (difference to ORR control group)
30%	27.3% (-2.7%)	33.6% (+3.6%)
40%	34.8% (-5.2%)	46.7% (+6.7%)
43.3 %	37.6% (-5.7%)	51.2% (+7.9%)
50%	42.4% (-7.6%)	60.3% (+10.3%)
60%	50.0% (-10.0%)	74.2% (+14.2%)

Table 15.1.3:1. Analysis based on the 90% CI for the ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) within the interval (0.736, 1.359). *(Calculation: ADDPLAN®, version 6.0.4, assuming 330 subjects per treatment arm. Calculated from a two one-sided tests approach without covariates. The final model will depend on the actual allocation of subjects to strata used as covariates in the primary analysis model.)*

Avastin® arm	BI 695502 arm	
ORR	Minimal ORR to declare equivalence (difference to ORR control group)	Maximal ORR to declare equivalence (difference to ORR control group)
30%	28.2% (-1.8%)	32.4% (+2.4%)
40%	36.1% (-3.9%)	45.5% (+5.5%)
43.3 %	38.5% (-4.8%)	49.7% (+6.4%)
50%	43.6% (-6.4%)	58.8% (+8.8%)
60%	50.9% (-9.1%)	72.7% (+12.7%)

Table 15.1.3:2. Analysis based on the 95% CI for the ratio in best ORR by Week 18 (BI 695502 versus US-licensed Avastin®) within the interval (0.736, 1.359). *(Calculation: ADDPLAN®, version 6.0.4, assuming 330 subjects per treatment arm. Calculated from a two one-sided tests approach without covariates. The final model will depend on the actual allocation of subjects to strata used as covariates in the primary analysis model.)*

15.1.3.1. **Primary analysis, global CTP**

The null hypothesis will be rejected in favor of equivalence if the two-sided 90% CI for the ratio in best ORR between the treatments falls completely within the range defined by the equivalence margin (0.736, 1.359).; i.e., the comparison will be based on two one-sided tests (TOST) with a 5% type I error rate. The TOST procedure controls the overall type I error rate at alpha=5%.
The primary efficacy analysis will be performed for the FAS.

The statistical model for the analysis of the best ORR will be:

(M1) log (E{Best ORR}) = treatment + sex + smoking status + NSCLC stage + ethnicity

The difference in log(best ORR) between BI 695502 and US-licensed Avastin® will be estimated, with 90% and 95% CIs, adjusted for sex, smoking status, NSCLC stage, and ethnicity. The estimate and CI will be exponentiated to return to the ratio scale.

<u>Handling of sparse data covariates for primary analysis model:</u>

The protocol specifies that in the case of sparse data in one (or more) strata which affects the convergence of the model, the respective factors may be omitted in the model. That is to say, if the log-binomial model with all four covariates does not converge, then the first covariate to be dropped will be according to the strata which has the least number of subjects. The log-binomial model will then be re-run using the remaining three strata. If this model still does not converge, then the next covariate to be dropped will be according to the next strata with the least number of subjects. This process will continue until the model converges.

For example, if the strata 'male' has the least number of subjects compared to the other seven stratas (female, East Asian, non-East Asian, never smoked, current/past smoker, recurrent NSCLC, stage IV NSCLC), then the covariate 'sex' will be the first covariate to be dropped from the model.

If the log-binomial model still does not converge and the strata 'stage IV NSCLC' has the least number of subjects compared to the other remaining stratas (East Asian, non-East Asian, never smoked, past smoker, recurrent NSCLC), then the covariate 'NSCLC stage' will also be dropped from the model.

Handling of missing covariates for primary analysis model:
For the purposes of the primary endpoint primary analysis, covariates (Sex / Smoking status / NSCLC stage / Asian ethnicity) with missing values based on eCRF data will be imputed with the corresponding value based on IXRS data.

15.1.3.2. Primary analysis, local protocol amendment Japan:

For the Japanese subgroup analysis, equivalence will be declared if the two-sided 95% CI for the Best ORR ratio between BI 695502 and US-licensed Avastin® using same model falls completely between the lower margin bound of 0.736 and the upper margin bound of 1.359. This is applicable to the Primary Analysis only.

15.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE(S)

15.1.4.1. Primary analysis – PPS

To assess the robustness of the results, the primary analysis will be repeated using the subjects in the PPS. The same model will be employed as for the primary analysis.

15.1.4.2. Sensitivity analysis - Equivalence margin

15.1.4.7. Primary analysis – Stratification Factors

Sensitivity analysis of the primary endpoint will be reported that uses the IXRS stratification factors (as per randomised strata) in place of the eCRF. This will take into account any potential differences in reporting between the two sources.

15.2. SECONDARY EFFICACY

For the pre-switch period, the secondary efficacy analyses will be performed on the full analysis set (FAS). Secondary efficacy analyses will not be performed for the post-switch period.

15.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

The following secondary efficacy endpoints will be analyzed using the Cox model on the FAS. Kaplan Meier estimates including Kaplan-Meier medians will also be presented. The CI for the median will be calculated according to the Brookmeyer and Crowley method [5]. No sensitivity analyses are planned for the analyses of the secondary efficacy variables:

- Progression free survival until end of study, investigator assessment
- Overall survival
- Duration of response (first CR/PR until progression), investigator assessment

15.2.1.1. Progression-free survival

Progression-free survival (PFS) is defined as the time from randomization (as defined in Section 9) until disease progression as per investigator assessment or death from any cause, whichever occurs first. For non-switched subjects, PFS time will be censored on the date of the last adequate tumor assessment for subjects who do not have an event (PD or death) or for subjects with an event after two or more subsequent missing response assessments.
For the SWS, PFS time will be censored at the last tumor assessment at or prior to the Switch Visit.
Data from subjects who do not have any post-baseline tumor assessments will be censored at randomization (as defined in Section 9) unless death occurred on or before the time of the

second planned tumor assessment in which case the death will be considered as an event.

15.2.1.2. **Overall survival**

Overall survival (OS) is defined as the time from randomization (as defined in Section 9) until death from any cause during the pre-switch period.

For subjects alive overall survival time will be censored at the last date on which they were known to be alive during the pre-switch period.

15.2.1.3. **Duration of response**

Duration of response (DOR) is defined as the time from first documented CR or PR until time of progression as per investigator assessment in the pre-switch period.
This definition applies only to subjects who experienced CR/PR in the pre-switch period.

One missed tumor assessments is defined as no tumor assessment within one time window as defined in Section 6.4.
Two consecutively missed tumor assessments is defined as no tumor assessment within two consecutive time windows as defined in Section 6.4.

15.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

For imputing missing parts of dates for the efficacy analyses (except OS), the missing day in a date will be imputed as the 15th of the month, if month and year is documented. If the imputation is earlier than the date of randomization, then the day of randomization (as defined in Section 9) will be taken and if the imputation is later than the date of death, then the day of death will be taken. In all other cases, missing or incomplete dates will not be imputed.
For missing date of death, refer to the censoring tables in Section 15.2.1.2.
For imputing missing day of death date, if month and year is available, then the day will be imputed by 15, unless this results in an earlier date or the same date as the date the subject is known to be alive. In that case, the date of death will be imputed by the last date known to be alive + 1.

15.2.3. Analysis of Secondary Efficacy Variables

For the progression-free survival, overall survival and duration of response, a Cox-proportional hazards model using the same adjustment factors as for the best ORR ratio will be used. Handling of sparse data covariates will be done as for the primary analysis primary model. Kaplan-Meier estimates will also be presented.

Swimmer plots will also be presented for DOR and treatment duration, with arrow for cases where an event is still ongoing. A table summarizing the overall duration of response using observed data only (not Kaplan-Meier estimates), will also be presented, differentiated by ongoing/stopped, and overall, where stopped is defined as subjects who experienced PD or death. Kaplan-Meier estimates of duration of follow-up will also be presented, with the 'event' defined as the point at which the subject was censored for the original survival analysis. For this analysis, subjects who died are considered to be censored at the time at which the death occurred.

16. SAFETY OUTCOMES

For the pre-switch period, all outputs for safety outcomes will be based on the TS.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section. Limited safety outcomes will be presented for the post-switch period as noted in the relevant sections below. Unless specified, safety outcomes will be tabulated for the pre-switch period only. All post-switch safety outcomes will be listed.

Safety endpoints in this trial are:

Adverse events selected for comparability assessment (secondary endpoint)

- The proportion of subjects with the following selected AEs will be evaluated in comparability assessment of BI 695502 and US-licensed Avastin®:
  1. Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions
  2. Arterial and venous thromboembolic events
  3. Febrile neutropenia
  4. Gastrointestinal perforations
  5. Hypertension
  6. Proteinuria
  7. Pulmonary hemorrhage
  8. Other hemorrhages
  9. Wound-healing complications/abscess/fistulas.

Other Endpoints:

- The proportion of subjects with AEs
- The proportion of subjects with AEs related to trial treatment
- The proportion of subjects with Grade 3 or 4 AEs according to NCI-CTCAE version 4.0[2]
- The proportion of subjects with Grade 3 or 4 AEs according to NCI-CTCAE version 4.0[2] related to trial treatment
- The proportion of subjects with AEs potentially related to immunogenicity
- The proportion of subjects with adverse events of special interest (AESIs).

[2] Version 4.0 or the latest version available at the time of the analysis

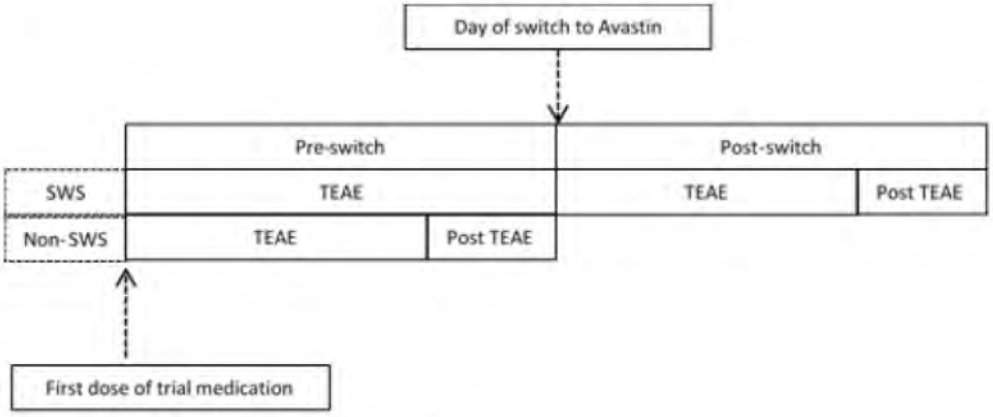
16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 19.0 or higher if available at the time of the data cut-off.

Treatment Emergent Adverse Events:

Figure B below provides an overview of the relationship between pre-switch and post-switch Treatment Emergent Adverse Events (TEAEs) and post AEs for subjects that switched (SWS) and those that did not switch (non-SWS).

Figure B – Treatment Emergent Adverse Events, Pre-Switch and Post-Switch period



For further details, see Appendix 10.

Note: Post TEAEs are not tabulated for the post-switch period.

See APPENDIX 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, then the AE will be classified by the worst case; i.e. treatment emergent.

For the Pre-Switch period, an overall summary of the number of subjects within each of the

categories described in the sub-sections below (16.1.1-6.1.13), will be provided as specified in the shells. For the post-switch period AEs to be tabulated are noted in the relevant sub-sections below.

In tables showing system organ classes and preferred terms, the system organ classes will be sorted by internationally agreed EMA SOC order (refer to APPENDIX 4), preferred terms will be sorted by decreasing frequencies in BI 695502 treatment arm (within system organ class).

A combined listing will be produced on all AEs (including TEAEs and Non-TEAEs) for the pre and post-switch periods.

Unless otherwise stated, other AE listings below will i) include only TEAEs and ii) be combined for the pre and post-switch periods.

16.1.1. POST-TREATMENT AEs

Frequency and percentage of post-treatment AEs will be presented by System Organ Class (SOC) and Preferred Term (PT). Post-treatments AEs are tabulated for the non-switched subjects. All post treatment AEs will be listed.

16.1.2. TEAEs SPECIFIC DERIVATION

16.1.2.1. Patient-Years incidence rate

Patient-years incidence rate per 1000 years for AEs meeting the specific criterion will be calculated as follows:
(Number of subjects with AE meeting the specific criterion) / (Patient-Years) * 1000,
where Patient-Years is the cumulative time at risk for all subjects (calculated in days) in the treatment group divided by 365.25.

16.1.2.2. **Risk ratio**

The risk ratio (RR) will be displayed together with the associated 95% exact confidence interval.

16.1.2.3. Wilson score Confidence Limits

PROC FREQ with option BINOMIAL will be used for programming purpose, for the Wilson score CI (Wilson, 1927 [6]).

16.1.3. ALL TEAEs

Frequency and percentage of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to trial medication. Patient-years incidence rate (as defined in Section 16.1.2.1) will be displayed.

In addition, a summary of frequencies, percentages and number of events by SOC, PT and by NCI-CTCAE grade will be displayed for the pre-switch period.

For the post-switch period, an overview of TEAEs will be presented as well as patient-years incidence rate (as defined in Section 16.1.2.1).

All TEAEs will be listed separately for the pre-switch and post-switch period.

16.1.3.1. Intensity

TEAE intensity is classified from Grade 1 to Grade 5, according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) v4.0. If a subject reports a TEAE more than once within that SOC/ PT, then the AE with the worst case intensity will be used in the corresponding by intensity summaries. The categories "Any grade", "Grade 1", "Grade 2", "Grade 3", "Grade 4", "Grade 5" and "Missing grade" will be displayed.

16.1.3.2. Relationship to Trial Medication

A related TEAE is defined as a TEAE with a relationship to trial medication ticked "yes" according to the investigator. TEAEs with a missing relationship to trial medication will be regarded as related to trial medication. If a subject reports the same AE more than once within that SOC/PT, then the AE with the worst case relationship to trial medication will be used in the corresponding relationship summaries.
For TEAE with a relationship to trial medication, a summary of frequencies, percentages and number of events by SOC and PT will be prepared and also listed. Patient-years incidence rate (as defined in Section 16.1.2.1) will also be displayed.
In addition, a summary of frequencies, percentages and number of events by SOC, PT and by NCI-CTCAE grade will be displayed.

16.1.3.3. Medical Concepts: Anaemia and Neutropenia

A summary of frequencies, percentages and number of TEAEs and related TEAEs by the medical concepts Anaemia and neutropenia will be prepared. Patient-years incidence rate (as defined in Section 16.1.2.1) will also be displayed.

16.1.4. TEAEs Leading to Interruption of Trial Medication, Paclitaxel or Carboplatin

TEAEs leading to temporary interruption of trial medication, Paclitaxel or Carboplatin will be identified by using the "Drug interrupted" category on the AE page of the eCRF.
For TEAEs leading to temporary interruption of trial medication, Paclitaxel and Carboplatin, summaries of frequencies, percentages and number of events by SOC and PT will be prepared.
In this context 'temporary interruption' refers to any interruption during the administration of the trial medication. TEAEs leading to treatment drug interruption will be listed, for trial medication, Paclitaxel and Carboplatin.

16.1.5. TEAEs Leading to Discontinuation of Trial Medication, Paclitaxel or Carboplatin

TEAEs leading to permanent discontinuation of trial medication, Paclitaxel or Carboplatin will be identified by using the "Drug Withdrawn" category on the AE page of the eCRF.
For TEAEs leading to permanent discontinuation of trial medication, Paclitaxel and Carboplatin, summaries of frequencies, percentages and number of events by SOC and PT will be prepared.
TEAEs leading to permanent discontinuation of trial medication due to progression disease will be identified by using the "Progressive disease" category on the EOT page of the eCRF.
For TEAEs leading to permanent discontinuation of trial medication due to progression of disease, a listing will be prepared.
TEAEs leading to treatment discontinuation will be listed, for trial medication, Paclitaxel and Carboplatin.

16.1.6. TEAEs Leading to Reduction of Chemotherapy

TEAEs leading to reduction of Paclitaxel (resp. Carboplatin) will be identified by using the "Dose reduced" category on the AE page of the eCRF.
For TEAEs leading to reduction of Paclitaxel (resp. Carboplatin), a summary of frequencies, percentages and number of events by SOC and PT will be prepared.
TEAEs leading to Paclitaxel reduction, as well as TEAEs leading Carboplatin reduction, will be listed.

16.1.7. Serious TEAEs

Serious adverse events (SAEs) are those events for which the investigator ticked "Yes, specify" to the item "Is this a serious adverse event?" on the AEs page of the eCRF.
A table of the number of subjects, percentages and number of events of Treatment Emergent SAEs by SOC and PT will be prepared. Patient-years incidence rate (as defined in Section 16.1.2.1) will be displayed. This information will also be presented for the post-switch period.
Serious TEAEs will be listed for the pre and post-switch periods.

16.1.8. Non-Serious TEAEs

Non-serious TEAEs are those events for which the investigator ticked "No" to the item "Is this a serious adverse event?" on the AEs page of the eCRF.
Frequency of subjects, number of events and incidence of subject with non-serious TEAEs will be presented by SOC and PT, if preferred term incidence is >5%.

16.1.9. TEAEs Leading to Death

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF.
For TEAEs leading to Death, a summary of frequencies, percentages and number of events by SOC and PT will be prepared. Subject-year incidence rate (as defined in Section 16.1.2.1) will also be displayed.
TEAEs leading to Death will be listed.

16.1.10. AEs Selected for Comparability Assessment (Secondary Endpoint)

The number of subjects and percentages with associated 95% Wilson score confidence interval (as defined in Section 16.1.2.3) of AEs selected for comparability assessment will be displayed in a separate table as well as the risk ratios (as defined in Section 16.1.2.2) and Patient-year incidence rates (as defined in Section 16.1.2.1) overall and per AE category.
In addition, a summary of frequencies, percentages and number of events by category and PT will be displayed. This summary description will also be presented for the post-switch period.

According to the protocol, the selected AEs for comparability assessment are the following:

1. Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions
2. Arterial and venous thromboembolic events
3. Febrile neutropenia
4. Gastrointestinal perforations
5. Hypertension
6. Proteinuria
7. Pulmonary hemorrhage
8. Other hemorrhages
9. Wound-healing complications/abscess/fistulas.

Identification of these categories will be based on pre-specified MedDRA terms according to medical input – see APPENDIX 8.
AEs selected for comparability assessment will be listed separately for the pre and post-switch period.

Frequency of subjects with at least one AE selected for comparability, as well as the 9 individual AEs selected for comparability will be analyzed for each of the levels of the subgroups as defined in Section 7.5. The risk ratio will be the observed one, and the Score exact method will be used to determine the risk ratio and corresponding 95% CI. These estimates will be produced

by subsetting the data to the individual levels within the subgroup.
Only the endpoint of subjects with at least one AE selected for comparability will be presented in the Forest plot.

16.1.11. TEAEs Of Special Interest

AESI reported by investigators are those events recorded as "Adverse Event of Special Interest" equal to "Yes" on the Adverse Events page of the eCRF.

A table of the number of subjects, percentages and number of events of Treatment Emergent AESI reported by investigators by the categories described in the sub-sections below and by PT with each AESI category will be provided.
TEAESI reported by investigator will be listed. TEAESI reported by investigator will also be summarized and listed separately for the post-switch period.

16.1.11.1. Hepatic Injury

Hepatic injury events are those events identified by medical advisor on the subset of AEs for subjects presenting laboratory potential Hepatic injury findings (refer to Section 16.4.1.1).
Hepatic injuries considered to be AESI are those events identified as both hepatic injury adverse events related to trial medication and recorded as "Adverse Event of Special Interest" equal to "Yes" on the Adverse Events page of the eCRF.
Hepatic injury TEAEs will be listed. The listing will include the "Adverse Event of Special Interest" equal to "Yes" information from the Adverse Events page of the eCRF as a flag.

16.1.11.2. Gastrointestinal Perforations

Gastointestional perforations (GI) are those events recorded as MedDRA code in the pre-defined Standardized MedDRA Queries (SMQ) = "Gastrointestinal perforation" (narrow).
GI perforations considered to be AESI are those events identified as both GI perforations and recorded as "Adverse Event of Special Interest" equal to "Yes" on the Adverse Events page of the eCRF.
GI perforation TEAEs will be listed. The listing will include the "Adverse Event of Special Interest" equal to "Yes" information from the Adverse Events page of the eCRF as a flag.

16.1.11.3. Anaphylactic Reactions

Anaphylactic reactions are those events recorded as MedDRA code in the pre-defined Standardized MedDRA Queries (SMQ) = "Anaphylactic reactions" (narrow).

Anaphylactic reactions considered to be AESI are those events identified as both Anaphylactic reactions and recorded as "Adverse Event of Special Interest" equal to "Yes" on the Adverse Events page of the eCRF.
Anaphylactic reaction TEAEs will be listed. The listing will include the "Adverse Event of Special Interest" equal to "Yes" information from the Adverse Events page of the eCRF as a flag.

16.1.11.4. Pulmonary Hemorrhage

Pulmonary hemorrhage are those events recorded in BIcMQ "Pulmonary hemorrhage" (refer to APPENDIX 8).

Pulmonary hemorrhage AEs considered to be AESI are those events identified as both Pulmonary hemorrhage and recorded as "Adverse Event of Special Interest" equal to "Yes" on the Adverse Events page of the eCRF.
Pulmonary hemorrhage TEAEs will be listed. The listing will include the "Adverse Event of Special Interest" equal to "Yes" information from the Adverse Events page of the eCRF as a flag.

16.1.11.5. Other AESIs

Other AESIs are those not falling into any of the above mentioned MedDRA categories and recorded as "Adverse Event of Special Interest" equal to "Yes" on the Adverse Events page of the eCRF.
Other AESIs will be listed. The listing will include the "Adverse Event of Special Interest" equal to "Yes" information from the Adverse Events page of the eCRF as a flag.

16.1.12. TEAEs POTENTIALLY RELATED TO IMMUNOGENICITY

A table of the number of subjects, percentages and number of TEAEs potentially related to immunogenicity will be prepared. TEAEs potentially related to immunogenicity will also be presented for the post-switch period.

Identification of these TEAEs potentially related to immunogenicity will be based on preferred terms (PT) according to medical input.
The following process will be used:

- 1. Identify subjects with ADAs or nADAs
- 2. For these subjects, identify AEs from the AEs for comparability categories "anaphylactic reactions", "hypersensitivity reactions" and "infusion-related reactions"

- 3. Medical review of these TEAEs to determine whether some of them should be classified as TEAEs potentially related to immunogenicity

This process will be performed prior to the unblinding of the database.
TEAEs potentially related to immunogenicity will also be listed for the pre and post switch periods.

16.1.13. GRADE 3 OR 4 TEAES

Grade 3 or 4 TEAEs are those events with a Grade 3 or a Grade 4 intensity according to NCI-CTCAE v4.0[2]. If a subject reports a TEAE more than once within a SOC/ PT, then the worst case intensity won't be used and in case of Grade 3 or a Grade 4 intensity at least once, the AE will be counted in the Grade 3 or 4 TEAEs summaries.

For Grade 3 or 4 TEAEs, a summary of frequencies, percentages and number of events by SOC and PT will be prepared. A similar summary will also be performed for Grade 3 or 4 TEAEs with a relationship to trial medication. Grade 3 or 4 TEAEs and Grade 3 or 4 TEAEs with a relationship to trial medication will also be listed.

16.2. EXEMPTED EVENTS OF DISEASE PROGRESSION

Progression of disease and death due to progression are considered as disease outcome and therefore, are exempted from reporting as a (S)AE. Frequency and percentage of these events will be summarized and listed by treatment group.

16.3. DEATHS

If any subject dies during the study

the information will be presented in a summary table and listed. The SWS will be noted on the associated listing, so that any deaths occurring for the SWS will be attributed to the post-switch period.

16.4. LABORATORY EVALUATIONS

All laboratory analyses will be presented on the treated set. All laboratory evaluations (16.4.1-16.4.2) will be analyzed only for the pre-switch period. Combined listings of laboratory evaluations for the pre and post-switch period will be provided.

Laboratory values taken after the first dose of trial medication up to a period of 16 weeks after the last dose of the trial medication will be assigned to the treatment phase for evaluation. Baseline and treatment phase assessments will be used in summary tables. All assessments will be presented in listings. Results from the central laboratory will be included in the reporting of this study for Hematology, Serum Chemistry, Urinalysis and Coagulation. A list of laboratory assessments to be included in the outputs is included in APPENDIX 3. Laboratory parameters will be ordered as in APPENDIX 3.

In general, laboratory evaluations will be summarized in System International (SI) units. Additionally, the data will be summarized in US units, if applicable. Listings will present both SI and US units in case of differences, otherwise only SI units will be presented.
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.
The handling of retests, unscheduled and end of study measurements are described in Section 6.3.

16.4.1. REGULAR SAFETY LABORATORY EVALUATIONS

summaries and listings will be provided for laboratory data:

16.4.1.1. **Laboratory Specific Derivations**

- Potential Hy's law categories:
  - Category 1: ALT or AST >=3xULN and TBL >=2xULN within the same sample
  - Category 2: TBL >=2xULN within 30 days after transaminase peak (ALT or AST >=3 ULN)

  Potential Hy's Law subjects are defined as subjects with laboratory data in at least one Potential Hy's law category at any time point of the study.

16.4.1.2. Laboratory Reference Ranges and Markedly Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI and US units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

16.4.1.3. CTC Grading for Laboratory Data

Laboratory results will be classified according to the National Cancer Institute Common Terminology Criteria v.4.0. Only programmable parts of definitions will be performed. The "Grade 0" will be introduced to indicate that a certain laboratory value can be seen as "normal" and does not fulfill the criteria of NCI-CTC grading either within the reference range or elevated in the other direction than defined in the NCI-CTC document. For uncertain cases (for example when the values can be assigned to grade 0 based on the normal range and grade 1 or 2 based on the toxicity criteria), a medical check will be performed, to determine the correct grade.

16.4.2. OTHER SAFETY LABORATORY EVALUATIONS

16.4.2.1. **Infection screen**

Descriptive table per visit will present hepatitis B and hepatitis C results by treatment group and results will also be listed.

16.4.2.2. **Human immunodeficiency virus test**

Descriptive table per visit will present human immunodeficiency virus (HIV) test results by treatment group and also be listed.

16.4.2.3. **Tuberculosis test**

Descriptive table per visit will present Tuberculosis (TB) test results by treatment group and the TB test results will be listed.

16.4.2.4. **Pregnancy test**

Descriptive table per visit will present pregnancy results for females by treatment group and pregnancy results will be listed.

16.5. HYPERTENSION

All hypertension analyses will be performed on the treated set for the pre-switch period.

16.6. BRAIN LESION

If any subject has a brain lesion during the study as recorded on the "non-target lesion" and "New lesion" pages of the eCRF, the information will be listed.

16.7. ECG EVALUATIONS

Results from ECGs will be summarized and listed by visit using the categories as recorded in the eCRF page "12-Lead-ECG" ("normal", "abnormal, not clinically significant" and "abnormal, clinically significant").

16.8. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Temperature (°C)
- Weight (kg)
- BSA (m^2) (where Paclitaxel is administered)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit.

A combined listing of Vital Signs for the pre and post-switch periods will be provided.

16.9. PHYSICAL EXAMINATION

Incidence of evaluation categories (normal, abnormal) at baseline and post-baseline visits will be provided and listed for physical examination data.

16.10. ECOG

ECOG performance status at baseline and post-baseline visits will be listed.

17. REFERENCES

[1] Spiegelman D and Hertzmark E. Easy SAS Calculations for Risk or Prevalence Ratios and Differences. Am J Epidemiol. 2005;162:199–200.

[2] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

[3] Multiple imputation for non-response in surveys. New York: John Wiley & Sons. 1987.

[4] Confidence interval of difference of proportions in logistic regression in presence of covariates. Statistical Methods in Medical Research. 2016. DOI : 10.1177/0962280216631583

[5] Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

[6] Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. Statistical Science. 2001;16:101-133.

APPENDIX 3. LABORATORY ASSESSMENTS

Laboratory parameter	Gradable with NCI-CTC	SI unit	US unit
Serum chemistry			
ALT	X	IU/L	IU/L
AST	X	IU/L	IU/L
Gamma glutamyl transpeptidase (g-GT)	X	IU/L	IU/L
Bilirubin	X	umol/L	mg/dL
Total cholesterol		mmol/L	mg/dL
Total protein		g/L	g/dL
Albumin	X (Hypoalbuminemia)	g/L	g/dL
Glucose	X (Hypoglycemia/Hyperglycemia)	mmol/L	mg/dL
Alkaline phosphatase	X	IU/L	IU/L
Calcium	X (Hypocalcemia/Hypercalcemia)	mmol/L	mg/dL
Creatinine	X	umol/L	mg/dL
Sodium	X (Hyponatremia/ Hypernatremia)	mmol/L	mEq/L
Potassium	X (Hypokalemia/Hyperkalemia)	mmol/L	mEq/L
Chloride		mmol/L	mEq/L
Hematology			
Hemoglobin	X (Anemia/ Hemoglobin increased)	g/L	g/dL
White blood cells	X (White blood cell decreased/Leukocytosis)	10^9/L	10^3/uL
Neutrophils	X	10^9/L	10^3/uL
Lymphocytes	X (Lymphocyte count decreased/Lymphocyte count increased)	10^9/L	10^3/uL
Platelets	X	10^9/L	10^3/uL
Hematocrit		v/v	v/v

Laboratory parameter	Gradable with NCI-CTC	SI unit	US unit
Urinalysis			
Protein	Gradable proteinuria is only reported at screening which is not reported (as per Section 16.4)	g/L	g/dL
Glucose		mmol/L	mg/dL
Blood		N/A	N/A
Coagulation			
INR	X		
PTT	X	second	second
PT		second	second

APPENDIX 4. EMA SOC ORDER FOR PRESENTATION OF THE AE IN THE TABLES

Order	System Organ Class
0	Uncoded
1	Infections and infestations
2	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
3	Blood and lymphatic system disorders
4	Immune system disorders
5	Endocrine disorders
6	Metabolism and nutrition disorders
7	Psychiatric disorders
8	Nervous system disorders
9	Eye disorders
10	Ear and labyrinth disorders
11	Cardiac disorders
12	Vascular disorders
13	Respiratory, thoracic and mediastinal disorders
14	Gastrointestinal disorders
15	Hepatobiliary disorders
16	Skin and subcutaneous tissue disorders
17	Musculoskeletal and connective tissue disorders
18	Renal and urinary disorders
19	Pregnancy, puerperium and perinatal conditions
20	Reproductive system and breast disorders
21	Congenital, familial and genetic disorders
22	General disorders and administration site conditions
23	Investigations
24	Injury, poisoning and procedural complications
25	Surgical and medical procedures
26	Social circumstances
27	Product issues

APPENDIX 5. CUT-OFF APPLICATION RULES

Cut-off rules are detailed in a separate document named "BI1302.5_SDTM_cut_off_01MAY2018".

APPENDIX 6. ADDITIONAL SUBGROUP ANALYSIS FOR JAPAN – PRIMARY ANALYSIS ONLY

For the primary analysis a set of outputs from the analysis in the Primary Analysis CTR will be selected for the Japanese subgroup. Some selected outputs will be included as an appendix in the Primary Analysis CTR, but the same outputs as produced for the global population subgroups will be produced in general for the Japanese subgroup as well. This Japanese subgroup analysis will not be described in the text of the Primary Analysis CTR.

For the primary analysis the Japanese subgroup analysis will use the same shells as the corresponding global population outputs.
Japanese subgroup will have 2 categories:

- Japanese subjects (Race = Asian and country site = "JPN")
- non-Japanese subjects (Overall population except Japanese subjects)

In general, TFLs will only be produced for the Japanese subjects category.

Japanese subgroup analysis will not be performed for the Final Analysis CTR.

APPENDIX 7. IMPORTANT PROTOCOL VIOLATIONS

Important protocol violations are detailed in a separate document named "BI1302.5_Important protocol violations_08AUG2017".

APPENDIX 8. BIcMQs, SMQs AND SELECTED PTs

For each safety concern, one or more MedDRA PT will be selected (e.g. per SMQ or per BIcMQ). A PT will be selected if it is part of the medical concept of the safety concern.

SMQs identification is based on separate external excel file named:

- SMQ_spreadsheet_21_0_

Safety concern
Anaphylactic reactions/hypersensitivity reactions/infusion-related reactions
Arterial and venous thromboembolic events
GI perforations
Hypertension
Proteinuria
Pulmonary hemorrhage
Other haemorrhages
Wound-healing complications including abscess and fistulas
Febrile neutropenia

BIcMQs identification is based on separate external excel file named:

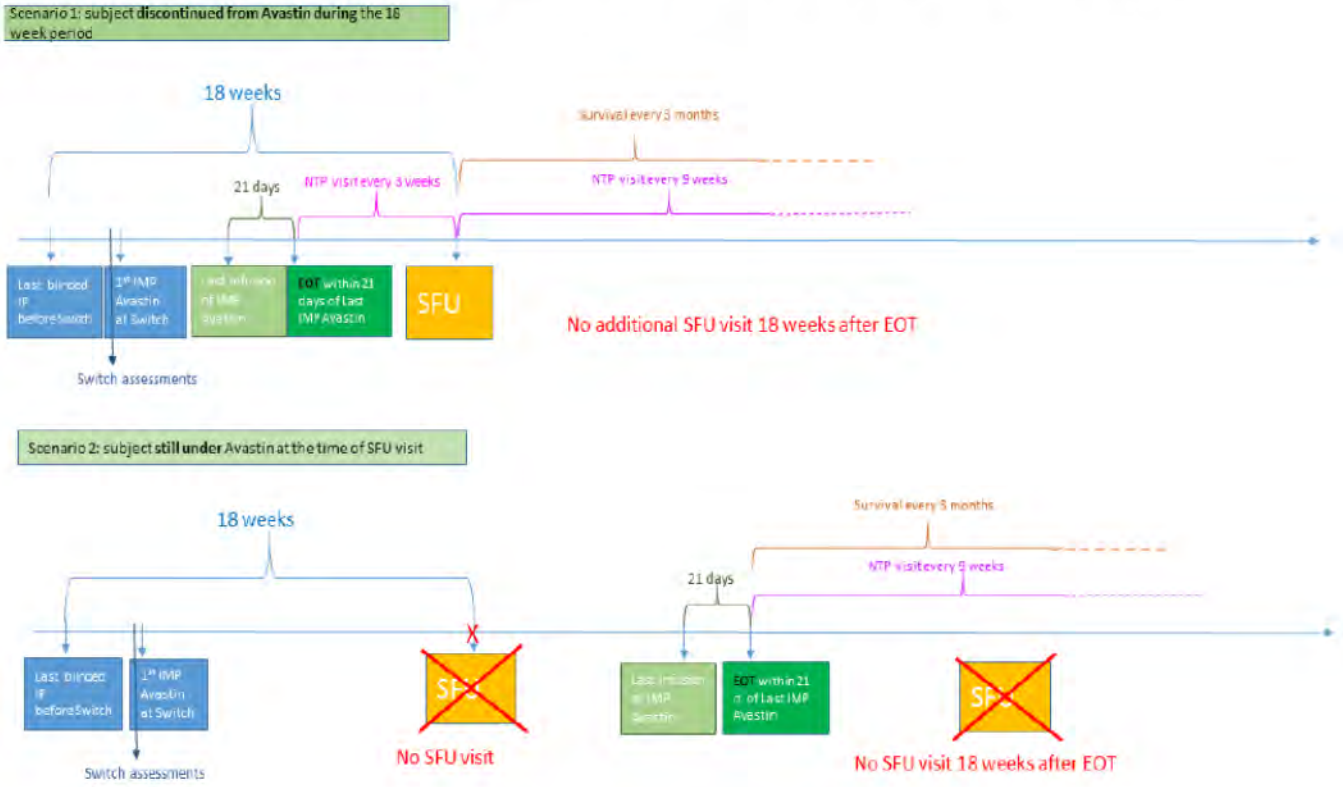
- BI 695502_MedDRA 21.0_BIcMQ_Pulmonary hemorrhage (or higher if available)

Adverse events selected for comparability and adverse events potentially related to immunogenicity are listed in a separate document named:

- BI1302 5_AEs Selected_v8.0_MedDRA21.0_Final (or higher if available)

Note: all external files for the Primary Analysis are based on MedDRA version 20.0. Files will be upgraded to the higher MedDRA version available at the time of each data cut-off or at final database lock.

APPENDIX 10. SAFETY FOLLOW UP AND EOT VISITS POST-SWITCH PERIOD



Overview of Safety Follow Up and End of Treatment Visits in the post-switch period.