BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-301
Study Protocol Title:	A Randomized, Open-label, Multi-center Phase 3 Study to Compare the Efficacy and Safety of BGB-A317 versus Sorafenib as First-Line Treatment in Patients with Unresectable Hepatocellular Carcinoma
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Approval

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Antidrug antibody
AE	Adverse event
BCLC	Barcelona Clinic Liver Cancer
BID	Twice daily
BIRC	Blinded Independent Review Committee
BOR	Best overall response
CBR	Clinical benefit rate
COVID-19	Coronavirus disease of 2019
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EQ-5D	European Quality of Life 5-Dimensions
EORTC QLQ-HCC 18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Hepatocellular Carcinoma 18 Questions
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio

HRQoL	Health-related quality of life
iDMC	Independent Data Monitor Committee
ITT	Intent-to-Treat
IV	Intravenous
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NA	Not assessable
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-L1	programmed cell death ligand-1
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PO	Orally
PP	Per-Protocol
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
RMST	Restricted Mean Survival Time
RPSFT	Rank Preserving Structural Failure Time
ROW	Rest of world
Q2W	Once every 2 weeks

Q3W	Once every 3 weeks
SD	Stable disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
QTcF	Fridericia's correction formula
TTP	Time to progression

1 INTRODUCTION

This SAP is developed for study closeout CSR.

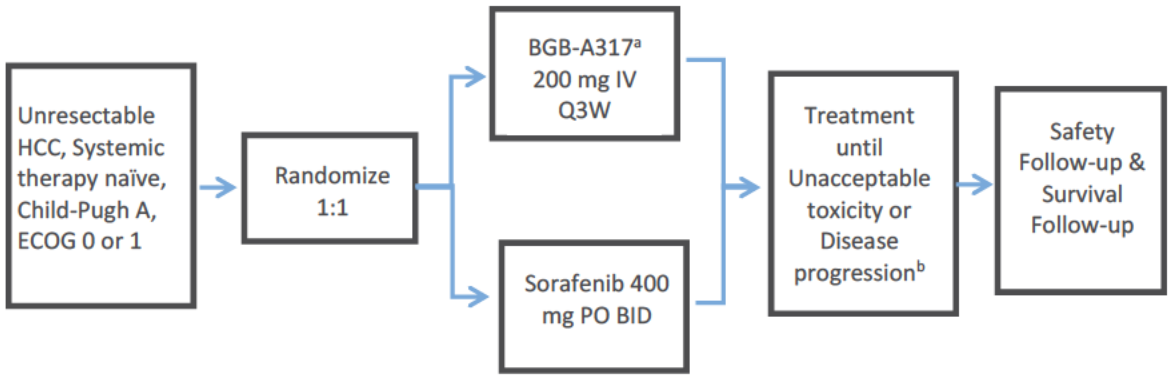
Reference materials for this statistical analysis plan include the protocol amendment BGB-A317-301 (version 5.0, dated as 11May2020) and the study SAP for primary CSR (Final version 2.0, dated as 21APR2022).

All statistical analyses will be conducted using SAS® (SAS Institute, Inc., Cary, NC, USA), Version 9.4 or higher.

2 STUDY OVERVIEW

2.1 STUDY DESIGN

This is a randomized, open-label, multicenter Phase 3 study to compare the efficacy and safety of tislelizumab to that of sorafenib as first-line treatment in adult patients with unresectable HCC. The study design schema is as follows:



a. The initial infusion (Cycle 1, Day 1) will be administered over a period of 60 minutes. If this infusion is well tolerated, subsequent infusions may be administered over 30 minutes. After tislelizumab infusion, patients will be further monitored for a period of 2 hours during Cycles 1 and 2. From Cycle 3 onward, a post-infusion monitoring period of ≥ 30 minutes will be required.
b. At the discretion of the Investigator, patients may be treated beyond disease progression under protocol-defined conditions (see Section 7.13.1 of the protocol).

After providing written informed consent, completing all Screening assessments, and being confirmed as eligible for study participation, approximately 640 patients will be randomized in a 1:1 ratio to receive (on an open-label basis) either tislelizumab or sorafenib.

At randomization, patients will be stratified by the following 5 factors:

- Macrovascular invasion (present vs absent)
- Extrahepatic spread (present vs absent)
- ECOG (0 vs 1)

- Etiology (hepatitis C virus [HCV] vs other [includes HBV])
- Geography (Asia [excluding Japan] vs Japan vs Rest of World)

Patients with HBV and HCV co-infection will be grouped along with HBV into the "other" category of etiology for randomization. Patients will then begin open-label treatment with 1 of the following regimens:

- Arm A: tislelizumab 200 mg intravenously (IV) once every 3 weeks (Q3W)
- Arm B: Sorafenib 400 mg orally (PO) twice daily (BID)

All study treatment is to be continually administered until intolerable toxicity, withdrawal of informed consent, or the time point at which, in the opinion of the Investigator, the patient is no longer benefiting from study therapy.

Treatment beyond the initial Investigator-assessed, RECIST v1.1-defined disease progression is permitted in both treatment arms provided the patient meets the criteria described in protocol Section 7.13.1.

Regarding study objectives, study endpoints, sample size considerations, interim analysis, there is no update since last SAP (final version, dated as 21APR2022), so in this SAP for closeout analysis, the above sections will not be repeated, details can be found in study SAP for primary CSR.

3 STATISTICAL METHODS

3.1 ANALYSIS SETS

Intent-to-Treat (ITT) Analysis Set – Includes all randomized patients. Patients will be analysed according to their randomized treatment arm (i.e., either tislelizumab or sorafenib). This will be the primary analysis population for all efficacy analyses.

Safety Analysis Set – Includes all randomized patients who received at least one dose of their assigned study drug. (tislelizumab or sorafenib). This will be the analysis population for all safety analyses. Patients will be analysed according to the study treatment they received. Patients will be classified according to treatment received, where treatment received is defined as (i) the intended treatment if it was received at least once, or (ii) the first treatment received when starting therapy with study medication if intended treatment is never received. Each patient will be classified into and analysed consistently within one (and only one) treatment arm.

3.2 DATA ANALYSIS GENERAL CONSIDERATIONS

3.2.1 Definitions and Computations

Study day: Study day will be calculated in reference to the first dose date. For assessments conducted on or after the date of first dose date, study day will be calculated as (assessment date –first dose date + 1). For assessments conducted before first dose date, study day is calculated as (assessment date – first dose date). There is no study day 0.

Baseline Measurements:

- For efficacy evaluation: a baseline value is defined as the last non-missing value

collected prior to the randomization.

- For safety: a baseline value is defined as the last non-missing value prior to the first study drug administration.
- For toxicity grade of certain laboratory tests: two baseline toxicity grades should be derived according to the directions (lower (Hypo) or higher (Hyper)). For example, a baseline hemoglobin with value between 10.0 g/dL and Lower limit of normal, two baseline toxicity grades: Grade 1 for Hypo and Grade 0 for Hyper will be derived.

Study Follow-up Duration (SFD): Study follow-up duration is defined as the duration from the randomization date to the study discontinuation date (e.g. death, consent withdrawal, lost to follow-up) or to cutoff date if a patient is still ongoing.

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

3.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25.
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Time-to-event or duration of event endpoints based on tumor assessment will be based on the actual date the radiograph was obtained rather than the associated visit date.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- The unit of time duration is month unless otherwise specified.

3.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere inthis document.

Specific rules for handling of missing or partially missing dates for adverse events, prior/concomitant medications/procedures, and subsequent anti-cancer therapy are provided in Appendix 6.1, 6.2, 6.3, and 6.4 .

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

3.3 PATIENT CHARACTERISTICS

3.3.1 Patient Disposition

The number (percentage) of patients who signed informed consent, enrolled in the study, died before enrollment, and screen-failed failure will be summarized. The number (percentage) of screen failure reason will also be summarized.

The number (percentage) of patients randomized, treated, discontinued from study drug and discontinued from the study will be summarized. The primary reason for end of treatment (study drug discontinuation) and end of study will be summarized by categories. The reasons for treatment/study discontinuation related to COVID-19 impact will also be summarized. Study follow up duration will be summarized descriptively.

Patient disposition will also be summarized by region (Asia [excluding Japan], Japan, and Rest of World) for ITT analysis set.

3.3.2 Protocol Deviations

Protocol deviation criteria will be established together with its category/term of important and not important. Important protocol deviation is defined as an event related to study inclusion or exclusion criteria, conduct of the trial, patient management, patient assessment, and/or a significant non-compliance that significantly affects or has the potential to significantly affect human subject protection or reliability of the trial's results, per International Council for Harmonisation (ICH) Guidelines E3. Patients with important protocol deviations will be identified and documented before the database lock. Important protocol deviations will be summarized for all patients in the ITT analysis set.

Critical protocol deviation that may significantly impacts efficacy will be reviewed prior to data base lock according to the criteria defined in protocol deviation specification. The patient with the following critical protocol deviations will be excluded from per protocol analysis set:

- Do not have histologically confirmed diagnosis of HCC
- Do not sign the inform consent form at study entry
- Receive different study drug from assigned treatment
- The ECOG PS score at screening is greater than 1
- Received any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, standard/investigational agents [including Chinese (and other Country) herbal medicine and patent medicines] for the treatment of cancer), or extensive radiation therapy (except for local, palliative radiotherapy to bone

3.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the ITT analysis set using descriptive statistics. Continuous variables will be summarized using number of patients, mean,

standard deviation, median, minimum, and maximum. Categorical variables will be summarized using number of patients and percentage in relevant categories.

Demographic and other baseline characteristics include:

- Age
- Age group (< 65 vs ≥ 65 years)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)

Demographic and other baseline characteristics will also be summarized by region (Asia [excluding Japan] and ROW) for ITT analysis set.

In addition, the stratification factors per IWRS and per eCRF will be summarized based on ITT analysis set:

- Macrovascular Invasion (yes vs. no)
- Extrahepatic Spread (yes vs. no)
- ECOG (0 vs 1)
- Etiology (hepatitis C virus [HCV] vs other [includes hepatitis B virus (HBV)])
- Geography (Asia [excluding Japan] vs Japan vs Rest of World)

3.3.4 Disease History and Baseline Disease Characteristics

The following disease history and baseline disease characteristics will be summarized in ITT analysis set:

- Time since initial cancer diagnosis to date of randomization
- Time since advanced/metastatic disease diagnosis to date of randomization
- BCLC Initial Staging
- BCLC stage at study entry
- Child-Pugh (CP) classification/scores
- Histological Tumor differentiation grade
- Macrovascular invasion
- Extrahepatic spread
- Distant metastases and location
- Number of metastatic sites involved (0, 1, 2, ≥3)

- Hepatitis virus infection status (hepatitis B, hepatitis C, non-viral)
- Prior loco-regional procedures (present vs. absent)
- Alpha-fetoprotein at baseline (numeric, and categories: < 200 ng/ml, >= 200 ng/ml, < 400 ng/ml, >=400 ng/ml)

The hepatitis virus infection status comes from the relevant medical history collected from HCC history and characteristics case report form.

Detail of HCC relevant medical history including but not limited to Hepatitis B, Hepatitis C, History of Alcohol Abuse, baseline Child-Pugh score with its components, and HBV/HCV laboratory test values at baseline will also be summarized.

Cancer associated symptoms at baseline will also be summarized by SOC, preferred term and CTCAE grade.

Disease history and baseline disease characteristics will also be summarized by region (Asia [excluding Japan] and ROW) for ITT analysis set.

3.3.5 Prior and Concomitant Medication and Therapy

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term by phase in the safety analysis set. Prior medications are defined as medications that stopped before the first dose date. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose or initiation of a new anti-cancer therapy, whichever occurs earlier. In addition, concomitant medication also includes medications associated with an immune-mediated adverse event recorded up to 90 days after last dose of study drug. Patients who received concomitant systemic corticosteroid/immunosuppressant will also be summarized.

Patient data listings of prior and concomitant medication will be provided.

3.4 Post-Study Anti-Cancer Therapy

Post-study anti-cancer therapy is defined as the anti-cancer therapy started after the last dose date of study drug. A summary of number and pecentage of patients who received subsequent systematic anticancer therapy/immune checkpoint inhibitors (single treatment), and combination therapy of immune checkpoint inhibitors and tyrosine kinase inhibitors will be provided by arm based on ITT analysis set.

Patient data listings of post-study anti-cancer therapy, procedure, radiotherapy, embolization, or surgery will be provided.

3.5 EFFICACY ANALYSIS

Overall survival is the primary endpoint of the study. One interim analysis of OS for efficacy is planned when approximately 80% (403) of the targeted death events (504) have been observed. Only superiority of OS will be tested at IA and noninferiority test will be skipped. At final, the superiority of tislelizumab over sorafenib will be tested for OS using a stratified log-rank test in the ITT analysis set only when noninferiority is demonstrated.

3.5.1 Primary Efficacy Endpoints

Variable:

Overall survival is defined as time from randomization date to the documented death date for patients who died prior to or on the clinical cutoff date. For patients who are alive by the clinical cutoff date, OS will be censored at the last known alive date (LKADT). The last known alive date will be defined as either the clinical data cutoff date for patients who are still on treatment, or last known alive date or cut-off date whichever comes first for other alive patients.

The 95% CI of $HR_{A/B}$ will be estimated in the ITT analysis set using a Cox proportional hazard model with treatment arm as a factor and stratified by the actual pooled stratification factors including region (Asia vs. ROW), macrovascular invasion and/or extrahepatic spread (present vs. absent), etiology (HCV vs. other) and ECOG (0 vs. 1). Efron's method will be used in tie handling.

The nominal p-value will be calculated from a stratified log-rank test for descriptive purpose.

The median OS and the cumulative probability of OS estimated at every 6 months will be calculated using Kaplan-Meier estimates for each treatment arm and presented with 2-sided 95% CIs computed by Brookmeyer and Crowley method using the log-log transformation.

3.5.2 Secondary Efficacy Endpoints

3.5.2.1 *ORR, PFS, DOR, and TTP assessed by the Investigator*

ORR, PFS, DOR, and TTP assessed by Investigator will be analyzed similarly to the approach used in assessment by BIRC.

3.5.2.2 Disease Control Rate (DCR) and Clinical Benefit Rate (CBR) by Investigators

Disease control rate (DCR) defined as the proportion of patients whose best overall response (BOR) is CR, PR, or SD. Clinical benefit rate (CBR) defined as the proportion of patients who have CR, PR, or SD of $\geq$ 24 weeks in duration.

Both DCR and CBR will be analyzed similarly to ORR in the ITT analysis set.

3.6 SAFETY ANALYSES

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v4.03. Laboratory values (e.g., hematology, clinical chemistry), vital signs, ECGs, and PEs, will also be used in determining safety. Descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables) will be used to analyze all safety data in the safety analysis set.

3.6.1 Extent of Exposure

The following exposure parameters will be summarized with descriptive statistics for each study drug. One cycle is defined as 21 days of treatment. Specifically:

Treatment duration (TD) for tislelizumab: The treatment duration will be calculated as (last date of exposure – date of first dose + 1)

- If patients discontinued treatment (with non-missing EOT date), using min (CUOFFDT, death date, last dose date + 20) as the "last date of exposure"
- otherwise if patient has treatment ongoing, using cutoff date as the "last date of exposure" for calculation of TD

Treatment duration for sorafenib: date of the last dose of sorafenib – date of first dose of sorafenib + 1). If the first dose starts in PM or the last dose stops in AM, only half day will be counted.

Total Cumulative Dose for tislelizumab and sorafenib = sum (all actual dosages per administration at all visits prior to the cut-off date).

Actual Dose Intensity (ADI) for tislelizumab (mg/cycle) = 21*total cumulative dose (mg) / (last dose date prior to cut off date+ 21 - first dose date).

Actual Dose Intensity for sorafenib (mg/cycle) = (total cumulative dose (mg) / TD for sorafenib) * 21.

Planned Dose Intensity for tislelizumab (mg/cycle) = 200 mg/cycle.

Planned Dose Intensity for sorafenib (mg/cycle) = 16800 mg/cycle.

Relative Dose Intensity (%) = Actual Dose Intensity/Planned dose intensity *100%

Number of cycles received is defined as the sum of number of cycles with at least one non-missing doses (dose>0). If patient take at least one sorafenib in 21-days period, this cycle will be counted. For tislelizumab, if patient did not take the IV during 21-days period, this cycle will not be counted.

Average cycle length of tislelizumab = (date of the last dose of tislelizumab – date of first dose + 21) / the number of cycles received.

Average cycle length of sorafenib = treatment duration for sorafenib / the number of cycles received.

The number of patients with dose reductions (sorafenib only), dose omissions, dose delays, dose interruptions, and treatment discontinuation and their reasons will be summarized by counts and percentages according to study drug. In addition, frequency of dose reductions (sorafenib only), dose omission, dose delays and dose interruptions will be summarized by categories (0, 1, ≥2).

Patient data listings will be provided for all dosing records, and for the above calculated summary statistics.

3.6.2 Adverse Events

The AE verbatim descriptions (Investigator's description from the eCRF) will be classified into

standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to MedDRA (Version 23.0 or higher) lower level term closest to the verbatim term. The linked MedDRA System Organ Class (SOC) and Preferred Term are also classified. All adverse event summaries are based on safety analysis set.

The immune-mediated adverse event (imAE) programmatic method per imAE identification charter (VV-PVG-001366) will be applied for identification of imAE, and the imTEAE results will be presented for both treatment arm and control arm.

In this trial, a TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever occurs first. TEAEs also includes all immune-mediated adverse events up to 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

3.6.2.1 Treatment Emergent Adverse Event

An overall summary of TEAEs will summarize the number (%) of patients with

- At least one TEAE
- At least one TEAE with NCI-CTCAE grade ≥3
- At least one treatment-related TEAE
- At least one serious TEAE
- At least one TEAE leading to death
- At least one TEAE leading to discontinuation of study drug
- At least one TEAE leading to dose modification of study drug
- At least one immune-mediated adverse event
- At least one immune-mediated adverse event with NCI-CTCAE grade ≥3
- At least one infusion-related reaction
- At least one infusion-related reaction with NCI-CTCAE grade ≥3

Summaries of the following TEAEs will be provided:

- All TEAEs
    - All TEAEs by SOC
    - All TEAEs by SOC and PT
    - Most frequently reported (incidence ≥10% in any treatment arm) TEAE by SOC and PT
    - Treatment-related TEAE by SOC and PT

- Most frequently reported (incidence ≥10% in any treatment arm) Treatment-related TEAE by SOC and PT

- Serious TEAEs by SOC and PT
  - Most frequently reported (incidence ≥ 5% in any treatment arm) serious TEAE by SOC and PT
  - Treatment-related Serious TEAE by SOC and PT
- TEAEs with NCI-CTCAE grade ≥3 by SOC and PT
  - Treatment-related TEAE with NCI-CTCAE grade ≥ 3 by SOC and PT
- Most frequently reported (incidence ≥ 5 % in any treatment arm) TEAE with NCI-CTCAE grade ≥ 3 by SOC and PT.
- TEAEs leading to death by SOC and PT
  - Treatment-related TEAE Leading to Death by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT
  - Treatment-related TEAE Leading to Treatment Discontinuation by SOC and PT
- TEAEs leading to dose modification by SOC and PT
  - Treatment-related TEAE Leading to Dose Modification by SOC and PT

3.6.2.2 Immune-mediated Adverse Event

Summaries of the following incidence of immune-mediated adverse events will be provided:

- Immune-mediated adverse events by category and maximum severity
- Immune-mediated adverse events with NCI-CTCAE grade ≥3 by category
- Immune-mediated adverse events leading to treatment discontinuation by category
- Immune-mediated adverse events leading to death by category
- Immune-mediated adverse events leading to dose modification by category
- Immune-mediated adverse events treated with systematic corticosteroid by category

4 CHANGES IN THE PLANNED ANALYSIS

Not applicable.

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6 APPENDIX

6.1 IMPUTE PARTIAL DATES FOR CONCOMITANT MEDICATION

When the start date or end date of a medication/therapy/procedure is partially missing, the date will be imputed to determine whether the medication/therapy/procedure is prior or concomitant. The following rules will be applied to impute partial dates for medications.

If start date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed start date > death date, then set to death date

If end date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

6.2 IMPUTE PARTIAL DATES FOR ADVERSE EVENTS

If year of the start date is missing or start date is completely missing, do not impute. Impute AE end date first if both AE start date and end date are partially missing.

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

If year of the end date is missing or end date is completely missing, do not impute. If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month
- If the imputed AE start date is after AE end date (maybe imputed), then update AE start date with AE end date as final imputed AE start date. If the imputed end date >

death date, then set to death date.

6.3 IMPUTE PARTIAL DATES FOR SUBSEQUENT ANTI-CANCER SURGERY/PROCEDURE

When the start date of subsequent anti-cancer therapy is partially missing, the following rules will be applied to impute partial dates.

If start date of is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

If year of the start date is missing, do not impute. If imputed start date is after study discontinuation date, then set to study discontinuation date.

6.4 IMPUTE PARTIAL DATES FOR PRIOR ANTI-CANCER THERAPY (DRUG, SURGERY/PROCEDURE, RADIOTHERAPY)

The following rules will be applied to impute partial dates such as initial diagnosis date, initial BCLC staging date, relapse date, therapy date (start/end date), or surgery date etc.

- If start date of a disease history or prior therapy is partially missing, impute as follows:
- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If the imputed start date > first dose date then set to first dose date – 1

If end date of a disease history or prior therapy is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > first dose date, then set to first dose date -1

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute. If imputed start date/end date is after randomization date - 14 , then set to randomization date - 14.

6.5 PROGRESSION FREE SURVIVAL CENSORING RULE

No.	Situation	Date of Progression or Censoring	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
1	No baseline tumor assessments and without death within 10 weeks after randomization	Randomization date	Censored	Censored	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed	Progressed	Progressed***
3	No progression at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored	Censored	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored	-	Censored
5	Death before first PD assessment	Date of death	Progressed	Progressed	Progressed***
6	Death between adequate assessment visits*	Date of death	Progressed	Progressed	Progressed***
7	Death or progression after more than one missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored	Censored	Progressed or died
8	Discontinued due to Clinical PD but no documented PD	Date of clinical progression	-	-	-