STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-fruquintinib-201
Study Protocol Title:	A MULTICENTER, OPEN-LABEL PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TISLELIZUMAB IN COMBINATION WITH FRUQUINTINIB IN PATIENTS WITH SELECTED SOLID TUMORS
Date:	27 February 2024
Version:	1.0
NCT Number	NCT04716634

SIGNATURE PAGE

Author: [redacted]	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I am the author of this document Signing Time: 27-Feb-2024 | 22:56:13 PST [redacted] Signature Date: 27-Feb-2024 | 22:56:59 PST

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug Antibody
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BGB-A317	Tislelizumab
CI	Confidence Interval
CR	Complete Response
CRC	Colorectal cancer
CT	Computed Tomography
DCR	Disease Control Rate
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
imAE	immune-mediated Adverse Event
GC	Gastric Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MSS	Microsatellite stable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed cell Death protein-1
PD-L1	Programmed cell Death Ligand-1
PFS	Progression-Free Survival
PK	Pharmacokinetic

Abbreviation	Definition
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SMC	Safety Monitoring Committee
SOC	System Organ Class
TA	Tumor Assessment
TEAE	Treatment-Emergent Adverse Event
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB-A317-fruquintinib-201: a multicenter, open-label phase 2 study to evaluate the efficacy and safety of tislelizumab in combination with fruquintinib in patients with selected solid tumors. This SAP is based on BGB-A317-fruquintinib-201 Protocol Amendment 1.0, dated on 16 December 2020. The focus of this SAP is for the final analysis specified in the study protocol.

2. STUDY OVERVIEW

2.1. Study Design

This is an open label, multicenter, phase 2 study designed to assess the efficacy and safety of tislelizumab in combination with fruquintinib in patients with advanced or metastatic, unresectable GC, MSS CRC and PD-L1 positive (defined as TC ≥1% by SP263 IHC) NSCLC. The study will be conducted in 2 parts (Figure 1).

2.1.1. Part 1 (Safety Run-in)

Part 1 of the study will be the safety run-in stage during which the first 6 patients will be enrolled and assessed for DLTs during the 28-day DLT observation period. Study drug administration will begin at the full dose of fruquintinib (5 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) in combination with tislelizumab (300 mg once every 4 weeks). A lower dose level of fruquintinib (4 mg daily, 3 weeks on followed by 1 week off every 4-week cycle) will be explored as necessary depending on observed toxicity. Only DLTs during the first 28 days of treatment will be assessed. Once they complete the DLT assessment, each patient who still receive study treatment will continue with the same dosage.

- If 0-1 of 6 patients experience a DLT, the study may proceed at the current dose of both drugs.
- If 2 or more patients experience a DLT, then, following consultation with the SMC, the study will proceed with enrollment in the next defined lower dose (Dose Level -1), an additional 6 patients will be enrolled, and the 28-day DLT observation period will be repeated.
- If 2 or more patients experience a DLT in Dose Level -1, enrollment in the study will cease.

The SMC will evaluate the safety and tolerability of the combination therapy when the first 6 DLT-evaluable patients have completed the first 28 days of treatment or when ≥ 2 DLTs at the tested dose level occur. Safety information including but not limited to the DLTs, all TEAEs, and laboratory abnormalities will be reviewed by the SMC. The SMC will make recommendations on safety management, including resumption of enrollment, de-escalation of fruquintinib to one lower dose level, or termination of enrollment. The final decision will be made by sponsor. Once

the sponsor has determined that the combination therapy could proceed, the current dose will be confirmed as the RP2D, and enrollment for Part 2 will begin at RP2D.

2.1.2. Part 2 (Expansion)

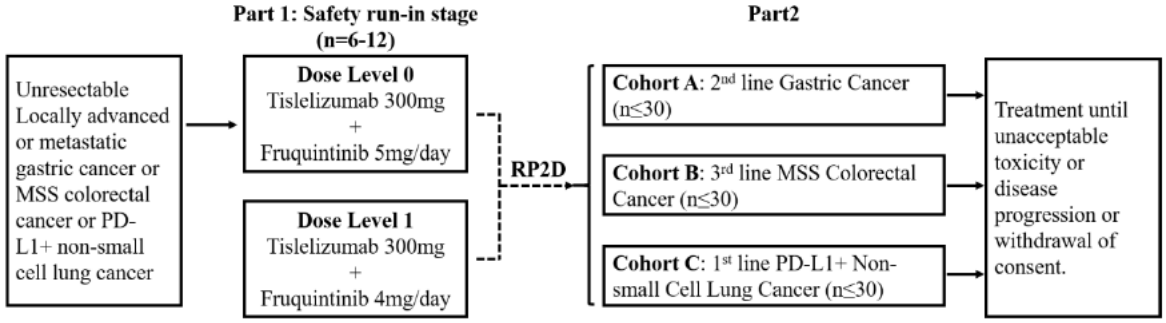
Patients enrolled in Part 1 at RP2D will be counted towards Part 2 by the diagnosis of the tumor types; up to approximately 30 patients per cohort will be enrolled at RP2D.

There will be a total of 3 cohorts in part 2.

- Cohort A: second line gastric cancer
- Cohort B: third line MSS colorectal cancer
- Cohort C: first line PD-L1 positive non-small cell lung cancer

The study schema is in Figure 1.

Figure 1: Study Schema



Abbreviations: DLT, dose limiting toxicity; RP2D, recommended Phase 2 dose; SMC, Safety Monitoring Committee.

Notes: The first 6 patients will be enrolled and assessed for DLTs during the 28-day DLT observation period. Dosing will begin at Dose Level 0. Dose Level -1 will be explored as necessary depending on observed toxicity. The SMC will evaluate the safety and tolerability of the combination therapy when the first 6 DLT-evaluable patients have completed the DLT observation period or when ≥ 2 DLTs at the tested level occur. Enrollment for Part 2 will begin once the sponsor has determined that the combination could proceed and confirmed the RP2D of fruquintinib in combination with tislelizumab.

- Tislelizumab will be administered intravenously on Day 1 of every 4-week cycle.
- Fruquintinib will be administered daily, orally with 3 weeks on followed by 1 week off for every 4-week cycle.

2.2. Study Assessments

Tumor Assessments:

Tumor assessments will be performed by the investigator using RECIST v1.1 criteria (Eisenhauer et al 2009). Tumor imaging (computed tomography [CT] with oral/IV contrast, unless contraindicated, or magnetic resonance imaging [MRI]) must be performed within 28 days prior to enrollment. On-study tumor assessments will occur every 8 weeks (±7 days) during the first 56 weeks and every 12 weeks (±7 days) thereafter until PD. If a patient discontinues study treatment due to any reasons other than PD, tumor assessments will continue to be performed as scheduled until disease progression, loss to follow up, initiation of subsequent therapy, withdrawal of consent, death, or until the study terminates, whichever occurs first.

Safety Assessment:

All patients will be closely monitored for AEs throughout the study and for up to 30 days after the last dose of study drug(s). AEs will be graded according to the NCI-CTCAE v5.0. Refer to protocol for additional and specific information regarding AE monitoring and reporting. After informed consent has been signed but before the administration of the study drug(s), only SAEs should be reported. After the first dose of study drug(s), all AEs and SAEs, regardless of relationship to study drugs, will be reported until either 30 days after last dose of study drug(s) (including fruquintinib) or initiation of new anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the investigator should be reported regardless of time since the last dose of treatment.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To assess the safety and tolerability of tislelizumab in combination with fruquintinib.
- To confirm the RP2D of fruquintinib in combination with tislelizumab.
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by investigator in patients with selected solid tumors as measured by the overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

3.2. Secondary Objective

- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the progression free survival (PFS) per RECIST v1.1.
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the disease control rate (DCR) per RECIST v1.1.
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the clinical benefit rate (CBR) per RECIST v1.1.
- To assess the efficacy of tislelizumab in combination with fruquintinib as assessed by the investigator in patients with selected solid tumors as measured by the duration of response (DOR) per RECIST v1.1.
- To assess the efficacy of tislelizumab in combination with fruquintinib as in patients with selected solid tumors as measured by overall survival (OS).
- To assess the safety of tislelizumab in combination with fruquintinib.

3.3. Exploratory Objective

- To characterize the immunogenicity of tislelizumab and its time-pairing pharmacokinetic (PK) when given in combination with fruquintinib
- To assess the PK of fruquintinib when given in combination with tislelizumab

4. STUDY ENDPOINTS

4.1. Primary Endpoint(s)

- Safety and tolerability will be assessed throughout the study by monitoring adverse events (AEs) characterized by type, frequency, severity per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, timing, seriousness, and relationship to study drug(s); and other safety assessments.
- RP2D of fruquintinib in combination with tislelizumab.
- ORR – defined as the proportion of patients whose best overall response is confirmed complete response (CR) or partial response (PR) as assessed by investigator per RECIST v1.1.

4.2. Secondary Endpoints

- PFS – defined as the time from the date of first dose to the date of the first determination of an objectively documented tumor progression as assessed by investigator per RECIST v1.1, or death, whichever occurs first.
- DCR – defined as the as the proportion of patients whose best overall response is CR, PR, or stable disease (SD) as assessed by investigator per RECIST v1.1.
- CBR – defined as the as the proportion of patients whose best overall response is CR, PR, or durable SD (Durable SD is defined as a SD with at least 24 weeks in duration) as assessed by investigator per RECIST v1.1.
- DOR – defined as the time from the first occurrence of documented objective response to the time of progression as assessed by investigator per RECIST v1.1 or death from any cause, whichever occurs first.
- OS - defined as the time from the date of first dose to the date of death due to any cause.
- AEs characterized by type, frequency, severity (as graded by the NCI-CTCAE v5.0), timing, seriousness, and relationship to study drug(s); and other safety assessments.

4.3. Exploratory Endpoints

- Incidence of anti-tislelizumab antibodies (ADA), and its time-pairing serum concentration of tislelizumab.
- Plasma concentrations and derived PK parameters of fruquintinib as data permit.

5. SAMPLE SIZE CONSIDERATIONS

Approximately 6 to 12 DLT evaluable patients will be enrolled at Part 1. Patients enrolled in Part 1 at RP2D will be counted towards Part 2 by tumor types. Approximately 96 patients will be enrolled at maximum, and about 30 patients will be enrolled at RP2D per cohort to evaluate the preliminary efficacy, safety, and clinical pharmacokinetics.

The study plans to enroll approximately 90 patients at RP2D :

- Cohort A: Gastric cancer (n = 30)
- Cohort B: Colorectal cancer (n = 30)
- Cohort C: Non-small cell lung cancer (n=30)

No formal hypothesis testing is planned in this trial.

The 95% CIs when observing different numbers of responders among 30 patients in each cohort are presented in Table 1.

Table 1: Estimate of 95% CI (%) Using Clopper-Pearson When Observing Different Number of Responders in 30 Patients

Number of responders (ORR observed)	2 (6.7%)	3 (10.0%)	5 (16.7%)	6 (20.0%)	8 (26.7%)	9 (30.0%)
(95% CI) (%)	(0.82, 22.07)	(2.11, 26.53)	(5.64, 34.72)	(7.71, 38.57)	(12.28, 45.89)	(14.73, 49.40)

Abbreviations: CRC, colorectal cancer; GC, gastric cancer; MSS, microsatellite stable; NSCLC, non-small cell lung cancer; ORR, overall response rate.
Notes: The historical response rate for the standard of care (SOC) in each cohort are the following:
ORR data of the SOC for 3rd line MSS CRC: Fruquintinib (4.7%, Li et al 2018) / regorafenib (4%, Li et al 2015)
ORR data of the SOC for 2nd line GC: Paclitaxel (16%) (Wilke et al 2014).
ORR data of the SOC for 1st line PD-L1+ NSCLC: pembrolizumab (27%) (Mok et al 2019)

6. STATISTICAL METHODS

6.1. Analysis Sets

The Safety Analysis Set (SAS) includes all patients who received ≥ 1 dose of study drug(s). This will be the primary analysis set for the safety and efficacy analyses.

The Evaluable Analysis Set (EAS) includes all patients who received ≥ 1 dose of study drug(s), have evaluable disease at baseline, and have ≥ 1 evaluable postbaseline tumor response assessment unless any clinical PD or early death (within 17 weeks of first dose date). Outcomes in the Evaluable Analysis Set will be evaluated as a sensitivity analysis.

The DLT Evaluable Analysis Set includes all patients who received at least 85% of the assigned total dose of fruquintinib and at least 67% (approximately two-thirds) of the assigned total dose of tislelizumab for the DLT assessment period. Additionally, patients who had a DLT event will

also be considered evaluable. Only patients from Part 1 are eligible for inclusion in the DLT Evaluable Analysis Set. This will be the analysis set for the DLT analyses.

The PK Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have ≥ 1 quantifiable postbaseline PK data.

The ADA Analysis Set includes all patients who received ≥ 1 dose of study drug(s) and have a baseline and at least 1 postbaseline ADA result.

6.2. Multiplicity Adjustment

Not applicable.

6.3. Data Analysis General Considerations

6.3.1. Definitions and Computations

Study drugs: Study drugs include tislelizumab and fruquintinib.

Reference date: Reference date is defined as the date of the first dose of any study drugs.

Study Day: Study Day will be calculated in reference to the date of the first dose of any study drug. For assessments conducted on or after the date of the first dose, the study day will be calculated as (assessment date – the first dose date + 1). For assessments conducted before the date of the first dose, study day is calculated as (assessment date – the first dose date). There is no study day 0. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix 1.

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the first dose of study drug(s).

Study Follow-up Duration (SFD): Study follow-up duration is defined as the duration from the reference date to death date if the patient died prior to data cutoff, or the study discontinuation date if the patient discontinued from study prior to data cutoff, otherwise to the data cutoff date.

All calculations and analyses will be conducted using SAS® Version 9.4 or higher.

6.3.2. 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'.
- Duration of image-based event endpoints (such as PFS) will be based on the actual date the radiograph was obtained rather than the associated visit date.
- For lab 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).
- For discrete endpoints, summary statistics will include frequencies and percentages.
- The unit of time duration is month unless otherwise specified.

6.3.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events, disease history and prior therapy, prior/concomitant medications/procedures and subsequent anticancer therapy. Specific rules for the handling of missing or partially missing dates are provided in Appendix 1.

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.

6.4. Patient Characteristics

6.4.1. Patient Disposition

The number (percentage) of patients enrolled, treated, discontinued from the study, reasons for discontinued from the study, and the study follow-up duration will be summarized in the safety analysis set. The patients who discontinued treatment and the primary reason for the end of treatment will be summarized among patients who were treated.

6.4.2. Protocol Deviations

Important protocol deviation criteria will be established, and patients with important protocol deviations will be identified and documented. Important protocol deviations will be summarized for all patients in the safety analysis set. They will also be listed by each category. Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per patient.

6.4.3. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using descriptive statistics in the safety analysis set, including but not limited to the following variables:

- Age (continuously and by categories [<65 or ≥65 years])
- Sex
- Race
- Country
- Weight
- BMI
- ECOG performance status at baseline

6.4.4. Disease History

The number (percentage) of patients reporting a history of disease characteristics, as recorded on the eCRF, will be summarized in the safety analysis set. Disease characteristics include disease stage at initial diagnosis, metastatic disease at study entry, time from initial diagnosis to first dose date, time from initial diagnosis of metastatic disease to first dose date, histology/cytology, histologic grade.

6.4.5. Prior Anticancer Drug Therapies and Surgeries

Prior anti-cancer drug therapies, prior anti-cancer radiotherapy, and prior anti-cancer surgeries will be summarized in the safety analysis set. The variables include number of patients with any prior anti-cancer drug therapy, number of prior lines, reason(s) for discontinuation of last prior anticancer drug therapy, best overall response to the last prior anticancer drug therapy, time from end of last prior anticancer drug therapy to first dose date, treatment setting for prior anti-cancer drug therapies, number of patients with any prior anticancer surgery, time from last prior anticancer surgery to first dose date and number of patients with any prior anticancer radiotherapy, time from last prior anticancer radiotherapy to first dose date. The last prior anticancer drug therapy/surgery/radiotherapy is defined as the anticancer drug therapy/surgery/radiotherapy with the last end date. Prior anti-cancer drug therapies with the same sequence/regimen number are counted as one prior therapy.

6.4.6. Prior and Concomitant Medications

Prior medications are defined as medications that started before the first dose of study drug. 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 the initiation of a new anti-cancer therapy.

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes version for the study at the time of database lock. They 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 name in the safety analysis set.

6.4.7. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version for the study at the time of database lock. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the safety analysis set.

Patient data listings of medical history will be provided.

6.5. Efficacy Analysis

No formal hypothesis testing is planned for efficacy analysis. All efficacy analyses will be performed descriptively by tumor types.

6.5.1. Primary Efficacy Endpoint(s)

ORR by Investigators

Best Overall Response (BOR) which is defined as the best response recorded from the start of the study drug until progressive disease (PD), death, data cut or start of new anticancer therapy, whichever comes first.

The ORR is defined as the percentage of patients whose BOR is confirmed CR or confirmed PR assessed by investigators per RECIST v1.1. Patients with no post-baseline response assessment (for any reason) will be considered as non-responders. The ORR will be summarized with descriptive statistics by tumor types and the corresponding two-sided 95% CIs calculated from Clopper-Pearson exact method will be also presented. The primary analysis of ORR is based on Safety Analysis Set and the sensitivity analysis of ORR is based on the Evaluable Analysis Set.

A swimmer plot of time on treatment (i.e., duration of exposure), with indicators for the start and end of each response episode, will also be provided for selected tumor types with sufficient sample size. The patients will be ordered by the duration of exposure. Patients with the longest duration will be presented at the top of the plot.

6.5.2. Secondary Efficacy Endpoints

Progression Free Survival (PFS)

Kaplan Meier methodology will be used to estimate median PFS, Q1 and Q3 of PFS, and the event-free rates at selected timepoints, e.g., 3, 6, 9, and 12 months based on Safety Analysis Set. 95% Cis for median and other quantiles of PFS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley, 1982). And 95% Cis for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926). Kaplan Meier curves will be

constructed to provide a visual description of the PFS change with time for each tumor type. The censoring rules for the primary analysis of PFS are presented in Table 2.

Table 2: Censoring Rules for Progression-free Survival Per RECIST Version 1.1

	Derivation rules	**Outcome**
No progression at the time of data cut-off or withdrawal from study or lost to follow up	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
New anticancer therapy started prior to disease progression or death	Last adequate disease assessment before the new anticancer therapy	Censored
No baseline or post-baseline tumor assessments without death within 17 weeks after date of the first dose	Date of the first dose	Censored
No baseline or post-baseline tumor assessments and died within 17 weeks after the first dose	Date of death	Event
Death or progression after more than one missed tumor assessment *	Date of last adequate radiologic assessment before missed tumor assessments	Censored
Progression documented at or between scheduled visits	Date of first radiologic PD assessment	Event
With baseline and post -baseline tumor assessment and death before the first disease progression	Date of death	Event

* More than one missed tumor assessment is identified in Appendix 2.

Disease control rate (DCR)

DCR is defined as the proportion of patients whose best overall response is CR, PR, or stable disease (SD) as assessed by investigator per RECIST v1.1. DCR will be analyzed using methods similar to those described for ORR based on the Safety Analysis Set.

Clinical benefit rate (CBR)

CBR is defined as the proportion of patients whose best overall response is CR, PR, or durable SD (Durable SD is defined as a SD with at least 24 weeks in duration) as assessed by investigator per RECIST v1.1. CBR will be analyzed using methods similar to those described for ORR based on the Safety Analysis Set.

Duration of Response (DOR)

DOR is defined as the time from the first determination of an objective response until the first documentation of PD as assessed by the investigator per RECIST v1.1, or death, whichever comes first. Duration of response analysis will only include patients with confirmed CR/PR. The censoring rule for DOR will follow the PFS censoring rule. Kaplan Meier methodology will be used to estimate the median duration, and the 95% confidence interval for the duration of response will be provided based on Safety Analysis Set.

Waterfall plots will be provided for the maximum tumor shrinkage based on target lesion(s). The maximum tumor shrinkage based on target lesion(s) used in the plots will be listed for selected tumor types with sufficient sample size.

Overall survival (OS)

OS is defined as the time from first dose 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. The last known alive date will be defined as either the clinical data cutoff date for patients who are still on treatment, or last available date showing patients alive or cut-off date whichever comes first for other alive patients.

Every effort should be made to ensure complete death dates. In the rare case, if day of death date is missing, death date is imputed as the max (last available date showing patients alive + 1, first day of month of death date). The patient with imputed death date will be considered as an event for OS analysis.

The distribution of OS, including median, Q1, and Q3, and event-free rates at 3, 6, 9 and 12 months, will be estimated using the Kaplan-Meier method by tumor types. 95% CIs for median, Q1, and Q3 of OS will be estimated using the method of Brookmeyer and Crowley (Brookmeyer and Crowley, 1982). The 95% CIs for event-free rates will be estimated using Greenwood's formula (Greenwood, 1926). Kaplan-Meier survival probabilities over time will be plotted.

OS will be analyzed in the Safety Analysis Set.

6.5.3. Post-Treatment Subsequent Anti-Cancer Therapy

Post treatment anti-cancer therapy is defined as the anti-cancer therapy started after the last dose of study drug(s).

A summary of number and percentage of patients who received any subsequent systemic anticancer therapy, radiotherapy, immunotherapy will be provided by tumor types based on safety analysis set.

Separate flags of start date of new anti-cancer therapy for efficacy and safety analyses are derived individually.

- As for efficacy analysis, start date of new anti-cancer therapy will be the earliest date of prohibited anti-cancer therapy taken during treatment.

- The start date of new anti-cancer therapy in defining TEAE for safety analysis is always the first date of new systemic anti-cancer therapy taken after the last study treatment.

Tumor response per RECIST or event driven endpoints have not been commonly used for the efficacy evaluation of TCM. ORR, PFS or OS benefit of Chinese herbal medicines or Chinese patent medicines has not yet been established. Therefore, TCM will not be considered as new anti-cancer therapy in the efficacy and safety analysis.

Patient data listings of post-treatment anti-cancer therapy, procedure, radiotherapy will be provided.

6.6. Safety Analyses

All safety analyses will be performed by tumor types based on safety analysis set except for analysis of DLT which is only applicable to patients in DLT Evaluable Set. Safety and tolerability will be assessed, where applicable, by incidence, severity, and change from baseline values for all relevant parameters including AEs, laboratory values (hematology, clinical chemistry and coagulation), vital signs, ECG findings and physical examination.

6.6.1. Extent of Exposure

The following measures of the extent of exposure will be summarized：

Duration of exposure (months):

- For tislelizumab, duration of exposure (months) is defined as (last date of exposure - first dose date + 1) / 30.4375. For treatment ongoing patients, use cutoff date as the 'last date of exposure'; for patients discontinued from treatment, 'last date of exposure' is defined as the earliest date of cutoff date, death date, or last dose date + 27.
- For fruquintinib, duration of exposure (months) is defined as (last date of exposure – first dose date + 1) / 30.4375. For treatment ongoing patients, use cutoff date as the 'last date of exposure'; for patients discontinued from treatment, 'last date of exposure' is defined as the earliest date of cutoff date, death date, or last dose date + 7.

Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study drug is administered.

Total dose received per patient (mg): defined as the cumulative dose of the study drug during the treatment period of the study.

Actual dose intensity (mg/cycle): defined as the total dose received by a patient divided by the duration of exposure. For tislelizumab, it will be calculated as

$$\frac{\text{cumulative dose} * 28}{\text{date of last dose} + 28\ \text{days} - \text{date of first dose}}$$

For fruquintinib, it will be calculated as

$$\frac{\text{cumulative dose} * 28}{\text{date of last dose} + 8\ \text{day} - \text{date of first dose}}$$

Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity. Planned dose intensity is defined as the planned one cycle dose (mg). Planned dose intensity for tislelizumab and fruquintinib is 300mg/cycle and 5mg*21/cycle, respectively.

Number (%) of patients with dose delay.

Number (%) of patients with dose interruptions.

Number (%) of patients with dose modifications.

For tislelizumab, dose modifications include dose delay, administration interruption and infusion rate decrease.

Reasons for dose delay, interruptions and modification of tislelizumab.

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

6.6.2. Adverse Events

AEs will be graded by the investigators using CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA (Version for the study at the time of database lock) lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

6.6.2.1 Treatment Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an AE that had onset or increase in severity level date on or after the date of the first dose of study drug through 30 days after the last dose (any component of combination treatment whichever is last) or the initiation of new anti-cancer therapy, whichever is earlier. Treatment-related TEAEs include those events considered by the investigator to be related to study drug or with a missing assessment of the causal relationship. Summary tables will generally focus on TEAEs and treatment-related TEAEs. An AE overview table, including the number and percentage of patients with TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with Grade 3 or above, TEAEs that led to death, TEAEs that led to treatment discontinuation, TEAEs that led to dose modification, treatment-related TEAEs, treatment-related version of any of the above categories will be provided by tumor types. The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT. Summaries of the number (%) of patients with the below types of TEAE will be generated by tumor types:

- All TEAEs
    - TEAEs by SOC and PT (Any Grade and ≥Grade 3)
    - TEAEs by PT
    - Tislelizumab related TEAEs by SOC and PT (Any Grade and ≥Grade 3)
    - Fruquintinib related TEAEs by SOC and PT (Any Grade and ≥Grade 3)

  - Tislelizumab related TEAEs by PT
  - Fruquintinib related TEAEs by PT
- Serious TEAEs
  - Serious TEAEs by SOC and PT
  - Tislelizumab related serious TEAEs by SOC and PT
  - Fruquintinib related serious TEAEs by SOC and PT
  - Serious TEAEs by PT
- TEAEs leading to death
  - TEAEs leading to death by SOC and PT
  - Tislelizumab-related TEAEs leading to death by SOC and PT
  - Fruquintinib related TEAEs leading to death by SOC and PT
- TEAEs leading to treatment discontinuation by SOC and PT
  - TEAEs leading to discontinuation of tislelizumab by SOC and PT
  - TEAEs leading to discontinuation of fruquintinib by SOC and PT
- TEAEs leading to treatment modification by SOC and PT
  - TEAEs leading to dose modification of tislelizumab by SOC and PT
  - TEAEs leading to dose modification of fruquintinib by SOC and PT

In addition, Dose-Limiting Toxicity Treatment-Emergent Adverse Events will be summarized by tumor types in DLT Evaluable Analysis Set.

Patient data listings of all AEs, treatment-emergent or otherwise will be provided.

6.6.2.2 Immune- Mediated Adverse Event

Immune-mediated AEs (imAE) will be identified from all AEs that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug and up to 90 days from the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE.

An overall summary table and separate summaries of the following incidence of immune-mediated adverse events will be provided:

- imAEs by category and PT (Any Grade and ≥Grade 3)
- Summary of imAEs Treated with Systemic Corticosteroids by Category
- imAEs Outcome, Time to Onset, and Duration by Category

Patient data listings of imAEs will be provided.

6.6.2.3 Infusion-related Adverse Event

For infusion related reaction (IRR)s, a summary of incidence by SOC and PT (Any Grade and ≥Grade 3) will be provided.

6.6.2.4 Death

All deaths and causes of death will be summarized by tumor types, including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

Patient data listings of deaths will be provided.

6.6.3. Laboratory Values

Laboratory safety tests will be evaluated for selected parameters described in Table 3.

Laboratory parameters (e.g., hematology, chemistry, and coagulation) that are graded in NCI CTCAE Version 5.0 or higher will be summarized by shifts from baseline CTCAE grades to maximum post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately. The summary tables will report laboratory assessments up to 30 days of the last dose date.

Box-whisker plots will be generated for parameters of interest.

Laboratory parameters for potential Hy's Law for liver injury and abnormal thyroid function will also be summarized.

Table 3: Clinical Laboratory Assessment

Serum Chemistry	**Hematology**	**Coagulation** [a]	**Thyroid Function**
Alkaline phosphatase	Hemoglobin	Prothrombin time	TSH
Alanine aminotransferase	Platelet counts	Partial thromboplastin time or activated partial thromboplastin time	T3
Aspartate aminotransferase	White blood cell count	International normalized ratio	T4
Albumin	Lymphocyte count		
Total bilirubin	Neutrophil		

	count		
Direct bilirubin			
Potassium			
Sodium			
Total calcium [a]			
Creatinine			
Lactate dehydrogenase			
Total protein			
Creatine Kinase (CK) [b]			
CK-MB [b]			

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme;

[a] Total calcium values will be corrected for patients with hypoproteinemia.

[b] All patients will have creatine kinase and CK-MB testing at screening, and to be repeated at all scheduled visits during the first 2 treatment cycles, all predose assessments from Cycle 3 onwards, and at the End-of-Treatment/Safety Follow-up visit. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead.

6.6.4. Vital Signs

Patient data listings of vital signs will be provided.

6.6.5. Electrocardiograms (ECG)

The number and percentage of patients satisfying the following QTcF conditions at any time post-baseline will be summarized:

- > 450, > 480, or > 500 msec
- > 30 or > 60 msec maximum increase from baseline

6.6.6. Eastern Cooperative Oncology Group (ECOG) Performance Status

A shift table from baseline to worst post-baseline in ECOG performance status will be summarized. ECOG status will be summarized by visit.

6.7. Pharmacokinetic Analyses

The following analysis plan provides the framework for the summarization of the PK data from this study. The objective is to assess serum tislelizumab and plasma fruquintinib and its major metabolite M11 (also known as HM5025423) PK profile. The PK analysis will be performed on PK analysis set.

6.7.1. Pharmacokinetic Analysis of Fruquintinib

For fruquintinib and its major metabolite M11 (also called HM5025423), serial and sparse PK samples will be collected for part 1 and sparse samples will be collected for part 2.

- Part 1 serial PK: pre-dose, 1h, 2h, 4h, 6h, 8h post dosing on C1D1
- Part 1 sparse PK: pre-dose on C1D15, C2D1, C2D15, C4D1, C7D1, and C13D1
- Part 2 sparse PK: pre-dose and 4h post dosing of C1D1; pre-dose on C1D15, C2D1, C2D15, C4D1, C7D1, and C13D1

Pharmacokinetic Concentrations Analysis

The concentration and time data of fruquintinib and M11 will be listed individually and summarized using descriptive statistics for both serial and sparse PK samples. The PK analyst will appropriately flag and annotate treatment of any anomalous concentrations, exclusions and any special treatment for descriptive statistics and plots.

The following conventions will be used for reporting descriptive statistics for concentration data.

- PK concentrations should be reported in listings at the same level of precision as that in the source data.
- If a concentration at a given time point is below the assay quantification limit (BLQ), the concentration shall be reported as the term “BLQ” with the lower limit of quantitation (LLOQ) defined in the footnotes. BLQ values shall be treated as zero for computation of descriptive statistics. BLQ values will not be included for calculations of geometric mean and geometric coefficient of variation (CV%).
- If a concentration at a given time point is missing, it shall be reported as a missing value. Missing values may be defined in a bioanalytical source as “NS” (no sample), “NR” (no result), “IS” (insufficient sample), etc. If missing data are not identified in the bioanalytical source (i.e., the record is missing), the reporting convention of “NS" shall be utilized.
- If the calculated mean concentration is BLQ, the mean value shall be reported in outputs (such as tables) as BLQ and SD and geometric CV% shall be reported as ND (not determined). Minimum, median, and maximum may be reported.

Plots of Pharmacokinetic Plasma Concentrations

For patients with serial plasma samples, plasma concentration versus time data will be plotted individually (using actual time) and summarized (using plan time) graphically using arithmetic mean (±SD) plots by analyst, respectively. Each plot will be showed in linear (i.e., original) scale and semi-logarithmic scale of time. Arithmetic mean concentrations that are BLQ shall be set to zero for plotting on linear scale but not shown on log-linear scale.

PK Parameters Analysis

Actual dose and blood draw times will be used to calculate the PK parameters. Parameters will be listed individually and summarized using descriptive statistics. PK parameters will be estimated based on non-compartmental analysis methods and will be computed using Phoenix WinNonlin® Version 8.0. or higher. Calculation and presentation of PK parameters will be based on the Work Instruction: Best Practice Guidance: Non-Compartmental Pharmacokinetic Data Analysis for Clinical Studies. Version 1.0, Document Number VV-QDOC-13140.

The PK parameter estimates profile includes but is not limited to the following.

Parameter (Units)	Definition	Method of Determination
AUC_t (ng*h/mL)	Area under the concentration-time curve from time zero to time t (8 hour)	Calculated using the linear up/log down variant of the trapezoidal rule
AUC_{inf} (ng*h/mL)	Area under the concentration-time curve from time zero to infinite time with extrapolation of the terminal phase	Calculated using the linear up/log down variant of the trapezoidal rule
C_{max} (ng/mL)	Maximum observed concentration	Reported value
T_{max} (h)	Time of the maximum observed concentration	Actual elapsed time for observed C_{max}
T_{last} (h)	Time of the last quantifiable concentration	Actual elapsed time for observed the last quantifiable concentration
$t_{1/2}$ (h)	Apparent terminal elimination half-life	$\ln(2)/\lambda_z$, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
CL/F (L/h)	Apparent drug clearance	Calculated as Dose/(AUC_{inf}*F), where F is the fraction of dose absorbed
V_z/F (L)	Apparent volume	Calculated as CL/F/λ_z, where λ_z is the first-order rate constant of drug associated with the terminal portion of the curve
$\%AUC_{extrap}$ (%)	Percentage of AUC due to extrapolation from the last quantifiable concentration to infinity	Calculated as (AUC_{inf}-AUC_{last})/AUC_{inf}*100

The parameters C_{max}, T_{max} and T_{last} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, T_{max} will be assigned to the first occurrence of C_{max}.

The PK analyst will appropriately flag and annotate treatment of any anomalous PK parameters, exclusions and any special treatment for descriptive statistics. The following conventions will be used for reporting descriptive statistics for PK parameters data:

- All the PK parameters except T_{max}, T_{last} and $t_{1/2}$ should have at least the following summary statistics: sample size (n), mean, standard deviation (SD), coefficient of variance (CV%), median, minimum, maximum, geometric mean, geometric CV%.
- For in-text tables, geometric mean (geometric CV%) will be the default method of reporting PK parameters. T_{max} and T_{last} should be presented as median, range (minimum, maximum), when presenting the summary statistics.
- For any parameters that $n \leq 2$, SD should not be presented.
- The units for all PK parameters will be provided.
- It is recognized that the number of decimals in reported concentrations, for example: "9632.94401 ng/mL" or "9.963294401 ug/mL" are highly improbable and will be queried (since bioanalytical assays generally do not have this level of precision). Usually the first-in-human dose escalation trial will provide the numerical range of PK parameters e.g., AUC range from 10 to 10,000 ng.hr/mL and C_{max} range from 1 to 1000 ng/mL.
- In this scenario, for reporting PK parameters such as AUC and C_{max}, the following guidance is provided for rounding:

  - If the numerical value is below 100 then one decimal place may be used e.g., 0.1 or 99.9.

  - For values ranging from >100, whole numbers should be used e.g., 100 or 9999.

  - If > 10,000 the clinical pharmacologist may decide on changing units e.g., from ng/ml to µg /ml.

  - For reporting times e.g., for T_{max}, T_{last} or $t_{1/2}$, if <1 hour uses 2 decimals; time up to 24 hour should be reported to one decimal place e.g., 23.5 hour, time >24 hour should be rounded to nearest whole number e.g. 105 hr.

6.7.2. Pharmacokinetic Analysis of Tislelizumab

Blood samples will be collected for tislelizumab PK evaluation at predose (C_{trough}) and postdose (C_{max}); the serum concentration data will be tabulated and summarized using descriptive statistics by the visit/cycle at which these samples are collected.

6.8. Immunogenicity Analyses

In part 1 and part 2, ADA samples for tislelizumab should be collected on Day 1 (Predose of tislelizumab, -60 min) of Cycles 1, 2, 4, 7 and 13, and at the mandatory safety follow-up visit. All samples should be drawn at the same time as the PK blood collection for pre-dose of tislelizumab.

The scope of ADA calculations used for characterizing clinical immunogenicity depend on the incidence and kinetics of detected (ADA). Therefore, not all parameters described below may be derived or additional parameters may be added.

The immunogenicity results will be summarized using descriptive statistics by the number and percentage of subjects who develop detectable ADAs. The incidence of positive and neutralizing ADAs will be reported for ADA-evaluable subjects according to the following definitions:

- ADA-evaluable patient: Number of patients with reportable non-missing baseline result and at least one reportable sample taken after tislelizumab administration during the treatment or follow-up observation period with reportable result (used for computing treatment-induced ADA incidence). Baseline-positive ADA-evaluable patient is an ADA-evaluable patient with positive ADA result.
- Treatment-emergent ADA: The sum of both treatment-boosted and treatment-induced ADA-positive patients. Synonymous with "ADA Incidence".
- Treatment-induced ADA: ADA-evaluable patients that were ADA-negative at baseline and ADA-positive following administration of tislelizumab.
- Treatment-boosted ADA: Baseline-positive ADA-evaluable patient with significant increases (4-fold or higher) in ADA titer after tislelizumab administration.
- Persistent ADA response: Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer, or treatment induced ADA incidence in the last sampling time point.
- Transient ADA response: Treatment-induced ADA that is not considered as persistent ADA.
- Neutralizing ADA: patients with positive NAb.

The individual immunogenicity results will also be listed.

Additional ADA analyses (such as the effect of immunogenicity on PK, efficacy, and safety) may be conducted if deemed necessary and will be described in a separate analysis plan.

7. INTERIM ANALYSES

No interim analysis is planned.

8. CHANGES IN THE PLANNED ANALYSIS

Table 4 summarizes the major changes in the planned analyses from BGB-A317-fruquintinib-201 Protocol Amendment 1.0, dated on 16 December 2020. The changes are all made before database lock and not based on any comparative data.

Table 4: Statistical Analysis Plan Changes

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
1.0	This version	Protocol	To clarify the definition	Change the "death occurred before the first

		Amendment 1.0	of the evaluable analysis set.	postbaseline tumor assessment" from the definition of evaluable analysis set in the protocol into "early death (within 17 weeks of the first dose date)" in the SAP.
1.0	This version	Protocol Amendment 1.0	To align with BeiGene's current standard.	The definition of TEAE is different between protocol and SAP. In the protocol, "TEAE classification also applies to imAEs recorded up to 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy." In this SAP, "If an imAE occurs outside of the above-mentioned TEAE window, it will not be classified as a TEAE". The update of TEAE window streamlines the TEAE derivation so all TEAEs can be identified programmatically instead of relying on the manual medically review of imAE.

9. REFERENCES

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Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224-35.

APPENDIX 1. IMPUTATION OF MISSING OR PARTIALLY MISSING DATES

In general, missing or partial dates will not be imputed at the data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

1.1 Prior/concomitant medications/procedures

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.

1.2 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 > min(death date, end of study date), then set to min (death date, end of study 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 > min (death date, end of study date), then set to min (death date, end of study date)

1.3 Disease history and prior therapy (drug, surgery/procedure, radiotherapy)

For prior therapy, impute end date first.

If end date of a 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 start date of a 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 > end date, then set to end date

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 date of a disease history 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 date > first dose date, then set to first dose date – 1

If diagnosis date of metastatic disease/locally advanced 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 date > first dose date, then set to first dose date – 1
- If the imputed date < (imputed) date of initial diagnosis date, then set to initial diagnosis

date.

If the date of response to 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 date > first dose date, then set to first dose date – 1

If the imputed date < the start date of prior therapy, then set to the start date of prior therapy +1.

1.4 Subsequent anti-cancer therapy

If start date of subsequent anti-cancer 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 start date > min (death date, study discontinuation date, data cutoff date, start date of the next subsequent anti-cancer therapy), then set to min (death date, study discontinuation date, data cutoff date, start date of the next subsequent therapy)

If stop 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 stop date > min (death date, study discontinuation date, data cutoff date, start date of the next subsequent anti-cancer therapy), then set to min (death date, study discontinuation date, data cutoff date, start date of the next subsequent therapy)

The (imputed) stop date must be after or equal to the (imputed) start date

If year of the start date/stop date is missing, do not impute.

Note: if the imputed subsequent anti-cancer therapy date collected from CRF “post-treatment discontinuation anti-cancer systemic therapy” or “post-treatment discontinuation anti-cancer procedure” page is before the last dosing date, send data query.

1.5 Fruquintinib administration date and actual dose

If end dose date of fruquintinib for certain cycle is missing, set to start dose date of this cycle.

If actual dose is ‘other’, but other dose is not specified, set actual dose as 0.

APPENDIX 2. RULES FOR IDENTIFYING MISSING TUMOR ASSESSMENTS

Identifying two missing tumor assessments

1) Input scheduled TA visit list
    a. (8wk-16wk-24wk-32wk-40wk-48wk-58wk) for this study with TA as every 8 weeks for the first 56 weeks, then every 12 weeks thereafter
2) Identify last evaluable TA before PD or death (--LPTADT) and map it to the closest scheduled visit (--LPTADT_WK).
    a. In the event of unscheduled TA, choose the closest scheduled visit number (e.g., 8wk) as –LPTADT_WK. It can be achieved programmatically by following the classification rule (e.g., defining thresholds) depicted in Table 5 below. (The team can consider mapping all tumor visits if the scheduled visits are uncleaned or questionable)
    b. Otherwise, assign the scheduled visit number (assuming it is coded correctly) to --LPTADT_WK
3) Find the 2nd TA visit after LPTADT_WK according to the list in step 1 (-LPTADT_WK_2)
    a. If LPTADT_WK_2+1wk (assuming 1 week TA window) < earliest of PD/death date, then censor PFS at the –LPTADT
    b. Otherwise, PFS event at the earliest of PD/death date

Table 5 shows how to assign unscheduled TA to a schedule visit. The threshold column is defined as the mid-point between current and next visit (except for baseline); it is the upper limit for LPTADT to be mapped to the prior scheduled assessment (step 2a above). For example, if LPTADT is Week 44 for an unscheduled visit, it will be mapped to Week 40 TA since it is within the threshold for Week 40. Assuming it is SD and the subsequent TA of the patient is PD after Week 57, PFS will be censored at LPTADT (Week 40); had the PD occurred prior to Week 57, it would be counted as an PFS event.

Table 5: Example of scheduled tumor assessments with time window

Weeks	Scheduled week -1	Scheduled week	Scheduled week+1	Threshold
Baseline		Baseline		
Every 8 weeks for the first 56 weeks	Week 7	Week 8	Week 9	Week 12
	Week 15	Week 16	Week 17	Week 20
	Week 23	Week 24	Week 25	Week 28
	Week 31	Week 32	Week 33	Week 36
	Week 39	Week 40	Week 41	Week 44
	Week 47	Week 48	Week 49	Week 52
	Week 55	Week 56	Week 57	Week 62
Every 12 weeks	Week 67	**Week 68**	Week 69	Week 74
	Week 79	Week 80	Week 81	Week 86

thereafter	Week 91	Week 92	Week 93	…
	…	…	…	…