Document Type:	Statistical Analysis Plan
Official Title:	An international, multicenter, Phase 1b/2 study of rogaratinib (BAY1163877) in combination with atezolizumab as first-line treatment in cisplatin-ineligible patients with FGFR-positive locally advanced or metastatic urothelial carcinoma
NCT Number:	NCT03473756
Document Date:	05 APR 2022

Title page

An international, multicenter, Phase 1b/2 study of rogaratinib (BAY 1163877) in combination with atezolizumab as first-line treatment in cisplatin-ineligible patients with FGFR-positive locally advanced or metastatic urothelial carcinoma

Phase 1b/2 study of rogaratinib (BAY 1163877) in combination with atezolizumab in urothelial carcinoma

Bayer study drug	BAY 1163877 / rogaratinib / pan FGFR inhibitor		
Study purpose:	Dose finding		
Clinical study phase:	Ib	**Date:**	05 APR 2022
Study No.:	19131 – Part A	**Version:**	4.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

A	Asian
AE	Adverse event
AJCC	American Joint Committee on Cancer
B	Black
b.i.d./BID	*bis in die* (twice daily)
BL	Baseline
C_{max}	Maximum observed drug concentration in measured matrix after single dose
CI	Confidence interval
CR	Complete response
CV	Coefficient of variation
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of repsonse
e.g.	*exempli gratia* (for example)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Efficacy analysis set
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
F	Female
FGFR	Fibroblast growth factor receptor
i.e.	*id est* (that is)
ICF	Informed consent form
iCPD	Confirmed progressive disease according to iRECIST
iRECIST	Response Evaluation Criteria in Solid Tumors Modified for Immune-based Therapeutics
iUPD	Unconfirmed progressive disease according to iRECIST
KM	Kaplan Meier
LLOQ	Lower limit of quantification
M	Male
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
NA	Not applicable
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NE	Not evaluable
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
PD	Progressive disease
PD-1	Programmed death protein 1
PD-L1	Programmed death-ligand 1
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic analysis set
PR	Partial response

PRO	Subject-reported outcomes
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Stable disease
TA	Tumor assessment
TCGA	The Cancer Genome Atlas
TEAE	Treatment-emergent adverse event
TEADR	Treatment-emergent drug-related adverse events
TNM	Classification of Malignant Tumors (T = tumor, N = lymph node, M = metastasis)
t_{last}	Time of last plasma concentration above LLOQ
t_{max}	Time to reach C_{max} (in case of two identical C_{max} values, the first t_{max} will be used)
UPM	Unit probability mass
W	White
WHO-DD	World Health Organization – Drug Dictionary

1. Introduction

This Statistical Analysis Plan (SAP) is based on the Clinical Study Protocol No. BAY 1163877 / 19131, Version 4.0, dated 04 OCT 2021 [1].

The study 19131 is planned to evaluate the safety, tolerability, pharmacokinetics (PK) and efficacy of oral twice daily rogaratinib in combination with atezolizumab in subjects with fibroblast growth factor receptor (FGFR)-positive locally advanced or metastatic urothelial carcinoma who are cisplatin-ineligible and have had no prior systemic treatment for locally advanced or metastatic disease.

Urothelial cancer is a highly immunogenic tumor, in large part as a result of the relatively high level of mutations, which represents at least one of the mechanisms for the generation of tumor neo-antigens for the host immune system to recognize. Programmed death-ligand 1 (PD-L1) overexpression in the tumor microenvironment and its binding to programmed death protein 1 (PD-1) on tumor antigen-specific T cells is a mechanism for immune escape in urothelial cancer.

Dysregulation of FGFRs has been identified in bladder cancer as compared with normal bladder. Increased expression was associated with mutation, 85% of mutant tumors showed high level expression, overall 42% of tumors with no detectable mutation showed over-expression including many muscle invasive. This may represent a non-mutant subset of tumors in which FGFR3 signaling contributes to the transformed phenotype and which may benefit from FGFR-targeted therapy.

It was shown that FGFR3 expression is associated with a non-T-cell-inflamed phenotype in tumor tissue of subjects with urothelial bladder cancer. Expression analysis of PD-L1 in archival biopsy samples collected in study 16443, showed that PD-L1 level is lower in subjects with FGFR mRNA overexpression. A similar correlation was detected in subjects with non-small-cell lung carcinoma using publically available TCGA data sets. It is assumed that a causal relationship between FGFR expression and T-cell exclusion leads to the observed findings and to a poorer response to inhibition of the PD-L1 axis by recently approved checkpoint inhibitors. Potentially, inhibition of FGFR can overcome this interaction and render tumors targetable by the immune system.

Atezolizumab is a PD-L1 antibody that demonstrated durable responses in urothelial bladder cancer as first-line and second-line treatment for subjects with locally advanced or metastatic urothelial carcinoma. It is assumed that subjects with FGFR overexpression exhibit a poorer response to atezolizumab treatment based on the non-T-cell-inflamed phenotype. Therefore it is suggested, that a combination of rogaratinib and atezolizumab can overcome this immune evasion improving immune-checkpoint inhibitor efficacy and disease response.

2. Study Objectives

Study 19131 originally comprised two separate parts: Phase 1b (Part A) and Phase 2 (Part B). The study parts differ in design, objectives, and treatment. Part B of the study will no longer be conducted.

The primary objectives of this Part A of the study are:

- To determine the safety and tolerability of rogaratinib in combination with atezolizumab in subjects with FGFR-positive locally advanced or metastatic urothelial carcinoma.
- To determine the recommended Phase 2 dose (RP2D) of rogaratinib in combination with atezolizumab in this subject population.

The secondary objectives of this Part A of the study are:

- To assess the efficacy of the combination of rogaratinib and atezolizumab in this subject population.
- To characterize the PK of rogaratinib in combination with atezolizumab in this subject population.

The exploratory objectives of this Part A of the study are:

- To assess new potential predictive or prognostic biomarkers and their association with tumor-related biomarkers, disease response, drug-resistance and subject outcome.
- To evaluate further biomarkers to investigate the drug (i.e. mode-of-action-related effect and / or safety) and / or the pathomechanism of the disease.
- To evaluate the combination of rogaratinib and atezolizumab with regard to subject-reported outcomes (PRO).

3. Study Design

This study 19131 Part A is an open-label, single-arm, international, multicenter, Phase 1b study of rogaratinib in combination with atezolizumab in subjects with FGFR-positive locally advanced or metastatic urothelial carcinoma.

The primary objectives of this Phase 1b study (Part A) are to determine the safety, tolerability, RP2D and PK of rogaratinib in combination with atezolizumab in these subjects. For all study objectives, see Section 2.

Before entering the screening, subjects are to be tested for FGFR1 and 3 mRNA expression levels. Only subjects with FGFR-positive tumors (RNA scope score of +3 or +4) can enter the study.

The study will comprise the following periods:

- Pre-treatment period, including FGFR testing and screening,

- Treatment period, and
- Follow-up period, including active follow-up and long-term follow-up.

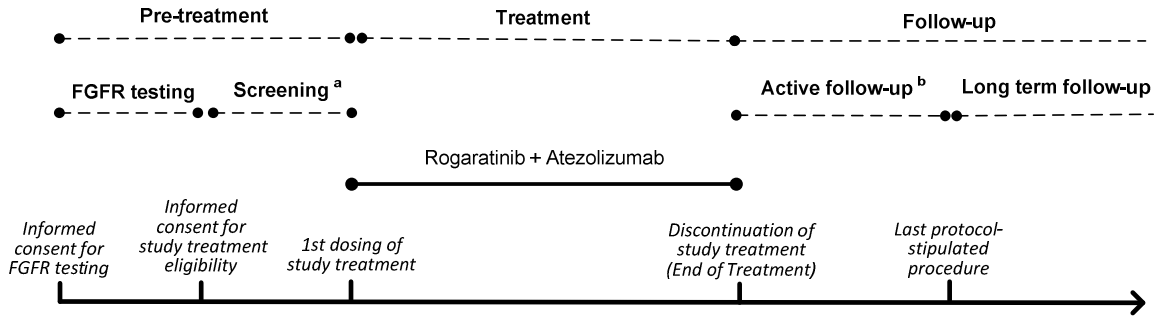
An overview of the study design is presented in Figure 3-1.

The study is conducted in subjects who are cisplatin-ineligible and have had no prior systemic treatment for locally advanced or metastatic disease.

Treatment is divided into cycles. A cycle consists of 21 days of BAY 1163877 twice daily.

Subjects will receive rogaratinib plus atezolizumab combination treatment.

Figure 3-1: Study 19131 Part A – Design overview



FGFR = Fibroblast growth factor receptor
a: Only FGFR positive subjects can enter screening.
b: Safety information is collected for all discontinued subjects for at least 30 (up to +7) days after the last administration of study treatment, and both safety and efficacy information is collected for subjects who discontinue study treatment without radiological disease progression.

Dose selection

The dose selection part of the study 19131 will assess the safety and tolerability of the combination. The maximum tolerated dose (MTD) will be determined by using stepwise dose selection design based on a modified toxicity probability interval (mTPI) method. Dose selection will stop after 20 valid subjects are available, and are evaluable for the MTD assessment. At the end of the DLT observation period of 20 subjects, the recommendations from the mTPI method will be regarded as guidance and will be integrated with the clinical assessments of the available PK and safety data to determine the MTD. A total of approximately 26-30 evaluable subjects will be enrolled to obtain additional safety data for confirming the MTD and to determine the RP2D that will be used in the Part B of the study.

The mTPI provides a practical dose-finding scheme guided by the posterior inference for a simple Bayesian model. The MTD is defined as the highest dose level that could be given so that the toxicity probability is closest to 30%. The starting dose of rogaratinib will be 800 mg b.i.d. Initially, at least 4 (4-6) subjects will be enrolled. The next group of subjects will be enrolled once the decision regarding the next dose level is made based on all available PK and safety data and the occurrence of DLTs. The decision about time of enrollment and the number of subjects evaluable for DLTs on a dose level will be made by the sponsor in consultation with investigators during regularly held safety calls. For details on what constitute DLTs, please refer to Section 7.4.3.1 of the protocol.

Safety will be regularly assessed during each cycle for potential adverse events, DLTs and disease-related signs and symptoms. Rogaratinib dosing will be interrupted/delayed or reduced in case of clinically significant toxicities. Atezolizumab dosing will not be adjusted,

however dosing will be interrupted or delayed in case of clinically significant toxicities. For more detailed information on dose modifications see Section 7.4.3 of the protocol.

The mTPI method will recommend de-escalation, re-escalation or expansion of the current dose level on basis of the observed DLTs. The first dose finding action on a dose level will be performed after at least 4 subjects are available on that dose level and are evaluable for DLTs. The possible dose finding actions are 'E'=escalate to next higher dose level (800 mg b.i.d. being the highest possible dose), 'S'=stay at the current dose level, 'D'=de-escalate to next lower dose level and 'DU'= de-escalate to next lower dose level and exclude the current and higher dose levels from the further dose escalation due to unacceptably high toxicity. If the probability that a dose is above the MTD is greater than 95%, the dose will be declared as toxic and only lower doses will be given in subsequent cohorts. If the highest dose is reached, escalation ('E') leads to staying at that dose. At the lowest dose level de-escalation ('D') or de-escalation with unacceptable high toxicity ('DU') lead to stop of the study. Details are provided in Section 6.4.1.

Intra-subject dose escalation is not permitted. Part B will start once safety and efficacy data are found to support study continuation.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

All variables will be analyzed by descriptive statistical methods. The number of data available and mean, standard deviation, minimum, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

Due to the exploratory character of this Part A of the study, no confirmatory analysis will be performed. All calculated p-values and confidence intervals are to be interpreted in the exploratory sense.

Data displays will follow the standard table catalogs for oncology standards, global standards, and clinical pharmacology standards, respectively.

All summaries will be performed by dose group. The dose groups "Rogaratinib XX mg BID+ Atezolizumab" will be analyzed, in which "XXmg" stands for the assigned dose. Pooled summary statistics (or frequency counts) will be provided where appropriate. Listings will also be provided by dose group.

4.2 Handling of Dropouts

Pre-screening failure = Subject signed ICF for FGFR testing but, for any reason, did not sign the ICF for study treatment eligibility.

Screening failure = Subject signed ICF for study treatment eligibility but, for any reason (e.g. failure to satisfy the selection criteria), terminated the study before start of study treatment.

Dropout = Subject discontinued study participation prematurely for any reason after start of study treatment. The start of the treatment period is defined by the first administration of study treatment.

Replacement of subjects may occur in Part A in order to ensure the necessary number of evaluable subjects for dose selection (at least 4 subjects per tested dose level, a total of 20 evaluable subjects) and to ensure at least 26 valid subjects for assessment of the RP2D. Subjects maybe replaced in the following circumstances:

Dose selection:

- Subjects who discontinue or took less than 80% of the per protocol required total dose of either study drug (rogaratinib or atezolizumab) during the first cycle due to any reason other than a DLT (*note*: protocol-defined dose reductions will not be considered incompliant).

Efficacy:

- Subjects who took less than 80% of the per protocol required total dose of either study drug (rogaratinib or atezolizumab) during the first two cycles or subjects without an efficacy assessment.

4.3 Handling of Missing Data

Missing data will not be replaced. Analyses will be performed considering all data observed for the respective analysis sets.

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form.

4.4 Interim Analyses and Data Monitoring

Safety data will be reviewed on an ongoing basis during this study. Additional analysis, as Bayesian dose-response and / or PK / PD modeling of DLTs rates and CTCAE version 4.03 gradings may be performed on selected groups of subjects in order to generate additional relevant information for the adaptive dose selection decisions. The sponsor together with all investigators will review all available data and make the final decision as to dose escalation, de-escalation or group expansion during the adaptive dose selection part. This group of sponsor and investigators will also determine when to implement predefined stopping rules.

No formal interim analysis of the data collected during Part A is planned.

4.5 Data Rules

4.5.1 Baseline

The baseline values will be the latest valid pre-administration available value.

4.5.2 Repeated Measurements

If control measurements for a planned timepoint before study drug administration are available, the last value (i.e. of the measurement closest to the study drug administration) will be used for the calculation of descriptive statistics. If control measurements for a planned time point after study drug administration are available, the first value (i.e. of the planned measurement) will be used for the calculation of descriptive statistics.

4.5.3 Laboratory Values Outside the Calibration Range

Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit. In tables showing

mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked. Differences (e.g. changes from baseline) will only be calculated if at least one measurement is not substituted.

4.6 Blind Review

This phase 1 study is performed in a non-blinded design because this is considered adequate to meet the study objectives.

The results of the validity review meeting will be documented in the Validity Review Report and may comprise decisions and details relevant for statistical evaluation. Any changes to the statistical analysis prompted by the results of the validity review meeting will be documented in an amendment and, if applicable, in a supplement to this SAP or will be documented in the clinical study report.

5. Analysis Sets

5.1 Assignment of analysis sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see section 4.6).

All subjects who signed the informed consent form (ICF) for FGFR testing will be included in the 'All enrolled subjects' evaluations. All subjects assigned to treatment will be included in the 'All subjects assigned to treatment' evaluations.

Safety analysis set (SAF)

All subjects who received at least one dose of study drug (i.e. rogaratinib or atezolizumab) and have post-treatment safety data available will be included in the safety evaluation.

MTD analysis set (MTD)

All subjects who completed Cycle 1 and who took at least 80% of the required total dose (protocol-defined dose reductions will not be considered incompliant) of either study drug (rogaratinib or atezolizumab) during Cycle 1 or discontinued during Cycle 1 due to a DLT will be included in the MTD evaluation.

Only subjects from the dose selection part are to be considered for the MTD analysis set.

Efficacy analysis set (EFS)

All subjects who have received at least one dose of study drug and who have post-baseline efficacy data available will be included in the efficacy evaluation.

Pharmacokinetics analysis set (PKS)

All subjects who have received at least one dose of study drug and with at least one valid concentration after first dosing and no important protocol deviations affecting the validity will be included in the PK evaluation.

6. Statistical Methodology

6.1 Population characteristics

Analysis for population characteristics will be performed on the SAF, unless otherwise specified.

6.1.1 Subjects Validity and Disposition

The number of subjects enrolled and included in each analysis set will be tabulated by region, country and center. The number of countries and study centers will be presented. A summary table will also be presented for the number of subjects enrolled and the number and percentage of subjects in each of the defined analysis sets. The reasons for subjects excluded from each of the analysis sets will also be tabulated. In addition, the number of subjects who were enrolled, treated and discontinued will be summarized. Reasons for discontinuation of study treatment will be tabulated. Important deviations will be summarized using frequency tables. These analyses will be performed on appropriate analysis sets like 'All subjects assigned to treatment' or 'All enrolled subjects'.

6.1.2 Demographics and Other Baseline Characteristics

Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) and frequency counts (for qualitative data) will be provided for demographics.

Demographics variables include sex, race, ethnicity, region, age in years (as reported in the CRF), weight, height and body mass index (BMI). If the PKS, MTD analysis set or EFS differ from the SAF, summary statistics and frequency tables for PKS and/or MTD analysis set and/or EFS will be provided as well.

Medical history findings will be summarized using MedDRA (Medical Dictionary for Regulatory Activities) terms (version 20.0 or later).

Cancer baseline characteristics will also be summarized. Variables include for example baseline Eastern Cooperative Oncology Group (ECOG) Performance Status, number of target lesions, number of non-target lesions, cancer type, histology, grade at initial diagnosis, stage at study entry, time since initial diagnosis. Please note that the list of the above mentioned parameters may not be exhaustive.

In addition, demographics (sex, race, ethnicity and age) and cancer baseline characteristics will be summarized for all subjects who signed the ICF for FGFR testing ("all enrolled subjects").

6.1.3 Prior and Concurrent Medication/Therapy

Prior anti-cancer therapy and surgical therapeutic procedures will be summarized. The counts and percentages of subjects who were previously treated using radiotherapy, local anti-cancer therapy, systemic anti-cancer therapy, and who had any diagnostic and therapeutic procedure(s) will be presented. The number of subjects with radiotherapy and systemic or local anti-cancer therapy will be presented by intent of procedure and number of regimens/procedures. In addition, concurrent radiotherapy, diagnostic and therapeutic procedures will be summarized. Systemic anticancer therapy and type of systemic anticancer therapy during follow-up will be summarized. Immunotherapy during follow-up will be listed. Prior and concomitant medications will be coded to generic terms using the World Health Organization Drug Dictionary (WHO-DD) version 2005/Q3 or later and will be

provided in two tables, one for 'Prior medication' (i.e. medications that are ongoing at, or began before the start of study drug) and one for 'Concomitant medication' (i.e. medications that are ongoing at, or began after the start of study drug). The version used in analyses will be presented in the clinical study report.

6.1.4 Medical and Surgical History

Medical history findings will be summarized by primary system organ class, high level term and preferred term of MedDRA version 20.0 or later. The version used in analyses will be presented in the clinical study report.

6.2 Efficacy

Efficacy analyses will be performed on the EFS, unless otherwise specified.

All efficacy variables evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 are linked to the secondary and exploratory objectives of the study Part A. All variables evaluated using the Response Evaluation Criteria in Solid Tumors Modified for Immune-based Therapeutics (iRECIST) version 1.1 are exploratory only.

Efficacy data will be summarized using descriptive statistics and will be graphically displayed if appropriate. The correlation between pharmacodynamic parameters and selected safety, efficacy, or PK parameters may be graphically displayed. Further statistical analyses may be conducted.

Response as defined by RECIST version 1.1: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). Response and progression will be evaluated in this trial using the new international criteria proposed by the RECIST committee for solid tumor.

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

Best overall tumor response according to RECIST criteria will be summarized using frequency counts. Best % change in Target Lesion sum of diameter from baseline will be displayed graphically for all subjects from worst to best in a waterfall plot.

6.2.1 Primary Efficacy Variable

Not applicable.

6.2.2 Secondary Efficacy Variable

The efficacy variable linked to the secondary objective of this study is the objective response rate.

Objective response rate (ORR) is defined as the percentage of subjects whose best response is either a CR or PR. Subjects for whom best tumor response is not CR or PR, as well as subjects without any efficacy assessment will be considered non-responders. According to RECIST version 1.1, confirmation of PR and CR is not required considering the nature of the study and the protocol requirements.

6.2.3 Exploratory Efficacy Variables

Exploratory efficacy variables defined according to RECIST version 1.1 will include disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) (according to both RECIST and iRECIST), time to progression (TTP), time to response (TTR), overall survival (OS) and follow-up time.

These variables are defined as below:

Follow-up time is defined as the time from the date of first study treatment until death or the date of last contact, if the subject is still alive at the time of analysis.

Disease control rate (DCR) is defined as the percentage of subjects whose overall best response was not progressive disease (i.e. CR, PR, SD or Non CR/Non PD). Tumor assessments with SD as response, that is performed prematurely after assignment to treatment of the subject (i.e. substantially earlier than the first planned radiological tumor assessment at 9 weeks), will not be taken into account.

Duration of response (DOR) (for PR and CR) is defined as the time (days) from the first documented objective response of PR or CR, whichever is noted earlier, to disease progression or death (if death occurs before progression is documented). DOR will be defined for responders only, i.e. subjects with a CR or PR. The actual dates the tumor scans were performed will be used for this calculation. DOR for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment.

Kaplan-Meier (KM) product-limit estimates for median, 25th and 75th percentile with its 95% CI together with total number of subjects, total censored and total events will be provided for DOR per dose group. In addition KM survival curves will be presented for each dose group.

Progression-free survival (PFS) is defined as the time (days) from start of study treatment to date of first observed disease progression (investigator's radiological or clinical assessment) or death due to any cause, if death occurs before progression is documented. The actual date that the tumor scan was performed will be used for this calculation. If a tumor assessment is performed over more than one day (e.g. scans for chest and abdomen done on different days for the same evaluation), the earliest date will be used for the calculation of PFS. For subjects without documented radiological or clinical progression or death at the time of analysis, PFS will be censored at the last actual visit date of tumor evaluation.

Kaplan-Meier (KM) product-limit estimates for median, 25th and 75th percentile with its 95% CI together with total number of subjects, total censored and total events will be provided for PFS per dose group. In addition KM survival curves will be presented for each dose group.

Overall survival (OS) is defined as the time (days) from start of study treatment to death due to any cause. Subjects alive at the date of data cut-off for analysis will be censored at the last date known to be alive. If a subject is lost to follow-up before any assessment after assignment to treatment, this subject will be censored at day 1.

KM product-limit estimates for median, 25th and 75th percentile with its 95% CI together with total number of subjects, total censored and total events will be provided for OS per dose group. In addition KM survival curves will be presented for each dose group.

Time to progression (TTP) is defined as the time (days) from start of study treatment to date of first observed disease progression (radiological or clinical). TTP for subjects without disease progression at the time of analysis will be censored at the last date of tumor evaluation. TTP for subjects who have no tumor assessments after baseline will be censored at day 1.

KM product-limit estimates for median, 25th and 75th percentile with its 95% CI together with total number of subjects, total censored and total events will be provided for TTP. In addition KM survival curves will be presented for each dose group.

Time to Response (TTR) is defined as the time (days) from start of study treatment to the date of first observed partial or complete response. Only subjects with a partial or complete response are considered for TTR.

KM product-limit estimates for median, 25th and 75th percentile with its 95% CI together with total number of subjects, total censored and total events will be provided for TTR. In addition KM survival curves will be presented for each dose group.

6.2.4 Health-Related Quality of Life

Subjects' health-related quality of life and health utility values will be measured using the EORTC QLQ-C30. A PRO information sheet will be provided and completed by the study nurse/investigator at each visit in which the protocol requires the questionnaires to be administered, whether or not the questionnaire was completed by the subject, in order to document information on questionnaire assessment such as questionnaire completion, date of completion, if assistance was needed, and reasons for non-completed questionnaires.

The EORTC QLQ-C30 includes 5 functional scales (physical, role, emotional, social, and cognitive functioning), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status scale, and a number of single items assessing additional symptoms (dyspnea, sleep disturbances, constipation, and diarrhea), and perceived financial impact.

For the majority of the EORTC QLQ-C30 items a 4-point Likert-type response scale is used. The only exception is the global health status/quality of life scale in which a 7-point Likert-type scale is used. For ease of interpretation, all scales and individual item responses are linearly converted to a 0 to 100 scale. For the functional and global quality of life scales a higher score represents better level of functioning. However in regard to symptom scales and single items a higher score reflects a greater degree of symptomatology. Summary statistics and changes from baseline by visit will be provided for EORTC QLQ-C30 for day 1 of each cycle, end of treatment visit and active follow-up based on the efficacy analysis set.

6.3 Pharmacokinetics/ Pharmacodynamics

6.3.1 Biomarker/ Pharmacodynamics

Retrospective exploratory biomarker/ pharmacodynamic data may be summarized using descriptive statistics and may be graphically displayed if appropriate. All pharmacodynamics analysis may be performed on the SAF population. The correlation between biomarker or pharmacodynamic parameters and selected safety, efficacy, or PK parameters may be

evaluated and graphically displayed. Further exploratory statistical analyses may be conducted. Biomarker data and analyses may be reported separately.

6.3.2 Pharmacokinetics

Analyses will be performed on the PKS.

The concentration-time courses of rogaratinib in Cycle 1 will be tabulated. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and CV, minimum, median, maximum value and the number of measurements. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked.

Individual and geometric mean concentration vs. time curves of all analytes (using the actual sampling times for individual plots and the planned sampling times for mean plots) will be plotted using both linear and semilogarithmic scale.

PK characteristics (t_{max} , t_{last} , R_{start}, R_{end}, points terminal and %AUC [t_{last}-∞] excluded) will be summarized by the statistics mentioned above. t_{max} and t_{last} will be described utilizing minimum, maximum and median as well as frequency counts.

Concentration data from cycle 2 to 5 of rogaratinib and all concentration data of Atezolizumab will only be listed.

6.4 Safety

Analyses will be performed on the SAF, unless otherwise specified.

Duration of treatment will be summarized using summary statistics. Actual dose, total amount of dose, and percent of planned dose during study period will be also summarized. Dose modification will be summarized.

6.4.1 Determination of MTD

The objective of the dose selection phase is to determine the MTD or confirm that the start dose level of rogaratinib (800 mg b.i.d.) is safe. The MTD is defined as the highest dose that can be given so that toxicity probability is closest to the target toxicity P_T=30%. Estimation of the MTD will be based on the estimation of the observed dose dependent incidence rate of DLT in the first 21 days of dosing.

The modified toxicity probability interval (mTPI) design will be applied to guide the dose selection decisions in the study. The equivalence interval of the toxicity probability for the MTD is set to [25%, 35%], in which any dose with a toxicity probability falling into this interval is considered as an estimate close to the true MTD. The dose selection part will be finished after 20 subjects are evaluable for the MTD assessment. A beta-binomial Bayesian model with Beta(1,1) prior will be used to compute the posterior probabilities that the true rate of DLT is contained in each of the 3 toxicity intervals:

- [0, 25%] under-dosing (below the MTD)
- [25%, 35%] target dosing (close to the MTD)
- [35%, 100%] over-dosing (above the MTD)

The mTPI method calculates the unit probability mass (UPM) for above intervals with safety rules to stop due to excessive toxicity. In addition doses that are estimated to have excessive toxicity will be excluded from the trial.

The UPM for a given interval is defined as the probability of the interval divided by the length of the interval. Then an appropriate dose-finding action will be chosen based on the interval with the largest UPM. Specifically, if the UPM for the under-dosing interval is the largest, the dose is considered lower than the MTD and the recommendation is to escalate to the next higher dose (800 mg b.i.d. being the highest possible dose) or to stay on the dose level if current dose is the highest possible dose (letter **E** in Table 6-1); if the target dosing interval has the largest UPM, the mTPI design will recommend remaining at the current dose (letter **S** in Table 6-1); if the over-dosing interval has the largest UPM, the design will recommend de-escalating to the previous lower dose (letter **D** in Table 6-1). If the safety stopping rule is met, the toxicity of the current dose will be considered as unacceptable high and never be used again in the remainder of the trial (letters **DU** in Table 6-1). The safety rule is triggered if the posterior probability that the current dose is above the MTD is greater than 95%. All of these rules are summarized and precalculated in Table 6-1 below. No decision is made before data of at least 4 subjects are available on the first dose level and are evaluable for DLTs. The sponsor in consultation with the investigators will decide how many additional subjects need to be evaluable for DLTs on the same dose level before the next decision.

The decision on the number of additional subjects and on the next dose level will be based on the recommendations from the mTPI, clinical assessment, all available PK and safety data.

The dose selection part will be finished after 20 subjects are evaluable for DLT assessment and are available for the MTD determination. The RP2D will be defined once sufficient data is available. The final decision about the RP2D will be made by the sponsor in consultation with the investigators.

Table 6-1: Possible dose finding actions

Number of subjects with observed DLTs	Number of subjects treated at current dose																
	4	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E
3	DU	D	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E
4	DU	DU	DU	D	D	S	S	S	S	S	S	S	S	S	S	S	S
5		DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S	S	S
6			DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S	S	S
7				DU	DU	DU	DU	DU	DU	DU	D	S	S	S	S	S	S
8					DU	DU	DU	DU	DU	DU	DU	DU	DU	D	S	S	S
9						DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	S
10							DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
11								DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
12									DU	DU	DU	DU	DU	DU	DU	DU	DU
13										DU	DU	DU	DU	DU	DU	DU	DU
14											DU	DU	DU	DU	DU	DU	DU
15												DU	DU	DU	DU	DU	DU
16													DU	DU	DU	DU	DU
17														DU	DU	DU	DU
18															DU	DU	DU
19																DU	DU
20																	DU

The column represents the number of subjects treated at a given dose level in the trial. Each row represents the number of subjects treated at the dose level and who have experienced dose-limiting toxicity (DLT) events. The letters in each cell provides the dose-assignment decision based on the data readout from the row and column numbers.

E: Escalate to the next higher dose (or stay if current dose is the highest possible dose)
S: Stay at the same dose
D: De-escalate to the previous lower dose (or stop if current dose is lowest possible dose)
DU: De-escalate to the previous lower dose and the current dose will never be used again.

6.4.2 Adverse Events (AEs)

Individual listings of AEs will be provided. AEs will be reported using MedDRA terms (version 20.0 or later) and graded according to NCI CTCAE version 4.03.

AEs will be considered to be treatment-emergent if they have started or worsened after first administration of study drug up to 30 days after the last dose of rogaratinib or 90 days after the last atezolizumab administration, whichever comes later.

The incidence of treatment-emergent adverse events (TEAEs), drug-related adverse events (TEADRs), treatment-emergent and drug-related serious adverse events (SAEs), respectively, will be summarized by MedDRA system organ class and worst NCI-CTCAE grade. TEAEs, SAEs, TEADRs, and drug-related SAEs for events of Grade 3/4/5 will be summarized similarly.

Subject listings of all AEs, SAEs, AESI, TEAEs leading to dose reduction, TEAEs leading to dose interruption, TEAEs leading to discontinuation, AEs leading to DLTs and deaths will be presented. For death, two listings ("during treatment and within 30 days post permanent treatment discontinuation" and "after 30 days post permanent treatment discontinuation") will be provided.

6.4.3 Clinical Laboratory Data

The incidence of laboratory data outside the reference range (low, high) will be summarized in frequency tables. The incidence of hematological and biochemical laboratory values will be summarized by worst NCI CTCAE version 4.03 grade. Frequency tables will be provided for the changes of worst NCI CTCAE version 4.03 grade after start of treatment versus baseline and under treatment Descriptive statistics (number of observations, mean, standard deviation, minimum, median and maximum values) will be presented for clinical laboratory tests (hematology, general chemistry and coagulation), their changes from baseline (including baseline value). Mean and standard deviation will be graphically displayed as well.. The number of subjects with urinalysis results will be tabulated by visit. Subjects will also be presented subdivided into classes according to their calcium phosphate product lower than 70 mg^2/dL^2 and equal to or higher than 70 mg^2/dL^2.

6.4.4 COVID-19 additional analysis

Due to the global pandemic, listings of all COVID-19 related important PDs, COVID-19 related study disruptions and subjects with COVID-19 related AEs will be provided.

6.4.5 Other Safety Data

Quantitative data (such as vital signs, electrocardiogram) will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data, such as ECG findings and interpretation.

The average of triplicate quantitative ECG parameters at all ECG time points will be used for all analyses.

ECOG performance status will be summarized by visit for observed values and changes from baseline using summary statistics. Ophthalmologic interpretation will be tabulated in frequency tables.

Number of women taking a pregnancy test and the result will be tabulated by visit.

7. Document history and changes in the planned statistical analysis

- SAP, Version 1.0, 19 JUN 2018

- SAP Amendment, 02 APR 2020
    - Wording was harmonized throughout the document;
    - Added wording changes from protocol amendment 2;
    - Added definitions for pre-screening failures and screening failures;
    - Added information on the validity review meeting;
    - Clarified that only subjects from the dose selection part are to be considered for the MTD analysis set;
    - Planned analysis for prior immunotherapy, duration of treatment, TTP, dose modifications;
    - Added plan for the biomarker/pharmacodynamics analysis.
- SAP Amendment, 05 OCT 2021
    - PK concentration data of only rogaratinib (previously also atezolizumab) will be tabulated in Cycle 1
    - Addition of TTR definition
    - Addition of Covid-19 analyses
    - Wording change: patient replaced by subject
    - Specification of CSP reference: Section 7.4.3
- SAP Supplement, 05 APR 2022
    - Section 2: Addition of wording about part B not being conducted
    - Section 6.1.1: Addition of presentation of countries and study centers
    - Section 6.1.2: Deletion of NYHA in demographic variables
    - Section 6.1.2: Deletion of status of primary tumor and clinical status at study entry in cancer baseline characteristics
    - Section 6.1.3: Addition of wording about therapies during follow-up
    - Section 6.2.3: Addition of Follow-up time definition and more detailed wording
    - Section 6.2.4: Addition of visits of the summary statistics of EORTC QLQ-C30 and the analysis set
    - Section 6.4.2: Deletion of frequency tables for change of CTCAE grade from pre-treatment
    - Section 6.4.3: Deletion of listing of laboratory data outside the reference range with abnormal values flagged
    - Section 6.4.3: Addition of more details about clinical laboratory data analysis
    - Section 6.4.5: Addition of more details about other safety data

8. References

[1] Clinical Study Protocol No. BAY 1163877 / 19131, version 4.0, 04 Oct 2021