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A prospective international multicenter phase II study to evaluate the efficacy, safety and quality of life of oral daily pazopanib in patients with advanced and/or metastatic renal cell carcinoma after previous therapy with checkpoint inhibitor treatment

Statistical Analysis Plan (SAP) – Amendment1

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24-Aug-2018	Prior to DB lock	To implement changes in Protocol amendment 1		Section 2.2 (Table 2-3) : Per protocol set deifinition has been removed. Section 2.2.1 : Subgroup of Interest has beed updated Section 2.5.4 : Supportive analysis based on PPS has beed removed. Forest plot also removed. Section 2.7.1 Secondary endpoints (Sub-group analysis added for OS and ORR) Section 2.8: Safety analysis: (Sub-group analysis added for AE and LAB) Section 2.8.1: AESI listing have been removed. Section 2.8.3: Lab shift tables and overall patient listings have been removed.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 2.8.4: Other safety data: Overall patient listings have been removed. Section 2.9 : Patient reported outcome (The EQ-5D-5L index score and patient listings have been removed)  Section3: Sample size calculation Section5.3.1: Added to define the MSKCC and IMDC risk roup imputation
11-Feb-2020	Prior to DB lock	To make changes in subgroup population cut-off for final analysis		Section 2.2.1 : Subgroup cut-off has beed updated

Table of contents

Table of contents 4
1 Introduction 8
1.1 Study design 8
1.2 Study objectives and endpoints 9
2 Statistical methods 11
2.1 Data analysis general information 11
2.1.1 General definitions 11
2.2 Analysis sets 15
2.2.1 Subgroup of interest 15
2.3 Patient disposition, demographics and other baseline characteristics 16
2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance) 18
2.4.1 Study treatment / compliance 18
2.4.2 Prior, concomitant and post therapies 19
2.5 Analysis of the primary objective 20
2.5.1 Primary endpoint 20
2.5.2 Statistical hypothesis, model, and method of analysis 21
2.5.3 Handling of missing values/censoring/discontinuations 21
2.5.4 Supportive analyses 22
2.6 Analysis of the key secondary objective 23
2.7 Analysis of secondary efficacy objective(s) 23
2.7.1 Secondary endpoints 23
2.7.2 Statistical hypothesis, model, and method of analysis 25
2.7.3 Handling of missing values/censoring/discontinuations 26
2.8 Safety analyses 26
2.8.1 Adverse events (AEs) 26
2.8.2 Deaths 27
2.8.3 Laboratory data 27
2.8.4 Other safety data 28
2.9 Patient-reported outcomes 30
[redacted] 31
2.11 Other Exploratory analyses 31
2.12 Interim analysis 32
3 Sample size calculation 32

3.1 Primary analysis....32
3.2 Power for analysis of key secondary variables....33
4 Change to protocol specified analyses....33
5 Appendix....34
5.1 Imputation rules....34
5.1.1 Study drug....34
5.1.2 AE, ConMeds and safety assessment date imputation....35
5.1.3 Imputation for MSKCC risk group and IMDC risk group....36
5.1.4 Other imputations....37
5.2 AEs coding/grading....38
5.3 Laboratory parameters derivations....38
5.4 Statistical models....39
5.4.1 Primary analysis....39
6 Reference....40

List of abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
bid	bis in diem/twice a day
BMI	Body Mass Index
BOR	Best Overall Response
CBR	Clinical Benefit Rate
CI	Confidence Interval
CR	Complete Response
CRO	Contract Research Organization
CRS	Case Retrieval Strategy
CSR	Clinical Study report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DAR	Dosage Administration Record
DB	Database Lock
DD	Drug Dictionary
DI	Dose Intensity
DOR	Duration of Response
DRL	Drug Reference Listing
FAS	Full Analysis Set
FKSI-DRS	Functional Assessment of Cancer Therapy- Kidney Symptom Index- Disease related Symptoms
FPFV	First Patient First Visit
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
HR	Heart Rate
IWR	Interactive Web Response
IMDC	International Metastatic Renal Cell Carcinoma Database Consortium
KPS	Karnofsky Performance Status
LLOQ	Lower Limit of Quantification
LPFV	Last Patient First Visit
LPLV	Last Patient Last Visit

LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mRCC	Metastasic Renal Cell Carcinoma
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
o.d.	Once Daily
ORR	Overall Response Rate
OS	Overall Survival
PD	Progression Disease
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PPS	Per-Protocol Set
PR	Partial Response
PRO	Patient-reported Outcomes
PT	Prefered Term
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RCC	Renal Cell Carcinoma
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SOC	System Organ Class
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings
ULOQ	Upper Limit of Quantification
UNK	Unknown
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the clinical study report(s) (CSR) of study CPZP034A2410, a prospective international multicenter phase II study to evaluate the efficacy, safety and quality of life of oral daily pazopanib in patients with advanced and/or metastatic renal cell carcinoma after previous therapy with checkpoint inhibitor treatment.

The content of this SAP is based on protocol PZP034A2410 v01. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is a multi-center, open-label, single-arm phase II study to determine the efficacy, safety and quality of life of treatment with pazopanib in patients with advanced and/or metastatic renal cell carcinoma (RCC) following prior treatment with immune checkpoint inhibitors. A total of approximately 100 patients are planned to be enrolled (with an approximately 40 patients receive pazopanib as 2nd line treatment.) and treated in this study.

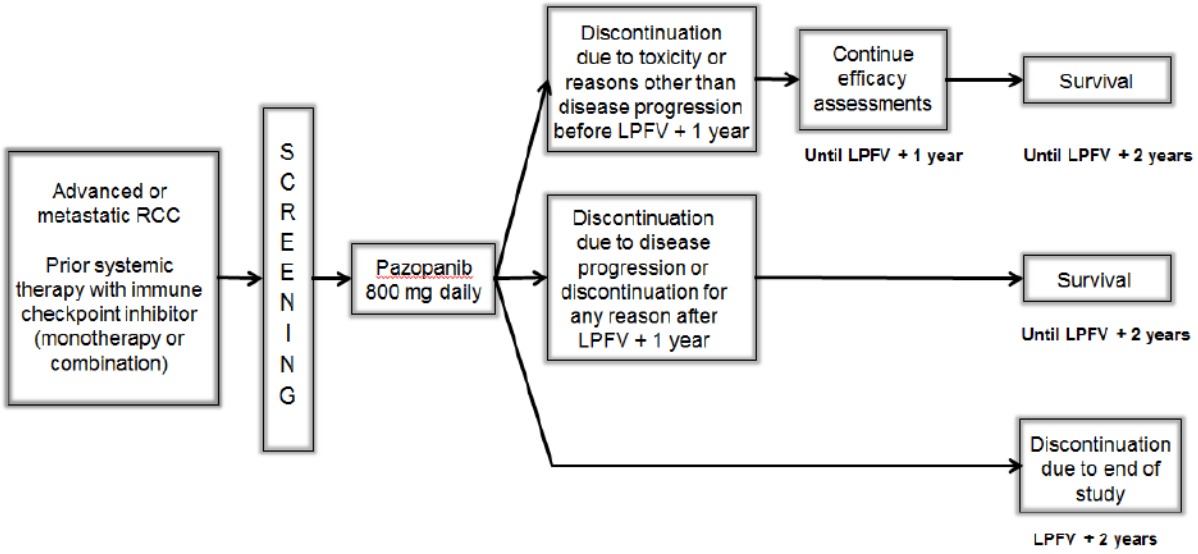
Patients will receive standard dose of pazopanib daily until disease progression, unacceptable toxicity, death, pregnancy, start of a new anti-neoplastic therapy, discontinuation at the discretion of the investigator or patient, lost to follow-up, end of study or study is terminated by the sponsor, whichever comes first. Dose modifications will be allowed for patients who do not tolerate the standard starting dose of 800 mg daily. Patients will be followed for survival (except if consent is withdrawn or patient is lost to follow-up).

Progression free survival (PFS) as assessed by local investigator review of tumor assessments and using RECIST v1.1 criteria is the primary endpoint in this study.

The primary analysis for PFS is planned after all patients have received a minimum of 6 cycles of study treatment or have discontinued study treatment early.
No formal interim analysis is planned for this trial.

The cut-off date for the primary analysis will be established after all patients have received a minimum of 6 cycles of study treatment or have discontinued study treatment early. The primary analysis data will be summarized in the primary clinical study report (CSR).

Figure 1-1 Study design



1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
To assess the progression free survival (PFS) based on local investigator assessment	PFS based on local investigator assessment using RECIST v1.1 defined as the time from the first administration of study treatment until the first documented progressive disease (PD) or death due to any cause.
Secondary	
To assess overall response rate (ORR) and clinical benefit rate (CBR) based on local investigator assessment	ORR defined as the proportion of patients with best overall response of confirmed complete response (CR) or partial response (PR) based on local investigator's assessment according to RECIST v1.1 CBR defined as the proportion of patients with a best overall response of CR or PR or an overall lesion response of stable disease (SD), or Non-CR/Non-PD lasting ≥ 24 weeks based on local investigator's assessment according to RECIST v1.1.
To assess overall survival (OS)	Overall survival (OS) defined as the time from the first administration of study treatment until death due to any cause.
To assess duration of response (DOR) in patients with CR or PR	DOR defined as the time from the date of first documented response (confirmed CR or PR) to the date of tumor progression.
To evaluate the safety and tolerability	Type, frequency and severity of AEs per NCI-CTCAE v4.03. Type, frequency and severity of laboratory toxicities per NCI-CTCAE v4.03.
To assess quality of life	Quality of life as assessed by the EuroQoL EQ-5D-5L and FKSI-DRS health questionnaires.
[redacted]	

2 Statistical methods

2.1 Data analysis general information

The primary and final analyses will be performed by Novartis and/or a designated CRO. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

Data included in the analysis

The cut-off date for the primary analysis of study data will be established after all enrolled patients have completed 6 cycles of treatment or have discontinued study. The final analysis cut-off date will be established 2 years after the last patient has started treatment. All statistical analyses will be performed using all data collected in the database up to the data cut-off date. All data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date will be included in the analysis. Any data collected beyond the cut-off date will not be included in the analysis and will not be used for any derivations.

All events with start date before or on the cut-off date and end date after the cut-off date will be reported as 'ongoing'. The same rule will be applied to events starting before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

General analysis conventions

Pooling of centers: Unless specified otherwise, data from all study centers will be pooled for the analysis. Due to expected small number of patients enrolled at centers, no center effect will be assessed.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum and in addition when specified 25th and 75th percentiles).

2.1.1 General definitions

Investigational drug and study treatment

Investigational drug, ***study treatment*** and ***study drug*** will refer to the pazopanib only.

Study treatment will be used throughout this document.

Date of first administration of study treatment

The date of first administration of study treatment is defined as the first date when a non-zero dose of study treatment is administered and recorded on the Dosage Administration Record (DAR) eCRF. The date of first administration of study treatment will also be referred as ***start of study treatment***.

Date of last administration of study treatment

The date of last administration of study treatment is defined as the last date when a non-zero dose of study treatment is administered and recorded on DAR eCRF. The date of last administration of study treatment will also be referred to as end of study treatment.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) – reference start date if event precedes the reference start date.

The reference date for all assessments (safety, efficacy, QoL/PRO, etc.) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

The cycle length is 28 days from day 1 to day 28.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of study treatment is defined as "baseline" assessment.

If patients have no value as defined above, the baseline result will be missing.

On-treatment assessment/event and observation periods

For adverse event reporting the overall observation period will be divided into three mutually exclusive segments:

1. ***pre-treatment period***: from day of patient's informed consent to the day before first administration of study treatment

2. ***on-treatment period***: from date of first administration of study treatment to 30 days after date of last actual administration of any study treatment (including start and stop date)
3. ***post-treatment period***: starting at day 30+1 after last administration of study treatment.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on-treatment and post-treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

Windows for multiple assessments of PRO

In order to summarize PRO measures and performance status (PS) collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If two assessments within a time window are equidistant from the target date, then the worst of the two assessments will be used. If multiple assessments on the same date then the worst case will be used. Data obtained at the end of treatment will be classified as other assessment in the corresponding time window. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

Note that only data collected under treatment (i.e. while the patient is treated) will be included in the time to definitive deterioration. The end of treatment assessment will be included if collected within 30 days of the last dose intake.

Table 2-1 Time windows for EQ-5D-5L, KPS and FKSI-DRS assessments

Assessment	Target day of	Time Interval
Baseline		≤ Day 1
Cycle 2 Day 1	29	Day 2 to day 42
Cycle 3 Day 1	57	Day 43 to day 70
Cycle 4 Day 1	85	Day 71 to day 98
Cycle 5 Day 1	113	Day 99 to day 126
Cycle 6 Day 1	141	Day 127 to day 154
Cycle 7 Day 1	169	Day 155 to day 196
Cycle 9 Day 1	225	Day 197 to day 252
Cycle 11 Day 1	281	Day 253 to day 308
Cycle 13 Day 1	337	Day 309 to day 378
Cycle 16 Day 1	421	Day 379 to day 462

Every 3rd cycle until EOT Cycle k Day 1 (k≥19)	d=(k-1)*28+1	Day d-42 to day d+41
End of Treatment		Assessment taken at the end of treatment visit Note: EOT data visit are included if obtained within 30 days of last non-0 dose intake.

Study Day 1 = start date of study treatment
Post treatment study day 1=end of treatment date + 1 day
30 days is considered to be the time until total drug elimination

Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 2-1 Last contact date data sources

Source data	Conditions
Start date of study treatment	No condition
Last contact date/last date patient was known to be alive from 'Survival Information' page	Patient status is reported to be alive.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
Tumor (RECIST) assessment date	Evaluation is marked as 'done'.
Laboratory collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

The last contact date is defined as the latest complete date from the above list on or before the data cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the last contact date. Partial date imputation is allowed only for event (death)/censoring if coming from 'Survival information' eCRF.

The last contact date will be used for censoring of patients in the analysis of overall survival.

2.2 Analysis sets

Full Analysis Set

The **Full Analysis Set** (FAS) comprises all patients to whom study treatment has been assigned and who received at least one dose of pazopanib.

Safety

The **Safety set** includes all patients who received at least one dose of pazopanib. The safety set and the FAS are the same for this single arm phase II study.

Other

Not applicable.

Pharmacokinetic analysis set (PAS)

Not applicable.

Patient Classification:

Patients may be excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific patient classification rules defined in Table 2-3.

Table 2-2 Patient classification based on protocol deviations and non-protocol deviation criteria

Analysis set	Protocol deviations leading to exclusion	Non protocol deviation leading to exclusion
FAS	No written informed consent	No dose of study medication
Safety set	No written informed consent	No dose of study medication

Withdrawal of Informed Consent

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

[redacted]

2.2.1 Subgroup of interest

The primary efficacy will be summarized by the following subgroups to examine the homogeneity of treatment effect based on the FAS:

- Age category (< 65 years, ≥ 65 years)

- MSKCC risk groups: poor (≥ 2 risk factors), intermediate (1risk factors), favorable (0 risk factor)
- IMDC risk groups: poor (> 2 risk factors), intermediate (1-2 risk factors), favorable (0 risk factor)
- Line of therapy (2^{nd} / 3^{rd}):
  - Second-Line therapy: all patients who received only one line of prior antineoplastic therapy before start of the study treatment
  - Third-Line therapy: all patients who received two lines of prior antineoplastic therapies before start of the study treatment

No formal statistical test of hypotheses will be performed for the subgroups, only point estimate of the treatment effect and 95% confidence intervals will be provided (see Sections 2.5.4 and 2.7.1 for further analysis details). The objective of the efficacy subgroup analysis is to evaluate homogeneity of treatment effect in the above subgroups.

Summary tables will only be performed if at least 20% of patients are present in each subgroup. Some grouping of classes may be considered for some subgroups (e.g. therapy type).

2.3 Patient disposition, demographics and other baseline characteristics

The Full Analysis Set (FAS) will be used for all baseline and demographic summaries and listings unless otherwise specified.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed. Categorical data (e.g. gender, age groups: < 65 and ≥ 65 years, race, ethnicity, Karnofsky performance status, MSKCC, IMDC risk group etc.) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body mass index etc.) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum, 25th and 75th percentiles). BMI (kg/m2) will be calculated as weight[kg] / (height[m]2) using weight at Baseline.

Baseline stratification factors

Not applicable.

Diagnosis and extent of cancer

Summary statistics will be tabulated for diagnosis and extent of cancer. This analysis will include the following: details of tumor histology/cytology, histological grade, stage at initial diagnosis, time since initial diagnosis, stage at time of study entry, presence/absence of target

and non-target lesions, metastatic sites involved. Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Presence/absence of metastatic sites will be based on diagnosis page.

Medical history

Medical history and ongoing conditions, including cancer-related conditions and symptoms entered on (e) CRF will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The MedDRA version used for reporting will be specified in the CSR and as a footnote in the applicable tables/listings.

Other

Other data collected at baseline including child bearing potential will be listed.

Patient disposition

The number (%) of treated patients included in the FAS will be presented. The number (%) of patients in the FAS who are still on treatment, who discontinued the study phases and the reason for discontinuation will be presented.

The following summaries will be provided (with % based on the total number of FAS patients):

- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Phase Disposition' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Phase Disposition' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Phase Disposition' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Phase Disposition' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the 'End of Post-treatment phase disposition' page);
- Reasons for discontinuation from the post-treatment follow-up (based on 'End of Post-treatment phase disposition' page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Post-treatment phase disposition' page and 'End of Treatment Phase Disposition' page).

Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Study Specification Document). All protocol deviations will be listed.

Analysis sets

The number (%) of patients in each analysis set (defined in Section 2.2) will be summarized.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure to pazopanib (expressed in months), actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized. Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number(%) of patients in each interval. The number (%) of patients who have dose reductions or interruptions, and the reasons, will be summarized.

Patient level listings of all doses administered on treatment along with dose change reasons will be produced.

The safety set will be used for all summaries and listings of study treatment.

Duration of exposure to study treatment

Duration of exposure to study treatment is considered by taking into account the duration of exposure to pazopanib:

Duration of exposure to pazopanib (*months*) =((last date of exposure to pazopanib) – (date of first administration of pazopanib) + 1) / (365.25/12).

The last date of exposure to pazopanib is the latest of the last dates of exposure to pazopanib (see section 2.1.1.)

Summary of duration of exposure of pazopanib in appropriate time units will include categorical summaries (<3 months, 3-<6 months, 6-<12 months, 12-<18 months, ≥ 18 months) and continuous summaries (i.e. mean, standard deviation etc.) using appropriate units of time.

Cumulative dose

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized.

The **planned cumulative dose** for a study treatment refers to the total planned dose as per the protocol up to the last date of study treatment administration.

The **actual cumulative dose** refers to the total actual dose administered, over the duration for which the patient is on the study treatment as documented in the Dose Administration eCRF.

For patients who did not take any drug the cumulative dose is by definition equal to zero.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

Dose intensity and relative dose intensity

Dose intensity (DI) for patients with non-zero duration of exposure is defined as follows:

DI (mg/day) = Actual Cumulative dose (mg) / Duration of exposure to study treatment (day).

For patients who did not take any drug the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (mg/day) = Planned Cumulative dose (mg) / Duration of exposure (day).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (mg/day) / PDI (mg/day).

DI and RDI will be summarized. RDI will also be summarized by the following categories: ≤75%, >75-90%, >90-110% and >110%.

Dose reductions, interruptions or permanent discontinuations

The number of patients who have dose reductions or interruptions, and the reasons, will be summarized.

'Dose interrupted' and 'Dose changed' fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions and dose interruptions.

The corresponding fields 'Reason for dose change/dose interrupted' will be used to summarize the reasons.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as separate interruptions. However, if the reason is the same in this mentioned multiple entries on consecutive days, then it will be counted as one interruption.

Reduction: A dose change where the prescribed dose level is lower than the previous prescribed dose level. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is collected in the CRF, number of reductions will be derived programmatically based on the change and the direction of the change.

Missing data: If dose is recorded but regimen is missing or entered as 'none', it is assumed that the study treatment was taken as per-protocol.

2.4.2 Prior, concomitant and post therapies

Prior anti-cancer therapy

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized. Prior anti-neoplastic medications will be summarized by lowest ATC class and preferred term.

Separate listings will be produced for prior anti-neoplastic medications and surgery.

Anti-neoplastic medications will be coded using the WHO Drug Dictionary (WHO-DD); anti-neoplastic surgery will be coded using MedDRA. Details regarding MedDRA and WHO-DD version will be included in the footnote in the tables/listings.

The above analyses will be performed using the Full Analysis Set.

Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class and preferred term by means of frequency counts and percentages using the Full Analysis Set.

Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

2.5 Analysis of the primary objective

The primary objective of the study is to evaluate the efficacy of pazopanib as assessed by progression-free survival (PFS) in patients with locally recurrent or metastatic RCC with predominantly clear cell component after previous therapy with immune checkpoint inhibitor treatment.

2.5.1 Primary endpoint

The primary endpoint of the study is PFS, defined as the time from the date of start of study treatment to the date of the first documented progression or death due to any cause. For the primary efficacy analysis, PFS will be based on local investigators review of tumor assessments using RECIST v1.1 criteria (see Appendix 2 of the study protocol). The primary analysis will be based on FAS and will include all data observed up-to the cut-off date. If a patient has not progressed or died at the analysis cut-off date, PFS will be censored at the date of the last adequate tumor evaluation date before the cut-off date. PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST v1.1. documented disease progression or

death) will be considered for the primary analysis provided tumor assessments continue after initiation of new cancer therapy (See Section 2.5.3 for additional details regarding censoring rules and determination of date of last adequate tumor assessment). Discontinuation due to disease progression (collected on the 'End of treatment' and 'End of post treatment follow up' disposition pages) without supporting objective evidence satisfying progression criteria per RECIST v1.1 will not be considered disease progression for PFS derivation.

2.5.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis will be tested in the study.
The survival distribution of PFS will be estimated using the Kaplan-Meier method. The results will be plotted graphically. The median, 25th and 75th percentiles of PFS along with 95% confidence intervals will be presented. The survival probabilities at every 2 months up to12 months, and the associated 95% confidence intervals will be summarized.

The primary efficacy analysis will be performed on the FAS.

2.5.3 Handling of missing values/censoring/discontinuations

In the primary analysis, PFS will be censored at the date of the last adequate tumor assessment if no PFS event (disease progression or death due to any cause) is observed prior to the analysis cut-off date.

PFS events documented after the initiation of new anti-neoplastic therapy (i.e. RECIST v1.1. documented disease progression or death) will be considered for the primary analysis provided tumor assessments continue after initiation of new cancer therapy.

The date of last adequate tumor assessment is the date of the last tumor assessment with overall lesion response of CR, PR or SD before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment will be used. If no post-baseline assessments are available (before an event or a censoring reason occurred) then the date of start date of treatment will be used.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after two or more missing tumor assessments. The term "missing adequate tumor assessment" is defined as a tumor assessment (TA) not performed or tumor assessment with overall lesion response of "UNK". The rule to determine number of missing TAs is based on the time interval between the date of last adequate tumor assessment and the date of an event. If the interval is greater than twice the protocol-specified interval between the TAs and 2 times the protocol-allowed time window around assessments, then the number of missing assessments will be 2 or more.

Refer to Table 2-4 for censoring and event date options and outcomes for PFS.

Table 2-4 Outcome and event/censor dates for PFS analysis

Situation	Date	Outcome
No baseline assessment	Date of start of study treatment	Censored
Progression or death at or before next scheduled Assessment	Date of progression (or death)	Progressed

Situation	Date	Outcome
Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
Progression or death after two or more missing assessments	Date of last adequate assessment prior to missed assessment	Censored
No progression (or death)	Date of last adequate assessment	Censored
Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	Date of last adequate assessment	Censored
New anticancer therapy given prior to protocol defined progression	Ignore the new anticancer therapy and follow situations above	As per above situations
Death before first PD assessment	Date of death	Progressed

2.5.4 Supportive analyses

NA

Subgroup analyses for the primary endpoint

The primary endpoint of PFS will be summarized for the subgroups specified in Section 2.2.1 and using the same conventions as for the primary analysis.
For each of the subgroups, the following analyses will be performed using the FAS:

- Kaplan-Meier estimates of the survival distribution of PFS

Efficacy analyses in subgroups are intended to explore the consistency (homogeneity) of treatment effect. No inferential statistics (p-values) will be produced for the subgroups.

Censoring pattern of PFS

Number of patients with a PFS event and number of patients censored for the PFS analysis will be summarized. In addition, a summary of reasons for PFS censoring will be provided based on the following reasons:

1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: Event after >=2 missing tumor assessments

The PFS censoring reasons are defined in the following way.

If the time interval between the last adequate TA date and the earliest of the following dates is smaller or equal to interval of 2 missing tumor assessments (see Section 2.5.3 for definition):

1. Analysis cut-off date,
2. Date of consent withdrawal,
3. Visit date of study treatment discontinuation or end of post-treatment follow-up discontinuation due to lost to follow-up.

Then the PFS censoring reason will be:

1. 'Ongoing without event',
2. 'Withdrew consent',
3. 'Lost to follow-up',

If the time interval is larger than the interval of 2 missing tumor assessments with no event observed then the PFS censoring reason will always default to 'Adequate assessment no longer available'. If the time interval between the last adequate tumor assessment date and the PFS event date is larger than the interval of 2 missing tumor assessments then the patient will be censored and the censoring reason will be 'Event documented after two or more missing tumor assessments'.

These summaries on censoring reasons will be produced.

2.6 Analysis of the key secondary objective

There is not key secondary objective in this single arm study.

2.7 Analysis of secondary efficacy objective(s)

The other secondary efficacy objectives are to:

- Evaluate pazopanib effect on overall survival (OS)
- Evaluate pazopanib effect with respect to overall response rate (ORR) and clinical benefit rate (CBR)
- Describe the duration of response (DOR) in the subset of patients with confirmed CR / PR
- Evaluate pazopanib effect with respect to PRO assessments by EQ-5D-5L and FKSI-DRS questionnaires.

2.7.1 Secondary endpoints

Overall Survival (OS)

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

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

The OS analyses will also be provided by the line of therapy subgroups defined in Section 2.2.1.

Overall Response Rate (ORR)

ORR is defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) according to RECIST 1.1 (see Appendix 2 of the study protocol). ORR will be calculated based on the FAS using local investigators review of tumor assessment data. Tumor assessments performed before the start of any further antineoplastic therapy (i.e. any additional secondary antineoplastic therapy or surgery) will be considered in

the assessment of BOR. Palliative radiotherapy is not allowed as per protocol and those will be considered as anti-neoplastic therapy usage.

The ORR analyses will also be provided by the line of therapy subgroups defined in Section 2.2.1.

Clinical benefit rate (CBR)

CBR is defined as the proportion of patients with a best overall response (BOR) of confirmed CR or PR, or SD or Non-CR/Non-PD lasting 24 weeks or longer, according to RECIST v1.1 criteria. A patient will be considered to have SD for 24 weeks or longer if a SD response is recorded at (24 -1) weeks or later from start of study treatment, allowing for the ±1 week visit window for tumor assessments. CBR will be calculated using the FAS based on the investigators' tumor assessments.

Duration of response (DOR)

DOR only applies to patients whose best overall response is complete response (CR) or partial response (PR) according to RECIST v1.1 based on local investigators review of tumor assessment data. The start date is the date of first documented response of CR or PR (i.e., the start date of response, not the date when response was confirmed), and the end date is defined as the date of the first documented progression or death due to underlying cancer. Patients continuing without progression or death due to underlying cancer will be censored at the date of their last adequate tumor assessment using the censoring rule described for PFS analysis.

Time to response

Time to response (CR or PR) is the time from date of start of treatment to first documented response of CR or PR (which must be confirmed subsequently) using local investigators review of tumor assessment data and according to RECIST v1.1. All patients in the FAS will be included in the time to response calculation. Patients who did not achieve a confirmed PR or CR will be censored at:

- the maximum follow-up time (i.e. FPFV - LPLV used for the analysis) for patients who had a PFS event (i.e. either progressed or died due to any cause);
- the last adequate tumor assessment date for all other patients.

Waterfall plot to depict anti-tumor activity

Waterfall graphs will be used to depict the anti-tumor activity using FAS. These plots will display the best percentage change from baseline in the sum of diameters of all target lesions for each patient. Only patients with measurable disease at baseline will be included in the waterfall graphs. Special consideration is needed for assessments where the target lesion response is CR, PR or SD, but the appearance of a new lesion or a worsening of non-target lesions results in an overall lesion response of PD. As a conservative approach, such assessments will not be considered for display as bars in the graph, since the percentage change in the sum of diameters of target lesions reflects the non-PD target lesion response, but the overall lesion response is PD. A patient with only such assessments will be represented by a special symbol (e.g. ✶) in the waterfall graph. Assessments with "unknown" target lesion

response and assessments with unknown overall response will be excluded from the waterfall plots. Patients without any valid assessments will be completely excluded from the graphs.

- The total number of patients displayed in the graph will be shown and this number will be used as the denominator for calculating the percentages of patients with tumor shrinkage and tumor growth. Footnote will explain the reason for excluding some patients (due to absence of any valid assessment).
- All possible assessment scenarios are described in Table 2-5.

Table 2-5 Inclusion/exclusion of assessments used in waterfall graph

	Criteria for inclusion/exclusion			Possible sources of contradictions	
case	Target response	Overall lesion response	Include in waterfall?	Non-target response	New lesion?
1	CR/PR/SD	PD	Yes but as " only	PD	any
2	CR/PR/SD	PD	Yes but as " only	any	Yes
3	UNK	UNK or PD	No	any	any
4	CR/PR/SD	UNK	No	UNK	No
5	CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
6	PD	PD	Yes as a bar	any	any

Patient-reported outcomes (PRO)

Statistical analyses are described in Section 2.9.

2.7.2 Statistical hypothesis, model, and method of analysis

Overall Survival

The survival distribution of OS distribution will be estimated using the Kaplan-Meier method. The Kaplan-Meier curve will be graphically presented, and the median, 25th and 75th percentiles will be shown along with the corresponding 95% confidence intervals [Brookmeyer and Crowley 1982] along with the proportion of patients alive at 6, 12 and 24 months and the associated 95% confidence intervals will be presented.

ORR (same for CBR)

ORR and CBR will be summarized using descriptive statistics (N, %) along with two-sided exact binomial 95% CIs [Clopper and Pearson 1934].

DOR (same for time to response)

DOR will be summarized for all patients in the FAS with confirmed BOR of CR or PR. DOR will be estimated using the Kaplan-Meier method. The Kaplan-Meier curve will be graphically presented and median, 25th and 75th percentiles, and the corresponding 95% confidence intervals will be provided.

2.7.3 Handling of missing values/censoring/discontinuations

Overall Survival

If a patient is not known to have died at the time of analysis cut-off, then OS will be censored at the date of last known date patient was alive, i.e., last contact date (see Section 2.1.1).

ORR (same for CBR)

Patients with unknown or missing best overall response (BOR) will be counted as failures. If there is no baseline tumor assessment, all post-baseline overall lesion responses are expected to be 'Unknown'. If no valid post-baseline tumor assessments are available, the best overall response must be "Unknown" unless progression is reported. For the computation of ORR, these patients will be included in the FAS and will be counted as 'failures'.

2.8 Safety analyses

All safety analyses will be based on the safety set.
The overall observation period will be divided into three mutually exclusive segments:
1. pre-treatment period: from day of patient's informed consent to the day before first dose of study medication;
2. on-treatment including safety follow-up period: from day of first dose of study medication to 30 days after last dose of study medication;

3. post-treatment period: starting at day 31 after last dose of study medication.

2.8.1 Adverse events (AEs)

AE summaries will include all AEs occurring during on treatment period. All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date outside of on-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency.

The following adverse event summaries will be produced; overview of adverse events and deaths, AEs by SOC and PT, summarized by relationship, seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome.

The summary of overview of all adverse events will be presented for line of therapy subgroups as specified in Section 2.2.1.

2.8.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data. AESIs are discussed in detail in the Investigator Brochure. The latest Case Retrieval Strategy (CRS) available at the time of the Primary/Final analysis will be used.

AESIs for this trial include hepatic toxicity, hypertension, thyroid-related disorders (hypothyroidism) and cardiac dysfunction.

Data analysis of AESIs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound pazopanib. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad. For each specified AESI, number and percentage of patients with at least one event of the AESI occurring during on treatment period will be summarized.

Summaries of these AESIs will be provided, (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption etc.).

2.8.2 Deaths

Separate summaries for on-treatment and all deaths will be produced by system organ class and preferred term.

All deaths will be listed, post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened patients.

2.8.3 Laboratory data

On analyzing laboratory, data from all sources (central and local laboratories) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 2.1.1).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status) will be presented for safety population . Each patient will be counted only for the worst grade observed post-baseline.

The following listing will be produced for the laboratory data:

- Listing of all CTC grade 3 or 4 laboratory toxicities.

Liver function parameters

Liver function parameters of interest are total bilirubin (TBL), ALT, AST and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values as per Novartis Liver Toxicity guidelines will be summarized:

The following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

Potential Hy's Law events are defined as those patients with concurrent occurrence of AST or ALT > 3xULN and TBL > 2xULN and ALP < 2xULN in the same assessment sample during the on-treatment period. Further medical review has to be conducted to assess potential confounding factor such as, liver metastases, liver function at baseline etc.

2.8.4 Other safety data

NA

2.8.4.1 ECG and cardiac imaging data

Data handling

In case the study requires ECG replicates at any assessment, the average of the ECG parameters at that assessment should be used in the analyses.

Data analysis

Local 12-lead ECGs including HR, PR, QRS, and QT intervals will be obtained for each patient at baseline, during the study treatment period and at the end of treatment. ECG data will be read and interpreted locally.

The number and percentage of patients with notable ECG values will be presented.

- QT or QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

A listing of notable vauel of ECG paremeters will be produced and the assessments collected during the post-treatment period will be flagged.

2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Data handling

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

Data analysis

For analysis of vital signs the clinically notable vital sign criteria are provided in Table 2-6 below.

Table 2-6 Clinically notable changes in vital signs

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Weight (kg)	increase > 10% from Baseline	decrease > 10% from Baseline
Systolic blood pressure (mmHg)	>=150 with increase from baseline of >=20	<=90 with decrease from baseline of >=20

Vital sign (unit)	Clinically notable criteria	
	above normal value	**below normal value**
Diastolic blood pressure (mmHg)	>=100 with increase from baseline of >=15	<=50 with decrease from baseline of >=15
Pulse rate (bpm)	>=100 with increase from baseline of >25%	<=50 with decrease from baseline of > 25%
Body temperature	>= 39.1	-

The number and percentage of patients with notable vital sign values (high/low) will be presented.

A listing of notable values of vital sign parameters will be produced and the assessments collected outside of on-treatment period will be flagged.

2.8.4.3 Additional Analyses: Echocardiogram/MUGA

Data handling

In case the study requires ECHO/MUGA replicates at any assessment, the average of the LVEF at that assessment should be used in the analyses.

Data analysis

Local echocardiogram or MUGA will be obtained for each patient will be obtained at baseline, during the study treatment period and at the end of treatment. The number and percentage of patients with notable post-baseline values of left ventricular ejection fraction (LVEF) based on NCI-CTCAE v4.03 will be summarized on the Safety Set:

- Grade 2: LVEF between >= 40 and <= 50 % and/or decrease from baseline between >= 10 and < 20 %
- Grade 3: LVEF between < 40 and <= 20 % and/or decrease from baseline between > 20 %
- Grade 4: LVEF < 20 %

In addition, the following notable post-baseline values will also be described on the Safety Set:

- Number of patients with new LVEF (%) <50%
- Number of patients with new LVEF (%) <50% and decrease >10%
- Number of patients with new LVEF (%) <50% and decrease >20%

2.9 Patient-reported outcomes

This study is a single arm study. Therefore, the PRO analyses will be descriptive and no statistical models will be provided.

The EQ-5D-5L is a general health status and health utility measure (Rabin 2001) and measures 5 dimension of health state: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression each assessed by a single question on a five-point ordinal scale EQ-5D Visual Analog Scale (VAS) is also included. The FKSI-Disease Related Symptoms (FKSI-DRS) is a 9-item questionnaire specifically designed to evaluate symptoms that are directly attributable to kidney cancer (Cella 2007) and includes patient's symptoms in the past seven days such as lack of energy, pain, bone-pain, shortness of breath, fatigue, blood in urine, etc. The scoring of these instruments will be done in accordance with the respective user's manual of the instrument.

Handling of missing data and generation of standard scores for the analysis will be performed in accordance with the respective scoring manual.

The FAS will be used for analyzing PRO data unless specified differently.

The PRO instruments are planned to be administered during screening and every 4 weeks after first day of treatment during the first 6 months, every 8 weeks thereafter until the first 11 months and then every 12 weeks until the end of treatment.

The baseline is defined as the last PRO assessment on or prior to first day of treatment.Distribution of patients on the 5 dimensions by level of problem at each schedule visit for EQ-5D-5L will be tabulated. The VAS scores from the EQ-5D-5L and FKSI-DRS will be displayed as mean profiles, presented over time using time windows as described in Table 2.1. Change from baseline scores at the time of each assessment will also be summarized on patients with an evaluable baseline score and at least one evaluable post baseline score during the treatment period.

Compliance to the schedule of administration of PRO will be summarized, for baseline and post-baseline on treatment assessments points. The following categories, as collected on the eCRF, will be used to describe whether the questionnaire was completed at a specific time point:

1. yes, fully completed
2. yes, partly completed
3. no, other.

[redacted]

2.11 Other Exploratory analyses

Karnofsky Performance Scale

The Karnofsky performance score (KPS) allows patients to be classified as to their functional impairment. The score runs from 100 down to 0, where 100 is "perfect" health and 0 is death. The definition of scores in relation to the performance status is given in Table 2-8.

Table 2-8 Karnofsky Performance Scale

Score	Performance Status
100	Normal: no complaints, no evidence of disease
90	Able to carry on normal activity; minor symptoms
80	Normal activity with effort; some symptoms
70	Cares for self; unable to carry on normal activities
60	Requires occasional assistance; cares for most needs
50	Requires considerable assistance and frequent care
40	Disabled: requires special care and assistance
30	Severely disabled: hospitalized but death not imminent
20	Very sick: active supportive care needed
10	Moribund: fatal processes are progressing rapidly
0	Dead

All collected data will be presented in data listings.

Duration of follow-up

Study follow-up will be summarized using the following methods:

- Summary of duration between start date of treatment and cut-off date, and follow-up times for PFS/OS, which are defined as follows:
  - Duration between start date of treatment and data cut-off date = (Cut-off date – Date of start of treatment + 1) / 30.4375 (months). This item will be summarized overall.
  - Follow-up time = (Date of event or censoring – Date of start of treatment + 1) / 30.4375 (months) regardless of censoring. Date of censoring is defined as the last adequate tumor assessment date for PFS or last contact date for OS. This item will be summarized.

All summaries will be reported in months. The calculations for PFS will be based on local assessment. Date of censoring is the same as defined for the PFS and OS analysis.

2.12 Interim analysis

No formal interim analysis is planned for this trial.

3 Sample size calculation

3.1 Primary analysis

Single arm study with PFS as primary endpoint

Since there is no formal hypothesis testing, sample size for this study is not based on any statistical power consideration. A total of approximately 100 patients (with approximately 40 patients receiving pazopanib as 2nd-line therapy) are planned to be enrolled and treated in this study. In a retrospective study, Nadal et al. reported median PFS (mPFS) of 6.9 months (95% Cl: 3.7 to 10.1) in mRCC patients treated with VEGFR-TKI therapy after any PD-1combination

(Nadal et al 2016). Based on this data, the median PFS for this patient population treated with pazopanib following prior treatment with immune checkpoint inhibitors is assumed approximately 6 months or less. Considering a recruitment period of 12 months and 6 months of follow up after LPFV, the expected 95% CIs for a median PFS for overall, 2nd line, and 3rd line patients with different sample sizes are presented in Table 3-1.

Table 3-1 Sample size and estimated 95% CI for median PFS

Patient population	Median PFS	Sample size	95%CI of median PFS (month)	Width (months)
Overall	5 months	90	3.96, 6.31 2.35	3.96, 6.31 2.35
		100	4.01, 6.24 2.23	4.01, 6.24 2.23
		110	4.05, 6.17 2.12	4.05, 6.17 2.12
2nd line	6 months	30	3.95, 9.12 5.18	3.95, 9.12 5.18
		40	4.17, 8.62 4.45	4.17, 8.62 4.45
		50	4.34, 8.30 3.96	4.34, 8.30 3.96
3rd line	4 months	50	2.96, 5.40 2.44	2.96, 5.40 2.44
		60	3.04, 5.26 2.22	3.04, 5.26 2.22
		70	3.10, 5.16 2.05	3.10, 5.16 2.05

3.2 Power for analysis of key secondary variables

Not applicable.

4 Change to protocol specified analyses

To follow the Novartis standard, prior, concomitant and post therapies will be provided on the Full Analysis Set instead of the Safety Set as per protocol.

Per Protocol Set (PPS) was defined in the original protocol, however, analysis by PPS population (including PPS definition) will not be conducted due to the fact that (i) sample size reduction and (ii) SAP leaning principal.

AESI main risk names were updated according to the last CRS available at the time of the SAP finalization.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The following rule should be used for the imputation of the dose end date for a given study treatment component:

Scenario 1: If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as on-going:

The patient should be treated as on-going and the cut-off date should be used as the dose end date.

Scenario 1 should not applicable for final CSR. All patients should have EOT page complete before the Database lock for Final CSR.

Scenario 2: If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

Use Dec31yyyy

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

Use EOT date

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

Use last day of the Month (mm)

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

Use the treatment start date

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

5.1.2 AE, ConMeds and safety assessment date imputation

Table 5-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates

day, month	• If available year = year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  ○ Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

day	• If available month and year = month and year of study treatment start date then
	  ○ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  ○ Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE, CM)

Missing Element	**Rule** (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

The above imputations are only used for analyses of time to and duration of AEs and concomitant medications.

5.1.3 Imputation for MSKCC risk group and IMDC risk group

If any of the following 3 factors are missing the rule below will be use for assign the MSKCC risk group.

1. Karnofsky performance status (< 80%)
2. Low serum hemoglobin (≤ 13 g/dL for males and < 11.5 g/dL for females)
3. High corrected serum calcium (≥ 10 mg/dL)

Number of missing factor(s)	Response from non-missing factor(s) [Yes => patient met the criteria]	Risk group
0	As collected in data base	Use protocol define criteria
1	2 Yes	Poor
1	1 Yes and 1 No	Missing
1	2 No	Missing
2	1 Yes	Missing
2	1 No	Missing
3	NA	Missing

If any of the following 6 factors are missing the rule below will be use for assign the IDMC risk group.

1. Haemoglobin <LLN,
2. Platelet >ULN,
3. Neutrophil >ULN,
4. Corrected serum calcium >ULN,
5. Karnofsky performance status [KPS] <80 and
6. <1 year from diagnosis to first-line targeted therapy

Number of missing factor(s)	Response from non-missing factor(s) [Yes => patient met the criteria]	Risk group
0	As collected in data base	· If the patient has 0 factor : Favorable prognosis · If the patient has 1-2 factors : Intermediate prognosis · If the patient has 3-6 factors : Poor prognosis
5 factors missing	1 or 0 Yes	Missing
4 factors missing	2, 1 or 0 Yes	Missing
3 factors missing	2, 1 or 0 Yes	Missing
3 factors missing	3 Yes	Poor
2 factor missing	≥3 Yes	Poor
2 factor missing	2, 1 or 0 Yes	Missing
1 factor missing	≥3 Yes	Poor
1 factor missing	2 Yes	Missing
1 factor missing	1 Yes	Intermediate
1 factor missing	0 Yes	Missing

5.1.4 Other imputations

Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

Incomplete assessment dates for tumor assessment

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if

the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

Applying the cut-off to tumor assessment

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date , then the evaluation is considered post-cut-off date and will be excluded from analysis.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Note: The latest available MedDRA version at the time of the analyses should be used. The MedDRA version used should be specified in the footnote of relevant tables.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (specify version used in the RAP). The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading

5.4 Statistical models

5.4.1 Primary analysis

Analysis of time to events Data

Hypothesis and test statistic

Not applicable.

Kaplan-Meier estimates

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

Median survival for each treatment group will be obtained along with 95% confidence intervals calculated from PROC LIFETEST output using the method of [Brookmeyer and Crowley 1982]. Kaplan-Meier estimates of the survival function with 95% confidence intervals at specific time points will be summarized. The standard error of the Kaplan-Meier estimate will be calculated using Greenwood's formula [Collett 1994].

Treatment of ties

The STRATA statement in LIFETEST procedure will be used to analyze time to event data with ties.

Analysis of Binary Data

Single arm study

Confidence interval for response rate

Responses will be summarized in terms of percentage rates with $100(1-\alpha)\%$ confidence interval using exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way table [Clopper and Pearson 1934].

Multiplicity adjustment

Not applicable.

Key secondary analysis

Not applicable.

6 Reference

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