J2G-GH-JZJK Statistical Analysis Plan v3

A Phase 2 Study of Oral Selpercatinib in Patients with Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation

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1. Statistical Analysis Plan: J2G-GH-JZJK: A Phase 2 Study of Oral Selpercatinib in Patients with Advanced Solid Tumors, Including *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors with RET Activation

LY3527723

This is an open label, multi-center Phase 2 study in patients with advanced solid tumors, including *RET* fusion-positive solid tumors (e.g., non-small cell lung cancer [NSCLC], thyroid, pancreas, colorectal), *RET*-mutant MTC, and other tumors with RET activation (e.g., mutations in other tumor types or other evidence of RET activation)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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SAP Version 2 electronically signed and approved by Lilly on 31-Aug-2020 GMT

SAP Version 3 electronically signed and approved by Lilly on the date provided below

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3. Revision History

SAP Version 1 was approved prior to first database lock.

SAP Version 2 was approved prior to first database lock. New analyses were added for: prior therapy, TTR, CNS ORR/DOR, and subgroup analysis for ORR/DOR.

SAP Version 3 was approved prior to second database lock. The following changes were made:

1) Section on interim analysis was added
2) Section on clinical trial registry analysis was added
3) A new exploratory objective, "subsequent radiographic progression date", was added in Section 4.3
4) The subgroup of patients with measurable disease and at least 1 post-baseline tumor assessment is renamed to "response evaluable subgroup" in Section 6.12.
5) Re-define RET fusion gene type to "KIF5B/CCDC6/NCOA4", "Other" and "Unknown" in baseline RET characteristics as well as subgroup definition.

4. Study Objectives

4.1. Primary Objective

To assess the anti-tumor activity of selpercatinib by determining objective response rate (ORR) using Response Evaluation in Solid Tumors version 1.1 (RECIST 1.1), as assessed by independent review committee (IRC).

4.2. Secondary Objectives

- To assess the anti-tumor activity of selpercatinib by determining:
  - ORR based on RECIST 1.1, as assessed by Investigator;
  - Duration of response (DOR) as assessed by IRC and Investigator;
  - Central nervous system (CNS) ORR based on RECIST 1.1 as appropriate to tumor type, as assessed by IRC (for patients with brain metastases);
  - CNS DOR as assessed by IRC (for patients with brain metastases);
  - Time to response (TTR) based on RECIST 1.1 as appropriate to tumor type, as assessed by IRC and Investigator;
  - Time to best response (TTBR) based on RECIST 1.1 as appropriate to tumor type, as assessed by IRC and Investigator;
  - Clinical Benefit Rate (CBR), as assessed by IRC and Investigator;
  - Progression-free survival (PFS) as assessed by IRC and Investigator;
  - Overall survival (OS) following initiation of selpercatinib.
- To determine the safety profile and tolerability of selpercatinib.
- To characterize the PK properties of selpercatinib.

4.3. Exploratory Objectives

- To determine the relationship between PK and drug effects, including efficacy and safety.
- To evaluate the serum tumor markers, carcinoembryonic antigen (CEA) and calcitonin (for patients with MTC), thyroglobulin (for patients with non-MTC thyroid cancer, unless not measurable due to presence of anti-thyroglobulin antibodies), and adrenocorticotropic hormone (ACTH)/cortisol (for patients with Cushing's disease related to their cancer), before, during, and at the end of treatment with selpercatinib.
- To characterize RET gene fusions and mutations and concurrently activated oncogenic pathways from circulating free deoxyribonucleic acid (cfDNA)
- To collect patient-reported outcomes (PRO) data to explore disease-related symptoms and health-related quality of life (HRQoL).

- To collect the time from initial progressive disease (PD_1) to subsequent PD (PD_2) to explore whether patients continue to benefit from study treatment after disease progression.

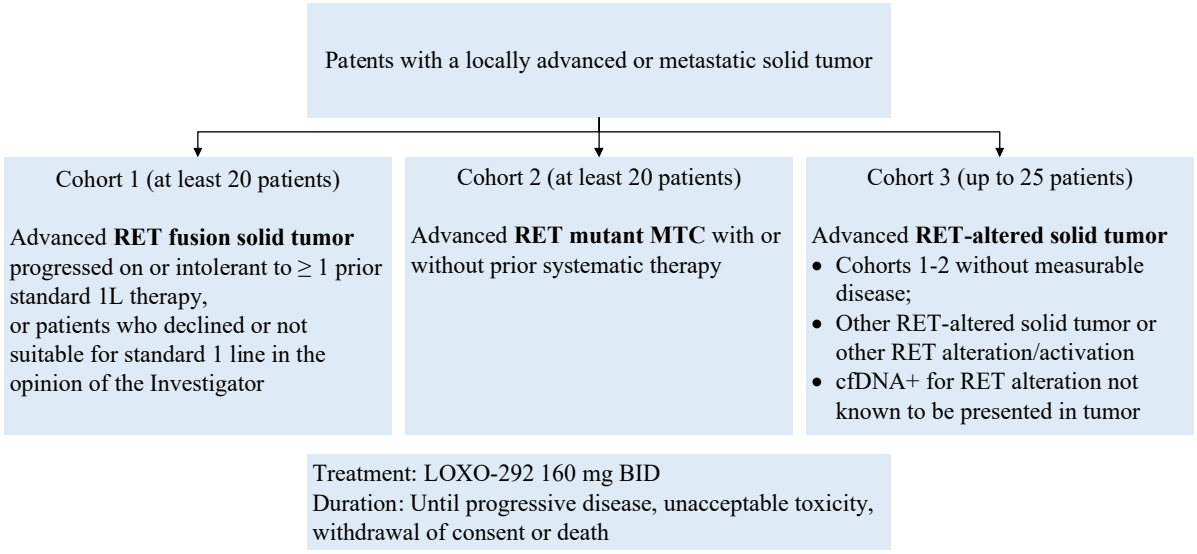
5. Study Design

5.1. Summary of Study Design

This is an open label, multi-center Phase 2 study in patients with advanced solid tumors, including *RET* fusion-positive solid tumors (e.g., non-small cell lung cancer [NSCLC], thyroid, pancreas, colorectal), *RET*-mutant MTC, and other tumors with RET activation (e.g., mutations in other tumor types or other evidence of RET activation).

Figure 5.1 illustrates the study design.

Figure 5.1. Study Schema.



5.2. Determination of Sample Size

For Cohort 1-2, at least 20 patients will be targeted for enrollment in each cohort. The main objective is to provide for a preliminary assessment of the antitumor activity of selpercatinib in Chinese patients with RET alterations. Table 5.1 presents the lower bounds of 2-sided exact 95% confidence intervals (CI) based on different choices of sample size and observed ORR. If the observed ORR is high (i.e., exceeds 45%) within a cohort of 20 patients, then the corresponding lower limit of a 2-sided exact 95% confidence interval will exclude true response rates that are considered marginal or uninteresting.

Up to 25 patients will be enrolled into Cohort 3 based on clinical considerations.

In addition, with an overall sample size of 75, the probability of observing one or more instances of a specific AE with a true incidence rate of 2% and 5% is approximately 80% and 98%, respectively.

Table 5.1. Lower bounds of 2-sided exact 95% CI based on different sample sizes and ORR

Observed ORR	0.4	0.45	0.5	0.55	0.6	0.65
n = 10	0.12	0.15	0.19	0.22	0.26	0.30
n = 20	0.19	0.23	0.27	0.32	0.36	0.41
n = 25	0.21	0.25	0.30	0.34	0.39	0.44
n = 30	0.23	0.27	0.31	0.36	0.41	0.46
n = 40	0.25	0.29	0.34	0.38	0.43	0.48
n = 50	0.26	0.31	0.36	0.40	0.45	0.50
n = 60	0.28	0.32	0.37	0.42	0.47	0.52

6. A Priori Statistical Methods

6.1. General Considerations

6.1.1. Analysis Populations

Entered population: will include all patients who signed the informed consent form

Enrolled population: will include all eligible patients.

Safety population: will included all enrolled patients who received at least one dose of selpercatinib. This population will be used for safety anlaysis.

Primary efficacy analysis population/primary analysis set (PAS): will include all treated patients enrolled in Cohort 1 and 2 who have *confirmed* RET fusion positive solid tumor or RET mutant MTC by central lab, respectively. The primary efficacy analysis will be conducted on this population.

Per-protocol population: will include all patients in the primary efficacy analysis population who are compliant with the study protocol without major protocol violations.

CNS response analysis population: will include all treated patients in Cohort 1 with confirmed *RET*-fusion positive solid tumor who have IRC-assessed CNS metastases at baseline.

Baseline diarrhea population: will include patients in Cohort 2 who had diarrhea at baseline. All analyses of bowel diary will be based on this population.

6.1.2. Definitions and Conventions

The **baseline value** is the last value observed prior to the first dose of study drug

The **study day** will be calculated in reference to the first dose date of selpercatinib as follows:

- assessment date/event date – first dose date + 1, if assessment date or event date ≥ first dose date,
- assessment date/event date – first dose date, if assessment date or event date < first dose date.

Unless otherwise noted, **summaries of continuous variables** will include a mean, median, standard deviation, minimum, and maximum.

Unless otherwise noted, **summaries of categorical variables** will include the frequency and percentage (relative to the population being analyzed) of each category.

Duration is calculated as:

- Duration (days): (End date – Start date + 1)
- Duration (weeks): (End date – Start date + 1) / 7
- Duration (months): (End date – Start date + 1) / 30.4375
- Duration (years): (End date – Start date + 1) / 365.25

6.2. Adjustments for Covariates

No adjustment for covariates is planned for this study.

6.3. Handling of Dropouts or Missing Data

Missing data will not be imputed with the exception of dates. The method of imputation for any dates is described in relevant section.

6.4. Mutiple Comparisons/Multiplicity

No adjustment for multiplicity is planned for this study.

6.5. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, reasons for discontinuation from study treatment, and reasons for discontinuation from the study. Reason for discontinuation from both study treatment and the study will be listed by the pre-determined categories. If the reason for discontinuation is adverse event (AE) or death, the associated AE or cause of death will be reported. All patients entered in the study will be included in the summary.

The number and percentage of patients will be summarized by the enrolling study center. In the event a patient transferred to another center during the study, the center of original enrollment will be used for this tabulation.

Patients with progressive disease may be allowed to continue study drug if, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment, and continuation of treatment is approved by the Sponsor. The number and percentage of such patients continuing to receive study drug after the documentation of disease progression will be presented.

6.6. Patient Characteristics

6.6.1. Demographics

The following variables will be summarized for all enrolled patients and PAS:

- Age
- Age group (<60, >=60)
- Sex (male, female)
- Height (cm)
- Weight (kg)
- Body mass index (BMI)
- ECOG performance status
- Smoking history (never smoked, current smoker, former smoker)

6.6.2. Baseline Disease Characteristics

The following disease characteristics will be summarized for all enrolled patients

- Stage of disease at enrollment (I–IV)
- Time since initial diagnosis (months)
- Metastatic disease at enrollment (yes, no)
- Time since initial diagnosis of metastatic disease (months)
- CNS metastasis by IRC assessment (yes, no)

Missing or partially missing dates for initial disease diagnosis will be imputed. If the month and year of the diagnosis are provided but the day is missing, the missing day is imputed as 15. If only the year is provided, then the missing month and day are imputed as July 1st for the calculation.

Stage of disease and disease metastasis will be derived from TNM staging. If M = M1, then the subject has metastatic disease, and vice versa.

Time since initial diagnosis will be calculated as (First dose date – Initial diagnosis date + 1) / 30.4375. Time since initial diagnosis of metastatic disease will be derived similary.

6.6.3. Pre-existing Conditions and Historical Illnesses

Historical illnesses are clinically relevant events in the past that ended before the screening visit, while pre-existing conditions are events that are still ongoing during the screening visit. Both will be summarized for all enrolled patients and PAS by MedDRA PT.

6.6.4. Prior Therapies

The following variables will be summarized for all enrolled patients:

- prior systemic treatments (yes, no)
- prior radiotherapy (yes, no)
- prior cancer-related surgery (yes, no)
- type of prior systemic treatments (e.g., platinum-based chemotherapy, anti-PD-1/PD-L1 antibody, selective TKI inhibitors (EGFR, ALK, ROS1, etc), multikinase inhibitors (cabozantinib, vandetanib, etc), other prior systemic therapies)
- number of prior multikinase inhibitors used (0, 1, 2)
- number of prior systemic regimens (0, 1, 2, ≥ 3)
- number of prior systemic regimens (as a continuous variable)
- number of prior treatment lines (0, 1, 2, ≥ 3)
- best overall response to most recent prior systemic regimen (CR, PR, SD, PD, NE, unknown)

The number of prior treatment lines is defined as the number of distinct dates of progressive disease.

6.6.5. Post-Discontinuation Therapies (PDT)

Post-discontinuation anti-cancer therapies, including systemic therapies, radiotherapies and surgeries, will be summarized for all enrolled patients and PAS. Systemic therapies will also be summarized by medication class and specific medication terms. The number of patients who received 1, 2, 3… subsequent regimens will be summarized.

Patient-level listings of PDT will be provided.

6.6.6. RET Alteration

The following variables will be summarized for all enrolled patients and PAS to describe the distribution of known *RET* alterations at enrollment:

- *RET* alteration documented (fusion, mutation)
- *RET* fusion gene (KIF5B/CCDC6/NCOA4, other, unknown)
- *RET* testing sample (tissue, blood)
- *RET* testing lab for eligibility (local, central)
- Consistency between local and central testing results
- *RET* mutation type (M918T, extracellular cysteine mutation, other)
    - Extracellular cysteine mutation is defined as mutation including at least 1 of the following: C609*, C611*, C618*, C620*, C630# and C634*, where * is any letter in {F, G, R, S, W, Y}, and # is any letter in {R, Y}

The presence of *RET* fusion genes and *RET* mutations will be based on local testing performed prior to enrollment or during the screening phase of the study.

6.6.7. Tumor Burden

The following variables will be summarized for all enrolled patients and PAS to characterize the extent of disease at enrollment:

- Number of measurable lesions
- Sum of the diameters of target lesions (mm)

Findings from investigator assessments of baseline radiographic scans will be used to characterize the disease burden of patients at baseline. Assessments will be performed using RECIST 1.1. Additionally, findings from the IRC assessments of the baseline radiographic scans will be summarized in the same manner.

6.7. Treatment Compliance

Treatment compliance of selpercatinib will be measured by capsule counts and summarized over the whole treatment period for the safety population. Compliance will be calculated as the ratio of total dose taken to the total dose expected to take (taking into account any dose adjustments and dose omission). More specifically:

- Total dose expected to take = total dose prescribed – total dose omitted
- Total dose prescribed = sum of (prescribed dose level * corresponding dosing period)
- Total dose omitted = sum of (prescribed dose level * corresponding withheld period)

6.8. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be listed and

summarized using the preferred name for the safety population.

6.9. Efficacy Analyses

6.9.1. General Considerations

This section describes the statistical methods to be used for analyses intended to demonstrate the effectiveness of selpercatinib in patients with *RET* alteration solid tumors.

Disease assessments for key efficacy endpoints in this study are derived from the IRC. An Imaging Review Charter outlines the procedures governing this process. This document includes operational guidelines for the imaging schedule and parameters, data management, guidelines for the reader, and management details. Additional analyses based on investigator assessment will be provided.

The **primary analysis** of efficacy endpoints will be based on PAS, and performed separately on each tumor type subgroup as warranted by data, e.g.:

- RET fusion positive NSCLC confirmed by central lab
- RET fusion positive TC confirmed by central lab
- RET mutant MTC confirmed by central lab

Supportive efficacy analyses will be based on enrolled population, and performed on tumor type subgroups pooled across cohorts, namely:

- All NSCLC patients
- All TC patients
- All MTC patients

Additionally, supportive efficacy analyses will be performed by *cohort*:

- Cohort 1
- Cohort 2

6.9.2. Objective Response Rate (ORR)

6.9.2.1. Primary Analysis

ORR is a summary measure of best overall response (BOR) as defined by RECIST Version 1.1. BOR is defined as the best response designation for each patient that is recorded between the date of the first dose of selpercatinib and the date of documented disease progression per RECIST 1.1 or the date of subsequent therapy, whichever occurs first. Each patient's BOR will be categorized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or not evaluable (NE).

Response (PR or CR) must be confirmed by a repeat assessment performed no less than 28 days after the criteria for response are first met. In the event that the confirmation of a CR or PR occurs at a time point following an NE assessment, the best overall response will be CR or PR. That is, the sequence of time point responses CR-NE-CR (or PR-NE-PR/CR) will be considered a best overall response of CR (or PR). When stable disease is believed to be the best response, it must also meet the minimum interval of 6 weeks (42 days) from the start of study treatment. If

the minimum time is not met when stable disease is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has stable disease at the first assessment, progressive disease at the second and does not meet minimum duration for stable disease, will have a best response of progressive disease. The same patient lost to follow-up after the first stable disease assessment will be considered inevaluable.

The ORR is defined as the number of patients who achieve a BOR of CR or PR that are confirmed divided by the total number of patients in the analysis population. The point estimate will be accompanied by a 2-sided 95% exact binomial CI using the Clopper-Pearson method.

The primary analysis of ORR is based on the response assessment by the IRC. The efficacy of selpercatinib will be demonstrated primarly on the primary efficacy analysis population. ORR will also be summarized by cohort (1 & 2), as well as by major tumor types across cohorts.

6.9.2.2. Supportive Analysis

The analysis will be repeated based on investigator assessment of response.

The tumor-burden change will be calculated for each patient in the PAS as the percentage change from baseline in the sum of diameters of target tumor lesions at each assessment time point. The best tumor-burdern change will be summarized descriptively by calculating the median and interquartile range across patients. Waterfall plots will be used to depict graphically the best change for each patient. Swimmer plots will be used to show the occurrence of clinical outcomes of interest over time (e.g. TTR, DOR, PD, treatment discontinuation, death).

Additional supportive analyses may be performed.

6.9.3. Time to Response (TTR)

TTR is defined as the number of months elapsed between the date of the first dose of selpercatinib and the first documentation of objective response (CR or PR, whichever occurs earlier) that is subsequently confirmed. IRC assessments will serve as the principal data source. Additional analyses based on investigator assessment will be provided.

TTR will be calculated as follows for patients who have a best overall response of confirmed CR or confirmed PR:

$$\text{TTR (months)} = (\text{Response Start Date} - \text{First Dose Date} + 1) / 30.4375$$

TTR will be summarized descriptively by calculating the median, IQR, minimum and maximum values. The number and percentage of patients with TTR by the following time points, measured relative to the date of first dose will be tabulated:

- <2 months
- 2 to 4 months
- 4 to 6 months
- 6 to 9 months
- ≥ 9 months

Kaplan-Meier curves will be used to present graphically the TTR distribution over time.

6.9.4. Time to Best Response (TTBR)

TTBR is defined as the number of months elapsed between the date of the first dose of selpercatinib and the first documentation of CR (if patient's BOR is confirmed CR) or PR (if patient's BOR is confirmed PR) that is subsequently confirmed. IRC assessments will serve as the principal data source. Additional analyses based on investigator assessment will be provided.

TTBR will be calculated as follows for patients who have a best overall response of confirmed CR or confirmed PR:

TTBR (months) = (Best Response Start Date – First Dose Date + 1) / 30.4375

TTBR will be summarized descriptively in the same manner as TTR.

6.9.5. Duration of Response (DOR)

DOR is defined as the number of months from the start date of PR or CR (whichever response is recorded first), and subsequently confirmed, to the date of disease progression or death, whichever occurs earlier. Patients with time point responses such as PR-NE-PR or PR-Stable-PR will be considered confirmed. For such patterns of response, the start date will be based on the date of the initial response. IRC assessments will serve as the principal data source. Additional analyses based on investigator assessment will be provided.

DOR will be calculated as follows for patients who have a best overall response of confirmed CR or confirmed PR:

DOR (months) = (Event/Censoring Date – Response Start Date + 1) / 30.4375

DOR will be right-censored for patients who meet one or more of the following conditions:

- Subsequent anticancer therapy in the absence of documented disease progression
- Died or documented disease progression after missing two or more consecutively scheduled disease assessment visits
- Alive and without documented disease progression on or before the data cutoff date

If a patient meets more than one of these conditions, then the scenario that occurs first will be used for the analysis. The event or censoring date will be determined based on the conventions listed in Table 6.1.

Table 6.1. Date of Event or Censoring for DOR

Situation	Date of event or censoring	Outcome
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event

Subsequent anticancer treatment started before disease progression or death (without disease progression beforehand)	Date of last evaluable disease assessment prior to start of subsequent anticancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments	Date of last evaluable disease assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last evaluable disease assessment	Censored

The patient's overall response status as of the data cutoff date will be summarized by tabulating the number and percentage of patients with confirmed CR or PR as follows:

- Response continuing
- Subsequent anticancer therapy without documented disease progression beforehand
- Documented disease progression
- Died (for patients who did not have documented disease progression beforehand)

DOR will be summarized descriptively using the Kaplan-Meier method with the 95% CI about the median calculated using Greenwood's formula.

6.9.6. Clinical Benefit Rate (CBR)

CBR will be calculated based on the proportion of patients with best overall response confirmed CR, PR, or stable disease lasting 16 or more weeks. Stable disease will be measured from the date of the first dose until the criteria for disease progression are first met. The analysis of CBR will be based on the methods described for ORR and will be presented in the summary table of best overall response and ORR.

6.9.7. Progression-Free Survival (PFS)

PFS is defined as the number of months elapsed between the date of the first dose and the earliest date of documented disease progression or death (whatever the cause). IRC assessments will serve as the principal data source. Additional analyses based on investigator assessment will be provided. If warranted by data, the analysis methods described for DOR will be used for PFS. Patient-level listing of PFS will be provided.

PFS will be calculated as follows:

PFS (months) = (Event or Censoring Date – First Dose Date + 1) / 30.4375

PFS will be right-censored for patients who met one or more of the following conditions:

- No post-baseline disease assessments unless death occurred prior to the first planned assessment (in which case death will be considered a PFS event)
- Subsequent anticancer therapy in the absence of documented disease progression

- Died or documented disease progression after missing two or more consecutively scheduled disease assessment visits
- Alive and without documented disease progression on or before the data cutoff date

If a patient meets more than one of these conditions, then the scenario that occurs first will be used for analysis. The event or censoring date will be determined based on the conventions listed in Table 6.2.

Table 6.2. Date of Event or Censoring for PFS

Situation	Date of event or censoring	Outcome
Death before first planned disease assessment	Date of death	Event
Death or disease progression between planned disease assessments	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
No postbaseline disease assessments	Date of first dose	Censored
Subsequent anticancer treatment started before disease progression or death (without disease progression beforehand)	Date of last evaluable disease assessment prior to start of subsequent anticancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments	Date of last evaluable disease assessment visit without documentation of disease progression before the first missed visit	Censored
Alive and without disease progression	Date of last evaluable disease assessment	Censored

6.9.8. Overall Survival (OS)

OS is defined as the number of months elapsed between the date of the first dose and the date of death (whatever the cause). Patients who are alive or lost to follow-up as of the data cutoff date will be right-censored. The censoring date will be determined from the date the patient was last known to be alive. Based on these considerations, OS will be calculated as follows:

$$\text{OS (months)} = (\text{Death or Censoring Date} - \text{First Dose Date} + 1) / 30.4375$$

If warranted by data, the duration of OS will be summarized descriptively using the Kaplan-Meier method with the 95% CI about the median calculated using Greenwood's formula.

6.9.9. CNS ORR and CNS DOR

Analyses of CNS ORR and CNS DOR will be conducted on the CNS response analysis population. The CNS ORR and CNS DOR will be assessed by IRC and will be analyzed using the same method described above for the analyses of ORR and DOR if data warrant.

Waterfall plot for change of CNS tumor burden from baseline will be provided.

6.10. Patient-Reported Outcomes

6.10.1. EORTC QLQ-C30

Data from the EORTC QLQ-C30 (Aaronson et al. 1993) instrument will be scored as described by the European Organization for Research and Treatment of Cancer (EORTC) scoring manual (Fayers et al. 2001).

Following the scoring instructions given by the EORTC Quality of Life Study Group, the raw EORTC QLQ-C30 subscale scores will be linearly transformed to 0–100. Missing values will be handled as outlined in the EORTC QLQ-C30 scoring manual if at least 50% of the items on a scale or subscale are reported; no values will be imputed. The raw score will be computed if at least 50% of the items on a scale or subscale are complete. The scoring for EORTC QLQ-C30 is detailed in Appendix 1.

Descriptive analyses will report median/quartile, mean/standard deviation (SD), and will include mean change/standard error (SE) from baseline for each subscale at each study visit for the predefined study cohorts. Additionally, mean scores across time will be presented in a line plot for each subscale.

For each subscale, mean change from baseline scores across time will be presented in a line plot.

For all change-from-baseline measures, the analysis set will include all treated patients who have baseline and at least one post-baseline PRO assessment on the QLQ-C30 subscale being evaluated.

A clinically meaningful difference will be defined as 10-point difference from the baseline assessment value for each patient. Each scale at every assessment time point will be compared to its baseline value and be categorized as follows (Osoba et al. 1998):

- **Worsening**: Defined as an increase of $\geqslant$10 points for the symptom scales or a decrease of $\geqslant$10 points for the functional scales and global health status/QoL scale.
- **Improvement**: Defined as a decrease of $\geqslant$10 points for the symptom scales or an increase of $\geqslant$10 points for the functional scales and global health status/QoL scale.
- **Stable**: Defined as no change or an increase/decrease of <10 points.

The number and percentage of patients improving, stable and worsening relative to their own baseline measurement will be reported at each post-baseline clinic visit time point for all patients reporting data. For each subscale, the number and proportion of patients experiencing definite improvement and time to definite improvement (defined as the first improvement from baseline of $\geq$10 points without any further deterioration in score $\geq$10 points) will be summarized. Similarly, number and proportion of patients experiencing definite worsening (defined as the first worsening from baseline, a $\geq$10 point decrease, without any further improvement of $\geq$10 points) and time to definite worsening will also be summarized.

Time to first improvement and to first worsening, respectively, will be evaluated using Kaplan-Meier method. For time to first improvement, patients who did not improve will be censored at

the date of their last EORTC assessment; Similary, for time to first worsening, patients who did not worsen will be censored at the date of their last EORTC assessment.

Questionnaire compliance will be summarized. Compliance rates will be calculated at each assessment time point. Compliance at an assessment time point is defined as the number of patients who were assessed divided by the expected number of patients at that time point. The expected number of patients:

- at baseline is equal to the number of patients enrolled
- at any post-baseline visit is equal to the number of patients who are alive and have not progressed

A patient who answers at least one item at a time point is considered to have been assessed. Reasons for non-compliance will be tabulated by assessment time point.

6.10.2. Bowel Diaries

The bowel diary questionnaire is a modified version of the STIDAT (Systemic Therapy Induced Diarrhea Assessment Tool), a standardized patient-reported questionnaire used to assess systemic therapy-induced diarrhea in oncology patients (Lui et al. 2017). The questionnaire used in this study contains 11 questions and assesses the patient's perception of having diarrhea, daily number of bowel movements, daily number of diarrhea episodes, the presence of urgency, presence of abdominal discomfort, fecal incontinence, patient's perception of diarrhea severity, and QoL. In the case of missing items in the QoL subscale, the scale will be excluded from the analysis and no imputation will be made.

This questionnaire uses a weighted scoring system, which will not be applied in this study due to the modification of the tool used in this study that invalidates the weights and could produce incorrect findings.

The mean/SD and median/range total QoL score, mean (SD) number of bowel movements (item 3), mean (SD) number of diarrheal episodes (item 2), and number/proportion of patients experiencing diarrhea (item 1), categorical response to severity of diarrhea (item 1 for those with diarrhea), urgency (item 4), abdominal discomfort (item 5), and fecal incontinence (item 6), respectively, will be summarized descriptively at each time point at which the data were collected for all patients, and separately for those who had diarrhea at baseline.

Item level mean/SD and median/range values will be reported for each QoL scale (items 8-12) at each study visit. Additionally, mean scores across time will be presented in a line plot for items 8-12. Change of score from baseline will also be summarized for each scale at each visit, and be presented in a line plot.

Worsening on the bowel diary is defined as any stepwise categorical decline in the diarrhea item 1 (such as, no diarrhea to minimal, moderate or severe; minimal to moderate or severe; moderate to severe), and improvement is defined as any stepwise improvement (such as minimal to no diarrhea, moderate to minimal or no diarrhea, severe to moderate, minimal or no diarrhea).

For all change-from-baseline measures, the analysis set will include all treated patients who have baseline and at least one post-baseline PRO assessment on the item being evaluated.

The number and proportion of patients experiencing worsening or improvement from baseline will be reported at each study visit at which the bowel diary is collected. Kaplan-Meier method will be used to evaluate time to first improvement (among the baseline diarrhea population) and time to first worsening (for the entire Cohort 2), respectively. For patients in the baseline diarrhea population, those who didn't experience any improvement or worsening will be censored at the date of their last bowel diary assessment. For patients in Cohort 2 who didn't have diarrhea at baseline, time to first worsening will be censored at the date of data cutoff.

For patients with improvement, the duration of improvement (defined as time from first improvement to the return to or below the baseline categorical level) will be reported as median, range, mean/SD days. Similarly, the duration of worsening (defined as time from first worsening to the return to or above the baseline categorical level) will be reported as median, range, mean/SD days.

6.11. Safety Analyses

Safety analyses will be conducted on the safety population. Additionally, safety endpoints may be summarized by tumor type (NSCLC, TC, and MTC) pooled across cohorts.

6.11.1. Extent of Exposure

Exposure to selpercatinib will be summarized based on the following:

- Time on treatment
- Dose intensities
- Dosage modifications

6.11.1.1. Time on Treatment

Time on treatment (TOT) will be summarized descriptively. For patients who permanently discontinued selpercatinib as of the data cutoff date, TOT will be calculated as follows:

$$\text{TOT (weeks)} = (\textit{Last Dose Date} - \textit{First Dose Date} + 1)/7$$

The first and last dose dates reported on the "Exposure: First Dose" and "Exposure: Last Dose" case report form pages, respectively, will be used for the above calculation.

For patients continuing to receive selpercatinib as of the data cutoff date, TOT will be calculated as follows:

$$\text{TOT (weeks)} = (\textit{Last Visit Date} - \textit{First Dose Date} + 1)/7$$

6.11.1.2. Dose Intensities

Dose intensities will be summarized descriptively as actual dose intensity (ADI), planned dose intensity (PDI) and relative dose intensity (RDI).

- The actual dose intensity of selpercatinib (mg/day) will be calculated as the actual cumulative dose of selpercatinib (mg) received divided by TOT (days).

- The planned dose intensity of selpercatinib (mg/day) will be as follows:
  - PDI (mg/day) = assigned dose level (mg) x 2/day = 320 mg/day
- The relative dose intensity is the percentage of dose received relative to the planned dose and is defined as follows:

$$\text{RDI (\%)} = \left(\frac{ADI}{PDI}\right) * 100\%$$

6.11.1.3. Dosage Modifications

The number and percentage of patients with 1 or more dose reductions, dose omissions, and dose increases will be tabulated with the reason for each dose modification.

6.11.2. Adverse Event

The reported AE term will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). AE verbatim text will be mapped by the sponsor or designee to corresponding terminology within MedDRA, and the resulting System Organ Class (SOC) and Preferred Term (PT) will be used for AE summary. The severity of each AE will be graded by the Investigator based on version 5 of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). For AEs without matching terminology within the NCI-CTCAE, Version 5, the investigator will be responsible for selecting the appropriate SOC and assessing severity grade based on the intensity of the event. The causal relationship between the occurrence of an AE and study drug will be judged by the Investigator, and reported by answering yes/no in CRF.

Consolidated AE: Consolidated terms comprising clinically synonymous MedDRA preferred terms have been defined in order to assist in identifying relevant safety differences between treatment arms. Summaries of the incidence of these consolidated terms will supplement the summaries by MedDRA PTs specified in this section. The MedDRA PTs that are grouped under each of the consolidated terms will be provided in compound-level safety document.

A **serious adverse event** (SAE) is any AE during this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization (except for study drug administration)
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

An AE will be regarded as **treatment-emergent**, if

- Its onset date occurs any time on or after the date of first dose up to 28 days after the last dose (or up to any time if serious and considered related to study treatment); or
- It occurs prior to first dose date and worsens while on therapy or up to 28 days after the last

dose of study treatment (or up to any time if serious and considered related to study treatment)

AEs will be summarized based on the number and percentage of patients experiencing events by MedDRA SOC and PT. If a patient experiences repeat episodes of the same AE (as defined by the MedDRA SOC and PT), the patient will only be counted once on the most severe CTCAE grade and the closest relationship to treatment.

The following TEAE/SAE listings and summaries will be provided:

- Overview of AEs
- Summary of TEAE/SAE by PT
- Summary of TEAE/SAE by SOC and PT
- Summary of TEAE/SAE by SOC and PT and maximum CTCAE grade (grades 1~5 and grade ⩾3)
- Listing of SAE

The summaries above will be repeated for TEAE/SAE related to study treatment.

6.11.2.1. Other Notable Adverse Events

AEs leading to discontinuation of study drug, AEs leading to dose modification, and AEs leading to death will be summarized by SOC and PT (all grades and grade ⩾3), and by maximum CTCAE grade. Patient-level listings of above AEs will be provided.

6.11.2.2. Adverse Events of Special Interest

Based upon information available to date and/or known class effects of this compound, several categories of AE have been designated to be of special interest. These include the following which are discussed below:

- Hepatic effects/potential liver toxicity (elevated levels of ALT, AST, total bilirubin, direct bilirubin, and ALP)
- Hypersensitivity
- Hypertension
- Thrombocytopenia

Liver function tests will be presented using conventional summary statistics, toxicity shift table analysis, and by time-to-event plots. Possible drug-induced liver injury will be assessed as defined in FDA guidance. Hy's Law cases of drug-induced liver injury have the following components:

- The drug causes hepatocellular injury as evidenced by an elevation of ALT or AST to 3-fold or greater of the upper limit of normal (ULN) relative to control (or in this context to baseline levels)

- In addition to the transaminase increases, an associated (i.e. concomitant) elevation of total serum bilirubin to 2-fold or greater of the ULN without initial findings of cholestasis (elevated alkaline phosphatase)
- No other explanation can be found for the combination of increased transaminase(s) and total bilirubin such as viral hepatitis, pre-existing acute liver disease, or concomitant drug capable of causing the observed injury

Events of hypersensitivity will be identified using search terms that include the preferred terms *Hypersensitivity* and *Drug hypersensitivity* under the *Immune System Disorders* MedDRA system organ class.

Events of hypertension will be identified using the preferred terms *Blood pressure abnormal* and *Blood pressure increased* under the *Investigations* system organ class, as well as the preferred term *Hypertension* under the *Vascular Disorders* system organ class.

Events of thrombocytopenia will be identified using the preferred term *Thrombocytopenia* under the *Blood and lymphatic system disorders* system organ class, as well as the preferred term *Platelet count decreased* under the *Investigations* system organ class.

Additional AEs of special interest may be added based on review of the safety data before the final data extraction.

6.11.3. Deaths

Incidences of deaths are to be reported, along with the primary cause of death in a summary table. All deaths including on-study death (deaths that occurred within 28 days of treatment discontinuation) and primary cause of death will be presented in a patient listing.

6.11.4. Clinical Laboratory Evaluations

Blood samples for the following clinical laboratory tests were collected and analyzed for safety:

- Hematology: hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)
- Serum chemistries (nonfasting): alkaline phosphatase, albumin, ALT, AST, blood urea nitrogen, total cholesterol, creatinine, glucose, lactate dehydrogenase, total and direct bilirubin, total protein, sodium, potassium, calcium, chloride, bicarbonate, magnesium, phosphate, and urea
- Coagulation: prothrombin time (PT), activated partial thromboplastin time (aPTT), and prothrombin international normalized ratio (INR)
- Thyroid panel: thyroid-stimulating hormone/thyrotropin (TSH), free triiodothyronine (T3),

and free thyroxine (T4)

Additional laboratory tests include:

- Urine chemistry: protein, glucose, blood, leukocyte esterase, specific gravity, pH, and ketones
- Biochemical response markers: carcinoembryonic antigen (CEA), calcitonin, and thyroglobulin
- Adrenocorticotropic hormone (ACTH)/cortisol

Whenever defined, laboratory values will be assigned toxicity grades based on CTCAE Version 5. For some laboratory tests, these criteria may include qualifying definitions (e.g. clinical AE and/or requirement for concomitant medication) in addition to the specific laboratory value used for the definition of the toxicity grades. For such tests, the qualifying definitions will not be used for the assignment of toxicity grades.

The maximum or "worst" change in each laboratory value occurring during treatment will be assessed by means of shift tables showing the number and proportion of patients with directional shifts in CTCAE grades relative to baseline. For laboratory variables without CTCAE toxicity grades (such as thyroid function), similar tables will be constructed showing shifts to outside (above or below) the local laboratory normal range relative to baseline. Baseline lab values will also be summarized in a descriptive manner.

6.11.5. Vital Signs and Other Physical Findings

The following vital signs and other physical findings were measured at screening and at periodic time points (including end of treatment and safety follow-up) following the initiation of selpercatinib:

- body weight (kg)
- systolic and diastolic blood pressures (mmHg)
- body temperature (degrees Celsius)
- respiration rate (breaths per minute)
- heart rate (beats per minute)
- ECOG performance status

The parameters and shift from baseline will be summarized by cycle for the safety population. A patient-level listing of vital signs will be provided.

6.11.6. Electrocardiograms (ECG)

ECG results will be summarized by cycle for the safety population.

6.12. Subgroup Analyses

If warranted by data, the point estimates of ORR (and 95% CI) and median DOR (and range)

based on IRC and investigator assessments will be calculated for the subgroups defined by the following:

- age (< 60 years, ≥ 60 years)
- sex (male, female)
- ECOG performance status at baseline (0, 1–2)
- smoking status (never smoked, current smoker, former smoker)
- *RET* fusion gene (KIF5B/CCDC6/NCOA4, other)
- *RET* mutation type (M918T, extracellular cysteine mutation, other)
- Prior systemic therapy use (treatment naïve vs pre-treated)
- type of prior systemic therapies (MKI including RET, other MKI, non-MKI)
- type of prior systemic therapies 2 (anti-PD-1/PD-L1 antibody, other)
- best overall response to most recent prior systemic therapy (CR, PR, SD, PD, NE)

Treatment naïve patients include patients who received no prior systemic therapies or who received only adjuvant/neo-adjuvant therapies; Otherwise, patients are categorized as pre-treated.

As a supportive analysis, ORR will be summarized on the **response evaluable subgroup**, defined as patients with measurable disease (at least 1 target lesion) and at least 1 post-baseline tumor assessment.

6.13. Protocol Deviation

Protocol deviations will be identified throughout the study. Important protocol deviations (IPDs) that potentially compromise the data integrity and patients' safety will be summarized. These deviations will include deviations that can be identified programmatically and those that can only be identified by the clinical research associate during monitoring. IPDs are described in the Trial Issue Management Plan (TIMP) within the study Trial Master File.

After further review, a comprehensive listing of patients with major protocol deviations (MPDs) among IPDs that might have significantly affected the interpretation and integrity of data or patient safety will be provided. Patients with MPDs will be excluded from PP population.

A listing of patients with MPDs will be defined prior to database lock, and the PP population will be derived using this list. The PP population may be used for select sensitivity analyses of the efficacy data.

IPDs and MPDs will be summarized by treatment arm and by the category and subcategory of deviation.

6.13.1. Protocol Deviation due to COVID-19

A listing of protocol deviations (both important and non-important) caused by COVID-19 will be provided.

6.14. Interim Analyses and Data Monitoring

An interim analysis is planned to trigger early interaction with regulatory authorities. The data cutoff date is expected to be 31 July 2020, determined such that approximately half of enrolled patients will have received at least one post-baseline tumor assessment.

The primary analysis will be performed after all enrolled patients have been followed up for a sufficient amount of time (with at least two post-baseline tumor assessments, except for patients discontinued early). The primary analysis may be updated upon request from regulatory authorities.

6.15. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and 'Other' Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An adverse event is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
    - the number of participants at risk of an event
    - the number of participants who experienced each event term
    - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

7. Unblinding Plan

Since this study is an open-label single-arm study, no blinding will be applied when patients are randomized in the IWRS system.

8. References

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9. Appendices

Appendix 1. Scoring for the EORTC QLQ-C30 Questionnaire Version 3.0

EORTC QLQ-C30 will be scored according to the scoring manual including transforming the raw score to the final score and handling of missing item responses as follows:

- Raw Scores (RS):
  a) Global Health Status:
     - Global Health Status (QL2) = (Q29+Q30)/2
  b) Functional Scales:
     - Physical Functioning (PF2) = (Q1+Q2+Q3+Q4+Q5)/5
     - Role Functioning (RF2) = (Q6+Q7)/2
     - Emotional Functioning (EF) = (Q21+Q22+Q23+Q24)/4
     - Cognitive Functioning (CF) = (Q20+Q25)/2
     - Social Functioning (SF) = (Q26+Q27)/2
  c) Symptoms/Items:
     - Fatigue (FA) = (Q10+Q12+Q18)/3
     - Nausea and Vomiting (NV) = (Q14+Q15)/2
     - Pain (PA) = (Q9+Q19)/2
     - Dyspnea (DY) = Q8
     - Insomnia (SL) = Q11
     - Appetite Loss (AP) = Q13
     - Constipation (CO) = Q16
     - Diarrhea (DI) = Q17
     - Financial Difficulties (FI) = Q28
- Transformed Scores (TS):
  a) For Global Health Status: TS = (RS-1)/6*100
  b) For Symptom Scales/Items: TS = (RS-1)/3*100
  c) For Functioning Scales: TS = [1-(RS-1)/3]*100
- Missing Data:

If there are missing items, raw scores derived from more than one question can be prorated so long as the respondent completed >50% of the items on a given subscale:

a) For status/scales/items derived from an odd total number of questions:
   [(Number of questions answered+1)/2] questions must be answered
b) For status/scales/items derived from an event total number of questions:
   [Number of questions answered/2] questions must be answered

Prorated raw score = [Sum of answered item scores] / [Number of items answered]

If any subscale has >50% missing items, then the subscale total score will be missing.

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