Official Title:	**A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumor Malignancies Harboring Activating FGFR Mutations or Translocations (FIGHT-207)**
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Statistical Analysis Plan

INCB 54828-207

A Phase 2, Open-Label, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib in Participants With Previously Treated Locally Advanced/Metastatic or Surgically Unresectable Solid Tumor Malignancies Harboring Activating FGFR Mutations or Translocations (FIGHT-207)

IND Number:	[redacted]
EudraCT Number:	**2018-004768-69**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803** **United States**
Protocol Version:	**Protocol Amendment 2 dated 14 JAN 2020**
CRF Approval Date:	**12 APR 2020**
SAP Version:	**Original**
SAP Author:	[redacted] **Biostatistics**
Date of Plan:	**23 SEP 2020**

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
CI	confidence interval
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
[redacted]	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
NE	not evaluable
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PP	per protocol
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SAP	Statistical Analysis Plan
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 2, open-label, single-arm, multicenter study in participants with previously treated locally advanced/metastatic or surgically unresectable solid tumor malignancies harboring activating FGFR mutations or translocations. Section 2 of the Protocol provides a detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with pemigatinib.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCB 54828-207 Protocol.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 54828-207 Protocol Amendment 2 dated 14 JAN 2020 and CRFs approved on 12 APR 2020. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancy with an activating FGFR mutation or translocation.	• ORR in Cohort A, defined as the proportion of participants in Cohort A who achieve a CR or PR based on RECIST v1.1 or RANO. • ORR in Cohort B, defined as the proportion of participants in Cohort B who achieve a CR or PR based on RECIST v1.1 or RANO. • An independent radiological review committee will determine response.

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary	
• To evaluate other clinical efficacy measurements of pemigatinib in participants with locally advanced/metastatic or surgically unresectable solid tumor malignancy with an activating FGFR mutation and/or translocation. • Safety and tolerability of pemigatinib.	• PFS, defined as the time from first dose until PD (according to RECIST v1.1 or RANO and assessed by an ICR) or death (whichever is first) in Cohorts A and B, respectively. • DOR, defined as the time from the date of first assessment of CR or PR until the date of the first PD by an ICR per RECIST v1.1 or RANO, or death (whichever is first) in Cohorts A and B, respectively. • OS, defined as the time from first dose of study drug to death of any cause in Cohorts A and B, respectively. • Safety and tolerability, as assessed by the occurrence of TEAEs and treatment-related AEs according to NCI CTCAE v5.0, physical exam changes, vital sign changes, laboratory evaluations, and ECGs in each cohort.
[redacted]	

3. STUDY DESIGN

This is an open-label, monotherapy study of pemigatinib in participants with advanced/metastatic or surgically unresectable solid tumor malignancy harboring an activating FGFR mutation or translocation. This study consists of 3 cohorts, Cohort A, Cohort B, and Cohort C and will enroll approximately 60 participants, 90 participants, and 20 participants, respectively (see Figure 1). Participants will receive a QD dose of pemigatinib at 13.5 mg continuously as long as participants are receiving benefit and have not met any criteria for study withdrawal. Participants with local laboratory test results (eg, tissue or plasma-based molecular assays) documenting an activating FGFR1, FGFR2, or FGFR3 mutation or gene rearrangement are eligible to enroll as long as the results meet the cohort criteria. Confirmatory testing through the central genomics laboratory will be performed for all participants; however, results from the central genomics laboratory are not required before enrollment. Centralized genomic testing results will allow participants to be assigned to a cohort:

- Cohort A: FGFR1-3 in-frame fusions or FGFR2 rearrangements* (n = 60)
- Cohort B: Known or likely activating mutations (excluding kinase domain) in FGFR1-3 included in Appendix C of Protocol Amendment 2 dated 14 JAN 2020 (n = 90)
- Cohort C: Known activating mutations in the kinase domain of FGFR1-3, other likely activating FGFR1-3 mutations or FGFR1/FGFR3 rearrangements* (requires consultation with the sponsor) (n = 20)

*Only FGFR fusions or rearrangements with an intact kinase domain are eligible.

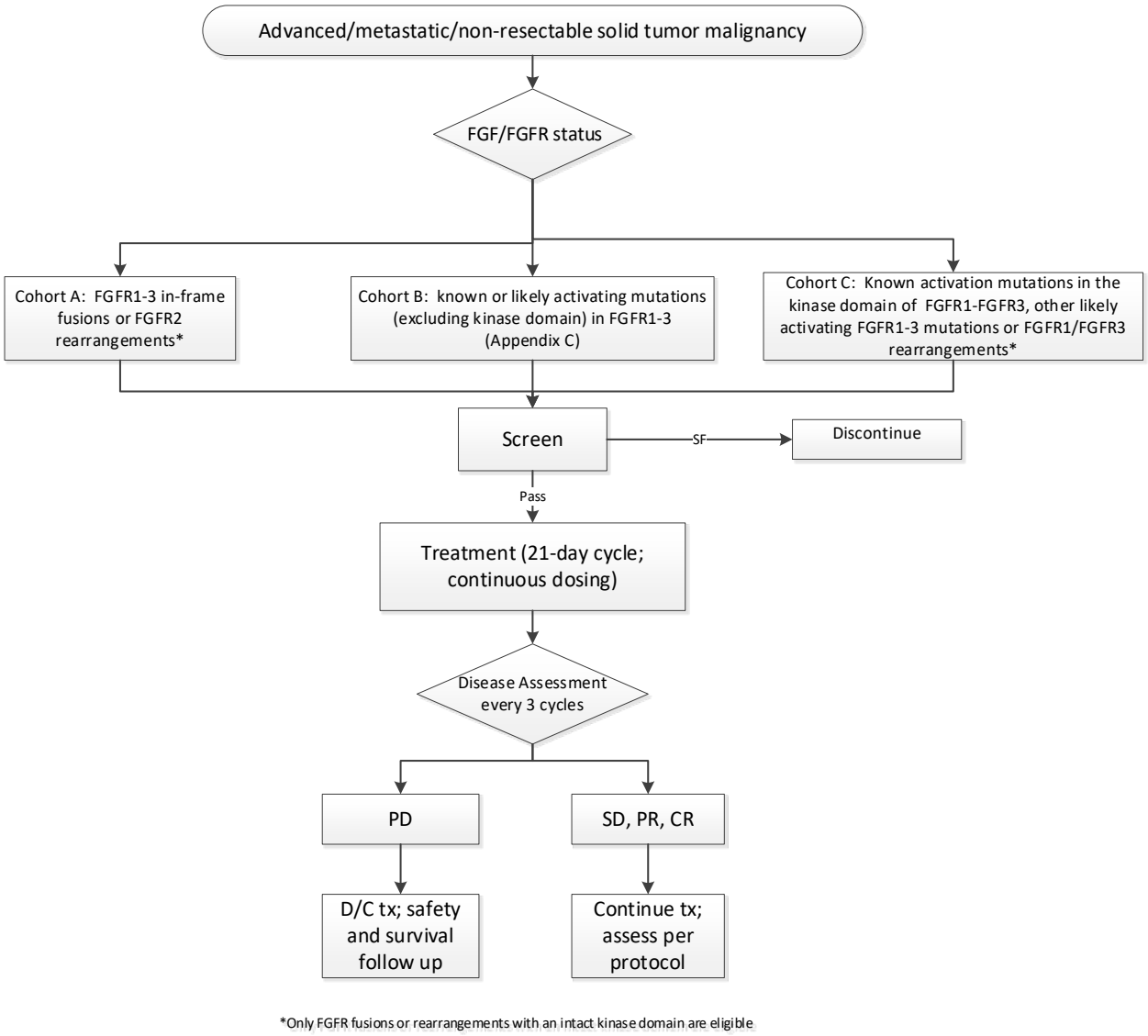
Please note that there is no difference in the treatment regimen between the cohorts. The sponsor may choose to cap enrollment of any one tumor type and/or FGFR alteration to allow representation of multiple tumor types and avoid analysis being influenced by any one tumor type. The sponsor may also choose to cap enrollment of any one tumor type if no benefit is being seen in previous participants enrolled.

For participants with FGFR2-rearranged cholangiocarcinoma, enrollment is limited to no more than 10 participants into Cohort A; for participants with FGFR3 mutation or fusions bladder cancer, enrollment is limited to no more than 10 participants into Cohort A or B combined. Participants from either group noted must have mandatory baseline and at least 1 on-treatment biopsy.

PPD

A fresh biopsy at baseline (or archival tissue that was collected less than 12 months from date of screening) and at least 1 on-treatment biopsy is required for participants with safely accessible lesions. Treatment will start on Day 1. Participants will undergo regular safety assessments during treatment as well as regular efficacy assessments. Participants will be allowed to continue administration in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

Figure 1: Study Design Schema



CR = complete response; D/C = discontinue; FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; PD = progressive disease; PR = partial response; SD = stable disease; SF = screen failure; tx = treatment.

3.1. Randomization

Not applicable.

3.2. Control of Type I Error

For the primary endpoint, the overall 1-sided Type I error is 0.025. The primary endpoint in Cohort A and Cohort B will be tested sequentially at 1-sided 0.025. If ORR in Cohort A is significant, then ORR in Cohort B will be tested.

3.3. Sample Size Considerations

For Cohort A, approximately 60 participants are planned. Assuming the true ORR is 35% for the intervention in this group, 60 participants are needed to ensure that there is at least 90% power to reject the null hypothesis of ORR ≤ 15%. This calculation assumes 1-sided test at the overall 0.025 level of significance.

For Cohort B, approximately 90 participants are planned. Assuming the true ORR is 30% for the intervention in this group, 90 participants are needed to endure that there is at least 90% power to reject the null hypothesis of ORR ≤ 15%. This calculation assumes 1-sided test at the overall 0.025 level of significance.

For Cohort C, approximately 20 participants will be enrolled, which will provide at least 80% chance of observing at least 4 responders in this cohort if the underlying ORR is 30%.

3.4. Schedule of Assessments

Refer to Protocol Amendment 2 dated 14 JAN 2020 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Day 1

Day 1 is the date that the first dose of pemigatinib is administered to the participants.

4.1.2. Study Day

If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as

Day # = (visit/reporting date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.3. Baseline Value

Baseline is the last nonmissing measurement obtained before the first administration of pemigatinib. When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following convention to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

4.1.4. Handling of Missing and Incomplete Data

In general, values for missing data will not be handled unless methods for handling missing dates are specified in this section or relevant sections. The original reported dates collected on the eCRF should be used in all relevant listings. The following rules will be used for handling partial dates for analyses requiring dates.

When calculating time since diagnosis of cancer, partial cancer diagnosis date will be handled as follows in the calculation:

- If only the day is missing, then use the first day of the month.
- If both the month and day are missing, then use 01 JAN of the year.
- Time since diagnosis will be missing if the diagnosis date is completely missing.

When date of last dose is used in deriving variables such as duration of treatment or TEAE flag, missing or partial date of last dose will be handled as follows:

- If only the day is missing, then use the earlier date of the last day of the month or the date that the participant discontinued treatment.
- Otherwise, the date that the participant discontinued treatment will be used as the date of the last dose.

For relevant efficacy endpoints, partial date of death will be handled as follows in the calculation:

- If mmyyyy for the last known alive date = mmyyyy for the death date, then the death date will be set to the day after the last known alive date.
- If mmyyyy for the last known alive date < mmyyyy for the death date, then the death date will be set to the first day of the death month.
- Otherwise, the partial death date will not be handled.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of pemigatinib is administered. Scheduled cycle length is 21 days. Actual Day 1 of subsequent cycles will correspond with the first day of administration of pemigatinib in that cycle.

4.1.6. Analysis Window

For parameters that will be summarized by visit, the nominal visit as recorded on the eCRF will be used. There will be no additional analysis windowing done based on the assessment date.

4.2. Variable Definitions

4.2.1. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of pemigatinib.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the date of first administration of pemigatinib and is ongoing throughout the study or ends on/after the date of first study drug administration.
- On/after the date of first administration of pemigatinib and is ongoing or ends during the course of study drug administration.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after first dose of pemigatinib. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9 or later) will be used for the generation of all tables, graphs, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analyses are planned for this study as defined in Section 9.

5.2. Treatment Groups

This is an open-label, single-treatment group study. Participants will be summarized by treatment cohort and by total. Cohort determination will be based on FGFR mutation or gene rearrangement results from central genomics laboratory.

5.3. Analysis Populations

5.3.1. Efficacy Evaluable Population

The efficacy evaluable population includes all enrolled participants in Cohorts A, B, and C who received at least 1 dose of pemigatinib. The efficacy evaluable population will be used for analyses of all efficacy data.

5.3.2. Safety Population

The safety population includes all enrolled participants who received at least 1 dose of pemigatinib. The safety population will be used for the summary of demographics, baseline characteristics, participant disposition and all safety analyses.

5.3.3. Per Protocol Population

The PP population includes all efficacy evaluable population participants who are sufficiently compliant with the Protocol.

The following procedures will be performed to identify those participants who are to be excluded from the PP population :

- Clinical review of Protocol deviations
- Clinical review of concomitant medications as defined in Section 6.6 of the Protocol
- Clinical review of the dose administration and drug accountability listing

The determination of participants being considered for exclusion from the PP population by the clinical team will be prepared and signed before database freeze.

The PP population will be used in the supportive sensitivity analyses for efficacy endpoints.

5.3.4. RECIST Evaluable Population

The RECIST evaluable population includes all efficacy evaluable population participants who have at least 2 objective tumor response assessments per independent centralized radiological review or who discontinued from the study.

RECIST evaluable population will be used for ORR analysis in the interim.

6. BASELINE, EXPOSURE, AND DISPOSITION

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

6.1.1. Demographics and Baseline Characteristics

The following demographics characteristics will be summarized for the safety population: age, sex, race, ethnicity, weight, and height.

6.1.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for the safety population: ECOG performance status, baseline parathyroid hormone, and baseline phosphate.

6.1.3. Disease History

For those who have solid tumor cancer history in the safety population, time since diagnosis, solid tumor cancer type, TNM classification at diagnosis and baseline, current stage, current sites of disease, and tumor marker test result will be summarized.

For those who have glioblastoma cancer history in the safety population, time since diagnosis, basis of initial diagnosis, time since reoccurrence, initial and current tumor WHO grade, infratentorial, supratentorial and CSF involvement at diagnosis and baseline, cerebral hemisphere involvement at diagnosis and baseline, multifocal disease at baseline and current sites of disease, and MGMT status will be summarized.

Time since diagnosis will be calculated as follows:

Time since diagnosis (years) = (Day 1 date – date of diagnosis + 1) / 365.25.

Time since reoccurrence will be calculated as follows:

Time since reoccurrence (months) = (Day 1 date – date of reoccurrence + 1) / 30.44.

6.1.4. Prior Therapy

The number of prior systemic cancer therapy regimens will be summarized for all participants in the safety population. The component drugs of prior systemic therapy regimens will be coded using the WHO Drug Dictionary. Number and percentage of participants with each drug will be summarized by WHO drug class and WHO drug PT. Regimen name, component drugs, start and stop date, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

The number of participants who received prior radiation will be summarized for the safety population. Radiotherapy type, body site, reason for regimen, start and stop date, total dose, and best response will be listed.

The number of participants who received prior radiotherapy for glioblastoma will be summarized for the safety population. Body type, start and stop date, total dose, radiation therapy technique, radiation method, and best response will be listed.

The number of participants who had prior surgery or surgical procedure for disease under study and for glioblastoma will be summarized for the safety population. Date and description of the surgery/procedure will be listed for disease under study and glioblastoma, extent of resection for glioblastoma will also be listed.

The number of participants who had prior loco-regional therapy will be summarized for the safety population. Therapy/treatment name, start and stop date, best response, reason for discontinuation and date of relapse/progression will be listed.

6.1.5. Medical History

For participants in the safety population, medical history will be summarized by assigned cohort. This summation will include the number and percentage of participants with significant medical history for each body system/organ class as documented on the eCRF.

6.2. Disposition of Participant

The number and percentage of participants who were treated, who were ongoing with study treatment, who discontinued study treatment with a primary reason for discontinuation, who were still in study, and who withdrew from the study with a primary reason for withdrawal will be summarized for the safety population.

The number and percentage of participants who were screened and enrolled will be summarized.

6.3. Protocol Deviations

Protocol deviations recorded on the eCRF will be summarized and listed.

6.4. Exposure

For participants in the safety population, exposure to pemigatinib will be summarized descriptively as the following:

- **Number of treatment cycles:** Number of cycles with a nonzero dose of pemigatinib.
- **Duration of treatment with pemigatinib (days):**

  Date of last dose of pemigatinib − date of first dose of pemigatinib + 1.
- **Average daily dose of pemigatinib (mg/day):**

  Total actual pemigatinib dose taken (mg) / duration of treatment with pemigatinib (days).
- **Pemigatinib dose modifications:** Number of participants who had pemigatinib dose reduction, and interruption will be summarized.

6.5. Study Drug Compliance

For participants in the safety population, overall compliance (%) for pemigatinib will be calculated for all participants as

Compliance (%) = 100 × [total dose actually taken] / [total prescribed dose].

The total prescribed dose is defined as the sum of the doses prescribed by the investigator accounting for dose modifications.

The total actual dose taken will be calculated based on information entered on the Drug Accountability eCRF. If there are dispensed drugs that have not been returned yet, the actual dose taken starting from the dispense date of the unreturned drugs will be imputed by the dose taken as reported on the Dosing eCRF.

6.6. Prior and Concomitant Medication

Prior medications and concomitant medications will be coded using the WHO Drug Dictionary. Number and percentage of participants in the safety population for each prior and concomitant medications will be summarized by WHO drug class and WHO drug PT.

7. EFFICACY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

7.1. Efficacy Hypotheses

Objective Response Rate (Primary Endpoint): Administration of pemigatinib to participants in Cohort A and B improves ORR from 15%. Assume ORR_A and ORR_B are the ORRs for cohort A and B respectively.

The hypotheses for Cohort A are as follows:

- H_0 (null hypothesis): $ORR_A \leq 15\%$
- H_A (alternative hypothesis): $ORR_A > 15\%$

The hypotheses for cohort B are as follows:

- H_0 (null hypothesis): $ORR_B \leq 15\%$
- H_A (alternative hypothesis): $ORR_B > 15\%$

7.2. Analysis of the Primary Efficacy Parameter

7.2.1. Primary Efficacy Analysis

The primary endpoints of the study are ORR in Cohort A and Cohort B, respectively. Objective response rate is defined as the proportion of participants who achieved a CR or a PR based on RECIST v1.1 or RANO, as assessed by an independent centralized radiological review committee. Confirmation of CR and PR is required and documented in the Independent Central Review Charter. This analysis will be based on the efficacy evaluable population. Participants

who do not have sufficient baseline or on-study response assessment information to be adequately assessed for response status will be included in the denominators in the calculation of ORR. The 95% CI for the ORR will be estimated using the Clopper-Pearson method. The p-value from the exact binomial test will be provided.

The ORR will also be analyzed based on the PP population as a sensitivity analysis.

7.2.1.1. Response Criteria

Overall disease status will be categorized using RECIST v1.1 (Eisenhauer et al 2009) and RANO. Participants will have their overall response evaluated as CR, PR, SD, PD, or NE at each postbaseline radiological assessment. Assessments using RECIST v1.1 are based on changes in target lesions, nontarget lesions, and appearance of new lesions. Assessments using RANO are based on enhancing measurable lesions, enhancing nonmeasurable/nontarget lesions, nonenhancing T2/FLAIR/nontarget lesions, new lesions, steroid use, and clinical status.

7.2.1.2. Objective Response Rates and Best Overall Response

A participant is considered an objective responder if they have a best overall response of CR or PR at any postbaseline visit before first PD.

In general, under RECIST v1.1 and RANO, best overall response is the best response recorded postbaseline before and including the first PD, in the order of CR, PR, SD, PD, and NE. The best overall response will be determined from response assessments before or on the same day as new anticancer therapy. If any alternative cancer therapy is taken while on study, any subsequent assessments will be excluded from the best overall response determination.

In the case of SD, measurements must meet the SD criteria at least once after the date of first dose at a minimum interval of 42 days. Participants who fail to meet this criterion will have best overall response of PD if the next available assessment indicates PD or NE if there is no additional assessment available.

7.2.2. Subgroup Analyses for Primary Endpoint

Subgroup analysis of the primary endpoint will be performed based on appropriate intrinsic and extrinsic factors if needed.

7.2.3. Sensitivity and Supportive Analyses for Primary Endpoint

The ORR will be analyzed based on the PP population as a sensitivity analysis.

7.3. Analysis of the Secondary Efficacy Parameters

7.3.1. Progression-Free Survival

Progression-free survival is defined as the time from date of first dose of study drug to the earliest date of PD or death, whichever is first. Progressive disease is evaluated based on RECIST v1.1 or RANO, by the ICR. Partial death dates will be handled using the rules described in Section 4.1.4. Participants who are alive without progression before analysis cutoff date will be censored. Censoring for PFS will follow the algorithm outlined in Table 2, which is

based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2015, FDA 2018).

Table 2: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessments	Censored	Day 1
No valid postbaseline response assessments	Censored	Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of PD
No progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last valid radiologic assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last valid radiologic assessment (not NE and not missing)

Table 2: Evaluation and Censoring of Progression-Free Survival (Continued)

Situation	Outcome	Date of Progression or Censoring
New anticancer treatment started	Censored	Date of last valid radiologic assessment (not NE and not missing) on/before starting a new anticancer treatment
Death before first progressive response assessment	Progressed	Date of death
Death between adequate response assessments	Progressed	Date of death
Death or progression after 2 or more missed assessments	Censored	Date of last valid radiologic assessment (not NE and not missing)

NE = not evaluable.

Progression-free survival data will be analyzed by the Kaplan-Meier method in Cohorts A and Cohort B, respectively. The number of participants who progressed or died and the number of participants censored will be summarized. The KM estimate of median PFS will be presented with its 95% CI. The 95% CI will be calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

7.3.2. Duration of Response

For objective responders, the duration of response is defined as the time from the date that a participant first achieves CR or PR based on RECIST v1.1 or RANO as assessed by ICR, until the date of first documented disease progression based on RECIST v1.1 or RANO as assessed by ICR, or death. Partial death dates will be handled using the rules described in Section 4.1.4. Participants who are alive without progression before analysis cutoff date will be censored. Censoring of DOR will follow the same algorithm as the censoring of PFS (see Section 7.3.1).

Duration of response data will be analyzed by the Kaplan-Meier method in Cohorts A and B, respectively. The total number of responders, the number of participants who progressed or died, and the number of participants censored will be summarized. The KM estimate of median DOR will be presented with its 95% CI. The 95% CI will be calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

7.3.3. Overall Survival

Overall survival is defined as the time from date of first dose of study drug to the date of death due to any cause. Date of death will be determined using the Death Report, the Survival Follow-Up, and the Participant Status eCRFs. Participants who are lost to follow-up or still alive at the time of analysis will be right-censored at the earlier of the date the participant was last known alive and the clinical data cutoff date for the analysis. The last known alive date is defined as the later of the last study visit and the date the participant was last known alive from the Survival Follow-Up and Participant Status eCRFs. Partial death dates will be handled using the rules described in Section 4.1.4.

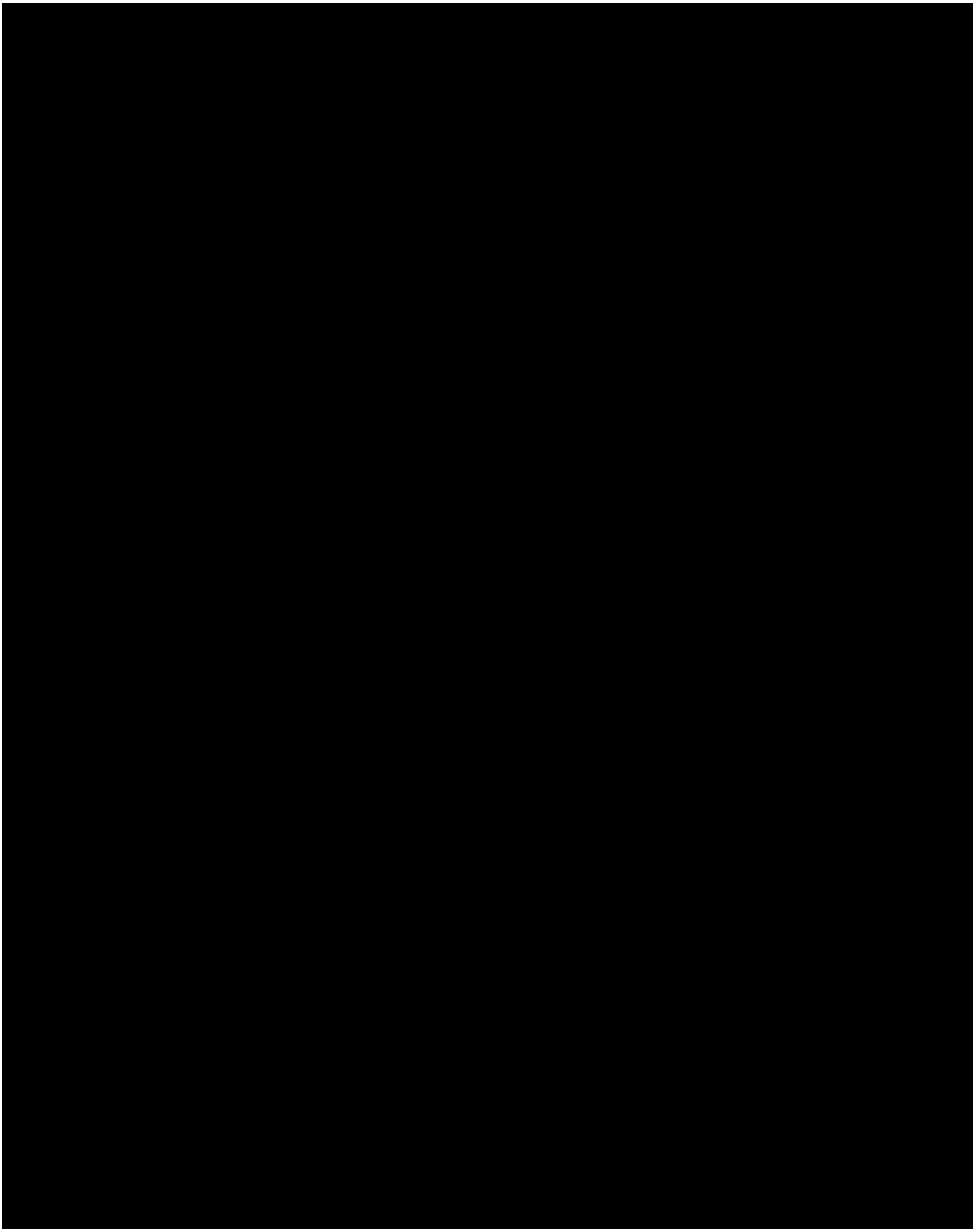
Overall survival will be analyzed by the Kaplan-Meier method in Cohorts A and B, respectively. The number of participants who died and the number of participants censored will be summarized. Median survival will be estimated using the Kaplan-Meier method. The 95% CIs for median survival time will be calculated using the generalization of Brookmeyer and Crowley's method (1982) with log-log transformation (Klein and Moeschberger 1997).

7.4. Other Efficacy Analyses

7.4.1. Largest Percentage Reduction in Sum of Diameters of Target Lesions

For each participant in the efficacy evaluable population with target lesions at baseline, target lesion sizes will be measured by sum of diameters. The best percentage change from baseline, defined as the largest decrease in target lesion size for each participant, will be summarized descriptively, and a waterfall plot of the best percentage change will be generated.

Per RECIST criteria, target lesions considered "too small to measure" will be assigned a default value of 5 mm for purposes of this analysis. Likewise, target lesions identified as "not present" at postbaseline assessments will be assigned 0 mm for this analysis. In the event a target lesion is unaccounted for in a particular postbaseline timepoint (ie, assessment missing or not evaluable), then the overall sum of diameters for target lesions will not be evaluable for that postbaseline timepoint.



8. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays. Sample data displays are included in a separate document.

8.1. General Considerations

The analyses for this section will be provided for the safety population. Summary tables may be replaced with listings when appropriate. For instance, an AE frequency table may be replaced with a listing if it only contains a few unique PTs reported on relatively few participants.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug until 30 days after the last dose of study drug. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study drug administration. For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment emergent.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE v5.0. The CTCAE reporting guidelines and grading details are available on the CTEP website.

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v5.0 criteria, it will be graded on a scale of 1 to 5 as follows: 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, and 5 = fatal. All toxicities will be graded based on the worst level reached, not the level they may have reached if they had not been treated. When the intensity of an AE changes over time for a reporting period (eg, between visits), each change in intensity will be reported as an AE until the event resolves.

The subset of AEs considered by the investigator to be related to study drug will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study drug, the AE will be considered to be treatment-related. The incidence of AEs and treatment-related AEs will be tabulated. In addition, SAEs will also be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

8.2.2. Clinically Notable Adverse Events

Specific groupings of clinically notable AEs will be considered and the number of participants with at least 1 event within each grouping will be reported. Such groups consist of AEs for which there is a specific clinical interest in connection with pemigatinib or AEs that are similar in nature (although not identical). The groups are defined as per Table 4. All clinically notable AEs are defined through reviewing PT according to the current MedDRA v21.1.

Table 4: Clinically Notable Adverse Events Groupings

Categories	Preferred Terms
Serous retinal detachment	Serous retinal detachment, detachment of macular retinal pigment epithelium, detachment of retinal pigment epithelium, retinal detachment, subretinal fluid, chorioretinopathy, retinal pigment epitheliopathy, chorioretinal disorder, retinopathy, maculopathy, retinal disorder, retinal thickening, chorioretinal folds, chorioretinal scar
Nail toxicity	Nail toxicity, nail bed tenderness, nail bed disorder, nail bed bleeding, nail disorder, nail discolouration, nail discomfort, nail dystrophy, nail hypertrophy, nail ridging, nail infection, onychalgia, onychoclasis, onycholysis, onychomadesis, onychomycosis, paronychia, fungal paronychia
Hyperphosphatemia	Hyperphosphataemia, blood phosphorus increased
Hypophosphatemia	Hypophosphataemia, blood phosphorus decreased
Dry eye	Dry eye, meibomian gland dysfunction, lacrimation increased, keratitis, punctate keratitis, pinguecula, pterygium
eyelash changes	Eyelash changes, growth of eyelashes, trichiasis, trichomegaly
vision blurred	vision blurred, visual impairment, visual acuity reduced
vitreous detachment	Vitreous detachment, vitreous floaters

8.2.3. Adverse Event Summaries

An overall summary of AEs by cohorts will include:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants reporting any serious TEAEs
- Number (%) of participants reporting any Grade 3 or higher TEAEs
- Number (%) of participants reporting any TEAEs related to pemigatinib
- Number (%) of participants who temporarily interrupted pemigatinib because of TEAEs
- Number (%) of participants who permanently discontinued pemigatinib because of TEAEs
- Number (%) of participants with pemigatinib dose reductions because of TEAEs
- Number (%) of participants who had a fatal TEAE

The following summaries will be produced by MedDRA term:

- Summary of TEAEs by MedDRA SOC and PT
- Summary of TEAEs by MedDRA PT in decreasing order of frequency
- Summary of TEAEs by MedDRA SOC, PT, and maximum severity
- Summary of TEAEs by MedDRA SOC, PT, and CTCAE Grade Category
- Summary of Grade 3 or higher TEAEs by MedDRA SOC and PT
- Summary of Grade 3 or higher TEAEs by MedDRA PT in decreasing order of frequency
- Summary of serious TEAEs by MedDRA SOC and PT
- Summary of serious TEAEs by MedDRA PT in decreasing order of frequency
- Summary of pemigatinib treatment-related AEs by MedDRA SOC and PT
- Summary of pemigatinib treatment-related TEAEs by MedDRA PT in decreasing order of frequency
- Summary of Grade 3 or higher pemigatinib treatment-related TEAEs by MedDRA SOC and PT
- Summary of pemigatinib treatment-related serious TEAEs by MedDRA SOC and PT
- Summary of TEAEs with a fatal outcome by MedDRA SOC and PT
- Summary of TEAEs leading to pemigatinib dose reduction by MedDRA SOC and PT
- Summary of TEAEs leading to pemigatinib dose interruption by MedDRA SOC and PT
- Summary of TEAEs leading to discontinuation of pemigatinib by MedDRA SOC and PT

- Summary of sponsor-defined clinically notable TEAEs by category and PT
- Summary of Grade 3 or higher sponsor-defined clinically notable TEAEs by category and PT
- Summary of serious sponsor-defined clinically notable TEAEs by category and PT
- Summary of sponsor-defined clinically notable TEAEs leading to pemigatinib dose reduction by category and PT
- Summary of sponsor-defined clinically notable TEAEs leading to pemigatinib dose interruption by category and PT
- Summary of sponsor-defined clinically notable TEAEs leading to discontinuation of pemigatinib by category and PT

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by visit for numeric laboratory parameters. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, additional rules may be provided after consultation with the medical monitor to delineate which value will be defined as baseline.

Laboratory test values outside the normal range will be assessed for severity based on the numerical component of CTCAE v5.0.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from central laboratories will be reported in SI units. All tests with numeric values will have a unique unit. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units.

For numeric laboratory values, baseline value, postbaseline value, change from baseline, and percentage change from baseline will be summarized descriptively by visit. The number and percentage of participants with the laboratory values being low, normal, and high will be summarized by visit. In addition, mean change from baseline will be plotted over time for selected laboratory parameters, including phosphate.

Severity grades will be assigned to laboratory test values based on the numerical component of CTCAE v5.0. Shift tables will be presented showing change in CTCAE grade from baseline to worst grade postbaseline. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category. The number of participants who experienced worsening of laboratory abnormalities will be summarized by maximum severity.

8.3.3. Potential Hy's Law Events

The participants with elevated ALT or AST > 3 × upper limit of normal range and alkaline phosphatase < 2 × upper limit of normal range accompanied by total bilirubin > 2 × upper limit of normal range at the same visit will be listed by cohort.

8.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including weight, systolic blood pressure, diastolic blood pressure, pulse, temperature, and respiratory rate will be summarized descriptively.

Normal ranges for vital sign values are defined in Table 5. The abnormal values for participants exhibiting vital sign abnormalities will be listed along with their cohort. Alert vital signs are defined as an absolute value outside the defined normal range and percentage change greater than 25%. Note that the definition of alert vital signs does not apply for body temperature and weight. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 5: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Temperature	> 38°C	< 35.5°C
Respiratory rate	> 24 breaths/min	< 8 breaths/min

8.5. Electrocardiograms

Twelve-lead ECGs including the heart rates and PR, QT, QRS, and QTc intervals will be obtained for each participant during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized for each ECG parameter. Baseline will be determined as the average of all nonmissing values before the first administration of pemigatinib.

Normal ranges for ECG values are defined in Table 6. ECG values will also be considered abnormal if the absolute percentage change from baseline is more than 25% (QRS 30%). Participant exhibiting ECG abnormalities will be listed with study visit and assigned cohort. Abnormal values for participant with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed. Outliers of QT, and QTc values, defined as absolute values > 450 ms, > 500 ms, or change from baseline > 30 ms, will be summarized.

Table 6: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
HR	> 100 bpm	< 45 bpm
PR	> 220 ms	< 75 ms
QT	> 500 ms	< 300 ms
QRS	> 120 ms	< 50 ms
QTc	> 460 ms	< 295 ms

9. INTERIM ANALYSIS

For Cohort A, futility analysis will be performed when approximately 25 participants are enrolled into the cohort and have at least 2 objective tumor response assessments per independent centralized radiological review or are discontinued from the study. Cohort A can be stopped for futility if ≤ 4 responders are observed, for which there is < 10% probability of claiming ORR > 15% at final analysis. This rule is just a guidance and nonbinding.

For Cohort B, futility analysis will be performed when approximately 35 participants are enrolled into the cohort and have at least 2 objective tumor response assessments per independent centralized radiological review or are discontinued from the study. Cohort B can be stopped for futility if ≤ 6 responders are observed, for which there is approximately 14% probability of claiming ORR > 15% at final analysis. This rule is just a guidance and nonbinding.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 7.

Table 7: Statistical Analysis Plan Versions

SAP Version	Date
Original	23 SEP 2020

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

Not applicable.

11. REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29-41.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. 2015.

Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. New York: Springer-Verlag. 1997.

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures and listings for the clinical study report. Shells are provided in a separate document for tables that are not in the Standard Safety Tables.

The lists of tables, figures, and listings are to be used as guidelines. Modifications of the lists that do not otherwise affect the nature of the analysis will not warrant an amendment to the SAP.

Tables

Table No.	Title	Population
Baseline and Demographic Characteristics		
1.1 Disposition		
1.1.1	Analysis Populations	All Enrolled
1.1.2	Summary of Participant Disposition	Safety
1.1.3	Summary of Number of Participants Enrolled by Country and Site	Safety
1.1.4	Summary of Protocol Deviations	Safety
1.2 Demography and Baseline Characteristics		
1.2.1	Summary of Demographics and Baseline Characteristics	Safety
1.3 Baseline Disease Characteristics		
1.3.1.1	Summary of Baseline Disease Characteristics	Safety
1.3.1.2	Summary of Baseline Disease Characteristics – Glioblastoma	Safety
1.3.2	Summary of Prior Systematic Cancer Therapy by WHO Drug Class and Preferred Term	Safety
1.3.3	Summary of Prior Cancer Therapy	Safety
1.4 Prior Medication and Concomitant Medication		
1.4.1	Summary of Prior Medications	Safety
1.4.2	Summary of Concomitant Medications	Safety
1.5 General Medical History		
1.5.1	Summary of General Medical History	Safety
Efficacy		
2.1 Primary Efficacy		
2.1.1	Summary of Best Response and Objective Response Rate – Cohort A and B	Efficacy
2.1.2	Summary of Best Response and Objective Response Rate – Cohort A and B	Per Protocol
2.2 Secondary Efficacy		
2.2.1	Summary of Progression-Free Survival – Cohort A and B	Efficacy
2.2.2	Summary of Duration of Response – Cohort A and B	Efficacy
2.2.3	Summary of Overall Survival – Cohort A and B	Efficacy
2.2.4	Summary of Best Change in Target Lesion Size	Efficacy
[redacted]		

Table No.	Title	Population
[redacted]		
Safety		
3.1 Dose Exposure		
3.1.1	Summary of Exposure and Duration of Exposure to Pemigatinib	Safety
3.1.3	Summary of Study Drug Compliance	Safety
3.2 Adverse Events		
3.2.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
3.2.2	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.3	Summary of Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.4	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and Maximum Severity	Safety
3.2.5	Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Grade Category	Safety
3.2.6	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.7	Summary of Grade 3 or Higher Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.8	Summary of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.9	Summary of Serious Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.10	Summary of Pemigatinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.11	Summary of Pemigatinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.12	Summary of Grade 3 or Higher Pemigatinib Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.13	Summary of Pemigatinib Treatment-Related Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.14	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety
3.2.15	Summary of Treatment-Emergent Adverse Events Leading to Pemigatinib Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety
3.2.16	Summary of Treatment-Emergent Adverse Events Leading to Pemigatinib Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety
3.2.17	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Pemigatinib by MedDRA System Organ Class and Preferred Term	Safety
3.2.18	Summary of Sponsor-Defined Clinically Notable TEAEs by Category and Preferred Term	Safety
3.2.19	Summary of Grade 3 or Higher Sponsor-Defined Clinically Notable TEAEs by Category and Preferred Term	Safety
3.2.20	Summary of Serious Sponsor-Defined Clinically Notable TEAEs by Category and Preferred Term	Safety
3.2.21	Summary of Sponsor-Defined Clinically Notable TEAEs Leading to Pemigatinib Dose Reduction by Category and Preferred Term	Safety

Table No.	Title	Population
3.2.22	Summary of Sponsor-Defined Clinically Notable TEAEs Leading to Pemigatinib Dose Interruption by Category and Preferred Term	Safety
3.2.23	Summary of Sponsor-Defined Clinically Notable TEAEs Leading to Discontinuation of Pemigatinib by Category and Preferred Term	Safety
3.3 Laboratory		
3.3.1.1	Summary of Laboratory Values – Hematology	Safety
3.3.1.2	Summary of Laboratory Values – Chemistry	Safety
3.3.1.3	Summary of Laboratory Values – Coagulation	Safety
3.3.1.4	Summary of Laboratory Values – Urinalysis	Safety
3.3.3.1	Shift Summary of Hematology Laboratory Values in CTC Grade – to the Worst Abnormal Value	Safety
3.3.3.2	Shift Summary of Chemistry Laboratory Values in CTC Grade – to the Worst Abnormal Value	Safety
3.3.3.3	Shift Summary of Coagulation Laboratory Values in CTC Grade – to the Worst Abnormal Value	Safety
3.3.3.4	Treatment-Emergent Worsening of Laboratory Abnormalities – Hematology	Safety
3.3.3.5	Treatment-Emergent Worsening of Laboratory Abnormalities – Chemistry	Safety
3.3.3.6	Treatment-Emergent Worsening of Laboratory Abnormalities – Coagulation	Safety
3.4 Vital Signs		
3.4.1	Summary of Systolic Blood Pressure	Safety
3.4.2	Summary of Diastolic Blood Pressure	Safety
3.4.3	Summary of Pulse	Safety
3.4.4	Summary of Respiration Rate	Safety
3.4.5	Summary of Body Temperature	Safety
3.4.6	Summary of Weight	Safety
3.5 ECG		
3.5.1	Summary of PR Interval (ms) From 12-Lead ECG	Safety
3.5.2	Summary of QRS Interval (ms) From 12-Lead ECG	Safety
3.5.3	Summary of QT Interval (ms) From 12-Lead ECG	Safety
3.5.4	Summary of QTc Interval (ms) From 12-Lead ECG	Safety
3.5.5	Summary of Heart Rate (bpm) From 12-Lead ECG	Safety
3.5.6	Summary of Outliers of QT, QTcB, and QTcF Interval Values (ms) From 12-Lead ECG	Safety
3.5.7	Summary of Clinically Significant ECG Abnormality	Safety

Figures

Figure No.	Title
4.1.1	Kaplan-Meier Estimates of Progression -Free Survival
4.2.1	Kaplan-Meier Estimates of Duration of Response
4.2.2	Kaplan-Meier Estimates of Overall Response
4.3.1	Waterfall Plot of Best Percentage Change in Sum of Target Lesions
4.3.2	Swimmer Plot of Duration of Treatment
4.6.1	Line Graph of Selected Laboratory Values by Study Visit

Listings

Listing No.	Title
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2.1.1	Participant Enrollment and Disposition Status
2.1.2	Participant Inclusion and Exclusion Criteria Violations
2.1.4	Survival Follow-up
2.2 Protocol Deviation	
2.2.1	Protocol Deviations
2.3 Data Excluded From Efficacy, and/or Safety Analyses	
2.3.1	Analysis Population
2.4 Demographic and Baseline Characteristics (Including Prior and Concomitant Medications)	
2.4.1	Demographic and Baseline Characteristics
2.4.2.1	Disease History
2.4.2.2	Disease History – Glioblastoma
2.4.3.1	Prior Radiation Treatment – Solid Tumor
2.4.3.2	Prior Radiation Treatment – Glioblastoma
2.4.4	Prior Systemic Therapy
2.4.5.1	Prior Surgery or Surgical Procedure – Solid Tumor
2.4.5.2	Prior Surgery or Surgical Procedure – Glioblastoma
2.4.6	Prior Loco-Regional Therapy
2.4.7	Medical History
2.4.8	Prior and Concomitant Medication
2.4.9	Procedures and Non-Drug Therapy
2.4.10	Post Therapy
2.5 Drug Compliance	
2.5.1	Study Drug Compliance
2.5.2	Study Drug Administration
2.6 Efficacy	
2.6.1	Deaths
2.6.2	Best Overall Response, Duration of Response, and Progression-Free Survival
2.6.3.1	Overall Response Assessment by Visit – RECIST
2.6.3.2	Overall Response Assessment by Visit – RANO
2.6.4.1	Response Assessment: Target Lesions – RECIST
2.6.4.2	Response Assessment: Measurable Lesions – RANO
2.6.5.1	Response Assessment: Nontarget Lesions – RECIST
2.6.5.2	Response Assessment: Nonmeasurable Lesions – RANO
2.6.6.1	Response Assessment: New Lesions – RECIST
2.6.6.2	Response Assessment: New Lesions – RANO
2.6.7	Tumor Tissue
2.6.8	ECOG Status
[redacted]	
2.7 Adverse Events	
2.7.1	Adverse Events

Listing No.	Title
2.7.2	Serious Adverse Events
2.7.3	Grade 3 and Higher Adverse Events
2.7.4	Fatal Adverse Events
2.7.5	Treatment-Related Adverse Events
2.7.6	Adverse Events Leading to Interruption, Reduction, or Discontinuation of Pemigatinib
2.7.7	Sponsor-Defined Clinically Notable Adverse Events
2.8 Laboratory Data	
2.8.1	Clinical Laboratory Values – Hematology
2.8.2	Clinical Laboratory Values – Chemistry
2.8.3	Clinical Laboratory Values – Coagulation
2.8.4	Clinical Laboratory Values – Urinalysis
2.8.5	Abnormal Clinical Laboratory Values – Hematology
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2.8.7	Abnormal Clinical Laboratory Values – Coagulation
2.8.8	Potential Hy's Law Events
2.8.9	Serology Lab Test
2.8.10	Pregnancy Test
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2.9.2	Abnormal Vital Sign Values
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2.10 ECG	
2.10.1	12-Lead ECG Values
2.10.2	Abnormal 12-Lead ECG Values
2.10.3	Alert 12-Lead ECG Values
2.11 Physical Examinations	
2.11.1	Eye Examination