Official Title:	**A Phase 2, Open-Label, Single-Agent, Multicenter Study to Evaluate the Efficacy and Safety of Pemigatinib (INCB054828) in Subjects With Metastatic or Surgically Unresectable Urothelial Carcinoma Harboring FGF/FGFR Alterations - (FIGHT-201)**
NCT Number:	NCT02872714
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STATISTICAL ANALYSIS PLAN

INCB 54828-201

A Phase 2, Open-Label, Single-Agent, Multicenter Study to Evaluate the Efficacy and Safety of INCB054828 in Subjects With Metastatic or Surgically Unresectable Urothelial Carcinoma Harboring FGF/FGFR Alterations

IND Number:	[redacted]
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Protocol Version:	**Protocol Amendment 6 dated 20 NOV 2018**
CRF Approval Date:	**03 OCT 2018**
SAP Version:	**Amendment 1**
SAP Author:	[redacted]**, Biostatistics**
Date of Plan:	**12 JUN 2019**

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
BMI	body mass index
CI	confidence interval
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	not evaluable
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PP	per protocol
PR	partial response
QTcF	Fridericia correction
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SI	international system of units
TEAE	treatment-emergent adverse event
TNM	TNM Classification of Malignant Tumors
WHO	World Health Organization

1. INTRODUCTION

This is a Phase 2, open-label, monotherapy study of INCB054828 in subjects with metastatic or surgically unresectable urothelial cancer harboring FGF/FGFR alterations. A detailed description of the investigational product, target patient population, rationale for doses to be examined, and potential risks and benefits of treatment with INCB054828 is provided in Section 1 of the Protocol.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the Study INCB 54828-201 Protocol.

2. INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on INCB 54828-201 Protocol Amendment 6 dated 20 NOV 2018 and case report form (CRF) approved on 03 OCT 2018. Unless superseded by an amendment, this SAP will be effective for all subsequent protocol amendments and eCRF versions.

2.2. Study Objectives

2.2.1. Primary Objective

- To evaluate the objective response rate (ORR) of INCB054828 as a monotherapy in the treatment of metastatic or surgically unresectable urothelial carcinoma with fibroblast growth factor receptor 3 (FGFR3) mutations or fusions.

2.2.2. Secondary Objectives

- To evaluate the efficacy of INCB054828 in subjects with advanced/metastatic or surgically unresectable urothelial cancer with different molecular subgroups.
- To evaluate the safety and tolerability of INCB054828.
- To evaluate other clinical efficacy measurements, including duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

[redacted]

2.3. Study Endpoints

2.3.1. Primary Endpoint

- Objective response rate in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and INCB054828 administered using a continuous dose regimen (Cohort A-CD). Response will be based on a review of scans by a centralized radiological review committee.

2.3.2. Secondary Endpoints

- Objective response rate in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and using an intermittent dose regimen (Cohort A-ID). Response will be based on review of scans by a centralized radiological review committee.
- Objective response rate in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and using a continuous dose regimen (Cohort A-CD). Response will be based on review of scans by centralized radiological review committee.
- Objective response rate in all subjects receiving INCB054828 administered as continuous dose regimen or intermittent dose regimen (Cohorts A-ID, A-CD, and B combined). Response will be based on review of scans by a centralized radiological review committee.
- Objective response rate in subjects with all other FGF/FGFR alterations (Cohort B). Response will be based on a review of scans by a centralized radiological review committee.
- PFS (Cohort A-ID, Cohort A-CD, and Cohort B, separately).
- DOR (Cohort A-ID, Cohort A-CD, and Cohort B, separately).
- OS (Cohort A-ID, Cohort A-CD, and Cohort B, separately).
- Safety and tolerability, assessed by monitoring frequency, duration, and severity of adverse events (AEs); through physical examinations; by evaluating changes in vital signs and electrocardiograms (ECGs); and through clinical laboratory blood and urine sample evaluations.

[redacted]

3. STUDY DESIGN

This is an open-label monotherapy study of INCB054828 in subjects with metastatic or surgically unresectable urothelial cancer harboring FGF/FGFR alterations. Subjects will receive INCB054828 at a once daily starting dose of 13.5 mg on a 2-weeks-on-therapy and 1-week-off-therapy schedule.

Protocol Amendment 5 introduces a new dose regimen for INCB054828 (13.5 mg continuous dose regimen [no planned dose holiday]). Subjects receiving a continuous dose regimen will be enrolled in a new cohort (Cohort A-CD). *Note*: Subjects enrolled in the current Cohort A (intermittent dose regimen [Cohort A-ID]) will continue to receive treatment with INCB054828 as 2-weeks-on/1-week-off therapy. Subjects in Cohort A-ID will not switch to a continuous dose regimen.

Subjects can enroll if they have a known FGF/FGFR alteration and have either: (a) failed at least 1 previous treatment for their metastatic or surgically unresectable urothelial carcinoma (ie, chemotherapy, immunotherapy) or (b) have not received chemotherapy for metastatic or surgically unresectable urothelial carcinoma due to poor performance status (ie, ECOG performance status of 2) and have insufficient renal function (ie, creatinine clearance < 60 mL/min or local guidelines).

Potential subjects can be screened/enrolled based on local genomic sequencing but must have their tumor samples sequenced through the sponsor's central laboratory. The results from the central laboratory will be considered final. In cases where the central laboratory does not show an alteration, the investigator will decide if continuing treatment is in the best interest of the subject; however, the subject will not be included in the efficacy analyses and may be replaced.

The study will enroll approximately 240 subjects:

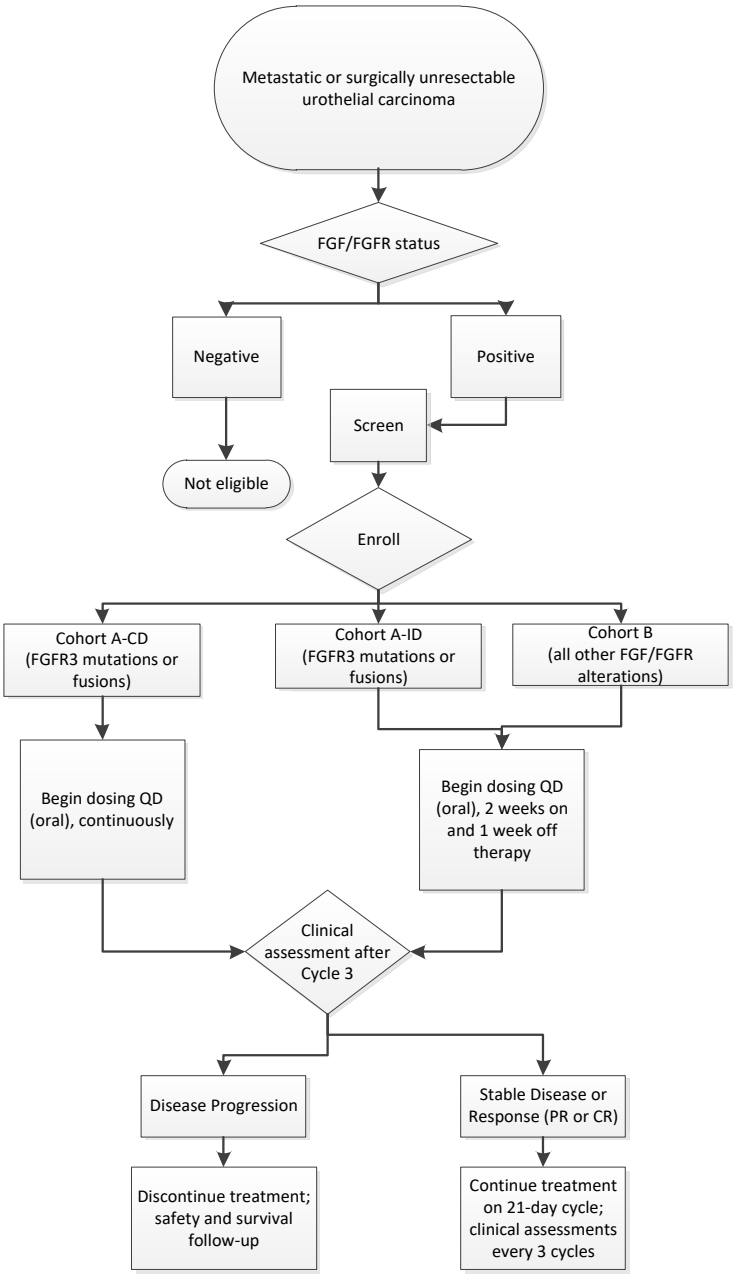
- Cohort A-ID: FGFR3 mutations or fusions (n = 100); this cohort will complete enrollment before Cohort A-CD begins enrolling subjects.
- Cohort A-CD: FGFR3 mutations or fusions (n = 100).
- Cohort B: all other FGF/FGFR alterations (n = 40).

Once a subject has completed screening and has enrolled into the study, treatment will start on Day 1. Subjects will undergo routine safety assessments during treatment as well as routine efficacy assessments. Subjects will be allowed to continue receiving study drug in 21-day cycles until documented disease progression or unacceptable toxicity is reported.

In addition to introducing continuous dosing, up-titration will be implemented. Any subject who does not reach the target serum phosphate level of > 5.5 mg/dL will increase the daily dose to 18mg.

The overall study design is shown in Figure 1.

Figure 1: Study Design



3.1. Control of Type I Error

All statistical analyses are exploratory in nature. Unless otherwise specified, all confidence intervals (CIs) provided will be at the 95% confidence level.

3.2. Sample Size Considerations

Approximately 100 subjects who have FGFR3 mutations or fusions based on central genomics laboratory results are planned per each Cohort A-ID and Cohort A-CD. An agent used in the second-line setting that has an ORR of 35% would be considered clinically meaningful. With the assumed rates of 35% for the intervention, a sample size of approximately 100 subjects per each Cohort A-ID and Cohort A-CD would provide a 95% CI with a lower limit of > 25%, assuming 10% lost to follow-up. Approximately 40 subjects will be enrolled in Cohort B (all other FGF/FGFR alterations), which will provide > 80% chance of observing at least 6 responders if the underlying ORR is 20%.

Subjects enrolled without known FGF/FGFR alteration from the sponsor's central laboratory will not be included in the efficacy analyses and may be replaced.

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 first dose of study drug (INCB054828) is administered to the subjects.

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 the Day 1 date, 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 defined as the last nonmissing measurement obtained prior to the first administration of INCB054828. 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 imputed unless methods for handling missing data are specified in this section or relevant sections.

Partial disease/cancer diagnosis date will be handled as follows:

- If only the day is missing, then the imputed day will be the first of the month.
- If both the month and day are missing, then the imputed day and month will be 01 JAN.
- No imputation will be done if the date is completely missing.

For relevant efficacy endpoints, partial death date will be imputed as follows:

- If mmyyyy for the last contact date = mmyyyy for the death date, then the death date will be set to the day after the last contact date.
- If mmyyyy for the last contact 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 imputed.

4.1.5. Cycle Length and Duration

Cycle 1 Day 1 is the day that the first dose of INCB054828 is administered. Scheduled cycle length is 21 days, with first day of each cycle corresponding with the first day of INCB054828 administration 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

The following variables will only be calculated if not reported on the eCRF.

4.2.1. Age

Subject age will be calculated as the integer part of the number of years from date of birth to the date of signing the informed consent form, using the following formula:

Age = integer part of (date of informed consent – date of birth + 1) / 365.25

4.2.2. Body Mass Index

BMI will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2

4.2.3. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the first dose of INCB054828.

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

- Before the date of first administration of INCB054828 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 INCB054828 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 INCB054828. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant medication.

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; v9.1 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 subjects in each category.

5.2. Treatment Groups

This is an open label, single-treatment group study. Subjects will be summarized by cohort and by total.

5.3. Analysis Populations

5.3.1. Efficacy Evaluable Population

The efficacy evaluable population includes all subjects enrolled in the study who have a known FGF/FGFR alteration from the sponsor's central laboratory and received at least 1 dose of INCB054828. The efficacy evaluable population will be used for analyses of all efficacy data.

5.3.2. Per Protocol Population

Subjects in the efficacy evaluable population who are considered to be sufficiently compliant with the Protocol compose the PP population.

The following procedures will be performed to identify those subjects who are to be excluded from the PP population before the database freeze:

- Clinical review of Protocol deviations/violations.
- Clinical review of concomitant medications as defined in Section 5.6 of the Protocol.
- Clinical review of the dose administration and drug accountability listing.

The determination of subjects 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.

5.3.3. Safety Population

The safety population includes all enrolled subjects who received at least 1 dose of INCB054828. All safety analyses will be conducted using the safety population.

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of data displays and sample data displays.

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

Demographic and baseline characteristics, disease history, and prior therapy will be summarized for the efficacy evaluable population and safety population and listed.

6.1.1. Demographics

The following demographic characteristics will be summarized for the efficacy evaluable population and safety population (if needed): age, sex, race, ethnicity, weight (by gender), height, and BMI.

6.1.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized for the efficacy evaluable population and safety population (if needed): ECOG performance status and baseline phosphate.

6.1.3. Disease History

Time since diagnosis, stage at diagnosis, bladder cancer location at diagnosis, histology at diagnosis and baseline, and current TNM classification will be summarized.

Time since diagnosis will be calculated as:

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

6.1.4. Prior Therapy

Number of subjects who received prior systemic cancer therapy and number of prior systemic cancer therapy regimens, number of subjects who received prior cisplatin, as well as the number of subjects who received prior immune therapy will be summarized for the efficacy evaluable population and safety population (if needed). Immune therapy includes but not is not limited to the following terms: atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab, tremelimumab, and ipilimumab. Regimen name, component drugs, start and stop dates, purpose of the regimen, best response, reason for discontinuation, and date of relapse/progression will be listed.

Number of subjects who received prior radiation will be summarized for the efficacy evaluable population. Radiotherapy type, body site, start and stop dates, total dose, and best response will be listed.

Number of subjects who had prior surgery or surgical procedure for the malignancies under study will be summarized for the efficacy evaluable population. Date and description of the surgery/procedure will be listed.

6.1.5. Medical History

For subjects in the efficacy evaluable population and safety population, medical history will be summarized by system organ class and preferred term and will be listed.

6.2. Disposition of Subjects

The number and percentage of subjects who were treated, discontinued study treatment with a primary reason for discontinuation, and discontinued from the study with a primary reason for withdrawal will be summarized for the efficacy evaluable population and safety population (if needed).

6.3. Protocol Deviations

Protocol deviations collected on the eCRF will be summarized descriptively and listed.

6.4. Exposure

For subjects in the safety population, exposure to INCB054828 will be summarized descriptively as the following:

- **Number of treatment cycles:** Number of cycles with a nonzero dose of INCB054828
- **Duration of treatment (days):** date of last dose of INCB054828 – date of first dose of INCB054828 + 1
- **Average daily dose (mg/day):** total actual INCB054828 dose taken (mg) / duration of treatment (days)

6.5. Study Drug Compliance

Overall compliance, total prescribed dose, and total actual dose of INCB054828 will be summarized descriptively and listed for subjects in the safety population.

Overall compliance (%) for INCB054828 will be calculated for all subjects 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 is dispensed drug that has not been returned yet, the actual dose

taken starting from the dispense date of the unreturned drug 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. For subjects in the safety population, the number and percentage of subjects with prior and concomitant medications will be summarized by WHO drug class and WHO drug term. In the data listing, each medication will be recorded as prior, concomitant, or both prior and concomitant.

7. EFFICACY

Appendix A provides a list of data displays and sample data displays.

7.1. Efficacy Hypotheses

Not applicable.

7.2. Analysis of the Primary Efficacy Parameter

7.2.1. Primary Efficacy Analysis

The primary endpoint of the study is ORR in subjects with FGFR3 mutations or fusions based on the central genomics laboratory results and on a continuous dose regimen, defined as the proportion of subjects with best response of CR or PR based on review of scans by an independent centralized radiological review committee per RECIST v1.1 (Eisenhauer et al 2009). Confirmation of CR and PR is required and documented in the Independent Review Charter. This analysis will be based on the efficacy evaluable population. Subjects 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 calculated using the Clopper-Pearson method.

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

7.2.1.1. Response Criteria

Objective assessment of tumor status will be evaluated by an independent central radiological review committee based on RECIST v1.1, and response status will be logged into the eCRF.

Response status will be recorded at each response assessment visit as CR, PR, SD, PD, or NE.

7.2.1.2. Overall Response Rate and Best Response

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

In general, best overall response is the best response recorded postbaseline prior to and including the first PD, in the order of CR, PR, SD, PD, and NE. A best overall response of CR or PR needs to be confirmed, and confirmation method is described in the Independent Review Charter. 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 49 days. Subjects that 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 Analysis for the Primary Endpoint

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

7.3. Analysis of the Secondary Efficacy Parameters

7.3.1. Secondary Endpoints Involving Objective Response Rate

The secondary endpoints involving ORR in this study include the following:

- ORR in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and using an intermittent dose regimen (Cohort A-ID). Response will be based on review of scans by a centralized radiological review committee.
- ORR in subjects with FGFR3 mutations or fusions based on central genomics laboratory results and using a continuous dose regimen (Cohort A-CD) and intermittent dose regimen (Cohort A-ID). Response will be based on review of scans by centralized radiological review committee.
- ORR in all subjects receiving INCB054828 administered as continuous dose regimen and intermittent dose regimen (Cohorts A-ID, A-CD, and B, combined). Response will be based on review of scans by a centralized radiological review committee.
- ORR in subjects with all other FGF/FGFR alterations (Cohort B). Response will be based on review of scans by a centralized radiological review committee.

The secondary endpoints involving ORR will be analyzed in the same way as the primary endpoint, and the 95% CI for ORR will be calculated using exact method for binomial distribution. Confirmation of CR and PR is required and documented in the Independent Review Charter.

7.3.2. Progression-Free Survival

Progression-free survival is defined as the length of time from the start of the study drug (Day 1) to the earlier of death or disease progression by RECIST v1.1, as assessed by the independent centralized radiological review committee. The date of PD will be the timepoint at which progression is first recorded. Censoring for PFS will follow the algorithm outlined in Table 1, which is based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2015, FDA 2018).

The number of subjects who progressed or died and the number of subjects censored will be summarized. The Kaplan-Meier estimate of median PFS will be presented with its 95% CI. The 95% CI will be calculated using the Brookmeyer and Crowley's method (Brookmeyer and Crowley 1982). The PFS analysis will be conducted for Cohorts A-ID, A-CD, and B.

Table 1: Evaluation and Censoring of Progression-Free Survival

Situation	Outcome	Date of Progression or Censoring
No baseline tumor assessment	Censored	Day 1
No adequate postbaseline response assessment	Censored	Day 1
Progression documented between scheduled response assessments	Progressed	Date of first overall response of progressive disease
No progression	Censored	Date of last adequate response assessment (not NE and not missing)
Study discontinuation for undocumented progression	Censored	Date of last adequate response assessment (not NE and not missing)
Study discontinuation for toxicity or other reason	Censored	Date of last adequate response assessment (not NE and not missing)
New anticancer treatment started	Censored	Date of last adequate response assessment (not NE and not missing) prior to starting of the new anticancer treatment
Death before first progressive disease assessment	Progressed	Date of death
Death between adequate assessment visits	Progressed	Date of death
Death or progression after more than 1 missed assessment	Censored	Date of last adequate response assessment (not NE and not missing)

7.3.3. Overall Survival

Overall survival is defined as the length of time from the start of the study drug (Day 1) until the date of death due to any cause. Date of death will be determined using the Death Report and the Survival Follow-Up eCRFs. Subjects 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 subject was last known alive and the clinical data cut-off date for the analysis. The last known alive date is defined as the later of the last study visit and the date the subject was last known alive from the Survival Follow-Up and Subject Status eCRFs.

The number of subjects who died and the number of subjects censored will be summarized. The Kaplan-Meier estimate of median OS will be presented with its 95% CI. The 95% CI will be calculated using the Brookmeyer and Crowley's method (Brookmeyer and Crowley 1982). The OS analysis will be conducted for Cohorts A-ID, A-CD, and B.

7.3.4. Duration of Response

For objective responders, DOR is the time from the first overall response contributing to an objective response as assessed by an independent centralized radiological review committee to the earlier of death or first overall response of PD occurring after the first overall response contributing to the objective response. Censoring of DOR will follow the same algorithm as the censoring of PFS (see Section 7.3.2).

The total number of responders, the number of subjects who progressed or died, and the number of subjects censored will be summarized. The Kaplan-Meier estimate of median DOR will be presented with its 95% CI. The 95% CI will be calculated using the Brookmeyer and Crowley's method (Brookmeyer and Crowley 1982). The DOR analysis will be conducted for Cohorts A-ID, A-CD, and B.

7.4. Other Efficacy Analyses

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

For subjects with measurable lesions at baseline, target lesion sizes will be measured by sum of diameters. The best percent change from baseline, defined as the largest decrease in target lesion size during the study, will also be summarized, and a waterfall plot of best percent change will be generated.

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, the assessment is missing or NE), then the overall sum of diameters for target lesions will not be evaluable for that postbaseline timepoint.

7.4.2. Investigator-Assessed Efficacy Parameters

ORR, PFS, and DOR based on review of scans by investigator per RECIST v1.1 will be analyzed in a similar fashion as those parameters assessed by an independent centralized radiological review committee. Confirmation of CR and PR is not required.

ORR and DOR assessed by an independent centralized radiological review committee per RECIST v1.1 without requirement of CR and PR confirmation will also be analyzed.

7.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG performance status and changes in status at scheduled assessment times will be summarized.

8. SAFETY AND TOLERABILITY

Appendix A provides a list of data displays and sample data displays.

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 preferred terms reported on relatively few subjects.

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 and within 30 days of 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 to study drug administration.

Adverse events will be tabulated by MedDRA preferred term and system organ class. Severity of AEs will be described and graded using the NCI CTCAE v4.03. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website.

A grading (severity) scale is provided for each AE term. If the toxicity is not included in the CTCAE v4.03 criteria, it will be rated on a scale of 1 to 4 as follows: 1 = mild, 2 = moderate, 3 = severe and 4 = life-threatening. 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. The incidence of AEs and treatment-related AEs will be tabulated. Serious adverse events will also be tabulated.

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

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

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment emergent.

8.2.2. Adverse Event Summaries

An overall summary of AEs by treatment group will include:

- Number (%) of subjects reporting any TEAEs
- Number (%) of subjects reporting any serious TEAEs
- Number (%) of subjects reporting any Grade 3 or 4 TEAEs

- Number (%) of subjects reporting any TEAEs related to INCB054828
- Number (%) of subjects who temporarily interrupted INCB054828 because of TEAEs
- Number (%) of subjects who permanently discontinued INCB054828 because of TEAEs
- Number (%) of subjects with INCB054828 dose reductions because of TEAEs
- Number (%) of subjects who had a fatal TEAE

The following summaries will be produced by MedDRA term (if ≤ 10 subjects appear in a table, a listing may be appropriate):

- Summary of TEAEs by system organ class and preferred term
- Summary of TEAEs by preferred term in decreasing order of frequency
- Summary of TEAEs by system organ class, preferred term, and maximum severity
- Summary of Grade 3 or higher TEAEs by system organ class and preferred term
- Summary of Grade 3 or higher TEAEs by preferred term in decreasing order of frequency
- Summary of INCB054828 treatment-related AEs by system organ class and preferred term
- Summary of treatment-related AEs by preferred term in decreasing order of frequency
- Summary of Grade 3 or higher INCB054828 treatment-related AEs by system organ class and preferred term
- Summary of TEAEs leading to death by system organ class and preferred term
- Summary of serious TEAEs by system organ class and preferred term
- Summary of treatment-related serious TEAEs by system organ class and preferred term
- Summary of TEAEs leading to INCB054828 dose interruption by system organ class and preferred term
- Summary of TEAEs leading to INCB054828 dose reduction by system organ class and preferred term
- Summary of TEAEs leading to discontinuation of INCB054828 by system organ class and preferred term
- Summary of TEAEs and Grade 3 or Higher TEAEs by preferred term in decreasing order of frequency
- Summary of treatment-emergent non-SAEs by system organ class and preferred term

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

For numeric laboratory results, the change and percentage change from baseline will be calculated. Baseline will be determined according to Section 4.1.3. If there are multiple values that meet the criteria for baseline, the value from the central laboratory has priority over the value from the local laboratory. Thereafter, 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 CTCAE grade or similar criteria where clinical intervention is required for CTCAE grading.

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 per test. 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 percent change from baseline will be summarized by visit. In addition, laboratory values and mean change from baseline will be plotted over time for selected laboratory parameters, including creatinine, parathyroid hormone, phosphate, sodium, 25-hydroxyvitamin D, and 1,25-dihidroxyvitamin D.

For the laboratory parameters that have CTCAE grading, shift tables will also be presented showing change in CTCAE severity grade from baseline to worst grade postbaseline. The denominator for the percentage calculation will be the number of subjects in the baseline category.

Categorical laboratory data will be tabulated by visit at baseline and postbaseline visits where appropriate.

8.4. Vital Signs

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

Criteria for clinically notable vital sign abnormalities are defined in Table 2. The abnormal values for subjects exhibiting clinically notable vital sign abnormalities will be listed. Alert vital signs are defined as an absolute value outside the defined range and percentage change from baseline greater than 25%. The abnormal values for subjects exhibiting alert vital sign abnormalities will also be listed.

Table 2: 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	> 38ºC	< 35.5ºC
Respiratory rate	> 24/min	< 8/min

8.5. Electrocardiograms

Twelve-lead ECGs including PR, QRS, QT, and QTcF intervals, as well as heart rate, will be obtained for each subject during the study. Values at each scheduled visit, change, and percent change from baseline will be summarized for each ECG parameter. Change and percent change from baseline will be calculated using the average of all nonmissing values before the first administration of INCB054828 as the baseline value.

Criteria for clinically notable ECG abnormalities are defined in Table 3. The abnormal values for subjects exhibiting clinically notable ECG abnormalities will be listed with study visit. Alert ECG values are defined as both the absolute value outside the defined range and the percentage change greater than 25% (QRS 30%). The abnormal values for subjects exhibiting alert ECG abnormalities will be identified and listed.

Table 3: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTcF	> 460 msec	< 295 msec
PR	> 220 msec	< 75 msec
QRS	> 120 msec	< 50 msec
QT	> 500 msec	< 300 msec

9. INTERIM ANALYSES

A futility analysis will be performed when approximately 45 subjects with FGFR3 mutations or fusions who have been treated and have had at least 1 tumor assessment or have permanently discontinued study treatment in Cohort A-ID. The study will be stopped for futility if 10 or fewer responders are observed, for which there is less than 15% probability of claiming ORR > 25% at final analysis.

10. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 4.

Table 4: Statistical Analysis Plan Versions

SAP Version	Date
Original	16 MAY 2017
Amendment 1	12 JUN 2019

10.1. Changes to Protocol-Defined Analyses

Not applicable.

10.2. Changes to the Statistical Analysis Plan

10.2.1. Original to Amendment 1

The original SAP has been updated to incorporate Protocol Amendments 4, 5, and 6. Specific changes are outlined below:

- Moved analysis of largest percentage reduction in sum of diameters of target lesions from Section 7.3, Analysis of the Secondary Efficacy Parameters to Section 7.4, Other Efficacy Analyses.
- Summaries of prior cisplatin use and prior immune therapy have been added.
- Average daily dose has been updated to use duration of treatment as the denominator.
- Investigator-assessed efficacy parameters have been added as other efficacy analyses.
- Summary of weight has been moved from efficacy section to vital sign section.

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. https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf. Accessed March 5, 2019.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. 2015. https://www.fda.gov/downloads/drugs/guidances/ucm259421.pdf. Accessed March 5, 2019.

APPENDIX A. PLANNED TABLES, FIGURES, AND LISTINGS

This appendix provides a list of the planned tables, figures, and listings for the CSR. Standard tables will follow the conventions in the Standard Safety Tables initial version. Shells are provided for nonstandard tables. In-text tables are identical in structure and content as appendix tables, but follow a Rich Text Format.

The list of tables, figures, and listings and the shells are to be used as guidelines. Modifications of the lists or shells 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		
1.1.1	Analysis Populations	All Enrolled
1.1.2	Summary of Subject Disposition	Efficacy
1.1.3	Summary of Number of Subjects Enrolled by Country and Site	Efficacy
1.1.4	Summary of Protocol Deviations	Efficacy
1.2.1	Summary of Demographics and Baseline Characteristics	Efficacy
1.2.2	Summary of Disease History	Efficacy
1.2.3	Summary of Prior Systemic Cancer Therapy	Efficacy
1.3	Summary of General Medical History	Efficacy
1.4.1	Summary of Prior Medications	Efficacy
1.4.2	Summary of Concomitant Medications	Efficacy
Efficacy		
2.1.1	Summary of Best Response and Overall Response Rate	Efficacy
2.1.2	Summary of Best Response and Overall Response Rate	Per Protocol
2.2.1	Summary of Duration of Response	Efficacy
2.2.2	Summary of Progression-Free Survival	Efficacy
2.2.3	Summary of Overall Survival	Efficacy
2.2.4	Summary of Best Change in Target Lesion Size	Efficacy
2.3.1	Summary of ECOG Performance Status	Efficacy
Safety		
3.1.1	Summary of Study Drug Exposure	Safety
3.1.2	Summary of Study Drug Compliance	Safety
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 Grade 3 or Higher Adverse Events by MedDRA System Organ Class and Preferred Term	Safety

Table No.	Title	Population
3.2.6	Summary of Treatment-Emergent Grade 3 or Higher Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.7	Summary of Treatment-Related Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.8	Summary of Treatment-Related Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.9	Summary of Treatment-Related Grade 3 or Higher Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.10	Summary of Treatment-Emergent Adverse Events With a Fatal Outcome by MedDRA System Organ Class and Preferred Term	Safety
3.2.11	Summary of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.12	Summary of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.13	Summary of INCB054828 Treatment-Related Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
3.2.14	Summary of Treatment-Emergent Adverse Events Leading to INCB054828 Dose Interruption by MedDRA System Organ Class and Preferred Term	Safety
3.2.15	Summary of Treatment-Emergent Adverse Events Leading to INCB054828 Dose Reduction by MedDRA System Organ Class and Preferred Term	Safety
3.2.16	Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of INCB054828 by MedDRA System Organ Class and Preferred Term	Safety
3.2.17	Summary of Treatment-Emergent Adverse Events and Grade 3 or Higher Adverse Events by MedDRA Preferred Term in Decreasing Order of Frequency	Safety
3.2.18	Summary of Treatment-Emergent Non-Serious Adverse Events by MedDRA System Organ Class and Preferred Term	Safety
Laboratory		
3.3.1	Summary of Laboratory Values - Hematology	Safety
3.3.2	Shift Summary of Hematology Values in CTC Grade - To the Worst Abnormal Value	Safety
3.3.3	Summary of Treatment-Emergent Worsening of Laboratory Abnormalities - Hematology	
3.3.4	Summary of Laboratory Values - Chemistry	Safety
3.3.5	Shift Summary of Chemistry Values in CTC Grade - To the Worst Abnormal Value	Safety
3.3.6	Summary of Treatment-Emergent Worsening of Laboratory Abnormalities - Chemistry	
3.3.7	Summary of Laboratory Values - Coagulation	Safety
3.3.8	Shift Summary of Coagulation Values in CTC Grade - To the Worst Abnormal Value	Safety
3.3.9	Summary of Treatment-Emergent Worsening of Laboratory Abnormalities - Coagulation	Safety
3.3.10	Summary of Laboratory Values - Urinalysis	Safety

Table No.	Title	Population
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 Body Temperature	Safety
3.4.5	Summary of Respiratory Rate	Safety
3.4.6	Summary of Body Weight	Safety
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 and QTc Interval Values From 12-Lead ECG	Safety
3.5.7	Summary of Clinically Significant ECG Abnormalities	Safety

Figures

Figure No.	Title
4.2.1	Kaplan-Meier Estimates of Duration of Response (Efficacy)
4.2.2	Kaplan-Meier Estimates of Progression-Free Survival (Efficacy)
4.2.3	Kaplan-Meier Estimates of Overall Survival (Efficacy)
4.3.1	Waterfall Plot of Best Percent Change from Baseline in Target Lesion Size (Efficacy)
4.3.2	Swimmer Plot of Duration of Treatment (Efficacy)
4.6	Line Graph of Mean Change From Baseline for Selected Laboratory Values (Safety)

Listings

Listing No.	Title
2.1.1	Analysis Population
2.1.2	Subject Enrollment and Disposition Status
2.1.3	Subject Inclusion and Exclusion Criteria
2.2	Protocol Deviations/Violations
2.4.1	Demographic and Baseline Characteristics
2.4.2	Bladder Cancer Disease History
2.4.3	Prior Systemic Therapy
2.4.4	Prior Surgery
2.4.5	Prior Radiotherapy
2.4.6	Post Therapy
2.4.7	Medical History
2.4.8	Prior and Concomitant Drug Treatments
2.4.9	FGF and FGFR Alterations
2.5	Study Drug Compliance
2.6.1	Best Overall Response, Duration of Response, Progression-Free Survival and Overall Survival
2.6.2	Investigator Reported Assessment by RECIST Criteria

Listing No.	Title
2.6.3	Response Assessment: Target Lesions
2.6.4	Response Assessment: Non-Target Lesions
2.6.5	Response Assessment: New Lesions
2.6.6	Tumor Tissue
2.6.7	ECOG Status
2.7.1	Study Drug Administration
2.7.2	Adverse Events
2.7.3	INCB054828 Treatment-Related Adverse Events
2.7.4	Adverse Events Leading to Interruption, Reduction, or Discontinuation of INCB054828
2.7.5	Serious Adverse Events
2.7.6	Adverse Events Leading to Death
2.8.1.1	Clinical Laboratory Values - Hematology
2.8.1.2	Clinical Laboratory Values - Chemistry
2.8.1.3	Clinical Laboratory Values - Coagulation
2.8.1.4	Clinical Laboratory Values - Urinalysis
2.8.2.1	Abnormal Clinical Laboratory Values - Hematology
2.8.2.2	Abnormal Clinical Laboratory Values - Chemistry
2.8.2.3	Abnormal Clinical Laboratory Values - Coagulation
2.9.1	Vital Signs
2.9.2	Abnormal Vital Sign Values
2.9.3	Alert Vital Sign Values
2.10.1	12-Lead ECG Values
2.10.2	Abnormal 12-Lead ECG Values
2.10.3	Alert 12-Lead ECG Values
2.11.1	Eye Examinations