Official Title:	**A Phase1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB054828 in Subjects With Advanced Malignancies (FIGHT-101)**
NCT Number:	NCT02393248
Document Date:	Clinical Study Protocol Version 10: 27 March 2020

Clinical Study Protocol

INCB 54828-101

A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB054828 in Subjects With Advanced Malignancies (FIGHT-101)

Product:	**INCB054828 (pemigatinib)**
IND Number:	[redacted]
EudraCT Number	**2016-002831-14**
Phase of Study:	**1/2**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol (Version 0):	**17 OCT 2014**
Amendment (Version) 1:	**19 NOV 2014**
Amendment (Version) 2:	**11 JUN 2015**
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Amendment (Version) 5:	**27 SEP 2016**
Amendment (Version) 6:	**26 JUN 2017**
Amendment (Version) 7:	**10 AUG 2018**
Amendment (Version) 8:	**11 DEC 2018**
Amendment (Version) 9:	**02 JUL 2019**
Amendment (Version) 10:	**27 MAR 2020**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, 312, and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for INCB054828. I have read the INCB 54828-101 Protocol Amendment 10 (Version 10 dated 27 MAR 2020) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

_____

(Printed Name of Investigator)

_____ _____

(Signature of Investigator) (Date)

SYNOPSIS

Name of Investigational Product: INCB054828 (pemigatinib)

Title of Study: A Phase 1/2, Open-Label, Dose-Escalation, Safety and Tolerability Study of INCB054828 in Subjects With Advanced Malignancies (FIGHT-101)

Protocol Number: INCB 54828-101	**Study Phase:** 1/2

Primary Objectives:

- To evaluate the safety, tolerability, and dose-limiting toxicities (DLTs) and to determine the pharmacologically active dose (PAD) and maximum tolerated dose (MTD) of INCB054828, alone as a monotherapy and in combination with other therapies.
- To assess the pharmacodynamics (PD) of INCB054828.

Secondary Objectives:

- To assess preliminary efficacy by assessing the overall response rate (ORR) of INCB054828 in subjects with measurable disease, alone as a monotherapy and in combination with other therapies.
- To evaluate the pharmacokinetics (PK) of INCB054828 and the effect of food and other therapies on the PK of INCB054828.

[redacted]

Overall Study Design:

This is an open-label, dose-escalation study of the fibroblast growth factor receptor (FGFR) inhibitor INCB054828 in subjects with advanced malignancies. Subjects will receive once daily (QD) doses of INCB054828 on a 2-weeks-on therapy and 1-week-off therapy schedule. A continuous administration regimen will also be explored, which will include a twice daily (BID) regimen. The study will be conducted in 3 parts. Part 1 (monotherapy dose escalation) will determine the MTD of INCB054828 and/or doses/regimen that produce substantial evidence of pharmacologic target inhibition (increased serum phosphate). Part 2 (monotherapy dose expansion) will evaluate the dose(s) selected in Part 1 as a monotherapy in specific indications where activity of FGFR is particularly relevant and that have amplification, mutation, or translocation of FGFR 1, 2, or 3, or alteration of FGF 1 through 23. In Part 1, approximately 20 subjects with moderate ($n \approx 10$) and severe ($n \approx 10$) renal impairment will be enrolled for safety and PK evaluation, with moderate renal impairment enrolled first.

Additionally, as part of the dose expansion (Part 2), all subjects enrolling in the tumor-specific cohorts ($n = 20$ total, $n = 5$ per cohort) will have mandatory biopsies, and approximately 8 subjects will participate in a food-effect study. Part 3 will begin with dose-finding to determine recommended Part 2 doses (RP2Ds) of INCB054828 in combination with gemcitabine + cisplatin, docetaxel, pembrolizumab, trastuzumab, or INCMGA00012 in subjects for which these treatments or PD-1–directed treatment is relevant. Dose expansion will further evaluate the RP2Ds selected in these populations harboring FGF/FGFR alterations, including up to 6 subjects per combination for mandatory baseline and on-treatment biopsies.

Treatment may continue as long as subjects are receiving benefit and have not met any criteria for study withdrawal. Subjects who discontinue study drug will continue to be followed for subsequent anticancer treatments and survival.

Part 1 Dose Escalation

Approximately 60 subjects will be enrolled. The study will begin with an open-label dose escalation with an accelerated titration design based on observing each dose level for a period of 21 days before enrolling the next cohort and administering the next dose level. In Part 1, subjects who receive at least 11 out of 14 doses of study drug at the level assigned to that cohort or have a DLT will be considered evaluable for determining tolerability of the dose. Subjects enrolling but not meeting these criteria may be replaced in order to fill the cohort.

The starting dose will be 1 mg. The initial cohorts will consist of at least 1 subject each, and the doses may be increased up to 2-fold in successive cohorts until a Grade 2 or greater toxicity (excepting toxicities with a clear alternative explanation or transient abnormal laboratory values without clinically significant signs or symptoms) or hyperphosphatemia (HP; serum phosphate > 5.5 mg/dL) is observed, at which time that cohort will be expanded to at least 3 subjects. From the point where a single-subject cohort is first expanded to 3 subjects, subsequent cohorts will enroll at least 3 subjects, and increases to study drug dose will be limited to no more than 50% in successive cohorts. If no DLTs are observed in the initial 3 subjects, then the next cohort will begin enrollment. If 1 DLT is observed in the first 3 subjects, then 3 additional subjects will be enrolled in the cohort. If a DLT occurs in 2 or more subjects in a cohort of 3 or 6, then the MTD will be deemed to have been exceeded, and the next lower dose level will be deemed to be the MTD. Thus, the MTD will be defined as 1 dose level below that at which one-third or more of subjects in a particular cohort report a DLT. If a DLT is observed at the initial dose of 1 mg QD, then a dose decrease to 0.5 mg may be considered. An intermediate dose level may also be explored. If toxicities specifically relevant to a type of malignancy are observed, a separate dose escalation or dose decrease group will be initiated for subjects with this malignancy.

Continuous administration of INCB054828

Continuous study drug administration will be tested in separate dose-escalation cohorts both in monotherapy cohorts and combination cohorts. The starting dose of continuous administration will be lower than the MTD identified in the 2-weeks-on therapy/1-week-off therapy schedule. Subjects who receive at least 18 of 21 doses of study drug at the level assigned to that cohort or who have a DLT will be considered evaluable for determining tolerability of the dose. Subjects enrolling but not meeting these criteria may be replaced in order to fill the cohort.

Twice daily administration of INCB054828

Twice daily administration will be tested in a dose-escalation cohort as monotherapy only. The BID starting dose will be 7.5 mg on a continuous dosing schedule (no planned dose hold). Subjects who receive at least 35 of a possible 42 doses of study drug at the level assigned to that cohort or have a DLT will be considered evaluable for determining tolerability of the dose. Subjects enrolling but not meeting these criteria may be replaced in order to fill the cohort. A total of approximately 21 subjects will be enrolled in this cohort for Part 1.

Renal Impairment

A subgroup of approximately 20 subjects (approximately 10 subjects with moderate renal impairment and 10 with severe) will be enrolled in Part 1 at the 13.5 mg continuous administration regimen to assess the effect of renal impairment on the safety and PK of INCB054828.

Pharmacodynamic Target

Dose escalation will proceed in the absence of an MTD to a PAD. The PAD is defined as the point where approximately 67% (2 out of 3) of subjects attain HP; in a cohort of 3 subjects, if 2 out of 3 have HP, the cohort will be expanded to 6 (while dose escalation continues as described above). Once the PAD is achieved, a new cohort will be enrolled where subjects will be treated with diet modification (decreased

phosphate intake) and phosphate binders, and dose escalation will continue to determine the dose at which at least one-third of subjects attain HP and an MTD is identified. Alternative PAD can be defined by molecular endpoint such as the inhibition of FGFR and/or at least a 1.5-fold increase of serum phosphate.

Recommended Part 2 Dose

The RP2D (dose and/or regimen) will be the lower of the MTD or the PAD with or without concomitant phosphate binders; different RP2Ds may be determined for interval administration and continuous administration. Multiple RP2Ds may be used going in to Part 2 and Part 3.

Lower Dose Level Expansion

Up to 3 additional subjects may be enrolled at any dose level for the interval and continuous administration monotherapy regimens, as well as the combination regimens, that is deemed to be pharmacodynamically active (hyperphosphatemia observed in two-thirds of treated subjects) if that dose level is below the MTD. Subjects must have FGF/FGFR alteration and are required to have a baseline biopsy and at least 1 on-treatment biopsy (recommended at Cycle 2 Day 14 but allowed to be performed at any cycle; must be performed on a study drug administration day, preferably between Day 8 and Day 14). Additionally, an end of treatment (EOT)/at time of progression biopsy is requested but not required. [redacted]

Part 2 Dose Expansion

When the recommended doses and/or regimen for investigation in Part 2 (RP2D) have been determined, enrollment will proceed for Part 2. It is possible that a different dose and/or regimen will be chosen for subjects with different types of malignancies.

Approximately 120 subjects will be treated in expansion groups to further determine safety, tolerability, efficacy, PK, food effect ($n \approx 8$), and PD in specific populations. In addition, all subjects enrolling in the tumor-specific cohorts ($n = 20$ total, $n = 5$ per cohort) will have mandatory biopsies. For the BID dosing regimen, approximately 10 subjects with FGFR3 mutated or fusion-positive advanced/metastatic bladder cancer will be enrolled and use the BID RP2D.

Subjects who attain HP should follow HP management guidelines as per Protocol. Subjects that do not attain HP or at least a 1.5-fold increase in serum phosphate after the first cycle of treatment should have their dose increased each cycle to the next previously study-assessed dose until HP or the maximum safely tested dose/MTD is reached.

Part 3 Combination Dose Finding and Expansion

Part 3 will comprise treatment groups evaluating INCB054828 when administered in combination with standard therapies for select solid tumors. Part 3 will include dose finding and dose expansion. Dose finding will be 3 + 3 enrollment to evaluate different doses of INCB054828 in combination with agents utilized in the treatment of solid tumors. The dose expansion is to further evaluate the safety and preliminary efficacy of the combination in select tumor types at the selected INCB054828 dose.

Approximately 60 subjects will be enrolled in the dose-finding group. The starting dose for Part 3 will be the RP2D(s).

Initially, at least 3 subjects will be enrolled in each treatment group for dose finding. The treatment groups include INCB054828 in combination with gemcitabine/cisplatin, docetaxel, pembrolizumab, trastuzumab, or INCMGA00012 at the doses, schedules, and routes described below. If in each group no DLTs are observed, then enrollment of the corresponding expansion will begin. If 1 DLT is observed, then at least 6 subjects will be enrolled in the dose-finding treatment group. If DLTs are observed in 2 or more subjects in a 3- or 6-subject group, then the dose of INCB054828 will be reduced by 25% to 50%. Dose assessment and dose decrease may be repeated once more. The combination MTD will be the highest dose of INCB054828 in each combination at which $\leq 0/3$ or $1/6$ subjects experience DLTs. The combination RP2D will be a dose less than or equal to the MTD/PAD dependent on emergent PD, PK, and safety data and may be specific to the different combination therapies. Up to 3 additional subjects with known FGF/FGFR alterations may be enrolled at any Part 3 dose level if that dose level is below the

MTD/PAD. In addition, the subjects enrolled in the lower dose level cohort per treatment combination are required to have baseline biopsy and at least 1 on-treatment biopsy (recommended at Cycle 2 Day 14 but allowed to be performed at any cycle; must be performed on a study drug administration day, preferably between Day 8 and Day 14). Additionally, an EOT/at time of progression biopsy is requested but not required. [redacted]

In the Part 3 combination expansion treatment groups, a total of approximately 75 subjects will be enrolled across 4 treatment groups (trastuzumab will not be expanded), including up to 6 subjects per combination for mandatory baseline and on-treatment biopsies.

Study Drug, Regimen, and Mode of Administration:

INCB054828 will be self-administered as a QD oral treatment on a 2-weeks-on therapy and 1-week-off therapy schedule; a continuous administration regimen will also be explored, which will include a BID dosing regimen. Each dose of INCB054828 should be taken without regard to timing of meals. On days when PK samples will be collected, subjects should fast for 8 hours before taking study drug in the clinic and fast for 1 additional hour after taking study drug. Tablets will be available in strengths of 0.5 mg and 2 mg; a 4.5 mg tablet will be available. The initial starting dose for dose escalation will be 1 mg. Dose escalation will proceed as described above. One cycle will be defined as 21 days of treatment.

Part 3: Combination

- Gemcitabine + cisplatin combination regimen will be administered as open-label, commercial products. Gemcitabine will be administered at 1000 mg/m^2 intravenously (IV) on Days 1 and 8 of each 21-day cycle. Cisplatin will be administered at 70 mg/m^2 IV once every 3 weeks on Day 1 of each 21-day cycle.
- Docetaxel will be administered as an open-label, commercial product at a starting dose of 75 mg/m^2 IV once every 3 weeks on Day 1 of each 21-day cycle.
- Pembrolizumab will be administered as an open-label, commercial product at a starting dose of 200 mg IV once every 3 weeks on Day 1 of each 21-day cycle.
- Trastuzumab will be administered as an open-label, commercial product at an initial dose of 8 mg/kg over a 90-minute IV infusion, followed by 6 mg/kg over a 30- to 90-minute IV infusion once every 3 weeks.
- INCMGA00012 will be administered as an open-label product at an initial dose of 500 mg over a 60-minute IV infusion once every 4 weeks. This will be a 28-day cycle.

Reference Therapy, Regimen, and Mode of Administration: Not applicable.

Duration of Participation: Subjects may continue on study until withdrawal criteria are met. Treatment duration will vary significantly between subjects, but is expected to average approximately 6 months.

Study Population:

Subjects with advanced malignancies who have failed a prior therapy and for whom no effective standard anticancer therapy is available.

Key Inclusion Criteria:

- Male or female subjects, age 18 years or older.
- Part 1: Any advanced solid tumor malignancy.
- Part 1: Subset subjects with moderate renal impairment (eGFR: ≥ 30 to < 60 mL/min/m^2) and severe renal impairment (eGFR: < 30 mL/min/m^2).

  Part 2: Subjects with measurable disease with documented FGF/FGFR alteration, including multiple myeloma and MPNs. For subjects enrolling in Part 2 with head and neck, vulvar, or anal cancer, must have evidence of positive HPV status.

Part 3:

1) Dose finding: subjects with solid tumor malignancies that have measurable disease for which treatment with gemcitabine + cisplatin, docetaxel, trastuzumab, and PD-1–directed therapies is relevant.
2) Dose expansion: subjects with solid tumor malignancies that have measurable disease and also harboring FGF/FGFR alterations for which treatment with gemcitabine + cisplatin, docetaxel, trastuzumab, and PD-1–directed therapies is relevant.

- Has progressed after prior therapy and either there is no further effective standard anticancer therapy available (including subject refuses or is intolerant) or the prescribed combination therapy for subjects enrolling in Part 3 is considered a relevant therapy for their diagnosis.
- Life expectancy > 12 weeks.
- ECOG performance status:
  - Part 1: 0 or 1.
  - Parts 2 and 3: 0, 1, or 2.
- Archival tumor specimen (tumor block or 25 unstained slides, minimum number of slides is approximately 15) or willingness to undergo a pretreatment tumor biopsy to provide a tumor block or 25 unstained slides (minimum number of slides is approximately 15). Archival tumor biopsies are acceptable at baseline and should be no more than 2 years old (preferably less than 1 year old and collected since the completion of the last treatment); subjects with samples older than 2 years old and/or with sequencing report from Foundation Medicine require approval from the sponsor medical monitor for exemption from the need for tumor biopsy or tumor sample requirement.
  - NOTE: For subjects in Part 1, fresh tumor biopsies for the purpose of determining study eligibility should be limited to tumors where tissue can be safely accessed. The medical monitor should be contacted before the subject is enrolled.

Key Exclusion Criteria:

- Treatment with other investigational study drug for any indication for any reason, or receipt of anticancer medications within 28 days before first dose of study drug (6 weeks for mitomycin-C or nitrosoureas, 7 days for tyrosine kinase inhibitors), but may be eligible with approval from the sponsor's medical monitor.
  - Subjects must have recovered (≤ Grade 1 or pretherapy baseline) from adverse events (AEs) due to previously administered therapies.
- Prior receipt of a selective FGFR inhibitor within the last 6 months.
- Laboratory parameters outside Protocol-defined range.
- Part 1 Dose Escalation:
  - Hemoglobin < 10.0 g/dL (transfusions are permitted with approximately 2 weeks of washout required before enrollment).
  - Platelet count < 100×10^9/L.
  - Absolute neutrophil count < 1.5×10^9/L.
  - Total bilirubin > upper limit of normal (ULN) unless associated with subject's primary cancer and/or metastases and with medical monitor approval.
  - Aspartate aminotransferase or alanine aminotransferase > ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval.
  - Alkaline phosphatase > ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval.

  - Creatinine clearance ≤ 60 mL/min (< 30 mL/min for urothelial carcinoma) based on the site's standard formula, except for a subset of subjects with moderate renal impairment (eGFR: ≥ 30 to < 60 mL/min/m^2) and severe renal impairment (eGFR: < 30 mL/min/m^2) based on the MDRD formula who will be allowed to enter the study.
  - Serum calcium outside of the institutional normal range, or serum albumin-corrected calcium outside of the institutional normal range if serum albumin is outside of the institutional normal range.
  - Serum phosphorus outside of the ULN of the institutional normal range.
  - Parathyroid hormone > 1.5 × ULN of the institutional normal range.
- Part 2 Expansion:
  - Hemoglobin ≤ 9.0 g/dL (transfusions are permitted with approximately 2 weeks of washout required before enrollment).
  - Platelet count ≤ 75 × 10^9/L.
  - Absolute neutrophil count ≤ 1.0 × 10^9/L.
  - Total bilirubin ≥ 1.5 × institutional ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval.
  - Aspartate aminotransferase or alanine aminotransferase ≥ 3 × ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval.
  - Alkaline phosphatase ≥ 2.5 × ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval.
  - Creatinine clearance ≤ 40 mL/min (< 30 mL/min for multiple myeloma or urothelial carcinoma) based on the site's standard formula.
  - Serum calcium outside of the institutional normal range, or serum albumin-corrected calcium outside of the institutional normal range if serum albumin is outside of the institutional normal range.
  - Serum phosphorus outside of the ULN of the institutional normal range.
  - Parathyroid hormone > 1.5 × ULN of the institutional normal range.
- Note: Hematological parameters do not apply to subjects with MPN.
- Part 3 Combination:
  - Hemoglobin < 9.0 g/dL (transfusions are permitted with approximately 2 weeks of washout required before enrollment).
  - Platelet count ≤ 75 × 10^9/L.
  - Absolute neutrophil count < 1.5 × 10^9/L.
  - Total bilirubin ≥ 1.5 × institutional ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval.
  - Aspartate aminotransferase or alanine aminotransferase ≥ 3 × ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval.
  - Alkaline phosphatase ≥ 2.5 × ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval.
  - Creatinine clearance ≤ 40 mL/min based on the site's standard formula (< 30 mL/min for urothelial carcinoma).
  - International normalized ratio or prothrombin time > 1.5 × ULN, unless on warfarin.
  - Activated partial thromboplastin time > 1.5 × ULN.
  - Serum calcium outside of the institutional normal range, or serum albumin-corrected calcium outside of the institutional normal range when serum albumin is outside of the institutional normal range.

  - Serum phosphorus outside of the ULN of the institutional normal range.
  - Parathyroid hormone > 1.5 × ULN of the institutional normal range.
- History of calcium and phosphate homeostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues, such as the skin, kidney, tendons, or vessels due to injury, disease, and aging, in the absence of systemic mineral imbalance).
- Current evidence of clinically significant corneal disorder/keratopathy (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis), or retinal disorder (including but not limited to macular/retinal degeneration, diabetic retinopathy, retinal detachment), confirmed by ophthalmologic examination.
- History or presence of an abnormal electrocardiogram (ECG) that in the investigator's opinion is clinically meaningful. A screening QTc interval > 470 milliseconds, as corrected by Fridericia, is excluded. For subjects with an intraventricular conduction delay (QRS interval 120 msec), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTc.
- Prior radiotherapy within 2 weeks of study treatment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. Evidence of fibrosis within a radiation field from prior radiotherapy is permitted with medical monitor approval. A 1-week washout period is permitted for palliative radiation to non–central nervous system disease with medical monitor approval.
  - Subjects enrolled into Part 3 (pembrolizumab or INCMGA00012 combination), should have a minimum of a 6-month washout period after thoracic radiotherapy if > 30 Gy was received.
- History of human immunodeficiency virus infection.
- Untreated brain or CNS metastases or brain/CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases). Subjects with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT scan) during the screening period, and they are on a stable or decreasing dose of corticosteroids for at least 1 week.
- Active chronic or current infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment within 2 weeks prior to enrollment (subjects with asymptomatic chronic infections on prophylactic treatment are allowed).
- History of clinically significant or uncontrolled cardiac disease including unstable angina, acute myocardial infarction within 6 months from Day 1 of study treatment administration, New York Heart Association Class III or IV congestive heart failure, or uncontrolled arrhythmia requiring therapy (subjects with pacemaker or with atrial fibrillation and well-controlled heart rate are allowed).
- History of allergic reactions to INCB054828, any of the excipients of INCB054828 or similar compounds, gemcitabine, cisplatin, docetaxel, pembrolizumab, trastuzumab, or INCMGA00012. History of infusion allergic reactions to antibodies (eg, pembrolizumab, trastuzumab, or INCMGA00012) that are able to be managed with standard measures (eg, H2 blockers and/or steroids) are allowed.
- Unable or unwilling to swallow INCB054828 or significant gastrointestinal disorder(s) that could interfere with the absorption, metabolism, or excretion.
- Pregnant or nursing women or subjects expecting to conceive or father children within the projected duration of the study, starting with the screening visit through completion of safety follow-up visit (30-35 days after last dose). Subjects enrolled in Part 3 combination with INCMGA00012 should avoid pregnancy or fathering a child starting at screening through 6 months after the last dose of INCMGA00012.

- Any condition that would in the investigator's judgment interfere with full participation in the study, including administration of study medication and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
- Subjects being considered for treatment in the trastuzumab combination group (Part 3) with left ventricular ejection fraction of < 50% on echocardiogram or multigated acquisition scan.
- Evidence of active hepatitis B virus or hepatitis C virus infection (defined as subjects with elevated transaminases or cirrhosis. Subjects with chronic HBV/HCV infection with no cirrhosis and no elevated transaminases are allowed).
- Any prior PD-1– or PD-L1–directed treatment for which permanent discontinuation of therapy is recommended, per USPI.
- Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids.
- Subjects receiving pembrolizumab or INCMGA00012 and have received a live vaccine within 28 days of planned start of study treatment.
  - Note: Examples of live vaccines include but are not limited to the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live-attenuated vaccines and are not allowed.
- Evidence of interstitial lung disease or active, noninfectious pneumonitis.

Study Schedule/Procedures:

Subjects will have regularly scheduled study visits at the clinical site as part of a 21-day cycle.

Study visits are as follows:

- Prescreening (allowed for subjects who require genomic sequencing for lower dose level cohorts, Part 2 or Part 3)
- Screening: Days -28 through -1
- Cycle 1: Day 1, Day 2, Day 8, Day 14, Day 15, Day 16
- Cycles 2 through 6: Day 1, Day 8, Day 15
- Cycles 7+: Day 1 only
- Cycle 2 (Part 2 only, food-effect study): Day 14, Day 15
- End of treatment
- Safety follow-up: 30 days (+ 5 days) after end of treatment
- Follow-up for disease status and survival: Disease status follow-up every 57 days (± 5 days) for subjects who discontinue for a reason other than disease progression. Survival follow-up every 12 weeks (± 7 days) after discontinuation.

Local laboratory tests:

Study visits will include sample collection for hematology, chemistry, coagulation, endocrine monitoring, lipid panel, and urinalysis testing to be conducted at a local laboratory. Additionally, the screening visit will include serology and fertility/pregnancy testing conducted at a local laboratory. Subjects with multiple myeloma or MPNs will have bone marrow aspirate/biopsy evaluations and laboratory assessments as part of the disease response assessment performed by a local laboratory.

Central laboratory tests:

Pharmacodynamic and PK samples will be collected at some visits and shipped to the sponsor or designee for analysis.

Clinical assessments:

Adverse event assessments, vital signs, electrocardiograms, physical examinations, ECOG performance status, comprehensive eye examination, skeletal survey, and tumor and disease response assessments will be performed by the investigative site.

An objective assessment of disease status will be performed at screening, appropriate to the malignancy type. For example:

- Computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT, bone marrow aspirate/biopsy (as applicable by subtype).

Subsequently, disease measurable by CT, MRI, or PET/CT will be assessed approximately every 9 weeks with the same methodology; for disease status assessed in bone marrow, on-treatment bone marrow aspirates/biopsies will occur only on a limited schedule if clinically indicated for the subject's diagnosis, if needed to confirm response or to assess PD response (optional).

A central facility will be responsible for the genomic sequencing of all subjects enrolled in Part 2 and 3. Subjects who are not confirmed per the analysis performed at the central facility will be considered unevaluable and may be replaced.

Primary Endpoints:

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs; through physical examinations; by evaluating changes in vital signs and ECGs; and through clinical laboratory blood and urine sample evaluations.
- Pharmacodynamics of INCB054828 including serum phosphorus level.

Secondary Endpoints:

- Tumor response rates in those subjects with measurable disease as determined by the investigator assessment of response.
- C_{max}, t_{max}, C_{min}, $AUC_{0\text{-}t}$, $t_{½}$, and Cl/F.

[redacted]

Planned Number of Subjects: Approximately 325 subjects.

Planned Number of Study Sites: Approximately 25 sites.

Principal Coordinating Investigator: Mansoor Saleh, MD

Estimated Study Duration:

Date first subject enrolled: FEB 2015

Estimated date last subject completed: JUN 2020

Statistical Methods:

Descriptive statistics (eg, mean, standard deviation, range) will be derived where appropriate. Subject enrollment, disposition, demographics, and medical history will be summarized at baseline. The rate of DLTs will be summarized for each cohort in Part 1 and Part 3 dose finding. Dose exposure and density will be calculated. Safety and disease response data will be compared over time to assess change from baseline, during treatment, and follow-up. Pharmacokinetic and PD data will be analyzed with appropriate standard nonlinear analytic software.

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LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this clinical study Protocol.

Term	Explanation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	twice daily
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRF	case report form (electronic)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
[redacted]	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	epidermal growth factor receptor
EOT	end of treatment
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FISH	fluorescent *in situ* hybridization
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HBV	hepatitis B virus
HCV	hepatitis C virus
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act of 1996
HNC	head and neck cancer
HP	hyperphosphatemia

Term	Explanation
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IMWG	International Myeloma Working Group
IN	Investigator Notification
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenously
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MPN	myeloproliferative neoplasm
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
NSAID	nonsteroidal anti-inflammatory drug
NOAEL	no-observed-adverse-effect level
NSCLC	non–small cell lung cancer
OCT	organic cation transporter
ORR	overall response rate
PAD	pharmacologically active dose
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction
PD	pharmacodynamics
PD-1	programmed cell death-1
PET	positron emission tomography
[redacted]	[redacted]
P-gp	P-glycoprotein
PK	pharmacokinetics
PR	partial response
PT	prothrombin time
Q2W	every 2 weeks
Q4W	every 4 weeks
QD	once daily

Term	Explanation
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Part 2 dose
RPED	retinal pigmented epithelium detachment
SAE	serious adverse event
SD	stable disease
SmPC	Summary of Product Characteristics
SRD	serous retinal detachment
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Package Insert

1. INTRODUCTION

1.1. Background

INCB054828 is an inhibitor of the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases that is proposed for the treatment of malignant diseases. Aberrant signaling through FGFR resulting from gene amplification or mutation, chromosomal translocation, and ligand-dependent activation of the receptors has been demonstrated in multiple types of human cancers. Fibroblast growth factor receptor signaling contributes to the development of malignancies by promoting tumor cell proliferation, survival, migration, and angiogenesis. Incyte is proposing to study INCB054828 for the treatment of advanced malignancies. Refer to the Investigator's Brochure (IB) for additional background information on INCB054828.

1.1.1. Fibroblast Growth Factor Receptor Inhibition in Oncology

The mammalian FGFR family is composed of 4 highly conserved receptors (FGFR1, FGFR2, FGFR3, and FGFR4) that have an extracellular ligand binding domain, a single transmembrane domain, and an intracellular tyrosine kinase domain. Eighteen fibroblast growth factor (FGF) ligands, divided into canonical and hormonal FGFs, bind to FGFRs leading to receptor dimerization, activation of the kinase domain, and transphosphorylation of the receptors (Eswarakumar et al 2005). Subsequent signal transduction occurs through phosphorylation of substrate proteins such as FGFR substrate 2 that leads to activation of the RAS–mitogen-activated protein kinase and PI3 kinase–protein kinase B pathways and phospholipase Cγ that activates the protein kinase C pathway. In some cellular contexts, signal transducer and activator of transcription proteins are also activated by FGFRs. Signaling through the FGF-FGFR pathway is tightly controlled through feedback regulation. Mitogen-activated protein kinase phosphatases and Sprouty proteins are upregulated upon FGFR stimulation and antagonize FGF-dependent activation of extracellular signal-regulated kinases. In many cases, FGFR pathway activation promotes cell proliferation, survival, and migration; however, cellular context plays an important role, and in certain tissues, FGFR signaling results in growth arrest and cellular differentiation (Dailey et al 2005).

Fibroblast growth factor ligands and FGFRs are widely expressed during development, and FGF-FGFR signaling is essential during embryonic development. Knockout mouse models of many FGF and FGFR genes exhibit lethal phenotypes from impaired organogenesis (Eswarakumar et al 2005). Activating mutations in FGFR3 are associated with congenital skeletal dysplasias such as achondroplasia and thanatophoric dysplasia, and activating mutations in FGFR2 are associated with a number of autosomal dominant craniosynostotic disorders including Crouzon and Apert syndromes. In adults, FGF-FGFR signaling is involved in angiogenesis during wound healing. The hormonal FGF ligands contribute to regulation of metabolic pathways involving lipid, glucose, phosphate, and Vitamin D (Itoh 2010). Genetic defects in the FGF23 signaling pathway lead to disordered phosphate metabolism: loss of function mutations in FGF23 or its signaling result in retention of phosphate and tissue mineralization, while gain of function mutations in the FGF23 pathway manifests as hypophosphatemic Rickets syndrome (Farrow and White 2010).

There is strong genetic and functional evidence that dysregulation of FGFR can lead to the establishment and progression of cancer. Genetic alterations in FGFR1, FGFR2, and FGFR3 have been described in many tumor types (Knights and Cook 2010, Turner and Grose 2010). These include activating mutations, translocations, and gene amplification resulting in ligand-independent, constitutive activation of the receptors or aberrant ligand-dependent signaling through FGFRs. Fibroblast growth factor receptor 1 is activated primarily through amplification of the 8p11 locus found in approximately 15% of squamous lung cancer and 10% of estrogen receptor–positive breast cancer (Weiss et al 2010, Elbauomy Elsheikh et al 2007). The FGFR1 kinase domain is also found to be translocated to a variety of gene loci in 8p11 myeloproliferative neoplasms (MPNs) that leads to constitutive kinase activity of the FGFR1 fusion protein (Goradia et al 2008). Fibroblast growth factor receptor 2 is found to be activated by gene amplification in a number of tumor types including gastric cancer and breast cancer and by mutation in endometrial cancer (Kunii et al 2008, Dutt et al 2008). Mutations that lead to activation of FGFR3 occur in 50% to 70% of superficial bladder cancer. The most prevalent FGFR3 mutations are Ser to Cys changes in the extracellular domain that promote autodimerization and ligand-independent activation of signaling (di Martino et al 2009, Cancer Genome Atlas Research Network 2014). These mutations match germline mutations in FGFR3 that are described in congenital skeletal dysplasias (Greulich and Pollock 2011). Translocations involving FGFR3 have been also been described in bladder cancer including the intrachromosomal rearrangement generating the FGFR3-TACC3 fusion (Williams et al 2013). Fibroblast growth factor receptor 3 is a target of the t(4;14) translocation that affects approximately 15% of multiple myeloma subjects (Chesi et al 1997). This balanced translocation adjoins the FGFR3 coding sequence to the strong IgH enhancer elements in plasma cells and drives high levels of FGFR3 expression. Finally, recent large-scale tumor sequencing efforts have uncovered multiple, but rare, transforming alterations in FGFR genes across a number of tumor histologies (Liao et al 2013, Wu et al 2013). In addition to these examples where FGFR dysregulation is a primary driver of tumorigenesis, FGFR has been reported to be a mechanism for resistance to hormone therapy in breast cancer and to epidermal growth factor receptor (eGFR) inhibitors in non–small cell lung cancer (NSCLC) by providing an alternative survival pathway (Turner et al 2010, Ware et al 2010).

Dysregulation of FGF ligands has also been reported in many human cancers. Preclinical studies have shown that high levels of FGF ligands such as FGF2 promote cancer cell resistance to radiation, chemotherapeutics, and targeted cancer drugs (Fuks et al 1994, Pardo et al 2002, Terai et al 2013). In triple negative breast cancer, upregulation of both FGF ligands and FGFR creates an autocrine loop that supports tumor cell growth and survival (Sharpe et al 2011). Clinically, detection of high levels of FGF2 in tumors is associated with poorer outcome in several tumor types including NSCLC (Donnem et al 2009, Rades et al 2012).

A substantial body of evidence supports that genetically activated FGFR pathway sensitizes FGFR-altered cancer cells to knockdown or inhibition of these receptors (Kunii et al 2008, Qing et al 2009, Weiss et al 2010, Lamont et al 2011). A large screen of more than 500 tumor cell lines with a selective FGFR inhibitor demonstrated that only a small percentage (5.9%) of all cells are sensitive to FGFR inhibition, and growth suppressed cell lines were highly enriched for FGFR alterations (Guagnano et al 2012). These results demonstrate that FGFR inhibitors are active in a targeted manner against cancers with activated FGFR pathway. An implication of these data is that selection based on molecular-, genetic-, or protein-based diagnostic tests for

specific FGFR alterations in tumors may be important for identifying subjects most likely to benefit from an FGFR inhibitor.

Results from early clinical studies of selective FGFR inhibitors have shown a tolerable safety profile for the class and have shown preliminary signs of clinical benefit in subjects selected for lesions of FGFRs. The safety and clinical activity of AZD4547 was evaluated in a Phase 1 study where subjects were prospectively selected for FGFR1 or FRFR2 gene amplification by fluorescent *in situ* hybridization (FISH). Of 21 subjects dosed with AZD4547, 7 subjects had FGFR amplifications and 3 subjects (one each squamous NSCLC, breast cancer, and bladder cancer) had target lesion shrinkage or prolonged disease stabilization (Kilgour et al 2014). In a Phase 1 expansion of subjects with previously treated Stage IV FGFR1-amplified squamous NSCLC, 14 subjects were evaluable for tumor response and there was 1 partial response (PR) and 4 stable disease (SD) observed (Paik et al 2014). In a separate expansion cohort of 13 subjects with advanced/metastatic gastric and gastroesophageal cancer, preliminary efficacy of AZD4547 was demonstrated with 1 PR and 4 SD; all 4 subjects had an FGFR amplification (Arkenau et al 2014). In the first in human study of JNJ-42756493, 37 subjects were treated on a once-daily (QD) continuous treatment schedule at 6 different rising dose levels. One dose-limiting toxicity (DLT) of Grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation was observed at the highest dose level and 9 mg QD was identified as the recommended Part 2 dose (RP2D). As of the data cutoff, 8 subjects were enrolled with an FGFR aberration and there was 1 PR in bladder cancer with an FGFR3-TACC3 translocation and 1 near complete response (CR) in a subject with urothelial cancer of the renal pelvis with an FGFR2 truncation. Four subjects with FGFR1 amplification (2 lung cancer, 1 chondrosarcoma, and 1 breast cancer) had SD (Bahleda et al 2014). An ongoing Phase 1 study of the selective pan-FGFR inhibitor BGJ398 has also shown a tolerable safety profile and preliminary efficacy in multiple tumor types. The study enrolled subjects with any type of FGFR genetic alteration. A 125 mg QD dose of BGJ398 was identified as the maximum tolerated dose (MTD). Preliminary data shows activity in urothelial carcinoma with FGFR3-activating mutations, FGFR1-amplified SCC lung cancer, cholangiocarcinoma with an FGFR2 gene fusion, and FGFR1-amplified breast cancer (Sequist et al 2014).

An on-target pharmacologic effect of FGFR inhibition in clinical studies is hyperphosphatemia (HP). In the Phase 1 study of BGJ398, at the MTD (125 mg QD dose), HP was reported in 78% of subjects (n = 41 subjects). Hyperphosphatemia was managed with diet modifications, phosphate-lowering therapy, or dose reductions. In future clinical studies of BGJ398, a 3-week on-therapy and 1-week off-therapy treatment schedule will be used based on the improved safety profile (Sequist et al 2014). JNJ-42756493 has shown a similar profile for HP. In the Phase 1 study where 6 dose levels were evaluated, 60% of subjects (n = 37 subjects) had HP reported and it was managed successfully with concomitant phosphate-lowering therapy and dose interruptions. A 9-mg QD continuous treatment schedule was chosen as the RP2D (Dienstmann et al 2014, Bahleda et al 2014).

Based on these preliminary data, targeting FGFR may be efficacious in several human cancers where alterations in the FGF-FGFR pathway have been established. INCB054828 is a potent selective inhibitor of FGFR1, FGFR2, and FGFR3 and is proposed for the treatment of advanced malignancies with FGFR alterations.

1.2. Overview of INCB054828

1.2.1. Pharmacology of INCB054828

INCB054828 is an inhibitor of the FGFR family of receptor tyrosine kinases that is proposed for the treatment of malignant diseases. In vitro, INCB054828 inhibits the kinase activity of FGFR1, FGFR2, and FGFR3 with IC_{50} values ranging from 0.39 to 1.2 nM. In enzyme assays versus a panel of non-FGFR kinases, INCB054828 is highly selective. In cellular assays, INCB054828 inhibits autophosphorylation of FGFR proteins with IC_{50} values of 3.1 to 3.7 nM and potently inhibits signal transduction by FGFR to downstream markers of pathway activation. Cancer cell lines that have genetic alterations in FGFR1, FGFR2, and FGFR3 are sensitive to INCB054828 with growth inhibitory IC_{50} values in the range of 3 to 50 nM; however, cancer cell lines or normal cells without FGFR dependence are much less sensitive (IC_{50} > 1500 nM). In a human whole blood assay, INCB054828 blocked phosphorylation of FGFR2 with an IC_{50} value of 10.9 nM. These data indicate that INCB054828 is potent and selective inhibitor of FGFR1, FGFR2, and FGFR3.

In vivo, INCB054828 was evaluated in 3 FGFR-dependent tumor models including H1581 FGFR1-dependent lung, KATOIII FGFR2-dependent gastric, and RT112 FGFR3-dependent bladder cancer. Pharmacokinetic-pharmacodynamic (PK-PD) analysis of pFGFR2 inhibition in tumors revealed an in vivo IC_{50} value of 22.6 nM. Maximum tumor inhibition was observed with once-daily doses of 0.3 to 1 mg/kg in all 3 models and corresponded to plasma drug levels that exceeded the whole blood IC_{50} for greater than 12 hours. At the clinical target dose of 6 mg QD, the whole blood IC_{50} is anticipated to be covered for the treatment interval and therefore is supported by the preclinical data. Serum phosphate, an endogenous PD marker for FGFR inhibition, increased in a dose-dependent manner in mice following a single dose of INCB054828.

In summary, pharmacological data obtained in both in vitro and in vivo model systems support the potential utility of orally administered INCB054828 in the treatment of cancer.

1.2.2. Nonclinical Drug Metabolism and Pharmacokinetics of INCB054828

The absorption, distribution, metabolism, and excretion of INCB054828 have been studied in Sprague Dawley rats, cynomolgus monkeys, and beagle dogs. The systemic clearance of INCB054828 was low in monkeys and dogs (8% and 10% of hepatic blood flow, respectively), but moderate in rats (31% of hepatic blood flow). INCB054828 exhibits a low to moderate volume of distribution in all 3 species, ranging from 0.584 (monkey) to 3.49 (dog) L/kg. The terminal elimination half-life following intravenous (IV) administration ranged from 4.0 hours (rat) to 15.7 hours (dog). The renal excretion of intact INCB054828 was 9% in rats, while these values were 36% and 22% in monkeys and dogs, respectively. Metabolism and renal clearance are the major elimination routes for INCB054828. The unbound renal clearance of INCB054828 exceeds the glomerular filtration rate in dogs and monkeys, suggesting active secretion mediated by transporters. The distribution of INCB054828 across the rat blood-brain barrier is limited, presumably due to interactions with efflux transporters. INCB054828 was absorbed rapidly with t_{max} values ranging from 0.56 hours to 2.0 hours. The oral bioavailability of INCB054828 was 29% in monkeys, 98% in dogs, and complete in rats.

Interactions of INCB054828 with some of the commonly encountered uptake and efflux transporters were determined in vitro. The permeability of INCB054828 is high in Caco-2 cells (11×10^{-6} cm/sec) at a nominal concentration of 50 μM. In vitro transport studies indicate that INCB054828 is a substrate of both P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP); however, the efflux mediated by P-gp and BCRP was saturated at concentrations of 1 μM and 30 μM, respectively, in vitro. Therefore, it is unlikely that efflux by these 2 transporters plays an important role in the oral absorption of INCB054828. INCB054828 is also an inhibitor of P-gp, with an IC_{50} value of 4.8 μM, and a potent inhibitor of organic cation transporter (OCT) 2, with an IC_{50} value of 0.075 μM. The ratio of total unbound C_{max}/IC_{50} for OCT2 is above 0.1. A physiologically based pharmacokinetic (PBPK) model was developed to evaluate DDIs with P-gp and OCT2 substrates. Based on the in vitro data and PBPK modeling, in vivo drug interaction studies for INCB054828 as a P-gp inhibitor and as an OCT2 inhibitor are not needed. INCB054828 is not an inhibitor of OATP1 B1 or OAT 1.

The plasma protein binding of INCB054828 is high in all species tested with ex vivo free fraction of 4.0% and 8.6% in rats and monkeys, respectively. The free fraction in humans is 9.4%, the average value from in vitro serum and plasma protein binding determinations.

INCB054828 is predominantly metabolized by cytochrome P450 (CYP) 3A4. INCB054828 is not a potent reversible inhibitor of the major CYPs evaluated or there was no evidence of metabolism-dependent inhibition noted (IC_{50} values > 25 μM). Therefore, the potential for INCB054828 to cause clinical DDIs via inhibition of CYP is low at the projected clinical dose. The major in vivo metabolites identified were M2, an O-demethylated metabolite, in rat plasma, and M5, a bis-hydroxylated metabolite, in cynomolgus monkey plasma. The most abundant in vitro metabolite was M6, an oxidative metabolite. There were no human-specific metabolites noted using in vitro systems. There is no evidence of chemical reactivity subsequent to metabolism.

1.3. Study Rationale

Cancer has several common characteristics that can be observed across numerous tumor types. One common characteristic is the uncontrolled growth and survival of cells and their ability to become invasive throughout the body. Fibroblast growth factor signaling produces mitogenic, anti-apoptotic, and angiogenic responses in cells, which leads to a deregulated state. Evidence from several in vitro and in vivo tumor models has established the FGFs and FGFRs as oncogenes and their expression has been found in numerous solid tumors or hematological malignancies. Several genetic alterations have been shown to generate overexpression of the FGF receptor, produce a receptor that is constitutively active, or lead it to a state where there is reduced dependence on ligand binding for activation (Knights and Cook 2010).

Tyrosine kinases are an especially important target in cancer therapy as they have a key role in growth factor signaling. Several tyrosine kinase inhibitors have been shown to be effective antitumor agents and have been approved in multiple oncology indications (Arora and Scholar 2005). In NSCLC, eGFR inhibitors have been shown to significantly improve survival (Shien et al 2014). Preliminary data from ongoing Phase 1 studies with the selective FGFR inhibitors AZD4547, JNJ-42756493, and BGJ398 have shown a tolerable safety profile for the class and signs of efficacy in tumors that have FGFR genetic alterations. INCB054828 is a potent inhibitor of the kinase activity of FGFR1, FGFR2, and FGFR3 and has been shown to

inhibit growth in several tumor models. Several tumor types such as squamous NSCLC, gastric cancer, and urothelial cancer are of particular interest due to the prevalence of FGFR genetic alterations. Subjects who have an FGFR alteration may benefit from treatment with a selective FGFR inhibitor and may be identified through the use of a companion diagnostic device.

The planned study will evaluate the safety, tolerability, and pharmacological activity of INCB054828 in subjects with advanced malignancies. An expansion phase will further evaluate the safety, tolerability, and preliminary efficacy of the RP2D of INCB054828 in selected indications that have been shown to have prevalent alterations in FGFRs. The following indications have been selected for expansion: squamous NSCLC (10%-22% have FGFR1 amplification), gastric cancer (5%-10% have FGFR2 amplification), urothelial cancer (10%-15% of muscle-invasive bladder cancers have FGFR3 mutation, 50%-60% of noninvasive bladder cancers have FGFR3 mutation, and 6% of muscle-invasive bladder cancers have FGFR3 translocation), endometrial cancer (10% have FGFR2 mutation), multiple myeloma (15% have FGFR3 translocation), and MPNs (8p11 myeloproliferative syndrome is a rare hematological malignancy characterized by FGFR1 translocation) (Turner and Grose 2010, Weiss et al 2010, Heist et al 2012).

1.3.1. Rationale for Evaluating Safety and Pharmacokinetics in Subjects With Renal Impairment

It is important to characterize the PK of INCB054828 in subjects with various degrees of renal impairment since cancer, and in particular urothelial cancer, can lead to renal dysfunction and ultimately renal impairment. The administration of INCB054828 poses a low risk to renally impaired subjects because INCB054828 is mainly eliminated by CYP3A4 metabolism and has been shown to have low renal excretion. Preliminary results from the mass balance study, INCB 54828-105, show a mean total radioactivity of 12% of the administered [^{14}C]-INCB054828 dose recovered in the urine. Results from study INCB 54828-101 will provide information on the safety, tolerability, and PK exposure of INCB054828 in subjects with renal impairment compared to subjects with normal renal function, which may inform dose selection in renally impaired subjects enrolled in future Phase 3 studies. This study will also evaluate the effects of plasma protein binding of INCB054828 in subjects with renal impairment compared to subjects with normal renal function.

1.3.2. Rationale for Combining INCB054828 With Chemotherapy, Pembrolizumab, Trastuzumab, and INCMGA00012

Conventional chemotherapies such as gemcitabine/cisplatin or docetaxel remain as the standards of care in many tumor types, and the blockade of immune inhibitory pathways, such as by programmed cell death-1 (PD-1) inhibitors, is emerging as an important therapeutic modality for the treatment of cancer. Although chemotherapeutic agents and immunotherapeutic agents have shown antitumor activity as monotherapies, refractory or relapsed diseases almost always occur. Since targeted therapies and chemotherapeutic or immunotherapeutic agents target tumors by different mechanisms, combination therapies may be able to achieve optimal therapeutic effect in order to increase clinical response duration and overall survival (Quezada and Peggs 2013). Recently it has been demonstrated that the FGFR3/AKT axis as an escape pathway contributing to development of trastuzumab resistance [redacted] (Piro et al 2016).

1.3.3. INCMGA00012

INCMGA00012 is a humanized, hinge-stabilized, IgG4κ mAb that recognizes human PD-1. INCMGA00012 contains a human IgG4 Fc domain to limit effector function while retaining neonatal FcR binding to extend circulating half-life. INCMGA00012 is designed to target PD-1 expressing cells, including T cells, and sustain/restore their effector function by blocking checkpoint inhibitory interactions between PD-1 and its 2 ligands, PD-L1 and PD-L2.

In vitro studies with INCMGA00012 have demonstrated high affinity binding to both recombinant human and cynomolgus monkey PD-1 as well as to PD-1 naturally expressed on the cell surface, including on T cells. Consistent with its intended mechanism of action and functional properties, INCMGA00012 has been shown to inhibit the binding of PD-L1 and PD-L2 to PD-1, to disrupt the PD-1/PD-L1 inhibitory axis, and to enhance IFN-γ secretion in human PBMCs stimulated with the superantigen, staphylococcal enterotoxin B, with activity comparable to replicas of pembrolizumab and nivolumab (generated by MacroGenics, Inc. based on the published sequences of these antibodies). INCMGA00012 does not induce ADCC or CDC, mitogenic activity, hemolysis, or cytokine release.

Administration of INCMGA00012 via IV infusion once weekly at levels of 10, 40, or 150 mg/kg was well tolerated in cynomolgus monkeys. The only findings related to INCMGA00012 were modest decreases in lymphocytes after the first infusion and microscopic changes at the IV administration site, consisting of minimal multifocal perivascular mononuclear cell infiltrates within the superficial dermis (an expected reaction to repeated injection of an exogenous protein). Other microscopic changes consisted of diffuse patterns of immune cell infiltration, consistent with the mechanism of action of anti–PD-1 antibodies, and similar to what has been reported in repeat-dose studies in monkeys with nivolumab or pembrolizumab (FDA Pharmacology Reviews for Keytruda and Opdivo).

Phase 1 results of INCMGA00012 in subjects with advanced cancer (N = 37) have been presented (Lakhani et al 2017). Doses ranging from 1 to 10 mg/kg of INCMGA00012 demonstrated acceptable tolerability with no DLT observed at any dose level. An MTD was not reached. Treatment-related AEs ≥ Grade 3 occurred in 4/37 (10.8%) subjects, and included increased lipase (n = 3) and vulvovaginal ulceration/inflammation (n = 1). The most common treatment-related AEs were fatigue (n = 9, 24.3%), rash (n = 5, 13.5%), nausea (n = 5, 13.5%), tumor flare (n = 4, 10.8%), and pruritus (n = 4, 10.8%). A single treatment-related SAE of aphasia (occurring in the setting of new brain metastases) was reported. Immune-related AEs were limited to rash (n = 5, 13.5%), hypothyroidism (n = 3, 8.1%), hyperthyroidism (n = 2, 5.4%), vaginal ulceration/inflammation (n = 1, 2.7%), and infusion-related reaction (n = 1, 2.7%). For both the 3 and 10 mg/kg dose levels C_{max} and AUC_{∞} were dose proportional. $T_{½}$ (β) was approximately 17 days, and steady state was achieved in approximately 85 days. Full and sustained receptor occupancy of INCMGA00012 on both CD4+ and CD8+ T cells along with complete loss of competing fluorescently labeled anti–PD-1 staining (eJBio105 clone) were seen at all dose levels.

INCMGA00012 is currently being evaluated in expansion cohorts of 35 subjects each (INCMGA 0012-102). These include: cervical cancer, non–small cell lung cancer, selected sarcoma subtypes, and endometrial cancer (including MSI-H, dMMR, and/or POLE exonuclease domain mutation positive disease).

Interim results for the expansion cohorts have recently been presented (Mehnert et al 2018). A total of 132 subjects were enrolled into the disease-specific expansion cohorts and another 30 in the tumor agnostic flat dosing cohorts at 500 and 750 mg Q4W. Subjects were predominantly Caucasian and female; the median age ranged from 44 for the sarcoma cohort to 64 for endometrial cancer. The most frequently reported TEAEs (> 10%) in subjects receiving body-weight based dosing were fatigue, diarrhea, and dyspnea. The most frequently reported TEAEs (≥ 20%) in subjects receiving the fixed dose of 500 mg Q4W were fatigue, blood alkaline phosphatase increased, and blood bilirubin increased. Overall, 23/199 (12%) of subjects exposed to INCMGA00012 in the study have experienced irAEs. Most irAEs were transient, with the exception of endocrine-related irAEs. Non-endocrine irAEs that did not resolve were lipase increased, stomatitis, proctitis, diarrhea, ALT increased, and blood bilirubin increased (all 1 subject each). There were no fatal irAEs. Confirmed RECIST responses were seen in all of the expansion cohorts.

INCMGA00012 will be evaluated in combination with INCB054828 in the proposed study.

1.4. Potential Risks

1.4.1. Potential Risks of INCB054828 Based on Preclinical Safety

The most prominent findings following repeat-dose exposure to INCB054828 in both rats and monkeys were HP, physeal dysplasia, and soft tissue mineralization. Mineralization was observed in numerous tissues including the kidney, stomach, arteries (gastric and pulmonary), ovaries (monkey only), and eyes (cornea; rat only). Soft tissue mineralization was not reversible, while physeal and cartilage findings were reversible.

Hyperphosphatemia, physeal dysplasia, and soft tissue mineralization have been reported in rodents and large animals following administration of selective FGFR inhibitors (Brown et al 2005, Brown 2010, Wöhrle et al 2011, Yanochko et al 2013). These observations can be explained by the pharmacological action of FGFR inhibition. Fibroblast growth factor 23 (FGF-23)–mediated signaling negatively affects renal vitamin D biosynthesis by transcriptional repression of CYP27B1, which catalyzes the production of the biologically active vitamin D metabolite 1,25(OH)2D3, and by induction of CYP24A1, which converts 1,25(OH)2D3 into a metabolite that is less biologically active. Additionally, it has been published that FGF-23 suppresses renal phosphate reabsorption by decreasing the expression of the sodium-phosphate cotransporters NPT2A and NPT2C in the brush-border membrane of proximal tubule epithelial cells (Baum et al 2005, Shimada et al 2001, Shimada et al 2004a, Shimada et al 2004b). Wöhrle et al (2011) demonstrated that FGFR inhibition by oral administration of PD176067 counteracts the biologic activity of FGF-23 in the kidney, leading to HP and hypervitaminosis D.

In rats, the mineralization was similar in distribution and morphology to that occasionally observed in normal animals; thus it is likely that the increased incidence of mineralization in various tissues at these doses represents a test article–related exacerbation of a spontaneously occurring condition. While soft tissue mineralization was not reversible during 28-day recovery period, there was also no evidence of progression or worsening of this effect. Soft tissue mineralization in monkeys was observed only at 3 mg/kg per day in the 10-day range-finding study and was not assessed for reversibility. No evidence of mineralization was found at the doses tested in the 28-day study in monkeys.

Moderate lens opacities (capsule, posterior) in one 0.33 mg/kg per day and one 1 mg/kg per day males and slight attenuation of retinal vessels in one 1 mg/kg per day female were observed in monkeys at the end of treatment (EOT) period on the 28-day Good Laboratory Practice (GLP) study. These findings were not present during the pretest period and thus a relationship to INCB054828 cannot be dismissed. However, lens opacities are occasionally observed in normal cynomolgus monkeys of similar age and origin according to the testing facility historical control data. Persistence of lens opacity in 1 animal at the end of recovery period suggests that this finding is not reversible.

Fully reversible mild-to-moderate elevation of ALT and AST were noted at the EOT period in the 28-day monkey study at doses ≥ 0.33 mg/kg per day; these changes were not associated with changes in other hepatobiliary parameters or microscopic changes in the liver. These changes may be related to FGFR4 inhibition, which is known to result in increases in liver function tests without histological correlates (Pai et al 2012).

In the 28-day study in rats, no severe toxicity was observed; the no-observed-adverse-effect level (NOAEL) was determined as 1.05 mg/kg per day (6.3 mg/m^2 per day), the highest dose tested. The human equivalent dose (HED) associated with 1.05 mg/kg per day based on standard body surface area conversion is 10.1 mg, and one-tenth of this dose is 1.01 mg. In the 28-day monkey study, no severe toxicity was observed. The NOAEL was considered to be 1 mg/kg per day (12 mg/m^2 per day), the highest dose tested. The HED associated with 1 mg/kg per day based on standard body surface area conversion is 19.2 mg; one-sixth of this dose is 3.2 mg. Taking a conservative approach and using one-tenth the NOAEL in the more sensitive species (rat), 1 mg is proposed as the starting clinical dose for Part 1.

It is estimated that a dose of 6 mg (QD) with an AUC of approximately 0.63 µM·h (≈ 0.06 µM·h, unbound) will be needed to exceed the IC_{50} at trough which has been shown to be efficacious in preclinical tumor models. The AUC at the proposed starting clinical dose of 1 mg is estimated to be approximately 0.1 µM·h (≈ 0.01 µM·h, unbound). The unbound AUC at the proposed starting dose is approximately 14-fold lower (monkey) and approximately 11-fold lower (male rats) than the unbound AUC values for the NOAELs determined in the 28-day GLP studies.

1.4.2. Potential Risks of INCB054828 Based on Clinical Experience

The comprehensive safety data that are included in IB Edition 5 used a data cutoff of 25 NOV 2018. As of the data cutoff date, a total of 562 participants (78 healthy participants and 484 participants with advanced malignancies) were enrolled in the ongoing clinical studies and received at least 1 dose of pemigatinib. Based on preliminary unaudited data from these ongoing studies, the most frequently occurring TEAEs (ie, incidence > 20%) were (in descending order of frequency) hyperphosphatemia, diarrhea, alopecia, fatigue, dry mouth, stomatitis, constipation, dysgeusia, nausea, decreased appetite, and anemia. Additional details for the current study INCB 54828-101 are presented in the following section.

1.4.2.1. Study INCB 54828-101

Of the 150 participants with advanced malignancies who have been enrolled in Study INCB 54828-101 as of the data cutoff date, 43 participants have been administered pemigatinib in Part 1 (monotherapy dose escalation), 63 participants in Part 2 (monotherapy dose expansion), and 44 participants in Part 3 (pemigatinib combined with gemcitabine and cisplatin [8 participants], docetaxel [7 participants], pembrolizumab [23 participants], and trastuzumab [6 participants]).

Dose-limiting toxicities informed dose escalation procedures during Part 1 of the study. Among participants in Part 1, 28 received pemigatinib at doses of 1 to 20 mg QD on a 2-weeks-on/1-week-off therapy schedule (ie, interval dose regimen), and 15 participants received pemigatinib at doses of 9, 13.5, or 20 mg QD on a continuous schedule (ie, continuous dose regimen). There were no DLTs for the monotherapy dose regimens, and the monotherapy MTD was not reached. The recommended Part 2 dose for pemigatinib was determined to be 13.5 mg based on PD and clinical effect, and the recommended Phase 2 dose regimens for pemigatinib based on safety and PK data and preliminary signals of clinical benefit (data not shown) were 13.5 mg QD following the interval schedule and 13.5 mg QD following the continuous schedule.

Overall, 105 participants (99.1%) who received pemigatinib monotherapy (all doses and dose regimens combined) in Study INCB 54828-101 had TEAEs. Treatment-emergent AEs occurring in ≥ 10% of participants who received pemigatinib monotherapy (Parts 1 and 2 combined) are presented by dose and dose regimen and overall in Table 1. Consistent with the expected pharmacological effect of FGFR inhibition on serum phosphate levels, the most frequently occurring TEAE was hyperphosphatemia (74 participants [69.8%]; serum phosphate > 5.5 mg/dL). Other frequent TEAEs (> 30%) included fatigue in 43 participants (40.6%), dry mouth in 39 participants (36.8%), and alopecia in 35 participants (33.0%). Comparison of the most frequently occurring TEAEs for the continuous and interval dose regimens suggests higher incidences of hyperphosphatemia (76.7% vs 67.1%), stomatitis (46.7% vs 22.4%), dry mouth (43.3% vs 34.2%), diarrhea (43.3% vs 22.4%), constipation (40.0% vs 25.0%), alopecia (40.0% vs 30.3%), and nausea (33.3% vs 22.4%) with continuous dosing. Other TEAEs that occurred more frequently with continuous dosing included dry eye, pain in extremity, hypercalcemia, onycholysis, and paronychia.

Forty-five participants (42.5%) who received pemigatinib monotherapy had at least 1 SAE; the overall incidence of SAEs for the continuous dose regimen (56.7%) was higher than was seen for the interval dose regimen (36.8%). Pneumonia in 7 participants (6.6%) was the most frequently occurring SAE. Other SAEs occurring in more than 1 participant included back pain and disease progression in 4 participants (3.8%) each; abdominal pain, dehydration, fatigue, hyponatremia, and acute renal failure in 3 participants (2.8%) each; and blood bilirubin increased, cerebrovascular accident, constipation, hypotension, pain in extremity, pleural effusion, and pyrexia in 2 participants (1.9%) each. Within the eye disorders SOC, a single participant had an SAE of ocular hyperemia (Grade 2), which was considered unrelated to pemigatinib by the investigator.

A total of 11 participants (10.4%), 7 participants (9.2%) on an interval dose regimen and 4 participants (13.3%) on a continuous dose regimen, had SAEs with a fatal outcome: disease progression in 4 participants (3.8%) and pneumonia, malignant neoplasm progression (ie, disease progression), cerebrovascular accident, intracranial hemorrhage, multiorgan failure, esophageal

varices hemorrhage, pneumonia, respiratory failure, and acute respiratory failure secondary to acute anemia (verbatim term) in 1 participant (0.9%) each. None of these fatal events were assessed as related to pemigatinib by the investigator.

Eleven participants (10.4%) discontinued pemigatinib monotherapy due to TEAEs; pneumonia in 3 participants (2.8%) and dehydration and small intestinal obstruction in 2 participants (1.9%) each were the only TEAEs leading to discontinuation of pemigatinib that occurred in more than 1 participant.

More detailed information about the known and expected benefits and risks (clinical safety and nonclinical toxicology) and reasonably expected AEs of pemigatinib are provided in the IB.

Table 1: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 10% of Participants on Pemigatinib Monotherapy in Study INCB 54828-101 (Parts 1 and 2 Combined) in Decreasing Order of Frequency

	Pemigatinib Interval Dose Regimen[a]						Pemigatinib Continuous Dose Regimen[b]				
MedDRA Preferred Term, n (%)	1/2/4 mg (N = 3)	6 mg (N = 4)	9 mg (N = 13)	13.5 mg (N = 50)	20 mg (N = 6)	Subtotal (N = 76)	9 mg (N = 8)	13.5 mg (N = 16)	20 mg (N = 6)	Subtotal (N = 30)	Total (N = 106)
Hyperphosphataemia	0	1 (25.0)	8 (61.5)	38 (76.0)	4 (66.7)	51 (67.1)	4 (50.0)	14 (87.5)	5 (83.3)	23 (76.7)	74 (69.8)
Fatigue	1 (33.3)	1 (25.0)	7 (53.8)	19 (38.0)	2 (33.3)	30 (39.5)	5 (62.5)	5 (31.3)	3 (50.0)	13 (43.3)	43 (40.6)
Dry mouth	0	1 (25.0)	6 (46.2)	17 (34.0)	2 (33.3)	26 (34.2)	2 (25.0)	7 (43.8)	4 (66.7)	13 (43.3)	39 (36.8)
Alopecia	0	0	7 (53.8)	15 (30.0)	1 (16.7)	23 (30.3)	2 (25.0)	7 (43.8)	3 (50.0)	12 (40.0)	35 (33.0)
Constipation	0	0	3 (23.1)	14 (28.0)	2 (33.3)	19 (25.0)	3 (37.5)	5 (31.3)	4 (66.7)	12 (40.0)	31 (29.2)
Stomatitis	0	0	3 (23.1)	11 (22.0)	3 (50.0)	17 (22.4)	4 (50.0)	7 (43.8)	3 (50.0)	14 (46.7)	31 (29.2)
Diarrhoea	0	1 (25.0)	2 (15.4)	12 (24.0)	2 (33.3)	17 (22.4)	1 (12.5)	8 (50.0)	4 (66.7)	13 (43.3)	30 (28.3)
Nausea	1 (33.3)	1 (25.0)	5 (38.5)	8 (16.0)	2 (33.3)	17 (22.4)	2 (25.0)	7 (43.8)	1 (16.7)	10 (33.3)	27 (25.5)
Decreased appetite	0	2 (50.0)	2 (15.4)	12 (24.0)	1 (16.7)	17 (22.4)	0	4 (25.0)	2 (33.3)	6 (20.0)	23 (21.7)
Dysgeusia	1 (33.3)	0	5 (38.5)	8 (16.0)	2 (33.3)	16 (21.1)	1 (12.5)	3 (18.8)	3 (50.0)	7 (23.3)	23 (21.7)
Anaemia	1 (33.3)	0	3 (23.1)	10 (20.0)	2 (33.3)	16 (21.1)	3 (37.5)	2 (12.5)	1 (16.7)	6 (20.0)	22 (20.8)
Abdominal pain	0	0	3 (23.1)	11 (22.0)	1 (16.7)	15 (19.7)	1 (12.5)	4 (25.0)	1 (16.7)	6 (20.0)	21 (19.8)
Vomiting	1 (33.3)	0	4 (30.8)	8 (16.0)	1 (16.7)	14 (18.4)	1 (12.5)	2 (12.5)	2 (33.3)	5 (16.7)	19 (17.9)
Aspartate aminotransferase increased	1 (33.3)	0	4 (30.8)	7 (14.0)	0	12 (15.8)	2 (25.0)	4 (25.0)	0	6 (20.0)	18 (17.0)
Hypophosphataemia	0	0	2 (15.4)	10 (20.0)	1 (16.7)	13 (17.1)	0	4 (25.0)	1 (16.7)	5 (16.7)	18 (17.0)
Dehydration	1 (33.3)	1 (25.0)	0	7 (14.0)	1 (16.7)	10 (13.2)	2 (25.0)	2 (12.5)	1 (16.7)	5 (16.7)	15 (14.2)
Dry eye	0	0	1 (7.7)	7 (14.0)	1 (16.7)	9 (11.8)	0	5 (31.3)	1 (16.7)	6 (20.0)	15 (14.2)
Pain in extremity	0	1 (25.0)	3 (23.1)	3 (6.0)	1 (16.7)	8 (10.5)	1 (12.5)	5 (31.3)	1 (16.7)	7 (23.3)	15 (14.2)
Alanine aminotransferase increased	1 (33.3)	0	4 (30.8)	4 (8.0)	0	9 (11.8)	2 (25.0)	3 (18.8)	0	5 (16.7)	14 (13.2)
Cough	1 (33.3)	0	1 (7.7)	6 (12.0)	2 (33.3)	10 (13.2)	1 (12.5)	3 (18.8)	0	4 (13.3)	14 (13.2)
Vision blurred	1 (33.3)	1 (25.0)	2 (15.4)	4 (8.0)	2 (33.3)	10 (13.2)	0	3 (18.8)	1 (16.7)	4 (13.3)	14 (13.2)
Weight decreased	2 (66.7)	0	2 (15.4)	5 (10.0)	2 (33.3)	11 (14.5)	1 (12.5)	0	2 (33.3)	3 (10.0)	14 (13.2)
Blood alkaline phosphatase increased	1 (33.3)	0	3 (23.1)	6 (12.0)	0	10 (13.2)	2 (25.0)	1 (6.3)	0	3 (10.0)	13 (12.3)
Hypercalcaemia	1 (33.3)	0	1 (7.7)	5 (10.0)	0	7 (9.2)	2 (25.0)	3 (18.8)	1 (16.7)	6 (20.0)	13 (12.3)
Back pain	1 (33.3)	0	4 (30.8)	4 (8.0)	0	9 (11.8)	1 (12.5)	2 (12.5)	0	3 (10.0)	12 (11.3)
Onycholysis	0	0	1 (7.7)	5 (10.0)	0	6 (7.9)	1 (12.5)	5 (31.3)	0	6 (20.0)	12 (11.3)
Paronychia	0	0	1 (7.7)	2 (4.0)	2 (33.3)	5 (6.6)	1 (12.5)	4 (25.0)	2 (33.3)	7 (23.3)	12 (11.3)
Arthralgia	0	1 (25.0)	3 (23.1)	2 (4.0)	2 (33.3)	8 (10.5)	0	2 (12.5)	1 (16.7)	3 (10.0)	11 (10.4)
Hyponatraemia	0	0	1 (7.7)	5 (10.0)	1 (16.7)	7 (9.2)	0	3 (18.8)	1 (16.7)	4 (13.3)	11 (10.4)
Nail discolouration	0	0	2 (15.4)	5 (10.0)	0	7 (9.2)	1 (12.5)	2 (12.5)	1 (16.7)	4 (13.3)	11 (10.4)

Note: Participants were counted once under each MedDRA preferred term. Adverse events are ordered by the descending frequency in the total column.
Note: Treatment-emergent AEs are any AEs either reported for the first time or worsening of a pre-existing event after first dose of study drug.
[a] Pemigatinib was administered QD on a 2-weeks-on/1-week-off therapy schedule.
[b] Pemigatinib was administered QD.

Treatment-emergent AEs occurring in ≥ 10% of participants on combination therapy in Study INCB 54828-101 (Part 3) are presented by treatment group and overall in Table 2. The most frequently occurring TEAEs for each treatment combination were as follows:

- **Pemigatinib + Gemcitabine + Cisplatin:** Anemia (8/8 participants); blood creatinine increased, constipation, fatigue, and nausea (5/8 participants each); and ALT increased, AST increased, diarrhea, hyperphosphatemia, hyponatremia, thrombocytopenia, and WBC count decreased (4/8 participants each).
- **Pemigatinib + Docetaxel:** Hyperphosphatemia, diarrhea, and dysgeusia (6/7 participants each); fatigue and dehydration (5/7 participants each); and nausea (4/7 participants).
- **Pemigatinib + Pembrolizumab:** Hyperphosphatemia (17/23 participants), anemia (11/23 participants), and diarrhea and decreased appetite (10/23 participants each).
- **Pemigatinib + Trastuzumab:** Alopecia, cough, and hyperphosphatemia (4/6 participants each) and decreased appetite, diarrhea, and dry mouth (3/6 participants each).

A single participant who received pemigatinib + docetaxel had DLTs of fatigue (Grade 3) and dehydration (Grade 3). No other participants on combination therapy had a DLT.

A total of 18 participants (40.9%) on combination therapy had at least 1 SAE: 4/8 participants on pemigatinib + gemcitabine + cisplatin, 6/7 participants on pemigatinib + docetaxel, and 8/23 participants on pemigatinib + pembrolizumab. The most frequently occurring SAEs across all combination therapy cohorts were dehydration in 3 participants (6.8%) and anemia and acute renal failure in 2 participants (4.5%) each. By treatment combination, the only SAE occurring in more than 1 participant was dehydration in 2 participants in the pemigatinib + docetaxel cohort. Two participants (4.5%) had SAEs with a fatal outcome: completed suicide (pembrolizumab + pemigatinib 9 mg) and disease progression (gemcitabine + cisplatin + pemigatinib 13.5 mg). Neither of these events was assessed as related to pemigatinib.

Five participants (11.4%) on combination therapy had TEAEs leading to discontinuation of pemigatinib. No event leading to discontinuation occurred in more than 1 participant.

Table 2: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 10% of Participants on Pemigatinib Combination Therapy in Study INCB 54828-101 (Part 3) in Decreasing Order of Frequency

	Pemigatinib + GEM + CIS		Pemigatinib + DOC	Pemigatinib + PEM				Pemigatinib + TRAS	
	Interval Dose Regimen[a]		Interval Dose Regimen[a]	Interval Dose Regimen[a]			Continuous Dose Regimen[b]	Interval Dose Regimen[a]	
MedDRA Preferred Term, n (%)	9 mg (N = 1)	13.5 mg (N = 7)	13.5 mg (N = 7)	9 mg (N = 3)	13.5 mg (N = 14)	Subtotal (N = 17)	13.5 mg (N = 6)	13.5 mg (N = 6)	Total (N = 44)
Hyperphosphataemia	1 (100.0)	3 (42.9)	6 (85.7)	3 (100.0)	11 (78.6)	14 (82.4)	3 (50.0)	4 (66.7)	31 (70.5)
Anaemia	1 (100.0)	7 (100.0)	3 (42.9)	1 (33.3)	8 (57.1)	9 (52.9)	2 (33.3)	2 (33.3)	24 (54.5)
Diarrhoea	0	4 (57.1)	6 (85.7)	1 (33.3)	7 (50.0)	8 (47.1)	2 (33.3)	3 (50.0)	23 (52.3)
Fatigue	0	5 (71.4)	5 (71.4)	1 (33.3)	5 (35.7)	6 (35.3)	1 (16.7)	2 (33.3)	19 (43.2)
Alopecia	0	1 (14.3)	3 (42.9)	0	6 (42.9)	6 (35.3)	2 (33.3)	4 (66.7)	16 (36.4)
Constipation	1 (100.0)	4 (57.1)	3 (42.9)	0	5 (35.7)	5 (29.4)	1 (16.7)	2 (33.3)	16 (36.4)
Decreased appetite	0	2 (28.6)	1 (14.3)	0	9 (64.3)	9 (52.9)	1 (16.7)	3 (50.0)	16 (36.4)
Dry mouth	1 (100.0)	2 (28.6)	1 (14.3)	0	4 (28.6)	4 (23.5)	4 (66.7)	3 (50.0)	15 (34.1)
Dysgeusia	0	2 (28.6)	6 (85.7)	0	3 (21.4)	3 (17.6)	3 (50.0)	1 (16.7)	15 (34.1)
Nausea	1 (100.0)	4 (57.1)	4 (57.1)	0	3 (21.4)	3 (17.6)	1 (16.7)	2 (33.3)	15 (34.1)
Stomatitis	1 (100.0)	2 (28.6)	2 (28.6)	1 (33.3)	5 (35.7)	6 (35.3)	1 (16.7)	2 (33.3)	14 (31.8)
Blood creatinine increased	1 (100.0)	4 (57.1)	1 (14.3)	1 (33.3)	4 (28.6)	5 (29.4)	0	1 (16.7)	12 (27.3)
Dehydration	1 (100.0)	2 (28.6)	5 (71.4)	1 (33.3)	2 (14.3)	3 (17.6)	1 (16.7)	0	12 (27.3)
Aspartate aminotransferase increased	0	4 (57.1)	0	0	5 (35.7)	5 (29.4)	1 (16.7)	1 (16.7)	11 (25.0)
Cough	0	1 (14.3)	1 (14.3)	0	5 (35.7)	5 (29.4)	0	4 (66.7)	11 (25.0)
Alanine aminotransferase increased	0	4 (57.1)	0	0	5 (35.7)	5 (29.4)	1 (16.7)	0	10 (22.7)
Dyspnoea	0	2 (28.6)	0	1 (33.3)	4 (28.6)	5 (29.4)	1 (16.7)	2 (33.3)	10 (22.7)
Vomiting	0	3 (42.9)	3 (42.9)	1 (33.3)	2 (14.3)	3 (17.6)	1 (16.7)	0	10 (22.7)
Dry eye	0	0	1 (14.3)	0	4 (28.6)	4 (23.5)	2 (33.3)	2 (33.3)	9 (20.5)
Hyponatraemia	1 (100.0)	3 (42.9)	2 (28.6)	1 (33.3)	2 (14.3)	3 (17.6)	0	0	9 (20.5)
Hypomagnesaemia	1 (100.0)	1 (14.3)	1 (14.3)	1 (33.3)	4 (28.6)	5 (29.4)	0	0	8 (18.2)
Abdominal pain	1 (100.0)	1 (14.3)	1 (14.3)	0	2 (14.3)	2 (11.8)	2 (33.3)	0	7 (15.9)
Back pain	0	0	2 (28.6)	1 (33.3)	2 (14.3)	3 (17.6)	1 (16.7)	1 (16.7)	7 (15.9)
Blood alkaline phosphatase increased	0	1 (14.3)	1 (14.3)	1 (33.3)	2 (14.3)	3 (17.6)	1 (16.7)	1 (16.7)	7 (15.9)
Hypercalcaemia	0	1 (14.3)	1 (14.3)	1 (33.3)	4 (28.6)	5 (29.4)	0	0	7 (15.9)

Table 2: Summary of Treatment-Emergent Adverse Events Occurring in ≥ 10% of Participants on Pemigatinib Combination Therapy in Study INCB 54828-101 (Part 3) in Decreasing Order of Frequency (Continued)

	Pemigatinib + GEM + CIS		Pemigatinib + DOC	Pemigatinib + PEM				Pemigatinib + TRAS	
	Interval Dose Regimen[a]		Interval Dose Regimen[a]	Interval Dose Regimen[a]			Continuous Dose Regimen[b]	Interval Dose Regimen[a]	
MedDRA Preferred Term, n (%)	9 mg (N = 1)	13.5 mg (N = 7)	13.5 mg (N = 7)	9 mg (N = 3)	13.5 mg (N = 14)	Subtotal (N = 17)	13.5 mg (N = 6)	13.5 mg (N = 6)	Total (N = 44)
Hypoalbuminaemia	1 (100.0)	0	1 (14.3)	1 (33.3)	2 (14.3)	3 (17.6)	0	1 (16.7)	6 (13.6)
Hypokalaemia	1 (100.0)	2 (28.6)	0	0	3 (21.4)	3 (17.6)	0	0	6 (13.6)
Hypotension	0	0	2 (28.6)	1 (33.3)	3 (21.4)	4 (23.5)	0	0	6 (13.6)
Neutropenia	0	3 (42.9)	3 (42.9)	0	0	0	0	0	6 (13.6)
Pyrexia	1 (100.0)	0	0	0	1 (7.1)	1 (5.9)	2 (33.3)	2 (33.3)	6 (13.6)
Vision blurred	0	1 (14.3)	1 (14.3)	0	3 (21.4)	3 (17.6)	0	1 (16.7)	6 (13.6)
Dizziness	0	3 (42.9)	0	0	2 (14.3)	2 (11.8)	0	0	5 (11.4)
Headache	0	1 (14.3)	1 (14.3)	0	1 (7.1)	1 (5.9)	0	2 (33.3)	5 (11.4)
Hyperglycaemia	0	1 (14.3)	1 (14.3)	1 (33.3)	2 (14.3)	3 (17.6)	0	0	5 (11.4)
Oedema peripheral	0	1 (14.3)	2 (28.6)	0	1 (7.1)	1 (5.9)	1 (16.7)	0	5 (11.4)
Paronychia	0	0	2 (28.6)	0	2 (14.3)	2 (11.8)	0	1 (16.7)	5 (11.4)
White blood cell count decreased	1 (100.0)	3 (42.9)	0	0	1 (7.1)	1 (5.9)	0	0	5 (11.4)
Weight decreased	0	1 (14.3)	3 (42.9)	0	0	0	1 (16.7)	0	5 (11.4)

CIS = cisplatin; DOC = docetaxel; GEM = gemcitabine; PEM = pembrolizumab; TRAS = trastuzumab.
Note: Participants were counted once under each MedDRA preferred term. Adverse events are ordered by the descending frequency in total column.
Note: Treatment-emergent AEs are any AEs either reported for the first time or worsening of a pre-existing event after first dose of study drug.
a Pemigatinib was administered QD on a 2-weeks-on/1-week-off therapy schedule.
b Pemigatinib was administered QD.

1.4.2.2. Pharmacokinetic/Pharmacodynamic Summary

Following QD oral doses of INCB054828 on a 2-weeks-on/1-week-off dosing schedule, an approximately linear relationship was observed for INCB054828 exposure (C_{max} and AUC) over the dose range studied in Study INCB 52828-101 (1 to 20 mg). INCB054828 is rapidly absorbed, attaining peak plasma concentrations in approximately 1 to 2 hours after oral administration, and the geometric mean $t_{½}$ is 15.4 hours. At the 13.5 mg QD dose, geometric mean of steady-state C_{max} value is 236 nM and AUC_{0-24} is 2620 nM·h, the geometric mean steady-state oral clearance of INCB054828 is low (10.6 L/h), and apparent steady-state volume of distribution is moderate (235 L). The PK parameters for continuous administration are similar to those for intermittent dosing. The projected average inhibition of FGFR2 based on PK and in vitro potency of INCB054828 ranged from 41% at 1 mg to 97% at 20 mg. Consistent with this projection, the observed inhibition of pFGFR2 in KATOIII cells spiked to ex vivo whole blood samples collected from subjects at trough was 82% after the 13.5 mg QD dose and 64% after the 9 mg QD dose. The steady-state plasma concentrations of INCB054828 after 13.5 mg QD dose that exceeded in vivo IC_{50} over a 24-hour dosing period is showed in Figure 1. The magnitude and frequency of HP was also dose-dependent. In the 9-mg cohort, 1 of 3 subjects developed HP in Part 1; 3 additional subjects were enrolled at 9 mg in Part 2. Of a total of 6 subjects administered 9 mg, 4 experienced HP; in the 13.5-mg cohort, all 6 subjects developed HP, which was managed with a low-phosphate diet and introduction of phosphate binders. Further, the increase in serum phosphorus observed after treatment with INCB054828 was exposure-dependent (see Figure 2).

Figure 1: INCB054828 Plasma Concentrations (Mean ± SE) at Steady State Following Once-Daily Dosing of Pemigatinib as Monotherapy

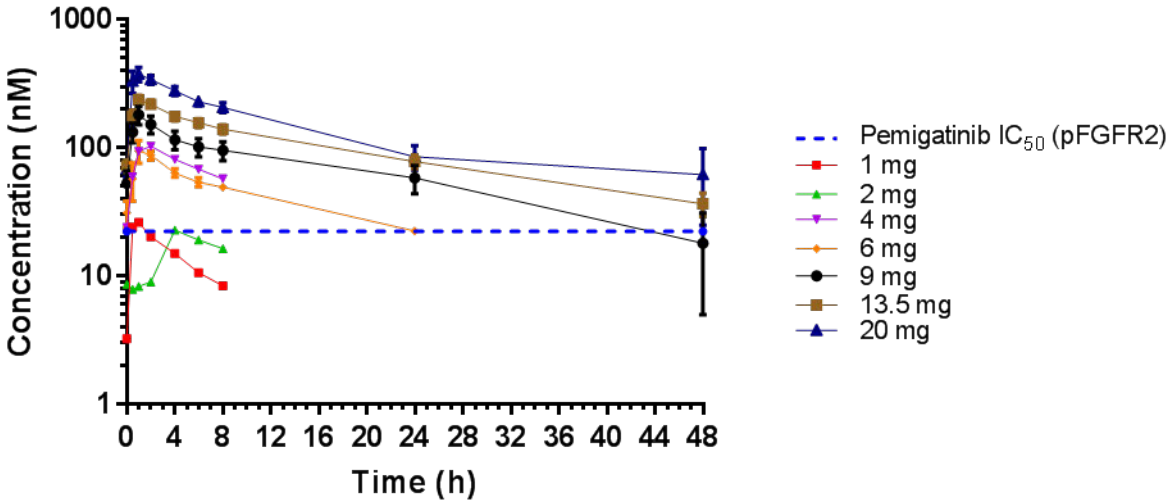
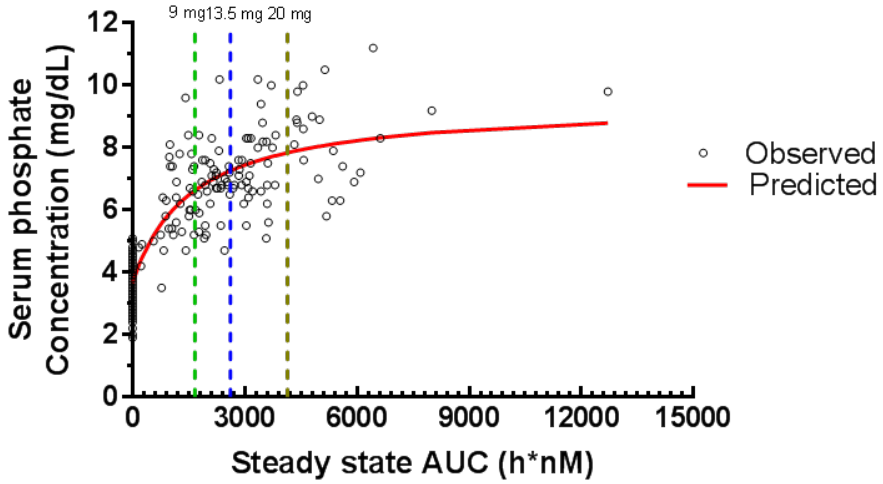


Figure 2: Serum Phosphate Versus Exposure



Subjects will be monitored on an ongoing basis throughout this study as per the schedule of laboratory assessments (see Table 20).

1.4.3. Potential Risks of Gemcitabine and Cisplatin

Gemcitabine is a nucleoside analog with structural similarity to cytarabine and is currently approved to treat breast cancer, NSCLC, ovarian cancer, and pancreatic cancer either alone or in combination with other chemotherapy agents.

Cisplatin is a platinum-containing alkylating agent and is currently approved to treat ovarian germ cell cancer, invasive bladder cancer, ovarian cancer, and testicular germ cell cancer either alone or in combination with other chemotherapy agents.

The combination of gemcitabine and cisplatin are indicated for use in the treatment of biliary tract cancer, bladder cancer, cervical cancer, malignant mesothelioma, NSCLC, ovarian cancer, and pancreatic cancer and are also being investigated in treating other cancers

Risks associated with use of gemcitabine include myelosuppression, which is the principal DLT. Gemcitabine can suppress bone marrow function as manifested by leukopenia, thrombocytopenia, and anemia. Subjects should be monitored for myelosuppression during therapy. The most common adverse reactions as a monotherapy are nausea; vomiting; anemia; increased ALT, AST, and alkaline phosphatase (ALP); neutropenia; leukopenia; proteinuria; fever; hematuria; rash; thrombocytopenia; and dyspnea. A complete discussion of risks associated with gemcitabine can be found in the United States Package Insert (USPI) or in the Summary of Product Characteristics (SmPC).

The following cisplatin side effects are common (occurring in > 30%): nausea, vomiting, kidney toxicity (dose related and typically reversible), neutropenia, leukopenia, and anemia. Less common side effects (occurring in 10-29%) include the following: peripheral neuropathy; paresthesia; sensory loss; numbness and tingling; difficulty walking (some effects may be irreversible); tinnitus; anorexia; dysgeusia; increased ALT, AST, and ALP; and alopecia. A complete and detailed list of risks associated with cisplatin use can be found in the USPI or SmPC.

1.4.4. Potential Risks of Docetaxel

Docetaxel is an antimitotic chemotherapy medication that works by interfering with cell division and is a member of the taxane class of drugs. It is indicated for use in subjects with breast cancer, NSCLC, prostate cancer, gastric cancer, bladder cancer, and head and neck cancer.

The most serious adverse reactions from docetaxel are toxic deaths, hepatotoxicity, neutropenia, hypersensitivity, and fluid retention. These are noted in the black box warning on the product label.

The reporting and incidence of AEs associated with docetaxel vary by dose and by indication; however, the most common adverse reactions across all docetaxel indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. A complete and detailed list of risks associated with docetaxel use can be found in the USPI or in the SmPC.

1.4.5. Potential Risks of Pembrolizumab

Pembrolizumab is a PD-1 inhibitor that works by blocking the inhibitory ligand of programmed cell death 1 receptor. It is part of a class of drug called the immune checkpoint inhibitors.

The following immune-mediated adverse reactions have been reported with use of pembrolizumab (2mg/kg): pneumonitis, colitis, hepatitis, endocrinopathies, renal failure, and nephritis. Additional notable (>30%) drug-related AEs (all grades) reported include fatigue, nausea, cough, pruritus, anemia, hyperglycemia, hyponatremia, and hypoalbuminemia.
A complete and detailed list of risks associated with pembrolizumab use can be found in the USPI or in the SmPC.

1.4.6. Potential Risks of Trastuzumab

Trastuzumab is a humanized monoclonal antibody that selectively binds to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2.

The most significant AE observed in subjects who receive trastuzumab is cardiac dysfunction, reflected by asymptomatic decreases in left ventricular ejection fraction (LVEF) and, less frequently, by clinically symptomatic congestive heart failure. Risk factors for cardiac failure in the setting of trastuzumab treatment include coadministration with anthracycle-based chemotherapy, increasing age, a declining LVEF during treatment to below the lower limit of normal, and the use of antihypertensive medications (Tan-Chiu 2005). Subjects receiving trastuzumab should undergo frequent monitoring of cardiac function. Discontinuation of trastuzumab therapy should be strongly considered in subjects who develop clinically significant congestive heart failure. Refer to the USPI or the SmPC for more information.

1.4.7. Potential Risks of INCMGA00012

INCMGA00012 is an IgG4 humanized mAb that has been designed to restore T-cell immune function, similar to other PD-1 inhibitors that have been extensively studied. Therefore, safety experience with other drugs should be considered when administering INCMGA00012. Potentially serious irAEs include:

- Pneumonitis
- Hepatitis
- Colitis
- Nephritis
- Endocrinopathies (thyroiditis, hypophysitis, Type I diabetes)
- Encephalitis
- Myocarditis
- Skin reactions (including Stevens-Johnson Syndrome/toxic epidermal necrolysis)
- Rejection of organ transplants

Other reactions (including arthritis, uveitis, myositis, Guillain-Barré syndrome, myasthenia gravis, vasculitis, pancreatitis, and hemolytic anemia).

The occurrence of any of these syndromes may dictate interruption and potential discontinuation of study drug administration pending further evaluation, and reporting them to the sponsor as AEs of special interest. Most low-grade immune-related AEs (irAEs) can be managed symptomatically. Persistent low-grade or moderate toxicities may require treatment with corticosteroids or, in refractory cases, other immune suppressing agents such as mycophenolate or infliximab. High-grade immune-related toxicities will, in almost all cases, require treatment with corticosteroids.

Temporary interruptions of INCMGA00012 may be required in the event of treatment-related immune-related toxicity. General guidelines for specific toxicity regarding dosing and treatment are provided in Section 5.8.6. All toxicities will be graded according to NCI CTCAE v4.03.

1.4.8. Potential Risks Related to the Combination Regimens

The effects of concomitant INCB054828 with gemcitabine + cisplatin, docetaxel, pembrolizumab, trastuzumab, or INCMGA00012 are being assessed in this Protocol. As described above, the most common AEs associated with these medications are neutropenia, anemia, thrombocytopenia, cardiac dysfunction, and immune-related events. The most common AE associated with INCB054828 has been HP. There is not an expected overlap or interaction between these profiles. Hematology and blood chemistry parameters will be closely monitored in all study subjects. In addition, all AEs will be monitored to identify occurrences of new safety signals or potentiation of any gemcitabine-related, cisplatin-related, docetaxel-related, pembrolizumab-related, trastuzumab-related, or INCMGA00012-related sided effects.

1.5. Justification of Route, Dose Regimen, and Treatment Period

1.5.1. INCB054828

INCB054828 is being developed as a new investigational drug for oral administration. Oral drug administration is generally the most convenient and cost-effective method of drug delivery for medications requiring continuous exposure. INCB054828 tablets will be administered orally QD on a 2-week on-therapy and 1-week off-therapy schedule, a continuous dosing schedule, and for a small subset of subjects a twice daily (BID) continuous dosing schedule. One cycle will be defined as 21 continuous days; treatment for subjects in this study will consist of repeating 21-day cycles (ie, 14 days on therapy and 7 days off therapy). Justification for the initial dose regimen (2 weeks on and 1 week off) came from a preclinical toxicology study in rats where INCB054828 was administered daily for 14 days followed by a 7-day nontreatment period. Additionally, INCB054828 was well tolerated in all dose levels tested in a 28-day continuous treatment toxicology study in cynomolgus monkeys.

Based on preclinical data, the terminal elimination half-life of INCB054828 in humans is projected to be approximately 16 hours. A clinical dose of 6 mg QD is estimated to provide a C_{ave} of approximately 0.025 μM, which is roughly twice the whole blood IC_{50} (0.011 μM). Following a 6 mg QD dose, the steady-state plasma AUC is estimated to be approximately 0.6 μM·h, the C_{max} is estimated to be approximately 0.05 μM, and the C_{min} is expected to exceed the whole blood IC_{50}. Preclinical data suggest that the whole blood IC_{90} for INCB054828 is approximately 0.077 μM. Thus, it is reasonable to expect that full pharmacologic inhibition can be achieved with INCB054828 at a feasible clinical dose.

Based on the findings in preclinical toxicology experiments in rats and monkeys, HP, physeal dysplasia, and soft tissue mineralization are toxicities of concern. These toxicities have been reported in rodents and large animals following administration of selective FGFR inhibitors and can be explained by the pharmacological action of FGFR inhibition. Data from ongoing clinical studies of selective FGFR inhibitors have confirmed that HP is an on-target pharmacologic effect of FGFR inhibition, and that it can be managed with phosphate-binding therapy, dose interruptions, and dose reductions. Clear guidance for the management of HP has been provided in this Protocol to initiate a low-phosphate diet, phosphate-binding therapy, phosphaturic agents, and dose interruptions and reductions depending on the serum phosphate level, which will be monitored weekly (at least twice weekly if abnormal). Additional safety measures have been added to the Protocol to require regular ophthalmological examinations and to exclude subjects with a history of a calcium/phosphate homeostasis disorder, a history and/or current evidence of ectopic mineralization/calcification, or current evidence of corneal disorder/keratopathy and retinal disorders.

Based on preclinical toxicology, the highest non–severely toxic dose in the most sensitive species is 1.05 mg/kg per day (6.3 mg/m^2 per day), the highest dose tested in the rat. This produces a HED of 10.1 mg, and using a conservative approach, one-tenth of this dose is 1.01 mg, thus the proposed starting dose is 1 mg.

Dose escalation will be conducted in an accelerated titration design (approximately 1 subject per cohort) and will switch to a 3 + 3 design once a Grade 2 or greater toxicity or HP (serum phosphate > 5.5 mg/dL) is observed. Subsequent cohorts will have increases in the dose of INCB054828 limited to no more than 50%.

An expansion (Part 2) of approximately 140 subjects with advanced malignancies that have genetic alterations in FGF or FGFR genes will be treated with the selected dose, either the MTD or the pharmacologically active dose (PAD) of INCB054828, to further determine safety, tolerability, efficacy, PK, food effect, and PD. Once enrollment in the expansion begins, approximately 8 subjects will be evaluated in the food-effect study.

The sponsor may implement alternate regimens such as intermediate doses or alternate administration schedules depending on PK, PD, and safety results.

1.5.2. Continuous Administration of INCB054828

1.5.2.1. Nonclinical

The nonclinical toxicology program for INCB054828 was conducted to support clinical studies in subjects with cancer and was designed in accordance with ICH S9 (FDA 2010). The studies successfully supported the selection of a safe starting dose and entry into the current Phase 1 clinical study in subjects with cancer (INCB 54828-101). The toxicology studies are outlined in Table 3 and detailed in IND 124358.

Table 3: INCB054828 Toxicology Program

Study Type (Compliance) and Duration	Species/Test System	Route of Administration
Single-dose toxicity (non-GLP)	Rat and monkey	Oral gavage
Repeat-dose toxicity (non-GLP) Daily for 9-10 days	Rat and monkey	Oral gavage
Repeat-dose toxicity (GLP)		
Intermittent dosing: 14 days dosing followed by 7 days nondosing followed by 14 days dosing	Rat	Oral gavage
Daily for 28 days	Monkey	Oral gavage

The target organ profile in both species was consistent with INCB054828 pharmacology (FGFR inhibition) and included hyperphosphatemia, physeal dysplasia, and soft tissue mineralization. Mineralization was observed in numerous tissues and was not reversible (after 4-week recovery periods), while physeal and cartilage findings were reversible.

At the NOAEL in the 28-day rat study, findings were minimal and considered to be exacerbation of normal background findings. The rat NOAEL was associated with $AUC_{0\text{-}24h}$ values of 2.88 and 3.39 µM·h in males and females, respectively. At the NOAEL in the 28-day monkey study, findings were limited to reversible, minimal to mild alterations in the femoral physis and sternal cartilage (synchondrosis). The monkey NOAEL was associated with $AUC_{0\text{-}24h}$ values of 1.78 and 1.65 µM·h in males and females, respectively.

The dose proposed for continuous (QD) dosing in INCB 54828-101 is 9 mg. In subjects given this dose on an intermittent schedule (2 weeks on and 1 week off per cycle), the $AUC_{0\text{-}\tau}$ was 1.7 µM·h; similar to the NOAEL-AUCs determined for rats administered study drug on an intermittent schedule and in monkeys administered study drug QD for 28 days.

1.5.2.2. Pharmacokinetics

INCB054828 exhibits linear PK over the dose range examined to date (1-13.5 mg; PK data not yet available for 20 mg). In both preclinical and clinical studies, change in serum phosphorus can be used as a surrogate marker for FGFR1 signaling. In study INCB 54828-101, using the 2-weeks-on and 1-week-off treatment schedule, increase in serum phosphorus is observed to be dose- as well as exposure-dependent (plasma AUC of INCB054828), with normalization occurring rapidly after treatment interruption (ie, it is readily reversible). The increase in serum phosphorus is minimal at 6 mg QD, moderate at 9 mg QD, and more consistent at doses > 9 mg QD. Based on these observations, 9 mg QD appears to be a PAD. Further, the 2 objective clinical responses observed to date in study INCB 54828-101 were at the 9 mg QD dose level. Therefore, the proposed starting dose for continuous administration is 9 mg QD. Serum phosphorus [redacted] will be monitored carefully, and the daily dose will be decreased if serum phosphorus is consistently elevated.

1.5.3. Twice-Daily Administration of INCB054828

Erdafitinib is an inhibitor of FGFR approved for treatment of bladder cancer. The long effective half-life of erdafitinib (59 hours) in cancer patients predicts low steady-state peak-to-trough fluctuation for target (pFGFR2) inhibition (93.6%-95.1% at therapeutic dose of 9 mg QD; Table 4). With administration of pemigatinib 13.5 mg QD, relatively high steady-state peak-to-trough fluctuation for pFGFR2 inhibition (82.7%-96.2%; Table 4) is predicted due to the relatively short half-life of pemigatinib (15 hours) compared to erdafitinib. Simulations suggest that BID administration of pemigatinib at a dose level above 9 mg can produce similar or higher pFGFR2 inhibition compared to erdafitinib 9 mg QD. Therefore, BID dosing of pemigatinib is proposed to improve the efficacy of FGFR inhibition.

Table 4: Comparison of Projected pFGFR2 Inhibition for Erdafitinib and Pemigatinib in Various Dose Regimens

Drug/Dose Regimen	I_{max}	I_{ave}	I_{min}
Erdacitinib 9 mg QD	95.1%	94.5%	93.6%
Pemigatinib 13.5 mg QD	96.2%	90.0%	82.7%
Pemigatinib 13.5 mg BID	97.8%	96.6%	95.2%
Pemigatinib 9 mg BID	96.1%	94.1%	91.5%
Pemigatinib 6 mg BID	93.1%	89.1%	85.4%

The target for the BID dosing schedule will be subjects with advanced/metastatic bladder cancer with FGFR3 alterations (mutations or fusions) in Part 2 (approximately 10 subjects).

1.5.4. Gemcitabine + Cisplatin

Gemcitabine + cisplatin combination regimen will be administered as open-label, commercially available product to be supplied by the clinical site. Gemcitabine is typically administered intravenously at 1000 mg/m^2 on Days 1, 8, and 15 of a 28-day cycle. Since the cycle for INCB054828 is 21 days, gemcitabine will be administered on Days 1 and 8 of the 21-day cycle. Cisplatin will be administered intravenously at 70 mg/m^2 once every 3 weeks on Day 1 of each 21-day cycle. Dose modifications can be made to manage toxicity.

1.5.5. Docetaxel

Docetaxel will be administered as open-label, commercially available product to be supplied by the clinical site. Docetaxel will be administered intravenously at a starting dose of 75 mg/m^2 once every 3 weeks on Day 1 of each 21-day cycle. Dose modifications can be made to manage toxicity.

1.5.6. Pembrolizumab

The dose of pembrolizumab planned to be studied in this study is 200 mg every 3 weeks. The dose recently approved in the United States for treatment of melanoma subjects is 2 mg/kg every 3 weeks. Information on the rationale for selecting 200 mg every 3 weeks is summarized below.

An integrated body of evidence suggests that 200 mg every 3 weeks is expected to provide similar response to 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg every 3 weeks are expected to lie within this range and will be close to those obtained with 2 mg/kg every 3 weeks dose. The 2 mg/kg every 3 weeks dose is the approved dose for metastatic melanoma in the United States.

The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose is predicted to considerably overlap those obtained with the 2 mg/kg dose and, importantly, will maintain individual subject exposures within the exposure range established in melanoma as associated with maximal clinical response. The slight increase in PK variability predicted for the fixed dose relative to weight-based dose administration is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 mg/kg and 10 mg/kg to provide similar efficacy and safety.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the antitumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types. Thus, the 200 mg every 3 weeks fixed dose regimen is considered an appropriate fixed dose for other solid tumor indications as well. Dose modifications can be made to manage toxicity.

1.5.7. Trastuzumab

The initial approved dose of trastuzumab in breast cancer was 4 mg/kg initial dose followed by a 2 mg/kg dose given every 7 days. This regimen was based on clinical efficacy in a randomized Phase 3 study (Bang et al 2010). Since the initial approval, the half-life of trastuzumab has been determined to be approximately 28.5 days, which supports administration every 3 weeks versus weekly. The average exposure at any time during the treatment is comparable between the 2 regimens. The every-3-week regimen has been used in subjects with breast cancer as well as gastric cancer (refer to the USPI and SmPC).

1.5.8. INCMGA00012

INCMGA00012 in combination with INCB054828 will be tested in this study. A fixed dose of INCMGA00012 will be used. Fixed doses have several advantages over weight-based doses, including convenience of preparation and administration, reducing errors in preparation calculation, and minimization of drug waste. Body weight–based doses and fixed doses of monoclonal antibodies have been evaluated, and the 2 approaches performed similarly, with body size–based doses not always offering an advantage in reducing variability of exposure (Bai et al 2012, Wang et al 2009).

The proposed flat dose regimen of 500 mg Q4W is based on modeling of clinical PK data from the ongoing first-in-human monotherapy study (NCT03059823) and benchmarking to pembrolizumab. This dose-escalation study of INCMGA00012 evaluated 37 subjects at the following doses: 1 mg/kg Q2W, 3 mg/kg Q2W, 3 mg/kg Q4W, 10 mg/kg Q2W, and 10 mg/kg Q4W. While supra dose proportionality was observed for AUC and C_{max} for the first dose escalation from 1 mg/kg to 3 mg/kg, linear PK was shown from 3 mg/kg to 10 mg/kg. No dose-limiting toxicity was observed at any dose level, and an MTD was not reached.

A population PK analysis was performed on these subjects to characterize the effect of body weight on the PK of INCMGA00012. The plasma concentrations of INCMGA00012 can be adequately described by a 2-compartment model with first-order elimination. Higher clearance of INCMGA00012 was estimated for 1 mg/kg than the other dose groups. Body weight dependence of clearance was characterized by a power relationship with an exponent of 0.911.

A simulation was conducted to investigate the use of body weight–based dosing and flat dosing for INCMGA00012, with the aim of targeting a steady-state trough concentration of ≈ 21 µg/mL, the median trough concentration for pembrolizumab (Freshwater, 2017). The median INCMGA00012 exposure and distribution around the median at 500 mg Q4W were similar to 7 mg/kg Q4W in the simulated population, which justified clinical exploration in an expansion cohort of the study. The median steady-state concentration at 500 mg Q4W was 24.8 µg/mL, and 58% of subjects had trough concentrations greater than target concentration.

Pharmacokinetic data were obtained from 15 subjects who received INCMGA00012 500 mg Q4W in the Cohort Expansion Phase of Study INCMGA 0012-101. The observed AUC_{∞} for 500 mg Q4W was close to the steady-state AUC_t based on the population PK analysis of weight-based dosing, as was the estimated clearance. The estimated $t_{½}$ (333 hours) was slightly shorter than that of the previous estimate of 409 hours. The mean trough plasma concentration on Cycle 2 was 17.1 µg/mL and the mean projected plasma $C_{min,ss}$ was 23.1 µg/mL (which meets or slightly exceeds the targeted concentration based on pembrolizumab data) with a mean accumulation index of 1.50. Overall, the 500-mg Q4W dose had very similar PK properties to 3 mg/kg dosing, and has ≈ 77% probability for steady-state trough plasma concentration ≥ 10 µg/mL, which is associated with maximum target engagement and greatest probability of efficacy. Based on these observations, 500 mg Q4W was chosen as the dosing regimen for further development in combination with INCB054828.

INCMGA00012 will be administered over a 60-minute IV infusion. The INCMGA00012 + INCB054828 cohorts will include:

- Dose Level 1: INCB054828 9 mg QD, continuously + INCMGA00012 500 mg Q4W
- Dose Level 2: INCB054828 13.5 mg QD, continuously + INCMGA00012 500 mg Q4W

Additional regimens of INCB054828 may be explored in combination with INCMGA00012 (eg, 2 weeks on/1 week off), as well as other doses/regimens of INCMGA00012 to determine the RP2D.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objectives

- To evaluate the safety, tolerability, and DLTs and to determine the PAD and MTD of INCB054828, alone as a monotherapy and in combination with other therapies.
- To assess the PD of INCB054828.

2.2. Secondary Objectives

- To assess preliminary efficacy by assessing the overall response rate (ORR) of INCB054828 in subjects with measurable disease, alone as a monotherapy and in combination with other therapies.
- To evaluate the PK of INCB054828 and the effect of food and other therapies on the PK of INCB054828.

[redacted]

3. SUBJECT ELIGIBILITY

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

3.1. Subject Inclusion Criteria

The following criteria are required for inclusion in the study:

1. Male or female subjects, age 18 years or older on day of signing consent.
2. Willingness to provide written informed consent for the study.
3. Part 1: Any advanced solid tumor malignancy.

   Part 1: Subset of subjects with moderate renal impairment (eGFR: ≥ 30 to < 60 mL/min/m^2) and severe renal impairment (eGFR: < 30 mL/min/m^2).

   Part 2: Subjects with measurable disease with documented FGF/FGFR alterations, including multiple myeloma and MPNs. For subjects enrolling in Part 2 with head and neck, vulvar, or anal cancer, must have evidence of positive HPV status. For BID dosing in Part 2, subjects must have a documented FGFR3 mutation or fusion-positive with advanced/metastatic bladder cancer.

   Part 3:

   1) Dose finding: subjects with solid tumor malignancies that have measurable disease for which treatment with gemcitabine + cisplatin, docetaxel, trastuzumab, and PD-1-directed therapies is relevant.
   2) Dose expansion: subjects with solid tumor malignancies that have measurable disease and are also harboring FGF/FGFR alterations for which treatment with gemcitabine + cisplatin, docetaxel, trastuzumab, and PD-1-directed therapies is relevant.
4. Has progressed after prior therapy and either there is no further effective standard anticancer therapy available (including subject refuses or is intolerant) or the prescribed combination therapy for subjects enrolling in Part 3 is considered a relevant therapy for their diagnosis.
5. Life expectancy > 12 weeks.
6. ECOG performance status:

   Part 1: 0 or 1.

   Parts 2 and 3: 0, 1, or 2.

7. Archival tumor specimen (tumor block or 25 unstained slides, minimum number of slides is approximately 15) or willingness to undergo a pretreatment tumor biopsy to provide a tumor block or 25 unstained slides (minimum number of slides is approximately 15). Archival tumor biopsies are acceptable at baseline and should be no more than 2 years old (preferably less than 1 year old and collected since the completion of the last treatment); subjects with samples older than 2 years old and/or with sequencing report from Foundation Medicine require approval from the sponsor medical monitor for exemption from the need for tumor biopsy or tumor sample requirement.

   NOTE: For subjects in Part 1, fresh tumor biopsies for the purpose of determining study eligibility should be limited to tumors where tissue can be safely accessed. The medical monitor should be contacted before the subject is enrolled.

8. Women of childbearing potential (defined as women who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy and are not postmenopausal or sterilized from chemo/radiotherapy, defined as ≥ 12 months of amenorrhea) must have a negative serum pregnancy test at screening and prior to the first dose on Cycle 1 Day 1. All women and men of childbearing potential must agree to take appropriate precautions to avoid pregnancy or fathering children (with at least 99% certainty) from screening through the safety follow-up visit (30-35 days after last dose). Subjects enrolled in Part 3 combination with INCMGA00012 should avoid pregnancy or fathering a child starting at screening through 6 months after the last dose of INCMGA00012. Permitted methods that are at least 99% effective in preventing pregnancy (Appendix A) should be communicated to the subject and their understanding confirmed.

3.2. Subject Exclusion Criteria

If met, any of the following criteria will lead to subject exclusion from the study:

1. Treatment with other investigational study drug for any indication for any reason, or receipt of anticancer medications within 28 days before first dose of study drug (6 weeks for mitomycin-C or nitrosoureas, 7 days for tyrosine kinase inhibitors), but may be eligible with approval from the sponsor's medical monitor.
   a. Subjects must have recovered (≤ Grade 1 or pretherapy baseline) from AEs due to previously administered therapies.
2. Prior receipt of a selective FGFR inhibitor within the last 6 months.
3. Inadequate laboratory parameters as indicated below. All screening laboratory tests should be performed within 14 days of treatment initiation.

   Part 1 Dose Escalation:

   a. Hemoglobin < 10.0 g/dL (transfusions are permitted with approximately 2 weeks of washout required before enrollment).
   b. Platelet count < 100×10^9/L
   c. Absolute neutrophil count < 1.5×10^9/L
   d. Total bilirubin > upper limit of normal (ULN) unless associated with subject's primary cancer and/or metastases and with medical monitor approval

e. AST or ALT > ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval
f. ALP > ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval
g. Creatinine clearance ≤ 60 mL/min (< 30 mL/min for urothelial carcinoma) based on the site's standard formula, except for a subset of subjects with moderate renal impairment (eGFR: ≥ 30 to < 60 mL/min/m^2) and severe renal impairment (eGFR: < 30 mL/min/m^2) based on the MDRD formula who will be allowed to enter the study
h. Serum calcium outside of the institutional normal range, or serum albumin-corrected calcium outside of the institutional normal range if serum albumin is outside of the institutional normal range
i. Serum phosphorus outside of the ULN of the institutional normal range
j. Parathyroid hormone > 1.5 × ULN of the institutional normal range

Part 2 Expansion:

a. Hemoglobin ≤ 9.0 g/dL(transfusions are permitted with approximately 2 weeks of washout required before enrollment).
b. Platelet count ≤ 75 × 10^9/L
c. Absolute neutrophil count ≤ 1.0 × 10^9/L
d. Total bilirubin ≥ 1.5 × institutional ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval
e. AST or ALT ≥ 3 × ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval
f. ALP ≥ 2.5 × ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval
g. Creatinine clearance ≤ 40 mL/minute (< 30 mL/min for multiple myeloma or urothelial carcinoma) based on the site's standard formula
h. Serum calcium outside of the institutional normal range, or serum albumin-corrected calcium outside of the institutional normal range if serum albumin is outside of the institutional normal range
i. Serum phosphorus outside of the ULN of the institutional normal range
j. Parathyroid hormone > 1.5 × ULN of the institutional normal range

Note: Hematological parameters do not apply to subjects with MPN.

Part 3 Combination:

k. Hemoglobin ≤ 9.0 g/dL (transfusions are permitted with approximately 2 weeks of washout required before enrollment).
l. Platelet count ≤ 75 × 10^9/L
m. Absolute neutrophil count ≤ 1.5 × 10^9/L
n. Total bilirubin ≥ 1.5 × institutional ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval
o. AST or ALT ≥ 3 × ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval
p. ALP ≥ 2.5 × ULN unless associated with subject's primary cancer and/or metastases and with medical monitor approval

q. Creatinine clearance ≤ 40 mL/minute (< 30 mL/min for urothelial carcinoma) based on the site's standard formula
r. International normalized ratio or prothrombin time > 1.5 × ULN, unless on warfarin
s. Activated partial thromboplastin time > 1.5 × ULN
t. Serum calcium outside of the institutional normal range, or serum albumin-corrected calcium outside of the institutional normal range when serum albumin is outside of the institutional normal range
u. Serum phosphorus outside of the ULN of the institutional normal range
v. Parathyroid hormone > 1.5 × ULN of the institutional normal range

4. History of calcium and phosphate homeostasis disorder or systemic mineral imbalance with ectopic calcification of soft tissues (exception: commonly observed calcifications in soft tissues, such as the skin, kidney, tendons, or vessels due to injury, disease, and aging, in the absence of systemic mineral imbalance).
5. History of hypersensitivity to any of the study drugs.
6. History and/or current evidence of ectopic mineralization/calcification, except intratumoral calcification secondary to tumor necrosis or previous treatment (eg, transarterial chemoembolization, chemotherapy) and calcified lymph nodes and asymptomatic arterial or cartilage/tendon calcification. Combined with #4 in Protocol Amendment 7.
7. Current evidence of clinically significant corneal disorder/keratopathy (including but not limited to bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis), or retinal disorder (including but not limited to macular/retinal degeneration, diabetic retinopathy, retinal detachment), confirmed by ophthalmologic examination.
8. History or presence of an abnormal electrocardiogram (ECG) that in the investigator's opinion is clinically meaningful. A screening QTc interval > 470 msec, as corrected by Fridericia, is excluded. For subjects with an intraventricular conduction delay (QRS interval 120 msec), the JTc interval may be used in place of the QTc with sponsor approval. The JTc must be ≤ 340 milliseconds if JTc is used in place of the QTc.
9. Prior radiotherapy within 2 weeks of study treatment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. Evidence of fibrosis within a radiation field from prior radiotherapy is permitted with medical monitor approval. A 1-week washout period is permitted for palliative radiation to non–central nervous system (CNS) disease with medical monitor approval.
    a. Subjects enrolled into Part 3 (pembrolizumab or INCMGA00012 combination), should have a minimum of a 6-month washout period after thoracic radiotherapy if > 30 Gy was received.
10. Use of any potent CYP3A4 inhibitor or inducer or moderate CYP3A4 inducer within 14 days or 5 half-lives (whichever is longer) of the first dose of study drug (see Section 5.12).
11. History of human immunodeficiency virus infection.

12. Untreated brain or CNS metastases or brain/CNS metastases that have progressed (eg, evidence of new or enlarging brain metastasis or new neurological symptoms attributable to brain/CNS metastases). Subjects with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT scan) during the screening period, and they are on a stable or decreasing dose of corticosteroids for at least 1 week.
13. Active chronic or current infectious disease requiring systemic antibiotic, antifungal, or antiviral treatment within 2 weeks prior to enrollment (subjects with asymptomatic chronic infections on prophylactic treatment are allowed).
14. History of clinically significant or uncontrolled cardiac disease including unstable angina, acute myocardial infarction within 6 months from Day 1 of study treatment administration, New York Heart Association Class III or IV congestive heart failure, or uncontrolled arrhythmia requiring therapy (subjects with pacemaker or with atrial fibrillation and well-controlled heart rate are allowed).
15. History of allergic reactions to INCB054828, any of the excipients of INCB054828 or similar compounds, gemcitabine, cisplatin, docetaxel, pembrolizumab, trastuzumab, or INCMGA00012. History of infusion allergic reactions to antibodies (eg, pembrolizumab, trastuzumab, or INCMGA00012) that are able to be managed with standard measures (eg, H2 blockers and/or steroids) are allowed.
16. Unable or unwilling to swallow INCB054828 or significant GI disorder(s) that could interfere with the absorption, metabolism, or excretion.
17. Inadequate recovery from toxicity and/or complications from a major surgery prior to starting therapy.
18. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, prostate intraepithelial neoplasm, carcinoma *in situ* of the cervix, or other noninvasive or indolent malignancy that has undergone potentially curative therapy.
19. Pregnant or nursing women or subjects expecting to conceive or father children within the projected duration of the study, starting with the screening visit through completion of safety follow-up visit (30-35 days after last dose). Subjects enrolled in Part 3 combination with INCMGA00012 should avoid pregnancy or fathering a child starting at screening through 6 months after the last dose of INCMGA00012.
20. Any condition that would in the investigator's judgment interfere with full participation in the study, including administration of study medication and attending required study visits; pose a significant risk to the subject; or interfere with interpretation of study data.
21. Subjects who require hemodialysis. Removed in Protocol Amendment 7.
22. Subjects being considered for treatment in the trastuzumab combination group (Part 3) with LVEF of < 50% on echocardiogram or multigated acquisition (MUGA) scan.

23. Evidence of active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection (defined as subjects with elevated transaminases or cirrhosis. Subjects with chronic HBV/HCV infection with no cirrhosis and no elevated transaminases are allowed).
24. Any prior PD-1– or PD-L1–directed treatment for which permanent discontinuation of therapy is recommended, per USPI.
25. Active autoimmune disease requiring systemic immunosuppression in excess of physiologic maintenance doses of corticosteroids.
26. Subjects receiving pembrolizumab or INCMGA00012 and have received a live vaccine within 28 days of planned start of study treatment.

    Note: Examples of live vaccines include but are not limited to the following: measles, mumps, rubella, chicken pox/zoster, yellow fever, rabies, Bacillus Calmette-Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live-attenuated vaccines and are not allowed.
27. Evidence of interstitial lung disease or active, noninfectious pneumonitis.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This is an open-label, dose-escalation study of the FGFR inhibitor INCB054828 in subjects with advanced malignancies. Subjects will receive QD doses of INCB054828 on a 2-weeks-on therapy and 1-week-off therapy schedule; a continuous administration regimen will also be explored, which will include BID administration as well. The study will be conducted in 3 parts (Figure 3). Part 1 (monotherapy dose escalation) will determine the MTD of INCB054828 and/or doses/regimen that produce substantial evidence of pharmacologic target inhibition (increased serum phosphate), and approximately 20 subjects will participate in the effect of renal impairment on safety and PK (approximately 10 moderate and 10 severe).

Part 2 (monotherapy dose expansion) will evaluate the dose(s) selected in Part 1 as a monotherapy in specific indications where activity of FGFR is particularly relevant and that have amplification, mutation, or translocation of FGFR 1, 2, or 3, or alteration of FGF 1 through 23. Additionally, as part of the dose expansion, all subjects enrolling in the tumor-specific cohorts (n = 20 total, n = 5 per cohort) will have mandatory biopsies, and approximately 8 subjects will participate in a food-effect study. Approximately 10 subjects will be enrolled into a very specific cohort to further evaluate the BID dosing regimen. Subjects will be required to have FGFR3 mutated or fusion-positive advanced/metastatic bladder cancer.

Part 3 will begin with dose-finding to determine RP2Ds of INCB054828 in combination with gemcitabine + cisplatin, docetaxel, pembrolizumab, trastuzumab, or INCMGA00012 in subjects with tumors for which gemcitabine + cisplatin, docetaxel, pembrolizumab, trastuzumab, or INCMGA00012 treatment is relevant. Dose-expansion will further evaluate the RP2Ds selected in these populations harboring FGF/FGFR alterations.

Treatment may continue as long as subjects are receiving benefit and have not met any criteria for study withdrawal. Subjects who discontinue study drug will continue to be followed for subsequent anticancer treatments and survival.

4.1.1. Part 1 Dose Escalation

The study will begin with an open-label dose escalation with an accelerated titration design based on observing each dose level for a period of 21 days before enrolling the next cohort and administering the next dose level. In Part 1, subjects who receive at least 11 out of 14 doses of study drug at the level assigned to that cohort or have a DLT will be considered evaluable for determining tolerability of the dose. Subjects enrolling but not meeting these criteria may be replaced in order to fill the cohort. Up to approximately 60 subjects will be enrolled.

The initial cohorts will consist of at least 1 subject each, and the doses may be increased up to 2-fold in successive cohorts until a Grade 2 or greater toxicity (excepting toxicities with a clear alternative explanation [eg, due to disease progression] or transient [≤ 72 hours] abnormal laboratory values without clinically significant signs or symptoms) or HP (serum phosphate > 5.5 mg/dL) is observed, at which time that cohort will be expanded to at least 3 subjects. From the point where a single-subject cohort is first expanded to 3 subjects, subsequent cohorts will enroll a minimum of 3 subjects, and increases to study drug dose will be limited to no more than 50% in successive cohorts, utilizing QD doses. If no DLTs are observed in the initial 3 subjects, then the next cohort will begin enrollment. If 1 DLT is observed in the first 3 subjects, then 3 additional subjects will be enrolled in the cohort. If a DLT occurs in 2 or more subjects in a cohort of 3 or 6, then the MTD will be deemed to have been exceeded, and the next lower dose level will be deemed to be the MTD. Thus, the MTD will be defined as 1 dose level below that at which one-third or more of subjects in a particular cohort report a DLT. If a DLT is observed at the initial dose of 1 mg QD, then a dose decrease to 0.5 mg may be considered. An intermediate dose level may also be explored. See Section 5.6 for DLT definitions. If toxicities specifically relevant to a type of malignancy are observed, then a separate dose escalation or dose decrease group will be initiated for subjects with this malignancy.

The effect of renal impairment on the safety and PK of INCB054828 will be conducted in a subset of subjects (approximately 10 with moderate renal impairment and 10 with severe) enrolled in Part 1 at 13.5 mg continuous administration.

Continuous study drug administration will be tested in separate dose-escalation cohorts. The starting dose of continuous administration will be lower than the MTD identified in the 2-weeks-on therapy/1-week-off therapy schedule. Subjects who receive at least 18 of 21 doses of study drug at the level assigned to that cohort or who have a DLT will be considered evaluable for determining tolerability of the dose. Subjects enrolling but not meeting these criteria may be replaced in order to fill the cohort.

Twice daily administration will be tested in a dose-escalation cohort as monotherapy only. The BID starting dose will be 7.5 mg on a continuous dosing schedule (no planned dose hold). Subjects who receive at least 35 of a possible 42 doses of study drug at the level assigned to that cohort or have a DLT will be considered evaluable for determining tolerability of the dose. Subjects enrolling but not meeting these criteria may be replaced in order to fill the cohort. A total of approximately 21 subjects will be enrolled in this cohort for Part 1.

4.1.1.1. Pharmacodynamic Target

Dose escalation will proceed in the absence of an MTD to a PAD. The PAD is defined as the point where approximately 67% of subjects (2 out of 3) attain HP; in a cohort of 3 subjects, if 2 out of 3 have HP, then the cohort will be expanded to 6 (while dose escalation continues as described above). Once the PAD is achieved, a new cohort will be enrolled where subjects will be treated with diet modification (decreased phosphate intake) and phosphate binders, and dose escalation will continue to determine the dose at which at least one-third of subjects attain HP and an MTD is identified. Alternative PAD can be defined by molecular endpoint such as the inhibition of FGFR and/or at least a 1.5-fold increase of serum phosphate.

4.1.1.2. Recommended Part 2 Dose

Based on safety and tolerability data and the PD measure of serum phosphate levels, the RP2D(s) (dose and/or regimen) will be defined and will be the lower of the MTD or the PAD with or without prophylactic concomitant phosphate binders; different RP2Ds may be determined for interval administration and continuous administration. Multiple RP2Ds may be used moving into Part 2 and Part 3.

4.1.1.3. Lower Dose Level Expansion

Up to 3 additional subjects may be enrolled at any dose level for the interval and continuous administration monotherapy regimens, as well as the combination regimens, that is deemed to be pharmacodynamically active (hyperphosphatemia observed in two-thirds of treated subjects) if that dose level is below the MTD. Subjects enrolled in the lower dose level cohort must have FGF/FGFR alteration and are required to have a baseline biopsy and at least 1 on-treatment biopsy (recommended at Cycle 2 Day 14 but allowed to be performed at any cycle; must be performed on a study drug administration day, preferably between Day 8 and Day 14). Additionally, an EOT/at time of progression biopsy is requested but not required. [redacted]

4.1.2. Part 2 Dose Expansion

When the recommended doses and/or regimen for Part 2 investigation have been determined, enrollment will proceed for Part 2. It is possible that a different dose and/or regimen will be chosen for subjects with different types of malignancies.

Approximately 120 subjects with advanced malignancies that have been evaluated and confirmed to harbor genetic alterations in FGF or FGFR genes will be treated in the dose-expansion cohort to further determine safety, tolerability, efficacy, PK, food effect, and PD. A subject's FGFR alteration can be based on local laboratory results and retrospectively confirmed by a central laboratory.

Approximately 70 subjects will be enrolled in Part 2, regardless of tumor type but harboring a FGF/FGFR alteration. Approximately 20 subjects will be enrolled into 1 of 4 potential tumor type-cohorts: cholangiocarcinoma (FGFR2 translocated only) (n = 5), bladder (n = 5), lung (n = 5), and HPV positive with FGFR-alteration tumors, including but not limited to head and neck (HNC), vulvar, and anal tumors (n = 5). A specific cohort of approximately 10 subjects with FGFR3 mutated or fusion-positive advanced/metastatic bladder cancer will be included in Part 2 as well. All subjects in each tumor-type cohort will be required to undergo a baseline

biopsy and at least 1 on-treatment biopsy (recommended at Cycle 2 Day 14 but allowed to be performed at any cycle; must be performed on a study drug administration day, preferably between Day 8 and Day 14). Additionally, an EOT/at time of progression biopsy is requested but not required. NOTE: Subjects who consent to the mandatory biopsy and withdraw consent after starting study treatment will be considered Protocol deviations.

A food-effect study will be conducted in approximately 8 subjects who will already be enrolled in Part 2 to determine if INCB054828 PK is affected by food (see Section 7.7.2).

Treatment will be initiated at an RP2D(s). Subjects who attain HP should follow guidelines for HP management as per Section 0. Subjects that do not attain HP or at least a 1.5-fold increase from baseline of serum phosphate after the first cycle of treatment should have their dose increased each cycle to the previously study assessed doses or 25% dose increments (whichever is a smaller increment) until HP or the maximum safely tested dose is reached.

4.1.3 Part 3 Combination Dose Finding and Expansion

Part 3 will comprise treatment groups evaluating INCB054828 administered in combination with standard therapies for select solid tumors. Part 3 will include dose finding and dose expansion. Dose finding will be a 3 + 3 enrollment design that will evaluate different doses of INCB054828 in combination with agents utilized in the treatment of solid tumors. The dose expansion is to further evaluate the safety and preliminary efficacy of the combination in select tumor types at the selected INCB054828 dose.

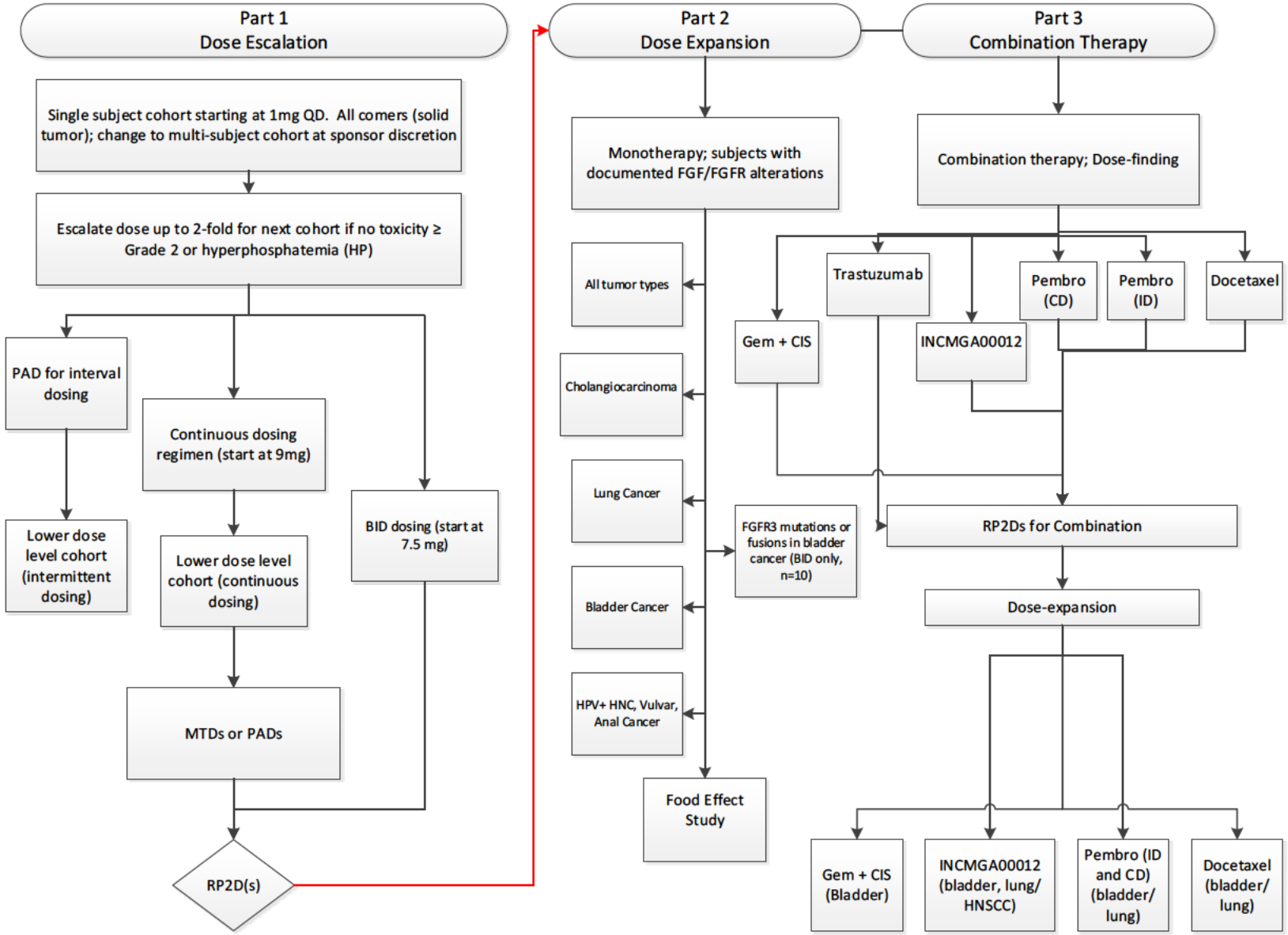
Approximately 60 subjects will be enrolled in the dose-finding group. The starting dose for Part 3 will be the RP2D(s).

Initially, at least 3 subjects will be enrolled in each treatment group for dose finding. The treatment groups include INCB054828 in combination with gemcitabine/cisplatin, docetaxel, pembrolizumab, trastuzumab, or INCMGA00012 at the doses, schedules, and routes described below. If in each group no DLTs are observed, then enrollment of the corresponding expansion will begin. If 1 DLT is observed, then at least 6 subjects will be enrolled in the dose-finding treatment group. If DLTs are observed in 2 or more subjects in a 3- or 6-subject group, then the dose of INCB054828 will be reduced by 25% to 50%. Dose assessment and dose decrease may be repeated once more. The combination MTD will be the highest dose of INCB054828 in each combination at which ≤ 0/3 or 1/6 subjects experience DLTs. The combination RP2D will be a dose less than or equal to the MTD/PAD dependent on emergent pharmacodynamics, PK, and safety data and may be specific to the different combination therapies.

Up to 3 additional subjects with known FGF/FGFR alterations may be enrolled at any Part 3 dose level if that dose level is below the MTD. In addition, the subjects enrolled in the lower dose level cohort per treatment combination are required to have a baseline biopsy and at least 1 on-treatment biopsy (recommended at Cycle 2 Day 14 but allowed to be performed at any cycle; must be performed on a study drug administration day, preferably between Day 8 and Day 14). Additionally, an EOT/at time of progression biopsy is requested but not required. [redacted]

In the Part 3 combination expansion treatment groups, approximately 75 subjects will be enrolled, including approximately 6 subjects per combination (if appropriate) for mandatory baseline and on-treatment biopsies.

Figure 3: Study Design



4.2. Study Endpoints

4.2.1. Primary Endpoints

- Safety and tolerability will be assessed by monitoring frequency, duration, and severity of AEs; through physical examinations; by evaluating changes in vital signs and ECGs; and through clinical laboratory blood and urine sample evaluations.
- Pharmacodynamics of INCB054828 including serum phosphorus level.

4.2.2. Secondary Endpoints

- Tumor response rates in those subjects with measurable disease as determined by investigator assessment of response.
- C_{max}, t_{max}, C_{min}, AUC_{0-t}, $t_{½}$, and Cl/F.

[redacted]

4.3. Measures Taken to Avoid Bias

This is an open-label study; no comparisons will be made between subjects or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions are made.

4.4. Number of Subjects

Approximately 325 subjects (total) are planned for enrollment.

4.5. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB or IEC in writing of the study's completion or early termination, and send a copy of the notification to the sponsor or sponsor's designee and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively, if required by regulatory decision. If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and regulatory bodies of the decision and reason for termination of the study.

5. TREATMENT OF SUBJECTS

5.1. Treatment Groups and Administration of Study Drug

5.1.1. Treatment Regimen for INCB054828

Subjects will self-administer study drug using an oral QD regimen in a 2-weeks-on therapy and 1-week-off therapy schedule; a continuous administration regimen will also be explored. Study drug can be taken with or without food. On days when PK samples will be collected, subjects should fast for 8 hours before taking study drug in the clinic and fast for 1 additional hour after taking study drug. If a dose is missed by more than 4 hours, the subject should skip the dose and take the next scheduled dose at the usual time. Any missed doses reported by the subject should be recorded in the subject's source documents.

One cycle will be defined as 21 continuous days of planned study treatment. The treatment cycle regimen consists of the following:

- Days 1 through 14: INCB054828 orally QD (suggested in morning). Extension of INCB054828 treatment into the recovery period is not permitted.
- Days 15 through 21: treatment break.

The continuous dosing regimen will still adhere to the 21-day cycle but instead of a planned dose hold from Days 15 to 21, subjects will continue taking study medication with no planned dose hold.

The BID regimen will also adhere to the 21-day cycle, but subjects will take study medication 2 times per day (AM and PM) and will also follow the continuous dosing regimen (no planned dose hold).

5.1.2. Treatment Regimen for Gemcitabine + Cisplatin (Part 3 Only)

Subjects will receive gemcitabine intravenously starting at 1000 mg/m^2 (30 minutes) on Days 1 and 8 of each 21-day cycle. Cisplatin will be administered intravenously starting at 70 mg/m^2 (1-4 hours) once every 3 weeks on Day 1 of each 21-day cycle. Both gemcitabine and cisplatin doses can be adjusted for toxicity management per commercial labeling. The investigator may choose to interrupt, modify, or discontinue chemotherapy with medical monitor approval. INCB054828 administration may continue during the toxicity break of gemcitabine/cisplatin.

5.1.3. Treatment Regimen for Docetaxel (Part 3 Only)

Subjects will receive docetaxel intravenously starting at 75 mg/m^2 (1 hour) once every 3 weeks on Day 1 of each cycle. The dose can be adjusted for toxicity management per commercial labeling. The investigator may choose to interrupt, modify, or discontinue chemotherapy with medical monitor approval. INCB054828 administration may continue during the toxicity break of docetaxel.

5.1.4. Treatment Regimen for Pembrolizumab (Part 3 Only)

Subjects will receive pembrolizumab intravenously at 200 mg (30 minutes) once every 3 weeks on Day 1 of each cycle. The dose can be adjusted for toxicity management per commercial labeling. The investigator may choose to interrupt, modify, or discontinue pembrolizumab with medical monitor approval. INCB054828 administration may continue during the toxicity break of pembrolizumab.

5.1.5. Treatment Regimen for Trastuzumab (Part 3 Only)

Trastuzumab will be administered as an open-label, commercial product at an initial dose of 8 mg/kg over a 90-minute IV infusion, followed by 6 mg/kg over a 30- to 90-minute IV infusion once every 3 weeks. The dose can be adjusted for toxicity management, per commercial labeling. The investigator may choose to interrupt, modify, or discontinue trastuzumab with medical monitor approval. INCB054828 administration may continue during the toxicity break of trastuzumab.

5.1.6. Treatment Regimen for INCMGA00012 (Part 3 Only)

INCMGA00012 will be administered as an open-label product at an initial dose of 500 mg over a 60-minute IV infusion. It will be administered once Q4W on a 28-day cycle. Table 5 shows the different dose level options for each cohort.

Table 5: Dose Levels for INCMGA00012 in Combination With INCB054828

Cohort	INCB054828	INCMGA00012
1	9 mg QD, continuous	500 mg Q4W
2	13.5 mg QD, continuous	500 mg Q4W

5.2. Treatment Compliance

Subjects should be counseled by the investigator to maintain strict adherence to the study regimen as prescribed and to keep a record of any missed doses. The subject will be instructed to bring all unopened, empty, and opened/partially used bottles of study drug to each study visit, at which time compliance will be assessed.

5.3. Randomization and Blinding

Not applicable.

5.4. Duration of Treatment and Subject Participation

Subjects will be treated in continuous cycles indefinitely; this may include temporary interruptions. If INCB054828 is permanently discontinued, the subject will be withdrawn from the study. All subjects will attend study visits weekly during the first 6 cycles. Treatment duration will vary significantly between subjects, but is expected to average approximately 6 months.

5.5. Rationale for Dose Modification

Selections and modifications to regimen of study drug are planned for dose-escalation cohorts. Also, dose interruptions and modifications may occur for individual study subjects. The identification of DLTs will define the doses used in planned cohorts. Further, the occurrence of DLTs and other toxicities (related or unrelated to study drug) will guide decisions for treatment interruptions and discontinuation for individual subjects.

Subjects enrolled in the dose escalation portion of the study will have the option of escalating to a dose found to be tolerated in a subsequent cohort.

5.6. Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose for INCB054828

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 6 occurring up to and including study Day 21, except those with a clear alternative explanation (eg, due to disease progression) or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination. All DLTs will be assessed by the investigator using the current CTCAE v4.03 criteria (NCI 2010). Subjects who receive at least 11 out of 14 doses of study drug in the first 2 weeks of cycle (Days 1 through 14) at the level assigned or have a DLT will be considered evaluable for determining tolerability of the dose.

Individual subject dose reductions may be made based on events observed at any time during treatment with INCB054828; however, for the purposes of dose cohort escalation/dose decrease, expanding a dose cohort, and determining the MTD of INCB054828, decisions will be made based on events that are observed from the first day of INCB054828 administration through and including the final day of Cycle 1 (Day 21). A lower RP2D may subsequently be determined based on relevant toxicities that become evident after Day 21.

Subjects with dose interruptions (but not meeting DLT criteria) during the first cycle who had not received at least 11 days of the prescribed dose for that cohort will not be considered evaluable for the purposes of determining the MTD and will be replaced.

Table 6: Definition of Dose-Limiting Toxicity and Maximum Tolerated Dose of INCB054828

Toxicity
Nonhematologic
• Any ≥ Grade 3 nonhematologic toxicity EXCEPT the following: – Nausea, vomiting, and diarrhea adequately controlled with medical therapy within 48 hours. – Asymptomatic changes in cholesterol and triglycerides – An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity. • Hy's Law: ALT > 3.0 × ULN, ALP < 2 × ULN, and bilirubin ≥ 2.0 × ULN; no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation.
Hematologic
• Grade 3 thrombocytopenia with bleeding. • Grade 4 thrombocytopenia. • Febrile neutropenia (ANC < 1.0×10^9/L and fever > 101°F/38.5°C). • Grade 4 neutropenia that does not recover to ≤ Grade 2 in ≤ 3 days after interrupting the INCB054828 dose. • Grade 4 anemia.

Table 6: Definition of Dose-Limiting Toxicity and Maximum Tolerated Dose of INCB054828 (Continued)

Toxicity
Hyperphosphatemia
• Serum phosphorus ≥ 10 mg/dL recurrent or persistent for more than 1 week despite appropriate management. • Serum phosphorus ≥ 7 mg/dL with clinical symptoms of acute HP (eg, muscle cramps, tetany, and numbness or tingling.
MTD of INCB054828
• One dose level below that at which ≥ one-third of subjects in a particular cohort have DLTs. Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in ***this table*** occurring up to and including study Day 21.

ANC = absolute neutrophil count.
Note: Transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination will not be considered a DLT.

5.6.1. Management of Dose-Limiting Toxicities or Other Urgent Situations

In all cases, investigators are free to employ any measures or concomitant medications, following discussion with the sponsor (whenever possible), necessary to optimally treat the subject.

5.6.2. Follow-Up of Dose-Limiting Toxicities

Any DLT should be followed until it resolves to baseline or appears to have stabilized for a minimum of 4 weeks. During follow-up, subjects should be seen as often as medically indicated to assure safety.

5.7. Procedures for Cohort Review and Dose Escalation of INCB054828

Telephone conferences will be scheduled by the sponsor with study investigators in order to review cohort-specific data and overall safety data, to agree on dose escalation, adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

5.8. Dose Modification of Study Drug

5.8.1. Planned Dose Modifications for INCB054828

Dose escalations to determine the RP2D(s) in Part 1 are described in Section 4.1.

Dose escalation will be allowed in Parts 1 and 2 (except in subjects with BID dosing), provided that the following criteria are met:

- The Protocol eligibility criteria are met at the time of escalation.
- The subject has received 1 cycle of study drug and has not had drug-related toxicity ≥ Grade 2.
- The next dose level has been determined to be safe based on the MTD criteria.
- The subject has not achieved HP at the current dose.
- The subject is willing to submit to the *PK sampling schedule* from Cycle 1.

- In the opinion of the investigator, the subject does not have any concurrent condition or circumstance that would complicate the dose escalation, PK sampling, or pose increased risk to the subject.
- The intrasubject dose escalation has been approved by the sponsor.

Any subject treated at 13.5 mg should be titrated up to 18 mg QD using their current dose regimen with approval from the medical monitor if they meet the following criteria:

- have been on study drug for at least 1 cycle,
- have been compliant with taking study drug,
- have no ongoing Grade 2 or higher treatment-related AE,
- have not achieved hyperphosphatemia defined as a serum phosphate level of > 5.5 mg/dL.

Subjects who are titrated up to 18 mg QD will begin the next cycle at the new dose level and must agree to all Cycle 1 assessments (PK and safety assessments [hematology and blood chemistry]). Up-titration may occur no earlier than Cycle 2 Day 1, so that subjects are observed for phosphate level and AEs for at least 1 cycle.

5.8.2. Criteria and Procedures for Interruption of INCB054828

Treatment with INCB054828 may be delayed up to 2 weeks (14 days), including the planned dose hold to allow for resolution of toxicity. It is recommended that subjects with suspected or documented serous retinal detachment be discussed with the Incyte medical monitor before adjusting the study drug regimen.

Subjects may resume treatment if no medical condition or other circumstance exists that, in the opinion of the investigator, would make the subject unsuitable for further participation in the study. The treating investigator should contact the sponsor's medical monitor to discuss the case of any subject whose treatment has been delayed for more than 14 days before restarting treatment with INCB054828.

Day 1 of each study cycle will correspond with the first day of INCB054828 administration in that cycle; thus, study cycles may become out of sync with the originally planned schedule if treatment is delayed for safety. In this event, tumor assessments will remain on the original schedule. All other assessments will shift to coincide with the revised treatment (cycle) schedule. The treating investigator should contact the sponsor's medical monitor to discuss any case in which a subject's study drug was interrupted to determine the best place to restart the subject's study drug.

For subjects who present with possible or confirmed serous retinal detachment/retinal pigmented epithelium detachment (SRD/RPED) based on optic coherence tomography, the guidelines in Table 7 should be followed. It is recommended to discuss the findings with the Incyte medical monitor before making changes to the subject's treatment.

Per CTCAE v4.03, there is a grading for retinal detachment; however, this refers to rhegmatogenous retinal detachment (when a hole occurs in the retina) or exudative detachment (fluid accumulation due to inflammatory diseases). There is no exact CTCAE grading term for SRD/RPED secondary to FGFR inhibition (there is no hole in the macula, just fluid

accumulation or detachment of retinal pigmented epithelium). Therefore, grading should be based on the CTCAE term "retinopathy."

Because subjects may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, these dose reduction rules are provided as guidelines (Table 7). Individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug and the subject's underlying condition.

Table 7: Guidelines for Interruption and Restart of INCB054828

Toxicity/CTCAE Grade	Action Taken
Chemistry	
• AST and/or ALT is > 5.0 × ULN • ALP > 5 × ULN Note: In subjects with bone metastasis-related elevations at baseline, contact sponsor to discuss clinical management and possible dose reductions.	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 except by approval of the medical monitor. **Step 2:** If assessed as related to study drug, restart study drug at next lower dose tested; monitor as clinically indicated.
Hy's law: ALT > 3.0 × ULN, ALP < 2 × ULN, and bilirubin ≥ 2.0 × ULN; no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation.	Discontinue treatment.
Hematology	
• ANC < 1.0 × 10^9/L unless due to underlying disease • Platelet count is 50 × 10^9/L to < 75 × 10^9/L unless due to underlying disease	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until the toxicity has resolved to ≤ Grade 1 or pretherapy baseline. **Step 2:** Restart study drug at same dose and monitor as clinically indicated. *If neutropenia is rapidly reversible after stopping study drug, subjects will be allowed to stay on their dose as long as ANC > 1.0 × 10^9/L.
• Grade 4 ANC (< 0.5 × 10^9/L) • ≥ Grade 3 ANC with an oral temperature of at least 38.5°C OR with ≥ Grade 3 infection • Platelet count is < 50 × 10^9/L	**Step 1:** Interrupt study drug up to 2 weeks (14 days) until resolved to ≤ Grade 1. **Step 2:** If assessed as related to study drug, restart study drug at next lower dose tested; monitor as clinically indicated, except if Grade 4 neutropenia resolves in ≤ 7 days, in which case restart at the same dose. Dose interruptions and reductions in MPN subjects should be considered on an individual basis and should be discussed with the sponsor.
• MPN: ≥ 50% decrease from baseline platelet count (subjects with baseline platelet count < 75 × 10^9/L only) • ≥ 50% decrease from baseline ANC (subjects with baseline ANC < 1.0 × 10^9/L only)	**Step 1:** Hold until resolved to baseline level. **Step 2:** Restart study drug at next lower dose; monitor as clinically indicated.

Table 7: Guidelines for Interruption and Restart of INCB054828 (Continued)

Toxicity/CTCAE Grade	Action Taken
Other toxicities, including SRD/RPED	
Any Grade 1 or Grade 2 toxicity	Continue study drug treatment and treat the toxicity; monitor as clinically indicated. For increased serum phosphate, see Section 0 for the recommended approach for HP management. Subjects who have abnormal serum phosphate or calcium levels should have their levels monitored at least twice a week.
Any Grade 3 toxicity, if clinically significant and not manageable by supportive care	**Step 1:** Interrupt study drug up to 2 weeks (14 days), until toxicity resolves to ≤ Grade 1. **Step 2:** If assessed as related to study drug, restart study drug at next lower dose tested; monitor as clinically indicated.
Any recurrent Grade 3 toxicity after 2 dose reductions	Discontinue study drug treatment and follow-up per Protocol.
Any other Grade 4 toxicity	Discontinue study drug treatment and follow-up per Protocol.

The sponsor recommends a maximum of 2 dose level reductions: subjects administered 13.5 mg can decrease to 9 mg and if additional dose reduction is required, subjects can decrease to 4.5 mg. Subjects enrolled before Amendment 10 may have had their dose reduced to 6 mg. The frequency of dosing (either intermittent or continuous) remains the same. A dose below 4.5 mg is not allowed.

Subjects who were up-titrated to 18 mg from 13.5 mg can be dose reduced back down to a dose of 13.5 mg, then 9 mg, then 4.5 mg. A dose below 4.5 mg is not allowed.

5.8.3. Management of Hyperphosphatemia

Hyperphosphatemia is an expected on-target pharmacologic effect of FGFR inhibition. Hyperphosphatemia should be managed with diet modifications, phosphate binders and diuretics, or a dose reduction per the recommendations in Table 8.

The use of diet modifications alone include food exchanges from high-phosphate foods to low-phosphate foods and can be implemented once serum phosphate levels are above the ULN but do not exceed 7.0 mg/dL.

Diet modification should continue with the inclusion of phosphate binders once serum phosphate levels exceed 7.0 mg/dL. Examples of phosphate binders are sevelamer HCl (examples of name brands: Renegel® or Renvela®) or lanthanum HCl; phosphate binders should be administered 3 times per day (eg, with each meal) to reduce absorption of phosphate. Doses and frequency of doses must be based on the subject's tolerance for the binder and the control of the serum phosphate. If binders are used to manage hyperphosphatemia during treatment, it is recommended to stop binders, together with the low-phosphate diet, at the same time pemigatinib is stopped to reduce the risk of hypophosphatemia.

Table 8: Recommended Approach for Hyperphosphatemia Management

Serum Phosphate Level	Supportive Care	Guidance for Interruption/Discontinuation of INCB054828	Guidance for Restarting INCB054828
> 5.5 mg/dL and ≤ 7 mg/dL	Initiate a low-phosphate diet	No action.	Not applicable.
> 7 mg/dL and ≤ 10 mg/dL	First occurrence: Initiate low-phosphate diet and phosphate-binding therapy until return to ≤ 7 mg/dL. Second/continued occurrence: initiate/continue low-phosphate diet and start/adjust phosphate binding therapy until return to ≤ 7 mg/dL. Monitor serum phosphate at least twice a week.	If serum phosphate level continues to be > 7 mg/dL and ≤ 10 mg/dL with concomitant phosphate-binding therapy for 2 weeks, *interrupt* study drug for up to 2 weeks (including the planned dose interruptions per treatment cycle for subjects receiving the interval regimen).	Restart at the same dose when serum phosphate is ≤ 7 mg/dL. If, after restarting, serum phosphate level recurs at > 7 mg/dL, study drug dose should be reduced.
> 10 mg/dL	First occurrence: Initiate a low-phosphate diet, phosphate-binding therapy, and phosphaturic agent until return to normal range. Second/continued occurrence: start/continue low-phosphate diet and start/adjust phosphate-binding therapy and phosphaturic agent until return to ≤ 7 mg/dL. Continue to monitor serum phosphate at least twice a week.	If serum phosphate level continues to be > 10 mg/dL for 1 week after supportive measures, *interrupt* study drug for up to 2 weeks (including the planned dose interruptions per treatment cycle for subjects receiving the interval regimen). If there is recurrence of serum phosphate level in this range after 2 dose reductions, *permanently discontinue* study drug.	Restart study drug at reduced dose with phosphate binders when serum phosphate is ≤ 7 mg/dL. If, after restarting, serum phosphate level recurs at > 10 mg/dL, study drug dose should be reduced.

5.8.4. Criteria for Permanent Discontinuation of INCB054828

The occurrence of unacceptable AEs will require that the study drug be permanently discontinued. Unacceptable AEs are defined as:

- Occurrence of an AE, which in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- AEs requiring more than 2 dose reductions (unless dose was increased) below the starting dose of INCB054828 or PAD of INCB054828 if the PAD has been established.
- Persistent AEs (including hyperphosphatemia) requiring a delay of therapy for more than 2 weeks (14 days), including the planned dose hold, unless a greater delay has been approved by the medical monitor.
- Serum phosphate levels in line with Table 6 and Table 8.
- Concurrent elevation of ALT > 3 × ULN and total bilirubin > 2 × ULN in subjects who do not have evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevations.

If study drug is permanently discontinued, see Sections 6.3 and 6.4 for follow-up assessments.

5.8.5. Dose Modifications and Management of Adverse Events Associated With Gemcitabine + Cisplatin, Docetaxel, Pembrolizumab, or Trastuzumab

If an AE or safety issue is considered to be associated with gemcitabine, cisplatin, docetaxel, pembrolizumab, or trastuzumab, then institutional guidelines for its management should be followed, and/or each drug label should be consulted, and if needed, the sponsor's medical monitor should be consulted.

5.8.6. Dose Modification and Management of Adverse Events for INCMGA00012

Pre-treatment criteria that should be met prior to treatment from Cycles 2 and onward include:

- Hemoglobin ≥ 8 g/dL.
- ANC ≥ 1.0×10^9/L.
- Platelet count ≥ 75×10^9/L.
- ALT/AST/bilirubin ≤ Grade 2.
- Resolution of all immune-related toxicity to ≤ Grade 1 (with the exception of endocrinopathy that is controlled on hormonal replacement).
- Resolution of all non–immune-related toxicity to Grade ≤ 1 or baseline (with the exception of alopecia or non–transfusion-dependent anemia).

  Note: Transient asymptomatic laboratory elevations ≤ Grade 3 do not require dose interruption or reduction if the subject is asymptomatic and the elevation is clinically insignificant and has been discussed with the medical monitor (eg, amylase, lipase).
- Daily dose of corticosteroid ≤ 10 mg prednisone or equivalent.

Subjects unable to restart study drug treatment ≤ 12 weeks from the start of the treatment delay due to toxicity will be permanently discontinued from receiving INCMGA00012. However, INCB054828 may continue if the investigator believes the subject is receiving benefit and obtains medical monitor approval to continue monotherapy of INCB054828.

Treatment breaks of greater than 12 weeks for reasons other than toxicity (eg, for targeted radiotherapy) will be considered on a case-by-case basis by the medical monitor.

INCB054828 can continue during any toxicity break that is considered related to INCMGA00012.

5.8.6.1. Management of Suspected Infusion Reactions

Premedication prophylaxis for infusion reactions is not required for INCMGA00012 but should follow institutional preferences. Guidelines for management of suspected infusion reactions are provided in Table 9. Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor regardless of whether criteria for reporting as an SAE are met.

Table 9: Guidelines for Management of Suspected Infusion Reactions

Grade	Description[a]	Treatment	Subsequent Infusions
1	Mild reaction; infusion interruption not indicated; intervention not indicated.	Monitor vital signs closely until medically stable.	Additional prophylaxis not required.
2	Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	**First occurrence:** Stop infusion and initiate appropriate medical measures (eg, IV fluids, antihistamines NSAIDS, acetaminophen/paracetamol, narcotics, per institutional preferences). Monitor vital signs until medically stable. If symptoms resolve within 1 hour, infusion may be resumed at 50% of the original infusion rate. **Subsequent occurrences (after recommended prophylaxis):** Permanently discontinue treatment.	Premedicate at least 30 minutes before infusion with antihistamines (eg, diphenhydramine 50 mg PO) and acetaminophen/paracetamol (500-1000 mg PO). Additional supportive measures may be acceptable (per institutional preference) but should be discussed with medical monitor.
3 or 4	**Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates). **Grade 4:** Life-threatening; pressor or ventilatory support indicated.	Stop infusion and initiate appropriate medical therapy (eg, IV fluids, antihistamines NSAIDS, acetaminophen/paracetamol, narcotics, oxygen, pressors, epinephrine, corticosteroids, per institutional preferences). Monitor vital signs frequently until medically stable. Hospitalization may be indicated.	Discontinue study drug.

a Per NCI CTCAE v4.03, appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study drug administration.

5.8.6.2. Management of Suspected Immune-Related Adverse Events

Adverse events of a potential immunologic etiology or irAEs may be defined as an AE of unknown etiology, associated with drug exposure, and consistent with an immune phenomenon. Immune-related AEs may be predicted based on the nature of the compounds, their mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes before labeling an AE as an irAE. Algorithms for evaluation of selected immune toxicities that have previously been attributed to PD-1 inhibitors (Brahmer et al 2018) are provided in the Study Procedures Manual.

Recommendations for management of specific immune-mediated AEs known to be associated with other PD-1 inhibitors (eg, pembrolizumab, nivolumab) are detailed in the sections below.

Management guidance for irAEs not detailed elsewhere in the Protocol should follow the established guidelines (Brahmer et al 2018).

5.8.6.3. Immune-Mediated Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving study drug and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug–associated pneumonitis, the suggested treatment plan is detailed in Table 10.

Table 10: Recommended Approach to Handling Pneumonitis

Study Drug–Associated Pneumonitis	Withhold/Discontinue Study Drug[a]	Supportive Care
Grade 1 (asymptomatic)	No action.	Intervention not indicated.
Grade 2	Withhold study drug.	Systemic corticosteroids are indicated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate.
Grades 3 and 4 or recurrent Grade 2	Permanently discontinue study drug.	Systemic corticosteroids are indicated.

[a] Criteria for restarting study drug are in Section 5.8.6.

5.8.6.4. Immune-Mediated Colitis

Subjects should be carefully monitored for signs and symptoms of colitis (such as diarrhea, abdominal pain, mucus, or blood in stool, with or without fever). In symptomatic subjects, infectious etiologies should be ruled out, and endoscopic evaluation should be considered for persistent or severe symptoms. Recommendations for management of enterocolitis are shown in Table 11.

Table 11: Recommended Approach for Handling Enterocolitis/Diarrhea

Study Drug–Associated Enterocolitis/Diarrhea	Withhold/Discontinue Study Drug[a]	Supportive Care
Grade 1	No action.	All subjects who have diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. An antidiarrheal can be started.
Grade 2	Withhold study drug.	Systemic corticosteroids are indicated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. Treatment with infliximab is acceptable per institutional guidelines.
Grade 3	Withhold study drug.	Treatment with systemic corticosteroids should be initiated. Treatment with infliximab is acceptable per institutional guidelines.
Grade 4 or recurrent Grade 3	Permanently discontinue study drug.	

[a] Criteria for restarting study drug are located in Section 5.8.6.

5.8.6.5. Immune-Mediated Hepatitis

Liver chemistry testing (hepatic transaminase and bilirubin levels) should be monitored and subjects assessed for signs and symptoms of hepatotoxicity before each dose of INCMGA00012. In subjects with hepatotoxicity, infectious or malignant causes should be ruled out, and frequency of liver chemistry monitoring should be increased until resolution. Recommendations for management of hepatitis are shown in Table 12.

Table 12: Recommended Approach for Handling Hepatitis

Study Drug–Associated Hepatitis	Withhold/Discontinue Study Drug[a]	Supportive Care
Grade 1	No action.	Increase frequency of liver chemistry monitoring to twice per week until liver chemistry tests return to baseline.
Grade 2	Withhold study drug.	Systemic corticosteroids are indicated (initial dose of 0.5-1 mg/kg per day of prednisone or equivalent). Taper as appropriate.
Grades 3 and 4	Permanently discontinue study drug.	Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate.

[a] Criteria for restarting study drug are located in Section 5.8.6.

5.8.6.6. Immune-Mediated Endocrinopathies

5.8.6.6.1. Hypophysitis

Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Recommendations for management of hypophysitis are shown in Table 13.

Table 13: Recommended Approach for Handling Hypophysitis

Study Drug–Associated Hypophysitis	Withhold/Discontinue Study Drug[a]	Supportive Care
Grade 1	No action.	Administer corticosteroids and hormone replacement as clinically indicated.
Grade 2	Withhold study drug.	
Grade 3	Withhold or discontinue study drug.	
Grade 4	Permanently discontinue study drug.	

[a] Criteria for restarting study drug are located in Section 5.8.6.

5.8.6.6.2. Thyroid Disorders

Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Recommendations for management of thyroid disorders are shown in Table 14.

Table 14: Recommended Approach for Handling Thyroid Disorders

Study Drug–Associated Thyroid Disorders	Withhold/Discontinue Study Drug[a]	Supportive Care
Grades 1 and 2	No action.	Administer replacement hormones for hypothyroidism and manage hyperthyroidism with thionamides and beta-blockers as appropriate.
Grade 3	Withhold or discontinue study drug.	
Grade 4	Permanently discontinue study drug.	

[a] Criteria for restarting study drug are located in Section 5.8.6.

5.8.6.6.3. New Onset Diabetes Mellitus

Monitor subjects for hyperglycemia or other signs and symptoms of diabetes. Recommendations for management of diabetes mellitus are shown in Table 15.

Table 15: Recommended Approach for Handling New Onset Diabetes Mellitus

Study Drug–Associated Diabetes Mellitus	Withhold/Discontinue Study Drug[a]	Supportive Care
Grades 1 and 2	No action.	Intervention not indicated.
Grade 3	Withhold study drug.	Administer insulin for Type 1 diabetes and administer antihyperglycemics in subjects with severe hyperglycemia.
Grade 4	Permanently discontinue study drug.	

[a] Criteria for restarting study drug are located in Section 5.8.6.

5.8.6.7. Immune-Mediated Nephritis and Renal Dysfunction

Monitor subjects for changes in renal function. Recommendations for management of nephritis and renal dysfunction are shown in Table 16.

Table 16: Recommended Approach for Handling Nephritis and Renal Dysfunction

Study Drug–Associated Nephritis and Renal Dysfunction	Withhold/Discontinue Study Drug[a]	Supportive Care
Grade 1	No action.	Intervention not indicated.
Grade 2	Withhold study drug.	Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate.
Grades 3 or 4	Permanently discontinue study drug.	

[a] Criteria for restarting study drug are located in Section 5.8.6.

5.8.6.8. Immune-Mediated Hematologic Toxicities

Monitor subjects for changes in hematology. Recommendations for management of hematological toxicities are shown in Table 17.

Table 17: Immune-Mediated Hematologic Toxicities

Study Drug–Associated Hematologic Toxicities	Withhold/Discontinue Study Drug[a]	Supportive Care
Grade 1	No action	Intervention not indicated
Grade 2	Withhold study drug	Systemic corticosteroids are indicated (initial dose of 0.5-1 mg/kg per day of prednisone or equivalent). Taper as appropriate.
Grade 3 or 4	Permanently discontinue study drug	Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate.

[a] Criteria for restarting study drug are in Section 5.8.6.

5.8.6.9. Immune-Mediated Skin Reactions

Immune-mediated rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid, can occur. Monitor subjects for suspected severe skin reactions and exclude other causes. Recommendations for management of skin reactions are shown in Table 18.

Table 18: Recommended Approach for Handling Skin Reactions

Study Drug–Associated Skin Reactions	Withhold/Discontinue Study Drug[a]	Supportive Care
Grade 1	No action.	Intervention not indicated.
Grade 2	Withhold study drug.	Treatment with systemic corticosteroids should be initiated (initial dose of 1-2 mg/kg per day of prednisone or equivalent). Taper as appropriate. *Note:* May consider IV immunoglobulin or cyclosporine as an alternative or in corticosteroid-refractory cases, for Grade for SCARs, DIHS/DRESS.
Grade 3 or suspected Stevens-Johnson syndrome or toxic epidermal necrolysis	Withhold study drug.	
Grade 4 or confirmed Stevens-Johnson syndrome or toxic epidermal necrolysis	Permanently discontinue study drug.	

DIHS/DRESS = drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; SCARs = severe cutaneous adverse reactions syndrome.
[a] Criteria for restarting study drug are located in Section 5.8.6.

5.8.7. Permanent Discontinuation of INCMGA00012 Due to Toxicity

The occurrence of unacceptable toxicity not caused by the underlying disease will require that the study treatment be permanently discontinued. Unacceptable toxicity is defined as follows:

- Occurrence of a treatment-related AE that, in the judgment of the investigator or the sponsor's medical monitor, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest.
- Persistent treatment-related AE requiring a delay of therapy for more than 12 weeks.
- Any AE defined in the dose modifications management guidelines (see Section 5.8.6) requiring the study treatment be discontinued.

5.9. Withdrawal of Subjects From Study Treatment

5.9.1. Withdrawal Criteria

Subjects **must** be withdrawn from study treatment for the following reasons:

- Further treatment would be injurious to the subject's health or well-being, in the investigator's medical judgment. Subject should still be followed for disease progression and survival.
- The subject becomes pregnant.
- Consent is withdrawn. NOTE: Subjects may choose to discontinue study treatment and remain in the study to be followed for disease progression and survival.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Unacceptable toxicity (Section 5.8.4) has occurred.
- Disease progression has occurred. NOTE: A subject may be allowed to continue receiving study drug if the investigator believes that the subject is receiving clinical benefit and no other treatment options are available for the subject.

A subject **may** be withdrawn from the study as follows:

- If, during the course of the study, a subject is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the subject should be withdrawn from the study. See Section 11.3, Protocol Adherence. This includes cases where the local genomic testing results are positive for an FGF/FGFR alteration, but the central genomic testing is not.
- If a subject is noncompliant with study procedures or study drug administration in the opinion of the investigator, the sponsor should be consulted for instruction on handling the subject.

5.9.2. Withdrawal Procedures

Once the decision is made to permanently discontinue the study drug, the following steps should be followed:

- The study monitor or sponsor must be notified.
- The reasons for withdrawal and the date of last dose of study drug must be documented in the subject's medical record and CRF (case report form).
- The EOT visit should be performed.
- Subjects must be followed for safety through the time of the follow-up visit or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer.

Reasonable efforts should be made to have the subject return for a follow-up visit. These visits are described in Section 6.

5.10. Concomitant Medications and Measures

The following must be recorded in the subject's medical record and CRF from the time of signing consent through and including the 30 days from date of last dose of study drug:

- All concomitant medications and treatments.
- Any prior medication received up to 30 days before enrollment (Cycle 1 Day 1).
- Concomitant treatments and/or procedures that are required to manage a subject's medical condition during the study.

5.11. Restricted Medications and Measures

The use of mild or moderate CYP inhibitors or mild inducers should involve careful monitoring. It is recommended that additional PK samples be obtained when such agents are coadministered with INCB054828, using the same PK sampling schedule as in Cycle 1 Day 14.

Calcium-based phosphate-binding medications are not recommended due to a concern for potential of soft tissue mineralization. Aluminum-based phosphate binders are not recommended due to potential toxicities associated with use.

5.12. Prohibited Medications and Measures

The following medications and measures are prohibited:

- The concomitant administration of potent CYP3A4 inhibitors and inducers and moderate CYP3A4 inducers is prohibited. Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.
- Any concomitant use of a selective FGFR inhibitor is prohibited.
- Investigational study drug for any indication is prohibited.
- Use of any anticancer medications other than the study medication from 21 days before Day 1 is prohibited.
- Subjects receiving pembrolizumab and INCMGA00012: Live vaccines within 28 days before first administration of study drug, throughout the treatment phase of the study, and for a duration of 90 days after the last dose of study drug.

6. STUDY ASSESSMENTS

For instructions on study assessments, see Section 7. All study assessments will be performed as outlined in Table 19 and Table 20. Required analytes are shown in Table 21 (all indications) and Table 22 (multiple myeloma).

Table 19: Schedule of Assessments

Procedure	Protocol Section	Screening	Treatment Phase												EOT	Post-Treatment			Notes
			Cycle 1						Cycles 2-6			Cycle 2		Cycles 7+		Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up	
												Food Effect (Part 2 Only)							
		Days -28 to -1	D1	D2	D8 ± 3 Days	D14	D15	D16	D1 ± 3 Days	D8 ± 3 Days	D15	D14	D15	D1 ± 3 Days	+ 5 Days	30 Days (+ 5 Days) After EOT	57 Days (± 5 Days) After D/C	Every 12 Weeks (± 7 Days)	
Informed consent	7.1	X																	
Contact IRT	7.2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Inclusion/ exclusion criteria	3	X	X																
Medical/cancer history	7.3.1	X																	
Concomitant medications	7.3.2, 7.3.3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
INCB054828 in clinic	5.1.1		X	X	X	X						X							
Gem + CIS in clinic	5.1.2		X		X				X	X				X					
Docetaxel in clinic	5.1.3		X						X					X					
Pembrolizumab in clinic	5.1.4		X						X					X					
Trastuzumab in clinic	5.1.5		X						X					X					
INCMGA00012 in clinic	5.1.6		X						X*					X*					*Based on Q4W regimen
New anticancer therapy	6.4.2																X		
Survival status	6.4.3																	X	
Comprehensive PE	7.4.2	X													X	X			
Targeted PE	7.4.3		X		X	X			X	X	X	X	X	X					

Table 19: Schedule of Assessments (Continued)

Procedure	Protocol Section	Screening	Treatment Phase												EOT	Post-Treatment			Notes
			Cycle 1						Cycles 2-6			Cycle 2		Cycles 7+		Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up	
												Food Effect (Part 2 Only)							
		Days -28 to -1	D1	D2	D8 ± 3 Days	D14	D15	D16	D1 ± 3 Days	D8 ± 3 Days	D15	D14	D15	D1 ± 3 Days	+ 5 Days	30 Days (+ 5 Days) After EOT	57 Days (± 5 Days) After D/C	Every 12 Weeks (± 7 Days)	
ECOG	7.6.1	X	X	X	X	X			X			X		X	X				
Vital signs/weight	7.4.4	X	X	X	X	X	X		X			X		X	X	X			
12-lead ECG (triplicate) (anytime)	7.4.5	X													X				
12-lead ECG (triplicate) (predose)	7.4.5 Table 23		X		X	X													Approximately 5 minutes before the predose PK blood draw
12-lead ECG (triplicate) (postdose)	7.4.5 Table 23		X			X													1, 2, and 4 hours postdose approximately 5 minutes before the PK blood draw
Echo/MUGA	7.4.6	X							X					X	X				Only subjects taking trastuzumab.

Table 19: Schedule of Assessments (Continued)

			Treatment Phase													Post-Treatment			
			Cycle 1						Cycles 2-6			Cycle 2		Cycles 7+					
												Food Effect (Part 2 Only)							
		Screening	D1	D2	D8	D14	D15	D16	D1	D8	D15	D14	D15	D1	EOT	Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up	
Procedure	**Protocol Section**	**Days -28 to -1**			**± 3 Days**				**± 3 Days**	**± 3 Days**				**± 3 Days**	**+ 5 Days**	**30 Days (+ 5 Days) After EOT**	**57 Days (± 5 Days) After D/C**	**Every 12 Weeks (± 7 Days)**	**Notes**
Eye examination (including slit lamp, visual acuity, fundoscopy with digital imaging, and optic coherence tomography)	7.4.7	X							X*					X*	X				*Every 3 cycles starting with Cycle 3 (± 14 days).
Adverse events	7.4.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Tumor tissue	7.5, 7.8.4	X							X*						X*				*Refer to Section 7.8.4 for details.

Table 19: Schedule of Assessments (Continued)

			Treatment Phase													Post-Treatment			
			Cycle 1						Cycles 2-6			Cycle 2		Cycles 7+					
												Food Effect (Part 2 Only)							
		Screening	D1	D2	D8	D14	D15	D16	D1	D8	D15	D14	D15	D1	EOT	Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up	
Procedure	**Protocol Section**	**Days -28 to -1**			**± 3 Days**				**± 3 Days**	**± 3 Days**				**± 3 Days**	**+ 5 Days**	**30 Days (+ 5 Days) After EOT**	**57 Days (± 5 Days) After D/C**	**Every 12 Weeks (± 7 Days)**	**Notes**
Disease assessment	6.4.2, 7.5, Appendix D, Appendix E	X*							X**					X**	X		X		*Multiple myeloma subjects; initial assessment 28 days before C1D1. **Solid tumors: every 3 cycles starting at the end of Cycle 3.
Skeletal survey (multiple myeloma only)	Appendix D	X							X*										*Every 8 weeks after baseline.

D/C = discontinuation; PE = physical examination.

Table 20: Laboratory Assessments

Procedure	Protocol Section	Screening	Treatment Phase: Cycle 1 D1	Cycle 1 D2	Cycle 1 D8	Cycle 1 D14	Cycle 1 D15	Cycle 1 D16	Cycles 2-6 D1	Cycles 2-6 D8	Cycles 2-6 D15	Cycle 2 Food Effect (Part 2 Only) D14	Cycle 2 Food Effect (Part 2 Only) D15	Cycles 7+ Day 1	EOT	Safety Follow-Up	Notes
		Days -28 to -1			± 3 Days				± 3 Days	± 3 Days	± 3 Days			± 3 Days	+ 5 Days	30 Days (+ 5 Days) After EOT	
Comprehensive serum chemistry	7.4.8.1	X	X	X	X		X		X	X	X		X	X	X	X	
Hematology with differential	7.4.8.1	X	X	X	X		X		X	X	X		X	X	X	X	
Coagulation panel	7.4.8.1	X	X						X						X		
Lipid panel	7.4.8.1	X	X						X						X		
Parathyroid hormone	7.4.8.1	X	X						X					X	X	X	
Urinalysis	7.4.8.2	X							X								
Serum or urine pregnancy test	7.4.8.3	X	X												X		
Serology	7.4.8.1	X															
Total urine	7.7.3					X											
Cytogenetics (MPN only)	Appendix E	X							X*						X		*As needed.
Serum protein electrophoresis, urine protein electrophoresis, quantitative immunoglobulins, serum free light chains (multiple myeloma only)	Appendix D	X							X								
Beta-2 microglobulin (multiple myeloma only)	Appendix D	X	X						X								
JAK-2 mutation (MPN only)	Appendix E	X															
Pharmacokinetic sampling	7.7		X	X	X	X	X	X				X*	X*				*Part 2 food effect only.

Table 20: Laboratory Assessments (Continued)

Procedure	Protocol Section	Screening	Treatment Phase: Cycle 1						Cycles 2-6			Cycle 2		Cycles 7+	EOT	Safety Follow-Up	Notes
			D1	D2	D8	D14	D15	D16	D1	D8	D15	Food Effect (Part 2 Only) D14	Food Effect (Part 2 Only) D15	Day 1			
		Days -28 to -1			± 3 Days				± 3 Days	± 3 Days	± 3 Days			± 3 Days	+ 5 Days	30 Days (+ 5 Days) After EOT	
PK plasma protein binding (postdose)	7.7.3		X			X			X*	X*	X*						Renally impaired subjects; PK blood sample for determination of plasma protein binding will be obtained at 4 hours postdose. *BID dosing: testing Days 1, 8, and 15 through end of Cycle 3.
[redacted]																	
Tissue biopsy	7.8.4	X							X*					X	X**		*At least 1 on-treatment biopsy. **EOT biopsy requested but not required.

Table 21: Laboratory Tests: Required Analytes for All Indications

<table>
<tr><th>Serum Chemistry</th><th>Hematology</th><th>Other</th></tr>
<tr><td rowspan="4">Albumin
Amylase
Alkaline phosphatase
ALT
AST
Bicarbonate
Blood urea nitrogen or urea
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase
Lipase
Phosphate
Potassium
Sodium
Total bilirubin
Direct bilirubin (if total bilirubin is elevated above ULN)
Total protein
Uric acid
Vitamin D (25-hydroxyvitamin D and 1,25-dihidroxyvitamin D)</td><td rowspan="4">Complete blood count, including the following:
Hemoglobin
Hematocrit
Platelet count
Red blood cell count
White blood cell count

Differential count, including the following:
Basophils
Eosinophils
Lymphocytes
Monocytes
Neutrophils

Absolute values must be provided for the following:
WBC differential laboratory results:
Lymphocytes
Neutrophils</td><td>Serology:
Hepatitis B surface antigen/antibody
Hepatitis B core antibody
HCV antibody
NOTE: If any of the above are positive, HBV-DNA, HCV-RNA to assess risk of reactivation.</td></tr>
<tr><td>Pregnancy test:
Female subjects of childbearing potential only require a serum test at screening and a urine pregnancy test before the first dose on Cycle 1 Day 1 and at EOT.
Pregnancy tests (serum or urine) should be repeated if required by local regulations.</td></tr>
<tr><td>Urinalysis with microscopic examination:
Color and appearance
pH and specific gravity
Bilirubin
Glucose
Ketones
Leukocytes
Nitrite
Occult blood
Protein
Urobilinogen (optional)</td></tr>
<tr><td>Coagulation:
PT
PTT or aPTT
INR</td></tr>
<tr><th>Endocrine Monitoring</th><th>Lipid Panel</th><th>Subjects With Myeloproliferative Neoplasm</th></tr>
<tr><td>Parathyroid hormone</td><td>Total Cholesterol
Triglycerides
LDL
HDL</td><td>Bone marrow aspirate and biopsy
JAK-2 mutation status
Cytogenetics</td></tr>
</table>

aPTT = activated partial thromboplastin time.

Table 22: Laboratory Tests: Required Analytes for Multiple Myeloma Subjects

Laboratory Test
Serum protein electrophoresis and immunofixation (M protein quantification) Urine protein electrophoresis (M protein quantification) Quantitative immunoglobulins Serum-free light chains Beta-2 microglobulin
Bone marrow aspirate and biopsy FISH Cytogenetics

6.1. Screening Phase

Prescreening is allowed for subjects without genomic testing results (Part 2 and Part 3). For subjects not requiring a genomic testing report (Part 1) or having a genomic testing report for Part 2 or 3, the screening phase will be up to 28 days. The screening phase is the interval between the signing of the informed consent form (ICF) and the first dose of study drug (Cycle 1 Day 1). Informed consent must be obtained before performing any study-specific procedures. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during this phase.

Results from the screening visit evaluations will be reviewed to confirm subject eligibility before randomization or the administration of study drug. Tests with results that fail eligibility requirements may be repeated once during the screening phase if the investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process 1 time if the investigator believes that there has been a change in eligibility status (eg, following recovery from an infection).

Additionally, the screening phase will be utilized to determine the baseline assessments of clinical condition and disease status. Tumor assessments appropriate to the type of malignancy will be performed and recorded in the CRF.

6.2. Treatment Phase

The treatment begins on the day the subject receives the first dose of study drug; this is defined as Cycle 1 Day 1 through the point at which the PI determines the subject will be permanently discontinued from study drug. Dates for subsequent study visits will be determined based upon this day and should occur within 3 days (+/-) of the scheduled date unless delayed for safety reasons. At Cycle 1 Day 1, results from screening visit evaluations should be reviewed to determine if the subject continues to meet the eligibility requirements as specified in the Protocol.

During the treatment phase, regular study visits (physician visits) will occur during the first 6 treatment cycles (ie, Days 1, 2, 8, 14, 15, and 16 of Cycle 1) and thereafter at the beginning of each 21-day treatment cycle, provided that subjects do not have more than a stable Grade 2 toxicity and have obtained approval from the medical monitor.

At certain study visits as indicated in Table 20, subjects will attend the study visit having fasted, having recorded the time of the prior study drug administration and time of last meal, and having withheld the dose of the study drug. At these visits, PK and/or PD sampling will be conducted.

6.3. End of Treatment

Once a decision is made that the subject will permanently discontinue study drug, the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT page in the CRF. The subject should be encouraged to return for the follow-up visit.

6.4. Follow-Up Phase

6.4.1. Safety Follow-Up

The safety follow-up phase is the interval between the EOT visit and the scheduled safety follow-up visit. Adverse events and SAEs must be reported up until at least 30 days after the last dose of study drug, the date of the safety follow-up visit, or until study drug–related toxicities resolve, return to baseline, or are deemed irreversible, death, or initiation of a new anticancer treatment, whichever occurs first. Reasonable efforts should be made to have the subject return for the follow-up visit and report any AEs that may occur during this phase. If the subject is unable to return to the site for the 30-day safety follow-up visit, a follow-up phone call can be conducted by the site at the time of the scheduled 30-day safety follow-up visit to collect any new safety information that occurred between EOT and the safety visit. If a subject is planned to start new anticancer therapy before the end of the 30-day safety follow-up period, the safety follow-up visit should be performed before the initiation of the new anticancer therapy. Once new anticancer therapy has been initiated, the subject will move into the survival follow-up phase.

6.4.2. Disease Status Follow-Up

Subjects who discontinue study treatment for a reason other than disease progression will move into the disease status follow-up phase and should be assessed every 57 ± 5 days by radiologic imaging (or by the relevant disease response assessment) to monitor disease status. Every effort should be made to collect information regarding disease status until:

- The start of new antineoplastic therapy
- Disease progression
- Death
- End of the study

6.4.3. Survival Follow-Up

Once a subject has confirmed disease progression or starts a new anticancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone, email, or visit at least every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.5. Unscheduled Visits

Unscheduled visits may occur at any time as medically warranted. Any assessments performed during those visits should be recorded in the CRF.

6.6. Beginning and End of Study

The study begins when the first subject signs the informed consent. The end of the study may be designated as the timepoint when all subjects have discontinued the study or the sponsor terminates the study.

7. CONDUCT OF STUDY ASSESSMENTS AND PROCEDURES

7.1. Administration of Informed Consent Form

Valid informed consent must be obtained from the study subject before conducting any study-specific procedures. The granting of informed consent for study participation must be documented in writing, using an ICF that contains all the elements required by ICH E6 and describes the nature, scope, and possible consequences of the study in a form understandable to the study subject. Local and institutional guidelines for ICF content and administration must be followed; a copy of the signed ICF must be provided to the study subject. Subjects of childbearing potential must agree to take appropriate measures to avoid pregnancy in order to participate in the study (Appendix A).

7.2. Interactive Response Technology Procedure

The Interactive Response Technology (IRT) will be contacted by the site to obtain a subject ID number when a subject enters the screening phase. Upon determining that the subject is eligible for study entry, IRT will be contacted to obtain study drug assignment. Additionally, IRT will be contacted on Day 1 of each regular study visit to register the subject visit and update the study drug supply.

7.3. Demography and History

7.3.1. Demographics and Medical History

Demographic data and a complete medical and medication history will be collected at screening by the investigator or qualified designee and will include date of birth, race, ethnicity, medical and surgical history, and concurrent illnesses assessed using the NCI CTCAE v4.03 (NCI 2010). Medical history should include all active conditions and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding ***the disease for which the subject has enrolled in this study*** (eg, date of diagnosis, primary tumor histology, prior systemic therapies, surgeries, radiation therapy, and stage of cancer) will be recorded separately and not listed in medical history.

7.3.2. Prior Medications

Prior and ongoing medications will be reviewed to determine study eligibility. The investigator or qualified designee will review prior medication use, including any Protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the study. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.3.3. Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the study. Concomitant medications include any prescription, over-the-counter, or natural/herbal preparations taken or administered during the study period. All medications related to reportable SAEs should be recorded as defined in Section 8.1.1.

7.4. Safety Assessments

7.4.1. Adverse Events

Adverse events will be monitored from the time the subject signs the ICF. Subjects will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, subjects will be asked general, nonleading questions such as "How are you feeling?" All AEs (serious and nonserious) must be recorded on the source documents and CRFs regardless of the assumption of a causal relationship with the study drug or the combination agents. The definition, reporting, and recording requirements for AEs are described in Section 8.

7.4.2. Comprehensive Physical Examination

Physical examinations must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant, or an advanced Registered Nurse Practitioner, as local law permits.

The comprehensive physical examination should include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; lymph nodes; and a brief neurological examination. Before the first dose of study treatment, clinically significant abnormal findings should be recorded as medical history. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

7.4.3. Targeted Physical Examination

A targeted physical examination will be a symptom-directed evaluation conducted by the investigator or designee. The targeted physical examination will include assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings. If the subject does not report any symptoms, then a targeted physical examination is not required.

7.4.4. Vital Signs

Vital sign measurements (blood pressure, heart rate, respiratory rate, and body temperature) will be taken with the subject in the recumbent, semirecumbent, or sitting position after approximately 5 minutes of rest. Height will be measured at screening only.

7.4.5. Twelve-Lead Electrocardiograms

Triplicate 12-lead ECGs will be obtained on the days and times noted in the schedule of assessments (Table 19) and Table 23 below. All timed 12-lead triplicate ECGs will be conducted predose and then at 1, 2, and 4 hours postdose, approximately 5 minutes before the PK blood draw at the corresponding timepoint. The specified postdose timepoint may be adjusted based on emerging PK data. All 12-lead ECGs will be performed with the subject in a recumbent or semirecumbent position after approximately 5 minutes of rest. Baseline ECG intervals will be equal to the average of all ECG intervals obtained before the first study drug dose administration. All 12-lead ECGs obtained at subsequent timepoints during the study will be compared with these baseline 12-lead ECG intervals. For ECG morphology, the ECG performed closest to the time of administration on Day 1 of Cycle 1 will be used as the baseline.

Twelve-lead ECGs will be acquired using an ECG analysis system with analysis and printing capabilities, as well as digital transmission capabilities to a central capture module at the central ECG laboratory. The investigator and research staff will receive adequate training by a qualified person on the use and operation of the analysis system. The successful digital submission of a 12-lead ECG, meeting quality standards, to the central ECG laboratory by the site must be ensured before enrollment of the first subject. The study manual for procedures that must be followed for the recording and transmission of ECGs and the operator's manual with instructions for operating the digital capture module will be shipped to the site along with the device. The 12-lead ECGs will be interpreted by the investigator at the site and will be used for immediate subject management. The decision to include or exclude a subject or discontinue a subject's participation in the study based on an ECG flagged as "Abnormal, Clinically Significant" is the responsibility of the investigator, in consultation with the sponsor's medical monitor, as appropriate. Twelve-lead ECGs that are identified by the investigator as "Abnormal, Clinically Significant" will be sent to the sponsor's medical monitor for review.

The overall ECG interpretation will be indicated by a flagging system that will help distinguish between a normal ECG, ECG abnormalities where no further investigation is required, and ECG abnormalities where study exclusion, further cardiovascular investigation, and/or prompt action may be necessary depending on the clinical context. A suitable flag will be included in the "Overall ECG Interpretation" section of the report when an ECG is considered to be technically unacceptable or uninterpretable. If several different abnormalities exist corresponding to different levels of flagging, the label will reflect the most severe level. Flagging by the central expert cardiologist of these significant abnormalities should only be regarded as a suggestion. This service is intended to assist the investigator in his/her interpretation of the ECG and decision-making. It is not intended to replace the investigator's expert judgment and knowledge of the subject's medical condition.

Table 23: Electrocardiogram Timed Measurements

Study Time	Timing of ECG
Cycle 1, Day 1	• Predose[a] • 1, 2, and 4 hours postdose[b]
Cycle 1, Day 8	• Predose[a]
Cycle 1, Day 14	• Predose[a] • 1, 2, and 4 hours postdose[b]

[a] Approximately 5 minutes before the predose PK blood draw.
[b] Approximately 5 minutes before the respective postdose PK blood draw.

7.4.6. Echocardiogram/Multigated Acquisition Scan

An echocardiogram/MUGA scan will be required **only** for subjects enrolling in the Part 3 trastuzumab group. Subjects will need this completed before enrollment (screening) and then on Day 1 of every cycle and at EOT.

7.4.7. Comprehensive Eye Examination

A comprehensive eye examination should be performed by a qualified ophthalmologist at screening, once every 3 cycles (± 14 days, starting at Cycle 3), at EOT, and as clinically indicated. The eye examination should include a visual acuity test, slit-lamp examination, funduscopy with digital imaging, and optic coherence tomography. Every effort should be made to ensure that all subsequent examinations are performed by the same ophthalmologist.

7.4.8. Laboratory Assessments

A laboratory local to the study site and subject may perform all clinical laboratory assessments for safety (eg, serum chemistry, hematology assessments, and urinalysis). The investigative site will enter the local laboratory results and laboratory normal ranges into the CRF. All local laboratory assessments should be performed using standard procedures on the days indicated in Table 20. Table 22 lists the required laboratory tests for multiple myeloma subjects, and Table 21 lists the required laboratory tests for all other indications. Additional tests may be performed if clinically indicated. Subjects who have abnormal on-study calcium and phosphorus levels should have their levels monitored at least twice a week.

Laboratory tests for screening should be performed within 14 days before the first dose of treatment. Predose laboratory procedures can be conducted up to 72 hours before study drug administration. Results must be reviewed by the investigator or qualified designee and found to be acceptable before starting study treatment.

7.4.8.1. Chemistry, Hematology, Coagulation Panel, Fertility, Serology, and Endocrine Function Testing

Chemistry, hematology, coagulation panel, serology, and endocrine function will all be analyzed by the local site laboratory.

7.4.8.2. Urinalysis

Urinalysis will be analyzed by the local site laboratory.

7.4.8.3. Pregnancy Testing

Serum pregnancy tests will be analyzed by the site laboratory at screening. Subsequently, pregnancy tests (either serum or urine) may be conducted as medically indicated or as required per local guidelines.

If a subject inadvertently becomes pregnant while on treatment with INCB054828, the subject will immediately be withdrawn from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the sponsor and followed as described above and in Section 8.

7.4.9. Evaluation of FGF and FGFR Genetic Alterations

Subjects may be evaluated for FGF and FGFR alterations by the investigational site's local sequencing laboratory (eg, FISH, immunohistochemistry, sequencing, next-generation sequencing, or gene expression analyses). All subjects will have a retrospective analysis conducted by the sponsor's designated central laboratory assay if it was not utilized initially for confirmation of study eligibility in Part 2 and Part 3 (dose expansion). If the FGFR/FGF genetic alteration cannot be confirmed in subjects in Part 2 and Part 3 (dose expansion), additional subjects may be enrolled as replacements. The continuation of the treatment in subjects with discordant tumor genetic information will be at the investigator's discretion.

7.5. Efficacy Assessments

Objective assessment of tumor status is required using appropriate disease-specific techniques and the investigator's assessment will be used to determine responses and will be logged into the CRF. For solid tumors, the RECIST 1.1 (Eisenhauer et al 2009) will be used and the recommended method for measuring and following tumor burden will be computed tomography (CT) scan, to include the thorax, abdomen, pelvis, and neck if needed. Alternative modalities may be substituted for a CT scan at the discretion of the investigator, provided that the same modality is used throughout the study and the methodology is consistent with RECIST 1.1.

For subjects with multiple myeloma, the assessments will be based on the IMWG Multiple Myeloma response criteria, see Appendix D (Durie et al 2006).

For subjects with MPNs, the response criteria in Appendix E will be used to assess response.

The schedule for efficacy assessments will be at screening (this will be considered the baseline scan) and every 3 cycles (starting with Cycle 3) throughout the study. Efficacy assessments should occur at the end of the cycle. Multiple myeloma subjects should have response assessments performed around Day 14 of every cycle (± 2 days). Subjects with MPN should have a bone marrow aspirate and biopsy performed approximately 3, 6, and 12 months after Day 1 and then every 12 months on the nearest Cycle Day 14 (± 2 days) after the first dose of treatment and as clinically indicated.

For subjects who discontinue treatment for reasons other than disease progression, every effort should be made to continue monitoring disease status until (1) start of new antineoplastic therapy, (2) documented disease progression, (3) death, or (4) the end of study, whichever occurs first.

7.6. Performance and Quality of Life Assessments

7.6.1. Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG performance status (Appendix C) at screening and before the administration of each cycle of study treatment in the clinic and EOT as specified in the schedule of assessments (Table 19). No quality-of-life instrument will be used in this study.

7.7. Pharmacokinetic Assessments

7.7.1. Blood Sample Collection

Pharmacokinetic samples will be obtained at the visits indicated in Table 20, and collection times and windows are described in Table 24 and Table 25. The exact date and time of the PK blood draws will be recorded in the CRF along with the date and time of the last dose of study drug preceding the blood draw and the time of the most recent meal. Instructions for sample preparation and shipping will be provided in the Laboratory Manual. Subjects will receive reminder cards/diaries in advance of the study visit providing instruction to hold the dose of study drug on the day of the visit, a place to record the time of the prior dose of study drug, and a place to record the time of the most recent meal or snack consumed.

During Cycle 1, PK samples will be obtained on Days 1, 2, 8, 14, 15, and 16. On these designated days, study subjects will refrain from eating 8 hours prior to arriving at the research unit. A trough (predose) PK sample will be drawn early in the study visit; the sample must be drawn approximately 1 hour prior to study drug administration. Subjects then need to fast for 1 additional hour after taking study medication. Once the subject takes the study drug, any subsequent timed samples will be taken.

Subjects on the BID dosing schedule will have PK sampling performed as indicated above during Cycle 1, but additional PK samples will be drawn on Day 1, Day 8, and Day 15 of Cycles 2 and 3 (predose only).

7.7.2. Food-Effect Study (Part 2 Only)

This cohort is closed to enrollment, as of Protocol Amendment 8.

On Cycle 2 Day 14, only study subjects who are selected to participate in the food-effect study in the expansion (Part 2, n ≈ 8) will be required to undergo PK testing in a fed state.

- Pharmacokinetic testing conducted on Cycle 2 Day 14 will be similar to that on Cycle 1 Day 14 with respect to the timing of sample collection and evaluations. Subjects may be excused from the food-effect part of the study if they are unable to consume the meal or feel they are unable to consume the meal.
- Subjects receiving INCB054828 in the fed state will have been fasted from food (not including water) overnight for at least 8 hours. A standardized high-fat, high-calorie breakfast will be given to these subjects approximately 30 minutes before administration of study drug. Subjects must consume the entire breakfast within 25 minutes, and study drug administration will begin 5 minutes after completing breakfast.
- The high-fat, high-calorie breakfast (50% kcal from fat) will consist of:
  - 2 eggs fried in butter
  - 2 strips of bacon
  - 1 English muffin with butter
  - 4 oz hash brown potatoes
  - and 8 oz whole milk

- Alternative menus with the same caloric and fat content may be substituted with the prior approval of the study sponsor.

Adjustments to the timing of blood sampling postdose may be made based upon emerging PK data; however, no more than 6 postdose timepoints will be used.

Table 24: Pharmacokinetic Blood Sampling (Parts 1 and 3)

Study Visit	Predose	Postdose					
		0.5 h	1 h ± 15 min	2 h ± 15 min	4 h ± 15 min	6 h ± 30 min	8 h ± 30 min
C1D1	X	X	X	X	X	X	X
C1D2	X						
C1D8	X						
C1D14	X	X	X	X	X	X	X
C1D15	X[a]						
C1D16	X[b]						

[a] The PK sample collected on C1D15 should be collected within 24 hours of the C1D14 study drug administration, with a ± 2-hour window.
[b] The PK sample collected on C1D16 should be collected within 48 hours of the C1D14 study drug administration with a ± 4-hour window.

Table 25: Pharmacokinetic Blood Sampling (Part 2)

Study Visit	Predose	Postdose					
		0.5 h	1 h ± 15 min	2 h ± 15 min	4 h ± 15 min	6 h ± 30 min	8 h ± 30 min
C1D1	X	X	X	X	X	X	X
C1D2	X						
C1D8	X						
C1D14	X	X	X	X	X	X	X
C1D15	X[a]						
C1D16	X[a]						
C2D14[b]	X	X	X	X	X	X	X
C2D15[b]	X[a]						
C2D1[c]	X						
C2D8[c]	X						
C2D15[c]	X						
C3D1[c]	X						
C3D8[c]	X						
C3D15[c]	X						

[a] The PK sample collected on C1D15 and C2D15 should be collected within 24 hours of the C1D14 and C2D14 study drug administration, respectively, with a ± 2-hour window. The C1D16 sample should be collected within 48 hours of the C1D14 study drug administration.
[b] For subjects who will participate in the Part 2 food-effect study only.
[c] For subjects who receive study drug BID.

7.7.3. Renal Impairment Cohort

Subjects with moderate and severe renal impairment will be enrolled in 2 separate subcohorts in Part 1. The following MDRD formula will be used to estimate the eGFR:

- MDRD formula (mL/min/1.73 m^2) = 175 × (serum creatinine) - 1.154 × (age) - 0.203 × (0.742 if female) × (1.212 if African American).

Subjects with an eGFR of ≥ 30 to < 60 mL/min/m^2 will be eligible to be enrolled in the moderate renal impairment cohort. Subjects with an eGFR of < 30 mL/min/m^2 but not receiving dialysis will be eligible to be enrolled in the severe renal impairment cohort. Pharmacokinetic (PK) samples will be obtained at the visits indicated in Table 20, and collection times and windows are described in Table 24 (see Section 7.7.1). An additional blood sample will be obtained to measure protein binding of INCB054828 in plasma.

Subjects will receive 13.5 mg continuous administration of INCB054828.

7.7.4. Urine Sample Collection (Total Urine [8-hour])

Urine will be collected from each subject at Cycle 1 Day 14. A predose sample will be collected and kept separate from the remaining urine collected throughout the day. Following INCB054828 administration, urine will be collected over an 8-hour interval (total urine). Urine containers should be kept at reduced temperature (refrigerated or ice bath) during collection. After the interval, the total urine volume should be measured and recorded in the individual CRF. The postdose urine will be mixed thoroughly, and a 200-mL aliquot will be collected into a prelabeled, polypropylene storage bottle and frozen at or below -20°C. Shipping and handling instructions will be provided in the Laboratory Manual.

7.7.5. Bioanalytical Methodology and Analysis

The plasma samples will be analyzed for INCB054828 by a validated assay. If there is sufficient urinary excretion of unchanged INCB054828 for assay, the urine samples will be assayed for INCB054828 by a validated assay. [redacted]
These samples will be analyzed by Incyte Corporation (Wilmington, Delaware) or its designee.

For each subject who completes study participation, pharmacokinetic parameters will be calculated from the plasma concentrations of INCB054828 according to the model independent approach. See Appendix B for a detailed list and description of the PK parameters.

7.8. Pharmacodynamic Assessments

Blood samples will be obtained for plasma PD and whole blood PD, studies as designated in Table 20. Sample collection times are indicated in Table 26.

Table 26: Sample Collection Times for Pharmacodynamic Assessments

Study Visit	Timing of Sample Relative to INCB054828 Administration	
	Plasma PD	**Whole Blood PD**
C1D1	Predose	Predose and in conjunction with timed PK samples (up to 6 h) listed in Table 24.
C1D2		Predose
C1D8		
C1D14	Predose	Predose and in conjunction with timed PK samples (up to 6 h) listed in Table 24.
C1D15		Predose if continuous administration, 24 hours postdose if 2 weeks on treatment/1 week off treatment
C2D1	Anytime during visit	
Day 1 subsequent cycles	Anytime during visit	

[redacted]

7.8.4. Tumor Biopsy

Subjects must have an archival tumor biopsy sample (obtained within the last 2 years) available or be willing to undergo a pretreatment tumor biopsy at baseline. For Part 1 subjects, fresh tumor biopsies for the purpose of determining study eligibility should be limited to tumors where tissue can be safely accessed. The medical monitor should be contacted to determine the potential risk of a tumor biopsy. Details and methods for obtaining, processing, and shipping the fresh tumor biopsy samples and for processing and shipping the archived tumor tissue samples will be provided in the Laboratory Manual for the study.

Tumor lesions used for biopsy should not be selected as RECIST target lesions, unless there are no other lesions suitable. If a RECIST target lesion is used for biopsy, the lesion must be ≥ 2 cm in the longest diameter.

The constituents of the tumor as well as the tumor microenvironment may be examined by histology, immunohistochemistry (using markers of cell populations, growth, signaling, cell cycling, apoptosis, etc.), and other exploratory methods, including analysis of RNA-based transcriptional profiles and somatic mutations to identify characteristics that may be associated with safety, response, or resistance to treatment with the study drug. Potential somatic mutations in tumor samples may be confirmed by assessing the specific sequence change in a normal sample obtained by buccal swab. These analyses will be conducted by Incyte Corporation (Wilmington, DE) or Incyte's designee.

Optional tumor biopsy specimens: May be obtained while the subject is receiving study drug in subjects with accessible tumors to assess intratumoral changes that might be associated with safety, response, or resistance to treatment.

Mandatory tumor biopsy specimens: Biopsies are mandatory for any subjects enrolled a lower dose level cohort in Part 1 or Part 3 or Part 2 (tumor-specific cohorts). A baseline biopsy (performed any time after last treatment) and at least 1 on-treatment biopsy (recommended at Cycle 2 Day 14, but allowed to be performed at any cycle; must be performed on a study drug administration day, preferably between Day 8 and Day 14). Additionally, an EOT/at time of progression biopsy is requested but not required. [redacted] NOTE: Subjects who withdraw consent for mandatory biopsy after enrollment will be reported as a Protocol deviation.

7.9. Other Study Procedures

7.9.1. Administration of INCB054828

Subjects will self-administer INCB054828 orally, with water, QD on a 2-week on-therapy and 1-week off therapy schedule, as directed by the investigator. Study drug can be taken with or without food.

Subjects enrolled in the continuous administration cohort(s) will take INCB054828 orally with water QD for the 21-day administration cycle, as directed by the investigator.

Study drug will be administered in the study clinic on days as indicated in Table 19, and Section 7.7.1; subjects will attend the study visit having fasted, having recorded the time of the prior administration of study drug and prior meal, and having withheld the dose of study drug. At this visit, PK and PD sampling will be conducted.

7.9.2. Dispensing of INCB054828

An initial bulk supply of INCB054828 will be provided to investigative sites prior to enrollment of the first subject. Thereafter, the site staff will contact the sponsor for resupply of INCB054828. When dispensing to subjects, the investigator or designee will remove the appropriate quantity of study drug from their stock, dispense the medication, and enter the amount dispensed into the CRF and drug accountability log. Full details will be provided in the Study Manual.

7.9.3. Assessment of Compliance With INCB054828

The study subject will return all full, empty, and opened/partially used bottles of study drug at the beginning of each treatment cycle, and a compliance check (tablet count) will be performed by the clinic staff at each visit; therefore, appropriate steps should be taken to optimize compliance.

7.9.4. Distribution of Subject Reminder Cards

Subjects will be provided with subject reminder cards at each visit. The subject reminder cards will indicate the date and time of the next visit. The reminder cards will have a field for the subject to enter the date and time of the last dose taken before the visit and to record the time of the last meal. Reminder cards will include instructions specific to study visits when the PK/PD sample is collected, at which time the subject will refrain from taking the study drug at home in the morning prior to the clinic visit. All necessary instructions, such as those for study drug administration, concomitant medications, and laboratory tests should be provided to the subject in writing on this reminder card or on accompanying written materials.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definitions and Reporting

For the purposes of this Protocol, an adverse event (AE) is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after a subject provides informed consent. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (eg, hematologic abnormality that requires transfusion), or require changes in the study drug(s).

Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events page of the CRF. Conditions that were already present at the time of informed consent should be recorded on the Medical History page of the CRF. Adverse event monitoring should be continued for at least 30 days after the last dose of study drug. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

Adverse events will be assessed according to the CTCAE version 4.03. The CTCAE severity Grade 5 (death) will not be used in this study; rather, information about deaths will be collected as an outcome of the event. The occurrence of AEs should be sought by nondirective questioning of the subject during the screening process after signing the ICF and at each visit during the study. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments.

Note that a grading scale for hyperphosphatemia (elevated serum phosphate) is not included in CTCAE v 4.03. Grading should be applied using the table below and referencing the "investigations-other, specify" category in CTCAE v 4.03. Hyperphosphatemia should be graded based on clinical severity (eg, symptoms) and medical intervention measures taken (eg, phosphate binders) and not on phosphate levels.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.

As far as possible, each AE should be evaluated to determine:

- The severity grade (CTCAE Grade 1 to 4).
- Reasonable possibility that the AE is related to the study treatment: unrelated (no) or related (yes).
- Start and end dates, unless unresolved at final examination.
- Action taken with respect to study drug (eg, none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable).
- Outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- Whether it is serious, as per SAE definition provided in Section 8.3.1.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see Section 8.3.2.

All AEs should be treated appropriately. If a concomitant medication or nondrug therapy is given, this action should be recorded on the AE and Prior/Concomitant medications pages of the CRF.

Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Disease progression should not be regarded or reported as an AE itself, unless it is associated with a separate AE.

8.2. Laboratory Test Abnormalities

8.2.1. Definitions and Reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug), should be recorded on the AE page of the CRF. Whenever possible, a diagnosis rather than a symptom should be provided (eg, anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory test result corresponds to a sign or symptom of a previously reported AE, it is not necessary to separately record the laboratory test result as an additional event.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as AEs. A Grade 3 or 4 (severe) AE, as per CTCAE, does not automatically indicate an SAE unless it meets the definition of serious, as defined in Section 8.3.1, and/or per the investigator's discretion. A dose interruption or adjustment for the laboratory abnormality may be required (see Section 5.8) and should not contribute to the designation of a laboratory test abnormality as an SAE.

8.3. Serious Adverse Events

8.3.1. Definitions

A SAE is defined as an event that meets 1 of the following criteria:

- Is fatal or life-threatening (ie, immediate risk of dying).
- Results in persistent or significant disability or incapacity.
- Constitutes a congenital anomaly or birth defect.
- Is clinically meaningful (ie, defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above). Considered meaningful by the investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is a result of:
  - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
  - Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF.
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.

- Social reasons and respite care, in the absence of any deterioration in the subject's general condition.
- Any SAEs that are expected due to the condition being treated, including if the SAE is a primary outcome measure, or where there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere.

8.3.2. Reporting

To ensure subject safety, every SAE, regardless of suspected causality, occurring after the subject has signed the ICF and up to the last study visit, or up to 30 days after the subject has stopped study treatment, whichever is later, must be reported to the sponsor (or designee) within 24 hours of learning of its occurrence. Any SAEs experienced after this period should be reported to the sponsor (or designee) only if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as the follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Previously planned (before providing informed consent) surgeries should not be reported as SAEs unless the underlying medical condition worsens over the course of the study.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than 1), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the sponsor or its designee. The investigator must assess if there is a reasonable possibility that the SAE is related to the study treatment: unrelated (no) or related (yes).

Serious AEs related to unblinded comparator drugs or concomitant medications/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The telephone and facsimile number of the sponsor's contact persons, specific to the study, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the CRF documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each recurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation, or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, a sponsor's associate may urgently require further information from the investigator for reporting to health authorities.

The sponsor or its designee may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

8.4. Emergency Unblinding of Treatment Assignment

Not applicable.

8.5. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed, the following procedures should occur:

- The investigator must notify the sponsor or its designee immediately.
- The study drug must be discontinued immediately.
- The subject must be withdrawn from the study.
- The EOT visit evaluations must be performed.
- The investigator must complete and submit the Pregnancy Initial and Follow-Up Report forms to the sponsor or its designee.
- A serum pregnancy test must be performed to confirm the urine pregnancy test result. (The serum test should be performed at the investigative site to ensure that the test will be performed promptly and the result available immediately for review.)

If a negative serum test does not confirm the urine pregnancy test result, then:

- The investigator will use his or her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine if it is in the subject's best interest to resume study drug and continue participation in the study.

To ensure subject safety, each pregnancy in a subject during maternal or paternal exposures to study drug must be reported within 24 hours of learning of its occurrence. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation. Follow-up to each pregnancy should be conducted to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the sponsor's study drug of any pregnancy outcome and follow-up to the first well-baby visit. **Any SAE experienced during pregnancy must be reported on the SAE Report Form and to the sponsor or its designee.**

8.6. Warnings and Precautions

No evidence available at the time of the approval of this study Protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications (INs). Any important new safety information should be discussed with the subject during the study as needed. If new, significant risks are identified, they will be added to the ICF.

8.7. Data Monitoring Committee

Not applicable.

8.8. Adverse Events of Special Interest

Not applicable.

8.9. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint and any associated AEs via email or other written communication to the Incyte contact.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9. STATISTICS

9.1. Study Populations

The populations to be analyzed include the following:

The Efficacy Evaluable Population/Safety Population consists of subjects enrolled in the study who received at least 1 dose of study drug.

The PK/PD population consists of all enrolled subjects who had PK/PD data.

9.2. Selection of Sample Size

Approximately 325 subjects will be enrolled into this study. Part 1 of the study is a standard dose-escalation design, and the sample size depends on the occurrence of safety findings such as DLTs. Approximately 1 to 6 subjects will be enrolled in each dose level. For Part 2, approximately 120 subjects will be enrolled, which will provide > 90% chance of detecting at least 17 responders if the underlying response rate is 30%. For Part 3, approximately 3 to 6 subjects will be enrolled per combination therapy for dose finding, and approximately 24 subjects per combination therapy for dose expansion (except docetaxel cohort), which will provide > 90% chance of detecting at least 4 responders in expansion group if the underlying response rate is 30%.

9.3. Level of Significance

This is an exploratory study and no formal statistical tests will be performed. All confidence intervals will be 95%.

9.4. Statistical Analyses

Data will be summarized overall and by treatment cohorts based on the dose regimen initially assigned.

9.4.1. Primary Analyses

The clinical safety data (vital signs, ECGs, routine laboratory tests, and AEs) will be summarized using descriptive statistics (eg, mean, frequency) using the safety population.

9.4.2. Secondary Analyses

The proportion of subjects who meet the response criteria (CR + PR) as appropriate for the tumor type will be summarized.

[redacted]

[redacted]

9.4.4. Safety Analyses

9.4.4.1. Adverse Events

A TEAE is any AE either reported for the first time or worsening of a pre-existing event after first dose of study drug, including combination products. Analysis of AEs 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 the MedDRA preferred term and system organ class. Severity of AEs will be based on the NCI CTCAE v4.03 (NCI 2010).

The subset of AEs considered by the investigator to have a relationship 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 or the combination products, the AE will be considered treatment related. The incidence of AEs and treatment-related AEs will be tabulated.

9.4.4.2. Clinical Laboratory Tests

Laboratory test values outside the normal range will be assessed for severity based on the normal ranges for the clinical reference laboratory. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

Laboratory data will be classified into CTC grades for AEs (CTCAE v4.03). The following summaries will be produced for the laboratory data:

- Number and percentage of subjects with worst postbaseline CTC grade (regardless of baseline value). Each subject will be counted only for the worst grade observed postbaseline.
- Shift tables using CTC grades to compare baseline with the worst postbaseline value will be produced with CTC grade.
- For laboratory parameters where CTC grades are not defined, shift tables to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.

9.4.4.3. Vital Signs

Descriptive statistics and mean change from baseline will be determined for vital signs (blood pressure, heart rate, respiratory rate, and body temperature) at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities (see Table 27), and subjects exhibiting clinically notable vital sign abnormalities will be listed. A value will be considered an "alert" value if it is outside the established range and shows a > 25% change from baseline.

Table 27: 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/min	< 8/min

9.4.4.4. Electrocardiograms

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities according to predefined criteria (see Table 28). Subjects exhibiting clinically notable ECG abnormalities will be listed. Adverse events will be reported for clinically notable abnormalities that are considered clinically significant in the judgment of the investigator.

Table 28: Criteria for Clinically Notable ECG 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
RR	> 1330 msec	< 600 msec

QTcF = Fridericia correction.

9.4.5. Pharmacokinetic Analysis

The PK parameters of C_{max}, t_{max}, C_{min}, AUC_{0-t}, and Cl/F (INCB054828) will be calculated from the blood plasma concentrations of INCB054828 using standard noncompartmental (model-independent) PK methods. Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin® (Pharsight Corporation, Mountain View, CA). Nominal times will be used in all cases, except when the difference between the actual time and nominal time is greater than 15 minutes for samples collected up to 4 hours after administration and greater than 30 minutes for samples collected more than 4 hours after administration; in these cases, actual time will be used for PK analysis.

If there is a sufficient amount of plasma concentration data from this study, the data will be analyzed by standard population PK methods using appropriate software (eg, NONMEM).

9.4.5.1. Food Effect and Renal Impairment

The log-transformed PK parameters will be compared between the fasted and fed study drug administration groups in the food-effect cohort and between the renal impairment cohort and the normal renal function group using a 1-factor ANOVA. The geometric mean ratio and 90% confidence intervals for INCB054828 C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ will be calculated to assess the magnitude of the effect of food or renal impairment on the PK of INCB054828.

9.5. Data Monitoring Committee

Not applicable.

9.6. Interim Analysis

Not applicable.

10. STUDY DRUG MATERIALS AND MANAGEMENT

In Part 3, commercially available and commercially packaged gemcitabine, cisplatin, docetaxel, pembrolizumab, or trastuzumab will be utilized for this study. See Section 10.3 for information on INCMGA00012.

10.1. Investigational Product Description: INCB054828

10.1.1. Packaging, Labeling, and Preparation of INCB054828

All medication labels will be in the local language and will comply with the legal requirements of each country.

10.1.2. Formulation and Chemical Properties of INCB054828

INCB054828 is formulated as 0.5-mg, 2.0-mg (free base equivalent), and 4.5-mg tablets. Each tablet contains the active ingredient and commonly used compendial excipients such as microcrystalline cellulose, sodium starch glycolate, and magnesium stearate.

10.1.3. Storage and Stability of INCB054828

INCB054828 drug product should be stored at room temperature, 15°C to 30°C (59°F-86°F).

10.2. Accountability, Handling, and Disposal of INCB054828

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until the end of the study. The investigator or designee must maintain records that document:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug including pill or unit counts from each supply dispensed.
- Return of study drug to the investigator or designee by subjects.

These records should include dates, quantities, batch or serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the correct study drug specified.

Completed accountability records will be archived by the site. At the completion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Incyte.

10.3. Investigational Product Description: INCMGA00012

10.3.1. Packaging, Labeling, and Preparation of INCMGA00012

INCMGA00012 will be provided in a 250-mg vial. All medication labels will be in the local language and will comply with the legal requirements of each country. INCMGA00012 will be administered at 500 mg, diluted in 100 mL of 0.9% sodium chloride injection USP (normal saline), and given as an IV infusion, over 60 minutes through a filter. Further guidance and information can be found in the Pharmacy Manual.

10.3.2. Formulation and Chemical Properties of INCMGA00012

INCMGA00012 drug product is provided as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow or pale brown solution with a protein concentration of 25 mg/mL. The product is formulated in 0.95 mg/mL sodium acetate trihydrate, 0.18 mg/mL acetic acid, 90 mg/mL sucrose, and 0.1 mg/mL polysorbate 80 in sterile water for injection, USP, at a pH of 5.1.

10.3.3. Storage and Stability of INCMGA00012

INCMGA00012 drug product should be stored upright under refrigeration at 2°C to 8°C (36°F-46°F) and protected from light.

10.3.4. Accountability, Handling, and Disposal of INCMGA00012

Responsibility for drug accountability at the study site rests with the investigator; however, the investigator may assign some of the drug accountability duties to an appropriate pharmacist or other designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities.

The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until the end of the study. The investigator or designee must maintain records that document the following:

- Delivery of study drug to the study site.
- Inventory of study drug at the site.
- Subject use of the study drug vial counts from each supply dispensed.

These records should include dates, quantities, batch or serial numbers (if available), and the unique code numbers (if available) assigned to the investigational product and study subjects.

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the subjects were provided the correct study drug specified.

Completed accountability records will be archived by the site. At the completion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional standard operating procedures. If local procedures mandate site destruction of investigational supply, prior written approval must be obtained from Incyte.

11. STUDY ADMINISTRATION

11.1. Data Management

11.1.1. Data Collection

The investigator will be provided with access to an electronic CRF; a set of forms will be completed for each subject. Entries made in the CRF must be verifiable against source documents; any discrepancies should be explained and documented. The investigator will be responsible for reviewing all data and CRF entries and will sign and date the designated pages in each subject's CRF, verifying that the information is true and correct. The investigator is responsible for the review and approval of all responses.

11.1.2. Data Management

Data management will be performed from CRFs. All CRF data are entered directly into a validated database by the study site. All data entry, verification, and validation will be performed in accordance with the current standard operating procedures of the Data Management Department at the sponsor or its designee. The database will be authorized for lock once all defined procedures are completed.

11.2. Study Monitoring

Qualified representatives of the sponsor or its designee, "study monitors," will monitor the study according to a predetermined monitoring plan. Monitoring visits provide the sponsor with the opportunity to:

- Evaluate the progress of the study.
- Verify the accuracy and completeness of CRFs.
- Assure that all Protocol requirements, applicable laws and/or regulations, and investigator's obligations are being fulfilled.
- Resolve any inconsistencies in the study records.

The investigator must allow the study monitors to periodically review, at mutually convenient times during the study and after the study has been completed, all CRFs and office, hospital, and laboratory records supporting the participation of each subject in the study. The CRFs and other documentation supporting the study must be kept up-to-date by the investigator and the research staff at the investigative site. These study materials must be available for review by the study monitor, and/or other qualified representatives of the sponsor or its designee, at each monitoring visit.

The study monitor will review the various records of the study (CRFs, subject medical and laboratory records, and other pertinent data). The study monitor will verify the CRF data against original source documentation for accuracy and completeness. The study monitor will identify data discrepancies and collaborate with the investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a "Protocol Deviation Log." The study monitor will follow an "Issue Escalation" plan in order to ensure that each issue identified during a monitoring visit is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements.

11.3. Protocol Adherence

The principal investigator must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval and all materials approved by the IRB or IEC for this study including the subject ICF and recruitment materials must be maintained by the investigator and made available for inspection.

Each investigator must adhere to the Protocol as described in this document and agree that changes to the Protocol, with the exception of medical emergencies, must be discussed and approved, firstly, by the sponsor or its designee and, secondly, by the IRB or IEC. Each investigator is responsible for enrolling subjects who have met the Protocol inclusion and exclusion criteria. The IRB or IEC that granted original approval, or the IRB or IEC currently responsible for overseeing the conduct of the study, must be notified of all changes in and deviations from the Protocol that may increase risk to the subject, and/or that may adversely affect the rights of the subject or validity of the investigation. The investigator must send a copy of the approval letter from the IRB or IEC to the sponsor or its designee and retain the original in the site study regulatory file.

Major eligibility deviations must be reported to the IRB or IEC in accordance with the IRB or IEC requirements. During the course of the study, the monitor must notify the sponsor or its designee of subjects found not to have met eligibility criteria. The medical monitor, in collaboration with the investigator, will determine if the subject should be withdrawn from the study.

11.4. Financial Disclosure

All clinical investigators participating in clinical studies subject to FDA Regulation Title 21 Code of Federal Regulations (CFR) Part 54 – Financial Disclosure by Clinical Investigators, are required before study initiation to submit a completed Clinical Investigator Financial Disclosure Request Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, clinical investigator is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects, including the spouse and each dependent child of the clinical investigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new investigators or subinvestigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Request Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligation to report to the sponsor or its designee any changes to the financial information previously reported. The clinical investigators will also be reminded that they must report any changes in their financial information for a period of 1 year after completion of the covered clinical study.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Sponsor Audits

At some point during the study, individuals from the sponsor's Quality Assurance department and/or their authorized representative may visit the investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the investigator's adherence to the Protocol, applicable regulations, and the sponsor's procedures, in addition to assessing the accuracy of the study data. Before initiating this audit, the investigator will be contacted by the sponsor to arrange a convenient time for this visit. The investigator and staff are expected to cooperate with the auditors and allow access to all subject records supporting the CRFs and other study-related documents.

12.2. Inspection by Regulatory Authorities

At some point during the investigational product's development program, a regulatory authority may visit the investigator to conduct an inspection of the study and the site. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the CRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

13. ETHICS

13.1. Ethical Conduct of the Study

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, GCPs as defined in Title 21 of the US CFR Parts 50, 54 56, 312, and Part 11, as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

13.2. Written Informed Consent

Informed consent documentation that includes both information about the study and the ICF will be prepared and given to the subject. This document will contain all elements required by the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject and must specify who informed the subject. Where required by local law, the person who informs the subject must be a physician.

The principal investigator at each center will ensure that the subject is given full and adequate verbal and written information about the nature, purpose, and the possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue study drug and withdraw from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated ICF must be obtained before conducting any study procedures. The principal investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject. The investigator should inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

Preparation of the ICF is the responsibility of the investigator and must include all elements required by the ICH GCP, and applicable regulatory requirements, and must adhere to the ethical principles that have their origin in the Declaration of Helsinki. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and approve all changes to site-specific ICFs. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to subject records. Before the beginning of the study, the IRB or IEC must provide the investigator with written approval/favorable opinion of the written ICF and any other information to be provided to the subjects.

13.3. Ethics Review

It is the responsibility of the investigator to assure that all aspects of the ethics review are conducted in accordance with the Declaration of Helsinki as described in the ICH E6: Guideline for GCP, and/or local laws, whichever provides the greatest level of protection for the study participants. The Protocol and any information supplied to the subject to obtain informed consent, including written ICFs, subject recruitment procedures (eg, advertisements), and written information to be provided to subjects (information leaflets), must be reviewed and approved by a qualified IRB/IEC before enrollment of participants in the study. Before initiation of the study,

the sponsor or its designee must receive documentation of the IRB or IEC approval, which specifically identifies the study/protocol, and a list of the committee members.

The principal investigator is responsible for informing the IRB or IEC of any amendment to the Protocol in accordance with local requirements. Protocol amendments and revisions to the ICF must be submitted to and approved by the IRB or IEC.

Investigators must submit progress reports to the IRB or IEC in accordance with the IRB or IEC requirements and local regulations. Annual re-approval of the study must be obtained. Copies of progress reports and annual re-approvals must be sent to the sponsor or its designee.

The principal investigator is also responsible for providing the IRB or IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The sponsor or its designee will provide this information to the principal investigator.

When the sponsor or its designee provides the investigator with a safety report, the investigator must promptly forward a copy to the IRB or IEC.

After completion or termination of the study, the investigator must submit a final report to the IRB or IEC and to the sponsor or its designee.

The investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB or IEC.

Each clinical investigator is responsible to conduct the study in accordance with the Protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

13.4. Data Privacy

The investigator and the sponsor or its designee must adhere to applicable data privacy laws and regulations. The investigator and the sponsor (or its designee) are responsible for ensuring that sensitive information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

14. DATA HANDLING AND RECORDKEEPING

14.1. Inspection of Records

The sponsor or its designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The investigator must ensure that all records pertaining to the conduct of the clinical study (as listed above) are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal termination of clinical development of the investigational product.

14.2. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the termination of the test article for investigation. If it becomes necessary for the sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records.

The investigator must not destroy any records associated with the study without receiving approval from Incyte. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable, provided it is legible and is a verified copy of the original document.

All CRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original CRF data and audit trail.

14.3. Confidentiality

Subject names will not be supplied to the sponsor or its designee if applicable. Only the subject number and subject's initials will be recorded in the CRF, where permitted; if the subject's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed that representatives of the sponsor or its designee, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

15. PUBLICATION POLICY

By signing the study Protocol, the investigator and his or her institution agree that the results of the study may be used by the sponsor, Incyte Corporation (Incyte), for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. The signed agreement is retained by the sponsor or its designee.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For Subjects Participating in the Study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- Intrauterine device (IUD)[2]
- Intrauterine hormone-releasing system (IUS)[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
[2] Contraception methods that in the context of this guidance are considered to have low user dependency.
[3] Vasectomised partner is a highly effective method provided of avoiding pregnancy that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
[4] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Source: CTFG 2014.

APPENDIX B. PHARMACOKINETIC ANALYTICAL PARAMETERS

C_{ave}	Average steady-state plasma concentration ($AUC_{0\text{-}12h}$/12h or $AUC_{0\text{-}24h}$/24h)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration during the dosing interval
T_{max}	Time to maximum plasma concentration
$AUC_{0\text{-}t}$	Area under the single-dose plasma concentration-time curve from Hour 0 to the last quantifiable measurable plasma concentration, calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
$AUC_{0\text{-}\tau}$ (ie, $AUC_{0\text{-}12h}$ or $AUC_{0\text{-}24h}$)	Area under the steady-state plasma concentration-time curve over 1 dosing interval (ie, from Hour 0 to 12 for BID administration or from Hour 0 to 24 for QD administration), calculated by the linear trapezoidal rule for increasing concentrations and the log trapezoidal rule for decreasing concentrations
λ_z	Apparent terminal phase disposition rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{½}$	Apparent plasma terminal phase disposition half-life (whenever possible), where $t_{½} = (\ln 2) / \lambda_z$
Cl/F	Oral dose clearance
V_z/F	Apparent oral dose volume of distribution
Fluctuation	Steady-state fluctuation ($[C_{max} – C_{min}]/C_{ave}$)

In addition, the following PK parameters may be calculated, whenever possible, for each subject based on the urine INCB054828 concentrations:

A_e	Amount of drug excreted in the urine over sampling interval
CL_R	Renal clearance, where $CL_R = A_e/AUC$
% Excreted or f_e	percent excreted in the urine, where % Excreted = 100 (A_e/dose)

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as WinNonlin® (Pharsight Corporation, Mountain View, CA). Additional details of analyses will be described in the data analysis plan.

APPENDIX C. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al 1982.

APPENDIX D. RESPONSE ASSESSMENT CRITERIA FOR MULTIPLE MYELOMA

Table 5 International Myeloma Working Group uniform response criteria: CR and other response categories

Response subcategory	*Response criteria*[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.
[a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
[b]Confirmation with repeat bone marrow biopsy not needed.
[c]Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of >4:1 or <1:2.
[d]Refer to Table 4 for definitions of measurable disease.

Table 6 International Myeloma Working Group uniform response criteria: disease progression and relapse

Relapse subcategory	*Relapse criteria*
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ⩾25% from baseline in Serum M-component and/or (the absolute increase must be ⩾0.5 g/dl)[b] Urine M-component and/or (the absolute increase must be ⩾200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be ⩾10%[c] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b] It is not used in calculation of time to progression or progression-free survival but is listed here as as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ⩾2 g/dl [1.25 mmol/l] (see Table 3 for further details) 5. Rise in serum creatinine by 2 mg/dl or more [177 μmol/l or more]
Relapse from CR[a](To be used only if the end point studied is DFS)[d]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ⩾5% plasma cells in the bone marrow[c] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR, complete response; DFS, disease-free survival.
[a]All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[b]For progressive disease, serum M-component increases of ⩾1 gm/dl are sufficient to define relapse if starting M-component is ⩾5 g/dl.
[c]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d]For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Source: Durie et al 2006.

APPENDIX E. RESPONSE ASSESSMENT CRITERIA FOR SUBJECTS WITH MYELOPROLIFERATIVE NEOPLASMS

Response Criteria for Myeloproliferative Neoplasms With Genetic Alterations in FGF or FGFR Gene

Complete Response	**Criteria**
Hematologic	Durable peripheral blood count remission, defined as: absence of circulating blasts, hemoglobin ≥ 100 g/L and < ULN, platelet count ≥ 100×10^9/L and < ULN, WBC and neutrophil count within institutional normal range. For subjects with baseline eosinophilia: eosinophils < 1.5×10^9/L.
Bone marrow	Cellularity appropriate for age, resolution of abnormal morphology, blasts ≤ 5%.
Spleen	For subjects with splenomegaly at baseline: < 25% increase in spleen size by palpation or imaging if baseline spleen is < 10 cm or < 50% if baseline spleen is ≥ 10 cm.
Lymph nodes	For subjects with lymph node disease: target nodes/nodal masses must regress to ≤ 1.5 cm in longest transverse diameter of lesion, no extralymphatic sites of disease, no new lesions present. Must be PET negative, if positive at baseline.
Cytogenetic CR	Meets above criteria and MPN-associated cytogenetic abnormalities are no longer detected (requires that abnormalities were found at baseline).
Molecular CR	Meets above criteria and MPN-associated molecular abnormalities (eg, by PCR) are no longer detected (requires that abnormalities were found at baseline)
Partial Response	
Hematologic	Hemoglobin ≥ 100 g/L and < ULN, 50% reduction in WBC and neutrophil count, 50% reduction in circulating blasts. For subjects with eosinophilia: > 50% reduction in eosinophil count.
Bone marrow	> 50% reduction in blasts.
Spleen	For subjects with splenomegaly: < 25% increase in spleen size by palpation or imaging if baseline spleen is < 10 cm or < 50% if baseline spleen is ≥ 10 cm.
Lymph nodes	For subjects with lymph node disease: ≥ 50% decrease in the sum of the product of the perpendicular diameters of up to 6 target measureable nodes and extranodal sites, no new lesions present.
Cytogenetics	No new abnormalities detected.
Molecular markers	No new abnormalities detected.
Stable Disease	
	Failure to achieve at least Partial Remission, but no evidence of progression for at least 9 weeks.
Progressive Disease	
Hematologic	WBC: > 2 times increase compared with baseline count in the absence of a concurrent acute or subacute medical illness. For subjects with circulating blasts: ≥ 50% increase in circulating blasts.
Bone marrow	≥ 50% increase in blasts.
Spleen	For subjects with splenomegaly: > 25% increase in spleen size by palpation or imaging if baseline spleen is < 10 cm and > 50% if baseline spleen is ≥ 10 cm or appearance of new splenomegaly.
Lymph nodes	If lymph node disease is present: a single node must be abnormal with the longest transverse diameter > 1.5 cm and ≥ 50% increase in the sum of measureable lesions or new or clear progression of pre-existing nonmeasured lesions.

CR = complete response; MPN = myeloproliferative neoplasm; PCR = polymerase chain reaction; PET = positron emission tomography; ULN = upper limit of normal; WBC = white blood cell.

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment (Version) 1:	19 NOV 2014
Amendment (Version) 2:	11 JUN 2015
Amendment (Version) 3:	02 NOV 2015
Amendment (Version) 4:	09 MAR 2016
Amendment (Version) 5:	27 SEP 2016
Amendment (Version) 6:	26 JUN 2017
Amendment (Version) 7:	10 AUG 2018
Amendment (Version) 8:	11 DEC 2018
Amendment (Version) 9:	02 JUL 2019
Amendment (Version) 10:	27 MAR 2020

Amendment 10 (27 MAR 2020)

Overall Rationale for the Amendment: To incorporate administrative changes and include updated language for comprehensive eye examination, per FDA feedback.

1. **Section 5.8.2, Criteria and Procedures for Interruption of INCB054828**

   Description of change: Added guidance for dose reduction and for . treatment associated with SRD/RPED.

   Rationale for change: To provide specific guidance.

2. **Section 5.8.4, Criteria for Permanent Discontinuation of INCB054828**

   Description of change: Dose reduction language was revised.

   Rationale for change: For clarification.

3. **Section 5.8.3, Management of Hyperphosphatemia**

   Description of change: Updated to include information on diet modification and phosphate binders.

   Rationale for change: To provide more specific guidance on the management of hyperphosphatemia.

4. **Section 6, Study Assessments (Table 19: Schedule of Assessments); Section 7.4.7, Comprehensive Eye Examination**

   Description of change: Language added to include optic coherence tomography as part of the regularly scheduled eye examinations.

   Rationale for change: Per FDA requirement.

5. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 9 (02 JUL 2019)

Overall Rationale for the Amendment: To add a BID dosing regimen and update the clinical experience section.

1. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Added language to hemoglobin exclusion criteria regarding transfusion allowance with appropriate washout before enrollment.

   Rationale for change: To allow transfusions to elevate low hemoglobin but requiring washout to ensure durable hemoglobin levels and not transient following transfusion.

2. **Synopsis; Section 4.1, Overall Study Design; Section 9.2, Selection of Sample Size**

   Description of change: Updated the number of subjects per study.

   Rationale for change: Added another cohort to Part 1 and Part 2.

3. **Synopsis; Section 1.5, Justification of Route, Dose Regimen, and Treatment Period; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design (including Figure 3: Study Design); Section 5.1.1, Treatment Regimen for INCB054828; Section 6, Study Assessments (Table 20: Laboratory Assessments); Section 7.7, Pharmacokinetic Assessments (including Table 25: Pharmacokinetic Blood Sampling [Part 2])**

   Description of change: Added BID dosing regimen for INCB054828 and amended the PK assessment schedule for BID dosing.

   Rationale for change: To Increase dose exposure with BID dosing.

4. **Section 1.4.2, Potential Risks of INCB054828 Based on Clinical Experience**

   Description of change: Updated the clinical experience section.

   Rationale for change: To provide updated information from the current IB.

5. **Section 5.8.2, Criteria and Procedures for Interruption of INCB054828**

   Description of change: Added recommendation to discuss suspected or documented serous retinal detachment with the medical monitor before modifying the INCB054828 dose.

   Rationale for change: To allow conversation with an Incyte representative before treatment is modified.

6. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 8 (11 DEC 2018)

Overall Rationale for the Amendment:

Changes were made to the Protocol based on FDA feedback after review of Amendment 7. Additional changes include the modification of ECG sampling times and the addition of a 4.5-mg tablet across all sites/countries.

1. **Synopsis; Section 1.5.1, INCB054828; Section 4.1.2, Part 2 Dose Expansion; Section 4.4, Number of Subjects; Section 9.2, Selection of Sample Size**

   Description of change: The number of subjects in Part 2 and the total sample size have been increased.

   Rationale for change: Additional treatment groups have been added.

2. **Synopsis; Section 3.1, Subject Inclusion Criteria; Section 3.2, Subject Exclusion Criteria**

   Description of change: Inclusion criterion 8 and exclusion criterion 19 have been revised to indicate that subjects enrolled in Part 3 combination with INCMGA00012 should avoid pregnancy or fathering a child through 6 months after the last dose of INCMGA00012. Exclusion criterion 9 has been revised to indicate the minimum washout period for subjects enrolled in Part 3 (pembrolizumab or INCMGA00012).

   Rationale for change: Additional time is needed for contraception for subjects receiving INCMGA00012 and pembrolizumab due to the half-life of the product.

3. **Synopsis; Section 3.2, Subject Exclusion Criteria; Section 5.12, Prohibited Medications and Measures**

   Description of change: Language has been added to indicate that the use of live vaccines is prohibited for subjects receiving pembrolizumab or INCMGA00012.

   Rationale for change: The restriction is standard for immune-modulating drugs.

4. **Synopsis; Section 5.1.1, Treatment Regimen for INCB054828; Section 7.9.1, Administration of INCB054828**

   Description of change: Language has been added regarding the administration of INCB054828 regardless of food.

   Rationale for change: The food effect study has shown no impact of food on INCB054828; therefore, restrictions have been lifted.

5. **Synopsis; Section 10.1.2, Formulation and Chemical Properties of INCB054828**

   Description of change: The specification that the 4.5-mg tablet will be for Denmark only has been removed.

   Rationale for change: The 4.5-mg tablet will be available in all regions of the study.

6. **Section 1.3.3, INCMGA00012**

   Description of change: Updated safety data from study INCMGA 0012-102 were added.

   Rationale for change: New information for INCMGA00012 is available.

7. **Section 1.4.7, Potential Risks of INCMGA00012**

   Description of change: Language has been added to specify potentially serious irAEs and other reactions.

   Rationale for change: Updated information from the INCMGA00012 program is available.

8. **Section 3.2, Subject Exclusion Criteria; Section 5.11, Restricted Medications and Measures; Section 5.12, Prohibited Medications and Measures**

   Description of change: Language has been modified to allow or restrict different medications.

   Rationale for change: Based on recent information, the use proton pump inhibitors is unrestricted and administration of moderate CYP inducers is prohibited.

9. **Section 5.1.2, Treatment Regimen for Gemcitabine + Cisplatin (Part 3 Only); Section 5.1.3, Treatment Regimen for Docetaxel (Part 3 Only); Section 5.1.4, Treatment Regimen for Pembrolizumab (Part 3 Only); Section 5.1.5, Treatment Regimen for Trastuzumab (Part 3 Only)**

   Description of change: Language has been added for dosing delays and restarting of drug.

   Rationale for change: Based on FDA feedback after review of Amendment 7.

10. **Section 5.6, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose for INCB054828 (Table 6: Definition of Dose-Limiting Toxicity and Maximum Tolerated Dose of INCB054828)**

    Description of change: The reference to INCMGS00012 and immune-related toxicity has been deleted and Hy's Law criteria have been added.

    Rationale for change: The FDA provided feedback to add Hy's Law criteria. INCMGA00012 and immune-related toxicity were deleted because they are not applicable to INCB054828.

11. **Section 5.8.1, Planned Dose Modifications for INCB054828**

    Description of change: The criteria were updated to provide instructions for up-titration.

    Rationale for change: To allow up-titration for subjects without hyperphosphatemia due to possible low drug exposure.

12. **Section 5.8.5, Dose Modifications and Management of Adverse Events Associated with Gemcitabine + Cisplatin, Docetaxel, Pembrolizumab, Trastuzumab; Section 5.8.6, Planned Dose Modification and Management of Adverse Events for INCMGA00012 (including Table 9 through Table 18); Section 5.8.7, Permanent Discontinuation of INCMGA00012 Due to Toxicity**

    Description of change: Language regarding toxicity management has been modified.

    Rationale for change: The language has been updated based on FDA feedback on INCB 54828-101 Protocol Amendment 7 and changes to INCMGA00012 Protocols.

13. **Section 6, Study Assessments (Table 19: Schedule of Assessments); Section 7.4.5, Twelve-Lead Electrocardiograms (including Table 23: Electrocardiogram Timed Measurements)**

    Description of change: The testing schedule for ECGs has been modified.

    Rationale for change: To pair ECG testing with PK draws.

14. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 7 (10 AUG 2018)

Overall Rationale for the Amendment:

The Protocol has been updated to include 1) a new combination treatment arm, 2) a renally impaired treatment arm, and 3) mandatory biopsies. Additional revisions are noted below.

1. **Synopsis; Section 1.3.1, Rationale for Evaluating Safety and Pharmacokinetics in Subjects With Renal Impairment; [redacted] Section 3.1, Subject Inclusion Criteria; Section 3.2, Subject Exclusion Criteria; Section 4.1, Overall Study Design; Section 4.1.1, Part 1 Dose Escalation; [redacted] Section 6, Study Assessments (Table 20: Laboratory Assessments); Section 7.7.3, Renal Impairment Cohort; Section 9.4.5.1, Food Effect and Renal Impairment**

   Description of change: Language has been added to include in Part 1 a subset of subjects with moderate and severe renal impairment. Pharmacokinetic assessments will be conducted on these subjects and overall analysis of the data will be done.

   Rationale for change: The change allows for the inclusion of renally impaired subjects for treatment and analysis in this study.

2. **Synopsis; Section 4.1, Overall Study Design; Section 4.1.2, Part 2 Dose Expansion; Section 6, Study Assessments (Table 20: Laboratory Assessments); Section 7.8.4, Tumor Biopsy**

   Description of change: Language has been added to indicate that all subjects entered into the tumor-specific cohorts in Part 2 and Part 3 must undergo mandatory biopsies.

   Rationale for change: To adjust the mandatory biopsy requirement for any subject enrolled in the tumor-specific cohort.

3. **Synopsis; Section 1, Introduction; Section 3, Subject Eligibility; Section 4.1, Overall Study Design; Section 4.1.3, Part 3 Combination Dose Finding and Expansion; Section 5, Treatment of Subjects; Section 6, Study Assessments (Table 19: Schedule of Assessments); Section 10.3, Investigational Product Description: INCMGA00012**

   Description of change: Sections and corresponding tables and figures have been added or updated to include a new combination therapy (INCMGA00012) to Part 3 of this study.

   Rationale for change: A new combination therapy (INCMGA00012) has been added to Part 3 of this study.

4. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Language for several of the exclusion criteria have been modified.

   Rationale for change: To update the inclusion and exclusion criteria to match recent clinical experience or updated preclinical experience or new guidance in industry (ie, ASCO).

5. **Synopsis; Section 4.4, Number of Subjects; Section 9.2, Selection of Sample Size**

   Description of change: Total sample size has been increased.

   Rationale for change: Total sample size was increased due to changes in cohort sizes.

6. **Section 1.2.2, Nonclinical Drug Metabolism and Pharmacokinetics of INCB054828; Section 1.4.2.1, Pharmacokinetic/Pharmacodynamic Summary**

   Description of change: Revised with updated data.

   Rationale for change: To provide updated PK data.

7. **Section 1.4.2, Potential Risks of INCB054828 Based on Preliminary Clinical Experience**

   Description of change: Revised with updated clinical data.

   Rationale for change: To provide updated risk language based on new clinical data.

8. **Section 4.1.2, Part 2 Dose Expansion**

   Description of change: Adding a specific cholangiocarcinoma with FGFR2 translocation cohort with required biopsies.

   Rationale for change: To enroll subjects in a target population in order to obtain tissue samples for analysis.

9. **Section 6, Study Assessments (Table 19: Schedule of Assessments); Section 7.4.5, Twelve-Lead Electrocardiograms**

   Description of change: Updated postdose ECG times to include 4 hours and added timing details to Table 19.

   Rationale for change: Clarification.

10. **Section 6, Study Assessments (Table 19: Schedule of Assessments); Section 7.4.7, Comprehensive Eye Examination**

    Description of change: Language has been added to list additional required assessments and optical coherence tomography for clinical symptoms.

    Rationale for change: Based on clinical data generated to date, the need for more comprehensive eye toxicity monitoring is required.

11. **Section** [redacted]

    Description of change: Language has been added to specify analyses to be completed on samples.

    Rationale for change: To provide a comprehensive list of analyses on samples collected.

12. **Section 8.1.1 Definitions and Reporting**

    Description of change: Language has been added to specify how hyperphosphatemia should be reported.

    Rationale for change: The current CTCAE v 4.03 does not list hyperphosphatemia; therefore, guidance has been added to the Protocol for hyperphosphatemia since it is an on-target event.

13. **Appendix F, Inhibitors of CYP3A; Appendix G, Inducers of CYP3A**

    Description of change: These appendices have been deleted.

    Rationale for change: These lists will no longer be provided as part of the Protocol.

14. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 6 (26 JUN 2017)

The primary purpose of this amendment is to increase the number of subjects in Part 2 and make changes to clarify and/or simplify the current study design.

1. **Synopsis; Section 1.5.1, INCB054828; Section 3.1, Subject Inclusion Criteria; Section 4.1, Overall Study Design (including Figure 1, Study Design); Section 4.1.2, Part 2 Dose Expansion; Section 4.4, Number of Subjects; Section 9.2, Selection of Sample Size**

   Description of change: Part 2 was revised to include approximately 15 subjects with specific tumor types (5 bladder cancer, 5 lung cancer, and 5 HPV-positive with FGFR-alteration tumors); approximately 6 of these subjects (2 per tumor type) will have mandatory biopsies. The number of subjects was updated accordingly.

   Rationale for change: Additional on-treatment tissue required to assess impact of INCB054828 on specific tumor types.

2. **Synopsis; Section 4.1.1, Part 1 Dose Escalation; Section 5.1.1, Treatment Regimen for INCB054828; Section 7.9.1, Administration of INCB054828**

   Description of change: Updated to reflect that a continuous study drug administration regimen **will** be explored and added language to explain required dosing completion for an evaluable subject and how INCB054828 should be administered in that regimen.

   Rationale for change: To clarify evaluability of subjects receiving the continuous study drug administration regimen.

3. **Synopsis; Section 4.1.1.3, Lower Dose Level Expansion; Section 4.1.2, Part 2 Dose Expansion; Section 4.1.3, Part 3 Combination Dose Finding and Expansion; Section 7.8.4, Tumor Biopsy**

   Description of change: Added language to specify requirements for mandatory biopsy tissue collection.

   Rationale for change: To simplify the process and provide clarity to timepoints.

4. **Section 1.4.2, Potential Risks of INCB054828 Based on Preliminary Clinical Experience**

   Description of change: Updated section with more recent clinical experience data.

   Rationale for change: Updated to match the Investigator's Brochure.

5. **Synopsis; Section 3.2, Subject Exclusion Criteria**

   Description of change: Adjustment was made to criterion regarding previous receipt of anticancer medication to 28 days (criterion 1). Added language to adjust serum phosphorus and parathyroid hormone requirements (criterion 3). Added language for ectopic mineralization/calcification to exclude certain circumstances that do not apply to this criterion (criterion 6). A new criterion was added to exclude previous anti-PD1 therapy in subjects in the Part 3 pembrolizumab group (criterion 24).

Rationale for change: To minimize the window of previous exposure to anticancer medications and to adjust the exclusion criterion for laboratory parameters and ectopic mineralization/calcification. New criterion was added to exclude previous exposure to anti-PD1 treatments.

6. **Synopsis; Section 6.1, Screening Phase**

   Description of change: Added language to allow prescreening for subjects without genomic testing results (Part 2 and Part 3).

   Rationale for change: Subjects in Part 2 and Part 3 require documentation of genomic sequencing results. Subjects who do not have this may be sequenced prior to signing the study informed consent and are subjected to the 28-day screening window.

7. **Section 5.1.2, Treatment Regimen for Gemcitabine + Cisplatin (Part 3 Only); Section 5.1.3, Treatment Regimen for Docetaxel (Part 3 Only); Section 5.1.4, Treatment Regimen for Pembrolizumab (Part 3 Only); Section 5.1.5, Treatment Regimen for Trastuzumab (Part 3 Only)**

   Description of change: Added language to allow discontinuation of chemotherapy/immunotherapy.

   Rationale for change: Chemotherapy/immunotherapy may be administered for a finite period of time, but INCB054828 may be given indefinitely. The added language allows investigators to stop chemotherapy/immunotherapy based on their discretion.

8. **Section 3.1, Study Population**

   Description of change: Section 3.1 was deleted.

   Rationale for change: Section was redundant with the inclusion/exclusion criteria sections.

9. **Section 5.7.3, Management of Hyperphosphatemia (Table 6, Recommended Approach for Hyperphosphatemia Management)**

   Description of change: Added language specifically for subjects in the continuous study drug administration cohorts.

   Rationale for change: Subjects in the continuous study drug administration cohorts do not have planned dose holds; therefore, the language needed to include statements for interruption and reductions for this group of subjects.

10. **Section 5.8, Withdrawal of Subjects From Study Treatment**

    Description of change: Added language to provide more clarity.

    Rationale for change: To provide more clarity on the withdrawal process and follow-up.

11. **Section 5.10, Restricted Medications and Measures; Section 5.11, Prohibited Medications and Measures**

    Description of change: Moved calcium-based binders from Section 5.11 to Section 5.10 and added aluminum-based phosphate binders to Section 5.10.

Rationale for change: To clarify that calcium-based and aluminum-based binders are not contraindicated, so they should not be prohibited.

12. **Section 6, Study Assessments (Tables 7 and 8, Schedule of Assessments and Laboratory Assessments)**

    Description of change: The schedule of assessments and laboratory assessments for subjects with multiple myeloma (original Tables 9 and 10) were deleted, and the information was added to Tables 7 and 8. The tables were updated to include notes in the table body (vs footnotes) and cross-references to applicable Protocol sections.

    Rationale for change: The assessment tables were combined and updated for clarity, easier readability, and consistency with other sections of the Protocol.

13. **Section 7.8, Pharmacodynamic Assessments (Table 13, Sample Collection Times for Pharmacodynamic Assessments);** [redacted]

14. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 5 (27 SEP 2016)

The primary purpose of this amendment is to revise the study design in order to add a continuous dosing cohort, a trastuzumab combination cohort in Part 3, and a lower dose level cohort in Part 1 and Part 3 with mandatory biopsies, and to increase the number of subjects in this study.

1. **Synopsis; Section 1.5.2, Rationale for Continuous Administration of INCB054828; Section 4.1, Overall Study Design; Section 4.1.1.3, Lower Dose Level Expansion; Section 4.1.3, Part 3 Combination Dose Finding and Expansion; Section 4.4, Number of Subjects; Section 5.1.1, Treatment Regimen for INCB054828; Section 6, Study Assessments (Table 7); Section 7.8.4, Tumor Biopsy**

   Description of change: A continuous study drug administration regimen has been added to Part 1. Lower dose level cohorts have been added to Part 1 and Part 3, with paired biopsies required. The number of subjects in Part 1 and Part 3 have been increased.

   Rationale for change: The continuous administration regimen is being added to allow for an additional dose regimen option. The lower dose level cohorts were added to obtain more data at the dose level below the RP2D and allow paired biopsies to be collected.

2. **Synopsis; Section 1.3.1, Rationale for Combining INCB054828 with Chemotherapy, Programmed Cell Death-1 Inhibitor and Trastuzumab; Section 1.4.6, Potential Risks of Trastuzumab; Section 1.4.7, Potential Risks Related to the Combination Regimens; Section 1.5.6, Trastuzumab; Section 3, Subject Eligibility; Section 4.4, Number of Subjects; Section 5.1.5, Treatment Regimen for Trastuzumab (Part 3 Only); Section 5.7.5, Management of Adverse Events Associated with Gemcitabine + Cisplatin, Docetaxel, Pembrolizumab, or Trastuzumab; Section 6, Study Assessments (Table 7); Section 7.4.6, Echocardiogram/Multigated Acquisition Scan; Section 10, Study Drug Materials and Management**

   Description of change: A trastuzumab combination cohort was added to Part 3. Relevant sections have been updated accordingly, including background information and dose regimen for trastuzumab (Part 3 only). An exclusion criterion was added for subjects being considered for treatment in the trastuzumab combination arm (left ventricular ejection fraction < 50% on echocardiogram or MUGA scan).

   Rationale for change: A trastuzumab combination cohort was added for exploration of an additional combination therapy, and relevant sections were updated accordingly. Exclusion criterion added per labeled criterion for subjects receiving trastuzumab.

3. **Synopsis; Section 3.1, Study Population; Section 4.1, Overall Study Design**

   Description of change: Specific tumor types for Part 2 have been deleted and the inclusion criterion outlining the different tumor types allowed in Part 2 have been removed.

   Rationale for change: All subjects with a documented FGF/FGFR alteration will be allowed to enroll.

4. **Synopsis; Section 3.3, Exclusion Criteria; Section 6, Study Assessments (Table 11)**

   Description of change: Separated the HIV and hepatitis language into 2 criteria; revised language for hepatitis.

   Rationale for change: Revision of HIV and hepatitis language to be clearer for selection of subjects.

5. **Synopsis; Section 9.2, Selection of Sample Size**

   Description of change: The effect size of this section was changed to account for the increase in number of subjects in each part.

   Rationale for change: The number of subjects in Part 3 has increased. Additionally, the tumor type "buckets" have been removed from Part 2.

6. **Section 1.4.2, Potential Risks of INCB054828 Based on Preliminary Clinical Experience**

   Description of change: Updated with clinical data as of 09 AUG 2016.

   Rationale for changes: To provide investigators with current information.

7. **Section 1.5.3, Gemcitabine + Cisplatin; Section 5.1.2, Treatment Regimen for Gemcitabine + Cisplatin (Part 3 Only); Section 6, Study Assessments (Table 7)**

   Description of change: Gemcitabine dose regimen has been changed to administration on Days 1 and 8 only.

   Rationale for change: The gemcitabine regimen is based on a 28-day cycle. INCB054828 is a 21-day cycle. The additional dose on Day 15 did not allow subjects to have enough of a break in between cycles.

8. **Section 5.7.2, Criteria and Procedures for Interruption of INCB054828 (Table 5)**

   Description of change: In Table 5 (Guidelines for Interruption and Restart of INCB054828), guidance regarding restarting study drug at "25% reduction if in expansion, rounded down to the nearest tablet strength" has been deleted.

   Rationale for change: Dose reductions are limited to doses tested (13.5 mg down to 9 mg; 9 mg down to 6 mg).

9. **Section 5.7.3, Management of Hyperphosphatemia (Table 6)**

   Description of change: Language has been added to Table 6 (Recommended Approach for Hyperphosphatemia Management) for subjects receiving INCB054828 as a continuous dose.

   Rationale for change: To provide guidance for subjects receiving the continuous administration regimen.

10. **Section 5.8.1, Withdrawal Criteria**

    Description of change: Language has been added to allow subjects to continue receiving INCB054828 even after progressive disease is noted.

    Rationale for change: In cases where the investigator believes the subject is receiving benefit and there are no other treatment options, this added language will allow subjects to continue to receive study drug, with medical monitor approval.

11. **Section 10.1, Investigational Product Description**

    Description of change: Language has been modified for INCB054828 labeling and storage requirements.

    Rationale for change: Study is no longer US only and has been modified for rest-of-world language requirements.

12. **Appendix A, Information Regarding Effectiveness of Contraceptive Methods**

    Description of change: Appendix A has been changed to include Clinical Trial Facilitation Group contraception methods.

    Rationale for change: Updated with approved contraception language.

13. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 4 (09 MAR 2016)

The primary purpose of this amendment is to adjust language in the Protocol to allow more flexibility for enrollment based on accumulated safety data. The secondary purpose is to adjust the management guidelines for hyperphosphatemia (HP).

1. **Synopsis; Section 3, Subject Eligibility; Section 4.1, Overall Study Design**

   Description of change: The Part 2 indications of gastric cancer and endometrial cancer were revised to gastric/cholangiocarcinoma cancer and endometrial/breast cancer.

   Rationale for change: To allow more flexibility for enrollment.

2. **Synopsis; Section 4.1.1, Pharmacodynamic Target**

   Description of change: Revised as follows: "The PAD is defined as the point where approximately 67% (2 out of 3) of subjects attain HP; in a cohort of 3 subjects, if 2 out of 3 have HP, the cohort will be expanded to 6 *(while dose escalation continues as described above)*. Once *the PAD*~~this target~~ is achieved ~~in a cohort of 6 subjects~~…"

   Rationale for change: To allow more flexibility for enrollment and management parameters associated with HP.

3. **Synopsis; Section 4.1.1.2, Recommended Part 2 Dose**

   Description of change: Revised to indicate that the recommended Phase 2 dose(s) (RP2D[s]) will be the lower of the maximum tolerated dose (MTD) or the pharmacologically active dose (PAD) *with or without prophylactic* concomitant phosphate binders.

   Rationale for change: To allow more flexibility for enrollment and management parameters associated with HP.

4. **Synopsis; Section 4.1.2, Part 2 Dose Expansion; Section 5.7.3, Management of Hyperphosphatemia**

   Description of change: In the Synopsis and Section 4.1.2, specific guidelines for subjects who attain HP were replaced with a cross-reference to Section 5.7.3. In Section 5.7.3, Table 3 (Recommended Approach for Hyperphosphatemia Management) was updated. The serum phosphate level column was revised to include 3 levels: 1) > 5.5 mg/dL and ≤ 7 mg/dL, 2) > 7 mg/dL and ≤ 10 mg/dL, and 3) > 10 mg/dL, and the recommended approach for each was revised.

   Rationale for change: To adjust the threshold for initiating phosphate binder use; this will allow more flexibility for the management parameters associated with HP.

5. **Synopsis; Section 3.2, Subject Inclusion Criteria; Section 6, Study Assessments (Table 4)**

   Description of changes:

   - Inclusion criterion 3 was revised to indicate that Part 2 subjects must have measurable disease with documented fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) alteration in tumor types.
   - Inclusion criterion 7 was revised to indicate that subjects with archival tumor samples older than 2 years old *and/or with sequencing report from Foundation Medicine* require approval from the sponsor medical monitor *for exemption from the need for tumor biopsy or tumor sample requirement*. This was also noted in Table 4, footnote h.

   Rationale for changes:

   - Inclusion criterion 3: To state requirement for measurable disease in Part 2.
   - Inclusion criterion 7: To provide biopsy sample flexibility for subjects who have existing Foundation Medicine genetic sequencing reports.

6. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of changes:

   - Exclusion criterion 1 was clarified to indicate that subjects who have received treatment with other investigational study drug or anticancer medications may be eligible with the sponsor's medical monitor approval.
   - Exclusion criterion 3 (laboratory parameters outside Protocol-defined range)

     Part 1 Dose Escalation:
     - Criteria 3d-f revised to indicate total bilirubin, AST/ALT, and ALP parameters > upper limit of normal (ULN) excluded *unless associated with subject's primary cancer and/or metastases and with medical monitor approval*.
     - Criterion 3g revised to indicate creatinine clearance < 30 mL/min for urothelial carcinoma.
     - Criteria 3h and j (serum calcium and serum albumin) combined to indicate serum calcium outside of the institutional normal range, or serum albumin-corrected calcium outside of the institutional normal range if serum albumin is outside of the institutional normal range.

     Part 2 Expansion:
     - Criteria 3d-e revised to indicate total bilirubin, AST/ALT, and ALP > upper limit of normal (ULN), and excluded *unless associated with subject's primary cancer and/or metastases and with medical monitor approval*.
     - Criterion 3g revised to indicate creatinine clearance ≤ 40 mL/min (< 30 mL/min for multiple myeloma *or urothelial carcinoma*)

Part 3 Combination:

- Criteria 3d-f revised to indicate total bilirubin, AST/ALT and ALP > upper limit of normal (ULN), and excluded *unless associated with subject's primary cancer and/or metastases and with medical monitor approval*.
- Criterion 3g revised to indicate creatinine clearance ≤ 40 mL/min *(< 30 mL/min for urothelial carcinoma)*.
- Criterion 3h revised to indicated international normalized ratio or prothrombin time > 1.5 × ULN*, unless on warfarin.*

Rationale for changes:

- Exclusion criterion 1: To provide more flexibility for enrollment.
- Exclusion criterion 3: To provide more flexibility for enrollment based on abnormal laboratory parameters that may be the result of the location of a subject's primary tumor or metastases.

7. **Section 1.4.2, Potential Risks of INCB054828 Based on Preliminary Clinical Experience**

   Description of change: Preliminary safety data have been updated.

   Rationale for change: To provide investigators with current information.

8. **Section 3, Subject Eligibility**

   Description of change: Updated to indicate that deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the Protocol is essential.

   Rationale for change: New standard language in all Incyte Protocols regarding waivers.

9. **Section 5.6, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Table 1)**

   Description of change: In Table 1 (Definition of Dose-Limiting Toxicity and Maximum Tolerated Dose of INCB054828), the nonhematologic toxicity section was updated to indicate "*Asymptomatic* changes in cholesterol and triglycerides," and "asymptomatic changes in lipid profiles" was deleted. The hyperphosphatemia section was updated to indicate "Serum phosphorus ≥ 10 mg/dL *recurrent or persistent for more than 1 week despite appropriate management*."

   Rationale for change: To refine the HP management guidelines based on revised criteria for initiating treatment with binders.

10. **Section 5.7.4, Criteria for Permanent Discontinuation of INCB054828**

    Description of change: The list of unacceptable AEs was updated to include serum phosphate levels in line with Table 3 (Recommended Approach for Hyperphosphatemia Management).

    Rationale for change: To refine the criteria for discontinuation based on the revised HP management guidelines

11. **Section 6, Study Assessments (Tables 4-7)**

    Description of changes: In Tables 4 and 6 (schedules of assessments for solid tumors/MPN and multiple myeloma), efficacy assessments (radiologic tumor assessments and IMWG multiple myeloma disease response assessment) were deleted from Cycles 2-6 Day 1 and moved to Cycles 2-6 Day 15. In Tables 5 and 7 (laboratory assessments for solid tumors/MPN and multiple myeloma), total urine collection was deleted from Cycle 1 Day 1.

    Rationale for changes: To ensure consistency between tables and Protocol text.

12. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 3 (02 NOV 2015)

The primary purpose of Amendment 3 is to add Part 3, Combination Therapy. In Part 3, INCB054828 will be paired with 3 different treatment regimens that are already being used for cancer treatment. Amendment 3 also contains changes to the inclusion/exclusion criteria and corrections to the Schedule of Assessment tables.

1. **Synopsis; Section 3.1, Study Population; Section 4.1, Overall Study Design; Section 4.1.3, Part 3 Combination Dose Finding and Expansion; Section 4.4, Number of Subjects; Section 5.1.2, Treatment Regimen for Gemcitabine + Cisplatin (Part 3 Only); Section 5.1.3, Treatment Regimen for Docetaxel (Part 3 Only); Section 5.1.4, Treatment Regimen for Pembrolizumab (Part 3 Only)**

   Description of change: Language was added to each section to describe Part 3, Combination Therapy. Combination therapies include gemcitabine + cisplatin, docetaxel, and pembrolizumab. Figure 1 (study design) was revised to include Part 3, and the number of subjects was updated.

   Rationale for change: Early exploration of INCB054828 in combination with different therapies in the treatment of different tumor types.

2. **Synopsis; Section 4.1.2, Part 2 Dose Expansion**

   Description of change: The definition of hyperphosphatemia was revised to serum phosphate > 5.5 mg/dL *or at least 1.5-fold change from baseline*.

   Rationale for change: Some subjects will have significant changes in serum phosphate baseline, while others will exceed the 5.5 mg/dL threshold. The high degree of variability in serum phosphate requires flexibility in declaring the PAD.

3. **Synopsis; Section 4.1.1.1. Pharmacodynamic Target**

   Description of change: The pharmacodynamic endpoint is now defined as approximately 67% (2 out of 3 subjects) instead of 80% (5 out of 6 subjects).

   Rationale for change: Some subjects will have significant changes in serum phosphate baseline, while others will exceed the 5.5 mg/dL threshold. The high degree of variability in serum phosphate requires flexibility in declaring the PAD.

4. **Section 1.3.1, Rationale for Combining INCB054828 With Chemotherapy and Programmed Cell Death-1 Inhibitor**

   Description of change: This new section was added with information on combining targeted therapies such as INCB054828 and chemotherapeutic and immunotherapeutic agents.

   Rationale for change: To provide a rationale for the combination of INCB054828 with the different agents proposed in Part 3.

5. **Section 1.4, Potential Risks; Section 1.5, Justification of Route, Dose Regimen, and Treatment Period**

   Description of change: New sections were added to the Introduction to outline the risks associated with INCB054828, gemcitabine and cisplatin, docetaxel, and pembrolizumab independently as well in combination, and to include dose and administration information for gemcitabine and cisplatin, docetaxel, and pembrolizumab.

   Rationale for change: New agents are being added to the study in Part 3, and the potential risks and dose and administration information must be included.

6. **Synopsis; Section 2, Study Objectives and Purpose**

   Description of change: The study objectives were updated to include the combination therapies.

   Rationale for change: Additional analyses will be performed to include data generated from subjects treated with the combination therapies.

7. **Synopsis; Section 3.2, Subject Inclusion Criteria; Section 3.3, Subject Exclusion Criteria**

   Description of change: Modifications were made to some of the inclusion/exclusion criteria and criteria were added for Part 3 subjects.

   Rationale for change: To allow more flexibility in the inclusion/exclusion criteria and to add parameters for Part 3 subjects.

8. **Section 5.7.5, Management of Adverse Events Associated With Gemcitabine + Cisplatin, Docetaxel, or Pembrolizumab**

   Description of change: New section has been added to outline the management of adverse events associated with gemcitabine, cisplatin, docetaxel, and pembrolizumab. Institutional guidelines should be followed and/or each drug label should be consulted, and if needed, the sponsor medical monitor should be consulted.

   Rationale for change: To provide instructions on how to handle adverse events or safety issues associated with the therapies that will be used in combination with INCB054828 in Part 3.

9. **Section 6, Study Assessments, Table 4: Schedule of Assessments (Solid Tumors and MPN)**

   Description of changes:

   a) Deleted 3-day window on Cycle 1 Day 15.
   b) Contact IRT: X's added on Days 8, 14, and 16 of Cycle 1; X deleted for Disease Status Follow-Up.
   c) INCB054828 in clinic: deleted X in Cycles 2-6 Day 15 and Cycle 7+ Day 1.
   d) Gem + Cis in clinic: added to D1, D8 and D15 for all cycles.
   e) Docetaxel in clinic: added to Day 1 for all cycles.
   f) Pembrolizumab in clinic: added to Day 1 for all cycles.

g) Targeted PE: added X's on Cycles 2-6 Days 8 and 15, Cycle 2 Day 15 (food effect), and Cycle 7+ Day 1.
h) ECOG: deleted X on Cycle 1 Day 15 and added X on Cycle 7+ Day 1.
i) Vitals signs: added X on Cycle 7+ Day 1
j) 12-lead ECG: deleted X on Safety Follow-Up.
k) Tumor tissue or bone marrow aspirate/biopsy collection: added X to Cycle 1 Day 14 and deleted X on Cycle 1 Day 15.
l) Radiologic tumor assessments: Add X on Cycles 2-6 Day 1 with footnote "k" indicating that assessments are done every third cycle on Day 14.
m) New footnote "d": Part 3 only; subjects should only receive the combination therapy to which they have been prescribed.
n) New footnote "e": Part 3 only; subjects on gemcitabine + cisplatin going into Cycle 7 or more should continue dose administration in clinic on Days 1, 8, and 15.

Rationale for changes: To correct when assessments need to be completed and to add assessments for Part 3 therapies.

10. **Section 6, Study Assessments, Table 5: Laboratory Assessments (Solid Tumors and MPN)**

Description of changes:

a) Deleted 3-day window for Cycle 1 Day 15; added 3-day window for Cycles 2-6 Day 15.
b) Comprehensive serum chemistry and Hematology with differential: Added X's for Cycle 1 Day 2, Cycles 2-6 Days 8 and 15, and Cycle 2 Day 15 (food effect).
c) Deleted second coagulation panel near bottom of the list of assessments (listed twice).
d) Total urine: Added X on Cycle 1 Day 1.
e) Blood sample for plasma PD assessments: deleted X on Cycle 1 Day 15; added X on Cycles 2-6 Day 1; deleted X on Cycles 2-6 Day 15.
f) Amended footnote "g" to include, "a predose sample will be collected separately; the postdose samples are collected….."
g) Blood sample for whole blood PD: added new footnote "j" (indicating "predose only") to Cycle 1 Days 2 and 15; added new footnote "k" (indicating "Serial sampling based on timing noted in Sections 7.7 and 7.8") to Cycle 1 Days 1 and 14.
h) [redacted]
i) Blood sample for INCB054828 PK: added footnote "k" to Cycle 1 Days 1 and 14, and Cycle 2 Day 14 for food effect; added footnote "j" to Cycle 1 Days 2 , 8, 15, and 16, and Cycle 2 Day 15 for food effect.

Rationale for changes: To correct when the assessments are to be performed.

11. **Section 6, Study Assessments, Table 6: Schedule of Assessments (Multiple Myeloma)**

Description of changes:

a) Deleted 3-day window on Cycle 1 Day 15.
b) Contact IRT: X's added on Days 15 and 16 of Cycle 1, Cycles 2-6 Days 8 and 15, and Cycle 2 Day 15 (food effect). X deleted for Disease Status Follow-Up.
c) INCB054828 in clinic: deleted X in Cycle 7+ Day 1.
d) Targeted PE: added X's on Cycles 2-6 Days 8 and 15, and on Cycle 7+ D1; deleted X at EOT.
e) ECOG: added X on Cycle 1 Day 15.
f) Vital signs and weight: deleted X's on Cycle 1 Day 16 and Cycles 2-6 Days 8 and 15.
g) 12-lead ECG: added X at EOT.
h) Eye examination: added X on Cycle 7+ Day 1.
i) IMWG: Added X on Cycle 1 Day 14 and Cycles 2-6 Day 1 with footnote "j" indicating that assessments are done every third cycle on Day 14.
j) Amended footnote "j" to read, "Response assessments should be performed every cycle on Day 14 (± 2 days)."

Rationale for changes: To correct when the assessments are to be performed.

12. **Section 6, Study Assessments, Table 7: Laboratory Assessments (Multiple Myeloma)**

Description of changes:

a) Deleted 3-day window for Cycle 1 Day 15; added 3-day window for Cycles 2-6 Day 15.
b) Safety Follow-Up: added "30 Days (+ 5 Days) After EOT" for evaluation window.
c) Comprehensive serum chemistry and Hematology with differential: Added X's on Cycle 1 Day 2, Cycles 2-6 Days 8 and 15, and Cycle 2 Day 15 (food effect).
d) Added Total Urine with X's on Cycle 1 Days 1 and 14.
e) Multiple myeloma response assessment: added X's on Cycle 1 Day 14 and Cycle 2-6 Day 1 with footnote "i" indicating that assessments are done every cycle on Day 14 (± 2 days).
f) Blood sample for plasma PD assessments: deleted X on Cycle 1 Day 15; added X on Cycles 2-6 Day 1; deleted X on Cycles 2-6 Day 15.
g) Blood sample for whole blood PD: added new footnote "l" (indicating "predose only") to Cycle 1 Days 2 and 15; .added new footnote "m" (indicating "Serial sampling per schedule in Sections 7.7 and 7.8") to Cycle 1 Days 1 and 14.
h) [redacted]
i) Blood sample for INCB054828 PK: added footnote "m" to Cycle 1 Days 1 and 14, and to Cycle 2 Day 14 for food effect; added footnote "l" to Cycle 1 Days 2, 8, 15, and 16.

Rationale for changes: To correct when the assessments are to be performed.

13. **Section 7.7, Pharmacokinetic Assessments, Table 11: Pharmacokinetic Blood Sampling (Parts 2 and 3)**

    Description of change: Added "Part 3" to table title and a predose blood sample on Cycle 1 Day 16 with an addition to footnote "a" indicating that the Cycle 1 Day 16 sample should be collected within 48 hours of the Cycle 1 Day 14 study drug administration.

    Rationale for change: To include Part 3 subjects in PK assessments and to add parameters for pulling the Day 16 sample- 48 hours after the last dose (Day 14).

14. **Section 7.8, Pharmacodynamic Assessments, Table 12: Sample Collection Times for Pharmacodynamic Assessments**

    Description of change: For plasma PD, deleted sample collection on Cycle 1 Day 15 and added "Any time during visit" to Cycle 2 Day 1. Changed whole blood PD on Cycle 1 Day 15 and whole blood for correlative studies on Cycle 1 Day 14 to "predose."

    Rationale for change: To correct assessment times and align with schedule of laboratory assessments.

15. **Synopsis; Section 9.2, Selection of Sample Size**

    Description of change: Language added to include Part 3 subjects for both the dose finding and the dose expansion.

    Rationale for change: To add subjects for Part 3.

16. **Section 10, Study Drug Materials and Management**

    [redacted]

    Rationale for change: To indicate how combination products will be made available.

17. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the red-line/strike-out version of the amendment.

Amendment 2 (11 JUN 2015)

The objective of this Protocol Amendment is to refine procedural language regarding pharmacokinetics (PK) and food effect, ophthalmologic examination frequency, ECG monitoring, and biopsy requirements.

1. **Synopsis; Section 5.1.1, Treatment Regimen; Section 7.7.1, Blood Sample Collection**

   Description of change: Per Protocol Amendment 1, subjects self-administer study drug without regard to meals except on days when PK is assessed. In Amendment 2, language was added to ensure that subjects administer study drug after a 2-hour fast and then fast for another hour after taking their dose of study drug. On days when PK samples will be collected, subjects will be asked to fast for 8 hours prior to taking study drug and then 1 hour after taking study drug.

   Rationale for change: Per FDA request. Standardized language has been added regarding meals with respect to study drug administration and overnight fasting prior to PK draws.

2. **Section 6, Study Assessments (Tables 4 and 6, Schedule of Assessments); Section 7.4.6, Comprehensive Eye Examination**

   Description of change: The timing for ophthalmologic testing during the treatment phase has been changed from every 4 cycles on Day 1 (± 14 days) to every 3 cycles (± 14 days) starting at Cycle 3 Day 1. Additional eye examinations are allowed when medically justified (eg, vision change).

   Rationale for change: The FDA requested more frequent ophthalmologic testing. The change from every 4 cycles to every 3 cycles shifts the testing from once every 12 weeks to once every 9 weeks (± 14 days).

3. **Section 6, Study Assessments (Tables 4 and 6, Schedule of Assessments); Section 7.4.5, Twelve-Lead Electrocardiogram**

   Description of change: The single 12-lead ECG was changed to a triplicate 12-lead ECG at each planned timepoint and will be matched as closely to the PK sampling time as possible.

   Rationale for change: The triplicate methodology is to maximize tracing quality and minimize intrasubject variability that may occur due to placement of electrodes, subject movement, etc.

4. **Synopsis; Section 1.5, Justification of Route, Dose Regimen, and Treatment Period; Section 2.2, Secondary Objectives; Section 4.1, Overall Study Design; Section 6, Study Assessments (Tables 4-7, Schedule of Assessments and Laboratory Assessments); Section 7.7.2, Food-Effect Study (Part 2 Only)**

   Description of change: A food-effect study will be performed on a subset of subjects (n = 8) enrolled into Part 2 of the study. On Cycle 2 Day 14, the subset of subjects will ingest a high-fat meal within 25 minutes, and study drug administration will begin 5 minutes after completion of the meal.

   Rationale for change: To study the impact of food on the PK of INCB054828.

5. **Synopsis; Section 6, Study Assessments (Tables 5 and 7, Laboratory Assessments); Section 7.7, Pharmacokinetic Assessments; Section 7.9.4, Distribution of Subject Reminder Cards**

   Description of change: Pharmacokinetic sampling times have been revised to refine the determination of the half-life of INCB054828. Serial sampling will be performed on Cycle 1 Day 1 and Day 14. One additional sample collection was added on Cycle 1 Day 16. Subjects will now have blood drawn on Days 1, 2, 8, 14, 15, and 16 in Cycle 1 only.

   Rationale for change: The purpose of the additional blood draws is to better characterize the PK profile for INCB054828.

6. **Synopsis; Section 3, Subject Eligibility; Section 4.1, Overall Study Design; Section 4.1, Number of Subjects; Section 7.4.8, Evaluation of FGF and FGFR Genetic Alterations**

   Description of change: Language has been added to clarify that for Part 2 (Dose Expansion), subjects will be allowed to enroll in the study based on sequencing data generated by the local institution in which they are being treated. However, all subjects will be evaluated via a central laboratory. Additional subjects may be enrolled if a subject has been enrolled based on a genetic alteration identified per a local assay, but it was not confirmed with the central laboratory assay. In addition, more subjects with tumor types other than what is defined in the Protocol will be allowed to participate in the expansion cohort, with medical monitor approval.

   Rationale for change: The purpose of this change is to minimize the number of potential screen failures. While it is understood that due to possible discordance between the local intuition's procedures and Foundation Medicine that there will still be a fair number of screen failures but pulling already sequenced subjects from each institution's database will increase the chance of eligible subjects being enrolled from the start. The addition of the cohort for subjects with FGFR/FGF alterations not fitting to one of the named tumor types will allow exploration of other tumor types with this alteration for potential future indications.

7. **Synopsis; Section 3.2, Subject Inclusion Criteria; Section 3.3, Subject Exclusion Criteria**

   Description of change: Modifications have been made to the inclusion/exclusion criteria: a) adjustments have been made to several laboratory parameter requirements for Part 1 and Part 2 (ie, hemoglobin, creatine clearance, total bilirubin); b) medical monitor approval is needed to enroll tumor types other than what is specified in the Protocol; c) subjects who require hemodialysis will be excluded from the study.

   Rationale for change: The purpose of these changes are to ensure that the inclusion and exclusion criteria are not too stringent as to restrict otherwise viable subjects, but also maintain proper guidance for the safe enrollment of the right subjects for this study. No signals have been seen in the study to date, nor have there been issues noted in other FGFRi trials or INCB54828 preclinical data.

8. **Synopsis; Section 1.5, Justification of Route, Dose Regimen and Treatment Period; Section 4.1.2, Part 2 Expansion; Section 4.4, Number of Subjects**

   Description of change: The number of sites participating in the study has increased to approximately 15 sites. The number of subjects participating in Part 2 (expansion) has increased to 50, which increases the total number of subjects to 90.

   Rationale for change: The integration of the central laboratory review of all subject tissue samples for FGFR alterations in Part 2 may result in discordance in results between a local laboratory (which will allow entry into the study) and the central laboratory (which will be confirmatory). This may result in different outcomes and may require replacement of subjects. As such, the number of subjects for Part 2 has been increased.

9. **Synopsis; Section 4.2.2, Secondary Endpoints**

   Description of change: Addition of $t_{½}$ to PK parameters being evaluated.

   Rationale for change: Due to intersubject variability, formal assessment of $t_{½}$ is needed to fully illustrate the PK profile of INCB54828.

10. **Section 6, Study Assessments (Tables 5 and 7, Laboratory Assessments, and Table 8, Laboratory Tests: Required Analytes for All Indications)**

    Description of change: A pregnancy test has been added at the end of treatment.

    Rationale for change: To ensure that the female subject has not become pregnant during the course of the study.

11. **Section 7.8, Pharmacodynamic Assessments (Table 12, Sample Collection Times for Pharmacodynamic Assessments)**

    Description of change: Adjustments have been made to the collection of samples. A timeframe range has now been provided as well as a shift from Day 15 to Day 14.

    Rationale for change: The purpose of the change is to align with the PK sampling schedule change.

12. **Section 7.5, Efficacy Assessments**

    Description of change: Efficacy assessments have been moved from Day 15 to Day 14 of each cycle.

    Rationale for change: The shift from Day 15 to Day 14 allows for alignment with the last day of study drug administration.

13. **Section 6.4.1, Safety Follow-Up**

    Description of change: Language has been added regarding the steps needed to complete a subject enrolled on this study if the subject is starting a new anticancer therapy.

    Rationale for change: Once a subject discontinues or completes the study and begins a new anticancer therapy, steps need to be completed to ensure that the full complement of data is collected for the study prior to the initiation of the new therapy.

14. **Section 5.7.2, Criteria and Procedures for Interruption (Table 2, Guidelines for Interruption and Restart of Study Drug)**

    Description of change: The guidelines for interruption have been refined (eg, Hy's Law).

    Rationale for change: The additional guidelines and parameters will ensure subject safety and provide clearer instructions for interrupting and discontinuing study drug.

15. **Section 5.10, Restricted Medications and Measures**

    Description of change: A sentence has been added to limit the use of proton pump inhibitors (PPIs) due to the possible impact of study drug PK profile.

    Rationale for change: The pH level of stomach may impact the dissolution of INCB54828; therefore, extensive use of PPIs might adverse effect the PK profile of study drug.

16. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the red-line/strike-out version of the amendment.

Amendment 1 (19 NOV 2014)

The objective of this Protocol Amendment is to address FDA's November 17, 2014, clinical deficiencies.

1. **Synopsis; Section 1.5, Justification of Route, Dose Regimen, and Treatment Period; Section 4.1.1, Part 1 Dose Escalation; Section 4.1.2, Part 2 Expansion (Figure 1: Study Design)**

   Description of change: The Protocol was updated to remove the duration of ≥ 1 week from the definition of hyperphosphatemia, such that once a subject develops hyperphosphatemia of any duration, in the accelerated titration portion of the study cohorts will be expanded to at least 3 subjects and subsequent dose escalations will be limited to 50%.

   Rationale for change: Required by FDA.

2. **Synopsis; Section 3.3, Subject Exclusion Criteria**

   Description of change: Exclusion criteria for subjects to be enrolled in Part 2 was updated to exclude subjects with a creatinine clearance ≤ 70 mL/min and also exclude subjects with serum calcium, serum phosphorus, and parathyroid hormone values outside of the institutional normal range. The creatinine clearance criterion in Part 1 was updated to be ≤ 70 mL/min rather than < 70 mL/min to be in alignment with the Part 2 exclusion criterion.

   Rationale for change: Required by FDA.

3. **Section 1.5, Justification of Route, Dose Regimen, and Treatment Period; Section 5.7.2, Criteria and Procedures for Interruption (Table 2: Guidelines for Interruption and Restart of Study Drug); Section 5.7.3, Management of Hyperphosphatemia (Table 3: Recommended Approach for Hyperphosphatemia Management); Section 6, Study Assessments (Table 5: Laboratory Assessments, and Table 7: Laboratory Assessments [Multiple Myeloma]); Section 7.4.7, Laboratory Assessments**

   Description of change: Protocol was updated to monitor calcium and phosphorus levels at least twice weekly in subjects who have abnormal levels on-study.

   Rationale for change: Required by FDA.

4. **Section 3.1, Study Population**

   Description of change: Added clarification to state that in addition to progressing on at least 1 line of therapy, subjects should have no further effective standard anticancer therapy available to be consistent with wording elsewhere in the Protocol.

   Rationale for change: Required by FDA.

5. **Section 5.6, Dose-Limiting Toxicity and Determination of Maximum Tolerated Dose (Table 1: Definition of Dose-Limiting Toxicity and Maximum Tolerated Dose)**

   Description of change: Added Grade 3 thrombocytopenia with bleeding as a dose-limiting toxicity. Also, to be consistent with wording elsewhere in the Protocol, added a note in this table stating that transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms based on investigator determination will not be considered a dose-limiting toxicity.

   Rationale for change: Required by FDA.

6. **Section 5.7.4, Criteria for Permanent Discontinuation of Study Drug**

   Description of change: New criteria were added to require discontinuation of study drug upon evidence of disease progression or a concurrent elevation of ALT > 3 × ULN and total bilirubin > 2 × ULN in subjects who do not have evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevations.

   Rationale for change: Required by FDA.

7. **Section 5.11, Prohibited Medications and Measures**

   Description of change: Calcium-based phosphate-binding medications were added to the prohibited medication list.

   Rationale for change: Required by FDA.

8. **Section 6, Study Assessments (Table 4: Schedule of Assessments, and Table 6: Schedule of Assessments [Multiple Myeloma]); Section 7.2, Interactive Response Technology Procedure**

   Description of change: An additional procedure was added to the study assessments tables to require sites to contact the IRT system. Associated language was also added in Section 7.2.

   Rationale for change: The Protocol was updated to include the use of IRT for the management of study drug supply.

9. **Section 6, Study Assessments (Table 4: Schedule of Assessments, and Table 6: Schedule of Assessments [Multiple Myeloma])**

   Description of change: Comprehensive physical examinations were added at Cycle 2 Day 1 and Day 1 of subsequent cycles.

   Rationale for change: Required by FDA.

10. **Section 6, Study Assessments (Table 4: Schedule of Assessments, footnote m); Section 6.4.2, Disease Status Follow-up**

    Description of change: Added clarification to state that the relevant disease response assessment should be performed in subjects who discontinue study treatment for a reason other than disease progression in the disease status follow-up phase.

    Rationale for change: Clarification was needed to specify that the relevant disease response assessment should be used to continue to monitor disease status.