Official Title: A Phase 1/2 Dose Finding Study of Poziotinib in Japanese Patients With Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

NCT Number: NCT04402008

Document Date: Protocol Amendment 2: 04 March 2020

CONFIDENTIAL

CLINICAL STUDY PROTOCOL

TITLE PAGE

Study Title:	**A Phase 1/2 Dose Finding Study of Poziotinib in Japanese Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)**
Study Number:	**SPI-POZ-104**
Study Phase:	Phase 1/2
Study Drug:	Poziotinib
IND Number:	135,719
Sponsor:	Spectrum Pharmaceuticals, Inc. Research and Development Office 157 Technology Drive Irvine, CA 92618 USA
In-Country Caretaker for Clinical trial (ICCC)	IQVIA Services Japan K.K. 4-10-18 Takanawa, Minato-ku, Tokyo, 108-0074, Japan
Protocol Version/Date:	Amendment 2/04 Mar 2020

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312, ICH guidelines, MHLW Article 14, Paragraph 3 and Article 80-2 of the "Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices", and MHLW "Ministerial Ordinance on GCP for Drugs"), applicable government regulations and applicable Institutional research policies and procedures.

INVESTIGATOR SIGNATURE

Protocol Number: SPI-POZ-104

A Phase 1/2 Dose Finding Study of Poziotinib in Japanese Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

I have read this protocol and agree that it contains all the necessary details for performing the study in accordance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP).

I will provide copies of the protocol and of the clinical and preclinical information on the investigational drug, which was furnished to me by the Sponsor (Spectrum Pharmaceuticals, Inc.), to all members of the study team responsible to me who participate in the conduct of this study. I will discuss this material with them to assure that they are fully informed regarding the investigational drug and the conduct of the study.

I will perform the study according to the specifications outlined in this protocol and agree to implement protocol requirements only after the protocol and patient information/Informed Consent form have been approved by the Institutional Review Board/Ethics Committee (IRB/EC). I will submit any protocol modifications (amendments) and/or any Informed Consent form modifications to the IRB/EC, and approval from the IRB/EC will be obtained before any modifications are implemented.

I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of this study will be released without prior written consent from Spectrum Pharmaceuticals, Inc., unless this requirement is superseded by the applicable territory's regulatory authority (e.g., PMDA).

_____

Principal Investigator Name (PLEASE PRINT):

Signature: _____ Date _____

SYNOPSIS

Title of Study: A Phase 1/2 Dose Finding Study of Poziotinib in Japanese Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

Name of Sponsor: Spectrum Pharmaceuticals, Inc.

Name of Investigational Product: Poziotinib

Study Centers: Approximately 20 study centers in Japan

Duration of Study: Approximately 3 years

Planned Number of Patients:	**Clinical Phase:** 1/2
Phase 1 – Dose-Finding: Approximately 36 patients **Phase 2 - Efficacy:** 40 patients (20 patients per cohort)	

Objectives:

To evaluate the following in NSCLC patients treated with poziotinib:

Primary Objective

- **Phase 1: Dose-Finding - Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD)**
- **Phase 2: Efficacy - Objective Response Rate (ORR)**

Secondary Objectives

- **Phase 1: Dose-Finding**
  - **Pharmacokinetics of poziotinib and M1 and M2 metabolites**
  - **Safety and Tolerability**
- **Phase 2: Efficacy**
  - **Disease Control Rate (DCR)**
  - **Duration of Response (DoR)**
  - **Progression-Free Survival (PFS)**
  - **Pharmacokinetics of poziotinib and M1 and M2 metabolites**
  - **Safety and Tolerability**

Exploratory Objective

- **Overall Survival**

Duration of Study:

It is estimated that the first patient will be enrolled in June 2020 and the last patient visit will occur approximately March 2025. The duration of study participation for each patient, in general, includes the following segments:

- **Screening Period:** up to 30 days
- **Treatment Period:** 28 days per cycle for up to 24 months of treatment or until disease progression, death, intolerable adverse events (AEs), or other protocol-specified reason for patient withdrawal
- **Safety Follow-up Visit:** 35 (±5) days after the last dose of poziotinib
- **Long-Term Follow-up:** After study drug discontinuation, patients who have consented will be contacted every 3 months, for up to 2 years after patient's first dose of poziotinib, for survival assessment

Study Design and Treatment Plan:

This is a Phase 1/2, open-label, multicenter dose finding study to determine the MTD/MAD of poziotinib when administered once daily (QD) or twice daily (BID) to Japanese participants with locally advanced or metastatic NSCLC.

Phase 1: Dose-Finding and Safety

Phase 1 is a dose finding study with two parallel, randomized dose groups. Each group will undergo dose-finding scheme using a 3+3 design with the assessment of dose-limiting toxicities (DLTs) at up to three dose levels. Patients will be hospitalized for the first 2 weeks of Cycle 1.

- **Group 1 (once daily dosing [QD]):** Starting dose of 8 mg.
- **Group 2 (twice daily dosing [BID]):** Starting dose of 4 mg BID.

The DLT assessment will be conducted in Cycle 1 of the Phase 1 of the study. Poziotinib dose-finding will proceed based on the occurrence of DLTs during Cycle 1. Although DLTs will be evaluated based on the list of criteria specified below, toxicity related to the onset of any unexpected adverse events will be evaluated as well in addition to the DLTs. The MTD or MAD will be determined in each group independently. The DLTs for MTD/MAD will be assessed by the Medical Monitor in consultation with the site Principal Investigator. In addition to the defined DLTs, dose advancement/MTD will be decided based on all safety information, including adverse events that the subject experiences that are not defined as DLTs. A DLT will be any of the following treatment-related adverse events that occur during Cycle 1, despite optimal medical supportive therapy:

Non-Hematological Toxicity:

- Grade 3 or higher toxicity based on NCI-CTCAE (version 5.0), except for alopecia
- Grade 3 or higher nausea and vomiting, despite treatment with oral anti-emetics at the highest dose
- Grade 3 or higher diarrhea, despite diarrhea treatment at the highest dose

Hematological Toxicity:

- Grade 4 or higher neutropenia (ANC$<0.5\times10^9$/L) sustained for 7 days or more
- Febrile neutropenia (ANC$<1.0\times10^9$/L with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour)
- Neutropenic infection: Grade 3 or higher infection accompanying Grade 4 neutropenia (ANC$<0.5\times10^9$/L) (requiring IV antibiotic, antifungal or antiviral agent administration/ requiring radiation or surgical therapy)
- Grade 4 thrombocytopenia (PLT<25,000/mm^3) or any grade thrombocytopenia requiring platelet transfusion

However, in case of ANC$<0.5\times10^9$/L, conduct a repeat test on at least the 7th day in order to verify if it is lasted for 7 days or more.

Because Phase 1 is for DLT assessment and dose finding, poziotinib dose modifications are not permitted during Cycle 1 in Phase 1. Dose modifications are permitted beginning with Cycle 2 based on Sponsor recommendations.

Phase 2: Efficacy

Once the MTD/MAD is determined, 40 additional NSCLC patients with EGFR (20 patients) or HER2 (20 patients) exon 20 insertion mutations (including duplication mutations) will be enrolled to evaluate the efficacy of poziotinib at the dose and dosing regimen determined in Phase 1. The choice of QD or BID for Phase 2 will be determined by the sponsor and the treatment regimen is selected by the Sponsor, Dose modifications are permitted based on Sponsor recommendations and notification of the Medical Monitor.

During each 28-day cycle, patients who are eligible for participation will receive poziotinib at the assigned dose, orally, QD or BID, depending on the dose identified in Phase 1, continuously. All patients will be treated for up to 24 months or until disease progression, death, intolerable adverse events (AEs), other protocol-specified reasons for patient withdrawal.

Patient Replacement Strategy: Patients in Phase 1 who discontinue from the study before completing Cycle 1 treatment for reasons other than DLTs will be replaced.

Inclusion & Exclusion Criteria:

Inclusion Criteria:

1. Patient is at least 20 years of age
2. Patient must be willing and capable of giving written Informed Consent, adhering to dosing and visit schedules, and meeting all study requirements
3. **Phase 2:** If an archival tissue sample is not available, a tumor biopsy will be required.
4. Previously treated patient with histologically or cytologically confirmed (archival tissue accepted) locally advanced or metastatic non-small cell lung cancer (NSCLC) and is not a candidate for definitive therapy
   - **Phase 1**: No test for mutational status is required
   - **Phase 2**: Documented EGFR or HER2 exon 20 insertion mutation (including duplication mutations) in NSCLC patients. Patients will be enrolled based on documentation of mutational status using PCR or a validated next generation sequencing detection analysis test.
     - Documented *EGFR* exon 20 insertion mutation, including D770_N771insSVD, D770_N771insNPG, V769_D770insASV, H773_V774insNPH, or any other *EGFR* exon 20 in-frame insertion mutation (including duplications).
     - Documented *HER2* exon 20 insertion mutation, including A775_G776insYVMA, G776_V777insVC, or P780_Y781insGSP, or any other *HER2* exon 20 in-frame insertion mutation (including duplications).
5. Patient has measurable NSCLC disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Metastatic lesions in bone, CNS, or in brain cannot be used for target lesions.
6. Prior treatment status:
   - **Phase 1:** Patient with refractory NSCLC to available standard therapies
   - **Phase 2**: Progression after at least one systemic therapy for locally advanced or metastatic disease
7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
8. Patient has recovered from prior systemic therapy for metastatic disease to Grade ≤1 for non-hematologic toxicities (except for Grade ≤2 peripheral neuropathy) and has adequate hematologic, hepatic, and renal function at Baseline, as defined by:
   - Leukocytes $\geq 3.0 \times 10^9$/L
   - Absolute neutrophil count (ANC) must be $\geq 1.5 \times 10^9$/L
   - Platelet count $\geq 100 \times 10^9$/L
   - Hemoglobin ≥9.0 g/dL
   - Total bilirubin ≤2 mg/dL; if hepatic metastases are present, ≤2.5×ULN
   - SGOT (AST) and SGPT (ALT) ≤2.5×ULN with the following exception; Patients with liver metastases AST, ALT ≤5×ULN
9. Patient is willing to practice 2 forms of contraception, one of which must be a barrier method. Female patients of childbearing potential must use an effective method of birth control (e.g., oral contraceptive, intrauterine device, bilateral tubal ligation/occlusion, condoms, diaphragm, not engaging in sexual intercourse) during treatment period and 3 months thereafter. Males must use an effective method of birth control (e.g., condoms, vasectomy, or not engaging in sexual intercourse) during treatment period and 3 months thereafter.
10. Females of childbearing potential must have a negative pregnancy test within 7 days prior to Cycle 1, Day 1. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) with no other medical reasons or who are surgically sterilized do not require this test.

Exclusion Criteria:

1. **Phase 2:** Patient has EGFR T790M mutation or any other acquired EGFR exon 20 point mutation
2. **Phase 2 Only:** Patient has had previous treatment with poziotinib. The currently approved TKIs that are not considered to be exon 20 insertion-selective are permissible.
3. Patient is concurrently receiving chemotherapy, biologics, immunotherapy for cancer treatment; systemic anti-cancer treatment or investigational treatment should not be used within 2 weeks prior to Cycle 1, Day 1; local radiation therapy for bone pain may be allowed.
4. Patient has used strong inhibitors/inducers of CYP3A4 and CYP2D6 within 1 month prior to Cycle 1, Day 1.
5. Patient has brain metastases and is clinically symptomatic, requires high dose or increasing doses of systemic corticosteroids, or needs any anticonvulsant therapy for metastatic brain disease.
6. Patient has a high risk for or history of congestive heart failure (CHF) Class III/IV according to the New York Heart Association (NYHA) Functional Classification or serious cardiac arrhythmias requiring treatment. Cardiac ejection fraction <50% as determined by either echocardiogram (ECHO) or multi-gated acquisition (MUGA) during Screening.
7. Patient has had another primary malignancy within 3 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ
8. Patient is confirmed to have clinically significant or recent acute gastrointestinal disease presenting as diarrhea and/or coloenteritis as a main symptom (ie, acute enteritis, malabsorption, or Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) Grade 2 or above diarrhea due to other etiologies
9. Patient has an active Grade ≥2 skin disorder, rash, mucositis, or skin infection that needs medication or therapy or existing Grade ≥2 skin toxicity from previous therapies; Grade >2 neuropathy, Grade ≥2 pneumonitis.
10. Patient is unable to take drugs orally due to disorders or diseases that may affect gastrointestinal function, such as inflammatory bowel diseases (eg, Crohn's disease, ulcerative colitis) or malabsorption syndrome, or procedures that may affect gastrointestinal function, such as gastrectomy, enterectomy, or colectomy
11. Patient has an active liver disease or biliary tract disease (except for Gilbert's disease, asymptomatic biliary stones, liver metastasis, or stabilized chronic liver diseases). Patient has active HBV or HCV infection.
12. Patient is HIV antibody positive.
13. Patient currently has or has had interstitial lung disease in the past.
14. Patient has known hypersensitivity to poziotinib or has a history of allergic reactions attributed to chemically similar compounds or other tyrosine kinase inhibitors (TKIs)
15. Patient has an active uncontrolled infection, underlying medical condition, or other serious illness that would not be appropriate for this study
16. Patient has unstable, uncontrolled, active bleeding disorders that the investigator considers that the patient could be at increased risk or not be suitable for treatment in this study
17. Patient is pregnant.
18. Women who are breastfeeding or women who are not willing to stop breastfeeding during study treatment period and for 30 days after the last dose of study drug.

Investigational Product, Dose, and Route of Administration:

Poziotinib is supplied as 8-mg tablets and 2-mg tablets. Poziotinib should be taken orally with food and a glass of water (approximately 240 mL) at approximately the same time(s) each day.

Once a Day Dosing:

- **Phase 1, Days 1 to 14:** Patients will be administered poziotinib every 24 (±1) hours.
- **Phase 1 post-Hospitalization and Phase 2:** If the daily dose is missed, this dose may be administered any time during the day, but at least 8 hours prior to the next scheduled dose.

Twice a Day Dosing:

- **Phase 1, Days 1 to 14:** Patients will be administered poziotinib every 12 hours (±30 minutes)
- **Phase 1 post-Hospitalization and Phase 2:** The first dose should be taken in the morning and the second dose should be taken approximately 8 to 12 hours later. If a dose is missed, and there is less than 8 hours before the next scheduled dose, the dose should be skipped and the next dose taken as scheduled.

Reference Therapy, Dose, and Route of Administration: None

Efficacy Assessments:

Clinical staging will be performed at Baseline, with follow-up at 4 weeks, 8 weeks, and every 8 weeks thereafter. Efficacy will be based on the radiologic assessment by the site's Principal Investigator using RECIST 1.1 criteria.

Primary Endpoint:

- **Phase 1: Dose-Finding: MTD or MAD**
- **Phase 2: Efficacy: Objective Response Rate** (**ORR,** complete response+partial response)

Secondary Endpoints:

- **Phase 1: Dose-Finding**
  - **Pharmacokinetics of poziotinib and M1 and M2 metabolites**
  - **Safety and Tolerability**
- **Phase 2: Efficacy**
  - **Disease Control Rate** (**DCR,** complete response+partial response+stable disease)
  - **Duration of Response (DoR)**
  - **Progression-Free Survival (PFS)**
  - **Safety and Tolerability**

Exploratory Endpoint:

- **Overall Survival**

Pharmacokinetic Assessments: The pharmacokinetics of poziotinib and the M1 and M2 metabolites will be characterized.

Phase 1 - Dose-Finding and Safety: On Cycle 1, Day 1 and Cycle 1, Day 13, all patients will have intensive PK blood samples drawn predose and 30 minutes, 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose. In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea, pneumonitis), PK blood samples will be collected as soon as possible following the onset of the AE and the time of the last dose and the time of blood draw should be recorded .

Phase 2 - Efficacy: All patients will have blood samples drawn predose and at 1 hour and 2 hours postdose on Cycle 1, Day 1 and Cycle 2, Day 1 for sparse PK sampling and time-matched concentration-ECG analysis. Blood samples will also be collected at each imaging session in order to correlate poziotinib concentrations with circulating tumor DNA (ctDNA) and efficacy; the time of the last dose and the time of blood draw should be recorded.

In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea, pneumonitis), a blood sample will be collected as soon as possible following the onset of the AE, and the time of the last dose and the time of blood draw should be recorded.

Safety Assessments:

Safety will be assessed by reported/elicited adverse events (AEs), laboratory assessments including hematology and biochemistry, vital signs, physical examination, and neurological examination. The assessment of treatment-emergent AEs (TEAEs) includes SAEs, AEs leading to study drug discontinuation, and AEs related to the study drug. The grade of TEAEs will be assessed based on CTCAE, version 5.0.

Adverse Event and Serious Adverse Event Reporting:

Adverse events will be recorded from the first dose of study drug administration until 35 (±5) days after the last dose of study drug is administered. From the time Informed Consent is signed to the first dose of study drug administration, all serious adverse events (SAEs) will be reported. In addition, SAEs that occur after 35 (±5) days after the last dose of study treatment where a causal relationship with the study drug is suspected will also be recorded.

Statistical Methods:

Sample Size Justification:

The total sample size for this study is approximately 76 patients. Phase 1 is a dose finding study using "3+3" design to determine the MTD/MAD in each dosing group (QD or BID). Up to 18 patients (up to 3 dose levels, up to 6 patients each level) will be included for DLT evaluation in each dosing group for a total of 36 patients in Phase 1. Patients who discontinue from the study before completing Cycle 1 treatment for reasons other than DLTs are not qualified for DLT evaluation and will be replaced.

A total of 40 patients (20 patients each in EGFR and HER2 mutation cohorts) will be enrolled in the dose confirmatory group in Phase 2 to confirm the activity in the identified poziotinib dose and schedule. The sample size of 20 patients in each mutation cohort in Phase 2 will provide a width for 95% confidence interval of 0.424 for the expected ORR of 30%.

Efficacy Analysis:

The primary efficacy variable ORR will be analyzed descriptively along with the 95% CI for each cohort. The determination of the ORR will be based upon radiographic assessment by the site's Principal Investigator using RECIST Version 1.1. The secondary outcomes, DCR, DoR, and PFS, will be analyzed using descriptive statistics, for each cohort, and with 95% CI for DCR and Kaplan-Meier plot for DoR and PFS.

Analysis Populations:

The following analysis populations have been defined for each cohort:

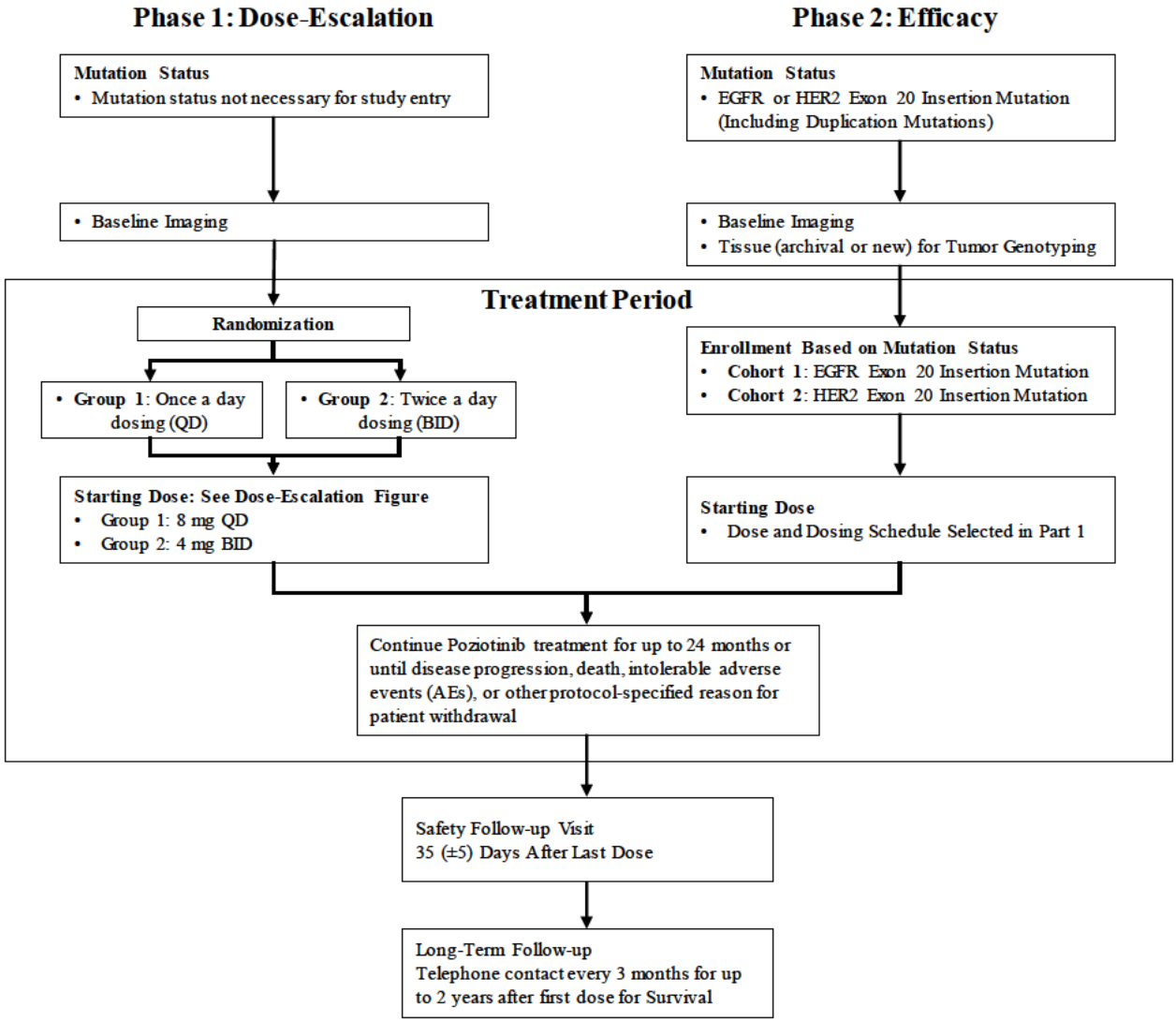
- The **Evaluable Population** consists of all patients in Phase 2 who are enrolled, complete at least 1 cycle of poziotinib treatment, and are evaluable for tumor response based on RECIST, Version 1.1 criteria. The efficacy data will be analyzed using the Evaluable Population.
- The **Safety Analysis Population** includes all patients who signed Informed Consent, enrolled, and received at least 1 dose of poziotinib. All demographics, Baseline characteristics, and safety data will be analyzed using the Safety Analysis Population.

Safety and Tolerability:

The following variables will be summarized and analyzed descriptively for each cohort: number of completed cycles; number and percentages of patients with TEAEs, SAEs, TEAEs leading to study drug discontinuation, TEAEs related to the study drug; and the severity of TEAEs based on the grading by CTCAE, Version 5.0.

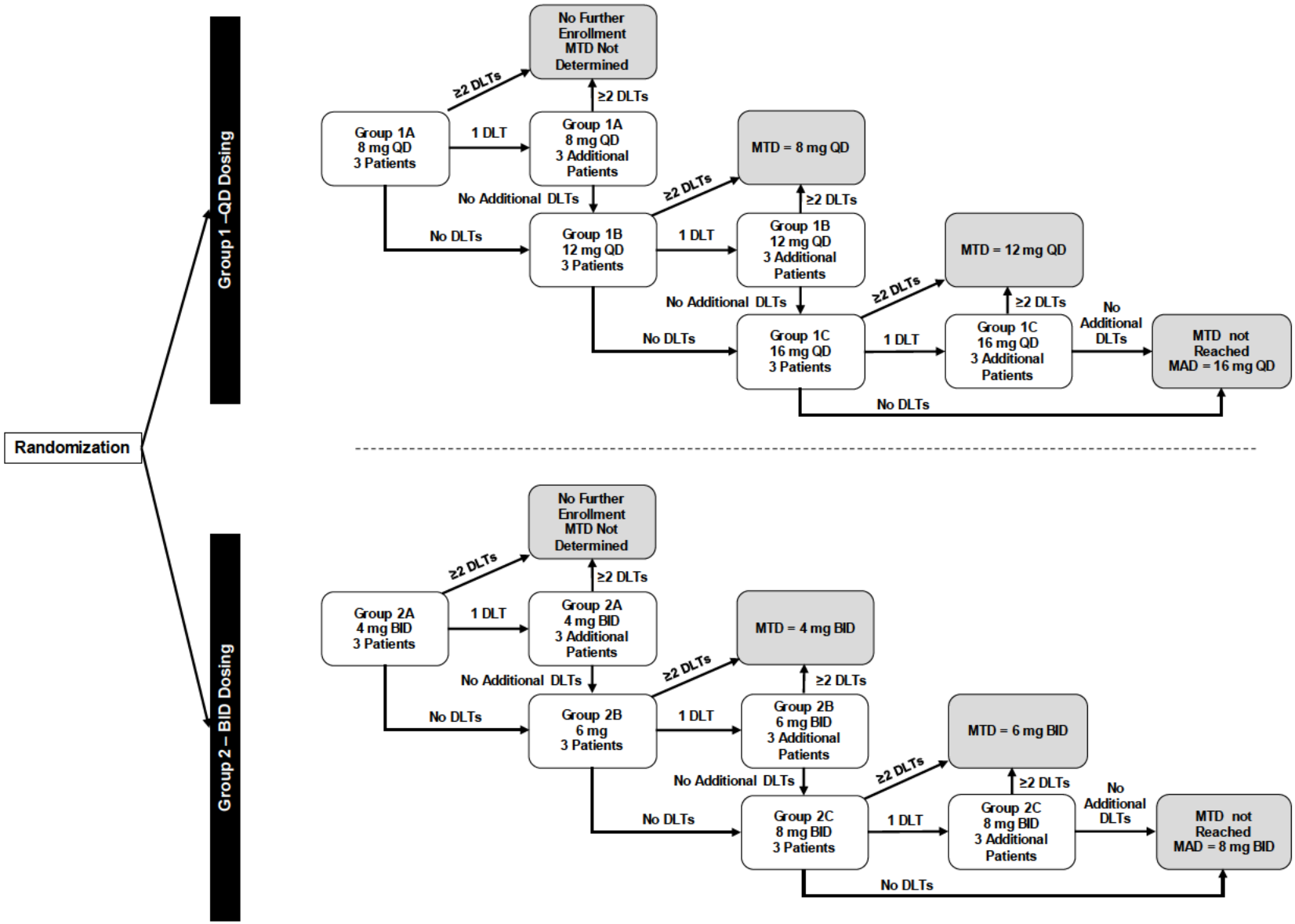
Protocol Version/Date: Amendment 2/04 Mar 2020

Study Design Diagram



Note: Phase 2 will start once the dose and dosing schedule have been determined in Phase 1.

Dose-Finding Diagram



PHASE 1 SCHEDULE OF ASSESSMENTS AND PROCEDURES

Phase 1 Assessment	Screening	Treatment Period [a] (Each Cycle=28 [±3] Days)							Safety Follow-up /End-of-Study Visit	Long-Term Follow-up
		Cycle 1					Cycle 2+			
	Day -30 to Day-1	Day				Day (±2 days)			35 (±5) Days After Last Dose	Every 3 months After Discontinuation
		1	7	13	14	22	1	15		
		Hospitalization								
Informed Consent	x									
Relevant Medical History	x									
Demographic Data	x									
Height and Weight [b]	x	x					x		x	
Physical Examination [c]	x	x	x		x		x		x	
Vital signs [d]	x	x	x		x		x		x	
Resting O_2 Saturation [e]	x	Daily					x		x	
Pulmonary Function [f]	x	x	x		x		x		x	
ECOG Performance Status [g]	x	x	x		x		x		x	
Pregnancy Test [h]	x	x					x		x	
Hepatitis B Surface Antigen Test [i]	x									
Hepatitis B Core Antibody Test [i]	x									
Hepatitis B Surface Antibody Test [i]	x									
Hepatitis C Antibody Test [j]	x									
HIV Antibody Test [k]	x									
Tumor Assessment [l]	x						x		x	
Whole Blood (metabolic profile) [,m]	x									
CBC with 5-part differential and platelets [n]	x	x	x		x		x		x	
Serum Chemistry, including KL-6 and C-reactive protein [o]	x	x	x		x		x		x	
Electrocardiogram [p]	x	x	x		x		x[p]		x	
Echocardiogram or MUGA Scan [q]	x									
PK Blood Samples [r]		x		x						
Dispense Poziotinib [s]		Daily					x			
Dispense Supportive Care Medications, as needed		Daily					x			
Adverse Event Assessment [t]	x	Daily					x		x	
Concomitant Medications	x	x	x		x		x		x	
Patient Diary Dispensed/Collected					x		x		x	

Phase 1 Assessment	Screening	Treatment Period [a] (Each Cycle=28 [±3] Days)							Safety Follow-up /End-of-Study Visit	Long-Term Follow-up
		Cycle 1						Cycle 2+		
	Day -30 to Day-1	Day				Day (±2 days)			35 (±5) Days After Last Dose	Every 3 months After Discontinuation
		1	7	13	14	22	1	15		
		Hospitalization								
Telephone Contact [u]						x		x		x

a) Patients must visit the site at the beginning of each cycle.
b) Height only needs to be recorded during the Screening Visit.
c) A complete physical examination, including auscultation, is required at Screening, Day 1 of each cycle, and at the Safety Follow-up Visit. Symptom-directed exams are required at other visits. In addition, a physical examination will be done on Days 7 and 14 of Cycle 1, while the patient is in the hospital.
d) Vital signs will be measured at Screening, on Day 1 of each cycle, and at the Safety Follow-up Visit. In addition, vital signs will be measured on Days 7 and 14 of Cycle 1 while the patient is in the hospital.
e) Resting O_2 saturation will be assessed daily for the first 2 weeks of Cycle 1, while the patient is hospitalized, on Day 1 of each subsequent cycle, and at the Safety Follow-up Visit.
f) Routine monitoring for evidence of interstitial lung disease (ILD) will be done at Screening, on Day 1 of Cycles 1-3, every 8 weeks thereafter, and at the Safety Follow-up Visit. In addition, evidence of ILD will be assessed on Cycle 1, Days 7 and 14 while the patient is in the hospital.
g) The patient's ECOG score will be evaluated at Screening, on Day 1 of each cycle, and at the Safety Follow-up Visit. In addition, the ECOG will be evaluated on Days 7 and 14 of Cycle 1, while the patient is in the hospital.
h) A urine or plasma pregnancy test (β-hCG), in women of child-bearing potential, is required at Screening, Day 1 of each cycle, and at the Safety Follow-up. A urine sample is only needed if a urine pregnancy test is done.
i) Tests will be for hepatitis B surface antigens and hepatitis B core and surface antibodies. If the hepatitis B surface antigen test is positive, the patient will be excluded from the study. If only the hepatitis B core antibody and/or hepatitis B surface antibody are positive, a serum hepatitis HBV DNA test will be done. If this test is positive the patient will be excluded from the study.
j) If the hepatitis C antibody test is positive, an HCV RNA test will be done. If this test is positive the patient will be excluded from the study.
k) Whole blood samples will be used for the HIV test. If this test is positive, the patient will be excluded from the study.
l) Screening tumor assessment within 28 days prior to Cycle 1, Day1 and additional assessments will be made at 4 weeks (Cycle 2, Day 1 [up to Cycle 2, Day 10]), at 8 weeks (Cycle 3, Day 1 [up to Cycle 3, Day 10, with at least 28 days from previous tumor assessment]), and then every 8 weeks (±10 days) thereafter for up to 24 months, or until disease progression, death, intolerable adverse events (AEs), or other protocol-specified reason for patient withdrawal. Assessment is also done at Safety Follow-up Visit unless the patient has documented disease progression or has undergone a tumor assessment within 8 weeks of the Safety Follow-up Visit.
m) Whole blood samples (4 mL) will be drawn at Screening for CYP2D6 metabolic profile testing.
n) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained at Screening, within 7 days prior to Day 1 of each cycle, at which time, platelet count must be $\geq 100\times10^9$/L and ANC must be $\geq 1.5\times10^9$/L before dispensing poziotinib for the next cycle of treatment, and at the Safety Follow-up Visit. In addition, CBC will be done on Days 7 and 14 of Cycle 1, while the patient is in the hospital. If the Screening Visit is within 14 days of Cycle 1 Day 1, the Baseline CBC is not required.
o) Blood for chemistry, including KL-6 and C-reactive protein, is to be collected at Screening, within 7 days prior to poziotinib administration on Day 1 of each cycle, and at the Safety Follow-up Visit; measurement of KL-6 is not required on Cycle 1, Day 1 if it was already measured during Screening. In addition, blood chemistry will be done on Days 7 and 14 of Cycle 1, while the patient is in the hospital. If the Screening Visit is within 14 days of Cycle 1, Day 1, the Baseline serum chemistry panel is not required
p) ECGs will be performed at Screening, predose and at 1 and 2 hours (±15 min) postdose on Cycle 1, Day 1 and Cycle 2, Day 1 as indicated for time-matched concentration-ECG analysis, and at end of study. In addition, for Phase 1 patients, ECGs will be done on Days 7 and 14 of Cycle 1, while the patient is in the hospital. ECGs are not required on Day 1 of other cycles.
q) Cardiac ejection fraction will be evaluated using echocardiogram or multi-gated acquisition (MUGA) scan at Screening. The Investigator can order subsequent tests based on patient standard of care.

r) On Cycle 1, Day 1 and Cycle 1, Day 13, patients will have intensive pharmacokinetic (PK) samples drawn (4 mL whole blood at each time point) predose and 30 minutes, 1 and 2 (±15 minutes) postdose, and 3, 4, 6, 8, 12, 14 (±30 minutes) postdose, and 24 hours (±1 hour) postdose. In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea, pneumonitis), blood samples will be collected as soon as possible following the onset of the AE and the time of the last dose and the time of blood draw should be recorded

s) Poziotinib will be dispensed on Day 1 of each cycle. Poziotinib should be taken with food and a glass of water (approximately 240 mL) at approximately the same time(s) each day.

t) During the Screening Period, only SAEs will be recorded . All AEs will be collected from Cycle 1, Day 1 through the Safety Follow-up Visit. Patients will be hospitalized during the first 2 weeks of the study and will be monitored for safety assessments including AEs, vital signs, ECGs on Day 7 and Day 14 of Cycle 1. Adverse events will be assessed daily while hospitalized.

u) Telephone contact for AE and concomitant medication assessment on Cycle 1, Day 22 (±2 days), weekly during Cycle 2 and then Day 15 (±2 days) in subsequent cycles. During the long-term follow-up patients will be contacted every 3 months to assess survival.

PHASE 2 SCHEDULE OF ASSESSMENTS AND PROCEDURES

Phase 2 Assessment	Screening	Treatment Period[a] (Each Cycle=28 [±3] Days)						Safety Follow-up /End-of-Study Visit	Long-Term Follow-up
		Cycle 1				Cycle 2+			
	Day -30 to Day-1	Day 1	Day (±2 days)					35 (±5) Days After Last Dose	Every 3 months After Discontinuation
			8	15	22	1	15		
Informed Consent	x								
Relevant Medical History	x								
Demographic Data	x								
Height and Weight [b]	x	x				x		x	
Physical Examination [c]	x	x	x	x		x		x	
Vital signs [d]	x	x	x	x		x		x	
Resting O_2 Saturation [e]	x	x	x	x		x		x	
Pulmonary Function [f]	x	x	x	x		x		x	
ECOG Performance Status [g]	x	x	x	x		x		x	
Pregnancy Test [h]	x	x				x		x	
Hepatitis B Surface Antigen Test [i]	x								
Hepatitis B Core Antibody Test [i]	x								
Hepatitis B Surface Antibody Test [i]	x								
Hepatitis C Antibody Test [j]	x								
HIV Antibody Test [k]	x								
Tumor Assessment [l]	x	X				X		X	
Tissue Samples [m]	x							x	
Whole Blood (metabolic profile) [n]	x								
Whole Blood (plasma ctDNA) [o]	x					x		x	
CBC with 5-part differential and platelets [p]	x	x				x		x	
Serum Chemistry, including KL-6 and C-reactive protein [q]	x	x				x		x	
Electrocardiogram [r]	x	x				x		x	
Echocardiogram or MUGA Scan[s]	x								
PK Blood Samples [t]		x				x			
Dispense Poziotinib [u]		x				x			
Dispense Supportive Care Medications, as needed		x	x	x					
Adverse Event Assessment [v]	x	x	x	x		x		x	
Concomitant Medications [w]	x	x	x	x		x		x	

Phase 2 Assessment	Screening	Treatment Period[a] (Each Cycle=28 [±3] Days)						Safety Follow-up /End-of-Study Visit	Long-Term Follow-up
		Cycle 1				Cycle 2+			
	Day -30 to Day-1	Day 1	Day (±2 days)					35 (±5) Days After Last Dose	Every 3 months After Discontinuation
			8	15	22	1	15		
Patient Diary Dispensed/Collected		x				x		x	
Telephone Contact [x]					x		x		x

a) Patients must visit the site at the beginning of each cycle.
b) Height only needs to be recorded during the Screening Visit.
c) A complete physical examination, including auscultation, is required at Screening, Cycle 1, Days 1, 8, and 15, Day 1 of each subsequent cycle, and at the Safety Follow-up Visit. Symptom-directed exams are required at other visits.
d) Vital signs will be measured at Screening, Cycle 1, Days 1, 8, and 15, Day 1 of each subsequent cycle, and at the Safety Follow-up Visit.
e) Resting O_2 saturation and will be assessed at Screening, Cycle 1, Days 1, 8, and 15, Day 1 of each subsequent cycle, and at the Safety Follow-up Visit.
f) Routine monitoring for evidence of interstitial lung disease (ILD) will be done at Screening, on Day of Cycles 1-3, every 8 weeks thereafter, and at the Safety Follow up Visit. In addition, it will be assessed on Days 8 and 15 of Cycle 1.
g) The patient's ECOG score will be evaluated at Screening, Cycle 1, Days 1, 8, and 15, Day 1 of each subsequent cycle, and at the Safety Follow-up Visit.
h) A urine or plasma pregnancy test (β-hCG), in women of child-bearing potential, is required at Screening, Day 1 of each cycle, and at the Safety Follow-up. A urine sample is only needed if a urine pregnancy test is done.
i) Tests will be for hepatitis B surface antigens and hepatitis B core and surface antibodies. If the hepatitis B surface antigen test is positive, the patient will be excluded from the study. If only the hepatitis B core antibody and/or hepatitis B surface antibody are positive, a serum hepatitis HBV DNA test will be done. If this test is positive the patient will be excluded from the study.
j) If the hepatitis C antibody test is positive, an HCV RNA test will be done. If this test is positive the patient will be excluded from the study.
k) Whole blood samples will be used for the HIV test. If this test is positive, the patient will be excluded from the study.
l) The Screening/Baseline tumor assessment will be performed within 28 days prior to, or on Cycle 1, Day 1, and additional assessments will be made at 4 weeks (Cycle 2, Day 1 [up to Cycle 2, Day 10]), at 8 weeks (Cycle 3, Day 1 [up to Cycle 3, Day 10, with at least 28 days from previous tumor assessment]), and then every 8 weeks (±10 days) thereafter for up to 24 months. Assessment is also done at Safety Follow-up visit unless disease progression is documented or assessment has been done within 2 months of Safety-follow up visit.
m) If an archival tissue sample is not available, a tumor biopsy will be required. A tumor genotyping report is required to confirm patient mutation eligibility. Collecting a tissue sample at progression is optional but is highly encouraged. Tumor tissue FFPE samples will be stored at room temperature.
n) Whole blood samples (4 mL) will be drawn at Screening for CYP2D6 metabolic profile testing.
o) Whole blood samples (20 mL) for plasma will be drawn as per site standard procedures at Screening, Cycle 2 Day 1, Cycle 3 Day 1 and then every 8 weeks. If the patient progresses a sample collection is optional, but highly encouraged. Samples will be processed into plasma at the site and shipped to the lab for storage at -70°C until ready for testing (companion diagnostic development and resistance mechanism study).
p) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained at Screening, within 7 days prior to Day 1 of each cycle, at which time, platelet count must be $\geq 100\times10^9$/L and ANC must be $\geq 1.5\times10^9$/L before dispensing poziotinib for the next cycle of treatment, and at the Safety Follow-up Visit. If the Screening Visit is within 14 days of Cycle 1 Day 1, the Baseline CBC is not required.
q) Blood for chemistry, including KL-6 and C-reactive protein, is to be collected at Screening, within 7 days prior to poziotinib administration on Day 1 of each cycle, and at the Safety Follow-up Visit; measurement of KL-6 is not required on Cycle 1, Day 1 if it was already measured during Screening. If the Screening Visit is within 14 days of Cycle 1, Day 1, the Baseline serum chemistry panel is not required
r) ECGs will be performed at Screening, predose and at 1 and 2 hours (±15 min) postdose on Cycle 1, Day 1 and Cycle 2, Day 1 as indicated for time-matched concentration-ECG analysis, and at Safety Follow-up Visit. ECG are not required on Day 1 of other cycles.

s) Cardiac ejection fraction will be evaluated using echocardiogram or multi-gated acquisition (MUGA) scan at Screening. The Investigator can order subsequent tests based on patient standard of care.
t) Patients will have blood samples drawn predose and at 1 hour and 2 hours (±15 min) postdose on Cycle 1, Day 1 and Cycle 2, Day 1 for sparse PK sampling and time-matched concentration-ECG analysis. Blood samples will be collected at Cycle 3 Day 1 and then every 8 weeks in order correlate poziotinib concentrations with plasma ctDNA and efficacy; the time of the last dose and the time of blood draw should be recorded. In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea, pneumonitis), blood samples will be collected as soon as possible following the onset of the AE and the time of the last dose and the time of blood draw should be recorded.
u) Poziotinib will be dispensed on Day 1 of each cycle. Poziotinib should be taken with food and a glass of water (approximately 240 mL) at approximately the same time(s) each day.
v) During the Screening Period, only SAEs will be recorded . All AEs will be collected from Cycle 1, Day 1 through the Safety Follow-up Visit.
w) Concomitant medications will be collected at Day 1 of each cycle, Day 8 and Day 15 during Cycle 1, and at the Safety Follow-up Visit.
x) Telephone contact will be made to collect AE and concomitant medication information from patients on Cycle 1, Day 22, every week in Cycle 2, and **Day 15 (±2 days)** in each cycle thereafter. During the long-term follow-up patients will be contacted every 3 months to assess survival.

Poziotinib Dosing Recommendations

In Phase 1 of the study (Dose-Finding), dosing modifications are not allowed during Cycle 1 but are allowed beginning with Cycle 2. Dosing modifications are allowed at any time during Phase 2 of the study. Dosing modifications are described in the table below. If needed, doses will be reduced by 2 mg/dose (i.e., if on QD, the reduction will be a total of 2 mg/day or if on BID, the reduction will be a total of 4 mg/day), regardless of starting dose, and will be at the Investigator's discretion; the Sponsor should be notified. Dose modifications not described in the table below must be discussed with Medical Monitor for approval. After dose reductions, if the patient has a documented confirmed progression, the patient's dose can be increased up to the starting dose.

Recommendations for Dose Reductions after Cycle 1 in Phase 1 and During Phase 2

<table>
<tr><th>Related Adverse Event</th><th>Triggering Criteria</th><th>First Occurrence</th><th>Subsequent Occurrences</th></tr>
<tr><td rowspan="2">Diarrhea</td><td>Grade ≥3 (Despite optimal anti-diarrhea management)</td><td rowspan="6">Stop poziotinib treatment until the AE has improved to Grade ≤1 and then continue treatment at the same dose.
or
Reduce poziotinib dose by 2 mg/dose</td><td rowspan="6">Reduce poziotinib dose by 2 mg/dose</td></tr>
<tr><td>Grade ≥2 for ≥48 hours (Despite optimal diarrhea management)</td></tr>
<tr><td>Fatigue</td><td>Grade ≥3</td></tr>
<tr><td>Mucositis/Stomatitis</td><td>Grade ≥3 (Despite optimal management)</td></tr>
<tr><td rowspan="2">Nausea and/or Vomiting</td><td>Grade ≥3 (Despite optimal anti-emetics)</td></tr>
<tr><td>Grade ≥2 for ≥48 hours (Despite optimal anti-emetics)</td></tr>
<tr><td>LVEF Dysfunction</td><td>Grade ≥3</td><td></td><td></td></tr>
<tr><td>Rash</td><td>Any Grade</td><td colspan="2">Refer to Rash Management Recommendations (Appendix 4)</td></tr>
<tr><td rowspan="2">Pneumonitis</td><td>Grade 1</td><td>Stop poziotinib treatment, assess pulmonary function, and monitor the patient as clinically indicated. Contact the Sponsor to discuss continuing treatment, if resolved.</td><td>Discontinue Treatment</td></tr>
<tr><td>Grade ≥2</td><td>Discontinue treatment. Assess pulmonary function and monitor the patient as clinically indicated.</td><td>NA</td></tr>
</table>

Dose interruptions should be minimized in order to reduce the risk of progression. Supportive medications, including early steroid use, should be considered even in the presence of low-grade "on-target" toxicity (eg, rash, diarrhea). The respiration and pulmonary function of the patient will be assessed throughout Cycle 1. Interstitial lung disease (ILD) is a clinical diagnosis and if

in the opinion of the Principal Investigator the patient has developed signs or symptoms of Grade ≥2 pneumonitis (CTCAE Version 5.0), the patient would stop dosing and depending on the response/recovery may be discontinued from the study. If the patient has developed signs or symptoms of Grade 1 pneumonitis, the Investigator can stop treatment after consultation/discussion with the Medical Monitor.

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1 INTRODUCTION

1.1 Background

1.1.1 Human Epidermal Growth Factor Receptor Family and Cancer

The human epidermal growth factor receptor (EGFR) family consists of four receptor sub-type members: epidermal growth factor receptor (EGFR/HER1 or ErbB-1), HER2 (ErbB-2), HER3 (ErbB-3), and HER4 (ErbB-4), all of which regulate cell growth, apoptosis, migration, adhesion, and differentiation. Hyperactivation of these receptors triggers a complex, multilayered network of interrelated signaling pathways including downstream up-regulation of the mitogen activated protein kinase (MAPK), phosphoinositide-3-kinase/ AKT (PI3K/AKT), and Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathways, which can promote cancer growth **[1]**.

Several solid tumor malignancies, including lung, breast, stomach, colorectal, head and neck, and pancreatic carcinomas, are associated with a mutation in or overexpression of members of the EGFR receptor family **[2]**. HER2 and other members of the EGFR receptor family are overexpressed in roughly 20% to 25% of breast cancers and is a prognostic marker **[3, 4]**. HER2-positive breast cancers are characterized as being more clinically aggressive and more invasive than HER2-negative subtypes, are associated with increased growth rates, early systemic metastasis, and worse outcome **[4, 5]**. HER2 is also overexpressed in several other solid tumor malignancies. Treatments that specifically target HER2 have been shown to be particularly beneficial to patients with HER2-positive breast cancers, and several targeted drug therapies have been approved by Ministry of Health, Labour and Welfare（MHLW） and the US Food and Drug Administration (FDA) to treat patients with HER2-positive breast cancer, including trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1) **[3, 4]**.

1.1.1.1 EGFR Exon 20 Mutation Non-Small Cell Lung Cancer

Despite years of research and prevention strategies, lung cancer continues to be the most common cause of cancer-related deaths worldwide. Activating epidermal growth factor receptor (EGFR) mutations are key drivers of non-small cell lung cancer (NSCLC) in 10% to 15% of patients of European descent and approximately 40% of patients of East Asian descent **[6]**.

Patients with the most common activating EGFR mutations, exon 21 L858R and deletions in exon 19 (del19), typically have initial substantial response to therapy with EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib or afatinib. In contrast, mutations in exon 20 of EGFR, which account for 5% to 10% of all EGFR mutations, have been generally associated with de novo resistance to EGFR TKIs. The reported response rate of patients with EGFR exon 20 insertions to gefitinib and erlotinib is low at 5% with a median PFS of 1.5 months. A combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3 and LUX-Lung 6 clinical trials showed that the response rate to afatinib is 8.7% with a median PFS of 2.7 months in EGFR exon 20 insertions patients **[7]**. This is in contrast with the activity of erlotinib, gefitinib, and afatinib in classical EGFR mutations where the response rate is 70% with a median PFS of 10-13 months.

The activity of other irreversible EGFR TKIs like neratinib and dacomitinib EGFR TKIs is limited for EGFR exon 20 mutations. In a Phase II trial of neratinib, three patients with exon 20 EGFR insertions NSCLC did not have radiographic responses. In an initial Phase I trial of

dacomitinib, six patients with EGFR exon 20 insertions were included and only one (with delAsn770insGlyTyr) had a response [8].

1.1.1.2 HER2 Exon 20 Mutation Non-Small Cell Lung Cancer

Human epidermal growth factor 2 (HER2 ErbB-2/neu) is a member of the ErbB receptor tyrosine kinase family. The ErbB2 gene, which encodes for HER2, is a major proliferative driver that activates downstream signaling through PI3K-AKT and MEK-ERK pathways. HER2 mutations consist of in-frame insertions in exon 20, leading to constitutive activation of the receptor and downstream AKT and MEK pathways [9].

HER2 mutations have been identified in approximately 1% to 4% of NSCLC. In an initial report, mutations in the HER2 kinase domain were identified in 4.2% of 120 primary NSCLC overall and 9.8% in adenocarcinomas. A subsequent study of 671 primary resected NSCLC, HER2 mutations were found in 1.6% of samples overall, but in 3.9% of adenocarcinoma samples, and more frequently in Asian ethnicity [9]. The largest retrospective series published to date, comprising 65 patients with NSCLC and HER2 mutations, provides important insights into the clinic-pathological features and correlates: mutations were found exclusively in patients with adenocarcinoma subtype, and predominantly in female patients and non-smokers, a population similar to the EGFR-mutated NSCLC.

There is no FDA approved targeted therapy[10] for HER2 exon 20 insertion mutation NSCLC. Chemotherapy remains the standard of care for metastatic disease with severe side effects and modest efficacy.

Patients with HER2 mutated NSCLC treated with lapatinib, a pan HER inhibitor, experienced progressive disease. The most promising data to date have been obtained using irreversible TKIs targeting HER2/3 and EGFR, such as afatinib, neratinib and dacomitinib. Three out of eight HER2 mutant NSCLC patients treated with afatinib achieved a partial response. Dacomitinib demonstrated an overall 13% response rate in the 26 HER2-mutant patients [9].

1.1.2 Poziotinib

1.1.2.1 Pharmacology of Poziotinib

Poziotinib (HM781-36B) is a novel, oral, quinazoline-based pan-HER inhibitor that irreversibly blocks signaling through the EGFR family of tyrosine-kinase receptors, including human epidermal growth factor receptor (HER1/ErbB1/EGFR), HER2 (ErbB2), and HER4 (ErbB4), as well as HER receptor mutations. This, in turn, leads to inhibition of the proliferation of tumor cells that overexpress these receptors. It is well established that several malignancies, including lung, breast, stomach, colorectal, head, and neck, and pancreatic carcinomas, are associated with a mutation in or overexpression of members of the EGFR receptor family [2].

1.1.2.2 Drug Product Description

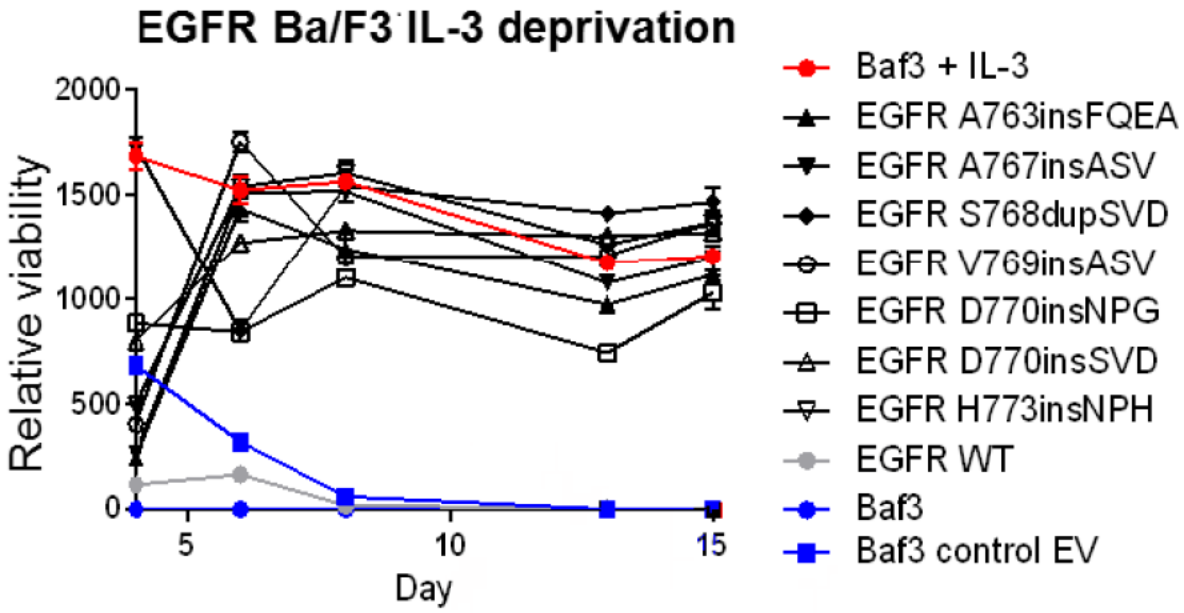
Poziotinib (HM781-36B) is formulated as a hydrochloride salt of poziotinib. The chemical formula of poziotinib is (1-[4-[4-(3,4-dichloro-2-fluorophenylamino)-7-methoxyquinazolin-6-yloxy]-piperidin-1-yl]prop-2-en-1-one hydrochloride). For clinical trials conducted in the United States, the drug product will be supplied as tablets for oral administration, which contain 2.0 mg or 8.0 mg of poziotinib (as salt form), respectively.

1.1.2.3 Poziotinib Nonclinical Studies

1.1.2.3.1 Poziotinib in Tumor Models with EGFR Exon 20 Insertion Mutations

Preclinical testing indicates that poziotinib is active against cell lines with a range of *EGFR* exon 20 mutations *in vitro* when using the standard Ba/F3 model. Ba/F3 is an interleukin (IL)-3 dependent pro-B cell line that has been widely used to study oncogenic activity of genes and development of drugs that target oncogenic drivers. This system was used this system to test several *EGFR* exon 20 insertion mutations for their effects on IL-3-independent cell survival, signaling, and drug responsiveness **[11]**. Stable expression of *EGFR* exon 20 insertion mutations rendered Ba/F3 cells IL-3 independent suggesting that these mutations are activating **(Figure 1)** **[11]**.

Figure 1 IL-3-Independent Survival of Ba/F3 Cells Stably Expressing *EGFR* Exon 20 Mutations



Ba/F3 cells with EGFR exon 20 insertions were then screened with a number EGFR TKIs including erlotinib, afatinib, osimertinib, rociletinib, EGF-816, and poziotinib. Ba/F3 expressing *EGFR* exon 20 insertions showed marked sensitivity to poziotinib **(Figure 2)**. Moreover, poziotinib led to suppression of EGFR phosphorylation and decreased downstream signaling, that was associated with increased level of cleaved PARP suggesting that treatment with poziotinib leads to cell apoptosis **(Figure 3)** **[11]**.

Figure 2 Poziotinib (HM781-36B) is a Potent Inhibitor of Cell Lines with *EGFR* Exon 20 Insertions

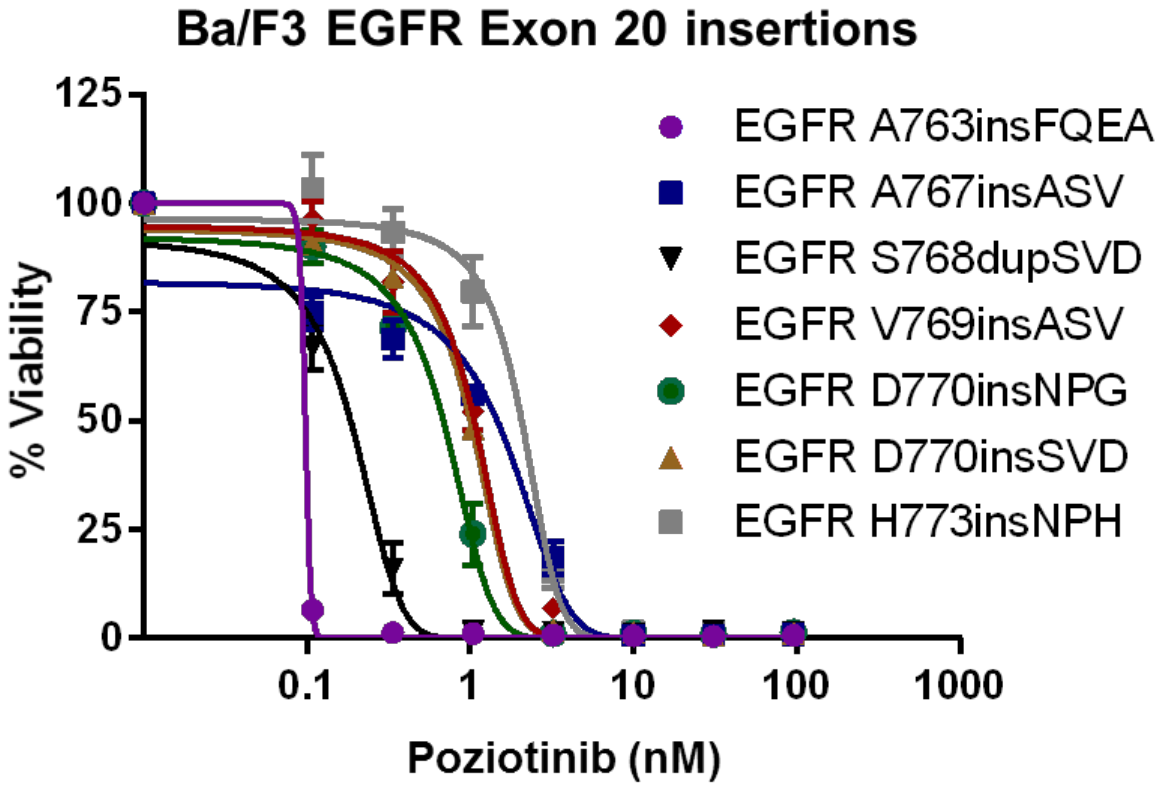
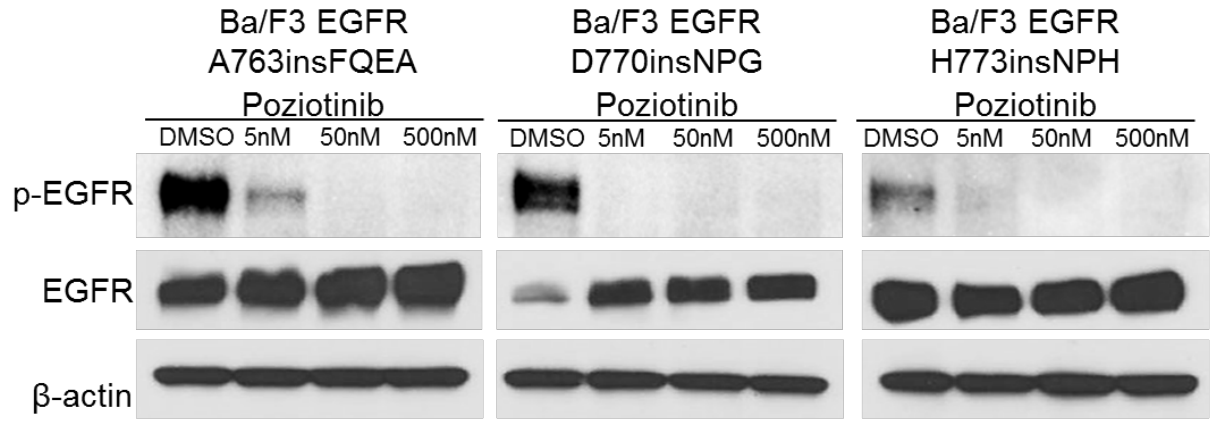
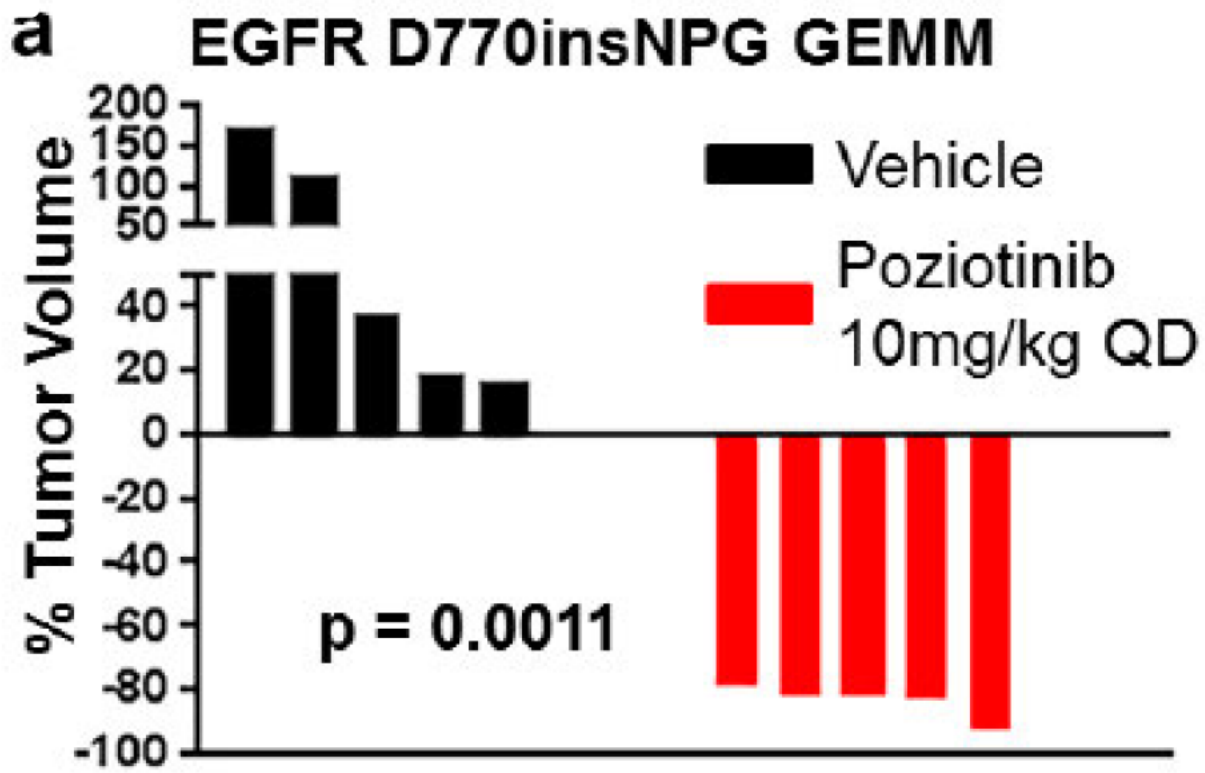


Figure 3 Effect of Poziotinib (HM781-36B) on EGFR Phosphorylation and Downstream Signaling



In vivo studies were also conducted to test the effect of poziotinib in genetically-engineered mice with EGFR exon 20 insertion mutations. Mice were treated daily with vehicle or 10 mg/kg poziotinib for 4 weeks. Waterfall plots of tumor volume change as measured by MRI demonstrated approximately 80% tumor inhibition at 4 weeks **(Figure 4) [11]**.

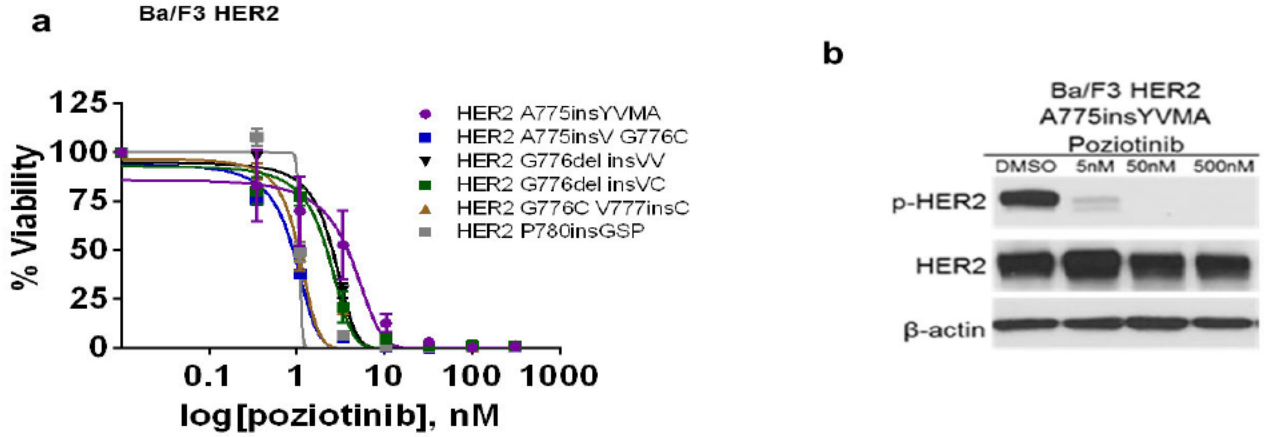
Figure 4 Tumor Volume Change in Mice with EGFR Exon 20 Insertion Mutations Treated with Poziotinib Vs Vehicle



1.1.2.3.2 Poziotinib in Tumor Models with HER2 Exon 20 Insertion Mutations

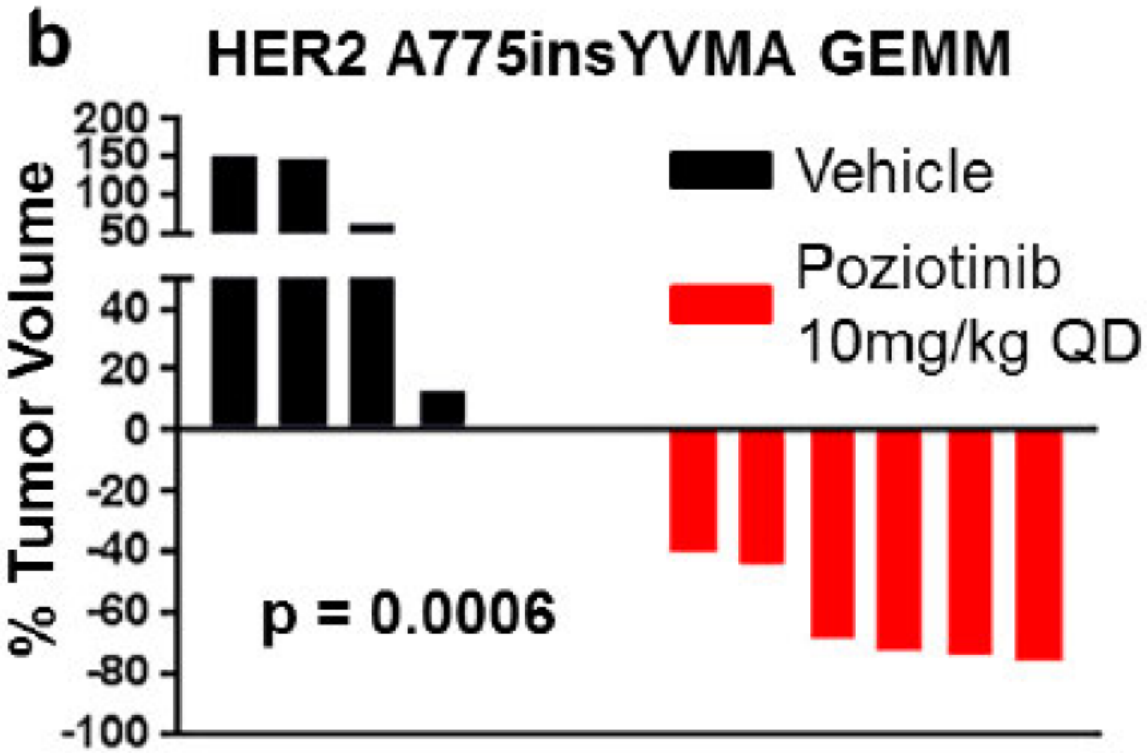
Robichaux et al stably expressed 11 clinically observed HER2 mutations in Ba/F3 cells **[11]**. Similar to cell lines with EGFR exon 20 mutations, it was observed that poziotinib potently inhibited cell lines with HER2 mutations in vitro. Poziotinib effectively inhibited the growth of HER2 exon 20 mutation Ba/F3 cells with an average IC50 value of 1.9 nM (**Figure 5a**) and was over 200 times more potent than osimertinib. These results were validated by Western blotting where poziotinib inhibited phosphorylation of HER2 at concentrations as low as 5nM (**Figure 5b**) **[11]**.

Figure 5 a) Ba/F3 Cells Expressing *HER2* Mutations are Sensitive to Poziotinib
b) Poziotinib Inhibits HER2 Phosphorylation



In vivo studies were also conducted to test the effect of poziotinib in genetically-engineered mice with HER2 exon 20 insertion mutations. Mice were treated daily with vehicle or 10 mg/kg poziotinib for 4 weeks. Waterfall plots of tumor volume change as measured by MRI demonstrated approximately 60% tumor inhibition at 4 weeks **(Figure 6) [11]**.

Figure 6 Tumor Volume Change in Mice with HER2 Exon 20 Insertion Mutations - Treated with Poziotinib vs Vehicle



Taken together, these results suggest that poziotinib is a potent inhibitor of tumors with *EGFR* and HER2 exon 20 insertion mutations and that its use in this patient population merits further investigation in the clinic.

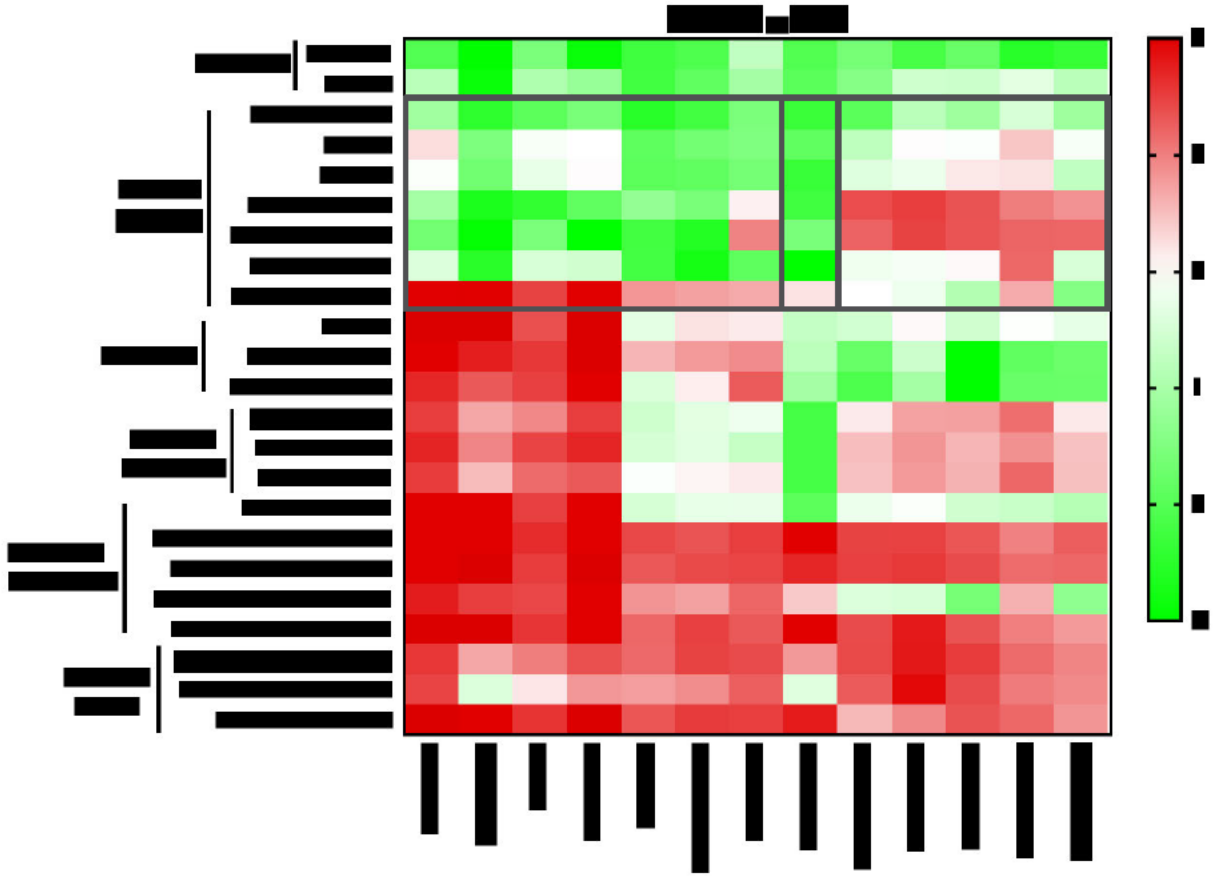
1.1.2.4 Poziotinib in Tumors with Atypical EGFR and HER2 Mutations

Poziotinib has also been studied in vitro in mutations that are classified as "atypical mutations" in both EGFR and HER2. In NSCLC, atypical EGFR mutations include mutations that are neither an exon 20 insertion mutation nor classified as classical (Ex19del or L858R).

1.1.2.4.1 Atypical EGFR Mutations

Unpublished data from first, second, and third generation TKIs tested against Ba/F3 cell lines expressing selected EGFR mutations has been provided through a personal communication by J. Heymach, MD Anderson Cancer Center. In addition to activity against EGFR exon 20 insertion mutations, there was high poziotinib activity against the atypical mutations evaluated (IC50 values ≤10 nM), including L861Q, G719A, L858R/V834L, L858R/C797S, and L858R/L792H, and Ex19del/C797S. There was less activity against Ex19del/L792H (**Figure 7**). In a separate study, Ba/F3 cell lines expressing osimertinib resistant EGFR point mutations L718Q/V and L747S were sensitive to poziotinib (IC50 values ≤1.0 nM) **[12]**.

Figure 7 Poziotinib Inhibits Growth of Atypical EGFR Mutant Ba/F3 Cell Lines



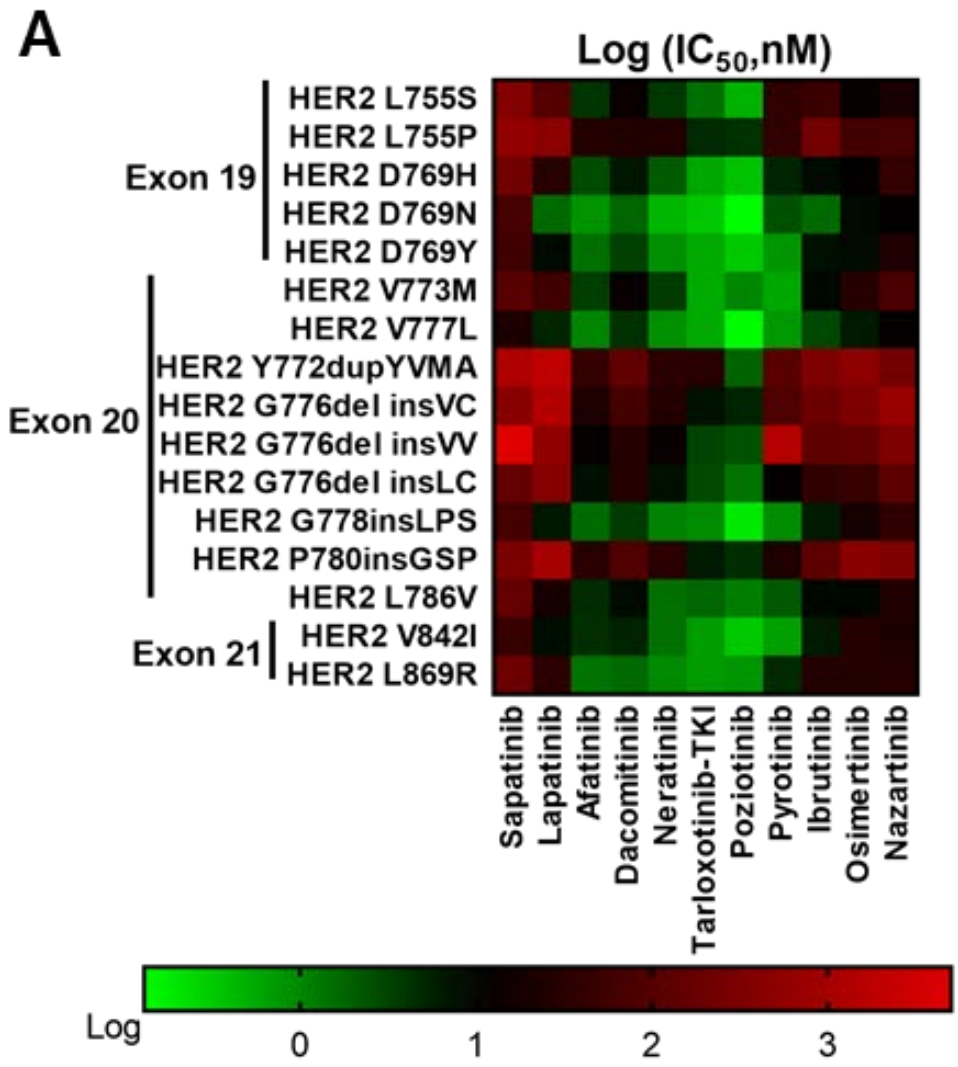
Source: Personal communication, J. Heymach, MD Anderson Cancer Center, 03 Apr 2019

1.1.2.4.2 Atypical HER2 Mutations

Several atypical HER2 mutations that are sensitive to poziotinib in vitro have been identified **[13]**. Poziotinib was tested in Ba/F3 cell lines expressing selected atypical HER2 mutations. Poziotinib was active against all exons 19, 20, and 21 point mutations **(Figure 8)**. Poziotinib was significantly more potent than either afatinib, neratinib, or tarloxotinib-TKI against HER2 exon 19 and 20 mutations, but there was no significant difference in average IC50 for exon 21 mutations.

Although no studies have been conducted with poziotinib, activating HER2 mutations have been identified in other cancers. Both I655v **[14]** and I767M **[15]** have been found in breast cancer tumors and S310F **[16]**, a mutation located in the extracellular region of HER2.

Figure 8 Poziotinib Inhibits Growth of Atypical HER2 Mutant Ba/F3 Cell Lines



1.1.2.5 Poziotinib Absorption, Distribution and Metabolism

Poziotinib is a compound with high plasma clearance, moderate oral bioavailability, high protein binding, slow metabolism in vitro, and extensive metabolism in vivo. Exposure to poziotinib increased with increase in dose, and pharmacokinetic profiles were similar between males and females in nonclinical species. Poziotinib was widely distributed in tissues and was concentrated in the uveal tract and eye. Poziotinib was extensively metabolized in the rat following intravenous and oral administration of the drug; 10 metabolites were identified. Metabolites identified in vitro were similar to those identified in vivo, and in the clinic; M1 (dihydroxy-poziotinib) and M2 (*O*-demethyl-poziotinib) were the major metabolites. Metabolite formation was NADPH-dependent, suggesting a role for cytochrome P450 (CYP450) enzymes. CYP3A4 was the primary enzyme in the formation of M1, and CYP2D6 was the primary enzyme in the formation of M2. Both the M1 and M2 metabolites are pharmacologically active, but M2 is much more potent than M1 **[17]**.

In vitro studies have shown that the solubility of poziotinib is pH dependent. Poziotinib is highly soluble at acidic pH, its solubility is significantly reduced at neutral or basic pH. Between pH 1-4, the solubility of poziotinib is 80 µg/mL whereas the solubility is less than 5 µg/mL at pH 6.8 (data on file). Similar trends have been observed with other EGFR tyrosine kinase inhibitors such as erlotinib and gefitinib. Although the effect of pH on systemic exposure of poziotinib has not been established, based on the solubility profile, it is quite likely that the absorption of poziotinib could be lower at higher pH.

Because proton pump inhibitors (PPIs), H2 histamine receptor antagonists, and antacids increase the gastric pH, we recommend that if possible, concomitant administration of long-acting PPIs or H2 receptor antagonists with poziotinib should be avoided, which is similar to the instructions for other TKIs. If needed, patients may take short acting antacids (e.g., Maalox®) at least 4 hours before or after poziotinib administration.

1.1.2.6 Poziotinib Toxicity Studies

The toxicity of single and repeated daily doses of oral poziotinib was assessed in rats and dogs. In the 13-week toxicity study, rats tolerated poziotinib up to a daily dose of 0.45 mg/kg. Adverse toxicological effects included an increase in the incidence of skin lesions (degeneration/atrophy, erosion/ulcer, epidermal hyperplasia, exudates), stomach toxicity (histopathological epithelial hyperplasia, hyperkeratosis, inflammation and erosion/ulcer) and increased neutrophil counts secondary to inflammation. The NOAEL for the 13-week study was 0.15 mg/kg/day. The MTD for the study was 0.45 mg/kg/day, based on reductions in mean body weight in males (-18.7%) and females (-7.1%).

In the 13-week canine toxicity study, dogs tolerated up to 0.15 mg/kg/day. The NOAEL following dose reduction was 0.075 mg/kg/day. The MTD following dose reduction was 0.15 mg/kg/day, based on reductions in body weight (13.2% and 13.9%) and food consumption (75.8% and 85.0%) in males and females, respectively. The major target organs were skin (hyperplasia, ulcer, and inflammation), gastrointestinal tract (inflammation, attenuation of luminal epithelium), eye (atrophy of the corneal epithelium), and lymphoid organ (lymphocyte depletion/necrosis). There were no cardiovascular effects (electrocardiogram [ECG], blood pressure, heart rate, and QT interval) in poziotinib doses up to 0.15 mg/kg/day.

Poziotinib and its M1 and M2 metabolites were not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or in the Chinese hamster ovary chromosome aberration assay. They were not clastogenic in an in vivo rat bone marrow micronucleus test at doses of up to 1000 mg/kg in males and 500 mg/kg in females. Poziotinib was evaluated in an embryo-fetal study in rats and rabbits. Effects of poziotinib on embryo-fetal development were limited and restricted to high doses. High-dose poziotinib exposure was associated with a reduction in the mean number of viable fetuses and this was correlated with increased post implantation loss and resorptions. Neither the rat nor the rabbit showed evidence of teratogenicity. Poziotinib did not show any evidence of skin irritation in male New Zealand White rabbits or any evidence of phototoxicity to BALB/c 3T3 clone A31 cells.

The toxicological findings in animal studies have been entirely consistent with the adverse events reported in human clinical trials. The most frequent adverse events reported in human clinical trials conducted in South Korea to date include diarrhea, stomatitis, rash, decreased appetite, and pruritus. These toxicological effects observed in rats, dogs and humans with poziotinib mirror those observed with other EGFR inhibitors **[18-21]**, suggesting that poziotinib toxicity is a class effect of EGFR tyrosine kinase inhibition. Since the poziotinib metabolite M2 exhibits in vitro EGFR inhibitory activity nearly identical to poziotinib (IC_{50} values = 5.6 nM and 5.4 nM, respectively), one cannot exclude the possibility that *in vivo* poziotinib EGFR inhibitory activity is due to systemic levels of both poziotinib and M2. As the formation of M2 is dependent on the variable activity of the human polymorphic CYP2D6 enzyme, accounting for poziotinib and M2 may be the most accurate estimate of TKI activity and hence toxicity. The mean safety margin at the NOAEL in dogs in the 13-week toxicity study, compared to humans at the MTD of 24 mg/day, was 0.8-fold using poziotinib exposure alone and 2.1-fold using poziotinib + M2 exposure.

These values are consistent with the results of Phase 1 studies completed in South Korea, in which patients were treated with poziotinib doses ranging from 0.5 mg to 32 mg (**HM-PHI-101**). The dose-limiting toxicity (DLT) in these clinical trials was observed at 32 mg, and 24 mg was the MTD for the intermittent (14 days on treatment and 7 days off) dosing schedule. Taken together, these data support the planned and ongoing clinical trials utilizing doses of poziotinib up to 24 mg/day.

In addition, the photo-cytotoxicity of poziotinib was evaluated in BALB/c 3T3 clone A31 cells in the presence and absence of *uv* light. Based on the results of this study, poziotinib did not show any evidence of phototoxicity on BALB/c 3T3 clone A31 cells under the conditions of this study.

1.1.3 Poziotinib Clinical Studies

The clinical development program for poziotinib is ongoing in collaboration with Hanmi in Korea. To date, a total of 11 studies have been conducted in Korea, of which four are ongoing Investigator Initiated studies (IIS). Clinical studies completed in Korea include:

- Two Phase 1 studies (**HM-PHI-101** and **HM-PHI-102**) conducted in patients with advanced cancers (solid tumors) are PK/PD and dose finding studies.
- Four Phase 2 studies (**NOV120101-202, HM-PHI-A201**, **NOV12010-201,** and **NOV12010-203**) conducted in patients with EGFR-mutant NSCLC, advanced gastric cancer and breast cancer (HER2 positive).

In the United States, the following poziotinib are ongoing:

- A Phase 1 study (**SPI-POZ-101**) in HER2+ breast cancer in combination with T-DM1
- A Phase 2 study (**SPI-POZ-201**) in HER2+ MBC with ≥2 prior HER2 directed therapies
- A Phase 2 study (**SPI-POZ-202**) in NSCLC with EGFR or HER 2 exon 20 insertion mutation in pretreated and treatment naïve patients.
- A US Investigator Initiated Study (**IIS-POZ-001**) in NSCLC with EGFR or HER2 exon 20 insertion/mutation

To date, more than 800 patients have received poziotinib monotherapy in open-label clinical trials and compassionate uses at doses ranging from 0.5 mg to 32 mg on an intermittent dosing schedule and from 8 mg to 24 mg on a continuous dosing schedule, or as combination therapy with trastuzumab and paclitaxel. Clinical activity was observed in patients on poziotinib monotherapy and in combination with other anti-cancer agents, as defined by objective response rates or prolonged stabilization of disease. Clinical benefit has been observed in patients with several solid tumors.

1.1.3.1 Summary of Clinical Efficacy

NOV120101-202 was a Phase 2, prospective, open-label, multicenter, exploratory study conducted in adult patients with Stage 3B or 4 NSCLC (including lung adenocarcinoma) with acquired resistance to first-generation EGFR TKIs (gefitinib or erlotinib). This study was conducted by Hanmi and National OncoVenture. Patients were not screened for EGFR or HER2 exon 20 mutations.

The primary study endpoint was Progression-free Survival (PFS). In addition, a number of secondary and exploratory endpoints were also assessed, including PFS rate at 16 weeks of treatment, Objective Response Rate (ORR), Disease Control Rate (DCR), overall survival (OS), time to progression (TTP), time to objective response, duration of objective response, duration of disease control, and change in quality of life: EQ visual analog scale (EQ VAS) and EQ-5D index to measure levels of mobility, self-care, activity, pain/discomfort, and anxiety/depression. Exploratory endpoints included a population PK profile and a subgroup analysis of genetic information confirmed from tumor tissue and blood samples. The primary and secondary endpoints of ORR and DCR are discussed in this section.

Poziotinib was administered orally at a dose of 16 mg/day once daily for 28-day (4-week) continuous cycles until the patient exhibited PD or intolerable AEs that led to drug discontinuation. The planned enrollment for this study was 40 patients. Tumor response was assessed periodically at protocol-designated times.

Forty patients were enrolled, and 39 patients were included in the Full Analysis Set and the Safety Analysis Set. One patient was not treated with poziotinib and was excluded from the analyses. The Per Protocol Analysis Set included 35 patients; 3 were excluded because of noncompliance with treatment, and 1 was excluded because of an inclusion criterion deviation. The majority of patients withdrew from the study due to PD or lack of efficacy (72.5%, 29/39) followed by withdrawal of consent (17.5%, 7/39), AEs (5%, 2/39), and other (2.5%, 1/39).

In the Full Analysis Set, the majority of patients had an event, 87.18% (34/39) versus 92.31% (36/39), after independent and Investigator review, respectively. Regardless of the censoring rule used, the number of events remained uniform. The median PFS was 2.70 months by independent

review (regardless of censoring rule) versus 3.52 or 3.65 months by Investigator assessment with censoring Rule 1 and Rule 2, respectively. In the Per Protocol Analysis Set, 4 patients were removed from the analysis, but the results were similar to the results presented in the Full Analysis Set.

1.1.3.2 Summary of Safety

Patients in the completed poziotinib studies experienced adverse events (AEs) that were either expected for the underlying malignancies or commonly seen with other HER2-targeted therapies (e.g., diarrhea, rash, and stomatitis). **Table 1** summarizes the most common (≥10%) treatment-emergent AEs in the 4 mg, 8 mg, 12 mg, and 16 mg/day cohorts of Studies **HM-PHI-101, HM-PHI-102, HM-PHI-A201**, **NOV120101-201**, **NOV120101-202,** and **NOV120101-203**.

Table 1 Most Common Treatment-Emergent Adverse Events (≥10% in Group Total for each Study) in patients receiving 12 mg Per Day and 16 mg Per Day Poziotinib in Completed Phase 1 and Phase 2 Studies

Preferred Term	HM-PHI-101[a]				HM-PHI-102 [b]		HM-PHI-A201[a]			NOV120101-201[b]	NOV120101- 202[b]	NOV120101-203[a]
	4 mg n (%)	8 mg n (%)	12 mg n (%)	16 mg n (%)	12 mg n (%)	16 mg n (%)	8 mg n (%)	12 mg n (%)	8 mg n (%)	12 mg n (%)	16 mg n (%)	12 mg n (%)
Any TEAE	**3 (100)**	**3 (100)**	**6 (100)**	**6 (100)**	**3 (100)**	**39 (100)**	**7 (100)**	**5 (100)**	**32 (100)**	**21 (95)**	**39 (100)**	**106 (100)**
Diarrhea	2 (67)	2 (67)	6 (100)	6 (100)	3 (100)	36 (92)	7 (100)	5 (100)	30 (94)	18 (82)	36 (92)	105 (99)
Rash	2 (67)	3 (100)	6 (100)	6 (100)	2 (67)	30 (77)	4 (57)	3 (60)	22 (69)	8 (37)	30 (77)	67 (63)
Stomatitis	0	2 (67)	6 (100)	6 (100)	3 (100)	23 (59)	4 (57)	2 (40)	16 (50)	19 (86)	23 (59)	98 (93)
Decreased Appetite	3 (100)	1 (33)	5 (83)	5 (83)	2 (67)	21 (54)	1 (14)	1 (20)	19 (59)	14 (64)	21 (54)	32 (30)
Pruritus	1 (33)	2 (67)	4 (67)	2 (33)	2 (67)	25 (64)	1 (14)	2 (40)	7 (22)	16 (73)	25 (64)	67 (63)
Paronychia	0	0	1 (17)	2 (33)	2 (67)	21 (54)	1 (14)	1 (20)	3 (9)	11 (50)	21 (54)	7 (7)
Nausea	1 (33)	1 (33)	3 (50)	2 (33)	0	5 (13)	1 (14)	3 (60)	10 (31)	7 (32)	5 (13)	22 (21)
Vomiting	1 (33)	1 (33)	2 (33)	4 (67)	0	4 (10)	2 (29)	2 (40)	8 (25)	2 (9)	4 (10)	14 (13)
PPE Syndrome [c]	0	0	5 (83)	2 (33)	1 (33)	3 (8)	0	0	0	1 (5)	3 (8)	11 (10)
Fatigue	1 (33)	0	2 (33)	3 (50)	0	15 (38)	0	0	9 (28)	7 (32)	15 (38)	12 (11)
Mucosal Inflammation	0	2 (67)	1 (17)	0	0	18 (46)	1 (14)	2 (40)	3 (9)	3 (14)	18 (46)	21 (20)

a) Continuous daily dosing for 2 weeks, Off for 1 week

b) Continuous daily dosing

c) PPE = palmar-plantar erythrodysesthesia syndrome

Note: Adverse events are listed by decreasing order of highest percent in any study.

MedDRA version: 14.0 was used for Studies **HM-PHI-101, HM-PH1-102**, and **HM-PHI-A201**; MedDRA version 17.0 was used for **NOV120101-202,** MedDRA version: 18.0 was used for **NOV120101-201**; MedDRA version: 19.0 was used for **NOV120101-203**

1.2 Rationale for the Current Study

Poziotinib is an orally administered, irreversible pan-HER inhibitor with activity against HER1, (ErbB1; EGFR), HER2 (ErbB2), and HER4 (ErbB4), as well as HER receptor mutations. The clinical results and safety profile of poziotinib to date in various studies involving patients with relapsed or refractory solid tumors as either a single agent or as combination therapy, have demonstrated that poziotinib may be a good option for patients harboring these mutations. These data support the expectation that poziotinib will be efficacious and well tolerated in solid tumor patients that overexpress EGFR or HER2 or that harbor mutations in EGFR or HER2.

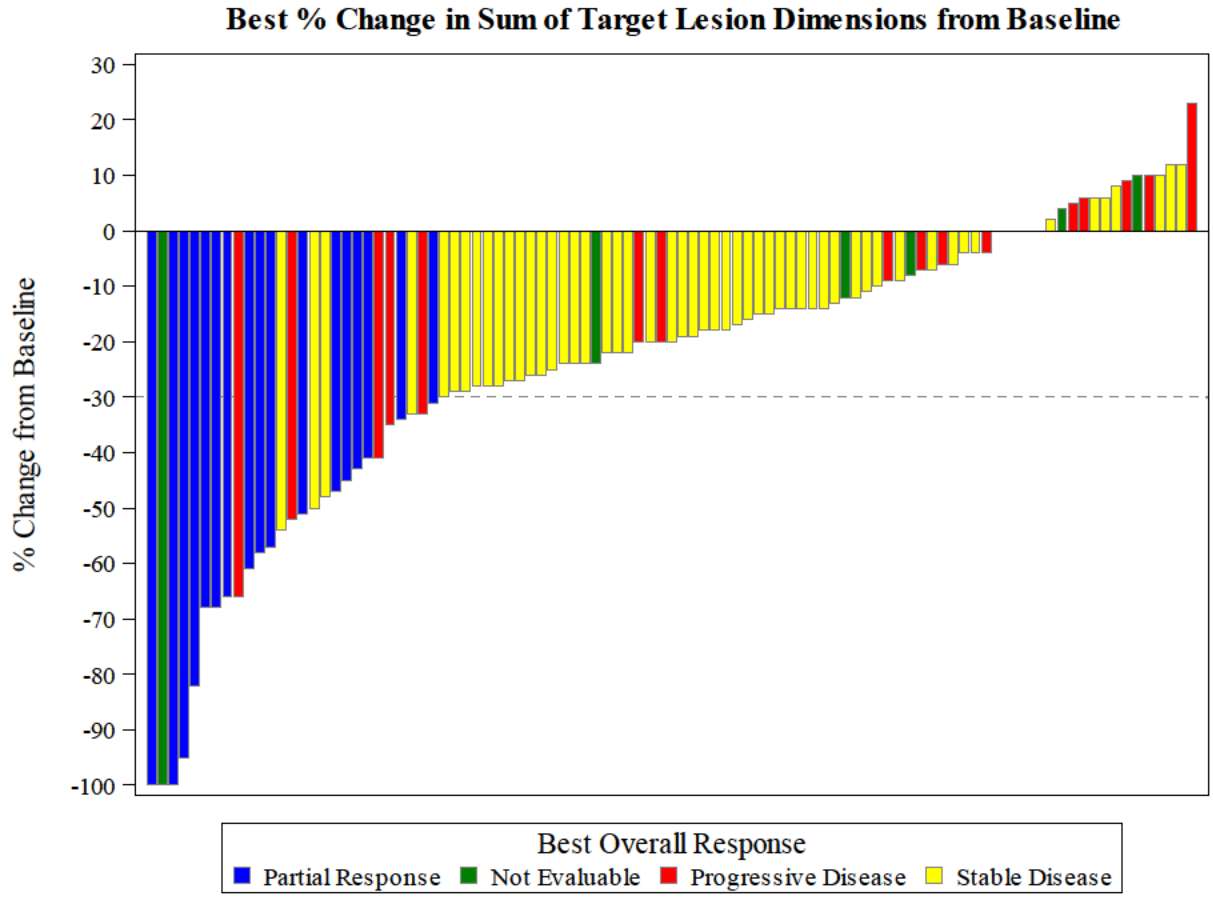
Doses from 0.5 mg to 32 mg for 14 days of a 21-day cycle were evaluated in a Phase 1 study (**HM-PHI-101**) in Korean patients with advanced solid tumors. Grade 3 diarrhea was reported as a DLT in one patient each in the 12-mg, 16-mg, and 24-mg dose groups. Two patients had Grade 3 diarrhea in the 32-mg group. No DLTs were reported in patients given <12 mg poziotinib. The MTD was determined to be 24 mg for intermittent dosing.

In another Phase 1 study (**HM-PHI-102**), Korean patients with advanced solid tumors were treated with doses of 12 mg, 18 mg, or 24 mg continuously for 28 days. One patient treated with 18 mg poziotinib had a DLT of Grade 3 decreased appetite. A patient treated with 24 mg poziotinib experienced two DLTs of Grade 3 diarrhea and Grade 3 decreased appetite. None of the patients treated with 12 mg poziotinib experienced DLTs and it was determined that the MTD for continuous dosing was 18 mg.

SPI-POZ-202 is an ongoing, multinational, Phase 2 study of poziotinib treatment in patients with locally advanced or metastatic lung cancer with EGFR or HER2 exon 20 insertion mutations. The starting dose for this study is 16 mg once daily. Enrollment into Cohort 1 (previously treated patients with EGFR mutations) and Cohort 2 (previously treated patients with HER2 mutations) in that study has been completed. Preliminary data from Cohort 1 for the primary endpoint (ORR) have been analyzed.

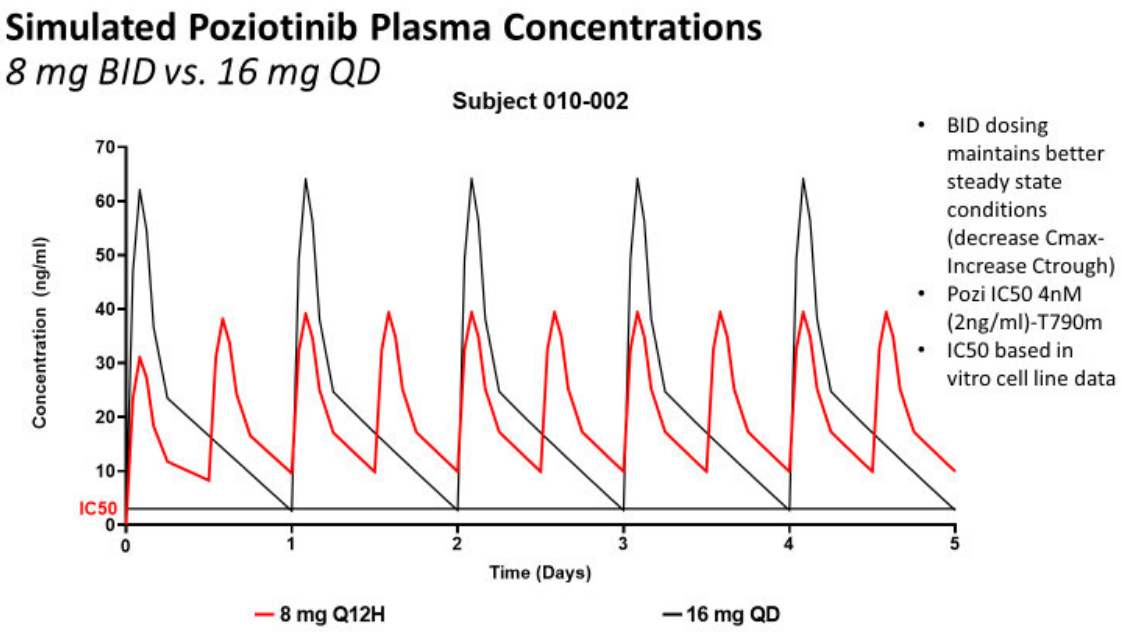
Cohort 1 enrolled a total of 115 patients who received 16 mg/day of poziotinib. The Intent-to-Treat analysis showed that 17 patients had a response (by RECIST) and 62 patients had stable disease for a 68.7% disease control rate (DCR). The confirmed objective response rate (ORR) was 14.8% (95% CI; 8.9%-22.6%). The median duration of response was 7.4 months. The best change in target lesion dimensions from Baseline is presented in **Figure 9**. The safety profile was at the high end of expected toxicities but in-line as to type of AE with other second-generation EGFR tyrosine kinase inhibitors. Permanent drug discontinuation related to AEs was seen in only 10% of patients but temporary drug interruption was seen in 88% of patients and dose reduction was seen in 68% of patients as permitted by protocol.

Figure 9 Best Percent Change in Sum of Target Lesion Dimension from Baseline



This study is being conducted to evaluate the safety of poziotinib in Japanese patients, a dose-escalating study beginning at 8 mg poziotinib QD and 4 mg BID is being conducted. Pharmacokinetic modeling of the 8 mg BID and 16 mg QD doses (the highest potential doses in the study), shows that BID dosing decreases fluctuations (i.e., difference between peak and trough concentrations) compared to QD dosing with a lower C_{max} **(Figure 10)** and the predicted AUC is expected to be similar for equivalent total daily doses. In Study HM-PHI-101, the 8-mg QD dose was well-tolerated in Phase 1 patients. In addition, activity and safety of BID dosing with poziotinib has not been previously investigated.

Figure 10 Simulated Poziotinib Plasma Concentrations Following QD and BID Dosing



2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the following in NSCLC patients treated with poziotinib:

- **Phase 1: Dose-Finding - Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD)**
- **Phase 2: Efficacy - Objective Response Rate (ORR)**

2.2 Secondary Objectives

- **Phase 1: Dose-Finding**
  - **Pharmacokinetics of poziotinib and M1 and M2 metabolites**
  - **Safety and Tolerability**
- **Phase 2: Efficacy**
  - **Disease Control Rate (DCR)**
  - **Duration of Response (DoR)**
  - **Progression-Free Survival (PFS)**
  - **Pharmacokinetics of poziotinib and M1 and M2 metabolites**
  - **Safety and Tolerability**

2.3 Exploratory Objective

- **Overall Survival**

3 INVESTIGATIONAL PLAN

3.1 Study Design and Treatment Plan

This is a Phase 1/2, open-label, multicenter dose finding study to determine the MTD/MAD of poziotinib when administered once daily (QD) or twice daily (BID) to Japanese participants with locally advanced or metastatic NSCLC.

3.1.1 Phase 1: Dose-Finding

Phase 1 is a dose finding study with two parallel, randomized dose groups. Each group will undergo dose-finding scheme using a 3+3 design with the assessment of dose-limiting toxicities (DLTs) at up to three dose levels. Patients will be hospitalized for the first 2 weeks of Cycle 1.

- **Group 1 (once daily dosing [QD]):** Starting dose of 8 mg.
- **Group 2 (twice daily dosing [BID]):** Starting dose of 4 mg BID.

The DLT assessment will be conducted in Cycle 1 of the Phase 1 of the study. Poziotinib dose-finding will proceed based on the occurrence of DLTs during Cycle 1. Although DLTs will be evaluated based on the list of criteria specified below, toxicity related to the onset of any unexpected adverse events will be evaluated as well in addition to the DLTs. The MTD or MAD will be determined in each group independently. The DLTs for MTD/MAD will be assessed by the Medical Monitor in consultation with the site Principal Investigator. In addition to the defined DLTs, dose advancement/MTD will be decided based on all safety information, including adverse events that the subject experiences that are not defined as DLTs. A DLT will be any of the following treatment-related adverse events that occur during Cycle 1, despite optimal medical supportive therapy:

- **Non-Hematological Toxicity:**
  - Grade 3 or higher toxicity based on NCI-CTCAE (version 5.0), except for alopecia
  - Grade 3 or higher nausea and vomiting, despite treatment with oral anti-emetics at the highest dose
  - Grade 3 or higher diarrhea, despite diarrhea treatment at the highest dose
- **Hematological Toxicity:**
  - Grade 4 or higher neutropenia (ANC$<0.5\times10^9$/L) sustained for 7 days or more
  - Febrile neutropenia (ANC$<1.0\times10^9$/L with a single temperature of >38.3°C (101.0°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour)
  - Neutropenic infection: Grade 3 or higher infection accompanying Grade 4 neutropenia (ANC$<0.5\times10^9$/L) (requiring IV antibiotic, antifungal or antiviral agent administration/ requiring radiation or surgical therapy)
  - Grade 4 thrombocytopenia (PLT<25,000/mm^3) or any grade thrombocytopenia requiring platelet transfusion

However, in case of ANC$<0.5\times10^9$/L, conduct a repeat test on at least the 7th day in order to verify if it is lasted for 7 days or more.

Because Phase 1 is for DLT assessment and dose finding, poziotinib dose modifications are not permitted during Cycle 1 in Phase 1. Dose modifications are permitted beginning with Cycle 2

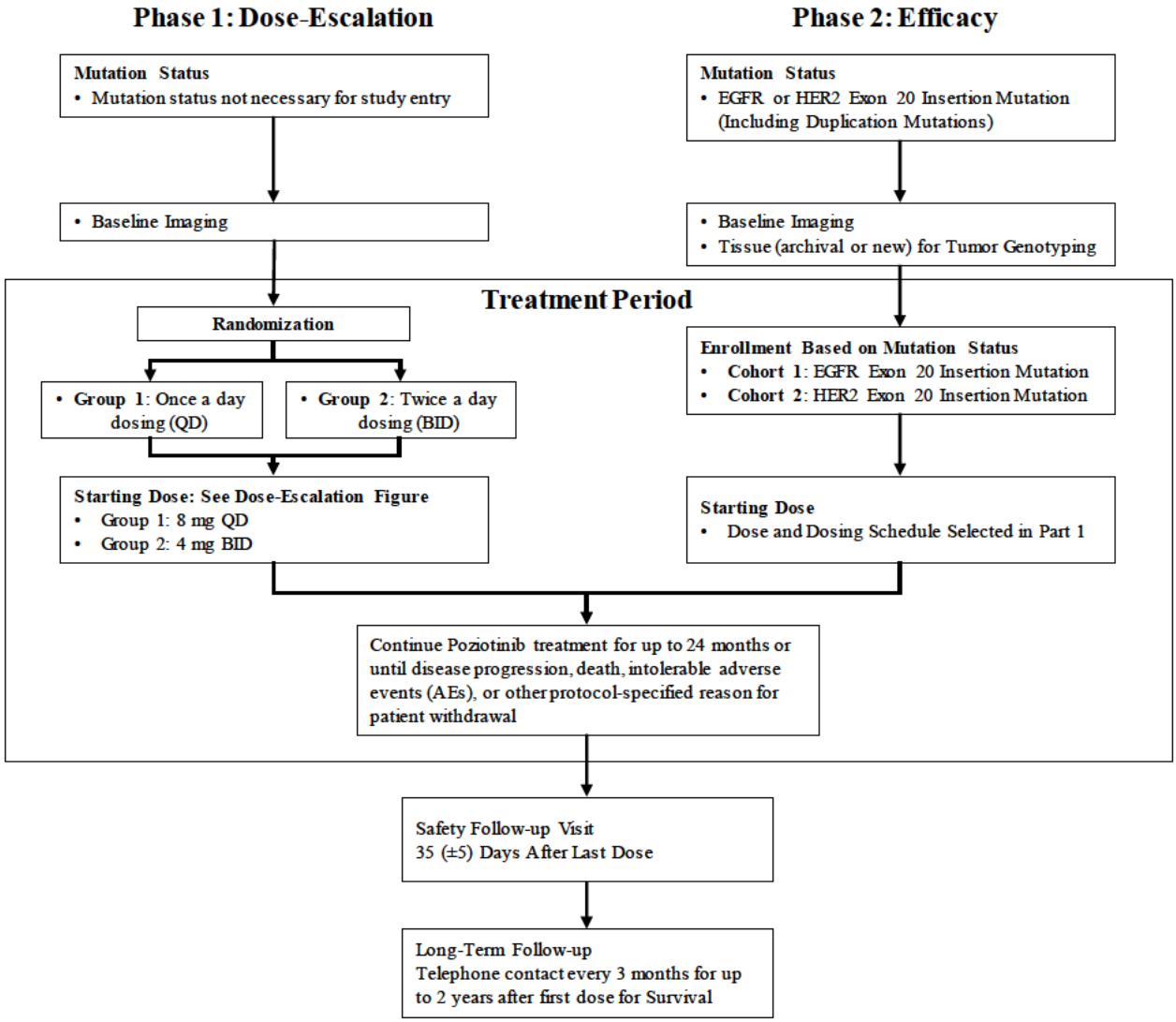
based on Sponsor recommendations. Patients who discontinue from the study for reasons other than DLTs will be replaced.

3.1.2 Phase 2: Efficacy

Once the MTD/MAD is determined, 40 additional NSCLC patients with EGFR (20 patients) or HER2 (20 patients) exon 20 insertion mutations (including duplication mutations) will be enrolled to evaluate the efficacy of poziotinib at the dose and regimen determined in Phase 1. The choice of QD or BID for Phase 2 will be determined by the sponsor when Phase 1 of the study is complete. If the patient is EGFR positive, then they go in the EGFR group. If the patient is HER2 positive, then they go in the HER2 group. Dose modifications are permitted based on Sponsor recommendations and notification of the Medical Monitor.

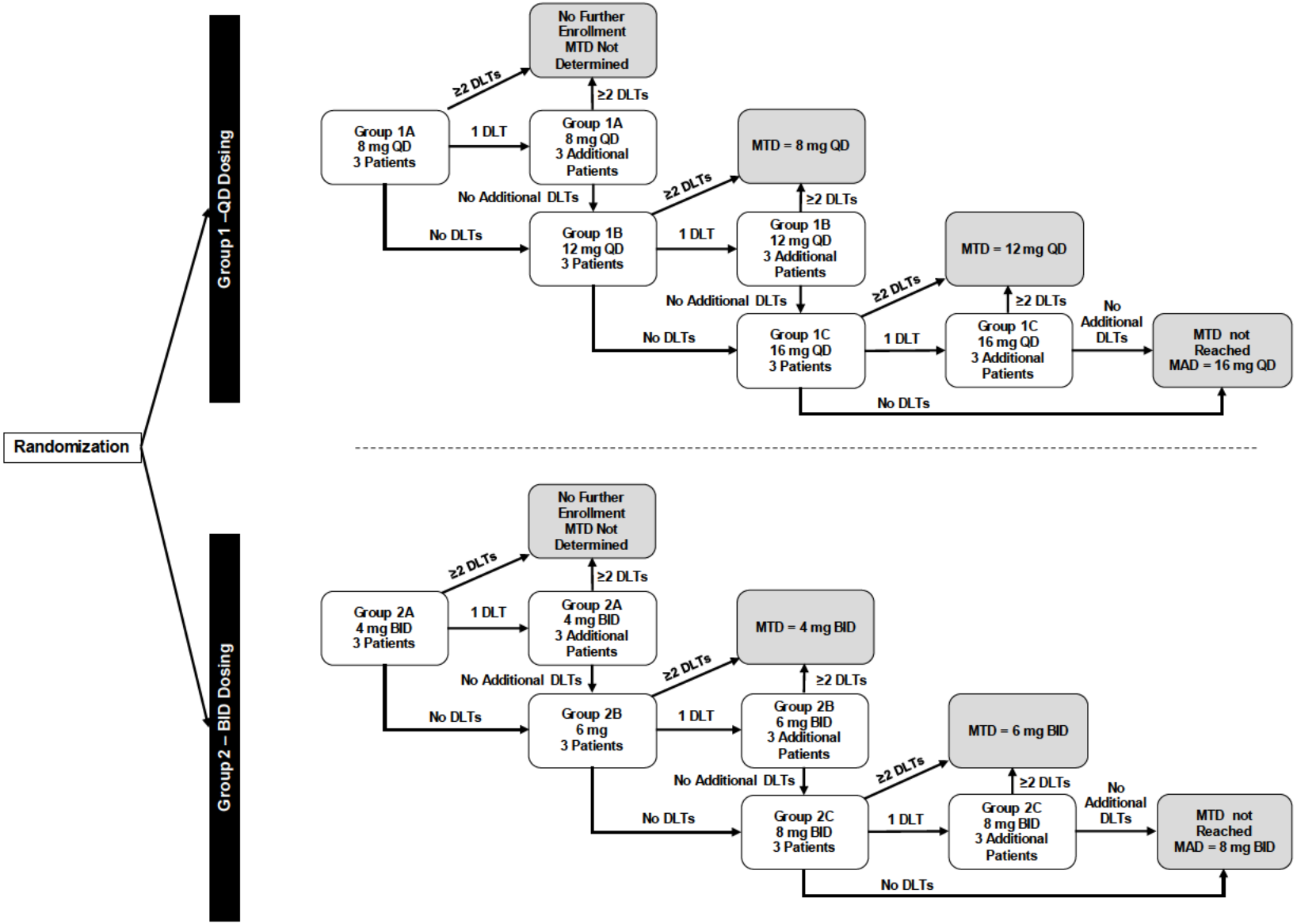
During each 28-day cycle, patients who are eligible for participation will receive poziotinib at the assigned dose, orally, QD or BID depending on the dosing group, continuously. All patients will be treated for up to 24 months or until disease progression, death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal.The study design diagram in presented in **Figure 11**, the dose-finding diagrams are presented in **Figure 12**, and the schedule of study assessments and procedures is presented in **Appendix 1** for Phase 1 and in **Appendix 2** for Phase 2.

Figure 11 Study Design Diagram



Note: Phase 2 will start once the dose and dosing schedule have been determined in Phase 1.

Figure 12 Dose-Finding Diagram



3.2 Study Duration

It is estimated that the first patient will be enrolled in January 2020 and the last patient visit will occur approximately March 2025.The duration of study participation for each patient, in general, includes the following segments:

- **Screening Period:** up to 30 days
- **Treatment Period:** 28 days per cycle for up to 24 months of treatment or until disease progression, death, intolerable adverse events (AEs), or other protocol-specified reason for patient withdrawal
- **Safety Follow-up Visit:** 35 (±5) days after the last dose of poziotinib
- **Long-Term Follow-up:** After study drug discontinuation, patients who have consented will be contacted every 3 months, for up to 2 years after patient's first dose of poziotinib, for survival assessment

4 PATIENT POPULATION

4.1 Inclusion Criteria

1. Patient is at least 20 years of age
2. Patient must be willing and capable of giving written Informed Consent, adhering to dosing and visit schedules, and meeting all study requirements
3. **Phase 2:** If an archival tissue sample is not available, a tumor biopsy will be required.
4. Previously treated patient with histologically or cytologically confirmed (archival tissue accepted) locally advanced or metastatic non-small cell lung cancer (NSCLC) and is not a candidate for definitive therapy
    - **Phase 1**: No test for mutational status is required
    - **Phase 2**: Documented EGFR or HER2 exon 20 insertion mutation (including duplication mutations) in NSCLC patients. Patients will be enrolled based on documentation of mutational status using PCR or a validated next generation sequencing detection analysis test.
        - Documented *EGFR* exon 20 insertion mutation, including D770_N771insSVD, D770_N771insNPG, V769_D770insASV, H773_V774insNPH, or any other *EGFR* exon 20 in-frame insertion mutation (including duplications).
        - Documented *HER2* exon 20 insertion mutation, including A775_G776insYVMA, G776_V777insVC, or P780_Y781insGSP, or any other *HER2* exon 20 in-frame insertion mutation (including duplications).
5. Patient has measurable NSCLC disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Metastatic lesions in bone, CNS, or in brain cannot be used for target lesions.
6. Prior treatment status:
    - **Phase 1:** Patient with refractory NSCLC to available standard therapies
    - **Phase 2:** Progression after at least one systemic therapy for locally advanced or metastatic disease
7. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

8. Patient has recovered from prior systemic therapy for metastatic disease to Grade ≤1 for non-hematologic toxicities (except for Grade ≤2 peripheral neuropathy) and has adequate hematologic, hepatic, and renal function at Baseline, as defined by:
   - Leukocytes $\geq 3.0 \times 10^9$/L
   - Absolute neutrophil count (ANC) must be $\geq 1.5 \times 10^9$/L
   - Platelet count $\geq 100 \times 10^9$/L
   - Hemoglobin ≥9.0 g/dL
   - Total bilirubin ≤2 mg/dL; if hepatic metastases are present, ≤2.5×ULN
   - SGOT (AST) and SGPT (ALT) ≤2.5×ULN with the following exception; Patients with liver metastases AST, ALT ≤5×ULN
9. Patient is willing to practice 2 forms of contraception, one of which must be a barrier method. Female patients of childbearing potential must use an effective method of birth control (e.g., oral contraceptive, intrauterine device, bilateral tubal ligation/occlusion, condoms, or diaphragm, not engaging in sexual intercourse) during treatment period and 3 months thereafter. Males must use an effective method of birth control (e.g., condoms, vasectomy, not engaging in sexual intercourse) during treatment period and 3 months thereafter.
10. Females of childbearing potential must have a negative pregnancy test within 7 days prior to Day 1. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) with no other medical reasons or who are surgically sterilized do not require this test.

4.2 Exclusion Criteria

1. **Phase 2 :** Patient has EGFR T790M mutation or any other acquired EGFR exon 20 point mutation
2. **Phase 2 :** Patient has had previous treatment with poziotinib. The currently approved TKIs that are not considered to be exon 20 insertion-selective are permissible.
3. Patient is concurrently receiving chemotherapy, biologics, immunotherapy for cancer treatment; systemic anti-cancer treatment or investigational treatment should not be used within 2 weeks prior to Cycle 1, Day 1;local radiation therapy for bone pain may be allowed.
4. Patient has used strong inhibitors/inducers of CYP3A4 and CYP2D6 within 1 month prior to Cycle 1, Day 1.
5. Patient has brain metastases and is clinically symptomatic, requires high dose or increasing doses of systemic corticosteroids, or needs any anticonvulsant therapy for metastatic brain disease.
6. Patient has a high risk for or history of congestive heart failure (CHF) Class III/IV according to the New York Heart Association (NYHA) Functional Classification or serious cardiac arrhythmias requiring treatment. Cardiac ejection fraction <50% as determined by either echocardiogram (ECHO) or multi-gated acquisition (MUGA) during Screening.

7. Patient has had another primary malignancy within 3 years prior to starting study treatment, except for adequately treated basal or squamous cell carcinoma of the skin or cancer of the cervix in situ
8. Patient is confirmed to have clinically significant or recent acute gastrointestinal disease presenting as diarrhea and/or coloenteritis as a main symptom (ie, acute enteritis, malabsorption, or Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) Grade 2 or above diarrhea due to other etiologies)
9. Patient has an active Grade ≥2 skin disorder, rash, mucositis, or skin infection that needs medication or therapy or existing Grade ≥2 skin toxicity from previous therapies; Grade >2 neuropathy, Grade ≥2 pneumonitis.
10. Patient is unable to take drugs orally due to disorders or diseases that may affect gastrointestinal function, such as inflammatory bowel diseases (eg, Crohn's disease, ulcerative colitis) or malabsorption syndrome, or procedures that may affect gastrointestinal function, such as gastrectomy, enterectomy, or colectomy
11. Patient has an active liver disease or biliary tract disease (except for Gilbert's disease, asymptomatic biliary stones, liver metastasis, or stabilized chronic liver diseases). Patient has active HBV or HCV infection.
12. Patient is HIV antibody positive.
13. Patient currently has or has had interstitial lung disease in the past
14. Patient has known hypersensitivity to poziotinib or has a history of allergic reactions attributed to chemically similar compounds or other tyrosine kinase inhibitors (TKIs)
15. Patient has an active uncontrolled infection, underlying medical condition, or other serious illness that would not be appropriate for this study
16. Patient has unstable, uncontrolled, active bleeding disorders that the investigator considers that the patient could be at increased risk or not be suitable for treatment in this study
17. Patient is pregnant.
18. Women who are breastfeeding or women who are not willing to stop breastfeeding during study treatment period and for 30 days after the last dose of study drug.

4.3 Patient Discontinuation/Withdrawal Criteria

Patients can withdraw from participation in this study at any time, for any reason, specified or unspecified, and without prejudice.

All treated patients must be withdrawn from study drug administration for the following reasons:

- Development of an adverse event (AE) that interferes with the patient's participation
- Initiation of non-protocol therapy
- Development of progressive disease (PD)
- Patient withdrawal of informed consent
- Delay of poziotinib administration for >28 days since last poziotinib administration
- Investigator decision
- Sponsor decision

- Lost to follow-up
- Pregnancy
- Death

The reason for the patient discontinuing study treatment or terminating from the study must be recorded on the case report form (CRF). Patients who discontinue treatment or who are withdrawn from treatment will return for a Safety Follow-up Visit 35 (±5) days after the last dose of poziotinib or prior to beginning a new treatment, whichever is first. If death is recorded as the reason for study discontinuation, the cause of death should be recorded on the CRF.

After study drug discontinuation, patients who have consented will be contacted every 3 months, for up to 2 years after patient's first dose of poziotinib, for survival assessment.

All patients will be withdrawn from the Long-Term Follow-up for the following reasons:

- Patient withdrawal of informed consent
- Investigator decision
- Sponsor decision
- Lost to follow-up
- Death

5 STUDY PROCEDURES

The Schedules of Study Assessments and Procedures is presented in **Appendix 1** and **Appendix 2**.

5.1 Screening

Informed Consent is to be obtained prior to the start of any protocol-specified assessments or procedures. The procedures and evaluations required for enrollment into the study are summarized below. All potential study patients will undergo a Screening Visit and eligibility determined up to 30 days prior to Day 1. The results of any procedures or laboratory assessments performed prior to the signing of Informed Consent as part of the site's routine standard of practice may be allowed for use as a Screening Assessment with Sponsor's approval. This information is to be discussed with the Medical Monitor before the patient is enrolled in the study. All procedures are to be performed as outlined in **Appendix 1** and **Appendix 2** prior to the start of study treatment, unless otherwise noted.

5.2 Patient Assignment

Each patient who signs an Informed Consent Form for participation in this study will be assigned a unique Patient ID according to the instructions provided in the study binder.

Confirmation of eligibility is to be received by the investigational site from Spectrum or designated Contract Research Organization (CRO) prior to enrollment of a patient. After a patient has signed the ICF, the investigator or site staff should assign a Patient ID. The Patient ID will include two parts: the site number assigned by Spectrum will be comprised of 5 digits with a 2-digit alphabetic country code [Reference ISO 3166] followed by a 3-digit site specific numeric

code and a 3-digit patient sequential number, unique to a site, separated by a hyphen (ie, JP001-001).

A CRF will only be completed for patients who are enrolled and receive a Patient ID.

5.3 Timing of Assessments and Procedures

5.3.1 Screening Visit

Informed Consent must be obtained prior to any study procedures. The following assessments should be performed at the Screening Visit within 30 days of Day 1.

- Verify existing pathology and tissue-based mutation diagnostic records, and available imaging test reports from medical records before consenting the patient. Tumor assessment scans for eligibility assessment must be completed within 4 weeks of Cycle 1, Day 1.
- Informed Consent
- Patient ID
- Relevant medical history
- Demographic data
- Height and weight
- Complete physical examination, including auscultation
- Vital signs
- Resting O_2 saturation
- Pulmonary function assessment (Chest X-ray and pulmonary function test)
- Eastern Cooperative Oncology Group (ECOG) Performance Status assessment
- Pregnancy test (beta human chorionic gonadotropin [β-HCG]) in women of childbearing potential
- Hepatitis B tests (surface antigen, core antibody, and surface antibody)
- Hepatitis C antibody test
- HIV antibody test
- Screening/Baseline tumor assessment within 4 weeks prior to **Cycle 1**, **Day 1**
- Baseline brain MRI scan for patients with known brain metastases (if needed)
- Tissue and whole blood collection
  - Phase 2 only: Tissue sample (archival sample or tissue biopsy) for genotyping
  - Phase 2 only: Whole blood sample for plasma circulating tumor DNA (ctDNA) analysis
  - All patients: Whole blood sample for CYP2D6 genotyping (metabolic profile analysis)
- Complete blood count (CBC) with 5-part differential and platelets prior to poziotinib administration (may be obtained up to 14 days prior to **Cycle 1**, **Day 1**)
- Serum chemistry, including KL-6 and C-reactive protein (may be obtained up to 14 days prior to **Cycle 1**, **Day 1**)

- 12-lead electrocardiogram (ECG)
- Echocardiogram or MUGA scan to evaluate cardiac ejection fraction (ECHO or MUGA results within 6 months prior to Cycle 1, Day 1 is acceptable if there is no major known cardiac event during this period)
- Adverse event assessment using NCI CTCAE, version 5.0, record SAEs before the first dose of poziotinib
- Concomitant medications

5.3.2 Treatment Period – Cycle 1, Day 1

- Eligibility confirmation
- Admission to hospital (**Phase 1 – Dose-Finding only**)
- Weight
- Physical examination
- Vital signs
- Resting O_2 saturation
- Pulmonary function assessment (if not evaluated within the past 6 months)
- ECOG Performance Status assessment
- Pregnancy test in women of childbearing potential (if Screening pregnancy test was more than 7 days prior to **Day 1**)
- CBC with 5-part differential and platelets prior to poziotinib administration. If the Screening CBC is within 14 days of Cycle 1 Day 1, the Day 1 CBC test is not required.
- Serum Chemistry (including KL-6 and C-reactive protein if not assessed during Screening). If the Screening Serum Chemistry is within 14 days of Cycle 1 Day 1, the Day 1 test is not required.
- 12-lead ECG predose and at 1 hour and 2 hours (±15 min) postdose
- Pharmacokinetic blood sampling:
  - **Phase 1:** Intensive PK blood samples drawn predose and 30 minutes, 1 and 2 hours (±15 minutes) postdose, and 3, 4, 6, 8, 12, 14 (±30 minutes) postdose, and 24 hours (±1 hour) postdose
  - **Phase 2:** Sparse PK blood sampling taken predose and at 1 hour and 2 hours (±15 min) postdose
- Dispense poziotinib
- Dispense supportive care medications as needed
- Adverse event assessment using NCI CTCAE, version 5.0
- Concomitant medications review
- Patient Diary dispensed

5.3.3 Phase 1, Cycle 1, Days 2-14, in the Hospital

The following evaluations will be done on Days 7, and 14:

- Physical examination
- Vital signs
- Resting O_2 saturation
- Pulmonary Function Assessment
- ECOG Performance Status assessment
- CBC with 5-part differential and platelets,
- Serum Chemistry
- ECGs (predose)
- Pharmacokinetic blood sampling (Day 13 only):
  - Intensive PK blood samples drawn
    - Predose
    - 30 minutes, 1 and 2 hours (±15 minutes) postdose
    - 3, 4, 6, 8, 12, and 14 hours (±30 minutes) postdose
    - 24 hours (±1 hour) postdose
- Adverse event assessment using NCI CTCAE, version 5.0
- Concomitant medications
- Discussion and assessment of breathing signs and symptoms; assessment of pulse oximetry measurements

5.3.4 Criteria for Discharge After Day 14 During DLT Evaluation Period (Phase 1 only)

The patient must meet the following criteria for hospital discharge after Day 14 during the DLT evaluation period:

- In the Investigator's clinical judgement, the patient is healthy enough to be discharged based on the evaluations in Section 5.3.3.
  - If the patient doesn't acceptably pass all evaluations in Section 5.3.3, the patient must continue to be hospitalized until reaching the criteria in Section 5.3.4 or complete the DLT evaluation period (1 cycle). Only the assessments that the patient didn't pass to be discharged need to be repeated in order to be discharged. It is unnecessary to recheck all evaluations.
- The investigator has documented all evaluations and assessments on the medical record.
- Adverse events have returned to Grade $\leq$1 or Baseline level
- No ongoing SAE.
- It has been established that the patient has access to emergency medical care. If the patient lives far from the clinical site or has difficulty traveling to the site, it has been confirmed that the site and neighborhood medical institution are well-cooperated.
- It has been confirmed that family or caregiver cooperation is established.
- The patient has been instructed on how to contact the study physician and site. Patients will receive a study information card, including information for 24-hour contact access to the physician and the study site.

5.3.5 Phase 2, Cycle 1, Day 8 and 15 (±2 days) (Phase 2 Only)

- Physical examination
- Vital signs
- Resting O_2 Saturation
- Pulmonary Function Assessment
- ECOG Performance Status assessment
- Adverse event assessment using NCI CTCAE, Version 5.0
- Concomitant medications
- Dispense supportive care medications as needed
- Review patient diaries

5.3.6 Treatment Period - Telephone Contact (Both Phases)

Cycle 1, Day 22 (±2 days)
Cycle 2 - Days 8, 15, and 22 (±2 days)
Cycles 3+ - Day 15 (±2 days)

- Adverse event assessment using NCI CTCAE, Version 5.0
- Concomitant medications

5.3.7 Treatment Period Office Visit – Cycle 2+, Day 1

- Weight
- Physical examination
- Vital Signs
- Resting O_2 Saturation
- ECOG Performance Status assessment
- Pregnancy test in women of childbearing potential
- Complete blood count with 5-part differential
- Serum chemistry, including KL-6 and C-reactive protein
- Imaging Session
  - Tumor assessment (to be performed at approximately 4 weeks (Cycle 2, Day 1 [up to Cycle 2, Day 10]), 8 weeks (Cycle 3, Day 1 [up to Cycle 3, Day 10, with at least 28 days from previous tumor assessment]), and approximately every 8 weeks [±10 days)]thereafter)
  - Whole blood samples (20 mL) on Cycle 2, Day 1, Cycle 3, Day 1, and then every 8 weeks
  - Pulmonary Function Assessment
- 12-lead ECG prior to that day's patient dose and 1 and 2 hours postdose (**Cycle 2 only**)

- Pharmacokinetic blood sampling (**4 mL**):
  - **Phase 2:** Predose and 1 and 2 hours postdose (±15 minutes) samples drawn on Cycle 2, Day 1 only and predose on Cycle 3, Day 1 and then every 8 weeks.
- Collect and dispense poziotinib
- Dispense supportive care medications as needed
- Adverse event assessment using NCI CTCAE, Version 5.0
- Concomitant medications
- Patient Diary collected and dispensed

5.3.8 Safety Follow-up/End-of-Study Visit (35 [±5] Days after Last Dose of Study Treatment)

The **Safety Follow-up Visit** is required 35 (±5) days after the last dose of poziotinib is administered. The following assessments are to be performed at this visit:

- Weight
- Physical examination
- Vital signs
- Pulmonary Function Assessment and Resting O_2 Saturation
- ECOG Performance Status assessment
- Pregnancy test in women of childbearing potential
- Tumor assessment (unless the patient has documented disease progression or has undergone a tumor assessment within the previous 8 weeks)
- Complete blood count with 5-part differential
- Serum chemistry, including KL-6 and C-reactive protein
- 12-lead ECG
- Newly biopsied tumor tissue taken from patients who progress (optional, but highly encouraged) (**Phase 2 only**)
- Whole blood samples for plasma ctDNA analysis if the patient progresses (optional) (**Phase 2 only**)
- Adverse event assessment using NCI CTCAE, Version 5.0
- Concomitant medications
- Patient diary collected

5.3.9 Long-Term Follow-up – Every 3 Months

- After study drug discontinuation, patients will be contacted every 3 months, for up to 2 years after patient's first dose of poziotinib, for survival assessment.

5.4 Description of Study Assessment Parameters

5.4.1 Relevant Medical History

At Screening, the patient's relevant medical history, including type of cancer, HER2 and EGFR status (optional in Phase 1), history of tobacco use, previous therapies, and current medications will be collected.

5.4.2 Physical Examination

A complete physical examination, including a description of external signs of the neoplastic disease and co-morbidities, will be performed at Screening and Day 1 of each cycle, and at the Safety Follow-up Visit. Symptom-directed examinations are required at other visits. In addition, physical examination will be done on days 7 and 14 of Cycle 1 while Phase 1 patients are in the hospital, and Cycle 1, Days 8 and 15 for Phase 2 patients. Physical examinations are to be completed by a physician or other health professional licensed to perform such examinations. Findings will be documented in the patient's medical record and on the appropriate CRF pages. Any abnormalities are to be recorded on the AE CRF.

5.4.3 Vital Signs

Vital signs, to include temperature, blood pressure, heart rate, and respiratory rate, are to be recorded at Screening and Day 1 of each cycle and at the Safety Follow-up Visit. In addition, vital signs will be taken on days 7 and 14 of Cycle 1 while Phase 1 patients are in the hospital, and Cycle 1, Days 8 and 15 for Phase 2 patients the patient is in the hospital. Heart rate and blood pressure will be recorded before poziotinib administration.

5.4.4 Pulmonary Function and Resting Oxygen Saturation

During the Screening Period the patient will be assessed for cofactors that may predispose to the development of pneumonitis including previous pneumonitis including radiation pneumonitis, radiation therapy to the lung fields, prior extensive chemotherapy, prior checkpoint inhibitor therapy, and connective tissue disease (rheumatoid arthritis, scleroderma, LES).

In Phase 1, resting O_2 saturation will be assessed at Screening, daily for the first 2 weeks of Cycle 1, while the patient is hospitalized, on Day 1 of all subsequent cycles, and at the Safety Follow-up Visit. In Phase 2, resting O_2 saturation will be assessed at Screening, Cycle 1, Days 1, 8, and 15, on Day 1 of all subsequent cycles, and at the Safety Follow-up Visit.

In both phases, screening and monitoring for evidence of interstitial lung disease (ILD) by verbal discussion with the patient regarding breathing signs and symptoms, physical examination including auscultation, and pulmonary function tests (spirometry) will be performed.

- In Phase 1, pulmonary function will be assessed at Screening, on Day 1 of Cycles 1-3, every 8 weeks thereafter, and at the Safety Follow-up Visit. In addition, evidence of ILD will be assessed on Cycle 1, Days 7 and 14 while the patient is in the hospital.
- In Phase 2, pulmonary function will be assessed at Screening, on Day 1 of Cycles 1-3, every 8 weeks thereafter, and at the Safety Follow-up Visit. In addition, evidence of ILD will be assessed on Cycle 1, Days 8 and 15.

5.4.5 ECOG Performance Status

Patients' Performance Status will be evaluated using criteria as developed by the Eastern Cooperative Oncology Group **(Appendix 3)** at Screening and Day 1 of each cycle and at the Safety Follow-up Visit. In addition, in Phase 1, ECOG will also be evaluated on days 7 and 14 of Cycle 1 while the patient is in the hospital and in Phase 2 will be assessed on Cycle 1, Days 8 and 15.

5.4.6 Tumor Assessment

Results of standard-of-care tests or examinations performed within 28 days prior to Cycle1, Day 1 may be used for the Screening/Baseline tumor assessment. Tumor assessments must be performed using computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI). The image will be reviewed by a local radiologist as the Baseline image for response assessment and per the Investigator's standard of care.

For patients with known brain metastases, a Baseline brain MRI scan (within 28 weeks prior to Cycle 1, Day1) will also be performed to assess the status of brain metastases if present.

Tumor assessments will also be performed at 4 weeks (Cycle 2, Day 1 [up to Cycle 2, Day 10]), 8 weeks (Cycle 3, Day 1 [up to Cycle 3, Day 10, with at least 28 days from previous tumor assessment]), and then every 8 weeks (±10 days) for up to 24 months or until disease progression, death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal or for a maximum of 24 months.

Tumor assessment will be performed at the Safety Follow up Visit unless the patient has documented disease progression or has undergone a tumor assessment within the previous 8 weeks.

Each subsequent tumor assessment must use the same baseline radiographic technique, either CT, PET/CT, or MRI. Tumor assessments will be made according to RECIST criteria, Version 1.1 **[22]** using appropriate radiographic imaging or other techniques. For radiographic assessment, CT, PET/CT, or MRI must be performed at every assessment. Patient enrollment and clinical decisions will be based on local review.

Measurable and non-measurable lesions that will not be followed by radiographic methods should be documented appropriately.

5.4.7 Tissue, Plasma, and Whole Blood Samples

Tissue and plasma samples (for mutational detection) are not required for patients in Phase 1 of the study.

5.4.7.1 Tissue and Whole Blood Samples

Tissue (Phase 2 Only): A tissue sample is required prior to Cycle 1, Day 1. If an archival tissue sample is not available, a tumor biopsy will be required.

The tissue from the biopsy will be processed according to site procedures into a Formalin-Fixed Paraffin-Embedded (FFPE) block. A tissue sample collected at disease progression is optional. Embedded tumor tissue will be shipped to the central laboratory and stored at room temperature. DNA and/or RNA will be extracted from FFPE samples and subjected NGS mutational detection analysis (companion diagnostic development and resistance mechanism study).

5.4.7.2 Whole Blood Samples

- **Phase 1 and Phase 2:** Whole blood samples (4 mL) will be collected once at Screening for CYP2D6 genotyping (metabolic profile analysis). Whole blood samples will be shipped at room temperature.
- **Phase 2 only:** Whole blood samples (20 mL) will be drawn for plasma ctDNA analysis at Screening and when the patient progresses (collecting a sample at progression is optional but is highly encouraged). Blood samples will be processed at the site and shipped to the lab for storage at -70°C until ready for testing (companion diagnostic development and resistance mechanism study). Blood samples will also be collected on Day 1 of Cycles 2 and 3 and then every 8 weeks thereafter in order to correlate poziotinib concentrations with ctDNA and efficacy.

5.4.7.3 Sample Retention

All samples will be banked at the lab for 5 years or for the duration that is compliant with local law. After this time, if no further analysis is planned, the Sponsor will request that the samples be destroyed as per local storage procedures.

Banked samples will not be returned to the patient for any reason, even if the patient withdraws consent during the term of the study or after the patient withdraws from the study. These samples will be destroyed as described above or upon the request for destruction from the subject. In addition, even if the patient withdraws consent to use/store the optional samples while participating in this study, the patient can continue participating in this study if they wish.

Genetic testing results will not be provided to patients unless requested by patients' physicians.

5.4.8 Pharmacokinetics

Phase 1: The pharmacokinetics of poziotinib and M1 and M2 metabolites evaluated. Patient will have intensive PK blood samples drawn (4 mL whole blood each time point) on **Cycle 1, Day 1** and **Cycle 1, Day 13** at the following timepoints:

- Predose
- Postdose
  - 30 minutes, 1, and 2 hours (±15 minutes)
  - 3, 4, 6, 8, 12, and 14 hours (±30 minutes)
  - 24 hours (±1 hour)

In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea, pneumonitis), PK blood samples will be collected as soon as possible following the onset of the AE, and the time of the last dose and the time of blood draw should be recorded.

Phase 2: All patients will have blood samples drawn predose and at 1 hour and 2 hours (±15 min) postdose for sparse PK sampling and time-matched concentration- ECG analysis on Day 1 of Cycle 1 and Day 1 of Cycle 2 for time-matched concentration- ECG analysis. In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea, pneumonitis), blood samples will be collected as soon as possible following the onset of the AE and the time of the last dose and the time of blood draw should be recorded. Blood samples will

also be collected predose on Cycle 3, Day 1 and every 8 weeks thereafter in order to correlate poziotinib concentrations with ctDNA and efficacy; the time of the last dose and the time of blood draw should be recorded.

5.4.9 Clinical Laboratory Tests

On Day 1 of each 28-day cycle, the patient's absolute neutrophil count (ANC) must be $\geq 1.5 \times 10^9$/L and platelet count must be $\geq 100 \times 10^9$/L before administering poziotinib. A local laboratory will be used to process all clinical specimens. The following clinical laboratory parameters will be evaluated in this study:

- **Complete Blood Count (CBC):** A CBC, including white blood cells (WBC), with 5-part differential, hemoglobin, and platelets will be performed at Screening, Day 1 of each cycle, and at the Safety Follow-up Visit. In addition, CBC will be done on Days 7 and 14 of Cycle 1 while the patient is in the hospital. The results of the laboratory assessments should be evaluated and medically accepted by the responsible physician before the start of each cycle. **If the Screening Visit is within 14 days of Day 1, the Day 1 CBC test is not required.**
- **Chemistry Panel:** A comprehensive chemistry and electrolytes, including blood urea nitrogen (BUN), AST/SGOT, ALT/SGPT, alkaline phosphatase (ALP), total bilirubin, albumin, calcium, lactate dehydrogenase, sodium, potassium, chloride, phosphate, magnesium, creatinine, glucose KL-6, and C-reactive protein, will be performed at Screening, Day 1 of each cycle, and at the Safety Follow-up Visit. **If the Screening Visit is within 14 days of Day 1, the Day 1 serum chemistry panel is not required.** In addition, a chemistry panel will be done on Days 7 and 14 of Cycle 1 while the patient is in the hospital.
    - **Special note for the Day 1 sampling of each cycle:** If possible, blood samples should be drawn on **Day 1** of each cycle (prior to treatment); however, for logistical reasons, it is also acceptable to draw samples for assessment up to 7 days prior to the start of a cycle. The results of the laboratory assessments should be evaluated and medically accepted by the responsible physician before the start of each cycle.
- **Pregnancy Test:** A urine or plasma β-hCG test will be performed at Screening, Cycle 1, Day 1 (if the Screening pregnancy test was more than 7 days prior to Day 1), Day 1 of each cycle, and at the Safety Follow-up Visit for all women of childbearing potential.

5.4.10 Hepatitis B, Hepatitis C, and HIV Tests

Tests will be for hepatitis B surface antigens and hepatitis B core and surface antibodies. If the hepatitis B surface antigen test is positive, the patient will be excluded from the study. If only the hepatitis B core antibody and/or hepatitis B surface antibody is positive, a serum hepatitis HBV DNA test will be done. If this test is positive the patient is excluded from the study.

If hepatitis C antibody test is positive, an HCV RNA test will be done. If this test is positive, the patient is excluded from the study.

Whole blood sample is used for the HIV test. If this test is positive the patient is excluded from the study.

5.4.11 Electrocardiogram

A 12-lead ECG will be performed at Screening, predose and at 1 hour and 2 hours (±15 min) postdose on Cycle 1, Day 1 and Cycle 2, Day 1 for time-matched concentration-ECG analysis, and at the patient's Safety Follow-up Visit. For Phase 1 patients, ECG will be performed predose on Days 7 and 14 of Cycle 1 while the patient is in the hospital. All ECGs will be sent for central analysis.

5.4.12 Cardiac Ejection Fraction

Cardiac ejection fraction will be assessed by either echocardiogram or multi-gated acquisition (MUGA) scan at Screening, and the Investigator can order subsequent tests based on patient standard of care. Results within 6 months prior to Cycle 1, Day 1 is acceptable if there is no major known cardiac event during this period.

5.4.13 Concomitant Medications

All medications administered from Screening to the Safety Follow-up Visit will be recorded on the CRF. A concomitant medication is any medication a patient is using from Cycle 1, Day 1 to the Safety Follow-up Visit. Poziotinib is not considered a concomitant medication.

All concomitant medications recorded at study entry must have a related, ongoing concomitant illness listed under the medical history at the time of patient entry into the trial. Patients may continue to use any ongoing medications not prohibited by the protocol.

All prescription and over-the-counter medications at trial entry as well as any new medications started during the trial must be documented on the CRF and in the source documents. The documentation should continue until 35 (±5) days after the last dose of poziotinib.

Premedications (such as antiemetics) used for supportive care are allowed as per institutional standards or guidelines and Investigator discretion.

Other supportive and palliative therapies may be allowed during the study upon prior authorization from Sponsor's Medical Monitor.

5.4.13.1 Possible Drug Interactions

Poziotinib is a substrate for cytochrome P450 (CYP) 3A4 and 2D6 enzymes. Patients may be taking medications that are strong inhibitors or inducers of these two enzymes **(Table 2)**. The plasma concentration of poziotinib could be different in these patients. The Investigator should try to substitute a medication that is not a strong inhibitor/inducer of these enzymes, if possible. If there is not an available substitute for a medication that a patient is taking, or the patient is not willing, to change medications, the Investigator must monitor the patient closely for possible AEs or changes in response.

Poziotinib is also a moderate inhibitor of CYP2C8 and CYP2D6; patients who take medications that are sensitive substrates for these two enzymes **(Table 2)** should be followed closely for possible changes in the patient's response to these medications. Patients should be told to avoid grapefruit juice, Seville oranges, and St. John's Wort during the study treatment.

Table 2 Examples of Important Clinical Inhibitors/Inducers/Substrates for P450 Enzymes Involved in the Metabolism of Poziotinib

CYP	Strong Inhibitor	Strong Inducer	Sensitive Substrate
2D6	Bupropion, Fluoxetine, Paroxetine, Quinidine, Terbinafine	None	Atomoxetine, Desipramine, Dextromethorphan, Eliglustat, Nebivolol, Nortriptyline, Perphenazine, Tolterodine, Venlafaxine
3A4	Boceprevir*, Cobicistat, Conivaptan*, Danoprevir* and Ritonavir, Elvitegravir* and Ritonavir, Grapefruit Juice, Indinavir** and Ritonavir, Itraconazole, Ketoconazole, Lopinavir and Ritonavir, Paritaprevir / Ritonavir / Ombitasvir** + Dasabuvir*, Posaconazole*, Ritonavir, Saquinavir** and Ritonavir, Telaprevir**, Tipranavir* and Ritonavir, Troleandomycin*, Voriconazole	Carbamazepine, Enzalutamide, Mitotane, Phenytoin, Rifampin, St. John's Wort	Not Applicable
2C8	Not Applicable	Not Applicable	Repaglinide

Source:
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

*: Not approved in Japan
**: Withdrawn from Japanese market

5.4.13.2 Premedication and Supportive Treatment

Pre-medications, as per Institutional standard of care as determined by the Investigator, should be administered before poziotinib on **Day 1**. All supportive medications for potential diarrhea and rash management should be distributed to the patient on **Day 1** with instructions on their use. During Cycle 1, use of growth factors is not allowed in the dose-finding phase of the study.

Preliminary information from **Cohort 1** in SPI-POZ-202 suggest that dose interruptions should be minimized in order to reduce the risk of progression. Supportive medications, including early steroid use, should be considered even in the presence of low-grade "on-target" toxicity (eg, rash, diarrhea).

5.4.13.3 Uses of Warfarin or Other Similar Anticoagulants

Warfarin or other similar anticoagulants should be used cautiously during treatment with poziotinib. When it cannot be avoided, regular monitoring of INR is required and prior authorization from the Sponsor's Medical Monitor is required.

5.4.13.4 Other Anticancer Therapies

No additional cytotoxic agents, biologic therapy, or immune response modifiers for cure-intent purpose are to be administered to patients until study treatment has been discontinued.

5.4.13.5 Drugs that Affect Gastric pH

In vitro studies have shown that the solubility of poziotinib is pH dependent. Poziotinib is highly soluble at acidic pH, its solubility is significantly reduced at neutral or basic pH. Although the effect of pH on systemic exposure of poziotinib has not been established, based on the solubility profile, it is quite likely that the absorption of poziotinib could be lower at higher pH.

Because proton pump inhibitors (PPIs), H2 histamine receptor antagonists and antacids increase the gastric pH, we recommend that if possible, concomitant administration of long-acting PPIs or H2 receptor antagonists with poziotinib should be avoided, which is similar to the instructions for other TKIs. If needed, patients may take short-acting antacids (e.g., Maalox®) at least 4 hours before or after poziotinib administration. Patients should also avoid drink water that is alkaline.

5.4.13.6 Prohibited Therapies or Medications

No other anti-cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or experimental medications, are permitted during the trial. Any disease progression that requires anti-tumor therapy will be cause for discontinuation from the study

5.4.14 Patient Discharge

All patients in the Phase 1 dose-finding phase will be hospitalized for at least 14 days from Cycle 1, Day 1 of the study. In order to be discharged from the hospital, the patient must not have any ongoing SAEs or DLTs, and in the Investigator's judgement, the patient is healthy enough to be discharged. At the discretion of the Investigator, the patient may continue to be hospitalized after Day 14 if in his or her clinical judgement this would be in the best interest of the patient. Hospitalization may continue for as long as medically necessary. Prior to patient discharge, the evaluations described in Section 5.3.3 of the protocol will be performed to assess and document the patient's readiness to be discharged according to the criteria in Section 5.3.4.

6 STUDY DRUG AND PHARMACEUTICAL INFORMATION

6.1 Poziotinib

Poziotinib will be supplied by Spectrum.

6.2 Poziotinib Composition

The poziotinib drug substance is a hydrochloride salt of poziotinib and is formulated as a tablet for oral administration.

6.3 Poziotinib Supply and Labeling

Poziotinib tablets are supplied in 2.0-mg and 8.0-mg dose strengths.

6.4 Poziotinib Storage and Handling

Poziotinib supplies must be stored in a secure, limited-access location under the storage conditions specified on the drug supply label.

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

6.5 Poziotinib Administration

Poziotinib should be taken with food and a glass of water (approximately 240 mL) at approximately the same time(s) each day.

Once a Day Dosing:

- **Phase 1, Days 1 to 14:** Patients will be administered poziotinib every 24 (±1) hours
- **Phase 1 post-Hospitalization and Phase 2:** If the daily dose is missed, this dose may be administered any time during the day, but at least 8 hours prior to the next scheduled dose.

Twice a Day Dosing:

- **Phase 1, Days 1 to 14:** Patients will be administered poziotinib every 12 hours (±30 minutes)
- **Phase 1 post-Hospitalization and Phase 2:** The first dose should be taken in the morning and the second dose should be taken approximately 8 to 12 hours later. If a dose is missed, and there is less than 8 hours before the next scheduled dose, the dose should be skipped and the next dose taken as scheduled.

6.6 Diarrhea Management

Tyrosine kinase inhibitors may cause diarrhea when taken. Prophylaxis for this is strongly encouraged and may be addressed by the Investigator using the Institute's standard of care. Any prophylaxis treatment will be recorded in the CRF and the source documents.

6.7 Poziotinib Dose Modification Recommendations

In Phase 1 of the study (Dose-Finding), dosing modifications are not allowed during Cycle 1 but are allowed beginning with Cycle 2. Dosing modifications are allowed at any time during Phase 2 of the study. Dosing modifications are described in **Table 3**. If needed, doses will be reduced by 2 mg/dose (i.e., if on QD, the reduction will be a total of 2 mg/day or if on BID, the reduction will be a total of 4 mg/day), regardless of starting dose, and will be at the Investigator's discretion; the Sponsor should be notified. Dose modifications not described in the table below must be discussed with Medical Monitor for approval. After dose reductions, if the patient has a documented confirmed progression, the patient's dose can be increased up to the starting dose.

Table 3 Recommendations for Dose Reductions after Cycle 1 in Phase 1 and During Phase 2

Related Adverse Event	Triggering Criteria	First Occurrence	Subsequent Occurrences
Diarrhea	Grade ≥3 (Despite optimal anti-diarrhea management)	Stop poziotinib treatment until the AE has improved to Grade ≤1 and then continue treatment at the same dose. or Reduce Poziotinib Dose by 2 mg/dose	Reduce poziotinib dose by 2 mg/dose
	Grade ≥2 for ≥48 hours (Despite optimal diarrhea management)		
Rash	Grade ≥3 (Despite adequate anti-rash management)		
Fatigue	Grade ≥3		
Mucositis/ Stomatitis	Grade ≥3 (Despite optimal management)		
Nausea and/or Vomiting	Grade ≥3 (Despite optimal anti-emetics)		
	Grade ≥2 for ≥48 hours (Despite optimal anti-emetics)		
Rash	Any Grade	Refer to **Appendix 4**	
LVEF Dysfunction	Grade ≥3	Discontinue Treatment	NA
Pneumonitis	Grade 1	Stop poziotinib treatment, assess pulmonary function, and monitor the patient as clinically indicated. Contact the Sponsor to discuss continuing treatment, if resolved.	Discontinue Treatment
	Grade ≥2	Discontinue treatment. Assess pulmonary function and monitor the patient as clinically indicated.	NA

Abbreviation: NA = not applicable.

Dose interruptions should be minimized in order to reduce the risk of progression. Supportive medications, including early steroid use, should be considered even in the presence of low-grade "on-target" toxicity (eg, rash, diarrhea). The respiration and pulmonary function of the patient will be assessed throughout Cycle 1. Interstitial lung disease (ILD) is a clinical diagnosis and if in the opinion of the Principal Investigator the patient has developed signs or symptoms of Grade ≥2 pneumonitis (CTCAE Version 5.0), the patient would stop dosing and depending on the response/recovery may be discontinued from the study. If the patient has developed signs or symptoms of Grade 1 pneumonitis, the Investigator can stop treatment after consultation/discussion with the Medical Monitor.

7 SAFETY ASSESSMENT

7.1 Safety Measures

It is the responsibility of the Principal Investigator to oversee the safety of the patients and to report all AEs/SAEs that are observed or reported during the study, regardless of relationship to study drug or clinical significance.

All patients taking study drug will be subject to DLT assessments, but patients in Phase 2 are unlikely to have DLTs, given that the dose of drug they are taking, is below the MTD determined in Phase 1.

The investigator together with the Sponsor's Medical Monitor will review all safety information per patient at each dose-finding meeting.

Safety data will also be reviewed on a regular basis by Spectrum's study monitoring team, which includes a Clinical Research Associate (CRA), Clinical Trial Manager (CTM), Medical Monitor, and other personnel from the company or its designee.

Adverse events will be characterized by intensity (severity), causality, and seriousness by the Investigator based on the regulatory definitions included below.

This study will utilize the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Scale Version 5.0 for AE grading.

7.2 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. A treatment-emergent AE (TEAE) is any AE that occurs from the first dose of study treatment until 35 (±5) days after the last dose of study treatment.

The study will record all AEs according to the information in **Section 7.3**.

Examples of AEs **include**:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration.
- Signs, symptoms, or the clinical sequelae of a suspected drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication.
- AEs may include pre-treatment or post-treatment events that occur as a result of protocol-mandated procedures, ie, invasive procedures.

Abnormal laboratory results are to be recorded as AEs, if any of the following conditions are met:

- The abnormal laboratory value leads to a therapeutic intervention.

- The abnormal laboratory value is considered to be clinically significant by the Investigator.
- The abnormal laboratory value is predefined as an AE in the protocol or in another document communicated to the Investigator by Spectrum or designee.

Examples of events that **do not** constitute AEs include:

- Medical or surgical procedures (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence does not occur (eg, social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Planned and prescheduled hospitalizations and procedures.
- Progressive disease and death due to disease progression.

The adverse events of special interest identified with poziotinib treatment in this study include diarrhea, skin rash, oral cavity mucositis/stomatitis, fatigue, and vomiting/nausea.

7.3 Guidelines for Recording and Attribution Scoring of Adverse Events

Timely and complete reporting of all AEs is required for all patients. Monitoring and documentation of all AEs allows for identification of potential study-drug or dose-related AEs, and for adherence to regulatory requirements. Please refer to the CRF Completion Guidelines located in the study binder for detailed instructions for AE reporting.

7.3.1 Recording of Adverse Events

All AEs that occur from the first dose of study treatment through 35 (±5) days after the last dose of study treatment is administered are to be recorded on the AE CRF. From the time the study Informed Consent is signed through the first dose of study drug administration, all SAEs are to be recorded. In addition, SAEs that occur after 35 (±5) days after the last dose of study treatment where a causal relationship with the study drug is suspected will also be recorded on the AE CRF.

The resolution of all AEs must be routinely recorded and be reconciled at the end of the study. The following conventions will be followed when patient completes or discontinues from the study:

- If a patient dies, the date of death should be the date of AE stop for all ongoing AEs at the time of death.
- The outcome of the AE is to be followed for 35 (±5) days from the date of discontinuation or until the AE has returned to Grade ≤1. The status of the AE and the date of last contact with the patient will be captured. If the AE has not returned to Grade ≤1 by the end of the study, the AE stop date should be left as ongoing.

All AEs will be classified by CTCAE Grade (**Section 7.3.2**), relationship to study drug (**Section 7.5**), and as serious or nonserious (**Section 7.7**) by the Investigator.

7.3.2 Grading of Adverse Events

This study will utilize the NCI CTCAE Scale, Version 5.0 for AE grading.

7.4 Follow-up of Adverse Events

All AEs and significant abnormal laboratory values are to be followed up in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements (eg, United States [US] Code of Federal Regulations [CFR]).

7.5 Relationship

The Investigator must make a causality assessment and document their opinion as to the relationship of all AEs and SAEs to study treatment **(Table 4)**.

Table 4 Investigator Assessment of Adverse Event Causality

Relationship	Description
Not Related	The event is clearly related to factors other than study treatment, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Unlikely Related	The temporal association, patient history and/or circumstances are such that the study drug or treatment is not likely to have had an association with observed event.
Possibly Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and/or follows a known response pattern to study treatment, but could have been produced by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Probably Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and follows a known response pattern to study treatment, and cannot be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient.
Definitely Related	The event follows a reasonable temporal sequence from the time of study treatment administration, and follows a known response pattern to study treatment, and cannot be reasonably explained by other factors, such as the patient's clinical state, therapeutic interventions, or concomitant medications administered to the patient. In addition, the event either occurs immediately following study treatment administration, improves on stopping study treatment, reappears on repeat exposure, or there is a positive reaction at the application site.

7.6 Expectedness

For investigational drugs, an AE is judged "expected" if its description agrees in nature and severity with the description of AEs previously noted with the study drug as detailed in the current Investigator's Brochure. An "unexpected" AE is one for which the specificity or severity is neither consistent with the current Investigator's Brochure nor the risk information described in the general investigational plan. The Sponsor will be responsible for assessing the expectedness of AEs.

The most common AEs associated with poziotinib treatment include:

- Diarrhea
- Rash
- Stomatitis
- Fatigue
- Vomiting
- Decreased Appetite
- Dry Skin
- Nausea

7.7 Serious Adverse Events

In the interest of patient care and to allow Spectrum to fulfill all regulatory requirements, any SAE, regardless of causal relationship to study treatment, is to be reported to the Sponsor within 24 hours of knowledge of the event. SAEs are defined (21 CFR 312.32, ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A Guideline) as those AEs that meet any of the following criteria:

- Results in death.
- Is life-threatening: ie, any event that, in the opinion of the Investigator, poses an immediate risk of death from that event.
- Requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for study therapy, disease-related procedures, or placement of an indwelling catheter, unless associated with other SAEs).
- Results in a persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Includes important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in this definition.

Adverse events that do not meet any of the above criteria for serious should be regarded as non-serious.

7.7.1 Serious Adverse Event Reporting

From the time the study Informed Consent is signed through the first dose of study drug administration, all SAEs are to be recorded. All SAEs that occur from the first dose of study drug administration through 35 (±5) days after the last dose of study treatment and SAEs that occur after 35 (±5) days after the last dose of study treatment where a causal relationship with the study drug is suspected are to be reported to Spectrum within 24 hours of knowledge of the event.

SAEs are to be reported and the serious adverse event report (SAER) faxed or e-mailed within 24 hours of knowledge of the event to the study Sponsor:

Spectrum Pharmaceuticals, Inc.
Primary Contact: Pharmacovigilance Department
Fax: + 1 (949) 861-6599
E-mail: drugsafety@sppirx.com

Spectrum may request additional information from the Principal Investigator to ensure the timely completion of accurate safety reports. Safety data that are critical to the reportability of an SAE, such as causality assessment and serious criteria, should be included in the initial faxed or e-mailed SAER. If omitted, a timely response to drug safety data queries received from Spectrum or designee is expected.

The Investigator is to take all appropriate therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE are to be recorded in the concomitant medication section of the patient's CRF.

SAEs that are study-treatment related will be followed until resolution or until they have returned to Grade 1, whichever is longer, or until it is determined that the outcome will not change with further follow-up.

Additionally, the SAE is to be entered in the AE section of the CRF. Follow-up SAERs need to be submitted to Spectrum within 24 hours, once additional information regarding the event becomes available (eg, final diagnosis is made, laboratory or test results, event course, outcome, etc).

The Sponsor or its designee will be responsible for reporting SAEs to the regulatory authorities in accordance with applicable expedited reporting regulatory guidelines. The Principal Investigator is responsible for submitting SAEs to his/her site's Institutional Review Board (IRB)/Ethics Committee (EC) through the head of the study site. Copies of each SAER, and documentation of IRB/EC notification and acknowledgement of receipt, will be kept in the Site's Regulatory Binder.

In addition, all deaths that occur on study will be reported on a death CRF page.

7.7.2 Exclusions to Serious Adverse Event Reporting Requirements

The following are not considered SAEs:

- Situations where an untoward medical occurrence did not occur (eg, social and/or convenience admission to a hospital, hospitalization for diagnostic tests such as CT scans).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected prior to first study treatment administration that do not worsen.
- Planned and prescheduled hospitalizations and procedures.
- Progressive disease and death due to disease progression.

7.8 Reproductive Risks

No adequate and well-controlled studies of poziotinib have been conducted in pregnant women. The effect of poziotinib on fertility and fetal development have not been studied in pregnant women. Poziotinib is not recommended for use during pregnancy.

Any pregnancy involving a study patient or a patient's partner that occur from the first dose of study treatment through 35 (±5) days after the last dose of study treatment is to be reported to the Sponsor within 24 hours after the Investigator has gained knowledge of the event via fax or e-mail (see contact information in **Section 7.7.1**). Pregnancies should be followed up until outcome and follow-up information regarding the outcome of the pregnancy should be faxed or e-mailed to Spectrum's Pharmacovigilance Department.

All patients who become pregnant during participation in this study are to be withdrawn from the study.

8 STATISTICAL PLAN

This section contains a brief overview of the statistical analyses planned for this study. A formal pharmacokinetic analysis plan, providing full technical details, will be finalized prior to database lock.

8.1 Sample Size

The current study will be conducted in 2-parts, and the total sample size is approximately 76 patients. Phase 1 is a dose-finding study using 3+3 design to determine the MTD/MAD in each dosing group (QD or BID). Up to 18 patients (up to 3 dose levels, up to 6 patients each level) will be included for DLT evaluation in each dosing group for a total of 36 patients in Phase 1. Patients who discontinue from the study before completing Cycle 1 treatment for reasons other than DLTs are not qualified for DLT evaluation and will be replaced.

Once the dose and regimen are identified, patients will be enrolled into Phase 2 to confirm the safety and evaluate the preliminary efficacy of poziotinib using the selected dose and schedule. In Phase 2, two cohorts of 20 patients each will be enrolled in previously treated NSCLC patients with EGFR Exon 20 insertion mutations and HER2 exon 20 insertion mutations respectively.

Although no a priori test of hypothesis and statistical powering is specified in this study, the statistical methods and test of comparison follows that of SPI-POZ-202, a global pivotal study. In that study, a single arm hypothesis testing to reject non-desired ORR of 17% vs. clinically meaningful ORR of 30% will be evaluated for previously treated NSCLC patients with EGFR Exon 20 insertion mutations and HER2 exon 20 insertion mutations respectively.

The above sample size of 20 patients in each mutation cohort will provide a width for 95% confidence interval of 0.424 for the expected ORR of 30%.

8.2 Method of Treatment Assignment

Patients in Phase 1 will be randomized. There is no randomization in Phase 2 and patients will be enrolled sequentially.

The study design for Phase 1 combines randomization and dose escalation. Randomization will be balanced for every 6 patients and stopped when the MTD/MAD is determined for either the QD or BID group. Patient enrollment will be on hold after 6 patients and resume when the next dose level is determined for both QD and BID groups. This process will continue for every 6 patients until MTD/MAD is determined for one of the dosing schemes, and randomization will be stopped. Then patient enrollment will resume and be on hold for every 3 patients until the

MTD/MAD is determined for the other dosing scheme. Patients who discontinue for reasons other than DLTs will be replaced.

8.3 Analysis Populations

Two analysis populations have been defined for each cohort as follows:

- The **Evaluable Population** consists of all patients in Phase 2 who are enrolled, complete at least 1 cycle of poziotinib treatment, and is evaluable for tumor response based on RECIST, Version 1.1 criteria. The efficacy data will be analyzed using the Evaluable Population.
- The **Safety Analysis Population** includes all patients who signed Informed Consent, enrolled, and received at least 1 dose of poziotinib. All demographics, Baseline characteristics, and safety data will be analyzed using the Safety Analysis Population.

8.4 General Statistical Methods

The Sponsor's Biostatistics and Data Management (BDM) group will be responsible for data management and statistical analysis of this study. All statistical analyses will be performed using SAS for Windows (version 9.3 or higher). Further details of the criteria and conduct of the statistical analyses will be included in the SAP for this study.

Descriptive statistics will be used to describe the recovery of radioactivity and PK parameters. Pharmacokinetic parameters will be computed and analyzed by standard analytical methods.

8.5 Efficacy Analyses

Phase 1: No efficacy analyses will be performed in Phase 1.

Phase 2: The primary efficacy variables, as described below, will be summarized and analyzed descriptively, along with 95% CI, for each cohort based on local radiographic review.

- **Objective Response Rate** (**ORR**) will be assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, version 1.1 **[22]** and is defined as the best response [Complete Response (CR) + Partial Response (PR)] recorded from the start of the study until the end of study in patients who received at least 1 dose of poziotinib. The ORR will be based on the Evaluable Population.

  The primary endpoint analysis will be performed using point estimate and the 95% CI.

8.5.1 Secondary Endpoints

- **DCR,** including CR, PR, and Stable Disease (SD), will be assessed using RECIST, version 1.1 and defined as the proportion of subjects who achieve CR, PR, and SD by the best response from the first dose of poziotinib to the end of study.
- **DoR** will be measured from the date that measurement criteria are first met for CR or PR (whichever status is recorded first) until the first subsequent date that progressive disease or death is documented.
- **PFS** is defined as the number of days from the treatment start date to the date of documented disease progression or death due to any cause. Disease progression will be determined by RECIST Version 1.1.

DCR, DoR, and PFS will be analyzed using descriptive statistics, for each cohort, and with 95% CI for DCR and Kaplan-Meier plot for DoR and PFS.

8.5.2 Exploratory Endpoints

- **Overall Survival** is defined as the number of days from the treatment start date to the date of death due to any cause. After study drug discontinuation, patients who have consented will be contacted every 3 months, for up to 2 years after patient's first dose of poziotinib, for survival assessment.

8.6 Safety Analysis

Safety analysis will include collection of adverse events, DLTs for determination of MTD/MAD, and pharmacokinetics.

8.6.1 Safety and Adverse Events

Safety will be assessed by reported/elicited AEs, laboratory assessments including hematology and chemistry, vital signs, physical examination, and neurological examination. The assessment of treatment-emergent AEs (TEAEs) includes SAEs, AEs leading to study drug discontinuation, and AEs related to the study drug.

The overall incidence of treatment-emergent AEs (TEAE) (ie, AEs occurring from the time the first dose of the study drug until 35 (±5) days after the last dose) and the proportion of patients who discontinue because of a TEAE are the primary safety outcome measures. The number and percent of patients with new-onset TEAEs will be summarized by the MedDRA system-organ-class (SOC) level and Preferred Term for all treated patients, for each cohort. The summary of TEAEs will be presented in the following categories:

- Number and percentage of patients with any TEAEs by SOC and Preferred Term.
- Number and percentage of patients with any SAEs by SOC and Preferred Term.
- Number and percentage of patients with related TEAEs by SOC and Preferred Term.
- Number and percentage of patients with TEAEs causing discontinuation of the study by Body System and Preferred Term.

In addition, the number and percent of patients with TEAEs by grade will be summarized. Serious adverse events reported prior to treatment but after IC will be provided in a listing.

The number of completed cycles will also be summarized and analyzed descriptively.

All laboratory abnormalities will be classified according to CTCAE version 5.0 and summarized by toxicity grade.

8.6.2 Pharmacokinetics

The pharmacokinetics of poziotinib and M1 and M2 metabolites evaluated. The timing for PK blood draws will be:

- **Phase 1:** All patients will have PK blood samples drawn predose and 30 minutes, 1, 2, 3, 4, 6, 8, 12, 14, and 24 hours postdose on Cycles 1, Days 1 and 13. In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea,

pneumonitis), PK blood samples will be collected as soon as possible following the onset of the AE and the time of the last dose and the time of blood draw should be recorded.

- **Phase 2:** All patients in Phase 2 will have blood samples drawn predose and at 1 hour and 2 hours postdose for sparse PK sampling and time-matched concentration- ECG analysis on Cycle 1, Day 1 and Cycle 2, Day 1 for time-matched concentration- ECG analysis. Blood samples will also be collected on Cycle 3, Day 1 then every 8 weeks thereafter in order correlate poziotinib concentrations with ctDNA and efficacy; the time of the last dose and the time of blood draw should be recorded. In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea, pneumonitis), blood samples will also be collected as soon as possible following the onset of the AE and the time of the last dose and the time of blood draw should be recorded.

9 ADMINISTRATIVE PROCEDURES AND STUDY MANAGEMENT

9.1 Investigator and Study Site Responsibilities

The study will be monitored by employees or representatives of Spectrum. CRAs will monitor the site on a periodic basis and perform verification of source documentation for each patient as well as other routine compliance reviews. The Sponsor's Safety Physician and Pharmacovigilance Department will review safety data and be responsible for ensuring timely reporting of expedited SAERs to regulatory agencies, the head of study site and Investigators.

9.1.1 Good Clinical Practice

It is the responsibility of the Principal Investigator to oversee the safety of the patients at their site. The Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, the clinical study protocol, standards stipulated in Article 14, Paragraph 3 and Article 80-2 of the "Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices (MHLW)", and "Ministerial Ordinance on Good Clinical Practice for Drugs (MHLW)". By signing the US Form FDA 1572, "Statement of Investigator", the Investigator commits to adhere to applicable sections of the US CFR parts 50 "Protection of Human Patients", 54 "Financial Disclosure by Clinical Investigators", 56 "Institutional Review Boards", and 312 subpart D "Responsibilities of Sponsors and Investigators". All Investigators will ensure adherence to ICH guidelines for GCP and Clinical Safety Data Management.

9.1.2 Institutional Review Board/Ethics Committee Approval

The head of study site shall assure that the IRB/EC will provide initial and continuing review of the study. Prior to screening and enrollment of study patients, documented IRB/EC approval of the protocol, ICF and any patient materials must be obtained and provided to Spectrum or its designee.

9.1.3 Informed Consent

The Investigator is responsible for preparing the written Informed Consent document for this study. The Sponsor or its designee will provide the Principal Investigator with an Informed Consent template. The Investigator may rearrange or reword the contents of the template, or may

add other elements or language, provided the meaning and content are not changed or deleted. The Sponsor or designee is to review and approve the Informed Consent document that is used by the Investigator for this study prior to IRB/EC submission through the head of the study site.

Written Informed Consent will be obtained from all patients participating in this study before any procedures are conducted, in accordance with ICH GCP and current regulatory requirements. The case history for each patient is to document that the Informed Consent process was obtained prior to participation in the study. The original Informed Consent document will be kept in the patient's record, and a copy will be provided to the patient.

9.1.4 Study Files and Retention of Records

The head of study site, the Investigator and IRB are to retain all study records until after the last approval of a marketing application in Japan or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product or until at least 3 years after the early termination or completion of the study whichever comes later as per GCP. These documents are to be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the head of study site and the Investigator when these documents no longer need to be retained. If the Investigator relocates, or for any reason desires to dispose of the records, the study records may be transferred to another institution, another Investigator, or to the Sponsor upon written agreement between the head of study site and the Sponsor.

9.2 Recording and Collecting of Data

In accordance with ICH and GCP guidelines, the Investigator will maintain complete, accurate, legible, and easily retrievable data, and will allow personnel authorized by the Sponsor access to all study data at any time. Such data shall also be secured in order to prevent loss of data.

9.2.1 Case Report Forms

At scheduled monitoring visits, CRFs will be verified against source documentation and submitted as final data. Any subsequent changes to the CRFs are to be performed in accordance with the Sponsor's standard operating procedures for editing and clarifying CRFs. Data entry will be performed by the sites using an electronic data capture (EDC) system. Comment fields on the CRFs will be used as a means of clarification and communication between the Investigator and the Sponsor; however, comments entered in these fields will not be edited or clarified.

9.2.2 Drug Accountability

In accordance with all applicable regulatory requirements, the Investigator or designated site staff is to maintain study treatment accountability records throughout the course of the study. This person(s) will document the date, time, and amount of poziotinib administered to patients. The CRA will review inventory and accountability documentation during monitoring visits.

The Investigator will not supply the investigational study drugs to any other investigators who are not contracted to perform the study. Investigational study drug use, other than as directed by this protocol, is not allowed.

All unused bottles of poziotinib are to be accounted for at the site and maintained in a secured, locked storage area with access limited to authorized study personnel only. Unused poziotinib

pills and bottles will be returned to the designated depot and destroyed according to local laws, and all applicable policies and procedures.

The head of study site has a responsibility of the investigational product control/accountability within the study site. Accurate records of all Poziotinib supplies received at, dispensed from, returned to, and disposed of by the study site should be recorded and preserved by the head of study site or the investigational product storage manager.

After study conclusion, all unused bottles of poziotinib may be returned to the designated depot following verification of accountability by a Sponsor representative.

9.3 Protocol Compliance

The Principal Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.4 Sponsor Responsibilities

9.4.1 Safety Monitoring

The clinical drug safety of study treatment will be continuously evaluated by the study Medical Monitor and Safety Physician or designee on an ongoing basis during the course of this clinical study. All SAEs related to study treatment in this study and all other ongoing clinical studies with study treatment will be processed in compliance with current regulatory guidelines by the Sponsor's Pharmacovigilance Department. This processing will include a formal assessment of each SAE by drug safety. In addition, a cumulative review of all SAEs from all sources will be assessed periodically.

9.5 Joint Investigator/Sponsor Responsibilities

9.5.1 Access to Information for Monitoring and Auditing

In accordance with ICH GCP guidelines and 21 CFR 312, the CRA/auditor is to have direct access to the patient's source documentation in order to verify the data recorded in the CRFs. The CRA is responsible for routine review of the CRFs at regular intervals throughout the study and to verify adherence to the protocol, as well as the completeness, consistency, and accuracy of the data being recorded. The CRA/auditor is to have access to any patient records needed to verify the entries on the CRFs, as well as access to all other study-related documentation and materials. The head of study site and the Investigator agrees to provide the monitor with sufficient time and facilities to conduct monitoring, and to cooperate with the monitor to ensure that any problems detected in the course of these monitoring/auditing visits are resolved.

9.5.2 Termination of the Study

For reasonable cause, either the Investigator, the head of study site or the Spectrum may terminate the Investigator's participation in this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement (CTA). In addition, the Sponsor may terminate the study at any time upon immediate notice for any reason, including but not limited to, Spectrum's belief that termination is necessary for the safety of patients.

9.6 Confidentiality

All information provided to the Investigator by the Sponsor, including nonclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator. All personnel will handle patient data in a confidential manner in accordance with applicable regulations governing clinical research. Upon request by a regulatory authority such as the US FDA, PMDA in Japan, and other regulatory authorities worldwide, the Investigator/institution is to make available for direct access all requested study-related records or reports generated as a result of a patient's participation in this study. This information may be related in confidence to the IRB/EC or other committee functioning in a similar capacity. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to the Sponsor, or in confidence to the IRB/EC or similar committee, except if required by law.

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Appendix 1 PHASE 1 SCHEDULE OF ASSESSMENTS AND PROCEDURES

Phase 1 Assessment	Screening	Treatment Period [a] (Each Cycle=28 [±3] Days)							Safety Follow-up /End-of-Study Visit	Long-Term Follow-up
		Cycle 1					Cycle 2+			
	Day -30 to Day-1	Day				Day (±2 days)			35 (±5) Days After Last Dose	Every 3 months After Discontinuation
		1	7	13	14	22	1	15		
		Hospitalization								
Informed Consent	x									
Relevant Medical History	x									
Demographic Data	x									
Height and Weight [b]	x	x					x		x	
Physical Examination [c]	x	x	x		x		x		x	
Vital signs [d]	x	x	x		x		x		x	
Resting O_2 Saturation [e]	x	Daily					x		x	
Pulmonary Function [f]	x	x	x		x		x		x	
ECOG Performance Status [g]	x	x	x		x		x		x	
Pregnancy Test [h]	x	x					x		x	
Hepatitis B Surface Antigen Test [i]	x									
Hepatitis B Core Antibody Test [i]	x									
Hepatitis B Surface Antibody Test [i]	x									
Hepatitis C Antibody Test [j]	x									
HIV Antibody Test [k]	x									
Tumor Assessment [l]	x						x		x	
Whole Blood (metabolic profile) [,m]	x									
CBC with 5-part differential and platelets [n]	x	x	x		x		x		x	
Serum Chemistry, including KL-6 and C-reactive protein [o]	x	x	x		x		x		x	
Electrocardiogram [p]	x	x	x		x		x[p]		x	
Echocardiogram or MUGA Scan [q]	x									
PK Blood Samples [r]		x		x						
Dispense Poziotinib [s]		Daily					x			
Dispense Supportive Care Medications, as needed		Daily					x			
Adverse Event Assessment [t]	x	Daily					x		x	
Concomitant Medications	x	x	x		x		x		x	

Phase 1 Assessment	Screening	Treatment Period [a] (Each Cycle=28 [±3] Days)							Safety Follow-up /End-of-Study Visit	Long-Term Follow-up
		Cycle 1					Cycle 2+			
	Day -30 to Day-1	Day				Day (±2 days)			35 (±5) Days After Last Dose	Every 3 months After Discontinuation
		1	7	13	14	22	1	15		
		Hospitalization								
Patient Diary Dispensed/Collected					x		x		x	
Telephone Contact [u]						x		x		x

a) Patients must visit the site at the beginning of each cycle.
b) Height only needs to be recorded during the Screening Visit.
c) A complete physical examination, including auscultation, is required at Screening, Day 1 of each cycle, and at the Safety Follow-up Visit. Symptom-directed exams are required at other visits. In addition, a physical examination will be done on Days 7 and 14 of Cycle 1, while the patient is in the hospital.
d) Vital signs will be measured at Screening, on Day 1 of each cycle, and at the Safety Follow-up Visit. In addition, vital signs will be measured on Days 7 and 14 of Cycle 1 while the patient is in the hospital.
e) Resting O_2 saturation will be assessed daily for the first 2 weeks of Cycle 1, while the patient is hospitalized, on Day 1 of each subsequent cycle, and at the Safety Follow-up Visit.
f) Routine monitoring for evidence of interstitial lung disease (ILD) will be done at Screening, on Day 1 of Cycles 1-3, every 8 weeks thereafter, and at the Safety Follow-up Visit. In addition, evidence of ILD will be assessed on Cycle 1, Days 7 and 14 while the patient is in the hospital.
g) The patient's ECOG score will be evaluated at Screening, on Day 1 of each cycle, and at the Safety Follow-up Visit. In addition, the ECOG will be evaluated on Days 7 and 14 of Cycle 1, while the patient is in the hospital.
h) A urine or plasma pregnancy test (β-hCG), in women of child-bearing potential, is required at Screening, Day 1 of each cycle, and at the Safety Follow-up. A urine sample is only needed if a urine pregnancy test is done.
i) Tests will be for hepatitis B surface antigens and hepatitis B core and surface antibodies. If the hepatitis B surface antigen test is positive, the patient will be excluded from the study. If only the hepatitis B core antibody and/or hepatitis B surface antibody are positive, a serum hepatitis HBV DNA test will be done. If this test is positive the patient will be excluded from the study.
j) If the hepatitis C antibody test is positive, an HCV RNA test will be done. If this test is positive the patient will be excluded from the study.
k) Whole blood samples will be used for the HIV test. If this test is positive, the patient will be excluded from the study.
l) Screening tumor assessment within 28 days prior to Cycle 1, Day1 and additional assessments will be made at 4 weeks (Cycle 2, Day 1 [up to Cycle 2, Day 10]), at 8 weeks (Cycle 3, Day 1 [up to Cycle 3, Day 10, with at least 28 days from previous tumor assessment]), and then every 8 weeks (±10 days) thereafter for up to 24 months, or until disease progression, death, intolerable adverse events (AEs), or other protocol-specified reason for patient withdrawal. Assessment is also done at Safety Follow-up Visit unless the patient has documented disease progression or has undergone a tumor assessment within 8 weeks of the Safety Follow-up Visit.
m) Whole blood samples (4 mL) will be drawn at Screening for CYP2D6 metabolic profile testing.
n) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained at Screening, within 7 days prior to Day 1 of each cycle, at which time, platelet count must be $\geq 100\times10^9$/L and ANC must be $\geq 1.5\times10^9$/L before dispensing poziotinib for the next cycle of treatment, and at the Safety Follow-up Visit. In addition, CBC will be done on Days 7 and 14 of Cycle 1, while the patient is in the hospital. If the Screening Visit is within 14 days of Cycle 1 Day 1, the Baseline CBC is not required.
o) Blood for chemistry, including KL-6 and C-reactive protein, is to be collected at Screening, within 7 days prior to poziotinib administration on Day 1 of each cycle, and at the Safety Follow-up Visit; measurement of KL-6 is not required on Cycle 1, Day 1 if it was already measured during Screening. In addition, blood chemistry will be done on Days 7 and 14 of Cycle 1, while the patient is in the hospital. If the Screening Visit is within 14 days of Cycle 1, Day 1, the Baseline serum chemistry panel is not required
p) ECGs will be performed at Screening, predose and at 1 and 2 hours (±15 min) postdose on Cycle 1, Day 1 and Cycle 2, Day 1 as indicated for time-matched concentration-ECG analysis, and at end of study. In addition, for Phase 1 patients, ECGs will be done on Days 7 and 14 of Cycle 1, while the patient is in the hospital. ECGs are not required on Day 1 of other cycles.
q) Cardiac ejection fraction will be evaluated using echocardiogram or multi-gated acquisition (MUGA) scan at Screening. The Investigator can order subsequent tests based on patient standard of care.

r) On Cycle 1, Day 1 and Cycle 1, Day 13, patients will have intensive pharmacokinetic (PK) samples drawn (4 mL whole blood at each time point) predose and 30 minutes, 1 and 2 (±15 minutes) postdose, and 3, 4, 6, 8, 12, 14 (±30 minutes) postdose, and 24 hours (±1 hour) postdose. In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea, pneumonitis), blood samples will be collected as soon as possible following the onset of the AE and the time of the last dose and the time of blood draw should be recorded

s) Poziotinib will be dispensed on Day 1 of each cycle. Poziotinib should be taken with food and a glass of water (approximately 240 mL) at approximately the same time(s) each day.

t) During the Screening Period, only SAEs will be recorded . All AEs will be collected from Cycle 1, Day 1 through the Safety Follow-up Visit. Patients will be hospitalized during the first 2 weeks of the study and will be monitored for safety assessments including AEs, vital signs, ECGs on Day 7 and Day 14 of Cycle 1. Adverse events will be assessed daily while hospitalized.

u) Telephone contact for AE and concomitant medication assessment on Cycle 1, Day 22 (±2 days), weekly during Cycle 2 and then Day 15 (±2 days) in subsequent cycles. During the long-term follow-up patients will be contacted every 3 months to assess survival.

Appendix 2 PHASE 2 SCHEDULE OF ASSESSMENTS AND PROCEDURES

Phase 2 Assessment	Screening	Treatment Period[a] (Each Cycle=28 [±3] Days)						Safety Follow-up /End-of-Study Visit	Long-Term Follow-up
		Cycle 1				Cycle 2+			
	Day -30 to Day-1	Day 1	Day (±2 days)					35 (±5) Days After Last Dose	Every 3 months After Discontinuation
			8	15	22	1	15		
Informed Consent	x								
Relevant Medical History	x								
Demographic Data	x								
Height and Weight [b]	x	x				x		x	
Physical Examination [c]	x	x	x	x		x		x	
Vital signs [d]	x	x	x	x		x		x	
Resting O_2 Saturation [e]	x	x	x	x		x		x	
Pulmonary Function [f]	x	x	x	x		x		x	
ECOG Performance Status [g]	x	x	x	x		x		x	
Pregnancy Test [h]	x	x				x		x	
Hepatitis B Surface Antigen Test [i]	x								
Hepatitis B Core Antibody Test [i]	x								
Hepatitis B Surface Antibody Test [i]	x								
Hepatitis C Antibody Test [j]	x								
HIV Antibody Test [k]	x								
Tumor Assessment [l]	x	X				X		X	
Tissue Samples [m]	x							x	
Whole Blood (metabolic profile) [n]	x								
Whole Blood (plasma ctDNA) [o]	x					x		x	
CBC with 5-part differential and platelets [p]	x	x				x		x	
Serum Chemistry, including KL-6 and C-reactive protein [q]	x	x				x		x	
Electrocardiogram [r]	x	x				x		x	
Echocardiogram or MUGA Scan[s]	x								
PK Blood Samples [t]		x				x			
Dispense Poziotinib [u]		x				x			
Dispense Supportive Care Medications, as needed		x	x	x					
Adverse Event Assessment [v]	x	x	x	x		x		x	
Concomitant Medications [w]	x	x	x	x		x		x	

Phase 2 Assessment	Screening	Treatment Period[a] (Each Cycle=28 [±3] Days)						Safety Follow-up /End-of-Study Visit	Long-Term Follow-up
		Cycle 1				Cycle 2+			
	Day -30 to Day-1	Day 1	Day (±2 days)					35 (±5) Days After Last Dose	Every 3 months After Discontinuation
			8	15	22	1	15		
Patient Diary Dispensed/Collected		x				x		x	
Telephone Contact [x]					x		x		x

a) Patients must visit the site at the beginning of each cycle.
b) Height only needs to be recorded during the Screening Visit.
c) A complete physical examination, including auscultation, is required at Screening, Cycle 1, Days 1, 8, and 15, Day 1 of each subsequent cycle, and at the Safety Follow-up Visit. Symptom-directed exams are required at other visits.
d) Vital signs will be measured at Screening, Cycle 1, Days 1, 8, and 15, Day 1 of each subsequent cycle, and at the Safety Follow-up Visit.
e) Resting O_2 saturation and will be assessed at Screening, Cycle 1, Days 1, 8, and 15, Day 1 of each subsequent cycle, and at the Safety Follow-up Visit.
f) Routine monitoring for evidence of interstitial lung disease (ILD) will be done at Screening, on Day of Cycles 1-3, every 8 weeks thereafter, and at the Safety Follow up Visit. In addition, it will be assessed on Days 8 and 15 of Cycle 1.
g) The patient's ECOG score will be evaluated at Screening, Cycle 1, Days 1, 8, and 15, Day 1 of each subsequent cycle, and at the Safety Follow-up Visit.
h) A urine or plasma pregnancy test (β-hCG), in women of child-bearing potential, is required at Screening, Day 1 of each cycle, and at the Safety Follow-up. A urine sample is only needed if a urine pregnancy test is done.
i) Tests will be for hepatitis B surface antigens and hepatitis B core and surface antibodies. If the hepatitis B surface antigen test is positive, the patient will be excluded from the study. If only the hepatitis B core antibody and/or hepatitis B surface antibody are positive, a serum hepatitis HBV DNA test will be done. If this test is positive the patient will be excluded from the study.
j) If the hepatitis C antibody test is positive, an HCV RNA test will be done. If this test is positive the patient will be excluded from the study.
k) Whole blood samples will be used for the HIV test. If this test is positive, the patient will be excluded from the study.
l) The Screening/Baseline tumor assessment will be performed within 28 days prior to, or on Cycle 1, Day 1, and additional assessments will be made at 4 weeks (Cycle 2, Day 1 [up to Cycle 2, Day 10]), at 8 weeks (Cycle 3, Day 1 [up to Cycle 3, Day 10, with at least 28 days from previous tumor assessment]), and then every 8 weeks (±10 days) thereafter for up to 24 months. Assessment is also done at Safety Follow-up visit unless disease progression is documented or assessment has been done within 2 months of Safety-follow up visit.
m) If an archival tissue sample is not available, a tumor biopsy will be required. A tumor genotyping report is required to confirm patient mutation eligibility. Collecting a tissue sample at progression is optional but is highly encouraged. Tumor tissue FFPE samples will be stored at room temperature.
n) Whole blood samples (4 mL) will be drawn at Screening for CYP2D6 metabolic profile testing.
o) Whole blood samples (20 mL) for plasma will be drawn as per site standard procedures at Screening, Cycle 2 Day 1, Cycle 3 Day 1 and then every 8 weeks. If the patient progresses a sample collection is optional, but highly encouraged. Samples will be processed into plasma at the site and shipped to the lab for storage at -70°C until ready for testing (companion diagnostic development and resistance mechanism study).
p) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained at Screening, within 7 days prior to Day 1 of each cycle, at which time, platelet count must be $\geq 100\times10^9$/L and ANC must be $\geq 1.5\times10^9$/L before dispensing poziotinib for the next cycle of treatment, and at the Safety Follow-up Visit. If the Screening Visit is within 14 days of Cycle 1 Day 1, the Baseline CBC is not required.
q) Blood for chemistry, including KL-6 and C-reactive protein, is to be collected at Screening, within 7 days prior to poziotinib administration on Day 1 of each cycle, and at the Safety Follow-up Visit; measurement of KL-6 is not required on Cycle 1, Day 1 if it was already measured during Screening. If the Screening Visit is within 14 days of Cycle 1, Day 1, the Baseline serum chemistry panel is not required
r) ECGs will be performed at Screening, predose and at 1 and 2 hours (±15 min) postdose on Cycle 1, Day 1 and Cycle 2, Day 1 as indicated for time-matched concentration-ECG analysis, and at Safety Follow-up Visit. ECG are not required on Day 1 of other cycles.

s) Cardiac ejection fraction will be evaluated using echocardiogram or multi-gated acquisition (MUGA) scan at Screening. The Investigator can order subsequent tests based on patient standard of care.
t) Patients will have blood samples drawn predose and at 1 hour and 2 hours (±15 min) postdose on Cycle 1, Day 1 and Cycle 2, Day 1 for sparse PK sampling and time-matched concentration-ECG analysis. Blood samples will be collected at Cycle 3 Day 1 and then every 8 weeks in order correlate poziotinib concentrations with plasma ctDNA and efficacy; the time of the last dose and the time of blood draw should be recorded. In addition, if a patient presents with a potentially drug-related Grade ≥3 TEAE (e.g., rash, mucositis, diarrhea, pneumonitis), blood samples will be collected as soon as possible following the onset of the AE and the time of the last dose and the time of blood draw should be recorded.
u) Poziotinib will be dispensed on Day 1 of each cycle. Poziotinib should be taken with food and a glass of water (approximately 240 mL) at approximately the same time(s) each day.
v) During the Screening Period, only SAEs will be recorded . All AEs will be collected from Cycle 1, Day 1 through the Safety Follow-up Visit.
w) Concomitant medications will be collected at Day 1 of each cycle, Day 8 and Day 15 during Cycle 1, and at the Safety Follow-up Visit.
x) Telephone contact will be made to collect AE and concomitant medication information from patients on Cycle 1, Day 22, every week in Cycle 2, and **Day 15 (±2 days)** in each cycle thereafter. During the long-term follow-up patients will be contacted every 3 months to assess survival.

Appendix 3 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCALE

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care 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.

Appendix 4 RASH MANAGEMENT RECOMMENDATIONS

Given the presence of wild type EGFR receptors in the skin, rash is a common, expected toxicity of tyrosine kinase inhibitor (TKI) compounds. For rash management, at the treating Investigator's discretion, the following interventions are strongly recommended.

Early and regular contact with the PI or dermatologist should be arranged for and provided prior to initiating dosing. At Baseline, an education session should be provided to the patient to inform them of likely skin events while on study and directions given on how to contact the appropriate member of the health care team. Visits on **Days 8** and **15** should include a focus on skin and mucosal assessment. Per protocol, visits or telephone contact should be made with the patient every week during **Cycles 1** and **2** and then every 2 weeks while being treated with study drug.

Supportive medications, including early steroid use, should be considered even in the presence of low-grade "on-target" toxicity (eg, rash).

Preliminary information from **Cohort 1** suggest that dose interruptions should be minimized in order to reduce the risk of progression.

CTCAE Severity Grading of Rash

Skin and subcutaneous tissue disorders	**GRADE**				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Rash Acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting selfcare ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death

Rash Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.

Abbreviations: ADL = activities of daily living; BSA = body surface area;

RECOMMENDATIONS FOR RASH MANAGEMENT

RASH SEVERITY	INTERVENTION
Start Prophylaxis for Rash (CTCAE Grade 0) Initiation of Poziotinib Treatment	• **Baseline Visit:** Expected skin events and management education session. • On initiation of Poziotinib therapy consider starting prophylactic treatment with doxycycline or minocycline for 4 weeks, if there are no contraindications.
Mild Rash (CTCAE Grade 1) Generally localized Minimally symptomatic No impact on ADL No sign of infection	• **For Face/Body Folds or Body:** Initiate low/moderate dose oral steroids (e.g., dexamethasone or prednisone). Start topical therapy (e.g., hydrocortisone 2.5% cream or ointment [Class VII topical steroid]) BID on the affected areas. • Consult dermatologist. • Continue poziotinib at the current dose level
Moderate Rash (CTCAE Grade 2) Generalized Mild symptoms (e.g., pruritus, tenderness) Minimal impact on ADL No sign of superinfection	• **For Face/Body Folds:** Initiate/continue with high-dose oral steroids (e.g., dexamethasone or prednisone) for 5-7 days and reassess. Start/change hydrocortisone to triamcinolone 0.1% cream or ointment (Class IV topical steroid) BID and consider adding topical clindamycin cream 1% BID on the affected skin area. • **For Body:** Initiate/continue with high dose oral steroids (e.g., dexamethasone or prednisone) for 5-7 days and reassess. Consider start/change triamcinolone to clobetasol or betamethasone 0.05% cream or ointment (Class I topical steroid) BID and add topical clindamycin cream 1% BID on the affected skin area. • Consult dermatologist. • Continue poziotinib at the current dose level
Severe Rash (CTCAE Grade 3) Generalized Severe symptoms (e.g., pruritus, tenderness) Potential for superinfection	• Initiate/continue with high dose oral steroids (e.g., dexamethasone or prednisone) for 5-7 days. Continue until improvement/stabilization of rash to Grade ≤1. • Continue all Grade 2 skin management above. Consult dermatologist. • Discuss with Sponsor's Medical Monitor and consider brief poziotinib dose interruption/lower dose. • A dose "hold" of poziotinib should be for as short a time as possible (<5-14 days). Restart at the current poziotinib dose or next lower dose upon discussion with Sponsor's Medical Monitor.
Severe or Extensive Rash; Possibly Life-Threatening (CTCAE Grade 4) Generalized severe or extensive symptoms; possibly life-threatening (e.g., pruritus, tenderness), associated with extensive superinfection	• Consult Sponsor's Medical Monitor • If considered life-threatening, discontinue poziotinib immediately

Dexamethasone may affect the metabolism of poziotinib (metabolized by CYP3A4). Steroids that do not affect poziotinib metabolism (e.g., hydrocortisone, methylprednisolone) should be considered as substitute. Consult the Sponsor's Medical Monitor if needed.

Modified from: http://www.aafp.org/afp/2009/0115/p135.pdf

- Hirsh, V. Managing Treatment-Related Adverse Events Associated with EGFR Tyrosine Kinase Inhibitors in Advanced Non-Small-Cell Lung Cancer. Current Oncology.18.3.126-138.