Official Title: A Phase 2 Study of Poziotinib in Patients with Non-Small Cell Lung Cancer (NSCLC), Locally Advanced or Metastatic, with EGFR or HER2 Exon 20 Insertion Mutation (ZENITH20)

NCT Number: NCT03318939

Document Date: Protocol Amendment 3: 14 February 2020

Study Title: **A Phase 2 Study of Poziotinib in Patients with Non-Small Cell Lung Cancer (NSCLC), Locally Advanced or Metastatic, with EGFR or HER2 Exon 20 Insertion Mutation (ZENITH20) (SPI-POZ-202)**

Protocol Version/Date: Amendment 3/14 Feb 2020

Deletions below are marked with red strikethrough text and additions are marked with red underlined text.

Summary of Significant Changes to the Protocol

Section	Change
Throughout Document	Minor edits for grammar, spelling, consistency, clarity, and typos.
Throughout Document: **General Explanation**	**Primary Reasons for Amendment:** **Reason 1** Preliminary results for the primary endpoint (ORR) for Cohort 1 are available. To help manage toxicity, patients in **Cohorts 4, 6,** and 7 will begin treatment with 8 mg BID (16 mg daily) dosing. In **Cohort 5**, the 10 mg QD group will continue and the 12 and 16 mg QD dose groups changed to 6 mg BID or 8 mg BID, for the same total daily dose; the predicted AUC for each BID dose group is expected be the same as the original QD dose groups. Except for Cohort 3 and the 10 mg group in **Cohort 5**, all new patients will now be treated with a BID dosing regimen. Most references to 16 mg are changed to 8 mg BID. The following dosing regimen changes are being made: **Cohort 4:** • The 16-mg QD group is closed. All new patients will receive 8 mg BID. **Cohort 5**: • The 12 and 16 mg QD dose groups are closed. All eligible patients entering **Cohort 5** will be randomized in a 1:1:1 ratio to starting doses of 10 mg QD, 6 mg BID (12 mg daily), or 8 mg BID (16 mg daily). If a treatment group(s) is stopped for futility, all newly enrolled patients will be randomized to the continuing dose group(s). • Dose escalation to 8 mg BID or maintenance at the patient's current dose after first progression is at the discretion of the Investigator based on the patient's tolerability to the drug and consideration of other available treatments but must be discussed and agreed with the Sponsor's Medical Monitor prior to implementation. **Cohorts 6, and 7**: • The dose of poziotinib is now 8 mg BID (16 mg daily). **Reason 2** Additional office visits on **Cycle 1, Day 8** and **Cycle 1, Day 15** are being added to help manage patient care; these visits were added to the Schedule of Assessments and Procedures Additional telephone contacts are being added in **Cycle 1** and **Cycle 2**; these contacts were added to the Schedule of Assessments and Procedures

Section	Change
Title Page **Footer** **Synopsis**	**Original Text:** Protocol Version/Date: ~~Amendment 2/28 May 2019~~ **New Text:** Protocol Version/Date: Amendment 3/14 Feb 2020
Title Page: Administrative Change	**Text Deleted:** ~~Spectrum Pharmaceuticals, Inc.~~ ~~Global Corporate Office~~ ~~11500 S. Eastern Ave, Suite 240~~ ~~Henderson, NV 89052~~ ~~USA~~
Synopsis: Planned Number of Patients **Throughout Document**	**New Text:** **Planned Number of Patients:** Up to ~~314~~349 patients enrolled in **Cohorts 1** to **4:** **(Cohort 1** – 87; **Cohort 2** – 87; **Cohort 3** – 70; **Cohort 4** – ~~70~~105) **Cohort 5** – approximately ~~180~~194 patients ~~(60 patients per dose group)~~; **Cohort 6** – 30 patients; **Cohort 7** – 30 patients **Reason:** • 35 patients are being added to Cohort 4 so that there will be a total of 70 patients treated with 8 mg BID
Synopsis: Exploratory Objectives **Section 2.3** **IMPORTANT CHANGES**	**New Text:** **Exploratory Objectives** • **Progression-free Survival (PFS)** • **Quality of Life (QoL)** • **Evaluate alternate poziotinib starting doses and schedules ~~(Cohort 5 only)~~** • **Evaluate poziotinib in patients who progressed while on treatment with first-line osimertinib (Cohort 6 only)** • **Evaluate poziotinib in patients with EGFR or HER2 activating mutations** • **Evaluate overall survival** • **Characterize the PK profile of poziotinib** **Reason:** • The Sponsor wants to characterize the PK profile after BID dosing with poziotinib. • Overall survival is being added as an exploratory objective.

Section	Change
Synopsis: Duration of Study **Throughout**	**New Text:** **Duration of Study:** The study will run for approximately 5 years. The total duration of the study for each patient will be approximately 2 years. However, some patients may receive longer treatment if responding to the treatment. The duration of study participation for each patient, in general, includes the following segments: • **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 **Reason:** A reference to the total duration of the whole study was added. In order to assess overall survival, a long-term follow-up was added.
Synopsis: Inclusion Criteria **Section 4.1** **IMPORTANT CHANGES**	**Original Text:** **Inclusion Criteria:** 5) Tissue and plasma samples for mutation confirmation: • **Cohort 6**: ~~A~~ tissue ~~sample must be provided~~ after osimertinib progression. 6) Patient is positive for EGFR or HER2 mutations based on: • **Cohort 6**: Documented acquired EGFR mutation who have progressed while on first-line osimertinib treatment using tissue tested with a next-generation sequencing assay. 12) Females of childbearing potential must have a negative pregnancy test within 30 days prior to enrollment. Females who are postmenopausal for at least 1 year (defined as more than 12 months since last menses) or who are surgically sterilized do not require this test. **New Text:** **Inclusion Criteria:** 5). Tissue and plasma samples for mutation confirmation: • **Cohort 6**: Either tissue or plasma samples after osimertinib progression. 6) Patient is positive for EGFR or HER2 mutations based on: • **Cohort 6**: Documented acquired EGFR mutation (tested after osimertinib progression) who have progressed while on first-line osimertinib treatment using tissue or plasma tested with a next-generation sequencing assay. 12) 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) or who are surgically sterilized do not require this test. **Reason:** 5) In Cohort 6, plasma samples are now allowed to identify mutations 6) The tissue or plasma used for mutation identification must be collected after progression on osimertinib 12) Pregnancy test requirements are stricter. The pregnancy test must be within 7 days prior to Day 1.

Section	Change
Synopsis: Exclusion Criteria **Section 4.2** **IMPORTANT CHANGES**	**Added Text:** **Exclusion Criteria:** 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 or 5 half-lives, whichever is longer; local radiation therapy for bone pain may be allowed **Reasons:** Exclusion Criteria: Making sure that prior therapy is cleared from the patient's blood prior to treatment.
Synopsis: Investigational Product, Dose, and Route of Administration **Section 6.1.3: Poziotinib Administration** **IMPORTANT CHANGES**	**Original Text:** Poziotinib is supplied as 8-mg tablets and 2-mg tablets. will be taken by the patient orally, ~~once daily~~ with food and a glass of water, at approximately the same time each ~~morning. If the morning dose is missed, this dose may be administered any time during the~~ day ~~preferably with food, but at least 8 hours prior to the next scheduled dose~~. **New Text:** Poziotinib is supplied as 8-mg tablets and 2-mg tablets. will be taken by the patient orally, with food and a glass of water, at approximately the same time(s) each day. **Once-Daily Dosing Regimen** If the morning 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-Daily Dosing Regimen** 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. **Reason:** More specific instructions for taking poziotinib were added for QD and BID dosing, including what to do if a dose is missed.
Synopsis: Pharmacokinetic Assessments **Section 5.4.8: Pharmacokinetics** **Section 8.7: Safety Analysis** **Schedule of Assessment and Procedures**	**Original Text:** All patients will have blood samples drawn pre-dose and at 1 hour and ~~3~~ hours (±15 min) post-dose for sparse PK ~~sampling~~ and time-matched concentration-~~QT~~ analysis ~~on Day 1 of Cycle 1 and pre-dose on Day 1 of Cycle 2 for time-matched concentration-QT analysis.~~ At ~~least 10~~ patients ~~from Cohorts 1 to 4, who have agreed to participate~~ in ~~this option and have signed~~ the ~~informed consent, will have~~ Intensive PK blood ~~samples drawn pre-dose and 30 minutes, 1, 1.5, 2, 3, 4, 6, and 24~~ hours post-dose on ~~Day 1 of Cycle 1.~~ In addition, if a patient presents with a potentially drug-related ~~SAE, PK~~ blood ~~samples may~~ be collected ~~during~~ the ~~clinic visit for PK analysis.~~ **New Text:**

Section	Change
	The PK profile of poziotinib and its metabolites (M1 and M2) will be characterized. All patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose on **Cycle 1, Day 1** and **Cycle 2, Day 1** for sparse PK and time-matched concentration-ECG analysis. At select study centers, patients (a minimum of 6 patients per dosing schedule) will be specifically consented for intensive PK in the 6 and 8 mg BID groups in **Cohort 5**. Intensive PK blood sampling will replace sparse PK blood sampling in **Cycle 1** and sparse sampling on **Cycle 2, Day 1** is not required in these patients. The schedule for intensive PK blood sampling will be pre-dose and 1, 2, 4, 8, 12, and 24 hours post-dose on **Cycle 1, Day 1** and **Cycle 1, Day 8 (±2 days)**. The 12-hour PK sample must be collected prior to the second daily dose (12-hour dose). Patient must be on drug at the time of blood sampling. In addition, if a patient presents with a potentially drug-related Grade ≥3 AE (e.g., rash, mucositis, diarrhea), a blood sample will be collected as soon as possible following the onset of the AE. **Reason:** • Intensive PK will be performed for some patients in Cohort 5 at select study sites on Cycle 1, Day 1 and Day 8. • Language changed from QT to ECG to clarify that a formal QT study is not be conducted. • Clarifying that we are characterizing the PK profile of poziotinib and its metabolites. • Samples for PK must be collected following a related Grade ≥3 AE and it is now a Grade ≥3 AE instead of an SAE.
Synopsis: Adverse Event and Serious Adverse Event Reporting **Throughout Document**	**Original Text:** 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, ~~only~~ serious adverse events (SAEs) ~~related to study procedures~~ will be reported. **New Text:** 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. **Reason:** • All SAEs will be recorded from the time of ICF to Day 1 instead of just SAEs related to study procedures. • After the safety follow-up visit, SAEs that could be related to poziotinib will be recorded during the long-term follow-up.

Section	Change
Synopsis: Statistical Methods **Section 8.1: Sample Size**	**Text Added:** The sample size of **Cohort 4** is revised to enroll a total of 70 patients treated with 8 mg BID using the same statistical test and pre-specification as described above. Patients who received 16 mg once daily prior to the protocol amendment will be analyzed separately. With the change in dose schedule to 8 mg BID, a sample size of 70 patients will provide 95% power, for a two-sided test with a significant level of 5% to reject a non-desired ORR of 20% if the observed ORR is 40% or higher. A two-stage design will be used to evaluate the primary endpoint of ORR in Cohort 5 once the futility analysis is complete in a test of single proportion using the same hypotheses as in Cohorts 1 and 2 (17% vs. 30%). In each dose group of Cohort 5 that remains after the futility analysis, a total of 19 patients will be enrolled and followed up for response evaluation to observe the number of responses in the first stage of two-stage design. If 2 or fewer responses are observed in the first stage, the dose group will be terminated. If 3 or more responses are observed in the first stage of a dose group, the dose group will continue to enroll in the second stage. All new patients will be randomized or enrolled to the remaining group that continues to enroll in the second stage. A total of 124 patients will be enrolled. If the number of responses is greater than 29, the corresponding dose group is considered to have met the primary endpoint. **Reason:** Accounted for the addition of patients treated with 8 mg BID in **Cohort 4**.
Synopsis: Statistical Methods **Section 8.2: Futility Analysis**	**Original Text:** ~~Since **Cohort 5** has~~ three randomized ~~treatment groups in which patients will be enrolled, the futility analysis decision will be made based on:~~ ~~1. If one of the two randomized~~ dose groups (10 mg or ~~12~~ mg) meets the criteria for futility, all new patients will be randomized into ~~either~~ the group ~~that continues or the 16 mg group for the rest of the Cohort.~~ ~~2. If both of the two randomized dose groups (10 mg and 12 mg) meet the criteria for futility, all new patients will be enrolled into the 16 mg dose group.~~ ~~3. No futility analysis will be conducted in the 16 mg dose group.~~ **New Text:** If one or two of the three randomized dose groups (10 mg QD or 6 mg or 8 mg BID) meets the criteria for futility, all new patients will be randomized or enrolled into the remaining group **Reason:** Simplified the language for the Cohort 5 futility analysis.

Section	Change
Synopsis: Statistical Methods **Section 8.3: Early Stopping Rules**	**Deleted Text:** ~~Early Stopping Rule~~ ~~Each of the first 4 cohorts also includes a stopping rule for efficacy based on conditional power (>99%) for the test of hypothesis in the ORR. The enrollment in **Cohorts 1** and **2** may be stopped when a total of 24 patients with confirmed responses (CR+PR) are observed at any post-baseline time point and the enrollment in **Cohorts 3** and **4** may be stopped when a total of 23 patients with confirmed responses (CR+PR) are observed at any post-baseline time point. No data dependent stopping rule for efficacy is specified for **Cohorts 5**, **6**, or **7**.~~ **Reason:** We are not expecting the response to be high enough to stop any of the cohorts.
Synopsis **Section 6.1.5: Poziotinib Dose Modification Recommendations**	**Original Text:** ~~No changes in dosing recommendations are being made for **Cohorts 1** to **4** in Amendment 2. Dosing modifications are recommended in . Dose reductions are in 2 mg,~~ regardless of starting dose and will be at the Investigator's discretion and the Sponsor should be notified. ~~Dose reductions~~ other than by 2 mg ~~increments require~~ Sponsor's Medical Monitor approval. After a dose reduction, a patient cannot be treated with a higher dose of poziotinib, except for patients in **Cohort 5**. Upon first progression, patients in **Cohort 5** can escalate to ~~16~~ mg or stay on therapy at their current dose at the discretion of the Investigator based on the patient's tolerability to the drug, and consideration of other available treatments but must be approved by the Sponsor's Medical Monitor prior to implementation. **New Text:** If needed, doses will be reduced by 2 mg (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 and the Sponsor should be notified. If doses are reduced by other than by 2 mg/dose Sponsor's Medical Monitor approval is required. After a dose reduction, a patient cannot be treated with a higher dose of poziotinib, except for patients in **Cohorts 5, 6**, and **7**. Upon first progression, patients in **Cohort 5** can escalate to a maximum of 8 mg BID or stay on therapy at their current dose at the discretion of the Investigator based on the patient's tolerability to the drug, and consideration of other available treatments but must be approved by the Sponsor's Medical Monitor prior to implementation. Dosing modifications are described in the table below. **Reason**: Instructions for dose reductions were adjusted to clarify that total dose reductions will be 2 mg/day for patients on a QD regimen and will be 4 mg/day for patients on a BID regimen. Each DOSE will be reduced by 2 mg.

CONFIDENTIAL

CLINICAL STUDY PROTOCOL

TITLE PAGE

Study Title:	**A Phase 2 Study of Poziotinib in Patients with Non-Small Cell Lung Cancer (NSCLC), Locally Advanced or Metastatic, with EGFR or HER2 Exon 20 Insertion Mutation (ZENITH20)**
Study Number:	**SPI-POZ-202**
Study Phase:	Phase 2
Study Drug:	Poziotinib
IND Number:	135,719
Sponsor:	Spectrum Pharmaceuticals, Inc. Research and Development Office 157 Technology Drive Irvine, CA 92618 USA
Protocol Version/Date:	Amendment 3/14 Feb 2020

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and applicable Institutional research policies and procedures.

Confidentiality Statement

The information contained in this document, particularly unpublished data, is the property or under control of Spectrum Pharmaceuticals, Inc. and is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board/Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in this protocol. You will not disclose any of the information to others without prior written authorization from Spectrum Pharmaceuticals, Inc. except to the extent necessary to obtain Informed Consent from those persons to whom the investigational drug may be administered.

INVESTIGATOR SIGNATURE

Protocol Number: SPI-POZ-202

A Phase 2 Study of Poziotinib in Patients with Non-Small Cell Lung Cancer (NSCLC), Locally Advanced or Metastatic, with EGFR or HER2 Exon 20 Insertion Mutation (ZENITH20)

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., FDA).

_____

Investigator Name (PLEASE PRINT):

Signature: _____ Date _____

SYNOPSIS

Title of Study: A Phase 2 Study of Poziotinib in Patients with Non-Small Cell Lung Cancer (NSCLC), Locally Advanced or Metastatic, with EGFR or HER2 Exon 20 Insertion Mutation (ZENITH20)	
Name of Sponsor: Spectrum Pharmaceuticals, Inc.	
Name of Investigational Product: Poziotinib	
Study Centers: Approximately 75 study centers globally	
Duration of Study: Approximately 5 years	
Planned Number of Patients: Up to 349 patients enrolled in **Cohorts 1** to **4:** (**Cohort 1 –** 87; **Cohort 2** – 87; **Cohort 3** – 70; **Cohort 4** –105) **Cohort 5** – approximately 194 patients; **Cohort 6** – 30 patients; **Cohort 7** – 30 patients	**Clinical Phase:** 2

Objectives:

To evaluate the following in NSCLC patients with EGFR or HER2 exon 20 insertion mutations (including duplication mutations) who are treated with poziotinib:

Primary Objective

- **Objective Response Rate** (**ORR**)

Secondary Objectives

- **Disease Control Rate** (**DCR**)
- **Duration of Response** (**DoR**)
- **Safety and tolerability**

Exploratory Objectives

- **Progression-free Survival** (**PFS**)
- **Quality of Life** (**QoL**) (**Cohorts 1** to **4** only)
- **Evaluate alternate poziotinib starting doses and schedules**
- **Evaluate poziotinib in patients who progressed while on treatment with first-line osimertinib (Cohort 6 only)**
- **Evaluate poziotinib in patients with EGFR or HER2 activating mutations**
- **Evaluate overall survival**
- **Characterize the PK profile of poziotinib**

Duration of Study: The study will run for approximately 5 years. The total duration of the study for each patient will be approximately 2 years. However, some patients may receive longer treatment if responding to the treatment. 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 until 24 months of treatment, disease progression (except for first progression in **Cohort 5**), death, intolerable adverse events (AEs), or other protocol-specified reasons 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 2, open-label, multicenter study to evaluate the efficacy and the safety/tolerability of poziotinib in four patient cohorts for up to 174 previously treated NSCLC patients with any systemic therapy (**Cohort 1**: 87 patients with EGFR exon 20 insertion mutations, **Cohort 2**: 87 patients with HER2 exon 20 insertion

mutations), up to 175 treatment-naive NSCLC patients (**Cohort 3**: 70 patients with EGFR exon 20 insertion mutations, **Cohort 4**: 105patients with HER2 exon 20 insertion mutations). , Approximately 194 patients in **Cohort 5** (see statistics section), 30 patients in **Cohort 6**, and 30 patients in **Cohort 7** are being enrolled**.**

The **Screening** period (**Day -30** to **Day -1**) lasts up to approximately 30 days prior to **Cycle 1**, **Day 1**. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. Eligible patients will provide written Informed Consent prior to any study procedures.

Each treatment cycle is 28 calendar days in duration. There will be 7 patient cohorts and eligible patients will be enrolled into each cohort in parallel based on EGFR or HER2 exon 20 mutation status and prior treatment status:

- **Cohort 1 (ZENITH20-1):** Previously treated patients with EGFR exon 20 insertion mutation positive NSCLC
- **Cohort 2 (ZENITH20-2):** Previously treated patients with HER2 exon 20 insertion mutation positive NSCLC
- **Cohort 3 (ZENITH20-3):** Treatment naïve patients with EGFR exon 20 insertion mutation positive NSCLC
- **Cohort 4 (ZENITH20-4):** Treatment naïve patients with HER2 exon 20 insertion mutation positive NSCLC
- **Cohort 5 (ZENITH20-5):** Patients who meet the criteria for enrollment in **Cohort 1** to **4**, but the enrollment in the respective cohort has been closed
- **Cohort 6 (ZENITH20-6):** Patients with acquired EGFR mutation who progressed while on treatment with first-line osimertinib
- **Cohort 7 (ZENITH20-7):** Patients with EGFR or HER2 activating mutations

Toxicity will be assessed based on the severity grade of the adverse events using CTCAE version 4.03.

On **Day 1** of each 28-day cycle, the patient's absolute neutrophil count (ANC) must be $\geq 1.5\times10^9$/L and platelet count must be $\geq 100\times10^9$/L before administering poziotinib. All patients will be treated until disease progression (except for first progression in **Cohort 5**), death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal. Upon first progression, patients in **Cohort 5** can escalate up to a maximum of 8 mg BID or stay on therapy at their current dose at the discretion of the Investigator based on the patient's tolerability to the drug, and consideration of other available treatments but must be discussed with the Sponsor's Medical Monitor prior to implementation.

Patient Replacement Strategy: Patients who discontinue from the study will not be replaced.

Inclusion & Exclusion Criteria:

Inclusion Criteria:

1. Patient is at least 18 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. Patient has histologically or cytologically confirmed locally advanced or metastatic non-small cell lung cancer (NSCLC) that is not amenable to treatment with curative intent
4. Prior treatment status:
   - **Cohorts 1** and **2**: Patient has had at least one prior systemic treatment for locally advanced or metastatic NSCLC
   - **Cohorts 3** and **4**: Patient is treatment-naïve for locally advanced or metastatic NSCLC and eligible to receive first-line treatment with poziotinib as determined by the Investigator. Adjuvant/neo-adjuvant therapies (chemotherapy, radiotherapy, or investigational agents) are permissible as long as they end at least 15 days prior to study entry
   - **Cohort 5**: Patients who meet the criteria for enrollment in **Cohorts 1** to **4**, but the enrollment in the respective cohort has been closed

- **Cohort 6:** Patients with EGFR mutation-positive NSCLC who progressed while on treatment with first-line osimertinib.
- **Cohort 7:** Patient has had at least one prior systemic treatment for locally advanced or metastatic NSCLC

5. Tissue and plasma samples for mutation confirmation:
   - **Cohorts 1** to **5**: Patient has adequate tumor tissue obtained from a biopsy or surgical procedure to enable molecular profiling for retrospective central laboratory confirmation of the mutation. If tissue is not available, the patient must have biopsy accessible disease and must be willing to undergo a biopsy to provide an appropriate tissue sample prior to receiving treatment in the study.
   - **Cohort 6**: Either tissue or plasma samples after osimertinib progression.
   - **Cohort 7**: Either tissue or plasma samples .
6. Patient is positive for EGFR or HER2 mutations based on:
   - **Cohorts 1 and 3**: Documented EGFR exon 20 insertion mutation (including duplication mutations) using a next generation sequencing diagnostic test, such as OncoMine Comprehensive Assay (OCA) or FoundationOne Assay, or by an FDA approved test (eg, cobas® EGFR mutation test v2 or therascreen EGFR RGQ PCR kit) performed by a US CLIA certified and locally licensed clinical laboratory or similarly accredited lab for ex-US sites using tissue samples
   - **Cohorts 2 and 4**: Documented HER2 exon 20 insertion mutation (including duplication mutations) using a next generation sequencing diagnostic test, such as OncoMine Comprehensive Assay (OCA) or FoundationOne Assay, performed by a US CLIA certified and locally licensed clinical laboratory or similarly accredited lab for ex-US sites using tissue samples
   - **Cohort 5**: Documented EGFR or HER2 exon 20 insertion mutations using tissue samples using the criteria described for **Cohorts 1 to 4**.
   - **Cohort 6**: Documented acquired EGFR mutation (tested after osimertinib progression) who have progressed while on first-line osimertinib treatment using tissue or plasma tested with a next-generation sequencing assay.
   - **Cohort 7**: Documented EGFR or HER2 activating mutations (see table below) using tissue or plasma tested with a next-generation sequencing assay .

EGFR	HER2
E709X	S310F
E709_T710del insD	I655V
L718X	L755X
G719X	I767M
I740_K745dupIPVAIK	D769X
L747X	V777X
A750P	L786V
S768I	V842I
L833V	L869R
L861Q	

7. Patient has measurable NSCLC disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Metastatic lesions in CNS or in brain cannot be used for target lesions
8. Brain metastases may be allowed if patient's condition is stable, defined as clinically asymptomatic, no requirement for high dose or increasing dose of systemic corticosteroids, and no need for any anticonvulsant therapy for metastatic brain disease. For the patient who has had radiation therapy, sequential post-treatment MRI tests, at least 4-6 weeks apart, should show no increases in brain lesion size/volume within 4 weeks prior to the study.
9. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and has a life-expectancy of more than 6 months

10. 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
    - Creatinine clearance ≥50 mL/min according to the Cockcroft-Gault equation
11. Patient is willing to practice 2 forms of contraception, one of which must be a barrier method, from study entry until at least 30 days after the last dose of poziotinib
12. 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) or who are surgically sterilized do not require this test.

Exclusion Criteria:

1. Patient has:
    - **All Cohorts**: EGFR T790M
    - **Cohorts 1 to 5**: EGFR exon 20 point mutation
    - **Cohort 7**: EGFR Exon 19 deletion and L858R or HER2 T798I mutations, EGFR and HER2 Exon 20 insertion mutation
2. Patient has had previous treatment with poziotinib or any other EGFR or HER2 exon 20 insertion mutation-selective tyrosine kinase inhibitor (TKI) prior to study participation. The currently approved TKIs (ie, erlotinib, gefitinib, afatinib, osimertinib) are not considered to be exon 20 insertion-selective and are permissible (**Cohorts 1** and **2**).
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 or 5 half-lives, whichever is longer; local radiation therapy for bone pain may be allowed
4. Patient has a 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
5. Patient has a high risk of cardiac disease, as determined by the Investigator, may undergo either echocardiogram (ECHO) or multi-gated acquisition (MUGA) during **Screening** and has a cardiac ejection fraction <50%
6. Patient has had other malignancies within the past 3 years, except for stable non-melanoma skin cancer, fully treated and stable, early-stage prostate cancer, or carcinoma in situ of the cervix or breast without need of treatment
7. 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 4.03) Grade 2 or above diarrhea due to other etiologies)
8. 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
9. 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

10. 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)
11. Patient has known hypersensitivity to poziotinib or has a history of allergic reactions attributed to chemically similar compounds or other tyrosine kinase inhibitors (TKIs)
12. Patient has an active uncontrolled infection, underlying medical condition, or other serious illness that would not be appropriate for this study
13. 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
14. Patient is pregnant or breast-feeding
15. **Cohort 5 only**: Patient is eligible for treatment in an open cohort (**Cohorts 1 to 4)**

Investigational Product, Dose, and Route of Administration:

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

Once-Daily Dosing Regimen

If the morning 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-Daily Dosing Regimen

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.

Cohorts 1 to 3:

- The dose of poziotinib is 16 mg, once a day (QD)

Cohort 4:

- The 16-mg QD group is closed. All new patients will receive 8 mg BID.

Cohort 5:

- The 12 and 16 mg QD dose groups are closed. All eligible patients entering **Cohort 5** will be randomized in a 1:1:1 ratio to starting doses of 10 mg QD, 6 mg BID (12 mg daily), or 8 mg BID (16 mg daily). If a treatment group(s) is stopped for futility, all newly enrolled patients will be randomized or enrolled to the continuing dose group(s).
- Dose escalation to 8 mg BID or maintenance at the patient's current dose after first progression is at the discretion of the Investigator based on the patient's tolerability to the drug and consideration of other available treatments but must be discussed and agreed with the Sponsor's Medical Monitor prior to implementation.

Cohorts 6, and 7:

- The dose of poziotinib is now 8 mg BID (16 mg daily).

Reference Therapy, Dose, and Route of Administration: None

Efficacy Assessments:

Efficacy will be based on central radiographic evaluation by an Independent Radiologic Review Committee.

Primary Endpoint:

- **Objective Response Rate** (**ORR,** complete response+partial response)

Secondary Endpoints:

- **Disease Control Rate** (**DCR,** complete response+partial response+stable disease)
- **Duration of Response** (**DoR**)
- **Safety and Tolerability**

Exploratory Endpoint

- **Progression-free Survival** (**PFS**)
- **Quality of Life (QoL) (Cohorts 1 to 4 only)**
- **Overall survival (OS)**

Pharmacokinetic Assessments:

The PK profile of poziotinib and its metabolites (M1 and M2) will be characterized.

All patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose on **Cycle 1**, **Day 1** and **Cycle 2**, **Day 1** for sparse PK and time-matched concentration-ECG analysis.

At select study centers, patients (a minimum of 6 patients per dosing schedule) will be specifically consented for intensive PK in the 6 and 8 mg BID groups in **Cohort 5** . Intensive PK blood sampling will replace sparse PK blood sampling in **Cycle 1** and sparse sampling on **Cycle 2**, **Day 1** is not required in these patients. The schedule for intensive PK blood sampling will be pre-dose and 1, 2, 4, 8, 12, , and 24 hours post-dose on **Cycle 1**, **Day 1** and **Cycle 1**, **Day 8 (±2 days)**. The 12-hour PK sample must be collected prior to the second daily dose (12-hour dose). Patient must be on drug at the time of blood sampling.

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

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.

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:

A formal statistical analysis plan (SAP) providing full technical details of the planned analyses will be finalized prior to database lock.

Sample Size Justification:

The study has 7 patient cohorts, and each one is considered to be a standalone study. Each of the first 4 cohorts is powered for testing hypothesis of the primary endpoint separately. No *a priori* test of hypothesis is planned and no sample size calculation is provided for **Cohorts 5** to **7**. The statistical analysis of primary as well as secondary outcomes will be performed separately for each cohort.

Cohort 1 will enroll patients with previously treated EGFR exon 20 insertion-mutation positive NSCLC and **Cohort 2** will enroll patients with previously treated HER2 exon 20 insertion-mutation positive NSCLC. Each cohort will be a single-arm and the primary test of hypotheses will be based on a single proportion. Sample size

calculation is based on single arm hypothesis testing to reject non-desired ORR of 17% vs. clinically meaningful ORR of 30%. A sample size of 87 patients in each cohort will provide 85% power, for a two-sided test with a significant level of 5% to reject a non-desired ORR of 17% if the observed ORR is 30% or higher. A sample size of 87 patients in each cohort will also provide 95% CI that contains 30% and rules out 17% as the lower bound is above 17%.

For **Cohorts 3** and **4**, patients who are treatment-naïve for exon 20 mutation positive NSCLC, each cohort will be single-arm and the primary test of hypotheses will be based on a single proportion. Based on the literature, an ORR of 20% is considered to be the lower threshold of efficacy in our study. Sample size calculation is based on the single arm hypothesis testing to reject non-desired ORR of 20% vs. clinically meaningful ORR of 40% in the study. A sample size of 70 patients in each cohort will provide 95% power, for a two-sided test with a significant level of 5%, to reject a non-desired ORR of 20% if the observed ORR is 40% or higher. A sample size of 70 patients in each cohort will also provide 95% CI that contains 40% and rules out 20% as the lower bound is above 20%.

The sample size of **Cohort 4** is revised to enroll a total of 70 patients treated with 8 mg BID using the same statistical test and pre-specification as described above. Patients who received 16 mg once daily prior to the protocol amendment will be analyzed separately. With the change in dose schedule to 8 mg BID, a sample size of 70 patients will provide 95% power, for a two-sided test with a significant level of 5% to reject a non-desired ORR of 20% if the observed ORR is 40% or higher.

A two-stage design will be used to evaluate the primary endpoint of ORR in **Cohort 5** once the futility analysis is complete in a test of single proportion using the same hypotheses as in **Cohorts 1** and **2** (17% vs. 30%). In each dose group of **Cohort 5** that remains after the futility analysis, a total of 19 patients will be enrolled and followed up for response evaluation to observe the number of responses in the first stage of two-stage design. If 2 or fewer responses are observed in the first stage, the dose group will be terminated. If 3 or more responses are observed in the first stage of a dose group, the dose group will continue to enroll in the second stage. All new patients will be randomized or enrolled to the remaining group that continues to enroll in the second stage. A total of 124 patients will be enrolled. If the number of responses is greater than 29, the corresponding dose group is considered to have met the primary endpoint.

There is no statistical power or sample size determined for **Cohorts 6** and **7**. A total of 30 patients will be enrolled in **Cohort 6** and 30 patients will be enrolled in **Cohort 7**. A sample size of 30 patients in each **Cohorts 6** and **7** will provide a width of 0.31 to 95% confidence interval for a point estimate of 20% (95% CI: 7.71, 38.57%) in 2-sided exact test of proportion in single-arm trial.

Futility Analyses

The study includes a futility analysis to be conducted in each patient cohort, separately, when the response evaluation is complete for the first 20 patients in **Cohorts 1** to **4** and for the first 10 patients in each dose group in **Cohort 5** and **Cohorts 6 and 7**. A patient cohort (**Cohorts 1** to **4**, **Cohort 6** and **7**) or treatment group (**Cohort 5**: 10 mg QD, 12 mg QD, 16 mg QD, 6 mg BID, and 8 mg BID groups) will be stopped for futility if the ORR is <10%. No adjustment to multiplicity will be made for the futility analysis.

If one or two of the three randomized dose groups (10 mg QD or 6 mg or 8 mg BID) meets the criteria for futility, all new patients will be randomized or enrolled into the remaining group(s)

Efficacy Analysis:

The primary efficacy analysis will include all treated patients for **Cohorts 1** to **4**, including patients treated with 8 mg BID using the same statistical criteria as defined in Amendment 2. The primary efficacy variable ORR will be analyzed descriptively along with the 95% CI for each cohort. The determination of ORR will be based upon assessment by an Independent Radiologic Review Committee. The other outcomes, DCR, DoR, and PFS for all cohorts and QoL for **Cohorts 1** to **4** only, will be analyzed using descriptive statistics and with 95% CI for DCR and Kaplan-Meier plot for DoR, PFS, and OS. The same analysis method, except for QoL, will be used for **Cohorts 5** to **7**.

Analysis Populations:

The following analysis populations have been defined for each cohort:

- The **As-Treated Population** will be the primary analysis population and include all patients who receive at least one dose of study medication.

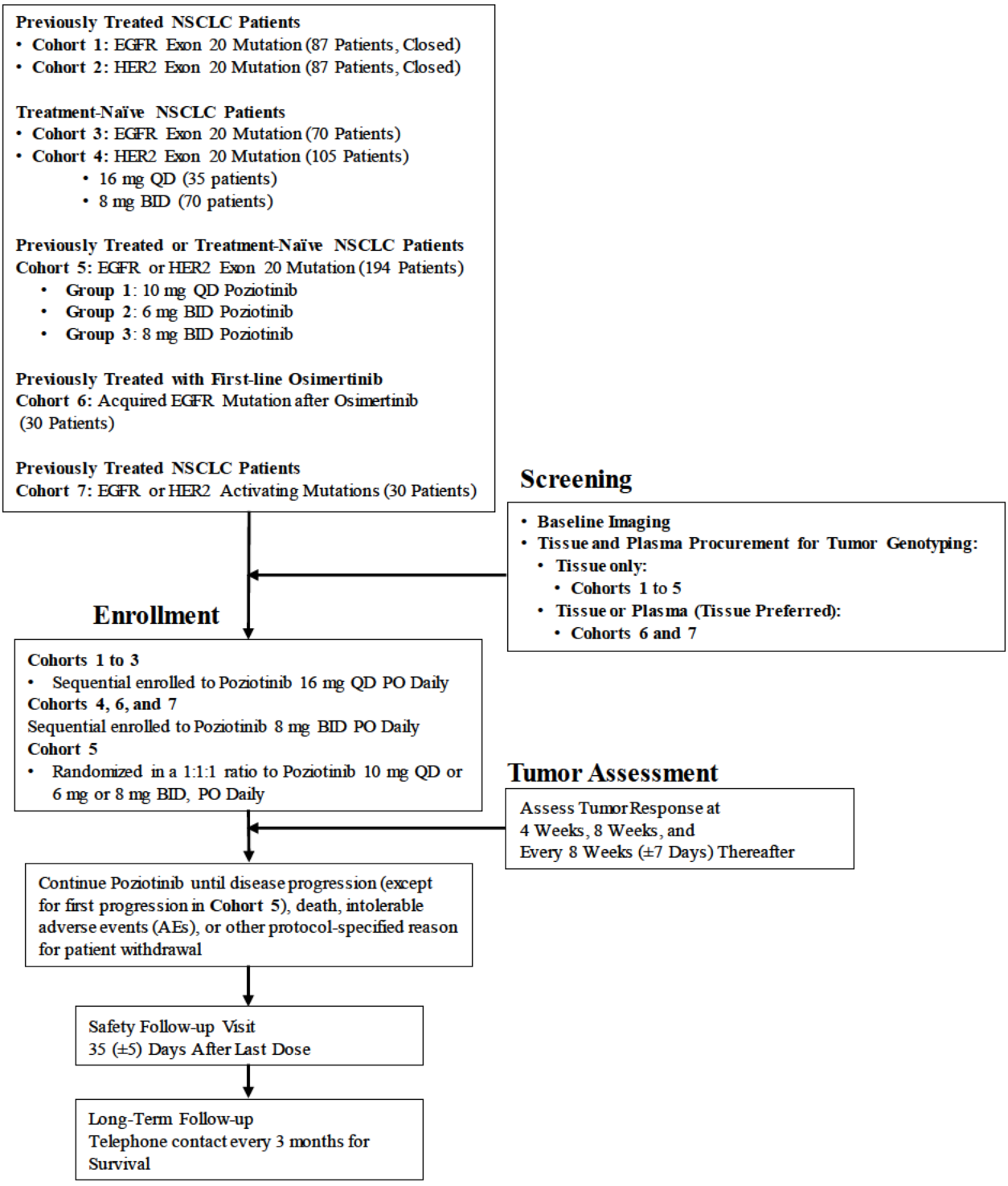
- The **Evaluable Population** consists of all patients who are enrolled, complete at least 1 cycle of poziotinib treatment, and is evaluable for tumor response based on RECIST, Version 1.1 criteria. The efficacy data will also be analyzed using the **Evaluable Population**.
- The **Safety Analysis Population** 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 CTCAE, Version 4.03.

Protocol Version/Date: Amendment 3/14 Feb 2020

Study Design Diagram



SCHEDULE OF ASSESSMENTS AND PROCEDURES

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)			Day 1	35 (±5) Days After Last Dose	Ongoing
			8	15	22			
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	x	x	x	x		x	x	
ECOG Performance Status	x	x				x	x	
Pregnancy Test (urine) [d]	x	x				x	x	
Tumor Assessment	x [e]	x [f]				x	x	
QoL Questionnaire [g]		x				x	x	
Tissue Samples [h]	x					x		
Plasma Samples [i]	x					x	x	
Whole Blood Samples [j]	x							
CBC with 5-part differential and platelets [k]	x	x				x	x	
Serum Chemistry [l]	x	x				x	x	
Electrocardiogram [m]	x	x				x	x	
Echocardiogram or MUGA Scan [n]	x							
PK Samples [o]		x	x			x		
Dispense Poziotinib [p]		x				x		
Dispense Loperamide		x				x		
Adverse event assessment	x [q]	x	x	x		x	x	x
Concomitant medications	x	x	x	x		x	x	
Patient Diary Dispensed/Collected		x	x	x		x	x	
Telephone Contact [r]		x			x	x		x

a) If a visit is delayed during a cycle, the subsequent schedules will be delayed sequentially.
b) Height only needs to be recorded during the **Screening Visit**.
c) A complete physical examination is required at **Screening**, **Day 1** of each cycles, and at the **Safety Follow-up Visit**. Symptom-directed exams are required at other visits.
d) Urine pregnancy test (β-HCG) in women of child-bearing potential.
e) The **Screening** tumor assessment will be based on scans performed before the patient signed the ICF. Brain MRI scans for patients with known brain metastases should also be performed per standard of care.

f) **Baseline** tumor assessment will be performed within 2 weeks 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 7**]), at 8 weeks (**Cycle 3**, **Day 1** [up to **Cycle 3**, **Day 7**, with at least 28 days from previous tumor assessment]), and then every 8 weeks (±7 days) thereafter until disease progression (except for first progression in **Cohort 5**), death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal.

g) **Cohorts 1** to **4** only: The QoL Questionnaire, EORTC QLQ-C30 and QLQ-LC13, will be performed on **Cycle 1**, **Day 1** (pre-dose), at each tumor imaging session, and at the **Safety Follow-up Visit**.

h) Tumor genotyping report for tissue samples from a local lab is required to confirm patient mutation eligibility for **Cohorts 1** to **6**. For **Cohort 7**, tissue samples are preferred, but results from plasma samples are acceptable if tissue is not available. For **Cohort 6**, plasma or tissue samples must be collected after osimertinib progression. All tissue samples should be retained for retrospective confirmatory central analysis. Collecting a tissue sample at progression is optional but is highly encouraged.

i) Plasma samples will be drawn from all patients at Screening and on the day of each on-study imaging session, beginning at the 8-week imaging session, and when the patient progresses, for biomarker analysis (optional). For **Cohort 7**, plasma samples are acceptable for patient mutation confirmation if a tissue sample is not available.

j) Whole blood samples will be drawn at Screening for pharmacogenomic analysis or at the next scheduled visit.

k) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained within 7 days prior to **Day 1** of each cycle, at which time, platelet count must be $\geq 100 \times 10^9$/L before and ANC must be $\geq 1.5 \times 10^9$/L dispensing poziotinib for the next cycle of treatment.

l) Blood for chemistry is to be collected within 7 days prior to poziotinib administration on **Day 1** of each cycle.

m) For all patients, 12-lead ECGs will be performed pre-dose and 1 and 2 hours post-dose on **Cycle 1**, **Day 1** and **Cycle 2**, **Day 1** for time-matched concentration-ECG analysis. ECGs are not required on **Day 1** of other cycles.

n) Cardiac ejection fraction may be evaluated at **Screening** in patients who are considered at high risk of cardiac disease, as determined by the Investigator, using echocardiogram or multi-gated acquisition (MUGA) scan. The investigator can order subsequent tests based on patient standard of care as determined by the Investigator.

o) All patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose on **Cycle 1**, **Day 1** and **Cycle 2**, **Day 1** for sparse PK sampling and time-matched concentration-ECG analysis . For intensive PK patients, Cycle 1, Day 1 and Cycle 1, Day 8 clinical evaluations can be done within 24 hours prior to first dose administration. At select study centers, patients (a minimum of 6 patients per dosing schedule) will be specifically consented for intensive PK in the 6 and 8 mg BID groups in **Cohort 5** . Intensive PK blood sampling will replace sparse PK blood sampling in **Cycle 1** and sparse sampling on **Cycle 2**, **Day 1** is not required in these patients. The schedule for intensive PK blood sampling will be pre-dose and 1, 2, 4, 8, 12, , and 24 hours post-dose on **Cycle 1**, **Day 1** and **Cycle 1**, **Day 8 (±2 days)**. The 12-hour PK sample must be collected prior to the second daily dose (12-hour dose). Patient must be on drug at the time of blood sampling. In addition, if, during any visit, a patient presents with a potentially drug-related Grade ≥3 adverse event (e.g., rash, mucositis, diarrhea), a blood sample will be collected as soon as possible following the onset of the AE. PK blood samples are not required on **Day 1** of other cycles.

p) Poziotinib will be dispensed on **Day 1** of each cycle.

q) From the time the ICF is signed through the first dose of study drug administration, all SAEs are to be recorded. 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 be recorded. Patients must visit the clinic for AE assessment on **Cycle 1**, **Days 8** and **15** (±2 days).

r) Telephone contact will be made with the patient every week during **Cycles 1** and **2** and then every other week while being treated with study drug, except for weeks that the patient visits the clinic. 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.

Poziotinib Dosing Recommendations

If needed, doses will be reduced by 2 mg (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 and the Sponsor should be notified. If doses are reduced by other than by 2 mg/dose Sponsor's Medical Monitor approval is required. After a dose reduction, a patient cannot be treated with a higher dose of poziotinib, except for patients in **Cohorts 5**, **6**, and **7**. Upon first progression, patients in **Cohort 5** can escalate up to a maximum of 8 mg BID or stay on therapy at their current dose at the discretion of the Investigator based on the patient's tolerability to the drug, and consideration of other available treatments but must be approved by the Sponsor's Medical Monitor prior to implementation. Dosing modifications are described in the table below.

Poziotinib Dose Modification Recommendations

<table>
<tr><th rowspan="2">Related Adverse Event</th><th rowspan="2">Grade</th><th colspan="2">Occurrence</th></tr>
<tr><th>1</th><th>Each Additional Occurrence</th></tr>
<tr><td>Diarrhea</td><td>Grade ≥3 (Despite adequate anti-diarrhea management)</td><td rowspan="6">Stop poziotinib treatment until AE Grade ≤1 and then continue treatment at the same dose [a]
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 adequate diarrhea management)</td></tr>
<tr><td>Fatigue</td><td>Grade ≥3</td></tr>
<tr><td>Mucositis/ Stomatitis</td><td>Grade ≥3 (Despite adequate management)</td></tr>
<tr><td rowspan="2">Nausea and/or Vomiting</td><td>Grade ≥3 (Despite adequate anti-emetics)</td></tr>
<tr><td>Grade ≥2 for ≥48 hours (Despite adequate anti-emetics)</td></tr>
<tr><td>Rash</td><td>Any Grade</td><td colspan="2">Refer to Appendix 6</td></tr>
<tr><td>LVEF Dysfunction</td><td>Grade ≥3</td><td colspan="2">Discontinue Treatment</td></tr>
</table>

a. Preliminary information from **Cohort 1** 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).

TABLE OF CONTENTS

TITLE PAGE 1
INVESTIGATOR SIGNATURE 2
SYNOPSIS 3
TABLE OF CONTENTS 15
List of Tables 17
List of Figures 18
LIST OF ABBREVIATIONS 19
1 INTRODUCTION 22
1.1 Background 22
1.1.1 EGFR Exon 20 Mutation Non-Small Cell Lung Cancer 22
1.1.2 HER2 Exon 20 Mutation Non-Small Cell Lung Cancer 22
1.1.3 Poziotinib 23
1.1.4 Poziotinib Nonclinical Studies 23
1.1.5 Poziotinib Clinical Studies 31
1.2 Rationale for the Current Study 34
1.2.1 Rationale for Amendment 3 34
2 STUDY OBJECTIVES 36
2.1 Primary Objective 36
2.2 Secondary Objectives 36
2.3 Exploratory Objectives 36
3 INVESTIGATIONAL PLAN 37
3.1 Study Design and Treatment Plan 37
3.2 Study and Treatment Duration 39
4 PATIENT POPULATION 40
4.1 Inclusion Criteria 40
4.2 Exclusion Criteria 42
4.3 Patient Discontinuation/Withdrawal Criteria 43
5 STUDY PROCEDURES 44
5.1 Screening 44
5.2 Patient Assignment 44
5.3 Timing of Assessments and Procedures 44
5.3.1 Screening (Day -30 to Day -1) 44
5.3.2 Treatment Period – Cycle 1, Day 1 45
5.3.3 Treatment Period Clinic Visit – Cycle 1, Day 8 (±2 days) and 15 (±2 days) 46
5.3.4 Treatment Period - Telephone Contact to Assess Adverse Events 46
5.3.5 Treatment Period – Cycle 2+, Day 1 46
5.3.6 Safety Follow-up/End-of-Study Visit (35 [±5] Days after Last Dose of Study Treatment) 47
5.3.7 Long-Term Follow-up – Every 3 Months 47

5.4 Description of Study Assessment Parameters 48
5.4.1 Relevant Medical History 48
5.4.2 Physical Examination 48
5.4.3 Vital Signs 48
5.4.4 ECOG Performance Status 48
5.4.5 Tumor Assessment 48
5.4.6 Tissue, Plasma, and Whole Blood Samples Retained 49
5.4.7 Clinical Laboratory Tests 50
5.4.8 Pharmacokinetics 50
5.4.9 Electrocardiogram 51
5.4.10 Cardiac Ejection Fraction 51
5.4.11 Quality of Life Questionnaire 51
5.4.12 Concomitant Medications 51

6 STUDY DRUG AND PHARMACEUTICAL INFORMATION 54

6.1 Poziotinib 54
6.1.1 Poziotinib Composition 54
6.1.2 Poziotinib Supply and Labeling 54
6.1.3 Poziotinib Administration 54
6.1.4 Poziotinib Storage and Handling 55
6.1.5 Poziotinib Dose Modification Recommendations 55
6.2 Comparator Treatment 56

7 SAFETY ASSESSMENT 56

7.1 Safety Measures 56
7.2 Adverse Events 57
7.3 Guidelines for Recording and Attribution Scoring of Adverse Events 58
7.3.1 Recording of Adverse Events 58
7.3.2 Grading of Adverse Events 58
7.4 Follow-up of Adverse Events 58
7.5 Relationship 58
7.6 Expectedness 59
7.7 Serious Adverse Events 60
7.7.1 Serious Adverse Event Reporting 60
7.7.2 Exclusions to Serious Adverse Event Reporting Requirements 61
7.8 Reproductive Risks 61

8 STATISTICAL PLAN 62

8.1 Sample Size 62
8.2 Futility Analyses 64
8.3 Method of Treatment Assignment 64
8.4 Analysis Populations 64
8.5 General Statistical Methods 64
8.6 Efficacy Analyses 65
8.6.1 Primary Endpoint 65
8.6.2 Secondary Endpoints 65
8.6.3 Exploratory Endpoints 65

8.6.4 Data Stratification 66
8.7 Safety Analysis 66
8.8 Clinical Laboratory Evaluations 67
9 ADMINISTRATIVE PROCEDURES AND STUDY MANAGEMENT 67
9.1 Investigator Responsibilities 67
9.1.1 Good Clinical Practice 67
9.1.2 Institutional Review Board/Ethics Committee Approval 68
9.1.3 Informed Consent 68
9.1.4 Study Files and Retention of Records 68
9.2 Recording and Collecting of Data 68
9.2.1 Case Report Forms 68
9.2.2 Drug Accountability 69
9.3 Protocol Compliance 69
9.4 Sponsor Responsibilities 69
9.4.1 Safety Monitoring 69
9.5 Joint Investigator/Sponsor Responsibilities 69
9.5.1 Access to Information for Monitoring and Auditing 69
9.5.2 Termination of the Study or Study Cohorts 70
9.5.3 Publication Policy 70
9.6 Confidentiality 70
10 REFERENCES 72
APPENDIX 1 SCHEDULE OF ASSESSMENTS AND PROCEDURES 74
APPENDIX 2 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCALE 76
APPENDIX 3 SAMPLE EORTC QLQ-C30 QUESTIONNAIRE 77
APPENDIX 4 SAMPLE EORTC QLQ-LC13 79
APPENDIX 5 DIARRHEA MANAGEMENT RECOMMENDATIONS 80
APPENDIX 6 RASH MANAGEMENT RECOMMENDATIONS 82

List of Tables

Table 1 Most Common Treatment-Emergent Adverse Events (≥30% in any Study) in Descending Order by Preferred Term (Safety Population) - Phase 1 and Phase 2 Completed Studies with Poziotinib (16 mg/day) 33
Table 2 Examples of Important Clinical Inhibitors/Inducers/Substrates for P450 Enzymes Involved in the Metabolism of Poziotinib 52
Table 3 Poziotinib Dose Modification Recommendations 56
Table 4 Investigator Assessment of Adverse Event Causality 59

List of Figures

Figure 1 IL-3-Independent Survival of Ba/F3 Cells Stably Expressing *EGFR* Exon 20 Mutations....24
Figure 2 Poziotinib (HM781-36B) is a Potent Inhibitor of Cell Lines with *EGFR* Exon 20 Insertions....25
Figure 3 Effect of Poziotinib (HM781-36B) on EGFR Phosphorylation and Downstream Signaling....25
Figure 4 Tumor Volume Change in Mice with EGFR Exon 20 Insertion Mutations Treated with Poziotinib Vs Vehicle....26
Figure 5 a) Ba/F3 Cells Expressing *HER2* Mutations are Sensitive to Poziotinib b) Poziotinib Inhibits HER2 Phosphorylation....27
Figure 6 Tumor Volume Change in Mice with HER2 Exon 20 Insertion Mutations - Treated with Poziotinib vs Vehicle....27
Figure 7 Poziotinib Inhibits Growth of Atypical EGFR Mutant Ba/F3 Cell Lines....28
Figure 8 Poziotinib Inhibits Growth of Atypical HER2 Mutant Ba/F3 Cell Lines....29
Figure 9 Best Percent Change in Sum of Target Lesion Dimension from Baseline....35
Figure 10 Stimulated Poziotinib Plasma Concentrations....36
Figure 11 Study Design Figure....39

LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Definition
ACS	American Cancer Society
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
β-hCG	Beta human chorionic gonadotropin
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CR	Complete Response
CRA	Clinical research associate
CRF	Case report form
CT	Computed tomography
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450
DCF	Data clarification form
DCR	Disease Control Rate
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EP	Evaluable Population
ER	Estrogen receptor
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridization
GCP	Good Clinical Practice
HER2	Human epidermal growth factor receptor 2

Abbreviation/ Acronym	Definition
hERG	Human ether-a-go-go
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
MedDRA®	Medical Dictionary for Regulatory Activities
M1	Metabolite 1 (of poziotinib)
M2	Metabolite 2 (of poziotinib)
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
MUGA	Multi-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Limit
NYHA	New York Heart Association
ORR	Objective response rate
PD	Progressive Disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial Response
PR	Progesterone receptor
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAER	Serious adverse event report
SAF	Safety analysis population
SAP	Statistical analysis plan
SD	Stable Disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TEAE	Treatment-emergent adverse event
TTP	Time to Progression
ULN	Upper limit of normal
US	United States

Abbreviation/ Acronym	Definition
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

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 **[1]**.

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 **[2]**. 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 **[3]**.

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 **[4]**.

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 **[4]**. 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**[5]** 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 **[4]**.

1.1.3 Poziotinib

1.1.3.1 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 **[6]**.

1.1.3.2 Drug Product Description

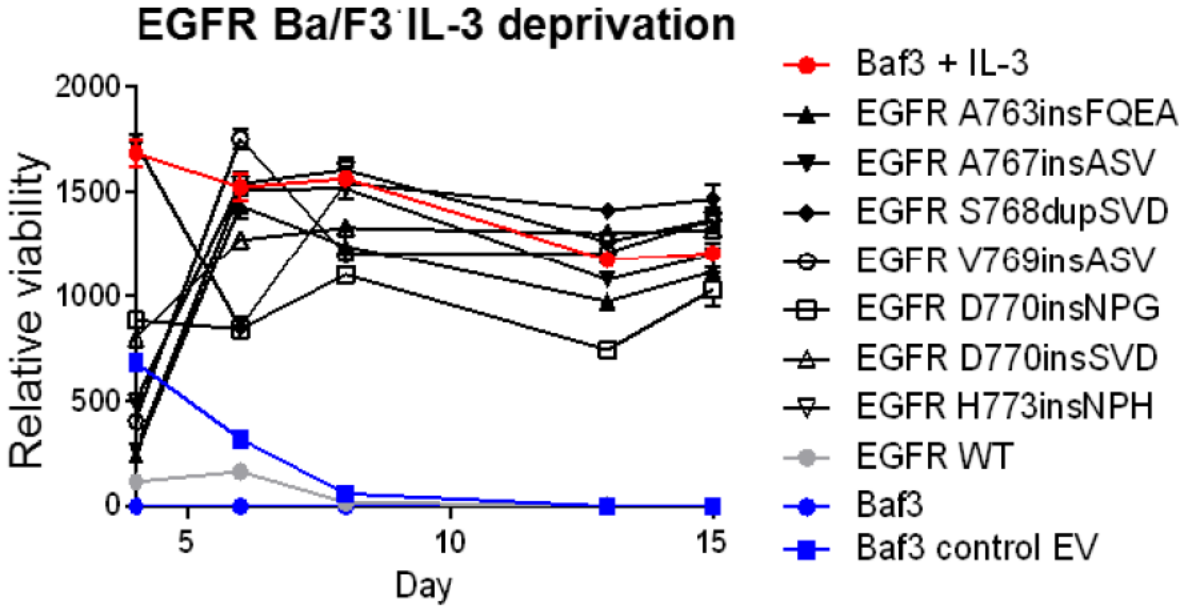
Poziotinib (HM781-36B) is formulated as a hydrochloride salt of poziotinib. The chemical formula of poziotinib is (1-[4-[4-(3,4-dichloro-2-fluorophenylamino)-7-methoxyquinazolin-6-yloxy]-piperidin-1-yl]prop-2-en-1-one hydrochloride). For clinical trials conducted in the United States, the drug product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

1.1.4 Poziotinib Nonclinical Studies

1.1.4.1 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 **[7]**. Stable expression of *EGFR* exon 20 insertion mutations rendered Ba/F3 cells IL-3 independent suggesting that these mutations are activating **(Figure 1) [7]**.

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) [7]**.

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

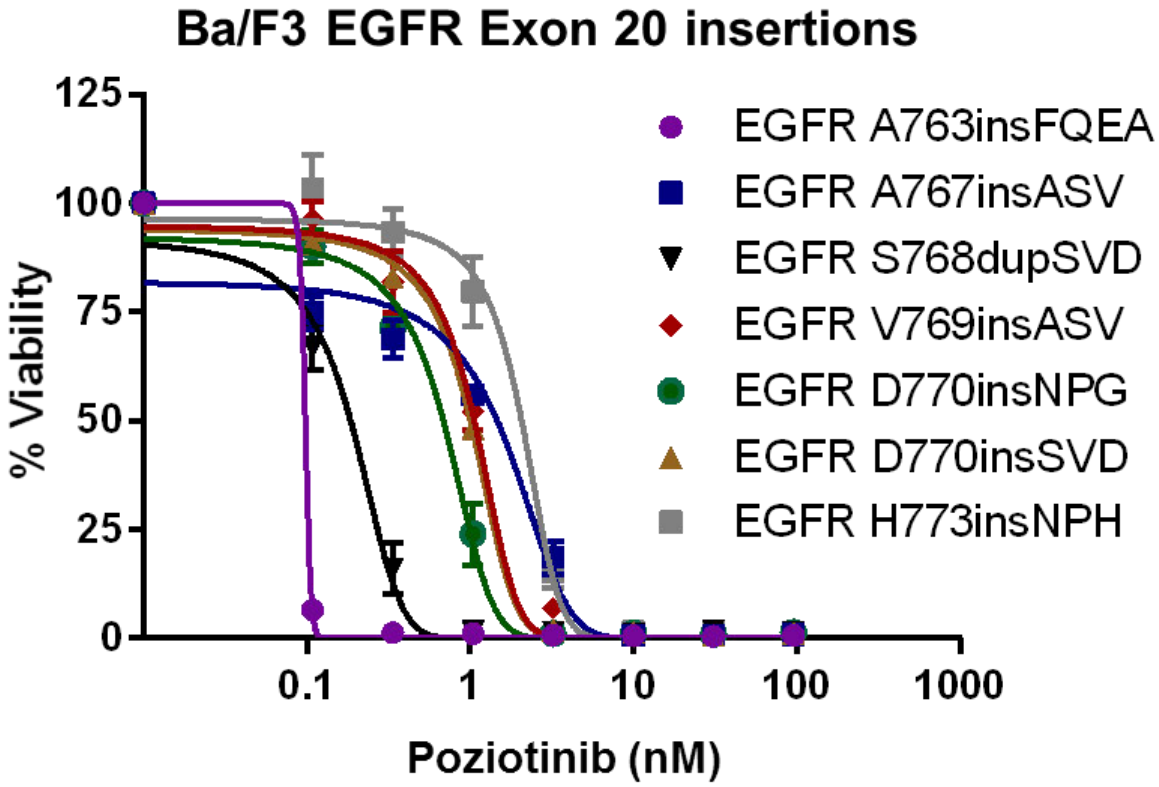
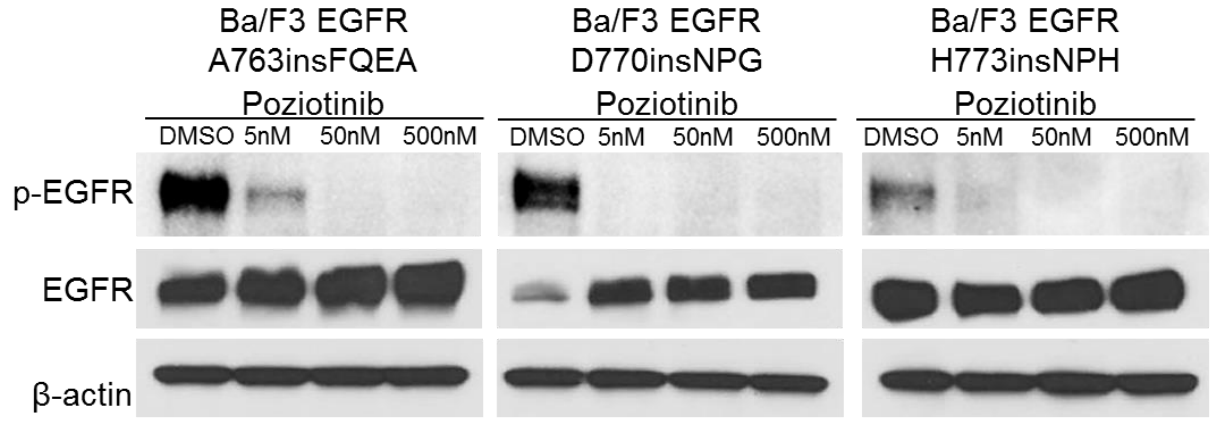
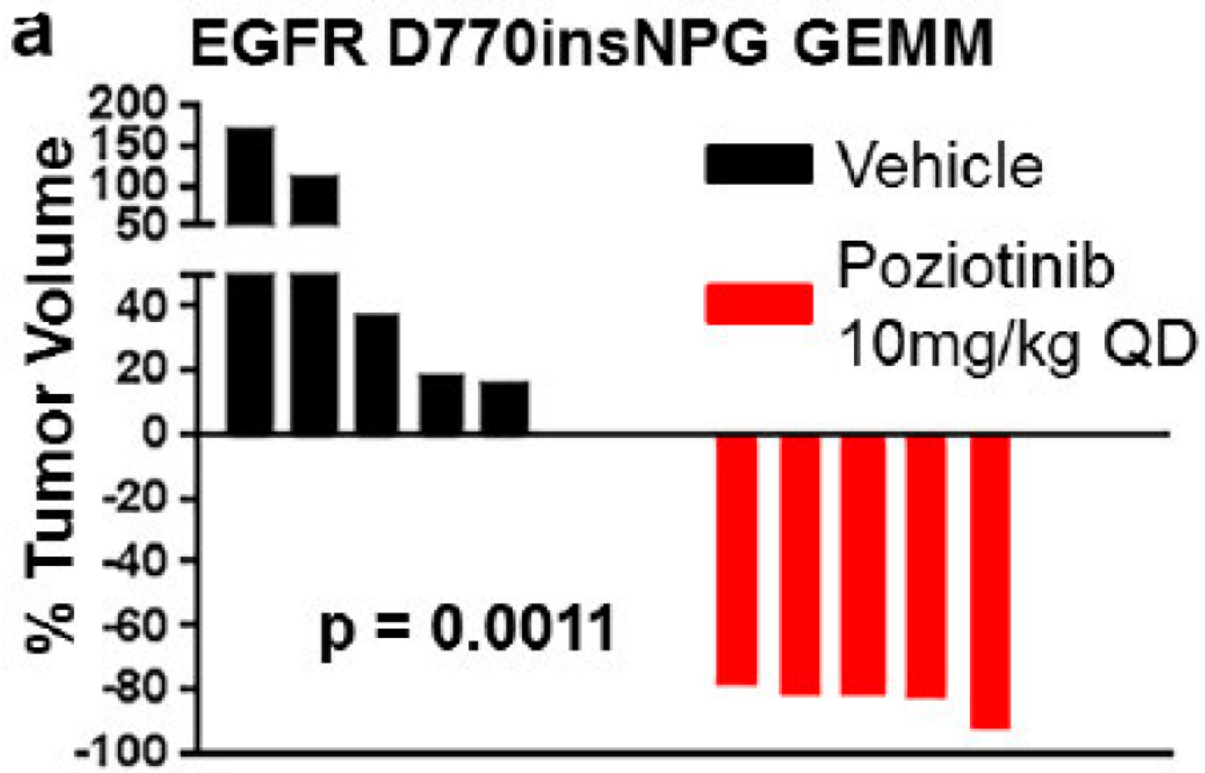


Figure 3 Effect of Poziotinib (HM781-36B) on EGFR Phosphorylation and Downstream Signaling



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) [7]**.

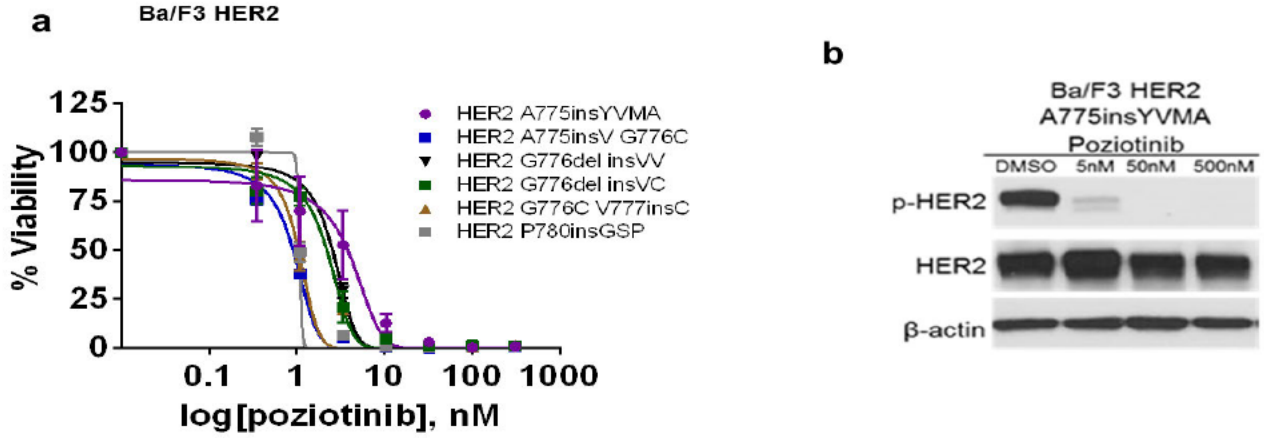
Figure 4 Tumor Volume Change in Mice with EGFR Exon 20 Insertion Mutations Treated with Poziotinib Vs Vehicle



1.1.4.2 Poziotinib in Tumor Models with HER2 Exon 20 Insertion Mutations

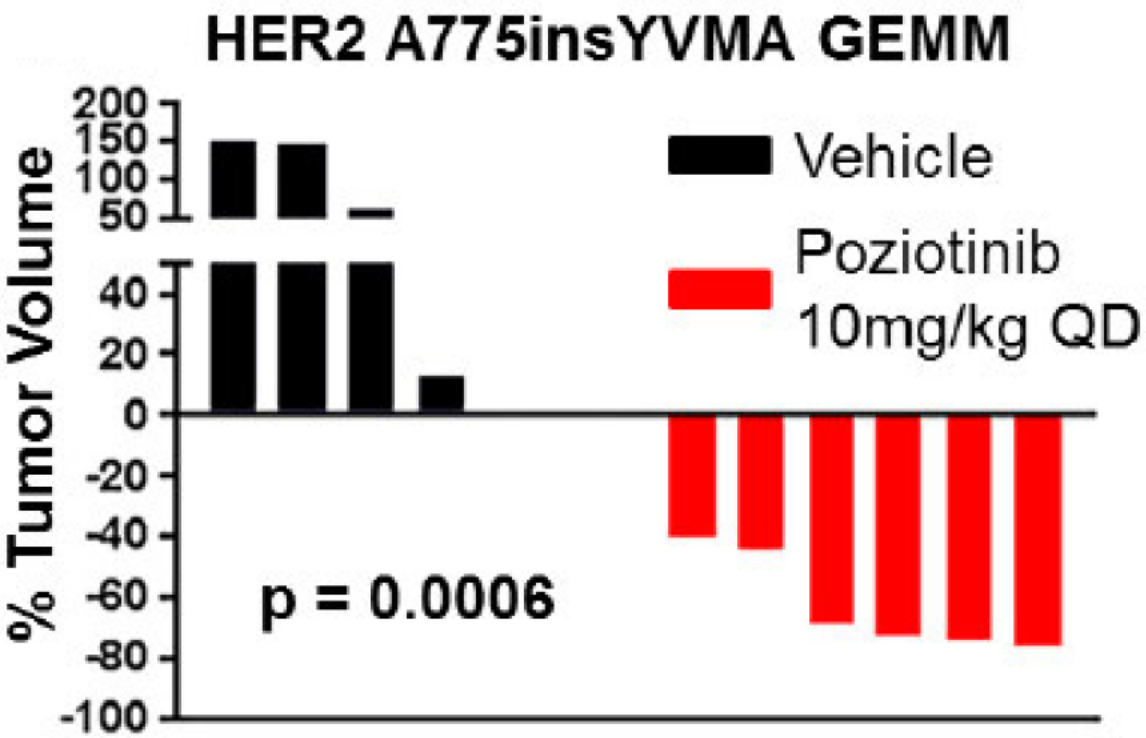
Robichaux *et al* stably expressed 11 clinically observed *HER2* mutations in Ba/F3 cells [7]. Similar to cell lines with *EGFR* exon 20 mutations, it was observed that poziotinib potently inhibited cell lines with *HER2* mutations *in vitro*. Poziotinib effectively inhibited the growth of *HER2* exon 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**) **[7]**.

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**) [7].

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.

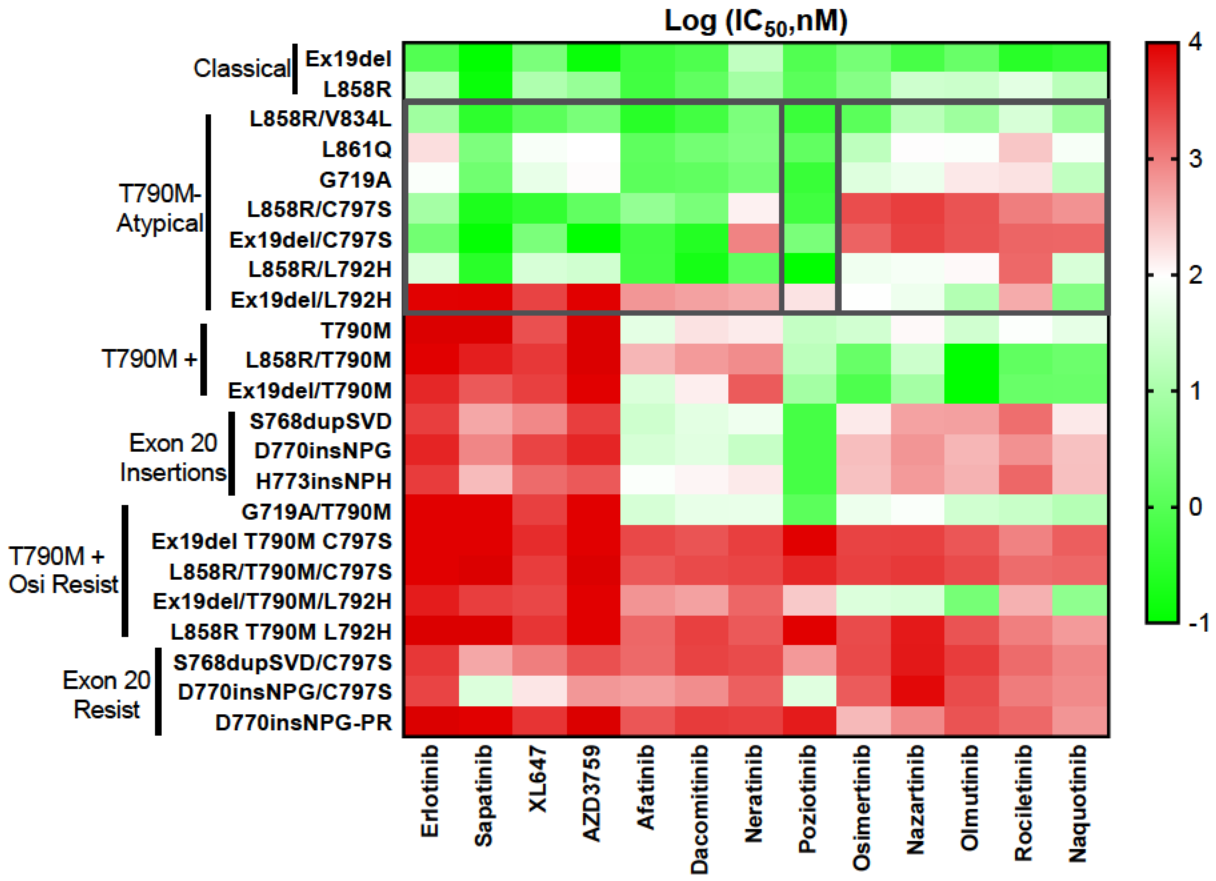
1.1.4.3 Poziotinib in Tumors with Atypical EGFR and HER2 Mutations

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).

1.1.4.3.1 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) **[8]**.

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



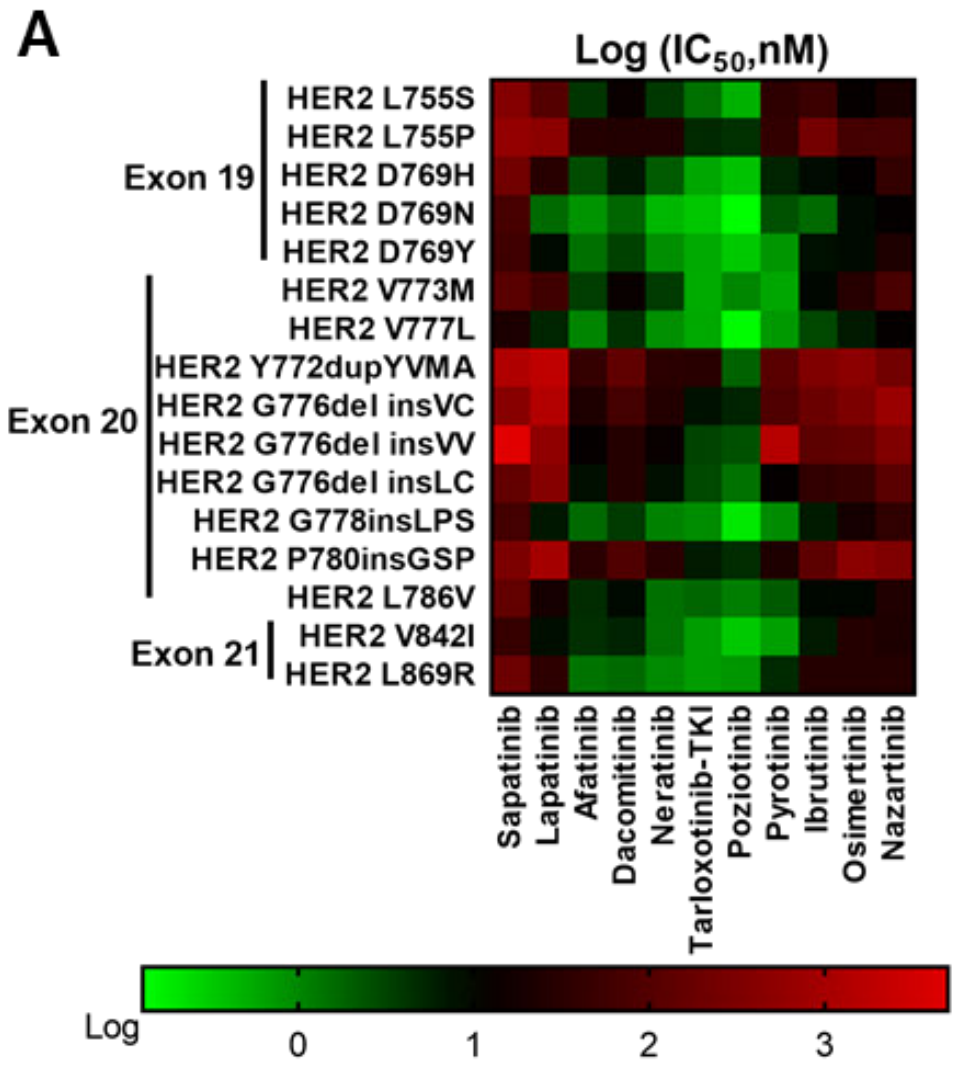
Source: Personal communication, J. Heymach, MD Anderson Cancer Center, 03 Apr 2019

1.1.4.3.2 Atypical HER2 Mutations

Several atypical HER2 mutations that are sensitive to poziotinib in vitro have been identified [9]. 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 [10] and I767M [11] have been found in breast cancer tumors and S310F [12], a mutation located in the extracellular region of HER2.

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



1.1.4.4 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 **[13]**.

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 (ie, Tums®, Maalox®) at least 4 hours before or after poziotinib administration.

1.1.4.5 Poziotinib Toxicity Studies

The toxicities of single or repeated daily doses of oral poziotinib were 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 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). In regard to cardiovascular effects (electrocardiogram [ECG], blood pressure, heart rate, and QT), there were no changes up to 0.15 mg/kg/day of poziotinib in the 13-week dog toxicity study.

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; and, 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 **[14-17]**, 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 in line with the 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.

1.1.5 Poziotinib Clinical Studies

To date, the clinical development program for poziotinib comprises 3 completed and 9 ongoing clinical studies in patients with advanced cancers.

- Two completed Phase 1 studies conducted in patients with advanced cancers (solid tumors) (**HM-PH1-101** and **HM-PH1-102**)
- One completed Phase 2 study conducted in patients with advanced NSCLC (**NOV120101**)
- Eight ongoing Phase 2 studies conducted in patients in various malignancies, including three Phase 2 studies being performed in NSCLC
- Compassionate-Use studies conducted in patients with NSCLC and breast cancer

To date, more than 800 patients have received poziotinib monotherapy in open-label clinical trials 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.

1.1.5.1 Overview of 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 Rat**e (**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**.

1.1.5.2 Overview of Safety

Poziotinib monotherapy utilizing an oral dose of 16 mg/day on either an intermittent (2 weeks on, 1 week off) or continuous dosing regimen can induce partial response or disease stabilization in patients with several advanced solid tumor types (**HM-PH1-102**). For the cancer indications being investigated, the patients 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).

Despite the fact that most patients treated in poziotinib clinical trials have had advanced and heavily pre-treated disease, the safety profile described for poziotinib in these trials and the anti-tumor activity noted suggests a favorable benefit-risk ratio and provides justification for the continued development of poziotinib for the treatment of multiple EGFR- or HER2-driven solid tumor indications.

The most commonly reported treatment-emergent AEs in all three completed studies were diarrhea, rash, stomatitis, decreased appetite, paronychia and pruritus (**Table 1**).

Table 1 Most Common Treatment-Emergent Adverse Events (≥30% in any Study) in Descending Order by Preferred Term (Safety Population) - Phase 1 and Phase 2 Completed Studies with Poziotinib (16 mg/day)

Preferred Term	Number (%) Patients		
	HM-PHI-101 N=55	HM-PHI-102 N=20	NOV120101-202 N=39
Any Adverse Event	**6 (100)**	**8 (100)**	**39 (100)**
Diarrhea	6 (100)	8 (100)	36 (92)
Rash	6 (100)	7 (88)	30 (77)
Stomatitis	6 (100)	6 (75)	23 (59)
Paronychia	2 (33)	7 (88)	21 (54)
Decreased Appetite	5 (83)	6 (75)	21 (54)
Vomiting	4 (67)	4 (50)	4 (10)
Pruritus	2 (33)	6 (75)	25 (64)
Acne	4 (67)	0	0
Fatigue	3 (50)	1 (13)	15 (38)
Mucosal Inflammation	0	3 (38)	18 (46)
Nausea	2 (33)	3 (38)	5 (13)
Rhinorrhea	2 (33)	3 (38)	4 (10)
Palmar-Plantar Erythrodysesthesia Syndrome	2 (33)	1 (13)	3 (8)
Weight Decreased	2 (33)	0	6 (15)
Dry skin	0	2 (25)	15 (38)
Pain of Skin	0	3 (38)	2 (5)

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 and HM-PH1-102**; MedDRA version 17.0 was used for **NOV120101-202.**

Source: Adapted from **Poziotinib IB Table 13**.

The most commonly reported treatment-related AEs (≥50% incidence in any 16 mg/day cohort) in **HM-PHI-101**, **HM-PHI-102**, and **NOV120101** were as follows:

- Diarrhea (100%, 100%, 95%)
- Stomatitis (100%, 75%, 59%)
- Vomiting (17%, 50%, 5%)
- Rash (100%, 88%, 77%)
- Pruritus (33%, 75%, 64%)
- Acne (67%, 0%, 0%)
- Decreased appetite (50%, 63%, 49%)
- Paronychia (33%, 88%, 54%)

The most commonly reported Grade 3 TEAEs (≥20% incidence in any 16-mg/day cohort) in **HM-PHI-101**, **HM-PHI-102**, and **NOV120101** were as follows:

- Rash (0%, 0%, 59%)
- Mucosal Inflammation (0%, 0%, 26%)

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.

In HER2 overexpressing tumors, clinical activity was shown in a variety of solid tumors in the Phase 1 studies of poziotinib. Additionally, clinical activity has been shown in a Phase 2 study in EGFR-mutation NSCLC at dose of 16 mg once daily (**NOV120101-202**).

In preclinical studies, consistent with reported clinical data, tumors with exon 20 insertions are resistant to first and second-generation tyrosine kinase inhibitors. Preclinical models indicate marked sensitivity of both EGFR and HER2 exon 20 insertion mutations to poziotinib **[18]**.

Based on the promising clinical data and acceptable safety profile from studies in HER2-overexpressed tumors and the preclinical data suggesting activity against EGFR and HER2 exon 20 insertion mutations, a single-center Phase 2 Investigator Initiated Study (IIS) was started to evaluate poziotinib in the patients with NSCLC and EGFR or HER2 exon 20 insertion mutations. The design of SPI-POZ-202 is similar to the IIS and is intended for further evaluation of the efficacy and safety of poziotinib in this NSCLC patient population.

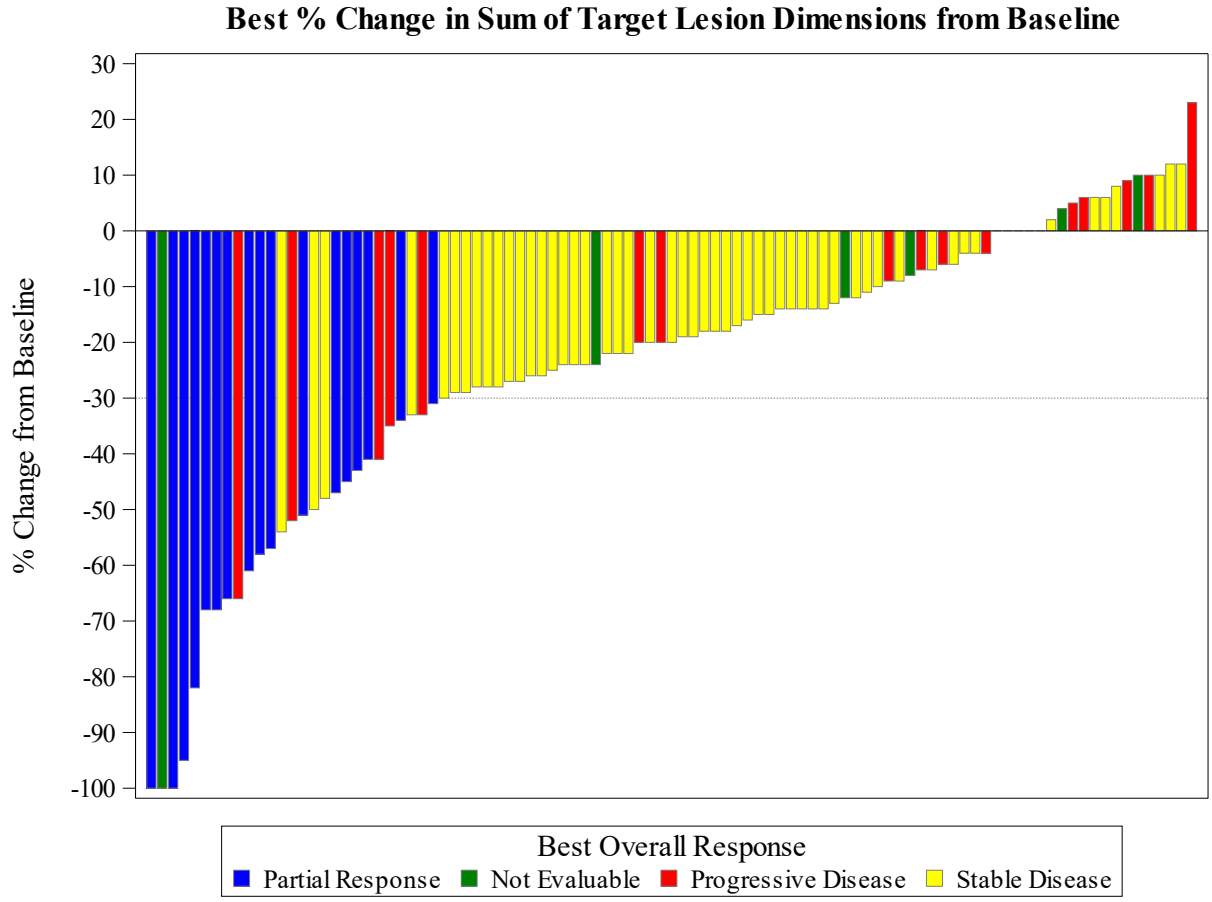
1.2.1 Rationale for Amendment 3

The starting dose for this study was 16 mg QD for all cohorts. Enrollment into **Cohort 1** (previously treated patients with EGFR mutations) and **Cohort 2** (previously treated patients

with HER2 mutations) in the study have been completed and the preliminary results for the primary endpoint (ORR) for **Cohort 1** are available.

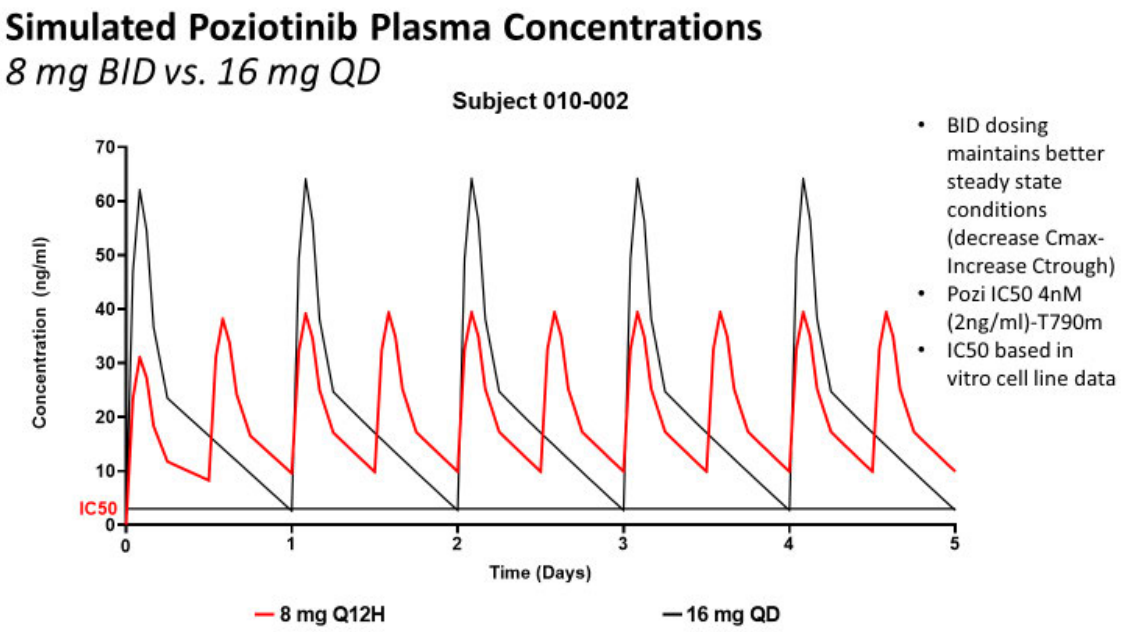
Cohort 1 enrolled a total of 115 patients who received 16 mg/day of poziotinib. The Intent-to-Treat analysis showed that 17 patients had a response (by RECIST) and 62 patients had stable disease for a 68.7% disease control rate (DCR). The confirmed objective response rate (ORR) was 14.8% (95% CI; 8.9%-22.6%). 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



Pharmacokinetic modeling for the 8 mg BID and 16 mg QD doses, 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)**. 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 Stimulated Poziotinib Plasma Concentrations



Because enrollment for **Cohort 3** is nearly complete, dosing for this cohort will not be changed. To help manage toxicity, patients in **Cohorts 4, 6,** and **7** will begin treatment with 8 mg BID (16 mg daily) dosing. In **Cohort 5**, the 10 mg QD group will continue and the 12 and 16 mg QD dose groups changed to 6 mg BID or 8 mg BID, for the same total daily dose; the predicted AUC for each BID dose group is expected be the same as the original QD dose groups.

2 STUDY OBJECTIVES

To evaluate the following in NSCLC patients with EGFR or HER2 exon 20 insertion mutations (including duplication mutations) who are treated with poziotinib.

2.1 Primary Objective

- **Objective Response Rate (ORR)**

2.2 Secondary Objectives

- **Disease Control Rate (DCR)**
- **Duration of Response (DoR)**
- **Safety and tolerability**

2.3 Exploratory Objectives

- **Progression-free Survival (PFS)**
- **Quality of Life (QoL) (Cohorts 1 to 4 only)**
- **Evaluate alternate poziotinib starting doses and schedules**

- **Evaluate poziotinib in patients who progressed while on treatment with first-line osimertinib (Cohort 6 only)**
- **Evaluate poziotinib in patients with EGFR or HER2 activating mutations**
- **Evaluate overall survival**
- **Characterize the PK profile of poziotinib**

3 INVESTIGATIONAL PLAN

3.1 Study Design and Treatment Plan

This is a Phase 2, open-label, multicenter study to evaluate the efficacy and the safety/tolerability of poziotinib in four patient cohorts for up to 174 previously treated NSCLC patients with any systemic therapy (**Cohort 1**: 87 patients with EGFR exon 20 insertion mutations, **Cohort 2**: 87 patients with HER2 exon 20 insertion mutations), up to 175 treatment-naive NSCLC patients (**Cohort 3**: 70 patients with EGFR exon 20 insertion mutations, **Cohort 4**: 105 patients with HER2 exon 20 insertion mutations).

Approximately 194 patients in **Cohort 5** (See **Section 8.1**), 30 patients in **Cohort 6**, and 30 patients in **Cohort 7** are being enrolled**.**

The **Screening** period (**Day -30** to **Day -1**) lasts up to approximately 30 days prior to **Cycle 1**, **Day 1**. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. Eligible patients will provide written Informed Consent prior to any study procedures.

Each treatment cycle is 28 calendar days in duration. There will be 7 patient cohorts and eligible patients will be enrolled into each cohort in parallel based on EGFR or HER2 exon 20 mutation status and prior treatment status:

- **Cohort 1 (ZENITH20-1):** Previously treated patients with EGFR exon 20 insertion mutation positive NSCLC (N=87)
- **Cohort 2 (ZENITH20-2):** Previously treated patients with HER2 exon 20 insertion mutation positive NSCLC (N=87)
- **Cohort 3 (ZENITH20-3):** Treatment naïve patients with EGFR exon 20 insertion mutation positive NSCLC (N=70)
- **Cohort 4 (ZENITH20-4):** Treatment naïve patients with HER2 exon 20 insertion mutation positive NSCLC (N=105)
- **Cohort 5 (ZENITH20-5):** Patients who meet the criteria for enrollment in **Cohorts 1** to **4**, but the enrollment in the respective cohort has been closed
- **Cohort 6 (ZENITH20-6):** Patients with acquired EGFR mutation who progressed while on treatment with first-line osimertinib
- **Cohort 7 (ZENITH20-7):** Patients with EGFR or HER2 activating mutations

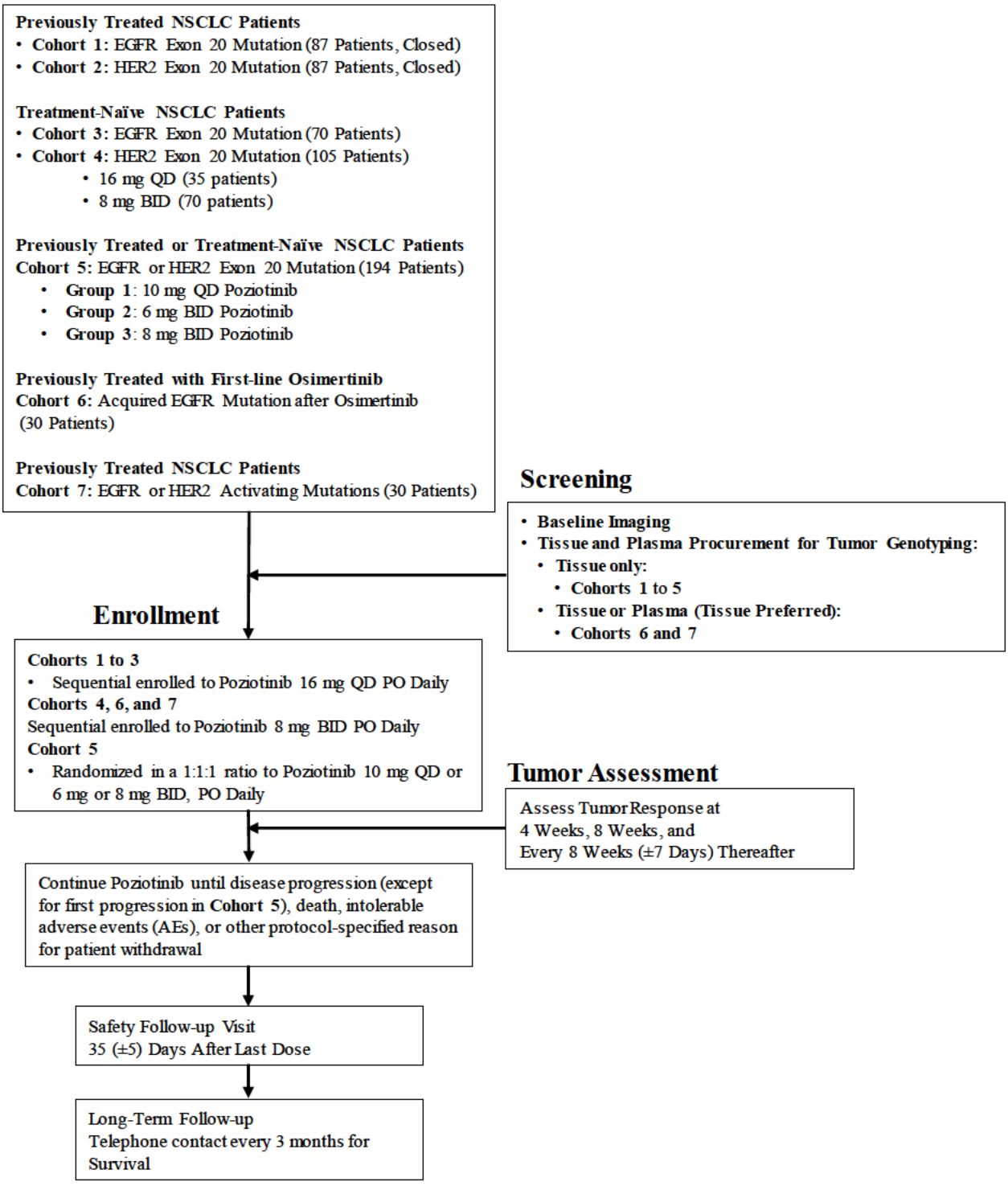
Toxicity will be assessed based on the severity grade of the adverse events using CTCAE version 4.03.

On **Day 1** of each 28-day cycle, the patient's absolute neutrophil count (ANC) must be $\geq 1.5\times10^9$/L and platelet count must be $\geq 100\times10^9$/L before administering poziotinib.

All patients will be treated until disease progression (except for first progression in **Cohort 5**), death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal.

The study design diagram is presented in **Figure 11**, and the Schedule of Study Assessments and Procedures is presented **Appendix 1**.

Figure 11 Study Design Figure



3.2 Study and Treatment Duration

The total duration of the study will be approximately 2 years. However, some patients may receive longer treatment if responding to the treatment. 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 until 24 months of treatment, disease progression (except for first progression in **Cohort 5**), death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal
- **Safety Follow-up Visit:** 35 (±5) days after the last dose of poziotinib

4 PATIENT POPULATION

4.1 Inclusion Criteria

1. Patient is at least 18 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. Patient has histologically or cytologically confirmed locally advanced or metastatic non-small cell lung cancer (NSCLC) that is not amenable to treatment with curative intent
4. Prior treatment status:
   - **Cohorts 1** and **2**: Patient has had at least one prior systemic treatment for locally advanced or metastatic NSCLC
   - **Cohorts 3** and **4**: Patient is treatment-naïve for locally advanced or metastatic NSCLC and eligible to receive first-line treatment with poziotinib as determined by the Investigator. Adjuvant/neo-adjuvant therapies (chemotherapy, radiotherapy, or investigational agents) are permissible as long as they end at least 15 days prior to study entry.
   - **Cohort 5**: Patients who meet the criteria for enrollment in **Cohorts 1** to **4**, but the enrollment in the respective cohort has been closed
   - **Cohort 6:** Patients with EGFR mutation-positive NSCLC who progressed while on treatment with first-line osimertinib.
   - **Cohort 7:** Patient has had at least one prior systemic treatment for locally advanced or metastatic NSCLC
5. Tissue and plasma samples for mutation confirmation:
   - **Cohorts 1** to **5**: Patient has adequate tumor tissue obtained from a biopsy or surgical procedure to enable molecular profiling for retrospective central laboratory confirmation of the mutation. If tissue is not available, the patient must have biopsy accessible disease and must be willing to undergo a biopsy to provide an appropriate tissue sample prior to receiving treatment in the study
   - **Cohort 6**: Either tissue or plasma samples after osimertinib progression
   - **Cohort 7**: Either tissue or plasma samples
6. Patient is positive for EGFR or HER2 mutations based on:
   - **Cohorts 1 and 3**: Documented EGFR exon 20 insertion mutation (including duplication mutations) using a next generation sequencing diagnostic test, such as OncoMine Comprehensive Assay (OCA) or FoundationOne Assay, or by an FDA approved test (eg, cobas® EGFR mutation test v2 or therascreen EGFR RGQ PCR kit) performed by a US CLIA certified and locally licensed clinical laboratory or similarly accredited lab for ex-US sites using tissue samples

- **Cohorts 2 and 4**: Documented HER2 exon 20 insertion mutation (including duplication mutations) using a next generation sequencing diagnostic test, such as OncoMine Comprehensive Assay (OCA) or FoundationOne Assay, performed by a US CLIA certified and locally licensed clinical laboratory or similarly accredited lab for ex-US sites using tissue samples
- **Cohort 5**: Documented EGFR or HER2 exon 20 insertion mutations using tissue samples using the criteria described for **Cohorts 1 to 4**
- **Cohort 6**: Documented acquired EGFR mutation (tested after osimertinib progression) who have progressed while on first-line osimertinib treatment using tissue or plasma tested with a next-generation sequencing assay
- **Cohort 7**: Documented EGFR or HER2 activating mutations (see table below) using tissue or plasma tested with a next-generation sequencing assay

EGFR	HER2
E709X	S310F
E709_T710del insD	I655V
L718X	L755X
G719X	I767M
I740_K745dupIPVAIK	D769X
L747X	V777X
A750P	L786V
S768I	V842I
L833V	L869R
L861Q	

7. Patient has measurable NSCLC disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). Metastatic lesions in CNS or in brain cannot be used for target lesions.
8. Brain metastases may be allowed if patient's condition is stable, defined as asymptomatic, no requirement for high dose or increasing dose of systemic corticosteroids, and no need for any anticonvulsant therapy for metastatic brain disease. For the patient who has had radiation therapy, sequential post-treatment MRI tests, at least 4-6 weeks apart, should show no increases in brain lesion size/volume within 4 weeks prior to the study.
9. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and has a life-expectancy of more than 6 months
10. 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
- Creatinine clearance ≥50 mL/min according to the Cockcroft-Gault equation

11. Patient is willing to practice 2 forms of contraception, one of which must be a barrier method, from study entry until at least 30 days after the last dose of poziotinib
12. 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) or who are surgically sterilized do not require this test.

4.2 Exclusion Criteria

1. Patient has:
   - **All Cohorts**: EGFR T790M
   - **Cohorts 1 to 5**: EGFR exon 20 point mutation
   - **Cohort 7**: EGFR Exon 19 deletion and L858R or HER2 T798I mutations, EGFR and HER2 Exon 20 insertion mutation
2. Patient has had previous treatment with poziotinib or any other EGFR or HER2 exon 20 insertion mutation-selective tyrosine kinase inhibitor (TKI) prior to study participation. The currently approved TKIs (ie, erlotinib, gefitinib, afatinib, osimertinib) are not considered to be exon 20 insertion-selective and are permissible (**Cohorts 1** and **2**).
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 or 5 half-lives, whichever is longer; local radiation therapy for bone pain may be allowed
4. Patient has a 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
5. Patient has a high risk of cardiac disease, as determined by the Investigator, may undergo either echocardiogram (ECHO) or multi-gated acquisition (MUGA) during **Screening** and has a cardiac ejection fraction <50%.
6. Patient has had other malignancies within the past 3 years, except for stable non-melanoma skin cancer, fully treated and stable early-stage prostate cancer, or carcinoma in situ of the cervix or breast without need of treatment
7. 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 4.03) Grade 2 or above diarrhea due to other etiologies)
8. 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
9. 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

10. 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)
11. Patient has known hypersensitivity to poziotinib or has a history of allergic reactions attributed to chemically similar compounds or other tyrosine kinase inhibitors (TKIs)
12. Patient has an active uncontrolled infection, underlying medical condition, or other serious illness that would not be appropriate for this study
13. 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
14. Patient is pregnant or breast-feeding.
15. **Cohort 5 only:** Patient is eligible for treatment in an open cohort (**Cohorts 1 to 4**)

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) except for the first progression in patients in **Cohort 5**
- 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.

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 study design diagram is presented in **Figure 11,** and the Schedule of Study Assessments and Procedures is presented **Appendix 1**.

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 be screened, and eligibility determined prior to enrollment. 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 will be allowed for use as a Screening Assessment at the discretion of the Sponsor. 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** 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 screening number according to the instructions in the study binder.

Confirmation of eligibility is to be received by the investigational site from Spectrum 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, US001-001).

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 (Day -30 to Day -1)

The following screening assessments should be performed within 30 days prior to **Cycle 1, Day 1**. Obtain Informed Consent prior to any study procedures.

- Verify existing pathology and tissue-based mutation diagnostic records, and available imaging test reports from medical records before consenting the patient
- Informed Consent
- Relevant medical history
- Demographic data
- Height and weight
- Complete physical examination
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) Performance Status assessment
- Urine pregnancy test (beta human chorionic gonadotropin [β-HCG]) in women of childbearing potential

- Baseline brain MRI scan for patients with known brain metastases (if needed)
- Tissue sample for tumor genotyping (mandatory for **Cohorts 1** to **6**
- Plasma sample for biomarker analysis
- Whole blood sample for pharmacogenomic analysis
- Complete blood count (CBC) with 5-part differential and platelets prior to poziotinib administration (may be obtained up to 7 days prior to **Cycle 1**, **Day 1**)
- Serum chemistry (may be obtained up to 7 days prior to **Cycle 1**, **Day 1**)
- 12-lead electrocardiogram (ECG)
- Echocardiogram or MUGA scan to evaluate cardiac ejection fraction (only for patients who have a high risk of cardiac disease, as determined by the Investigator)
- Adverse event assessment using NCI CTCAE, version 4.03, record SAEs
- Concomitant medications

5.3.2 Treatment Period – Cycle 1, Day 1

- Eligibility confirmation
- Patient ID
- Weight
- Physical examination
- Vital signs
- ECOG Performance Status assessment
- Urine 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
- Serum Chemistry
- QoL questionnaire: EORTC QLQ-C30 and QLQ-LC13 (prior to first dose) (**Cohorts 1** to **4** only)
- 12-lead ECG pre-dose and at 1 hour and 2 hours (±15 min) post-dose
- Baseline tumor assessment if not already performed within 2 weeks prior to **Cycle 1**, **Day 1**
- Dispense poziotinib and loperamide
- **For intensive PK patients, clinical evaluations can be done within 24 hours prior to first dose administration.**
- Pharmacokinetic blood sampling:
  - Sparse PK blood sampling taken pre-dose and at 1 hour and 2 hours (±15 min) post-dose (**All patients**)

    OR
  - Intensive PK blood sampling pre-dose and 30 minutes, 1, 2, 4, 8, 12, and 24 hours post-dose (**Cohort 5 only at select sites**)

- Dispense supportive care medications as needed
- Adverse event assessment using NCI CTCAE, version 4.03
- Concomitant medications review
- Patient Diary dispensed

5.3.3 Treatment Period Clinic Visit – Cycle 1, Day 8 (±2 days) and 15 (±2 days)

- Physical examination
- Vital signs
- Adverse event assessment using NCI CTCAE, version 4.03
- Concomitant medications review
- Patient Diary collected
- Intensive PK for consented patients in **Cohort 5** (**Day 8 visit only; Intensive PK Patients only**)

5.3.4 Treatment Period - Telephone Contact to Assess Adverse Events

- **Cycle 1, Day 22 (±2 days)**
- **Cycle 2** - every week
- **Cycles 3+** - every 2 weeks

5.3.5 Treatment Period – Cycle 2+, Day 1

- Weight
- Physical examination
- Vital Signs
- ECOG Performance Status assessment
- Urine pregnancy test in women of childbearing potential
- Complete blood count with 5-part differential
- Serum chemistry
- Tumor assessment (to be performed at approximately 4 weeks (**Cycle 2**, **Day 1** [up to **Cycle 2**, **Day 7**]), 8 weeks of treatment (**Cycle 3**, **Day 1** [up to **Cycle 3**, **Day 7**, with at least 28 days from previous tumor assessment]), and approximately every 8 weeks (±7 days) thereafter)
- Plasma collection for later biomarker analysis (At the tumor imaging visit beginning at **Cycle 3**, **Day** 1 [up to **Cycle 3**, **Day 7**]), and approximately every 8 weeks (±7 days) thereafter)
- QoL questionnaire: EORTC QLQ-C30 and QLQ-LC13 (at each tumor imaging session) (**Cohorts 1** to **4** only)
- 12-lead ECG pre-dose and at 1 hour and 2 hours (±15 min) post-dose (**Cycle 2** only)
- Pharmacokinetic blood sampling (**Cycle 2** only):

- Sparse PK blood sampling taken pre-dose and at 1 hour and 2 hours (±15 min) post-dose (**All patients**)
- Dispense poziotinib and loperamide
- Dispense supportive care medications as needed
- Adverse event assessment using NCI CTCAE, Version 4.03
- Concomitant medications
- Patient Diary dispensed

5.3.6 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
- ECOG Performance Status assessment
- Tumor assessment (unless the patient has documented disease progression or has undergone a tumor assessment within the previous 8 weeks)
- Urine pregnancy test in women of childbearing potential
- Complete blood count with 5-part differential
- Serum chemistry
- QoL questionnaire: EORTC QLQ-C30 and QLQ-LC13 (**Cohorts 1** to **4** only)
- 12-lead ECG
- Newly biopsied tumor tissue taken from patients who progress for biomarker analysis (optional, but highly encouraged)
- Plasma sample for biomarker analysis if the patient progresses (optional)
- Adverse event assessment using NCI CTCAE, Version 4.03
- Concomitant medications
- Patient Diary collected

5.3.7 Long-Term Follow-up – Every 3 Months

- 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.
- Record SAEs where a causal relationship with the study drug is suspected.

5.4 Description of Study Assessment Parameters

5.4.1 Relevant Medical History

At **Screening**, the patient's relevant medical history will be collected, to include the history of lung cancer, documentation of EGFR or HER2 exon 20 insertion mutation confirmation, previous therapy, as well as significant and relevant past diseases and current medications.

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, Cycle 1, Days 1, 8,** and **15** and **Day 1** of each subsequent cycle, and **Day 1** of each cycle, and at the **Safety Follow-up Visit**. Symptom-directed examinations are required at other visits. 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, Cycle 1, Days1, 8,** and **15** and **Day 1** of each subsequent cycle, and at the **Safety Follow-up Visit**. Heart rate and blood pressure will be recorded before poziotinib administration.

5.4.4 ECOG Performance Status

Patients' Performance Status will be evaluated using criteria as developed by the Eastern Cooperative Oncology Group **(Appendix 2)** at **Screening** and **Day 1** of each cycle and at the **Safety Follow-up Visit**.

5.4.5 Tumor Assessment

The **Screening** tumor assessment for patient eligibility will be based on the scans performed before the patient signed the ICF. Tumor assessments must be performed using computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI). The **Baseline** tumor assessment must be performed within 2 weeks prior to, or on **Cycle 1**, **Day 1** as the **Baseline**. The image will be sent to central radiographic review by an Independent Radiologic Review Committee for response evaluation analysis.

For patients with known brain metastases, a Baseline brain MRI scan 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 7**]), 8 weeks (**Cycle 3**, **Day 1** [up to **Cycle 3**, **Day 7**, with at least 28 days from previous tumor assessment]), and then every 8 weeks (±7 days) until disease progression (except for first progression in **Cohort 5**), death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal.

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 **[19]** 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 and the efficacy assessments for final analysis will be based on the central image review.

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

5.4.6 Tissue, Plasma, and Whole Blood Samples Retained

5.4.6.1 Tissue Samples

Patients will be enrolled based upon confirmation of mutational status from the results of a tissue-based test such as OncoMine Comprehensive Assay (OCA) or FoundationOne Assay, or by an FDA approved test (eg, cobas EGFR mutation test v2 or therascreen EGFR RGQ PCR kit) performed by a US CLIA certified and locally licensed clinical laboratory or similarly accredited lab for ex-US sites using tissue samples. Patients must have documentation of mutation as noted below:

- **Cohorts 1 and 3:** 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).

  or
- **Cohorts 2 and 4:** 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).
- **Cohort 5**: Documented EGFR or HER2 exon 20 insertion mutations using tissue samples using the criteria described for **Cohorts 1** to **4**
- **Cohort 6**: Documented acquired EGFR mutation who have progressed while on first-line osimertinib treatment using tissue tested with a next-generation sequencing assay.
- **Cohort 7**: Documented EGFR or HER2 activating mutations (see table below) using tissue tested with a next-generation sequencing assay or plasma tested with a Guardant assay.

EGFR	HER2
E709X	S310F
E709_T710del insD	I655V
L718X	L755X
G719X	I767M
I740_K745dupIPVAIK	D769X
L747X	V777X
A750P	L786V
S768I	V842I
L833V	L869R
L861Q	

Tissue samples acquired prior to **Cycle 1**, **Day 1** during the screening period will be sent for retrospective central laboratory confirmation of receptor mutations and for companion diagnostic

development. If possible, tumor tissue samples from a biopsy when progression occurs during the study should be collected. This is not mandatory, but it is highly encouraged.

5.4.6.2 Plasma Samples

For all patients, plasma samples will be collected at Screening, at each imaging session, beginning at the 8-week imaging session, and if the patient progresses for biomarker analysis (optional). Plasma samples will not be used for eligibility verification in **Cohorts 1** to **6** but are allowed for eligibility verification for **Cohort 7** if a tissue sample is not available.

5.4.6.3 Whole Blood Samples

Whole blood samples will be collected once at Screening for pharmacogenomic analysis.

5.4.7 Clinical Laboratory Tests

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**. The results of the laboratory assessments should be evaluated and medically accepted by the responsible physician before the start of each cycle.
- **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, and glucose, will be performed at **Screening**, **Day 1** of each cycle, and at the **Safety Follow-up Visit**.
  - **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 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.

5.4.8 Pharmacokinetics

The PK profile of poziotinib and its metabolites (M1 and M2) will be characterized.

All patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose on **Cycle 1**, **Day 1** and **Cycle 2**, **Day 1** for sparse PK and time-matched concentration-ECG analysis.

At select study centers, patients (a minimum of 6 patients per dosing schedule) will be specifically consented for intensive PK in the 6 and 8 mg BID groups in **Cohort 5** . Intensive PK blood sampling will replace sparse PK blood sampling in **Cycle 1** and sparse sampling on **Cycle 2**, **Day 1** is not required in these patients. The schedule for intensive PK blood sampling will be

pre-dose and 1, 2, 4, 8, 12, , and 24 hours post-dose on **Cycle 1**, **Day 1** and **Cycle 1**, **Day 8 (±2 days)**. The 12-hour PK sample must be collected prior to the second daily dose (12-hour dose). Patient must be on drug at the time of blood sampling.

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

5.4.9 Electrocardiogram

A 12-lead ECG will be performed at **Screening,** pre-dose and 1- and 2-hours post-dose 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**. In addition, if a patient presents with a potentially drug-related Grade ≥3 AE (e.g., rash, mucositis, diarrhea), an ECG will be performed at the clinic visit. All ECGs will be sent for central analysis.

5.4.10 Cardiac Ejection Fraction

For patients who are at high risk of cardiac disease, as determined by the Investigator, cardiac ejection fraction may 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 as determined by the Investigator.

5.4.11 Quality of Life Questionnaire

Quality of life (QoL) will be evaluated for **Cohorts 1** to **4**, only, using the EORTC QLQ-C30 **(Appendix 3)** and QLQ-LC13 **(Appendix 4)** questionnaire on **Cycle 1**, **Day 1** (pre-dose), at every imaging session, and at the **Safety Follow-up Visit**.

5.4.12 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 on **Cycle 1, Days 1, 8,** and **15, Day 1** of each subsequent cycle, and 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.

5.4.12.1 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, so 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 advised that grapefruit juice and St. John's Wort should be avoided 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 and Ritonavir and (Ombitasvir and/or 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

5.4.12.2 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.

Preliminary information from **Cohort 1** 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).

5.4.12.2.1 Diarrhea Management

Spectrum will supply loperamide for diarrhea management. Diarrhea should be monitored very closely. Diarrhea can be managed per standard of care as determined by the Investigator, Institutional Guidelines, or considering the algorithm in **Appendix 5**.

5.4.12.2.2 Mucositis Management

Mucositis/stomatitis can be treated in a supportive manner aiming to control symptoms. Prophylactic methods to reduce or prevent mucositis/stomatitis include:

- Avoidance of spicy, acidic, or irritating foods and alcoholic drinks
- Use of solutions such as saline (diluted solution with saltwater and baking soda by dissolving ½ teaspoon of salt and 1 teaspoon of baking soda in approximately 1 liter of water) and using this solution every 4 hours
- Use of Nystatin solution
- Use of Magic Mouthwash (for instance, combination of viscous lidocaine 2% + Mylanta + diphenhydramine elixir + prednisolone solution)

5.4.12.2.3 Rash Management

Rash may be managed according to the algorithm in **Appendix 6** and/or per standard of care as determined by the Investigator or Institutional Guidelines.

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

5.4.12.3 Uses of Warfarin or Other Coumadin-Derived Anticoagulants

Warfarin or other coumadin-derived 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.

5.4.12.4 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.

5.4.12.5 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 (ie, Tums®, Maalox®) at least 4

hours before or after poziotinib administration. Patients should also avoid drink water that is alkaline.

5.4.12.6 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.

6 STUDY DRUG AND PHARMACEUTICAL INFORMATION

Study treatment is to be handled and administered according to the study sites' regulations for the handling and administration of cytotoxic anticancer agents.

6.1 Poziotinib

Poziotinib will be supplied by Spectrum.

6.1.1 Poziotinib Composition

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

6.1.2 Poziotinib Supply and Labeling

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

6.1.3 Poziotinib Administration

Poziotinib will be taken by the patient orally, with food and a glass of water, at approximately the same time(s) each day. during each 28-day cycle.

Once-Daily Dosing Regimen

If the morning 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-Daily Dosing Regimen

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.

Patients who initiated therapy prior to Amendment 3 will remain on their assigned dosage and schedule.

- **Cohorts 1 to 3:**
  - The dose of poziotinib is 16 mg, once a day (QD).
- **Cohort 4:**
  - The 16-mg QD group is closed. All new patients will receive 8 mg BID.
- **Cohort 5**:

- The 12 and 16 mg QD dose groups are closed. All eligible patients entering **Cohort 5** will be randomized in a 1:1:1 ratio to starting doses of 10 mg QD, 6 mg BID (12 mg daily), or 8 mg BID (16 mg daily). If a treatment group(s) is stopped for futility, all newly enrolled patients will be randomized or enrolled to the continuing dose group(s).
- Dose escalation to 8 mg BID or maintenance at the patient's current dose after first progression is at the discretion of the Investigator based on the patient's tolerability to the drug and consideration of other available treatments but must be discussed and agreed with the Sponsor's Medical Monitor prior to implementation.

- **Cohorts 6 and 7:**
  - The dose of poziotinib is now 8 mg BID (16 mg daily).

6.1.4 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.

6.1.5 Poziotinib Dose Modification Recommendations

If needed, doses will be reduced by 2 mg (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 and the Sponsor should be notified. If doses are reduced by other than by 2 mg/dose Sponsor's Medical Monitor approval is required. After a dose reduction, a patient cannot be treated with a higher dose of poziotinib, except for patients in **Cohorts 5**, **6**, and **7**. Upon first progression, patients in **Cohort 5** can escalate up to a maximum of 8 mg BID or stay on therapy at their current dose at the discretion of the Investigator based on the patient's tolerability to the drug, and consideration of other available treatments but must be approved by the Sponsor's Medical Monitor prior to implementation. Dosing modifications are described in the table below.

Table 3 Poziotinib Dose Modification Recommendations

Related Adverse Event	Grade	Occurrence	
		1	Each Additional Occurrence
Diarrhea	Grade ≥3 (Despite adequate anti-diarrhea management)	Stop poziotinib treatment until AE Grade ≤1 and then continue treatment at the same dose [a] or Reduce Poziotinib Dose by 2 mg/dose	Reduce Poziotinib Dose by 2 mg/dose
	Grade ≥2 for ≥48 hours (Despite adequate diarrhea management)		
Fatigue	Grade ≥3		
Mucositis/ Stomatitis	Grade ≥3 (Despite adequate management)		
Nausea and/or Vomiting	Grade ≥3 (Despite adequate anti-emetics)		
	Grade ≥2 for ≥48 hours (Despite adequate anti-emetics)		
Rash	Any Grade	Refer to **Appendix 6**	
LVEF Dysfunction	Grade ≥3	Discontinue Treatment	

a) Preliminary information from **Cohort 1** 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) (**Appendix 6**).

6.2 Comparator Treatment

No comparator will be used in this study.

7 SAFETY ASSESSMENT

7.1 Safety Measures

It is the responsibility of the Principal Investigator to oversee the safety of the patients at their site and to report all AEs/SAEs that are observed or reported during the study, regardless of relationship to the investigational drug or clinical significance. The decision to modify the dose of study treatment will be determined by the Investigator based on the decision rules shown in **Section 6.1.5**.

Safety data will also be reviewed on a regular basis by the Sponsor's study monitoring team, which includes a Clinical Research Associate (CRA), Medical Monitor, and other personnel from Spectrum Pharmaceuticals, Inc. 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 4.03 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 drug or a concurrent medication.
- AEs may include pre-treatment or post-treatment events that occur as a result of protocol-mandated procedures (eg, 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.

The adverse events of special interest identified with poziotinib treatment 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.
- If a patient discontinues due to an AE(s), 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 intensity/severity (**Section 7.3.2**), relationship to study drug (**Section 7.5**), and as serious or non-serious **(Section 7.7)** by the Investigator.

7.3.2 Grading of Adverse Events

This study will utilize the NCI CTCAE Scale, Version 4.03 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 to the patient 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 that 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 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 Investigator is responsible for submitting SAEs to his/her Institutional Review Board (IRB)/Ethics Committee (EC). Copies of each SAER, and documentation of IRB/EC notification and acknowledgement of receipt, will be kept in the Site's Regulatory Binder.

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.

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.

It is not known whether taking poziotinib can cause death, serious birth defects, or other harm to unborn babies or nursing children. Patients should not become pregnant or father a child while taking part in this study.

Any pregnancy involving a study patient or a patient's partner that occurs from the first dose of study treatment through 30 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 will be withdrawn from this study.

8 STATISTICAL PLAN

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

8.1 Sample Size

The reported response rate of patients with EGFR exon 20 mutations 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 mutant patients. In a pivotal study of crizotinib vs. chemotherapy, the response rate of chemotherapy-treated patients with previously treated ALK-positive NSCLC was 20%.

There is no approved treatment available for EGFR exon 20 insertion mutation NSCLC patients. Unlike other EGFR mutations, patients with EGFR exon 20 insertions rarely respond to gefitinib or erlotinib. A review of 84 patients with exon 20 insertion mutations across different series treated with either gefitinib or erlotinib demonstrated an RR of only 11% with a PFS of 2.4 months **[20]**. Similarly, treatment with afatinib in this patient population is also associated with a low RR and PFS (8.7% and 2.7 months, respectively **[2]**. Overall survival of patients with EGFR exon 20 insertion mutations is similar to that of patients without EGFR-mutant NSCLC but inferior to that of patients with EGFR exon 19 deletion or L858R advanced NSCLC **[21]**.

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.

The study has 7 patient cohorts, and each one is considered to be a standalone study. Each of the first 4 cohorts is powered for testing hypothesis of the primary endpoint separately. No *a priori* test of hypothesis is planned and no sample size calculation is provided for **Cohorts 5** to **7**. The statistical analysis of primary as well as secondary outcomes will be performed separately for each cohort.

Cohort 1 will enroll patients with previously treated EGFR exon 20 insertion-mutation positive NSCLC and **Cohort 2** will enroll patients with previously-treated HER2 exon 20 insertion-mutation positive NSCLC. Each cohort will be a single-arm and the primary test of hypotheses will be based on a single proportion. Sample size calculation is based on single arm hypothesis testing to reject non-desired ORR of 17% vs. clinically meaningful ORR of 30%. A sample size of 87 patients in each cohort will provide 85% power, for a two-sided test with a significant level of 5% to reject a non-desired ORR of 17% if the observed ORR is 30% or higher. A sample size of 87 patients in each cohort will also provide 95% CI that contains 30% and rules out 17% as the lower bound is above 17%.

For **Cohorts 3** and **4**, patients who are treatment-naïve for exon 20 mutation positive NSCLC, each cohort will be single-arm and the primary test of hypotheses will be based on a single proportion. Based on the literature, an ORR of 20% is considered to be the lower threshold of efficacy in our study. Sample size calculation is based on the single arm hypothesis testing to reject non-desired ORR of 20% vs. clinically meaningful ORR of 40% in the study. A sample

size of 70 patients in each cohort will provide 95% power, for a two-sided test with a significant level of 5%, to reject a non-desired ORR of 20% if the observed ORR is 40% or higher. A sample size of 70 patients in each cohort will also provide 95% CI that contains 40% and rules out 20% as the lower bound is above 20%.

The sample size of **Cohort 4** is revised to enroll a total of 70 patients treated with 8 mg BID using the same statistical test and pre-specification as described above. Patients who received 16 mg QD prior to the protocol amendment will be analyzed separately. With the change in dose schedule to 8 mg BID, a sample size of 70 patients will provide 95% power, for a two-sided test with a significant level of 5% to reject a non-desired ORR of 20% if the observed ORR is 40% or higher.

A two-stage design [22] will be used to evaluate the primary endpoint of ORR in **Cohort 5** once the futility analysis is complete in a test of single proportion using the same hypotheses as in **Cohorts 1** and **2** (17% vs. 30%). The details of the statistical design are described below.

Possible Designs For P0=0.170, P1=0.300, Alpha=0.025, Beta=0.100

N1	R1	PET	N	R	Ave N	Alpha	Beta	Constraints Satisfied
109	26	0.000	109	26	109.00	0.025	0.096	Single Stage
15	0	0.061	109	26	103.25	0.025	0.099	Minimax
19	2	0.350	124	29	87.25	0.023	0.099	Optimum

The optimal two-stage design to test the null hypothesis that the ORR ≤17% versus the alternative that the ORR ≥30% has an expected sample size of 87.25 and a probability of early termination of 0.35. If the drug is actually not effective, there is a 0.023 probability of concluding that it is (the target for this value was 0.025). If the drug is actually effective, there is a 0.099 probability of concluding that it is not (the target for this value was 0.100). After testing the drug on 19 patients in the first stage, the trial will be terminated if 2 or fewer respond. If the trial goes on to the second stage, a total of 124 patients will be studied. If the total number responding is less than or equal to 29, the drug is rejected.

In each dose group of **Cohort 5** that remains after the futility analysis, a total of 19 patients will be enrolled and followed up for response evaluation to observe the number of responses in the first stage of two-stage design. If 2 or fewer responses are observed in the first stage, the dose group will be terminated. If 3 or more responses are observed in the first stage of a dose group, the dose group will continue to enroll in the second stage. All new patients will be randomized or enrolled to the remaining group that continues to enroll in the second stage. A total of 124 patients will be enrolled. If the number of responses is greater than 29, the corresponding dose group is considered to have met the primary endpoint.

There is no statistical power or sample size determined for **Cohorts 6** to **7**. A total of 30 patients will be enrolled in **Cohort 6** and 30 patients will be enrolled in **Cohort 7**. A sample size of 30 patients in each **Cohorts 6** and **7** will provide a width of 0.31 to 95% confidence interval for a point estimate of 20% (95% CI: 7.71, 38.57%) in 2-sided exact test of proportion in single-arm trial.

8.2 Futility Analyses

The study includes a futility analysis to be conducted in each patient cohort, separately, when the response evaluation is complete for the first 20 patients in **Cohorts 1** to **4** and for the first 10 patients in **Cohort 5** and **Cohorts 6 and 7**. A patient cohort (**Cohorts 1** to **4**, **Cohort 6** and **7**) or treatment group (**Cohort 5**: 10 mg QD, 6 mg BID, and 8 mg BID groups) will be stopped for futility if the ORR is <10%. No adjustment to multiplicity will be made for the futility analysis.

Since dose schedule of **Cohort 5** is revised to 1:1:1 randomization to 10 mg QD, 6 mg BID, and 8 mg BID, a futility analysis will be conducted once the response evaluation of the first 10 patients is available in each dose group (10 mg QD, 6 mg BID and 8 mg BID). If one or two of the three randomized dose groups (10 mg QD or 6 mg or 8 mg BID) meets the criteria for futility, all new patients will be randomized or enrolled into the remaining group(s).

8.3 Method of Treatment Assignment

Cohorts 1 to **4** and **Cohorts 6** and **7** are not randomized. Patients will be enrolled sequentially and into the cohorts based on their mutation status and prior treatment status.

Patients enrolled in **Cohort 5** will be randomized in a 1:1:1 ratio to starting doses of 10 mg QD or 6 mg BID (12 mg daily), and 8 mg BID (16 mg daily).

8.4 Analysis Populations

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

- The **As-Treated Population** will be the primary analysis population and include all patients who receive at least one dose of study medication.
- The **Evaluable Population** consists of all patients who are enrolled, have at least one dose of poziotinib treatment, and is evaluable for tumor response based on RECIST, Version 1.1. The efficacy data will also be analyzed using the Evaluable Population.
- The **Safety Analysis Population** includes all patients who signed informed consent, enrolled, and received at least one dose of study treatment. All demographics, Baseline characteristics, and safety data will be analyzed using the Safety Analysis Population.

8.5 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.

Each patient cohort is a standalone study and the statistical analyses, tests of hypotheses are conducted independently of other cohorts. As specified in **Section 8.1**, the primary endpoint for **Cohorts 1** to **4** are powered independently and will be analyzed separately. No statistical powering is provided, and no test of hypothesis, will be conducted for **Cohorts 5**, **6**, and **7**. Although the study is continuing, the database for a patient cohort once complete will be closed and locked for the final analysis. All statistical summary tables, data listings, and figures will be produced separately for each cohort as if they are independent studies along with the

corresponding clinical study reports (ZENITH20-1, ZENITH20-2, ZENITH20-3, ZENITH20-4, ZENITH20-5, ZENITH20-6, ZENITH20-7).

8.6 Efficacy Analyses

8.6.1 Primary Endpoint

The primary efficacy variables for **Cohorts 1** to **4**, as described below, will be summarized and analyzed descriptively, along with 95% CI, for each cohort based on central radiographic review by an Independent Radiologic Review Committee.

- **Objective Response Rate** (**ORR**) will be assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, version 1.1 **[19]** 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 primary analysis population. The ORR will be determined by an Independent Radiologic Review Committee using 2 independent readers and 1 adjudicator paradigm.

  The test of hypothesis of the primary endpoint will be performed using the 95% CI. The prespecified primary endpoint criteria for each cohort is stated in **Section 8.1**.

8.6.2 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.

8.6.3 Exploratory Endpoints

- **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.
- QoL will be evaluated in **Cohorts 1** to **4** only using the EORTC QLQ-C30 and QLQ-LC13 questionnaire at **Cycle 1, Day 1**, at every imaging session, and at the **Safety Follow-up Visit**. The global health status/QoL, functional scales, symptom scales, and lung cancer related symptoms will be summarized for each evaluation time point.
- **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.

The other outcomes of DCR, DoR, and PFS for all cohorts and QoL for **Cohorts 1** to **4** only, will be analyzed using descriptive statistics and with 95% CI for DCR and Kaplan-Meier plot for DoR and PFS. The same analysis method, except for QoL, will be used for **Cohorts 6** and **7**.

As the **Cohort 5** is amended to include 2 new dose groups (6mg BID and 8mg BID), the efficacy analysis of the **Cohort 5** will be conducted as follows:

- Futility analysis: will be conducted once response evaluation of the first 10 patients is available in each of dose groups (10mg QD, 6 mg BID, 8 mg BID). If one or two of the three randomized groups meets the criteria for futility, all new patients will be randomized or enrolled into the remaining dose groups. No adjustment to multiplicity will be made for the primary endpoint analysis.
- Two-stage design – Once the futility analysis is complete, the remaining dose groups individually will follow two-stage design (Simon, et al, 1989) for the primary efficacy analysis based on the optimal trial design simulation using the same criteria for statistical test as specified for Cohorts 1 and 2. The test of statistical hypotheses results in rejecting a non-desired ORR of 17% vs. desired ORR of 30% in a 2-sided test of proportion in a single arm study, the ORR endpoint is considered to be met.
- If more than one dose group meets the criteria of continuation to second stage of the two-stage design, a decision to continue one dose group may be made by taking into consideration conditional probability of rejecting non-desired ORR and the toxicity associated with the dose group.

8.6.4 Data Stratification

There will be no stratification of patients in all cohorts except for **Cohort 5**. Within each cohort, data for all exon 20 mutations will be pooled. A stratified analysis of **Cohort 5** will be performed as an exploratory analysis by mutation status (EGFR, HER2 exon 20) and by line of treatment (previously treated, treatment naïve).

8.7 Safety Analysis

- **Safety, including adverse events and pharmacokinetics**
  - **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.
  - **Pharmacokinetics:** The PK profile of poziotinib and its metabolites (M1 and M2) will be characterized. All patients will have blood samples drawn for sparse pharmacokinetic (PK) sampling pre-dose and at 1 hour and 2 hours (±15 min) post-dose on **Cycle 1**, **Day 1** and **Cycle 2**, **Day 1** for sparse PK and time-matched concentration-ECG analysis.

    At select study centers, patients (a minimum of 6 patients per dosing schedule) will be specifically consented for intensive PK in the 6 and 8 mg BID groups in **Cohort 5** . Intensive PK blood sampling will replace sparse PK blood sampling in **Cycle 1** and sparse sampling on **Cycle 2**, **Day 1** is not required in these patients. The schedule for intensive PK blood sampling will be pre-dose and 1, 2, 4, 8, 12, , and 24 hours post-dose on **Cycle 1**, **Day 1** and **Cycle 1**, **Day 8 (±2 days)**. The 12-hour PK sample must be collected prior to the second daily dose (12-hour dose). Patient must be on drug at the time of blood sampling.

In addition, if a patient presents with a potentially drug-related Grade ≥3 adverse event (e.g., rash, mucositis, diarrhea), a blood sample will be collected as soon as possible following the onset of the AE.

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 (version 17) 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. Adverse events reported prior to treatment but after IC will be provided in a listing.

Finally, the number of completed cycles will also be summarized and analyzed descriptively.

8.8 Clinical Laboratory Evaluations

Key laboratory parameters will be summarized using shift tables, which display a cross-tabulation of the Baseline grade versus the highest on-study grade for each laboratory parameter, for each cohort.

All laboratory abnormalities will be classified according to NCI CTCAE, Version 4.03 and summarized by worst grade severity and by cohort.

9 ADMINISTRATIVE PROCEDURES AND STUDY MANAGEMENT

9.1 Investigator Responsibilities

The study will be monitored by employees or representatives of Spectrum. CRAs will monitor each site on a periodic basis and perform verification of source documentation for each patient as well as other routine compliance and documentation reviews. The Sponsor's Medical Monitor and Pharmacovigilance Department will review safety data and be responsible for ensuring timely reporting of expedited SAERs to regulatory agencies 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, or with the laws and regulations of the country in which the research is conducted. 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 Investigator 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 prior to use.

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 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.

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 Investigator is to retain all study records until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product as per 21 CFR 312.62 and ICH GCP E6 4.9.5 and 5.5.12. 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 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 Investigator 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 preserve integrity and prevent loss or destruction 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.

The EDC system will house data for all patient cohorts. However, the database for each cohort will be locked once complete while the database will be open for the remaining cohorts.

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 not listed on the US Form FDA 1572 or equivalent. 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 destroyed per Institution, local laws, and all applicable policies and procedures. After study conclusion, all unused bottles of poziotinib may be destroyed at the site, 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 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 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 or Study Cohorts

For reasonable cause, either the Investigator or the Sponsor 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, or any cohorts, at any time upon immediate notice for any reason, including but not limited to, Sponsor's belief that termination is necessary for the safety of patients.

9.5.3 Publication Policy

To coordinate the dissemination of data from this study across all participating study sites, the Sponsor encourages the formation of a publication committee consisting of the Principal Investigator and appropriate Sponsor staff. The committee is expected to solicit input and assistance from other investigators and Sponsor staff as appropriate. Membership on the committee (both for investigators and Sponsor staff) does not guarantee authorship – the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirements for Manuscript Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

- Authorship credit should be based on the following; authors should meet all three conditions:
  1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
  2. Drafting the article or revising it critically for important intellectual content
  3. Final approval of the version to be published.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.
- All publications (eg, manuscripts, abstracts, oral/slide presentations, books chapters) based on this study must be submitted to the Sponsor for corporate review.

9.6 Confidentiality

All information provided to the Investigator/Institution by the Sponsor or its designees, including nonclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel actually 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 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 drug, 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 applicable law.

10 REFERENCES

1. Chatziandreou I, Tsioli P, Sakellariou S, Mourkioti I, Giannopoulou I, Levidou G, et al. Comprehensive Molecular Analysis of NSCLC; Clinicopathological Associations. PloS one. 2015;10(7):e0133859.
2. Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. The Lancet Oncology. 2015;16(7):830-8.
3. Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. The Lancet Oncology. 2012;13(1):e23-31.
4. Peters S, Zimmermann S. Targeted therapy in NSCLC driven by HER2 insertions. Translational lung cancer research. 2014;3(2):84-8.
5. Saridaki Z, Georgoulias V, Souglakos J. Mechanisms of resistance to anti-EGFR monoclonal antibody treatment in metastatic colorectal cancer. World journal of gastroenterology : WJG. 2010;16(10):1177-87.
6. Roskoski R, Jr. ErbB/HER protein-tyrosine kinases: Structures and small molecule inhibitors. Pharmacological research. 2014;87:42-59.
7. Robichaux JP, Tan Z, Elamin YY, Zhang S, Liu S, Li S, et al. Identification of molecular features of kinase inhibitors that circumvent steric hindrance induced by exon 20 insertions in EGFR and HER2 mutant NSCLC. 2017.
8. Robichaux JP, Le X, Elamin YY, Nilsson MB, Hu L, He J, et al. Activity of second-gen EGFR TKIs including poziotinib in atypical exon 18 P-loop and acquired osimertinib resistant mutations. Abstract. World Conference on Lung Cancer. 2019 (Submitted).
9. Robichaux JP, Elamin YY, Vijayan RSK, Nilsson MB, Hu L, Zhang F, et al. Pan-cancer landscape and functional analysis of HER2 mutations identifies poziotinib as a clinically active inhibitor and enhancer of T-DM1 activity. 2019 (Submitted).
10. Singla H, Kaur RP, Shafi G, Vashistha R, Banipal RPS, Kumar V, et al. Genomic alterations associated with HER2+ breast cancer risk and clinical outcome in response to trastuzumab. Molecular biology reports. 2019;46(1):823-31.
11. Ng CK, Martelotto LG, Gauthier A, Wen HC, Piscuoglio S, Lim RS, et al. Intra-tumor genetic heterogeneity and alternative driver genetic alterations in breast cancers with heterogeneous HER2 gene amplification. Genome biology. 2015;16:107.
12. Hyman DM, Piha-Paul SA, Won H, Rodon J, Saura C, Shapiro GI, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. Nature. 2018;554(7691):189-94.
13. Noh YH, Lim HS, Jung JA, Song TH, Bae KS. Population pharmacokinetics of HM781-36 (poziotinib), pan-human EGF receptor (HER) inhibitor, and its two metabolites in patients with advanced solid malignancies. Cancer chemotherapy and pharmacology. 2015;75(1):97-109.

14. Han SW, Hwang PG, Chung DH, Kim DW, Im SA, Kim YT, et al. Epidermal growth factor receptor (EGFR) downstream molecules as response predictive markers for gefitinib (Iressa, ZD1839) in chemotherapy-resistant non-small cell lung cancer. International journal of cancer Journal international du cancer. 2005;113(1):109-15.

15. Kim DW, Lee DH, Kang JH, Park KM, Han JY, Lee J-S, et al. Clinical activity and safety of HM61713, an EGFR-mutant selective inhibitor, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs). Journal of Clinical Oncology. 2014;32(15 Suppl. 1).

16. Landi L, Cappuzzo F. Irreversible EGFR-TKIs: dreaming perfection. Translational lung cancer research. 2013;2(1):40-9.

17. Wang X, Batty KM, Crowe PJ, Goldstein D, Yang JL. The Potential of panHER Inhibition in Cancer. Frontiers in oncology. 2015;5:2.

18. Yang JC-H, Sequist L, O'Byrne K, Schuler M, Mok T, Geater S, et al. Epidermal growth factor receptor (EGFR)-mediated adverse events (AEs) in patients (pts) with EGFR mutation positive (EGFR M+) non-small cell lung cancer treated with afatinib. European Journal of Cancer. 2013;49:S190.

19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer (Oxford, England : 1990). 2009;45(2):228-47.

20. Naidoo J, Sima CS, Rodriguez K, Busby N, Nafa K, Ladanyi M, et al. Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. Cancer. 2015;121(18):3212-20.

21. Oxnard GR, Lo PC, Nishino M, Dahlberg SE, Lindeman NI, Butaney M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2013;8(2):179-84.

22. Simon R. Designs for efficient clinical trials. Oncology (Williston Park). 1989;3(7):43-9; discussion 51-3.

Appendix 1 SCHEDULE OF ASSESSMENTS AND PROCEDURES

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)			Day 1	35 (±5) Days After Last Dose	Ongoing
			8	15	22			
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	x	x	x	x		x	x	
ECOG Performance Status	x	x				x	x	
Pregnancy Test (urine) [d]	x	x				x	x	
Tumor Assessment	x [e]	x [f]				x	x	
QoL Questionnaire [g]		x				x	x	
Tissue Samples [h]	x					x		
Plasma Samples [i]	x					x	x	
Whole Blood Samples [j]	x							
CBC with 5-part differential and platelets [k]	x	x				x	x	
Serum Chemistry [l]	x	x				x	x	
Electrocardiogram [m]	x	x				x	x	
Echocardiogram or MUGA Scan [n]	x							
PK Samples [o]		x	x			x		
Dispense Poziotinib [p]		x				x		
Dispense Loperamide		x				x		
Adverse event assessment	x [q]	x	x	x		x	x	x
Concomitant medications	x	x	x	x		x	x	
Patient Diary Dispensed/Collected		x	x	x		x	x	
Telephone Contact [r]		x			x	x		x

a) If a visit is delayed during a cycle, the subsequent schedules will be delayed sequentially.
b) Height only needs to be recorded during the **Screening Visit**.
c) A complete physical examination is required at **Screening**, **Day 1** of each cycles, and at the **Safety Follow-up Visit**. Symptom-directed exams are required at other visits.
d) Urine pregnancy test (β-HCG) in women of child-bearing potential.
e) The **Screening** tumor assessment will be based on scans performed before the patient signed the ICF. Brain MRI scans for patients with known brain metastases should also be performed per standard of care.

f) **Baseline** tumor assessment will be performed within 2 weeks 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 7**]), at 8 weeks (**Cycle 3**, **Day 1** [up to **Cycle 3**, **Day 7**, with at least 28 days from previous tumor assessment]), and then every 8 weeks (±7 days) thereafter until disease progression (except for first progression in **Cohort 5**), death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal.

g) **Cohorts 1** to **4** only: The QoL Questionnaire, EORTC QLQ-C30 and QLQ-LC13, will be performed on **Cycle 1**, **Day 1** (pre-dose), at each tumor imaging session, and at the **Safety Follow-up Visit**.

h) Tumor genotyping report for tissue samples from a local lab is required to confirm patient mutation eligibility for **Cohorts 1** to **6**. For **Cohort 7**, tissue samples are preferred, but results from plasma samples are acceptable if tissue is not available. For **Cohort 6**, plasma or tissue samples must be collected after osimertinib progression. All tissue samples should be retained for retrospective confirmatory central analysis. Collecting a tissue sample at progression is optional but is highly encouraged.

i) Plasma samples will be drawn from all patients at Screening and on the day of each on-study imaging session, beginning at the 8-week imaging session, and when the patient progresses, for biomarker analysis (optional). For **Cohort 7**, plasma samples are acceptable for patient mutation confirmation if a tissue sample is not available.

j) Whole blood samples will be drawn at Screening for pharmacogenomic analysis or at the next scheduled visit.

k) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained within 7 days prior to **Day 1** of each cycle, at which time, platelet count must be $\geq 100 \times 10^9$/L before and ANC must be $\geq 1.5 \times 10^9$/L dispensing poziotinib for the next cycle of treatment.

l) Blood for chemistry is to be collected within 7 days prior to poziotinib administration on **Day 1** of each cycle.

m) For all patients, 12-lead ECGs will be performed pre-dose and 1 and 2 hours post-dose on **Cycle 1**, **Day 1** and **Cycle 2**, **Day 1** for time-matched concentration-ECG analysis. ECGs are not required on **Day 1** of other cycles.

n) Cardiac ejection fraction may be evaluated at **Screening** in patients who are considered at high risk of cardiac disease, as determined by the Investigator, using echocardiogram or multi-gated acquisition (MUGA) scan. The investigator can order subsequent tests based on patient standard of care as determined by the Investigator.

o) All patients will have blood samples drawn pre-dose and at 1 hour and 2 hours (±15 min) post-dose on **Cycle 1**, **Day 1** and **Cycle 2**, **Day 1** for sparse PK sampling and time-matched concentration-ECG analysis . For intensive PK patients, Cycle 1, Day 1 and Cycle 1, Day 8 clinical evaluations can be done within 24 hours prior to first dose administration. At select study centers, patients (a minimum of 6 patients per dosing schedule) will be specifically consented for intensive PK in the 6 and 8 mg BID groups in **Cohort 5** . Intensive PK blood sampling will replace sparse PK blood sampling in **Cycle 1** and sparse sampling on **Cycle 2**, **Day 1** is not required in these patients. The schedule for intensive PK blood sampling will be pre-dose and 1, 2, 4, 8, 12, , and 24 hours post-dose on **Cycle 1**, **Day 1** and **Cycle 1**, **Day 8 (±2 days)**. The 12-hour PK sample must be collected prior to the second daily dose (12-hour dose). Patient must be on drug at the time of blood sampling. In addition, if, during any visit, a patient presents with a potentially drug-related Grade ≥3 adverse event (e.g., rash, mucositis, diarrhea), a blood sample will be collected as soon as possible following the onset of the AE. PK blood samples are not required on **Day 1** of other cycles.

p) Poziotinib will be dispensed on **Day 1** of each cycle.

q) From the time the ICF is signed through the first dose of study drug administration, all SAEs are to be recorded. 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 be recorded. Patients must visit the clinic for AE assessment on **Cycle 1**, **Days 8** and **15** (±2 days).

r) Telephone contact will be made with the patient every week during **Cycles 1** and **2** and then every other week while being treated with study drug, except for weeks that the patient visits the clinic. 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.

Appendix 2 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 housework, 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 3 SAMPLE EORTC QLQ-C30 QUESTIONNAIRE

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): ____
Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Specimen

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

© Copyright 1995 EORTC Quality of Life Group. All rights reserved. Version 3.0

Specimen

Appendix 4 SAMPLE EORTC QLQ-LC13



EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

SPECIMEN

© QLQ-C30-LC13 Copyright 1994 EORTC Quality of life Group. All rights reserved

Appendix 5 DIARRHEA MANAGEMENT RECOMMENDATIONS

RECOMMENDATIONS FOR DIARRHEA MANAGEMENT

For diarrhea management, the following interventions may be used based on the severity of the condition.

DIARRHEA SEVERITY	INTERVENTION
Start Diarrhea Prophylaxis *(CTCAE grade 0) Initiation of Pozionitib Treatment	- Start prophylactic therapy with Loperamide** 4mg orally twice daily when Poziotinib is initiated and continue for first 2 cycles - If patient becomes constipated, modify/discontinue Loperamide therapy appropriately - Upon development of diarrhea other etiologies including GI infection and inflammatory disorders must be ruled out. If Poziotinib related diarrhea is considered → follow the suggested approach per CTCAE severity as below:
Mild Diarrhea *(CTCAE Grade 1) Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	- Continue Loperamide 4 mg orally, 3 times a day, followed by 2 mg every 4 hours or after each loose stool - Start Doxycycline at 100 mg orally (or alternatively use Minocycline 100 mg orally) twice a day, continue for 2 weeks or until resolution of diarrhea - Continue Poziotinib at the current dose level
Moderate Diarrhea *(CTCAE Grade 2) Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	- Continue Loperamide 4 mg orally, 3 times a day, followed by 2 mg every 4 hours or after each loose stool - Continue Doxycycline at 100 mg orally (or alternatively use Minocycline 100 mg orally) twice a day, continue for 2 weeks or until resolution of diarrhea - Consider starting Cholestyramine 4 g orally, once or a twice day (30 minutes prior to the meals), continue till improvement of diarrhea to Grade 1 or a resolution OR Budesonide orally 9 mg daily for 4 weeks - Continue Poziotinib at the current dose level
Severe Diarrhea *(CTCAE Grade 3)	- Continue Loperamide 4 mg orally, 3 times a day, followed by 2 mg every 4 hours or after each loose stool

Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL		- Continue Doxycycline at 100 mg orally (or alternatively use Minocycline 100 mg orally) twice a day, continue for 2 weeks or until resolution of diarrhea - If started then continue Cholestyramine OR Budesonide (if started) - Consider Octreotide SubQ: 100 to 150 mcg every 8 hours; may increase to 500 to 1500 mcg IV or SubQ every 8 hours - Hold Poziotinib for one week and restart at the lower dose - Upon resolution or diarrhea improvement to ≤ Grade 1, Poziotinib dose escalation may be allowed after approval from the Sponsor

Gastrointestinal disorders	*GRADE				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Definition of Diarrhea: A disorder characterized by frequent and watery bowel movements

**** The maximum daily dose of Loperamide is 16 mg**

Version 1,

Dec, 12. 2017

Appendix 6 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.