Official Title: A Phase 2 Study of Poziotinib in Patients with EGFR or HER2 Activating Mutations in Advanced Malignancies

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Study Title: **A Phase 2 Study of Poziotinib in Patients with EGFR or HER2 Activating Mutations in Advanced Malignancies (SPI-POZ-203)**

Protocol Version/Date: Amendment 1/20 May 2021

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, and typos.
Throughout Document: **General Explanation**	**Primary Changes:** 1. The starting poziotinib dosing regimen changed from 16 mg QD to 8 mg twice per day (BID). • The 8 mg BID dose has demonstrated improved tolerability and retained or improved efficacy as the 16 mg QD dose. 2. The End-of-Treatment Visit was changed from 35 (±5) days to 30 (±5) days. • 30 days for the End-of-Treatment Visit is the standard for clinical studies at investigational sites. 3. A long-term follow-up period was added for survival assessment for up to 2 years. • Allows for the collection of additional outcome data. 4. Poziotinib dose modifications were altered to include dose reductions for BID dosing and **Table 2** was revised. **5.** Eligible patients who elect to continue treatment with poziotinib after disease progression in this study in will transition to an **Extension Study (SPI-POZ-501).** 6. At selected sites, intensive pharmacokinetic assessments have been added for up to 25 patients. • This sampling will allow the required PK analyses for 8-mg BID dosing.
Title Page **Footer** **Synopsis**	**Original Text:** Protocol Version/Date: ~~Original/19 Sep 2019 Final~~ **New Text:** Protocol Version/Date: Amendment 1/20 May 2021

Section	Change
Synopsis: Patient Replacement Strategy **Section 4.3: Patient Discontinuation/Withdrawal Criteria**	**Original Text:** Patients ~~who discontinue~~ from the study ~~for reasons other~~ than disease progression ~~and/or~~ toxicity ~~will be replaced~~. **New Text:** Patients not efficacy evaluable i.e. not completed at least 1 cycle of poziotinib treatment and have baseline and at least 1 post-baseline tumor response evaluation using RECIST, version 1.1 (and/or RANO for Cohort 4) will be replaced unless they have discontinued from treatment or from the study due to disease progression or probable disease progression (eg, clinical progression, initiation of new therapy) or due to toxicity. **Reason:** Clarification of patient replacement criteria.
Synopsis: Dosing Regimen, Investigational Product, Dose, and Route of Administration **Section 6.1.2: Poziotinib Administration**	**Original Text:** ~~Patients in all cohorts will self-administer~~ poziotinib ~~within 30 minutes after consumption of a meal~~ at approximately the same time each day. Poziotinib should be ~~administered with~~ approximately ~~240 mL (8 fluid ounces) of water~~. **New Text** The starting dose of poziotinib is 8 mg, twice per day (BID). Poziotinib will be self-administered by the patient orally, with food and a glass of water, at approximately the same time(s) each day during each 28-day cycle. 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, it should be taken once remembered or with the next dose if on the same day. **Reason** Instructions for twice daily dosing were added to replace once-daily dosing.
Synopsis: Inclusion Criteria **Section 4.1: Inclusion Criteria**	**Added Text:** **Inclusion Criteria:** 1) Patient is 18 years of age or older 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 a metastatic solid tumor that meets at least one of the following criteria: • ~~has progressed on a standard therapy~~ • ~~has~~ no available standard therapy • ~~in the opinion of the investigator, patient is not a candidate for or would be unlikely to tolerate or receive benefit from standard therapy~~ **Table A List of Activating Mutations Eligible for Enrollment** Activating Mutations **Cohorts 1-3: HER2 Activating Mutations (at least one of the following)**

Section	Change

Furin-Like/Extracellular	S310F/Y
Transmembrane	I655V, V659E, R678Q, V697L
Kinase Domain	Exon 20 insertion, T733I, L755X, I767M, ~~D769H/N/Y~~, V773M, ~~V777L/M~~, L786V, V842I, T862I, L869R
Cohorts 4-5: EGFR Activating Mutations (at least one of the following)	
Extracellular & Transmembrane	EGFRvIII, R108K, R222C, A289T, P596L, G598V
Kinase Domain	Exon 20 insertion, ~~E709K~~, G719X, V742I, E746_A750del, S768I, V769M, V774M, R831C, R831H, L858R, L861Q, A864V

8) Brain metastases may be allowed if patient's condition is stable. Stable ~~brain metastases are~~ defined as stable symptoms, no requirement for ~~high dose~~ or increasing doses of systemic corticosteroid (except **Cohort 4** where anti-seizure medication [Keppra] and dexamethasone up to or equivalent to 4 mg daily), nor progression ~~on imaging studies~~ for at least 4 weeks ~~prior to enrolment. If applicable~~, Patients must complete ~~brain radiation therapy~~ and return to ~~suitable~~ condition prior to eligibility assessment ~~of the study~~. for the patient who has had radiation therapy, post-treatment MRI tests should show no increases in brain lesion size/volume and ~~there should be~~ no new lesions compared to pre-treatment MRI (except **Cohort 4**) for at least 4 weeks. A new lesion is defined as lesion size greater than 5 mm and not previously present ~~and/or not requiring radiation therapy~~

New Text

1. Patient is 18 years of age or older
2. Patient must be willing and capable of giving written Informed Consent, adhering to dosing and visit schedules
3. Patient has an advanced or metastatic solid tumor with no available standard therapy option
4. Patient with breast cancer must have an NGS HER2 activating mutation (see Table A), and:

- IHC HER2-positive tumors (based on ASCO/CAP criteria) are included only when they have progressed on trastuzumab, pertuzumab, and T-DM1 which have been administered in the metastatic setting, unless disease recurred within 12 months of adjuvant or neoadjuvant treatment.
- IHC HER2-negative, ER/PR-positive breast cancer (based on ASCO/CAP criteria) may be included after 1st line endocrine therapy in the metastatic setting, either as a single agent or in combination with standard biological agents (eg aromatase inhibitor and CDK 4/6 inhibitor). Patients are permitted to continue single agent endocrine therapy concurrently with the study.

  IHC HER2-negative, ER/PR-negative tumors may be included after first-line treatment (any standard chemotherapy-based regimen) in the metastatic setting.

Section	Change
	5. Patient with colorectal cancer who are MSI-H and have confirmed progression on pembrolizumab or nivolumab or nivolumab/ipilimumab

Table A List of Activating Mutations Eligible for Enrollment

	Activating Mutations
Cohorts 1-3: HER2 Activating Mutations (at least one of the following)	
Furin-Like/Extracellular	S310F/Y
Transmembrane	I655V, V659E, R678Q, V697L
Kinase Domain	Exon 20 insertion, T733I, L755X, I767M, D769X, V773M, V777X, L786V, V842I, T862I, L869R
Cohorts 4-5: EGFR Activating Mutations (at least one of the following)	
Extracellular & Transmembrane	EGFRvIII, R108K, R222C, A289T, P596L, G598V
Kinase Domain	Exon 20 insertion, E709X, E709_T710del insD, L718X, G719X, I740_K745dupIPVAIK, I740_K745dup, V742I, L747X, E746_A750del, A750P, S768I, S768I/V769L, S768I/V774M, L833V, V769M, V774M, R831C, R831H, L858R, L861Q, A864V

8) Brain metastases may be allowed if the patient's condition is stable. Stable condition is defined as having stable neurological symptoms, with no requirement for anti-seizure medications or >2 mg/day dexamethasone equivalent or increasing doses of systemic corticosteroids (except **Cohort 4** where anti-seizure medication [Keppra] and dexamethasone up to or equivalent to 4 mg daily is allowed), and no evidence of CNS disease progression documented for at least 4 weeks after CNS-directed treatment (eg, whole brain radiation), as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Patients must complete CNS-directed treatment and return to stable condition prior to eligibility assessment for the study. For patients who have had radiation therapy, post-treatment MRI tests should show no increase in brain lesion size/volume and no new lesions compared to pre-treatment MRI (except **Cohort 4**) for at least 4 weeks. A new lesion is defined as lesion size greater than 5 mm and not previously present

Reason:

1) No change
2) The deleted statement was redundant
3) To clarify eligibility around prior treatment
4) Criteria were updated to reflect the current practice standards for the treatment of breast cancer
5) Eligible molecular mutations were updated and specified

Section	Change
	8) Clarification around eligibility was added for patients with brain metastases
Synopsis: Exclusion Criteria **Section 4.2: Exclusion Criteria**	**Original Text:** **Revised Text:** 2. ~~Patient with T798M or T798I mutations in HER2~~, 4. Patient has received anticancer chemotherapy, biologics, immunotherapy, targeted therapy (including HER2 targeted therapy), curative-intent radiotherapy, or other investigational treatment within 15 days local radiation therapy for bone ~~pain~~ may be allowed. Standard and approved hormonal therapies for hormonal receptor positive tumors are allowed. **New Text:** 2. Patients with the T790M mutation in EGFR 4. Patient has received anticancer chemotherapy, biologics, immunotherapy, targeted therapy (including HER2 targeted therapy), curative-intent radiotherapy, or other investigational treatment within 15 days of study entry. Palliative local radiation therapy for bone metastasis may be allowed. Standard and approved hormonal therapies for hormonal receptor positive tumors are allowed. For Cohort 4, patients who have prior single agent VEGF inhibitor therapy (eg bevacizumab) are excluded. **Reason:** 1.-4. Specific eligible molecular mutations now summarized in Table A 5. Exclusion criteria added for patients with GBM who have received single-agent VEGF inhibitor therapy due to limited expected response

Section	Change
Synopsis: Table A **Section 4.1**	**Original Text** **Poziotinib Dose Modifications** ~~Dosing modification recommendations are described in~~ the t~~able below. Dose reductions are in 2 mg~~ increments, regardless of starting dose and will be at the Investigator's discretion. the Sponsor should be notified. ~~Dose reductions other than by 2 mg increments require~~ the Sponsor's Medical Monitor approval. No dose reductions below 8 mg/day are allowed. If the patient ~~has a first documented confirmed~~ progression, ~~the patient may stay on therapy at their current dose or can be increased up to~~ the ~~starting dose of 16 mg/day at the discretion of the Investigator based on the patient's tolerability to the drug~~, investigator's opinion that the patient is still deriving clinical benefits and ~~consideration of~~ other available treatments but must be approved by the Sponsor's Medical Monitor prior to implementation. **New Text** **Poziotinib Dose Modification Recommendations** If needed, the initial dose (8 mg BID) may be reduced by 2 mg for each dose (ie 12 mg per day divided into 6 mg BID doses) at the Investigator's discretion and the Sponsor should be notified. If further dose reduction is required, the next dose should be reduced by a total of 2 mg/day (ie 10 mg per day divided into a 6 mg and 4 mg dose per day) and the Sponsor should be notified. Any further reductions in dose must be discussed a priori with the Sponsor's Medical Monitor and approval is required. No dose reductions below 8 mg total dose/day are allowed. If the patient experiences a radiographic progression, but in the investigator's opinion the patient is still deriving clinical benefit and isn't eligible for other available treatments, the patient may continue receiving poziotinib in Extension Study (SPI-POZ-501). Dosing following documented progressive disease must be approved by the Sponsor's Medical Monitor prior to implementation. **Reason** Information for BID dose reductions were added taking into consideration the currently available dose tablets (2 mg and 8 mg).

Section	Change
Synopsis: Pharmacokinetic Assessments **Section 5.4.6: PK Sample**	**Original Text:** ~~All patients will have blood samples for sparse PK drawn pre-dose and at 1 hour and 3 hours (±15 min) post-dose on **Day 1** of **Cycle 1** and pre-dose on **Day** 1 of Cycle 2. The PK of major active metabolites will also be characterized.~~ **New Text:** At select study centers, up to 25 patients may be specifically consented for intensive PK sampling and concurrent ECGs as defined below: **Schedule:** Intensive PK blood sampling will be at pre-dose and 2, 4, 8, 12, and 24 hours post-dose on **Cycle 1**, **Day 1** and on **Cycle 1**, **Day 8 (±3 days)**. The 12-hour and 24-hour PK samples must be collected prior to the second daily dose. A local 12-lead ECG will be obtained just **before** each PK blood sample on both Day 1 and Day 8. If the patient has interrupted continuous poziotinib dosing, clear dosing documentation must be done in order to assess suitability of further PK sampling and ECG recording. In addition, if a patient presents with a potentially drug-related Grade ≥3 AE, a PK sample should be collected as soon as possible, if feasible, following the onset of the AE in order to characterize the PK. Documentation of last dose timing prior to the event is required. **Reason:** Details for the intense PK sampling were added.
Section 1.1.2.5: Poziotinib Clinical Studies **Section 1.1.2.5.2: Overview of Safety** **Figure 16: Safety Comparison of 16 mg QD vs 8 mg BID**	Background information was added on completed and on-going studies to support the change in the starting dose of poziotinib. **Reason:** Updated data available around the safety and efficacy of poziotinib was added.

Section	Change
Section 5.4.7: **Electrocardiogram (ECG)**	**Original Text:** A 12-lead ECG will be performed at **Screening** and will be ~~repeated as needed during~~ the study. **New Text:** A 12-lead ECG will be performed at **Screening**. At select study centers, up to 25 patients may be specifically consented for intensive PK sampling and concurrent ECGs as defined below: **Schedule:** Intensive PK blood sampling will be at pre-dose and 2, 4, 8, 12, and 24 hours post-dose on **Cycle 1, Day 1** and on **Cycle 1, Day 8 (±3 days)**. The 12-hour and 24-hour PK samples must be collected prior to the second daily dose. A local 12-lead ECG will be obtained just before each PK blood sample on both Day 1 and Day 8. If the patient has interrupted continuous poziotinib dosing, clear dosing documentation must be done in order to assess suitability of further PK sampling and ECG recording. In addition, if a patient presents with a potentially drug-related Grade ≥3 AE, a PK sample should be collected as soon as possible, if feasible, following the onset of the AE in order to characterize the PK. Documentation of last dose timing prior to the event is required. **Reason:** ECG tracing prior to PK sampling added in order to evaluate potential cardiac effects of poziotinib.

CONFIDENTIAL

CLINICAL STUDY PROTOCOL

TITLE PAGE

Study Title:	A Phase 2 Study of Poziotinib in Patients with EGFR or HER2 Activating Mutations in Advanced Malignancies
Study Number:	SPI-POZ-203
Study Phase:	Phase 2
Study Drug:	Poziotinib
IND Number:	140296
Sponsor:	Spectrum Pharmaceuticals, Inc. Research and Development 157 Technology Drive Irvine, CA 92618 USA

Protocol Version/Date: Amendment 1 / 20 May 2021

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

Confidentiality Statement

INVESTIGATOR SIGNATURE

Protocol Number: SPI-POZ-203

A Phase 2 Study of Poziotinib in Patients with EGFR or HER2 Activating Mutations in Advanced Malignancies

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) Guideline for Good Clinical Practice (GCP) as presented adopted by FDA.

I will provide copies of the protocol and of the clinical and preclinical information on the investigational product, 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 study. I will discuss this material with them to assure that they are fully informed regarding the study drug and the conduct of the study.

I will perform the study according to specifications outlined in the protocol, applicable laws and regulations, and the applicable clinical trial agreement 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 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 the study will be released without prior consent from Spectrum Pharmaceuticals, Inc., unless this requirement is superseded by a regulatory authority (e.g., FDA) in which case I will follow the procedures for disclosure described in the applicable clinical trial agreement.

_____

Investigator Name (PLEASE PRINT):

Signature: _____ Date _____

SYNOPSIS

Title of Study: A Phase 2 Study of Poziotinib in Patients with EGFR or HER2 Activating Mutations in Advanced Malignancies

Name of Sponsor: Spectrum Pharmaceuticals, Inc.

Name of Investigational Product: Poziotinib

Study Centers: Approximately 25 study centers

Planned Number of Patients: Approximately 150 patients (30 patients per cohort)

Duration of Study: Approximately 4 years, including enrollment and follow-up	**Clinical Phase:** 2

Objectives:

Primary Objective

- To evaluate the Objective Response Rate (ORR) of poziotinib in patients with EGFR or HER2 mutation-positive malignant solid tumors.

Secondary Objectives

- To evaluate other efficacy variables of poziotinib in patients with EGFR or HER2 mutation-positive, malignant solid tumors, including the following:
  - Duration of Response (DoR)
  - Disease Control Rate (DCR)
- To evaluate the Safety and Tolerability of poziotinib in patients with EGFR or HER2 mutation-positive malignant solid tumors

Exploratory Objectives

- To evaluate the following additional efficacy outcomes:
  - ORR, DCR, and DoR in patients with baseline CNS metastases
  - Overall Survival (OS) and Progression-free Survival (PFS)
  - Relationship between molecular biomarkers and clinical outcome

Duration of Study: The total duration of the study will be approximately four (4) years, including enrollment and follow-up. The duration of study participation for each patient includes the following:

- **Screening Period:** Up to 30 days
- **Treatment Period:** 28 days per cycle for up to 24 months of treatment or until death, intolerable adverse events, progressive disease or other protocol-specified reasons for patient withdrawal
- **End-of-Treatment Visit:** 30 (±5) days after the last dose of poziotinib
- **Long-Term Follow-up:** After treatment period 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.

Patient Replacement Strategy: Patients not efficacy evaluable i.e. not completed at least 1 cycle of poziotinib treatment and have baseline and at least 1 post-baseline tumor response evaluation using RECIST, version 1.1 (and/or RANO for **Cohort 4**) will be replaced unless they have discontinued from treatment or from the study due to disease progression or probable disease progression (eg. clinical progression, initiation of new therapy) or due to toxicity.

Study Design and Methodology

This is a Phase 2 multicenter, open-label study to evaluate the efficacy and safety of poziotinib in patients with EGFR or HER2 mutation-positive malignant solid tumors.

The study is a basket trial with five cohorts. The primary analysis will be conducted for each cohort separately. The five cohorts are:

- **Cohort 1:** Patients that have HER2-positive or HER2-negative, breast cancer with HER2 activating mutations (see **Table A**) (N=30) (See **Inclusion Criteria #4**)
- **Cohort 2:** Patients that have colorectal cancer with HER2 activating mutations (see **Table A**) (N=30)
- **Cohort 3:** Patients that have solid tumors (except NSCLC, breast cancer, or colorectal cancer) with HER2 activating mutations (see **Table A**) (N=30)
- **Cohort 4:** Patients that have GBM with EGFR activating mutations (see **Table A**) (N=30)
- **Cohort 5:** Patients that have solid tumors (except NSCLC or GBM) with EGFR activating mutations (see **Table A**) (N=30)

This study includes a two-stage design in each cohort separately. The first-stage of each cohort will enroll 9 patients. Details of the two-stage design are provided in the statistical section. A cohort will enroll patients into the second-stage if the required responses are observed in 9 patients in the first-stage for each cohort.

Dosing Regimen

The starting dose of poziotinib is 8 mg, twice per day (BID). Poziotinib will be self-administered by the patient orally, with food and a glass of water, at approximately the same time(s) each day during each 28-day cycle.

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, it should be taken once remembered or with the next dose if on the same day.

All patients will be given loperamide for daily use, starting from the first day of the study (4 mg two to three times a day or according to the treating physician's instruction). Poziotinib dose modifications are allowed based on the guidelines provided (**Table 2**).

The Screening period (Day -30 to Day 1) lasts up to 30 days prior to Cycle 1, Day 1. Patients must provide written Informed Consent prior to undergoing any study procedure. Patients must meet all Inclusion/Exclusion Criteria in order to participate in the study. Each treatment cycle is 28 calendar days in duration, regardless of dosing interruptions. Tumor assessments are scheduled at Baseline/pre-dose, Week 4, Week 8 and every 8 weeks thereafter. In the event of a response (PR or CR), a confirmatory scan may be performed 4 weeks from the initial response. Pre-dose tumor assessments must be within 14 days prior to Cycle 1, Day 1 (Baseline assessments may be used if obtained within 14 days prior to Cycle 1, Day 1).

The treatment period for all patients will be from the time of the first dose of poziotinib to the first occurrence of disease progression, intolerable adverse events, the start of a new anti-cancer treatment, withdrawal of consent or death.

Following radiologic disease progression, the patient may continue to receive poziotinib in an Extension Study (SPI-POZ-501) only if the following criteria are met**:** absence of signs and symptoms indicating clinical deterioration due to progression of disease or drug toxicity and absence of decline in ECOG performance status, or the investigator and medical monitor agree that the patient continues to derive clinical benefit despite progressive disease.

SPI-POZ-501 Extension Study

Patients who wish to participate in the extension study must provide written Informed Consent. Treatment will begin after the patient has completed the End-of-Treatment (EOT) Visit in the Original Study (ie visit in SPI-POZ-203 study). Assessments obtained at the EOT visit in the Original Study will serve as Baseline data for the extension study.

Patients will continue to receive poziotinib at the last dose level and schedule received in the POZ-203 study. Poziotinib dose modifications will be allowed under the treating physician's discretion after consultation and approval from the Spectrum medical monitor.

Safety will continue to be followed during the extended treatment according to Standard of Care (SOC). Efficacy of continued poziotinib treatment will be evaluated by imaging according to the Institution's SOC, but at least every 2 cycles.

A patient may continue to receive poziotinib treatment as long as the patient is deriving clinical benefit, as judged by consensus of the investigator and Spectrum medical monitor, or until withdrawal of consent, unacceptable toxicity, the patient is lost to follow-up, poziotinib receives commercial approval in their country of residence, or

development of poziotinib is terminated by the Sponsor, whichever occurs first. There will be an End-of-Treatment (EOT) Visit 30 (±5) days after the last dose of poziotinib.

Inclusion & Exclusion Criteria:

Inclusion Criteria:

1. Patient is 18 years of age or older
2. Patient must be willing and capable of giving written Informed Consent, adhering to dosing and visit schedules
3. Patient has an advanced or metastatic solid tumor with no available standard therapy option
4. Patient with breast cancer must have an NGS HER2 activating mutation (see Table A), and:
   - IHC HER2-positive tumors (based on ASCO/CAP criteria) are included only when they have progressed on trastuzumab, pertuzumab, and T-DM1 which have been administered in the metastatic setting, unless disease recurred within 12 months of adjuvant or neoadjuvant treatment.
   - IHC HER2-negative, ER/PR-positive breast cancer (based on ASCO/CAP criteria) may be included after 1st line endocrine therapy in the metastatic setting, either as a single agent or in combination with standard biological agents (eg aromatase inhibitor and CDK 4/6 inhibitor). Patients are permitted to continue single agent endocrine therapy concurrently with the study.
   - IHC HER2-negative, ER/PR-negative tumors may be included after first-line treatment (any standard chemotherapy-based regimen) in the metastatic setting.
5. Patient with colorectal cancer who are MSI-H and have confirmed progression on pembrolizumab or nivolumab or nivolumab/ipilimumab
6. Patient's tumor is positive for EGFR or HER2 mutations based on DNA genetic testing of either tumor tissue or plasma samples. Patients with documented EGFR or HER2 mutations are identified by local testing from participating sites using next generation sequencing (NGS) test such as OncoMine Comprehensive Assay (OCA), Guardant360 Assay, or FoundationOne Assay that detects specific mutations, performed by a US CLIA certified and CAP accredited clinical laboratory or similarly accredited lab for ex-US sites using tissue or plasma samples. Patient has a solid tumor with at least one of the listed activating mutations (see **Table A**):
   - Cohort 1: Patients that have HER2-positive or HER2-negative breast cancer with HER2 activating mutations (see **Table A**) (N=30) (See **Inclusion Criteria #4**)
   - Cohort 2: Patients that have colorectal cancer with HER2 activating mutations (see **Table A**) (N=30)
   - Cohort 3: Patients that have solid tumors (except NSCLC, breast cancer, or colorectal cancer) with HER2 activating mutations (see **Table A**) (N=30)
   - Cohort 4: Patients that have GBM with EGFR activating mutations (see **Table A**) (N=30)
   - Cohort 5: Patients that have solid tumors (except NSCLC or GBM) with EGFR activating mutations (see **Table A**) (N=30)

Table A—List of Activating Mutations Eligible for Enrollment

	Activating Mutations
Cohorts 1-3: HER2 Activating Mutations (at least one of the following)	
Furin-Like/Extracellular	S310F/Y
Transmembrane	I655V, V659E, R678Q, V697L
Kinase Domain	Exon 20 insertion, T733I, L755X, I767M, D769X, V773M, V777X, L786V, V842I, T862I, L869R
Cohorts 4-5: EGFR Activating Mutations (at least one of the following)	

Extracellular & Transmembrane	EGFRvIII, R108K, R222C, A289T, P596L, G598V
Kinase Domain	Exon 20 insertion, E709X, E709_T710del insD, L718X, G719X, I740_K745dupIPVAIK, I740_K745dup, V742I, L747X, E746_A750del, A750P, S768I, S768I/V769L, S768I/V774M, L833V, V769M, V774M, R831C, R831H, L858R, L861Q, A864V

7. Patient has measurable disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) and/or RANO Criteria for **Cohort 4**. Target lesion(s) must be radiographically measurable. CNS metastatic lesions cannot be considered target lesions in **Cohorts 1-3** and in **Cohort 5**.
8. Brain metastases may be allowed if the patient's condition is stable. Stable condition is defined as having stable neurological symptoms, with no requirement for anti-seizure medications or >2 mg/day dexamethasone equivalent or increasing doses of systemic corticosteroids (except **Cohort 4** where anti-seizure medication [Keppra] and dexamethasone up to or equivalent to 4 mg daily is allowed), and no evidence of CNS disease progression documented for at least 4 weeks after CNS-directed treatment (eg. whole brain radiation), as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Patients must complete CNS-directed treatment and return to stable condition prior to eligibility assessment for the study. For patients who have had radiation therapy, post-treatment MRI tests should show no increase in brain lesion size/volume and no new lesions compared to pre-treatment MRI (except **Cohort 4**) for at least 4 weeks. A new lesion is defined as lesion size greater than 5 mm and not previously present.
9. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
10. Patient has recovered from prior systemic therapy for advanced or 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:
    - Absolute neutrophil count (ANC) $\geq 1.0\times10^9$/L
    - Platelet count $\geq 75\times10^9$/L
    - Hemoglobin ≥9.0 g/dL
    - Total bilirubin ≤1.5×ULN; if hepatic metastases are present, ≤2.0×ULN
    - Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) ≤2.5×upper limit of normal (ULN); if hepatic metastases are present, ≤5.0×ULN
    - Creatinine Clearance
        - Creatinine clearance ≥ 50 mL/min (calculated according to Cockcroft and Gault formula: CCr = {((l 40–age) x weight)/(72xSCr)}) x 0.85 (if female), Scr in mg/dL)

          or
        - GFR >= 45 ml/min/1.73m^2 as calculated by the CKD-EPI Creatinine Equation (2009) (https://www.kidney.org/professionals/kdoqi/gfr_calculator)
11. Patient with childbearing potential 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 serum pregnancy test within 7 days prior to study treatment. Females who are postmenopausal do not require this test (Postmenopausal is defined as any of: age ≥60 years, age <60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range, or prior bilateral oophorectomy, or if taking tamoxifen or toremifene, or age <60 years with FSH and plasma estradiol in postmenopausal ranges).

Exclusion Criteria:

1. Patient has primary tumors in central nervous system (CNS), meningeal carcinomatosis, leptomeningeal carcinomatosis, spinal cord compression, or unstable brain metastasis except if qualified under inclusion criteria for Cohort 4.
2. Patients with the T790M mutation in EGFR.
3. Patients with breast or gastric cancers without eligible HER2 mutations (see **Table A**).
4. Patient has received anticancer chemotherapy, biologics, immunotherapy, targeted therapy (including HER2 targeted therapy), curative-intent radiotherapy, or other investigational treatment within 15 days of study entry. Palliative local radiation therapy for bone metastasis may be allowed. Standard and approved hormonal therapies for hormonal receptor positive tumors are allowed. For Cohort 4, patients who have prior single agent VEGF inhibitor therapy (eg bevacizumab) are excluded.
5. Patient has used or will continue to use strong inhibitors/inducers of CYP3A4 and CYP2D6 within 2 weeks prior to or during the study.
6. Patient has not recovered (i.e, > Grade 1) from drug-induced pancreatitis or has a history of drug-induced pancreatitis.
7. Patient has interstitial lung disease (ILD) or history of ILD or pneumonitis or is less than 30 days from last dose of CPI.
8. Patient has ≥ Grade 2 skin disorders (rash), mucositis, or stomatitis within previous 15 days.
9. 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.
10. Patient has a high risk of cardiac disease, as determined by the Investigator. If patient is deemed to have a high cardiac risk, enrollment may be considered if echocardiogram (ECHO) or multi-gated acquisition (MUGA) during **Screening** demonstrates a cardiac ejection fraction >50%.
11. Patient has a QTc > 470 ms.
12. Patient has a history of other malignancies within the last 1 year, except for non-melanoma skin cancer, carcinoma in situ of the cervix, or PSA-stable, asymptomatic early stage prostate cancer or superficial bladder cancer without active treatment.
13. Patient has clinically significant or recent acute gastrointestinal disease presenting as diarrhea and/or coloenteritis as the main symptom (i.e. acute enteritis, malabsorption, or Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) Grade 2 or higher diarrhea due to other drug-related reasons within 15 days.
14. Patient is unable to take drugs orally due to disorders that may affect gastrointestinal function or has malabsorption syndrome.
15. Patient has an active liver disease or biliary tract disease (except for Gilbert's disease, asymptomatic biliary stones, liver metastasis, or stabilized chronic liver disease).
16. Patient has a medical condition that in the opinion of the investigator or medical monitor would put her/him at an unreasonable risk during the trial
17. Patient has known hypersensitivity to poziotinib or history of allergic reactions attributed to a compound of similar chemical composition to poziotinib.
18. Patient has an active or uncontrolled infection, active bleeding disorder, any underlying medical condition, or other serious illness that would impair the ability of the patient to receive protocol treatment.
19. Patient has had recent major surgery or invasive procedure within 15 days prior to starting study treatment.
20. Patient is pregnant or breast-feeding.

Investigational Product, Dose, and Route of Administration:

Poziotinib is supplied as 8-mg tablets and 2-mg tablets. The starting dose of poziotinib is 8 mg, twice per a day (BID). Patients will self-administer poziotinib orally with food and a glass of water, at approximately the same times each day (recorded in a diary). 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, it should be taken once remembered or with the next dose if on the same day.

Poziotinib Dose Modification will be permitted according to the dose modification guidelines (**Synopsis Table 2**).

Efficacy Assessments:

Efficacy will be based on the local radiology evaluation according to RECIST 1.1 (and/or RANO Criteria for **Cohort 4** as applicable).

Primary Endpoint:

- Objective Response Rate (ORR) - the rate of confirmed complete response + partial response

Secondary Endpoints:

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

Exploratory Endpoints:

- ORR and DoR in patients with baseline CNS metastases
- Overall Survival (OS) and Progression-free Survival (PFS)
- Relationship between molecular biomarkers and clinical outcome

Pharmacokinetic Assessments: At select study centers, up to 25 patients may be specifically consented for intensive PK sampling and concurrent ECGs as defined below:

Schedule: Intensive PK blood sampling will be at pre-dose and 2, 4, 8, 12, and 24 hours post-dose on **Cycle 1**, **Day 1** and on **Cycle 1**, **Day 8 (±3 days)**. The 12-hour and 24-hour PK samples must be collected prior to the second daily dose. A local 12-lead ECG will be obtained just before each PK blood sample on both Day 1 and Day 8.

If the patient has interrupted continuous poziotinib dosing, clear dosing documentation must be done in order to assess suitability of further PK sampling and ECG recording.

In addition, if a patient presents with a potentially drug-related Grade ≥3 AE, a PK sample should be collected as soon as possible, if feasible, following the onset of the AE in order to characterize the PK. Documentation of last dose timing prior to the event is required.

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 30 (±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) will be recorded and reported.

Statistical Methods:

Sample Size:

The statistical analysis of each cohort will be performed separately. A total of 30 patients in each cohort will be enrolled using Simon's two-stage design. The optimal two-stage design to test the null hypothesis that $p \leq 0.050$ *versus* the alternative that $p \geq 0.250$ has an expected sample size of 16.76 and a probability of early termination of 0.630. If the drug is not effective, there is a 0.049 probability of concluding that it is (the target for this value was 0.050). If the drug is effective, there is a 0.098 probability of concluding that it is not (the target for this value was 0.100). For each cohort, 9 patients will be evaluated in the first stage; the cohort will be terminated if 0 respond. If the cohort goes on to the second stage, a total of 30 patients will be studied. If the total number responding is less than or equal to 3, the cohort is closed.

Efficacy Analysis:

The primary efficacy variable ORR is the proportion of patients with confirmed Complete Response (CR) and Partial Response (PR) recorded from the start of the first dose of poziotinib to the end of study and will be analyzed descriptively along with the 95% CI for each cohort. The determination of ORR will be based upon an assessment of the local radiological review by the respective Principal Investigator using RECIST version 1.1 and/or RANO Criteria (for GBM).

The secondary endpoints are DCR and DoR, DCR is the proportion of patients with best response of CR, PR, and Stable Disease (SD) from the first dose of poziotinib to the end of study; and DoR is the time 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.

Exploratory endpoints are OS and PFS. OS is the time from the treatment start date to the date of death during the study; and PFS is the time from the treatment start date to the date of documented disease progression or death during the study.

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

Analysis Populations:

The following analysis populations will be defined.

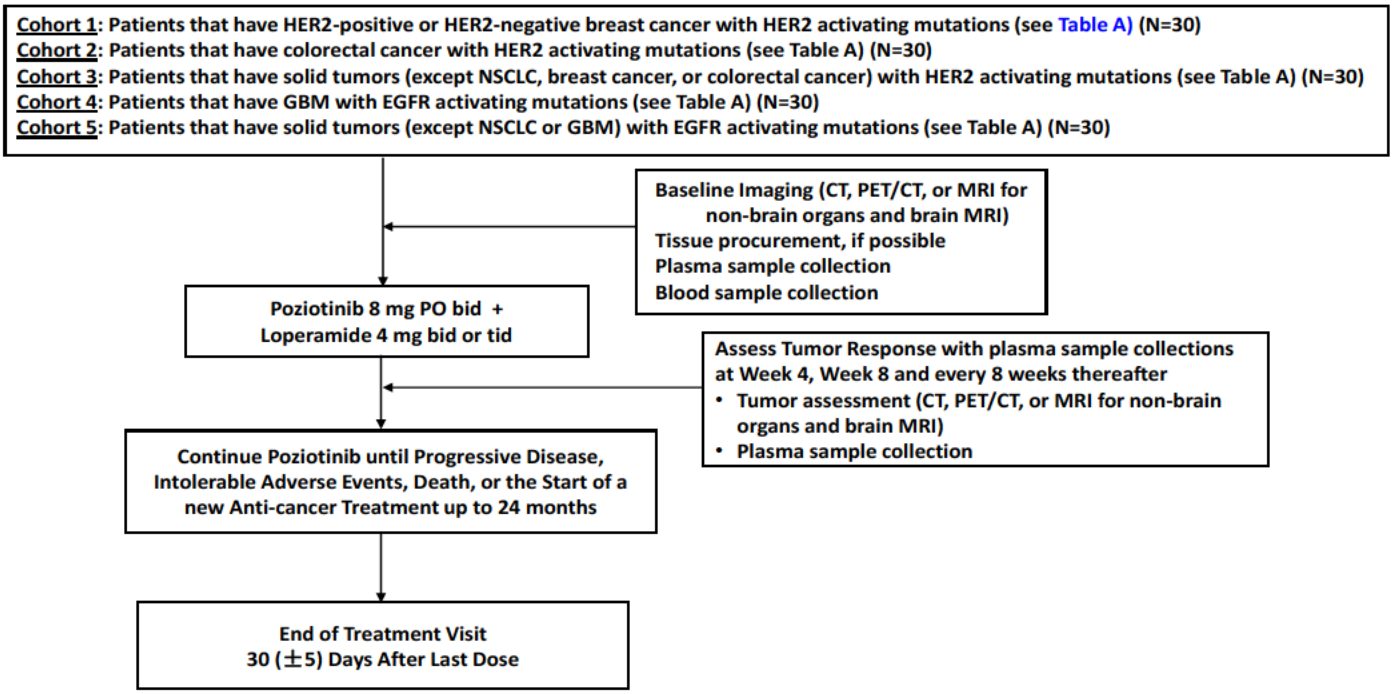
- The **Evaluable Population (EP)** consists of all enrolled patients who, completed at least 1 cycle of poziotinib treatment, and have baseline and at least 1 post-baseline tumor response evaluation using RECIST, version 1.1 (and/or RANO for **Cohort 4**) or progressed prior to any post-baseline image evaluation. All efficacy analyses will be done using the **Evaluable Population.**
- The **Safety Analysis Population (SAF)** includes all enrolled patients who received at least 1 dose of poziotinib. All demographics, Baseline characteristics, and safety data will be analyzed using the **SAF** population.

Safety and Tolerability:

The following variables will be summarized and analyzed descriptively for each cohort: number of completed cycles, relative dose intensity, 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 5.0.

Protocol Version/Date: Amendment 1/ 20 May 2021

Study Design Diagram



SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment	Screening (30 days prior to Day 1, Cycle 1)	Treatment Period[a] (Each Cycle=28 [±3] Days)						End of Treatment (EOT) Visit	Long-Term Follow-up
		Cycle 1[b]			Cycle 2		Cycle 3+		
	Day -30 to Day 1	Day 1	Day 8±1	Day 15±3	Day 1	Day 8±1	Day 1	30 (±5) Days After Last Dose[c]	Every 3 months for 2 years
Informed Consent	x								
Relevant Medical History	x								
Demographic Data	x								
Height and Weight	x	x			x		x	x	
Physical Examination[d]	x	x	x	x	x		x	x	
Vital signs	x	x	x	x	x		x	x	
ECOG Performance Status	x	x			x		x	x	
Pregnancy Test[e]	x	x			x		x	x	
Tumor Assessment	x[f]				x		x	x	
Tumor Histopathology Report[g]	x								
CBC with 5-part differential and platelets[h]	x	x	x		x	x	x	x	
Serum Chemistry[i]	x	x[i]			x		x	x	
Electrocardiogram (ECG)[j]	x	x	x						
Echocardiogram or MUGA Scan[k]	x								
Tissue Samples[l]	x							x	
Plasma Samples[m]	x				x		x[l]	x	
Whole Blood Sample[n]	x								
PK Samples[o]		x	x		x				
Dispense Poziotinib and Loperamide[p]		x			x		x		
Adverse Event Assessment	x[q]	x	x[r]	x	x	x[r]	x	x	x
Dispense and Collect Patient Diary		x	x		x	x	x	x	
Concomitant Medications review	x	x	x	x	x	x	x	x	
Telephone Contact[s]									x

a) Each treatment cycle is 28 days with a visit window of ± 3 day. If a visit is delayed during 1 Cycle, the subsequent schedules will be delayed sequentially.
b) Patients will be contacted by telephone on Days 3-8 and on Day 22 for assessment of adverse events.
c) An **End-of-Treatment Visit** will be performed 30 (±5) days after the last dose of poziotinib. An End of Study page will be recorded at that time.
d) A complete physical examination is required at **Screening**, **Day 1** of each Cycle, at Days 8 and 15 of Cycle 1, and at the **End-of-Treatment Visit**. Symptom-directed exams if clinically indicated are required at other visits.
e) Pregnancy test (β-HCG) in women of child-bearing potential. Blood pregnancy test is required at **Screening**. Urine pregnancy test is required on Day 1 of each Cycle starting from **Cycle 2** and at **Cycle 1**, **Day 1**, if Screening pregnancy test was more than 7 days prior to **Day 1**. Urine pregnancy test also required at **End-of-Treatment Visit**.

f) The **Screening** tumor assessment for patient eligibility will be based on scans performed within 30 days before the patient signed the ICF. Either CT, PET/CT, or MRI scans should be performed for non-brain organs and brain MRI scans should be performed locally per standard of care before the patient signed the ICF. **Baseline** tumor assessment (CT, PET/CT or MRI for non-brain and brain MRI) will be performed within 14 days prior to **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, death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal.

g) Tumor histopathology report (from local pathologist) and molecular test report for mutation diagnosis.

h) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained within 7 days prior to poziotinib administration on **Day 1** of each cycle, at which time, the patient's absolute neutrophil count $\geq 1.0 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L before administering the next dose of poziotinib. In addition, a CBC is to be performed on **Day 8** of **Cycles 1** and **2**.

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

j) ECGs will be performed at screening. At select study centers, up to 25 patients may be specifically consented for ECG as defined below:
Schedule: A local 12-lead ECG will be obtained just before each PK blood sample on both Day 1 and Day 8. If the patient has interrupted continuous poziotinib dosing, clear dosing documentation must be done in order to assess suitability of further PK sampling and ECG recording.

k) 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.

l) Tumor genotyping report from local lab is required to confirm patient mutation eligibility. Tissue sample (archival or fresh biopsy), if available, should be retained for retrospective analysis by FoundationOne CDx test. Collecting a tissue sample at progression is optional but is highly encouraged.

m) Plasma samples will be required at **Screening** and optional on the day of each on-study imaging session, beginning at the 4-week imaging session, once every 8 weeks with imaging scan and when the patient progresses for biomarker analysis. Guardant's 360 or FoundationACT assays will be used, Plasma sample collection and storage will follow vendors' standard procedures as described in the vendors' Laboratory Manual.

n) Whole blood samples will be drawn at **Screening** for pharmacogenomic analysis.

o) At select study centers, up to 25 patients may be specifically consented for intensive PK sampling as defined below:
Schedule: Intensive PK blood sampling will be at pre-dose and 2, 4, 8, 12, and 24 hours post-dose on **Cycle 1**, **Day 1** and on **Cycle 1**, **Day 8 (±3 days)**. The 12-hour and 24-hour PK samples must be collected prior to the second daily dose. If the patient has interrupted continuous poziotinib dosing, clear dosing documentation must be done in order to assess suitability of further PK sampling and ECG recording. In addition, if a patient presents with a potentially drug-related Grade ≥3 AE, a PK sample should be collected as soon as possible, if feasible, following the onset of the AE in order to characterize the PK. Documentation of last dose timing prior to the event is required.

p) Poziotinib and loperamide will be dispensed on **Day 1** of each cycle. Patients will take poziotinib orally twice daily with food and a glass of water at approximately the same times each day. Loperamide will be given prophylactically for diarrhea as follows: 4 mg twice daily (bid) to three times daily (tid or according to treating physician's instruction.

q) Adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) and during **Screening** only study-related SAEs to be recorded.

r) Weekly calls to patients will be conducted during the Days 3 to 8 of each cycle for the first 2 cycles as a follow up of expected adverse events.

s) Patients who have consented will be contacted by phone (or email or letter if specifically requested) every 3 months, for up to 2 years after patient's first dose of poziotinib, for survival assessment.

Poziotinib Dose Modification Recommendations

If needed, the initial dose (8 mg BID) may be reduced by 2 mg for each dose (ie 12 mg per day divided into 6 mg BID doses) at the Investigator's discretion and the Sponsor should be notified. If further dose reduction is required, the next dose should be reduced by a total of 2 mg/day (ie 10 mg per day dived into a 6 mg and 4 mg dose per day) and the Sponsor should be notified. Any further reductions in dose must be discussed a priori with the Sponsor's Medical Monitor and approval is required.

No dose reductions below 8 mg total dose/day are allowed.

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 rowspan="2">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 ~1 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 4.</td></tr>
<tr><td>LVEF Dysfunction</td><td>Grade ≥3</td><td colspan="2">Discontinue Treatment</td></tr>
</table>

a) Supportive medications, including early steroid use, should be considered even in the presence of low-grade "on-target" toxicity (eg, rash, diarrhea) (**Appendix 4**).

If the patient experiences a radiographic progression, but in the investigator's opinion the patient is still deriving clinical benefit and isn't eligible for other available treatments, the patient may continue receiving poziotinib in Extension Study (SPI-POZ-501). Dosing following documented progressive disease must be approved by the Sponsor's Medical Monitor prior to implementation.

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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
CPI	Check-Point Inhibitor
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
GBM	Glioblastoma

Abbreviation/ Acronym	Definition
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HER2	Human epidermal growth factor receptor 2
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
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial Response
PR	Progesterone receptor
RANO	Response assessment in neuro-oncology
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

Abbreviation/ Acronym	Definition
SGPT	Serum glutamic pyruvic transaminase
T-DM1	Trastuzumab emtansine
TEAE	Treatment-emergent adverse event
TTP	Time to Progression
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

1.1.1 Human Epidermal Growth Factor Receptor Family and Cancer

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

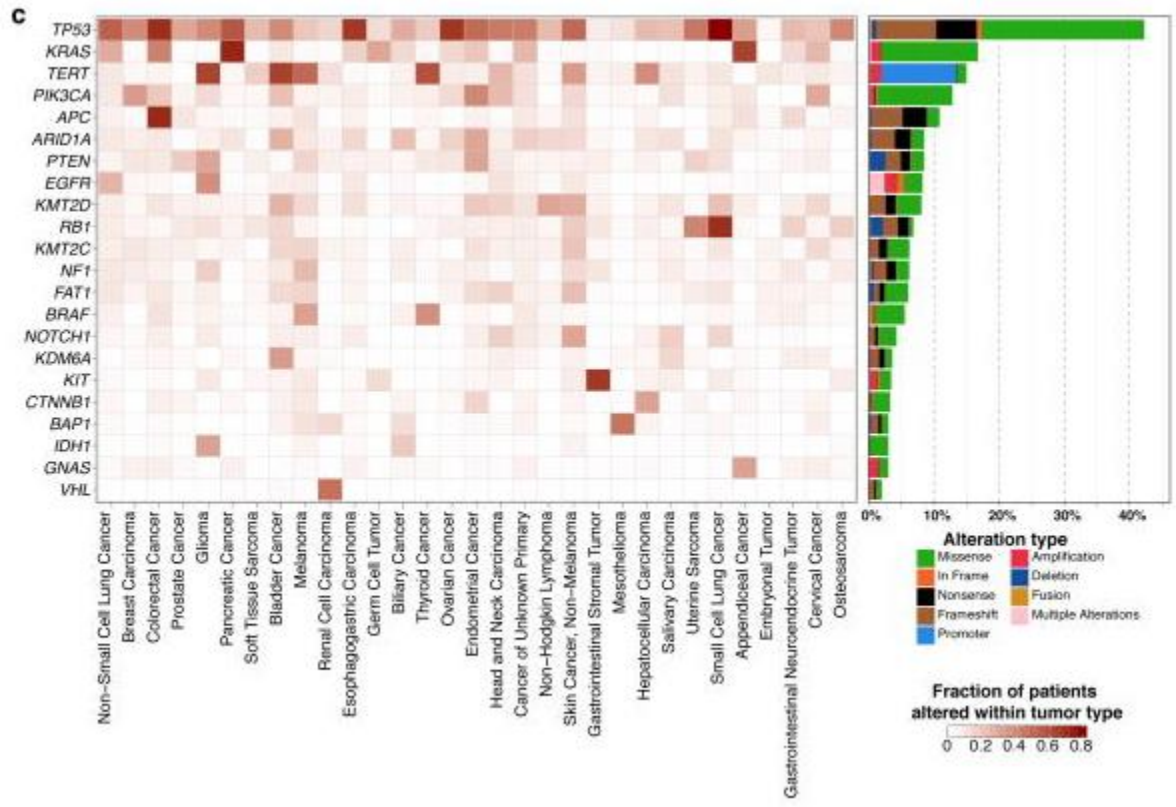
Many solid tumors, including lung, breast, bladder, head and neck, and other gastrointestinal cancers, are associated with either an activating mutation in or an overexpression of members of the ErbB receptor family, especially EGFR and HER2 **[2]**. EGFR and HER2 mutations, including exon 20 insertion mutations, have been identified in a variety of cancer types**.** Treatments that specifically target HER2 overexpression have been shown to be clinically beneficial to breast cancer patients and several targeted therapies have been approved by the FDA for treatment patients with NSCLC and breast cancer. Similarly, there are investigations of FDA-approved EGFR targeting agents in HER2 overexpressed and mutant colorectal, head and neck, and pancreatic cancers. In a recent basket trial of patients with lung, breast, bladder, colorectal, and several other solid tumors, HER2 mutations were shown to be clinically targetable with neratinib; although, outcomes were modest **[3]**. However, to date, excluding NSCLC, there are no FDA-approved targeted therapies for EGFR or HER2 mutant solid tumors. The results of nonclinical *in vitro* and *in vivo* studies show sensitivity of both EGFR and HER2 exon 20 mutations across tumor types to poziotinib, a novel oral, irreversible pan-HER inhibitor **[4]**. Clinical efficacy and safety data obtained to date indicate that poziotinib may be beneficial to patients with pretreated metastatic lung cancers that harbor these mutations **[5, 6]**. In addition, Spectrum has two compassionate therapy cases with one patient who received poziotinib for treatment of lung cancer with a HER 2, exon 19 mutation and in one patient with breast cancer with a HER2, exon 20 mutation (Case Reports).

1.1.1.1 EGFR Mutations in Various Malignancies and EGFR Mutational Hotspots by Cancer Type

Zehir et al. utilized a large-scale, prospective clinical sequencing, comprehensive assay, MSK-IMPACT, and compiled matched tumor and normal tissue sequence data from a unique cohort of more than 10,000 patients with advanced cancer **[7]**. Using these data, they identified EGFR clinically relevant somatic mutations most frequently in non-small cell lung cancer (NSCLC), glioma, head and neck carcinoma, stomach, esophagogastric carcinoma and breast **(Figure 1)**. Priestley et al. had further defined the EGFR activating alternations in metastatic solid tumors by analyzing data from TCGA and ICGC, 2,520 whole genome-sequenced tumor-normal pairs. They have reported that EGFR mutations occurred most frequently in cancers of the lung (14.5%), stomach (6.9%), esophagus (5.2%), head and neck (4.8%), liver (3%), breast (1.3%) and urinary tract (1.2%). EGFR activating mutations occurred most frequently in the exon 19, in frame deletion, and in the exon 20, codon L858, followed by exon 20 insertion/duplication

mutations, and mutations in codons G719, S768, L861 **[8]**. Currently, there are FDA-approved targeted therapies for EGFR mutant NSCLC with exon 19 deletion and L858R substitution in exon 21 (Afatinib, Erlotinib, and Gefitinib), but there is no FDA-approved targeted therapy for other solid tumor types.

Figure 1 EGFR Mutant Cancers



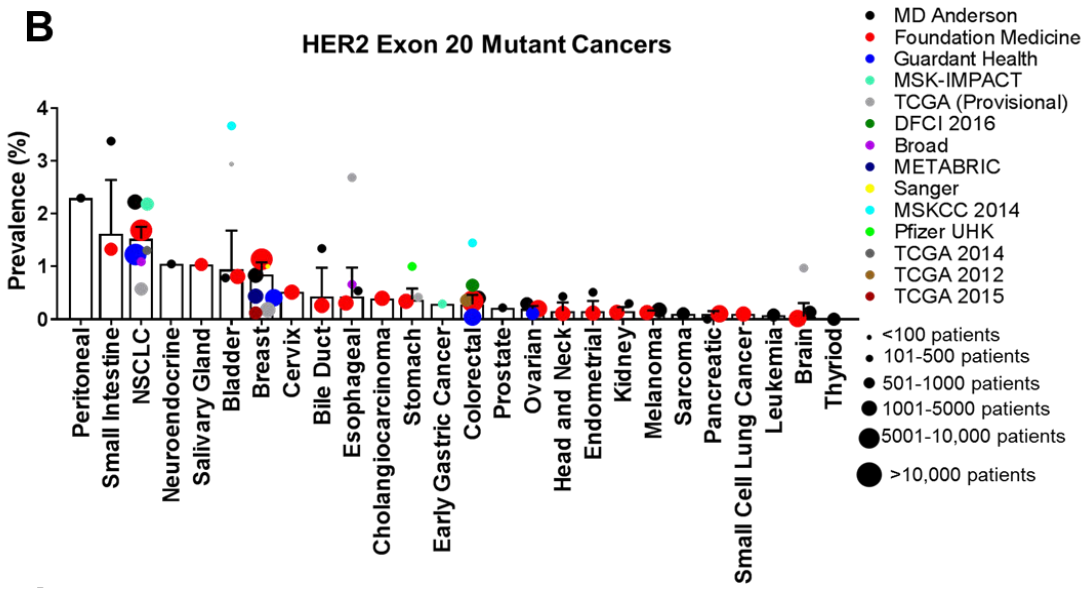
Overview of the MSK-IMPACT cohort. Recurrent somatic alterations across common tumor types. Genes with a cohort-level alteration frequency of ≥5% or a tumor type-specific alteration frequency of ≥30% are displayed. Bars indicate the percent of cases within each tumor type harboring different classes of genomic alterations.

1.1.1.2 HER2 Mutations Occur in Various Malignancies, and HER2 Mutational Hotspots Vary by Cancer Type.

Across four public and proprietary databases, HER2 mutations were analyzed within 26 different cancer types. HER2 mutations occurred most frequently in bladder, stomach, and bile duct cancers (unpublished manuscript); and HER2 exon 20 mutations occurred most frequently in cancers of the peritoneal, small intestine, and lung **(Figure 2)**. Across all cancer types, HER2 mutations occurred most frequently in the extra-cellular domain, followed by exon 20, exon 19, and exon 21 (unpublished manuscript). Mutational hotspots varied by malignancy type. These hotspot mutations have been tested *in vitro*, and have demonstrated as activating mutations **[5]** and (unpublished manuscript). A recent basket trial of neratinib enrolled 125 patients with HER2 mutations, 102 patients with hotspot mutations, and remaining patients with potentially oncogenic mutations determined by OncoKB, a curated knowledge database (**[3]**). Enrolled patients had lung, breast, bladder, colorectal, biliary, endometrial, and other solid tumors. The study has demonstrated that HER2 mutations are clinically targetable; however, the outcomes

with neratinib were modest. Currently, there are no FDA-approved targeted therapies for HER2 mutant solid tumors. However, there are two on-going Phase 2 clinical trials of poziotinib for patients with metastatic NSCLC harboring an exon 20 insertion mutation in either EGFR or HER2 (NCT03318939 and NCT03066206).

Figure 2 HER2 Mutant Cancers



HER2 mutations occur in a variety of cancer types with mutational hotspots occurring across the receptor. Bar plot of weighted averages of HER2 exon 20 mutation frequency by cancer. Bars are representative of the weighted average ± SEM. Dot sizes are representative of the number of patients in each database. (N=390,000). [6]

1.1.2 Poziotinib

1.1.2.1 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 a salt form), respectively.

1.1.2.2 Pharmacology of Poziotinib

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

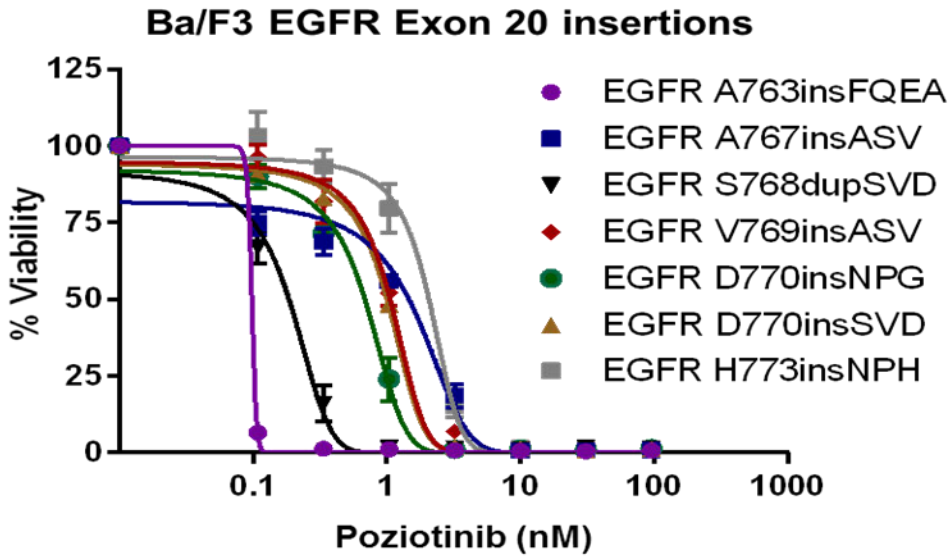
1.1.2.3 Nonclinical Data

1.1.2.3.1 Poziotinib in Tumor Models with EGFR Exon 20 Insertion Mutations

Poziotinib is active *in vitro* against cell lines with a range of *EGFR* exon 20 mutations 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 the oncogenic activity of genes and development of drugs that target oncogenic drivers. This system was used to test several *EGFR* exon 20 insertion mutations for their effects on IL-3-independent cell survival, signaling, and drug responsiveness **[5]**. Stable expression of *EGFR* exon 20 insertion mutations rendered Ba/F3 cells IL-3 independent, suggesting that these mutations are activating **[5]**.

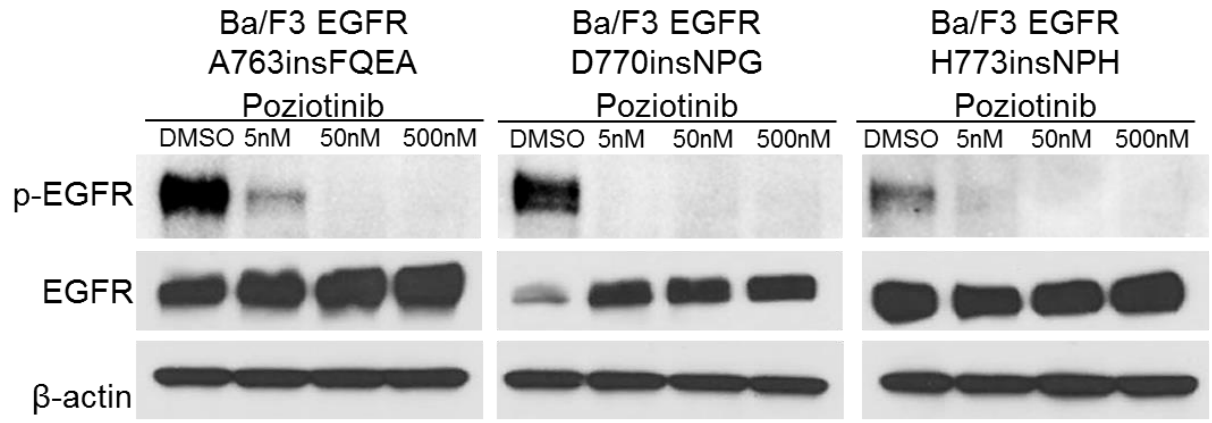
Ba/F3 cells with EGFR exon 20 insertions were then treated with poziotinib. Ba/F3 expressing *EGFR* exon 20 insertions showed marked sensitivity to poziotinib (**Figure 3**).

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



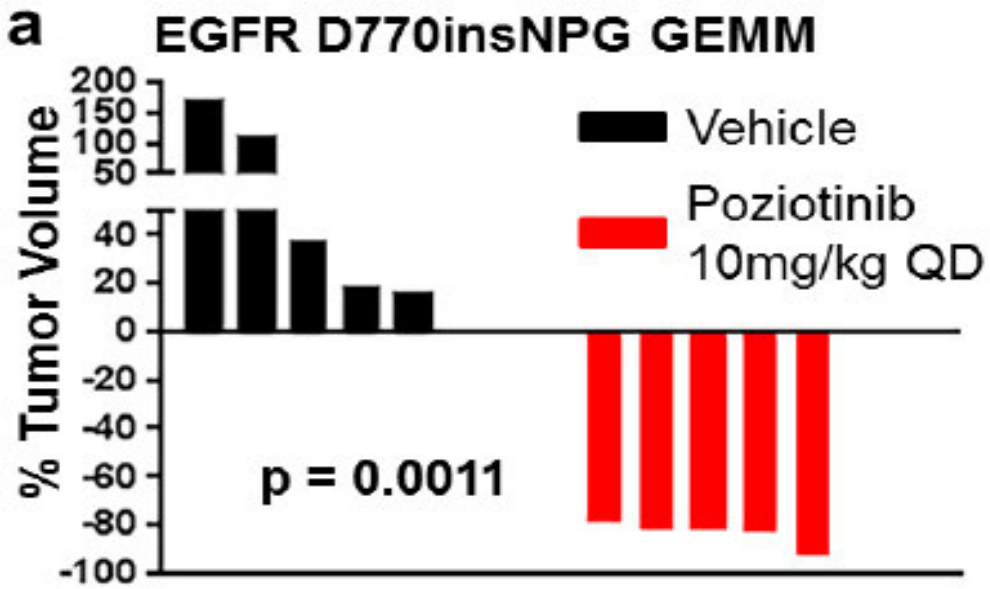
Moreover, poziotinib led to the suppression of EGFR phosphorylation and decreased downstream signaling, that was associated with an increased level of cleaved PARP suggesting that treatment with poziotinib leads to cell apoptosis **(Figure 4) [9]**.

Figure 4 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 5**) [9].

Figure 5 Tumor Volume Change in Mice with EGFR Exon 20 Insertion Mutations Treated with Poziotinib Vs. Vehicle



1.1.2.4 Poziotinib Inhibits HER2 exon 20 Insertion Mutations *in Vitro* and *In Vivo*

Figure 6 and Figure 7 present the results of recent *in vitro* nonclinical studies of poziotinib on HER2 exon 20 mutations in NSCLC and other malignancies. Ba/F3 cells with HER 2 exon 20 insertion A775insYVMA were screened with TKIs including poziotinib. Ba/F3 expressing this insertion mutation showed marked sensitivity to poziotinib (**Figure 6**) [10, 11]. We found that

across all HER2 mutations, poziotinib was one of the two most mutant-selective TKIs (Figure 7F, mutant/WT = 0.23) and across HER2 exon 20 mutations, poziotinib was the most mutant-selective TKI. Therefore, poziotinib was the most potent and mutant-selective inhibitor tested for HER2 mutations *in vitro* (**Figure 7**) [10].

Figure 6 Dose-Response Curves of the Cell Viability of HER2 Mutant A775insYVMA Ba/F3 Cells After TKI Treatment for 72 Hours

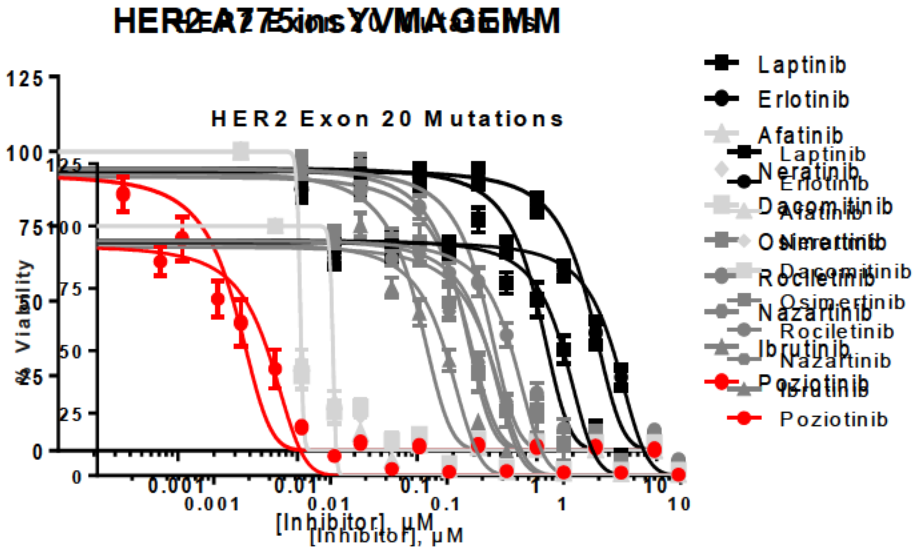
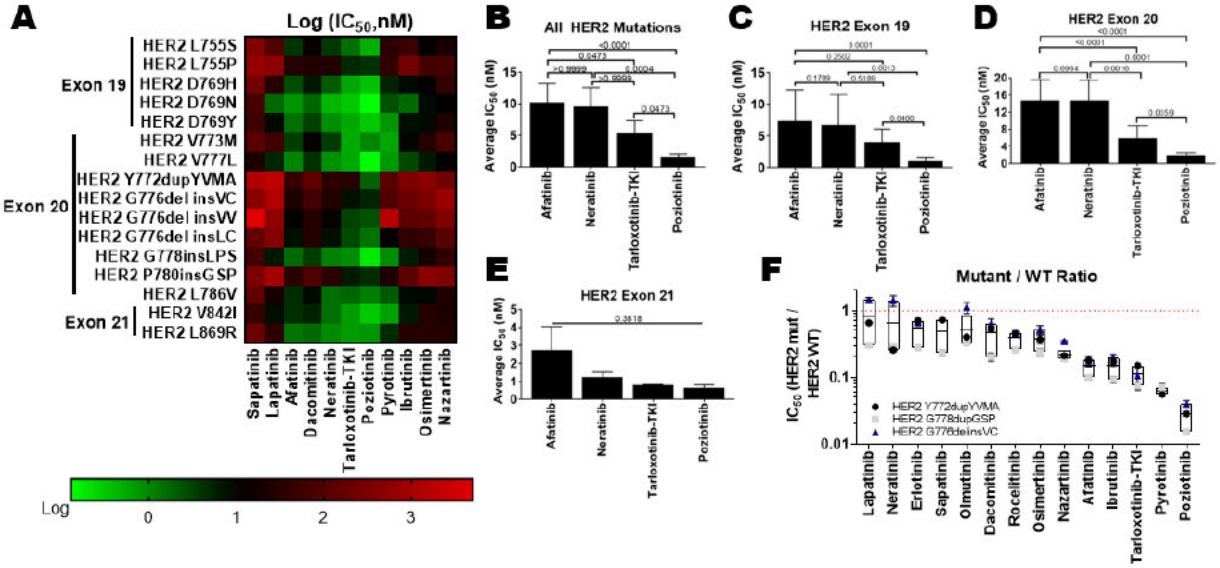


Figure 7 Poziotinib as a Potent Inhibitor for HER2 Mutations *in Vitro*

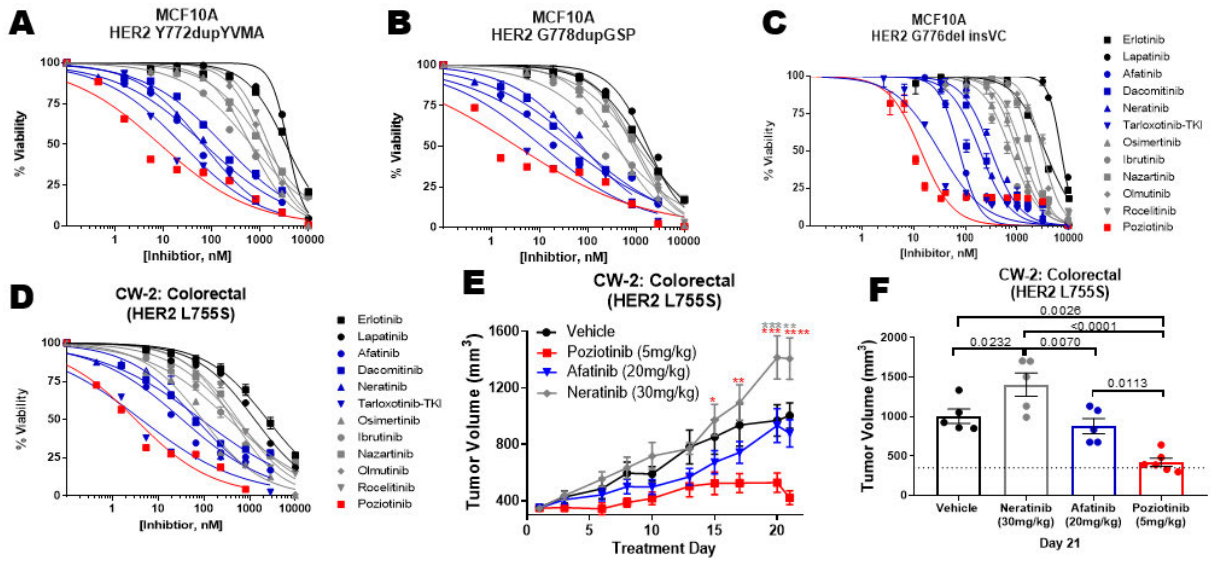


(A) Heatmap of log IC_{50} values of Ba/F3 cells stably expressing the indicated mutations after 72 hours of drug treatment. Cell viability was determined by the Cell Titer Glo assay (N≥3). Average IC_{50} values for all Ba/F3 cell lines expressing HER2 mutations **(B)**, HER2 exon 19 mutant cell lines **(C)**, HER2 exon 20 mutant cell lines **(D)**, or HER2 exon 21 mutant cell lines **(E)**

after drug treatment for 72 hours **(C-E)**. Dots are representative of mean ± SEM (N≥3). **(F)** Bar graph of MCF10A HER2 mutant to WT ratio where dots are representative of mean ± SEM for each cell line and bars are representative of mean ± min/max of all three cell lines.

In addition, human breast and colorectal cell lines and xenografts with HER2 mutations were highly sensitive to poziotinib *in vitro* and *in vivo* (**Figure 8**). Poziotinib is 2.6 and 19 times more potent than tarlox-TKI and neratinib, respectively (Figure 8A-C). Poziotinib was the most mutant selective TKI tested in MCF10A cell lines, followed by pyrotinib, and tarlox-TKI (Figure 8D). In a model of HER2 exon 19 mutant colorectal cancer (CW-2), differences in sensitivity between poziotinib, tarlox-TKI, and neratinib were less dramatic, albeit significant (p=0.02 and p=0.0004) with average IC50 values of 3.19nM, 4.24nM, and 68.8nM, respectively (Figure 8F) **[10]**.

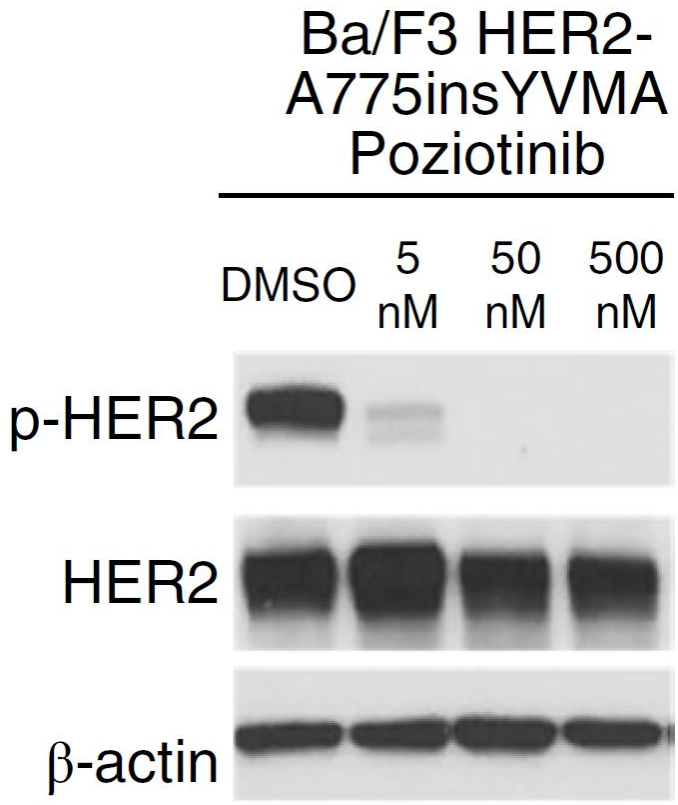
Figure 8 Human Breast and Colorectal Cell lines with HER2 Mutations Highly Sensitive to Poziotinib *in Vitro* and *in Vivo*



(A-C) Dose response curves of MCF10A cells expressing exon 20 insertion mutations or **(D)** CW-2 cells treated with indicated inhibitors for 72 hours. **(E)** Tumor growth curve of CW-2 cells (HER2 L755S) xenografts treated with indicated inhibitors. Two-Way ANOVA was used to determine statistical significance. Asterisk indicate significance between vehicle and poziotinib (red) or neratinib (grey). **(F)** Bar graph of CW-2 tumor volume at day 21. Dots are representative of individual tumors, and bars are representative of mean ± SEM. The dotted line indicates randomization at 350mm$^{3.}$ Statistical significance was determined by one-way ANOVA.

Moreover, poziotinib led to the suppression of HER2 phosphorylation and decreased downstream signaling, that was associated with an increased level of cleaved PARP suggesting that treatment with poziotinib leads to cell apoptosis **(Figure 9) [9]**.

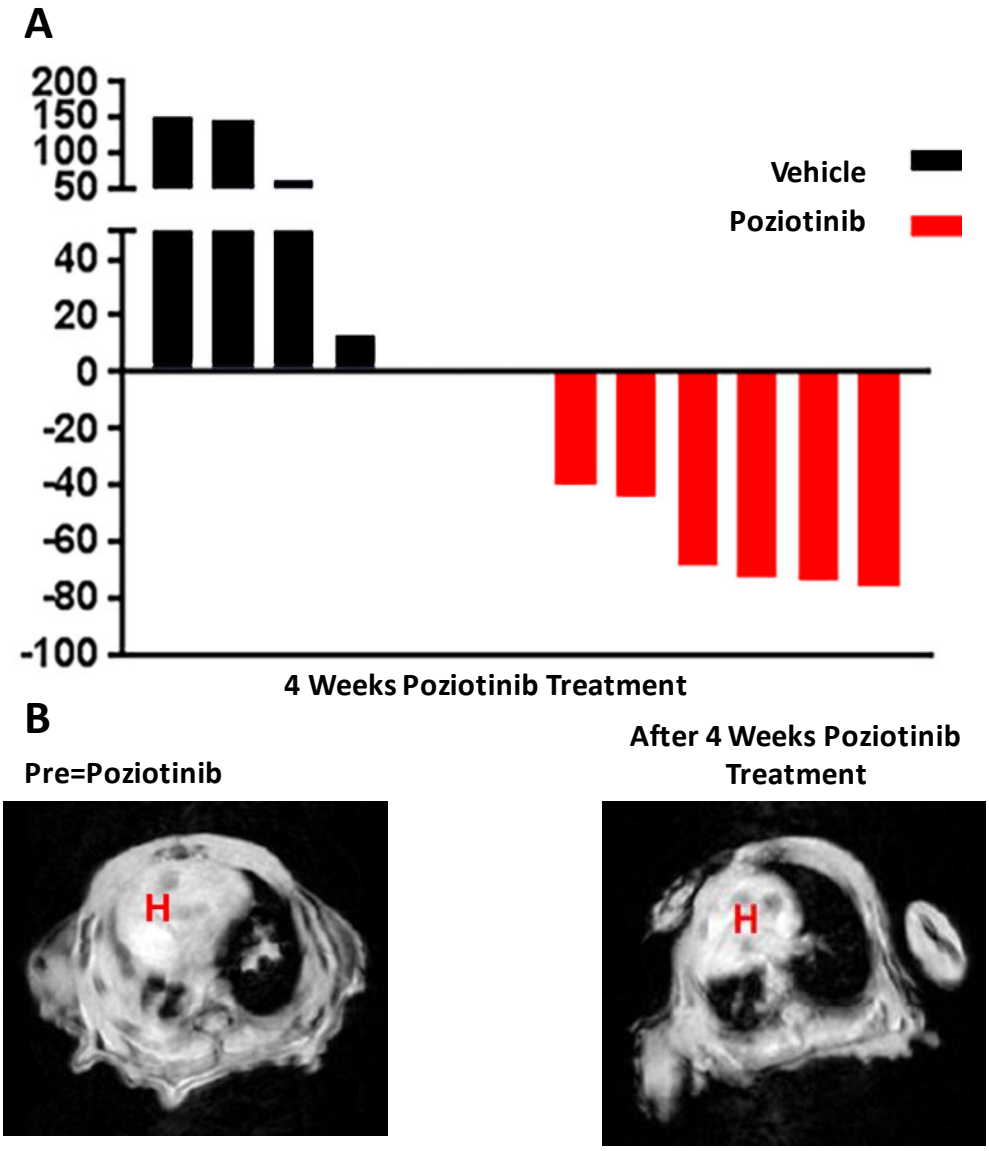
Figure 9 Effect of Poziotinib (HM781-36B) on HER2 Phosphorylation and Downstream Signaling



Western blotting confirms inhibition of p-HER2 in Ba/F3 cell lines after 2 hours of poziotinib treatment (n=2)

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 80% tumor inhibition at 4 weeks (**Figure 10A** and **B**) **[11]**.

Figure 10 MRI Results after Poziotinib Treatment



A) Waterfall plots of HER2 GEMM tumor volume change as measured by MRI after 4 weeks poziotinib treatment
B) DMRIs of HER2 GEM before and after 4 weeks poziotinib treatment.

In addition, in a model of HER2 exon 19 mutant colorectal cancer (CW-2), poziotinib demonstrated most potent inhibitory activity among other TKIs. Furthermore, in a xenograft mouse model of CW-2 colorectal cells, poziotinib treated animals had shown a significant tumor growth inhibition (TGI) (unpublished manuscript).

1.1.2.4.1 Poziotinib Absorption, Distribution and Metabolism

Poziotinib exhibits high plasma clearance, moderate oral bioavailability, high protein binding, slow metabolism *in vitro*, and extensive metabolism *in vivo*. Exposure to poziotinib increased with increasing 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 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 **[12]**.

1.1.2.4.2 Poziotinib Toxicity Studies

The toxicology of poziotinib has been evaluated in animal studies and 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 **[9-12]**, suggesting that poziotinib toxicity is a class effect of EGFR tyrosine kinase inhibition.

1.1.2.5 Poziotinib Clinical Studies

The clinical development program for poziotinib is ongoing in collaboration with Hanmi Pharmaceuticals, Inc. in Korea. To date, 10 studies have been conducted in Korea. Three of these are Investigator-initiated studies and are ongoing. The remaining seven trials have been completed and are listed below.

Poziotinib Clinical Trials Completed in Korea:

- Two (2) Phase 1 studies (HM-PHI-101 & HM-PHI-102) conducted in patients with advanced cancers (solid tumors) are PK/PD and dose finding studies
- Four (4) Phase 2 studies (NOV12010-201, NOV120101-202, HM-PHI-A201, and NOV12010-203) conducted in patients with EGFR-mutant NSCLC, advanced gastric cancer, and HER2+ breast cancer
- Investigator-Initiated study (NSCLC with HER2 mutations).

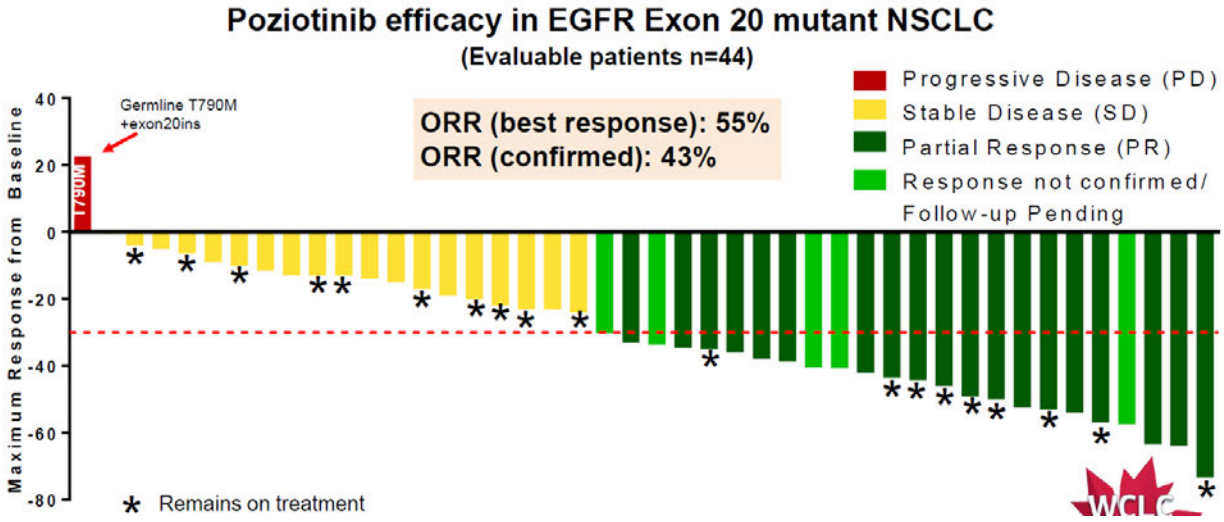
Ongoing Poziotinib Trials in the US:

- Phase 1 study (**SPI-POZ-101**) in HER2+ breast cancer in combination with T-DM1
- Phase 2 study (**SPI-POZ-201**) in HER2+ breast cancer with ≥2 prior HER2 directed therapies
- Phase 2 study (**SPI-POZ-202**) in NSCLC with EGFR or HER 2 exon 20 insertion mutation in pretreated and treatment naïve patients
- Phase 2, US Investigator-Initiated Study (NCT03066206) in NSCLC with EGFR or HER2 exon 20 mutation

The maximum tolerated dose was determined in two different Phase I studies. In the HM-PHI-101 study, poziotinib was administered on an intermittent schedule (2 weeks on and 1 week off) at doses ranging from 0.5 mg to 32 mg, and the maximum tolerated dose was determined as 24 mg in this schedule. In the HM-PHI-102 study, poziotinib was administered daily at doses

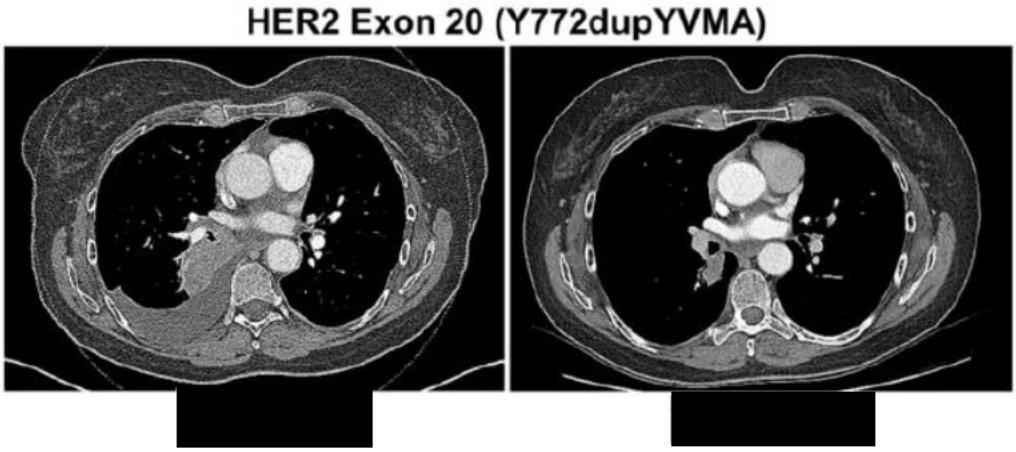
ranging from 12 mg to 24 mg. In this study, the maximum tolerated dose was determined as 18 mg, and the recommended dose was 16 mg. This is the basis for selecting the 16 mg dose for lung cancer studies where the drug is administered daily.Overall, 1143 patients have received poziotinib in 21 clinical studies (12 sponsored by Hanmi, 8 Sponsored by Spectrum, and 1 by MD Anderson Cancer Center) at doses ranging from 0.5 mg to 32 mg QD on an intermittent dosing schedule or 10 mg to 24 mg QD on a continuous dosing schedule. Combined, more than 500 patients have been treated orally with 16 mg QD as their starting daily dose representing a large safety dataset for this rare mutation. Poziotinib as monotherapy is being studied in NSCLC patients with EGFR and HER2 exon 20 mutations in an open-label, single-arm study Phase 2 study at the University of Texas MD Anderson Cancer Center (MDACC) (NCT03066206). In this study, a cohort of 50 patients with previously treated, locally advanced or metastatic NSCLC bearing mutations in EGFR exon 20 (except EGFR T790M) and another cohort of 30 patients with NSCLC HER2 exon 20 mutations were to be enrolled. The preliminary data on 50 patients in EGFR exon 20 cohort and 13 patients in HER2 exon 20 Cohort was presented at the International Association for the Study of Lung Cancer (IASLC) 2018. This phase 2 study demonstrated high anti-tumor activity for poziotinib with best response of PR in 55% of evaluable patients (43% confirmed ORR to date) in metastatic, heavily pretreated EGFR exon 20 mutant NSCLC Cohort (**Figure 11**) and showed an initial response in 50% (6/12) of evaluable HER2 exon 20 mutations patients to date **[6]**.

Figure 11 Poziotinib efficacy in patients with EGFR exon 20 mutant NSCLC



One of the patients with NSCLC harboring HER2 exon 20 (Y772dupYVMA) mutation who has been treated with poziotinib. The CT scans of this patient showed one (1) day before poziotinib treatment and 8 weeks after poziotinib therapy **(Figure 12)** (J. Heymach's unpublished data)

Figure 12 NSCLC Patient with HER2 exon 20 (Y772dupYVMA) mutation



1.1.2.5.1 Case Studies

1.1.2.5.1.1 Case 1 – Breast Cancer with HER2 Exon 20 Mutation

The first case was a [redacted]-year-old woman with breast cancer. The initial biopsy in [redacted] was an adenocarcinoma, estrogen receptor (ER) positive, progesterone receptor (PR) positive and HER2 equivocal. She was heavily treated with many regimens including paclitaxel, nab-paclitaxel, doxorubicin-cyclophosphamide, trastuzumab, letrozole, fulvestrant, tamoxifen, exemestane, trastuzumab/pertuzumab, trastuzumab-emtansine; and capecitabine. All of these therapies only resulted in 3 to 6 months of stable condition followed by progression and worsening of dyspnea, fatigue, and exercise intolerance.

In [redacted], she was diagnosed HER2 exon 20 insertion mutation (ERBB2 P780-Y781insGSP). From [redacted] to [redacted], she received lapatinib, nab-paclitaxel, eribulin, neratinib and gemcitabine. By [redacted], the patient developed severe dyspnea and high tumor burden in her liver and lungs on imaging (**Figure 13**).

In [redacted], she started a compassionate therapy with poziotinib 16 mg daily. Within 2 months in [redacted], her hepatic lesion was significantly reduced (**Figure 14**), and her CA 27.29 was dropped from over 400 in [redacted] to 27 in [redacted]. In [redacted] the patient had discontinued supplemental oxygen, and her exercise tolerance had improved markedly. However, from [redacted], her symptoms gradually worsened due to disease progression. The patient entered hospice care in late [redacted] and expired in [redacted].

Figure 13 CT of Abdomen, [redacted]

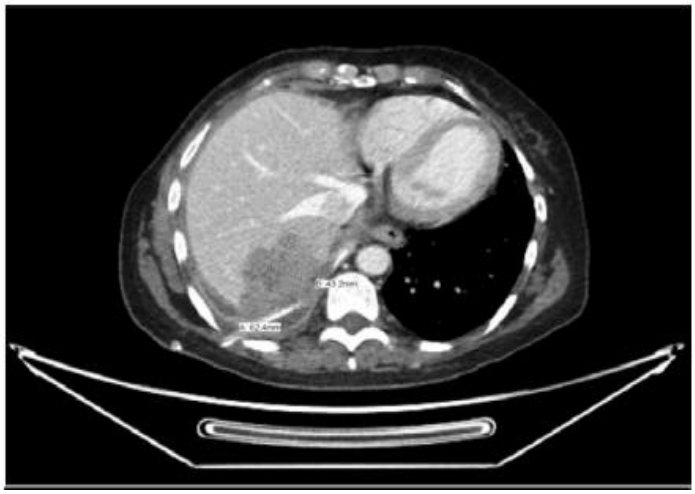
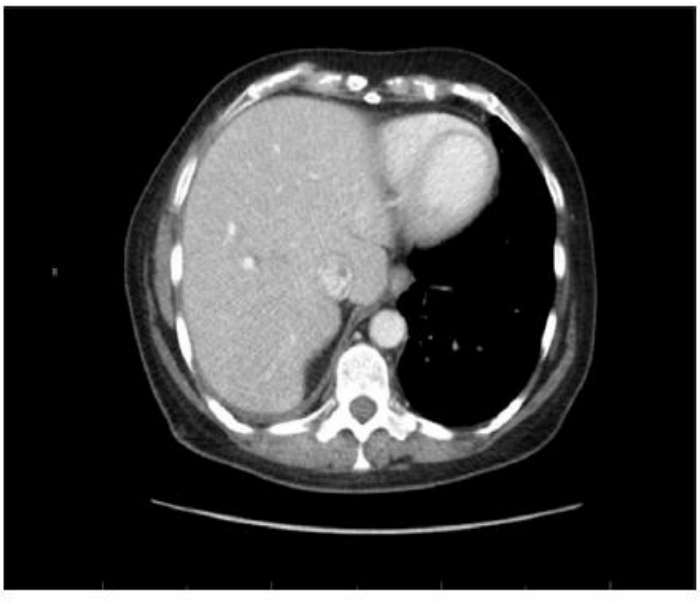


Figure 14 CT of Abdomen, [redacted]



This patient received poziotinib therapeutic benefit for about 6 months with clinical improvement and imaging/biomarker confirmation **[13].**

1.1.2.5.1.2 Case 2 – NSCLC with HER2 Exon 19 Mutation

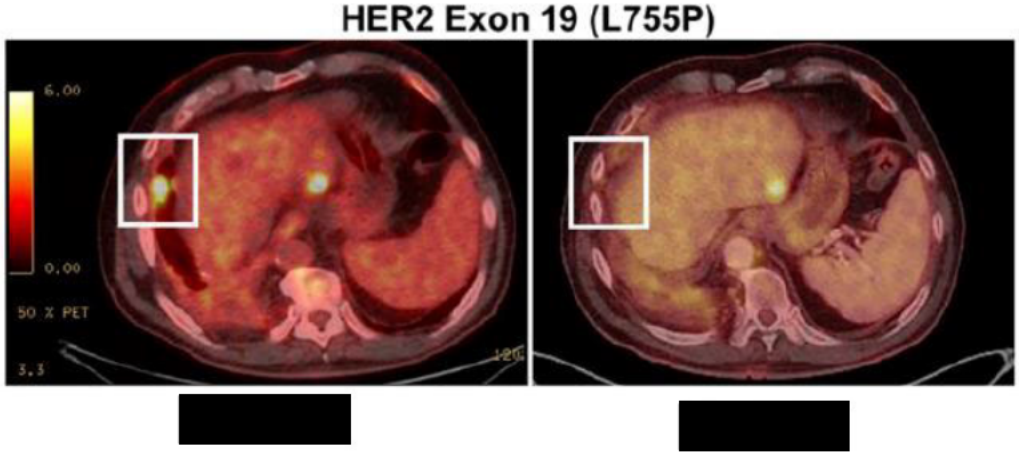
The second case was a [redacted]-year-old man and was a former smoker. He was diagnosed in [redacted] with adenocarcinoma of the right lower lung and underwent a right lower lobectomy. He received 4 cycles of adjuvant chemotherapy with cisplatin and pemetrexed in [redacted].

From [redacted], he had disease recurrence in the mediastinum and pleura which was biopsied and confirmed to be an adenocarcinoma. Molecular profiling diagnosed an ERBB2 (HER2) exon 19 L755P mutation. He received 6 cycles of carboplatin, pemetrexed and

trastuzumab from [redacted] until [redacted] with partial response, followed by pemetrexed, and trastuzumab maintenance until [redacted] when he developed disease progression. He started second-line nivolumab on [redacted] and had progression within 2 months. He received 3rd line therapy with afatinib. By [redacted], the patient developed disease progression and started 4th line T-DM1 (trastuzumab emtansine). On [redacted], he developed further disease progression in the lungs, pleura, and hilar lymph nodes.

This patient started a compassionate treatment with poziotinib at 16 mg daily on [redacted]. On [redacted], his CT scan showed lesion size reduction by 12% per RECIST. His stable disease condition was confirmed by the subsequent CT test on [redacted]. He had poziotinib dose reduction to 12 mg on [redacted], due to diarrhea and skin rash. He remained on poziotinib with disease control until [redacted] when PET scan showed disease progression and poziotinib was discontinued. The patient is clinically well and is dispositioned to receive further systemic therapy (**Figure 15**)(J. Heymach's unpublished data).

Figure 15 PET Scans of the Patient At 1 Day Before and 4 Weeks After Poziotinib Treatment



1.1.2.5.2 Overview of Safety

Overall, 1143 patients have received poziotinib in 21 clinical studies (12 sponsored by Hanmi, 8 Sponsored by Spectrum, and 1 by MD Anderson Cancer Center) at doses ranging from 0.5 mg to 32 mg QD on an intermittent dosing schedule or 10 mg to 24 mg QD on a continuous dosing schedule. Combined, more than 500 patients have been treated orally with 16 mg QD as their starting daily dose representing a large safety dataset for this rare mutation.

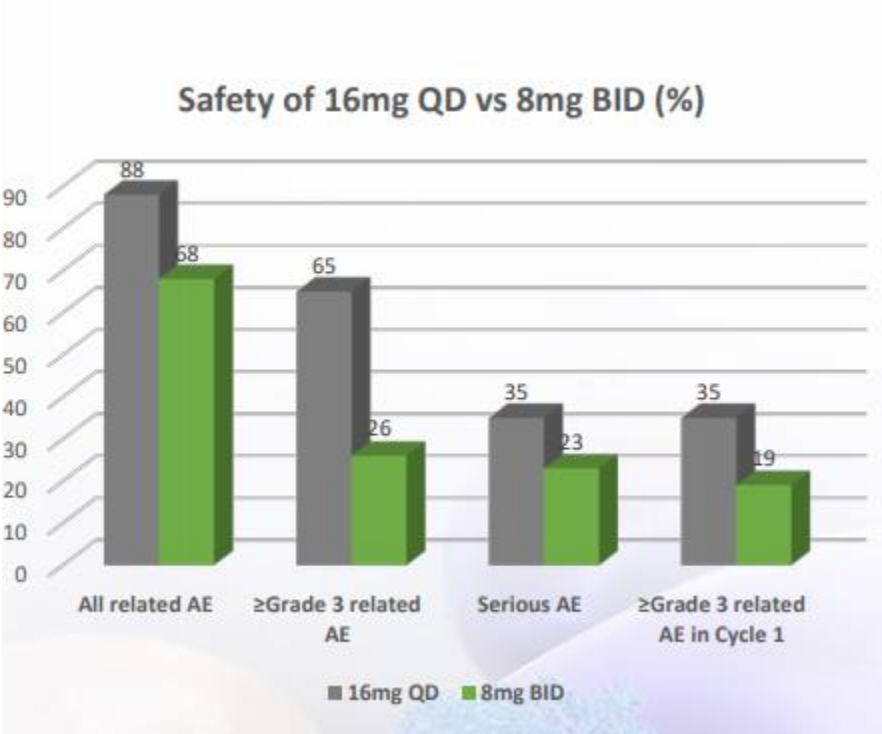
In **SPI-POZ-201**, a phase 2 study of patients with HER2-positive metastatic breast cancer, as of the cutoff date 12 Dec 2017, 32 (97.0%) patients in Cohort 1 have experienced treatment-emergent adverse events. The most common adverse event in Cohort 1 was diarrhea (87.9%), followed by rash (60.6%). In Cohort 1, 13 (39.4%) patients experienced serious adverse events.

In **SPI-POZ-202**, a phase 2 study of patients with locally advanced or metastatic non-small cell lung cancer with EGFR or HER2 exon 20 mutations, as of the cutoff date, 29 Jul 2018, 30 (96.8%) patients in Cohort 1 and 16 (84.2%) patients in Cohort 2 have experienced treatment-emergent adverse events. The most common TEAEs in Cohort 1 were also diarrhea (74.2%),

stomatitis (64.5%), and rash (48.4%). The most common TEAEs in Cohort 2 were diarrhea (73.7%), stomatitis (47.4%), and rash (52.6%). Diarrhea, stomatitis, and rash were also the most common treatment-related TEAEs in both cohorts.

In SPI-POZ-202, Cohort 5, poziotinib is being administered at varying doses (10 mg QD, 6 and 8 mg BID) to patients with NSCLC with EGFR and HER2 mutations. Patients treated with 8 mg BID have demonstrated improved tolerability and safety as compared to once daily dosing with 16 mg QD. As shown in **Figure 16**, patients treated with 8 mg BID had reduced treatment emergent ≥Grade 3 AES and treatment-related AEs [Le et al, 2021]. Preliminary response data also showed improved anti-tumor activity with 8 mg BID dosing compared to 10, 12, 16 mg QD or 6 mg BID. Patients are continuing to be enrolled at the 8 mg BID starting dose.

Figure 16 Safety Comparison of 16 mg QD vs 8 mg BID



1.2 Rationale for the Current Study

Many solid tumors, including lung, breast, bladder, head and neck, and other gastro-intestinal cancers, are associated with either an activating mutation in or overexpression of members of the ErbB receptor family, especially EGFR and HER2 **[2]**. Treatments that specifically target HER2 overexpression have been shown to be particularly beneficial to breast cancer patients and several targeted therapies have been approved by the FDA to treat EGFR mutant NSCLC. However, to date, excluding NSCLC, there are no FDA-approved targeted therapies for EGFR or HER2 mutant solid tumors. The results of nonclinical *in vitro* and *in vivo* studies indicate high sensitivity of both EGFR and HER2 activating mutations (including exon 20 insertion,

other point mutations in the kinase domain) across tumor types to poziotinib, a novel oral, irreversible pan-HER inhibitor (**[10]**, **[4]** and Study Report Dv-0080). Clinical efficacy and safety data obtained to date indicate that poziotinib may be beneficial to patients with lung and breast cancers that harbor EGFR or HER2 mutations (**[5]**, **[6]** and Case Reports in Section **1.1.2.5.1**). Based on the Phase 1 study, HM-PHI-102, the recommended Phase 2 dose is 16 mg daily. Combined, more than 260 patients have been treated with 16 mg as their starting dose. Poziotinib was well tolerated by majority of patients. Therefore, the current multi-center basket study is planned to evaluate 16 mg daily poziotinib in patients with EGFR and HER2-mutatation positive solid tumors in 5 different cohorts.

2 STUDY OBJECTIVES

2.1 Primary Objective

- To evaluate the Objective Response Rate (ORR) of poziotinib in patients with EGFR or HER2 mutation-positive malignant solid tumors

2.2 Secondary Objectives

- To evaluate other efficacy variables of poziotinib in patients with EGFR or HER2 mutation-positive, malignant solid tumors, including the following:
  - Duration of Response (DoR)
  - Disease Control Rate (DCR)
- To evaluate the Safety and Tolerability of poziotinib in patients with EGFR or HER2 mutation-positive malignant solid tumors

2.3 Exploratory Objectives

- To evaluate the following additional efficacy outcomes:
  - ORR, DCR, and DoR in patients with baseline CNS metastases
  - Overall Survival (OS) and Progression-free Survival (PFS)
  - Relationship between molecular biomarkers and clinical outcome

3 INVESTIGATIONAL PLAN

3.1 Study Design and Treatment Plan

This is a Phase 2 multicenter, open-label study to evaluate the efficacy and safety of poziotinib in patients with eligible EGFR or HER2 mutation-positive malignant solid tumors.

The study is a basket trial with five patient cohorts. The primary analysis will be conducted for each cohort separately. The five patient cohorts are:

- **Cohort 1:** Patients that have HER2-positive or HER2-negative breast cancer with HER2 activating mutations (see **Table A** in Section **4.1**) (N=30) (See **Inclusion Criteria #4**)
- **Cohort 2:** Patients that have colorectal cancer with HER2 activating mutations (see **Table A** in Section **4.1**) (N=30)

- **Cohort 3:** Patients that have solid tumors (except NSCLC, breast cancer, or colorectal cancer) with HER2 activating mutations (see **Table A** in Section **4.1**) (N=30)
- **Cohort 4:** Patients that have GBM with EGFR activating mutations (see **Table A** in Section **4.1**) (N=30)
- **Cohort 5:** Patients that have solid tumors (except NSCLC or GBM) with EGFR activating mutations (see **Table A** in Section **4.1**) (N=30)

This study includes a two-stage design in each cohort separately. The first-stage of each cohort will enroll 9 patients. Details of the two-stage design are provided in the statistical section. A cohort will enroll patients into the second-stage if the required responses are observed in 9 patients in the first-stage for each cohort.

The **Screening** period (Day -30 to Day 1) lasts up to 30 days prior to Cycle 1, Day 1. Patients must provide written Informed Consent prior to undergoing any study procedure. Patients must meet all Inclusion/Exclusion Criteria to participate in the study. Each treatment cycle is 28 calendar days in duration, regardless of dosing interruptions. Tumor assessments are scheduled at Baseline/pre-dose, Week 4, Week 8 and every 8 weeks thereafter. In the event of a response (PR or CR), a confirmatory scan may be performed 4 weeks from the initial response. Pre-dose tumor assessments must be within 14 days prior to Cycle 1, Day 1 (Baseline assessments may be used if obtained within 14 days prior to Cycle 1, Day 1).

The treatment period for all patients will be from the time of the first dose of poziotinib to the first occurrence of disease progression, intolerable adverse events, the start of a new anti-cancer treatment, or death.

Following radiological progression, the patient may continue to receive poziotinib in an Extension Study (SPI-POZ-501) only if the following criteria are met**:** absence of signs and symptoms indicating clinical deterioration due to progression of disease or drug toxicity and no decline in ECOG or performance status or if the investigator and medical monitor agree that the patient continues to derive clinical benefit. Disease imaging assessments must continue at the institutional standard of care interval. In addition, the patient will be made aware of other therapeutic options and reconsented if their decision is to continue poziotinib.

SPI-POZ-501 Extension Study: Patients who wish to participate in the extension study must provide written Informed Consent. Treatment will begin after the patient has completed the End-of-Treatment (EOT) Visit in the Original Study (ie visit in SPI-POZ-203 study). Assessments obtained at the EOT visit in the Original Study will serve as Baseline data for the extension study.

Patients will continue to receive poziotinib at the last dose level and schedule received in the POZ-203 study. Poziotinib dose modifications will be allowed under the treating physician's discretion after consultation and approval from the Spectrum medical monitor.

Safety will continue to be followed during the extended treatment according to Standard of Care (SOC). Efficacy of continued poziotinib treatment will be evaluated by imaging according to the Institution's SOC, but at least every 2 cycles.

A patient may continue to receive poziotinib treatment as long as the patient is deriving clinical benefit, as judged by consensus of the investigator and Spectrum medical monitor, or until withdrawal of consent, unacceptable toxicity, the patient is lost to follow-up, poziotinib receives commercial approval in their country of residence, or development of poziotinib is terminated by

the Sponsor, whichever occurs first. There will be an End-of-Treatment (EOT) Visit 30 (±5) days after the last dose of poziotinib.

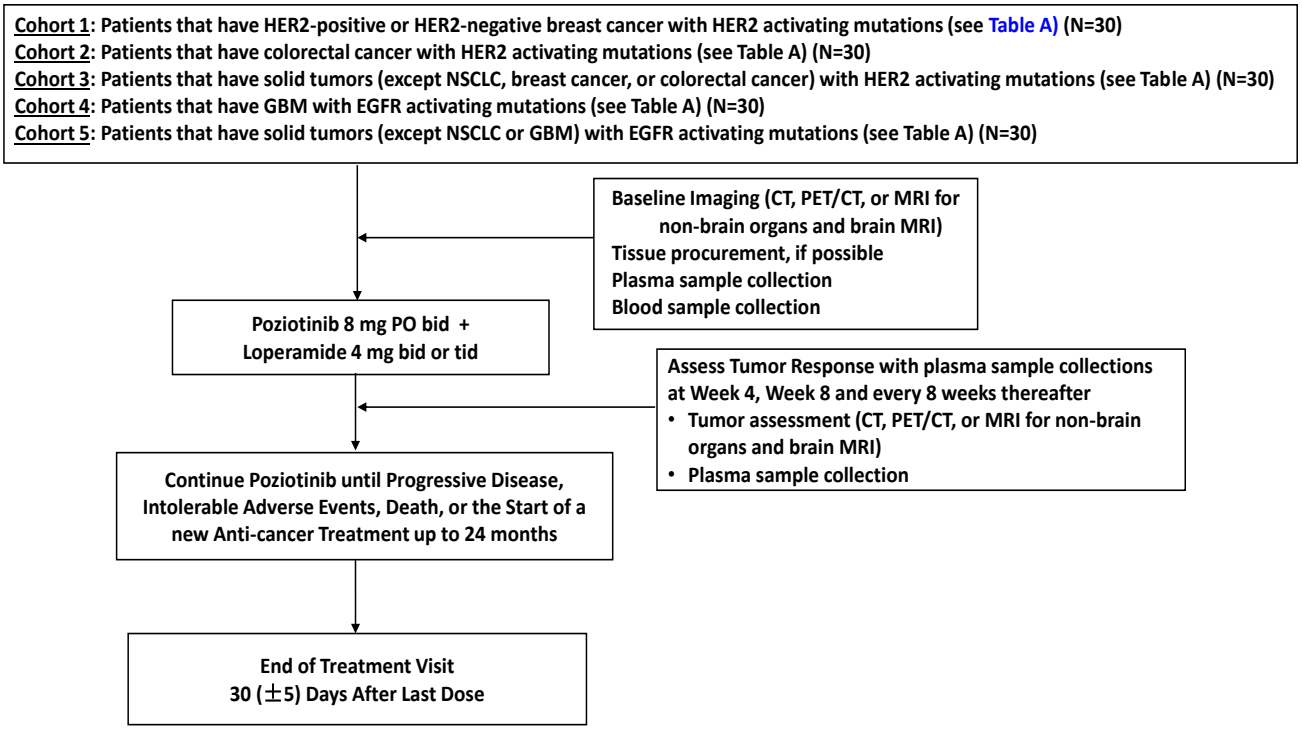
3.2 Study and Treatment Duration

The total duration of the study will be approximately 4 years although patients will be treated until meeting a discontinuation criterion. The duration of study participation for each patient includes the following:

- **Screening Period:** Up to 30 days
- **Treatment Period:** 28 days per cycle or until death, intolerable adverse events, progressive disease or other protocol-specified reasons for patient withdrawal
- **End-of-Treatment Visit:** 30 (±5) days after the last dose of poziotinib
- **Long-Term Follow-up:** After treatment period discontinuation in Study SPI-POZ-203, 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 study design diagram is presented in **Figure 17** and the Schedule of Study Assessments and Procedures is presented **Appendix 1**.

Figure 17 Diagram of Study Design



4 PATIENT POPULATION

The following inclusion and exclusion criteria must be met in order to participate in the study.

4.1 Inclusion Criteria:

1. Males or females 18 years of age or older
2. Patient must be willing and capable of giving written Informed Consent, adhering to dosing and visit schedules
3. Patient has an advanced or metastatic solid tumor with no available standard therapy option
4. Patients with breast cancer must have an NGS HER2 activating mutation (see Table A), and:
   - IHC HER2-positive tumors (based on ASCO/CAP criteria) are included only when they have progressed on trastuzumab, pertuzumab, and T-DM1 which have been administered in the metastatic setting, unless disease recurred within 12 months of adjuvant or neoadjuvant treatment.
   - IHC HER2-negative, ER/PR-positive breast cancer (based on ASCO/CAP criteria) may be included after 1st line endocrine therapy in the metastatic setting, either as a single agent or in combination with standard biological agents (eg aromatase inhibitor and CDK 4/6 inhibitor). Patients are permitted to continue single agent endocrine therapy concurrently with the study.
   - IHC HER2-negative, ER/PR-negative tumors may be included after first-line treatment (any standard chemotherapy-based regimen) in the metastatic setting.
5. Patient with colorectal cancer who are MSI-H and have confirmed progression on pembrolizumab or nivolumab or nivolumab/ipilimumab
6. Patient's tumor is positive for eligible EGFR or HER2 mutations based on DNA genetic testing of either tumor tissue or plasma samples. Patients with documented EGFR or HER2 mutations are identified by local testing from participating sites using next generation sequencing (NGS) test such as OncoMine Comprehensive Assay (OCA), Guardant360 Assay, or FoundationOne Assay that detects specific mutations, performed by a US CLIA certified and CAP accredited clinical laboratory or similarly accredited lab for ex-US sites using tissue or plasma samples. Patient has a solid tumor with at least one of the listed activating mutations (see **Table A**):
   - Cohort 1: Patients that have HER2-positive or HER2-negative breast cancer with HER2 activating mutations (see **Table A**) (N=30) (See **Inclusion Criteria #4**)
   - Cohort 2: Patients that have colorectal cancer with HER2 activating mutations (see **Table A**) (N=30)
   - Cohort 3: Patients that have solid tumors (except NSCLC, breast cancer, or colorectal cancer) with HER2 activating mutations (see **Table A**) (N=30)
   - Cohort 4: Patients that have GBM with EGFR activating mutations (see **Table A**) (N=30)
   - Cohort 5: Patients that have solid tumors (except NSCLC or GBM) with EGFR activating mutations (see **Table A**) (N=30)

Table A—List of Activating Mutations Eligible for Enrollment

	Activating Mutations
Cohorts 1-3: HER2 Activating Mutations (at least one of the following)	
Furin-Like/Extracellular	S310F/Y
Transmembrane	I655V, V659E, R678Q, V697L
Kinase Domain	Exon 20 insertion, T733I, L755X, I767M, D769X, V773M, V777X, L786V, V842I, T862I, L869R
Cohorts 4-5: EGFR Activating Mutations (at least one of the following)	
Extracellular & Transmembrane	EGFRvIII, R108K, R222C, A289T, P596L, G598V
Kinase Domain	Exon 20 insertion, E709X, E709_T710del insD, L718X, G719X, I740_K745dupIPVAIK, I740_K745dup, V742I, L747X, E746_A750del, A750P, S768I, S768I/V769L, S768I/V774M, L833V, V769M, V774M, R831C, R831H, L858R, L861Q, A864V

7. Patient has measurable disease, as per the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) and/or RANO Criteria for **Cohort 4**. Target lesion(s) must be radiographically measurable. CNS metastatic lesions cannot be considered target lesions in **Cohorts 1-3** and in **Cohort 5**.
8. Brain metastases may be allowed if the patient's condition is stable. Stable condition is defined as having stable neurological symptoms, with no requirement for anti-seizure medications or >2 mg/day dexamethasone equivalent or increasing doses of systemic corticosteroids (except **Cohort 4** where anti-seizure medication [Keppra] and dexamethasone up to or equivalent to 4 mg daily is allowed), and no evidence of CNS disease progression documented for at least 4 weeks after CNS-directed treatment (eg. whole brain radiation), as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period. Patients must complete CNS-directed treatment and return to stable condition prior to eligibility assessment for the study. For patients who have had radiation therapy, post-treatment MRI tests should show no increase in brain lesion size/volume and no new lesions compared to pre-treatment MRI (except **Cohort 4**) for at least 4 weeks. A new lesion is defined as lesion size greater than 5 mm and not previously present.
9. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
10. Patient has recovered from prior systemic therapy for advanced or metastatic disease to Grade ≤1 for non-hematologic toxicities (except for Grade ≤2 peripheral neuropathy or alopecia) and has adequate hematologic, hepatic, and renal function at Baseline, as defined by:
    - Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L
    - Platelet count $\geq 75 \times 10^9$/L
    - Hemoglobin ≥9.0 g/dL
    - Total bilirubin ≤1.5×ULN; if hepatic metastases are present, ≤2.0×ULN

- Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) ≤2.5×upper limit of normal (ULN); if hepatic metastases are present, ≤5.0×ULN
- Creatinine clearance
    - Creatinine clearance ≥ 50 mL/min (calculated according to Cockcroft and Gault formula: CCr = {((l 40–age) x weight)/(72xSCr)}) x 0.85 (if female), Scr in mg/dL)

      or
    - GFR >= 45 ml/min/1.73m^2 as calculated by the CKD-EPI Creatinine Equation (2009) (https://www.kidney.org/professionals/kdoqi/gfr_calculator)

11. Patient with childbearing potential 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 serum pregnancy test within 7 days prior to study treatment. Females who are postmenopausal do not require this test (Postmenopausal is defined as any of: age ≥60 years, age <60 years and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range, or prior bilateral oophorectomy, or if taking tamoxifen or toremifene, or age <60 years with FSH and plasma estradiol in postmenopausal ranges).

4.2 Exclusion Criteria:

1. Patient has primary tumors in central nervous system (CNS), meningeal carcinomatosis, leptomeningeal carcinomatosis, spinal cord compression, or unstable brain metastasis except if qualified under inclusion criteria for Cohort 4.
2. Patients with the T790M mutation in EGFR.
3. Patients with breast or gastric cancers without eligible HER2 mutations (see **Table A**).
4. Patient has received anticancer chemotherapy, biologics, immunotherapy, targeted therapy (including HER2 targeted therapy), curative-intent radiotherapy, or other investigational treatment within 15 days of study entry. Palliative local radiation therapy for bone metastasis may be allowed. Standard and approved hormonal therapies for hormonal receptor positive tumors are allowed. For Cohort 4, patients who have received prior single agent VEGF inhibitor therapy (eg bevacizumab) are excluded.
5. Patient has used or will continue to use strong inhibitors/inducers of CYP3A4 and CYP2D6 within 2 weeks prior to or during the study.
6. Patient has not recovered (i.e, > Grade 1) from drug-induced pancreatitis or has a history of drug-induced pancreatitis.
7. Patient has interstitial lung disease (ILD) or history of ILD or pneumonitis or is less than 30 days from last dose of CPI.
8. Patient has ≥ Grade 2 skin disorders (rash), mucositis, or stomatitis within previous 15 days.

9. 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.
10. Patient has a high risk of cardiac disease, as determined by the Investigator. If patient is deemed to have a high cardiac risk, enrollment may be considered if echocardiogram (ECHO) or multi-gated acquisition (MUGA) during **Screening** demonstrates a cardiac ejection fraction >50%.
11. Patient has a QTc > 470 ms.
12. Patient has a history of other malignancies within the last 1 year, except for non-melanoma skin cancer, carcinoma in situ of the cervix, or PSA-stable, asymptomatic early stage prostate cancer or superficial bladder cancer without active treatment.
13. Patient has clinically significant or recent acute gastrointestinal disease presenting as diarrhea and/or coloenteritis as the main symptom (i.e. acute enteritis, malabsorption, or Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) Grade 2 or higher diarrhea due to other drug-related reasons within 15 days.
14. Patient is unable to take drugs orally due to disorders that may affect gastrointestinal function or has malabsorption syndrome.
15. Patient has an active liver disease or biliary tract disease (except for Gilbert's disease, asymptomatic biliary stones, liver metastasis, or stabilized chronic liver disease).
16. Patient has a medical condition that in the opinion of the investigator or medical monitor would put her/him at an unreasonable risk during the trial.
17. Patient has known hypersensitivity to poziotinib or history of allergic reactions attributed to a compound of similar chemical composition to poziotinib.
18. Patient has an active or uncontrolled infection, active bleeding disorder, any underlying medical condition, or other serious illness that would impair the ability of the patient to receive protocol treatment.
19. Patient has had recent major surgery or invasive procedure within 15 days prior to starting study treatment.
20. Patient is pregnant or breast-feeding.

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 the study due to the following reasons:

- Development of an adverse event (AE) that interferes with the patient's participation
- Initiation of non-protocol therapy
- Development of progressive disease (PD)
- Patient withdrawal of informed consent
- Delay of poziotinib administration for >28 days since last study drug 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 an End-of-Treatment Visit 30 (±5) days after the last dose of poziotinib or prior to beginning a new treatment, whichever is first. If death is recorded as the reason for study discontinuation, the cause of death should be recorded on the CRF. Patients not efficacy evaluable i.e. not completed at least 1 cycle of poziotinib treatment and have baseline and at least 1 post-baseline tumor response evaluation using RECIST, version 1.1 (and/or RANO for **Cohort 4**) will be replaced unless they have discontinued from treatment or from the study due to disease progression or probable disease progression (eg. clinical progression, initiation of new therapy) or due to toxicity.

5 STUDY PROCEDURES

Refer to the Schedule of Study Assessments and Procedures presented in **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.

Patients must have disease that is resistant to or relapsed following available standard systemic therapy (according to NCCN or ASCO guidelines), or for which there is no standard systemic therapy or reasonable therapy in the physician's judgment likely to result in clinical benefit or if such therapy has been refused by the patient. Documentation of the reason must be provided for patients who have not received a standard therapy likely to result in clinical benefit.

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

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 hyphenated 3-digit patient sequential number, unique to a site, separated by a hyphen (i.e., 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 Visit (Within 30 Days of Cycle 1, 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.

- Informed Consent
- Patient ID
- Relevant medical history
- Demographic data
- Height and weight
- Complete physical examination
- Vital signs
- Eastern Cooperative Oncology Group (ECOG) Performance Status assessment
- Pregnancy test (blood beta-human chorionic gonadotropin [β-HCG]) in women of childbearing potential
- Tumor assessment: **Screening** tumor assessment for patient eligibility will be based on scans performed locally within 30 days before the patient signed the ICF; **Baseline** tumor assessment (either CT, PET/CT, or MRI for non-brain organs and brain MRI) will be performed within 2 weeks prior to, or on **Cycle 1**, **Day 1**
- Tumor histopathology report (from local pathologist) and molecular test report for mutation diagnosis
- 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 prior to poziotinib administration (may be obtained up to 7 days prior to **Cycle 1**, **Day 1**)
- 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)
- Tissue sample (from archival or fresh biopsy) or plasma for tumor genotyping
- Plasma sample for biomarker analysis
- Whole blood sample for pharmacogenomic analysis
- Adverse event assessment using NCI CTCAE, version 5.0. Only study-related SAEs to be recorded during **Screening**
- Concomitant medication review

5.3.2 Treatment Period – Cycle 1, Day 1

- Eligibility confirmation
- Height and 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
- Intense pharmacokinetic sampling (see schedule of sampling in section **5.4.6**)
- ECG before each PK sampling
- Dispense poziotinib and loperamide
- Adverse event assessment using NCI CTCAE, version 5.0
- Dispense Patient Diary
- Concomitant medications review

5.3.3 Treatment Period – Cycle 1, Days 8 and 15 (±3 Days)

- Physical exam
- Vital signs
- Complete blood count with 5-part differential and platelets
- Intense pharmacokinetic sampling can occur only on C1D8 +/- 3 days (see schedule of sampling in section **5.4.6**)
- ECG before each PK sample on Day 8 only
- Adverse events using NCI CTCAE, Version 5.0
- Patient Diary Review
- Concomitant medications review
- Contact patient by telephone calls between Day 3- 8 for any AE, such as skin rash and diarrhea, and take action according to **Appendices 3, 4, and 5**

5.3.4 Treatment Period – Cycle 1, Day 22 (±2 Days) (By Telephone)

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

5.3.5 Treatment Period – Cycle 2, Day 1

- Height and Weight
- Physical examination
- Vital Signs
- ECOG Performance Status assessment
- Urine pregnancy test in women of childbearing potential
- Tumor assessment: either CT, PET/CT, or MRI for non-brain organs and brain MRI (the same imaging acquisition method as the baseline should be used)
- Complete blood count with 5-part differential

- Serum chemistry
- Plasma sample for biomarker analysis
- Dispense poziotinib and loperamide
- Adverse event assessment using NCI CTCAE, Version 5.0
- Dispense and Collect Patient Diary
- Concomitant medications review

5.3.6 Treatment Period – Cycle 2, Day 8 (±1 Day)

- Complete blood count with 5-part differential and platelets
- Adverse event assessment using NCI CTCAE, Version 5.0; a telephone call to patient for the follow up of AEs between Days 3 to 8
- Patient Diary review
- Concomitant medications review

5.3.7 Treatment Period – Cycle 3+, Day 1

- Weight
- Physical examination
- Vital Signs
- ECOG Assessment
- Urine pregnancy test in women of childbearing potential
- Tumor assessment: either CT, PET/CT, or MRI for non-brain organs and brain MRI (unless the patient has documented disease progression or has undergone a tumor assessment with the previous 8 weeks; the same imaging acquisition method as the baseline should be used)
- Complete blood count with 5-part differential
- Serum chemistry
- Plasma sample for biomarker analysis
- Dispense poziotinib and loperamide
- Adverse event assessment using NCI CTCAE, Version 5.0
- Dispense and Collect Patient Diary
- Concomitant medications review

5.3.8 End-of-Treatment Visit (30 [±5] Days After Last Dose of Study Treatment)

The **End-of-Treatment Visit** is required 30 (±5) days after the last dose of poziotinib is administered. The following assessments are to be performed at this visit:

- Height and Weight
- Physical examination
- Vital signs

- ECOG Performance Status assessment
- Urine pregnancy test in women of childbearing potential
- Tumor assessment (either CT, PET/CT, or MRI for non-brain organs and brain MRI (unless the patient has documented disease progression or has undergone a tumor assessment within the previous 8 weeks; same imaging acquisition method as the baseline should be used)
- CBC with 5-part differential and platelets
- Serum chemistry
- Newly biopsied tumor tissue taken from patients who progress for biomarker analysis (optional, but encouraged)
- Plasma sample for biomarker analysis if the patient progresses (optional)
- Adverse event assessment using NCI CTCAE, Version 5.0
- Patient Diary Collection
- Concomitant medications review

5.3.9 Long-Term Follow-up – Every 3 Months

- After progressive disease is documented, regardless of possible treatment continuation, patients who have consented will be contacted by phone or email (or letter if specifically requested) 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 Visit**, the patient's relevant medical history will be collected, to include 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 Visit, Cycle 1, Days 1, 8,** and **15** and **Day 1** of each subsequent cycle, and **Day 1 of each cycle**, and at the **End-of-Treatment 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, Days 1, 8, and 15 and Day 1 of each subsequent cycle and at the End-of-Treatment 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 End-of-Treatment Visit.

5.4.5 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 and Day 8 of Cycle 1 and Cycle 2, Day 1 of each cycle, and at the End-of-Treatment 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, uric acid, and glucose, will be performed at Screening Visit, Day 1 of each cycle, and at the End-of-Treatment 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 blood β-hCG test will be performed for all women of childbearing potential at **Screening**. A urine pregnancy test is required on Day 1 of each Cycle starting from **Cycle 2** and at **Cycle 1**, **Day 1**, if Screening pregnancy test was more than 7 days prior to **Day 1**. Urine pregnancy test also required at **End-of-Treatment Visit**.

5.4.6 PK Sample

At select study centers, up to 25 patients may be specifically consented for intensive PK sampling and concurrent ECGs as defined below:

Schedule: Intensive PK blood sampling will be at pre-dose and 2, 4, 8, 12, and 24 hours post-dose on **Cycle 1**, **Day 1** and on **Cycle 1**, **Day 8 (±3 days)**. The 12-hour and 24-hour PK samples must be collected prior to the second daily dose. A local 12-lead ECG will be obtained just before each PK blood sample on both Day 1 and Day 8. If the patient has interrupted continuous poziotinib dosing, clear dosing documentation must be done in order to assess suitability of further PK sampling and ECG recording.

In addition, if a patient presents with a potentially drug-related Grade ≥3 AE, a PK sample should be collected as soon as possible, if feasible, following the onset of the AE in order to characterize the PK. Documentation of last dose timing prior to the event is required.

5.4.7 Electrocardiogram (ECG)

A 12-lead ECG will be performed at **Screening**. At select study centers, up to 25 patients may be specifically consented for intensive PK sampling and concurrent ECGs as defined below:

Schedule: Intensive PK blood sampling will be at pre-dose and 2, 4, 8, 12, and 24 hours post-dose on **Cycle 1**, **Day 1** and on **Cycle 1**, **Day 8 (±3 days)**. The 12-hour and 24-hour PK samples must be collected prior to the second daily dose. A local 12-lead ECG will be obtained just before each PK blood sample on both Day 1 and Day 8. If the patient has interrupted continuous poziotinib dosing, clear dosing documentation must be done in order to assess suitability of further PK sampling and ECG recording.

In addition, if a patient presents with a potentially drug-related Grade ≥3 AE, a PK sample should be collected as soon as possible, if feasible, following the onset of the AE in order to characterize the PK. Documentation of last dose timing prior to the event is required.

5.4.8 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 institutional standard of care.

5.4.9 Tumor Assessment

Tumor assessment for study patient's eligibility must be performed by Investigators using computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI) for non-brain organs and MRI for brain at **Screening** up to 30 days prior to **Cycle 1**, **Day** 1. Imaging studies performed prior to the signing of Informed Consent as part of the site's routine standard of practice are allowed at the discretion of the Sponsor as the Screening assessment. Brain MRI must be performed to assess the brain metastasis status at the screening per eligibility criteria. This information is to be discussed with the Sponsor's Medical Monitor before the patient is enrolled in the study. **Baseline** tumor assessment will be performed within 2 weeks prior to, or on **Cycle 1**, **Day 1.** Post-Baseline tumor assessments must be performed at **Cycle 2 Day 1**, at **Cycle 3 Day 1**, and every 8 weeks thereafter until patient discontinuation.

Each subsequent tumor assessment must use the same radiologic technique as in Baseline, either CT, PET/CT, or MRI. Tumor assessments will be made according to RECIST, version 1.1 **[14]** using appropriate radiologic imaging or other techniques. For radiographic assessment, CT, PET/CT, or MRI must be performed at every assessment.

In Cohort 4, tumor assessments will be made using appropriate radiologic imaging techniques as per RECIST 1.1 and/or the RANO criteria **[15]**.

Measurable and non-measurable lesions should be documented appropriately.

Tumor assessment is based on the study investigator's assessment with local radiology review and report according to the RECIST 1.1 and/or RANO (for **Cohort 4**) criteria for response evaluation.

5.4.10 Tissue, Plasma, and Whole Blood Samples Retained

5.4.10.1 Tissue Samples

Tissue samples at **Screening**, if available, are acquired prior to **Cycle 1**, **Day 1** during the screening period. If possible, tumor tissue samples from a biopsy when progression occurs during the study should be collected. This is not mandatory but is encouraged. The tumor tissue will be used for genetic analysis (DNA and or RNA sequencing) to understand poziotinib response and resistance mechanisms.

5.4.10.2 Plasma Samples

Plasma samples are required at baseline (prior to start of study treatment), and optional on the day of each on-study imaging session, beginning at the 8-week imaging session, once every 8 weeks with imaging scan. The plasma samples will be used for genetic analysis (DNA sequencing) to understand poziotinib response mechanism and progression of disease. Guardant's 360 or FoundationACT assays will be used, Plasma sample collection and storage will follow vendors' standard procedures as described in the vendors' Laboratory Manual.

5.4.10.3 Whole Blood Samples

Whole blood samples will be collected once at **Screening** or during the study for pharmacogenomic analysis.

5.4.11 Concomitant Medications

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

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

All prescription and over-the-counter medications at trial entry as well as any new medications started during the trial must be documented on the CRF and in the source documents. The documentation should continue until 30 (±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.

5.4.11.1 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 1)**. 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 1**) 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 1 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

5.4.11.2 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.

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

5.4.11.2.1 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 3**.

5.4.11.2.2 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 a 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, a combination of viscous lidocaine 2% + Mylanta + diphenhydramine elixir + prednisolone solution)

5.4.11.2.3 Rash Management

Rash may be managed according to the algorithm in **Appendix 4** and/or per standard of care as determined by the Investigator or Institutional Guidelines.

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

5.4.11.2.4 Paronychia management

Paronychia may be managed according to the algorithm in **Appendix 5** and/or per standard of care as determined by the Investigator or Institutional Guidelines

5.4.11.3 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.

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.

5.4.11.4 Prohibited Therapies or Medications

No other anti-cancer therapy, including chemotherapy, radiation therapy, immunotherapy, target therapy (including HER2 targeted therapy), biologics, or experimental medications, are permitted during the trial with the exception of focal radiation therapy for bone pain palliation. Any disease progression that requires anti-tumor therapy will be a 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 and Formulations

The poziotinib drug substance is a hydrochloride salt of poziotinib and is formulated as a tablet for oral administration. Poziotinib tablets are supplied in 2.0-mg and 8.0-mg dose strengths and contain 2.0 mg and 8.0 mg of poziotinib hydrochloride salt, respectively.

6.1.2 Poziotinib Administration

Poziotinib is supplied as 8-mg and 2-mg tablets and will be administered on an outpatient basis orally twice daily.

Dosing Regimen

The starting dose of poziotinib is 8 mg twice per a day (BID). Poziotinib will be self-administered by the patient orally, with food and a glass of water, at approximately the same time(s) each day during each 28-day cycle.

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, it should be taken once remembered or with the next dose if on the same day.

6.1.3 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.

6.1.4 Poziotinib Dose Modification Recommendations

If needed, the initial dose (8 mg BID) may be reduced by 2 mg for each dose (ie 12 mg per day divided into 6 mg BID doses) at the Investigator's discretion and the Sponsor should be notified. If further dose reduction is required, the next dose should be reduced by a total of 2 mg/day (ie 10 mg per day dived into a 6 mg and 4 mg dose per day) and the Sponsor should be notified. Any further reductions in dose must be discussed a priori with the Sponsor's Medical Monitor and approval is required.

No dose reductions below 8 mg total dose/day are allowed.

Table 2 Poziotinib Dose Modifications 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 ~1 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 4**.	

Related Adverse Event	Grade	Occurrence	
		1	Each Additional Occurrence
LVEF Dysfunction	Grade ≥3	Discontinue Treatment	

a) Supportive medications, including early steroid use, should be considered even in the presence of low-grade "on-target" toxicity (eg, rash, diarrhea)(**Appendix 4**).

6.2 Comparator Treatment

No comparator is 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 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 6.1.4**.

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 the 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 5.0 for AE grading.

7.2 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. A treatment-emergent AE (TEAE) is any AE that occurs from the first dose of study treatment until 30 (±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 (e.g., 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 (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence does not occur (e.g., 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 does not worsen
- Planned and prescheduled hospitalizations and procedures
- Progressive disease

The adverse events of special interest identified with poziotinib treatment include diarrhea, skin rash, stomatitis, paronychia, and pneumonitis.

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 30 (±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 30 (±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 30 (±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 5.0 for AE grading.

7.4 Follow-up of Adverse Events

All AEs and significant abnormal laboratory values are to be followed up in accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and other applicable regulatory requirements (e.g., United States [US] Code of Federal Regulations [CFR]). All AEs that are ongoing during the treatment period will be followed up for 30 (±5) days from the date of the last dose of poziotinib.

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 3**).

Table 3 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/Dermatitis acneiform
- Stomatitis/Mucosal inflammation
- Paronychia
- Decreased Appetite
- Dry Skin
- Vomiting
- Pruritus

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: i.e., 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 or substantial disruption of the ability to conduct normal life functions
- 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, only SAEs are to be recorded. All SAEs that occur from the first dose of study drug administration through 30 (±5) days after the last dose of study treatment and SAEs that occur after 30 (±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 the 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 (e.g., 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 (e.g., 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.
- Disease progression as the result of a 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 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 the study.

8 STATISTICAL PLAN

A Statistical Analysis Plan (SAP) will be provided before data base lock.

8.1 Sample Size

The statistical analysis of each cohort will be performed separately. A total of 30 patients in each cohort will be enrolled using Simon's two-stage design. The optimal two-stage design to test the null hypothesis that $p \leq 0.050$ *versus* the alternative that $p \geq 0.250$ has an expected sample size of 16.76 and a probability of early termination of 0.630. If the drug is not effective, there is a 0.049 probability of concluding that it is (the target for this value was 0.050). If the drug is effective, there is a 0.098 probability of concluding that it is not (the target for this value was 0.100). For each cohort, 9 patients will be evaluated in the first stage; the cohort will be terminated if 0 respond. If the cohort goes on to the second stage, a total of 30 patients will be studied. If the total number responding is less than or equal to 3, the cohort is closed.

8.2 Method of Treatment Assignment

This study is not randomized.

8.3 Analysis Populations

The following analysis populations will be defined.

- The **Evaluable Population (EP)** consists of all enrolled patients who completed at least 6 weeks of poziotinib treatment, and have baseline and at least 1 post-baseline tumor response evaluation using RECIST, version 1.1 (and/or RANO for Cohort 4) or

progressed prior to any post-baseline image evaluation. All efficacy analyses will also be done using the Evaluable Population.

- The **Safety Analysis Population (SAF)** includes all enrolled patients who received at least 1 dose of poziotinib. All demographics, Baseline characteristics, and safety data will be analyzed using the SAF population.

8.4 General Statistical Methods

The Sponsor's Biostatistics and Data Management group will be responsible for data management and statistical analysis of this study. All statistical analyses will be performed using SAS for Windows (Version 9.4 or higher). Patient data listings and tabular presentations of results will be provided. Further details of the criteria and conduct of the statistical analyses will be included in the SAP for this study.

8.5 Efficacy Analysis:

The primary efficacy variable ORR is the proportion of patients with confirmed Complete Response (CR) and Partial Response (PR) recorded from the start of the first dose of poziotinib to the end of study and will be analyzed descriptively along with the 95% CI for each cohort. The determination of ORR will be based upon an assessment of the local radiological review by the respective Principal Investigator using RECIST version 1.1 and/or RANO criteria (for GBM). Confirmatory assessments must be completed by the Investigator 4 weeks ± 3 days after the first assessment of CR or PR and only confirmed CR/PR can be deemed as CR/PR.

The secondary endpoints are DCR and DoR, DCR is the proportion of patients with best response of CR, PR, and Stable Disease (SD) from the first dose of poziotinib to the end of study; and DoR is the time 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.

Exploratory endpoints are OS and PFS. OS is the time from the treatment start date to the date of death during the study and PFS is the time from the treatment start date to the date of documented disease progression or death during the study.

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

8.6 Safety and Tolerability

The following variables will be summarized and analyzed descriptively for each cohort: number of completed cycles, relative dose intensity, 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 5.0.

8.7 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 5.0, and summarized by worst grade severity and by treatment.

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 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, and with the laws and regulations of the country in which the research is conducted as applicable. By signing the US Form FDA 1572, "Statement of Investigator", the Investigator commits to adhere to applicable sections of the US CFR Title 21 Parts 50 "Protection of Human Patients", 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, as well as all applicable laws and regulations, including US CFR Title 21 Part 54.

9.1.2 Institutional Review Board/Ethics Committee Approval

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

9.1.3 Informed Consent

The Investigator is responsible for preparing the written Informed Consent document for this study. The Sponsor or its designee will provide the 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 prevent unauthorized access to data, or unauthorized editing or loss of data.

9.2.1 Case Report Forms

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

9.2.2 Drug Accountability

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

The Investigator will not supply investigational study drugs to 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 vials 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. Used poziotinib vials/bottles will be destroyed per institution, local, and all applicable policies and procedures. After study conclusion, all unused vials of poziotinib may be destroyed at the site, following verification of accountability by a Spectrum 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

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

9.5.3 Publication Policy

To coordinate the dissemination of data from this study, the Sponsor encourages the formation of a publication committee consisting of the principal investigator and appropriate Spectrum 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 (e.g., 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 by the Sponsor, including nonclinical data, protocols, CRFs, information regarding poziotinib, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with the relevant CTA with Sponsor, including related to the confidentiality provisions and any right of publication granted to the Investigator in the CTA. All personnel will handle patient data in a confidential manner in accordance with applicable regulations governing clinical research and in accordance with the CTA. 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 in accordance with the procedures and requirements of the CTA. This information may be related in confidence to the IRB/EC or other committee functioning in a similar capacity. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to the Sponsor, or in confidence to the IRB/EC or similar committee, except if required by law and subject to the confidentiality and other provisions of the CTA.

10 REFERENCES

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Appendix 1

SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment	Screening (30 days prior to Day 1, Cycle 1)	Treatment Period[a] (Each Cycle=28 [±3] Days)						End of Treatment (EOT) Visit	Long-Term Follow-up
		Cycle 1[b]			Cycle 2		Cycle 3+		Every 3 months for 2 years
	Day -30 to Day 1	Day 1	Day 8±1	Day 15±3	Day 1	Day 8±1	Day 1	30 (±5) Days After Last Dose[c]	
Informed Consent	x								
Relevant Medical History	x								
Demographic Data	x								
Height and Weight	x	x			x		x	x	
Physical Examination[d]	x	x	x	x	x		x	x	
Vital signs	x	x	x	x	x		x	x	
ECOG Performance Status	x	x			x		x	x	
Pregnancy Test[e]	x	x			x		x	x	
Tumor Assessment	x[f]				x		x	x	
Tumor Histopathology Report[g]	x								
CBC with 5-part differential and platelets[h]	x	x	x		x	x	x	x	
Serum Chemistry[i]	x	x[i]			x		x	x	
Electrocardiogram (ECG)[j]	x	x	x						
Echocardiogram or MUGA Scan[k]	x								
Tissue Samples[l]	x							x	
Plasma Samples[m]	x				x		x[l]	x	
Whole Blood Sample[n]	x								
PK Samples[o]		x	x		x				
Dispense Poziotinib and Loperamide[p]		x			x		x		
Adverse Event Assessment	x[q]	x	x[r]	x	x	x[r]	x	x	x
Dispense and Collect Patient Diary		x	x		x	x	x	x	
Concomitant Medications review	x	x	x	x	x	x	x	x	
Telephone Contact[s]									x

a) Each treatment cycle is 28 days with a visit window of ± 3 day. If a visit is delayed during 1 Cycle, the subsequent schedules will be delayed sequentially.
b) Patients will be contacted by telephone on Days 3-8 and on Day 22 for assessment of adverse events.
c) An **End-of-Treatment Visit** will be performed 30 (±5) days after the last dose of poziotinib. An End of Study page will be recorded at that time.
d) A complete physical examination is required at **Screening**, **Day 1** of each Cycle, at Days 8 and 15 of Cycle 1, and at the **End-of-Treatment Visit**. Symptom-directed exams if clinically indicated are required at other visits.

e) Pregnancy test (β-HCG) in women of child-bearing potential. Blood pregnancy test is required at **Screening**. Urine pregnancy test is required on Day 1 of each Cycle starting from **Cycle 2** and at **Cycle 1**, **Day 1**, if Screening pregnancy test was more than 7 days prior to **Day 1**. Urine pregnancy test also required at **End-of-Treatment Visit**.

f) The **Screening** tumor assessment for patient eligibility will be based on scans performed within 30 days before the patient signed the ICF. Either CT, PET/CT, or MRI scans should be performed for non-brain organs and brain MRI scans should be performed locally per standard of care before the patient signed the ICF. **Baseline** tumor assessment (CT, PET/CT or MRI for non-brain and brain MRI) will be performed within 14 days prior to **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, death, intolerable adverse events (AEs), or other protocol-specified reasons for patient withdrawal.

g) Tumor histopathology report (from local pathologist) and molecular test report for mutation diagnosis.

h) Complete blood count (CBC), including white blood cells with 5-part differential, hemoglobin, and platelets, is to be obtained within 7 days prior to poziotinib administration on **Day 1** of each cycle, at which time, the patient's absolute neutrophil count $\geq 1.0 \times 10^9$/L and platelet count $\geq 75 \times 10^9$/L before administering the next dose of poziotinib. In addition, a CBC is to be performed on **Day 8** of **Cycles 1** and **2**.

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

j) ECGs will be performed at screening. At select study centers, up to 25 patients may be specifically consented for ECG as defined below:
Schedule: A local 12-lead ECG will be obtained just before each PK blood sample on both Day 1 and Day 8. If the patient has interrupted continuous poziotinib dosing, clear dosing documentation must be done in order to assess suitability of further PK sampling and ECG recording.

k) 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.

l) Tumor genotyping report from local lab is required to confirm patient mutation eligibility. Tissue sample (archival or fresh biopsy), if available, should be retained for retrospective analysis by FoundationOne CDx test. Collecting a tissue sample at progression is optional but is highly encouraged.

m) Plasma samples will be required at **Screening** and optional on the day of each on-study imaging session, beginning at the 4-week imaging session, once every 8 weeks with imaging scan and when the patient progresses for biomarker analysis. Guardant's 360 or FoundationACT assays will be used, Plasma sample collection and storage will follow vendors' standard procedures as described in the vendors' Laboratory Manual.

n) Whole blood samples will be drawn at **Screening** for pharmacogenomic analysis.

o) At select study centers, up to 25 patients may be specifically consented for intensive PK sampling as defined below:
Schedule: Intensive PK blood sampling will be at pre-dose and 2, 4, 8, 12, and 24 hours post-dose on **Cycle 1**, **Day 1** and on **Cycle 1**, **Day 8 (±3 days)**. The 12-hour and 24-hour PK samples must be collected prior to the second daily dose. If the patient has interrupted continuous poziotinib dosing, clear dosing documentation must be done in order to assess suitability of further PK sampling and ECG recording. In addition, if a patient presents with a potentially drug-related Grade ≥3 AE, a PK sample should be collected as soon as possible, if feasible, following the onset of the AE in order to characterize the PK. Documentation of last dose timing prior to the event is required.

p) Poziotinib and loperamide will be dispensed on **Day 1** of each cycle. Patients will take poziotinib orally twice daily with food and a glass of water at approximately the same times each day. Loperamide will be given prophylactically for diarrhea as follows: 4 mg twice daily (bid) to three times daily (tid or according to treating physician's instruction. .

q) Adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) and during **Screening** only study-related SAEs to be recorded.

r) Weekly calls to patients will be conducted during the Days 3 to 8 of each cycle for the first 2 cycles as a follow up of expected adverse events.

s) Patients who have consented will be contacted by phone (or email or letter if specifically requested) 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 house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 3 DIARRHEA MANAGEMENT

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; limiting instrumental ADL	- 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)**		
Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	→	- 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 - 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; limiting instrumental ADL	Increase of >=7 stools per day over baseline; 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 an increase in frequency and/or watery bowel movements.

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

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Dec, 12. 2017

Appendix 4 RASH MANAGEMENT RECOMMENDATIONS

RECOMMENDATIONS FOR ACNEIFORM RASH MANAGEMENT

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.

Appendix 5 PARONYCHIA MANAGEMENT RECOMMENDATIONS

RECOMMENDATIONS FOR PARONYCHIA MANAGEMENT

For paronychia management, at the treating investigator's discretion, the following interventions may be used based on the severity of the paronychia.

PARONYCHIA SEVERITY	INTERVENTION
Mild Paronychia ***(CTCAE Grade 1)**	
Nail fold edema or erythema; disruption of the cuticle	• Dilute white vinegar/dilute bleach soaks • Avoid trauma, wet-work, friction • Betamethasone diproprionate 0.05% lotion or gel: Apply once or twice daily to the effected nail after the soak • Clindamycin gel or gentamicin solution: Apply once or twice daily after the soak • Continue Poziotinib at the same dose level • Consider a dermatology consult
Moderate Paronychia ***(CTCAE Grade 2)**	
Local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	• If discharge from under or around the nail: Send wound discharge for culture • Betamethasone diproprionate 0.05% lotion or gel: Apply once or twice daily to the effected nail after the soak • Clindamycin gel/gentamicin solution: Apply once or twice daily after the soak • **Key intervention**: Consider consulting dermatology and chemical cautery with silver nitrate for periungual pyogenic granulomas • Consider partial nail avulsion if ingrown nail is visible. • Start antibiotics per wound culture or continue empiric Doxycycline 100 mg orally (or alternatively use Minocycline 100 mg orally) twice a day for 2-4 weeks or till resolution • Consider Poziotinib dose reduction after consultation with sponsor • Continue all CTCAE recommendations unless otherwise stated
Severe Paronychia ***(CTCAE Grade 3)**	• **Key intervention**: Consider chemical cautery with silver nitrate for periungual pyogenic granulomas

Operative intervention indicated; IV antibiotics indicated; limiting self-care ADL	→	• Consider partial or total nail avulsion if ingrown nail is visible. • Oral or IV antibiotics as per wound culture sensitivity • Hold Poziotinib • Continue all CTCAE recommendations unless otherwise stated

***CTCAE Severity**
Grading of paronychia:

Infections and Infestations **GRADE**

Adverse Event	1	2	3	4	5
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Operative intervention indicated; IV antibiotics indicated; limiting self-care ADL	-	-

Definition: A disorder characterized by an infectious process involving the soft tissues around the nail.

*CTCAE v5.0

Vinegar soaks: 1 part water to 1 part vinegar: soak 15 minutes daily

Dilute bleach soaks: 1 tablespoon bleach to 1 gallon water: soak 15 minutes daily

References:

Lacouture, ME et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer* (2011) 19:1079–1095.

Melosky, B et al. Management of egfr tki–induced dermatologic adverse events. *Curr Oncol* (2015) 22:123-132.

Version 1, Aug 2018