POZIOTINIB FOR THE TREATMENT OF PATIENTS WITH PREVIOUSLY TREATED LOCALLY ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER HARBORING HER2 EXON 20 INSERTION MUTATIONS

SPONSOR BRIEFING DOCUMENT

ONCOLOGIC DRUGS ADVISORY COMMITTEE

MEETING DATE: 22 SEPTEMBER 2022

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE

TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
AUC_{0-24h}	Area under the concentration-time curve extrapolated from time 0 to 24 hours
AUC_{0-inf}	Area under the concentration-time curve extrapolated from time 0 to infinity
BID	Twice daily
BMI	Body mass index
BOR	Best overall response
CI	Confidence Interval
C_{max}	Maximum serum concentration
CPI	Checkpoint inhibitor
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DoR	Duration of Response
%CV	Percent coefficient of variation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
HER2	Human epidermal growth factor receptor 2
IDMC	Independent Data Monitoring Committee
IIT	Investigator-initiated trial
ILD	Interstitial lung disease
IRC	Independent Review Committee
MDACC	MD Anderson Cancer Center
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NE	Not evaluable

Abbreviation	Definition
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron-emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PT	Preferred term
QD	Once daily
QLQ	Quality of life questionnaire
QoL	Quality of life
QTcB	QT Interval Corrected by Bazett's Formula
QTcF	QT Interval Corrected by Fridericia's Formula
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	Standard of care
T-DXd	Trastuzumab-deruxtecan
T-DM1	Trastuzumab-emtansine
SD	Stable disease
TKI	Tyrosine kinase inhibitors
T_{max}	Time to maximum serum concentration
US	United States

OVERVIEW

Spectrum Pharmaceuticals, Inc (Spectrum) is seeking accelerated approval of poziotinib for the treatment of patients with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring human epidermal growth factor receptor 2 (HER2, ErbB-2) exon 20 insertion mutations.

Poziotinib is a novel, irreversible tyrosine kinase inhibitor (TKI) of the ErbB family of receptors that has demonstrated consistent evidence of efficacy in previously treated patients with HER2 exon 20 insertions. As described throughout this Briefing Document, the drug has been thoroughly evaluated in a clinical program of 1,336 patients with NSCLC or other cancers, including 185 previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations, representing the largest cohort ever studied in a global multicenter study for this rare disease.

There are no large, randomized studies for chemotherapy specifically for HER2 exon 20 NSCLC patients. Currently, patients with NSCLC harboring HER2 exon 20 insertion mutations who have progressed after standard platinum-based chemotherapy ± checkpoint inhibitor (CPI) have no approved oral therapies and the only approved targeted treatment option is the recently approved antibody-drug conjugate (ADC) trastuzumab-deruxtecan (T-DXd), which may not be appropriate for all patients given the possibility of pulmonary and/or cardiac toxicities. In general NSCLC patients for which T-DXd is not suitable, or who progress on the drug, options include docetaxel (objective response rate [ORR] 10–12%, median progression-free survival [mPFS] 4 months)(Borghaei et al 2015; Herbst et al 2016), which is considered the comparator for randomized studies; docetaxel plus ramucirumab (ORR 23%, mPFS 4.5 months)(Garon et al 2014a) and CPIs which have limited efficacy (ORR 7–8%, median PFS 1.9–3.0 months) in patients with HER2 mutations (Mazieres et al 2019; Negrao et al 2021).

The data from the poziotinib clinical development program show consistent evidence of efficacy. In the pivotal study, Study 202 Cohort 2, the primary endpoint was ORR. The ORR was 27.8% (95% confidence interval [CI]: 18.9, 38.2), and the lower bound of 95% CI exceeded the pre-specified criterion of 17% in previously treated NSCLC patients harboring HER2 exon 20 insertion mutations. This efficacy is further supported by 2 independent studies in previously treated patients. An ORR of 40% was seen in Cohort 5 patients who received 16 mg once daily (QD) and an ORR of 26% in an Investigator-initiated study at MD Anderson Cancer Center (MDACC). Additionally, in Cohort 4, treatment-naïve patients with NSCLC harboring HER2 exon 20 insertion mutations treated with poziotinib 16 mg QD showed an ORR of 45%. Secondary efficacy analyses of disease control rate (DCR) and duration of response (DoR) supported the primary analyses. The drug has predictable and reversible side effects consistent with other 2nd-generation HER2/epidermal growth factor receptor (EGFR) inhibitors that are routinely managed by medical oncologists and with no chemotherapy type of side effects.

Poziotinib addresses a major unmet need for an oral treatment option in patients with NSCLC with HER2 exon 20 insertion mutation after treatment with platinum therapy. Overall, the efficacy and safety data support a favorable benefit-risk ratio to address this important unmet need for a population with limited treatment options and fulfill the requirements for an accelerated approval.

1 EXECUTIVE SUMMARY

1.1 Background and Unmet Need

Lung cancer is the most common cause of cancer-related death worldwide, and NSCLC accounts for approximately 85% of all lung cancers (Cheema et al 2019; SEER 2021; Siegel et al 2021). Since the discovery of classical EGFR mutations in NSCLC in 2004 as oncogenic drivers as well as the utility of tyrosine kinase inhibitors (TKIs) leading to tumor regression, numerous targeted therapies have been approved for a total of 9 oncogene drivers in NSCLC (Lynch et al 2004; Paez et al 2004; Pao et al 2004). Over the last two decades these targeted therapies have improved survival of patients with NSCLC (Howlader et al 2020).

1.1.1 HER2 Exon 20 Insertion Mutations in NSCLC

HER2, also known as ErbB-2, belongs to the ErbB family of receptor tyrosine kinases (RTK), together with three other family members: EGFR (also known as ErbB-1/HER1), ErbB-3 (HER3), and ErbB-4 (HER4). They are cytoplasmic membrane-anchored proteins that share structural and sequence similarities, containing an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain (Rubin and Yarden 2001). Mutations or insertions in the kinase domain of HER2 are oncogenic and can lead to lung cancer. Based on The Cancer Genome Atlas and other literature, HER2 mutations accounts for about 2–3% of all NSCLCs (Figure 1) (Cancer Genome Atlas Research Network 2014; Li et al 2016; Robichaux et al 2019; Skoulidis and Heymach 2019)). The majority of the HER2 oncogenic mutations are exon 20 insertions as reported in 80–90% in individual studies, which represents approximately 3,000 newly diagnosed patients per year in the United States (US) (Arcila et al 2012; Li et al 2022; Mazieres et al 2013; Nagasaka et al 2022; Ross et al 2014; Tomizawa et al 2011). In a large analysis for incidence of HER2 mutation in NSCLC, the most frequent HER2 mutation is exon 20 insertion at Y772_A775dupYVMA with a frequency of over 50% of all exon 20 insertions, followed by G776delinsVC and G778_P780dupGSP (Robichaux et al 2019).

Figure 1:   Targetable Oncogenic Driver Mutations in Metastatic NSCLC

HER2

~2%

Legend:
- **HER2 (including exon 20)**
- **KRAS non-G12C**
- **KRAS G12C**
- **EGFR non Exon 20**
- **EGFR Exon 20**
- **BRAF**
- **MET Exon 14**
- **ALK Fusion**
- **RET Fusion**
- **ROS1 Fusion**
- **NTRK 1/2/3 Fusion**
- **Other or not identified**

Pie values: 17%, 12%, 19%, 2%, 5%, 4%, 3%, 2%, 1%, 1%, 32%
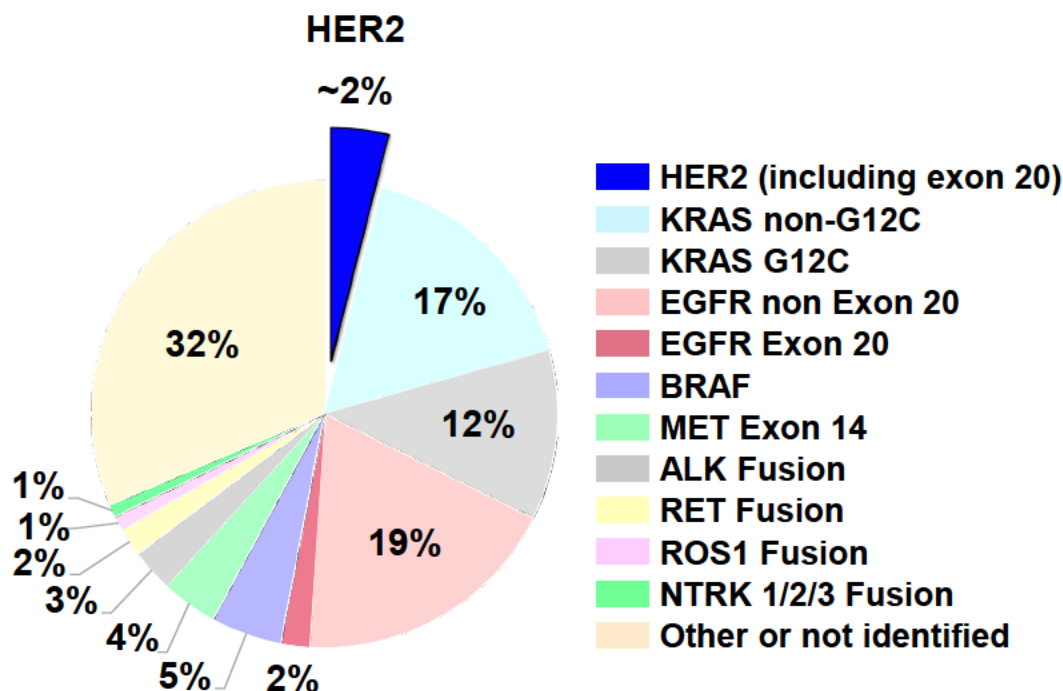
NSCLC=non-small cell lung cancer
Source: Adapted from (Thai et al 2021)

1.1.2   Landscape of Current Treatment Options for HER2 Exon 20 Insertion-NSCLC

1.1.2.1   First-line Therapy

Chemotherapy ± Checkpoint Inhibitors (CPI)

Currently there is no HER2 targeted therapy approved as first-line therapy specifically for patients with advanced NSCLC bearing HER2 exon 20 insertions, and randomized studies have not been reported for NSCLC patients with HER2 exon 20 insertions in any setting. The standard of care for this population remains chemotherapy with platinum-based chemotherapy, with or without CPI. In recent first-line trials for advanced NSCLC, when chemotherapy was used as a comparator arm, platinum-doublet resulted in an ORR of 18.9–30% with mPFS of 2.6–4.9 months (Gandhi et al 2018; Hellmann et al 2019).

The addition of CPI to chemotherapy has improved responses and prolonged survival in the advanced NSCLC population without EGFR or ALK mutations. For example, in the Keynote 189 study, the addition of pembrolizumab led to improved ORR (47.6%) and PFS (8.8 months), and now chemotherapy+CPI is commonly offered by oncologists to patients with advanced NSCLC lacking EGFR or ALK mutations (Gandhi et al 2018). These first-line studies did not specifically address outcomes in HER2 exon 20 insertion

patients, as this population is expected to receive less benefit from the addition of CPI. Like patients with EGFR mutations or ALK mutations, these patients are commonly never- or light-smokers, with low PD-L1 levels, low tumor mutation burden, and low responses to CPI monotherapy (Mazieres et al 2019; Negrao et al 2021). In EGFR-mutant NSCLC, independent studies have indicated that the addition of CPI to platinum-doublet chemotherapy did not confer additional clinical benefit with PFS remaining at 5.0–5.3 months (Hong et al 2022; White et al 2022).

Due to the rarity of NSCLC with HER2 mutations, the available literature for the use of chemotherapy in this patient population are mostly from small, retrospective studies. From a pooled group of 9 studies, the median (range) ORRs and PFS were 15% (0–62) and 4.9 months (2.1–6.7), respectively (Auliac et al 2019; Mazières et al 2016; Xu et al 2020; Yang et al 2021; Zhou et al 2020). Taken together, although lacking large, randomized trials for this population, the current first-line therapy of platinum-chemo ± CPI in HER2-mutant NSCLC is likely to benefit patients with ORR in the range of 20–30% and PFS 4–7 months.

1.1.2.2 Second-line+ Therapies After Platinum-based Therapy

Checkpoint Inhibitors (CPI) Monotherapy

CPI monotherapy is largely ineffective in patients with HER2-mutant NSCLC. For CPI monotherapy, the two largest retrospective studies comprising of three cohorts of 65 HER2-mutant patients, indicated a median PFS of 1.9–3.0 months and an ORR of 7–8% (Mazieres et al 2019; Negrao et al 2021). This was expected, and likely due to patient's never smoker status, low TMB, and low PD-L1 (Negrao et al 2021). HER2-mutant NSCLC patients derive very little clinical benefit from CPI therapies in the second-line setting.

Docetaxel ± Ramucirumab

Since 2000, docetaxel has been considered the SOC following platinum-doublet therapy (Fossella et al 2000). Docetaxel, established as a salvage option, rendered a response of approximately 11% (Fossella et al 2000). In more recent studies, docetaxel is often used as a comparator therapy for large, randomized studies. Docetaxel has demonstrated a consistent ORR of 10–14% with PFS of 3–4 months. For example, in the Checkmate-057 trial, docetaxel showed an ORR of 12% and PFS was 4.2 months in non-squamous NSCLC (Borghaei et al 2015). In the Keynote-010 trial, the ORR in the docetaxel group was 8% and the PFS was 4.1 months (Herbst et al 2016). The addition of ramucirumab was shown to enhance clinical benefit for docetaxel, as the REVEL study showed an ORR of 23% and PFS was 4.5 months with docetaxel (Garon et al 2014b) in all patients with NSCLC mutations. This approach of adding ramucirumab is not used in the majority of patients. Therefore, currently, docetaxel remains the primary salvage therapy for patients with metastatic NSCLC who have progressed on platinum-based therapy with or without a CPI and has been used as the standard comparator arm in randomized Phase 3 trials (Borghaei et al 2015) (Herbst et al 2016).

Anti-HER2 Antibody-Drug Conjugates

Current NCCN guidelines recommend the use of anti-HER2 ADCs for treating HER2-mutant NSCLC after platinum-based therapy, which includes T-DM1 and T-DXd. T-DM1 had an ORR of 50% and PFS of 5.0 months in HER2-mutant NSCLC (NCCN, 2022). In the study DESTINY-Lung01, T-DXd at the dose of 6.4 mg/kg Q3 weeks showed a 55% ORR with a PFS of 8.2 months (Li et al 2022). In August 2022, T-DXd received accelerated approval for use in patients with HER2-mutant NSCLC who have received a prior systemic therapy, based on the study of DESTINY-Lung02 (T-DXd at 5.4 mg/kg) showing ORR of 58% and consistent DoR response (FDA, 2022).

With T-DXd at 6.4 mg/kg dose, the drug is associated with a high rate of interstitial lung disease (ILD)/pneumonitis (26%) (Li et al 2022). In a pooled analysis for breast and lung cancer patients from various trials with different doses, the ILD/pneumonitis incidence was 15.4% for all Grade, including 2.2% of Grade 5 fatal events (Powell et al 2022). In the subsequent DESTINY-Lung02, the eligibility around ILD/pneumonitis was stricter in that it excluded not only patients with history and/or current ILD/pneumonitis, or prior pneumonectomy, but also excluded patients with "suspected ILD/pneumonitis that cannot be ruled out by imaging at screening." The other class of common adverse events (AEs) with anti-HER ADCs are cytopenia because the active payload of T-DM1 and T-DXd are cytotoxic chemotherapy. DESTINY-Lung01 had Grade 3 and greater neutropenia in 19% of patients (Li et al 2022); cytopenia remains to be a common side effect (> 20%) in DESTINY-Lung02 (FDA, 2022).

Anti-HER2 ADCs are mechanistically distinct from HER2 TKIs and available data thus far suggesting cross-resistance may be uncommon (Viray et al 2022). This may be due to distinct mechanisms of resistance; for example, anti-HER2 ADC resistance may be mediated by resistance to its chemotherapy payload (Aldonza et al 2016; Kinneer et al 2018). In preclinical studies HER2 TKIs cause upregulation of cell surface HER2 and can sensitize tumors to anti-HER2 ADCs (Robichaux et al 2019; Scaltriti et al 2009). Consistent with these observations, in a recent report three patients with HER2 mutations initially treated with poziotinib with progression after 3–8 months were subsequently treated with anti-HER2 ADCs with durable benefit (Viray et al 2022). Data regarding the use of TKIs after anti-HER2 ADCs is discussed below. These data support the potential benefits of the sequential use of mechanistically distinct targeted agents.

Reported Off-Label Use of Oral ErbB Tyrosine Kinase Inhibitors (TKIs)

Given the structural similarity between HER2 (ErbB-22) and EGFR (ErbB-1), TKIs that inhibit one receptor often inhibit the other to at least some extent. Given the mechanistic differences of TKIs from chemotherapy and ADCs, TKIs may provide an option to overcome chemotherapy resistance in HER2 mutations. Oral TKIs are a standard of care for NSCLC patients with classical EGFR or exon 20 insertion EGFR mutations, or HER2 positive breast cancer, but there are no FDA approved small molecule TKIs for patients with HER2 exon 20 insertion NSCLC (or more generally for any HER2 mutant

cancer) (2021a; 2022b) (2022a). Several of these TKIs have been tested in HER2 mutant or HER2 exon 20 insertion NSCLC. Neratinib is an approved HER2 targeting TKI for breast cancers. In a prospective trial, zero response was observed in 17 HER2-mutant NSCLC patients (NCT01827267). In a basket trial (SUMMIT trial, NCT01953926) treating HER2-mutant solid tumors, no response (0%) was observed in the HER2 exon 20 insertion patients (Gandhi et al 2014; Hyman et al 2018). Afatinib is a pan-ErbB inhibitor approved for EGFR-mutant NSCLC, a few prospective and retrospective analyses revealed responses ranging from 0–13.0% with PFS in the 2.0–3.9 months (Dziadziuszko et al 2019; Lai et al 2019). Dacomitinib was also studied in 26 HER2-mutant NSCLC patients and achieved an ORR of 12% and PFS of 3.0 months (Kris et al 2015). Taken together, the off-label use of approved TKIs have limited efficacy in HER2-mutant NSCLC.

Table 1:   Anti-Tumor Activity of "Off-label" Use of TKIs in NSCLC HER2 Mutations

TKI	Study	National Clinical Trial Number	N	ORR (%)	PFS (mos)
Neratinib	Sponsored [1]	NCT01827267	17 [a]	0	2.9
Neratinib	SUMMIT (US) [2]	NCT01953926	26 [a]	0	5.5
Afatinib	NICHE (Europe) [3]	NCT02369484	13 [a]	7.7	3.9
Afatinib	China Malaysia [4]	NCT02597946	18 [b]	0	2.8
Afatinib	US, Australia, Euro [5]	Meta-analysis	27 [b]	13	NR
Dacomitinib	US [6]	NCT00818441	26 [a]	12	3.0

HER2: human epidermal growth factor receptor 2; ORR: objective response rate; NR: not reported; PFS: progression-free survival; TKI: tyrosine kinase inhibitor; US: United States.
a. HER2 exon 20 mutation
b. HER2 mutations
1. *clinicaltrials.gov* 2. *(Hyman, 2018)* 3. *(Dziadziuszko et al 2019)*, 4. *clinicaltrials.gov* 5. *(Hellmann et al 2019)* 6. *(Kris et al 2015)*

Tolerability of TKIs

TKIs that inhibit HER2 and EGFR typically have reversible dose-related class effects related to inhibition of wild-type EGFR including a diffuse, papulopustular acneiform eruption which is noted in 60–90% of patients receiving these agents; diarrhea; and paronychia (Jacot et al 2004; Melosky et al 2015; Shepherd et al 2005; Wu et al 2017; Wu et al 2014). These symptoms are predictable and usually peak at 2–8 weeks after initiating therapy before typically improving. Given how common these cutaneous toxicities are, medical oncologists are usually familiar with managing them using preventative and therapeutic measures. Preventative measures include avoiding skin irritants, excessive sun exposure, and using alcohol-free moisturizers (Melosky et al 2015). Preemptive therapy with oral antibiotics in conjunction with topical corticosteroids significantly reduces TKIs cutaneous toxicities (Bachet et al 2012). Patients with severe cutaneous toxicities (Grade 3 or higher) can be managed by TKI dose interruption, dose reduction, retinoic acid analogs such as acitretin, oral corticosteroids, and antibiotics. Such interruptions or dose reductions are common; for example, the majority of patients treated with dacomitinib and afatinib underwent dose reductions (Corral et al 2019; Wu et al 2017; Yang et al 2015).

1.1.3 Sequential Use of Mechanistically Distinct Targeted Treatment Options for HER2-mutant NSCLC

1.1.3.1 Current Landscape of Treating Metastatic HER2-Mutant NSCLC

In treating patients with metastatic NSCLCs, sequential use of different therapies is a common strategy to prolong the totality of lifespan for patients, including for HER2-mutant NSCLC. Platinum-based chemotherapy remains the first-line systemic therapy for the majority of the patients and usually render a median PFS 2.1–6.7 months (averaging 4.5 months). The approval of T-DXd potentially adds another 8.2 months (median PFS) to the course. Docetaxel has been used by many oncologists as the next line options with another possible 3–4 months of disease control (Figure 2, top scenario).

There is also a population of patients, for whom trastuzumab ADCs may not be clinically suitable, including patients with underlying interstitial lung disease, impaired cardiac function, or cytopenia from prior chemotherapy. Those patients are receiving docetaxel or CPI or off-label use of TKIs. But as discussed above, those treatments have very limited efficacy in HER2-mutant NSCLC (Figure 2, bottom scenario).

Furthermore, all the currently available medications within the current landscape are intravenous (IV) drugs, which is also a barrier for certain patient populations, including the ones from rural areas and the ones with lower socioeconomic status who commonly have transportation challenges. Therefore, with those currently available drugs, there is still an unmet need for other effective drugs with different mechanism of actions, that can be used after resistance developed to chemotherapy and anti-HER2 ADC.

Figure 2: **Current Treatment Landscape of NSCLC HER2 Exon 20 Insertion Mutations**
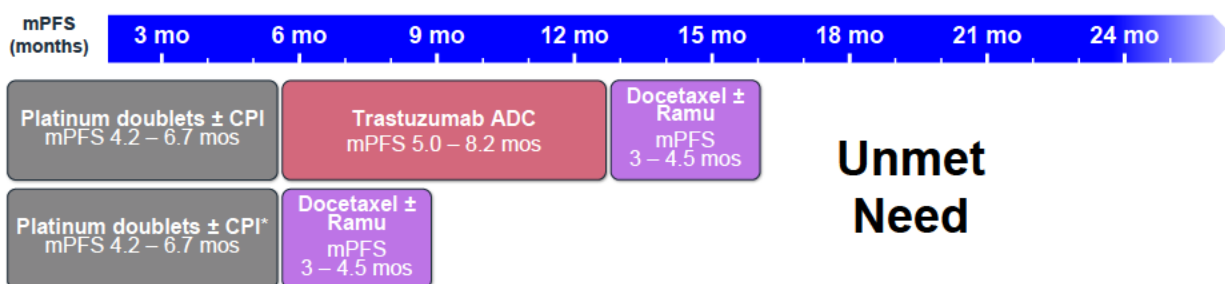
CPI: immune checkpoint inhibitor; mo: months; mPFS: median progression-free survival.
note: For patients who did not receive CPI with chemotherapy in first-line setting, it could be given as monotherapy in 2nd+ line setting.

1.2 Product Description

Poziotinib, if approved, would be the first therapy specifically indicated for patients with NSCLC harboring HER2 exon 20 insertion mutations, a serious and life-threatening disease for which therapies are urgently needed. Poziotinib is a novel, oral, irreversible,

TKI with a unique structure that allows for binding of HER2 receptors that have exon 20 insertion mutations (Figure 3). Insertion mutations in exon 20 of HER2 cause steric hindrance in the kinase domain, which renders available TKIs significantly less effective. Compared to other TKIs, poziotinib has a unique structural moiety, including a smaller terminal group and a flexible quinazoline core. In addition, poziotinib has smaller substituent groups linking the Michael acceptor group to the quinazoline core, can rotate freely around the amine and ether groups, and has increased halogenation of the terminal benzene ring compared to afatinib. The electron-rich moiety within the terminal group also interacts with basic residues of EGFR or HER to further stabilize its binding (Robichaux et al 2018). These features allow poziotinib to overcome the steric hindrance caused by exon 20 insertion mutations and permits effective drug pocket binding leading to kinase inhibition (Figure 4). This was confirmed in preclinical models, with poziotinib demonstrating potent anti-tumor efficacy in HER2-mutant cancer cells (Robichaux et al 2018).

The recommended dose for poziotinib is 16 mg orally QD. Reductions in dose are recommended to manage adverse reactions (see Table 39).

Figure 3:   Poziotinib Structure
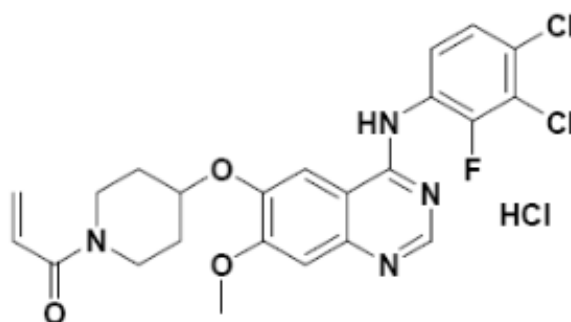
Figure 4: Potency and Specificity of HER2/EGFR TKIs for HER2 Exon 20 Mutations In Vitro
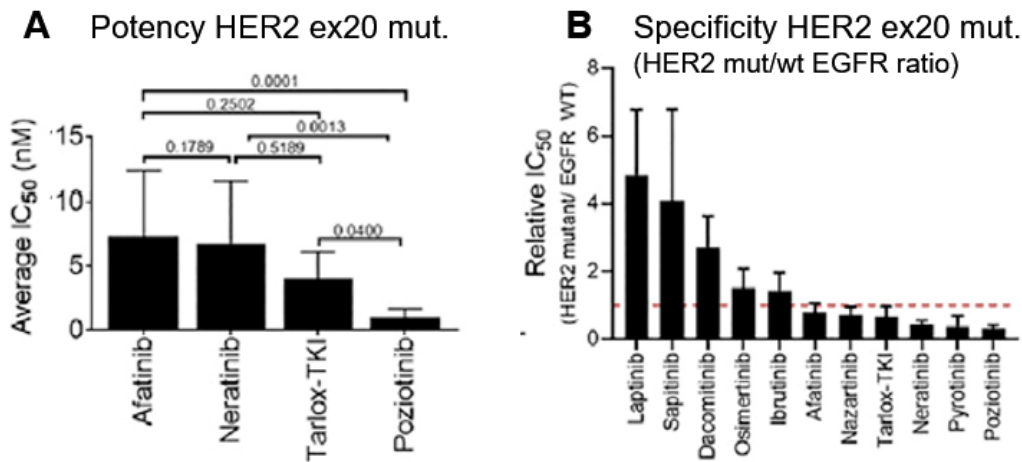
A. Potency of TKIs for Ba/F3 cell lines expressing HER2 exon 20 mutations. IC50 is average concentration for inhibiting 50% of cell growth for cell lines bearing 9 most common HER2 exon 20 mutations. B. Specificity of TKIs expressed as a ratio of IC50 for the HER2 ex20 mutation/wild-type EGFR. Lower bar denotes greater specificity for HER2 exon20 mutation. Error bars represent ± standard error of measurement.

1.3 Clinical Development Program

The overall clinical development program for poziotinib comprises 1,336 patients and 82 healthy volunteers in 22 studies and an expanded access program as of data cutoff 16 May 2022.

The clinical pharmacology, efficacy, and safety data to support poziotinib in the proposed indication primarily come from the ongoing Phase 2 multi-cohort study of poziotinib conducted in patients with locally advanced or metastatic NSCLC with HER2 exon 20 insertion mutations (Study SPI-POZ-202 [Study 202]). Each cohort in Study 202 is a standalone study (ie, the statistical analyses and tests of hypotheses for each cohort are conducted independently of other cohorts).

Cohort 2 is the pivotal study that demonstrates efficacy of poziotinib 16 mg QD in previously treated (second-line) patients (Figure 5). Supportive efficacy data in patients with HER2 exon 20 NSCLC in the second-line setting is derived from both Cohort 5, an exploratory dose-ranging study, and an independent investigator led study conducted at MDACC. Cohort 4, a study in first-line patients with NSCLC HER2 exon 20 insertion mutations, is also supportive and met its primary endpoint.

Figure 5:   **Studies Supporting Efficacy in Patients with NSCLC Harboring HER2 Exon 20 Insertion Mutations Receiving Poziotinib 16 mg QD**

	Second Line			First Line
	Pivotal Study	Supportive Data	Supportive Data	Additional Data
	Study 202 Cohort 2	Study 202 Cohort 5	MDACC Study[1]	Study 202 Cohort 4
N	90	10	27	47
ORR	28%	40%	26%	45%
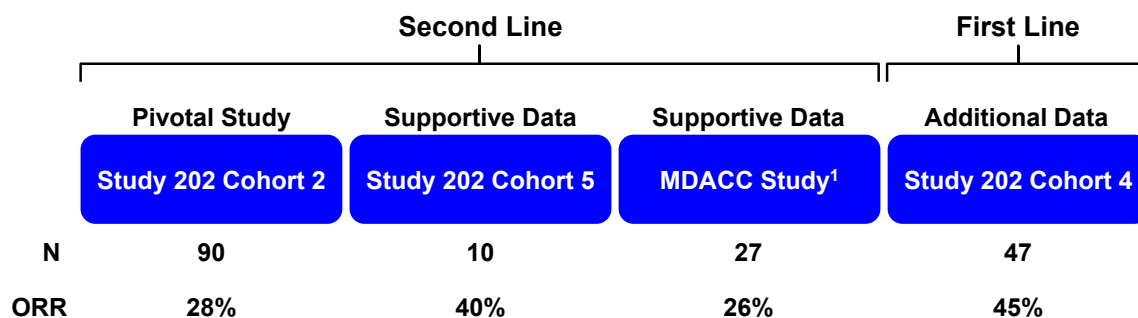
HER2: human epidermal growth factor receptor 2; MDACC: MD Anderson Cancer Center; NSCLC: non-small cell lung cancer; ORR: objective response rate; QD: once daily.
1. Elamin et al, 2022

1.4   Second-Line Efficacy Findings

1.4.1   Second-Line Efficacy Pivotal Study (Study 202-Cohort 2)

Design

Cohort 2 was a single-arm, open-label, global, multicenter Phase 2 study to evaluate the efficacy, safety, and tolerability of poziotinib in adult patients with NSCLC harboring HER2 exon 20 insertion mutations. Eligible patients had been previously treated for locally advanced or metastatic NSCLC with at least one systemic therapy.

Enrolled patients received poziotinib at a starting dose of 16 mg QD; per protocol, dose reductions were permitted to manage adverse reactions (see Section 5.3.1). Treatment was continued for 24 months or until disease progression, death, intolerable AEs, or other specified reason for patient withdrawal. An Independent Review Committee (IRC) assessed tumor response based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 criteria at weeks 4, 8, and every 8 weeks thereafter. Safety follow-up continued through 35 days after the last dose.

The primary objective was ORR (ie, complete response [CR] + partial response [PR]) in the As-Treated Population (patients who received at least one dose of poziotinib), based on central radiographic evaluations. Based on the literature available at the time of the study initiation as described in Section 1.1 above and per FDA discussion, an ORR of 17% was considered to be clinically meaningful ORR in this patient population as it is higher than the range of ORRs seen across all available therapies. Per the Study 202 Statistical Analysis Plan (SAP), a 17% lower bound of the 95% CI was pre-specified as the efficacy threshold for this study. Secondary efficacy objectives were to evaluate DCR (CR + PR + stable disease [SD]) and DoR. PFS and quality of life (QoL) were examined as exploratory objectives.

Patient Population

Demographics and other baseline characteristics of the study patient population were representative of a population of patients with NSCLC harboring exon 20 insertion mutations as described in the literature (Table 2) (Baraibar et al 2020). More than 95% of patients were previously treated with at least one platinum-based therapy and had histopathology of adenocarcinoma, 90% of patients were diagnosed with Stage IV disease, and 83% of patients had metastatic cancer.

Table 2:   Summary of Patient Demographics and Baseline Characteristics –Cohort 2 Previously Treated Patients with NSCLC Harboring HER2 Exon 20 Insertion Mutations

Category	Poziotinib 16 mg QD N=90
Age, years	
Mean (SD)	60 (11.69)
Min, Max	25, 86
< 65, n (%)	56 (62.2)
Female, n (%)	58 (64.4)
Hispanic or Latino, n (%)	5 (5.6)
Race, n (%)	
White	70 (77.8)
Black	4 (4.4)
Asian	12 (13.3)
Other	4 (4.4)
Never Smoked, n (%)	65.6
Mean BMI (kg/m^2) (SD)	25.16 (4.4)
ECOG Performance Status 1, %	57.8
Number of Line of Prior Systemic Therapy	
Median	2.0
Min, Max	1, 6

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; min: HER2: human epidermal growth factor receptor 2; minimum; max: maximum; NSCLC: non-small cell lung cancer; QD: once daily; SD: standard deviation.
Data cutoff: 05 Mar 2021

Most patients (72.2%) had tumors with the difficult to-treat Y772_A775dup insertion mutation, which is known to be most prevalent in this patient population (Robichaux et al 2019). The only other mutations present in at least 5% of patients' tumors were G776delinsVC and G778_P780dup, which are typical of this patient population reported in the literature.

Efficacy Results

Cohort 2 met its pre-specified primary endpoint, with an ORR of 27.8% (95% CI: 18.9, 38.2; Table 3) and the lower bound of the 95% CI exceeding the pre-specified criterion of 17%. In total, 67 patients (74.4%) experienced reduced tumor volume during poziotinib treatment, demonstrating clinical activity in the majority of patients in this population (see Figure 6). The DCR was 70.0%, and the median DoR was 5.1 months.

The median PFS was 5.5 months (95% CI: 3.9, 5.8). This single-arm study was not designed to follow patients for OS.

See Section 5.3.6 for complete efficacy analyses.

Table 3: Summary of Efficacy by Central Independent Radiographic Review –Cohort 2 Previously Treated Patients with NSCLC Harboring HER2 Exon 20 Insertion Mutations

	Poziotinib 16 mg QD N=90
Confirmed Best Overall Response [a], n (%)	
CR	0
PR	25 (27.8)
SD	38 (42.2)
PD	13 (14.4)
NE	14 (15.6)
ORR (CR+PR) [a], n (%)	**25 (27.8)**
95% CI [b] (%)	(18.9, 38.2)
DCR (CR+PR+SD) [a], n (%)	**63 (70.0)**
95% CI [b] (%)	(59.4, 79.2)
Median DoR [c] (months)	**5.1**
95% CI [c] (months)	(4.2, 5.5)
Median PFS [c] (months)	**5.5**
95% CI [c] (months)	(3.9, 5.8)

CI: confidence interval; CR: complete response; DCR: disease control rate; DoR: duration of response; HER2: human epidermal growth factor receptor 2; NE: not evaluable; ORR: objective response rate; PD: progressive disease; PFS: progression-free survival; PR: partial response; QD: once daily; SD: stable disease.
a. A patient had to be treated for at least 6 weeks to be assessed as SD/PR/CR. The confirmation scan for CR or PR had to be at least 4 weeks from the initial scan showing response.
b. Clopper-Pearson exact confidence limits.
c. Kaplan-Meier (product-limit) estimate.
Data cutoff: 05 Mar 2021

Figure 6: **Waterfall Plot Best Percent Change in Target Lesion Sum of Diameters from Baseline –
Cohort 2 Previously Treated Patients with NSCLC Harboring HER2 Exon 20 Insertion
Mutations**
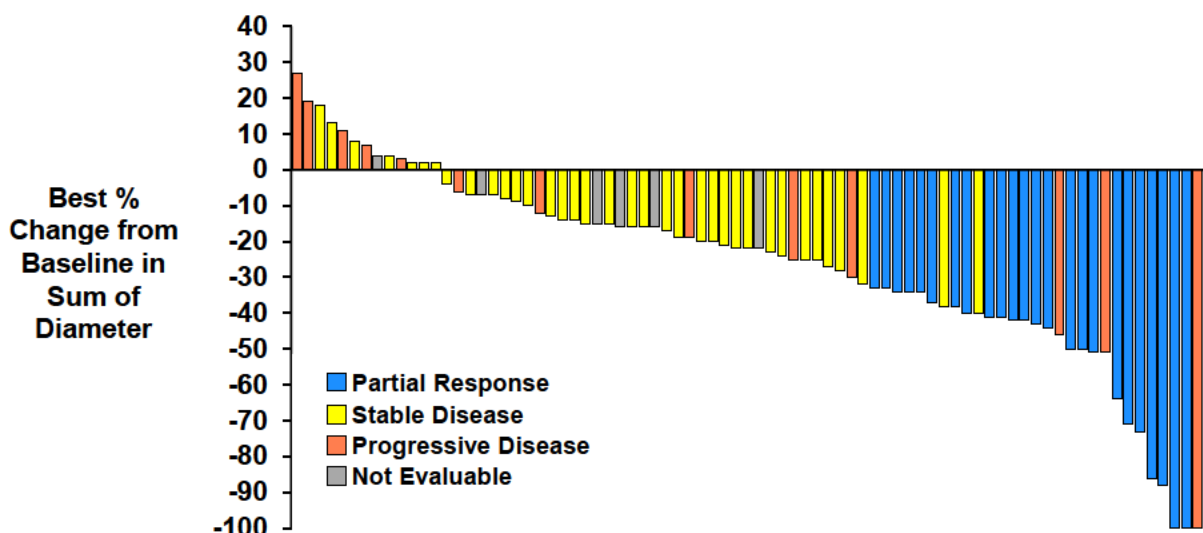
HER2: human epidermal growth factor receptor 2; NSCLC: non-small cell lung cancer
Data cutoff: 05 Mar 2021

1.4.2 Supportive Second-Line Efficacy Study (Study 202-Cohort 5 HER2 Exon 20)

Design

The efficacy of poziotinib is further supported by Cohort 5, an ongoing, randomized,
Phase 2, open-label, multicenter, two-stage dose-ranging study. An IRC assessed
tumor response in all treatment arms at weeks 4, 8, and every 8 weeks thereafter.

The primary objective was to assess the ORR in the As-Treated Population. Secondary
efficacy objectives were to evaluate DCR and DoR. PFS and OS were evaluated as
exploratory objectives.

For the purpose of the discussion of efficacy of the proposed dose for this New Drug
Application (NDA), only the results of the 16 mg QD are included here.

Patient Population

The demographics were consistent with the literature describing the target population of
patients. The mean age in the 16 mg arm was 62 years, and 60% of the patients overall
were younger than 65 years of age. Enrolled patients were predominantly female (70%)
and white (80%). See Section 5.4.2.

Most patients had never smoked, and baseline Eastern Cooperative Oncology Group
(ECOG) performance status was 1 in the majority of patients.

Efficacy Results

The primary endpoint of ORR in Cohort 5 16 mg QD provides supportive evidence of poziotinib efficacy with an ORR of 40%, DCR of 70%, DoR of 6.5 months and PFS of 7.3 months (Table 4).

Table 4: **Summary of Efficacy by Central Radiographic Review – Cohort 5 Previously Treated Patients with HER2 Exon 20 Mutation**

	Cohort 5 16 mg QD N=10
Confirmed Best Overall Response [a], n (%)	
CR	0
PR	4 (40.0)
SD	3 (30.0)
PD	0
NE	3 (30.0)
ORR (CR+PR) [a], n (%)	**4 (40.0)**
95% CI [b] (%)	(12.2, 73.8)
DCR (CR+PR+SD) [a], n (%)	**7 (70.0)**
95% CI [b] (%)	(34.8. 93.3)
Median DoR [c] (months)	**6.5**
95% CI [c] (months)	(3.7, NA)
Median PFS [c] (months)	**7.3**
95% CI [c] (months)	(5.5, NA)

CI: confidence interval; CR: complete response; DCR: disease control rate; DoR: duration of response; NA: not available; NE: not evaluable; ORR: objective response rate; PFS: progression-free survival; PD: progressive disease; PR: partial response; QD: once daily; SD: stable disease.
a. A patient had to be treated for at least 6 weeks to be assessed as SD/PR/CR. The confirmation scan for CR or PR had to be at least 4 weeks from the initial scan showing response.
b. Clopper-Pearson exact confidence limits.
c. Kaplan-Meier (product-limit) estimate.
Data cutoff: 16 May 2022

1.4.3 Supportive Second-Line Efficacy Study from the MD Anderson Cancer Center Study

Design

An independent Phase 2, open-label, Investigator-initiated study of the efficacy of poziotinib was conducted at MDACC. Patients with NSCLC harboring HER2 exon 20 insertion mutations were enrolled and treated with poziotinib 16 mg QD until objective disease progression. Patients were permitted to continue beyond progression for as long as the Investigator observed clinical benefit.

The primary endpoint was the proportion of patients who achieved an objective response as assessed by the Investigator according to RECIST version 1.1. Secondary efficacy endpoints included DCR, DoR, PFS, and OS.

Results

Thirty patients received poziotinib treatment out of which 27 patients were previously treated with a platinum-based therapy; 16 (53%) had two lines or more prior systemic therapies. Poziotinib provided a confirmed ORR of 27.0% overall and 26.0% in patients treated with platinum-based therapy (Table 5). Responses were observed across HER2 exon 20 insertion mutations subtypes. Furthermore, an additional 46% of patients achieved SD, for a DCR of 73%. The median PFS was 5.5 months, and the median OS was 15 months. One (3.7%) patient discontinued due to an AE. Additional details are provided in Section 5.5.

Table 5:   **Summary of Objective Response Rate in Patients with NSCLC Harboring HER2 Exon 20 Insertion Mutations – MDACC Study**

Response	
Overall population	**N=30**
ORR (%) [b] (95% CI)	**27.0 (12.0, 46.0)**
Confirmed Partial Response, n (%)	8 (27)
Stable Disease, n (%)	14 (46)
Progressive Disease [a], n (%)	8 (27)
Median OS, months (95% CI)	15.0 (9, NA)
Platinum-pretreated	**N=27**
ORR (%) [b] (95% CI)	**26.0 (11.0, 46.0)**

CI: confidence interval; HRE2: human epidermal growth factor receptor 2; MDACC: MD Anderson Cancer Center; NA: not available; NSCLC; non-small cell lung cancer; ORR: objective response rate; OS: overall survival
a. Includes one patient with early death that was deemed possibly related to poziotinib vs related to disease progression.
b. Confirmed objective response rate.

1.5   First-Line Supportive Efficacy from Cohort 4

Study 202 Cohort 4 provides additional evidence of poziotinib efficacy.

Design

Cohort 4 is an ongoing, open-label, multicenter, Phase 2 study in patients with locally advanced or metastatic NSCLC harboring HER2 exon 20 insertion mutations who are treatment-naïve. Patients received a starting dose of poziotinib of 16 mg QD or 8 mg twice daily (BID).

The primary objective was to assess the ORR (CR+PR) in the As-Treated Population based on central radiographic evaluations. Secondary efficacy objectives were to evaluate DCR and DoR. PFS and QoL were evaluated as exploratory objectives.

Results

Among the 70 patients treated with poziotinib, 47 were treated with poziotinib 16 mg QD and the remaining 23 were treated with 8 mg BID. For the purpose of this meeting, only the results of 16 mg QD dosing are presented. The ORR and DCR were 45% (95% CI:

30, 60%) and 75% (95% CI: 60, 86%), respectively. The median DoR was 5.7 months, and the median PFS was 5.6 months (95% CI: 0, 20.7).

Approximately 73% of patients achieved disease control and reductions in tumor size. Fourteen patients (20%) are still receiving poziotinib treatment.

1.6   Efficacy Overview in Patients with HER2 Exon 20

Table 6 below provides a summary of efficacy in HER2 exon 20 patients treated with poziotinib 16 mg QD as second-line as well as first-line. The data demonstrated consistent and reproducible efficacy with the poziotinib treatment. Pooled ORR of 29% across 2 independent studies in second-line treatment provides clinically meaningful efficacy from a large dataset.

Table 6:   Efficacy in First-and Second-Line Setting for Patients with NSCLC HER2 Exon 20 Insertion Mutations – Poziotinib 16 mg QD

	Cohort 2 Second-Line N=90	Cohort 5 Second-Line N=10	Pooled[a] Second-Line N=100	MDACC Second-Line N=27	Cohort 4 First-Line N=47
Confirmed Best Overall Response, n					
CR	0	0	0	0	1
PR	25	4	29	7	20
SD	38	3	41	12	14
PD	13	0	13	8	7
NE	14	3	17	0	5
ORR (CR+PR), n (%)	**25 (27.8)**	**4 (40.0)**	**29 (29.0)**	**7 (26.0)**	**21 (44.7)**
95% CI [b] (%)	(18.9, 38.2)	(12.2, 73.8)	(20.4, 38.9)	(11.1, 46.3)	(30.2, 59.9)
DCR (CR+PR+SD), n (%)	**63 (70.0)**	**7 (70.0)**	**70 (70.0)**	**19 (70.4)**	**35 (74.5)**
95% CI [b] (%)	(59.4, 79.2)	(34.8, 93.3)	(60.0, 78.7)	(49.8, 86.3)	(59.7, 86.1)
Median DoR [c], mos	**5.1**	**6.5**	**5.2**	**5.0**	**5.7**
95% CI [c] (mos)	(4.2, 5.5)	(3.7, NA)	(4.6, 6.4)	(4.0, NA)	(4.6, 11.9)
Median PFS [c], mos	**5.5**	**7.3**	**5.6**	**5**	**5.6**
95% CI [c] (mos)	(3.9, 5.8)	(5.5, NA)	(4.0, 6.2)	(2.0, 6.0)	(4.3, 9.1)

CI: confidence interval; CR: complete response; DCR: disease control rate; DoR: duration of response; HER2: human epidermal growth factor receptor 2; NE: not evaluable; NA: not available; ORR: objective response rate; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease.
a. Pooled data is the corresponding total of results from Cohorts 2 and 5 included in the first 2 columns.
b. Clopper-Pearson exact confidence limits.
c. Kaplan-Meier (product-limit) estimate.
Data cutoff: Cohort 2: 05 Mar 2021; Cohort 5, Cohort 4: 16 May 2022; Cohort 4

1.7 Safety Findings

Safety Populations

Across the clinical program, 1,336 patients with NSCLC or other cancers received poziotinib (data cutoff: 16 May 2022). Primary safety data supporting the proposed indication come from Cohort 2. Supportive safety data come from the safety population of Group 1, which is a dataset of 482 patients with NSCLC from all cohorts of Study 202 who received 16 mg QD or 8 mg BID, regardless of the oncogene, mutation, and line of treatment (data cutoff: 19 Nov 2021; described in Section 6.10).

Overview of Adverse Events in Cohort 2

AEs were reported in nearly all patients during the treatment period (Table 7). In Cohort 2, Grade 3 AEs were reported in 86% of patients and Grade 4 AEs in 11.1% of patients. Serious AEs (SAEs) were reported in 40.0% of patients. SAEs leading to death occurred in 10% of patients.

Table 7: Summary of Adverse Events – Cohort 2

Category, n (%)	Poziotinib 16 mg QD N=90
Any AE	90 (100.0)
Grade 3 AE	77 (85.6)
Grade 4 AE	10 (11.1)
AE leading to dose interruption [a]	81 (90.0)
AE leading to dose reduction [a]	52 (57.8)
Any AE leading to drug discontinuation [a]	21 (23.3)
Any treatment-related AE leading to discontinuation	11 (12.2)
Any SAE	36 (40.0)
SAE leading to death	9 (10.0)
Treatment-related SAE leading to death	1 (1.1)

AE: adverse event; HER2: human epidermal growth factor receptor 2; SAE: serious adverse event.
[a] Action taken on AE CRF recorded as drug withdrawn
Data cutoff: 19 Nov 2021

The most commonly reported AEs overall, were diarrhea, rash, stomatitis, and paronychia, and the most common Grade 3–4 AEs were diarrhea, rash, and stomatitis which were all AEs of Special Interest (AESIs). These events are considered mechanistically on-target with the TKI class of drugs and consistent with second-generation TKIs. Generally, the AEs were manageable with study protocol recommended prophylactics and the protocol management plan or institutional protocols.

The most common AE leading to poziotinib permanent discontinuation was rash (n=4; 4.4%).

Adverse Events of Special Interest (AESIs)

AESIs included were pneumonitis, rash-type AEs (multiple preferred terms [PTs]), diarrhea, stomatitis-type AEs (multiple PTs), and paronychia. Key findings for the AESIs are summarized below. Complete details are provided in Section 6.9.

- Onset of rash of any grade occurred with a median of 8 days after first dose of poziotinib. Approximately half of patients experienced Grade 3 AESI of rash; most were managed with dose reduction.

- Onset of diarrhea of any grade occurred a median of 6 days after first dose of study drug. Diarrhea was the most prevalent AESI.

- Onset of stomatitis of any grade occurred with a median of 7 days after first dose of poziotinib.

- Paronychia events were generally low in severity with only one Grade 3 AESI of paronychia.

- Pneumonitis occurred in 1 patient. The event was Grade 1, and the patient stayed on poziotinib treatment.

The proposed labeling contains specific statements on patient monitoring and management of these class types of AEs (see Section 6.13).

1.8   Confirmatory Study

A Phase 3, randomized, two-arm, active-controlled, open-label, multicenter study has been initiated to compare the efficacy and safety/tolerability of poziotinib versus docetaxel in previously treated patients with locally advanced or metastatic NSCLC harboring HER2 exon 20 mutations. Patients are being randomized 2:1 to oral poziotinib 8 mg BID or docetaxel 75 mg/m^2 administered IV on Day 1 of each cycle. The study will enroll approximately 268 patients.

The primary endpoint is a comparison of PFS (poziotinib vs docetaxel). Secondary endpoints include comparison of OS, ORR, and DCR. Topline study results are expected to be reported in 2026. Additional information on the confirmatory study is provided in Section 8.

1.9   Benefit-Risk Summary

Patients with NSCLC harboring HER2 exon 20 insertion mutations who have progressed on one or more lines of therapy have limited treatment options. The ADC T-DXd was recently approved for patients with HER2 mutant NSCLC. Not all patients may be suitable for treatment with T-DXd given its risk of neutropenia and, ILD which may be particularly problematic for patients with compromised pulmonary status, a common issue with lung cancer patients particularly given treatments they commonly

receive (lobectomy, radiation to the chest, etc). For patients not suitable for T-DXd or who progress on T-DXd, options include docetaxel (ORR 10–14%, mPFS 3 months), which is considered the comparator for randomized studies; docetaxel plus ramucirumab (ORR 23%, mPFS 4.5 months); and CPIs, which have distinct side effects and limited efficacy (ORR 7–8%, mPFS 1.9–3.0 months) in patients with HER2 mutations.

Poziotinib is a novel TKI with unique structural features that overcome the steric hindrance caused by HER2 exon 20 insertion mutations. It can fill an important unmet need by providing an oral targeted treatment option that is mechanistically distinct from ADCs and could be used upon progression on HER2 ADCs, or after platinum doublets patients not suitable for these HER2 ADCs or who favor oral therapy. Substantial activity was also observed in patients who had progressed after prior platinum doublets ± CPIs and docetaxel. Poziotinib therefore fills an important unmet need by providing patients with this rare mutation subtype, and physicians, with an oral treatment option that could possibly be used in previously treated patients.

Efficacy. Poziotinib met the pre-specified primary endpoint with an ORR 27.8% (95% CI: 18.9, 38.2), data further supported by the full 16 mg pooled group of 100 patients from Study 202 (29%); an even higher response rate in the treatment-naïve patients in Cohort 5 (40%) and an independent Investigator-initiated trail in a predominantly heavily pretreated population (26% [second-line]). Secondary efficacy analyses of DCR, DoR, and PFS supported the primary analyses. While these studies were not designed to assess OS as a primary endpoint, the OS observed (15–16 months) compares favorably with OS observed in patients who had progressed after prior platinum-based chemotherapy regimens (9–13 months). These represent the largest prospective treatment studies for this population reported to date that show consistent and reproducible efficacy in the proposed patient population.

Tolerability. As noted above, oral tyrosine kinases that inhibit HER2 and EGFR typically have reversible dose-related class effects related to inhibition of wild-type EGFR including dermatologic toxicities and diarrhea. These symptoms are predictable, typically peak at 2–8 weeks after initiating therapy before improving, and are manageable using established approaches with which medical oncologists who use these drugs have experience. Consistent with other drugs in the class, poziotinib at a starting dose of 16 mg require dose reductions and management of skin AEs and diarrhea although like with other drugs in this class the symptoms typically stabilize after the first two months. It is worth noting that Grade 3 or 4 pneumonitis rates were low (1.9% in 482 patients treated with 16 mg), even in heavily pretreated lung cancer patients, and no treatment-related cardiac toxicities were reported. Together the data support that dose-related AEs were predictable, in line with other drugs in the class, manageable using dose reduction and established supportive care, and typically improved over time.

Dose. Given the rate of dose reductions the question arose as to whether 16 mg QD is the most appropriate starting dose for patients, or whether starting at a lower dose (or BID dosing) may give comparable activity with fewer dose reductions. To address this, in Cohort 5, different dosing regimens were tested. While there was clear evidence of clinical activity at lower doses, and toxicity was reduced in a dose-dependent manner, there was a trend towards lower efficacy (ORR/mPFS was 40%/7.3 months [m] at 16 mg QD, 29%/7.4 months at 8 mg BID, 25%/5.6 months at 12 mg QD, and 13.3%/3.8 months at 6 mg BID). For this reason, Spectrum concluded that 16 mg QD would be the most appropriate starting dose, but that dose reductions to these lower doses would be appropriate where clinically indicated.

Summary. Poziotinib demonstrated clear and consistent evidence of efficacy in patients with HER2 exon 20 insertions previously treated with platinum-based chemotherapy regimens. Poziotinib has class-related, predictable toxicities requiring frequent dose reductions consistent with other FDA approved drugs in the class, but these are manageable using established approaches. Poziotinib would therefore address a major unmet need for an oral treatment option in this population after treatment with platinum therapy. In addition, consideration could be given after treatment with a HER2 ADC or provide a targeted treatment option for patients not suitable for a HER2 ADC or who prefer an oral agent. Overall, the efficacy and safety data support a favorable benefit-risk ratio to address this important unmet need for a population with limited treatment options and fulfill the requirements for an accelerated approval.

2   POZIOTINIB PRODUCT DESCRIPTION

Summary

- Poziotinib is a novel irreversible ErbB TKI with a proposed indication for the treatment of adult patients with locally advanced or metastatic NSCLC harboring HER2 exon 20 insertion mutations as detected by an FDA-approved test with disease progression on or after platinum-based chemotherapy.
- Poziotinib is administered orally, at a recommended dose of 16 mg QD.
- Poziotinib has unique structural features compared to class TKIs, including a smaller halogenated terminal group and flexible amine linker, that allow poziotinib to overcome the steric hindrance caused by exon 20 insertion mutations and permits effective drug pocket binding leading to kinase inhibition.

2.1   Proposed Indication, Administration, and Dosing

The proposed indication of poziotinib is for the treatment of adult patients with locally advanced or metastatic NSCLC harboring HER2 exon 20 insertion mutations as detected by an FDA-approved test with disease progression on or after platinum-based chemotherapy. The recommended starting dose is 16 mg poziotinib orally QD.

Recommended poziotinib dose reductions for managing adverse reactions, is presented in the proposed label, are provided in Table 39.

2.2   Poziotinib Product Overview and Mechanism of Action

Poziotinib, if approved, would be the first therapy specifically indicated for patients with NSCLC harboring HER2 exon 20 insertion mutations, a serious and life-threatening disease for which therapies are urgently needed. Poziotinib is a novel, oral, irreversible, TKI with a unique structure that allows for binding of HER2 receptors that have exon 20 insertion mutations. Insertion mutations in exon 20 of HER2 cause steric hindrance in the kinase domain, which renders available TKIs significantly less effective. Compared to other TKIs, poziotinib has a unique structural moiety, including a smaller terminal group and a flexible quinazoline core. In addition, poziotinib has smaller substituent groups linking the Michael acceptor group to the quinazoline core, can rotate freely around the amine and ether groups, and has increased halogenation of the terminal benzene ring compared to afatinib. The electron-rich moiety within the terminal group also interacts with basic residues of EGFR or HER to further stabilize its binding (Robichaux et al 2018). These features allow poziotinib to overcome the steric hindrance caused by exon 20 insertion mutations and permits effective drug pocket binding leading to kinase inhibition (Figure 4). This was confirmed in preclinical models, with poziotinib demonstrating potent anti-tumor efficacy in HER2-mutant cancer cells (Robichaux et al 2018).

3 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Successful pre-NDA meeting with the FDA on 9 Nov 2020 in support of the NDA for poziotinib in previously treated NSCLC patients with HER2 exon 20 insertion mutations.
- FDA granted poziotinib Fast Track Designation on 11 Feb 2021.
- The primary evidence supporting approval of poziotinib in previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations comes from 3 studies:
  - Primary efficacy: Cohort 2 – Phase 2 study to evaluate efficacy and safety of poziotinib in patients with NSCLC harboring HER2 exon 20 insertion mutations who had been previously treated for locally advanced or metastatic NSCLC.
- Supportive efficacy:
  - Cohort 5 – Phase 2 dose-ranging study in treatment-naïve or previously treated patients with NSCLC harboring HER2 or EGFR exon 20 insertion mutations.
  - MDACC – Investigator-initiated study to evaluate poziotinib in patients with Stage IV or recurrent NSCLC harboring HER2 exon 20 insertion mutations.

3.1 Regulatory Milestones

In 2021, FDA granted Fast Track Designation for poziotinib for the treatment of patients with locally advanced or metastatic NSCLC harboring HER2 exon 20 insertion mutations, reinforcing the unmet need that exists for this patient population.

Spectrum submitted the 505(b)(1) NDA for poziotinib on 24 Nov 2021. Spectrum requested accelerated approval following FDA regulations under 21 CFR 314.500 (Subpart H – Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) and current guidance based on meeting criteria listed in Table 8 (FDA 2014).

Table 8: Poziotinib Accelerated Approval Criteria

Qualifying Criteria	Poziotinib Fulfills Criteria
Treats serious condition	NSCLC HER2 exon 20 insertion mutation recognized as a rare, life-threatening disease [1]
Provides meaningful advantage over existing therapies	ORR of 28% with a distinct AE profile
Surrogate endpoint likely to predict clinical benefit	Demonstrated evidence of efficacy with protocol defined endpoint of ORR, an intermediate clinical endpoint that is reasonably likely to predict clinical long-term benefit (improved survival)
Post-approval trial required to confirm benefit	Confirmatory study, Study 301, currently underway to confirm clinical benefit in patients with NSCLC harboring HER2 exon 20 insertion mutations

AE: adverse event; HER2: human epidermal growth factor receptor 2; NSCLC: non-small cell lung cancer; ORR: objective response rate

1. National Organization for Rare Diseases (NORD)

3.2   Clinical Development Program

As of 16 May 2022, the overall clinical development program for poziotinib comes from 1,336 patients and 82 healthy volunteers from 22 studies and an expanded access program (Figure 7).

Figure 7:   Poziotinib Clinical Development Program
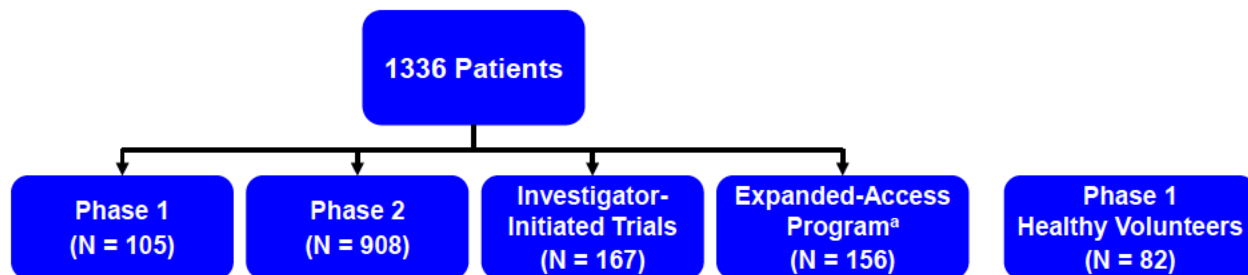
MDACC: MD Anderson Cancer Center
ª 11 patients already counted in other studies.
Data cutoff: 16 May 2022

After completing the Phase 1 studies, Spectrum conducted a Phase 2, open-label, multi-cohort, multicenter study to evaluate the efficacy and the safety/tolerability of poziotinib in adult (≥ 18 years of age) patients with NSCLC harboring EGFR or HER2 exon 20 insertion mutations (SPI POZ-202, ZENITH20). The study includes 7 cohorts, and each cohort was independently designed with different patient populations. Cohorts 1 to 4 were statistically powered with a pre-specified efficacy endpoints and analysis. For the current FDA submission, primary efficacy data comes from Cohort 2, where poziotinib treatment was in patients with previously treated NSCLC harboring HER2 exon 20 insertion mutations.

Primary safety data for the NDA was Safety Group 1 and comes from all Study Cohorts of Study 202 in which patients received a starting dose of 16 mg daily QD or 8 mg BID regardless of oncogenes and treatment status.

Additionally, clinical pharmacology studies were conducted in healthy subjects and patients with advanced solid tumors (described in more detail in Section 4).

4   CLINICAL PHARMACOLOGY

Summary

- Poziotinib was studied in 2 Phase 1 studies at doses ranging either from 0.5 to 32 mg QD on an intermittent schedule (2 weeks on/1 week off) or 10 to 24 mg QD on a continuous schedule.

    o On a continuous schedule, 18 mg QD is the maximum tolerated dose (MTD), and 16 mg QD is the recommended dose.

- Additional Phase 2 dose evaluation study (Cohort 5) supports the selection of 16 mg QD.

- More than 500 patients have been treated orally with 16 mg QD as the starting dose.

- Poziotinib is rapidly absorbed after oral administration, in a dose proportional manner with a median time to maximum serum concentration (T_{max}) between 0.8 and 2.9 hours. Oral bioavailability ranged from 37.1 to 64.4%.

- Poziotinib, and metabolites M1 and M2, are highly bound to human plasma proteins, and binding is not concentration dependent. Cytochrome P450 34A (CYP34A) is the primary pathway for the formation of M1, and Cytochrome P450 Family 2 Subfamily D Member 6 (CYP2D6) is the primary enzyme in the formation of M2.

    o The M1 metabolite was 172-fold and the M2 metabolite was 13.5-fold less potent than the parent poziotinib in tumors harboring HER2 insertion mutations.

    o Food had no effect on area under the concentration-time curve extrapolated from time 0 to 24 hours (AUC_{0-24h}) of poziotinib, but it decreased its maximum observed plasma concentration (C_{max}) by 27%, this may not be clinically significant.
- The mean elimination half-life is approximately 6 hours.
- Phase 1 metabolism of poziotinib was primarily mediated by CYP3A4 with minor contribution from CYP2D6.

- Coadministration of poziotinib with strong CYP3A4 or strong CYP2D6 inhibitors may increase poziotinib plasma concentrations. Therefore, it is recommended to avoid concomitant use of strong CYP3A4 or strong CYP2D6 inhibitors with poziotinib.

- Coadministration of poziotinib with strong CYP3A4 inducers may decrease poziotinib exposure, which may decrease efficacy of poziotinib; therefore, concomitant use of strong CYP3A4 inducers with poziotinib should be avoided.

4.1   Overview of Clinical Pharmacology Studies

The clinical pharmacology program evaluated poziotinib in healthy participants and patients with solid tumors in two Phase 1 studies (HM-PHI-101; HM-PHI-102) and the Phase 2 Study 202 to assess single and multiple dose pharmacokinetics (PK), potential for food effect, potential for drug-drug interactions, and final dose selection. In the two

Phase 1 studies, poziotinib was studied at doses ranging either from 0.5 to 32 mg QD on an intermittent schedule (2 weeks on/1 week off) or 10 to 24 mg QD on a continuous schedule. 18 mg QD was determined as the MTD and 16 mg QD was the recommended dose. Additional Phase 2 dose evaluation study (Cohort 5) supports the selection of 16 mg QD.

4.2 Pharmacokinetics

4.2.1 Human Absorption, Distribution, Metabolism, and Elimination

Absorption: After single and multiple dose administration, poziotinib was rapidly absorbed with C_{max} and AUC increased in a dose proportional manner over the dose range of 0.5 to 32 mg (0.03 to 2 times the recommended dose). Following a single oral dose of 16 mg poziotinib, the median (range) time to peak concentration (T_{max}) of poziotinib was 2 hours (1.5–3.9 hours).

At the recommended dose of 16 mg once daily, the steady state geometric mean [% coefficient of variation (CV%)] C_{max} and AUC_{0-24} of poziotinib was 76.1 ng/mL (60.3%) and 400 h•ng/mL (60.6%), respectively.

Distribution: At the recommended daily dose of 16 mg, the geometric mean (percent coefficient of variation [%CV]) apparent volume of distribution of poziotinib was 342 L (67%) at steady state. Poziotinib, and metabolites M1 and M2, were highly bound to human plasma proteins in vitro, and binding was not concentration dependent. The blood-to-plasma ratio was 0.53 for poziotinib, 0.60 for metabolite M1, and 0.54 for metabolite M2.

Metabolism: The Phase I metabolism of poziotinib is primarily mediated by CYP3A4 with minor contribution from CYP2D6 and CYP3A5. Formation of metabolites M1 (dihydrodiol-poziotinib), and M2 (O-demethyl-poziotinib), are mediated by CYP3A4 and CYP2D6, respectively. Following a single oral dose of 8 mg/100 µCi [14C] poziotinib hydrochloride to healthy participants, unchanged poziotinib (48%), M1 (14%) and M2 (12%) were the major circulating radioactive components. Metabolites M1 and M2 are pharmacologically less active than poziotinib and are not likely to contribute to efficacy at the recommended dose of poziotinib.

Elimination/Excretion: At the recommended dose of 16 mg daily, the geometric mean apparent oral clearance (%CV) of poziotinib at steady state was 37.6 L/h (62%). The mean (± standard deviation) plasma elimination half-life of poziotinib at steady state was 6.5 (1.7) hours. Following a single oral dose of 8 mg/100 µCi [14C] poziotinib hydrochloride (drug in capsule) to healthy participants, 64% and 1.73% of the administered radioactive dose was recovered in feces and urine, respectively. Unchanged drug was not detected in urine; however, unchanged drug represented approximately 20% of the radioactive dose recovered in feces. These findings indicate that poziotinib is hepatobiliary cleared with little to no renal clearance.

4.3　Dose Selection

4.3.1　Two Phase 1 Studies (16 mg QD)

HM-PHI-101

HM-PHI-101 was a Phase 1, multicenter, open-label, "3+3" dose-finding study to determine the MTD, dose-limiting toxicity, anticancer effect, and PK profile of poziotinib in patients with advanced solid tumors. Patients with advanced solid tumors included primarily patients with lung cancer, breast cancer, gastric cancer, and colorectal cancer. The study comprised a dose-escalation phase, consisting of administration of single oral doses of poziotinib ranging from 0.5 mg to 32 mg (n=43), and a dose-expansion phase, in which 12 additional patients were enrolled at the MTD. During dose-escalation, the dose was escalated to 0.5 mg, 1 mg, 2 mg, 4 mg, 8 mg, 12 mg, 16 mg, 20 mg, 24 mg, and 32 mg by level, with at least 3 patients treated for each dose level. Dose-limiting toxicity (Grade 3 diarrhea) occurred in 11.9% of patients overall and in 28.6% of patients treated with poziotinib 32 mg. In patients treated with poziotinib 16 mg, Grade 3 events of diarrhea, stomatitis, and rash occurred in 16.7%, 0%, and 0% of patients, respectively. Based on the safety results the MTD of poziotinib was determined to be 24 mg QD, and the recommended dose was 16 mg QD.

HM-PHI-102

HM-PHI-102 was a prospective, multicenter, open-label, Phase 1 study of poziotinib given continuously in patients with advanced solid tumors. The study consisted of a dose-escalation phase, with poziotinib administered as single oral doses ranging from 12 to 24 mg poziotinib (n=12), and a food effect phase (n=8) (results of food effect presented in more detail in Section 4.4.1). Twenty patients received ≥ 1 dose of poziotinib. Overall, 45.0% of patients reported Grade 3 AEs, the most common of which was diarrhea (3 patients). One patient had a Grade 4 event of blood amylase increased, which was not due to study drug. Based on safety results of a continuous dosage regimen, the MTD of poziotinib was determined to be 18 mg QD and the recommended dose was 16 mg QD.

Although the above studies were conducted in patients across multiple tumor types, poziotinib monotherapy utilizing an oral dose of 16 mg QD on either an intermittent or continuous dosing regimen induced a partial response or disease stabilization in patients with several advanced solid tumor types. For patients with locally advanced or metastatic NSCLC, patients experienced AEs that were either expected for their underlying malignancy or are commonly seen with other HER2 targeted therapies (eg, diarrhea, rash, and stomatitis). Based on these data, the 16 mg QD dose of poziotinib was the selected dose in Cohort 2, which enrolled NSCLC patients with HER2 exon 20 insertion mutations, who had been treated with prior systemic therapy.

4.3.2 Study 202 Cohort 5

Study 202 is a Phase 2, ongoing, open-label, multicenter, multi-cohort study to evaluate the efficacy and the safety/tolerability of range of poziotinib doses in patients with NSCLC with locally advanced or metastatic tumors harboring EGFR or HER2 insertion mutations (see Section 5.2). The study includes 5 randomized dosing arms (poziotinib 16 mg QD, 8 mg BID, 12 mg QD, 6 mg BID, and 10 mg QD arms). Poziotinib is administered continuously on each day of every 28-day cycle.

The efficacy and safety data presented in Section 7 support the selection of 16 mg QD as the starting dose.

4.3.3 Dose Selection Conclusions

Poziotinib 16 mg QD is the recommended starting dose based on results from the two Phase 1 studies (HM-PHI-101; HM-PHI-102) and Study 202 Cohort 5.

4.4 Extrinsic Factors Affecting Poziotinib Pharmacokinetics

4.4.1 Food Effect

Although most clinical trials were conducted in the fasted state, no clinically meaningful differences were observed under fed or fasting conditions.

4.4.2 Drug-Drug Interactions

Clinical Studies

Strong CYP3A Inhibitors: Coadministration of poziotinib with itraconazole, a strong CYP3A inhibitor, increased poziotinib C_{max} and area under the concentration-time curve extrapolated from time 0 to infinity (AUC_{0-inf}) by approximately 2-fold and 2-fold, respectively compared to an 8 mg dose of poziotinib administered alone.

Strong CYP3A Inducers: Coadministration of poziotinib with phenytoin, a strong CYP3A inducer, decreased poziotinib C_{max}, and AUC_{0-inf} by approximately 49% and 60% respectively, compared to a single dose of poziotinib administered alone.

Strong CYP2D6 Inhibitors: Coadministration of poziotinib with paroxetine, a strong CYP2D6 inhibitor, increased poziotinib AUC_{0-inf} by approximately 1.5-fold, while C_{max} remained unchanged, compared to an 8 mg dose of poziotinib administered alone.

CYP450 Substrates

Poziotinib is a reversible inhibitor, time-dependent inhibitor and an inducer of CYP3A but does not inhibit or induce CYP2D6, CYP1A2, CYP2B6, CYP2C9, or CYP2C19 at clinically relevant concentrations. Poziotinib is an inhibitor of CYP3A4 when testosterone was used as a substrate but not when midazolam was used as a substrate.

Coadministration of poziotinib with strong CYP3A4 inhibitors may increase poziotinib plasma concentrations, which may increase the risk of adverse reactions. Therefore, the proposed label recommends avoiding concomitant use of strong CYP3A4 inhibitors with poziotinib. Additionally, coadministration of poziotinib with strong CYP3A4 inducers may decrease poziotinib exposure, which may decrease efficacy of poziotinib therefore, concomitant use of strong CYP3A4 inducers with poziotinib should be avoided.

Concomitant use of a strong CYP2D6 inhibitor with POZENVEO increased poziotinib plasma concentrations, which may increase the incidence and severity of adverse reactions of POZENVEO. The effect of coadministration of a moderate CYP2D6 inhibitor with POZENVEO on poziotinib plasma concentrations has not been studied. Monitor for adverse reactions more frequently in patients co-administered a strong or moderate CYP2D6 inhibitor with POZENVEO and reduce the POZENVEO dosage based on the severity of the adverse reactions.

Poziotinib is a substrate of P-gp, but not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2K. Poziotinib is an inhibitor of P-gp and BCRP. At clinically relevant concentrations, clinical drug-drug interactions with OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, BSEP, MATE1 and MATE2K substrate drugs are not anticipated.

5   CLINICAL EFFICACY IN SECOND-LINE OF TREATMENT

Summary

- Poziotinib demonstrated efficacy in the pivotal study, Cohort 2, which is supported by consistent results in Cohort 5 and the Investigator-initiated MDACC study.

- The pivotal study, Cohort 2, evaluated the efficacy of poziotinib 16 mg QD in previously treated adult patients with NSCLC harboring HER2 exon 20 insertion mutations.

  - The ORR was 27.8% (95% CI: 18.9, 38.2), exceeding the pre-specified criterion of 17% for the 95% CI lower bound and demonstrating efficacy in a heavily pre-treated patient population with difficult-to-treat tumor mutations.

  - Clinical activity was observed in the majority of patients: 74.4% of patients had reduced tumor volume during treatment.

  - The DCR of 70.0%, PFS of 5.5 months, and DoR of 5.1 months support the primary efficacy results.

- Efficacy data from previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations in Cohort 5 provide supportive evidence of poziotinib 16 mg QD efficacy:

  - The ORR was 40% in 10 patients who received poziotinib 16 mg QD.

  - The DCR was 70%, median PFS was 7.3 months, and the median DoR was 6.5 months.

- The IIT conducted at MDACC also supports the findings of the pivotal study using poziotinib 16 mg QD in patients with Stage IV NSCLC or recurrent HER2 exon 20 insertion mutations.

  - The ORR was 27%.

5.1   Overall Efficacy in Previously Treated Patients with NSCLC with HER2 Exon 20 Insertion Mutations

Efficacy data for previously treated patients with NSCLC with HER2 exon 20 insertion mutations were analyzed as follows:

PIVOTAL EFFICACY DATA: Phase 2 Study (N=90)

> **SPI-POZ-202 Cohort 2:** A Phase 2, multicenter, open-label study of poziotinib (16 mg QD) in the treatment of previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations (N=90).

SUPPORTIVE EFFICACY DATA: Phase 2 study and an MDACC sponsored study (**NCT03066206**) (data cutoff: 16 May 2022)

SPI-POZ-202 Cohort 5: A randomized, Phase 2, multicenter, open-label study of poziotinib in patients with NSCLC harboring HER2 exon 20 insertion mutations (previously treated, poziotinib 16 mg QD N=10).

NCT03066206 (MDACC IIT): A Phase 2, multicenter, open-label study of poziotinib (16 mg QD) in the treatment of previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations (N=27).

Additional efficacy data in the first-line settings from Cohort 4 are included below.

5.2   Phase 2 Study 202 Overview

Study 202 is a Phase 2, open-label, multi-cohort study to evaluate the efficacy and the safety/tolerability of poziotinib. Study 202 data presented in this Briefing Document focuses on the previously treated patients with NSCLC harboring HER2 insertion mutations (Cohort 2 and Cohort 5). Importantly, each patient cohort in Study 202 was designed as standalone study (ie, the statistical analyses and tests of hypotheses are conducted independently of other cohorts).

5.3   Second-Line Efficacy Pivotal Study (Study 202 Cohort 2)

5.3.1   Overview

Cohort 2 is a Phase 2, open-label, multicenter study conducted at 34 active sites in the US, Canada, France, Italy, Netherlands, and Spain to evaluate the efficacy and the safety/tolerability of poziotinib in patients with NSCLC harboring HER2 exon 20 insertion mutations.

After screening, enrolled patients received poziotinib, administered orally as 16 mg QD (two 8-mg tablets) during each 28-day cycle (Figure 8). If needed, doses could be reduced by 2 mg/dose poziotinib at the Investigator's discretion based on protocol recommended dose modifications. Dose reductions other than by 2 mg increments required approval by the Sponsor's Medical Monitor.

Tumor assessments were performed using central radiographic review by an Independent Radiologic Review Committee. Tumor response was evaluated based on RECIST version 1.1 criteria. Baseline tumor assessments were performed within 2 weeks prior to, or on Cycle 1, Day 1; additional planned assessments were performed at 4 weeks, 8 weeks, and then every 8 weeks (± 7 days) thereafter until disease progression, death, intolerable AEs, or other protocol-specified reasons for patient withdrawal. Each subsequent tumor assessment was to use the same Baseline radiographic technique – computed tomography (CT), positron-emission tomography (PET)/CT, or magnetic resonance imaging (MRI) – at every assessment.

Figure 8:   Cohort 2 Design
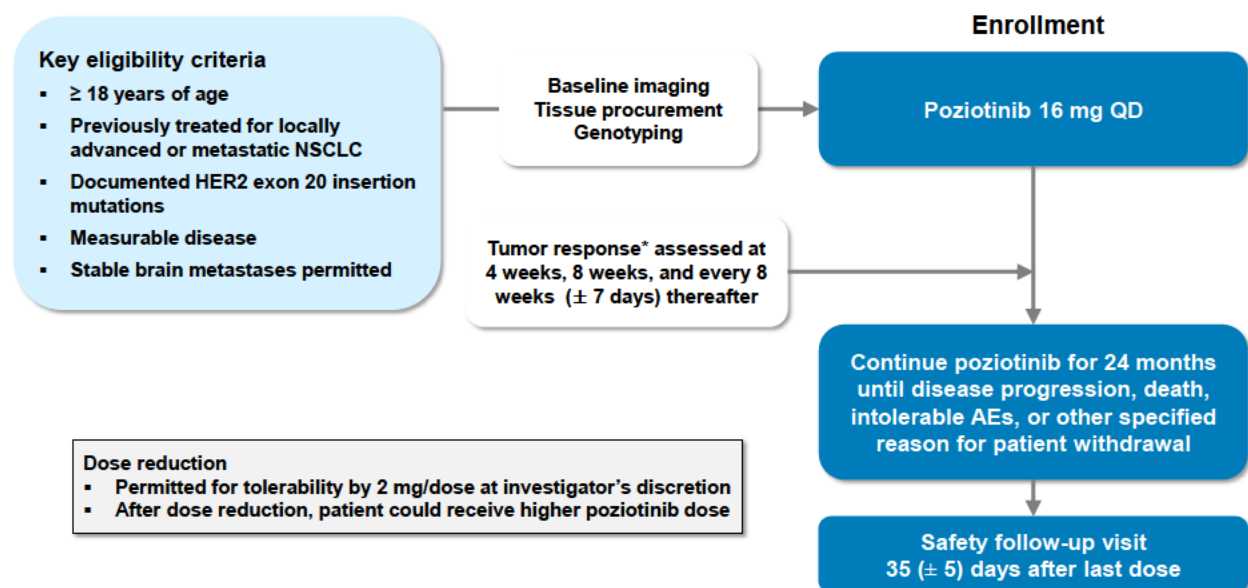
AE: adverse event; HER2: human epidermal growth factor receptor 2; NSCLC: non-small cell lung cancer; QD: once daily.

5.3.2   Key Enrollment Criteria

5.3.2.1   Inclusion Criteria

The key inclusion criteria included:

- Adults, at least 18 years old

- Diagnosis of histologically or cytologically confirmed locally advanced or metastatic NSCLC with documented HER2 exon 20 insertion mutations (including duplication mutations but excluding sensitive mutations such as point mutations)

- Received at least one prior systemic treatment

- ECOG performance status of 0 or 1

5.3.2.2   Exclusion Criteria

Key exclusion criteria included:

- Presence of EGFR T790M

- EGFR or HER2 exon 20 point mutations

- Previous treatment with poziotinib or any other EGFR or HER2 exon 20 insertion mutation selective TKI prior to study participation

- Currently approved TKIs (ie, erlotinib, gefitinib, afatinib, osimertinib) were not considered to be exon 20 insertion-selective and were permissible

5.3.3 Efficacy Endpoints

The primary efficacy endpoint was:

- ORR, defined as the proportion of patients whose best overall response was confirmed to be CR or PR from the first dose of poziotinib until the last tumor assessment on study

Tumor response was based on central radiographic review by an IRC.

Secondary efficacy endpoints included:

- DCR, defined as the proportion of patients whose best overall response (BOR) was CR, PR, or SD from the first dose of poziotinib until the last tumor assessment on study

- DoR, evaluated only for patients whose BOR was either CR or PR, was defined as the time (in months) from the date when response evaluation criteria were first met for CR or PR (whichever status is recorded first) until the first subsequent date when progressive disease (PD) or death was documented

Exploratory endpoints included:

- PFS, defined as the time from the treatment start date to the first date of documented PD or death was evaluated as an exploratory endpoint.

- Quality of Life (QoL) measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionaire-30 and -LC13 (EORTC-QLQ).

5.3.4 Statistical Methods

5.3.4.1 Sample Size

Cohort 2 was analyzed as a standalone study with individual primary endpoint and was powered for testing hypotheses separately. The sample size justification for Cohort 2 with previously treated patients with NSCLC HER2 exon 20 mutations was based on the literature available at that time. The literature available at that time was primarily in patients with EGFR exon 20 mutation and was mostly from small, non-controlled, and retrospective studies.

The reported response rate of patients with EGFR exon 20 mutations to gefitinib and erlotinib is low at 5% with a median PFS of 1.5 months. A combined post hoc analysis of LUX-Lung 2, LUX-Lung 3 and LUX-Lung 6 clinical trials showed that the response rate to afatinib is 8.7% with a median PFS of 2.7 months in EGFR exon 20 mutant patients.

The most promising data that were available when the study was initiated were obtained using irreversible TKIs targeting HER2/3 and EGFR, such as afatinib, neratinib, and dacomitinib. Three out of eight HER2 mutant NSCLC patients who were treated with afatinib achieved a PR. Dacomitinib demonstrated an overall 13% response rate in 26 patients with NSCLC harboring HER2 mutations.

Based on the literature available at the time of the study initiation, as described in Section 1.1 above and per FDA discussion, an ORR of 17% was considered to be clinically meaningful ORR in this patient population as it is higher than the range of ORRs seen across all available therapies. Per the Study 202 SAP, a 17% lower bound of the 95% CI was pre-specified as the efficacy threshold for this study. The sample size calculation was based on single-arm hypothesis testing to reject a non-desired ORR of 17% vs an expected ORR of 30%. A sample size of 87 patients provides 85% power for a two-sided test with a significance level of 5% to reject a non-desired ORR of 17%.

5.3.4.2   Analysis Populations

The As-Treated Population was the primary analysis population and included all patients who received at least one dose of study medication.

The Evaluable Population excludes patients from As-Treated Population who did not have baseline target lesion(s) identified by central review or who did not have evaluable best overall tumor response.

The Safety Population includes all patients who signed informed consent, enrolled, and received at least one dose of study treatment.

5.3.4.3   Efficacy Endpoint Analyses

The primary analysis of efficacy endpoints was based on the central imaging review by the IRC. Tumor response was evaluated using RECIST v1.1 criteria. CR or PR required confirmation at a subsequent visit that was ≥ 4 weeks later. A response of SD could only be made if the patient had been on treatment for ≥ 6 weeks.

DoR was evaluated only for patients whose BOR was CR or PR. The DoR of patients without documented PD or death was censored at the time of last tumor assessment.

The PFS time for patients without documented PD or death was censored at the date of last tumor assessment or the date of first treatment if there was no post-baseline tumor assessment.

ORR and DCR were estimated with count, percentage, and 95% CI (Clopper-Pearson method). The distribution of PFS and DoR was estimated using the Kaplan-Meier method; the median and quartiles of DoR and the DoR rate at 3, 6, 9, and 12 months were reported with corresponding 95% CI.

The QoL analyses were based on the As-Treated Population. The global health status/QoL, functional scales, symptom scales, and lung cancer-related symptoms were summarized for each evaluation time point using descriptive statistics.

5.3.4.4 Subgroup Analyses

Although not statistically powered, pre-specified subgroup analyses were performed for key efficacy endpoints by demographic and baseline characteristics, mutational subgroups, and subgroups based on patients' prior therapy(ies) for advanced or metastatic NSCLC.

5.3.5 Patient Population

5.3.5.1 Disposition

Ninety patients were enrolled and received at least one dose of poziotinib; these patients are included in the Safety Analysis Population and the As-Treated Population (Table 9). Seventy-four (82.2%) patients who had both baseline target lesion(s) identified by central review and an evaluable best overall tumor response were included in the Evaluable Population.

At the time of the primary endpoint analysis, 1 patient was ongoing, and all other patients have discontinued. The primary reason for discontinuation was disease progression. At the 19 Nov 2022 data cutoff, a total of 14 (15.6%) patients have discontinued due to AEs and 10 (11.1%) due to death as the primary reason.

Table 9:   Patient Disposition – Cohort 2

	N=90 n (%)
Patient Population	
As-Treated Population	90 (100.0)
Evaluable Population	74 (82.2)
Safety Population	90 (100.0)
Disposition	
Ongoing Treatment	1 (1.1)
Discontinued from Study, Primary Reason:	89 (98.9)
Adverse Event	14 (15.6)
Initiation of Non-Protocol Therapy	1 (1.1)
Disease Progression	52 (57.8)
Withdrew Consent	5 (5.6)
Delay of Poziotinib Administration for > 28 Days Since Last Administration	2 (2.2)
Lost to Follow-up	2 (2.2)
Death [a]	10 (11.1)
Other [b]	3 (3.3)

a. patient may have had adverse event during discontinuation, but the primary reason for discontinuation was death per Investigator.
b. One patient wished to stop taking study drug due to toxicities and two other patients discontinued because of likely clinical or disease progression, with one patient seeking hospice care.
Data cutoff: 19 Nov 2021

5.3.5.2   Demographics and Baseline Characteristics

Demographics and other baseline characteristics of the study patient population were representative of a population of previously treated patients with NSCLC harboring exon 20 mutations (Table 10).

The median patient age was 60.0 years, with the majority of patients being less than 65 years old. The majority of patients were female and predominantly White. The majority of patients were never smokers and had an ECOG performance status of 1 (ambulatory).

Table 10:   Summary of Patient Demographics – Cohort 2

Characteristic (Unit)	(N=90)
Age (years)	
Mean (SD)	60.0 (11.69)
Median (min, max)	60.0 (25, 86)
< 65 years	56 (62.2)
≥ 65 years	34 (37.8)
Sex, n (%)	
Male	32 (35.6)
Female	58 (64.4)
Ethnicity, n (%)	
Hispanic or Latino	5 (5.6)
Not Hispanic or Latino	85 (94.4)
Race, n (%)	
White	70 (77.8)
Black or African American	4 (4.4)
American Indian or Alaska Native	1 (1.1)
Asian	12 (13.3)
Other	3 (3.3)
Smoking Status, n (%)	
Never	59 (65.6)
Current	1 (1.1)
Former	30 (33.3)
Weight (kg)	
Mean (SD)	71.57 (16.301)
Median (min, max)	72.60 (39.5, 117.5)
ECOG Performance Status, n (%)	
0	38 (42.2)
1	52 (57.8)

ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; Max: maximum; Min: minimum; SD: standard deviation.
Data cutoff: 05 Mar 2021

The specific HER2 exon 20 NSCLC mutations that were present in patient's tumors at Screening are presented in Figure 9. The majority of patients enrolled into the study had tumors with the Y772_A775dup insertion mutation, which is known to be most prevalent in this patient population based on the literature (Robichaux et al 2019). The only other mutations present in ≥ 5% of patient's tumors were the G776delinsVC and G778_P780dup mutations.

Figure 9: Frequency of HER2 Exon 20 Mutations – Cohort 2
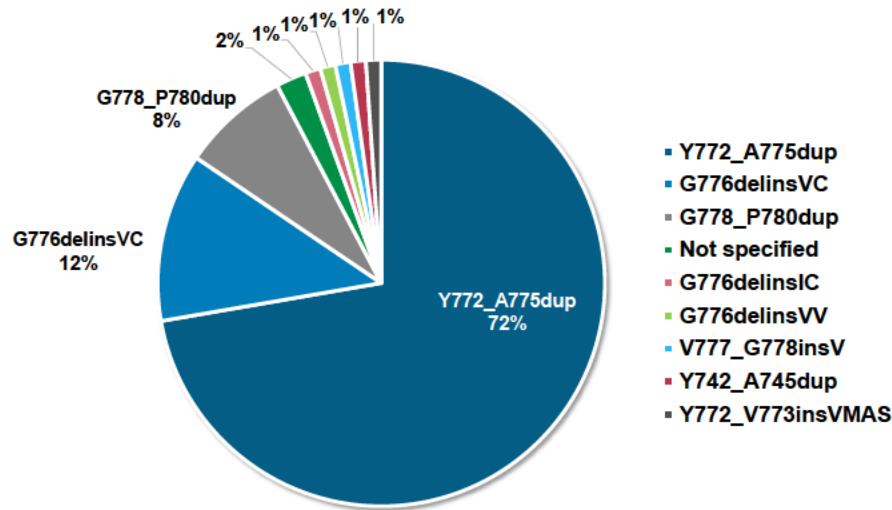
HER2: human epidermal growth factor receptor 2.
Data cutoff: 05 Mar 2021

In general, patients in this study were heavily pre-treated with a median of 2 lines of therapy (Table 11). A total of 38.9% of patients had received at least 3 prior lines of systemic therapy, and a large majority (96.7%) of patients had received prior platinum-based chemotherapy, whereas 67.8% of patients had received prior CPI therapy and 27.8% of patients had received prior HER2-targeted therapy. All patients had previously received one or more of the 3 types of prior therapies in combination or separately, including chemotherapy and CPIs but not HER2-targeted therapy; chemotherapy only; and chemotherapy, HER2-targeted therapy, and CPI. In addition to prior systemic therapies for advanced NSCLC, 48.9% of patients had prior surgery, and 57.8% had received prior radiation therapy for their cancer.

Table 11:   Summary of Prior Therapy for Cancer – Cohort 2

Characteristic (Unit)	N=90
Number of Line of Prior Systemic Therapy	
Median	2.0
Min, Max	1, 6
Number of Line of Prior Systemic Therapy, n (%)	
1 Line	27 (30.0)
2 Lines	28 (31.1)
3+ Lines	35 (38.9)
Type of Prior Systemic Therapy, n (%)	
Chemotherapy	88 (97.8)
Platinum-Based Chemotherapy	87 (96.7)
CPI	61 (67.8)
TKI-EGFR	12 (13.3)
HER2-Targeted Therapy	25 (27.8)
VEGF-Targeted Therapy	14 (15.6)
Multiple Prior Systemic Therapies [a], n (%)	
Chemotherapy Only	22 (24.4)
Chemotherapy, CPI	41 (45.6)
Chemotherapy, HER2-Targeted Therapy [b]	7 (7.8)
Chemotherapy, HER2-Targeted Therapy, CPI	18 (20.0)
CPI only	2 (2.2)
Other Previous Therapy for Cancer, n (%)	
Prior Cancer Surgery	44 (48.9)
Prior Radiation Therapy	52 (57.8)

CPI: checkpoint inhibitor; HER2: human epidermal growth factor receptor 2; TKI-EGFR: tyrosine kinase inhibitor for epidermal growth factor receptor; VEGF: vascular endothelial growth factor.
Note: Chemotherapy includes carboplatin, cisplatin, pemetrexed, docetaxel, paclitaxel, gemcitabine, vinorelbine, etoposide, decitabine, and irinotecan.
Note: Platinum-based chemotherapy includes carboplatin and cisplatin.
Note: CPI includes pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, ipilimumab, and tremelimumab.
Note: TKI-EGFR includes afatinib and erlotinib.
Note: HER2-targeted therapy includes trastuzumab, trastuzumab emtansine (T-DM1), pertuzumab, and neratinib.
Note: VEGF-targeted therapy includes bevacizumab and ramucirumab.
a. Administered separately or in combination.
b. One patient had only non-platinum-based chemotherapy.
Data cutoff: 05 Mar 2021

5.3.6   Efficacy Results

5.3.6.1   Objective Response Rate

The primary endpoint was met in Cohort 2. Based on independent central radiographic review in the As-Treated Population, 25 patients experienced PR, resulting in a modified

ORR of 27.8% (95% CI: 18.9, 38.2; Table 12). The lower bound of the 95% CI exceeded the pre-specified criterion of 17%.

The DCR by central imaging review was 70.0% (95% CI: 59.4, 79.2).

Table 12:   Summary of Efficacy by Central Independent Radiographic Review – Cohort 2

	As-Treated Population N=90	Evaluable Population N=74
Confirmed Best Overall Response [a,b], n (%)		
CR	0	0
PR	25 (27.8)	26 (35.1)
SD	38 (42.2)	35 (47.3)
PD	13 (14.4)	13 (17.6)
NE	14 (15.6)	0
ORR (CR+PR) [a,b], n (%)	**25 (27.8)**	**26 (35.1)**
95% CI (%) [c]	(18.9, 38.2)	(24.4, 47.1)
DCR (CR+PR+SD) [a], n (%)	**63 (70.0)**	**61 (82.4)**
95% CI (%) [c]	(59.4, 79.2)	(71.8, 90.3)

CI: confidence interval; CR: complete response; DCR: disease control rate; NE: not evaluable; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease

a. A patient had to be treated for ≥ 6 weeks to be assessed as having SD, PR, or CR. The confirmatory scan for CR or PR had to be ≥ 4 weeks from the initial scan showing a response.

b. For evaluable population, a confirmatory scan for CR or PR was required to be ≥ 3 weeks from the initial scan showing a response.

c. Exact (Clopper-Pearson) confidence limits.

Data cutoff: 05 Mar 2021

Based on independent central radiographic review in the Evaluable Population, the ORR was 35.1% (95% CI: 24.4, 47.1; Table 12). For evaluable population, the requirement for confirmatory scan was reduced from 4 weeks to 3 weeks due to scheduling permission in the original protocol. Therefore, there is one additional PR in the evaluable population.

Overall, 74.4% (67/90) patients experienced a reduction in tumor volume during treatment with poziotinib (Figure 10) demonstrating strong clinical activity in this patient population.

Figure 10: Waterfall Plot – Best Percent Change in Target Lesion Sum of Diameters from Baseline – Cohort 2
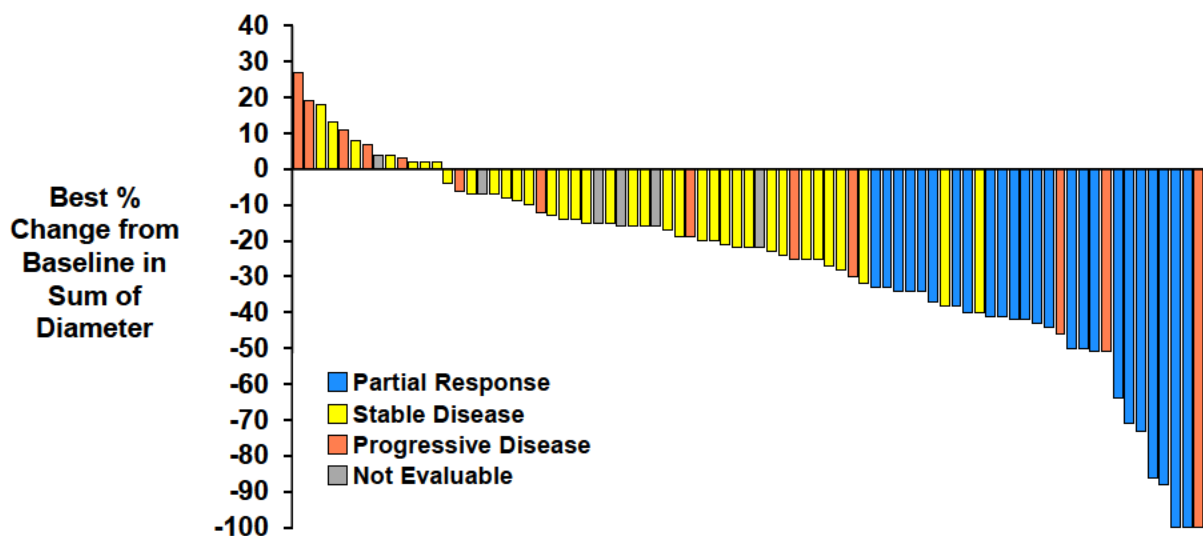
Data cutoff: 05 Mar 2021

5.3.6.1.1 Subgroups

Demographic and Baseline Characteristics

Subgroup analyses were carried out by region (US vs non-US), sex, age group (< 65 years vs ≥ 65 years), and ECOG performance status score (0 vs 1) for the key efficacy endpoints based on the independent central imaging review data in the As-Treated Population. ORRs were generally similar across all patient subgroups with an ORR ranging from 25% to 32.4% (Figure 11).

Prior Therapy Subgroup Analyses

Although, not statistically powered for stratified subgroup analyses, in patients with ≥ 3 lines of prior therapy, the ORR was 37.1% (95% CI: 21.5, 55.1) with the lower bound of the 95% CI exceeded 17%. In patients with 1 and 2 lines of prior therapy, the ORR was 22.2% and 21.4%, respectively. Also, ORRs in patients treated with prior platinum and CPIs and those were treated with HER2 targeted therapy such as trastuzumab, T-DM1, and other ADCs were 25.4% (95% CI: 15.0, 38.4) and 24.0% (95% CI: 9.4, 45.1), respectively, indicating that poziotinib showed similar clinical activity regardless of line of therapy or prior use of CPIs and/or HER2 targeted therapies.

Subgroup of Patients with Baseline Brain Lesion(s)

Based on the independent central imaging review in a subgroup of 14 patients with stable brain lesion(s) at baseline, ORR was 28.6% (95% CI: 8.4, 58.1).

Mutational Subgroup Analyses

Anti-tumor activity and radiographic responses were observed across all HER2 exon 20 mutation subgroups. Y772_A775dup, a difficult to-treat mutation, was the most common mutation in this study population, and the ORR in this subgroup was 20.0% (95% CI: 11.1, 31.8). In a subgroup of 7 patients whose tumors had the G778_P780dup mutation had confirmed PR, resulting in an ORR of 100% (95% CI: 59.0, 100).

Figure 11:   ORR Subgroup Analyses Based on Central Radiologic Review – Cohort 2

	N	ORR, % (95% CI)	ORR, % (95% CI)
All patients	90		27.8% (19, 38)
< 65 years	56		25.0% (14, 38)
≥ 65 years	34		32.4% (17, 51)
Female	58		25.9% (15, 39)
Male	32		31.3% (16, 50)
US	61		26.2% (16, 39)
Non-US	29		31.0% (15, 51)
ECOG = 0	38		31.6% (18, 49)
ECOG = 1	52		25.0% (14, 39)
1 prior line of therapy	27		22.2% (9, 42)
2 prior lines of therapy	28		21.4% (8, 41)
3+ prior lines of therapy	35		37.1% (22, 55)
With brain lesion	14		28.6% (8, 58)
Y772_A755dup	65		20.0% (11, 32)
G776delinsVC	11		27.3% (6, 61)
G778_P780dup	7		100% (59, 100)
Other	7		28.6% (4, 71)
Previously treated with TKI	12		50.0% (21, 79)
HER2 targeted therapy	25		24.0% (9, 45)
Plat. based chemo, immune CPI	59		25.4% (15, 38)

CI: confidence interval; CPI: checkpoint inhibitor; ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; plat: platinum; ORR: objective response rate; TKI: tyrosine kinase inhibitor; US: United States. Data cutoff: 05 Mar 2021

5.3.6.1.2   Efficacy Analyses Based on Local Imaging Review

The results of the local evaluation were consistent with that of central review. Based on local radiographic evaluation, in the As-Treated Population, there was 1 CR and 24 PRs, resulting in an ORR of 27.8% (95% CI; 18.9, 38.2). An analysis of inter-rater agreement on BOR between central and local imaging reviews found substantial agreement between the two methods. Seventy-two (80%) of 90 reviews matched, with a weighted kappa of 0.783 (95% CI: 0.682, 0.884).

In the Evaluable Population with local imaging review, the modified BOR was CR for 1 (1.4%) and PR for 25 (33.8%) patients, resulting in an ORR of 35.1%, which is identical to the ORR obtained in the analysis using central imaging review.

5.3.6.2 Secondary Efficacy Results – Duration of Response

The median DoR was 5.1 months (95% CI: 4.2, 5.5), with 24.0% of responders having a DoR ≥ 6 months (Table 13). The Kaplan-Meier plot for DoR by central imaging review is provided in Figure 12.

Table 13:   Summary of Duration of Response Confirmed by Central Radiographic Review – Cohort 2

	Patients with Best Overall Response of CR or PR N=25
Patients with Disease Progression or Death, n (%)	21 (84.0)
Patients Censored, n (%)	4 (16.0)
Length of Follow-up from First Response (months) [a]	
Median (Min, Max)	NR (1.0, 14.1)
Duration of Response (months) [a]	
First Quartile (95% CI)	4.2 (2.3, 4.9)
Median (95% CI)	5.1 (4.2, 5.5)
Third Quartile (95% CI)	6.4 (5.2, 11.2)
Min, Max	1.0, 14.1
Patients with Duration of Response, n (%)	
≥ 3 months	20 (80.0)
≥ 6 months	6 (24.0)
≥ 9 months	3 (12.0)
≥ 12 months	1 (4.0)

CI: confidence interval; CR: complete response; Max: maximum; Min: minimum; NR: not reached; PR: partial response.
a. Kaplan-Meier (productive-limit) estimate.
Data cutoff: 05 Mar 2021

Figure 12:   Kaplan-Meier Plot for Duration of Response in Patients with a Complete Response or Partial Response by Central Imaging Review – Cohort 2

	Poziotinib N = 25
Median DoR, % (95% CI)	5.1 (4.2, 5.5)
≥ 6 months, %	24%

Patients at risk: 25   20   6   3   1   0
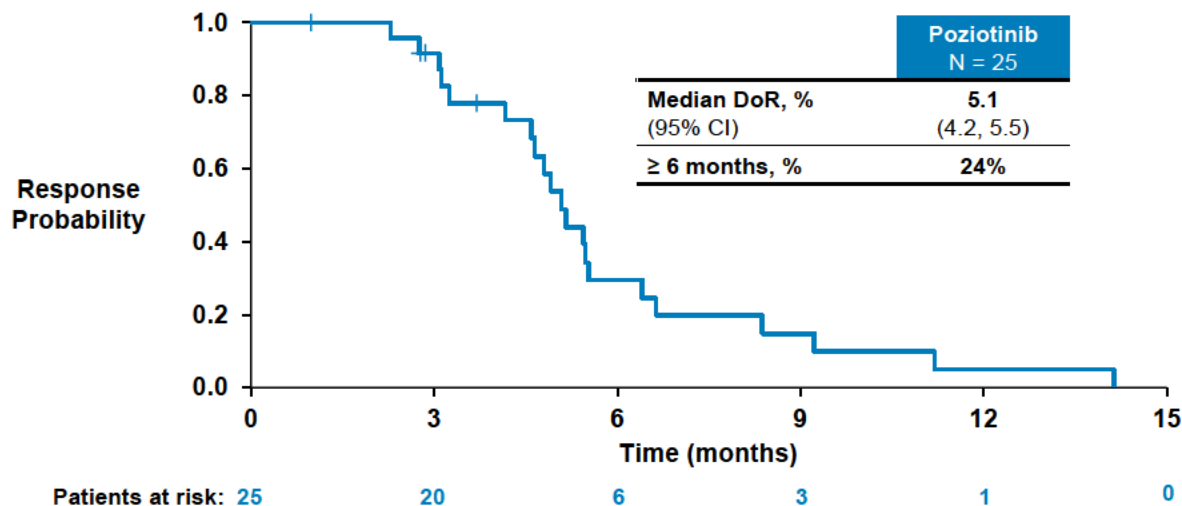
CI: confidence interval; DoR: duration of response
Data cutoff: 05 Mar 2021

5.3.6.3   Exploratory Efficacy Results – Progression-Free Survival

As of the data cutoff date and based on central imaging review in the As-Treated Population, 61.1% of patients experienced disease progression or death, with 38.9% of patients censored (Table 14). The median length of follow-up was 9.0 months (range, 0.0 [1 day] to 17.6 months), median PFS was 5.5 months (95% CI: 3.9, 5.8), and 37.8% of patients (95% CI: 25.5, 50.0) had not progressed or died at 6 months.

The Kaplan-Meier plot for PFS in the As-Treated Population is presented in Figure 13.

Table 14:   Summary of Progression-Free Survival by Central Imaging Review – Cohort 2

	N=90
Patients with Disease Progression or Death, n (%)	55 (61.1)
Patients Censored, n (%)	35 (38.9)
Length of Follow-up (months) [a]	
Median (Min, Max)	9.0 (0.0, 17.6)
Progression-free Survival (months) [a]	
First Quartile (95% CI)	3.5 (1.9, 3.9)
Median (95% CI)	5.5 (3.9, 5.8)
Third Quartile (95% CI)	7.4 (6.1, 12.1)
Progression-free Survival Rate (%) [a]	
At 3 months (95% CI)	77.7 (66.4, 85.5)
At 6 months (95% CI)	37.8 (25.5, 50.0)
At 9 months (95% CI)	22.0 (12.1, 33.8)
At 12 months (95% CI)	14.0 (5.8, 25.6)

CI: confidence interval; Max: maximum; Min: minimum.
a. Kaplan-Meier (product-limit) estimate.
Data cutoff: 05 Mar 2021

Figure 13:   Kaplan-Meier Plot for Progression-Free Survival by Central Imaging Review – Cohort 2
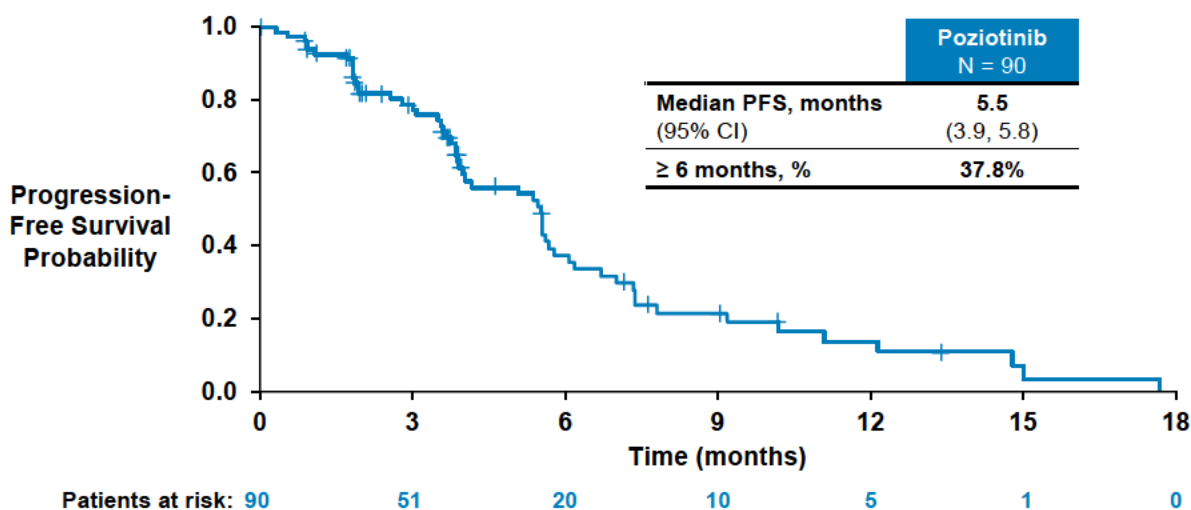
CI: confidence interval; PFS: progression-free survival.
Data cutoff: 05 Mar 2021

5.3.6.4   Exploratory Analysis – Overall Survival

Although the study was not designed to perform an analysis of OS, an exploratory analysis of OS was performed using reported death as the event during the treatment follow-up. Since the patients discontinued once the criteria of toxicity, disease progression or other reason was met, OS analysis is challenged by significant right

censoring. The median OS in the study was 16.8 months (95% CI: 8.9, not available [NA]) (Figure 14).

Figure 14:   Kaplan-Meier Plot for Overall Survival by Central Imaging Review – Cohort 2
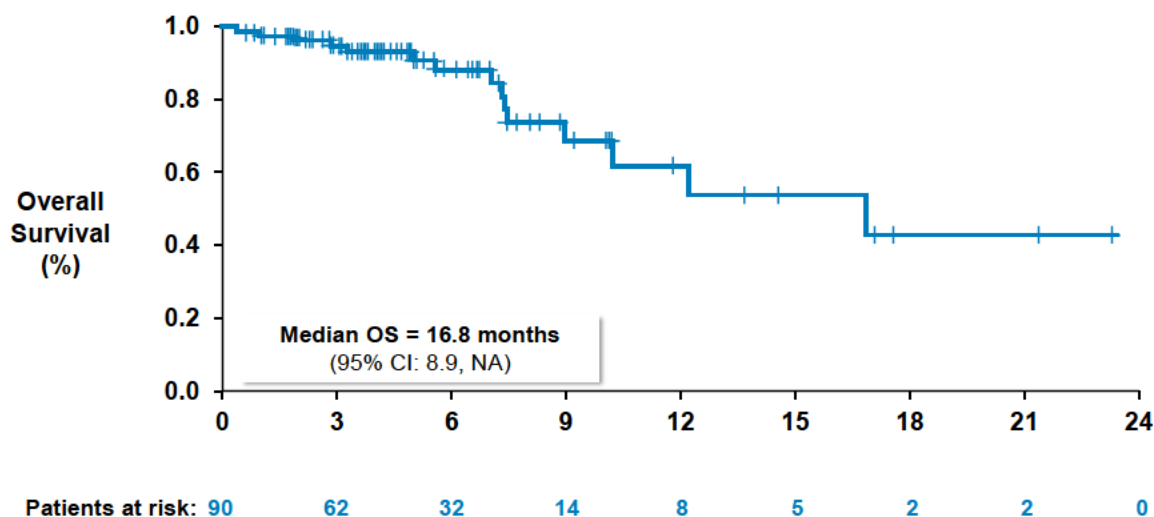
CI: confidence interval; NA: not available; OS: overall survival.
Note: Overall survival was not an efficacy endpoint for Study 2 Cohort 2, and thus patients were not followed for survival after disease progression.
Data cutoff: 05 Mar 2021

5.3.6.5   Exploratory Analysis – Quality of Life

In this single-arm study, validated QoL questionnaires were used (EORTC-QLQ-30 and -LC13). Global and Functional Scales showed no major improvement (ie, increase) or worsening (ie, decrease) over time at each Study visit (Figure 15). Major symptoms that got worse (increase > 10 points) with poziotinib treatment included diarrhea, sore mouth, and alopecia. A major improved symptom (decrease > 10 points) with poziotinib treatment was cough.

Figure 15: **Cohort 2 Change from Baseline in Lung Cancer Symptoms Over Time – As-Treated Population**
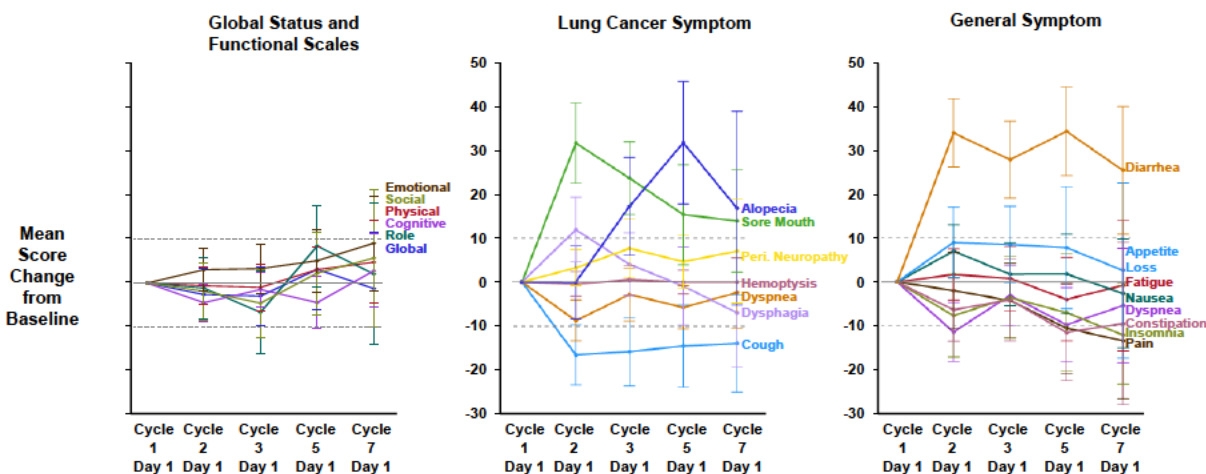
Number of patients completed QoL at Cycle 1, Cycle 2, Cycle 3, Cycle 5, and Cycle 7 were 90, 74, 66, 38, and 25, respectively.
Data cutoff: 05 Mar 2021

5.4 Second-Line Supportive Efficacy (Study 202 Cohort 5)

5.4.1 Overview

Study 202 Cohort 5 is an independent cohort in the ongoing randomized, Phase 2, open-label, multicenter, dose-ranging study evaluating the efficacy and the safety/tolerability of poziotinib.

The primary objective was to assess the ORR in the As-Treated Population. Secondary efficacy objectives were to evaluate DCR and DoR.

5.4.2 Patient Population

Since Cohort 5 enrollment is currently ongoing, the data presented here are updated from the data originally submitted NDA (data cutoff date of 05 Mar 2021) to the most recent data cutoff date of 16 May 2022. Upon completion of Stage-1 analysis, only 8 mg BID cohort continued while the rest of the dose arms were stopped for enrolment.

A total of 237 patients were enrolled into Cohort 5 across the 5 dose arms out of which 226 received at least one dose of poziotinib. As the focus of this Briefing Document is the proposed indication of previously treated HER2 exon 20 mutations, all data presented from here onwards will be only in the subset of the patients matching the proposed indication who were treated with poziotinib 16 mg QD (data cutoff date of 16 May 2022).

At the time of the data cut on 16 May 2022, all 10 patients had discontinued (Table 15). The primary reason for discontinuation was disease progression (60%).

Table 15: Patient Populations and Disposition – Cohort 5

Patient Population/Patient Disposition	Previously Treated HER2 Mutations 16 mg QD n (%)
Patient Population	
Enrolled Patients	10
As-Treated Population	10
Safety Population	10 (100.0)
Discontinued from Study	10 (100.0)
Reasons for Discontinuation	
Disease Progression	6 (60.0)
Adverse Event	1 (10.0)
Death	1 (10.0)
Withdrew Consent	1 (10.0)
Other	1 (10.0)

HER2: human epidermal growth factor receptor 2; QD: once daily
Data cutoff: 16 May 2022.

In Cohort 5, the mean age was 62 years (Table 16). Most patients were female (70.0%), White (80.0%) and never smokers (70.0%).

Table 16: Summary of Patient Demographics and Characteristics – Cohort 5

	16 mg QD N=10
Age (years)	
Mean (SD)	61.9 (8.77)
Median	62.0
Min, Max	44, 71
Sex, n (%)	
Male	3 (30.0)
Female	7 (70.0)
Race, n (%)	
White	8 (80.0)
Other	2 (20.0)
Smoking Status, n (%)	
Never	7 (70.0)
Former	3 (30.0)
ECOG Performance Status, n (%)	
0	3 (30.0)
1	7 (70.0)

BID: twice daily; EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2; Max: maximum; Min: minimum; QD: once daily; ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.
Previously Treated Patients with HER2 Exon 20 Insertion Mutations
Data cutoff: 16 May 2022

5.4.3 Efficacy Results

The ORR by independent image review and DCR results are summarized in Table 17.

The efficacy results of Cohort 5 (16 mg QD) in previously treated NSCLC HER2 exon 20 mutations support the findings of the pivotal study (Cohort 2) with an ORR of 40% and DCR of 70%.

Table 17: Summary of Objective Response Rate and Disease Control Rate Based on Central Imaging Review – Cohort 5

Response	16 mg QD N=10
Confirmed Best Overall Response [a], n (%)	
CR	0
PR	4 (40.0)
SD	3 (30.0)
PD	0
NE	3 (30.0)
ORR (CR+PR) [b], n (%)	**4 (40.0)**
95% CI [c] (%)	(12.2, 73.8)
DCR (CR+PR+SD) [b], n (%)	7 (70.0)
95% CI [c] (%)	(34.8, 93.3)

CI: confidence interval; CR: complete response; DCR: disease control rate; ORR: objective response rate; PD: progressive disease; PFS: progression-free survival; PR: partial response; QD: once daily; SD: stable disease.
Note: Presented for Previously Treated Patients with HER2 Exon 20 Insertion Mutations
Data cutoff: 16 May 2022
a. A patient had to be treated for at least 6 weeks to be assessed as SD/PR/CR. The confirmation scan for CR or PR had to be at least 4 weeks from the initial scan showing response.
b. Clopper-Pearson exact confidence limits.
c. Kaplan-Meier (product-limit) estimate.

In this updated analysis, with currently ongoing patients, median DoR was 6.5 months in 16 mg QD and the median PFS was 7.3 months respectively (Table 18).

Table 18: Summary of Duration of Response and Progression-free Survival by Central Radiographic Review – Cohort 5

Response	16 mg QD N=10
Duration of Response	
Patients with Best Overall Response as CR or PR, n	4
Patients with Disease Progression or Death, n (%) [a]	4 (100)
Median DoR (months) [b]	6.5
95% CI (months) [b]	(3.7, NA)
Progression-free survival	
Patients with Disease Progression or Death, n (%) [c]	6 (60.0)
Median PFS (months) [b]	7.3
95% CI (months) [b]	(5.5, NA)

CI: confidence interval; CR: complete response; DoR: duration of response; NA: not available; PFS: progression-free survival; PR: partial response; QD: once daily.
a. Percentage based on patients with Best Overall Response as CR or PR
b. Kaplan-Meier (product-limit) estimate
c. Percentage based on total patients
Note: Presented for Previously Treated Patients with HER2 Exon 20 Insertion Mutations
Data cutoff: 06 May 2022

5.5 Investigator-Initiated Trial in HER2 Exon 20 Insertion Mutation (MD Anderson Cancer Center Study) – Supportive Efficacy

5.5.1 Overview

This was a single-center, Phase 2, open-label, single-arm, multicohort, Investigator-initiated trial (NCT03066206). NSCLC patients with Stage IV or recurrent HER2 exon 20 insertion mutant lung cancer were eligible for the cohort reported here (Elamin et al 2022). Patients received poziotinib 16 mg QD. The primary endpoint was the ORR evaluated per RECIST version 1.1. Secondary efficacy endpoints included PFS, DoR, DCR, and OS. Tumor response was assessed by a thoracic radiologist at the institution imaging laboratory independent of the study team. Confirmation of objective responses was required by a second scan more than 28 days after initial response was noted.

Patients received poziotinib 16 mg orally QD, until objective disease progression, and could continue beyond progression for as long as clinical benefit was observed, as judged by the Investigator and in the absence of other discontinuation criteria (patient withdrawal, AE). Dose interruption or reduction occurred if patients had a Grade 3 or more non-disease related AE or unacceptable toxicity. If the AE resolved or reverted to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE) Grade 1, poziotinib treatment could be restarted at the same dose (16 mg) or a lower dose (12 mg). A second reduction of dose to 8 mg was allowed for reoccurrence of the same toxicity. If toxicity recurred following two dose modifications, poziotinib was discontinued.

5.5.2 Statistical Methods

A sample size of 30 patients ensured that, if the trial was not terminated early, a posterior 90% credibility interval for ORR will have width of 0.266 at most, under the assumption of a 30% ORR (Elamin et al 2022).

Best overall response and disease control and their exact 95% CIs were estimated. PFS, DoR, and OS outcomes were calculated using the Kaplan-Meier method. Data were analyzed using a 01 March 2021 data cutoff.

5.5.3 Patient Population

A total of 35 patients were screened, and 30 were enrolled and treated with poziotinib between 18 Sept 2017 and 22 Nov 2019. Of 30 patients, 27 patients were previously treated with a platinum-based therapy, 16 (53%) had two lines or more prior systemic therapies. The majority of patients (83%) had never smoked, and all had adenocarcinoma. Most patients had the Y772_A775dupYVMA insertion mutation (77%) or G778_P780dupGSP (17%). The median duration of follow-up at the time of data analysis (data cutoff 01 Mar 2021) was 14.0 months (range 2.0–42.5).

5.5.4 Efficacy Results

Based on MDACC independent laboratory review, poziotinib demonstrated a confirmed ORR of 27.0% overall and 26.0% in patients treated with platinum-based therapy (Table 19). Responses were observed across HER2 exon 20 insertion mutations subtypes. Furthermore, an additional 46% of patients achieved SD, for a DCR of 73%.

Figure 16 shows the waterfall plot of best response to treatment with poziotinib.

Table 19: Summary of Objective Response Rate in Patients with NSCLC Harboring HER2 Exon 20 Insertion Mutations – MDACC Study

Response	
Overall population	**N=30**
ORR (%) [b] (95% CI)	**27.0 (12.0, 46.0)**
Confirmed Partial Response, n (%)	8 (27)
Stable Disease, n (%)	14 (46)
Progressive Disease [a], n (%)	8 (27)
Median OS, months (95% CI)	15.0 (9, NA)
Platinum-pretreated	**N=27**
ORR (%) [b] (95% CI)	**26.0 (11.0, 46.0)**

CI: confidence interval; HRE2: human epidermal growth factor receptor 2; MDACC: MD Anderson Cancer Center; NA: not available; NSCLC; non-small cell lung cancer; ORR: objective response rate; OS: overall survival
a. Includes one patient with early death that was deemed possibly related to poziotinib vs related to disease progression.
b. Confirmed objective response rate.
Source: Elamin et al, 2022

Figure 16: Best Response to Treatment by RECIST version 1.1 Criteria – MDACC Study
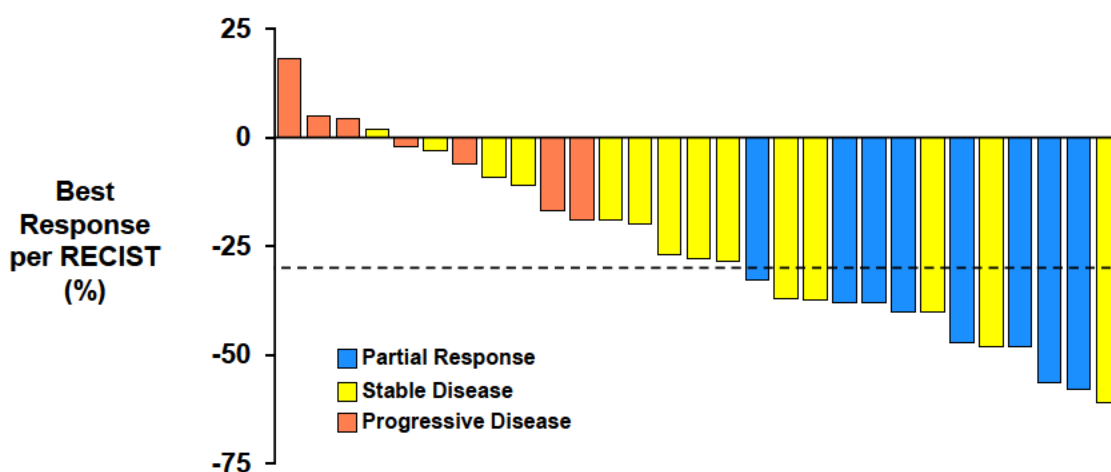
MDACC: MD Anderson Cancer Center; RECIST: Response Evaluation Criteria in Solid Tumors.
Source: Elamin et al, 2022

In a platinum-refractory subset of patients (n=27) the median PFS was 5.0 months (95% CI: 2.0, 6.0) and the 8-week ORR was 47% (95% CI: 25.0, 59.0), with a confirmed PR of 26% (95% CI: 13, 45). The median PFS in patients who received 2 or more prior lines of therapy (n=16) was 4.0 months (95% CI: 2.0, 6.0), and the 8-week ORR was 31% (95% CI: 14, 56) with confirmed PR rate of 19% (95% CI: 7, 43).

At data cutoff, 2 patients remained on treatment, 1 with a confirmed PR and 1 with prolonged SD. Notably, both patients remained on poziotinib after more than 3 years from starting treatment. In the overall population, 8 patients continued poziotinib treatment beyond radiological disease progression for a median of 2.0 months (range 1.5–8.2). The median OS was 15.0 months (95% CI: 9, not reported [NR]; Figure 17).

Figure 17: Overall Survival – MDACC Study
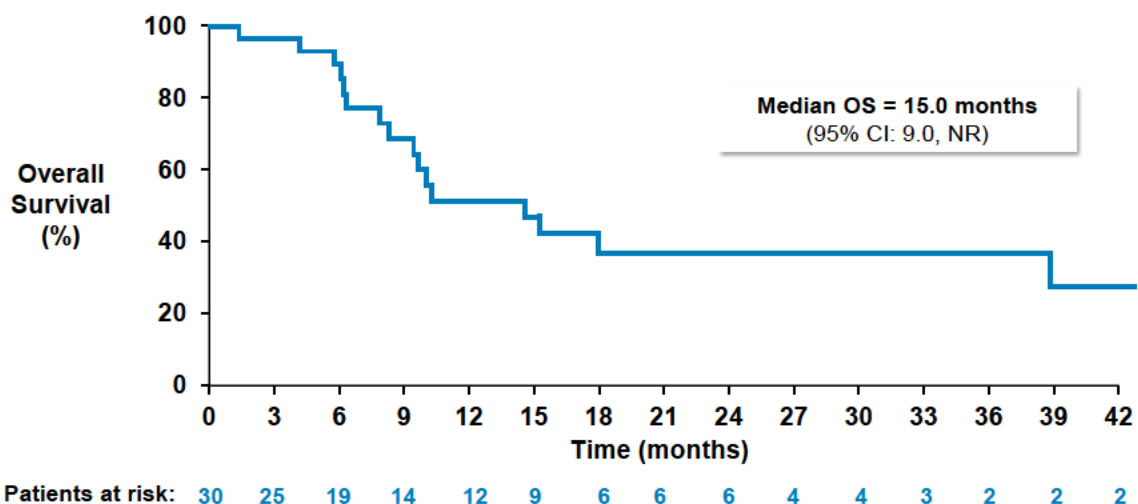
CI: confidence interval; MDACC: MD Anderson Cancer Center; NR: not reported; OS: overall survival.
Source: Elamin et al 2022

5.6 Poziotinib in Treatment-Naïve (First-Line) NSCLC Harboring HER2 Exon 20 Mutations – Additional Supportive Study

In addition to the above studies in previously treated HER2 exon 20 mutations, poziotinib was studied in treatment-naïve NSCLC HER2 exon 20 insertion mutations in Cohort 4.

5.6.1 Design Overview

Study 202 Cohort 4 is an ongoing, open-label, multicenter, Phase 2 study. Eligible patients include those with histologically or cytologically confirmed locally advanced or metastatic NSCLC harboring HER2 exon 20 insertion mutations who are treatment-naïve. Patients received a starting dose of poziotinib of 16 mg QD. Patients enrolled after protocol amendment 3 will receive 8 mg BID. Similar to the pivotal study (Cohort 2), dose reductions by 2 mg were permitted at the discretion of the Investigator to manage adverse reactions.

All patients are treated until disease progression, death, intolerable AEs, or other protocol-specified reason for patient withdrawal.

The primary objective was to assess the ORR (CR+PR) in the As-Treated Population based on central radiographic evaluations. Secondary efficacy objectives were to evaluate DCR and DoR. PFS and QoL were evaluated as exploratory objectives.

5.6.2 Patient Population

The demographics were consistent with the target population. The mean age was 61 years (range: 34–87 years; Table 20).

5.6.3 Results

The primary endpoint of ORR in Study 202 Cohort 4 provides proof-of-concept of poziotinib efficacy. Among the 70 patients treated with poziotinib, 47 were treated with poziotinib 16 mg QD and the remaining 23 were treated with 8 mg BID. The confirmed ORR and DCR by central imaging review were 45% (95% CI: 30, 60) and 75% (95% CI: 60, 86), respectively (Table 20; Figure 18). The median DoR was 5.7 months, and the median PFS was 5.6 months (range: 0- 22.7).

Approximately 75% of patients achieved disease control and reductions in tumor size.

Table 20: **Summary of Demographics and Efficacy – Cohort 4**

	Treated 16 mg QD (N=47)
Age, median (range), years	61 (34–87)
Female / Male, n	25 / 22
Duration of Treatment, median (range), months	4.5 (< 1–21)
Treatment Ongoing, n (%)	1 (2)
Objective Response Rate, n (%) 95% CI	**21 (45)** 30%–60%
ORR in Evaluable Population (n=41), n (%) 95% CI	21 (51) 35%–67%
Disease Control Rate, n (%) 95% CI	35 (75) 60%–86%
Duration of Response, median (range), months	5.7 (2.8–19.1)
Progression-free Survival, median (range), months	5.6 (0–22.7+)

CI: confidence interval; ORR: objective response rate
Patients with NSCLC HER2 Exon 20 Insertion Mutations
Source: Analysis from data presented by Sun, et al, 2022 ESMO TAT

Figure 18: **Waterfall Plot Best Response – Cohort 4**
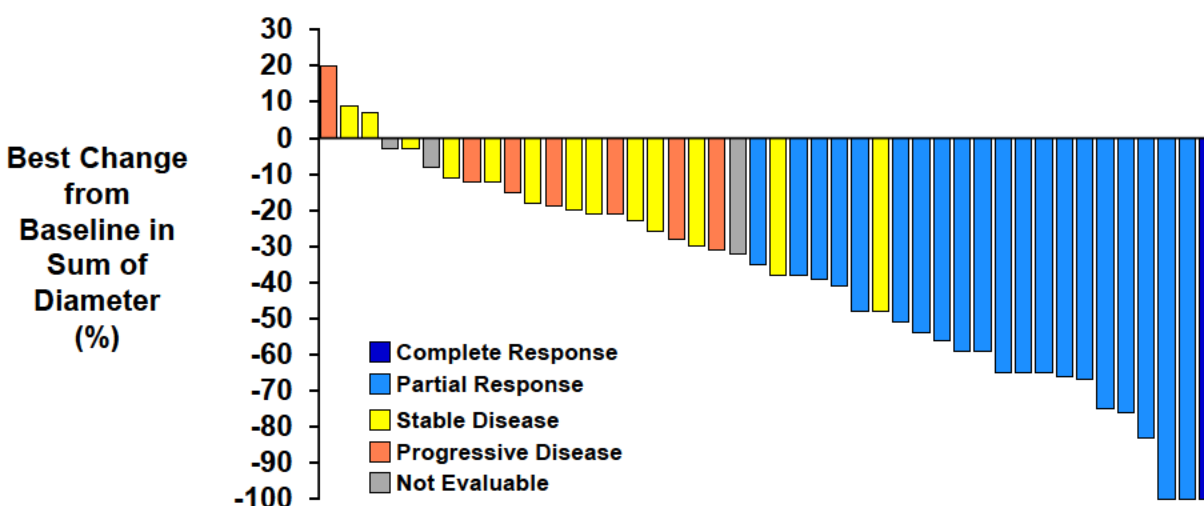
5.7 Summary of Exposure-Response Analysis

An exposure-response (ER) analysis was conducted by Model Answers division of Paraxel International, including data from Study 202 Cohort 2 and Study 202 Cohort 5 across a range of starting doses including 16 mg QD and 8 mg BID. A summary of ER analysis is provided below:

- Patients on starting daily dose of 16 mg tended to have higher relative dose intensity (RDI)-adjusted exposures leading to higher efficacy and showed a trend in dose proportionality across the range of doses.

- Patients on all starting dose experienced dose interruptions and reduction and starting dose < 16 mg daily dose tended to reduce their RDI-adjusted exposure to levels associated with poorer PFS.

- Based on the current data from Study 202 suggested that patients may experience maximum effectiveness by starting at 16 mg daily and be continuously monitored to balance effectiveness and safety.

5.8   Efficacy Conclusions

In Cohort 2, poziotinib demonstrated clinical efficacy in previously treated patients with NSCLC harboring HER2 exon 20 mutations. Based on the independent central imaging review, the primary efficacy endpoint in the As-Treated Population was met (ORR: 27.8% [95% CI: 18.9, 38.2]) and exceeded the pre-specified criterion for clinically meaningful efficacy (Table 21). In addition, the observed reductions in target lesion size during treatment with study drug show that poziotinib provides meaningful clinical activity in a majority of patients in this population.

These results were further supported by Study 202 Cohort 5 and an independent study conducted by MDACC with consistent and reproducible efficacy in the proposed patient population. In Study 202 Cohort 5, the ORR was 40.0% (95% CI: 12.2, 73.8) among patients who received poziotinib 16 mg. In the MDACC study, in the heavily pre-treated population with HER2 exon 20 mutant NSCLC, poziotinib demonstrated encouraging antitumor activity in both TKI-naïve and -refractory patients. Poziotinib provided a 26% confirmed response rate and a median PFS of 5 months in platinum-treated patients. An additional study conducted as a proof-of-concept, poziotinib also demonstrated clinical activity with an ORR of 45% and 75% achieved dose control and tumor reduction in treatment-naïve NSCLC patients with exon 20 insertion mutations.

Table 21:   Poziotinib 16 mg Efficacy in First-and Second-Line Setting for Patients with NSCLC HER2 Exon 20 Insertion Mutations – Poziotinib 16 mg

	Second-Line				First-Line
	Cohort 2 N=90	Cohort 5 N=10	Pooled[a] N=100	MDACC N=27	Cohort 4 N=47
Confirmed Best Overall Response, n					
CR	0	0	0	0	1
PR	25	4	29	7	20
SD	38	3	41	12	14
PD	13	0	13	8	7
NE	14	3	17	0	5
ORR (CR+PR), n (%)	**25 (27.8)**	**4 (40.0)**	**29 (29.0)**	**7 (26.0)**	**21 (44.7)**
95% CI[b] (%)	(18.9, 38.2)	(12.2, 73.8)	(20.4, 38.9)	(11.1, 46.3)	(30.2, 59.9)
DCR (CR+PR+SD), n (%)	**63 (70.0)**	**7 (70.0)**	**70 (70.0)**	**19 (70.3)**	**35 (74.5)**
95% CI[b] (%)	(59.4, 79.2)	(34.8, 93.3)	(60.0, 78.7)	(49.8, 86.3)	(59.7, 86.1)
Median DoR[c], mos	5.1	6.5	5.2	5.0	5.7
95% CI[c] (mos)	(4.2, 5.5)	(3.7, NA)	(4.6, 6.4)	(4.0, NA)	(4.6, 11.9)
Median PFS[c], mos	5.5	7.3	5.6	5	5.6
95% CI[c] (mos)	(3.9, 5.8)	(5.5, NA)	(4.0, 6.2)	(2.0, 6.0)	(4.3, 9.1)

CI: confidence interval; CR: complete response; DCR: disease control rate; DoR: duration of response; HER2: human epidermal growth factor receptor 2; NE: not evaluable; NA: not available; ORR: objective response rate; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease.
a. Pooled data is the corresponding total of results from Cohorts 2 and 5 included in the first 2 columns.
b. Clopper-Pearson exact confidence limits.
c. Kaplan-Meier (product-limit) estimate.
Data cutoff: Cohort 2: 05 Mar 2021; Cohort 5, Cohort 4: 16 May 2022; Cohort 4

6   CLINICAL SAFETY

Summary

- Across the clinical program, poziotinib demonstrated an AE profile that was mostly mechanism based.

- The types of AEs reported were similar to what has been reported for patients treated with other second-generation TKIs.
  - The most common AEs following poziotinib administration were diarrhea, stomatitis, and rash.
- The most common AEs leading to discontinuation were rash and diarrhea
- Approximately 40% of patients experienced at least one SAE; dyspnea and pneumonia were observed most often.
- In Cohort 2, there were 9 SAEs leading to death; 1 was assessed as possibly related to treatment.

- The AESI of the rash-type events, diarrhea, stomatitis-type events, and paronychia were manageable following the recommended prophylactic and management plan, and/or institutional protocol.

  - Most AESI were reversible after drug interruption or discontinuation.

- AEs were managed through dose interruptions and reductions as part of the study design described in the study protocol. Related AEs led to permanent discontinuation in 12% of patients.

- Overall, poziotinib demonstrated a manageable AE profile with safety findings similar to other second-generation TKIs.

6.1   Safety Populations

To characterize safety and efficacy in the same population of previously treated patients with NSCLC harboring HER2 exon 20 insertion mutations, the safety summary below is provided for Cohort 2 (data cutoff: 19 Nov 2021). Following the safety summary for Cohort 2, a high-level summary of safety is provided for Group 1, which includes Study 202 patients with NSCLC, locally advanced or metastatic EGFR or HER2 exon 20 insertion mutation who received poziotinib 16 mg QD or 8 mg BID (data cutoff: 19 Nov 2021).

6.2   Treatment Exposure

The median overall duration of treatment was 112.5 days in Cohort 2 (Table 22).

Table 22:   Summary of Poziotinib Exposure – Cohort 2

Parameter	N=90
Overall Duration ofTreatment (days) [a]	
Mean (SD)	149.6 (151.97)
Median	112.5
Min, Max	1, 972
Number of Cycles [b]	
Mean (SD)	5.4 (5.15)
Median	4.0
Min, Max	1, 33
Average Daily Dose (mg/day) [c]	
Mean (SD)	11.51 (3.147)
Median	11.45
Min, Max	3.3, 16.0
Relative Dose Intensity (%) [d]	
Mean (SD)	71.97 (19.667)
Median	71.53
Min, Max	20.8, 100.0

Max: maximum; Min: minimum; QD: once daily; SD: standard deviation.
a. Duration of Treatment = difference in days between first dose and last dose + 1.
b. Total Cycles was the last cycle reported when treatment was taken; 1 Cycle = 28 days.
c. Average Daily Dose = Total Dose Received/Duration of Treatment.
d. Relative dose intensity = 100 * Average Daily Dose/16.
Data cutoff: 19 Nov 2021

6.3   Dose Interruptions and Reductions

The data for the dose exposure came from patient diary as reported directly by patients. A dose reduction was considered occurring when a patient took a dose level lower than the assigned dose level for at least 2 consecutive days. A drug interruption was considered to have occurred when patient had not taken drug on any day. Thus, the reported dose reductions and drug interruptions based on patient diaries may not be complete and could be overestimated. Also, the rates of dose interruptions and reduction presented here are different than those presented in the AE section as those data were collected on the AE case report form. The dose interruptions and reductions guidance from a given starting dose in the presence of toxicity were pre-specified in the clinical study protocol.

In Cohort 2, 86.7% of patients reported drug interruptions and 76.7% patients had both an interruption and a reduction. The median time to first drug interruption was 16 days and time to first dose reduction was 36 days (Table 23).

Table 23: Dose Reductions and Interruptions – Cohort 2

	N=90
Patients with Dose Reduction [a]	69 (76.7)
Days to First Dose Reduction [a]	
Mean (SD)	50.1 (39.14)
Median	36.0
Patients with Drug Interruption [b], n (%)	78 (86.7)
Days to First Dose Interruption	
Mean (SD)	29.2 (41.60)
Median	16.0

SD: standard deviation
a. A dose level is considered as dose reduction if it is lower than 16 mg and has been taken for at least 2 consecutive days.
b. Drug interruption is any period of days without treatment administered, regardless of length or reason.
Data cutoff: 19 Nov 2021

6.4 Overview of Adverse Events

In Cohort 2, all patients experienced at least one AE (Table 7). The majority of events were Grade 1, 2, or 3. Grade 4 events were reported in 11% of patients. SAEs were reported in 40.0% of patients, and 10% of patients experienced an SAE that led to death.

Most patients experienced an AE that led to dose interruption, and approximately half of patients experienced AEs that led to dose reduction. Eleven patients experienced treatment-related AEs that led to permanent discontinuation.

6.5 Common Adverse Events

The most commonly reported AEs were consistent with the established safety profile of TKIs and were predominantly associated with either skin and subcutaneous tissue or gastrointestinal disorders. In Cohort 2, the most commonly reported AEs were diarrhea, rash, and stomatitis (Table 24). These events were also the most common Grade 3–4 AEs, further described in Section 6.6.

Table 24: Adverse Events in ≥ 20% of Patients by Preferred Term and Grade – Cohort 2

Preferred Term	N=90 n (%)	
	Any Grade	Grade 3 or 4
Any AE	90 (100.0)	80 (88.9)
Diarrhea	75 (83.3)	24 (26.7)
Rash	62 (68.9)	27 (30.0)
Stomatitis	60 (66.7)	21 (23.3)
Paronychia	36 (40.0)	1 (1.1)
Decreased appetite	35 (38.9)	2 (2.2)
Nausea	35 (38.9)	2 (2.2)
Dry skin	30 (33.3)	5 (5.6)
Fatigue	29 (32.2)	4 (4.4)
Alopecia	29 (32.2)	0
Vomiting	27 (30.0)	1 (1.1)
Pruritus	24 (26.7)	2 (2.2)
Anemia	21 (23.3)	4 (4.4)
Dyspnea	19 (21.1)	6 (6.7)
Weight decreased	19 (21.1)	1 (1.1)
Epistaxis	19 (21.1)	0
Rash maculo-papular	18 (20.0)	9 (10.0)

AE: adverse event.
Data cutoff: 19 Nov 2021

6.6 Adverse Events Grade 3 and Grade 4

In Cohort 2, the most commonly reported AEs Grade ≥ 3 were rash (30.0%), diarrhea (26.7%), and stomatitis (22.2%; Table 25). Dermatitis acneiform and rash maculo-papular each occurred in 10.0% of patients. All other Grade 3 AEs were reported in less than 6% of patients.

Grade 4 AEs of any causality were reported in 11.1% of patients. The following Grade 4 AEs were reported in 1 patient each, except as noted: dyspnea (in 3 patients), asthenia, hyperbilirubinemia, hypocalcemia, hypomagnesemia, hypophosphatemia, hypoxia, lipase increased, pericarditis, pancreatitis relapsing, pneumonia, and stomatitis.

Table 25: **Grade 3 and 4 Adverse Events Reported in ≥ 10% of Patients – Cohort 2**

Preferred Term	N=90 n (%)	
	Grade 3	Grade 4
Any AE	77 (85.6)	10 (11.1)
Rash	27 (30.0)	0
Diarrhea	24 (26.7)	0
Stomatitis	20 (22.2)	1 (1.1)
Rash Maculo-popular	9 (10.0)	0
Dermatitis Acneiform	9 (10.0)	0

AE: adverse event.
Data cutoff: 16 Nov 2021

6.7   Serious Adverse Events

In Cohort 2, the most commonly reported SAEs were dyspnea, pneumonia, acute kidney injury, pleural effusion, pulmonary embolism, and respiratory failure (Table 26).

Table 26: **Summary of Most Common Serious Adverse Events (≥ 2% of Patients) – Cohort 2**

Preferred Term	N=90 n (%)	
	Any Grade	Grade 3–4
Patients with ≥ 1 SAE	36 (40.0)	27 (30.0)
Dyspnea	6 (6.7)	5 (5.6)
Pneumonia	5 (5.6)	3 (3.3)
Acute kidney injury	4 (4.4)	3 (3.3)
Pleural effusion	4 (4.4)	3 (3.3)
Pulmonary embolism	4 (4.4)	3 (3.3)
Respiratory failure	4 (4.4)	1 (1.1)
Asthenia	3 (3.3)	2 (2.2)
Dehydration	3 (3.3)	3 (3.3)
Rash	3 (3.3)	3 (3.3)
Diarrhea	2 (2.2)	2 (2.2)
Fatigue	2 (2.2)	1 (1.1)
Hyponatremia	2 (2.2)	2 (2.2)
Hypoxia	2 (2.2)	2 (2.2)
Stomatitis	2 (2.2)	2 (2.2)

SAE: serious adverse event.
Data cutoff: 19 Nov 2021

6.8   Deaths in Cohort 2

At the data cutoff of 19 Nov 2021, there were a total of 15 patients who died while on study. The cause of death in 6 patients was disease progression and in 9 patients, the death was considered as an outcome of an SAE (Table 27). In 8 of the 9 patients with fatal SAEs, the events were deemed unrelated to treatment by the Investigator. The fatal SAEs were likely related to conditions associated with the progression of underlying disease. One patient died due to pneumonia with an onset 84 days after starting poziotinib; the death was judged by the Investigator to be possibly treatment related. By Spectrum assessment, the pneumonia is considered an acquired infection due to tumor obstruction and unlikely related to poziotinib.

Table 27: **Summary of 9 Serious Adverse Events with Death as the Outcome – Cohort 2**

SAEs PT	Relationship to Study Drug by Investigator	Relationship to Study Drug by Sponsor
Patients with SAE Leading to Death, n (%)	9 (10)	9 (10)
Acute Respiratory Failure/Anemia/Ischemic Stroke	Not Related	Unlikely Related
Respiratory Failure	Unlikely Related	Not Related
Respiratory Failure	Not Related	Not Related
Respiratory Failure	Not Related	Not Related
Pneumonia	Not Related	Not Related
Pneumonia	Possibly Related	Unlikely Related
Dyspnea	Not Related	Not Related
General Physical Health Deterioration	Not Related	Not Related
Cardio-Respiratory Arrest	Not Related	Not Related

PT: preferred term; SAE: serious adverse event
Data cutoff: 19 Nov 2021

6.9   Adverse Events of Special Interest

In the poziotinib program, AESIs included diarrhea, rash-type AEs (multiple preferred terms [PTs]), stomatitis-type AEs (multiple PTs), paronychia, and pneumonitis/ILD based on results from the Phase 1 studies and known AEs of the pharmacologic class. The occurrence rates and severities of the AESI were similar with literature reporting of other second-generation TKIs (2019; 2021b) and are summarized below.

6.9.1   Pneumonitis/Interstitial Lung Disease

Pneumonitis/ILD are associated with EGFR or HER2 TKIs. The occurrence rates (any Grade) reported in marketed EGFR TKIs has been reported from 1% to 5%. The rates of fatal events ranged 0.3 to 1.2% per labeling. For the same class of drug, mobocertinib (targeted EGFR exon 20 insertion mutations), ILD/pneumonitis occurred in 4.3% of patients including 0.8% Grade 3 events and 1.2% fatal events (Suh et al 2018).

In Cohort 2, 1 patient experienced Grade 1 pneumonitis. This patient continued on poziotinib treatment with a dose reduction. No severe or serious events were reported, and there were no deaths due to pneumonitis (Table 28).

Table 28: Summary of Pneumonitis/ILD Adverse Events – Cohort 2

Patient with ≥ 1:	N=90 n (%)
Pneumonitis/ILD AE	1 (1.1)
Pneumonitis/ILD AE related to treatment	1 (1.1)
Grade ≥ 3 pneumonitis/ILD AE related to treatment	0
Pneumonitis/ILD SAE	0
Pneumonitis SAE/ILD related to treatment	0
Pneumonitis AE/ILD leading to death	0

AE: adverse event; ILD: interstitial lung disease; SAE: serious adverse event.
Data cutoff: 19 Nov 2021

6.9.2   Stomatitis

Stomatitis is a mechanism based adverse event of TKIs. Therefore, per the protocol, prophylactic methods including avoidance of spicy, acidic food, and alcoholic beverages; use of saline and Nystatin solutions; and use of mouthwash containing lidocaine, Mylanta, diphenhydramine, and prednisolone were used to reduce or prevent stomatitis.

The AESI of stomatitis was examined using the PTs of mucosal inflammation, mucosal toxicity, and stomatitis. These events occurred in most patients and almost all were associated with study drug treatment (Table 29). The most frequently reported PT in the AESI was stomatitis.

Table 29: Summary of Stomatitis Adverse Events of Special Interest – Cohort 2

Category	Cohort 2 N=90 n (%)
Any stomatitis-type AE	64 (71.1)
Any stomatitis-type AE related to treatment	62 (68.9)
Any Grade 3 stomatitis-type AE	21 (23.3)
Any Grade 3 stomatitis-type AE related to treatment	21 (23.3)
Grade 4	1 (1.1)
Any stomatitis-type SAE	2 (2.2)
Any stomatitis-type SAE related to treatment	2 (2.2)

AE: adverse event; SAE: serious adverse event.
Data cutoff: 19 Nov 2021

6.9.3   Paronychia

Paronychia is one of the most common side effects reported with TKIs.

The median onset of paronychia events was 51.5 days (range 8 to 155 days). One Grade 3 event occurred, which had an onset of 49 days after first administration of study drug, leading to dose reduction and dose interruption (Table 30).

Table 30: Summary of Paronychia Adverse Events of Special Interest – Cohort 2

Category	Cohort 2 N=90 n (%)
Any paronychia AE	36 (40.0)
Any paronychia AE related to treatment	35 (38.9)
Any Grade ≥ 3 paronychia AE	1 (1.1)
Any Grade ≥ 3 paronychia AE related to treatment	1 (1.1)
Any paronychia SAE	0
Any paronychia SAE related to treatment	0

AE: adverse event; SAE: serious adverse event.
Data cutoff: 19 Nov 2021

For Grade ≥ 3 events where adequate medical management does not address, the label will recommend dose interruption and resuming poziotinib at the same or reduced dose depending on severity.

6.9.4 Rash

Given the presence of wild-type EGFR receptors in the skin, rash is a common, expected toxicity of TKIs. Per the protocol, prophylactic treatment with doxycycline or minocycline was recommended for 4 weeks following initiation of poziotinib treatment. Supportive topical medications including early use of steroids were also recommended.

The AESI of Rash-Type Adverse Events was a collection of PTs that included rash, dermatitis acneiform, rash maculo-papular, rash erythematous, rash generalized, rash papular, palmar-plantar erythrodysesthesia syndrome, rash macular, rash pruritic, mucocutaneous rash, and rash pustular. In Cohort 2, Rash-Type AEs frequently occurred and were commonly considered related to study drug treatment (Table 31). The incidence of Grade ≥ 3 Rash-Type AEs related to treatment was 48.9% for Cohort 2.

Table 31:   Summary of Rash-Type Adverse Events of Special Interest – Cohort 2

Category	N=90 n (%)
Any rash-type AE	82 (91.1)
Any rash-type AE related to treatment	82 (91.1)
Any Grade ≥ 3 rash-type AE	44 (48.9)
Any Grade ≥ 3 rash-type AE related to treatment	44 (48.9)
Any rash-type SAE	3 (3.3)
Any rash-type SAE related to treatment	3 (3.3)

AE: adverse event; SAE: serious adverse event.
Data cutoff: 19 Nov 2021

In Cohort 2, the most frequently reported Rash-Type PTs were rash, rash maculo-papular, and dermatitis acneiform (Table 32). Approximately half of these patients experienced these AEs as Grade 3 events.

Table 32:   Rash Adverse Events of Special Interest Treatment-Emergent Adverse Events – Cohort 2

Preferred Term	N=90 n (%)	
	Any Grade	Grade 3*
Any Rash Event	82 (91.1)	44 (48.9)
Rash	62 (68.9)	27 (30.0)
Rash maculo-papular	18 (20.0)	9 (10.0)
Dermatitis acneiform	16 (17.8)	9 (10.0)
Rash generalized	4 (4.4)	3 (3.3)
Rash erythematous	3 (3.3)	1 (1.1)
Rash macular	2 (2.2)	1 (1.1)
Rash papular	2 (2.2)	1 (1.1)
Palmar-plantar erythrodysesthesia syndrome	1 (1.1)	0
Rash pustular	1 (1.1)	0

*No Grade 4 or 5 events were reported.
Data cutoff: 19 Nov 2021

There were no fatal Rash-Type AEs for Cohort 2. For Cohort 2 the onset of AEs (n=82) occurred a median of 8 days after first dose (range 1,148) with the onset of AEs of ≥ Grade 3 (n=44) occurring later, a median of 48 days after the first dose of poziotinib (range 4, 172).

Per the protocol, AEs were managed with supportive therapies including topical and oral corticosteroids and antibiotics. Dose interruption with subsequent reduction was recommended for severe events.

The clinical trial experience with poziotinib has demonstrated that the majority of cases can be managed medically with or without dose reduction with few serious cases. Accordingly, based on clinical experience, Rash-Type events, which are anticipated for

the pharmacologic class of TKIs, can be managed with supportive care and dose modifications when required. The proposed label includes recommendations to initiate topical corticosteroids and antibiotics as clinically indicated, withhold or reduce poziotinib for persistent Grade 2 or Grade 3 rash, and discontinue treatment for Grade 4 rash (see Table 39).

6.9.5 Diarrhea

Diarrhea is recognized as a common adverse event occurring with TKIs, although the exact mechanisms are not fully understood. The AESI of diarrhea was represented by the single PT of diarrhea. Consistent with the pharmacologic class, patients receiving poziotinib in Cohort 2 experienced a high overall rate of diarrhea (83.3); however, most cases were mild to moderate in intensity, with severe diarrhea occurring in 26.7% of patients in Cohort 2 (Table 33). There were no fatal events of diarrhea reported.

Table 33: Summary of Diarrhea Adverse Events of Special Interest – Cohort 2

Category	N=90 n (%)
Any diarrhea AE	75 (83.3)
Any diarrhea AE related to treatment	75 (83.3)
Any Grade 3 diarrhea AE	24 (26.7)
Any Grade 3 diarrhea AE related to treatment	23 (25.6)
Any Grade 4 diarrhea AE	0
Any diarrhea SAE	2 (2.2)
Any diarrhea SAE related to treatment	2 (2.2)
Any diarrhea AE leading to discontinuation	2 (2.2)
Any diarrhea AE leading to death	0

AE: adverse event; SAE: serious adverse event.
Data cutoff: 19 Nov 2021

The onset of diarrhea of any grade (N=75) occurred at a median of 6 days after initiation of poziotinib (range 1,141) with the onset of Grade ≥ 3 events (N=24) reported as a median of 13 days after initiation of poziotinib (range 2, 246). The majority of diarrhea events were non-serious with only 4 patients experiencing SAEs (N=2) or requiring dose discontinuation (N=2). Per the protocol, medical management included administration of loperamide as prophylaxis for diarrhea with initiation of doxycycline or cholestyramine for mild to moderate events or managed per institutional guidelines. Dose interruption and subsequent reduction was recommended for severe cases of diarrhea. In Cohort 2, there were 17 patients who required poziotinib dose reductions for the management of diarrhea.

Based on the clinical trial experience with poziotinib, the AESI of diarrhea can be managed through prophylaxis with loperamide, other supportive medical management and with dose reductions when needed. There was a low rate of SAEs or AEs requiring discontinuation. Accordingly, the proposed label for poziotinib includes

recommendations regarding initiation of anti-diarrheal prophylaxis and consideration of withholding or dose reduction for recurrent Grade 2 or Grade 3 events.

6.10 Group 1 Safety

Group 1 includes 482 patients with NSCLC from all cohorts of Study 202 who received 16 mg QD or 8 mg BID, regardless of the oncogene, mutation and line of treatment (data cutoff: 19 Nov 2021).

In Group 1, most patients experienced at least one AE (Table 34). The majority of events were Grade 1, 2, or 3, and Grade 4 and 5 events were each reported in < 10% of patients. SAEs were reported in 40.0% of patients. Most patients experienced an AE that led to dose interruption, and approximately half of patients experienced AEs that led to dose reduction.

Table 34:   Overall Summary of Adverse Events – Cohort 2 and Group 1

Patients with ≥ 1:	Cohort 2 N=90 n (%)	Group 1 N=482 n (%)
Any AE	90 (100.0)	470 (97.5)
Grade 1–2	89 (98.9)	464 (96.3)
Grade 3–4	80 (88.9)	393 (81.5)
Grade 3	77 (85.6)	390 (80.9)
Grade 4	10 (11.1)	41 (8.5)
AE leading to dose interruption [a]	81 (90.0)	373 (77.4)
AE leading to dose reduction [a]	52 (57.8)	247 (51.2)
Any AE leading to drug discontinuation [a]	21 (23.3)	85 (17.6)
Any treatment-related AE leading to discontinuation	11 (12.2)	52 (10.8)
Any SAE	36 (40.0)	193 (40.0)
SAE resulting in death	9 (10.0)	28 (5.8)

AE: adverse event; SAE: serious adverse event.
[a] Action taken on AE CRF recorded as drug withdrawn
Data cutoff: 19 Nov 2021

The most commonly reported AEs were consistent with established safety profile of TKIs and were predominantly associated with either skin and subcutaneous tissue or gastrointestinal disorders. In Group 1, the most commonly reported AEs were diarrhea, rash, and stomatitis (Table 35). These events were also the most common Grade 3–4 AEs.

Table 35:   Adverse Events in ≥ 20% of Patients by Preferred Term and Grade – Cohort 2 and Group 1

Preferred Term	Cohort 2 (N=90) n (%)		Group 1 N=482	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any AE	90 (100.0)	80 (88.9)	470 (97.5)	393 (81.5)
Diarrhea	75 (83.3)	24 (26.7)	393 (81.5)	108 (22.4)
Rash	62 (68.9)	27 (30.0)	287 (59.5)	122 (25.3)
Stomatitis	60 (66.7)	21 (23.3)	336 (69.7)	88 (18.3)
Paronychia	36 (40.0)	1 (1.1)	231 (47.9)	26 (5.4)
Decreased appetite	35 (38.9)	2 (2.2)	183 (38.0)	16 (3.3)
Nausea	35 (38.9)	2 (2.2)	180 (37.3)	16 (3.3)
Dry skin	30 (33.3)	5 (5.6)	153 (31.7)	15 (3.1)
Fatigue	29 (32.2)	4 (4.4)	174 (36.1)	22 (4.6)
Alopecia	29 (32.2)	0	144 (29.9)	0
Vomiting	27 (30.0)	1 (1.1)	145 (30.1)	16 (3.3)
Pruritus	24 (26.7)	2 (2.2)	117 (24.3)	13 (2.7)
Anemia	21 (23.3)	4 (4.4)	75 (15.6)	15 (3.1)
Dyspnea	19 (21.1)	6 (6.7)	94 (19.5)	22 (4.6)
Weight decreased	19 (21.1)	1 (1.1)	109 (22.6)	4 (0.8)
Rash maculo-papular	18 (20.0)	9 (10.0)	88 (18.3)	39 (8.1)
Epistaxis	19 (21.1)	0	62 (12.9)	0
Dermatitis acneiform	16 (17.8)	9 (10.0)	108 (22.4)	41 (8.5)

AE: adverse event
Data cutoff: 19 Nov 2021

Safety results of Group 1 were similar to Cohort 2 except for pneumonitis/ILD which was seen at a frequency of 3.3% in Group 1 and of 1.1% in Cohort 2. There were 16 patients (3.3%) in Group 1 who experienced an event of pneumonitis or ILD, and most events (14) were assessed as related to poziotinib (Table 36). There were 4 fatal events of pneumonitis (0.8%). One of the events of fatal pneumonitis was pre-existing and assessed as unlikely related by the Investigator and Spectrum; three other fatal events were assessed as related to poziotinib (Table 37). The deaths were confounded by the progression of disease and other comorbidities.

Table 36: Pneumonitis and Interstitial Lung Disease Adverse Events – Cohort 2 and Group 1

	Cohort 2 N=90 n (%)	Group 1 N=482 n (%)
Pneumonitis/ILD AE	1 (1.1)	16 (3.3)
Pneumonitis/ILD AE related to treatment	1 (1.1)	14 (2.9)
Grade ≥ 3 pneumonitis/ILD AE related to treatment	0	9 (1.9)
Pneumonitis/ILD SAE	0	11 (2.3)
Pneumonitis/ILD SAE related to treatment	0	9 (1.9)
Pneumonitis/ILD SAE leading to discontinuation of study drug	0	7 (1.5)
Pneumonitis/ILD SAE leading to death	0	4 (0.8)
Pneumonitis/ILD SAE related to treatment leading to death	0	3 (0.6)

AE: adverse event; ILD: interstitial lung disease.
Data cutoff: 19 Nov 2021

Table 37: Fatal Pneumonitis / Interstitial Lung Disease – Group 1

Age / Sex	PT	Mutation	Cohort	Previous Treatment for NSCLC	Initial Dose	Time to Onset (days)	Relation to Study Drug (INV)	Relation to Study Drug (Sponsor)
51 / M	Pneumonitis	HER2 exon 20 insertion mutation	4	N/A	16 mg QD	73	Possibly related	Possibly related
73 / M	Pneumonitis	EGFR exon 20 insertion mutation	3	N/A	16 mg QD	82	Possibly related	Possibly related
54 / F	Pneumonitis	EGFR exon 20 insertion mutation	3	N/A	16 mg QD	174	Probably related	Probably related
62 / F	Pneumonitis	EGFR activating	7	Cisplatin / Pemetrexed / Palliative radiation right lung	8 mg BID	13	Unlikely related	Unlikely related

BID: twice daily; EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2; INV: investigator; NSCLC: non-small cell lung cancer; PT: preferred term; QD: once daily.

6.11 Laboratory Values

Changes in values from baseline were also evaluated for each laboratory test as shifts in CTCAE grade relative to the normal range.

In general, clinically significant changes from normal baseline to Grade 3+ were uncommon Table 38.

Table 38: Select Laboratory Abnormalities (> 20%) That Worsened from Baseline in Patients with NSCLC – Group 1

Laboratory Abnormality	Grade 3 or 4 (%)
Decreased albumin	1.5
Worsened sodium	2.7
Increased alkaline phosphatase	1.7
Worsened glucose	1.7
Increased aspartate aminotransferase	0.4
Decreased hemoglobin	2.3

6.12 Cardiac Safety

Cardiac safety was assessed in Study 202 through comprehensive electrocardiogram (ECG) recordings and by central analysis (eRT). No patient developed clinically significant abnormal ECGs in Cohort 2.

Additionally, there were no clinically meaningful changes in cardiac parameters (heart rate and P-R interval, QRS, and QT intervals, QT Interval Corrected by Bazett's Formula [QTcB], and QT Interval Corrected by Fridericia's Formula [QTcF]), and no patients had a new QTcF > 500 ms or had a > 60 ms change from baseline for QTcF. Poziotinib had no significant effect on cardiac repolarization.

6.13 Management and Monitoring of Adverse Events of Special Interest

Based on the known safety profile of TKIs and poziotinib clinical data, Spectrum has included the following in the Warning and Precautions section of the proposed label:

- Diarrhea: Diarrhea may lead to dehydration or electrolyte imbalance with or without renal impairment. Withhold, dose reduce or permanently discontinue [poziotinib] based on severity.

- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Withhold [poziotinib] for suspected ILD/pneumonitis and permanently discontinue [poziotinib] if ILD is confirmed.

- Dermatologic Adverse Reactions: May cause dermatologic adverse reactions, including rash, that can be severe. Withhold, dose reduce or permanently discontinue [poziotinib] based on severity.

- Keratitis: Promptly refer patients with signs and symptoms of keratitis to an ophthalmologist for evaluation.

- Mucositis: Withhold, dose reduce or permanently discontinue [poziotinib] based on severity.

- Nail Toxicity: Withhold, dose reduce or permanently discontinue [poziotinib] based on severity

Recommended dose modifications included in the proposed label are shown in Table 39.

Table 39:   Poziotinib Recommended Dose Reductions for Adverse Reactions

Adverse Reaction	Severity [a]	Dosage Modification
Diarrhea	Intolerable or recurrent Grade ≥ 2 (or Grade 2 for ≥ 48 hours despite adequate antidiarrheal management) or Grade ≥ 3	Withhold poziotinib until recovery to ≤Grade 1. Resume poziotinib at the same dose or reduced dose depending on severity.
Interstitial Lung Disease (ILD)/ Pneumonitis	Grade ≥ 1	Withhold poziotinib. If diagnosis of ILD/pneumonitis is confirmed, permanently discontinue poziotinib.
Dermatologic Adverse Reactions	Persistent Grade 2 or Grade 3	Withhold poziotinib until recovery to ≤Grade 1. Resume poziotinib at reduced dose.
	Grade 4	Permanently discontinue poziotinib.
Ocular Toxicity	Grade 2	Withhold poziotinib until recovery to ≤ Grade 1. Resume poziotinib at the same dose.
	Grade ≥ 3	Withhold poziotinib until recovery to ≤ Grade 1. Resume poziotinib at reduced dose.
Mucositis	Grade 2	Withhold poziotinib until recovery to ≤ Grade 1. Resume poziotinib at the same dose.
	Grade 3	Withhold poziotinib until recovery to ≤ Grade 1. Resume poziotinib at reduced dose.
	Grade 4	Permanently discontinue poziotinib.
Nail Disorders	Grade 2	Withhold poziotinib until recovery to ≤Grade 1 Resume poziotinib at the same or reduced dose, depending on severity.
	Grade 3	Withhold dosing until recovery to ≤ Grade 1 Resume poziotinib at the same or reduced dose depending on severity.
Other Adverse Reactions	Grade ≥ 3	Withhold poziotinib until recovery to ≤ Grade 1. Resume poziotinib at the same or reduced dose depending on severity.

6.14 Safety Conclusions

Poziotinib development program comprise a large number of patients (N=482) at the efficacious daily dose (16 mg QD or 8 mg BID) and therefore, the safety signals are well

characterized for a rare disease indication. Based on the safety analyses of Study 202, the most common AEs following poziotinib administration were diarrhea, stomatitis, and rash. The safety profile of poziotinib has been consistent, manageable, and similar between studies in respect to common AEs. In this relatively large safety database for a rare disease, the incidence of the most serious class AEs of ILD/pneumonitis and QTc prolongation are low or absent with poziotinib.

7 RATIONALE FOR PROPOSED POZIOTINIB DOSE OF 16 MG QD

7.1 Dosing Regimen (Intermittent vs Continuous)

Based on mouse allometric scaling to human, the human dose was projected to be 15 mg QD. The Phase 1 studies determined the MTD of poziotinib to be 18 mg QD daily or 24 mg QD with 2 weeks on and 1 week off dosing.

In Study 201, two dosing regimens, intermittent dosing of 24 mg 2 weeks on 1 week off and continuous 16 mg daily dosing were evaluated in patients with HER2 positive breast cancer. Although the efficacy between dosing groups was similar with ORR of 30%, there were more CRs, higher DCR, median PFS and median DoR in 16 mg QD continuous dosing schedule (Table 40). Therefore, the continuous daily dosing regimen was selected as the dosing regimen for the Phase 2 studies. The MDACC IIT then used the 16 mg QD as the starting dose.

Table 40: Study 201 Efficacy Results Intermittent vs Continuous Dosing

Parameter	24 mg Intermittent N=30	16 mg Continuous N=27
ORR: CR + PR, % (95% CI)	30 (14.7, 49.4)	30 (13.8, 50.2)
CR, %	0	19
PR, %	30	11
DCR: CR + PR + SD, % (95% CI)	60 (40.6, 77.3)	78 (57.7, 91.4)
Median TTP, months (95% CI)	4.1 (1.5, 5.6)	4.9 (1.8, 7.4)
Median PFS, months (95% CI)	4.1 (1.5, 5.6)	4.9 (1.8, 7.4)
Median DoR, months (95% CI)	5.7 (1.8, NA)	13.0 (2.2, NA)

CI: confidence interval; CR: complete response; DCR: disease control rate; DoR: duration of response; NA: not available; ORR: objective response rate; PFS: progression-free survival; PR: partial response; SD: stable disease; TTP: time to progression
Data cutoff: 05 Mar 2021

7.2 Dose Selection

Cohort 5, an independent cohort in the ongoing randomized, Phase 2, open-label, multicenter study, was a dose-ranging study designed to evaluate the efficacy and the safety/tolerability of poziotinib. Cohort 5 includes a population of patients with NSCLC harboring HER2 or EGFR insertion mutations who are treatment-naïve or previously treated.

The randomization scheme employed is described below:

- Protocol Amendment 2: Initiated Cohort 5 and randomized allocation to 10, 12, and 16 mg QD dose arms
- Protocol Amendment 3: Randomized allocation to 10 mg QD, 6 mg BID, and 8 mg BID dose arms. 12 mg QD and 16 mg QD dose arms were stopped

- Stage 1 analysis: 10 mg QD and 6 mg BID closed based on lack of efficacy; 8 mg BID dose arm – continued to Stage 2 and is currently ongoing

In the HER2 exon 20 previously treated subset of Cohort 5, the 16 mg QD dosing arm had the highest proportion of responses compared to other dosing arms (Table 41). Although Grade ≥ 3 treatment-related AEs were higher in the 16 mg QD arm than with the BID dosing arm, the proportion of patients who reduced or interrupted their dose was similar across doses levels. The results of efficacy and safety for the range of doses and schedule evaluated in Cohort 5 show a trend in dose proportionality and support the selection of 16 mg QD as the starting dose.

Table 41:   Study 202 Cohort 2 and Second-Line Cohort 5 Safety Summary of Drug-Related AEs

	Cohort 2	Cohort 5				
	16 mg QD (N=90)	16 mg QD (N=10)	8 mg BID (N=40)	12 mg QD (N=16)	6 mg BID (N=15)	10 mg QD (N=14)
ORR (CR+PR), n (%)	25 (28)	4 (40)	9 (23)	4 (25)	2 (13)	1 (7)
DCR (CR+PR+SD), n (%)	63 (70)	7 (70)	22 (55)	10 (63)	10 (67)	8 (57)
Grade ≥ 3 Treatment-related AE, n (%)	73 (81)	9 (90)	26 (65)	10 (63)	6 (40)	9 (64)
Grade ≥ 3 Rash Treatment-related	44 (48.9)	4 (40)	13 (32.5)	7 (43.8)	3 (20.0)	4 (28.6)
Grade ≥ 3 Diarrhea Treatment-related	23 (25.6)	2 (20)	5 (12.5)	2 (12.5)	2 (13.3)	5 (35.7)
Grade ≥ 3 Stomatitis Treatment-related	22 (24.4)	5 (50.0)	9 (22.5)	0	1 (6.7)	1 (7.1)
Grade ≥ 3 Paronychia Treatment-related	1 (1.1)	0	1 (2.5)	1 (6.3)	0	0
Patients with Dose Reduction, n (%)	69 (77)	5 (50)	24 (60)	11 (69)	5 (33)	5 (36)
Patients with Dose Interruption, n (%)	78 (87)	7 (70)	29 (73)	14 (88)	12 (80)	9 (64)

AE: adverse event; BID: twice daily; CR: complete response; DCR: disease control rate; ORR: objective response rate; PR: partial response; QD: once daily; SD: stable disease.
Data cutoff: Cohort 2 efficacy: 05 Mar 2021, Cohort 2 safety: 19 Nov 2021; Cohort 5:16 May 2022

8   CONFIRMATORY STUDY

8.1   Study Design

8.1.1   Overview

The confirmatory study, Study 301, has been designed in consultation with the FDA (Figure 19). Study 301 is a Phase 3, randomized, two-arm, active-controlled, open-label, multicenter study to compare the efficacy and safety/tolerability of poziotinib versus docetaxel in previously treated patients with locally advanced or metastatic NSCLC harboring HER2 exon 20 mutations. Patients will be randomized 2:1 to:

- Poziotinib: 8 mg orally BID, or

- Docetaxel 75 mg/m^2 IV on Day 1 of each cycle.

Patients will receive study treatments until progressive disease, intolerable toxicity, death, or withdrawal of consent. Patients in the docetaxel arm may cross over to poziotinib treatment after the Investigator has documented PD. Dose interruptions will be recommended for treatment-related AEs Grade $\geq$ 3 until severity lessens to Grade $\leq$ 2. Patients can then restart at 8 mg BID or reduce to 6 mg BID, at the discretion of the Investigator.

Each cycle consists of 21 ($\pm$3) days.

Figure 19:   Study 301 Confirmatory Study Design
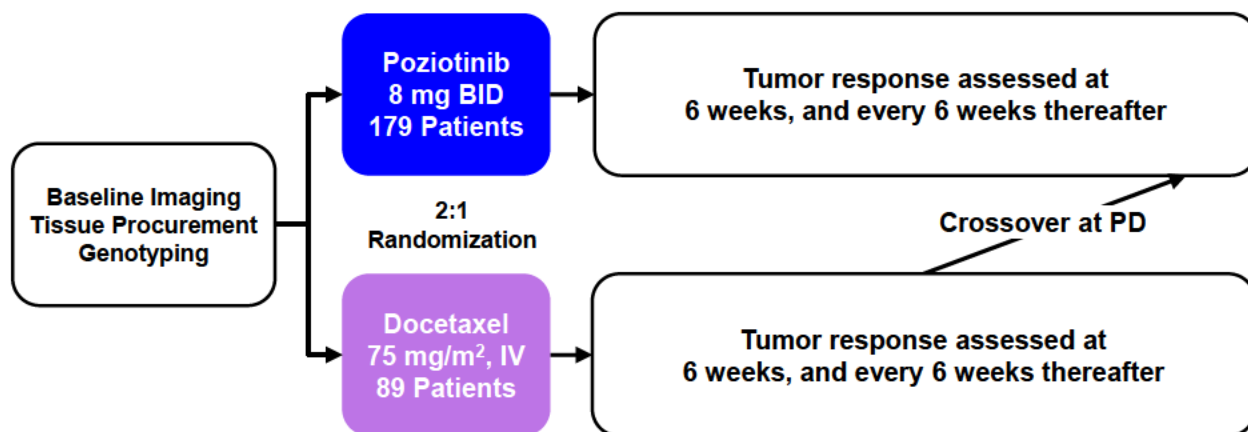
- **Designed to enroll 268 patients**
- **Up to 150 sites globally**
- **Estimated top-line results: 2026**

BID: twice daily; IV: intravenous; PD: progressive disease.

The primary objective is to compare the PFS in patients with locally advanced or metastatic NSCLC harboring HER2 exon 20 mutations when treated with poziotinib versus docetaxel. Secondary objectives include comparison of OS, ORR, and DCR in patients with locally advanced or metastatic NSCLC harboring HER2 exon 20 mutations when treated with poziotinib versus docetaxel.

8.1.2 Statistical Methods

For the purpose of the statistical powering and sample size calculation of the comparison of median PFS between two treatment arms in this randomized controlled study in patients previously treated with 1 or more prior lines of therapy, median PFS of 6 months will be considered for poziotinib arm and 3.5 months for the docetaxel arm.

A sample size of 268 patients with 193 PFS events in a 2:1 randomization ratio will provide 95% power to test the hypothesis of the superiority of poziotinib over docetaxel for a hazard ratio of ≤ 0.58 (poziotinib 6 months vs docetaxel 3.5 months) using a one-sided log-rank test at 2.5% level of significance. This also considers a 20% dropout rate in each arm.

The primary efficacy analysis will be carried out once a total of 193 PFS events have been accrued, and all secondary endpoint analyses will be conducted at the time of the primary analysis.

A futility analysis will be conducted by an Independent Data Monitoring Committee (IDMC) when 30% of the PFS events combined are accrued (approximate 58 events). The study will stop for futility if the hazard ratio is > 1.27 (Z > 0.873) using a beta spending function with gamma (-4) distribution.

8.2 Feasibility

Study 301 will be conducted at approximately 150 global study centers and will run for approximately 5 years. Substantial efforts are underway to activate multi-regional clinical trial sites for this rare NSCLC mutation and enroll patients as soon as possible in this rare disease population (Figure 20):

- Spectrum has identified 55 sites globally that have collaborated on prior Spectrum studies with exon 20 mutations and is engaging directly with them.

- Spectrum has retained PPD (Spectrum's contract research organization) who has identified an additional 375 sites worldwide in 29 countries that have significant experience in NSCLC studies.

- A total of 91 sites have been qualified as of 19 Aug 2022.

Enrollment projection is shown in Figure 21 below. The analysis of topline data is expected to be completed in 2026.

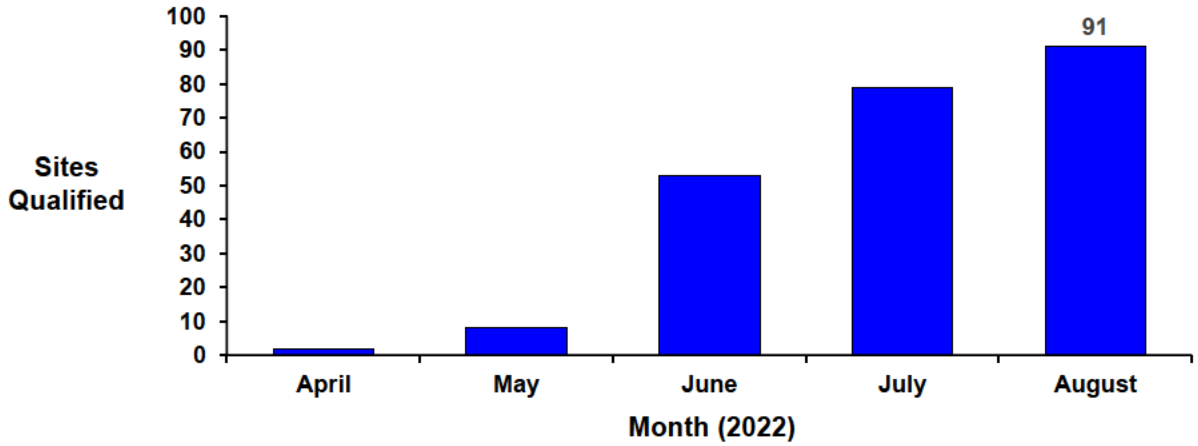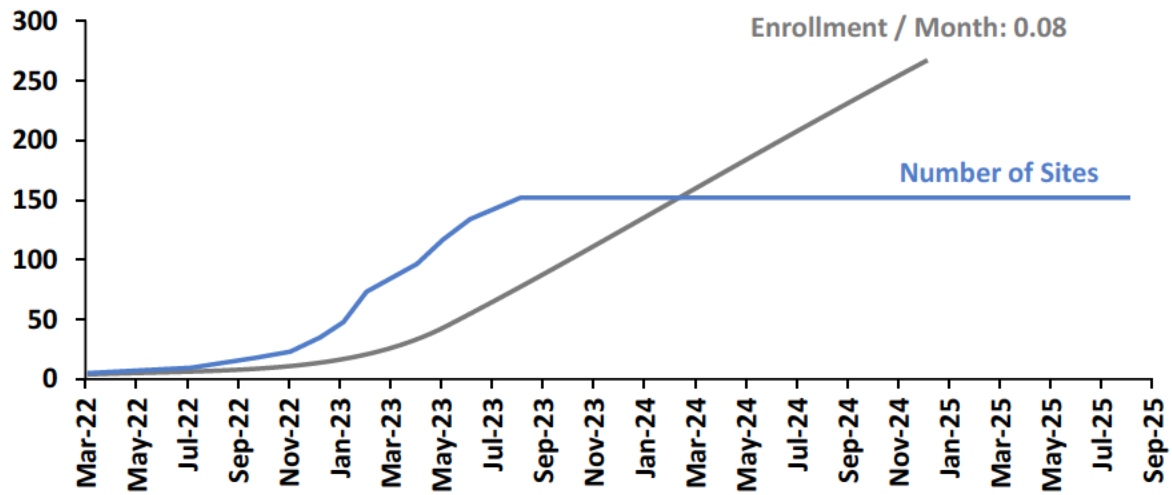**Figure 20:   Study 301 Site Qualification**

Figure 21:   Study 301 Enrollment Rate Projection

9   REFERENCES

Food and Drug Administration. FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for HER2-mutant non-small cell lung cancer. [updated August 2022]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-fam-trastuzumab-deruxtecan-nxki-her2-mutant-non-small-cell-lung.]

Lung Cancer - Non-Small Cell. [updated November 2021]. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell.]

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer Version 3.2022. National Comprehensive Cancer Network. [updated March 2022]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.]

National Institute of Health. Afatinib in NSCLC With HER2 Mutation. [updated October 2019]. Available from: https://clinicaltrials.gov/ct2/show/NCT02597946.]

National Institute of Health. Neratinib With and Without Temsirolimus for Patients With HER2 Activating Mutations in Non-Small Cell Lung Cancer. [updated July 2018]. Available from: https://clinicaltrials.gov/ct2/show/NCT01827267.]

Gilotrif (afatinib) [Package Insert]. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. 2019.

Exkivity (mobocertinib) [Package Insert]. Takeda Pharmaceuticals America, Inc, Lexington, MA 02421. 2021a.

Iressa (gefitinib) [Package Insert]. AstraZeneca Pharmaceuticals LP, Wilmington, DE. 2021b.

Nerlynx (neratinib) [Package Insert]. Puma Biotechnology, Inc, Los Angeles, CA. 2022a.

Tagrisso (osimertinib) [Package Insert]. AstraZeneca Pharmaceuticals LP, Wilmington, DE. 2022b.

Aldonza MB, Hong JY, Alinsug MV, Song J, Lee SK. Multiplicity of acquired cross-resistance in paclitaxel-resistant cancer cells is associated with feedback control of TUBB3 via FOXO3a-mediated ABCB1 regulation. Oncotarget. 2016;7(23):34395-419.

Arcila ME, Chaft JE, Nafa K, Roy-Chowdhuri S, Lau C, Zaidinski M, et al. Prevalence, clinicopathologic associations, and molecular spectrum of ERBB2 (HER2) tyrosine kinase mutations in lung adenocarcinomas. Clin Cancer Res. 2012;18(18):4910-8.

Auliac JB, Dô P, Bayle S, Doubre H, Vinas F, Letreut J, et al. Non-Small Cell Lung Cancer Patients Harboring HER2 Mutations: Clinical Characteristics and Management in a Real-Life Setting. Cohort HER2 EXPLORE GFPC 02-14. Adv Ther. 2019;36(8):2161-6.

Bachet JB, Peuvrel L, Bachmeyer C, Reguiai Z, Gourraud PA, Bouche O, et al. Folliculitis induced by EGFR inhibitors, preventive and curative efficacy of tetracyclines in the management and incidence rates according to the type of EGFR inhibitor administered: a systematic literature review. Oncologist. 2012;17(4):555-68.

Baraibar I, Mezquita L, Gil-Bazo I, Planchard D. Novel drugs targeting EGFR and HER2 exon 20 mutations in metastatic NSCLC. Crit Rev Oncol Hematol. 2020;148:102906.

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015;373(17):1627-39.

Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. Nature. 2014;511(7511):543-50.

Cheema PK, Rothenstein J, Melosky B, Brade A, Hirsh V. Perspectives on treatment advances for stage III locally advanced unresectable non-small-cell lung cancer. Curr Oncol. 2019;26(1):37-42.

Corral J, Mok TS, Nakagawa K, Rosell R, Lee KH, Migliorino MR, et al. Effects of dose modifications on the safety and efficacy of dacomitinib for EGFR mutation-positive non-small-cell lung cancer. Future Oncol. 2019;15(24):2795-805.

Dziadziuszko R, Smit EF, Dafni U, Wolf J, Wasąg B, Biernat W, et al. Afatinib in NSCLC with HER2 mutations: results of the prospective, open-label phase II NICHE trial of European Thoracic Oncology Platform (ETOP). Journal of thoracic oncology. 2019;14(6):1086-94.

Elamin YY, Robichaux JP, Carter BW, Altan M, Gibbons DL, Fossella FV, et al. Poziotinib for Patients With HER2 Exon 20 Mutant Non-Small-Cell Lung Cancer: Results From a Phase II Trial. J Clin Oncol. 2022;40(7):702-9.

Guidance for Industry Expedited Programs for Serious Conditions - Drugs and Biologics. May 2014. . 2014. Available from: https://www.fda.gov/media/86377/download.

Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000;18(12):2354-62.

Gandhi L, Bahleda R, Tolaney SM, Kwak EL, Cleary JM, Pandya SS, et al. Phase I study of neratinib in combination with temsirolimus in patients with human epidermal growth factor receptor 2-dependent and other solid tumors. J Clin Oncol. 2014;32(2):68-75.

Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(22):2078-92.

Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014a;384(9944):665-73.

Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014b;384(9944):665-73.

Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019;381(21):2020-31.

Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.

Hong L, Lewis WE, Nilsson M, Patel S, Varghese S, Rivera MJ, et al. Limited Benefit from the Addition of Immunotherapy to Chemotherapy in TKI-Refractory EGFR-Mutant Lung Adenocarcinoma. Cancers (Basel). 2022;14(14).

Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The Effect of Advances in Lung-Cancer Treatment on Population Mortality. N Engl J Med. 2020;383(7):640-9.

Hyman DM, Piha-Paul SA, Won H, Rodon J, Saura C, Shapiro GI, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. Nature. 2018;554(7691):189-94.

Jacot W, Bessis D, Jorda E, Ychou M, Fabbro M, Pujol JL, et al. Acneiform eruption induced by epidermal growth factor receptor inhibitors in patients with solid tumours. Br J Dermatol. 2004;151(1):238-41.

Kinneer K, Meekin J, Tiberghien AC, Tai YT, Phipps S, Kiefer CM, et al. SLC46A3 as a Potential Predictive Biomarker for Antibody-Drug Conjugates Bearing Noncleavable Linked Maytansinoid and Pyrrolobenzodiazepine Warheads. Clin Cancer Res. 2018;24(24):6570-82.

Kris MG, Camidge DR, Giaccone G, Hida T, Li BT, O'Connell J, et al. Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. Ann Oncol. 2015;26(7):1421-7.

Lai WV, Lebas L, Barnes TA, Milia J, Ni A, Gautschi O, et al. Afatinib in patients with metastatic or recurrent HER2-mutant lung cancers: a retrospective international multicentre study. Eur J Cancer. 2019;109:28-35.

Li BT, Ross DS, Aisner DL, Chaft JE, Hsu M, Kako SL, et al. HER2 Amplification and HER2 Mutation Are Distinct Molecular Targets in Lung Cancers. J Thorac Oncol. 2016;11(3):414-9.

Li BT, Smit EF, Goto Y, Nakagawa K, Udagawa H, Mazieres J, et al. Trastuzumab Deruxtecan in HER2-Mutant Non-Small-Cell Lung Cancer. N Engl J Med. 2022;386(3):241-51.

Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004;350(21):2129-39.

Mazières J, Barlesi F, Filleron T, Besse B, Monnet I, Beau-Faller M, et al. Lung cancer patients with HER2 mutations treated with chemotherapy and HER2-targeted drugs: results from the European EUHER2 cohort. Ann Oncol. 2016;27(2):281-6.

Mazieres J, Drilon A, Lusque A, Mhanna L, Cortot AB, Mezquita L, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. Ann Oncol. 2019;30(8):1321-8.

Mazieres J, Peters S, Lepage B, Cortot AB, Barlesi F, Beau-Faller M, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. Journal of clinical oncology. 2013;31(16):1997-2003.

Melosky B, Leighl NB, Rothenstein J, Sangha R, Stewart D, Papp K. Management of egfr tki-induced dermatologic adverse events. Curr Oncol. 2015;22(2):123-32.

Nagasaka M, Singh V, Baca Y, Sukari A, Kim C, Mamdani H, et al. The Effects of HER2 Alterations in EGFR Mutant Non-small Cell Lung Cancer. Clin Lung Cancer. 2022;23(1):52-9.

Negrao MV, Skoulidis F, Montesion M, Schulze K, Bara I, Shen V, et al. Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. J Immunother Cancer. 2021;9(8).

Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004;304(5676):1497-500.

Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A. 2004;101(36):13306-11.

Powell CA, Modi S, Iwata H, Takahashi S, Smit EF, Siena S, et al. Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open. 2022;7(4):100554.

Robichaux JP, Elamin YY, Tan Z, Carter BW, Zhang S, Liu S, et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20–selective kinase inhibitor in non–small cell lung cancer. Nature medicine. 2018;24(5):638-46.

Robichaux JP, Elamin YY, Vijayan R, Nilsson MB, Hu L, He J, et al. Pan-cancer landscape and analysis of ERBB2 mutations identifies poziotinib as a clinically active inhibitor and enhancer of T-DM1 activity. Cancer Cell. 2019;36(4):444-57. e7.

Ross JS, Wang K, Gay LM, Al-Rohil RN, Nazeer T, Sheehan CE, et al. A high frequency of activating extracellular domain ERBB2 (HER2) mutation in micropapillary urothelial carcinoma. Clin Cancer Res. 2014;20(1):68-75.

Rubin I, Yarden Y. The basic biology of HER2. Ann Oncol. 2001;12 Suppl 1:S3-8.

Scaltriti M, Verma C, Guzman M, Jimenez J, Parra JL, Pedersen K, et al. Lapatinib, a HER2 tyrosine kinase inhibitor, induces stabilization and accumulation of HER2 and potentiates trastuzumab-dependent cell cytotoxicity. Oncogene. 2009;28(6):803-14.

SEER. SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2018/, based on November 2020 SEER data submission, posted to the SEER web site,2021 [July 7, 2022]. Available from: https://seer.cancer.gov/archive/csr/1975_2018/.]

Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005;353(2):123-32.

Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33.

Skoulidis F, Heymach JV. Co-occurring genomic alterations in non-small-cell lung cancer biology and therapy. Nat Rev Cancer. 2019;19(9):495-509.

Suh CH, Park HS, Kim KW, Pyo J, Hatabu H, Nishino M. Pneumonitis in advanced non-small-cell lung cancer patients treated with EGFR tyrosine kinase inhibitor: Meta-analysis of 153 cohorts with 15,713 patients: Meta-analysis of incidence and risk factors of EGFR-TKI pneumonitis in NSCLC. Lung Cancer. 2018;123:60-9.

Thai AA, Solomon BJ, Sequist LV, Gainor JF, Heist RS. Lung cancer. Lancet. 2021;398(10299):535-54.

Tomizawa K, Suda K, Onozato R, Kosaka T, Endoh H, Sekido Y, et al. Prognostic and predictive implications of HER2/ERBB2/neu gene mutations in lung cancers. Lung Cancer. 2011;74(1):139-44.

Viray H, Rangachari D, Costa DB. Trastuzumab Deruxtecan in Non-Small-Cell Lung Cancer. N Engl J Med. 2022;386(18):1769-70.

White MN, Piper-Vallillo AJ, Gardner RM, Cunanan K, Neal JW, Das M, et al. Chemotherapy Plus Immunotherapy Versus Chemotherapy Plus Bevacizumab Versus Chemotherapy Alone in EGFR-Mutant NSCLC After Progression on Osimertinib. Clin Lung Cancer. 2022;23(3):e210-e21.

Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(11):1454-66.

Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(2):213-22.

Xu F, Yang G, Xu H, Yang L, Qiu W, Wang Y. Treatment outcome and clinical characteristics of HER2 mutated advanced non-small cell lung cancer patients in China. Thorac Cancer. 2020;11(3):679-85.

Yang JC, Sequist LV, Geater SL, Tsai CM, Mok TS, Schuler M, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol. 2015;16(7):830-8.

Yang S, Wang Y, Zhao C, Li X, Liu Q, Mao S, et al. Exon 20 YVMA insertion is associated with high incidence of brain metastasis and inferior outcome of chemotherapy in advanced non-small cell lung cancer patients with HER2 kinase domain mutations. Translational lung cancer research. 2021;10(2):753-65.

Zhou J, Ding N, Xu X, Zhang Y, Ye M, Li C, et al. Clinical outcomes of patients with HER2-mutant advanced lung cancer: chemotherapies versus HER2-directed therapies. Ther Adv Med Oncol. 2020;12.