1172P

High Activity of Poziotinib in G778_P780dup *HER2* Exon 20 Insertion Mutations in Non-Small Cell Lung Cancer (NSCLC)

SPECTRUM PHARMACEUTICALS
Redefining Cancer Care

Xiuning Le[1]; Sophie Sun[2]; Eric Haura[3], Erin Bertino[4], Christina Baik[5]; Hirva Mamdani[6], Sharon Leu[7]; Arunthi Thiagalingam[8], Jaba Kokhreidze[7], Francois Lebel[7]; Mark Socinski[9]

[1]MD Anderson Cancer Center, Houston, TX; [2]British Columbia Cancer, Vancouver, Canada; [3]Moffitt Cancer Center & Research Institute, Tampa, FL; [4]The Ohio State University, Columbus, OH; [5]Seattle Cancer Center Alliance, Seattle, WA; [6]Karmanos Cancer Institute, Detroit, MI; [7]Spectrum Pharmaceuticals, Irvine, CA; [8]Spectrum Pharmaceuticals, Boston, MA; [9]AdventHealth Cancer Institute, Orlando, FL

BACKGROUND

- Human epidermal growth factor receptor 2 (HER2, also known as ErbB2) has long been recognized as an oncogenic driver across a variety of cancers[1]
  - The frequency of HER2 mutation is estimated to be 2-3% in patients with non-small cell lung cancer (NSCLC)[1]
- Patients harboring exon 20 insertion mutations (ex20ins) comprise 80-90% of all HER2 mutations
  - The G778_P780dup (G778) mutation is the 2nd to 3rd most common HER2 ex20ins mutations in NSCLC, representing 9–19% of HER2 insertion mutations
  - Previous studies have reported an overall response rate ranging from 10–60% with tyrosine kinase inhibitors (TKIs) in patients with G778 mutations
- Poziotinib is an oral pan-*ErbB* TKI that has demonstrated clinical activity and a tolerable safety profile in NSCLC[2]
- Here we report the effects of poziotinib in a relatively large population of treatment-naïve and previously treated patients with NSCLC with HER2 ex20ins G778 mutations

OBJECTIVE

To assess the effects of poziotinib in patients with the HER2 ex20ins G778 mutation in a population of previously treated (C2) and treatment-naïve (C4) patients with NSCLC

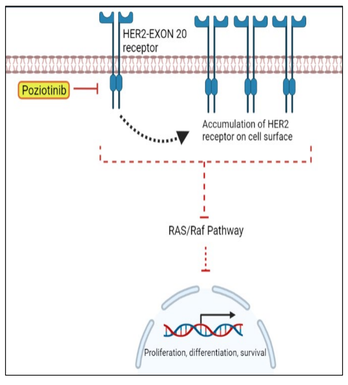
Poziotinib

Poziotinib is an oral pan-ErbB TKI with activity in patients with HER2 exon 20 mutated NSCLC. HER2 exon 20 insertion mutations are a rare subset accounting for approximately 2-4% in NSCLC. There is no approved therapy for either treatment-naïve or previously treated NSCLC with HER2 exon 20 mutations.

Poziotinib MoA

Poziotinib inhibits tyrosine kinase phosphorylation in patients harboring HER2 exon 20 mutations resulting in inhibition of the RAS/RAF pathway.

Poziotinib treatment also increases HER2 receptor expression on surface of tumor cells harboring exon20 insertion mutations. (Cartoon)



Study Design

ZENITH20 STUDY (NCT03318939)

- A Phase 2, open-label, prospective, multi-center study evaluating the efficacy and safety/tolerability of poziotinib in seven patient cohorts
- Cohorts 2 and 4 (C2, C4) included previously treated (C2) or treatment naive (C4) adult patients with locally advanced or metastatic NSCLC harboring HER2 ex20ins
  - Tumor mutational status was assessed via NGS
  - C2 patients received 16 mg poziotinib once a day (QD)
  - C4 patients received 16 mg QD or 8 mg twice a day (BID)
- The primary endpoint was objective response rate (ORR) assessed by an Independent Radiologic Review Committee
  - Secondary endpoints included progression free survival (PFS), disease control rate (DCR), duration of response (DOR), and safety

Results

Demographics

- In total, 170 patients were enrolled and treated with poziotinib in these two cohorts, with 90 patients in C2 and 80 patients in C4
- Fourteen (8.2%) patients had the HER2 G778 GSP insertion (C2, n=7; C4, n=7)
- Median (range) age was 59 (34-80) years
- The demographics for the G778 group were similar to what has been reported in the literature for this group of patients

	Cohort 2 and Cohort 4 n=14
Age (years)	
Median (range)	59 (34–80)
Sex (male, n, %)	6 (42.9)
Race, n (%)	
Asian	2 (14.3)
White	11 (78.6)
Other	1 (7.1)
Smoking status, n (%)	
Former	6 (42.9)
Never	8 (57.1)
ECOG PS, n (%)	
0	6 (42.9)
1	8 (57.1)
Prior lines of therapy	
Median (range)	2[a] (1–5)

ECOG = Eastern European Oncology Group; PS = performance status; SD = standard deviation
a) For previously treated patients only

SAFETY

- The frequency of adverse events (AEs) were consistent with the overall population in ZENITH20 and adverse events were similar to other drugs in the TKI class.
- No pneumonitis was reported in this subset of patients.

Efficacy: Response

- 12 of 14 patients were evaluable; 1 patient discontinued due to an AE prior to any post-baseline scan and 1 with data not complete
- All 12 evaluable patients had a partial response (ORR 100%)
- The median DoR was 5.5 months (C2: 5.3 months; C4: 8.9 months)
- The median PFS was 7.8 months (C2: 7.6 months; C4: 9.8 months)

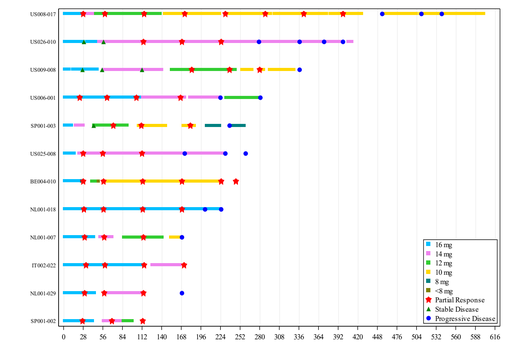
	Previously treated (C2), n=7	Treatment naïve (C4), n=7
Best Overall Response, n (%)		
Complete Response	0	0
Partial Response	7 (100)	5 (71.4)
Stable Disease	0	0
Progressive Disease	0	0
Not Evaluable	0	2 (28.6)
Objective Response Rate, % (95% CI)	100 (59.0, 100)	71.4 (29.0, 96.3)
Duration of response, months Median (Range)	5.3 (2.9, 6.6)	8.9 (4.6, 14.1)
Progression-Free Survival, months Median (Range)	7.6 (3.7, 11.1)	9.8 (0.03, 14.9)

C2 = Cohort 2; C4 = Cohort 4; CI = confidence interval.

Anti-Tumor Activity

- Most patients (9/12) had an initial response observed at the end of Cycle 1 (**Figure 1**)
- Target lesion decreased from baseline in both cohorts, ranged between 33% and 72% **(Figures 2 and 3)**

Figure 1. Efficacy and Dosing Over Treatment Period in the 12 Evaluable Patients[a] with HER2 G778 GSP Insertion Mutations



Swimmer plot for individual responders showing the duration of dosing and response.

Figure 2. Most Patients Across Both Cohorts Demonstrated a Reduction in Tumor Size from Baseline

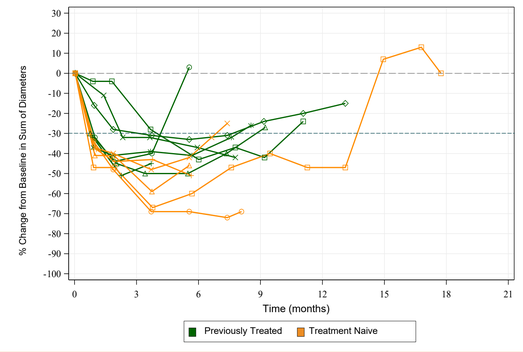
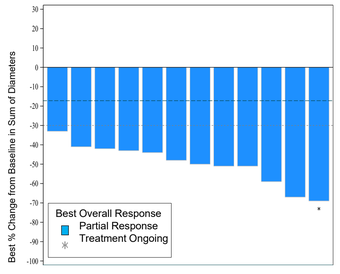


Figure 3. Best Overall Response in Patients with HER2 G778 GSP Insertion Mutations GSP Insertion Mutations



Best percentage change from baseline in target lesion size (based on RECIST Guidelines, v1.1 by BICR) in patients with advanced NSCLC and HER2 exon 20 insertions (evaluable population, n=12). BICR, blinded independent committee review; ex20ins, exon 20 insertion; NSCLC, non-small cell lung cancer; RECIST, response evaluation criteria in solid tumors.

CONCLUSIONS

- Poziotinib is highly active in G778 mutations in both treatment-naïve and previously treated patients with NSCLC
- PFS compared favorably to results previously reported (Cohort 2: 5.5 months[2]; Cohort 4: 5.6 months[3])
- To date, the ZENITH20 trial is the largest HER2 exon 20 insertion study in NSCLC that uses blinded central imaging for response analysis

References

1. Robichaux et al, Cancer Cell 2019;20(1):44-57.
2. Le X, et al., J Clin Oncol 2022;40(7):710–18
3. Sun et al, ESMO TAT 2022

Acknowledgement

We thank all the patients and their families

Poziotinib is an investigational drug that has not been approved by the Food and Drug Administration

Presenting author email: xle1@mdanderson.org

This study and publication were sponsored by Spectrum Pharmaceuticals, Inc. NCT03318939

Poster to be presented at the European Society for Medical Oncology (ESMO), Paris, France, September 9–13, 2022.
Editorial assistance was provided by Meridian HealthComms Ltd, funded by Spectrum Pharmaceuticals.