WCLC 2018: Poziotinib in Stage IV NSCLC With EX 20 EGFR Mutation

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Key Points

- Early results of a phase II study showed a total of 24 of 44 patients (55%) with exon 20 mutations in *EGFR,* and 6 of 12 patients (50%) with exon 20 mutations in the HER2 receptor, responded at 8 weeks after treatment with poziotinib.
- Median progression-free survival on the EGFR arm of the poziotinib trial was 5.5 months, and it has not been reached in the HER2 arm.

Findings presented at the International Association for the Study of Lung Cancer (IASLC) 19th World Conference on Lung Cancer (WCLC) showed poziotinib demonstrates clinical activity among patients with stage IV NSCLC with genetic mutations that have previously not responded to treatment. Researchers at The University of Texas MD Anderson Cancer Center reported early results from a phase II clinical trial (Abstract OA02.06) and showed that 24 of 44 patients (55%) with exon 20 mutations in the epidermal growth factor receptor (EGFR) and 6 of 12 patients (50%) with exon 20 mutations in the HER2 responded at 8 weeks after treatment with poziotinib.

Response rates of patients with an exon 20 point mutation to other targeted therapies aimed at EGFR and HER2 have been 12% or less, the researchers noted. There are no approved therapies for these patients. Researchers estimate exon 20 *EGFR* mutations occur in about 1% to 2% of NSCLCs and *HER2* exon 20 variations occur in about 3%.

“These findings confirm earlier observations that poziotinib is highly active against this previously untargetable mutation and durable responses are observed, with some patients on treatment now for more than a year,” said principal investigator **John Heymach, MD, PhD**, Professor and Chair of Thoracic/Head and Neck Medical Oncology at MD Anderson.

Previous early results had been reported for 11 patients with *EGFR* mutations, but Dr. Heymach’s presentation is the first to include patients with *HER2* mutations.

More Findings

Nineteen patients remain on treatment, six for more than a year. All responses so far are partial responses. The median progression-free survival on the EGFR arm of the poziotinib trial was 5.5 months, and it has not been reached in the HER2 arm.

In the EGFR cohort, 56% of patients had a side effect of grade 3 or higher, most commonly skin rash (34.9%), diarrhea (17.5%), and paronychia (9.5%); 1 patient stopped treatment due to grade 3

skin rash. Sixty percent of patients had dose reductions. Side effects in the HER2 cohort were similar. One death from pneumonitis in the HER2 cohort was considered to be possibly drug-related.

Selecting Poziotinib

Dr. Heymach's team decided to focus on patients with an exon 20 mutation while selecting projects for MD Anderson's Moon Shots Program. Review of a patient database found patients with an exon 20 mutation had a median progression-free survival of just 2 months.

In a series of cell line and mouse model experiments, combined with structural modeling of both *EGFR* and *HER2* mutations and available drugs to target them, the researchers found that poziotinib's structure made it a "good fit" for exon 20–mutated disease, even though it had largely failed to be effective against other mutations. The tighter target pocket on EGFR and HER2 tumors with exon 20 mutations also explained why other targeted therapies had been unable to bind with and inhibit the proteins.

Dr. Heymach and colleagues published their results in *Nature Medicine.*

The MD Anderson team continues to study resistance mechanisms to poziotinib and work with colleagues to study exon 20 insertions in other types of cancer. They have identified about 20 other cancer types that include exon 20 *EGFR* or *HER2* mutations and are planning a basket clinical trial of poziotinib in other malignancies.