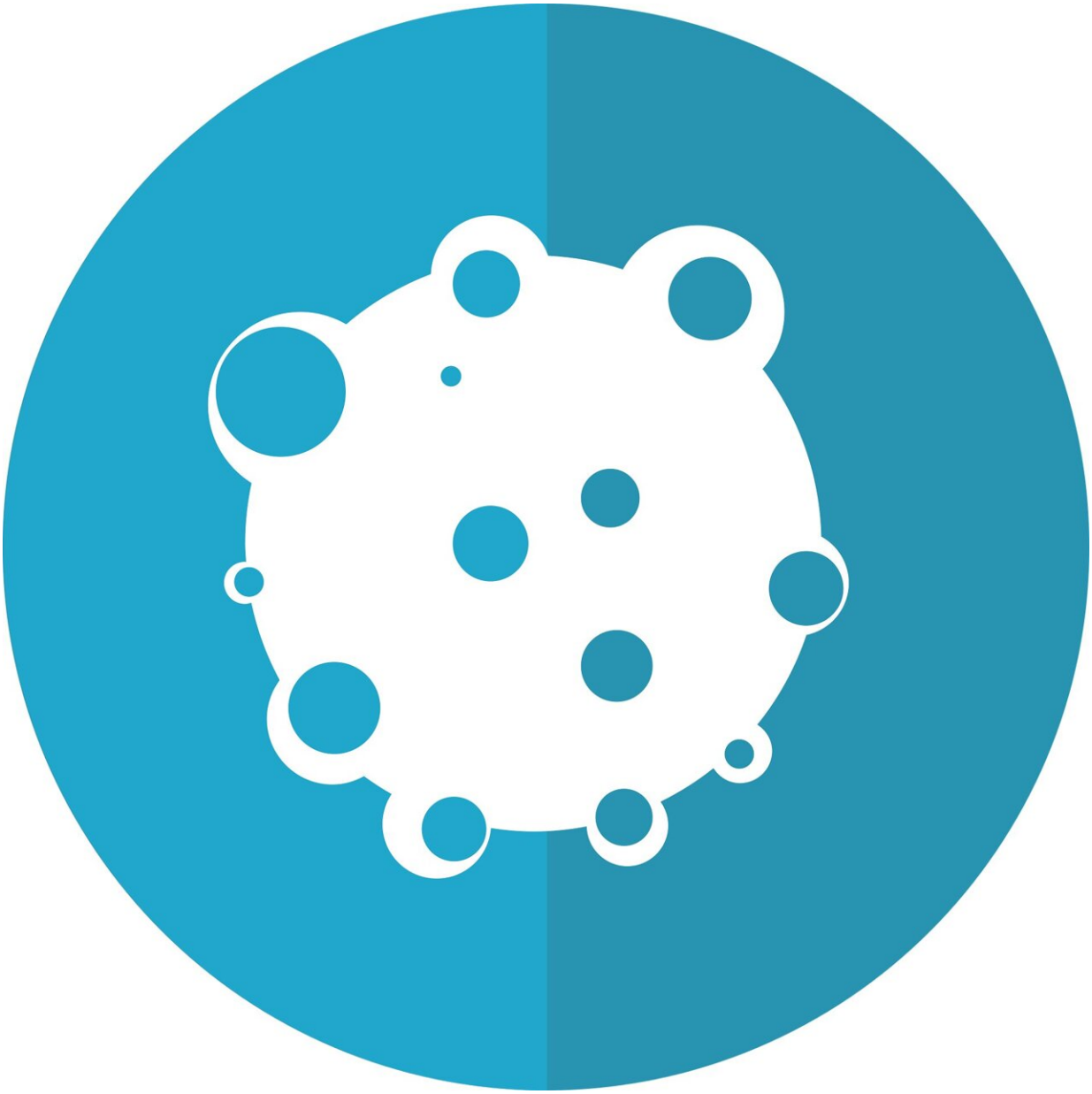
Poziotinib is active in EGFR exon 20 mutant non-small cell lung cancer

July 11 2022



Credit: Pixabay/CC0 Public Domain

A Phase II clinical trial of poziotinib for non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 mutations, led by researchers at The University of Texas MD Anderson Cancer Center, found the drug had significant antitumor activity and the efficacy was highly dependent on the location of the exon 20 loop insertion, which may impact future clinical trials for EGFR exon 20 targeted therapies.

The study, published today in *Cancer Cell*, showed an overall response rate of 32% across all patients with EGFR exon 20 mutations, but this efficacy varied depending on the location of the mutation: a 46% overall response rate was observed for "near-loop" insertions and a 0% response rate was observed for "far-loop" insertions. The results build on earlier findings published by the research team in *Nature Medicine* supporting the activity of the drug in patients with EGFR exon 20 mutations, as well as a study in *Nature* that demonstrated classifying EGFR mutations by structure and function can more accurately match NSCLC patients to effective treatments.

"EGFR exon 20 mutant lung cancers typically don't respond well to the types of tyrosine kinase inhibitors (TKIs) that have been largely successful in targeting classical EGFR mutations, leaving this patient population with few effective treatment options," said senior author John Heymach, M.D., Ph.D., chair of Thoracic/Head & Neck Medical Oncology. "Our study gives hope for not only a potentially beneficial treatment option, but for a new level of precision to better target EGFR exon 20 mutations and to design more effective clinical trials."

Exon 20 mutations are characterized by the insertion of additional amino

acids in the loop after the C-terminal end of the αC-helix, where exon 20 is folded within the EGFR protein. The insertions cause defects in the drug-binding pocket that can reduce sensitivity to some TKIs. Standard sequencing methods used to identify the mutation include the location of the inserted amino acids. In this study, the researchers defined near-loop insertions as amino acids A767 to P772, and far-loop insertions beyond P772.

Early trial results hinted at the importance of the insertion location, so the research team used pre-clinical models, including cell lines and molecular dynamics simulations, to investigate this observation. They discovered that poziotinib, a second-generation TKI, more effectively bound to the EGFR protein when exon 20 insertions were in the near loop versus the far loop. This finding was validated when the clinical responses were analyzed based on the insertion loop location.

"Defining EGFR exon 20 as a targetable mutation was a major step, and now we've taken one step further to find that even within exon 20, not all mutations are the same," said lead author Yasir Elamin, M.D., assistant professor of Thoracic/Head & Neck Medical Oncology. "While further research is needed, these findings may be applicable to other exon 20 inhibitors, and future clinical trials should take exon 20 insertion location into consideration."

Study met primary endpoint with manageable safety profile

The single-center study (NCT03066206) enrolled 50 patients with advanced NSCLC with point mutations or insertions in EGFR exon 20. Patients received poziotinib, a TKI identified and repurposed by Heymach's team for the treatment of exon 20 mutated NSCLC. The research to advance poziotinib in this setting was supported by MD

Anderson's Lung Cancer Moon Shot, part of the institution's Moon Shots Program, a collaborative effort to accelerate the development of scientific discoveries into clinical advances that save patients' lives.

The clinical trial enrollment population was 60% female, with a median age of 62. Racial demographics were 76% white, 16% Asian and 8% African American. Nearly all patients (94%) had received at least one prior systemic therapy.

The study met its primary endpoint of objective response rate (ORR) of 30% or greater, with 32% and 31% ORR as assessed by the investigator and blinded independent review, respectively. The median progression-free survival (PFS) was 5.5 months, median duration of response was 8.6 months and median overall survival was 19.2 months.

Translational findings showed that mechanisms of resistance fell into two recognized categories for EGFR inhibitors: EGFR-dependent mechanisms, such as acquired T790M and C797S mutations, and EGFR-independent mechanisms, such as epithelial-to-mesenchymal transition. These data provide the first confirmation that known mechanisms of resistance to EGFR inhibitors also apply to exon 20 inhibitors.

Most patients experienced grade 1 or 2 toxicities, with diarrhea (92%), skin rash (90%), oral mucositis (68%), paronychia (68%) and dry skin (60%) being the most comment adverse events. Patients were followed by a dermatologist after beginning treatment to help manage the skin toxicities. Only three patients (6%) discontinued treatment due to adverse events. A total of 36 patients (72%) had dose reductions due to adverse events; the median PFS was similar across the dose-reduction group and full study population.

Based on these results, several ongoing clinical trials are assessing poziotinib for EGFR exon 20 mutant NSCLC in larger, international

cohorts and testing alternate dosing strategies to reduce toxicity while maintaining efficacy.

More information: John V. Heymach, Poziotinib for EGFR exon 20 mutant NSCLC: clinical efficacy, resistance mechanisms and impact of insertion location on drug sensitivity, *Cancer Cell* (2022). DOI: 10.1016/j.ccell.2022.06.006. www.cell.com/cancer-cell/fullt … 1535-6108(22)00270-7

Provided by University of Texas M. D. Anderson Cancer Center