

# Targeted Therapies for *EGFR* Exon 20 Insertion-Positive NSCLC

In this **CancerNetwork® OncView™** program, faculty panelist Zofia Piotrowska, MD, explains the treatment options in this disease space and discusses recent drug approvals



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In a recent OncView™ discussion, **Zofia Piotrowska, MD**, an assistant professor of medicine at Harvard Medical School and a lung cancer medical oncologist at Massachusetts General Hospital, in Boston, Massachusetts, discussed the identification and targeting of *EGFR* exon 20 insertion mutations in non–small cell lung cancer (NSCLC).

Piotrowska opened the conversation with a background review of *EGFR* exon 20 insertions in this space, emphasizing that “the landscape of *EGFR* mutations in non–small cell lung cancer has gotten increasingly complex in recent years. It’s important not just to recognize that your patient may have an *EGFR* mutation on their molecular testing report, but specifically look at which type of mutation they have and think about what the implications are of that specific mutation for treatment.”

## Testing for *EGFR* Exon 20 Insertion Mutations

Piotrowska explained that many next-generation sequencing (NGS) assays being used in clinics today will detect *EGFR* exon 20 insertion mutations. “The important thing is to be able to notice that an *EGFR* mutation has been discovered and that this specific mutation may not be the same as the more common exon 19 deletions and L858R point mutations. It’s important to read the report carefully and distinguish

these different mutations.”

At the initial diagnosis, Piotrowska recommends doing molecular testing for patients. She explained, “It really is important to do testing for all of our patients, and ideally that testing should be done at the time of initial diagnosis so that we can help select the best first-line therapy.”

And although testing should be done for all patients with this disease, barriers to testing remain, according to Piotrowska. Specifically, she cites the lack of regular testing across treatment settings, struggles with performing the testing itself, and waiting times for results as common issues associated with testing.

There are several ways to increase access to testing. “Working closely with pathologists to make sure that the tissue is used carefully and as much as possible is saved for molecular testing, and then also thinking about the use of liquid biopsies are important steps that we can take to improve the rates of testing,” Piotrowska explained.

Furthermore, the ability to accurately interpret the results from these assays, and specifically identify which mutations are present, is an increasingly difficult challenge that care providers need to tackle, according to Piotrowska.

“The other big category is waiting for test results and being able to appropriately interpret NGS reports to identify

which mutations are present and help ensure that we're selecting the right treatment for patients," Piotrowska explained. "I've seen in my own practice that has gotten more and more complicated in recent years as we have new targeted therapies available for patients."

### Treatment Options and Patient Selection

A current problem for treating patients with *EGFR* exon 20 mutations revolves around the ineffectiveness of commonly used first- and second-generation *EGFR* inhibitors, such as erlotinib (Tarceva), gefitinib (Iressa), and afatinib (Gilotrif), to treat this specific mutation, according to Piotrowska.

"The data that we have so far certainly seem to show that these drugs are not as effective as they are for exon 19 deletions and L858R point mutations," Piotrowska continued.

Specifically in the first-line setting, standard chemotherapy remains a good option for patients with exon 20 insertion mutation–positive lung cancers. A gap in the field exists surrounding the benefit of immunotherapy for patients with *EGFR* exon 20 mutations as it compares with that observed in other mutation subtypes, as well as the potential use of immunotherapy plus chemotherapy combinations.

"The jury is still out on the role of immunotherapy, but certainly chemotherapy remains an important treatment option, as it has been historically for these patients."

One emerging agent in the second-line or later setting that recently received accelerated approval from the FDA for patients with *EGFR* exon 20 insertion–positive NSCLC is the *EGFR*-MET bispecific antibody amivantamab (Rybrevant).<sup>1</sup>

Amivantamab was approved based on the results of the phase 1 CHRYSALIS trial (NCT02609776).<sup>2</sup> In total, 81 patients with *EGFR* exon 20 insertion–mutant NSCLC who previously received

platinum-based chemotherapy were treated with amivantamab. The overall response rate (ORR) for the efficacy population was 40% (95% CI, 29%-51%), including 3 complete responses. Median duration of response was 11.1 months (95% CI, 6.9 to not reached [NE]) and median progression-free survival (PFS) was 8.3 months (95% CI, 6.5 - 10.9).

The most common any-grade adverse effect (AE) was rash, seen in 86% of patients. Common grade 3 or higher AEs included hypokalemia (5%), rash (4%), pulmonary embolism (4%), diarrhea (4%), and neutropenia (4%).

"It's great to have another option for patients with these mutations, and it's a very good option for patients," Piotrowska explained. "It's approved for second-line and later use, so it doesn't necessarily impact our first line of treatment for patients with *EGFR* exon 20 insertions as of today."

Another targeted therapy for the second-line or later setting is the oral *EGFR* tyrosine kinase inhibitor mobocertinib (Exkivity), which was granted accelerated approval by the FDA in September 2021.<sup>3</sup>

"Mobocertinib was the second drug approved for *EGFR* exon 20 insertion mutations," Piotrowska explained. "It's great to have 2 different targeted therapeutic options for these patients."

Approval was based on positive results from the phase 1/2 EXCLAIM trial (NCT02716116).<sup>4</sup> A total of 114 patients with *EGFR* exon 20 insertion–positive NSCLC who progressed on prior platinum-based chemotherapy were included in the study's population. The confirmed ORR was 28% (95% CI, 20% - 37%) by independent review committee assessment. Median duration of response was 17.5 months (95% CI, 7.4 - 20.3) and median PFS was 7.3 months (95% CI, 5.5 - 9.2).

Diarrhea was a common toxicity, seen in 91% of patients treated with mobocertinib, 21% of which were grade 3 or

higher events. Rash was also a common AE (45%), but most cases were categorized as low-grade.

Although these 2 approvals are promising developments for treating this subset of patients, Piotrowska emphasized the existing need for an effective first-line therapeutic option.

"Although we now have 2 approved targeted therapies for these patients, unfortunately neither of them is approved in the frontline setting," she explained. "There are some ongoing clinical trials looking at first-line treatment options for these patients, but as of today in 2021, the preferred first-line treatment for these patients is still platinum-based chemotherapy."

### Future Directions

"It's great to see the progress that we've made, but I would say there are still many unmet needs in this patient population," Piotrowska explained.

Specifically, although the response rates observed with these targeted therapies are encouraging, Piotrowska emphasized that the data are still not as promising as response results seen with osimertinib (Tagrisso) for more common *EGFR* mutation subtypes.

Moreover, toxicities exist with amivantamab and mobocertinib, including gastrointestinal and skin toxicities. Piotrowska suggests that alternative treatment options to minimize these AEs would be welcome.

Looking ahead, Piotrowska is excited for potentially more alternative targeted therapies for patients with NSCLC and mutations in *EGFR* subtypes.

"There are a number of drugs now in development that are trying to be more specific for that mutant *EGFR*, and a number of others that are in development that have the potential to be more effective and have a better safety profile," Piotrowska concluded. ■

➔ For references visit [cancernetwork.com/Piotrowska\\_12.21](https://cancernetwork.com/Piotrowska_12.21)