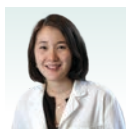


Amivantamab as Second-line Option in Advanced NSCLC *EGFR* Exon 20 Mutation



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In a *Between the Lines* program hosted by CancerNetwork®, Joshua K. Sabari, MD, and Helena A. Yu, MD, discussed treatment options for patients with advanced non-small cell lung cancer (NSCLC) who have *EGFR* exon 20 insertion mutations. Specifically, the conversation centered on the results of the phase 1 CHRYSALIS study (NCT02609776), which were presented at the European Lung Cancer Congress 2023 and designed to evaluate amivantamab-vmjw (Rybrevant) vs alternative real-world anticancer therapies.

Sabari, a medical oncologist at NYU Langone Health's Perlmutter Cancer Center, New York, New York, and Yu, an associate attending physician at Memorial Sloan Kettering Cancer Center, New York, New York, reviewed treatment options for patients with this specific mutation, results from CHRYSALIS, and how these results may affect clinical practice.

Treatment Options for the *EGFR* Exon 20 Population

Sabari launched the conversation by asking how common *EGFR* exon 20 insertion mutations are in patients with NSCLC. Yu commented that she rarely

sees patients with such mutations and that they make up about 2% to 3% of the total patient populations that she has.

Unfortunately, patients with this specific mutation face limited available treatment options. For those with exon 19 or exon 21 mutations, however, there is a plethora from which to choose.

Sabari wondered how Yu identified patients with exon 20 mutations. She responded, "At my institution, we use next-generation sequencing [NGS], and that allows us to look for all the mutations within the *EGFR* gene, but also look for other driver mutations. It's 1 test to identify all [mutations]."

Sabari said broad-panel NGS is used at NYU Langone Health, but many of his colleagues use immunohistochemistry-based assays. However, Yu commented that these assays may not be as sensitive and may miss different *EGFR* mutations.

Once an *EGFR* exon 20 mutation is discovered, clinicians are faced with determining what the first-line treatment should be. Yu will start her patients on platinum-based chemotherapy, and in the second line she will transition them

to amivantamab. Sabari said he uses a similar regimen.

A hot topic of conversation in this space has been using immunotherapy for patients with exon 20 mutations. Many trials have not ventured into evaluating immunotherapy for this population; therefore, clinicians do not have data on utilizing this type of therapy for these patients, and there may be added toxicities for this combination.

For patients with exon 20 mutations, Sabari would never choose osimertinib (Tagrisso). Even at doses of 80 mg or 160 mg, the data are nonexistent. The ECOG-ACRIN 5162 study (NCT03191149) evaluated the administration of osimertinib at 160 mg in this patient population, but the results were modest and not enough to consider using osimertinib in the first line.¹

Following first-line treatment, progression-free survival (PFS) is about 7 months for this population. Clinicians must then consider what they can offer patients in the second-line setting. Because Yu uses NGS prior to treatment, she can make an informed decision when she does see a patient progress, and move to treatments like amivantamab.

Patients with exon 20 mutations have shorter survival than those with other insertion mutations. “Until recently, we didn’t have targeted therapies for that population, so their armamentarium of treatments was quite limited. I still think the data that we have retrospectively [are] that they don’t respond as well to chemotherapy. They’re very likely to get brain metastases, so it’s a population where we want to stay on top of treatment and make sure that we give our best treatments as soon as possible,” Yu said.

CHRYSALIS Study

The conversation then turned to cohort D of CHRYSALIS, which analyzed amivantamab vs alternative treatments in patients with *EGFR* exon 20 insertion–mutated advanced NSCLC. This cohort enrolled 114 patients, with the primary end points being safety, overall response rate, and duration of response. Secondary end points included PFS, time to treatment failure, and overall survival.

Investigators consulted databases in the United States, such as Flatiron and ConcertAI, as well as in Europe. Using these databases allowed them to isolate patients with the exon 20 mutation to see whether they had prior lines of chemotherapy.

Regarding the major end points, results were consistently and statistically significant in favor of amivantamab. Yu noted a response rate of 40% and a PFS of 8.3 months.

With amivantamab shown to be a potential treatment option, Sabari asked how colleagues should be educated when using this agent, as it is given as an infusion in a clinic. “Education is key for our patients and our chemotherapy infusion staff, just so that they know what to expect,” Yu said. “The one unusual [adverse] effect [AE] of amivantamab is the infusion-related reactions. I have seen them primarily and almost exclusively on day 1 and because of that, the first dose is a split dose where you get part of the dose on day 1, and part of the dose on day 2. I always just instruct my patients that

if they feel anything is off, like they’re having some wheezing, some flushing, or pain anywhere, please let us know as soon as possible. As long as the medication is stopped promptly, medications are given, if appropriate, to address the reaction. After [managing the AEs], quite a few patients successfully go to day 2 [of therapy].”

Sabari reiterated the importance of education. “This is a drug that you need to educate your patients and your staff on,” he said. “Infusion-related reactions are quite common, with 65% to 70% of my patients having 1 cycle on day 1. When they have a reaction, most of the time it’s just flushing [occurring about] 30 minutes to 35 minutes into the infusion. We stop the medicine. I don’t usually continue it that day. I have patients come back for cycle 1, day 2, get the remainder of the infusion, and the infusion-related reaction for me in my clinic is less than 1% on the second day and thereafter very well tolerated over time in patients.”

Additional second-line treatment that Yu often sees is just standard chemotherapy, she said. Sabari noted that he sees a lot of osimertinib use, chemotherapy and immunotherapy, and occasionally the use of single-agent docetaxel or docetaxel plus ramucirumab (Cyramza).

Future Treatment Options

Many studies are evaluating first-line treatment for patients with *EGFR* exon 20 mutations. The phase 3 PAPILLON trial (NCT04538664) is evaluating amivantamab plus carboplatin-pemetrexed vs carboplatin-pemetrexed alone. Both Sabari and Yu said they were excited to see the results of this study.

When considering immunotherapy, Yu said there has not been a “synergy” shown for this population. Additionally, in retrospective studies that have been conducted, the single-agent response of immunotherapy was almost 0%. Sabari agreed, noting, “There is no clear role for immunotherapy in the frontline setting.” ■



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