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# Guidelines-recommended targeted therapies as second-line treatment options for patients with metastatic NSCLC

**Announcer:**
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**Dr. Yu:**
This is CME on ReachMD, and I'm Dr. Helena Yu.

**Dr. Paz-Ares:**
And I'm Dr. Luis Paz-Ares.

**Dr. Yu:**
Targeted therapies have now been incorporated into the second-line treatment for metastatic non-small cell lung cancer.

Luis, what are the guideline recommendations for patients with common sensitizing EGFR mutations or ALK rearrangements in the second-line setting?

**Dr. Paz-Ares:**
What we typically do on those patients with EGFR mutation at the time of progressions, we typically look at what was the initial therapy. Today, in most of the cases, we use third-generation TKIs such as osimertinib. So the time of relapse, we tend to do, if feasible, some type of biopsy, liquid or solid, or one after the other, depending on the result. If we really are able to see there is one genomic aberration that is targetable and responsible for the resistance, we may think about giving a specific therapy. In the case that we were not able to do a biopsy, in the case that we didn't find any clear mechanism of progression, I would say today the standard of care may be the MARIPOSA-2 type of regimen, which is a combination of amivantamab plus chemotherapy. In this very setting, it's been clear on the MARIPOSA-2 trial, that increased the response rate quite significantly, and also it really impacts on time-dependent outcomes such as PFS with a hazard ratio of 0.48. That means you're decreasing the risk of relapse by more than 50%.

In the case of ALK rearrangements, today I'm pretty sure that most of the patients would be started on lorlatinib, but maybe some patients are having other ALK inhibitors such as alectinib, and so the tumor relapsing depends on the therapy you had been using in first line; in the case lorlatinib had not been used, typically, we use lorlatinib at a time of relapse. In the case of lorlatinib had been the therapy used, there are a number of opportunities to use chemotherapy, among others, but also there are some novel drugs that are coming with promising data not yet being officially accepted by the agencies.

Okay. So my question for Helena would be, what are the guideline recommendations in the second-line setting for patients with some of the other actionable mutations?

**Dr. Yu:**
Yes. I think, Luis, you bring a great point that we used to have one option in the first-line setting, and it was very clear what the second

option is, but for now, for all of these, it really depends on what you get in the first-line setting, and that dictates what's available to you in the second-line setting.

So for KRAS G12C alterations, which are, of course, the most common type of KRAS alterations, most of those patients will get chemotherapy with immunotherapy in the first-line setting. And then in the second-line setting, the 2 approved drugs are sotorasib and adagrasib. I think that they behave actually quite similar in terms of efficacy with both. Both have an overall response rate around 35% to 40%. PFS is in that 6- to 7-month range. And so I think those are our solid second-line indications.

For HER2 alterations, we have trastuzumab deruxtecan. This is an FDA-approved NCCN-recommended second-line treatment for patients with HER2 mutations. And then there is an ongoing study looking to see if we can move that to the first line. So we'll see about that, just because it has excellent efficacy in that second-line setting. And then for ROS1, which is rare, about 1% to 2% of all lung cancers, there are different options. I think historically, perhaps, these patients might have gotten crizotinib, and so then lorlatinib or repotrectinib are both options for patients. And also, of course, if they had gotten chemotherapy up front, certainly, we could give repotrectinib as the first TKI.

Well, this has been a brief but great discussion. I hope we gave you something to think about. And thanks for tuning in.

**Announcer:**
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