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https://reachmd.com/programs/cme/targeted-therapy-for-treatment-naive-ret-fusion-positive-lung-cancers/14840/

Released: 12/07/2022
Valid until: 12/07/2023
Time needed to complete: 1h 03m

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Targeted Therapy for Treatment-Naïve *RET* Fusion-Positive Lung Cancers

Announcer:
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Dr. Drilon:
Hello, my name is Alexander Drilon. I'm a medical oncologist for Memorial Sloan Kettering Cancer Center. This presentation is on targeted therapy for treatment-naive RET fusion-positive lung cancers. We will first walk through the history of targeted therapy development for RET-dependent cancers, and the first point for you is that the older RET inhibitors were what we call multi-kinase inhibitors that inhibited RET and inhibited a bunch of other different kinases, and this occurred before 2017 with examples such as cabozantinib, vandetanib, and lenvatinib. Many of these drugs were repurposed to focus on RET inhibition and pulled off the shelf and not specifically designed to target RET. And so, in this slide, you'll see that in the yellow bubbles, the outcomes observed in terms of objective response rate and median progression-free survival were modest compared to other targeted therapies for ALK, EGFR, and ROS1.

Thankfully, selective RET inhibitors entered clinical testing in 2017. These are drugs that were rationally designed to more optimally inhibit RET and target activating RET alterations. And you'll see these Kinome dendrograms on the very right-hand portion of the slide with BLU-667 which is now called pralsetinib and LOXO-292 which is called selpercatinib. The take-home with these diagrams is that these drugs pretty much hit RET meaningfully while avoiding many of the other kinases that don't appear here as extra dots that you see with the older drugs like cabozantinib, vandetanib, and lenvatinib.

This presentation will focus on the outcomes achieved with the selective RET inhibitors in the regulatory-grade dataset for treatment-naive patients with RET fusion-positive lung cancers. And here, we will start with selpercatinib in this slide where you see a waterfall plot of all patients who are treatment-naive with RET fusion-positive lung cancers that got the drug. You'll note that there were 69 patients in this cohort with an objective response rate by IRC of 84%. You'll note that there were 6% of cases that had a CR, and that the frequency of primary progressive disease was low at 4%. On the waterfall plot here of measurable disease, you'll see that all patients basically had disease regression with therapy showing how well the drug works.

And in this next slide, we show you durability in the same treatment-naive population where you have the Kaplan-Meier curves for median duration of response on the left and median progression-free survival on the right. You'll note that the median duration of response as per this data cut was 20.2 months and the median progression-free survival was 22 months. Now you'll see that the one-year and two-year landmarks look favorable, especially compared to older agents for lung cancer, and even other systemic therapies that patients with non-small cell lung cancer receive.

Now, moving on to the second drug, here we have pralsetinib, which is also a selective RET inhibitor that's likewise approved for RET fusion-positive lung cancers. Here, we have the treatment-naive data in RET fusion-positive lung cancers with an overall response rate of 70%. Most patients had benefit with therapy. You see again here the waterfall plot showing disease regression in everyone with

measurable disease, complete response rate of 11%, and primary progressive disease was also low at 11%, so comparable results to selpercatinib.

You'll see here the durability in treatment-naive RET fusion-positive non-small cell lung cancers with the Kaplan-Meier curves for duration of response on the left, median progression-free survival on the right and the median DoR was nine months for pralsetinib while the median progression-free survival was 9.1 months.

Now, this next slide shows you that selective RET inhibitors also achieve molecular responses to therapy. This is admittedly a mixed bag of treatment-naïve and treatment-experienced patients, but for both selpercatinib and pralsetinib, you see the RET fusion-variant allele frequency go down substantially in many patients. That's unsurprising given the radiologic and clinical responses we're seeing with the therapy.

I also wanted to throw out there that the drugs can work very well in the CNS. These are intracranial waterfall plots for selpercatinib and pralsetinib. And in the middle, this is a patient who had a confirmed intracranial PR with complete resolution of leptomeningeal disease with selpercatinib.

So here, you have a table summarizing the activity of the selective RET inhibitors, selpercatinib, and pralsetinib, both of which were approved and explored on the LIBRETTO-001 and ARROW Trials respectively. You see here the objective response rates, median duration of response, and median PFS side by side for the treatment-naive population.

To confirm the data that you've seen thus far on the activity of selpercatinib and pralsetinib in the treatment-naive setting, there are two randomized Phase 3 trials that are ongoing. The first is shown on this slide, the AcceleRET Lung Study, that randomized RET fusion-positive non-small cell lung cancers with no prior systemic therapy for metastatic disease to either pralsetinib or investigator's choice of platinum-based chemotherapy plus/minus pembrolizumab. As you can see, the primary endpoint is progression-free survival with the secondary endpoints of response, overall survival, safety, tolerability, and the rest listed here.

The second study is the LIBRETTO-431 Study which has a similar design randomizing treatment-naïve patients with locally advanced or metastatic RET-fusion positive lung cancers to selpercatinib or chemotherapy plus/minus immunotherapy with pembrolizumab. Note that there is an optional crossover at progression in patients who develop PD after chemoimmunotherapy or chemotherapy at which point patients can receive selpercatinib. The primary endpoint is like the AcceleRET Trial progression-free survival with the secondary endpoints shown here. Thank you for your attention.

Announcer:
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