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Can I Use Targeted Therapy in *RET*-Positive mNSCLC in Pretreated Patients?

Announcer:
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Dr. Gainor:
Hello, my name is Dr. Justin Gainor from the Massachusetts General Hospital. Today I'll be focusing on the question of, Can I use targeted therapy in RET fusion-positive non-small cell lung cancer that has been previously treated. Over the last seven years, we've seen evolution in how we've approached RET fusion-positive non-small cell lung cancer. Early on we were using multikinase inhibitors with anti-RET activity in an experimental fashion. So, these were investigational trials that were really repurposing already approved drugs, but in a new context for RET fusion-positive lung cancer. And the activity of these agents such as Cabozantinib and Vandetanib was relatively modest and that was principally driven by we weren't hitting the target hard enough because of all of the off-target effects. More recently we've seen the emergence of two selective RET inhibitors, Pralsetinib and Selpercatinib. And both of these agents were explored in pivotal Phase 1, 2 studies with an early focus on patients who had been previously treated, specifically patients previously treated with platinum doublet chemotherapy. So, I'd like to take a few minutes and walk through those two studies with you.

So, on the next slide, we see the schema of the Libretto-001 study which investigated Selpercatinib. This study included a Phase 1 dose escalation study followed by a Phase 2 expansion arm. And within the phase two expansion, there were multiple different expansion cohorts. The registrational cohort for non-small cell lung cancer focused on individuals who had received prior platinum doublet chemotherapy which is really the standard of care before this study. On the right of this slide, you can see the initial waterfall plot published in the New England Journal by Alex Drilon and colleagues showing that among patients with non-small cell lung cancer that have been previously treated with platinum, the objective response rate was 64 to 70% depending on whether one was looking at investigator versus blinded independent review.

On the next slide, we have updated data that were just published in the Journal of Clinical Oncology from this same study, Libretto-001. And here we see a much larger cohort at 247 patients, but the objective response rate holds up with the larger cohort. We see an objective response rate of 61%. And we see a medium progression-free survival approaching 25 months. If we look at that two-year landmark, we see that over half of patients, 51.4%, are progression-free at the two-year landmark.

Importantly, Selpercatinib does have CNS activity. In this next slide, focusing on the CNS activity, we see that among patients with measurable brain metastases and this includes both previously treated and untreated patients, we see an intracranial objective response rate of 85%. Collectively, these data form the basis for the FDA approval of Selpercatinib and really establish this as one of two agents that are a standard of care for RET fusion-positive lung cancer including among patients who were previously treated. I should add that based upon these data; the activity is so robust with both Selpercatinib. And as you'll see with Pralsetinib, we really should be using these agents in the first-line setting. However, if someone had already received chemotherapy, then these agents still have robust clinical activity and should be used in that setting.

If we move on to the next slide which summarizes the schema for the ARROW Study, this was the corresponding Phase 1, 2 study of Pralsetinib, the other selective RET inhibitor. It had a very, very similar design in that there was a Phase 1 dose escalation portion followed by Phase 2, which focused on various expansion cohorts including RET fusion-positive lung cancer with an early focus on the registrational cohort which was in patients previously treated with platinum double chemotherapy. On the right of this slide, you'll see the waterfall plot from our publication last year focused on that cohort where we saw an objective response rate of 61% among patients previously treated with platinum.

On the next slide, we see updated data. These data were just published in Annals of Oncology earlier this year. And with a much larger cohort, we see a very similar objective response rate of 59%.

On the next slide, we see an intracranial response rate of 70% among 10 patients with measurable CNS metastases both patients previously treated in blue bars and patients who had received prior therapy but it was non platinum in the red bar. Nonetheless, this highlights the CNS penetrance of Pralsetinib as well. And altogether, these data also led to the FDA approval of Pralsetinib. As I mentioned with Selpercatinib, the activity of both agent is extremely robust, and I would argue that these agents should be used in the first-line setting. But if one encounters a patient who's been previously treated with chemotherapy for whatever reason perhaps in the adjuvant setting and requires therapy, I think these data justify using selective RET inhibitors in the next-line setting.

Here I'm just summarizing the data for both selective RET inhibitors. I've added the medium progression-free survival times. For both agents, you can see that Pralsetinib and I didn't show that capital markers, but in the updated data it's been 16.5 months. In terms of most common treatment-related adverse events between these agents, we see that the most common adverse events with Selpercatinib is dry mouth, diarrhea, hypertension, and elevated transaminase. And among patients treat with Pralsetinib, most common adverse events are neutropenia, AST increase, anemia, and alterations in white blood cell count. So, to summarize, both Selpercatinib and Pralsetinib have potent antitumor activity in both the treatment naive as well as in the post-platinum setting. And these agents should be a standard of care for RET fusion-positive lung cancer. Thank you so much.

Announcer:
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