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Emerging Agents and Combinations to Treat *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 emerging agents and combinations to treat RET fusion-positive lung cancers. We'll start with drugs that are generationally probably in the same bucket as selpercatinib and pralsetinib as far as we know based on the science that's been presented. One of these drugs is zeteletinib which is another selective RET inhibitor similar to the design of selpercatinib and pralsetinib and there's an ongoing phase 1 trial for which we've seen data in treatment-naive RET fusion-positive lung cancers from the dose escalation where you see an objective response rate of 30%. Remember that some of these patients had gotten doses below the recommended phase 2 dose, and interestingly, on the lower right you'll see that with this newer drug, we're seeing side effects like an increase in CPK that we haven't seen much of, really, with the approved agents selpercatinib and pralsetinib.

Another selective RET inhibitor is SYHA1815. So far, we've seen preclinical data showing that the drug is selective over other kinases like VEGFR2. It does inhibit RET fusions and gatekeeper mutations and a phase 1 trial is ongoing in China and we look forward to seeing the results from that drug. One interesting tidbit is that RET fusions can also be found in EGFR-mutant lung cancers or other non-RET but oncogene dependent non-small cell lung cancers as a mechanism of resistance to targeted therapy. The example here is patients with EGFR-mutant lung cancers treated with osimertinib acquiring a RET fusion, and thankfully in this data that you see on this slide with osimertinib and pralsetinib or osimertinib and selpercatinib by adding in a RET inhibitor, you can reestablish disease control in these patients who have progressed on the single agent TKI by giving the combination.

Now to talk about next-generation RET inhibitors, it's first important to speak to on-target resistance which essentially means that the cancers are likely still addicted to RET, and this can happen with the acquisition of kinase domain mutations on top of the fusion in RET-fusion positive lung cancers. And while we've seen a higher frequency of these mutations in other oncogene-driven lung cancers, the frequency in RET-dependent cancers is low, in the order of 8 to 10% with selpercatinib and pralsetinib as you can see in this slide, and a mutation that's commonly seen as the solvent front mutation, G810R, and G810S.

There are drugs that have been developed to target these resistant mutations including the solvent front mutation. This is TPX-0046. It's a small macrocycle that inhibits RET in addition to other kinases like TRKB, FGFR1, JAK2, and SRC. On the right, you'll see that the drug does target RET G810 R or S although it is less potent against the gatekeeper RET V804 M or E mutation.

The drug is currently being explored in the SWORD-1 phase 1 study. There was initial data showing that four out of five TKI naive patients had disease regression and two of them had a PR and three out of nine TKI pretreated patients had disease regression. Now, while that drug was a multikinase inhibitor, in this slide, we moved to the selective next-generation RET inhibitors. We're talking first about HM06 which addresses solvent front and gatekeeper resistance while being selective for RET. Then you'll see the design of the

drug on the upper right as well as the in vivo data both in KIF5B-RET PDXs, as well as KIF5B-RET PDXs that harbor the solvent front mutation. This drug is being explored on the phase 1/2 margaRET study which is open and accruing around the world. The first patient was dosed in December of 2021 and the scheme of the trial is shown here, taking patients with advanced RET fusion-positive non-small cell lung cancers.

A second selective RET inhibitor is LOXO-260 that also covers solvent front and gatekeeper resistance. Here you see the in vivo and in vitro data against RET G810 substitutions and RET V804 gatekeeper substitutions.

LOXO-260 is being explored on an ongoing phase 1/2 trial as well as an ongoing expanded access trial and we look forward to seeing the results of this trial, the schema of which is shown here. It is taking patients who have progressed on a prior RET inhibitor similar to the other drug, HMO6.

Another drug is EP0031. It's, as we know, a selective RET inhibitor that also covers solvent front resistance. There's an ongoing phase 1/2 trial in China and a trial in the United States that just opened in 2022. Finally, there's APS03118, also selective inhibitor that covers solvent front resistance with a clinical trial planned for 2022 and IND application that's already been approved in the United States with an NMPA submitted in China.

Finally, we'll talk about off-target resistance where RET fusion-positive lung cancers can acquire dependence on other genes like KRS or MET. Some of this can be targetable. Here, you'll see that some RET fusion-positive lung cancers will acquire MET amplification, and in that setting, if you look at the in vitro work and in vivo work here, if you add a MET inhibitor to the RET inhibitor, you can reestablish disease control in laboratory studies.

We've demonstrated proof of concept that laboratory data applies to patients and if you give a combination of a RET and MET inhibitor in this case, the patient got both selpercatinib and crizotinib, you can make these tumors shrink again and there's an ongoing phase 2 trial of cabozantinib, an older drug that inhibits RET, but also is a powerful MET inhibitor that's treating these patients. Thank you for your attention.

Announcer:
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