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What is the Recommended Monitoring Plan for Patients Receiving *RET*-Targeted Therapies?

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 what is the recommended monitoring plan for patients receiving RET-targeted therapies. On the next slide, we see a summary of the data for use of selpercatinib and pralsetinib in patience with RET fusion-positive non-small cell lung cancer. Both agents produce high response rates that are quite durable when measured with the standards of non-small cell lung cancer.

When I'm treating patients with newly diagnosed RET fusion-positive non-small cell lung cancer and I'm starting them on a targeted therapy such as selpercatinib or pralsetinib, I typically see patients every two weeks for a clinical assessment, either in person or virtually, with laboratory monitoring every two weeks up until the first scan which I typically obtain at the six-week mark. If patients are tolerating therapy well and the first scan shows evidence of the expected anti-tumor response, I typically then start spacing out my scans and visits. In my practice, I typically will then see patients every four to six weeks thereafter up until the six-month mark and then start spacing out my clinical visits to every three months or so. In terms of scans, I will typically scan every three months provided patients have achieved an initial response based upon that first repeat disease assessment. In terms of monitoring the brain, clearly among patients who have baseline brain metastases, I am performing routine brain MRIs as part of my CT scan surveillance. We do know that RET fusion-positive lung cancer patients can develop brain metastases despite the CNS penetrance of these agents. And so even among patients who don't have brain metastases at baseline, I'm typically obtaining surveillance brain MRIs every 6 to 12 months in order to monitor for focal CNS recurrence.

We do know that despite the activity of the selective RET inhibitors that patients will eventually develop resistance to therapy and so that underscores the importance of the serial scans, but also, we want to think through if we are seeing resistance to therapy, what are the mechanisms driving resistance to therapies? And is this something that we could actually use a local therapy such as radiation surgery to treat? I wanted to say a brief word on the molecular mechanisms of resistance that have been identified among patients progressing on RET inhibitors. The first reports shown here on this slide of RET inhibitor resistance involve the emergence of a RET solvent front mutation at this G810 residue that was seen in multiple sites within a given patient. This was a patient who ultimately had an autopsy and so one could see this convergent evolution around that solvent front mutation.

Subsequent studies show that RET point mutations are seen in approximately 10% of patients, so these are what we would characterize as on-target resistance mutations. In addition to that 10%, another 10% of patients or so will have bypass signaling pathways such as MET amplification.

We also have seen reports of alterations in the MAP kinase pathway as an alternative mechanism of resistance. And so, in my patients who repeat scans do identify the emergence of resistance, I do typically aim to repeat a biopsy or a liquid biopsy in order to try to

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understand the mechanism of resistance. And so, with that, I'd like to thank you for your attention.

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