Patterns of Resistance in ALK-Positive NSCLC

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TRANSCRIPT

My name is Alice Shaw, I am director of the Center for Thoracic Cancers at Massachusetts General Hospital in Boston.

Over the last several years, there has been many advances in the field of advanced ALK-positive lung cancer and I think the most exciting one for many patients has been the development of new what we call next generation ALK inhibitors.

There's a whole class of second-generation ALK inhibitors such as Ceritinib, Alectinib, and Brigatinib all of which have now have been approved for patients with ALK-positive lung cancer who have previously received Crizotinib. Over the last several years, we now realized that patients who fail on the first-generation inhibitor Crizotinib, most of them are still very ALK sensitive meaning that they will respond to a more potent ALK inhibitor such as Ceritinib, Alectinib, or Brigatinib. I would say one standard approach to treating patients with advanced ALK-positive lung cancer is to use sequential first followed by second-generation ALK inhibitors.

In just the last 6 months, we now actually have data on the use of these more potent second-generation inhibitors in the first-line setting. So, that means instead of treating patients with Crizotinib as their first therapy more and more of us are moving to second-generation inhibitors particularly Alectinib. In this setting, front-line setting, the second-generation inhibitors appear even more active than Crizotinib which is why they are becoming standard of care. However, despite this activity of second-generation drugs like Alectinib, Ceritinib, and Brigatinib we know that at some point almost all patients will develop resistance. This occurs at different times for different patients and also occurs in different ways.

We have spent many years now studying the development of resistance to ALK inhibitors starting with Crizotinib as the first-generation inhibitor but now really focusing on second-generation inhibitors trying to understand resistance to these agents so that we can we can develop new and effective therapies to overcome this resistance. We recently performed a large study of patients who were ALK-positive and had undergone repeat biopsies at the time of relapse on a second-generation ALK inhibitor primarily Ceritinib or Alectinib. These results were published about a year ago in Cancer Discovery. What we found is that the molecular mechanisms resistance to second-generation inhibitors are different compared to first-generation inhibitors. I would say most notably what we found is that whereas for Crizotinib resistance where only about 20% is mediated by Crizotinib resistance mutations, notably the gatekeeper mutation L1196M, in the setting of resistance to second-generation more potent inhibitors like Alectinib and Ceritinib a little over 50% of patients now have developed these specific on target resistance mutations. It is much more common for patients when they fail a more potent ALK inhibitor to now have an ALK resistance mutation emerging in their cancer.

The other very notable thing that we found is that depending on the specific second-generation ALK inhibitor, the exact spectrum and type of resistance mutations that can be impacted by that particular ALK inhibitor. For example, we see quite commonly I1171 mutations emerge when patients relapse on Alectinib. However, that mutation is really never seen on Ceritinib or Brigatinib because those two second-generation inhibitors are active against that mutation. We basically see a very distinct resistance mutation profile with each second-generation inhibitor. This is very important information to know because this now allows us to potentially tailor the selection of yet a third ALK inhibitor based on the resistance mutation that emerged.

Now one of the most common resistance mutations that we see emerge in all of the second-generation ALK inhibitors is the very refractory ALK mutation ALK G1202R. We see this in about 20-25% of patients who are relapsing on second-generation inhibitors. This mutation causes resistance, a kind of cross resistance to first and second-generation inhibitors. But, fortunately we now have at least one drug a third-generation ALK inhibitor, Lorlatinib, which is able to overcome the ALK G1202R resistance mutation both in pre-clinical studies and in a clinic.

In the Phase 1/2 study of Lorlatinib which completed already we have analyzed the patient's results based on their mutation and we have been able to show that patients with this particular resistance mutation, ALK G1202R, are highly responsive to Lorlatinib. They tend to respond and these responses tend to be durable. So, I would say for about half of the patients who relapse on a second-generation inhibitor and have an ALK resistance mutation we almost always will have the possibility of using another either second-generation inhibitor or the third-generation inhibitor Lorlatinib.

http://cancergrace.org/lung/2018/03/30/lung-cancer-video-library-patterns-of-resistance-in-alk-positive-nsclc/