Case Based Panel 2019 – Lung Cancer ALK Positive

Case Based Panel Discussion – 2019 ALK Pos, Developing Resistance to ALK Inhibitors and Next Steps

For this round of case based panel discussions, Dr. Jack West is joined by Drs. Jonathan Riess and Suki Padda. Jonathan W. Riess, MD MS is Associate Professor of Medicine in the Division of Hematology/Oncology at UC Davis Comprehensive Cancer Center. Sukhmani Padda MD is Assistant Professor of Medicine (Oncology) at the Stanford University Medical Center.

The doctors discuss a series of cases related to a diagnosis of ALK Positive NSCLC. In this video, they discuss developing resistance to Alk inhibitors, treatment approaches and biopsies, and what are the next steps.

Dr. Jack West: Let's turn to the situation of someone who has progression after two and a half years on Alecensa elective. They have an ALK rearrangement. They tolerated it well, but at this point they have multiple areas of progression, bone metastases and liver say what is your approach? Do you biopsy that in all cases? Do you think that that is a particularly high yield intervention, and what is your general go-to approach after that? If there isn't some clear indication of what to do based on the biopsy? Suki, can I start with you there?

Dr. Sukhmani Padda: Yeah, absolutely. So I think that my approach would be to biopsy with especially such a multifocal progression. And that biopsy is sort of helpful I think in two ways. One way is we know that unfortunately somehow our lung adenocarcinoma type tumors can change into a totally different kind of tumor and it looks completely different under the microscope and may have sort of implications in what we use for treatment next. And that I think has been shown including squamous transformation. That's another non small cell lung cancer type. And also small cell lung cancer transformation, which is of course we need to know about because the treatments are very different. So that's one way I think it's, it's helpful just to confirm that the tumor type looks the same under the microscope. I think the other important aspect of it is trying to sort of understand why this resistance happened and we can at least do that to some degree based on some of the clinically unfillable next generation sequencing testing we have available either in house, like we have internal testing in Stanford, but there's also of course commercial assays. And that may give us a sense, you know, is there a mutation, another mutation that developed in ALK that caused this resistance. There's some sort of guidelines in terms of what treatments we can do next based on that. Although it's not 100%, it's

more of like a guidance in terms of what we should do next based on the resistance mutation profile. And so I think those are the two ways that it can be helpful.

Dr. Jonathan Riess: So I agree with Suki. I generally do biopsy, I start with a plasma first approach because you can draw a tube of blood in clinic that day and hopefully get an answer in a week or two. I also think, you know, it helps determine treatment in certain situations. I think, you know, there's been published data by Dr. Shawn Colleagues that look at the circulating tumor DNA and they found an on target outward resistance mutations. So the you know, the alectinib is you know, is being outwitted by the cancer, by new ALK resistance mechanism within the ALK gene. Compared with not detecting that, you know, on average quarlatinib which has improved the response rates in about a third of patients. But if you detect that app resistance mutation in plasma, it was about 69% that had a very good tumor shrinkage, whereas it was only about 27% when that wasn't present. So I think that's one thing that's informative cause quarlatinib, which is a third generation ALK inhibitor, is now approved. And so with response, good tumor shrinkage being about a third of patients overall in that situation. But then if you get an on target resistance being almost 70%, that's something noteworthy. And then if I don't get that, I do generally look for a tissue biopsy and then once again to look for those on target resistance mutations where we can know looking at different ALK inhibitors, what mutation may be more sensitive to others. And also if there's other mechanisms that's not just ALK but something we call bypass track where the cancer outwits the drug by running around ALK through another protein. For example, you know, there's one called MEK, or crizotinib which is the first generation ALK inhibitor, also as a met inhibitor, was initially developed as a MEK inhibitor. We have clinical trials like one developed by my colleague Collin Blakely at UCSF with adding a MEK inhibitor, trametinib to Ceritinib. So that could all be informative. And but what's approved now vorlatinib is a next generation ALK inhibitor. But this is the way I think about how we treat ALK lung cancer. And you know, chemotherapy can be very effective in these patients too if they haven't had chemotherapy. There's a sense that that pemetrexed also called Alimta can be especially effective. And often we give that with, with carboplatin and other drugs. So that's the way about how I think of treating these patients.

Dr. Jack West: So, let me follow up. Suki, would Vorlatinib generally be your next approach? Let's say that you didn't get an informative result from the biopsy. Would you, as Jonathan mentioned, you could consider chemo, you could consider Vorlatinib, but there may be other choices. Jonathan, maybe you could plant a flag and say, would you favor Vorlatinib generally over chemo in this setting or after alectinib, or which would you prefer?

Dr. Jonathan Riess: You know, I mean, the response overall are fairly comparable. If you look at like find [inaudible] vorlatinib, but generally patients prefer taking a pill drug. It's got good CNS

activity. So generally favor vorlatinib. But you know, chemotherapy is also a good option.

Dr. Jack West: And in truth, it's not necessarily either or forever. It's just what next? Suki, what's your thought?

Dr. Sukhmani Padda: Yeah, so I think there's still a little bit of a question with all the available ALK inhibitors in terms.

Dr. Jack West: We haven't had any of these tested directly. It's all infamous.

Dr. Sukhmani Padda: Correct. So essentially, you know, I think vorlatinib is a great drug in the space is because we do at least have some data from a clinical trial setting showing that for a proportion of patients who have received alectinib before vorlatinib can work probably in around 30% of patients like Dr. Riess said. However, you know, any particular drug has its scope of toxicity and vorlatinib I think has a little bit of a unique toxicity profile that if physicians are going to this drug next to just be aware of because it can really impact our patient's quality of life, particularly some of the sort of cognitive toxicities, not feeling quite right, some depression, mood disorders that can occur with the drug that really do seem to be dose dependent, cholesterol, high triglycerides, swelling. So it says a little bit of a unique side effect profile that I think you know, it definitely has a purpose, but we just need to be aware of the side effects so that we can get at them early. The one thing I do want to emphasize is I think it's important what's going on in the brain at the time of progression on Alecensa because like Dr. Riess, yeah, we have vorlatinib, we potentially have other targeted therapies but we don't quite know where they fit. But we also have chemotherapy where pemetrexed can work for super long time and some of these patients with ALK. And I think if there's also both body progression and brain progression that I would favor doing vorlatinib because of the activity in the brain.

Dr. Jonathan Riess: Yeah. And I would just highlight for the audience, there's a great article in the oncologist on how to manage side effects with vorlatinib. So I'd refer folks there and take a look.

Dr. Jack West: Good to know. I would just take a step back as devil's advocate. Say that though, I appreciate the value of doing a repeat biopsy to see what's going on at this point. We don't have good evidence to say that it has a big impact, certainly outside of academic settings where the, the options are pretty limited. It's not a standard of care right now that has a clear proven benefit. And just along the lines of what Alice Shaw and Colleagues saw at Mass General with the different profiles and the probability of response to vorlatinib, the benefit of vorlatinib even in the less favorable is high enough that it's still a good choice. So it gets to the question of you could do this, but no, all roads lead to trying vorlatinib maybe next door or not.

Dr. Jonathan Riess: I would just comment one small. It's a minority of patients but sometimes we see early progression where it's more likely there's that squamous type self transformation that's been strapped. Small cell probably less commonly in the GFR, which even in the GFRs very uncommon. And then some of these bypass tracks like MEK so forth. So there are certain places, yeah.

Dr. Jack West: Yeah. If we don't look, we won't find. Yeah, that's for sure.