Can or Will Specific Molecular Characteristics Help Determine Which ALK Inhibitor to Choose?

Drs. Leora Horn, Ben Solomon, & Jack West review whether there are specific factors that should make one second generation ALK inhibitor more ideal than other competing options for a specific patient with an ALK rearrangement.

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Dr. West: Where does this leave crizotinib — a drug that still has activity that can be long-lasting for many patients, tends to be less active, though, than any or all of these second generation ALK inhibitors, and with less activity, but not none, in the brain. So, does your view change, that you would be inclined to move these second generation inhibitors up front, if they’re paid for, or would you still favor giving crizotinib until progression, and then getting whatever you can get from a second generation inhibitor; Leora?

Dr. Horn: So, we have trials that are going to answer that question, and it’s similar to with the EGFR front line trials, where I think the combined survival, when you’re on crizotinib, and then you get a second generation inhibitor, should be combined, compared to getting that second generation inhibitor up front. And, so, I heard this meeting, that the ALEX trial is closed, the 396 phase three trial is going to be opening, and so, we have studies that are going to answer these questions for us.

Dr. West: But it would have to be, when we’re looking at progression-free survival, a
statistically significant difference of four months, maybe enough to declare a winner as first line therapy, but that’s not the same thing as showing it’s the better strategy, compared with sequential first line crizotinib, followed by second line, second generation ALK inhibitors.

**Dr. Horn**: Correct, or can we see that, you know, 50% of patients on the second generation inhibitors do not get brain metastasis? You know, that will be something that will be meaningful.

**Dr. West**: And for you?

**Dr. Solomon**: Yeah, no, so I think crizotinib is a great treatment, and I think there’s — we still have patients who are on the original phase one trial of crizotinib, continuing on crizotinib...

**Dr. West**: You’ll retire before then!

**Dr. Solomon**: That’s right, I hope! I think that is the current bar, and I think the standard first line treatment for patients with ALK rearranged lung cancer, at present, is crizotinib...

**Dr. West**: Which is also, often, very well tolerated.

**Dr. Horn**: Yes.

**Dr. Solomon**: Yeah, and I do think the ALEX trial will be an important trial, because alectinib is another really well tolerated drug which does have better brain penetration, and I think that result will be an important result. But, again, I think we need to see how the data pans out, and I think we need to show that these drugs are better than crizotinib before moving them into first line.

**Dr. West**: How would you approach a patient who is on Xalkori (crizotinib) in the first line setting, and develops two small brain metastasis that you can treat pretty readily with stereotactic radiosurgery, Gamma Knife, CyberKnife, and continue them on Xalkori, if they have no progression outside of the brain, or are you inclined to change them to a second generation ALK inhibitor with the thought that it has better penetration in the brain? Ben, why don’t I start with you?

**Dr. Solomon**: Yes, so, in that particular instance, I think if the disease outside the brain was still really well controlled, and they were tolerating the crizotinib well, and my radiation oncology colleagues thought that those two lesions were suitable for stereotactic radiosurgery, I would go ahead with the stereotactic radiosurgery and continue the crizotinib. I think it would be a different situation, either if they had disease that was starting to progress outside the brain, or if they had multiple brain metastases that needed whole brain radiotherapy, and in that context, when we know that there are agents that can work in patients progressing on crizotinib, or that might work better in the brain, and therefore delay the time for them to need to have whole brain radiotherapy, that’s probably my trigger to switch.

**Dr. West**: Your thoughts?
Dr. Horn: I agree, I'd do the same.