2020 Target Therapy Forum

NTRK, BRAF, RET & MET Question and Answer Panel

Why Different Mutations have Different Progression Free Survival Averages

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Dr. Justin Gainor: So maybe Dr. Sands there's another questionnaire. It says, do we know why different fusions have such different PFS on selective TKIs? For example, 36 months for ALK versus 17 months for what RET, what can we do against this?

DR. Jacob Sands: Yeah. So keep in mind that the, you know, the initial drug for ALK was actually closer to the 17. It was actually less than, and it's really the newer drug now for ALK that's at 36. So, the specifics in the answer to this question really has to do with not only the fusion or we could also even say mutations. But so the, just to make it more broad, the genomic alterations, how effectively we're able to target that, and hit that. And even just the effectiveness of the drugs can come from some of the specifics in how effective we were able to target these cells. But on top of that then is potential resistance mutations that or alterations that developed. And so a drug may be very, very effective, but ends up having common resistance mutations that show up. So if we talk about this in EGFR mutations with, so the first one that as I outlined at the beginning of my talk, so erlotinib and gefitinib, those are the first generation EGFR, TKIs. So targeting these sensitive EGFR mutations, we would commonly see a mutation called T790M show up, and that would be, that would then be a resistance mutation.

Well, then the drug osimertinib developed, and that was a way of targeting T790M, but it also kind of more broadly hits a lot of the other targets that these first-generation EGFR TKIs hit as well. Not all of them, but a lot of them. And so now, osimertinib is a drug where we're seeing a longer disease control than we did on the initial drugs. And so we're seeing that both in mutations and infusions where we're developing more effective therapies that work for longer, are there inherent differences with ALK and with RET, where RET is something that we'll never be able to target as effectively as we have ALK and RET is much newer. So we have the drugs are newer. The drugs as Dr. Gainor outlined are pretty specific to rat. But is there a way that we can then improve upon that and what is the resistance pattern that develops, and then looking at that resistance pattern to try to find ways of preventing those mechanisms of resistance. This is a process going forward, and I'm very confident that further down the line we'll find better and better therapies for RET as well. But these initial ones are an excellent start as they're very effective and also well tolerated.

Dr. Justin Gainor: Yeah, I would echo that, you know, I would think of a question like this in three different categories, much like you did, which is there can be differences in just the fundamental biology of the driver that is, you know, ALK versus RET. So that's one like, the cancer cell may care more about one or one can be a more, more aggressive driver. That is, it sends signals that are just more powerful to the cell, or it leads to an earlier, a greater ability to metastasize. So, so there, there can be differences in that. It's hard to study that in the lab, but there can be biological differences as Dr. Sands was alluding to the second big thing is there can be drug differences. These are really the, ALK, you know, there are successive generations of targeted therapies, whereas these were the first approved RET inhibitors. But then the third thing that I would caution against is the statistical aspect, which is that, you know, when we see these medians if you look into it, these are probabilistic models based upon how long patients have been on the study.

And what's happened to the patients who are currently in the study, the RET trials have only been open for a little over three years. So it's hard to reach a median an average of three years, if the, you know, they haven't been opened now, you know, that long, most patients, you know, who have enrolled on the RET drugs have really enrolled in the last year or two. So, some of it also has to do with length of follow-up on the studies, because I think the point is that drug development has changed a lot, ALK, you know, it was discovered 2007. Whereas, and we had the ALK inhibitors in clinic, first [inaudible] 2011, which we've had a lot more follow up on those. Whereas these novel RET inhibitors really have only been in the clinic for three years. So that's another important part. So we definitely want to see what happens long-term with those drugs.

Dr. Jacob Sands: Yeah. That's an important point that, you know, the RET inhibitors in many but this wasn't all first-line. And so when we're talking about ALK, we're talking about first-line as well.