2020 Target Therapy Forum

NTRK, BRAF, RET & MET Question and Answer Panel

Clinical Trials for STK11 Mutation

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Dr. Jacob Sands: So, I do see there are some questions that we can start with the first one. Are there any promising clinical trials? Is the question I had mentioned HER2 and KRAS G12C as both being targets with ongoing, very promising clinical trials. Justin, is there anything you want to add to that?

Dr. Justin Gainor: Yeah. So I'm looking at this question, I think any promising clinical trials or treatments available for SDK 11 mutation. I think that's a very good question. And it I think raises a much broader question. I'm going to take a step back from that for a second and, and speak to that. There are I think it will illustrate two big points. The first point is genetic changes or mutations come in two flavors, everything that I've shown you right now has to do with a genetic change called oncogenes. Okay. So, oncogenes are when we have a mutation, they get activated. Okay. So, you know, the, the schematic I showed you at the beginning, you know, I had the lightning bolts around it. So when there's a genetic change there, it actually gains function. So it's just, it's lost the control. So it's gained function. The flip side of that, the other type of genetic alteration is what we call a tumor suppressor. So these are genes that are normally protecting us against cancer.

You know, they are, you know, the guardians of our genome. They, they try to protect us from some of these, the, these other mutations. So, they are things that help like repair DNA. And there, if you have a mutation, it's a mutation that causes you to lose the function. And so, you basically no longer have that proofreading capabilities. So, all

oncogenes they're activated tumor suppressors, they lose their activity. So one can imagine it's easier, like from a drug making standpoint, it's easier to block something that is overactive than it is to repair or refill a function in the body. And so, SDK 11 is one of those tumor suppressors, so it's mutations, there are loss of function. So that's one kind of thing to know. So it's not to say that we won't be able to target it. It's just means that we have to take different approaches for it. And then the second piece is, you know, the genetic alterations that we talked about so far are mutations that are largely mutually exclusive from one another.

So, if you have a RET fusion, you generally, you know, when you're initially diagnosed, you generally don't have BRAF, or you don't have MET Exon 14 skipping. There are rare examples of, you know, acquiring [inaudible], but by and large, you know, they're mutually exclusive SDK 11, these tumor suppressors that that's not the case. So, they can occur with other genetic changes. And so it can be tricky sorting out what is the true kind of driver of the cancer? So STK 11 is commonly co-mutated with KRAS. And in that context, we think of KRAS is the dominant driver in SDK 11 is a supportive, important mutation. And it in normally plays a role in metabolism, basically how tumors use energy sources. And I think there's some exciting work going on looking how you can exploit that. And so there are you know, some promising preclinical studies about trying to develop novel ways of trying to exploit SDK 11. But it's going to take a different approach than some of the approaches that we're just reviewing.

Dr. Jacob Sands: So that's a challenge then with SDK 11 and potentially affecting immunotherapy effectiveness also then leads to the next question is could telezotinib be promising for STK 11? And would it need to be done with the avalumab current clinical trial on these meds together States, but not in Canada? And that is a trial of a lung map trial. So this is a part of one of those studies that Dr. Gainor outlined where they're looking at widespread development testing and then using sub studies within this bigger umbrella, which is lung map. And in this case, those with an STK 11 mutations, then being eligible for this study of [inaudible] plus avalumab. So Justin kind of breaking this apart a little bit, avalumab is a checkpoint inhibitor. It is not an approved one-on-one at this time and actually the results from that single drug trial weren't as compelling as some of the other drugs we do have available, but checkpoint inhibitors in lung cancer are widely used.

So pembrolizumab, nivolumab, atezolizomab, Dirvalumab, these are all drugs that have a standard of care place within non-small cell lung cancer, although pembrolizumab is more commonly used in the first-line setting at this point. And what the checkpoint inhibitor does is helps immune cells to essentially, well helps in the interaction of immune cells with cancer cells, preventing cancer cells from downsizing things for the immune system. So essentially then keeping the immune system active against cancer

cells and therefore clearing them out. And when there's an STK 11 mutation, and there's still ongoing research around this and what the exact setting is, but in some of these cases with an STK 11 mutation whether that be in combination with some other genomic alterations or by itself, this can affect the effectiveness or prevent the effectiveness of these immunotherapy treatments.

So, in this setting, basically the trial that this person is asking about is saying, okay, in this setting where there's an STK 11 mutation, this is a population where we don't yet know the specifics, but there's concern about immunotherapy being effective in the population. And for this trial is then adding in telezopomib which is a PARP inhibitor. And there's a lot of interests around the potential for PARP inhibitors and immunotherapy drugs that combination, maybe we call it synergistic where essentially not one plus one equals two, but maybe one plus one equals four, in that as we bring these together, they're better than just the sum of the two parts. And so this is a trial as far as whether or not this is effective, we still need to wait and see results from that. This is an ongoing study. It's not necessarily targeted therapy in a sense of the different drugs that we've discussed within this topic. But rather drugs with two different mechanisms of action, PARP inhibitors tend to result in breaks in the DNA by finding part. And so this combination may be effective right now. There's not really a place for using any of these PARP inhibitors as part of a standard of care. So still more to watch from these trials.

Dr. Justin Gainor: Yeah. I would echo that. I think, you know, it's hard. I don't want to comment too specifically on a specific clinical scenario, but more broadly, I think there are some common themes of, you know, when people ask me about, you know this drug combination for X mutation I think as we try to show at the beginning, which is that not every mutation then is actually meaningful. And so, whenever I look at its mutation, you know, a report I want to know, you know, is this something that actually, you know, in the case of STK 11, you know, I said, this is a tumor suppressor, is this something that would be predicted to cause it to lose function? And you know, there are listings and things like that. So that's always one question. I asked myself, are there other mutations present?

And I think we will start seeing data that especially, you know especially for things like SDK 11 it's context specific. I do think that it's going to matter, you know, what the other mutations with it are. Both you know in, in terms of specifically about immunotherapy. So I think that's a piece too. And you know, I think trying to combine you know, PARP inhibitors which, you know, as Dr. Sands saying, you know, are working on the DNA with immunotherapy, I think is a strategy that's being applied, not just in the trial that was being asked about this is a broader you know, strategy that's being played out to many,

many different types of cancer. So I think it's a strategy that, you know, it is certainly an interesting strategy, but I think it depends on the individual scenario.

Dr. Jacob Sands: Excellent point about STK 11, just to highlight your comment there about, I mean, there's still a lot to know about just STK 11. And so that mutation in itself versus the specific combinations there's still a lot for us to know Justin just about the SDK 11. So these different trials of STK limited a little bit different than like the EGFR trials or the ALK trials, or some of the other ones that that Dr. Gainor laid out there. So a lot to still understand about that process.

Dr. Justin Gainor: Yeah. And that one is, you know, it also then raises the questions of you know, as we do broader and broader panel testing you know, tested for more and more genes, you see more genetic alterations, but, but how they relate to one another and the meaningfulness of them it raises important questions. You know, 10 years ago, not a single panel would have included STK 11 and now many panels still don't. So I think as we start doing broader, broader testing we're going to see many of these co-mutations in it. And I think the people are going to start paying a lot more attention from a research perspective of, you know, even for some of these bonafide drivers, like, ALK, EGFR and MET, are the different responses, you know, why does some person respond for five years and someone respond to one when it's the same mutation? And there could be some role for all these other mutations that go along with it.