2020 Target Therapy Forum

NTRK, BRAF, MET & RET Session:

Frontline Therapy for Uncommon Mutations

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Dr. Justin Gainor: My name is Dr. Justin Gainor. I'm the director of the center for thoracic cancers at MGH, as well as the director of targeted immunotherapy. And today I'm going to be talking to you on frontline therapy for uncommon mutations. I'm just going to now share my screen. I just wanted to first begin with my disclosures. And beyond that you know, I think it's helpful. I think Dr. Sands provided us an excellent overview of the various genetic alterations. And I wanted to touch on a few key topics because they're going to have relevance for how do we then, how do we go from having alterations then using a drug and what actually happens and what are some of the commonalities across these different genetic alterations? Because even though these may be uncommon mutations that I'm going to focus on today, we can actually draw some common lessons.

Okay. So the first thing is the central dogma of biology. This will be familiar to many of you. And this is just to say that we start with DNA. These are the blueprints DNA gets turned into RNA. So from two strands to one strand, and then the RNA gets turned into protein. And so when we're talking about mutations, where at the DNA level and when we're using drugs, like these kinase inhibitors or targeted therapies, we're blocking the resulting proteins. And so how might this work? Well, it's important to touch on how do normal cells first you know, communicate signals to grow. So I have a schematic here where here's the surface of the cell and we have our receptor here in purple. And essentially when something in its environment comes, it docks in, and then that creates this cascade. It's like a game of telephone where suddenly the cascade, and once it gets to the end, it says grow.

Now it's not as simple as this, because if you actually look at all of the various signaling in the cell, it gets very complicated very quickly, because it's not just this linear path. There are actually many, many, many different circuits. And back in the early two thousands, there was a lot of talk about how given this complexity, we would never really be able to develop targeted therapies because, you know, if you block one thing, if I blocked you know, up here near the top then things can easily get around it and nothing would really be able to, there were too many redundancies in the system. We've since learned, starting with the EGFR mutation that Dr. Sands described that there's this thing called oncogene addiction. And what that means is so many of the genetic changes that we're describing. So again, here we have a schematic of the cell, and now here's a little blue receptor on the surface. And now we have a change, a mutation in that we're suddenly a no longer need something to dock to it.

It's constantly on, you know, it's constantly sending those growth signals. And what ends up happening is the cell, the cancer cell first, this leads to a cancer. And then secondly, the cancer becomes reliant on this pathway. It becomes addicted to it and it becomes addicted to it because it's easier, you know, there are no controls to it. There's no on off switch, it's constantly on. So as a result, you know, these cells preferentially prefer this pathway. And so then if we block it, you know, the cells don't know what to do. So, that's really the basis for the, all of the targeted therapies that you're hearing today. And that applies from EGFR all the way to some of these less common alterations like ENTRK. The other thing I wanted to point out, and this is I think important when patients, families, providers alike are looking at their genetic reports that these reports can get quite complicated and that there are different types of mutations. And not every mutation essentially turns on that light switch.

So, I wanted to briefly talk to you a little bit about the different types of mutations, because the four genetic targeted therapies we're going to talk about today, you know involve different types of mutations. And sometimes the naming that we use for many of these gets confusing. I thought just providing that background may be helpful. So the simplest type of genetic alterations is called a point mutation. And it's just that imagine, you know, here's a gene, you know, so a long segment of DNA and there's just like one little change at one position. The analogy I give to my patients is imagine like a street. Okay. And it's a very long street and, you know, there are 600 houses on the street and suddenly there's a change only on app position house number 600. Right. So, that's an example of a point mutation. And so what that point mutations that are most meaningful is essentially taking the control switches, and basically always turning that gene on. Another type of genetic change is called a rearrangement.

And here, the naming can get really tricky because rearrangements or translocations or fusions essentially all mean the same thing. Okay. So you may hear us say like an ALK rearrangement or ALK fusion, ALK translocation all mean the same thing. And what they're describing is here I have, you know, say my gene of interest in green. And there's a second gene here, gene, number two essentially what ends up happening is they get the, they get chopped up. It recombined. So half of gene one and half of gene two, and they come together so it creates this fusion. That's a mixture of two different genes, and that's just a different way of removing the controls on the gene. And then a third way that this oncogene addiction can occur is simply by amplification of the gene. So here the gene is identical. So nothing has happened to that long street. It's just suddenly we have many more copies than we normally should, and that can also send increased growth signals to the rest of the body, to the tumor.

This is a different version of the pie charts that Dr. Sands showed you in. So today we're going to be focusing on four different alterations. We're going to be talking about RET, we're going to be talking about NTRK, BRAF, and met. So I'm going to start with a fusions just because the biology is similar. So I'm going to group those together and then we'll go to the others. So I, again, I'm going to start on the left here. So, RET fusions. So our RET rearrangements, these are found in one to 2% of lung cancers, but they're also found in other cancers. So their final, it sounded thyroid cancer. And then they're found in many other at very, very low frequencies in many other cancers. We don't really see RET mutations, those point mutations, just those little changes in lung cancer. We see them in other cancers but different genes can come together and be rearranged. So it's, when you see things like this, KIF5B CCDC6, it's just a fancy way of naming the two genes that have kind of fused together.

Okay. So that part of the nomenclature. What do we know about patients who have RET rearranged lung cancer? This was taken from a large series of over 160 patients, and what we know is that you know, in terms of age, they tend to be about you know a median age of 61. There's no gender predict preference between males and females, pretty even. They do occur more commonly in patients who have never smoked or and there are more commonly found in, in how to know carcinoma. This is just a schematic to show that, you know normally there are controls and then in the setting of these fusions, it leads to cancer formation. Now it's interesting, and this is kind of a historical note, but I think one that gives us some lessons. So back in 2011, it was December, 2011. I distinctly remember it, when RET fusions were first described. And at the time, you know, the field of thoracic oncology already knew about ALK. We already knew about ROS1 fusions.

And the initial papers that described RET seemed to relate a very similar biology, all three of those involve pieces of DNA that break apart and then combined together and, in the laboratory, it looked like they behaved very similarly. And so there was a rapid enthusiasm and like, this is likely another target that we can use targeted therapies for. And there was a concerted effort to try to repurpose drugs. You know, basically here's a whole list of drugs that were already approved for other things. But when we looked at the chemical structures, we found that they also targeted RET. And so it seemed like a great opportunity to like, Hey, let's just insert these new drugs. And while we saw a little activity, this is a waterfall plot. Some of you had probably seen these throughout the day, but essentially each bar represents a patient here. And if you're below zero. So in the minus side, this illustrates tumor shrinkage, if above that, that illustrates tumor growth. And in this study, this first study of one of these repurposed drugs, it was a fit underwhelming.

We saw only 28% of patients responding. And the responses were far too short, not only that is the drug was pretty toxic. And so, excuse me. And so, comparing this to ALK, ROS1, excuse me, comparing this to other targets, you know, it seemed like these weren't responding nearly as well. So there's a concerted effort to develop more targeted medicines against RET. So these are pictures that illustrate, these are all of the different genes that signal in that pathway that I showed you at the very beginning, that signal transduction. So these are trees and each dot here represents the drug blocking one of those different kinases until what you see with these early RET drugs is that they actually blocked far too many things, ideally in your perfect targeted therapy. It blocks only one thing. And so that's what essentially was recently developed. So you can see these newer RET drugs, these were specifically designed to block RET. So pralsetinib and celpercatinib.

So, you can see these same tree diagrams, but instead of blocking all these different things, you know, they blocked very, very few. So these are, and they really only block RET. So these are much more selective. And as a result, you know, when you look at these in RET fusion positive lung cancer, now we get much different waterfall plots. So this is the kind of the same type of figure where each bar represents a patient. And, you know, you always want to see waterfall plot, whether every single line is going down and that's more or less what we're seeing here is that the vast majority of patients are having a very robust responses to these drugs. This is just a similar waterfall plot, but looking at the activity within the brain treating brain metastases, this is a different way of showing it, but essentially these are, you know, each line means tumor shrinkage in the brain. And so both of these drugs as Dr. Sands alluded to both of these drugs were actually approved in the last three months to treat RET fusion positive lung cancer.

And I view them as now standards of care to treat anyone who has a RET fusion. So one can take a very similar approach. So for NTRK, so like RET in track is actually seen not just in lung cancer, it's actually seen in many, many different types of cancer types as illustrated here, including some pediatric cancers, the thing about NTRK is, you know, it's found very infrequently in some common tumor types. So it's very infrequent in lung cancer. But when you find it it's incredibly important. So this shows you the frequency of MTRK fusion. So this is looking at over 4,000 patients tested, finding only 11. So the frequency is 0.23%. And these were all the different, you know, fusions, all the naming, the different genes that come together. So many, many different types, but no it's really important to still test for this because as you'll see in the next few slides, when you find it, it can be transformative for the individual patient. These interact fusions are most commonly found in never smokers.

The patients pretty young, so 48 and with adenocarcinoma, but it also raises a question, if you have a genetic change, that's so rare, you know, 0.24%. How do you study that? Some of you may have heard of the different types of clinical trials and this is what leads me to the concept of a basket study. And so the NTRKs inhibitors were tested in a basket study, which is essentially you're testing one drug usually in, against one mutation, but in a variety of cancer types. So essentially, and I know you guys already had a talk this morning on tumor agnostic approaches, and this is really a tumor agnostic approach. And so here's entrectinib. This is, you know, you can hear it in his name TRK. So, here also, the naming's a little complicated, but NTRK is the gene name and that track is the protein name. So that's why, you know, you can see both listed there. So these are track inhibitors, and you could see in this PAN cancer analysis.

So, each bar representing a different patient, but you can see various different cancer types showing very good responses across various, all tutors are regardless of what type of tumor. It seems like your patients were responding to the track inhibitor entrectinib, and in lung cancer, 70% had had a response. The other track inhibitor is larotrectinib. It was the same type of design where various different tumors actually 17 different tumors, very nice waterfall plot. So, both of those drugs are now approved, and I would argue it would be the standard of care for patients with NTRK fusions. The important thing is actually finding those genetic alterations. Now, on to BRAF. So Dr. Sands mentioned that, you know, it's a specific type of BRAF mutation and here we're no longer talking about those fusions. We're talking about a point mutation. So just one change. And that change occurs at position 600, and it's a simple switch from a V to an E and then that sets off the cancer.

So, I bring up melanoma first, because this is an important lesson compared to the NTRK experience that I, and the RET experience that I showed you before. And this is actually one of those areas where speaks to the reason why we still have to do clinical trials. So here's one of the first trials of using a BRAF inhibitor in patients would be BRAF V600E melanoma. So again, one of those waterfall plots and we see everything going down. So if we look at colon cancer, so, you know, we saw close to 50% of patients with melanoma responding in colon cancer, the same exact mutation, BRAF V 600E. You use the same exact drug. Suddenly you're only seeing 5% of patients respond, so same exact mutation, but now it occurring in two different types of cancers and we're seeing fundamentally different response rates. And so this is something that's also playing out with KRAS mutations.

Now it looks like KRAS mutations and these drugs, the newer drugs targeting them have shown very promising response rates in lung cancer, but lower response rates in colon cancers, suggesting that there's some context dependence. It's worried about the experience in lung cancer, as it can be more like the experience in melanoma or more like the experience in colon cancer. Unfortunately, what we saw in a series of studies shown here it looks more akin to melanoma seeing response rates around 40%, if you just use a BRAF inhibitor. So just blocking that once you get a change but you know, there's some very elegant preclinical studies in the lab. It was recognized. So, normally when the pathway goes to BRAF, when this is active, it then activates MEK and then ERC and then grow. So what if you not only blocked BRAF, but if you block MET too? In melanoma, what we saw was that if you use them a BRAF inhibitor plus a MEK inhibitor, you actually did better than just the BRAF inhibitor.

And so, this is actually then been played out in lung cancer as well. Another one of those waterfall plots and what we're seeing we're not comparing the two strategies in one study, but if you look in these you know, single arm studies where every patient got Dabrafenib and trametinib, you know BRAF and the MEK inhibitor, much higher response rates. And so this is really the standard of care for BRAF V600E. Importantly not every mutation leads to the activation. So in lung cancer, only half of the BRAF mutations are V600E. That specific change the other half are not, and they generally don't respond to these drugs. So it's not enough just to see a mutation in a particular gene. It has to be the right mutation. And then the last three minutes, I wanted to talk a little bit about MET alterations and there are different types. So MET amplification is in about 1% and then MERT EXON 14 skipping. And that already sounds a bit more complicated.

So, what, what are these so magnification, I told you before amplification just means extra copies of, of the gene. And so if you have extra copies, it can, it can just send more signal. MET Exon 14 Skipping is a bit more complicated than that. Now I told you at the

beginning that that central dogma DNA goes to RNA goes to protein. Well, when you go from DNA to RNA, you actually lose some pieces. And those pieces, you know, are called introns and what ends up happening is in that splicing process, when you're cutting mop up, there can be mutations that lead to skipping. One part called Exon 14. And that's a really important part because usually it causes the cell to have to recycle MET, you know, every proteins in the cell also have some, you know, get reused to get recycled.

And essentially what this means is you have extra MET on the cell surface and so extra signaling going within the cell, and that kind of leads to tumor formation. So Met Exon 14 there've been a series of MET inhibitors that have been explored here. Dr. Sands alluded to that crizotnib, you know, wasn't designed as an ALK inhibitor. It was actually designed as a MET inhibitor. And so one of the first looks at that was looking at using crizotnib against MET Exon 14 and here we actually see that, again, this looks like an active you know, therapeutic target that we can induce to your responses. But the activity of crizotinib was not as robust as we had hoped. And so there are newer MET inhibitors, one called tepotinib. This was published in the New England Journal of Medicine. You can see here and again, any waterfall plot where most of the bars are going down, that\ represents a promising drug.

And so, we can see here to platinum caused responses in about half patients, you know, by responses. I mean, below this 30% tumor shrinkage, it's arbitrary, but that's usually what the field has established, but that also means that all these other patients who are deemed not having a response, but are also benefiting because they're having tumor shrinkage. Geometry one, this is a different MET inhibitor, but the same type of waterfall plots where most of these bars are going down, showed about our response rate of 60% in patients who had previously not had any treatments. And so Capmatinib was recently approved by the USFDA and is now considered a standard of care for patients with newly diagnosed, MET Exon 14, skipping tepotinib has been given priority review status, but it's not approved yet. So if we put all of the frontline FDA approved drugs, I'm listing here and the preferred agents are in bold.

For some, we don't know if one is better than the other. And so there, I just list both. We're going to move to questions in a minute, but I just wanted to summarize that targeted therapies are standard for patients with advanced lung cancer, harboring RET, NTRK, MET, and BRAF. The success of NTRK and RET highlight tumor agnostic approaches, but BRAF is a cautionary tale. As you heard from Dr. Sands, it's critical to genotype all these patients and efforts are ongoing now to really understand kind of the next lines of treatment, such as resistance, and overcoming resistance and expanding this whole approach to other genetic alterations. So with that, I'll conclude. And I think we can open it up to questions.