



2020 Target Therapy Forum

NTRK, BRAF, RET & MET Session:

Casting a Wide Net: The Need for Broad Molecular Testing

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Dr. Jacob Sands:

Hi, this is Jacob Sands. I am a thoracic medical oncologist at Dana Farber and excited to speak with you all today about casting a wide net and need for broad molecular testing. And I believe that you can see the slides. And so I'll start this. So I apologize. I'm having technical difficulties with my camera. So I've got on this nice suit jacket, and but, but I don't even get to share that with you. So I will, I do have slides though, so I will be going through the slides. And discussing this topic, I'm going to try and make sure that we really stay ahead on time because I do want to make sure that we have plenty of time for questions so that we can really address anything that, questions that come up from the talks as well as things that maybe people are brought in with questions. So we will get started. So when discussing the need for genomic testing, it really comes down to what exactly are we looking for?

How is this going to change what we do? And that's really at the basis of so much of our medical decision making. So when we look at this timeline, you know, back in 1984 to 2003, we knew about KRAS. But there really weren't other known genotypes. And even with KRAS, you know, we'll talk about later. That's not really yet something that we have an approved therapy for. So knowing about it without therapy options is a bit different than knowing about it with treatment options, because then it does change. 2004 EGFR was known, but really around 2009 was when there was the first clear demonstration that we are able to effectively target EGFR and treat the EGFR cancers. And around that time is also when we recognized the BRAF, HER2, ALK, PIK3CA. And then 2012, you can see now ROS1, MET, RET were known at that time. And so, it increased in the numbers of different genomic alterations that were recognized at that time.

So, this is to say that that these are those have really grown quite a bit through the years and they've continued to grow. And in fact, now shear on the right, this is the



percentage of genomic alterations when there is an identified genomic alteration. So seeing multiple others that now are being added and identifying these genomic alterations becomes very important. We often say mutations, and in some cases, these are fusions. And so the alterations is really a way of capturing really all of these changes to the DNA of these cells. And to be clear, these are changes to the cancer DNA, not changes to people's normal DNA cells. And there are rare circumstances where that does exist and it's related and then cancer develops as well. But by and large, these are really changes to the cancer DNA. And so what we're discussing on this is the importance of looking for these alterations, when there's lung cancer.

I will point out that there are specific circumstances where that's really more important than in others. So in most cases, we're talking about non-squamous non-small cell lung cancer. And so most commonly the term had no carcinoma was used. And in that setting, it is very, very important to really get broad testing. And that's the topic of this. And someone who has squamous cell lung cancer with an extensive smoking history, then looking for these alterations is not part of standard of care. And that's just because in general, we don't really see alterations that are then going to guide treatment. Those are different cancers. Similarly in small cell lung cancer, these are not really these aren't really present and therefore don't affect treatment options. That being said, in anybody with lung cancer, whether it be small cell or squamous if someone does not have a smoking history or a very remote and minimal smoking history, then looking for these alterations can be a part of care.

And there's a nuance to that, that I won't dive into further, but we can certainly discuss if there are questions. So 2009, this was the year that that avatar was big in the theaters. It was also the year of a publication called IPASS. And the IPASS trial was really the first clear, a definitive demonstration of a drug that can target EGFR and now there was an EGFR directed therapy already approved prior to this, what was not known with that prior approval that the drug erlotinib was really by and large effectively treating lung cancer that had an EGFR mutation, but that wasn't this full understanding wasn't present until really 2009 when this really became evident. And so this was a drug that was approved as a next line therapy for lung cancer. But once we really understood that we could identify the population of people that would really benefit from that drug most, then the approval really shifted to just those lung cancers with any EGFR mutation.

And there's a bit of a nuance to the EGFR mutations, it's not all of them that's really specified in there some resistant EGFR mutations. But I'm just going to say broadly EGFRs mutations but that is a nuance to it. So in 2009, this was understood. And that was since then now we have five approved drugs just in 11 years to treat EGFR so a lot of progress has been made and, and multiple others. So this was a timeline of this. So



erlotinib was approved in 2005. This is a drug that targets EGFR, but that wasn't really clearly understood at that time. 2009, I pointed out with the IPASS trial, gefitinib, a similar drug to her erlotinib was approved at that time. And, and we now have three other drugs that are FDA approved along with that, the standard of care now being a drug called osimertinib, which has really widely used as the first-line treatment option in the US. I'll also point out that there are real benefits, osimertinib is a drug that has fewer side effects.

People tolerate it better. It also works in the central nervous system. So sometimes brain metastases, for example, can be difficult to treat because we have a blood-brain barrier, which blocks the cross edge of toxins and compounds into our central nervous system which is a protective measure, but that can make it more difficult, more challenging to treat brain metastases. Whereas this drug post osimertinib crosses well. So it's a drug that works better. Also works in the central nervous system. Also has a better side effect profile, which is just to say that once we identify a target and we identify a drug that can effectively hit that target, the research doesn't stop there. And we now have other drugs that work better than those initial ones. On the bottom line, you see the ALK timeline, and this was a fairly quick timeline due to some good fortune. There was a drug that was called crizotinib, which had been developed for a different target. And then the EML4-ALK, this is, we say ALK fusion, or just ALK was discovered in 2007.

And with this drug already being present, then the first patient was dosed using that drug. And it was a fairly quick timeline to crizotinib then being approved. And since then now there are five ALK drugs that are used and alectinib being a drug that's widely used in the US as the first line. Which again, is to say that the target is discovered, the drug is found, and there's still a lot of research that happens for even better treatments. Now, since EGFR and ALK, there are now a handful of others that are approved targets with, excuse me, understood targets with approved drugs that are effective which increases the importance of doing this testing. So I mentioned alectinib, and I'll speak to this a little bit. I mentioned control in the, to treat brain metastases for EGFR with the drug with osimertinib. Similarly alectinib is also effective. And you can see on the right of this slide, there is so in the right, there are two scans there of the brain, and you can see the scan on the left side with this multiple white spots are brain metastases.

And this is pre-treatment. And then the one on the right is after having started taking alectinib, which is a pill. And in this case, you can see that that many of those are gone, if not much smaller. Just as a demonstration of the effectiveness of this drug in treating cancer that spread to the brain. At the same time on the left, there is a progression free survival curve. These are curves we look at for how long the disease is controlled with the drug. And I'll point out also that sometimes people will say, Oh, the median



progression free survival is the term we'll use, the median time before which this cancer grow was through with such and such a time. But at the same time, you know, I try and make sure everyone understands that, that median is not what we expect for everybody. There's still a broad range. And so with this drug, there are people controlled whether their treatment is controlled for many years, and there are some where it grows earlier than that median time.

That median time is not what it is for everybody, but the crizotinib, which is the red line there, is the first drug that was approved, the one that I mentioned on the prior slide and the blue line there is alectinib, and this was the trial demonstrating that alectinib was much more effective than crizotinib. Similar to the prior discussion, it was also better tolerated and worked well in the central nervous system too. So this is a better drug and in many different ways. So the, the research has continued the on this slide. So this is now the difference targets, and you can see them circled there in that initial pie chart. These are targets that have approved therapies. EGFR at 30%. We mentioned with the first trial was IPASS and that really started things. And then osimertinib now being the standard. ALK Fusion is on there. And you can see that that's just 4.4% in this pie charts. And that is the drugs that I just pointed out, but there are, there are others now.

So, Justin, Dr. Gainor is going to be talking about some of these as well. This shows MET amplification, as well as MET mutation, RET fusion BRAF. You can see as the 5.5%, it's not all BRAF, it's really these 600 either that we have approved therapy for. And then there's NTRK and TRK isn't on this, because it is actually very rare for lung cancer, but there's another one that does have target effective targeted therapy for. So we do see multiple of these. I'll also point out on here. You can see above MET amplification, which is the highest one with a circle is ERBB2, which is also HER2. So that's HER2 amplification, the further down is HER2 mutations. That is something that there are clinical trials really, that are very promising for HER2. And so and most recently, RET fusion and MET have new drugs that have been developed and are now approved. Actually RET fusion the newest. There was I believe it was a few months ago was the first drug that was approved for RET. And now very recently now a second drug approved for RET. So we're now seeing multiple drugs for other targets as well.

Well, as far as testing, I'm just going to touch on this because it does become important for saying, okay, well, you really need to test for all of those different things. We have approved therapy for those. So how do we go about doing the testing? And I'm going to speak very little about something where there there's much more nuance to this topic. And certainly other ways of doing it just broadly speaking, though, if we talk about preliminary chain reaction or as people commonly say PCR, and with PCR testing, this is a way of doing it. It can be done more quickly and less expensively, but essentially you



have to know exactly what you're looking for and that exact sequence of the DNA, essentially, you build probes that fit that sequence. So, it can kind of zip onto it like a zipper or like a magnet. It sticks to just that exact sequence. And when it binds to that sequence with these probes essentially there's a process to then build that out to be able to then see that in detect it.

So, you build probes for those exact sequences to then find those, and you find what you're looking for if it's there. So if we're looking for specific EGFR mutations, we can then find those specific ones with this. There's also next generation sequencing and next generation sequencing is actually a way of really putting together the exact sequence that exists in the DNA, in the specific area that you're looking for in the cancer DNA. And so with this, you can detect things that you're not necessarily expecting or not necessarily looking for. So more rare kinds of mutations. And then you can use that one sample for looking for multiple different mutations or alterations. This does take longer generally, and it also is more expensive technology to use. So we can detect, and I know this was discussed earlier, I believe. So I'll just barely touch on it, but we can detect that DNA with a couple of different ways. One of which is getting a specific biopsy of the tissue, that we then tested the DNA from.

The other is to look in the bloodstream and we see the DNA from the cancer cells circulating in the bloodstream. And to then detect that through these technologies. There are other things like circulating tumor cells exosomes. These are not as widely used. So before I finish here, I do want to kind of touch on some other things, but I'll leave these important points up. So first of all, I've outlined, let me go back. So I've outlined these different mutations, but I've also outlined others that are being tested in clinical trials. And that's actually a really important point because when we see that these different alterations exist and somebody is going to be treated right now than what shows up on that DNA testing on the cancer DNA testing is going to impact decision-making at this moment. But going forward, other drugs could end up being approved. And so someone has ongoing control for a while, whether it be on one of these or even if it was chemotherapy or immunotherapy.

Then further down the line when the cancer grows, if one of these other new, if there's a new treatment for one of these other genomic alterations, then that becomes really important. And I have a handful of stories, like the one that I'm about to mention, but I'll just mention this one specifically. I saw a guy who had had initially been diagnosed years ago and went on chemotherapy initially. And then when there was growth of the cancer, it was actually right when immunotherapy has first been approved as treatment when the cancer had progressed on chemotherapy, so it had just approved. He was one of the first people that was treated on approved next line immunotherapy and had good control for a long time. And so a couple years after that he had the cancer growing and



his oncologist had told him that there really wasn't any other good option that in his situation trying another chemotherapy regimen was unlikely to really help him because the first time he'd done chemo, I hadn't done a lot for him.

And so, the discussion was really around hospice and how to make sure he's comfortable at home and such, but using no other therapy thing that he wasn't really eligible. And when I saw him and looked back through his records, when he was first diagnosed, he had gotten the genomic testing for everything that was available at the time. So at his initial diagnosis, he had the full spectrum of testing, but it was focused testing. It wasn't one of the bigger, next generation sequencing panels. It was targeted for the different genomic alterations that had effective treatment at the time. And so, when I when I saw him and recognized this, then I sent a test to look for other mutations. And I sent a blood test in his case, and that came back showing BRAF V600E. So that has an approved therapy, a combination of two different pills, which at the time that he was first diagnosed was not the case. So he was appropriately tested at initial diagnosis, but at this time now being put on hospice, it turned out he actually had a great treatment option.

And so, I put him on those two pills that are approved for BRAF 600 E. And she did very well with significant shrinking of his cancer and improvement in his strength and appetite and all of that. And so, the appropriate amount of testing, of course, we need to make sure, happens at the time that somebody is diagnosed. But at this point with the number of new genomic alterations we're seeing, an increasing effective therapy. It's important that when there's progression of their cancer, that we look back and make sure that all of the DNA testing of the cancer that had been done incorporates all of the new progress that has happened since that initial diagnosis. Another exciting group of trials that's going on right now is as you see on the top, right, there is KRAS. And so, one of the more common KRAS mutations, which is KRAS G12C now has two drugs in clinical trials that have both been very promising, where we're seeing good responses and generally well tolerated drugs. And so this is another exciting area of potential progress.

There's, there's certainly more research that needs to happen. And those are not approved, but there's optimism that these are drugs that will effectively get there. So we'll see. You know, there was at the same time, I'll point out that the widespread testing of all of these although this really is the standard of care, it's surprisingly not being done for everybody. So this is an extremely important topic. And Dr. Jack West that I know this audience is very familiar with him. He wrote an excellent article about a study that had come out, showing that not everybody is getting tested. And surprisingly, even amongst the people that are getting tested, who have one of these alterations show up, not all of them are ending up on the treatment that is effectively targets that, and this is really important because we know that when there are these alterations, but



the best treatment in many of these cases, the best treatment is the targeted therapy. Now some of these alterations also tend to respond well to immunotherapy and that's a nuanced topic that I'm not diving into. But some of these are scenarios where, where immunotherapy doesn't tend to be effective for those cancers.

And so, when we detect one of these alterations, it's really important to them consider that specific targeted therapy and at initial diagnosis, sometimes there's you know, understandably it's very normal for when there's initial diagnosis, people wanting to get on treatment immediately. But waiting to do this DNA testing is important to that unless somebody really has symptoms that require immediate treatment. But in many cases we can wait to then do that testing. And what I often say is we need to do this testing to make sure that we put the person on the best treatment, not the first treatment. So for lung cancer, this is an incredibly important topic that can't be overstated. And although it is the standard of care, it's not happening enough. So really it's important for patients, for people who have a diagnosis of cancer or for loved ones as advocates of going in to make sure that the oncologist treating has tested for all of these and at any new points that they look back at what had been done and see if there's anything further that needs to be done as well. The other part then is that well, just as the final points, tumors with genomic alterations need to be treated with that targeted therapy. We need to use the best treatment, not the first one. And next generation sequencing really detects the most genomic alterations. Thank you very much for your attention.

