Podcast Transcript
Precision oncology – An overview of tumour agnostic therapies

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Tonke de Jong (COR2ED)
New potentially targetable molecular alterations have been identified in several types of tumours, and pan tumour approaches signal an important new paradigm in the clinical management of various cancers. Keep listening to hear the latest developments in tumour agnostic treatments.

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So today's topic is all about tumour agnostic treatments. I'm honoured to introduce to you two experts in the field of precision oncology, Professor David Hong, Medical Oncologist, and Dr Tracy Stockley, Pathologist and Geneticist. We're very excited to listen to your discussion.

David Hong
Well, hello. Welcome to this podcast. Where we're discussing tumour agnostic therapies. I'm Dave Hong. I'm a professor and deputy chair in the Department of Investigational Cancer Therapeutics here at MD Anderson Cancer Center in Houston, Texas. And today, I'm joined by my colleague, Dr Tracy Stockley. Thank you for joining me, Tracy. Could you introduce yourself to the listeners?

Tracy Stockley
Thanks, David. It's great to be here. So I'm a Molecular Geneticist in the lab medicine program at Princess Margaret Cancer Center in Toronto and a professor at the University of

Toronto. So in my day to day work, I oversee the genomic lab testing for oncology and work closely with our pathologists and clinicians in caring for cancer patients.

David Hong
So let's start by making sure we're all on the same page. Tracy, could you explain to me what we mean by tumour agnostic treatments for cancer and how are they different from other kinds of targeted therapies?

Tracy Stockley
Sure David. So as you know, for some time we've had access to drug treatments that are based on specific biomarkers in specific tumour types. So for example, we routinely test for EGFR mutations in non-small cell lung cancer that directs a specific therapy. But tumour agnostic treatment is an outcome of more recent research where drug treatments are found to be effective in multiple tumour types that harbour one specific biomarker.

So these treatments really are effective in many tissues with that biomarker, not just one tumour type. An important point about this is typically these biomarkers are at different frequencies in different tumour tissues, so more common in some and more rare in the others. But the benefit is, once you find this biomarker, any of those tumours can be targeted by the tumour agnostic treatment.

So it's really moving us into a more genomically informed treatment using new targets regardless of the tumour origin. Just to give a little more detail, these treatments typically have the following criteria. The tumours are enriched for one or more molecular alterations, and these changes predict a response to therapy. As I mentioned, they're found across a variety of cancer types and not just one cancer type.

And it really then does have a biomarker driven targeted therapy rather than a histology driven one. And I think finally, another important point is not all tumours respond equally well to these tumour agnostic treatments. So there is some variability.

David Hong
Thanks, Tracy. And I think these tumour agnostic treatments target multiple tumour types. And I think the development and the design of these trials differ from traditional anti-cancer therapy trials. I've run a number of these trials, and they're somewhat different, obviously, than traditional phase two trials where you are focused on one specific tumour type. They're oftentimes what are called 'basket studies' where the trial allows for the drug to be tested in a number of different tumour types. And they may not necessarily be the more common tumour types. They may be rare tumour types that harbour this specific mutation or genomic alteration.
There are other kind of interesting protocol designs where you may have, like, a master protocol or something called an umbrella or platform design, where you can eventually plug in additional tumour types or maybe even combinations of that specific drug or drugs that could then target that alteration.

Tracy, can you tell us which tumour agnostic treatments are currently approved and for which targets and also which tumours carry these gene alterations?

Tracy Stockley
Yeah, sure. I'm happy to give an overview. So far, there's several treatments that have FDA approval for tissue agnostic therapies. The most common maybe of which is the larotrectinib and entrectinib for tumours with the *NTRK* gene mutations. And for tumours that have demonstrated deficient mismatch repair status or are microsatellite instability high or have a high mutation tumour burden, there's pembrolizumab and there's also dostarlimab for tumours that have mismatch repair deficiency. Now thinking about tumours that might carry other mutations like the *BRAF* mutation V600E, there's dabrafenib and trametinib. And finally, selpercatinib for tumours that have *RET* gene mutations. And so as we talked about, we see these alterations across various tumour types and that really allows us to expand these in the lab to test for these and then hopefully expand use of these therapies.

Another example then might be RET mutations that are found in multiple tissues, including thyroid, lung, breast, skin and colon. And similarly for *NTRK*, these are found in many different cancer types, including breast, salivary, thyroid, lung, soft tissue, skin, colon and more.

And again, as we discussed, a key thing to remember is the likelihood of finding these tumour agnostic biomarkers really does vary between different tumour types. So some are much more common and some are very rare. So it really is the molecular testing that you need to have access to in order to identify these patients who might benefit from therapy.

So now let me ask you a question, David. As a medical oncologist, you've had firsthand experience using these therapies in your patients. So what sort of a response would you expect to see with these therapies? And are the effects similar irrespective of a tumour histologies?

David Hong
Yeah. That's a really good question. Most of the patients that I've treated on these tumour agnostic therapies really have been in the context of clinical trials. And some of the drugs that I helped develop have eventually developed a tumour agnostic indication. But I often tell other physicians who asked me about tumour agnostic that if, in some instances, if you find these alterations and they can be relatively rare such as *NTRK*, it's almost kind of like a lottery ticket to some of these patients who have metastatic, you know, chemo refractory cancer.

I mean, the data that we have now on over 200 some patients with larotrectinib, response rates are well above 70%. Some of these patients go into complete response. I still have a patient close to nine years who is still on from the phase one trial. And so the responses can be dramatic. And I think other physicians will tell you other targeted agents, whether it's selpercatinib with *RET*, in some instances, for example, in MSI-high tumours with pembro or TMB-High, these responses and duration of response, probably the most more importantly, can be profound. So I really encourage physicians and also patients, if they really run out of options to try to explore if they haven't already, obtain an NGS of some sort, next generation sequencing of their tumour to try to do that in the event that they could have one of these alterations.

Tracy Stockley
Yeah, I think that's such a great point. And I think again, from the lab side we know some of these are very rare, but just as you say, the response can be so phenomenal that, you know, there really is a huge benefit to being able to provide this testing.

So another question, so should we give tumour agnostic therapy to any patient who might have this relevant biomarker? So are these therapies relevant in all situations?

David Hong
That's also a really good question. I think as we've expanded the number of, you know, tumour agnostic indications and the number of patients on them, we're understanding, kind of, the nuances I think of these therapies. For example, although, you know, *BRAF* or *MEK* plus *BRAF* inhibition in *BRAF* V600E tumours can be profoundly effective, there are subsets of tumours that do not relatively respond to just *BRAF* inhibition alone, for example, colorectal cancer patients, which is a significant number of *BRAF* V600E patients. The chances of them responding and having clinical benefit from a *BRAF* inhibition is around single digits.

With that said, we now understand that if you combine it with cetuximab, an EGFR antibody, you can increase that response and in fact there is now encorafenib plus cetuximab is for example, approved. There are NCCN guidelines that suggest that, and this is a trial that I helped develop and run, which is irinotecan, vemurafenib and cetuximab. These all have significant clinical benefit, not just response rates, but overall survival benefit in these patients. But again, it is nuanced, even with larotrectinib. It's interesting, we've now known over a period of time as we've enrolled different tumour types that there are some differential response rates. If you take the whole pool of patients, it's like around 70% response.

But there are subsets of tumours that tend to have lower response rates. For example, primary CNS disease. We know that these drugs can cross the blood brain barrier, but in GBM [glioblastoma], adult GBM, the response rates still hover around 30% relative to 70% in other tumour types or even higher in other tumour types. Right? So why is that? It's not entirely clear, but 30% response, durable response rates in CNS patients in primary CNS glioblastoma patients is far better than what we currently standard of care have, right?

So it's still worth, I think, pursuing these patients and pursuing that subset of patients. Let me step back here a little bit, Tracy, and talk a little bit about tissue analysis and precision therapy in general. So the beauty of tissue agnostic precision oncology is the ability to treat cancers with relatively low incidence rates that have been less frequently studied or profiled. But there are obviously challenges with tumour agnostic development as well. And as a pathologist. Right. Can you tell us about some of the challenges from, you know, from a pathology perspective, histology, tumour perspective?

Tracy Stockley
Yeah, sure. Yeah. There are still certainly challenges from that perspective with, you know, the tumour agnostic testing and the therapy. So we know that there's still heterogeneity in

some of the drug effects in the different biomarker positive tumour types. So that's something that's been observed. Of course, there's always differences in tumour biology. And, you know, the natural history of a cancer that might affect their response. And it's not always very well understood. And as we talked about before, the different mutations frequencies among the different tissue types is a challenge. And sometimes there are also inherent resistant mechanisms that can present in some of the tumour types that lead to some challenges too. And David, from your perspective as a medical oncologist trying to access tests, what are some of the challenges that you might see with the testing or you know, access to testing that you might need?

David Hong
So in our institution, accessing testing is not that hard, to be honest. But we kind of live in a bubble in a way. I think in the community, it's not as easy as some place like MD Anderson. In MD Anderson it's almost like a reflex test. If they don't have NGS, we will go ahead and just order that. And it's RNA based NGS, which is probably a much more extensive next gen sequencing platform than standard DNA NGS. You know, if we don't have tissue to do the NGS, we'll even get cfDNA. Right?

Now, in the community, I think there's been now multiple kind of analysis done that, you know, even in a in a poster child of targeted therapy such as non-small cell lung cancer, the actual rates of obtaining next gen sequencing in that population is not where you would think that we would be given all the new targeted therapies in that space. And I think that's probably just logistically, there are a lot of issues more than the actual technology, right? We have cfDNA and we have NGS, which are all available in the community through vendors like Foundation or Guardians or etc., at least here in the United States. But I'm sure there are there are issues that I don't fully understand, such as the reimbursement issues, but also just, you know, turnaround time, even.

Right? Of the actual test, right? If you have a very sick patient in your clinic and you need to have that turnaround relatively quickly, you know, two weeks, may be too long or a week may be too long. I mean, it takes on average here in this institution at least two weeks for an NGS panel to come back to us. Right? And in some instances, you just don't have the liberty to do that, given the clinical condition of these patients.

My hope is, is that ultimately, you know, we're going to start getting NGS at all stages of cancer. Most, I think most NGS and other testing are often done in patients who are refractory right, not upfront, they're refractory, and they're in the metastatic setting, refractory to chemotherapy. And then they get NGS kind of as a last ditch effort. Hopefully as therapies go into the adjuvant, neoadjuvant setting, and then some, we will start, you know, getting NGS from the get go, even in earlier stage patients and also frontline patients with metastatic disease. And I think that will help us make some decisions sooner and quicker and faster with these patients.

Tracy Stockley
Yeah, I really think, I really think that is a needed move. And David maybe I'll just go back and just ask a little bit more about the trial design and implementation. So I guess I'm just

wondering like what challenges you see in terms of trial design and implementation for these tumour agnostic therapies?

David Hong
That's also really good question. I know I've run now multiple of these kind of 'basket' trials or kind of tumour agnostic studies. And I think, you know, obviously the design of these studies, a lot of it has to do with, you know, discussions with the FDA. Right. What are the hurdles in which they can, would lead to eventually a tumour agnostic approval?

There's not one formula. I mean, I just reviewed recently, kind of, the different characteristics of the tumour agnostic therapies. Most of them have at least 15 different tumour types and some of them are more common. The ones that have been approved to date have had at least a threshold of response. Whether you agree that that's necessarily the best surrogate marker or endpoint, that's what has eventually led to approval, a certain threshold response, a certain duration of response.

What's interesting on this is, is that there's been the companion diagnostic portion is interesting because most of the trials that have been approved have not necessarily been required to have, eventually a companion diagnostic development. I think there's one situation when, I think it may have been pembro or nivo that had the TMB indication, there was a post-marketing requirement of developing a companion TMB diagnostic.

But the vast majority is that people use non-companion diagnostics as a measure for treating these patients, partly because it was reimbursed right? But the challenges of these trials are multifold. One is obviously you've got to pick the right tumour type. Obviously you want to pick a certain number of arms.

It's difficult oftentimes to do these as randomised control studies because these tumours are so rare. Right. And so there's a lot of different complications of these studies. But I think that, the gist of it is, is I think you'll see more and more of these. At least in my clinic where I do mostly clinical trials, I see more and more of these trials and the attempt to get some kind of tumour agnostic approval down the line.

And I think you're going to see more and more of these indications FDA approved. And ultimately, you know, community oncologists who are listening to this will have to learn which indications that they can treat their patients with.

Tracy Stockley
Yeah. Yeah. Those are great points. Yeah. Thanks. And maybe just from the lab side, you know, if I could have, just thinking about the broader use of NGS for these tumour agnostic therapies a real challenge is having, you know, the right tissue and the right sources and informatics interpretive algorithms in order to develop these tests. This may be more relevant outside of the U.S., where we are making, often making our own or using our own NGS tests in-house.

And I think, again, one of the things about these tumour agnostic therapies and the rarity of some of these tumours harbouring these biomarkers is you really need large collaborative

studies and ring studies to bring together people to help validate the test. And certainly for the tumour agnostic therapies we've really seen some great work in that way to help bring people together, even internationally to share samples and work up algorithms to enable this testing.

David Hong
So when you think about five years out, or maybe even just a couple of years out, Tracy, do you see anything on the horizon that could be other targets for tumour agnostic treatment?

Tracy Stockley
Yeah, sure. So there are a few ongoing right now. So there's the DESTINY-PanTumor trial that's looking at HER2 directed antibody drug conjugate trastuzumab deruxtecan that has response against multiple HER2 expressing solid tumours so endometrial, cervical, ovarian, bladder and biliary cancers. Another emerging one are the *NRG1* fusions and these are a potential tumour agnostic therapy in multiple tumours including non-small cell lung, breast, cholangiocarcinoma, ovarian, pancreatic, renal, bladder and sarcomas.

David Hong
All right. Well, thanks again, Tracy. It's really been an enjoyable discussion with you on this topic. I just want to wrap up to kind of highlight some, I think, key points that I've gotten out of this discussion. Number one, tumour agnostic therapies are here and many of these therapies can have profound effects on your patients. So I think testing is key.

Whatever testing that you have the ability to get, specifically, ideally NGS testing. I think two, that there are going to be a lot more of these therapies in the near future. And you've just described a number of these that are coming down the pipe. So, you know, I think to ultimately help our patients and ultimately treat them with the most cutting edge therapies, we really need to be aware and conscious of these upcoming indications.

Tracy Stockley
Yeah, thanks. And for me, I think it's just really gratifying to see the outcome of so much of this research and this trial work that's really bringing these tumour agnostic therapies to help patients. Thanks, David. It's great to talk to you.

David Hong
All right. Thank you, Tracy, and thank you, all of the listeners. And we hope you enjoyed our discussion.

Tonke de Jong (COR2ED)
Thank you so much for sharing your insights, Professor Hong and Dr Stockley. We've learned a lot from your discussion on the latest developments in tumour agnostic treatments. If you liked this episode and want to find out more about precision oncology, then look on the Oncology Medical Conversation podcast under the account of COR2ED medical education. Also, don't forget to rate this episode, subscribe to our channel or inform your colleagues about it. Thank you for listening and see you next time.

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