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Emerging Therapeutic Strategies in Metastatic NSCLC

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Brian McDonough.

Dr. McDonough:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and joining me to discuss the evolving non-small cell lung cancer treatment landscape is Dr. Urs Weber. He's an Assistant Professor in the Division of Medical Oncology at the University of Colorado Anschutz Medical Campus. Dr. Weber, thanks for being here today.

Dr. Weber:
Pleasure to be here with you.

Dr. McDonough:
Now, for some background, immunotherapy-based combinations remain the foundation of first-line care, but we're seeing a growing influx of new therapies, like antibody-drug conjugates and novel immunotherapy combinations. So, Dr. Weber, how is this evolution impacting your day-to-day clinical decision-making?

Dr. Weber:
Yeah, it's an exciting time to be in oncology and to be focused on lung cancer. Specifically, we've had a lot of really exciting progress that's been made over the last 5 to 10 years. Even just the introduction of immunotherapy into the treatment of lung cancer has made a big difference for a lot of patients. I think for now, the combination of chemo and immunotherapy in some way, shape, or form remains the backbone of treatment for most patients with non-small cell lung cancer. You have to separate out the folks who have driver mutations that we can target with targeted therapies. But for the remainder of patients, chemoimmunotherapy is the standard.

I do think that many of us have the hope that we'll eventually be able to get away from conventional chemotherapy more and more. It's been around forever. It's a pretty crude tool. It does work, but it has significant side effects and the benefit tends to be time limited. And so I think that most of us in the field are eager to get away from that if we can and if the data's there.

Dr. McDonough:
With that background in mind, let's zero in on antibody-drug conjugates. Agents like trastuzumab deruxtecan and datapotumab deruxtecan have showed encouraging response rates in heavily pretreated patients. And ongoing trials are exploring their role in earlier lines of therapy. Given these data, can you walk us through how antibody-drug conjugates work and what role you see them playing in the treatment landscape?

Dr. Weber:
Absolutely. So antibody-drug conjugates are like the guided missiles of cancer treatment. We still have chemotherapy involved, but the chemotherapy is attached to an antibody. So instead of having that chemotherapy float around freely in the body and go wherever it drifts off to, you have an antibody that's designed to take that chemotherapy to a target on the cancer cell. The target preferentially is going to be something that is expressed—seen on the outside of the cancer cells and not seen so much in other parts of the body—because that's really how you're going to get that chemotherapy delivered to the cancer cell. And that's really where the crux of these antibody-drug conjugates lies is in the selection of the target.

So if you have a really good target like HER2, which is overexpressed in a lot of cancers—not just lung cancer, but breast cancer,

gastric cancer—and not heavily expressed elsewhere in the body, you're going to get a lot of chemotherapy exposure to the tumor and not so much to the rest of the body. So that's really where an antibody-drug conjugate can distinguish itself over conventional chemotherapy.

I think a lot of us want this to work out and want the efficacy of chemotherapy without the side effects. And I think that's really a promise that we potentially have with antibody-drug conjugates. I think it really rests on the selection of good targets, and that's where I think we're still really working is to find the right targets for lung cancer. They're also doing this in other tumor types so that we can really get that nice benefit to side effect ratio that we're looking for with these.

Dr. McDonough:
Now, some antibody-drug conjugates have been associated with toxicities like interstitial lung disease, which can be particularly concerning in patients with underlying pulmonary compromise. So how do these safety considerations influence the integration of these agents into care plans?

Dr. Weber:
That's a real concern that was first recognized with trastuzumab deruxtecan but has since been recognized with other antibody-drug conjugates as well. And so certainly, I would be very cautious to use an antibody-drug conjugate in a patient who has a history of interstitial lung disease. And even in patients who don't have that history, be very mindful of this risk in patients who are being treated with antibody-drug conjugates, take new respiratory symptoms very seriously, and work those up—high-resolution CT scans are the best modality to pick up drug-induced pneumonitis.

I'm a lung cancer specialist, and pretty much all of my patients don't have normal lungs at baseline, so this is a real challenge to try to distinguish what is shortness of breath and cough versus what is drug-induced pneumonitis. And so I work very closely with my pulmonary colleagues. We have an interstitial lung disease clinic here to really work through some of these tougher cases where patients have multiple things going on in their lungs that are abnormal, and we really try to suss that out.

But I would just counsel my colleagues out there to really be mindful of this risk of interstitial lung disease anytime they're using an antibody-drug conjugate because it does seem to be a risk that permeates the entire drug class to some extent.

Dr. McDonough:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Urs Weber about how we can navigate recent therapeutic shifts in metastatic non-small cell lung cancer.

So Dr. Weber, if we continue examining the evolving landscape, novel immunotherapy combinations are also being explored alongside antibody-drug conjugates. Building on established regimens like nivolumab and ipilimumab, newer strategies targeting pathways such as TIGIT, LAG-3, and TIM-3 have shown early promise in improving response rates, particularly in biomarker-low populations. However, some phase 3 trials—especially with TIGIT inhibitors—have not yet demonstrated consistent survival benefit. With all that being said, how do you interpret these mixed results?

Dr. Weber:
Yeah, so I think there's a lot of interest in developing novel immunotherapies and trying to harness the immune system to fight lung cancer, especially in patients who have biomarkers like the high PD-L1 expression that would predict a high likelihood of response to—I call them the classical immune checkpoint inhibitors even though they haven't been around for terribly long—your PD-1, PD-L1 axis inhibitors.

And so I think we're still really trying to fully define this interaction between our immune system and cancer. The whole tumor microenvironment is a very active area of research; we're trying to understand where do all of these different markers play in and how important are they to the interaction that's happening between the cancer cells and the immune system? Because really, it comes back down to target selection, similarly to what I was talking about with the antibody-drug conjugates. All of these markers are involved somehow in the tumor microenvironment in that interaction with the immune system, but they might not be as important to that interaction as we think they are. And that's where there might be a disconnect between what we're seeing in preclinical research and how things actually play out in clinical trials.

And so I think this is just going to be something that we keep plugging away at. One of these might end up being the next PD-L1, but it also might be none of these and we might find a new target that turns out to be a better target that's more important to that interaction.

So I think this isn't going away. I think immunotherapy and developing novel immunotherapies is going to be really important in the next years or decades. I think it's going to take some more plugging away and just finding the right target that's biologically relevant.

Dr. McDonough:

Now, as these new therapies emerge, sequencing becomes a central factor to consider. Based on what we currently know, do you foresee a potential shift regarding where antibody-drug conjugates and novel immunotherapy combinations fit in the overall treatment sequence?

Dr. Weber:
I do think that we're going to see some change here—maybe not in the next year and maybe not in the next two years, but definitely in the next 5 to 10 years, I do think we're going to see the landscape shift here. There's already ongoing trials where antibody-drug conjugates are challenging conventional chemotherapy in the first-line setting in lung cancer.

We also have novel immunotherapies that are making their way into that space. We didn't talk about bispecific antibodies, but that's another type of novel immunotherapy that's really getting a lot of attention with the first approval for a bispecific antibody in a solid tumor coming in small cell lung cancer a few years ago. There's a lot of interest in trying to bring that technology into non-small cell lung cancer as well. And so there's several companies that are developing bispecific antibodies that target both PD-1 and VEGF, and there's ongoing trials trying to integrate those into the treatment of non-small cell lung cancer even as early as in the first-line setting. And so I think we're going to get more options there, and I think there's a chance that one of these novel approaches beats out what we currently have in terms of conventional platinum double chemotherapy with immune checkpoint inhibition.

Dr. McDonough:
Before we close, Dr. Weber, let's look at one more aspect of the current landscape, which is the coexistence of established regimens and early-phase innovations. For instance, trials like KEYNOTE-189, KEYNOTE-407, and CheckMate 9LA have demonstrated durable survival benefits, while many emerging therapies are supported by shorter follow-up and surrogate endpoints. So how do you balance this mature, long-term evidence with the promise of newer agents when making treatment decisions?

Dr. Weber:
To me and I think to most people in the field, overall survival is still the gold standard. And I think that's a tangible number that a lot of patients want to know as well. How much longer is this treatment going to help me live? So overall survival is obviously the endpoint that takes the longest to get to—you need the most follow-up time—so for a lot of newer therapies, it's going to take a long time to get there.

I think the change here, especially with our frontline regimens, is going to be slow. I don't foresee big shifts in how the field treats certain patients based on an objective response rate or even a progression-free survival. It's really that overall survival data that drives the big shifts. And so especially in the first-line setting, we have pretty good therapies at this point. People are living years on these therapies, and so it's going to take time to really demonstrate benefit over those. Certainly in the latter-line settings where therapies aren't as good and there's less options, you might be able to generate some excitement and some movement in the field with some of those earlier markers like objective response rate, disease control rate, and progression-free survival. But certainly in the first line, I think overall survival remains the gold standard.

Dr. McDonough:
Well, given the emerging research on new therapeutic modalities, I want to thank my guest, Dr. Urs Weber, for joining me to discuss what the future of metastatic non-small cell lung cancer treatment might look like. Dr. Weber, it was great having you on the program.

Dr. Weber:
It was great being here. Thanks for your time.

Announcer:
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