Transcript Details

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Time needed to complete: 15 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Unlocking the Potential of TROP2-Targeted Therapy: Breakthroughs in NSCLC Therapeutic Approaches

Announcer:
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Dr. Levy:
TROP2 is emerging as a potential therapeutic target in non-small cell lung cancer, or NSCLC, and clinical trials are ongoing to evaluate the safety and efficacy of TROP2-targeted therapy in this patient population. Are you up to date with the most recent clinical trial data for TROP2-directed ADCs in non-small cell lung cancer? This is CME on ReachMD, and I'm Dr. Benjamin Levy.

Dr. Spira:
And I’m Dr. Alex Spira.

Dr. Levy:
So, to start things off, let's talk about TROP2 and its role in cancer regulation, Alex. I think we're all in the practice of parsing out non-small cell lung cancer into potential distinct molecular subsets, or even PD-L1 expression. And I think with the advent of ADCs, clearly we're starting to look at potential IHC markers that may predict efficacy to these drugs.

Now, TROP2 as of today is not predicting efficacy of these drugs, we can talk about this, but it's still relevant. So, TROP2 is a transmembrane glycoprotein. It's highly expressed in non-small cell lung cancer and other solid tumors. Interestingly, if you look at the data, TROP2 overexpression is seen in roughly 2/3rd or 3/4th of lung adenocarcinoma as well as squamous cell cancers. We've seen that high TROP2 expression is associated with poor prognosis. We've seen in at least preclinical models that increased TROP2 expression has been shown to accelerate tumor growth, where if you suppress it, you can slow the proliferation, the migration, the invasion of neoplastic cells. So, this makes a lot of sense as a target, not only because of its relevance as a poor prognostic marker in non-small cell lung cancer, but also because it's quite frequent in lung cancer, and we have ways to measure it. So you know, again, this is exciting for us to see.

Alex, we have an understanding of TROP2 overexpression, and its ability to potentially prognosticate outcomes for patients. but perhaps you can talk now about the drugs that we're using to target TROP2 ADCs, maybe starting out with mechanisms of actions of TROP2-directed ADCs and then getting into some of the data that we've had.

Dr. Spira:
Thanks, Ben. So, I think a couple of things. So first and foremost there's so many ADCs now in clinical trial development, I don't think either one of us could keep track. And they're all very simple molecules, right? They're an antibody drug conjugate, which is three parts: the antibody, a linker that helps keep this all attached, as well as a cytotoxic poison or warhead, that sits on the end of it. And all these antibody drug conjugates coming almost mixed and matched depending on where they come from.

And you know, the basic mechanism of action, they actually can work in a couple of different ways. as a simple way of thinking about it, they can just bind, they're an antibody, and by binding, you're blocking ligand signaling, and you're sometimes just turning off the signaling that way. most importantly, they're an antibody drug conjugate. So, I describe it as a targeted chemotherapy where you're bringing in a little bit of chemo directly to the cancer cells expressing whatever molecule. So, in this case, if you overexpress TROP2 or even express TROP2 in that situation, you'll target anything expressing that and you'll bring that cytotoxic in. So, people had various names for that over the long term. But I kind of describe it as a smart bomb, and it works very well.

The challenge is with all our ADCs is it's, A, it may not be that smart. And B, this is a pretty complex thing. We talk about it almost secondhandedly right now, but I think the real way to think about it is the side effects can be either binding of the antibody, so if TROP2 is expressed in normal cells. But these antibody drug conjugates are not necessarily perfect, right? So, you can get leakage of the drug conjugate into the systemic circulation, and that could lead to some of the side effects.

We already have sacituzumab which is approved for bladder cancer and breast cancer and datopotamab which we'll talk about right now as well. So, this has been longstanding, and the first one was approved almost 20 years ago for leukemia, and there's a lot out there.

But briefly about some of the studies, we have good data from some of the phase 1 studies. But TROPION-Lung01 was a registrational study. And TROPION-Lung01 was randomized people to either docetaxel the standard current second-line treatment, versus datopotamab deruxtecan, and deruxtecan is the warhead. That data just came out not that long ago, published at ESMO. And what it showed is that there was a clear increase in progression-free survival and higher response rates but only limited to the adenocarcinoma population. And this really wasn't understood before. If you look at the squamous cell population, patients did the same if not worse with datopotamab. But with this, we did see clear efficacy of datopotamab deruxtecan compared with docetaxel in the second-line setting, clear improvement in PFS as well as response rates, and now we're waiting for some of the overall survival data.

TROPION-Lung05 looked at patients similarly, most commonly adenocarcinoma, but those with actionable genomic alterations. So, what do we mean by that? We mean EGFR and ALK. Most of them were EGFR, which is not a surprise. And there, we clearly saw benefit versus docetaxel. So, the response rates were much better with datopotamab deruxtecan compared with docetaxel. Some of those patients were in TROPION-Lung, studied very well in this setting as well.

So again, we have the beginning of data right now that shows that this works. So, we have antibody drug conjugates. We knew they kind of worked in the phase 1, we now have randomized data. I think better overall in TROPION-Lung05 with actionable genomic alterations, but also compared with docetaxel in the all-comer a population of non-squamous cells.

Okay. So, with all that data right now in the second-line setting, the next step, of course, is to look at these drugs in the first-line setting. Ben, do you want to talk about some of those really ongoing studies? Of course, we don't have data right now, but maybe the scientific rationale?

Dr. Levy:
Yeah, I think it's a natural progression to look at these drugs in the second-line, then move them to frontline. You elegantly went over the second-line data. We now have some first-line data, it's small cuts, small data points. One is the EVOKE-02 study. This is looking at the ADC, sacituzumab govitecan, a TROP2 ADC. It has a monoclonal antibody with a linker, and the cytotoxic payload being SN-38. And a pretty clean study, in my mind looking at two separate cohorts, looking at sacituzumab govitecan in combination with pembro in cohort of patients with a PD-L1 greater than 50%. And then looking at the combination with pembro in a PD-L1 cohort less than 50%. Again, small numbers. But, you know, remarkably seeing some really good activity here. The objective response rate in the PD-L1 greater than 50% being around 70%, the objective response in the PD-L1 group less than 50%, around 40%. So, I think this is sort of just gaining traction, gaining some experience to show that you can use these drugs in the first-line specifically in combination with immunotherapy.

A trial that I was fortunate enough to be a part of is another study looking at ADCs or TROP2 ADCs in the frontline, and that's datopotamab deruxtecan, a drug you've already mentioned, Alex. This was a study looking at datopotamab deruxtecan in combination with pembrolizumab or in combination with pembrolizumab and carboplatin. Again, in the second-line, but also a cohort of patients in the first-line, asking the question: How did these drugs perform in the first-line? And we saw meaningful responses in the doublet and triplet arm. Objective response rates anywhere from 50 to 60%. Again, early cuts, a small number of patients. So, we'll have to see how this pans out.

Dr. Spira:
Especially in the frontline setting, what we're thinking about is two things. We're not just thinking about efficacy, but these are patients that are going to hopefully do well for a while. So, we want to think about toxicity and toxicity management, and what that is. Because at

the end of the day, especially in that frontline setting, it's going to come down to both the survival rates, PFS, and overall survival. But most importantly or just as importantly I should say, toxicities. How do we deal with that? And what are they?

So, let's now talk about some of those adverse events. I kind of think about them as a couple of things. There's a little bit of ocular toxicity. Mucositis is probably the biggest one and as well as pulmonary toxicity, which is rare, but real. So, Ben, do you want to talk to us a little bit more about those and how you think about them and manage them?

Dr. Levy:
Yeah. I look at the adverse events for these TROP2 ADCs through two separate prisms. I think the first prism is those common side effects that we see with other chemotherapies, because sometimes we view these ADCs as chemotherapy 2.0. So, we're talking about the cytopenias. We're talking about the GI toxicities. we're talking about alopecia, peripheral neuropathies, fatigue. Those are things that as we do with other chemotherapies, we need to be mindful. We need to be proactive. We need to be able to mitigate these. And I think that we have these strategies sort of ironed out when we've used these strategies so commonly with other chemotherapies. So clearly growth factor support for neutropenias, we're seeing that may be helpful for the sacituzumab govitecan compound. Transfusion support for anemias. Obviously for diarrhea, which is the most common side effect from sacituzumab govitecan using antidiarrheals, even atropine may be helpful. So, these are I think, strategies that we are well aware of, maybe some nuances but very, very important to get our patients through this journey with the ADCs.

Perhaps, and you mentioned this, Alex, more important is those AEs of special interest that we're seeing with these ADCs, these TROP2-directed ADCs. And there's probably three that come to mind for me that are important to talk about. First is stomatitis, and we'll touch upon this. Second is the ocular events that we're seeing with some of these TROP2 ADCs. And then there's the ILD.

And starting with stomatitis, interestingly we have two TROP2 ADCs that are gaining a lot of traction right now, datopotamab deruxtecan and sacituzumab govitecan, we're seeing stomatitis with datopotamab deruxtecan but we're not seeing it with sacituzumab govitecan, even though these drugs work very similarly. A lot of head scratching on why that is. We saw from the TROPION-Lung01 data that you discussed, Alex, that the stomatitis rate was more than 50% of patients. And so, we've got to be active and be mindful of that if this drug makes it into our clinic in everyday practice, there are mitigating strategies we can employ that include dexamethasone rinses, ice chips. So there are a lot of ways I think that we can be proactive and manage these patients before it happens.

The second thing that I'll mention are ocular events. Again, we see these mostly as grade 1 or grade 2. We saw them in TROPION-Lung01. ocular events usually clinically manifest as dry eyes. but this is something where we need to partner with our subspecialists like our ophthalmologists when these things occur.

The third thing that's important to talk about not only with TROP2-directed ADCs but all ADCs, and specifically HER2-directed ADCs are the ILD. Now the ILD signal came out first with trastuzumab deruxtecan, which is a HER2 ADC but we've seen some of this with the TROP2-directed ADCs, specifically from TROPION-Lung01. It's not that common. All-grade ILD, we saw was around 8%, 9% in the datopotamab deruxtecan arm. but we need to be active with managing ILD. We need to screen our patients. We need to ask questions. We need to scan them and be proactive. we need to suspend treatment. And then we need to consider steroids.

I would say the one thing about ILD that's important with ADCs that's a little different than immunotherapy, is that a grade 1 ILD with ADCs, you usually should interrupt the ADC until the ILD resolves. And that's a little different than what we have with immunotherapy. and then anything grade 2 or beyond, really need to consider stopping drug altogether.

So, you know, these are kind of the ways that I view these, so these two separate prisms. And, so Alex, you've had a chance to use both datopotamab deruxtecan and sacituzumab govitecan, what are the differences that you see between these two drugs?

Dr. Spira:
You talked about this very eloquently, Ben. But I think for me, the biggest difference is sacituzumab has more diarrhea, which is kind of expected, right? I mean, it's an SN-38 analog. For those of you who don't think about that, think of irinotecan, it's an irinotecan metabolite, we see that not uncommonly when you use that drug. So, that's typically what you see. It's also given on a more frequent schedule and a little bit more hassle for patients, day 1, day 8. So for me, there's a lot more GI side effects with that one.

For me, the one that scares me the most is of course ILD. It's very rare when you see it. I think it's pretty similar between datopotamab and sacituzumab. You know, I think all our ADCs really have some of it.

And I always remind everybody that, you know, the breast cancer world is a little bit different, you know, sacituzumab is already approved, trastuzumab deruxtecan is approved in both. And I think what our experience is that in lung cancer, we already have lung damage, the patient's pulmonary status is never normal. They may have gotten radiation to their chest before, either palliative or curative if they relapsed. And something you really got to watch very, very closely. So that's how I kind of use it.

Dr. Levy:
Yeah these are great points, Alex. I think you know, we have to remember even though there were stomatitis and ILD and ocular events from TROPION-Lung01, you know, if you look at the patients who got dose reduced, the dose was discontinued, that was more common in docetaxel arm than it was in the Dato-DXd arm, so – and I think we'll see the same trends.

Remember, we've got EVOKE-01 coming out very soon, which is the same as TROPION-Lung01, but using sacituzumab versus docetaxel. We'll have that data in I think Spring 2024. So, be interesting to see what comes out of that and how we do this apples-to-oranges comparison between two trials with a common comparator arm of docetaxel.

And that's all the time we have today. So, I want to thank our audience for listening in, and especially thank Dr. Spira for sharing his valuable insights. Alex, it was great speaking with you today.

Dr. Spira:
Great talking with you, Ben. Take care.

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