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https://reachmd.com/programs/cme/trop2-adcs-for-metastatic-nsclc-setting-the-stage-for-future-use/14416/

Released: 11/15/2022

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TROP2 ADCs for Metastatic NSCLC: Setting the Stage for Future Use

Announcer:
Welcome to CME on ReachMD. This activity, entitled “TROP2 ADCs for Metastatic NSCLC: Setting the Stage for Future Use” is provided by Prova Education.

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Dr. Levy:
The emergence of targeted therapy has shifted the treatment paradigm for advanced non-small cell lung cancer. Are you as excited as we are to see how Trop2-targeted antibody-drug conjugates, or ADCs, can help our patients?

This is CME on ReachMD, and I'm Dr. Benjamin Levy. Here with me for Chapter 1 is Dr. Becca Heist.

Dr. Heist:
Hi, Ben, thanks for having me here.

Dr. Levy:
So, Becca, let's drive right into a case. We have a 55-year-old patient with advanced metastatic non-small cell lung cancer. She's positive for EGFR and has no relevant identifiable mechanisms of resistance post-TKI. After progression on that tyrosine kinase inhibitor, she receives platinum-based chemotherapy, and unfortunately, again, develops disease progression 1 year later.

Dr. Heist, how would you approach a patient like this?

Dr. Heist:
Yeah, so this is a really interesting case. And you know, we're often faced with the situation, right, where somebody initially has a great response to a TKI and then they progress, and we try platinum chemotherapy, and then there's progression again. You know, I'm always looking to see if I can identify a mechanism of resistance. And as you know, there are multiple mechanisms described, including secondary mutations in EGFR, activation of other pathways, transformation to other histologies. But sometimes we don't find a clear mechanism of resistance, and then we’re left just trying to deal with the progression as best as we can.

In that setting, of course, there are standard of care treatments that we can do after platinum chemotherapy. And there are also clinical trials where we would test novel agents. And so I think this is a situation that we're faced with often. And when there's not a defined mechanism of resistance, it's hard to know exactly what the right next step is. But clearly, there are some newer agents that I think would be of high interest to look at in this situation.

Dr. Levy:
Yeah, great point. I think we can both agree that we're not too enthusiastic about docetaxel, which would probably be the standard of care here. You agree with that, Becca?

Dr. Heist:
I would agree with that. You know, docetaxel of course, is an approved regimen post-platinum therapy in advanced lung cancer. But you know, the response rates are generally quite low. We expect a response rate of about 10%. And although some more patients can

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get stabilization of disease, in general, we're looking for newer agents because we're not that enthusiastic about how active the drug is.

You know, doce[taxel] with ramucirumab is another combination that can be considered, and response rates are slightly higher with that combination. But again, we're still looking for newer agents in this space, and there's a real need for it.

Dr. Levy:
Yeah, I think docetaxel or docetaxel plus ramucirumab certainly are options here, standard care. Becca, is there a role for immunotherapy in this space as a potential therapeutic option in the EGFR-positive patient?

Dr. Heist:
So that's a great question. You know, in general, when we've looked at the immunotherapy studies—and there have been various meta-analyses looking at these—if you tease apart the patients who had EGFR [mutations] in the various, for example, immunotherapy, PD-1, PD-L1 inhibitor vs chemo studies. You know, the benefit that we saw with IO really did not accrue in the patients with EGFR mutations. My general sense here is that single-agent immunotherapy with a PD-1 or PD-L1 inhibitor is not expected to have much activity, even in the setting of a high PD-L1 when there's an EGFR mutation.

Dr. Levy:
So let's move to some of the more exciting options potentially coming down the pike. We mentioned docetaxel plus ramucirumab as probably the standard. We mentioned that single-agent IO probably doesn't have a role. What are your thoughts on some of the other drugs that are coming down and potentially some data points that we have on these drugs?

Dr. Heist:
So antibody-drug conjugates, I think, is a class of drugs that everyone's very excited about. And there have been a couple of ADCs that have been investigated in this setting. There's a HER3 ADC. This is patritumab deruxtecan. This is an ADC directed against HER3 attached via a linker to deruxtecan.

And there was a study that was reported of this drug after EGFR or TKI and other therapies. And in that particular study, there was a response rate that was, I believe, around the 39% range. And the interesting thing about that drug, of course, is that they saw activity across a range of resistance mechanisms. There are some really nice and interesting data that suggest that there are some newer therapies that could be of benefit in this situation.

Dr. Levy:
So, Becca, you did a nice overview of the HER3-directed ADCs specifically for EGFR-mutant lung cancer. Are there any other antibody-drug conjugates that look promising in this area?

Dr. Heist:
Yeah, I think datopotamab deruxtecan is actually a very interesting ADC in this area as well. So this drug, as you know, is an ADC directed to Trop2. There have been early reports of the activity of this drug in all lung cancer, actually, with some nice activity in unselected non-small cell lung cancer populations. But specifically, there's also been some data in patients with lung cancer who have genomic alterations. So TROPION-Lung01 is a study that was done in advanced lung cancer with actionable genomic alterations. And in a report at ESMO of last year some of the early data from that study were presented. And in that particular study, they accrued patients with a variety of alterations; the majority were EGFR. There were also some ALK, ROS, RET alterations included among the alterations there. So I think this Trop2 ADC is also actually quite an interesting one to think about in this population after they've had TKI and platinum chemotherapy.

Dr. Levy:
Yeah, great overview. And we're blessed to have all these new therapies coming down the pike.

Just briefly, Becca, if we back up and this patient didn't have an EGFR mutation, let's say this patient was treated initially with chemo/IO, you know, is there a role for these ADCs, as second line and in an unenriched group of patients? Are there others? Just a very high-level overview here.

Dr. Heist:
Yeah, absolutely. You know, I think if this patient did not have an EGFR mutation and we were looking at what are we to do after platinum IO, you know, here is, similar to what we were saying before, yes, you can use a drug like doce or doce/ram[ucirumab], but we are looking for options that are better and that have higher activity. So you know, Trop2 ADC, the datopotamab, the original data were in unselected non-small cell lung cancer; there's nice activity there. I think that's a consideration. I think ADCs in general in this space would be interesting to pursue and have some efficacy. So here I would be really looking for let's go beyond standard of care and look for a clinical trial of some agent that we think might have some activity, because I think there's a huge need to improve how we're doing

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in this space.

Dr. Levy:
Yeah, I always, when I'm talking to fellows in my clinic, I always say, you know, what's the next line of therapy post chemo/IO? And they wrestle with doce or doce/ram, and I say, “No, it's a clinical trial.” That's really where we're heading now. And I think we'll see some nice head-to-head data; maybe it'll pan out with ADCs vs docetaxel very soon. So very much looking forward to this.

So thank you, Becca.

In chapter 2, I'll be joined by Dr. Peter Illei, a pathologist who will discuss the importance of both immunohistochemistry and next-generation sequencing testing in patients diagnosed with non-small cell lung cancer. Stay tuned.

Dr. Levy:
So welcome back. We're going to shift gears from our patient case to focus on immunohistochemistry, or IHC, and next-generation sequencing, NGS. Dr. Peter Illei is joining us for this discussion.

Welcome, Peter.

Dr. Illei:
Hello, and thanks for having me.

Dr. Levy:
So, Peter, what's the importance of immunohistochemistry and next-generation sequencing testing after a patient is diagnosed with non-small cell lung cancer?

Dr. Illei:
Both of those methods can be used to identify targetable alterations. Immunohistochemistry is used to detect PD-L1 expression in order to determine eligibility for immunotherapy. And next-generation sequencing or other DNA- or RNA-based techniques are used to identify targetable genetic alterations, mutations, indels, and translocations.

Dr. Levy:
Yeah, so walk us through a little bit. You get the tissue and obviously you mentioned that PD-L1 needs to be done. It seems like that both DNA and RNA should be done. Are these done at the same time? Are they done sequentially? How does this work? And what do you think the optimal way is for this to work?

Dr. Illei:
So immunohistochemistry is using tissue sections. So that's done separately. And in the case of PD-L1, the indications are that all non-small cell carcinomas should be tested. In terms of molecular testing, currently the standard, at least at our institution, is to test all non-squamous non-small cell carcinomas. And we use a large panel, NGS platform, DNA-based platform to identify molecular alterations, and we also use a fusion panel identifying potential translocations and gene fusion products.

Dr. Levy:
Yeah, and I think that we've come a long way in the diagnostic algorithm for patients with non-small cell lung cancer. Clearly, you mentioned that we need tissue to identify these alterations and DNA- and RNA-based testing as well as PD-L1 testing. How common is it that you don't have enough tissue to do the testing that you need to do?

Dr. Illei:
Well, it's fairly common that we have to deal with a limited amount of tissue. About 70% of advanced-stage lung cancers are diagnosed on small biopsy or cytology specimen. So unfortunately, in our case, most of the time we have enough tissue to do some testing, at least the minimum recommended panel to perform on these tissues. But there’s great variation in different institutions. And in terms of what material you’re testing, whether there's sufficient tumor to do all the testing.

Dr. Levy:
Yeah, I think it's always a challenge for us to make sure that we're getting enough tissue to do this testing.

You know, we've talked about genomic alterations that are important, we've talked about PD-L1 as the bonafide biomarker for immunotherapy. There are other IHCs that may or may not be relevant with new drug therapies. One of the new drugs, obviously, is the Trop2 antibody-drug conjugate class of drugs that we're beginning to look at in clinical trials and are starting to make their way into clinical space. One of the ways that these drugs work is clearly to potentially bind to Trop2 protein on the cell surface and then deliver the warhead.

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Peter, what's the relevance of Trop2 expression right now in lung cancer? And do you see this playing a role potentially in the future?

Dr. Illei:
So we don't know yet. Trop2 immunohistochemistry has not been used, at least in our institutions, for clinical purposes. Trop2 is a surface glycoprotein that's expressed on the surface of many different adenocarcinomas, including lung adenocarcinoma, which is actually the majority of them. And it's not expressed or just minimally expressed in benign, non-neoplastic tissues. So the fact that it's differentially expressed in tumor cells, it makes it a potential biomarker, but whether this will be a predictive biomarker, we don't know yet.

Dr. Levy:
Yeah, I think we're in a waiting period here to see how this pans out and other predictive biomarkers as well, not just genomic alterations, the NGS and the PD-L1. But I think we are still in need of understanding other potential biomarkers to predict both efficacy and lack of efficacy for new drug therapies.

This has been great. Thank you, Peter. Next up, we'll be discussing targeting Trop2 in non-small cell lung cancer.

Dr. Levy:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Benjamin Levy, and here with me today is Dr. Rebecca Heist and Dr. Peter Illei. We're discussing Trop2 antibody-drug conjugates and setting the stage for their use in advanced-stage metastatic non-small cell lung cancer.

So welcome back. We just covered the importance of immunohistochemistry and next-generation sequencing with Dr. Illei. And now Dr. Becca Heist is back to discuss targeting Trop2 in non-small cell lung cancer.

So, Becca, what can you tell us about targeting Trop2 with antibody-drug conjugates in lung cancer?

Dr. Heist:
Yeah, so this is a really exciting new class of drugs. And the reason why we think about targeting Trop2, is Trop2 is overexpressed in cancer cells. It's expressed in a wide variety of normal human tissue, but it also is highly overexpressed in cancer cells. And so, when we think about an antibody-drug conjugate, so this is an antibody that attaches to an antigen that it recognizes, and it's attached via a cleavable or non-cleavable linker to a payload that is really the chemotherapy agent. And here, there are a variety of different chemotherapy agents that get attached to the antibody-drug conjugate. It's really a way to deliver chemotherapy in a targeted way to cancer cells. And I think this ability to really target the chemotherapy is leading to a lot of excitement and activity in lung cancer and in other cancers as well.

Dr. Levy:
Yeah, it's very exciting. I think the mechanism of action is exciting, as you mentioned, to have these 3 components with a warhead that may selectively deliver the chemotherapy to the cancer cells and potentially have a bystander effect. And I think, you know, we're learning how to manage these drugs and their tolerability, but more importantly, the efficacy. The preliminary efficacy that we've seen is quite exciting.

Becca, we have two Trop2 ADCs that are probably front and center. One is sacituzumab govitecan, which I know you've had experience with. The other is datopotamab deruxtecan, which I have some experience with.

So, Becca, what's the current regulatory status of datopotamab deruxtecan?

Dr. Heist:
So datopotamab deruxtecan is currently not approved for any indication in lung cancer.

Dr. Levy:
Yeah, I think we'll hopefully see some data soon that may change that. I look forward to seeing that. I think these drugs, or datopotamab deruxtecan, specifically, we'll see some data to support this, but may gain approval at some point in the second line. But we'll have to see how the data shakes out and whether or not it can outperform docetaxel in the second line.

Can you talk a little bit about the toxicity management of these Trop2 ADCs?

Dr. Heist:
Yeah, sure. And of course, they're a little bit different. So sacituzumab, as you mentioned, is approved in the breast cancer space. And in lung cancer, it does have some activity. There was an early study looking at non-small cell lung cancer, and sacituzumab had a response rate of around 19% or so in lung cancer. There, the warhead that's attached is an analogue of irinotecan. So the toxicities we see are hematologic toxicities; we see some GI toxicities like diarrhea.

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Datopotamab, another Trop2 ADC, the warhead is deruxtecan, which is slightly different. And the toxicities we see related to that are a little bit different than what we see with saci[tuzumab]. So common toxicities include some fatigue, some nausea, some stomatitis. With stomatitis, there are measures that you can use. For example, I use a fair amount of steroid swish and spits, to try to alleviate some of this stomatitis that we see. We see some things like dry eye, which can be quite bothersome to patients. And again, there, we work closely with our ophthalmologic colleagues to use various sorts of eyedrops to alleviate those toxicities.

So there are some idiosyncratic toxicities that we see with these various drugs that have to do with the attached warhead. And there's definitely a learning curve there in terms of managing the side effects that people have.

Dr. Levy:
Yeah, I think I'm biased, but I think the lung cancer community has always been on the leading edge of all these new therapies. For these, I think we are again learning from our colleagues. I agree with you that the stomatitis is an issue, and I think we have reasonable strategies to mitigate stomatitis. As you mentioned, the steroid swish and spit has, at least in our experience, been effective in, again, reducing the severity of stomatitis. I think using it preemptively may make sense in future studies and in current use and current studies. So it's very exciting.

I think we're moving leaps and bounds with some of these drugs, and we're starting to push the antibody-drug conjugates not only looking up in the second line, but starting to look at that in the first line. I was fortunate to present some of these data at World Lung 2022 in Vienna, the TROPION-Lung02 study, which was a phase 1b study looking at datopotamab deruxtecan or Dato-DX plus immunotherapy – there's a lot of rationale to look at the synergy of these 2 drugs – plus or minus platinum chemotherapy, specifically platinum, either carboplatin or cisplatin. And this was looked at in advanced non-small cell lung cancer. And this study looked at 6 cohorts. The first 2 cohorts were looking at a 4- or 6-mg/kg dose of datopotamab with pembrolizumab. And then the next 4 cohorts, 3 through 6, importantly, were looking at datopotamab plus pembrolizumab plus either carboplatin or cisplatin.

So this is the first time we've looked at these antibody-drug conjugates with immunotherapy and with platinum. This is the first reports of this, of potential outcomes and safety with these drugs. There were roughly 40 patients in the doublet arm and 48 patients in the triplet arm. And these drugs, the doublet or triplet arms, were given either in the treatment refractory setting, but also in the treatment-naïve setting. And again, this is the first data set we have. The bottom line is that response rates were roughly 37% and 41% in the doublet and triplet arm, respectively. But looking in the first line, looking at the doublet arm in the first line, the response rate was 62%. But looking at the triplet arm, the datopotamab, pembrolizumab, either carboplatin or cisplatin, the response rate was 50%.

So we'll have to see how this all pans out. Some of these responses were durable and meaningful and ongoing. And we will be increasing our patient population in this study and hopefully presenting it again. We didn't see any new safety signals. And we've talked about safety already. So this is exciting for us and for the Trop2 class of drugs.

So again, that's not the only study. Becca, are there other ongoing studies with Trop2 ADCs?

Dr. Heist:
Oh, yeah. So it's being looked at in a variety of settings, as you know. So in the first-line setting, or I should say in combination with PD-1 or chemotherapy, as you mentioned, that's some of the early data presented. These Trop2 ADCs are being looked at in clinical trials in comparison to, for example, docetaxel. So taking a step back, you know, before the first line – or after the first-line setting, if we can use it in second line or later. So both sacituzumab and datopotamab are being compared to docetaxel. So I think that'll be interesting to see if either of these Trop2 ADCs can actually do better than doce because we're always looking for something that would be more effective than docetaxel in the post-platinum IO space.

There are also studies looking at the Trop2 ADCs in specific populations with actionable genomic alterations. So again, there, even though patients have a variety of TKI options, there's always room for more drugs, because at some point people progress through the available TKIs. And so that's another interesting area where these drugs are being studied. So I think in the next several years, we'll see a lot of data come out, and we'll understand more about how best to use these.

Dr. Levy:
Yeah, great overview, Becca. I think we are seeing what I call the ADC blitz in non-small cell lung cancer, similar to the IO blitz, immunotherapy blitz that happened maybe 4 or 5 years ago, where we're starting to see these competing trials, these drugs that may work very differently. You know, you mentioned the Trop2 ADCs. There are CEACAM5-directed ADCs, drugs like tusamitamab ravtansine that are being looked at in both first line and second line. There's telisotuzumab, which is a MET-directed antibody-drug conjugate. That's, again, looking potentially in the second line, specifically for MET-positive patients. And we talked about this before, patritumab deruxtecan, this HER3 antibody-drug conjugate that's also being looked at in the EGFR mutant lung cancer space. So it's

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going to be tough to keep up with all this stuff.

And then, as you mentioned, Becca, the first line. Looking at these ADCs in the first line, 1 study that I'm fortunate to lead will be this TROPION-Lung08 study looking at datopotamab [deruxtecan] plus pembrolizumab vs pembrolizumab alone for those patients with a PD-L1 > 50% and asking the question: can we add datopotamab [deruxtecan] to pembro[lizumab] and achieve a better outcome and potentially reasonable safety vs pembro alone? We'll see where this goes and whether there'll be a role here or not. I think we have to really look at meaningful improvement here. Are we improving longevity and at the same time not sacrificing a quality of life or tolerability? So a very exciting time.

Becca, your final thoughts on where we're heading with these drugs? Is there a potential role in the adjuvant space, the neoadjuvant space? Are there biomarkers that may help us predict for efficacy of these drugs? Where are we heading here?

Dr. Heist:
Yeah, so Ben, as you say, it's a really exciting time with ADCs. And it's a little a bit hard to know exactly where things will pan out. As I think about it, I think there are a couple of things. One, it would be great if there were some biomarker where we could pre-select or highly select patients who are more likely to benefit. So far with the, for example, Trop2 ADCs, Trop2 expression itself hasn't correlated with response. And that may just have to do with the fact that so many cancers overexpress and highly express Trop2. But if there were some other biomarker that could predict who would be most likely to respond, I think that would be a great addition to the field. And that's an area of really high interest and high activity right now, as well.

You know, it seems to me that these drugs and their preliminary signals of activity do have some really interesting activity. And at some point, whether it's, you know, in the first-line setting, incorporated in some regimen, or in second-line or later settings, it seems to me that we're going to see more and more of these ADCs and Trop2 ADCs, in particular, being used. It seems likely to me.

And then of course, when we see activity in the metastatic setting, we are always thinking, can we move that up into the adjuvant or neoadjuvant space? Can we select patients in that space who would be most likely to benefit? And there, I think is where the biomarkers are going to be most important. And as you said, can we devise a regimen that would have high efficacy and also maintain excellent quality of life? And so, I think all of those areas are going to be explored. And we'll have more and more answers as the years go on.

Dr. Levy:
Yeah, I think it's going to mirror sort of the IO, or immunotherapy, experience, where we throw spaghetti on a wall and see what sticks. That's what's happened a lot with immunotherapy combinations. And I think we're going see that. That's not a bad thing. I think, you know, we learn a lot sometimes about these drugs when we look at them in combination and then try to figure out on the back end why that combination worked, which is sort of in reverse to what we usually do in lung cancer. We try to figure out how these therapies work and then leverage them in a specific space. I think in this setting, we're not really sure how these drugs work sometimes, and combinations need to be looked at. And we'll see what sticks and then work backwards to see why this worked and how to leverage it in our clinic.

Well, this has certainly been a fascinating conversation. And let me just summarize by saying, one, we are really moving this field forward with a lot of different therapies. And I think the antibody-drug conjugates are certainly front and center. And my guess is they will gain approval in the near future.

You know, despite that, I think there's a long way to go. I think we need to learn how these drugs work a little bit better than we know now. I think we need to look at combination approaches or look at these drugs in different settings.

I look forward to potentially seeing these drugs leveraged in earlier-staged disease at some point, either in combination with immunotherapy or chemotherapy. I also look forward to seeing these drugs being pushed into the frontline. And hopefully we'll see some exciting data there.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in, and thank Dr. Becca Heist and Dr. Peter Illei for joining me and for sharing all of their valuable insights. It was great speaking with you today, Becca.

Dr. Heist:
It was great to be here, Ben.

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