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https://reachmd.com/programs/cme/chairpersons-perspective-evidence-informed-clinical-decision-making-in-her2-overexpressed-and-trop2-targeted-nsclc/39894/

Released: 03/05/2026
Valid until: 03/05/2027
Time needed to complete: 15 minutes

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Chairperson's Perspective: Evidence-Informed Clinical Decision-Making in HER2-Overexpressed and TROP2-Targeted NSCLC

Opening:
Welcome to CE on ReachMD. This activity, titled **"Mastering New Standards: Evidence-Informed Clinical Decision Making in HER2-Overexpressed and TROP2-Targeted NSCLC"** is provided by **AstraZeneca and Daiichi Sankyo, Inc.**

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Dr. Levy:
Hello, everybody. This is CE on ReachMD. I'm Dr. Benjamin Levy. I'm Associate Professor at Johns Hopkins School of Medicine, and the Clinical Director for the Johns Hopkins Sidney Kimmel Cancer Center at Sibley Memorial Hospital in the National Capital Region in Washington, D.C. And we're going to be talking about decision-making with HER2-overexpressed and TROP2-targeted non-small cell lung cancer.

So, let's start with HER2 alterations in non-small cell lung cancer and IHC testing.

And we need to remember that HER2 alterations come in many different sizes, shapes, and forms, and we'll go over this briefly in the talk today. Importantly, when we talk about HER2 alterations, we're talking about HER2 gene amplification, HER2 gene mutation, and HER2 protein overexpression. All of those encompass HER2 alterations. It's important to try to delineate these when we're talking about interrogating lung cancer to decide what therapy that we're going to use.

Now, specifically in lung cancer, HER2 overexpression occurs in roughly 1 to 2%. HER2 mutations, which we know are actionable – specifically, HER2 exon-20, we know are actionable – occurs in around 5% of patients. And then, HER2 amplifications anywhere from 2 to 14%, and that's specifically in lung adenocarcinoma. They're a little bit higher for all non-small cell lung cancer.

HER2 overexpression is important now. We know that this is an actionable biomarker, and it has to be HER2 3+ that we're looking for. And the NCCN guidelines have come out and really made it clear that we do need to do HER2 testing by IHC at some point, either at the beginning of treatment or during disease progression to inform treatment decisions. So, really important that we're doing this now and tacking this on potentially, to our NGS platforms to help guide therapy, specifically with trastuzumab deruxtecan.

And this is just a schema, showing you what HER2 staining looks like by IHC and what the pathologist does.

This is a nice algorithm, showing you how HER2 testing should be done. And the bottom line here is for HER2 mutations, you should be doing both tissue and plasma, generally on all advanced non-small cell lung cancer patients. That is better able to interrogate and unearth HER2 mutations. And then the IHC needs to be done as well. And again, based on the results from both IHC and NGS, both in

tissue and plasma, we can make informed treatment decisions.

So, HER2 expression matters. It's important to know that with HER2 testing now, with IHC, if we have 3+, we are able to use that information and use it in real time for treatment decisions for trastuzumab deruxtecan, specifically in the refractory setting. And it's important that we learn how to streamline HER2 testing workflows in our practice, not only for IHC, but also for NGS.

So, important that yes, we're testing, but therapeutic strategies, we're going to go over these specifically in HER2 overexpressed non-small cell lung cancer.

And perhaps the first data signal that we had that trastuzumab deruxtecan was beneficial in patients that were HER2 overexpressed was from DESTINY-Lung01. This was a study that looked at both cohorts of HER2-overexpressed and HER2-mutated.

Now, we know in this study that HER2 mutations predicted response to trastuzumab deruxtecan, but importantly, there were signals for HER2 overexpressed lung cancers, that overexpression did predict better outcomes, specifically 3+. And this was our first signal.

Now, fast forward to DESTINY-PanTumor02, which was all solid tumors. And this study did include some lung cancer patients, but very few. Patients who had solid tumor malignancies, who had HER2 IHC 3+, who received trastuzumab deruxtecan in refractory disease, the response rates were north of 60%, duration of response 22 months, and the PFS was 12 months.

And because of that, FDA approved in April of 2024 trastuzumab deruxtecan for all solid tumors who have HER2 overexpression 3+. So, really important that we realize based on this, the data that trastuzumab deruxtecan is a bona-fide therapeutic strategy for HER2 overexpressed cancers, and lung cancer is one of those.

So, the NCCN guidelines have now adopted HER2 overexpression into the diagnostic algorithm, and clinicians can use trastuzumab deruxtecan for HER2 positive IHC 3+. Really important that we're doing that.

Now, there's been other data, specifically in lung cancer, that has shown that patients with lung cancer advanced stage who have HER2 3+, that does predict response. In DESTINY-Lung03 part 1, looking at this trastuzumab deruxtecan monotherapy, showing that patients with HER2 IHC 3+ have response rates around 57%, PFS of 7 months and OS of 16 months. And that is really just reinforcing the idea that this is an important therapeutic strategy.

And again, this is the waterfall plot from that study, showing you that predictive nature of IHC for monotherapy.

We need to keep in mind the adverse events with trastuzumab deruxtecan: left ventricular dysfunction, neutropenia, and I would say ILD is low on the list now, but it's there. It occurs at the 5.4 mg/kg dose of around 5 to 10%, so you need to keep your eye out for it.

Again, important that we have this therapeutic now. Important that we also are testing but also managing the toxicities of these compounds.

What about TROP2-directed therapies in non-small cell lung cancer?

TROP2 is overexpressed in non-small cell lung cancer, and importantly, it is prognostic for worse outcomes. So, this is a potential nice target to try to drug.

Two different ADCs have come into the market that have come into clinical investigation; sacituzumab govitecan and datopotamab deruxtecan.

Both have been evaluated in non-small cell lung cancer. The bottom line is both of these drugs, datopotamab deruxtecan and sacituzumab govitecan, have been evaluated in patients in the second-line compared to docetaxel. Unfortunately, these agents did not outperform docetaxel.

But all is not lost with TROP2 ADCs. And we know now that datopotamab deruxtecan is approved specifically in patients that are EGFR-positive. And while it did not show a benefit in the second-line versus docetaxel, we now have the data from TROPION-Lung05 and

TROPION-Lung01 – we'll talk about that – showing that in a group of patients with genomic alterations, and this is TROPION-Lung05, who were highly pre-treated, who received datopotamab deruxtecan 6 mg/kg, the response rates specifically in the patients that were EGFR-positive from this study, the response rates were north of 40%, PFS of around 6 months, and OS greater than 14 months.

This really was a signal that then the decision was, well, let's pull the analysis. Let's look at the EGFR patients from TROPION-Lung05, and let's look at the EGFR patients specifically from that TROPION-Lung01 study that would have evaluated datopotamab deruxtecan in the second-line and look at these together. One hundred seventeen patients who were pre-treated, who had received targeted therapy, who were all EGFR positive, who received datopotamab deruxtecan as a single agent.

And not surprisingly, here again, response rates north of 40%, PFS of around 6 months, and OS around 15 months.

And because of this, this pooled analysis, the FDA did approve a datopotamab deruxtecan specifically in the EGFR-positive patient population for patients who have received targeted therapy and chemotherapy, this is a bona fide FDA-approved therapy. Now, no new safety signals in the EGFR patient population versus what we saw from the larger data sets in the second-line. So, very encouraging data that we're seeing here.

This drug is now approved. And again, the NCCN appropriately has recommended the use of datopotamab deruxtecan specifically for patients who are EGFR positive, who've had disease progression on osimertinib and chemotherapy.

A lot of new emerging data for TROP2 ADCs in the EGFR setting. A very high-level overview of sacituzumab tirumotecan. Now, it's an IgG1 TROP2-directed monoclonal antibody. It has a belotecan payload, a little bit different, but still a topoisomerase payload. And there's been two studies that have been looked at this, both out of China. The first is the phase 2 OptiTROP-Lung03 comparing sacituzumab tirumotecan to docetaxel in the third-line for patients that are EGFR-positive, and improvement in response rates, improvements in progression-free survival, and OS really immature, but trending towards improvement, for this phase 2 study looking at sacituzumab tirumotecan versus docetaxel presented at ASCO last year, 2025, and really showing a real benefit here.

Fast forward to the second study that was presented at ESMO 2025. This was looking at sacituzumab tirumotecan versus chemotherapy in the second-line for patients that are EGFR-positive who've had disease progression on a third generation TKI.

And similar to OptiTROP-Lung03, there was an improvement in PFS and really strong signal here for OS. Now, we need to remember that this data was out of China, and we would like to get a global patient population to look at this but the bottom line here is that we're seeing really significant signals here with this compound in the EGFR refractory setting, either in second-line or in third-line. So, really important to keep your eyes out for this compound and where it lands in our clinics. Further studies will be done.

So, we talked about the TROP2 ADCs in the second-line, not outperforming docetaxel. We talked about datopotamab deruxtecan now being approved in the EGFR setting, and we talked about sacituzumab tirumotecan as an emerging TROP2 ADC in the EGFR setting. Now, let's fast forward to where we're heading with TROP2 ADCs and really looking at them in the first line.

And at a very high level, there's been a couple of studies that have evaluated either sacituzumab govitecan in the first-line, or datopotamab deruxtecan in the first-line. And the bottom line is, both of these studies have shown some encouraging response rates in PFS, but they are non-randomized.

This is the phase 2 EVOKE-02 study showing encouraging responses with sacituzumab govitecan, either with pembrolizumab or with pembrolizumab and platinum in the frontline, showing encouraging response rates.

And then the study that I was fortunate to present, datopotamab deruxtecan, also combined with pembrolizumab or pembrolizumab with platinum in the first-line. This is a phase 1b study.

But showing feasibility of giving these in the first-line showing encouraging PFSs with doublet, encouraging PFSs and outcomes with triplet, the triplet being datopotamab-pembrolizumab-platinum, the doublet being datopotamab and pembrolizumab alone, no platinum. But we're seeing signals here that will need to be further validated in larger data sets.

These drugs are great and are eliciting meaningful activity, but we need to be mindful of toxicities. Specifically, with sacituzumab

govitecan, it's really about febrile neutropenia and diarrhea. For datopotamab deruxtecan, it's about ocular events, it's about ILD, and it's about stomatitis. Those are the AEs of special interest that we need to keep in mind.

There are multiple algorithms to help us manage all of these AEs. And I would just say, importantly, in your clinic, now that datopotamab deruxtecan is approved, please grade these symptoms. It's important to grade them first. And then, how to manage them really, is going to be evolving. I would say dose delays and reductions are important. Steroid rinses are also important preemptively for stomatitis, as well as ice chips during therapy.

ILD is one of those things we see with immunotherapy, but remember, a grade 2 ILD is permanently discontinuing the drug, which is a little bit different than immunotherapy when you have a grade 2 ILD. But certainly, remember to grade these and then look them up. The NCCN does a wonderful job helping guide you on management of these adverse events. So, really important, again, that we are educating our patients and asking them. Educating them what the signs and symptoms would be, and important for them to report us. For ILD, it's shortness of breath, it's cough, really important. For stomatitis, it's difficulty eating, it's mouth sores.

Ocular surface toxicity is certainly there as well. We again, need to grade them. Partner with your ophthalmologist. It's really important when patients come in with dry eyes or even increased lacrimation. These are things where you really need to partner with your ophthalmologist to help out.

So again, we have current approved therapies in this space. Datopotamab deruxtecan now approved in the EGFR setting. Need to be mindful of the adverse events that come along with that, but certainly there. Keep your eye out for sacituzumab tirumotecan. We'll also see that drug, see how it performs in the EGFR space in a global population. And then really, it's all about grading the AEs with these compounds, and it's also about partnering with our subspecialists to help mitigate some of these toxicities.

Thank you so much. And it's a pleasure for me to be able to deliver this exciting new class of compounds in the non-small cell lung cancer space, specifically for now in the HER2 and the EGFR-positive space.

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