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The Evolving TROP2-directed ADC Landscape in Metastatic NSCLC

Announcer:
Welcome to ReachMD. This activity, titled “The evolving TROP2-directed ADC landscape in metastatic NSCLC” is brought to you by COR2ED and is supported by an Independent Educational Grant from AstraZeneca.

Dr. Lim:
Hello to everyone who's joined us today. So I'm going to be briefly talking over these next couple of minutes on the relevance of TROP2-directed therapy in metastatic non-small cell lung cancer, particularly in the context of antibody-drug conjugates. I'm going to touch a little bit on the biology and also some of the drugs that are gaining interest in this rapidly evolving landscape.

So why do we look at TROP2? Essentially, TROP2 is a transmembrane glycoprotein that's overexpressed, we know, in multiple solid tumor tissues. And in the context of non-small cell lung cancer, it's expressed in about 64% of adenocarcinomas and 75% of squamous cell carcinomas. And it's really this broad expression that makes it such an attractive target for antibody-drug conjugates. But, you know, it's not just in lung cancer that we see this TROP2 expression. We're also seeing it in a wide variety of other tumors, and that really explains why there is such an enlarging global program for these ADCs in oncology.

So what are antibody-drug conjugates? Essentially, these are specialized targeted forms of drug delivery. They consist of an antibody, a linker, and payload. So the antibody targets the antigen expressed on the tumor cell, in this case TROP2. The antibody is then internalized, and the linker is cleaved, and the payload released into the cell, causing cell death.

And one of the phenomena that you might, you know, hear us as oncologists bang on about is the bystander effect. And essentially this is when the payload is released into the tumor microenvironment, and you get cell death in antigen— in tumor cells that don't actually present high levels of the antigen. And it's a phenomenon we can manipulate and essentially target with these newer antibody-drug conjugates.

So currently globally there are probably three main drugs of interest in development in non-small cell lung cancer. All of them target TROP2, but they're quite different. So we've got sacituzumab govitecan, we've got datopotamab deruxtecan, and sacituzumab tirumotecan; quite a mouthful, and so we call them by the smaller names SG, Dato-DXd, and sac-TMT.

Essentially, they're all TROP2-directed drugs, but they differ quite substantially. So they differ in their drug-antibody ratio, they differ in their linker technology, and they differ in their payload biochemistry. And that's really important because it therefore shows that they've actually got different efficacies, they've got different toxicity profiles, which you will see later on in the talk, and essentially they've got different bystander antitumor effects. So yes, of course, they all belong to the same class of drugs, but actually you can't treat these drugs in the same way, and that's key.

This is my final slide before I'm going to pass it on to Professor Girard, who's actually going to talk about more of these ADCs and in detail the clinical trials that we're looking at. But essentially what we've shown is that TROP2, it makes sense to target TROP2 in non-small cell lung cancer because of its broad expression. We've seen that there's a lot of traction in terms of the drugs that are coming out looking in this area within lung cancer, and it'd be really interesting to see where these drugs sit once some of these big clinical trials read out in terms of our treatment landscape.

Thank you so much.

Dr. Girard:
Well, thank you, Louise, for this introduction. And now we will move to some of the clinical data, and I will first discuss the patients

without actionable genomic alterations.

We know that these patients may receive in the second-line setting docetaxel, which is a standard of care for the patients. Here is the algorithm from the ESMO Clinical Practice Guidelines for nonsquamous cell carcinomas. Docetaxel may be delivered as a single agent, and this is what we do in most of the patients, may be combined with some antiangiogenic agents, but at the end, this is docetaxel, which is the control arm in most of the randomized studies assessing the TROP2 antibody-drug conjugates in this second-line setting.

The first trial is the EVOKE-01 study with sacituzumab govitecan. So very simple design, sacituzumab govitecan versus docetaxel in patients who showed disease progression after platinum-based chemotherapy and an anti-PD-1 and anti-PD-L1 agent. The primary endpoint was overall survival, and this is a negative study in the ITT population. You can see that the patients have a similar overall survival curve.

There were some exploratory studies in the subgroup of patients with progression as the best response, so patients with a resistance to first-line treatment showing some more benefit with SG versus docetaxel, but at the end this is a negative trial.

With datopotamab deruxtecan, same population, second-line patients, TROPION-Lung01 is again randomization between Dato-DXd versus docetaxel. Most of the patients in this study had no actionable genomic alterations; some patients had, and Louise will discuss this later.

This was a dual primary endpoint, PFS/OS, in the ITT population, and this is a positive trial. We have a statistically significant benefit for PFS, although numerically it's quite limited. It's moving from 3.7 months with docetaxel to 4.4 months with Dato-DXd in the ITT population. We see here, looking at the histology subgroup, that the benefit is driven by the nonsquamous, and that the squamous cell carcinomas do not benefit from Dato-DXd. And subsequent development of Dato-DXd in lung cancer is restricted now to nonsquamous cell carcinomas. In the ITT population there was no difference in terms of overall survival, but again we see that nonsquamous cell carcinomas versus squamous cell carcinomas, we see the difference, and the squamous cell carcinomas clearly do not benefit from Dato-DXd in this study.

It's obviously interesting to look at the target of the antibody. As we discussed, it's one of the key components of the antibody-drug conjugate. So how to assess TROP2 as a biomarker? We have some data with this normalized membrane ratio, which is measured by quantitative continuous scoring. So basically this is IHC for TROP2, then an image analysis with a kind of artificial intelligence looking at expression of TROP2 in the membrane versus the global expression in the membrane and the cytoplasm.

And actually this score reflects internalization of TROP2. So the lower is the score, the better it is to predict the internalization of the antibody-drug conjugate. So NMR-QCS biomarker is considered positive if at least 75% of tumor cells have this low normalized membrane ratio. And when we apply this, which was developed in the landmark phase 1 study with datopotamab deruxtecan, when we apply that to TROPION-Lung01, we see here a significant benefit in those patients with TROP2 QCS NMR-positive in favor of datopotamab deruxtecan versus docetaxel. This is a hazard ratio of 0.52. So this is probably the subset of patients who clearly drive the benefit for the datopotamab deruxtecan versus docetaxel. You move from 4.1 months to 7.2 months. So this is also clinically meaningful.

We see that the safety profile of datopotamab deruxtecan is very clear now. We have some gastrointestinal disorders, hematological disorders, mostly grade 1-2. The adverse events of special interest include stomatitis, ocular events, and ILD. And this will be further discussed later in this webinar.

TROPION-Lung17 is actually replicating the design of TROPION-Lung01 in patients with TROP2 NMR-positive nonsquamous cell carcinomas to further demonstrate and validate these findings regarding the predictive value of TROP2 QCS-NMR in this second-line setting population.

How to move to first line, where the standard of care for most of the patients is chemotherapy plus immunotherapy, or immunotherapy alone in patients with high expression of PD-L1? Well, we have some data from phase 2 studies, starting with SG. This is the EVOKE-02 trial. Interestingly, here you have some complexity regarding first the histology, but also the PD-L1 expression status. Here in EVOKE-02, we add a combination of SG plus pembrolizumab in patients with PD-L1-high expression, and you also have some combination of chemotherapy, carboplatin plus pembrolizumab plus SG; SG kind of replacing pemetrexed or paclitaxel that we give as a standard of care in those patients.

What is of interest is that we see that we have some efficacy here in patients with a combination of SG plus pembrolizumab, 77% response rate, which is higher than what we have with pembrolizumab as a single agent in the landmark KEYNOTE-024. This is a 45% response rate, median PFS 13 months with combination in patients with a lower PD-L1 expression, clearly we have a lower efficacy, so not sure that those patients with a lower efficacy of PD-L1 actually derive a benefit.

The combination is considered feasible, even if we have some treatment-related adverse events, grade 3 or higher, reported in the

majority of the patients. So very important to also have this proactive management to make this combination feasible.

EVOKE-03 is a phase 3 randomized study in PD-L1-high patients randomizing SG plus pembrolizumab versus pembrolizumab, with PFS and OS as primary endpoints.

With datopotamab deruxtecan, we have similar strategies here in the phase 1b studies, TROPION-Lung02, TROPION-Lung04, basically looking at combinations of datopotamab deruxtecan plus pembrolizumab, or datopotamab deruxtecan plus durvalumab, or the triplet datopotamab deruxtecan plus pembro plus chemotherapy, datopotamab deruxtecan plus durvalumab plus chemotherapy. So multiple cohorts. The final dose for this combination is probably the 6-mg/kg, and we have here some of the key data. Interesting to see that whatever is the PD-L1 status, for the doublet or the triplet, we have quite high response rates, higher than 50%.

Look at the figures, the numbers of patients remains limited for the PD-L1-high patients. We see that with the doublet we reach a median PFS of 11 months, which is higher than what we have in historical studies. Not sure that the triplet is actually adding some additional efficacy, but this needs to be confirmed. And again in this TROPION-Lung02 study, we see the value of the TROP2 NMR-QCS, with the patients with a positive biomarker having a more prolonged PFS as compared to the patients negative for the biomarker.

Again, feasibility. We have a quite high number of patients showing grade 3 or higher side effects, mostly related to datopotamab deruxtecan, and so again it showed that it requires some more proactive management of the expected adverse events. Actually, for the doublet, less than 10% of the patients had serious treatment-related adverse events. Again, with the triplet, we see that more patients will show some of these side effects, mostly related to chemotherapy.

At the end, we see high response rates with the doublet, with the triplet, so it shows that we are probably increasing the efficacy of the standard of care when making these combinations.

TROPION-Lung04, in combination with durvalumab, we have similar data in this setting.

So we are waiting now for the phase 3 studies based on datopotamab deruxtecan in the first-line setting. We have the AVANZAR study, which is carboplatin plus datopotamab deruxtecan plus durvalumab, or datopotamab deruxtecan plus durvalumab, versus chemotherapy plus pembrolizumab. We have TROPION-Lung07 with a similar design, pembrolizumab being used as the immune checkpoint inhibitor for this study. Here, interesting to see that in these two trials, AVANZAR and TROPION-Lung07, not only the primary endpoints are PFS and OS in the ITT, but also in the TROP2 NMR-QCS-positive subgroup of patients.

We have TROPION-Lung08 in the PD-L1-high setting, here with the doublet datopotamab deruxtecan plus pembrolizumab versus pembro. And finally, TROPION-Lung10, which is Dato plus rilvegostomig, anti-TIGIT and anti-PD-1 bispecific immunotherapy.

So more to come in the first-line setting. We have this data suggesting high efficacy of these combinations. Now obviously we need to see these randomized studies.

With sacituzumab tirumotecan, we have this trial in patients with PD-L1-positive tumors, sac-TMT plus pembro versus pembro. We know that this trial showed a PFS benefit in favor of the combination and a positive trend for overall survival, but we need to see the data.

With sacituzumab tirumotecan, there are some combination trials that are ongoing, again focusing on the doublet sac-TMT plus pembro in patients with PD-L1-high. This is TroFuse-007, and in squamous cell carcinoma patients as maintenance treatment after chemotherapy plus pembrolizumab. So different strategies here on treatment sequencing for this sac-TMT-based combination.

With that, I will stop here and I pass it back to Louise for the patients with actionable genomic alterations.

Dr. Lim:
So in this section I'm going to be focusing specifically on the role of TROP2-directed ADCs in patients with genomic alterations, particularly EGFR mutations, because essentially this is the space that we're seeing the most mature and clinically relevant data.

So why look at TROP2 expression in EGFR-mutant disease? So what we've seen previously is that we have higher levels of TROP2 expression in EGFR-mutant disease compared to EGFR wild-type. We also know that TROP2 is enriched in TKI resistance states, and so it makes biological sense for us to look at these TROP2-directed ADCs on failure of our frontline TKIs.

This slide shows our current ESMO Clinical Practice Guidelines for EGFR-mutant non-small cell lung cancer. And as you can see, osimertinib forms the backbone for a lot of our frontline therapy regimens. And on progression, that's where it certainly becomes more challenging for us as clinicians as to what to do next. Historically, we've used platinum-based chemotherapy, but we know that that doesn't work that well, and essentially the question now arises as to whether or not we can use these TROP2-directed ADCs potentially in this setting.

So this slide shows the pooled data from the TROPION-Lung05 and TROPION-Lung01 study that Nicolas presented earlier. So this

looked at predominantly the EGFR mutation-positive patients, which we know formed the biggest cohort in the patients with actionable genomic mutations, and they received Dato-DXd on failure of frontline TKI and also platinum-based chemotherapy. So these were heavily pretreated patients.

And what we can see from the results is that we showed an overall response rate of 43%. We had improved PFS and also OS. And importantly, these were in patients who had prior osimertinib, so essentially you were seeing activity in, you know, resistant TKI states.

As shown from previous slides with Nicolas, you know the standard adverse events were seen, so nothing surprising. A majority got stomatitis, alopecia, nausea, fatigue, ocular surface events. But I guess what was reassuring is that there were low levels of drug-related ILD events, which, as you know, is an important adverse event that we as clinicians need to monitor. Most of AEs were grade 1 and grade 2.

This showed the results from the ORCHARD study. This was an early-phase study, and it looked at patients who had frontline osimertinib. We then challenged them with osimertinib plus Dato. And as you can see, results were encouraging despite it being an early study, improved PFS, and again similar adverse events, stomatitis, mucositis, but again low levels of ILD.

TROPION-Lung15 is the global phase 3 ongoing trial. It looks at patients who have progressed on osimertinib, who then go on to receive either Dato-DXd or Dato plus osi or platinum-based chemotherapy, and they've got dual primary endpoints. I think it'd be really interesting to see, you know, how this trial reads out, and certainly it's an area of interest for me because I've been running this trial at Barts.

Moving on to the other TROP ADC of interest, sac-TMT. This was the OptiTROP-Lung03 study. So this looked again at patients who had EGFR-mutant disease, who were heavily pretreated, having had platinum and a TKI upfront. They were then randomized to receive either sac-TMT or docetaxel. This trial was positive, and it showed that there was an improved OS, a median OS of 20.0 months in the sac-TMT arm versus docetaxel at 13.5 months, and there was also an improved PFS.

But interestingly, if you look at the toxicity and AE profile, it's different from actually Dato-DXd. And we kind of touched a little bit on this, and I'm sure Jacob and Stephanie will speak more about this a bit later, but you can see it was more hematological driven: anemia, neutropenia, alongside stomatitis and alopecia. But again, what was important was that there were few cases of ILD and pneumonitis.

This was the OptiTROP-Lung04, which moved the treatment paradigm a little bit earlier. So this was on failure of TKI, where they then got either sac-TMT or platinum-based chemotherapy. And again this was a positive study. Median PFS 8.3 versus 4.3, hazard ratio of 0.49. You know, overall response rate in the sac-TMT arm 60.6 versus 43.1, and you know, this was a consistent benefit that they saw across all the predefined subgroups. Again, the AEs were expected, hematologically driven, and with, you know, maybe some GI toxicity, some ocular surface toxicity. But reassuringly, no drug-related ILD or pneumonitis in either arm.

These are the ongoing global phase 3 trials. The two trials that we spoke about earlier were predominantly run in China, and so these are the global studies that are looking to see whether or not sac-TMT will beat platinum-based chemotherapy in the second-line setting, and it's against docetaxel in the third-line setting. And so it'd be interesting to see how these trials read out.

Interestingly, there is a biomarker and patient stratification component to these studies, and I think that's right because I think we do need to be able to identify which patients we select best for these treatments.

Even more interestingly, we've got a frontline study with Dato-DXd, where, you know, we're ignoring the fact about upregulation and TKI resistance, and actually we're just putting it head to head with osimertinib against Dato- with Dato against osi on its own, and it will be really interesting to see how this comes out.

I'm now going to move on. Essentially, these are just questions that, you know, we think is important after Nicolas' and my talk about where we are in terms of the current future landscape strategies and where these TROP2 ADCs sit. I think the question is whether or not these ADCs with IO will replace IO monotherapy in PD-L1 more than 50%. I think the question is whether or not we feel we need to intensify treatments, or really do we take a more clever approach of actually selecting our patients to see who needs what.

For me personally, whether or not this survival improvement justifies the added toxicity that I'm giving to my patients—and that's important—and really where all these ADCs are going to sit, and how we best position them because, you know, God knows there are so many new drugs and bispecifics that are coming out, and we need to know how best and where to put these, and which patients to select.

Dr. Sands:
Thank you. And while the efficacy is overwhelmingly important, and now the toxicities really are the other side of that equation, of course, as well. So we're very happy to go through this.

So we'll start a little bit here, and then I'll be talking a bit about interstitial lung disease and mucositis, and Stephanie, my colleague, we work so closely together in managing these patients in clinic, will talk about ocular surface toxicity and some of the cytopenias and GI toxicities as well.

All right, so we'll jump into oral mucositis and stomatitis. Well, the oral mucositis and stomatitis, we see this particularly with datopotamab deruxtecan. We also see it with sac-TMT. Now, an interesting thing to me in these, you know, we look at those two drugs as well as sacituzumab govitecan. On paper, these all look the same—TROP2 antibodies, topoisomerase inhibitor payloads, cleavable linkers, you know, broadly they're the same. Sacituzumab govitecan, dosed day 1, day 8. We see an efficacy signal that looks a bit different with those.

And from a toxicity signal we see sac-TMT and Dato-DXd both causing mucositis, stomatitis, which we'll discuss, as we don't see that as much with govitecan. I think the interesting thing to me in this is that I think of these as being very much TROP2-directed toxicities, and so we're seeing from a toxicity profile that Dato-DXd and sac-TMT have TROP2-directed toxicities, which means to me they're more likely really actually hitting the target and getting internalized in those cells versus the toxicity of sacituzumab govitecan, which is kind of more irinotecan toxicity that also fits the irinotecan-style dosing schedule.

Now, this often occurs early in the process. And I think one of the things to highlight here is that this is when we look at any grade, then okay, this is high in numbers. Now, a grade 1 is not necessarily symptomatic. That can be an individual where we just see something in their mouth, but they don't otherwise know that they have it.

The other thing to keep in mind is that nobody has this indefinitely. We're not continuing treatment in patients that have symptomatic mucositis either, so in someone who's having symptoms, then you're going to pause until essentially it's asymptomatic. You may still see it, but otherwise they're not feeling it. And then at that point, depending upon how that's gone, I may consider a dose reduction as well.

Now, in the early signal that we saw from Dato-DXd, and we're starting at a 6-mg/kg dose level, but the 4-mg/kg dose level also showed real efficacy. So if we have to reduce the dose, then okay, we still have seen an efficacy signal from that. That's where I have the majority of experience when I'm speaking to that, but sac-TMT as well. If you need to dose reduce, then you dose reduce.

And someone who has kind of a very mild grade 2 that lasted for a couple days, I would not dose reduce, frankly, in that setting, and often the mucositis can improve as you get further into the treatment. But there are things that you can do to potentially help reduce this.

So here are the signs and symptoms of mucositis that you see on the left there when you're looking and seeing ulceration or a discoloration. Questions to ask the patients, whether they're feeling, you know, for what they're feeling in the mouth now. Obviously, you know, when we think of mucositis, I think the worst is when someone has, like, a diffuse pain that's there, and that can get in the way of eating, swallowing, talking. That can be issue, and you know, if someone's experiencing that, and if it's more severe, but not requiring hospitalization, you know, something where it's really bothersome for many days, you know, those are scenarios where I'd say, okay, once they are no longer symptomatic, even if we're delaying dose, saying, okay, now we should really consider a dose reduction in that setting.

And now there are things we can do to manage that, although there's still a lot for us to learn about this, but the easiest is the good oral hygiene, gentle brushing, daily flossing, a bland rinse, being well hydrated. These are all important things that are really more straightforward and easy. Now, ice chips—holding ice chips in the mouth during the time of infusion, in particular minimizing the amount of first-pass blood flow to the oral mucosa—and things like the corticosteroid-containing mouthwash, using an oral mouthwash that's a steroid, this is something that has shown benefit in other drugs that cause mucositis. So I think there's still a lot for us to learn about these mouthwashes, but something that I'd recommend, although to me this is not critical for use.

On the right side, there are certain things to avoid that may also impact mucositis, stomatitis. You know, alcohol is always one where for some patients having a drink occasionally is something that to them is really meaningful. I think it's very easy for us to just tell people to never have alcohol again while they're on treatments and such, and I hear some patients who have oncologists that they say have told them that. You know, I think there's a balance in this. Maybe from the start have some time where you're not drinking alcohol because that may impact the mucositis, stomatitis. But you know, someone's a few cycles in and everything has gone fine, and so something like that I really don't hold a hard line on, and I'd say, well, let's give it a few cycles and see how you do, and then maybe at that point having a drink sometimes is okay.

Here's a case to go through. A 65-year-old man, performance status 0, ultimately gets diagnosed with lung adenocarcinoma that's metastatic, EGFR exon 19 deletion, started first-line combination chemotherapy and osimertinib which worked for about 20 months before then having progression at multiple sites, at which point started Dato-DXd q3-week dosing.

At cycle 2, patient notes about 4 days of painful mucositis. So is still eating, able to tolerate soft foods, but has altered essentially what they're eating, maintaining stable weight, but symptomatic. This is a grade 2 mucositis.

So upon examination now at the beginning of the next cycle, patient says the pain has resolved, but on an exam you're seeing evidence of mucositis, so it's now a grade 1. What is the best next step at this point? Do you hold treatment, and they haven't done the steroid mouthwash, hold treatment, tell them to start that? Do you start antibiotics? Can you go on to initiate the next cycle now, given that they're asymptomatic, it's a grade 1, and really encourage better, more intense oral care? Or permanently discontinue Dato-DXd?

C is the answer. Continue treatment because the patient is now asymptomatic, it's a grade 1. It's okay if you see something. We're really talking about symptoms, and in this case, you know, 4 days, depending on the patient and some of the other details, I would probably continue the same dose in this case, given that it was 4 days, they've had many days now of feeling better, they're back to eating normally. This can improve with later doses, and so, depending on the scenario, I may give the same dose and monitor from there.

Here's some of the more data, and you see that 36% is grade 1 which is essentially asymptomatic, so there's about 33% that are having symptoms, and you know, 9% is grade 3, so this is as severe. And so it can be severe. This is something certainly to be aware of. But only 14% lead to dose reduction, 8% dose delays. So it's just to point out that even not all grade 2s really need to be dose reduced or even dose delayed.

We've gone a bit through the management already, and I've described this a bit as well. So essentially the grade 2 is where you get broad variation. These can have somewhat more symptomatic, in which case you really would need to dose reduce, and others that you don't.

So with that, I'll pass on to ocular surface events, but I think that was kind of the biggest of all these to go through.

Ms. Stephanie McDonald:
Thank you. All right, so I'm going to be covering ocular surface events. They're another important toxicity class with TROP2 ADCs, especially Dato-DXd. Fortunately, many of the events are mild, but they require vigilance because the symptoms can escalate if they're ignored.

So common symptoms that we see, mostly dry eyes, excessive tearing, blurry vision, eye irritation, maybe some light sensitivity. This is an area where nursing, APPs, allied health, really, the assessment can make a major difference in preventing progression of symptoms. So our goal is really to identify symptoms early and intervene quickly and try to keep patients safely on treatment. And patients may describe this as like sand in my eyes, or you know, tearing, light sensitivity, or just may say that their eyes feel different. So those descriptions should be a trigger for further assessment. We should be getting baseline eye exams for patients, especially on Dato-DXd. It does not—I want to stress that it does not—need to delay the start of treatment to have this baseline eye exam, but we do want to try to get these, you know, as soon as possible, before or around, like kind of within the first month of starting treatment.

So now I like this slide because it turns toxicity monitoring into real patient language, right? Instead of asking only, "Are you having any eye problems?" we can ask more targeted questions that you can see listed here on the right side of the slide to be able to inquire more detail. So symptoms to be able to listen for, any complaints of increased tearing, eye pain, any foreign body sensation, if they're starting to have like red eyes or vision changes, dry eye complaints, and light sensitivity, you know. For grade 2 or higher ocular surface events, we are referring to an eye care specialist. And it's important that you understand that it doesn't just have to be an ophthalmologist. I say eye care provider because it can also be an optometrist. So- and even grade 1 symptoms, they may warrant a referral depending on kind of the persistence and the severity of the eye complaint. So the prescribing oncologist or APP really should be notified for any new or worsening symptoms if they develop.

So this case kind of illustrates like a realistic presentation of ocular surface toxicity. This is a 64-year-old woman with metastatic EGFR exon 19 deletion lung adenocarcinoma. She received first-line treatment with carboplatin and pemetrexed, ended up having progression after 8 months, and then started Dato-DXd on clinical trial.

So by cycle 4 she ended up developing this gritty sensation in both of her eyes. She had this mild burning sensation as well, increased tearing and light sensitivity, but she did not have vision loss or eye pain. The symptoms are mild, but they are definitely classic for ocular surface irritation. The absence of vision loss or eye pain, it is reassuring, but it does not mean that we ignore this, you know. This is the moment kind of where early symptom support, all the supportive care measures, and a referral can be helpful in preventing worsening symptoms.

So the question for polling: patient receiving Dato-DXd reports this gritty sensation, mild burning, tearing in both eyes without the vision loss or eye pain. What is the most appropriate initial management? Is it A, continue treatment without intervention and reassess at the next cycle; B, optimize supportive care with preservative-free lubricating eye drops and refer to an eye care provider; C, are we going to

be starting topical antibiotic eye drops and hold treatment; or D, permanently discontinue Dato-DXd?

So the answer is B. We're going to, you know, implement supportive care early. We do not have to wait until ocular toxicity becomes severe before acting, so we don't need to be holding treatment on these patients.

Okay, so as far as prophylaxis and monitoring, you know, prevention and monitoring, they are key components to ocular toxicity management. So we need to be educating our patients before starting therapy about eye symptoms to report. We do not need to delay, again, the starting treatment for baseline eye exams, but we want to try to get them early in the course of starting treatment.

And we are making recommendations to avoid contact lenses, but I've actually heard from some eye care providers that I've had discussions with that this is not an absolute need to, but I think we are telling our patients to just out of an abundance of caution decrease like infection.

And then patients are using artificial tears and lubricating preservative-free eye drops, starting with the first treatment. You know, maybe use as prophylaxis or early supportive care, depending on kind of your practice, but then, you know, usually we're recommending the drops about four times daily as needed, and then if the dry eyes or symptoms increase or initiate, then we're going up to kind of eight times a day and as needed.

And then the baseline eye history, I think, really matters. Like, do they use contact lenses daily? Do they have dry eye at baseline? Do they have any prior corneal disease or glaucoma? This really may affect their risk and kind of the referral decisions and our collaboration with an eye care specialist earlier on when they start treatment.

And then just monitoring really should be ongoing because these symptoms can develop after several cycles, as in the case kind of we just reviewed.

And then just kind of this slide just emphasizes grading and dose management decisions for, you know, ocular surface events. So management is going to be dependent on the severity. And just to highlight kind of grade 1, that's where you're doing the supportive care measures and considering the referral to the eye care specialist. Grade 2, you're now getting these patients into the eye care specialist, and treatment may need to be delayed. For grade 3, there's a treatment delay and dose reduction after the symptoms improve. And for grade 4, urgent ophthalmology, and these patients' treatment is likely being discontinued.

So the practical point is that we should not guess this. You know, the visual symptoms require structured grading and really early involvement of eye care specialists.

And with that, I will pass it back over to Dr. Sands to go over ILD.

Dr. Sands:
We really haven't seen more than grade 3 ILD. Now, that's not to say that it's not symptomatic in some ways, but we've not seen grade 5 events within the EGFR population. You can see the grade is 8% to 9% with Dato-DXd, 2% with sac-TMT, not reported with sacituzumab govitecan, 3.7% with Dato-DXd at grade 3, but as I said, there aren't grade 5s.

Now, the big thing about ILD, one, is identifying it early. The challenge is that waxing and waning inflammatory findings are something that we can see, and so this is something to be aware of. If you see something that you don't have a better explanation for, I think you really have to consider this to likely be ILD. Here are some of the questions on the right and symptoms you're looking for, but broadly you're just looking for respiratory symptoms, and is there something inflammatory you're seeing on the scans?

Here's an example on the right side of a patient treated with carbo-pem-pembro, then started second-line Dato-DXd, and the on-treatment. Now, this is a more extreme example of the flare, and it doesn't always look so diffuse, and I think that can be one of the challenges, is even some minimal findings you could call a grade 1, even, you know, if they're not symptomatic, and so being aware of even a lesser view of that.

Here's another one that's a grade 2 pneumonitis. This patient was kind of mildly symptomatic, but that does make it a grade 2.

So the ILD is not something we fully understand. We do see this across the deruxtecan payload in other antibodies as well, and so maybe related to that, although within sac-TMT, we are seeing some degree of this as well, although not as significant for grade 2. In all the trials, the drug would be stopped indefinitely. Admittedly, you know, I think in practice, if I see someone who's minimally—like, on a very minimal end of grade 2—then this is something that I might consider restarting, but one needs to really be aware.

Essentially, the short of this is there are higher-dose steroids for higher-degree suspected ILD. So remember, grade 1 is asymptomatic, you're just seeing it on scans, but still giving steroids, doing the workup, involving pulmonology. If they're symptomatic, the steroid dosing is higher, but multidisciplinary workup is really important.

Ms. Stephanie McDonald:
All right, so just jumping into GI and hematology events in ADCs; they differ across ADCs, so we need to know kind of the expected toxicity profile of the specific agent. Just this comparison kind of reinforces that TROP2 ADCs are not interchangeable from a toxicity standpoint. Saci-G is kind of particularly associated with diarrhea and neutropenia, consistent with that SN-38 payload. Dato-DXd kind of has a different toxicity pattern. We're not really seeing diarrhea and significant like significant neutropenia in this patient population. And then sac-TMT also has important kind of GI and hematologic considerations.

So just jumping into this case kind of highlights early diarrhea and kind of emerging neutropenia in a patient on saci-G. So, a 64-year-old man, metastatic non-small cell lung cancer, no actionable mutations. He received platinum-based chemo and immunotherapy, and then docetaxel, then is now receiving saci-G on clinical trial. So after the first infusion, he ends up developing diarrhea about five, six times a day, mild cramping and fatigue. By day 8, his ANC is down a little bit to 1.1, but treatment ends up being administered.

So this is kind of the exact situation where early diarrhea should raise a little bit of a concern, and we're watching these people a little bit more closely. We're also seeing the ANC trending down early, which kind of matters, especially because infection risk can complicate diarrhea and dehydration. So this patient kind of needs a little bit more closer monitoring.

So they end up, you know, now five days after cycle 1, day 8, the patient now has eight or more watery stools in the day, some nocturnal symptoms, poor oral intake, some dizziness. You can see mild hypotension and tachycardia. So this, you know, has grade 3 neutropenia. This patient's kind of a mess. I might be strongly considering kind of admitting this patient if we can't improve their symptoms and vitals in clinic, but this is no longer kind of mild diarrhea. Eight or more stools a day and the nocturnal symptoms definitely meet kind of a grade 3 scenario.

So the differential is here. You need to consider, you know, is it drug related, you know, from saci-G? Is there an infectious process going on? What about, particularly given kind of the prior immunotherapy exposure, depending on the timing of that, we should keep that on the differential. But kind of the immediate priorities for this patient are to hold therapy, assess their volume status. We want to correct their electrolytes in clinic, send the stool studies, test ruling out infectious or viral causes of their diarrhea, and evaluate for infection. I would also probably consider sending a stool calprotectin to assess for potential ICI colitis, just to make sure we rule it out in this patient. I'd rather be safe than sorry. We have had some rare scenarios where even if it's been a while since they got immunotherapy, it can rear its ugly head. And then because he's neutropenic, fever education and infection precaution is critical. And then just in patients on ADCs, diarrhea and neutropenia is always like a higher-risk combination than diarrhea. So we're really supporting these patients with aggressive antidiarrheal regimen. Hydration is key and kind of potentially home electrolytes in this patient's situation.

Quickly, which supportive care strategy helps reduce the risk of neutropenia with saci-G? A, giving antibiotics to all patients; B, using G-CSF in high-risk patients; C, giving steroids before all treatments; or D, hydration only? I will say that B, I'm hoping everybody guessed B, using G-CSF in high-risk patients.

The heme toxicities can be silent until they become kind of clinically significant. So neutropenia is often kind of asymptomatic. So we're getting our CBC for monitoring. We should ask more comprehensive questions about fevers, maybe recent ED visits, recent use of antibiotics, any systemic complaints, sore throat, cough, urinary complaints. Just get a comprehensive history on these patients each time we see them.

You can see kind of some of the risk factors. If they've had baseline cytopenias or nutritional deficiencies or other recent cytotoxic chemotherapies, we're going to be assessing for symptoms like fever, chills, and looking for oral ulcers, any vital sign changes. And kind of this is where our assessment skills become critical to kind of identify infection or other things that are going on early for these patients.

And just this slide just kind of gives the management framework for saci-G- you know, related hematologic AEs. So commonly seen, like I said, neutropenia, anemia, less commonly thrombocytopenia. Really the kind of the diagnostic workup begins with that CBC, and before each dose of treatment. ANC less than 1 is considered grade 3 or higher neutropenia. We need to be evaluating for fever and infectious complaints, like we said. For grade 3 or higher, we're holding treatment. The G-CSF should be considered for prolonged or recurrent grade 3 or higher neutropenia or prior neutropenic complications. And then treatment can typically resume after recovery, typically if the ANC is at least like 1.5, we can do dose reducing for any recurrent grade 3 neutropenia.

So, you know, kind of just have proactive ANC monitoring and early growth factor support for these patients because they can help them stay safely on treatment.

I'm just kind of going to breeze through this, just kind of going over symptoms and asking those targeted questions, and then the high risk for these patients for especially for kind of assessing for nausea. Females—younger age females typically are higher risk, but you

want to be assessing for nausea and vomiting and be specific. If it's not just, "Are you having nausea?" but is it interfering with your ability to eat and drink and keep up with hydration and nutrition?

Using your grading and managing these patients pretty aggressively, you know, ruling out, like I said, other signs of infection. This is pretty similar to the information I went over before.

And then just kind of one quick note just about managing nausea and vomiting. You know, these slides really focus on kind of practical self-management strategies, things that they can do at home. Nausea is an important side effect. You know, we want to be proactive with these patients. Many centers now, I know we do, have the triple antiemetic regimen with many of these higher nausea-causing drugs. So typically a 5-HT3 antagonist, dexamethasone, an NK1 receptor antagonist. We're also implementing olanzapine kind of prophylactically, you know, not before treatment, but when they go home, we're starting it after treatment. So 2.5 to 5 mg nightly for about, you know, five or seven nights after treatment. We really, for nausea, just small, frequent meals, avoiding strong smells.

We want to just be able to support these patients. The best thing you can do is prevent nausea and be aggressive, especially for that first week after treatment. And just kind of reinforcing for them to call their team for any uncontrolled symptoms and a low threshold to bring these patients into clinic to be able to support them and make sure they're not having any signs of dehydration or weight loss.

Just, it really just takes a multidisciplinary approach to care. It's a kind of all hands on deck. The patients at the center of the care. And depending on the symptom, you know, we're referring these patients out and having good communication with all healthcare specialists. You know, we really need to be supporting these patients from head to toe, physically, emotionally, and just making sure they have what they need to safely stay on treatment.

Dr. Girard:
So thank you. And thank you for the great overview on the management of side effects. This is something that we have to learn for sure. We learned how to manage the cytotoxic chemotherapy side effects. We need to learn with these ADCs, and obviously it's quite different than what we are used to do, but it's a multidisciplinary setting management.

We have some questions on the chat actually regarding the TROP2 expression and whether there are some correlation between the TROP2 expression and the side effects, first question, and also the role for TROP2 expression in the current approval for datopotamab deruxtecan in EGFR-mutated patients. Maybe Jacob, you can answer some questions.

Dr. Sands:
Yeah. So interestingly, we have not seen a TROP2 IHC correlating with outcomes, and that's a little contrary to what we expected from the beginning. What we have seen, though, is now an AI-generated test, which is a quantitative continuous scoring normalized membrane ratio, essentially where we're looking at the presence of TROP2 on the surface level of the cell as well as within the cytoplasm and looking at a ratio of these.

Now to be a positive test, essentially what we're seeing is relatively more within the cytoplasm than what we see on the cell surface, which was a little counterintuitive, but I think likely represents increased internalization when that surface-level receptor is bound.

This is a test that was developed for nonsquamous non-small cell without actionable genomic alterations. What we've seen is that within the EGFR population, that test does not help, and I think the reason it doesn't help is because the receptor is so much more reliably internalized than in the nonsquamous non-actionable genomic alteration population.

So I highlight that, and I appreciate the question because we will see studies coming out that are incorporating this in an all-comer nonsquamous population. In the first-line setting, we have three different trials which will report this out, and so some familiarity with the biomarker, I think, will be valuable. There is a trial also enrolling in the second line, randomizing docetaxel to Dato-DXd based upon biomarker positivity, so that test you'll hear more about.

Dr. Lim:
Can I just follow up on that? And I think you're absolutely right, Jacob, when you say actually the side effect profile that we're seeing in these TROP2s isn't directly linked to maybe the expression, but maybe the bystander effect, and I think that that's key to this as well. And essentially, you know, it is the fact that these drugs are getting out of the cell and they're causing the side effects as opposed to a cumulative effect of the TROP2 expression.

Dr. Girard:
Yeah, I agree with you, and obviously waiting for the clinical trials in the first-line setting to kind of validate this QCS-NMR and obviously learn on how to implement that in the routine biomarker testing for the non-small cell lung cancer patients.

I think it's time now to make the conclusion of this webinar, and this is for you, Louise.

Dr. Lim:
So thank you, everyone, who's taking part of this webinar today. And as you can see, there's a whole lot of information around these TROP2-directed ADCs. I mean, clearly they're a very promising therapeutic group of drugs that are coming across the landscape of non-small cell lung cancer. You know, Dato-DXd has already seen FDA approval, as we know, following TKI and platinum-based treatment in the US. We've got sacituzumab tirumotecan that's approved in China, and you know, we're seeing, you know, consistent but manageable safety profiles, as illustrated by Jacob and Stephanie. And it is the challenging us as clinicians to say, look, you know, we know these toxicities exist, we need to recognize them early, and we need to intervene early, because if not, we're going to obviously affect the patient outcomes because the patients just will not take these drugs, and that is the true, you know, challenge for us. There are ongoing phase 3 trials, as we've seen, that I think will clearly say where these drugs are going to position in this very rapidly, a very exciting changing field of non-small cell lung cancer.

Thank you, everyone.

Dr. Girard:
Thank you.

Announcer:
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