From Research to Real World: Antibody Drug Conjugate, Immunotherapy Combinations, and Sequencing in Metastatic Non-small Cell Lung Cancer

CEC Podcast Transcript

Marina Garassino, MD:

Hello, everyone. My name is Marina Chiara Garassino. I am a professor of medicine at the University of Chicago, and thank you for joining us for today's program, From Research to Real World: Antibody Drug Conjugate, Immunotherapy Combinations, and Sequencing in Metastatic Non-small Cell Lung Cancer.

I would like also to thank Creative Educational Concepts for supporting today's activity. Creative Educational Concepts jointly accredited by ACCME, ACP, and NCCC, enabling high-quality continuing education for the entire healthcare team. Some content today may involve also off-label investigational uses, and we will disclose them as they come up.

So, before we want to get started, I think it's important to introduce ourself. And so maybe you can just get started to introduce yourself, Vicky?

Victoria Sherry, DNP, ANP-BC, AOCNP:

Sure. Hi, everyone. My name is Vicky Shari. I am an adult oncology nurse practitioner. I have a dual appointment where I practice as a nurse practitioner at Penn Medicine's Abramson Cancer Center in Philadelphia. I specialize in lung cancer, and I've been in that position for the past 19 years. And I'm also on the faculty at the University of Penn School of Nursing where I teach undergraduate and graduate nurses. Welcome.

Marina Garassino, MD:

Thank you so much. And Atif?

Atif Hussein, MD, MMM, FACP:

OH, yes. Hi, everyone. I'm Atif Hussein. I'm the medical director of a large cancer program down in South Florida where the weather is very nice. And I hold faculty appointments at University of Miami, Florida International University, and the Florida Atlantic University. And I lead a 15, soon to become 21, hematology-oncology fellowship program.

Marina Garassino, MD:

Thank you so much. And I just want to remind also that today, you will hear also some perspectives from Dr. Biagio Ricciuti from Dana-Farber Cancer Center and also Dr. Helena Yu, Memorial Sloan Kettering.

Here are all the disclosures. So I think we can get started for the most important part of the program that is going through... Dr. Hussein will start walking us through the entire evolution of systemic therapy in metastatic non-small cell lung cancer. Thank you so much.

Atif Hussein, MD, MMM, FACP:

You are welcome, Marina. It has been so exciting in the world of oncology for us in the last 10 to 15 years. It's my pleasure to discuss with you the antibody-drug conjugates. But before discussing that in detail, I want to

briefly frame where they fit in the evolution of systemic therapy in metastatic small-cell lung cancer. I still remember around 20 years ago when there was a plenary session in ASCO about the major benefit of adding paclitaxel to carboplatin. It was a plenary session.

First, we had chemotherapy. We began with the platinum droplets and the alkylator-based chemotherapy, but they had limited survival benefit, limited durability, and significant toxicity. And this was largely non-selective cytotoxic therapy. Then, we got to the targeted therapy area. There came molecularly targeted therapy, identification of actionable oncologic drivers, including so many now. They are growing by the day. EGFR, ALK, MET, and others. They have very high response rate if used in selected patients targeting those agents. This was our first move towards precision medicine.

Then, we had the immune therapy era, and how exciting that was. Immune checkpoint inhibitors improved the outcome versus chemotherapy in almost every study. It became the frontline standard in many settings. This expanded benefit beyond oncogene-driven diseases and now, the antibody-drug conjugate. They are smart chemotherapy. They targeted delivery of the cytotoxic payloads activity in biomarker defined and broader populations, and we'll talk about that a lot.

Emerging role in earlier lines of therapy. ADCs combine the precision of targeted therapy with the potency of chemotherapy. If chemotherapy was non-specific and targeted therapy was mutation-specific, ADCs represent targeted cytotoxic delivery, bridging both words.

In this slide, I would like to review the currently FDA-approved antibody-drug conjugate in metastatic non-small cell lung cancer. Like I said, this is growing by the day. But at least for now, as long as ADCs are concerned, all ADCs consist of three parts, like you all know. The antibody target, the linker, which is very, very important, and then the cytotoxic payload. Therefore, whenever you look at ADC, you need to know these three components of the ADC.

The first one we are going to discuss today is telisotuzumab. It's a c-MET antibody-drug conjugate. It's indication in previously advanced non-small cell lung cancer. The biomarker here is c-MET overexpression where more than 50% of the cells have IHC over three-plus. Now ,remember, this is very different than the c-MET 14 exonic mutation. This is protein overexpression where if you have it, you can use telisotuzumab vedotin.

Then, we have the ADC that we use in almost every cancer, every stage. It's easier to tell you which one we don't use rather than the one we use, which is the trastuzumab deruxtecan, T-DXd. It's indicated in previously treated metastatic non-small cell lung cancer with activating HER2 mutations. Again, it is the mutation here, although it is indicated with IHC 3+. I'll talk about that later on.

The payload here is topoisomerase 1 inhibitor, deruxtecan. It has a very high drug-antibody ratio of around eight, and it has a bystander effect. And that's why it sometimes works even when there isn't a lot of overexpression. In lung cancer, they approve the mutation driven, not HER2 amplification or IHC co-expression as in breast cancer.

The third one we will talk about in this slide is the datopotamab deruxtecan, D2DXT, which is a TROP2 antibody-drug conjugate. Again, it's active in EGFR-mutant disease after prior chemotherapy and EGFR targeted tyrosine kinase inhibitor. The payload is Topoisomerase 1 inhibitor. It represents expression into broader tumor antigen targeting.

So across the various ADCs approved in metastatic non-small cell lung cancer, these are the ones that they target the HER2, the TROP2, and the c-MET. Subsequently, I'm going to discuss the use of the major antibody-drug conjugate in non-small cell lung cancer, and these are the studies that are ongoing.

The two main targets now. They are, really, the TROP2 and the HER2. But like I said, c-MET is also coming on the screen to be a major target. telisotuzumab vedotin. The payload is actually MMAE, which is a microtubule inhibitor, which is really very unique, and it's called Vedotin. We have another Vedotin that we use in Hodgkin lymphoma where the payload, not Topoisomerase 1, but a microtubule inhibitor. And this is one of the few based ADCs, like I said, with this very specific payload.

Now, the payload may enter, and we'll discuss that in future slides, like how can we sequence these antibody-drug conjugates. Maybe if drugs have the same payload or they target the same target, maybe they shouldn't be used. But you know what? We really don't know a lot about the sequencing, but let's just discuss each one at a time now.

The HER2 trastuzumab deruxtecan, T-DXd, it is a topoisomerase inhibitor. As I said, it has really very high drug-antibody ratio of eight. Now, we can discuss, "Does this really matter because the others is like three to four molecules per antibody? If we tag on more payload to an antibody, does this result in better efficacy? Does this result in better bystander effect?" We will be able to discuss that.

The TROP2 is definitely becoming a very active target in antibody-drug conjugates. We have two of them. The datopotamab deruxtecan, that is approved, like I said before, in EGFR-mutant non-small cell lung cancer after using an EGFR TKI and after using platinum-based chemotherapy. Therefore, it's third line. It's second-line if you use both. If you use TKI and platinum-based, you can use it as a second-line.

HER3. HER3, I really was very excited about patritumab deruxtecan, and I honestly believe this was going to be a major antibody-drug conjugate and a target. And although the phase 2 were very encouraging, as we all know, last year in ASCO 2025, the results of the HERTHENA-Lung02 trial was presented. This is in patients who received almost everything, and it was compared to Docetaxel. And unfortunately, the overall survival was the same in both the patritumab deruxtecan and chemotherapy. And that's why the company actually took their biologic application for approval of the market, at least in this group of patients. And I really hope that this will be pursued in more select actionable, targetable population of patients and not in everybody.

Marina Garassino, MD:

Thank you so much. I think that we can just take a look. First of all, I shared the enthusiasm that you shared of 20 years of incredible research in non-small cell lung cancer, where when I started practicing, there was only this place in gemcitabine and cisplatin/pemetrexed. And now we are talking about doing multiple choices for our patients and the last baby where the antibody just conjugates.

So I just want to review some clinical data. You reviewed very, very well the mechanism of action and also the need of testing. So the first, as you said, is the DESTINY-Lung02, where we have in the HER2 mutated population, we have an incredible response rate of 50% and 56% with the two doses. And now, we know also that we have also other drugs that are tyrosine kinase Inhibitors in this setting. So the future research here will be to decide which will come first.

Then, we have the Dato-DXd, and the Dato-DXd, we have to remember that the first clinical trial in the world-type population showed the benefit in terms of progression-free survival, but didn't show an overall survival

benefit. And we will review later also the QCS-NMR that is the new testing with the artificial intelligence that will become part of the future clinical trials with Dato-DXd in the world-type population.

And third, we have the use of Dato-DXd in very advanced lines with patients with antibody-drug conjugates, and there was a combined analysis that showed the benefit in particular in the population of EGFR non-small cell lung cancer after prior EGFR-direct therapy and also chemotherapy. And impressively, the response rate in this population that is already highly pre-treated is 35%, 36%, between 35% and 36% and 43%. And there is also some activity also for those patients with ALK translocation, so this population was represented.

And finally, we have the c-MET overexpressing population with Teliso-V. I think here, it's very, very important to say, again, that c-MET is not MET Exon 14 and is not MET amplification. Sometimes I see second opinions where there is some confusions. The c-MET overexpressing must be test with immunohistochemistry, while the MET Exon 14 is an NGS testing, and the same for the MET amplification.

So, here, we are talking about a test that must be done. We are doing a reflex at the University of Chicago. Must be done in the beginning of the treatment because this can represent quite a nice big population, and the response rate in this population is, again, 30%. So I recommend to start testing reflex both for HER2 and also for c-MET, all the patients with non-small cell lung cancer, because we have great results.

So we have an incredible number of new drugs that are happening in the field of non-small cell lung cancers, all the new drugs. And for this, I ask Dr. Hussein to go through all the data, so we can see one by one at least what is already usable today.

Atif Hussein, MD, MMM, FACP:

Thank you, Marina. I presented to you the data about the ADCs that are already approved, but there is a wealth of data available there that it's either under review for publication or even by the FDA. This slide summarizes the key investigational ADC trials in metastatic non-small cell lung cancer, primarily focusing on TROP2 directed agents. I will highlight the major signals rather than go through each number.

The EVOKE-01 trial, this was a phase 3 trial, post-platinum, post-immunotherapy, post-targeted therapy for actionable genomic alterations. The study was Sacituzumab Govitecan versus Docetaxel. Primary endpoint, overall survival. There was no significant overall survival improvement. The takeaway point here that the trial did not show significant improvement because it included patients from all groups on non-small cell lung cancer. This is really equivalent to the HERTHENA-Lung02 study... 03 study based on which patritumab deruxtecan did not show the same thing. Again, the lesson is when we do clinical trials, we need to not just include everybody, but rather a subgroup of patients.

Then, we have the EVOKE-02 because we learned from EVOKE-01 not to include everybody in EVOKE-02, but it's a phase 2. It's a first-line metastatic NSCLC without actionable genomic alteration. This is actually a phase 2 using sacituzumab and pembro, but we are learning from our colleagues in breast cancer because they are way ahead of us. They are not only in phase 2, they already published phase 3 ASCENT-04 in triple-negative breast cancer. But here, the overall response rate was the endpoint, and there was a major signal. The major signal is that patients with the PDL1 of at least 50%, 67% response rate, amazing, but less than 50... There were some responses, but not as high at 20%. Therefore, combination strategies may improve activity, particularly in PDL1 high disease, and that's exactly what the ASCENT-04 in breast cancer triple-negative showed.

Now, let's go to the OptiTROP studies. This is another TROP2 antibody-drug conjugate that is called sacituzumab tirumotecan. Let me call it sac-TMT phase 3 OptiTROP-Lung03. It included patients small EGFR-mutant non-small cell lung cancer after TKI and platinum. Very reasonable second line. The overall response rate versus paclitaxel was significant in favor of sac-TMT. 45% versus 15% is statistically significant. Again, very strong signal in EGFR-resistant disease.

The OptiTROP-Lung04 is a phase 3 that is post-EGFR-TKI setting, and there was an improvement in progression-free survival of 8.3 versus 4.3 months at a hazard ratio of around 0.5. This is one of the more compelling signals, actually, in metastatic and non-small cell lung cancer with EGFR-mutant disease.

Now, let's go to the TROPION studies, and they use Dato-DXd, TROPION-Lung02, and we'll talk that during the cases. First-line advanced metastatic non-small cell lung cancer. The doublet or triplet strategies with pembro with or without chemo management safety profile, there was an encouraging overall survival. The ADC here, they can be combined safely with frontline, especially immune checkpoint inhibitors.

The big picture here is that although there were mixed results in unselected populations, there were real strong signals in EGFR-mutant metastatic patients. A combination strategy is really the key. Also, moving these ADCs earlier. While not all the phase 3 trials have been positive, there is a clear cut about the EGFR patients, and this table in summary represents the maturation of ADC field from exploratory cell-free therapy to biomarker-driven and frontline integration strategies like we have seen in so many cancers.

Here, I'm going to talk about some of the investigational agents that are still not also in approval, and we talked about the c-MET Teliso-Vedotin. The TeliMET is actually a study going on, non-small cell lung cancer 01. It's a phase 3. Again, like Dr. Garassino said, this is about the c-MET overexpression 3-plus in at least 50% of the cells, has nothing to do with the mutation or amplification. And then we have the trastuzumab deruxtecan. We have DESTINY-Lung04 and DESTINY-Lung06.

Again, briefly, these are really of ADCs that are be brought the two hypotheses here to combine them and move them upfront because they have been proven to be very effective. Now, moving them upfront, we will encounter some issues, like how long to give them. Some of these ADCs are really hard to give for a very long period of time versus just monoclonal antibody or chemotherapy, which we can use for a long period of time. Therefore, there's a lot to learn, but this is so exciting now, ADCs at the forefront of metastatic non-small cell lung cancer, at least in the EGFR-mutant patients.

Marina Garassino, MD:

Okay. So as we consider these going to clinical trials and future sequencing strategies, we also have to consider the experience of the patients receiving these therapies. And so CE Concepts did a survey on patients and also caregivers to better understand which side effects have had the greatest impact on the daily life of these patients. The responses, I think that they provide an important context on how we think about the toxicity management, and I think that... Dr. Sherry, can you walk us through what we see here? I think you are the best person to comment on them.

Victoria Sherry, DNP, ANP-BC, AOCNP:

Sure. This survey shows really what worries patients and caregivers the most when dealing with side effects and symptoms, and I found this really eye-opening as a provider. So if you were to asked me this survey, I would've

said lung inflammation, pneumonitis, cough, shortness of breath. But you can see here how patients and caregivers, their worries are more focused on quality of life and physical symptoms. And I really think we have to think about this when we are managing these patients, and remember that we are treating the whole patient and that we are a team, and remember to... We need to put our priorities on... and align them with the patient's priorities as well. So this was a very interesting survey.

Marina Garassino, MD:

So I think that with this new wave of antibody-drug conjugates, we are seeing some toxicities that, I think, in the past, we have never seen with the other drugs, and I believe that they are more common as we were prepared. So if you, Vicky, want to go through the most clinical relevant toxicities, and also, I think it's important to flag when we can intervene also earlier and we can do something better for the patient.

Victoria Sherry, DNP, ANP-BC, AOCNP:

Absolutely. In patients with lung cancer, ILD symptoms, they can mimic so many other diagnoses, right? Tumor progression, pneumonia, pulmonary embolism. So when a patient reports a new or worsening dry cough, increased shortness of breath with or without a fever, those are definite red flags for me. I do not watch and wait. I hold the drug and evaluate immediately because early steroid intervention can prevent progression to something that could be life-threatening, as you said.

So if ILD is confirmed and the patient is asymptomatic, because sometimes we do pick up these things incidentally on routine CT imaging, or if symptoms are mild, like a grade 1 or early grade 2, we can treat and in select cases, consider rechallenge with very close monitoring. But with grades 3 or 4 events, we are looking at permanent discontinuation.

And when I think about ADC-related ILD versus immune-related pneumonitis, clinically, they can look almost identical at first presentation. That overlap is exactly what makes them challenging. Both typically present with a new cough, shortness of breath, sometimes low-grade hypoxia, and on imaging, you'll often see ground-glass opacities or patchy infiltrates. And there's no single defining radiographic feature that allows us to confidently say, "This is an ADC toxicity," or, "This is immune-mediated."

So distinguishing this overlap matters, because for many of our patients, these therapies, they receive them sequentially or even very close together. So when someone presents with respiratory symptoms, the question is not just like, "Is this pneumonitis?" It should be, "What is the mechanism driving it?" Treatment, again, will probably involve steroids in both cases, but the rechallenged decision is very, very different.

With IO pneumonitis, we sometimes rechallenge after complete resolution to a grade 1, especially if the patient is benefiting from therapy. With ADC-related ILD, particularly grade 2 or higher, permanent discontinuation is usually recommended and rechallenge carries substantial risk, so we need to be careful with that. So with ADC-ILD, I think structural lung injury, do not gamble. And with immunotherapy pneumonitis, I think immune inflammation, "Can we safely reset? Can we give this safely?"

Marina Garassino, MD:

Yes. Thank you. I think you said things perfectly. I think that in my clinical practice, but also sharing with my colleagues, the distinguishing the ILD that is ADC-related from other immune-related pneumonitis or

progression is not easy. And now, I think that we are also seeing an over-reporting of everything when the patients are using ADC that is like a bell to say, "Okay, I flag this because this can be an ILD."

And so this is the survey again for the healthcare professionals. And as you can see, several doctors and providers are saying that is challenging to attribute the ILD or the pneumonitis to the antibody to conjugate. And so I think that here, we really need a lot of education, education for the providers, education for the radiologists, and remembering also that the ILD is a restrictive disorder. For example, the pneumonia and pneumonitis are obstructive disorders. So working also with a pulmonologist, I think, is very, very important.

So, now, we spent quite a lot of time on the ILD, but I think there's another toxicity that can really create problems for the patient and can create problems also to the course of the diseases, the oral mucositis. So if you can walk through again what we can do actively for the mucositis, I think is great.

Victoria Sherry, DNP, ANP-BC, AOCNP:

Sure. So mucositis is a toxicity that really may seem minor at first, but it can quickly impact their nutrition and overall quality of life. So I always counsel patients starting with cycle 1 about proactive mouth care using the salt and baking soda rinses, the one to three ratio, and I ask them about their mouth pain or sores at every visit so that I can intervene before it becomes really dose-limiting.

In my experience, baking soda rinses are very effective. If needed, I will add in dexamethasone oral solution, half a milligram per 5-mls, and they swish 5-mls... swish and spit about three times a day. But also, educating our patients, avoiding alcohol-based mouthwashes, avoiding spicy or acidic foods, and making sure they're really staying well-hydrated, water and electrolytes, as hydration supports that oral mucose integrity.

For mild symptoms of mucositis, we can usually continue treatment with supportive care. And for moderate toxicity, I will hold treatment until symptoms improve to a grade 1, and then I will resume sometimes with dose modification depending. Grade 4 mucositis is a permanent discontinuation.

And then we have ocular toxicity. And as you noted, Marina, ocular toxicity for the profile... sorry, the provider survey, it was a side effect that they don't feel comfortable managing, and I think it's because it's just new and unfamiliar. When I had my first few patients on clinical trials with datopotamab and telisotuzumab, all my patients were seen by ophthalmology prior to their appointment. So this made managing the side effect super easy. Really, they would grade the toxicity, and my job was either to hold the drug or give the drug.

However, I don't have this luxury of having ophthalmology essentially on call when treating patients off trial. So I did learn through ophthalmology that ocular toxicity really often starts subtly and mild dryness, irritation, blurred vision. And I ask about vision changes at every visit and recommend starting a preservative-free lubricating eyedrops early on from their first symptom that they have.

In my experience, lubricating eyedrops tend to work better than the standard artificial tears, but that's just what I've seen in my practice. If patients wear contact lenses, they should switch to glasses during treatment to reduce the risk of infection. I encourage good eyelid hygiene, so I have them scrub with baby shampoo every night. And I also definitely get ophthalmology involved very early on rather than waiting for symptoms to escalate. And again, if their symptoms are mild, we can continue with treatment. If they're affecting their vision or functioning, we need to hold treatment. And with severe symptoms, we will discontinue treatment.

Marina Garassino, MD:

No, I agree. And then I think we should also educate the patients that sometimes, in particular, for those patients on Teliso-V, you see sometimes a change also in the face of the patients that really goes away once they stop the treatment. But I think that, again, the education here, I think, is crucial.

Victoria Sherry, DNP, ANP-BC, AOCNP:

Absolutely. I agree. I agree. And then a few other side effects of ADCs. Neutropenia. We commonly see this with sacituzumab govitecan and trastuzumab deruxtecan. And this is a 100% payload-related effect. So because of the frequency and potential severity of this adverse event, I'm proactive with all of my patients. Hands down, they get pegfilgrastim with every cycle. And this seems to work really well and keeps them out of the hospital from becoming immunocompromised.

Education here is critical. I think that's what we've been saying over and over. Patient education is critical here. I review neutropenic precautions carefully, make sure patients understand a call, and my rule of thumb is if you have a temperature of 100.4 or higher and you feel okay, call us right away. We'll bring you in for an evaluation. But if you have a fever of 100.4 or higher with shaking chills and you feel terrible, just go directly to the nearest emergency department. Sepsis is not something that we want to mess around with at all.

And then another unique toxicity to ADCs is peripheral neuropathy. It's commonly seen with telisotuzumab, and this is a slow progressive toxicity, and I find this toxicity incredibly difficult to manage. So, at every visit, I ask about numbness, tingling, burning, pain in the fingers and toes, and neuropathy typically follows a classic stocking glove pattern. So it starts at the tips of their fingertips or toes, and then it moves proximally.

I also ask if they're having discomfort, if it keeps them up at night. That's a big red flag for me. Early on, if symptoms are mild and not functionally limiting, I'll just monitor them. And again, asking them at every single visit. But once it begins to creep upward or interfere with sleep, activities, daily living, for example, I always ask them, "Are you having difficulty writing? Can you hold a cup of coffee or tea? Can you button your clothes? Are you tripping or falling while you're walking?" That's when I intervene. And at that point, I will initiate duloxetine, 30 milligrams daily for a week. And then if they tolerate that, I will increase it to 60 milligrams daily and keep them there.

I also discuss dose modification if symptoms are progressing. And several of my patients pursue acupuncture as well to treat their neuropathy, and many report meaningful benefit from it. So it's something to keep in mind. Unfortunately, it's not covered by all insurances and can be incredibly expensive. But if it is covered by insurance, I think it's an avenue that they should pursue, for sure. So, across all these toxicities, my general approach is very consistent. I anticipate them, educate patients clearly about what to report, and intervene at a grade 1 rather than reacting at a grade 3.

Marina Garassino, MD:

Oh, thank you so much, and I agree. And it's a learning curve experience for all of us. So I think also the centers that had the clinical trials may be treated, just maybe limited the number of patients. So as we did for other toxicities in the past, I think we will improve also in the management of all of them. And so now that we have reviewed the emerging toxicities and also some practical approaches for this kind of toxicities, let's bring all of that together in the context of a real worst scenario. And Atif, can you walk through the first clinical case?

Atif Hussein, MD, MMM, FACP:

Thank you so much. Yes, I will be glad to. Our patient, Sylvia, is a 58-year-old woman with metastatic non-small cell lung cancer, bilateral pulmonary nodules, extensive mediastinal lymphadenopathy, but no evidence of CNS disease. She is symptomatic at ECOG performance status of one most because of the extensive mediastinal lymphadenopathy. She's a former smoker, but she quit 20 years ago. She's 30-pack years. Comorbidities, she has some diabetes with grade 1, 2 peripheral neuropathy and intermittent exertional dyspnea since the diagnosis.

The pathology showed that her PDL1 score of CPS is 80%, and she was found to have an actionable genomic alteration of EGFR Exon 20 insertion and mutation. The patient received palliative radiation therapy during mediastinum because she was very symptomatic. First line in this patient is carboplatin, pemetrexed, pembrolizumab. Partial response, but unfortunately she progressed five months later. Second line, amivantamab with lazertinib. She had a partial response for around seven months with some symptomatic improvement. Therefore, she had already two lines of treatment in the last one year. The question here is, which systemic therapy would you most likely recommend next?

Yes. When we asked the audience, the majority of them said as a third line, they will use another tyrosine kinase inhibitor, knowing this patient already received in second line lazertinib with amivantamab with EGFR Exon 20 insertion and mutation.

Marina Garassino, MD:

And we asked also the same question to Dr. Ricciuti in Dana-Farber. Let's hear what he says.

Biagio Ricciuti, MD, PhD:

This patient has received, as you mentioned, chemoimmunotherapy, and then the second line was the amivantamab-lazertinib combination. Upon resistance to the second-line therapy today, my personal choice would be datopotamab deruxtecan, and it's based on the TROPION-Lung05 study. They've shown a pretty robust response rate of 43% in patients with EGFR mutations.

Now, the label is now restricted to the common sensitizing EGFR mutation, such as excellent index lesion and L858R mutation, but certainly, this would represent a good option for this patient instead of, let's say, using a single-agent immunotherapy, combination immunotherapies, or potentially single-gene chemotherapies such as docetaxel, gemcitabine, that have a very low response rate in the 15% range and a median progression-free survival that's usually three to four months. So it's certainly suboptimal for this patient who has a young 58-year-old person.

Marina Garassino, MD:

So we have asked several people what they are thinking about, the doctors in the community, Dr. Ricciuti, and now we asked also AI. Let's see the result.

So as you can see here, there is the AI answer, ChatGPT, and the vote was for docetaxel plus or minus ramucirumab. So this is why I think that the artificial intelligence should not be used for clinical decisions. So we have already data saying that the TROP2 are superior to docetaxel plus or minus ramucirumab.

So I think in a case like that, like Dr. Ricciuti, I would go with Dato-DXd. Also, if sac-TMT is not approved yet, but you have to remember that we have two clinical trials that showed that the TROP2 antibody-drug conjugates are

superior to the standard chemotherapy and also to docetaxel. So, also, sac-TMT is not exactly the same as Dato-DXD, but Dato-DXd is approved. I think in this case, I would go, of course, with the antibody-drug conjugate with TROP2, and I'm curious to hear also my colleagues.

Atif Hussein, MD, MMM, FACP:

Yes. I will definitely pick up the Dato-DXd because of the overall response rate and the progression-free survival advantage in TROPION-Lung05, although there was a numerical improvement in over-survival, but it was there. It was not statistically significant. It was too early. Now, having always a clinical trial is really amazing. I love combining Dato-DXd with immune checkpoint, but there is actually TROPION-Lung10, which is a phase 3 evaluating Dato Deruxtecan plus REL-V, which is actually a very unique biospecific monoclonal antibody that targets both PDL1 and PGF.

Victoria Sherry, DNP, ANP-BC, AOCNP:

I don't have too much to add besides when I looked at this question, I thought of a TKI as the option too, and my thought was, "Let's look a little bit more into this patient. Let's look into her social support. Let's see if she has rides to clinic, because we're talking about an oral therapy versus an IV therapy. And really, what would be best for the patient?" We can present all the data to the patients, but it really comes down that it's shared decision-making ultimately, but I would also go with the datopotamab in my practice as well.

Marina Garassino, MD:

Yes. Thank you. And I think it's always important to refer the patients for the clinical trials. I think that potentially, all the options are here that are listed are feasible. So, also, the future will help to understand which is the best sequence for this patient, but the evidence, also, if we don't have head-to-head clinical trials about sequencing, is favoring the antibody conjugate.

Atif Hussein, MD, MMM, FACP:

Marina, may I ask you a question?

Marina Garassino, MD:

Yes.

Atif Hussein, MD, MMM, FACP:

What do you think the main mechanism of resistant to some of these ADCs? I don't know how much work there is because we really need to understand that at least so that we don't have to do a million clinical trial about sequencing. I mean, the possibilities are endless. What do we know about mechanism of action to better be smarter in designing sequencing clinical trials?

Marina Garassino, MD:

So, as you illustrated very well in the beginning, some antibody-drug conjugates must be internalized to be active. And this is the case of Dato-DXd and also of sac-T. Other ADCs don't need to be internalized. This is the

case, for example, of sacituzumab govitecan, and they work with bystander effect. So this is a major difference, and maybe this can be also reflected in the use of the AI biomarker. And then we have to recognize that the payloads are basically different types of chemotherapy. Also, sometimes they are very similar, so we will see. I think we'll be learning the curve for us in the future as researchers.

Atif Hussein, MD, MMM, FACP:

Thank you.

Marina Garassino, MD:

So now that we have reviewed how can be difficult to make a decision in 2026 based on the data that we have, the uncertainties, the efficacy, the toxicity, and other things, we can go through another case if... Dr. Sherry, do you want to go through the new case?

Victoria Sherry, DNP, ANP-BC, AOCNP:

Absolutely. This is Peter. Peter is a 62-year-old man, newly diagnosed, non-squamous metastatic non-small cell lung cancer, has bilateral pulmonary nodules, bulky mediastinal lymphadenopathy, and no evidence of brain metastases. He has a very good performance status. He is a former smoker, 25-pack years. He did quit though, so kudos to Peter. Comorbidities, well-controlled hypertension. He has a high PDL1 of 60%, and no biomarkers were identified on the initial testing of his tissue.

Marina Garassino, MD:

So take a moment to select the option that in your opinion best reflects how would you manage this patient.

Now, let's see how the contributors approach this case.

Victoria Sherry, DNP, ANP-BC, AOCNP:

We surveyed a community oncologist who felt that enrollment in a clinical trial of a TROP-ADC plus immune checkpoint inhibitor would be the best treatment option for Peter.

Marina Garassino, MD:

And now, let's go back and hear what Dr. Ricciuti from Dana-Farber is saying about this case.

Biagio Ricciuti, MD, PhD:

But for this patient specifically, without knowing the remainder of his genetic profile, I would likely lean towards chemotherapy PD1 inhibition combination. For example, carboplatin, pemetrexed, and pembrolizumab.

I think for the PDL1, more than 50%, for example, population as this patient, I think it makes a lot of sense to combine datopotamab deruxtecan and pembrolizumab. And as you know, there is a randomized phase 3 study that's ongoing, and that's a very reasonable and also rational combination.

So I do try to offer clinical trials to all my patients, and I think when patients are embarking on their journey and they're starting on their first-line therapy, that is one of the best setting where to explore new combination,

where the immune system is still naive to systemic therapy, is more intact, and where you have higher chances of a synergy with ADCs and immune checkpoint blockade.

Marina Garassino, MD:

Yes. And we did the same test again for ChatGPT 2, 5.2, and the answer was platinum chemotherapy and immune checkpoint inhibitors. Then, this was much more aligned to what I would have selected, and apparently, also better to the previous question to the ChatGPT. But let's see what my colleagues are saying about that. Atif?

Atif Hussein, MD, MMM, FACP:

Yes, I definitely... Marina, like you said, I will definitely give chemotherapy and immune checkpoint inhibitor to this person, even with a PDL1 more than 50% because Peter is very symptomatic. Now, whether we give a couple of cycles of platinum-based and then you give Ipi-Nivo or you give four cycles of carboplatin, pemetrexed with pembrolizumab, single agent, it depends on some other factors, but either one will be very reasonable. But I will not give this patient just immune checkpoint inhibitor without chemo because he is really symptomatic.

Marina Garassino, MD:

Thank you.

Victoria Sherry, DNP, ANP-BC, AOCNP:

I would go the chemoimmunotherapy route, for sure. But I think in my practice, we will offer them a clinical trial as their first option. And I think both, Marina and Atif, you have said that the importance of offering clinical trials provides access to novel therapies. And really, I think it should be viewed as a preferred option for eligible patients who we can enroll onto these trials, if not chemoimmunotherapy.

Marina Garassino, MD:

I completely agree with you. Clinical trials, clinical trials, clinical trials, because in this way, maybe we can give options to the patient and move forward the science.

So as we consider the TROP2 directed antibody-drug conjugate in our practice, biomarker interpretation is becoming really crucial, and so how are the clinicians are incorporating TROP2 expression into their decision-making? And I just want also to remind you that the TROP2 expression by itself didn't show too much in the selection of the patients.

Here is the survey, and as you can see, that I would still offer TROP2 directed antibody conjugate, I would consider alternative therapy, and I am unsure how to interpret TROP2 immunochemistry in this setting. And I think I would completely agree with the first option, because first of all, we have to remember that TROP2 is expressed in almost 90% of all lung cancer patients, and we have seen multiple papers showing that the TROP2 immunosuppression does not reflect the activity to these patients. And so to put these survey findings into context, we also asked Dr. Yu from MSK her perspective on the TROP2 biomarker expression. Let's hear what she has to say.

Helena A. Yu, MD:

I would love if there was a biomarker that selected for better response to TROP2 ADCs, but I think there's pretty convincing evidence that TROP2, the degree of TROP2 surface expression really does not predict response to the ADC.

Marina Garassino, MD:

Yes, it's something that I completely agree. It's important to remember that there is a biomarker that is called QCS-NMR that I presented a couple of years ago to the World Lung Cancer Conference that is a biomarker that is AI-driven. And now, this biomarker that is created by an automatic system that is able to distinguish the tumor and the non-tumor, and is able based on the mechanism of action of the Dato-DXd that must be internalized to be active is able to score the optimal density of the expression of TROP2 in the cytoplasm and the ratio between the TROP2 in the cytoplasm and in the membrane is creating positive and negative. And apparently, this biomarker is able to distinguish those patients who are active with Dato-DXd from those patients in which the Dato-DXd is not active.

This is a biomarker that can be used tomorrow morning in the clinical practice, so let's going back to another clinical case that is the case of a 66-year-old man with metastatic non-small cell lung cancer in a new onset of pulmonary symptoms. He has oxygen, 95%, or room air, no fever, no phlegm, and no other infection symptoms. And he gradually progressive dyspnea on exertion, new dry cough over the last two, three weeks, and the biomarker profile showed HER2 mutation, and imaging findings showed a new bilateral patching ground-glass opacity. There's interlobular septa thickening, scattered subcentimeter nodular opacities, and findings were not present on prior images. I think we don't have images of the CT scan here, but I always teach my fellows always to go and see with their eyes the CT scans.

So the first line was cisplatin, pemetrexed, pembrolizumab with disease progression, and the last dose of Pembrolizumab was given four months ago. And currently, the patient is receiving trastuzumab deruxtecan with partial response on first-line... on treatment imaging. So please take a moment to select the option that best reflects how would you manage this patient in your own practice.

Let's see how our contributors approach this case.

Atif Hussein, MD, MMM, FACP:

Based on the community oncologist response, the main response was to discontinue treatment and change systemic therapy due concern for disease progression.

Marina Garassino, MD:

Okay. Let's hear what Dr. Yu is saying about this case.

Helena A. Yu, MD:

And I think it sounds like he is symptomatic with dyspnea and cough, but is not requiring oxygen. So I would put that at a level that probably doesn't require acute hospitalization. Obviously, if somebody is newly hypoxic, sending them to the hospital. So, for him, I would definitely hold treatment. I think that we know that T-DXd has

a reasonably high frequency of pneumonitis as a complication, and so definitely, when you are considering pneumonitis on a differential whole treatment.

And then I probably would do both where I'd touch base with pulmonary, and if they were able to set him up for a bronchoscopy relatively urgently within a few days, I might hold off on steroids. But if they said, "Oh, I can see him next week, and we can evaluate," then I would start empiric steroids.

In the setting of no infectious symptoms, no white count, I feel less strongly about a trial of antibiotics. You certainly could try. If anyone had increased sputum, or green sputum, or low-grade fevers, or a white count, then definitely, I'd be treating for infection as well. So it really depends on... I'd like the patient bronched. So if they can be bronched quickly, I would probably just proceed with that to get a gold standard diagnosis of what's going on. But otherwise, low threshold to start steroids.

Marina Garassino, MD:

Yes, I completely agree with what Helena said. So I think that also in my clinic, I hold the treatment. I am spoiled because it's very easy to have a bronch. So anytime that I have a case like this one, I start immediately with a bronch. Otherwise, I start again with steroids, unless there are some inflammatory symptoms, and I try always to involve the pulmonologist from the beginning in the case.

Atif Hussein, MD, MMM, FACP:

Marina, regarding the treatment, let's suppose this patient progressed on T-DXd. Have you used a TKI, like zongertinib or zanucutinib, post T-DXd and got responses?

Marina Garassino, MD:

Yes, we have some data on tyrosine kinase inhibitors after T-DXd. And while we don't have data of the opposite of T-DXd after the tyrosine kinase inhibitors, also, here, I think it's important in the future to try to understand which is the best sequence for these patients. But I think to your point, I think that the tyrosine kinase inhibitors in the case of an ILD can be a relevant option.

So I think we have done three cases, and we have seen how meaningful variation and how different contributors approach sequencing, trial enrollment, toxicity attribution. I think this is a study that will continue for, I think, at least until I will be retired. And rather than viewing those differences as right or wrong, I think that they offer insight into how evolving evidence is interpreted in the real-world practice. So let's summarize what each group has taught us. Vicky, do you want to go through?

Victoria Sherry, DNP, ANP-BC, AOCNP:

When we think about our patients, tolerability often drives decision-making just as much as efficacy. And the fear of serious or permanent toxicities, whether it's neuropathy or ILD, it can really significantly influence a patient's willingness to start or continue therapy. And that's why we've said this over and over again. Clear communication is essential. Patient education is essential. And we need to explain not only to the patients what to monitor for, but also let them know what side effects are reversible, how we can intervene early, and how closely the patients will be followed by us. So, ultimately, treatment selection must balance clinical benefit with the anticipated impact on their quality of life.

Marina Garassino, MD:

Yes. And Atif?

Atif Hussein, MD, MMM, FACP:

Yes. I mean, this has been a great discussion. I think we oncologists, and advanced practice nurses, and physician assistant, and our chemo nurses... Now, we call them “immunotherapy nurses” because our ED doctors, we need to educate them about all of this. It took us decades to teach ED medicine about neutropenic fever. And now, they see our patients, Marina and Vicky, and they are not vomiting, their hair is still on, their CBC is known. It's like, "You are fine. Go home." "I cannot breathe." "I will give you azithromycin." But they are really very quick to learn, and our next generation of physician is very important to learn.

I like to teach them where we were and where we are now, and it's so exciting where we are now. I think doctors and all healthcare professionals who are involved in cancer care, they really are special people. They really are into this field because they are special. They want to do something special, or else they will never be in it. And they all want to learn. And we learn from each other because no two patients are the same, like we are discussing. It's not the same sequence for everybody. Like Vicky mentioned, it's the toxicity, the quality of life, the economic, the driving. They all enter into the picture, and that's why it takes a village to take care of a cancer patient, and we are all very, very, very proud to be members of that village.

Marina Garassino, MD:

So thank you so much. I always think that what you say is completely true. And also during these couple of hours that we spend together, I learned so many things from you. I think my final message are... First of all, as I teach to the fellows, test, test, test, because if you don't test, you don't treat. So I just want to put again the accent on the importance of testing for c-MET in the immunohistochemistry that is not still widely used. And the same for HER2 immunohistochemistry together clearly with NGS and also with PDL1.

So testing is crucial to make the right decisions, and understanding the toxicity is important because we have seen that maybe the doctors are scared, and they stop the treatment too early because they are scared to have toxicity. So testing and learning the toxicity will help to shape better decisions for our patients. And having said that, I think that we heard now so many nuances on sequencing and toxicity. And Vicky, I will hand this over to you again.

Victoria Sherry, DNP, ANP-BC, AOCNP:

So, on this slide, you can see at the center of the model is, of course, the most important person, which is the patient. But surrounding the patient is an interconnected care team that contributes at different points along their treatment trajectory. A medical oncologist leads the systemic therapy decisions, but also relies really heavily on close collaboration with pathology and molecular diagnostics to ensure accurate biomarker identification and reassessment.

Radiology to help distinguish progression from treatment-related toxicities, which we've touched on frequently throughout this presentation today. Pulmonology. Again, we brought them up, particularly when evaluating suspected ILD or pneumonitis. Ophthalmology for ocular monitoring with certain ADCs. Pharmacists, oncology nurses who are critical for toxicity education, early detection, and dose modification guidance. Radiation

oncology and thoracic surgery when multimodality input is needed. And very importantly, we must integrate both palliative care and primary care providers to support proactive symptom management and optimize comorbid conditions.

As therapies become increasingly targeted and complex, coordinated communication across the care team becomes just as critical as the treatment themselves. I'm sure all of you reach out to primary care and all of the consults when you're dealing with all these adverse events, and so very important to include them and part of the team.

Marina Garassino, MD:

Yes. And I would add also the importance of the APPs and the nurse navigators because they are sometimes the people who are closest to the patient. And so the identification and the treatment of the side effects is crucial for the success of the treatment.

Victoria Sherry, DNP, ANP-BC, AOCNP:

Yes. Marina, thank you for bringing up nurse navigators. They're usually the first point of contact for our patients, and then they are... Throughout their treatment, they reach out to them frequently. So, yes. Thank you for bringing them up. They're key players on the team.

Marina Garassino, MD:

So I think... Thank you so much. I think as we close, the question becomes, what do we do differently starting tomorrow? And the SMART goals are designed to move beyond the knowledge and into implementation. And Dr. Hussein, can you walk us through these goals?

Atif Hussein, MD, MMM, FACP:

This slide focusing on translating discussions like this into action. We can keep on talking, but we need to put this into action using the SMART goals, which stand for Specific, Measurable, Achievable, Relevant, and Time-linked objective.

First, we aim to increase comprehensive biomarker testing and review, like you, Marina, have emphasized a couple of times, in patient with metastatic non-small cell lung cancer before selecting second and later-line treatment. This ensures optimal sequencing and targeted opportunities.

Second, we want to expand the appropriate ADC utilization, selecting patients based on tumor biology, prior therapy, and performance status. Third, we will proactively screen for ADC-associated toxicities, including ILD, ocular toxicities, mucositis, cytopenias during routine visits, not just when patients report symptoms. This is really important. If you don't ask and you don't try to find, you will never find something.

Fourth, we must improve timely differentiation between ACC toxicities and immune-related adverse events. Easier said than done, but Marina and Vicky both actually elaborated in that, especially in patients previously treated with immune therapy, because as we know, toxicity of immune therapy can happen month or even a year after you stop treatment completely.

Finally, we emphasize the multidisciplinary collaboration. And I mean, we mentioned all these people. I'm sure we forgot some. The pulmonologist, the ophthalmologist were managing these rare side effects. It took us time

to learn how to manage skin toxicity. Now, we are really very good in it, and now, we need to deal with the lung and with the ocular. The overarching takeaway is moving from awareness to structured implementation in daily practice.

Marina Garassino, MD:

So thank you so much, and I would thank both of you for this very interesting discussion today. If today's discussion raised additional questions you'd like to explore further, we encourage you to visit the website that you can see, ceconcept.com, for more information. And to receive credits for today's activity, simply follow the direction on the slide.

And I would like to thank you again for participating in this program. And we really hope that today's discussion enhances your confidence in integrating the antibody-drug conjugates into the management of metastatic non-small cell lung cancer. We really appreciate your commitment to improving patient care. And we are a community, so let's share our experiences, and we are all together. Thank you so much.