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Chairperson Perspective: Precision Payloads: Exploring ADC-Directed Therapies in HER2-Mutant and Overexpressing Lung Cancer

### Announcer:

Welcome to CME on ReachMD. This activity, titled Chairperson Perspective: Precision Payloads: Exploring ADC-Directed Therapies in HER2-Mutant and Overexpressing Lung Cancer is developed by AXIS Medical Education and is supported by an educational grant from AstraZeneca Pharmaceuticals and Daiichi Sankyo.

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Here's Dr. Joshua Reuss.

### Dr. Reuss:

Hello, my name is Dr. Joshua Reuss. I'm a Thoracic Medical Oncologist at MedStar Georgetown University Hospital in the Georgetown Lombardi Comprehensive Cancer Center. And today, we're going to be discussing antibody-drug conjugate-directed therapies in HER2-mutated and overexpressing lung cancer. So, with that, let's begin.

I think first, it's important to really review molecular testing, the clinical value and implications for HER2 testing in non-small cell lung cancer.

So, first and foremost, HER2 is a rather diverse oncogenic driver in cancer in general. HER2 itself, it's a receptor tyrosine kinase encoded by the ERBB2 receptor tyrosine kinase 2, or ERBB2 gene. This is activated via hetero and homodimerization with other family members with subsequent activation of downstream signaling pathways, PI3K/AKT/MEK activation, that promote oncogenesis and growth signaling.

There are 3 key types of alterations observed across solid tumors. One are HER2 gene mutations. This is what we most commonly are talking about in non-small cell lung cancer. HER2 gene amplifications, and then HER2 protein overexpression. The latter 2 we talk about more commonly in GI malignancies and breast cancer. In lung, we tend to think of HER2 mutations occurring in about 1 to 3% of patients.

So, how do we look for these genomic alterations? Obviously, we need to test for these because if we don't test for them, we won't know that they're there. It is absolutely critical to perform next-generation sequencing and genomic testing, really in all stages of advanced non-small cell lung cancer ranging from resectable to advanced. Comprehensive broad next-generation sequencing is our gold standard, utilizing both tissue and blood-based platforms. To assess HER2 mutations, again, comprehensive next-generation sequencing, or NGS, is preferred. However, some older platforms, Sanger sequencing, and targeted PCR techniques also can be utilized. Now, it is absolutely important to wait for these results before beginning systemic therapy in advanced non-small cell lung cancer. There's actually been data to support that waiting for these results actually associated with improved survival in advanced non-small cell lung cancer. However, if you're in a clinical scenario where you just can't wait, someone has significant symptoms, signs of organ dysfunction. In that scenario, I will deploy chemotherapy alone, which can oftentimes provide some cytoreduction allow you that time to wait for the results of the next-generation sequencing, before proceeding with appropriate molecular profile targeted therapy,

whether that's a targeted treatment or a chemoimmunotherapy treatment. And in general, these next-generation sequencing tests, tissue tests, tend to take about 2 to 3 weeks, calendar weeks to come back, and then the liquid tests may be more like 7 to 10 calendar days.

So, this is taken from the NCCN Guidelines just talking about biomarker testing in advanced non-small cell lung cancer. You can see that next-generation sequencing molecular testing carries a Category 1 recommendation for adenocarcinoma large cell non-small cell lung cancer, and non-small cell lung cancer not otherwise specified. It is also part of the guidelines for squamous cell non-small cell lung cancer, though it does not carry the Category 1 recommendation. I will say though, that in my practice I do obtain next-generation sequencing on patients with squamous cell non-small cell lung cancer, as well.

So, let's talk a bit further detail about tissue versus plasma-based testing considerations. So, for tissue, this is typically run on formalin-fixed paraffin-embedded samples. Typically cytopathology preparations, not processed by FFPE methods are not accepted, though I will say that for bronchoscopy samples, if you do get sufficient tissue with an FNA, as long as that can be put into a tissue block, that usually is sufficient, and even sometimes highly cellular pleural effusions can be turned into blocks sufficient for testing as well. But primarily, you want to make sure that you're getting sufficient tissue and really trying to limit your IHC testing so as to preserve tissue for next-generation sequencing.

Circulating tumor DNA, or ctDNA testing. This is liquid testing that, I tend to obtain upfront in conjunction with tissue testing. This also, very important platform to utilize. Oftentimes can come back quicker, and get you an answer sooner, when it comes to actionable driver mutations. And again, data does support the complementary use of ctDNA testing with tissue testing to reduce turn-around time and really increase your yield.

So, I think I told you my preferred method, which is to obtain tissue and liquid testing concurrently. This is one other algorithm that you can utilize. Whereas, if tissue testing is available for genotyping, and tissue is adequate, you can, for one, obtain concurrent testing as I do, or you could obtain the tissue testing and then wait. And if it's inadequate, then pursue liquid testing. Now, if tissue testing is inadequate, then one can, again, obtain liquid testing first, followed by tumor tissue testing. They can obtain repeat biopsy and then do tissue, followed by liquid, though again, if your current tissue sample is insufficient, I do tend to recommend obtaining a liquid biopsy while concurrently scheduling a tissue biopsy if that is needed.

Now, if tissue testing if tumor tissue is just unavailable period, plasma ctDNA, can be obtained upfront, again, with requesting the tissue testing if needed. Or you could obtain the plasma tissue testing followed by biopsy, if the plasma testing is negative. But again, I do tend to like to, if I know the tissue is insufficient, I tend to want to at least schedule the tissue biopsy, because oftentimes I can get that answer back from the liquid biopsy before the tissue repeat biopsy is obtained, thereby really limiting the amount of time I'm waiting to start treatment.

So, what do community clinicians need to keep in mind regarding genomic testing and why? I think really, the key take-home message here is really, every patient with advanced non-small cell lung cancer, and not only advanced, localized locally advanced. Really, across the spectrum of stages of non-small cell lung cancer should obtain molecular testing, ideally through next-generation sequencing testing. Again, I like to obtain both tissue and liquid concurrently, but really, one needs to be performing this testing before, starting appropriate systemic therapy in order to really best help our patients.

So, with that, let's talk a little bit more detail about clinical decision making for HER2-mutated and overexpressing non-small cell lung cancer.

Now, this figure here shows across the spectrum some of the therapies that have been tried over the years for HER2-altered non-small cell lung cancer. However, we're going to spend most of our time talking about what's in kind of the upper, midsection figure here, particularly, what's called DS-8201a, that was really the first name for what we now call trastuzumab deruxtecan, which is really broken through in advanced HER2-mutated non-small cell lung cancer.

So, what is an antibody-drug conjugate? Let's spend a little time homing in on that. There are really three key components here. One, the antibody, by nature the target that the antibody homes in on. Now, the target should be selectively expressed or overexpressed on tumor cells in order to prevent on-target, off-tumor toxicity. IgG-1 is the most common humanized, immunoglobulin utilized here. Now, the antibody is connected to a cytotoxic payload via a linker. Now, being a connection, the linker also helps to maintain stability of the antibody-drug conjugate in circulation. There are 2 key types of linkers, non-cleavable – these require trafficking to mature lysosomes for degradation, by nature of their biochemistry the compound has limited ability, the payload has limited ability to then traverse across cell membranes and exert effects on neighboring cells. The so-called bystander effect, which can be important in the efficacy of these compounds. These types of linkers were primarily used in earlier generation antibody-drug conjugates, and they were used in T-DM1, as an example. The second are cleavable linkers. These rely on cell physiology, pH, proteases, etcetera for payload linker uncoupling,

and because of their biochemistry, there is actually, typically, prominent bystander effect where the payload can diffuse across cell membranes and exert effect on neighboring cells. This is very, very important, tumors that have heterogeneous target expression and dense tumors that really require, permeation of that payload to affect the cancer cells. Now, the payload in these current generation ADCs is primarily a highly potent cytotoxin, such as a DNA-damaging agent, or topoisomerase inhibitor. These are almost, you could think of them like chemotherapeutics that are incredibly potent in the picomolar concentration. A related important aspect of this is called the drug-to-antibody ratio, or DAR. These are the number of payload moieties that are attached to a specific antibody. And the mechanism of action of how these compounds work primarily with payload delivery. However, antibody-dependent cell cytotoxicity, complement-mediated cytotoxicity, and in select cases, inhibition of oncogenic drivers, are all postulated as contributing to the anti-tumor effect of these compounds.

So, what is the rationale for antibody-drug conjugates in HER2-mutated non-small cell lung cancer? This is actually quite elegant work that came out of Bob Li's lab at Memorial Sloan Kettering, which showed that in HER2-mutated cancers compared to wild-type, there's actually increased internalization of the HER2 receptor which preclinically leads to increased internalization of ADC compounds which is showing, really, the rationale for how these compounds can be utilized in HER2-mutated non-small cell lung cancer.

So, the first antibody-drug conjugate that was shown to have efficacy in HER2-altered non-small cell lung cancer was ado-trastuzumab emtansine, or T-DM1. This is composed of anti-HER2 monoclonal trastuzumab, conjugated to the anti-microtubule agent DM1 via a non-cleavable linker. This was an agent that has been approved in subsequent therapy as advanced HER2-positive breast cancer. And importantly, efficacy signals are observed in HER2-mutated and amplified non-small cell lung cancer. This is primarily from a Phase 2 basket study of 49 patients, that have previously-treated advanced non-small cell lung cancer, where a response rate of 51%, with a median progression free survival of 5 months was observed. As you can see here in some of the breakdown of the data, responses were observed in both HER2-mutated and HER2-amplified non-small cell lung cancer, although interestingly, very minimal benefit was seen in those with HER2-overexpressing non-small cell lung cancer in multiple Phase 2 studies. Key toxicities of this compound include cytopenias, fatigue, elevated LFTs, and infusion reactions, and the component actually carries a category 2a recommendation for subsequent line therapy in advanced HER2-mutated non-small cell lung cancer, though of note, is not formally approved, by the FDA in this setting.

This is just a visual depiction of the figures showing the difference in response rates for T-DM1 in HER2-altered non-small cell lung cancer, between HER2-overexpressing non-small cell lung cancer and then HER2-mutated or HER2-amplified. And really efficacy observed was primarily in those with HER2-mutated, or HER2-amplified non-small cell lung cancer.

But moving on to really what was much more exciting in the field, was the emergence of the next-generation antibody-drug conjugate trastuzumab deruxtecan, or T-DXd, in advanced non-small cell lung cancer. So, T-DXd is composed of the HER2-targeted antibody trastuzumab conjugated to the, payload of deruxtecan, or T-DXd via cleavable linker with the drug-to-antibody ratio of 8. Now, because of this cleavable linker, as I alluded to earlier, this compound is able to elicit significant bystander effect supporting its use in tumors with heterogeneous HER2 expression. And prior to its accelerated approval in non-small cell lung cancer, this compound has been approved in patients with HER2-positive and HER2-low breast cancer, HER2-positive gastric or gastroesophageal junction adenocarcinoma.

So, what data do we have in, advanced non-small cell lung cancer? Now, the first data that emerged was from the DESTINY-Lung01 study. This was a large multi-center international 2-cohort Phase 2 study that looked at patients with unresectable metastatic previously treated non-squamous non-small cell lung cancer and enrolled them into 1 of 2 key cohorts. Cohort 1 was in HER2-overexpressing non-small cell lung cancer, and cohort 2 wherein patients with activating HER2 mutations, with a primary endpoint of objective response rate.

Now, homing in on those with HER2 mutations, this was really exciting data when it was first released here, showing a response rate of 55% in those with HER2 mutations. Importantly, activity was observed across HER2 mutation subtypes and irrespective of concurrent HER2 amplification, or HER2 expression status, with a median duration of response of 9.3 months.

Now, while this was the first data that was released, what the data that actually led the trial that led to the approval of this compound in advanced HER2-mutated non-small cell lung cancer was the DESTINY-Lung02 trial. Here we showed the design of this study. This study was randomized 2 to 1 in a non-comparative study of T-DXd 5.4 mgs/kg every 3 weeks, or 6.4 mgs/kg every 3 weeks, with the primary endpoint of a confirmed objective response rate.

This is the key data from this study. When comparing the 5.4 to 6.4 milligram per kilogram dose, very similar response rates, 49% with 5.4, 56% with 6.4 mgs/kg, with clinically similar progression free survival and overall survival.

And more recently, we saw the final results of this study presented at ASCO 2024 this year, which, very similar numbers. Though, of note, the final median survival in the study showed a T-DXd 5.4 mg/kg dose survival of 19 months. And at the 6.4 mg/kg dose of 17.3

months. So, maybe a numerically slightly higher survival with the lower dose, but I think the key take-home point here is, from an efficacy standpoint, very similar.

This is just another figure showing the efficacy at that 5.4 mg/kg dose, and as was observed in DESTINY-Lung01, efficacy observed irrespective of the type of HER2 mutation, and irrespective of concurrent HER2 amplification or overexpression status with an objective response rate of 49%. Though again, in the more recent presentation at ASCO, this response rate, was noted at 50%.

And again, similar efficacy, but importantly, much more favorable safety profile at the 5.4 mg/kg dose. You could see here, both in terms of toxicities that we commonly associate with chemotherapy, such as, cytopenias, nausea, fatigue, where that was numerically lower. In addition, grade 3 or higher treatment related adverse events were overall lower at the 5.4 mg/kg dose. And then, importantly, drug-related ILD was lower shown in the publication from last year. Any-grade ILD of 12.9% at 5.4 mg/kg dose, compared to 28% more recently at ASCO. This was updated to 14.9 versus 32%. Primarily these were lower grade AEs, grade 1 or 2. But importantly, again, the rate was over half at the 5.4 mg/kg dose, really further supporting its accelerated approval in patients with advanced HER2-mutated non-small cell lung cancer with progression on prior therapy.

So, in August of 2022, the FDA granted an accelerated approval for trastuzumab deruxtecan in patients with advanced HER2-mutated non-small cell lung cancer who have received prior systemic therapy. This was the first drug approval for HER2-mutated non-small cell lung cancer. And again, the recommended dose is 5.4 milligrams per kilogram once every 3 weeks.

Now, one might think that based off of the construct of these compounds, that they may have limited ability to traverse into the CNS illicit effects there. But as this data here highlights this actually is likely false and that we actually have observed significant CNS efficacy of T-DXd in HER2-mutated non-small cell lung cancer. This is pooled CNS efficacy data from DESTINY-Lung-01 and DESTINY-LUNG-02, including in patients that received no prior radiation treatment, there is efficacy in the CNS, including a very favorable CNS disease control rate and duration of response.

Now, as I mentioned earlier, in DESTINY-Lung-01, there was also a cohort of patients that were included that had HER2-overexpressing non-small cell lung cancer, including IHC of either 3 or 2 plus.

There was efficacy observed, although, probably, I would say less prominent, or more modest efficacy response rates ranging from 26 to 34%. And given the majority of patients enrolled were at the 2+ IHC level, it's really hard to delineate overall response between those with 3+ and 2+, though perhaps, maybe numerically slightly higher or at the 3+ level.

So, based off of this data and data from the DESTINY-PanTumor02 study, the FDA actually granted accelerated approval to T-DXd in patients with advanced unresectable solid tumors with HER2 overexpression defined by IHC 3+, who have received prior therapy and have no other satisfactory alternative treatments. Alluded to the DESTINY-Lung01, study data and then the PanTumor-02 response rates there at 51.4% with the median duration of response of 19.4 months.

So, what are the key perspectives from this data? What is most practice-changing? I think the number one most practice-changing here is really DESTINY-Lung02, trastuzumab deruxtecan in HER2-mutated non-small cell lung cancer. You know, this is now a treatment option for patients who have experienced disease progression on prior systemic therapy. The final response, duration of response, progression free and overall survival data from this study supported use of the 5.4 milligram per kilogram dose over the 6.4 milligram per kilogram dose given the favorable safety profile here. Regarding the data on HER2-overexpressing non-small cell lung cancer, it's excellent to have another option, though I do want to see more data to better assess how this compares to our other subsequent line therapy such as docetaxel, as well as to see what's really driving that response. Is it truly the HER2 overexpression, is it concurrent amplification, or some other factors that might be leading responses in select patients? So, I think these are all important things to keep in mind. Regarding frontline therapy for HER2-mutated non-small cell lung cancer I think it's up to the clinician whether to pursue chemotherapy alone or to add in immunotherapy. The data is mixed on use of immunotherapy in this population, but again, I think that really should be deferred to the treating clinician for HER2-mutated non-small cell lung cancer. For those with HER2-overexpressing non-small cell lung cancer. It's important to keep in mind that these patients should be treated, along traditional treatment algorithm for those without driver mutations, so really, following a treatment algorithm of an immunotherapy backbone approach, if that's appropriate for a particular patient.

Now, what about other data from ASCO find exciting here? So, there are some future targeted therapies to keep your eye out on. One is zongertinib that was showed in the BEAMION-Lung 01 study. And importantly, in early data in 41 patients with advanced non-small cell lung cancer, a response rate of 44% was observed with a median duration of 15.8 months. in addition, across enrolled cohorts in this study, patients who had received prior trastuzumab deruxtecan saw a response rate of fixed 36%. So, it's important to note that there are emerging targeted therapies out there that hopefully will make a major impact for our patients.

So, these are other ongoing trials of trastuzumab deruxtecan in non-small cell lung cancer. DESTINY-Lung03 is looking at the combination of T-DXd with other immunotherapies with or without chemotherapy in first-line treatment of advanced non-small cell lung cancer with HER2 overexpression. DESTINY-Lung-04 is a Phase 3 trial looking at T-DXd versus standard-of-care frontline setting for patients with advanced HER2-mutated non-small cell lung cancer. And the DESTINY-Lung-05 is a Phase 2 study looking at T-DXd in patients with HER2-mutated non-small cell lung cancer who have disease progression on or after at least one line of treatment.

So, a little bit more on DESTINY-Lung-04, is really asking is, can we bring T-DXd into the front-line treatment of patients with advanced HER2-mutated non-small cell lung cancer? So, this study is a Phase 3 randomized trial randomizing patients 1 to 1 to either T-DXd or to standard-of-care with platinum doublet chemotherapy plus pembrolizumab. And again, this includes patients, with activating HER2 mutations advanced non-small cell lung cancer that is treatment naive.

DESTINY-Lung03, so again, this is a multi-arm trial looking at various combinations of T-DXd with immunotherapies, with or without platinum, in patients with unresectable locally advanced or metastatic HER2-overexpressing non-squamous non-small cell lung cancer that is treatment naive.

So, I alluded to this a little bit earlier, but what role does immunotherapy play in HER2-mutated non-small cell lung cancer? So, this is just, a table summarizing some small retrospective studies talking about, talking about anti-PD-1 and PD-L1 monotherapy in HER2-mutated non-small cell lung cancer. And you could see that overall responses not particularly robust. But the real question here is, should we incorporate anti-PD1 and PD-L1 therapy with platinum doublet chemotherapy in the frontline management of advanced HER2-mutated non-small cell lung cancer?

Now again, as I alluded to earlier, this is really clinician decision. I know many colleagues where they would do platinum doublet chemotherapy alone and others do incorporate immunotherapy. I think you can make this decision as well on a case-by-case basis looking at the molecular profile. Is there anything, concurrent alterations there that would support benefit of immunotherapy? Is patient of prior smoker? Or are there any clear contraindications to immunotherapy, such as significant, autoimmune disease? So, I think all these things should be taken into consideration, when considering addition of immunotherapy to platinum doublet chemotherapy in the frontline treatment of advanced HER2-mutated non-small cell lung cancer. So, I will say that I typically do steer away from PD-1 monotherapy or immunotherapy alone in patients with HER2-mutated non-small cell lung cancer.

These are the NCCN guidelines for HER2-mutated non-small cell lung cancer. And just to highlight that they do show that one should follow frontline setting the adenocarcinoma or squamous cell carcinoma treatment approach. And then on progression considering T-DXd or trastuzumab emtansine, T-DM1, and then following progression there on appropriate standard therapy.

But as I alluded to earlier, this is kind of my approach where I would utilize platinum doublet chemotherapy with or without a PD-1/PD-L1 immunotherapy, again, with a patient-specific decision-making there, looking at computational profile, smoking status, etcetera, following disease progression. That's when I would consider T-DXd, and after that, assess subsequent line chemotherapy. T-DM1 after T-DXd, there's not a lot of data there, and overall when tried, minimal response is observed when T-DM1 followed T-DXd.

So, what about in patients with HER2-overexpressing non-small cell lung cancer? As I alluded to earlier, T-DXd now has a tumor agnostic approval for unresectable or metastatic HER2-positive IHC 3+ solid tumors. So, this can be considered as a subsequent line therapy in patients with advanced non-small cell lung cancer with 3+ IHC, HER2 overexpression in patients who have no other treatment options. I think it remains to be seen where this will settle out in the line of treatment in advanced non-small cell lung cancer, but really important, as I mentioned, that these patients should follow the non-driver algorithm, so basically an immunotherapy backbone approach with or without chemotherapy depending on, you know, things like PD-L1 expression, mutational profile. What one would undertake, would when patients without driver mutations in the frontline setting. But again, in the subsequent line setting, I think it's important that we have other options, though I do want to see further data as well as other things that might predict responses as HER2 amplification.

Another important, aspect here is surveillance of treatment-related adverse events. So, what are some key treatment-related adverse events with T-DXd and T-DM1, the HER2-targeted ADCs. With T-DM1, as I mentioned, transaminitis, thrombocytopenia, nausea, fatigue. Similarly in T-DXd we can see several of these, what we kind of view as kind of chemotherapy-like AEs, nausea, vomiting, fatigue, decreased appetite. but importantly, we also have to think about, one key side effect, interstitial lung disease, that has been observed in ADC's that incorporate this DXd payload.

So, a little further detail there. So, this was observed less frequently at the 5.4 mg/kg dose, as I alluded to earlier from the DESTINY-Lung02 study, with the data shown on the right. And just a reminder, updated data from ASCO 2024 showed ILD of 14.9% at the 5.4 mg/kg dose compared to 32% at the 6.4 mg/kg dose. Studies suggest median time to onset of about 88 days, and the majority of patients do receive steroids to treat this ILD. And at least in the studies, no patients were retreated.

So, how would I manage ILD if observed? I think it's important to maintain a high index of suspicion. New cough, shortness of breath, dyspnea on exertion, fever, etcetera – high index of suspicion, and if suspected, you must stop T-DXd and initiate steroids promptly. Workup should include a high-resolution chest CT, CBC, blood cultures, PFTs, pulse-ox, typically, we will also consider consulting pulmonology, as well as consider an infectious disease input because we really want to, you know, utilize an appropriate differential diagnosis here looking at other common things such as infection, cancer progression, radiation-related pneumonitis or ILD of another etiology. As I mentioned earlier, management here is prednisone, typically 1 mg/kg per day. and what about reinitiating T-DXd if ILD resolves? So, there's very limited data here. Per the FDA label, this can be considered in cases of grade 1 ILD, which by definition is asymptomatic ILD, and it is not recommended, if there are any symptoms or if it's grade 2 or higher ILD. But admittedly, we do need more data in this space.

This is just an algorithm, taken, from a publication by Tarantino et al. at JAMA Oncology that one can deploy with suspected ADC-related ILD.

So again, real-world considerations here, use of T-DXd in patients with non-small cell lung cancer really requires meticulous proactive monitoring for adverse events. you know, our more common, chemotherapy-related AEs that I think we're all relatively experienced in managing; nausea, vomiting, fatigue, cytopenias. but then, other things that are specific to trastuzumab-based therapies, such as left ventricular dysfunction. And then, importantly, specific to T-DXd ILD pneumonitis, and maintaining a high index of suspicion for that, and promptly initiating the steroids if that is suspected.

So, what do community clinicians need to keep in mind regarding treatment related adverse events? So, I think it's as I alluded to earlier, I think the key thing is you know, keeping an eye out for significant AEs. Now, if it's things like nausea, vomiting, fatigue, one can consider dose-reductions or spacing the dose needed. But for ILD, one really needs to maintain a high index of suspicion, promptly initiate steroids. And it's really uncommon to consider reinitiation. If it's clinically significant ILD, I would not reinitiate T-DXd. However, this can be considered if it's grade 1, so detected on imaging alone without symptoms.

So, let's move forward with a practical application case.

So, this is a 64-year-old female with newly diagnosed lung adenocarcinoma, metastatic to liver and bone, presents to clinic for management. She's a former half-pack-a-day smoker for 10 years, but quit 30 years ago, so a very modest smoking history. Quite fit. Liver biopsy unfortunately confirms TTF1 positive adenocarcinoma consistent with lung primary, and additional testing reveals PD-L1 of 80%.

So, which of the following is the most appropriate next step in care? Is it to begin ICI monotherapy with or without platinum doublet chemotherapy, begin platinum-doublet chemotherapy, begin afatinib (an older generation HER2 TKI), obtain next-generation sequencing, or unsure?

Because this patient is fit without significant symptoms, I would absolutely obtain next-generation sequencing, which is answer choice D. Now, if this patient had had a significant symptoms or you saw LFT increases, you were really worried about them declining quickly, you could begin platinum doublet chemotherapy while awaiting sequencing. But ideally, one waits for sequencing before beginning appropriate therapy.

So, in this case you obtain additional next-generation sequencing that reveals a pathogenic YVMA duplication, which is the most HER2 Exon 20 insertion mutation. You begin systemic therapy with platinum doublet chemo with immunotherapy. After 8 months, of initial response, unfortunately, there is disease progression that's biopsy-confirmed with NGS testing showing the HER2 Exon 20 insertion. Patient otherwise feels well apart from mild worsening fatigue.

So, in this setting, what would you consider? Atezolizumab monotherapy, docetaxel, trastuzumab deruxtecan 5.4 milligram per kilogram, trastuzumab deruxtecan 6.4 milligram per kilogram dose, or poziotinib (an older HER2 TKI studied)?

So, the answer here is T-DXd at 5.4 milligram per kilogram dose. This was the dose studied in the DESTINY-Lung02 trial. And again, important here why that dose over 6.4? More is not always better, and importantly, the efficacy at these two doses was similar with an improved safety profile, specifically less adjudicated ILD at the 5.4 milligram per kilogram dose.

So importantly, we also have a downloadable shared decision-making guide that accompanies this presentation, some of the things we discussed today on molecular testing, therapy selection, as well as giving details on key points of data on various of the HER2-targeted therapies that we discussed today.

So, what are key takeaways? Number one, alterations in HER2 mutations, gene amplification, and protein overexpression are all found in non-small cell lung cancer. But the only way you can find these is with broad next-generation sequencing to assess for these

mutations. Yes, could you use a more limited platform? You could, but you really want – the gold standard is to deploy broad next-generation sequencing to assess the genomic profile of non-small cell lung cancer, and then appropriately guide therapy from there. I typically use both tissue and liquid testing concurrently in the frontline setting in my practice. Assessment of HER2 amplification and HER2 overexpression, importantly though, is not routinely performed as part of the initial workup of advanced non-small cell lung cancer, and outside of a clinical trial or individual case-based decision HER2 amplification and overexpression do not factor into the frontline management of advanced non-small cell lung cancer. The initial management of HER2-mutated non-small cell lung cancer consists of platinum doublet chemotherapy with or without immunotherapy. The addition of immunotherapy should really be as a clinician-based decision, though again, I would steer away from immunotherapy alone in patients with HER2 mutations. Trastuzumab deruxtecan, or T-DXd, is the only HER2-directed therapy with an FDA approval. It carries an accelerated approval after progression on prior systemic therapy for those with HER2-mutated non-small cell lung cancer. T-DXd also has an approval in the subsequent line therapy space for patients with solid tumors with overexpression defined by IHC 3-plus. So, this is also an option in patients with overexpressing non-small cell lung cancer who have no other alternative systemic therapy. It's important for patients who are on T-DXd to watch closely for ILD, this is an important treatment-related adverse event. And if ILD is suspected, steroid should be started promptly with discontinuation of T-DXd and then in the course, doing further workup to look for other possible etiologies, infection, disease progression, and incorporating important colleagues for that pulmonology, for bronchoscopy lung function assessment, as well as infectious disease colleagues for assessment as well.

So, with that, I want to thank you for your attention and your participation in this activity.

**Announcer:**

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