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HER2-Targeted ADCs in Advanced NSCLC: A Case-Based Approach to Targeted Treatment for Metastatic Disease

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Chapter 1: Dr. Gainor- Progressive HER2-Altered NSCLC After Standard Frontline Therapies

Dr. Gainor:
Hello, my name is Dr. Justin Gainor. I'm the director for the Center for Thoracic Cancers Program at the Massachusetts General Hospital and an associate professor of medicine at Harvard Medical School.

Today we'll be discussing HER2- targeted antibody drug conjugates in advanced non-small cell lung cancer. We'll launch right in with a case, and this is a patient who I saw in my clinic a short time ago. This is a 76-year-old woman. She's a never smoker with a history of hypertension who initially presented with fevers and cough.

A chest X-ray showed a left hilar mass, and this was followed by a chest CT that showed a 6.4 centimeter left hilar mass, including the left lower lobe segmental bronchus, as well as multistage, mediastinal adenopathy and multiple hypodense lesions. We pursued a liver biopsy that showed adenocarcinoma consistent with lung origin, highlighted by TTF1 positivity. Of note, PDL1 tumor proportion score was 20%. At the time of the biopsy, we sent both liquid and tissue next generation sequencing, and these returned showing a HER2 mutation, G776 deletion insertion VC. The patient was initiated on first-line therapy with carboplatin, pemetrexed, and pembrolizumab, but unfortunately, repeat scans after only two cycles showed evidence of disease progression, with the interval growth of several liver lesions despite observing some tumor shrinkage in the left lung mass. So the main question is, what is the optimal management for this patient?

I think this is a nice segue to first talk a little bit about HER2 alterations and non-small cell lung cancer. In general, we, we should think about three alterations, HER2 mutations, HER2 amplifications and HER2 expression. At present, the only two alterations for which we have targeted therapies with antibody drug conjugates are HER2 mutations and HER2 overexpression. So let me take them one by one. So on the left I show various HER2 insertion mutations found, in non-small cell lung cancer. These are relatively uncommon found in about 2% of patients. When we look at the distribution of these alterations, we see that about a quarter of these are in the extracellular domain of the kinase, but 10% are in the transmembrane domain, and then the bulk of these alterations are in the kinase domain. So if we think back to our patient in case one, her alteration was in the kinase domain, specifically exon 20.

HER2 mutations, you know, have been known oncogenic driver in non-small cell lung cancer and generally mutually exclusive with other genetic alterations such as EGFR and ALK. We also know that patients with HER2 mutations have defined clinical pathologic characteristics. We generally see these, alterations in adenocarcinoma, and we generally see these alterations in patients who have a

never or light smoking history. So HER2 mutations were really the first alteration for which we had an approved, antibody drug conjugate. More recently, however, just within the last few months, we saw a new FDA approval, actually a tumor agnostic approval that is any solid tumor with HER2 overexpression assessed via immunohistochemistry. I showed here a slide showing the, the grading scale. So much like in other tumor types, zero indicates negative, and then we can have positivity of 1+, 2+, or 3+. Importantly, in that tumor agnostic approval, it is only for 3+ positivity. And so when we think about testing in non-small cell lung cancer, it should now be a standard of care to test for both HER2 mutations as well as HER2, overexpression via immunohistochemistry. So why is this important? Well, you know, this goes back to some data that we saw as of 2022 using the antibody drug conjugate trastuzumab deruxtecan.

First, the historical note. There have been a number of different strategies trying to target HER2 mutations, and these have range from small molecule inhibitors to, naked antibodies such as pertuzumab or trastuzumab. But really the major treatment shift was with the antibody drug conjugates. And that's because we saw much better anti-tumor activity than what we had previously seen with those other modalities. I'm showing data from the Destiny-Lung01 study, the initial publication that appeared in the New England Journal of Medicine in 2022.

We see a waterfall plot showing significant anti-tumor activity with a objective response rate of 55%. Notably, this occurred in patients with both kinase mutations as well as mutations in the extracellular domain. So both groups of patients were included in this study. You see the progression-free survival and the median PFS and the initial report was 8.2 months. Subsequently, we saw additional data from Destiny-Lung, and importantly, subsequent data started to look at dose optimization. So the initial data that is showing you on this previous, on the prior slide was using trastuzumab deruxtecan at a dose of 6.4 mg/kg. Now, one of the challenges at that dose, which we'll discuss in a few slides was we observed high rates of treatment related interstitial lung disease. And so there was concerted effort to explore that high dose versus, a lower dose of 5.4 mg/kg.

And so I show here the comparison of the two, with a 5.4 mg/kg highlighted above at the top. And we, what we can see is that, in this study that the response rates look quite comparable between the two. Again, response rates in that 50 to 56% range across a range of HER2 mutations, including extracellular kinase, domain mutations. In terms of progression-free survival, we see 9.9 months, versus 15.4 months. But importantly, duration of response remains quite good with a 5.4 mg/kg dose of 16.8 milligrams. What I'll add is that the FDA approved dose for trastuzumab deruxtecan actually is the 5.4 mg/kg dose. And this reflects a combination of the efficacy shown in this slide as well as the safety profile, which we'll review in the coming slides. A brief word on efficacy as relates to HER2 over expression. Obviously this was not what was seen in the first case that I presented, but nonetheless, I did wanna highlight this. These data were recently published in Lancet Oncology by Dr. Smit and colleagues, and we see that on the left is a waterfall plot for both HER2 overexpression of 2+ and 3+. But if you hone in on the 3+, which is the FDA approved group, we see a response rate that is fairly comparable to HER2 mutant, non-small cell lung cancer with a response rate of 52% in the median duration of response, a little bit shorter, so 6.9 months. What about safety profile? So, this slide summarizes the most common adverse events between the 5.4 and 6.4 mg/kg doses. We see that the most common adverse events include nausea, neutropenia, fatigue, and decreased appetite. So even though this is a targeted therapy in the sense that we're using a biomarker enrichment strategy, I do think it is important to note that that this is still chemotherapy. And so we still see, you know, relatively high rates of nausea, but seldom grade three or higher. So this does require typical antiemetics, et cetera, with, with this agent. The other thing I'd like to highlight in this slide is that if we compare the adverse event profile between the 5.4 and 6.4 dosing, we see in general the side effect profile looks better with a 5.4 dosing regimen.

So we see lower rates of any grade adverse events as well as lower rates of grade three or higher adverse events. I next wanted to spend a minute to focus on interstitial lung disease because this is one of those important adverse events that any clinician using this agent should know about. These are several examples of what interstitial lung disease can look like, in patients treated with trastuzumab deruxtecan. So, you know, two examples on the far left a baseline, and then we see in the middle pane there examples of pneumonitis and then examples of treatment following corticosteroids. The mainstay of treatment for ILD related to this agent is corticosteroids prompt initiation of corticosteroids. And I typically follow the same timeline in terms of tapers that I would say for a checkpoint inhibitor. So I'm typically tapering by about 10 mg/kg of prednisone per week. So I'm typically giving about a four to six week course of steroids. What about kind of the rates of interstitial lung disease and if there's a difference between the two doses? The short answer is yes, there is a difference between the two doses. So this is looking at adjudicated rates of drug related ILD in patients who had received a prior PD one inhibitor. We see at the high dose of 6.4 mgs per kg, the rate was 28%. Most of these though being grade one or grade two at the lower dose of 5.4 mg/kg, we see that the rates of ILD are cut in half, so around 14.9%. Importantly, it doesn't really look like with the high dose, there's a relationship with prior checkpoint inhibitor. The lower dose maybe it looks like their rates were even lower if patients had not received a prior PD one inhibitor. But really need more data in this regard to tease apart that association.

So with that, you know, what would be the next step for management of the patient? I presented in case one and the next step in my mind would be trastuzumab deruxtecan. Based upon the data that I just highlighted throughout these slides to summarize these data, I would add that testing for HER2 mutations and over expression is now a standard of care and advanced non-small cell lung cancer.

Trastuzumab deruxtecan is now approved for previously treated HER2 mutant non-small cell lung cancer and HER2 over expressing solid tumors via IHC 3+. We saw dose optimization studies from the destiny lung studies establishing that 5.4 mg/kg is the preferred dose of T-DXd, but clinician should be aware of important drug-related adverse events, most notably interstitial lung disease because it does require prompt initiation of therapy. So with that, I'd like to thank you for your attention and I hope that you found this useful in for your practice moving forward. Thank you very much.

Chapter 2: Beyond the Blood–Brain Barrier: Intracranial Activity of HER2-Targeted ADC Therapy in HER2-Altered NSCLC with Brain Metastases

Dr. Sands:
Hi, my name is Jacob Sands, Thoracic Medical Oncologist at Dana-Farber Cancer Institute, and I'm excited to join you today to talk about Beyond the Blood Brain Barrier. We're going to talk about intracranial activity of HER2-targeted antibody drug conjugate, namely trastuzumab/deruxtecan, which is an FDA approved therapy for HER2-mutant positive non-small cell lung cancer. In the setting of brain metastases, this becomes a more nuanced topic.

Let's start with a case, and then we'll go a bit more into the data. Sixty-two-year-old-woman with metastatic non-small cell lung cancer So, in this case patient came in with a cough, worsening shortness of breath and cough. Workup showed multiple lung nodules, mediastinal adenopathy, liver metastases and a right adrenal metastasis. Now, biopsy demonstrated the non-small cell lung cancer. Her oncologist wanted to start treatment due to worsening symptoms. That being said, genomic testing wasn't back yet at that time, and so our oncologist started carboplatin and pemetrexed without immunotherapy. In this case the patient did not have a smoking history, so further increasing the, likelihood of an actionable genomic alteration wasn't yet known at the time, and so started carboplatin and pemetrexed. I'll make the point, I think that's a really important thing to consider in someone, particularly where you suspect, some kind of actionable genomic alteration. To start with, carboplatin/pemetrexed alone while saving the immunotherapy. And that's really important, especially in the setting of an eGFR mutation being discovered. And those with sensitizing eGFR mutations where you'd consider then starting osimertinib, if they've been on, immunotherapy, there's a higher risk of developing a pneumonitis in the setting of starting osimertinib with the prior immunotherapy.

So, in this case, started carboplatin and pemetrexed, while awaiting the genomic testing. Now, the genomic testing came back showing a HER2 mutation. This is after having already started the chemotherapy. in this case, the patient had, a wonderful response to carboplatin and pemetrexed and was tolerating that well and continued on therapy. After about 8 more months on maintenance pemetrexed, scans showed progression, and at that time, an MRI was done for restaging, and this showed multiple brain metastases, up to 6mm. So, multiple small brain mets. they’re not symptomatic, and there was not any significant edema around them. So, asymptomatic multiple brain metastases.

What to do in those cases? Let's go into the data a little bit around this. So, first of all, brain metastases represent a challenging scenario, in many cases, for solid tumor management. Some targeted therapies are very effective. things like osimertinib, things like alectinib. More recently erlotinib, that we've seen for eGFR and ALK, mutations. But when we're talking about cytotoxics, there's often some limitations to that. Now with DESTINY-Lung01 and 02, these were the trials looking at trastuzumab/deruxtecan for HER2-positive non-small cell lung cancer. These trials did allow enrollment of asymptomatic untreated brain mets, and that's something to really look at. Many trials do not allow asymptomatic and untreated brain mets. Many require prior treatment of brain mets, so, when looking at a trial, this is something really important, evaluate, whether or not were allowed enrollment.

Now, first of all, what did the data show? DESTINY-Lung02 is what led to FDA approval, and this was a trial looking at two different dose levels, the 5.4 milligram per kilogram every 3 weeks, or 6.4 milligram per kilogram every 3 weeks, and you see the waterfall plots here. Now, both really show the kind of waterfall plots we hope to see in that the vast majority of patients did have regression of tumor and met at least a partial response. They look fairly similar between the two, and so, representing the fact that we see, still sufficient outcomes in the 5.4 milligram per kilogram dose level. At the same time, on the bottom left there, you see adjudicated ILD. Now interstitial lung disease is an important consideration in any of these antibody drug conjugates with a deruxtecan payload. We see interstitial lung disease show up across the various trials. In this case, at the lower dose level of 5.4 milligram per kilogram dose level, we see less, adjudicated ILD, drug-related ILD. And so, this led to the approval and the use of the 5.4 milligram per kilogram dose particularly in non-small cell lung cancer. This is something worth highlighting and underlining, because it is a different dose than what we see in breast cancer. At the same time, I'll point out that these are for HER2-mutant non-small cell lung cancer, which is also a difference from breast cancer. Now HER2, we've had as a part of a biomarker for work-up the treatment of breast cancer for many years, and that's HER2 expression. In this case, it's HER2 mutation. So, for non-small cell lung cancer, HER2 mutant, the dose is 5.4 milligrams per kilogram.

Now, for brain metastases, there were 33 patients, in the DESTINY-Lung01 study, 33 patients with brain metastases at baseline were included. Fourteen of them had prior treatment with radiation, 19 of them presumably had not had treatment. Of those 19, there were a

reported 10 that achieved a partial response. So, an indication of CNS efficacy. Among all of those 33 patients, so those are patients previously treated as well as some untreated or progressing brain mets, amongst those 33, the median progression-free survival was 7 months and median overall survival being 13.8 months. And the overall numbers, are similar to that, a little bit more. The overall numbers median progression-free survival was 8.2, relative to that 7.1 with the prior brain mets, and 17.8 months of median overall survival relative to the 13.8 months, median overall survival in those with brain mets. So, still seeing efficacy, some durability to that, numbers don't look quite numerically what we see in the overall population, but when we see brain metastases, that generally is a worse prognosis, and so this is holding up.

Now, when we look at pooled analysis from DESTINY-Breast01, 02, and 03, so this was taking three different studies and pulling all together, looking particularly at those with brain mets. You see here from the chart, on the left side there is, the trastuzumab/deruxtecan group in blue, and right is the comparator pool. And, scrolling all the way down, you see the prior treatment, about 30% of patients in both of the groups had not had prior treatment of their brain mets. now, also point out, though, that they define the untreated active events are new or progressive brain mets that have not been subjected to any CNS directed therapy since documented progression. So, some of those may have had prior treatment, but then progression, which is in systemic disease. We utilize that as a way of, we have to have seen some progression before you can call something active and measurable.

So, this is an important thing to look at, especially when looking at, these reported data around efficacy within the brain. Have they been treated? What was the prior treatment? sometimes you have to dig the manuscript to find that. So about 30% of patients in both groups, OK. Now, that being said, we're going to see the data that reports out on those with some prior treatment and without. So, here is the best intracranial response that we see across the two groups. And I really like the way that they separated these out, where on the left side you see the treated stable brain mets, and on the right side, within the blue and in both groups, the untreated and active brain mets. And the fact that we have the comparator pool there also gives us another way of evaluating this. Now, in both the treated and stable brain mets, as well as the untreated active brain mets, we do see numerically better responses. More complete responses, more partial responses, both of those groups. But I tend to focus more so on the untreated active. So, this is the ones where we know that there is disease there and it's growing. across that group, there were 7 patients, so not a huge number, but 7 with a complete response 13 with a partial response. But still, that's 45.5% of patients having a complete or partial response.

Now, further to this , you see the treated stable brain mets and the untreated active brain mets, curves, and so this is progression-free survival curves. And so, for the treated stable brain mass, these look quite a bit more similar. There's not as nearly as much separation, but there is still separation of the curves in advantage of trastuzumab/deruxtecan. And the untreated active brain mets is where we really see a very clear separation, and more stability than in that group that has, gotten trastuzumab/deruxtecan. So, we see a signal here. Even though they're low numbers, we do see a signal for some intracranial efficacy, as well as from a progression-free survival, an indication that there is some protection or some treatment preventing progression within the brain that group, as well.

We do have sufficient numbers here to say that there appears to be some intracranial activity. Now, that being said, to go back to our case, 62-year-old woman, metastatic non-small cell lung cancer, HER2 mutation with multiple new brain mets. Now remember, there were multiple less than 6mm brain mets, so asymptomatic, untreated in this case. Now, I think there are options. she could be started on trastuzumab/deruxtecan and monitor the, brain closely. it is something where there may be some durability to that. I don't think you necessarily have to rush to treating an asymptomatic, brain mets. but something that's symptomatic or a bit larger, particularly large to the point where you'd consider, neurosurgical resection. but even some where you're seeing some edema or some kind of symptoms, then getting radiation to that is probably an important consideration. Whether that's prior to starting trastuzumab/deruxtecan or later, and then potentially between cycles, I think is a clinical determination depending on the patient. And how much you need to treat any other disease is present beyond the brain.

So, there is, certainly more data to come, I'm sure, as this is now an FDA-approved widely-used drug, in the setting of HER2-positive non-small cell lung cancer. More data to come, from some of the toxicities that we're seeing, as well as then, brain efficacy in particular. But this is something that I think we can utilize in those with active brain mets that are asymptomatic, and a starting drug and monitoring closely. but in something that's bigger, I think starting treatment is important first.

I thank you for your attention.

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