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HER2-Driven Strategies in Metastatic NSCLC

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Dr. Liu:
Welcome to CME on Reach MD. I'm Dr. Stephen Liu, and today I'm joined by my colleagues, Dr. Joshua Sabari and Dr. Susan Scott. Today, we'll summarize why HER2 is an important target in lung cancer and review relevant clinical trial data.

Let's begin with the DESTINY trials. Susan, can you discuss some of the key findings from these studies?

Dr. Scott:
Yeah, so the DESTINY studies look at trastuzumab deruxtecan, an ADC targeting the HER2 protein in non-small cell lung cancer. So DESTINY-Lung01 had two main cohorts. One was HER2 overexpression by IHC, Cohort 1, and then Cohort 2 was HER2-mutated lung cancer, so activating mutations in the HER2 gene and protein.

The HER2 mutated cohort, Cohort 2, was really the first one to change our practice in lung cancer. This was a second-line study, patients previously treated with at least chemotherapy or chemoimmunotherapy. This demonstrated in the second-line, overall response rate of 55%, a median duration of 9.3 months, median progression-free survival of 8.2 months, and median overall survival of almost a year and a half, again, in this pretreated population. This study was run at the 6.4-mg/kg dose. And there was a high rate of ILD or lung toxicity from the trastuzumab deruxtecan.

The DESTINY-Lung02 study was actually comparing that 6.4-mg/kg dose to a slightly lower dose at 5.4 mg/kg. The highlight from this study was that it was a similar overall response rate, similar PFS, similar OS, but importantly, a lower rate of toxicity, fewer than half the rate of ILD cases. DESTINY-PanTumor02 kind of revisited the IHC overexpression HER2 group, and this led to the approval of trastuzumab deruxtecan in any tumor — any solid tumor with IHC 3+ expression. So this does apply to lung cancer, and we do have an approval for trastuzumab deruxtecan in pretreated patients with overexpression of HER2 in their tumor.

Dr. Liu:
Yeah. Well, we'll summarize there now. Given the emergence of HER2 now as a viable target in non-small cell lung cancer, now that we have drugs FDA approved here, how are you testing for HER2 mutations and overexpression? Is everyone getting tested up front? Josh?

Dr. Sabari:
Yeah, so all patients have broad panel NGS. That'll identify the HER2 exon 20 insertion mutation. It'll also identify the non-tyrosine kinase domain mutations that may fall outside of that exon 20. And then we do do protein expression by IHC in all patients, really, for the last 3 months here at our center, because of the broad approval in the 3+ patient population.

Dr. Liu:

Susan, similar approach?

Dr. Scott:
Yep, absolutely. We've started incorporating the IHC more recently after the approval of T-DXd in the HER2 overexpression population. And we send all the tumors to pathology for HER2 at the same time we do PD-L1.

Dr. Liu:
Yeah, I think it's important that we've started doing this. But if patients are progressing and they had their testing a year ago, 2 years ago, I kind of have to make a conscious note to go back and look if they've had HER2 IHC. And if not, to do that testing. If the tissue is exhausted, do we rebiopsy? So while practice going forward, I think, is set, we have to remember that we weren't checking for HER2 for MET IHC a year ago. So something we will want to keep in mind as patients progress in later lines. But earlier lines is certainly where we think this is going.

Josh, what about DESTINY-Lung 04? Do you eventually think T-DXd, trastuzumab deruxtecan, will be a frontline drug?

Dr. Sabari:
Yeah, so we heard from Susan that there's an accelerated approval in the second-line setting, 55% response rate, median PFS 8.3 months, and overall survival in that 17-18 month range. Can we move this into the frontline? And that's exactly what DESTINY-Lung04 is — a randomized phase 3 study, open-label, randomizing patients to T-DXd, trastuzumab deruxtecan, versus standard-of-care chemotherapy and immunotherapy in the frontline setting. Again, these are HER2-mutated patients, not overexpressed. And I do think there's a real opportunity here. I think the key issue for me with the ADCs is potential tox. So barring any new toxicity signal in the frontline setting, I think this could potentially move and become a standard of care in the frontline.

Dr. Liu:
Let's talk about some other HER2-targeted approaches. There are some tyrosine kinase inhibitors that I think are worth mentioning. Susan, can you tell us about BAY-2927088, otherwise known as sevabertinib?

Dr. Scott:
Yes, absolutely. This drug was investigated in the SOHO-01 trial. This was advanced non-small cell lung cancer with HER2-activating mutations. And then the two subgroups that we're highlighting here, are those that are either naïve to HER2-targeted therapy, that – so these patients would have likely received chemotherapy with or without immunotherapy in the frontline but had not received something like trastuzumab deruxtecan or another TKI targeting HER2. And then Cohort F was patients that were naïve to any systemic therapy. We see really robust response rates in both of these cohorts, particularly in the patients that had received prior systemic therapy. An overall response rate of 60% is really encouraging in a pretreated tumor.

We are also looking at high disease control rates, up to 84–85%. And relatively tolerable side effects. So we see some diarrhea and some cutaneous side effects that are from EGFR off-target effects of the HER2 inhibition. But really exciting to see new therapies that may come in sequence with our existing HER2 regimens.

Dr. Liu:
I think a very active drug. It's good to have active kinase inhibitors. While the rate of grade 3 adverse events was relatively low, 84% risk of diarrhea in that previously treated setting is on the higher end. Fortunately, most of those grade 1/grade 2.

It's not the only TKI we have in development. Josh, what do you know about zongertinib in this setting?

Dr. Sabari:
Yeah, so zongertinib, formerly known as BI 181, is a HER2-specific TKI. I think it differentiates from some of the other agents such as sevabertinib, which inhibits HER2 as well as EGFR. Really, zongertinib is HER2-selective in this patient population. And the Beamion LUNG-1 we presented at AACR, we saw an impressive 71% response rate in this patient population. What about patients who were previously treated with HER2 ADCs such as trastuzumab deruxtecan? 48% response rate. Median progression-free survival in Cohort 1, 12.4 months.

But I think the differentiator here is the selectivity. This is a very safe, well-tolerated medicine. Essentially no significant diarrhea events, no cutaneous events, and very safe in the sense of ILD.

So I do think there's an opportunity for this drug to move forward. We have an FDA approval pending date in August. And there is also the Beamion LUNG-2 trial, which is ongoing in the frontline setting, hopefully moving this agent into the frontline. And again, Steve, you said it's an exciting space. I think having more therapies for our patients is better.

Dr. Liu:

Absolutely. And as drugs get better tolerated, can we use them in combination? Can we use them in the earlier-stage setting? A lot of unanswered questions, but an exciting time. That is all the time we have for today, though. So thanks everybody for listening.

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