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The Emerging Role of HER2 (ERBB2) Mutations in NSCLC

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Dr. Bazhenova:
Do know that in non-small cell lung cancer, HER2 alterations are now considered the distinct molecular subtype? Although there are no currently approved therapies, several promising agents targeting HER2 mutations in non-small cell lung cancer are in clinical development.

This is CME me on ReachMD, and I'm Dr. Lyudmila Bazhenova.

Dr. Levy:
And I'm Dr. Benjamin Levy.

Dr. Bazhenova:
Let's get started. We know a lot about HER2 receptor from breast and gastric cancer, but HER2 is now an emerging biomarker for non-small cell lung cancer. Ben, what do you want our listeners to know about HER2 alterations in this setting?

Dr. Levy:
Yeah, I think it's really important to take a step back because HER2 alterations are quite heterogeneous. And there's really 3 types. There's HER2 gene amplification, there's HER2 overexpression, and there's HER2 point mutations, which I know we'll talk about later.

You know, HER2 expression, protein expression occurs in roughly 15% to 30% of all non-small cell lung cancer. Obviously, more frequent in adenocarcinomas, and we usually measure this by IHC [immunohistochemistry]. There's been some data to suggest that HER2 overexpression is prognostic for worse outcome. Although the data is conflicting in, at least, early-stage lung cancer. We, of course, have HER2 gene amplifications, as well. This is a little less frequent. It occurs in roughly 3% to 5% of lung adenocarcinomas. And it can occur in up to 15% of patients in the EGFR TKI-resistant setting. And this historically has been measured by FISH [fluorescence in situ hybridization].

But I think most important is HER2 mutations. I think it's important to note that it really is, in lung cancer, HER2 mutations that are predictive of response to all these therapies that we will talk about.

And also important is that there's very little overlap. If you’re HER2 amplified, that doesn't mean you're HER2 mutated. I think these are distinct alterations that don't necessarily coincide.

I think perhaps the most important thing is we have to identify these mutations. So contemporary next-generation sequencing [NGS] methods are important platforms. So DNA- and RNA-based sequencing, NGS sequencing is important, but liquid biopsies are also

important. We know if we add liquid biopsies to tissue that we can better identify these alterations.

So, Lyudmila, how common is HER2 in non-small cell lung cancer? And just how significant are these mutations?

Dr. Bazhenova:
In lung cancer, HER2 mutations are present in approximately 1% to 5% of patients. We know that most common site of HER2 mutation in lung cancer is in tyrosine kinase domain, specifically in exon 20. And most of those are insertions.

That's why when you hear us talking about HER2 mutations, we mostly talk about HER2 exon 20 insertions. It is, however, important to distinguish those mutations from other commonly mentioned exon 20 insertion mutations in EGFR receptor, for which we recently had 2 FDA approvals. Even though EGFR and HER2 belong to the same receptor family, treatment for HER2 exon 20 insertions and EGFR exon 20 insertions are completely different.

If one examines specifically mutations in HER2, the most common exon 20 insertion is so called YVMA. Other mutations in exon 20, as well as exon 19, are also reported. And all of those patients were included in a DESTINY trial that we will discuss later.

If you look at the patient population who have HER2 mutations, they tend to be our typical oncogenically driven patients, such as females, never-smokers, adenocarcinoma. However, I cannot underscore enough that when you decide who to test for molecular testing in our lung cancer patients, neither of those characteristics should play a role in your thinking. Currently, if your patient has non-small cell lung cancer, you need to be testing them regardless of phenotype. We know in the past, and this is the data that Ben has mentioned briefly, that patients with HER2 mutations in general have worse prognosis compared to patients with other oncogenic drivers, likely because we did not have any effective therapy for those patients.

So, Ben, since we're talking about response, what do we know about response of HER2 alterations to targeted therapies?

Dr. Levy:
A little historical perspective here on how we've tried to drug HER2 alterations. And probably this starts with taking a page out of the breast cancer book and using drugs like trastuzumab and pertuzumab, either a single agent or in combination with chemotherapy, in patients with lung cancer and an unselect group of patients or patients who are enriched for, let's say, HER2 overexpression by IHC. And I think, importantly, all of these trials have been relatively disappointing. And so I think because of that, the strategies of these monoclonal antibodies have in large part been abandoned in lung cancer. And we've moved on to other therapies.

The other therapies, of course, that we have looked at are tyrosine kinase inhibitors [TKIs]. And these have specifically been looked at in HER2-mutated lung cancer. And this is where HER2 mutations matter.

I think the drug that's probably worth mentioning is poziotinib, which the FDA has accepted a new drug application specifically for HER2 exon 20. And this is coming from the ZENITH20 trial looking at single-agent poziotinib, and a cohort of patients that were pretreated all with HER2 exon 20. The response rate was around 28% with a PFS of around 5 months.

I think we'll learn as we begin to continue to talk that there may be other better options for HER2-mutated lung cancer. This drug does have toxicities that are sometimes difficult to manage. But this does begin the story of how we start to think about targeting HER2 alterations, starting with monoclonal antibodies, moving on to TKIs. And then of course, we'll get to the next section with the important class of drugs that are moving into the clinic now.

Dr. Bazhenova:
For those just tuning in, you're listening to CME on ReachMD. I am Dr. Lyudmila Bazhenova, and here with me today is Dr. Ben Levy. We are discussing HER2 mutations and non-small cell lung cancer and current clinical trials that may change the therapeutic landscape for this patient population with currently limited options.

HER2-targeted therapies have shown substantial efficacy and survival benefit in patients with HER2-positive breast cancer. So the question is can we use those agents for HER2-positive non-small cell lung cancer? Before we get to the data, Ben, can you tell us what these agents are and how do they work?

Dr. Levy:
Yeah, these antibody-drug conjugates, or ADCs, I call them the new kids on the block for non-small cell lung cancer because we're just beginning to learn how to leverage them. Obviously, these drugs have been front and center for breast cancer.

This compound has 3 key elements of course. It has an antibody, which can be an IgG1, IgG2, IgG3, or 4. The antibody of course needs to have high affinity and avidity for a target antigen. That's the whole point of targeting a protein that's expressed on the tumor cell. It needs to have a long half-life. It needs to be stable.

The second component is the linker. And this also needs to be stable in blood circulation to prevent a premature offload of the warhead, which I'll talk about. And linkers can be both non-cleavable and cleavable.

And then finally, the payload, the warhead. This needs to be generally a chemotherapeutic agent; it's at the current time either a lot of them are microtubule inhibitors or DNA-damaging agents. And they need to have a defined mechanism of action. These drugs, of course, work by targeting a particular antigen on the cancer cell. Most of these antibody-drug conjugates are internalized in the tumor cells, so the payload is released causing cell death. But there's also this bystander effect where some of the payload can leak out and destroy other cells that may not have the target that still could be cancer cells.

I think we're still learning about how these drugs work. But a very exciting class of drugs for us to be leveraged for lung cancer patients.

So, Lyudmila, how effective are antibody-drug conjugates against HER2 mutations in non-small cell lung cancer? And perhaps we can start with the results of DESTINY-Lung01 study; what can you tell us about that?

Dr. Bazhenova:
DESTINY-Lung01 trial was a multicenter, phase 2, single-arm trial which enrolled 91 patients with metastatic HER2-mutant non-small cell lung cancer who are refractory to standard therapy. A separate cohort was also enrolled for patients who had HER2 overexpression. You hear us multiple times today discussing the difference between HER2 mutations and overexpression, and in the DESTINY-Lung01 trial, results were different for those patients. Patients received trastuzumab deruxtecan at 6.4 mg/kg every 3 weeks till progression or intolerable toxicity. Primary endpoint for the study was centrally confirmed overall response rate. Results of the study, it showed confirmed objective response rate of 55% in patients with HER2 mutation. Median duration of response was 9.3 months, and median progression-free survival was 8.2 months, and median overall survival was 17.8 months.

When you contrast that efficacy data to the efficacy data for patients with HER2 overexpression, the response rate for patients overexpressing HER2 was only 24%. Responses were not as durable, and median progression-free survival was 5.4 months.

As expected, toxicity was seen with antibody-drug conjugate T-DXd. Most common adverse event was nausea, and was seen in approximately two-thirds of the patients, vomiting in about one-third. Majority of the patients with nausea and vomiting had a grade 1 or 2 toxicities. Alopecia has been seen in approximately 50% of the patients. Most common grade 3 toxicity was neutropenia at 19% and anemia at 10%.

One important adverse event we need to be aware of is interstitial lung disease or pneumonitis, and that was seen in approximately 26% of the patients. The good news is that 75% of those ILD cases where grade 1 and 2.

Dr. Levy:
That's all really exciting. And you know, I think when we talk about trastuzumab deruxtecan, we can't ignore the other ADC that's been exploited in lung cancer, ado-trastuzumab emtansine, or T-DM1. This has also been looked at as a single agent specifically in a small number of patients with HER2-mutated lung cancer. That data doesn't look as good as we've seen with trastuzumab deruxtecan, but certainly showing a response rate of 40%, roughly, and a PFS around 5 months. So yet another option that we have, but I think, clearly, trastuzumab deruxtecan is leading the way as the ADC in HER2-mutated lung cancer.

The story is not over. There's going to be a lot of different studies evaluating trastuzumab deruxtecan. The DESTINY-Lung02 trial is a phase 2 study of trastuzumab deruxtecan in patients with HER2 advanced adenocarcinoma of the lung. And looking at 2 different doses, a 6.4 mg/kg dose given every 3 weeks versus a 5.4 mg/kg dose given every 3 weeks. So trying to demonstrate whether lowering the dose potentially could lessen the rate of ILD that, Lyudmila, you mentioned. And this will be, again, patients who've received 1 previous treatment. So this will be given as second line. But it'd be a good study to answer that dose question.

Perhaps the more important study will be the first-line study, the DESTINY-Lung04 study evaluating trastuzumab deruxtecan versus standard chemotherapy in treatment-naïve HER2-positive non-small cell lung cancer. So the chemotherapy will be platinum-pemetrexed-pembrolizumab, again, compared to trastuzumab deruxtecan. And my hope is that we see a benefit in the first line here and that we can start using this drug confidently in the first line. And I think this is a call for clinical trials. It really is. We got to enroll these trials so that we can get these answers and better understand how to sequence these exciting therapies for our lung cancer patients.

Dr. Bazhenova:
Yeah, I agree with you completely.

So, well, this has certainly been a fascinating conversation. But before we wrap up, Ben, can you share your one take-home message with our audience?

Dr. Levy:

You can't give these drugs unless you know the alteration. So identifying HER2 mutations is important. And we need to remember that HER2 mutation is not HER2 overexpression, is not HER2 amplification. It really is looking at the mutation. And that's best identified and discovered by contemporary next-generation sequencing panels like DNA- and RNA-based sequencing, including liquid biopsies.

Dr. Bazhenova:
I cannot agree with you more. And I'll add that once you made a decision to use whatever appropriate therapies we're going to have in the future, it is very important to be aware of the toxicity profile that the drug that you are administering. And make sure you're staying alert of the symptoms that the patient can develop as expected based on a toxicity of the Lung DESTINY-01.

Unfortunately, this is all the time we have today. So I want to thank our audience for listening and thank you, Dr. Ben Levy, for joining me and sharing your valuable insight. It was great speaking with you today.

Dr. Levy:
Thank you so much. It's been a pleasure speaking with you.

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