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An Evolving Clinical Landscape in HER2+ and HER2-Mutant Metastatic NSCLC: Critical Updates for Your Practice

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Dr. Jennifer Carlisle has indicated no real or apparent conflicts.

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Dr. Ramalingam:
Hi, I'm Dr. Suresh Ramalingam, Professor of Hematology and Medical Oncology at the Winship Cancer Institute of Emory University.

So the treatment of non–small-cell lung cancer has really become very personalized to the specific patient. Molecular profiling is

considered standard of care in patients with stage IV non–small-cell lung cancer. We have a number of targeted agents that are used to treat specific molecular subsets of non-small cell lung cancer. I'm going to talk about HER2 as a target in non–small-cell lung cancer over the next few minutes.

As you are very familiar with, HER2 is a target for therapy in certain other solid tumors, like breast cancer. In lung cancer, HER2 is emerging as a target, but it's not associated with proven therapies, at this point. But we're going to talk about some promising therapies that are in the horizon.

As you're very familiar with, HER2 is part of the epidermal growth factor receptor family of proteins. When this pathway is activated, it turns on downstream signals that include activation of cell cycle progression, proliferation, formation of new blood vessels, and overall, the cancer results in a very invasive phenotype. We see HER2 activation in breast cancer, gastroesophageal cancers, and non–small-cell lung cancer.

What do we know about the role of HER2 pathway activation in non–small-cell lung cancer? Well, HER2 pathway can be activated in the form of protein overexpression, gene amplification, or mutation. HER2 mutations are seen in approximately 2% to 3% of lung adenocarcinoma patients. For instance, in the Lung Cancer Mutation Consortium study, where close to 900 patients were screened, approximately 3% had HER2 insertion mutation.

What is the relevance of having the HER2 mutation? Well, we know that it is not yet a target for therapy, in which case, the current standard of care involves using chemotherapy, first-line therapy, second-line therapy, like we do for patients without a proven molecular target.

First point is HER2 mutations are seen more in women and also in patients with never-smoking status. The survival outcomes for HER2-mutated patients appears to be comparable to some of the other common subsets of non–small-cell lung cancer. When we look at the outcomes for chemotherapy, response rate is about 40%. Median PFS of approximately 6 months are noted. In the salvage therapy setting, when patients get agents such as docetaxel, the response rate is about 10%, and the median PFS is about 4 months.

A number of HER2-targeted therapies have been studied in patients with HER2-mutated non–small-cell lung cancer. These have shown very variable response rates. The overall efficacy of these agents has been relatively modest to date.

What about HER2 overexpression? This is detected by immunohistochemistry. A number of studies, adding up to close to 6000 patients, were included in the meta-analysis to look at the prognostic significance of HER2 overexpression. And here, it turns out that HER2 overexpression was associated with a suboptimal outcome compared to patients without HER2 overexpression, with a hazard ratio for death of approximately 1.5 in non–small-cell lung cancer

One other clinical context where you would see HER2 activation is in the setting of acquired resistance to EGFR-targeted therapies. In the FLAURA study, which looked at osimertinib as frontline therapy for EGFR exon 19- or 21-mutated patients, when patients have acquired resistance to osimertinib, approximately 2% of the patients developed acquired resistance through HER2 amplification. So this is another setting where HER2-targeted therapy might be appropriate.

So, in summary, HER2 mutations are seen in about 2% to 3% of the patients. These are the patients that are primarily being targeted in ongoing studies. The role of HER2 amplification and HER2 overexpression will be clarified by additional ongoing studies.

Dr. Carlisle:
Hi, I'm Dr. Jennifer Carlisle, Assistant Professor of Hematology and Medical Oncology at the Winship Cancer Institute of Emory University. Now, we will discuss differences in HER2 mutations, amplifications, and overexpression and data on what to target.

So first, let's define what we mean by HER2 amplification and overexpression. Unfortunately, there's no clear consensus definition in lung cancer. And unlike breast cancer, there's no clear association between protein overexpression and gene amplification.

On the left, you can see HER2 gene amplification as shown by fluorescence in situ hybridization, where amplification is defined by a HER2-to-centromere protein of at least 2%. And in the figure, HER2 is highlighted in red, and the CEP17 gene is highlighted in green. On the right, you can see HER2 protein overexpression as measured by immunohistochemistry staining. 0 to 1+ has little to no staining, where 2 and 3+ have progressively more extracellular IHC staining.

Some of the initial studies looked at trastuzumab, a monoclonal antibody targeting HER2, plus or minus chemotherapy, in patients with non–small-cell lung cancer and HER2 expression.

The CALGB Phase 2 study of trastuzumab looked at 24 patients with 2 to 3+ HER2 protein expression. Only 1 partial response was seen, and unfortunately, 1 treatment-related death from pulmonary toxicity.

Around that same time, platinum doublets were studied with and without trastuzumab. First, gemcitabine plus cisplatin was studied in 103 patients with 2 o 3+ HER2 expression. And while this combination was safe, the addition of trastuzumab did not improve response rates, progression, or overall survival.

In the ECOG Phase 2 trial of carbo, taxel, and trastuzumab, in 53 patients the response rate was 24%, with a median PFS of 3.3 months and OS of 10 months. However, you can see, in the Kaplan-Meier curve on the right that survival probability did not depend on HER2 IHC expression. In fact, patients with 1+ HER2 IHC had the highest 1-year overall survival.

Next, let's look at HER2 mutations in non–small-cell lung cancer. The HER2 gene is located on the long arm of chromosome 17. And while mutations are seen in the extracellular and transmembrane domain, most are in the TKI domain, namely, in exon 20. The most common insertion is a 12 base-pair insertion made by duplication of the amino acids YVMA. And you can see in the figure that 50% of patients have this particular exon 20 insertion. These mutations are tested via RT-PCR or broader next-generation sequencing panels, and as already mentioned by Dr. Ramalingam, have been reported concomitantly with EGFR mutations.

A variety of tyrosine kinase inhibitors have been studied in HER2-mutated non–small-cell lung cancer over the past 5 years. You can see the number of patients included in all of these Phase 2 trials is relatively small, anywhere from 11 to 33 patients.

Some of the first studies looked at dacomitinib and afatinib, which had very low response rates in the single agents to teens, where some of the newer agents, like poziotinib and pyrotinib, had higher response rates at 42 and 53%. But these were very small studies of 12 and 15 patients, respectively.

Here's the summary figure showing various HER2 alterations and the results with treatments that have been tested. Starting on the left, with the green symbols, we can see HER2 protein overexpression in 2% to 38% of patients with lung cancer. And here, cisplatin and pemetrexed-based chemotherapy has modest responses, to which the addition of trastuzumab does not add anything.

On the right, you can see the 2% to 4% HER2 gene-mutation cohort, where TKIs have been studied. Here lapatinib, which is a dual EGFR HER2 TKI, was also looked at with no responses, as well as pertuzumab, a monoclonal antibody that impairs dimerization. And these have been looked at in non-HER2 selected patients with non–small-cell lung cancer and had disappointing results.

What we're going to focus the remaining sections of this talk on are antibody-drug conjugates, namely, TDM-1 and DS8201 or trastuzumab deruxtecan. And here, we've seen more promising results in the HER2 gene-mutated group. Notably, we're still awaiting outcomes of studies looking at the HER2 gene-amplification cohort, of which 10% to 20% of patients with non–small-cell lung cancer have.

Now we will focus on the efficacy of HER2-targeted antibody-drug conjugates and non–small-cell lung cancer. The first studied was ado-trastuzumab emtansine, or TDM-1. This antibody-drug conjugate was made by linking trastuzumab via a thioether linker to TDM-1 as the payload.

And here I'm showing a report from Li and colleagues, in the *Journal of Clinical Oncology,* looking at a basket trial. Cohort 1 included patients with HER2-mutant lung cancer. Ado-trastuzumab emtansine was given at 3.6 mg/kg IV on day 1 of a 21-day cycle until disease progression or unacceptable toxicity. Here, 11 patients with HER2-mutant lung cancer were included, with a median age of 64 years, female predominance, including former and never-smokers with a good performance status. The majority of patients had 2 or more prior lines of therapy, including some prior HER2-targeted therapy with neratinib, afatinib, or trastuzumab.

The results shown with the waterfall plot on the left show a response rate of around 44%, with a number of patients with stable disease and only 3 with progressive disease. The median PFS was 5 months. And you can see the duration of responses in the swimmer's plot to the right, with a median duration of response of 4 months.

The authors note that response were seen in HER2 exon 20 insertion, point mutations in the kinase transmembrane, and extracellular domains, and that HER2 immunohistochemistry ranged from 0 to 2+ and did not predict response. In fact, responders had low HER2-protein expression as measured by mass spec.

Now we'll move on to the newest agent currently under investigation, trastuzumab deruxtecan. This is a novel antibody-drug conjugate designed, again, with 3 components. There's a humanized anti-HER2 monoclonal antibody, the same amino acid sequence as trastuzumab, linked by a tetrapeptide-based cleaver to a topoisomerase 1 inhibitor payload. And this construct was designed to have a high-potency payload, high drug-to-antibody ratio of 8, and a payload with a short systemic half-life.

Here's the schema for the DESTINY-Lung01 Phase 2 trial, which looked at patients with unresectable and metastatic nonsquamous non–small-cell lung cancer, refractory to standard treatment with either HER2 expression or HER2 mutations and no prior HER2-targeted therapy, outside of pan-HER TKIs. The primary endpoint was independently central reviewed objective response rate.

Thus far, we have data reported for cohort 2, which were HER2-mutated patients. You can see the baseline characteristics on the right of the 42 patients with a median age of 63, slight female predominance, and well distributed between Asia, North America, and Europe. The majority of patients had kinase domain mutations at 90%. And you can see that 45% had CNS metastases.

Most patients have had 2 prior lines of treatment, with platinum-based therapy at 90%, 50% having prior PD-1 pathway checkpoint blockade, and nearly 20% with salvage docetaxel.

The efficacy of trastuzumab deruxtecan is shown here in the very impressive waterfall plot. Here, you can see, in 39 evaluable patients, all with shrinkage from baseline of their tumor, 1 patient had a complete response. Of the 42, 25 had a partial response, 12 had stable disease, 2 had progressive disease, and 2 were not evaluable, leading to a disease control rate of 90.5%. The median PFS estimated was 14 months, and duration of response was not reached.

So this represents a very promising new study for patients with HER2-mutated non–small-cell lung cancer. And we await the results of patients with HER2 IHC expression non-small cell lung cancer in future cohorts.

Now let's focus on the safety of HER2-targeted antibody-drug conjugates in non–small-cell lung cancer. I want to focus, first, on practical considerations for managing HER2 antibody-drug conjugates based on their mode of action.

First, the antibody-drug conjugate binds the HER2 receptor. And then this complex is internalized by endocytosis, and the cytotoxic effect is induced by drug payload release. We can see bystander killing effect from a variety of mechanisms, including release of the drug payload from the antibody, after antigen binding and before internalization, or release of the drug payload from the intracellular space, if there is high drug membrane permeability.

It's important to note that drug payload release after linker cleavage helps patients get good antitumoral efficacy, despite low HER2 antigen density when drugs have a high drug-to-antibody ratio. So while these bystander killing effects may lead to cytotoxic toxicities that we attribute to the payload, they're also very important for their antitumoral effects, especially in patients that lose HER2 expression or with cells that develop lower HER2 protein expression. Careful attention should be given to lab parameters for dose delay and dose reduction as needed.

First, is the safety of ado-trastuzumab emtansine based on the basket trial study. Here, you can see, in this small study, a number of patients have elevated AST, ALT, thrombocytopenia, and fatigue and nausea, but these were low at grade 1. There were a few patients with infusion reactions or weight loss, seen at grade 2, and only one patient with grade 3 anemia.

Of note, the FDA package insert has warnings for ado-trastuzumab emtansine for the breast cancer indication, listing hepatotoxicity, liver failure, and death have occurred, with the need to monitor hepatic function prior to initiation and prior to each dose. Physicians should also be mindful that this may lead to reductions in left ventricular ejection fraction.

Moving on to the safety of trastuzumab deruxtecan in non–small-cell lung cancer. Here, in the DESTINY-Lung01 cohort of HER2-mutated non–small-cell lung cancer, treatment-emergent adverse events listed here in greater than 15% of patients, we can see a high number of patients with nausea, alopecia, anemia, decreased appetite, and neutropenia. In grade 3 AEs, that were more common, were nausea, anemia, and neutropenia.

Summary data, here, of the 42 patients thus far reported, showed all had at least one treatment-emergent adverse events, and these patients had a median treatment duration of 7 months. 52% had grade 3 or higher drug-related AEs, but only 17% had drug-related serious treatment-related AEs. The most common AEs associated with dose reduction were fatigue and nausea, whereas the most common AEs associated with dose interruption were neutropenia or lung infection. There were 5 patients who had death on the trial, but none were related to the treatment.

One adverse event of special interest is interstitial lung disease. Here, you can see, of the 42 patients thus far reported, only 5 had ILD. All were grade 2. The median time to onset was around 86 days. Four patients stopped treatment, and 1 had drug interruption. All received steroid treatment, and most are recovering at the time of data cutoff. Fortunately, no grade 5 ILD was observed in this cohort.

So, in summary, antibody-drug conjugates show reasonable safety and characteristic cytotoxic-related side effects that can be managed.

Dr. Ramalingam:
The exciting results of the DESTINY-01 trial have really paved the way for a potential targeted approach for HER2-mutated patients. Trastuzumab deruxtecan has shown a response rate of over 60% and a median PFS of approximately 14 months, in an early result from the ongoing study. The cohort had approximately 39 patients. So what does this mean for the field of HER2-mutated non–small-cell lung cancer, as we move forward?

So here are some key questions: Where does a targeted agent like trastuzumab deruxtecan fit in, into the treatment landscape?

What is the role of immunotherapy in HER2-mutated non–small-cell lung cancer?

And then, we talked about mutations. Where does a HER2-targeted agent fit in for a patient with HER2-amplified non–small-cell lung cancer?

And finally, can we move these agents, once we see substantial efficacy, into the treatment of earlier stages of non–small-cell lung cancer?

Now, with trastuzumab deruxtecan, monotherapy has yielded a promising response rate. The next question, obviously, is do we use this as monotherapy, or would we combine it with other strategies. And the most obvious approach would be to combine it with platinum-based chemotherapy for potential use in the frontline setting. This is similar to the chemo plus EGFR TKI approach that's currently being studied in randomized trials.

The other potential way to combine is, once we know about potential resistance mechanisms, to combine DS-8201 with other targeted agents that could delay the emergence of resistance or overcome resistance.

Finally, I think knowing which patient will do well and which patient will not do quite as well, based on biological and biomarker characteristics, we will be able to identify which patient needs monotherapy and which patient would require a combination approach.

Immune checkpoint inhibitors have become standard approaches in various patients with non–small-cell lung cancer. However, in patients with driver mutations, the response outcomes and clinical outcomes for patients with immunotherapy have been somewhat modest.

In this study reported last year, when you look at the outcome for immune checkpoint inhibition as monotherapy, in patients with driver mutations, we can see the majority of the patients have disease progression as the best response. Objective responses are not very common. For this reason, we do not recommend using IO agents as monotherapy.

Perhaps the combination of chemo plus IO may be helpful for these patients. And ultimately, efforts to improve the tumor microenvironment from being cold to hot in these patients' driver mutation will potentially yield successful results.

Now, we saw the response rate with the trastuzumab deruxtecan. The question, then, is if these results hold out in other cohorts of patients, what is the optimal setting in HER2-mutated metastatic non–small-cell lung cancer patients? We know that chemotherapy alone has a response rate of about 40%, and the median PFS is about 5 to 6 months. So if you look at trastuzumab deruxtecan, with its early results showing a response rate of 60% and a median PFS of about 14 months, I would say this could be used in the frontline treatment approach for patients with advanced stage non–small-cell lung cancer, since these results are comparable or better than what one would expect with platinum-based chemotherapy approaches.

What about HER2-amplified non–small-cell lung cancer? Can agents that target HER2 be used in this setting? Well, we know that HER2 amplification can be seen in a small percentage of non–small-cell lung cancer patients in the absence of EGFR mutation, and these events can be oncogenic for these patients. However, at this point, we don't have any definitive evidence to say that these patients can be treated with HER2-targeted approaches.

So we will have to see whether agents like trastuzumab deruxtecan will be efficacious, and will that be comparable to efficacy results that are being observed in patients with HER2-mutated disease.

And finally, another key question is where does this fit in in the treatment of early-stage non–small-cell lung cancer?

We have recently seen the early results of the ADAURA trial, which showed that for patients with EGFR-mutated non–small-cell lung cancer, the use of osimertinib after surgical resection for stage IB, II, and IIIA disease has resulted in substantial improvement in disease-free survival. This provides the rationale to study other targeted agents in the early-stage treatment setting.

Once we establish the optimal treatment of HER2-mutated non–small-cell lung cancer, I believe that these agents will be studied in patients with early-stage lung cancer. However, we have to keep in mind that HER2 mutations are much less common, compared to EGFR mutations in exons 19 and 21. Therefore, conducting the kind of randomized trials such as ADAURA will be difficult in patients who have less common targets. So we've all had to make some extrapolations from the overall literature to refine our approach for the treatment of early-stage non–small-cell lung cancer.

So overall, I will conclude by saying that HER2 mutations, which are seen in 2% or 3% of advanced-stage lung adenocarcinoma, could be targeted with the emerging class of antibody-drug conjugates led by trastuzumab deruxtecan.

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