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MET and Other Emerging Targets 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. We're going to discuss emerging targets in metastatic non-small cell lung cancer.

Let's begin with C-MET. Susan, what's going on in this MET space?

Dr. Scott:
Yeah, so we've gotten a new drug for MET overexpression in lung cancer. The teliso-v is an ADC targeting MET, or c-MET, and was investigated in overexpression. So MET by IHC 3+, which was defined as 75% of the cells with high expression of the c-MET protein. And this study looked at the use of teliso-v following prior treatment. They demonstrated an overall response rate of 28.6% in that c-MET kind of highest expression. The grade 3 or higher treatment-related adverse events were about 60%, so this is something that we're going to have to learn to use and understand better with time. But overall, teliso-v does have some durable responses in many of these tumors with really high expression of c-MET in non-squamous EGFR wild-type non-small cell lung cancer.

Dr. Liu:
So, Josh, we've got this drug approved now. How has this impacted your practice? Specifically, when are you testing for c-MET?

Dr. Sabari:
Yeah, I think all patients should be tested for c-MET up front. We know that this may be a biomarker that is dynamic. So we've been testing — because of the EGFR mutant patient population — all patients for about a year now. So we have this information on our patients. For sure if you don't have it up front, you should test at progression, especially your biomarker-negative patients. Because here you have a new FDA-approved therapy that clearly beats out docetaxel, in my opinion. There is higher peripheral neuropathy rates. This is an MMAE payload, and we know we are moving to more sort of topo I type payloads in the near future. But clearly an improvement for patients over docetaxel in this setting.

Dr. Liu:
Yeah, agreed. Susan, any differences there? Are you testing everyone for c-MET now?

Dr. Scott:
We are, but this is really one where we're kind of going back and looking because it's been so recent. So we are sending out right now for c-MET, but it's something that we need to incorporate for every patient, either at diagnosis or on progression, so that we make sure that they have all available options open to them.

Dr. Liu:

Yeah, c-MET, I think an important biomarker there. We don't want to mix it up with MET amplification, MET exon 14 mutations.

Josh, another target, B7-H3, may be less familiar to some clinicians. What's its role in lung cancer?

Dr. Sabari:
Yeah, so B7-H3 is an important, sort of immune, sort of marker. And we have therapies now, I-DXd, formerly known as DS-7300. More data really emerging in the small cell lung cancer space, but I'm sure this is going to be looked at as well in the non-small cell lung cancer space. But in the small cell lung cancer space, which we talked earlier, becoming saturated with so many excellent therapeutics, here for I-DXd, in small cell, patients who received prior therapies, we're seeing response rates north of 50%, and they are somewhat durable. So I think this is an exciting agent. It has a deruxtecan payload, a topo I payload, so similar toxicities that we've discussed with some of the other ADCs mentioned today in this program.

Dr. Liu:
Yeah. Unfortunately, there are many drugs in this space, so we're going to see which one emerges as the leading candidate.

Susan, what about KRAS? Any recent progress in that area?

Dr. Scott:
Yea, so we've got two approved KRAS G12C inhibitors, adagrasib and sotorasib, both with proven activity following initial chemotherapy and immunotherapy, with approvals in that setting. But both are being looked at in earlier lines, particularly adagrasib. We've gotten some recent data looking at adagrasib plus pembrolizumab in untreated patients, so up in the frontline. There was a nice response rate of 44%, median progression-free survival of 11 months, median overall survival 18.3 months. We're still looking at toxicity for these drugs and how they combine with immunotherapy and any overlapping toxicity. But we're looking at moving earlier with precision for the KRAS G12C inhibitors. There are also novel KRAS G12C inhibitors in development. So this is definitely a quickly evolving space where I think we're going to have more options, both in the frontline and later lines, in the coming months and years.

Dr. Liu:
And we have these pan-KRAS inhibitors. Excited about those. I think particularly KRASG12D, which often patients with no smoking history may not be as likely to get that immunotherapy benefit—really limited options there. So excited to see what more we can do with KRAS.

Josh, let's talk about something unlike KRAS, pretty common and also pretty rare, NRG1 gene fusions. What's the latest there?

Dr. Sabari:
Yeah. So 0.25% of my patient population with non-small cell lung cancer, more commonly seen in never smokers, very hard to target NRG1. So we have a bispecific antibody here, zenocutuzumab, which targets both HER2 and HER3, preventing dimerization. And we've seen on this trial leading to FDA approval, very nice efficacy. Duration of response here 11 months, progression-free survival in that 7-month range. There are some toxicities: diarrhea, fatigue, nausea. But this is the first FDA-approved therapy in the NRG1 space. So keep your eyes peeled on those NGS reports for these rare mutations. We now have FDA-approved matched targeted therapies.

Dr. Liu:
Yeah, absolutely. A reminder that this is a huge gene, mostly intronic, so we do need RNA sequencing to find these. If we're doing just DNA-based sequencing, we're going to miss these NRG1 fusions. And what we've shown retrospectively, these tumors don't do well. They do not respond well to chemotherapy or immunotherapy. They often have this lymphangitic pattern treated for pneumonitis when really it's disease growth. So good to have a targeted drug. Zenocutuzumab really preferred agent in that setting.

Another great discussion, both of you, but unfortunately our time is up. So thanks everyone for listening.

Announcer:
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