



2022 Case Based Panel Discussion

Treating HER2 Exon-20 Insertion NSCLC with Trastuzumab Deruxtecan (T-Dxd)

Speakers:

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TRANSCRIPT

Dr. Dagogo-Jack: It does have that next generation sequencing and it shows a HER2 Exon 20 insertion. So this is a mutation in the HER2 gene. It's rare, but a lot of these rare things because lung cancer is so common, do impact a significant proportion of patients. And this particular target is the focus of our case. Two, because we recently had approval of treatment of a particular type of therapy called an antibody drug conjugate for this. And so an antibody drug conjugate is a little bit of a different therapy than the immune therapy, chemotherapy and targeted therapy we talked about.

It's a bit of a maybe a smart or really vocally directed chemotherapy. It consists of several components that are joined by a linker. And so there's this antibody that is supposed to bind to a protein that is hopefully expressed more on a cancer cell than a normal cell. And so here it's binding to HER2 expression and attached to that same antibody drug conjugate is chemo. We call that a payload. And so when the antibody drug conjugate binds to the target, it's internalized.

So taken up by the cancer cell. Only then is it broken down into its component. The payload or the chemotherapy is released directly into the cancer cells. And the hope is that this type of strategy would minimize some of the toxicities associated with chemotherapy. And so we've recently had an approval of trastuzumab deruxtecan, or you might find your doctors calling it TDxD in this setting for her two mutant non-small cell lung cancer. And so we'll talk a little bit more about the data, but it's left us kind of scratching our heads in this setting about do you start with chemotherapy in the first line setting? Do you give chemo plus immunotherapy, or do you go right to trastuzumab deruxtecan or TDxD? And so before we kind of go into that first line discussion, Natalie, do you mind kind of walking us through the data and why did we need a study that was looking at two separate doses?



Dr. Vokes: Yeah, it's a great question. So we had very good data from the Destiny Lung 01 study that looked at the higher dose of this drug that showed that this drug worked very well for lung cancer patients with this HER2 alteration, it had very high response rates of about 50%, a much higher percentage than that had disease control. And this got everybody really excited that we might finally have an effective drug for this group of patients.

The problem was that there were also fairly high rates of toxicity, so about 20% of patients had higher rates of interstitial of- lung pneumonitis, which is a common side effect from this drug and is also a common side effect in our patients, since a lot of them have lung disease to begin with. And there were also two deaths on the study. Now, this was a drug that's also been approved and has we've had some experience with in breast cancer and other cancer types. And in those other diseases, two different doses of the drug had been tried.

And so there are some rationale to say, you know, hey, could we take this drug, which seems to work really well, use it at still a very high dose, but one that's been effective in other diseases and see whether we preserve the efficacy while minimizing some of those toxicities that we were seeing in Destiny Lung 01. And so that was the Destiny Lung 02 trial. It basically compared these two different doses of the drug. And what you can see the left column is showing the lower dose and the right column, the showing, the higher dose.

And you can see that in the lower dose, there was still an objective response rate of 53%. It was actually in this trial higher than the higher dose, which was 43%. And in both groups, there was an excellent disease control rate. So that's patients whose cancer didn't grow while on the drug of almost 100% and 90%. And you can also see that the rates of interstitial lung disease were much lower. So rather than being closer to 15, 20%, which is what we see with the higher dose, it went down to 6%.

And the number of people who are able to stay on the drug without having the dose reduced or without having to stop, it was also much higher. So you can see on the bottom that the percent of people who had to discontinue the drug went lower. So this was really great data for us because it showed that we could continue to give this drug that there is no decrease in the efficacy while we were also sparing our patients some of those side effects.

Dr. Dagogo-Jack: Yeah, I think it was very encouraging data, right. We always like when we have a new therapy for a new target and based on seeing this data, it's it's kind of begged the question, when should we be using this now that we know that we can reduce, we don't have a 20% risk of the inflammation of the lungs or that interstitial lung disease? Should we be using it first or should we be using it later down the line? And so there's a- there's a clinical trial for that called the Destiny 04 that will answer that exact question.



And this is the the clinical trial design here. And so untreated, a little bit different from the study that Natalie just discussed, where patients had previously received chemotherapy and or immunotherapy here untreated. And you'd be randomized 1 to 1. So half of the patients get one therapy, half get the other to chemotherapy, plus immune therapy or to receive this trastuzumab drugs or So this is another area to stay tuned for. I'm not going to put anyone on the spot and say, what what do you use first or what do you use later? Because think you might meet one doctor who says one thing and another doctor who says anything and think at the end of the day we have to go based on the data at hand, the data that will hopefully emerge from this trial.

But very, very encouraging to see a new therapy in this space.