Case Based
Panel Discussions
Lung Cancer 2018

Advanced Non-Squamous NSCLC, Low PD-L1 No Driver Mutation – Is there a Best Systemic Therapy Option?

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TRANSCRIPT

Dr. West: A common case that we will see is a patient who is fit, has a non-squamous or lung adenocarcinoma that is Stage 4, and who we've tested for driver mutations like EGFR and ALK and others and does not have these. We then routinely look for the level of PD-L1 staining, the protein on cancer cells that is a reflection of the probability of responding to immune therapy, although it's not a perfect predictor. And about a third of our patients have PD-L1 that's detectable but at a low level, say 4%. I mean, a lot of times patients will either be in the high range of more than 50% or be below 20% or 10%. Not that many are very much in between that.

So if you have someone who has low PD-L1, we have a few treatment options that have good evidence to support them and are FDA approved. One is the option of getting chemo with immunotherapy Keytruda (also known as pembrolizumab); and this agent or this combination has been shown, earlier in 2018, to have a significant survival benefit for patients with non-squamous non-small cell, regardless of their level of PD-L1, compared to chemotherapy alone. And so this is an option to really consider, the chemotherapy being either Cisplatin or Carboplatin with Alimta and now with Keytruda. So there's that option of chemo and Keytruda.

But at the ASCO 2018 meeting, which is our biggest cancer meeting of the year, there was a big presentation of a trial called Keynote-042 that gave Keytruda alone compared to chemotherapy in patients with any level of PD-L1 over 1%. So that's about two thirds of our patients. We've seen previously very good results for Keytruda alone for the patients with high PD-L1, and this trial opened it up to a broader population with low PD-L1. And the trial was positive, but not necessarily looking that great for the patients with low PD-L1. So it's very likely that this option of Keytruda alone is going to be FDA approved and something to consider. But I would ask the question to you, what would you be inclined to favour for your own patients who are fit and

could get justifiably Keytruda alone? Of course chemotherapy alone is a possibility, but I think the leading options would be Keytruda alone or in combination with chemo if they have this low PD-L1 level. Taofeek, what do you think here?

Dr. Owonikoko: The options for our patients are getting more and more complicated. Which is a good thing in one sense, that we have a lot to choose from.

Dr. West: These are all showing benefits.

Dr. Owonikoko: These are all showing benefits for patients. So the way I look at the recently presented data (the Keynote-042 study) in non-small cell lung cancer patients regardless of the level of expression where they showed benefit of pembrolizumab, is that is not the only data that we have. We also have other data showing that those with very high levels of PD-L1 expression derive significant benefit from Keytruda. So when I put these two data together, side by side, and I look at the patient in front of me, the decision you want to make is what is best for this patient in front of me? So when we have a patient with low PD-L1 expression, like the specific one that we are talking about now, we know that that patient would not qualify based on the Keynote-189 study, but will qualify based on the Keynote-042 study because of the low expression of PD-L1.

But when I look at the entirety of the data that we have to support what we do for patients, I'm probably less inclined to offer a patient with low PD-L1 expression single agent pembrolizumab, if they are otherwise able to get the combination of Keytruda and chemotherapy. But if there are other factors that will make me not want to give the patient the combination of chemotherapy and Keytruda, then we will have that discussion to say, when we look at the data and look at different sub-group of patients in this study, it seems that the greatest benefit applies to those with high PD-L1 expression. But regardless of that, when we look at the entire population of patients that seem to be benefit of chemotherapy alone over chemotherapy, and for that reason I might be inclined to offer the option of Keytruda as a single agent, even in the context of low PD-L1 expression, after having this discussion.

Dr. West: Yeah, I agree. It makes sense to individualize. But to my eye – and I think a lot of people looking at the evidence that came out from the Keynote-042 trial – it looked like the patients with high PD-L1 did very, very well with Keytruda, and the patients with low PD-L1 diluted that, and the trial was still positive, but it was really positive despite the addition of these patients. It wasn't helped in any way. And it's just really suggested you could get away with it, but that doesn't mean it's a good option. Zosia, what do you think here? Are they both good options or is one a better one?

Dr. Piotrowska: I would say, you know, overall from Keynote-042 what we saw is that we really saw a recapitulation of Keynote-24. And I recognize this gets to be a word and number salad here. But now we've had two studies that basically show us for high PD-L1 patients greater than 50%, Keytruda alone is a good option and chemo plus Keytruda together is probably also a very good option for those patients.

Really I think what was instructive about Keynote-042 is for the patients that were lower than 50%, still positive but low-level positive, when you looked at that subgroup in the study, they didn't seem to derive as much benefit from Keytruda alone over chemotherapy. And overall, I think for those patients, for the low-level PD-L1 positive, the best data that we have, the most promising data, is to combine chemotherapy and Keytruda. That being said, it's not the right thing for everyone; there are some patients where there are factors that may lead you not to use chemotherapy and Keytruda together, and that's certainly a patient by patient decision. But for a fit patient where you're kind of trying to pick the best and most likely to benefit the patient treatment regimen, I think chemotherapy and Keytruda together would be my preference.

Dr. West: I agree with that. I think one of the challenges is that in the way that Keynote-042 was designed, which is again the single agent Keytruda versus chemo, it did not allow cross-over in the trials. So the patients who were randomized, half the patients got chemo, but they didn't have a clear path to getting immune therapy as a second treatment, which in the United States is really a standard approach we know can benefit patients. So only 20% of the patients who were in this global trial ended up getting immune therapy, so that fact that, yes, they got the same overall survival as with the chemo, and you could say, well, there you go, it's not an option. But that's just as good as a very handicapped chemotherapy arm that I think did worse than, or would do worse than, if we were to give them fair access to chemotherapy sequentially.

Dr. Owonikoko: I think the other point I want to make here is, if you look at the earlier studies in the post-frontline setting for patients who had already failed chemotherapy before, so whether you look at the Checkmate-017 or 057 and the Keynote...

Dr. West: These are trials of second-line...

Dr. Owonikoko: Second-line or beyond. We had this struggle as well when we were comparing immunotherapy to Docetaxel chemotherapy in the absence of biomarkers. And we had all these discussions, too, with ourselves and with our patients as to whether or not we should use these drugs in somebody where the biomarker was not present. And I think the entire field agreed at that point around the consensus of, even when you do not have the biomarker being present, it did not appear that going on immunotherapy was worse than chemotherapy. It might not be as good as those with the biomarker being present, and I think one can make the same argument with the Keynote-042 data.

Even when we look at the subset of patients with low PD-L1 expression, of course the benefit we want is for the benefit to cut across all patients and to be very good. But in those with low-level PD-L1 expression, it wasn't as good, but it doesn't mean that it was worse than those who went on chemotherapy.

Dr. Piotrowska: Sometimes you have patients where you just don't think chemotherapy is going to be safe; you worry about the side effects of it. I agree with you. I think the study provides good rationale for using Keytruda alone, and I think this is really a very good option for those

patients. And so I certainly consider it. But I think for the very fit patients, where the side effects are less of a concern, the combination still is...

Dr. West: I think it depends. This would give license for patients to say, "I don't want to do chemo." And yes, there are people who just are truly adamant, and informed about it. My concern is that if you ask people, "Would you rather have chemo or not?" no one will choose it (or very few would). But I think part of it is due to a concept of the side effects of chemo that are not really applicable to the chemo regimens we're talking about, especially drugs like Carboplatin and Alimta that most patients do very well with and they're thinking of what their uncle got in 1987; and that is not the same world we're in. I am certainly more inclined to encourage people and educate people that they should not paint all chemo with one brush and just say that they're disinclined. I think, yes, if you are informed and are still adamant, fine. But I think that the chemo immunotherapy approach for these low PD-L1 patients is a stronger option.

Dr. Piotrowska: That's a conversation that I have with many patients in the clinic. Of course no one wants chemotherapy, but it is a very effective type of treatment. And, exactly as you say, I think a lot of people go into the thought of chemotherapy with misconceptions, whether those be formed by prior experiences with family members, what we see in the media or in movies or things like that. And the truth is everyone expects that all chemotherapy will make you lose your hair, you're going to be extremely nauseous, and that's just really not the case in the era of common chemotherapy supportive medications.

I think what's really been striking across all these studies is that even the combination of chemo and immunotherapy, all strong and effective medicines, together still have been quite tolerable for the majority of patients. And patients are really able to live very normal lives, coming into clinic often just once every three weeks once they've been on the treatment for a while. If they want to keep working and keep doing what they normally would be doing, even on these combination therapies that we're talking about.

Dr. Owonikoko: Yeah, and I think that is the reassuring thing about the chemo immunotherapy approach for our patients. I think all of us, when the initial Keynote-021 data came out, which was initially a [safety... finding study, 12:02], we were all worried whether anyone would be able to tolerate the combination of chemotherapy and immunotherapy. And we went into it gingerly, hoping not to see anything bad happen to patients, and fortunately it turned out to be quite well tolerated.

Dr. Piotrowska: I would say that in my clinic I have been able to give it to patients who are even well but elderly. I think it really depends. You have to look not just at one mark, anything like age or really other markers. You just have to make a decision based on patients, how functional they are, their other medical problems; and I think you can do it safely in many, many patients.

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