



Case Based Panel Discussions Lung Cancer 2018

Advanced Non-Squamous NSCLC, High PD-L1, Negative for a Driver Mutation: What is the Optimal First Line Treatment for this Patient?

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TRANSCRIPT

Dr. West: The first case is one that we see a fair bit of. It is someone with Stage 4 disease, advanced non-squamous adenocarcinoma lung cancer who is fit and who has testing for PD-L1, the protein that we look at on the surface of cancer cells, and if it's seen at a high level, it suggests that these patients have a good chance of responding to the immunotherapies that we commonly consider. Importantly, this patient also gets tested for EGFR and ALK and other driver mutations, because if they're positive for this we would favor a different approach of an oral therapy. But this particular patient does not have an EGFR mutation or ALK rearrangement, but has high PD-L1 of 80%. That's about a third of our patients have this level of high PD-L1.

This is a setting where we have a few different options, and in fact some different trials that were positive, even showing a survival benefit, one of them is called Keynote-024 that's out a couple of years ago in late 2016 that compared Keytruda (or pembrolizumab) to plain standard chemotherapy with two drugs, and was better for a whole bunch of ways of measuring activity and as well overall survival.

But in 2018 we've also gotten the results of another trial called Keynote-189 that gives chemotherapy and immunotherapy together. And this is with a combination of either Cisplatin or – we would commonly give Carboplatin with Alimta, also known as Pemetrexed, and then that was those chemo drugs alone or with Keytruda. And this showed that chemo and Keytruda together was a very strong option that also gives a survival benefit compared to double at chemotherapy. So we have the option of chemotherapy with Keytruda being better than chemo alone and Keytruda alone being better than chemotherapy. So how do you approach this for a

patient who comes into your clinic, when you can potentially give Keytruda with or without chemotherapy?

Dr. Piotrowska: I think that's a very good question and it's one that's actually coming up more and more in the clinic. In my mind, I think these are both very good options. You know, we have two different studies each showing really what we consider kind of the gold standard of what we consider to be really a demonstrable improvement in outcomes for patients. These drugs actually help patients to live longer, which is what we hope to see. So both I think Keytruda and the combination of chemotherapy and Keytruda together are good options. I think it really comes down to a discussion with patients.

It also comes down to a few other factors, like for example, the extent of disease, the burden of disease that patients have. We have seen in these studies that combining the two (the chemotherapy and the Keytruda together) leads to a little bit of a higher rate of response, of actually seeing a tumor shrinkage, which sometimes can be an important factor when patients are really symptomatic, they have a lot of symptoms related to their cancer, and you're looking to see that cancer shrink faster so that you can see an improvement in the symptoms that they're experiencing. For those patients I would say that I favour a chemotherapy together with Keytruda.

On the flipside, there are some patients where maybe, even though they're fit, you worry that they may not do as well with the side effects of the chemotherapy. Some patients are just worried about chemotherapy and would rather avoid it if possible. And for those patients I think it's very reasonable to do Keytruda alone. Ultimately, I think it's a patient by patient decision that we as doctors make, and most importantly that we make together in discussion with the patients and their families.

Dr. West: For a fit patient, these bits of evidence now or the support we have for chemo and Keytruda is new. And so we haven't had a lot of experience doing this, but what's your sense of how frequently you are likely to be favoring chemotherapy and Keytruda versus Keytruda alone in these patients who could go either way?

Dr. Piotrowska: I'd say, for the most part, I've been favouring the combination: chemotherapy and Keytruda together. You know, if you look – again, it's hard to compare across different clinical trials – but overall the outcomes of the Keynote-189 study were very promising and very good. And for patients where we think they can tolerate the combination, I think there's good rationale to give both drugs together.

Dr. West: Taofeek, what do you think?

Dr. Owonikoko: I agree with Zosia. We have a number of good options now for our patients. And what we really want to do is get the best treatment that the patient can tolerate and look at the entire situation that the patient is faced with. Unfortunately, what we would have loved to see

is a comparison of Keytruda by itself to Keytruda with chemotherapy, and in this patient population especially those with very high PD-L1 expression. Since we do not have that data, what we then have is two pieces of data to guide us and then to see what is best for the patient in front of us.

For me, I tend to do – I'm not necessarily married to either approach at this point. So I look at the patient, disease burden is an important consideration if you want the patient to actually have a good response and stay on treatment for a long period of time, perhaps coming with the combination of chemotherapy and Keytruda might give you that initial push to help the patient.

But also when you look at patients that we deal with now, now we have patients living years on treatment and we do not want patients to put their life on hold just because they're going through treatment. So I do have these discussions with some of my patients. Someone who is actively working who wants to come in and get their treatment and go back to work, that could be a consideration for me to say, either option would be good, but in this situation perhaps going with Keytruda alone could be better for your circumstance. A similar patient who is perhaps retired and doesn't mind maybe staying a little bit longer to get all the treatment in, I may not be as focused on the duration of treatment when they come into the office.

The other thing is when we look at the Keynote-189 study, at least in some of the patients there could be some overlap in toxicity between Alimta and the combination with Keytruda in terms of kidney function. So when I have a patient where there's a borderline concern or maybe a real concern about their ability to tolerate chemotherapy, a potential worsening of their kidney function, I might elect to go with just single agent Keytruda or either the combination of chemotherapy and Keytruda in that instance. But ultimately, it's going to be a joint decision with the patient and their caregivers to see that we are doing the best for the patient and taking into consideration every other aspect of their lives, not just the cancer.

Dr. West: This issue with the kidney toxicity, the side effects, that they did see not frequently but more than we might expect, has led some of the folks I've talked to, to say, "Hey, I'd be really cautious about giving Cisplatin" (a drug that's generally harder but particularly challenging on the kidneys). But at the same time, in my experience, when I have patients who are on Alimta a long time, more than a year or 18 months, usually that's a good problem to have, but I've had more patients who develop kidney issues in that setting than when we used to see progressing cancer in less than a year, and you don't have the time really to have the long-term side effects you don't see otherwise. So I wonder if that's a factor. I don't know if you have thoughts on this?

Dr. Piotrowska: I think it's a very good point. You know, we're seeing patients living longer and staying on one particular therapy for longer. And so I think some of the side effects that we're seeing, some of these late side effects, become much more of an important than when patients were just staying on a treatment for a short time. And so that's something that we're

going to have to really look at carefully in the studies that we have and in future studies. I think the kidney issue is just one example and we'll have to keep a close eye out for others.

Dr. West: Because typically in trials like this, where you give chemo with immune therapy, you drop the platin, the Carboplatin or the Cisplatin, but you'd often keep the Alimta going along with immunotherapy. And that can be a very long time.

END OF RECORDING