Lung Cancer News and Updates ASCO 2020

NSCLC Trial Updates - Checkmate 227

Opdivo (Nivolumab)/Yervoy (Ipilimumab) Combination Today?

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Dr. Jack West: Hi, I'm Dr. Jack West, I'm associate clinical professor in medical oncology at the City of Hope Comprehensive Cancer Center, and also the founder and president of GRACE, global resource for advancing cancer education. I'm very happy to be joined today for an ASCO highlights presentation in the field of lung cancer with two of my friends and colleagues from other parts of the country who are lung cancer experts with some different perspectives. And we're going to go through some of the key presentations and talk about what we think this means for patients. So first I have Dr. Helena Yu, who is medical oncologist at Memorial Sloan Kettering Cancer Center and Dr. David Spiegel, who is chief scientific officer and director of the Lung Cancer Program at the Sarah Cannon Cancer Center in Nashville, Tennessee. Thanks guys for joining.

One of the other issues that came up at ASCO 2020 was the potential use of an immunotherapy combination, specifically immunotherapy agents at the same time as now an FDA option, and the question of where that might fit in to our treatment plan. The combination of Opdivo, also known as nivolumab, and Yervoy, which is another hitting another target in immunotherapy management, ipilimumab, has been studied in a trial called Checkmate 227 that we've seen over the last several years. And at ASCO 2020, we saw three year results from this rather complex trial. And you could see that the study was broken down into whether patients who could either have squamous or nonsquamous non-small cell as first line treatment would get chemotherapy doublet, or if they had PD-L1 expression would get randomized to alternatively to nivolumab, Opdivo alone or the combination of Opdivo with Yervoy.

And in patients who did not have PD-L1 expression of 1% or higher would get randomized to chemotherapy, Opdivo with chemo, or the two-drug immunotherapy combination. And this study, and we saw or mature now three-year update presented by our colleagues Ramalingam. We see a significant improvement in overall survival for

the nivo IPI combination, Opdivo and Yervoy compared to chemotherapy, and a suggestion that maybe a [inaudible] on the curve, which is shown on these curves called Kaplan Meier curves, where time is going from left to right. And as you move further and further over time there is a drop-off, as patients will tend to die of the cancer, but we love to see what looks like a plateau at the right side as patients are potentially living even longer.

And one of 10 [inaudible] that is sometimes cited of this combination is that maybe is associated with a higher tail on the curve, more people alive at two or three or more years. So one of the questions is whether there may be a particular value to the nivo IPI combination, specifically for the possibility of giving longer term survival going out several years. But that said, what we have here is a positive trial and an FDA approved treatment option for these patients with PD-L1 of 1% or higher. Compared to chemotherapy, which is an older standard that we used in 2015, 16, 17, but for most of the last two years, we've moved on from that use chemo, immunotherapy combinations.

You can see that when we look at the results for patients with higher versus low PD-L1, you really see the same trend results in the patients who got the Opdivo Yervoy combination, overall the patients with higher or with a high PD-L1, or at least detectable PD-L1 just had better outcomes overall, no matter what regimen they got, but there was a relative benefit with this combination. And what we also saw is overall there were side effects with this combination but nothing that was especially [inaudible] here, I would highlight that we are talking a regimen with this combination that is lower doses, particularly of the Yervoy Ipilimumab, that can be very challenging in other settings at higher doses.

And so I wanted to turn to you to get a sense of what you think of this combination? And where it might fit in when we have other regimens that have also beaten chemotherapy alone. And the way we've been using for a couple of years, does this bubble up now as a compelling option? Or is this maybe too little too late, just a lateral move? And I'd like to start with you David. I know actually that Matt Hellman, who is at Memorial Sloan Kettering has been deeply involved with this trial. So I assume that Helena, you have some experience with seeing some of these patients maybe managing some, but I'd love to get, if David, you have a kind of more outside perspective where you see this.

Dr. David Spigel: Yeah, I think you said it best. I mean, 227 has been a study that all of us have been following for a little while now, and a little bit of a moving, you know, evolving or moving target, but evolving story, because initially the excitement was around TMB. One of the primary end points you pointed out PFS and high TMB. And yet the approval

is in patients with a PD-L1 expression, 1% or higher. So a little bit of a shift in how we were thinking about nivo, IPI being used, that it might be something we're using regardless of PD-L1 expression, but in our patients with high PD-L1 status, and now that's changed on us. Suffice it to say, it's an active regimen, it's improved survival. It is tolerable. You know, I think we followed Matt's kind of pivotal phase one study in Lancet oncology that looked at six week and 12 week dosing of Ipi. And, you know, six week dosing looked really good at one Mg per kg of ipilimumab. And I think that has made it a different kind of experience than our colleagues in melanoma who use higher doses of ipilimumab experience with their patients in terms of toxicity.

I guess the big question is, will it get used? And you think about your options in the first line setting, you have immuno alone, immuno immuno now with this regimen, or chemo immuno. And so how do we think about where to use this? And for me, I'm not sure yet where I'm going to use nivo IPI. We used it on a trial that was a companion study to this, and I've had actually some fantastic results in some patients, including complete responses or complete remissions, I should say, but I'm also had some toxicity that seems more than I would see with single agent checkpoint inhibitors or chemo immuno. So for me, right now, this regimen is one I would consider in my patients who have a good performance status, can tolerate immune-related toxicity, don't want chemo for some reason, you know, they make it clear that they just don't want chemo. And I probably want something that's a little more active than pembro, although there's no evidence that this is more active than pembro. I just had the feeling it might be.

Dr. Jack West: Yeah. Helena what are your thoughts? And particularly, I know there are patients out there who want to avoid chemotherapy, but my concern and question is that this is chemo free, but it's not side effects treatment. Even if it isn't prohibitive. It is essentially from at least looking at the numbers. And I do not have much experience directly using the regimen. It seems like it's kind of a lateral move in terms of the frequency and intensity of the side effects you'd see, but maybe more idiosyncratic than the pretty predictable side effect profile we have known for years to decades with these chemo combinations.

Dr. Helena Yu: Yeah. I definitely would agree with you there, Jack. I think it is you know, it would be like what David said, I think for a specific patient who for whatever reason did not want chemotherapy, but I would really reserve it for my patients that are fit and young, and maybe people who have less of a disease burden as well, or, or are asymptomatic. I think knowing that sometimes these medications, immunotherapies take a little bit of time to work and alleviate symptom burden. So and maybe somebody who wants something a little bit more out of the box looking to sort of be part of that tail of the curve, but I would say this is not something that I would routinely offer to sort of my run

of the mill patient that comes to see me about first line treatment exactly for the issues that you both brought up.

Dr. Jack West: Yeah. So I think that it is an option, but it's one that may struggle to find firm footing alongside of options that we've been generally happy with between pembro monotherapy, for the high PD-L1 patients and chemo, pembro, or some other options, perhaps.

Dr. David Spigel: You know, Jack, the one thing I'd say, you know, maybe the three of us are at a little bit of a disadvantage is our colleagues in the community that are generalists who maybe have more familiarity with this regimen, or Ipi I should say, in melanoma and renal cell, you know, maybe this will be attractive to them because it's probably easier regimen than the regimen in those disease settings. I don't know, but for folks like us, I guess that are a little more focused in lung cancer, you know, it's probably a newer regimen.