



Case Based Panel Discussion 2019- Lung cancer Unresectable NSCLC

Case Based Discussion Panel – Stage 3 NSCLC – Immunotherapy Combos Checkmate 227 a Treatment Option?

Dr. Millie Das specializes in the treatment of thoracic malignancies. She sees and treats patients both at the Stanford Cancer Center and at the Palo Alto VA Hospital. She is Chief of Oncology at the Palo Alto VA and also leads the VA thoracic tumor board on a biweekly basis.

Dr. Matthew Gubens is a thoracic oncologist who treats patients with lung cancer, mesothelioma and other thoracic malignancies, including thymoma and thymic carcinoma, which are rare tumors of the mediastinum. He is an Assistant Clinical Professor of Medicine at UCSF.

Dr. Jack West:

I'd like to explore the question of what the role might be for immunotherapy combinations. We've established that drugs like pembrolizumab or Keytruda combined with chemotherapy are a very good standard of care option, not the only one, Tacentriq or Atezolizumab has also been compared with chemotherapy combinations sometimes with the anti-angiogenic or blood vessel attacking drug Avastin. But there are also other immunotherapy drug classes, one called CTLA4 that works at a different part of the immune system than the ones that we've largely been concentrating on. Drugs like Keytruda to Centric and Opdivo. There was a study called Checkmate 227 that's been out and reported in some forms for more than a year, but just had new data presented in the fall of 2019 that show that the combination of the drug ipilimumab or Yervoy combined with nivolumab or Opdivo, this nivo-ipi combination is significantly better than chemotherapy alone for patients with PDL1 detectable, as well as PDL1 undetectable.

Interestingly, the results look particularly stronger in those with high PDL1 or zero PDL1, and not as good in the low PDL1, which is frankly difficult to understand. But this is also a setting where chemotherapy is no longer our treatment of choice. And we've kind of moved on from that. And so because of that, I'm interested in your impressions of how attractive this combination of nivo-ipi is compared to what we already have Whether that would be Keytruda alone for the high PDL1 group or commonly chemo with Keytruda for the negative or low. We like these combinations. They work. They're not



hard to tolerate in general. I think there's an appeal to the concept of a chemo free option, but this wasn't toxicity free either. The side effects are pretty comparable to chemo or they're just different. So really what do you see as the utility, presuming that we get an FDA approval for a two drug combination of nivo and IPI or Opdivo and Yervoy. You've got this, you could use it, but we also have other options that have also shown a benefit compared to chemotherapy. So where does it fit in?

Dr. Millie Das: Right. I mean I think this is where it gets confusing. Cause there's no head to head comparisons here. So I think it will add to our treatment options. There are some patients who would want a chemotherapy sparing regimen. So, you know, I suppose it's nice to have this as a chemo sparing regimen. Although, you know, you point out that there are significant potential for toxicities. Especially with that, you know, dual kind of PD1 CTLA4 inhibition. We know that the rate of autoimmune toxicities is significantly higher. So, you know, I don't think there's an absolute right or wrong answer. I think.

Dr. Jack West: Well, I was looking for the absolute right answer.

Dr. Millie Das: Right. And I wish I could provide that. But yeah, I think this is just one of the, it's going to be another regimen that we can offer. And I think it depends on the specific patient. You know, my tendency is to go with the chemo plus IO and I prefer the platinum pemetrexed pembro regimen. It tends to be pretty well tolerated. You know, it's relatively easy to administer. And so, you know, and I think we've been using this regimen probably longer. You know, than any of these other regimens that are, you know, kind of more newly approved or you know, in the case of nivo-ipi, it hasn't even been approved yet. And so I think time will tell and you know, I'm not, certainly when we do get the FDA approval I will probably use it. I just, I don't know that it's necessarily better or worse.

Dr. Jack West: Matt, who do you think you'd, where's the sweet spot for this? Where would you use this relative to the tools you already have?

Dr. Matthew Gubens: Well, you use sort of chemo sparing. I think there's also a case to be made, it's chemo saving, you know, part of the chemo and, Keytruda with carboplatin Olympus, pretty well tolerated, standard of care, better than chemo. But the one of the problems with using that is the minute a patient progresses on that, what do you do next? You kind of go on to crappy second line chemo and unfortunately our next lines of therapy as of today aren't that robust. Taxotere is a tough chemo drug that doesn't work in a lot of patients, so there is some intuitive appeal to saying if I can give a drug combination that clearly beats chemo in the first line but lets me keep chemo for the second line, there's some appeal there. I think there's something to be said for that. I think it always has to come with a caveat that double immunotherapy is tougher. These drugs have been approved as a doublet in melanoma for awhile now melanoma patients tend to be



younger and fitter and so we have to be really on the lookout for those kinds of side effects.

Dr. Jack West: It is not without risk in those people, of course.

Dr. Matthew Gubens: But I want to take a step back and say, you know, for those patients who get single agent PD1 or PDL1 inhibition, some of them get their two years of treatment and are alive five years later, they never do see that next chemo. So if I can offer that immunotherapy alone, which just has that more of that brass ring element that maybe I can get that longterm response, I think there's a subset of patients where with the discussion, that double immunotherapy might be a really good first line option and then I always have chemo in my back pocket.

Dr. Jack West: What about the question? There has been a suggestion looking at the data without any head to head comparison that the patients who get a two immunotherapy drug combo with like nivo-ipi can have more sustained benefit. You have more patients who are alive without progression at two years. We don't have three, four or five year results and we definitely don't have a comparison of nivo-ipi versus Keytruda alone in high PDL1 or chemo Keytruda in everybody. But do you think that that angle has traction of maybe giving you the better chance of having the patient still doing well at 18 months, two years or longer with an immunotherapy combo?

Dr. Millie Das: Yeah, I mean I think that's, that's where part of the appeal lies and you know, that's why I do think this is going to be something that we're going to be using and patients may also be asking for it for that reason. And for the reason also of just not having, needing the chemotherapy upfront and saving that potentially for later.

Dr. Matthew Gubens: Because so far I think the only patients we can reasonably give single agent immunotherapy to, Keytruda, are really those 50% or higher. So we can go into the debate about the one to 49 percenters. I don't do that. I think that data was, were flawed. That trial was flawed, but as you pointed out, there was this kind of subset analysis where the PDL1 0% patients, we don't think immunotherapy as a single agent works as well as other stuff. They did very well on this trial, wasn't powered to look at those patients particularly. But there's something maybe in the mechanism where that dual checkpoint inhibition, maybe there's a there that even in those low inflame tumors, those low PDL1, who are they? But is there an opportunity to give them an immunotherapy only option? Grab that brass ring. And again, maybe hold off on chemo.

Dr. Jack West: It's interesting, I think if you really look at it and suggest the paperwork, people with negative PDL1, they just do comparably well with nivo-ipi, whether they were high or low, but the chemo didn't do as well in these patients. So it's really the control arm that did disappointingly, which elevates the difference. That's makes it look so much better.



But these are interesting, unanswerable questions. But you know, I don't know if it's a blessing or a curse that [inaudible] live in interesting times. We do. So thank you so much for spending the time.