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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Assessing Nivolumab + Ipilimumab in mNSCLC: 6-Year Outcomes from CheckMate 9LA

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Jacob Sands.

Dr. Sands:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and joining me today is Dr. Martin Dietrich, a medical oncologist with the US Oncology Network Cancer Care Centers of Brevard and an Assistant Professor of Internal Medicine at the University of Central Florida in Orlando. Together, we'll be examining the final 6-year data from the CheckMate 9LA study on nivolumab plus ipilimumab and chemotherapy as a first-line treatment for metastatic non-small cell lung cancer with PD-L1 expression less than 1 percent. Dr. Dietrich, thanks for being here today.

Dr. Dietrich:
Well, thank you so much for having me.

Dr. Sands:
To begin with some background, Dr. Dietrich, why has the low PD-L1 subgroup remained such a critical focus when we look at first-line treatment strategies for metastatic non-small cell lung cancer?

Dr. Dietrich:
Well, PD-L1 negative disease is mostly unresponsive to the PD-1/PD-L1 inhibition. We've had significant setbacks in clinical trial development when we try to lower the PD-L1 threshold. We've seen in CheckMate 026 a single agent with a PD-L1 cutoff of 5 percent not reaching statistical significance. We've had really underwhelming responses in the PD-L1 low range from 1 to 49 percent, with the benefit being reserved for PD-L1/ PD-1 inhibition in the greater than 50 percent range, and we have never seen a signal either in chemotherapy plus PD-1 inhibitors or in single-agent PD-1 inhibitors where an impact was made over background chemotherapy.

So it's really hard to treat the disease subtype. The responses are typically very short-lasting, so the monotherapy and the combination therapy here with PD-1 inhibitors alone really poses a significant challenge. And that's, I think, where the combination of immunotherapies have really helped us sensitize from a different angle and allow us to look into studies like CheckMate 9LA and CheckMate 227, both of which evaluated CTLA-4 combinations in the PD-L1 negative space with a particular focus on that subset of patients.

Dr. Sands:
With that in mind, let's turn to the CheckMate 9LA trial. In terms of overall survival, what stands out to you about these 6-year results, specifically in patients with PD-L1 expression less than 1 percent?

Dr. Dietrich:
Oh yes, so we've seen long-term results now with 6 years follow-up, over the 6 to 8 months in follow-up here for the study. And what has continued is a trend that the tail of the curve really seems to rise far above what we would expect in the treatment. We've had a combination here of nivolumab/ipilimumab on an ongoing basis and on a reduced dosing schedule for ipilimumab, and at the 6-year mark, the general population did benefit.

But particularly of interest was that the PD-L1 negative patients here—less than 1 percent—maintained a 6-year overall survival rate of

about 20 percent, almost threefold compared to what we've seen with chemotherapy alone. In chemotherapy, the most common subsequent line of therapy based on the standard of care at the time was the PD-1 inhibitors in second line. So I think we're looking here at an indirect comparison of PD-1s in second line versus those that are getting ipilimumab/nivolumab and maintenance after a short course of induction chemotherapy.

And I think this difference is relatively consistent across all PD-L1 subgroups. So there is really no prognostic impact of PD-L1 anymore if we include ipilimumab as an additional agent for treatment here. So whether we have PD-L1 positive or PD-L1 negative disease, both arms really perform similarly, underscoring that we are sensitizing in the PD-L1 negative subset with the use of ipilimumab as a CTLA-4 inhibitor.

Dr. Sands:
Now, you commented on the tail of the curve, and one of the really important things about these combinations with immunotherapy is that durability, where we see patients do well for an extended time. With that context, can we talk about the progression-free survival and the duration of response? What do the data show in these patients?

Dr. Dietrich:
Yeah, the progression-free survival and overall survival as well as the duration of response are remarkably consistent between the different subgroups of PD-L1 levels. We've seen about a 3- or 4-month improvement in progression-free and overall survival independent of PD-L1 level, so moving from about 10 months in the chemotherapy-first approach to about 14 months in the combination.

I think what's very interesting is the positive prognostic impact of a response upfront—hopefully attributable to immunotherapy. We see here a very strong duration of response of 17.5 months in the PD-L1 negative subset. So that's a very strong number.

It's a little bit of my practice to move away from the medians, as we're mostly affecting a subset of patients, and start looking at landmarks; longer time readouts—4, 5, and obviously 6 years now—are very confirmatory that we're providing a long-term benefit that may not be as easily captured on the median progression-free survival numbers, but really looking at the landmark improvements over time. And we see at the tail of the curve that it is significantly elevated, going in a factor 2 or 3 improvement over our standard-of-care arm here.

So I think that's the most important dataset to consider for treatment selection in non-small cell lung cancer of any histology or any PD-L1 level for that matter.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Martin Dietrich about the final 6-year data from the CheckMate 9LA study on nivolumab plus ipilimumab and chemotherapy for patients with metastatic non-small cell lung cancer with PD-L1 expression less than 1 percent.

Now, if we switch gears and focus on safety, Dr. Dietrich, were there any new concerns in this data? Or did it mostly reinforce what we've already seen?

Dr. Dietrich:
Well, I think in general terms, the side effects really occur earlier. And I think this is the observation in the clinical trial; it may be a little bit early in the combination setting, not necessarily as intense as we used to see it, and mostly attributable, in my interpretation, to the new dosing schedule. We've seen the standard PD-1 dosing plus a significantly reduced exposure to ipilimumab with a lower dose of 1 mg/kg body weight and a lesser frequency of every 6 weeks. So it was an alternating schedule of dual- and mono-immunotherapy.

I think the safety signals at 6 years were consistent with what we've seen at the 5-year mark. I don't think there were any new safety signals. But overall, it's been a regimen that has been significantly better tolerated based on the new dosing regimen in CheckMate 9LA.

The data also showed that patients that had discontinuations due to the treatment related adverse events still had a 6-year overall survival rate that was around 34 percent, suggesting that the early discontinuation didn't negatively impact long-term benefit.

Dr. Sands:
Well, given the no change in safety signal and the results you've described, how does this shape the way we think about this treatment approach for patients with low PD-L1 expression?

Dr. Dietrich:
Well, in my practice—and I think this is a repetitive signal that we've seen in a number of studies now—the PD-L1 expression at the very top end obviously confers very good long-term responses to PD-1 expression alone. But conversely, the lower we get, especially in the

PD-L1 negative setting, we know we need to do more. And I think it reinforces that CTLA-4/PD-1 combinations with ipilimumab and nivolumab are a viable option to enhance durability of response; it's really what we want to achieve with immunotherapy, where monotherapy by itself wouldn't be as beneficial. And especially when we add additional high-risk factors of squamous cell histology and brain metastases, this is really a strong option and, in my practice, the preferred regimen for PD-L1 negative patients that are able to receive combination immunotherapy.

And when I think about the challenge for the 1/3 of patients that are PD-L1 negative, we're really underserving them with our standard PD-1 approaches. And the combination here becomes very attractive.

Dr. Sands:
As a follow-up to that, you've mentioned some patients or some characteristics for which you would favor this dual immunotherapy. You mentioned squamous, brain metastases, and low PD-L1 expression. Is there a certain patient or characteristic where you're broadly recommending it? Is it those three characteristics? Can you take us through a little bit of the algorithm that you would use when determining which patients to offer this combination to?

Dr. Dietrich:
Yeah, it's a very complex dataset. And I have to say, a lot of the observations are not prospectively evaluated. So part of it is my practice pattern. But I think in general terms, the less options patients have and the more I rely on immunotherapy as their mainstay of therapy, the more I believe that the combinations and the increase in toxicity—even though it is a modest increase, it's definitely more than we would expect from single-agent PD-1 alone—is justified.

I think the PD-L1 is a very good starting point. If the PD-L1 level here is negative, I believe that the PD-1s don't really have a proven dedicated dataset to point to them as necessarily particularly helpful.

I think we see histology as an area of concern. I think squamous is particularly difficult, as we see lesser chemotherapy sensitivity with squamous cell carcinoma. We don't have a good maintenance option, and we also have much less targeted therapy options for a second- and later-line setting. And so I think squamous is a high-risk feature contextualized to the biology.

I do extend it to other subgroups that I think are quite interesting, including the resistance mutations. So if I have a PD-L1 level that is negative but they carry mutations that we've seen in a resistance setting, like STK11 and KEAP1, it certainly warrants a consideration. We know that they confer an immunotherapy—at least a PD-1 immunotherapy—resistance that is of note, so I would extend that.

And then there's some compartments like the brain that are less immunotherapy-accessible. And for those, I believe the CTLA-4 addition, since the early melanoma days, has really been a marker of interest. And we see here really an equilibrium between PD-L1 negative patients that have similar benefits with combination immunotherapy and patients with brain metastases. So if patients have brain metastases at baseline, their long-term outcome is identical to those that don't have brain metastases at baseline at 6 years. And I think that's a very appealing part because we see brain metastases in 30-40 percent of patients at baseline, and it's clearly a compartment that we want to cover.

When I think about this in terms of sequencing, there are no really good options for second-line immunotherapy and follow-up. So the durability of response is really what we're hoping for. The best case scenario is that patients not only live with lung cancer but actually live with a controlled lung cancer beyond treatment.

I think it's a very appealing option to go all in in the first-line setting and continue with a combination immunotherapy approach in the first-line setting. We have to balance that with the toxicities, obviously. But if a patient is fit and interested in achieving the best long-term responses in these high-risk subgroups, I believe it's a very appealing option.

Dr. Sands:
Well, we've certainly covered a lot today. But before we close, where do you see the biggest opportunities for continuing to improve outcomes for these patients?

Dr. Dietrich:
Well, I think there is a three-dimensional construct of biomarkers that I think is very important. As I mentioned, I think we look at the genotypes. They are guiding us very much towards the expectations for immunotherapy, as well as the markers of immunotherapy sensitivity. Obviously, PD-L1 here is the most validated one. This is the marker on which all of our immunotherapies are based in the lung cancer space. But we also look at additional features. In CheckMate 9LA, high tumor mutational burden correlated with better outcomes.

So I think we really have to take into account many factors. It makes it a little bit more complicated, but with a starting point of PD-L1 negativity, the resistance mutations and certain clinical features really provide an opportunity for an underserved population that may

benefit particularly well from the addition of a second immunotherapy agent.

Dr. Sands:
Well, with those forward-looking comments in mind, I want to thank my guest, Dr. Martin Dietrich, for joining me to assess the long-term efficacy and safety outcomes from the CheckMate 9LA trial. Dr. Dietrich, it was wonderful having you on the program.

Dr. Dietrich:
No, thank you so much. It was my pleasure.

Announcer:
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