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6-Year Outcomes from CheckMate 9LA: Efficacy and Safety Across NSCLC Subgroups

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 to examine the six-year efficacy and safety data from the CheckMate 9LA study, which evaluated nivolumab plus ipilimumab and chemotherapy across key metastatic non-small cell lung cancer subtypes, is Dr. Millie Das. Dr. Das is a Clinical Professor of Medicine at Stanford University. Dr. Das, thank you for joining the program today.

Dr. Das:
It's great to be with you here today. Thank you.

Dr. Sands:
So let's just dive right in, Dr. Das. Can you walk us through the key patient subgroups that were analyzed in the 6-year CheckMate 9LA dataset?

Dr. Das:
Yes, absolutely. So I think this was an important trial, and of course, now we're excited to see this long-term follow-up data. So the data that we have from CheckMate 9LA includes stratification by histology, so we're seeing long-term outcomes for our squamous versus non-squamous histologies, and also outcomes for patients across the various PD-L1 levels, including PD-L1 negative and PD-L1 positive subgroups.

And then additionally, there were exploratory analyses evaluating efficacy according to KRAS mutation—whether or not patients had a KRAS mutation—and also whether or not patients had STK11, KEAP1, and TP53 mutations.

Dr. Sands:
With that in mind, let's focus on the long-term efficacy and safety of nivolumab plus ipilimumab and chemotherapy in each individual subgroup. Starting with the squamous histology subgroup, what did we learn? And how has that shaped the approach to first-line treatment decisions in these patients?

Dr. Das:
So with regard to squamous histology, what we're seeing is those patients who had squamous had a 14 percent six-year overall survival when treated with ipi/nivo/chemo compared to five percent in those patients getting just chemo alone. So what this shows me is that we know that these squamous patients in particular don't have as many treatment options, and they can be more challenging to treat. And what we're seeing here, I think, is quite reassuring, that this particular regimen does provide benefit. So this dual checkpoint inhibitor therapy in combination with chemotherapy does provide benefit compared to chemotherapy alone. And so this is certainly a treatment strategy that I would consider strongly in these patients with squamous histology.

Dr. Sands:
Let's talk a little more about that. You highlighted that squamous is a challenging subtype, and certainly that's, I think, many of our experiences. What about on the tail of the curve? I think sometimes with these immunotherapy drugs, the real benefit we tend to see

often is on the tail. What is the durability like within this group?

Dr. Das:
So yes, I think you bring up a great point about the tail of the curve. I think one of the exciting things about immunotherapy in general is the potential for long-term, durable responses and even for the potential of cure in these patients with metastatic disease.

What we are seeing from the six-year data from CheckMate 9LA is, even in these squamous patients, we're seeing the potential for durable responses. Again, I think this is quite exciting. I think there's clearly a difference here—the 14 percent versus five percent in terms of overall survival. And so I think, again, this is corroborating the benefit that we saw.

Dr. Sands:
Turning now to molecular features, what did the data show for patients with KRAS or STK11 mutations? And how does that influence the way you manage these cases?

Dr. Das:
So we know that the patients who were KRAS-mutant still saw an overall survival benefit when treated with the ipi/nivo/chemo combination compared to chemo alone—so at six years, 21 percent overall survival for those patients who were KRAS-mutant treated with the ipi/nivo/chemo versus 10 percent in those patients treated with chemo alone.

We know also that STK11 mutations typically confer poorer prognosis. These patients don't tend to respond as well to immunotherapy. Again, though, in this study of CheckMate 9LA, we are seeing improved outcomes in these patients who are STK11-mutant treated with ipi/nivo/chemo compared to chemo alone.

So when I'm seeing these patients in clinic who are KRAS-mutant and who are STK11 mutant, I do think about treatment escalation with the addition of a CTLA-4 inhibitor, particularly that STK11 mutation subgroup of patients, where I think retrospective data has shown that these patients do less well when treated with chemotherapy plus a checkpoint inhibitor alone. And so I do think that there's a role, potentially, for treatment escalation with the addition of a CTLA-4 inhibitor.

Dr. Sands:
Dr. Das, we've covered a lot of ground, particularly with these subpopulations. It'd be great if you could help us process this and share how it impacts your treatment decision-making. One of the complicating factors of this, of course, is that CheckMate 9LA compares to standard-of-care chemotherapy, but that is not currently really a standard-of-care option at this point. So of course, we need to make some cross-trial comparisons. So how are you using the 9LA data? And what is your algorithm for populations where you're specifically considering nivolumab and ipilimumab with a short course of chemotherapy?

Dr. Das:
Yeah, I think the patients that I'm really thinking more about this regimen for are the patients who are PD-L1 negative and those patients who are STK11 mutant. Again, I think the six-year data from CheckMate 9LA reassuringly shows us that these patients are doing quite well, even at six years, compared to when they are treated with chemo alone. And we know that those patient subgroups don't do as well with just a checkpoint inhibitor with chemotherapy.

So we need prospective trials here, but I think this data does provide me with some reassurance that there is efficacy with dual checkpoint inhibition with chemotherapy in these patients in particular.

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. Millie Das about data from the CheckMate 9LA study, which evaluated the six-year efficacy and safety of nivolumab plus ipilimumab and chemotherapy across metastatic non-small cell lung cancer subgroups.

Now, Dr. Das, it is really impressive that at a six-year timeframe—which is a really long time in lung cancer—we still see those curves separated out in a substantial way, especially in the PD-L1 low and squamous subgroups. Of course, we've also discussed the STK11 and KRAS.

Now, those benefits are impressive and exciting, but of course, the other side of that are the toxicities. Can you outline some of the toxicities from combination nivolumab plus ipilimumab, and then there's a short course of chemo? And also incorporate the importance of multidisciplinary collaboration and the other services you engage in managing some of these toxicities?

Dr. Das:
Absolutely. The addition of a CTLA-4 inhibitor to a checkpoint inhibitor is going to increase the potential for autoimmune toxicity. So this dual checkpoint inhibition does lead to a greater incidence of immune-related adverse events.

Reassuringly, from the six-year update from CheckMate 9LA, there were no new safety signals observed. Nonetheless, I think we all need to be mindful of the possibility of these autoimmune toxicities, and we absolutely need to continue to collaborate with our subspecialists, and a lot of it depends on the organ system involved.

So we know the most common organ systems involved tend to be the lung, colon, or skin, and so it's really common for us to be co-managing patients who have autoimmune toxicities relating to these organs with those disease specialists.

So, for example, a patient who develops suspected autoimmune pneumonitis, we're very closely following these patients along with our pulmonology colleagues. Oftentimes, the diagnosis of autoimmune pneumonitis can be quite challenging, and looking at it radiographically and trying to understand the time course, I think, is really critical.

And so, this is just one of those things that we all need to keep in the back of our minds. And we need to really optimize patient outcomes by thinking about the potential for autoimmune toxicities and starting steroids as early as possible. So again, having that collaboration with our disease specialists in this multidisciplinary way is really going to be important in order to ensure that our patients are getting timely initiation of steroids and that we can get them through that particular toxicity.

Dr. Sands:
Finally, based on this long-term dataset, where do you see the biggest unmet needs or areas that warrant more tailored research going forward?

Dr. Das:
Yeah, I think we alluded to this a little bit earlier. We do need prospective trials and data. A lot of the data that we have right now is retrospective—it's cross-trial comparisons—and so it would be really nice to have more data and trials that we can use to help guide us.

Short of that, I think we need to try to identify better biomarkers to try to predict who really needs dual checkpoint inhibitor therapy versus chemo–IO. I think, of course, with the knowledge that dual checkpoint inhibitors does increase the potential for autoimmune toxicities, we need to really be able to tailor that to the patients who need it.

And as we spoke about, I think the patients who we think really may need that dual checkpoint inhibitor therapy are those patients who are PD-L1 negative, patients who are STK11 mutant, and also potentially our squamous histology patients.

Dr. Sands:
Well, it's clear that we still have a lot to learn, especially when it comes to managing these complex cases. But for now, I want to thank my guest, Dr. Millie Das, for joining me to share the latest data on using nivolumab plus ipilimumab and chemotherapy to treat metastatic non-small cell lung cancer subgroups. Dr. Das, it was wonderful having you on the program.

Dr. Das:
Thank you so much, Dr. Sands, it's always a pleasure speaking with you.

Announcer:
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