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

6-Year CheckMate 9LA Data in PD-L1-Negative NSCLC: Implications for Care

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

Dr. Jackson:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Steve Jackson, and joining me to review the long-term survival and safety data from CheckMate 9LA in PD-L1-negative metastatic non-small cell lung cancer is Dr. Luda Bazhenova. She's a board-certified medical oncologist and a Professor of Medicine at UC San Diego Health. Dr. Bazhenova, thanks for being here today.

Dr. Bazhenova:
It's my pleasure to be here.

Dr. Jackson:
To begin, the latest update from CheckMate 9LA gives us one of the longest follow-ups we've seen in first-line metastatic non-small cell lung cancer, particularly in PD-L1-negative disease where median overall survival has historically been less than one year with chemotherapy alone. From your perspective, Dr. Bazhenova, what makes this data set clinically meaningful right now, and what should clinicians keep in mind when interpreting long-term follow-up data like this?

Dr. Bazhenova:
As we gain more experience with chemoimmunotherapy in metastatic lung cancer without driver alterations, the long-term outcomes are giving us confidence that some patients can do very well with that approach. CheckMate 9LA and CheckMate 227 are the only trials that have reported six years of follow-up data. But other studies, such as KEYNOTE-189, KEYNOTE-024, and KEYNOTE-042, have reported five-year survival outcomes. So I think with the overall wealth of the data, we are now confident in saying that some of the patients do extremely well with immunotherapy in combination with chemotherapy, both with dual immunotherapy and chemo-combination as well as chemotherapy and immunotherapy combinations.

The challenge now is figuring out who will benefit from the dual immunotherapy approach versus the chemoimmunotherapy approach and how to choose between several approved first-line options when we do not have head-to-head comparisons. And when we make those decisions at this point, we are forced to look at the subset analysis. And the subset analysis from CheckMate 9LA gives us some interesting hints about which patient subgroups may benefit more from chemotherapy plus dual immunotherapy. And based on the subgroup analysis, those appear to be patients with PD-L1 less than 1 or STK11 mutations.

Dr. Jackson:
Right. And with that context, let's look at the findings. The six-year data show that a subset of patients treated with nivolumab plus ipilimumab and two cycles of chemotherapy achieved prolonged survival beyond what was historically seen with chemotherapy alone. How should we interpret this long-term survival plateau, particularly in the PD-L1-negative patients?

Dr. Bazhenova:
I think tail of the curve is valuable. So we definitely see a tail of the curve. We think that maybe some of those patients will do very well with chemotherapy. Looking specifically at CheckMate 9LA and the PD-L1-negative subset analysis, I think we can be confident in that up to about 60 to 66 months. But if you look at the patients at risk afterwards, for example at 72 months, for the PD-L1 less than 1 population, there are only 13 and seven patients at risk, respectively, for the dual IO and chemotherapy arm.

While I like to see the tail of the curve because I like my patients to be on the tail of the curve, the challenge here is that I want to know when I start the patient on treatment if they're going to be on the tail. It is not helpful for me after I've been treating a patient for five years to tell them, "You're doing very well, so that means you're probably on the tail." We need to do something different in the beginning of the treatment and try to understand, again, which of the patients with PD-L1 less than 1 are going be on that tail and which of them are not and what we can do differently to intensify or do some other treatments to increase the plateau and the number of patients who reach the tail.

Dr. Jackson:
Now, we're also seeing that patients who achieve an objective response are more likely to maintain disease control over time. Can you tell us how you interpret this durability signal and what it suggests about the potential role of early immune priming with CTLA-4 inhibition?

Dr. Bazhenova:
I think this is consistent with what we know about targeted therapy, chemotherapy, and immunotherapy in oncology. Across those three different strategies, we have established that patients whose cancer respond to treatment are more likely to maintain the response over time compared to the patients who had stable disease. We also know that the depth of the response predicts the durability of the response in targeted therapy and immunotherapy trials.

So what I don't know right now is if this pattern is enhanced with dual IO inhibition or if it has the similar magnitude as the chemo IO with the single immunotherapy drugs. And at this point, we have to do cross-trial comparisons, which is very difficult here because we are comparing CheckMate 9LA, which enrolled both squamous and non-squamous, and KEYNOTE-189, which enrolled non-squamous. And then POSEIDON also enrolled both squamous and non-squamous. So I think preclinically, CTLA inhibition theoretically has the potential of being the agent responsible for durability of response. But again, I keep stressing that this only can be evaluated in head-to-head trials.

What I was surprised to see, however—and I think that underscores the need to do more trials for the PD-L1 less than 1 patients—is that chemotherapy did very poorly for patients with PD-L1 less than 1 percent. Their median duration of response was only four months compared to the median duration of response of 17 months with chemo dual IO. So it's clear that immunotherapy is necessary even if you do not express PD-L1. What we don't know for sure is if immunotherapy by itself is going to be good enough or if you need to do both CTLA-4 and PD-1 inhibition.

Dr. Jackson:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Luda Bazhenova about the long-term survival and safety outcomes from CheckMate 9LA in PD-L1-negative metastatic non-small cell lung cancer patients.

From a safety standpoint, the six-year follow-up shows no new or cumulative immune-related toxicities beyond what's been previously characterized, despite the inclusion of CTLA-4 inhibition. So how does this long-term safety profile shape your approach to using this regimen in clinical practice?

Dr. Bazhenova:
I think this is a very important observation because it gives me confidence that if the patient has done well up to a certain point, continuing immunotherapy does not seem to add additional adverse events. At this point, many of our first-line trials limit immunotherapy to two years. We do not know if continuation of immunotherapy in the first line improves patient outcomes because that study has never been done. But for those patients who would like to continue immunotherapy long term, it gives me confidence that if you haven't gotten into trouble by now, it is unlikely that the new adverse events are going present themselves.

Dr. Jackson:
All right, let's focus on how these findings compare with other first-line approaches, such as chemoimmunotherapy combinations or dual immunotherapy alone. Where do you see this regimen fitting into today's treatment landscape?

Dr. Bazhenova:
So CheckMate 9LA is one of the several approved options. We also have KEYNOTE-189 for patients with non-squamous non-small cell lung cancer doing platinum doublet plus immunotherapy for all comers, meaning all PD-L1 expressions. Then we have KEYNOTE-024, which is monotherapy immunotherapy for PD-L1 more than 50. And then we have KEYNOTE-042, which is a monotherapy immunotherapy for PD-L1 more than 1. We also have POSEIDON, which is very similar to CheckMate 9LA based on patient enrollment. The difference is that POSEIDON had four cycles of chemotherapy and CheckMate 9LA had two. And then we also have CheckMate 227, which is a chemotherapy-free approach using PD-1 and CTLA-4.

What gives me permission to use dual immunotherapy inhibition is we now have three trials using a dual IO inhibition, which is CheckMate 227, CheckMate 9LA, and POSEIDON. And all of those trials show that patients with PD-L1-negative disease consistently show better hazard ratios than patients with PD-L1-positive disease. However, we also need to be very aware that doing dual IO inhibition will result in increased toxicity compared to just single immunotherapy.

In my practice, I do believe that using regimens such as CheckMate 9LA, POSEIDON, or CheckMate 227 is okay for the PD-L1 less than 1 percent patient or PD-L1 patients with a STK11 and KEAP1 mutation. But this is a very controversial statement because we have to balance increased toxicity when using dual IO inhibition. And in the absence of head-to-head comparisons, we are forced to do a subset analysis and cross-trial comparisons, which are difficult to do and flawed to be misinterpreted.

Dr. Jackson:
Lastly, Dr. Bazhenova, how are these six-year outcomes influencing your approach to treatment selection and patient counseling in PD-L1-negative metastatic non-small cell lung cancer?

Dr. Bazhenova:
This is a challenging question to answer, and I think we've highlighted the controversies before. The issue, again, is that this is a subset analysis of the patients. And while it's positive and consistent with other dual immunotherapy trials, it is still a subset analysis. It has to be shared decision-making with the patient, highlighting the fact that dual IO inhibition will result in increased toxicity compared to monotherapy inhibition. You just have to be aware of the side effects. You have to be very proactive in managing those side effects. And it has to be shared decision-making, and this patient needs to be told that there is a potential for increased toxicity when you do dual IO therapy.

Dr. Jackson:
With those practical considerations in mind, I want to thank my guest, Dr. Luda Bazhenova, for joining me to evaluate the final six-year survival and safety findings from the CheckMate 9LA study and their implications for treating PD-L1-negative metastatic non-small cell lung cancer. Dr. Bazhenova, it was great having you on the program.

Dr. Bazhenova:
Thank you so much.

Announcer:
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