Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/long-term-survival-data-in-high-risk-nsclc-insights-from-real-world-practice/35995/

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

Long-Term Survival Data in High-Risk NSCLC: Insights from Real-World Practice

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:
This is *Project Oncology* on ReachMD, and I'm Dr. Jacob Sands. Here with me today is Dr. Joshua Sabari, who's an Assistant Professor in the Department of Medicine at NYU Grossman School of Medicine and a thoracic oncologist. Together, we'll be discussing a recent study that was presented at the 2025 AACR Annual Meeting, which evaluated the 5-year real-world survival outcomes in patients with advanced non-small cell lung cancer with PD-L1 expression less than 1 percent who received first-line immunotherapy-based regimens. Dr. Sabari, welcome to the program.

Dr. Sabari:
Thank you, Jacob, for having me. I'm really excited.

Dr. Sands:
To help set the stage for us, Dr. Sabari, focusing on long-term outcomes with first-line immunotherapy in advanced non-small cell lung cancer, what have major clinical trials found? And why is it important to explore these real-world datasets after those prior trials?

Dr. Sabari:
So first and foremost, it's critical to identify whether the patient in front of you has a driver alteration. For the discussion today, we're talking about patients who are driver mutation-negative, so those who do not have an EGFR or an ALK fusion. In that patient population—the driver mutation-negative patients—it's critical to understand their PD-L1 expression, understand their histology, and then look at other high-risk features. And we'll talk a lot about those today.

But really honing in on PD-L1 expression, if you look at one of the earliest studies, KEYNOTE-024, patients who have high PD-L1 expression—greater than 50 percent—actually do quite well with single-agent immunotherapy. Those patients with lower PD-L1 expression, particularly PD-L1 expression negative or 0, really do need further escalation of therapy. And KEYNOTE-189 showed that the combination of a platinum doublet plus a PD-1 inhibitor really did seem to improve outcomes for patients that were PD-L1 expression less than 50 percent.

So how does this all then play out in the real-world setting? Well, clinical trials have given us these benchmarks, but in the real world, my patients are often older, have more comorbidities, and are generally sicker than the patient population in the clinical trial. So understanding data from the real world really does sort of drive how I think about my clinical practice.

Dr. Sands:
With that background in mind, let's zero in on this real-world dataset that was presented at AACR and how it was designed. What kinds of patients were included, and how were the survival outcomes measured?

Dr. Sabari:
Yes, this is really an impressive undertaking, and I applaud the authors here. This is a retrospective analysis of over 17,000 patients from a real-world database. This is the Flatiron Health database. This dataset looked at patients with non-small cell lung cancer, and it excluded those patients who had actionable driver alterations, such as EGFR or ALK. They also excluded patients who had unknown

histology.

And this retrospective analysis looked at both overall survival and real-world progression-free survival out to 5 years. So we're looking at how well patients did over that 5-year course. And we looked at Kaplan-Meier estimates to assess this. And it's really important because overall survival is king, right? Whether that's in the real world or a clinical trial, when someone dies, if we have the data available—and these datasets are quite robust—we can really make an assumption or a generalization.

Real-world progression-free survival might be somewhat different because we don't generally have scans done at the exact same times as we do in clinical trials, but we can assess that based on clinical documentation, and some of these endpoints that are listed in the charts.

Dr. Sands:
With that background, let's focus on the results, and I like how you highlighted that with real-world outcomes. Because in some cases where we see radiographic progression, that doesn't mean the patient is no longer benefiting from the drug, and in many cases, patients sometimes end up continuing on treatment. And so one outcome is the duration of being on a drug itself, and that can be a meaningful endpoint that sometimes we see a bit more. With all of that, what were the long-term outcomes for patients receiving immunotherapy alone versus immunotherapy plus chemotherapy?

Dr. Sabari:
Yeah, so the 5-year overall survival was really modest across both groups: 17.5 percent 5-year overall survival for those patients who received immunotherapy alone, and 15.8 percent for those patients who received immunotherapy plus chemotherapy. And one could imagine that those patients who got immunotherapy alone probably had higher PD-L1 expression driving that longer 5-year overall survival. But for those patients who had PD-L1 expression that was low or negative—15.8 percent 5-year overall survival—clearly, we need to do better for our patients in our clinical practice setting.

When we looked at real-world progression-free survival—and this is the time from starting therapy to the time of progression—and Jacob, you made an extremely important point here that we don't always have exact timing of scans in the real-world datasets. We sometimes look at start of next treatment or sort of progression clinically. So we really assume that based on the data analysis in these real-world sets. But when we looked at real-world progression-free survival, it showed a pretty dismal similar trend, reinforcing that long-term disease control in this patient population remains a significant challenge.

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. Joshua Sabari about the 5-year real-world survival outcomes in advanced non-small cell lung cancer with PD-L1 expression less than 1 percent.

So given these findings, Dr. Sabari, how might they shape your approach to choosing first-line regimens in clinical practice?

Dr. Sabari:
These are really important results to me because when I walk into a room with a patient and their PD-L1 is greater than 50 percent, I'm pretty optimistic and hopeful that with single-agent immunotherapy, we can see long-term survival, potentially even cure, in about 1/3 of our patients in the prospective clinical trials.

When we're talking about patients who are PD-L1 negative less than 1, this is a patient population that I truly worry about, right? And if you dig deeper into the biology here, why does a patient have a low PD-L1 expression or PD-L1 negative? Maybe it's because of other co-alterations driving poor immune response, such as STK11 or KEAP1. And again, this goes back to looking at the genomics when you do next-generation sequencing to try to better understand the biology of these patients. So when I knock on the door for a new visit and the PD-L1 is negative or low, and on top of that, they have a low or a poor biology of their disease—STK11, KEAP1 co-altered—I do think about using more aggressive treatment in that patient population.

So factor their PD-L1 expression, their genomics, and also their comorbidities, right? Is a patient fit? Do they have COPD, hypertension, hyperlipidemia, or any cardiac disease? If patients are fit and have a very bad biology, I'm generally escalating therapy to use dual checkpoint inhibitors—a CTLA-4 inhibitor and a PD-1 inhibitor—plus/minus chemotherapy.

And we've seen prospective data from CheckMate 9LA—that's chemotherapy and ipilimumab and nivolumab. We've also seen data from CheckMate 227—ipilimumab and nivolumab—as well as more recently from the POSEIDON regimen of durvalumab, tremelimumab—a PD-L1 inhibitor—and a CTLA-4 inhibitor plus chemotherapy that these patients with low PD-L1 expression and high-risk genomics seem to benefit. And again, I think this real-world analysis here from the Waterhouse group really shows that in the real-world setting, we need to do more for this patient population.

So I think in a PD-L1 negative patient who's more fit, I would opt to use chemotherapy and immunotherapy and may even add a dual

checkpoint inhibitor in this population.

Dr. Sands:
I think one aspect of this real-world dataset that stood out was the especially poor outcomes in patients with squamous histology or low PD-L1 expression. So focusing on those subgroups, how do you interpret these results from this dataset? I think you've kind of alluded a little bit to that already, but what unmet needs does this highlight?

Dr. Sabari:
Yeah, we know that squamous histology, although less common in the United States now compared to adenocarcinoma, is a very high-risk disease, and unfortunately, we don't have actual genomic alterations. And I agree with you that for patients who are PD-L1 low and have squamous histology, which we know is very difficult to treat, I'm generally thinking about dual checkpoint inhibitors or chemotherapy and immunotherapy combinations. I very rarely use single-agent PD-1 or PD-L1 inhibitors in this patient population, even when they're PD-L1 high. I mean, the squamous cell population generally, for me, needs to be treated a bit more aggressively. And I think this real-world dataset really does show us that in the real-world setting, this is one of the most significant unmet needs in our clinical practice. Squamous cell histology as well as squamous cell histology that is PD-L1 negative is a group where I think we all should be escalating care.

One important point to make here, Jacob, is a lot of our squamous cell patients—and I'm sure you see this in your practice—are older, less fit, and have a heavy smoking history. So we do have to balance using aggressive regimens that have potentially higher side effect profile with patients' goals of care as well as their comorbidities.

Dr. Sands:
Yeah, certainly areas of need. I also just want to call out that if you compare this to 10 years ago, the fact that we're seeing patients surviving out beyond 5 years in these numbers, even with single agents, represents a real step forward. And then in the combinations in trials, we're seeing separation that looks like an even further step in those more difficult-to-treat subpopulations. And so I want to highlight that just in the prior years, we've really seen a lot of progress in lung cancer treatment.

But with all of this in mind, I do have one final question for you before we close, Dr. Sabari. Where do you see the most promising areas for research or new treatment approaches, especially for these high-risk patients?

Dr. Sabari:
Yeah, I think the fact that we're talking about different patient populations—I know when we both trained in practice, everyone got chemotherapy in the frontline setting, and our differentiator was histology alone. Now that we're looking at genomics and we're looking at PD-L1 expression, we're better able to subset populations that have higher-risk disease and may not benefit from conventional therapeutics that are available or approved now.

Some novel checkpoint pathways that we're looking at now, such as anti-TIGIT, unfortunately, have not seemed to pan out to date. LAG-3 is another novel checkpoint inhibitor that is still being looked at. But I think we're moving more into adoptive T-cell therapies and sort of personalizing our therapeutics for individual patients.

So when you see a patient with squamous cell histology with a low PD-L1 expression, we may look further at that patient; are they MTAP-deleted? This is a new sort of entity that we're thinking about. Would they benefit from a specific subset of medicines—PRMT5 inhibitors, for example—versus if you have an adenocarcinoma patient who has a low PD-L1 expression. We're starting to better sub-specialize or sub-segment out our populations in an effort to better escalate treatment there.

So I think that in the future—if I had a crystal ball here, Jacob, and curious about your thoughts as well—I think we're going to be delivering personalized medicine in the coming 5 to 10 years for our patients, so there's going to be a very steep learning curve for medical oncologists in this setting. Because right now, we still give similar treatments to all patients; I think we're going to start to give individualized treatments to particular patients, specifically those in higher-risk subgroups.

Dr. Sands:
I agree. There is a lot that is in the works that's exciting, and I'm so grateful to be practicing medicine in a time where we are seeing substantial ongoing progress, although obviously there's still a ton of work to do.

But with those final comments that bring us to the end of today's program, I want to thank my guest, Dr. Joshua Sabari, for joining me to discuss this data on the impacts of first-line immunotherapy combination regimens in patients with PD-L1 advanced non-small cell lung cancer. Dr. Sabari, it was wonderful having you on the program.

Dr. Sabari:

Dr. Sands, thanks for having me. I always appreciate discussing with you.

Announcer:
This episode of *Project Oncology* was sponsored by Bristol Myers Squibb. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!