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(866) 423-7849

Durable Outcomes in NSCLC: 6-Year Survival Findings 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:**
This is *Project Oncology* on ReachMD, and I'm Dr. Jacob Sands. Joining me today is Dr. Sandip Patel, who's a Professor of Medicine and medical oncologist at the University of California, San Diego. Together, we'll be reviewing the 6-year findings from the CheckMate 9LA study related to overall survival and response durability in patients with metastatic non-small cell lung cancer who discontinued first-line nivolumab plus ipilimumab and chemotherapy. Dr. Patel, welcome to the program.

**Dr. Patel:**
Thank you, Dr. Sands. Great to be joining you.

**Dr. Sands:**
So let's start with some background, Dr. Patel. Why has this particular regimen of nivolumab plus ipilimumab with a short course of chemotherapy become part of the treatment landscape for metastatic non-small cell lung cancer?

**Dr. Patel:**
It's a great question, and I think it fundamentally gets to the role of CTLA-4 inhibition with ipilimumab—in this case—in non-small cell lung cancer. We have a history where PD-1 monotherapy in the frontline setting really only works in a biomarker-selected population. And then given that the durability of response in patients with metastatic non-small cell lung cancer really comes to immunotherapeutic component, can we avoid the early drop-off that we see in the Kaplan-Meier curve in patients that are on IO-only regimens while limiting exposure to chemotherapy but retaining that long-term benefit?

And so the idea of giving two cycles of chemotherapy with a PD-1 inhibitor—nivolumab —with the CTLA-4 inhibitor ipilimumab and then continuing dual immune checkpoint blockade as maintenance after those two cycles of chemotherapy really try to represent an optimal way of delivering this therapy to avoid that early drop-off in patients who don't respond, give time for a patient's own immune system to catch up to the cancer and be activated against the tumor, and then continue the maintenance immunotherapeutic approach.

**Dr. Sands:**
Now, with that background, let's turn to the CheckMate 9LA study. Can you briefly remind us how it was designed?

**Dr. Patel:**
Yeah, so the CheckMate 9LA study was two cycles of chemotherapy with ipilimumab 1 mg/kg every 6 weeks and nivolumab given every 3 weeks versus chemotherapy alone. So I think it's important to know that when this trial was ongoing, chemotherapy alone was still a standard of care where this trial was conducted.

And the goal was to try to maximize the benefit of immunotherapy and limit the amount of chemotherapy that was needed to really just overcome that initial hump, both individually in patients in terms of getting their immune systems activated but also at a population level where we've seen in study across study—initially those IO-only studies—that patients did a little worse than patients on chemotherapy alone. And so can you have your cake and eat it too?

And this led to global approvals and guideline inclusion with overall survival and progression-free survival benefits compared to

chemotherapy alone.

**Dr. Sands:**
So as you highlighted, this did lead to a change in the standard of care as far as treatment options, I think one of multiple options, essentially. So with all of that background, let's zero in on the new 6-year results. What stood out to you about the overall survival data, especially in the patient subgroups like those with low PD-L1 or squamous histology?

**Dr. Patel:**
Yeah, it's a great question. And so this, I think, fundamentally goes to the question of: in which patient populations do I think about CTLA-4 inhibition, given the lack of prospective randomized controlled trials compared to chemo PD-1 regimens?

And so when we look at some of the subsets from CheckMate 9LA, the groups that really stand out to me are patients who are PD-L1 negative—which is about 1/3 of patients—patients with squamous histology, patients with brain metastasis, and patients with STK11/KEAP1 co-mutations.

Now, when we look at some of these cohorts and at the 6-year overall survival rates from this study, patients received up to 2 years of treatment. So many of these patients are years after their last dose of treatment—because the real drug now is their own immune system keeping the cancer away—and we see some durable benefit.

For example, in the PD-L1 less than 1 percent or PD-L1 negative population, the 6-year overall survival rate is 20 percent. So 1 in 5 patients, even if they're PD-L1 negative, are still alive, compared to 7 percent with chemotherapy alone. Where in squamous histology, 14 percent of patients are alive at 6 years compared to 5 on chemotherapy alone.

And so I think it really goes to the point that for certain subgroups of patients that have either more aggressive disease biology or disease characteristics, the addition of CTLA-4 inhibition really brings up the long-term durability of benefit. And we've seen this in melanoma. We've seen this in renal cell carcinoma. And I think with this dataset, we've seen that in subgroups of non-small cell lung cancer—especially PD-L1 negative, squamous histology, brain metastasis, and STK11/KEAP1—CTLA-4 inhibition in this study with ipilimumab helps these patients reach those durable remissions.

**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. Sandip Patel about the 6-year data from CheckMate 9LA evaluating overall survival and response durability in patients with metastatic non-small cell lung cancer.

Now, Dr. Patel, one of the more intriguing exploratory findings was the survival rate in patients who had discontinued treatment due to adverse events. What did the data show? And what do you make of that?

**Dr. Patel:**
Yeah, I think it's a really interesting phenomenon. We've seen it in multiple different clinical trials of immune checkpoint blockade. Melanoma really was at the vanguard of this. And so in patients in CheckMate 9LA for metastatic non-small cell lung cancer, those patients had to stop treatment due to treatment-related adverse events—immunologically-related adverse events in particular—and they had a 6-year overall survival rate of 34 percent.

And so this goes to what I think is best termed as “immunostat function,” suggesting that these patients get a degree of autoimmune activity due to overall immune activation. It's a true double-edged sword. And so it's cutting the tumor, but it's also leading to immune-related adverse events. But these patients actually have lasting benefit because those immune cells continue to persist and attack the tumor, but unfortunately, it also leads to autoimmune consequences that are hopefully optimally managed with steroids and other immunosuppression.

Now, this isn't to say that you must have an IRAE—or immune related adverse event—to get benefit; it’s just that those that do can still confer clinical benefit long term. And I think, to me, the real-world setting gets to the point that we don't want to be overly aggressive with immunotherapeutic re-challenge because many of these patients will get that lasting benefit long term without the risk of continued immunotherapy exposure.

**Dr. Sands:**
Alongside that, we also saw time to subsequent therapy and duration of response data that seemed to support a long tail of benefit. How do you think about the durability of responses here, especially after treatment discontinuation?

**Dr. Patel:**
When I think about immune checkpoint blockade, when you select the right patient population, there's a durability of response that

hopefully lasts for years and years. In this clinical trial, patients received 2 years of protocol-mandated treatment. We're talking about 6-year overall survival. And so these patients have been off treatment longer than they've been on treatment, and they're still getting durable remissions. And almost 1 in 5—or 19 percent—of patients with response in the combination arm with dual immune checkpoint blockade and two cycles of chemotherapy maintained that response out to 6 years.

And so I think that's why it's so important to select patients for the right treatment regimen, including those patients who may be optimal candidates for CTLA-4 blockade, because we're able to get 1 in 5 patients with metastatic disease out to 6 years. This is really a high water mark given that historically, the number of patients that would make it to even 5 years with non-small cell lung cancer in the metastatic setting was in the single digits and a handful really in historical case series.

**Dr. Sands:**
Given these findings—and you've described various subsets and their responses and highlighted the tail of the curve as well—how do you see this data shaping future strategies for the first-line management of metastatic non-small cell lung cancer? And also, I'd ask to add in which patients you're really focusing this treatment for—what is the change in your practice as far as the utility of this regimen?

**Dr. Patel:**
Yeah, it's a great question. I think the most important thing we can do for our patients is appropriate staging, right? And so we do radiographic staging and histologic diagnosis, but I think the molecular diagnosis is key. If you have a canonical-driving EGFR mutation, ALK fusion, or ROS1, these are patients better served via targeted therapy in addition to some other actionable driver mutations.

For those patients that lack those targetable frontline driver mutations for which their upfront therapy optimally is generally a pill, these patients benefit from immunotherapeutic strategies, in particular with smoking-related non-small cell lung cancer. And so chemo PD-1 strategies remain the standard of care in that setting.

In particular, when we talk about CheckMate 9LA and the introduction of CTLA-4 with a PD-1 with chemotherapy, patients who are PD-L1 negative, squamous histology, brain metastasis, and STK11/KEAP1 co-mutations benefit from the integration of these strategies.

So I think it's important to do that next-generation sequencing test, which can be done as a liquid biopsy as well, in order to best determine which patients benefit from targeted treatment versus chemo PD-1 versus chemo PD-1 CTLA-4, as in the CheckMate 9LA regimen.

**Dr. Sands:**
What do you see as the next steps in evaluating this combination regimen of nivolumab and ipilimumab in any other subpopulations where you think there's particularly something to study?

**Dr. Patel:**
Yeah, it's a great question, Dr. Sands. I think as we're looking at this regimen, I think we've learned a lot across multiple different disease types. I think the areas that we need to think about are, for example, when we're using chemo PD-1 in the neoadjuvant setting, is CTLA-4 either an option upfront or after treatment? And the early clinical data suggests maybe it's actually ADCs, for example—antibody-drug conjugates—that may be the best partner. Are radiation strategies with SBRT indicated? How much does CTLA-4 add compared to PD-1?

But I think when we look at the 6-year overall survival data, we see here a robust option for a subset of patients who have more immunotherapy-refractory disease, and many of whom can get long-term survival. Here we're looking at 6-year overall survival, even if they're PD-L1 negative, even if they have brain metastasis, and even if they're years after their last dose of treatment.

And so I think it's important for our patients to maximize their opportunities for long-term remission. And I think this is one of the regimens that can help us.

**Dr. Sands:**
As those forward-looking comments bring us to the end of today's program, I want to thank my guest, Dr. Sandip Patel, for joining me to discuss the survival and outcomes in those who discontinued for toxicity from the CheckMate 9LA trial. Dr. Patel, it was wonderful having you on the program.

**Dr. Patel:**
Thanks for having me, Dr. Sands.

**Announcer:**
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