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Optimizing First-Line Care for PD-L1–Low Metastatic NSCLC

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

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Joining me to evaluate the latest clinical evidence and strategies informing our first-line treatment decisions for patients with PD-L1–low or PD-L1–negative metastatic non-small cell lung cancer is Dr. Deepa Rangachari. She's an Assistant Professor of Medicine at Harvard Medical School and at the Thoracic Oncology Program at Dana-Farber Cancer Institute in Boston. Deepa, thanks for being here today.

Dr. Rangachari:
Terrific to be here with you, Charles.

Dr. Turck:
Well, to help set the stage for us, Deepa, would you tell us what makes first-line treatment decision-making particularly challenging in patients with PD-L1–low or PD-L1–negative metastatic non-small cell lung cancer?

Dr. Rangachari:
Well, first things first, the fact that we can even have a conversation about a question of this kind is really a reminder of the progress made, progress that needs to be made in this field still, and the inherent heterogeneity of this entity that we're calling metastatic non-small cell lung cancer. It's really not a monolithic entity, and we know that each individual patient can have a very different outcome depending on a variety of factors.

In this case, we're talking about a molecular biomarker—PD-L1—where multiple studies have now demonstrated that while these patients can derive benefits from checkpoint inhibitors, including the same tolerable and durable efficacious benefits that patients with high PD-L1 can experience, the relative proportion of patients with low or absent tumor PD-L1 expression that have that durable outcome is far less. So in general, when we're talking about the management of these patients, we're talking about combination therapy strategies, either combination chemotherapy with the checkpoint inhibitor, dual-checkpoint reinhibitor regimens, or even chemotherapy and dual-checkpoint inhibitor regimens.

And I think the biggest issue here is the Goldilocks issue; what we really are striving for in every patient, regardless of tumor PD-L1 expression, is what I want to think of as optimal therapy and outcome, which shouldn't be conflated with maximal therapy and outcome. Just because somebody has adverse features, that doesn't always mean that they're going to need the maximum number of drugs to have a good benefit.

But the problem is many patients with low or absent tumor PD-L1 will need more. And so I think in high tumor PD-L1, we have pretty good evidence to suggest that checkpoint inhibitor monotherapy is very durably and tolerably efficacious. And in low or absent tumor PD-L1, we're generally reaching for combination therapy strategies. But buried in there somewhere is always that unexpected patient with low or absent tumor PD-L1 expression who may have derived tremendous benefit from a more parsimonious regimen. And I think we should continue to look for tools to help us stratify these patients, appreciating that PD-L1 as a standalone is certainly the best-vetted molecular biomarker that we have, but it is an imperfect biomarker.

Dr. Turck:

Given those challenges, let's take a look at some of the latest clinical evidence. In both the KEYNOTE-189 and -407 trials, chemoimmunotherapy demonstrated overall survival benefit regardless of a patient's PD-L1 status. So with that being said, what do those findings tell us about the role of combination strategies in PD-L1–low and PD-L1–negative patients?

Dr. Rangachari:
Yeah, I think what these studies tell us is that the addition of some other category of agent to the checkpoint inhibitor backbone is one way that we can overcome some of the relative or intrinsic immune resistance that may be present in those tumors. But what's important about KEYNOTE-189 and -407 is there were patients with all levels of tumor PD-L1 expression. And it's not to say that the high PD-L1–expressing tumors and patients didn't benefit from the combination strategy. But in that case, it was more a question of, do we actually need to do all of that to get the desired benefit?

So I think it comes back to this idea about not conflating optimal therapy with maximal therapy. How do we get it just right for each patient? And for high PD-L1–expressing tumors and for most patients, single-agent checkpoint inhibitor is going to go the mile. But for those patients who have low or absent tumor PD-L1 expression, we really know that for the most part, we do need to give them combination regimens.

Dr. Turck:
So when combination therapy is the preferred approach, how do you balance the incremental efficacy we see in clinical trials with safety and tolerability concerns in real-world care?

Dr. Rangachari:
Yeah. So I think it really depends on which combination regimen we're talking about. When we combine platinum-doublet chemotherapy with a single-agent checkpoint inhibitor, we know the individual characteristics of the different drugs and their relative toxicities, and they're not necessarily terribly overlapping. But when we're talking about combination therapy that's defined by combining checkpoint inhibitors, for example, we know that there can be a roughly doubling of immune-related adverse events. And so I think that is something that we always need to think about when we're talking about combining drugs. We need to think about overlapping versus non-overlapping toxicities.

And then we really need to think about how those different mechanisms of toxicity will affect the patient—whether that means that we're going to have to modify the dose of the regimen in the setting of chemotherapy, or in the setting of checkpoint inhibitors, we're really not talking about dose modification. In that case, if someone experienced a significant toxicity, we're talking about holding or discontinuing the treatment altogether and/or administering steroids.

Dr. Turck:
For those just tuning in, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Deepa Rangachari about first-line decision-making strategies in PD-L1–low and PD-L1–negative metastatic non-small cell lung cancer.

So, Deepa, now that we have an understanding of the role of combination strategies, let's examine how patient-specific factors can shape those decisions in practice. Beyond PD-L1 status, what patient- or disease-related characteristics do you consider when selecting a first-line treatment?

Dr. Rangachari:
So I think this is incredibly important because as we've just talked about, PD-L1 has emerged as one of our best-vetted biomarkers, and yet it's not a comprehensive biomarker and it does not trump all of the other factors relevant to a patient's health, well-being, and future care.

So other things that I'm commonly thinking about in addition to or alongside PD-L1 status is first and foremost—and we're talking about the management of lung cancer in 2026—the molecular profile. Knowing the comprehensive tumor molecular profile is a mandate. It's imperative. We need to know. For example, is there an actionable driver genetic alteration or not? And some oncogenic driver alterations will render checkpoint inhibitor therapy and PD-L1 status irrelevant. Other oncogenic driver alterations like KRAS don't necessarily render discussions about immune checkpoint inhibitor therapy or tumor PD-L1 status irrelevant, but they may affect how we think about the optimal single-agent or multi-agent regimen.

Similarly, if we think beyond PD-L1 and tumor molecular profile and if we think about a patient that has very high disease burden, bulky disease burden, clinically threatening, and/or very symptomatic disease burden, if they are otherwise clinically and functionally brisk—even if the tumor PD-L1 expression is very high and there's no actionable alterations—that is another example of a patient where I may favor combination therapy rather than checkpoint inhibitor monotherapy because we may only have one chance in that patient's case; we have to put our best foot forward with the very first regimen that we try because we may be in that circumstance where we cannot try

one therapy, and if it doesn't work, intensify that therapy or try one therapy, and if it doesn't work, we may not have time to then pivot to a second-line therapy.

And then lastly, always we must think of the person before us and the priorities and values that they may have surrounding their treatment along with the schedule, side effects, and toxicity management. And also, we have to think about intrinsic things about who they are and their medical history, including things like autoimmune disease or baseline end-organ dysfunction that may also impact our therapeutic stratification.

Dr. Turck:
As a follow-up to that, how do actionable mutations like EGFR or ALK alterations influence your first-line treatment approach?

Dr. Rangachari:
Yeah. So this is a very critical question, and it comes down to what we said just now. In 2026, for all treatment-eligible and treatment-desiring patients with advanced and frankly even earlier stages of non-small cell lung cancer, comprehensive tumor molecular profiling is really a mandate. And the reason it's a mandate is because when we do such tests, we unearth whether the patient's tumor may have certain actionable genetic alterations. And we know that not all actionable genetic alterations are created equal in terms of their impact on upfront treatment selection.

For example, in the context of certain highly actionable genetic alterations like EGFR, ALK, and ROS1, these commonly occur in patients who develop lung cancer in the context of limited to no tobacco use. And what we know in that circumstance is regardless of what the tumor PD-L1 expression is, those patients really do not derive any meaningful benefit from upfront checkpoint inhibitor therapy; they really should be treated with upfront targeted therapy.

On the other hand, though, there are certain other types of actionable genetic alterations like KRAS where we know that we could, in theory, apply an oral targeted therapy. But because that alteration tends to occur in the context of significant tobacco exposure and other factors that render a more favorable immune microenvironment, upfront checkpoint inhibitor therapy is actually the right answer for somebody that has a KRAS mutation.

So I think knowing first and foremost what, if any, actionable alterations are present in the tumor and then understanding that different actionable alterations have different impacts on the tumor microenvironment and response to different types of therapies is of critical importance. Some of those alterations are not going to respond well to checkpoint inhibitor therapy regardless of tumor PD-L1 expression and should be treated with evidence-based frontline targeted therapies. Other categories of actionable genetic alterations do have a very favorable environment for use of checkpoint inhibitors, and those patients should be treated with checkpoint inhibitors plus or minus chemotherapy or dual-checkpoint blockade, depending on that profile.

The final thing to think about is that whenever we're thinking about targeted therapies and checkpoint inhibitor therapies, we really want to think about safety of sequencing these agents. We've seen a number of trials in the lung cancer space where combining targeted therapy and immune therapies or rapid cycling or sequencing of targeted therapy to checkpoint inhibitor can lead to excess rates of immune-related adverse events far more than we might otherwise suspect. And so whenever we're thinking about this question, we're not only thinking about optimal treatment efficacy, but we are also taking into consideration matters relating to safety of the therapy.

Dr. Turck:
Before we wrap up, Deepa, what's the key takeaway for clinicians treating patients with PD-L1–low or PD-L1–negative metastatic non-small cell lung cancer?

Dr. Rangachari:
So I think the bottom line here is in the setting of low or absent tumor PD-L1 expression, we are, in general, going to need to do more to achieve a meaningful and durable benefit for the patient. Checkpoint inhibitor monotherapy for most of these patients who are otherwise treatment-eligible and desiring and have adequate end-organ function should consist of some form of combination therapy. I think it's fair to say at this point that there is reasonable equipoise about which of the combination strategies might be preferred. Certainly, we can combine platinum-doublet chemotherapy with a checkpoint inhibitor, we could combine dual-checkpoint inhibitor therapy, or a third option is to combine platinum-doublet chemotherapy with dual-checkpoint inhibitor therapy.

And at the end of the day, treatment decisions should be made on an individualized basis, considering very person-specific and disease-specific factors as best as we can assess at this point in time.

Dr. Turck:
Well, with those key takeaways in mind, I want to thank my guest, Dr. Deepa Rangachari, for joining me to share these first-line treatment decision-making strategies for patients with PD-L1–low or PD-L1–negative metastatic non-small cell lung cancer. Deepa, it

was great having you on the program.

Dr. Rangachari:
Charles, thanks very much for an engaging discussion.

Announcer:
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