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Managing High-Risk Subgroups in 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 assess the clinical evidence that's guiding our treatment decisions for high-risk subgroups in metastatic non-small cell lung cancer are Drs. Melina Marmarelis and Deepa Rangachari. Dr. Marmarelis is an Assistant Professor of Medicine at the University of Pennsylvania in Philadelphia. Melina, welcome to the program.

Dr. Marmarelis:
Thanks so much for having me.

Dr. Turck:
And Dr. Rangachari is an Assistant Professor of Medicine at Harvard Medical School and at the Thoracic Oncology Program at Dana-Farber Cancer Institute. Deepa, it's great to have you with us as well.

Dr. Rangachari:
Charles, delighted to be here.

Dr. Turck:
Well, let's start our discussion with you, Deepa. When it comes to high-risk subgroups in metastatic non-small cell lung cancer, what makes these patients particularly difficult to treat?

Dr. Rangachari:
Well, I think this is a terrific place to start the conversation because it acknowledges a very important point that advanced-stage non-small cell lung cancer is a highly heterogeneous condition. And so for each individual patient, we need to think about unique disease biology and person-defining characteristics.

The first question, of course, then is, what is the definition of high-risk subgroups? And I think there are many evolving definitions of how we might think about that. High-risk may be defined by the tumor's molecular profile—what oncogenic driver alterations are present or not present as it may be. And in the setting of certain oncogenic driver alterations like KRAS, for example, we know that the presence of certain co-alterations in tumor suppressor genes like STK11/LKB1 can impact the response to therapy.

Similarly, if we move away from genetic alterations and think about molecular characteristics, things like low or absent tumor PD-L1 expression can impact whether we think of somebody as being high- or low-risk. And again, risk is not necessarily defined by the clinical threat that the disease burden presents; that's a different category of high-risk—for example, people who have clinically threatening disease, including brain metastases. But when we talk about molecular and genomic alterations, high- and low-risk are more defined by presence or absence of certain things and the predicted response to our standard therapies.

So I think, overall, it's a very important thing to acknowledge that there are different risk groups, that high- and low-risk can be defined variably by anatomic, pathologic, genomic, and molecular features, and that in general, when we identify the things that signal a higher-risk subgroup, we're often dealing with higher-grade or more aggressive disease biology. We're going to have to do more in terms of combining therapies or intensity of therapies to achieve the same outcome, the evidence-based strategies may provide less durable outcomes, or there may be more heterogeneity or equipoise as to what the optimal systemic therapy strategy should be.

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Dr. Turck:
Well, with that context in mind, let's turn to you now, Melina, and examine subgroup data from recent trials. In squamous non-small cell lung cancer, KEYNOTE-407 showed that pembrolizumab combined with carboplatin and a taxane improved overall survival across all PD-L1 subgroups. And this benefit was consistent despite the aggressive biology of this disease. So with all that being said, how do you interpret these findings when selecting a first-line therapy for patients in this subgroup?

Dr. Marmarelis:
I think the first thing this brings up is actually how heterogeneous PD-L1 is as a biomarker. So we know now that if you take biopsies of even different areas of the same tumor, you might get a different PD-L1. So certainly, the expression of PD-L1 increases your chance of having a response to immunotherapy, but the absence of PD-L1 does not mean, A, that it's not present elsewhere, and B, that you won't have a response to immunotherapy.

Then, of course, we know that chemotherapy in addition to immunotherapy can improve that response by exposing additional neoantigens potentially with the cells that are killed with chemotherapy. So it's really a synergistic combination approach that is suitable for all levels of PD-L1, both in squamous but also in non-squamous. So I think this was a huge trial in squamous cell lung cancer. It's very exciting to see this type of result in this very high-risk population.

Dr. Turck:
And for patients with brain metastases, subgroup analyses from KEYNOTE-189 and CheckMate 9LA suggest that immunotherapy-based combinations can improve survival, although outcomes can vary based on factors like steroid use and symptom burden. So if we come back to you, Deepa, what impact do these data have on your treatment decisions for these patients?

Dr. Rangachari:
Yeah, Charles, the brain metastasis question doesn't go away. This is something that our patients often face, and I think what data from these combination chemoimmunotherapy trials highlight is that the blood-brain barrier is not an impenetrable fortress. There is clearly a role for it, and patients can benefit from highly effective systemic therapy in the brain. But oftentimes, as these studies tell us, and as we have already talked about today, in order to control hard-to-reach or high-burden anatomic locations of disease, we often have to do more. And the "do more" in this case often can involve combining chemotherapy with a checkpoint inhibitor.

But I think a couple of things have to be considered. One, many of these people will benefit from some combination multimodality strategy that involves combinations of systemic therapy and local therapy or brain radiation. And as strategies for brain radiation have become more effective and less toxic—for example, stereotactic strategies—I think there are a lot of evolving unanswered questions about, is there an optimal sequence for drug and local therapy? Which one should go first? Do we do all of them in short order? And so I think that's one question that is not clearly answered by all of the data that we have.

And I think the other thing that we're always thinking about is the things that we have to do for damage control in and around management of brain metastases, things like steroids; how does that impact the systemic therapy that we are using? We know that corticosteroid doses as low as prednisone 10 to 20 milligrams per day can have lymphotoxic effects that can affect the responses with immune checkpoint inhibitors, and yet we should not read that as if somebody has symptomatic brain mets and intracranial edema, we're not going to give them steroids. So I think we're often balancing some competing factors, and there is both progress in figuring out how to do that and opportunity to do even better.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Melina Marmarelis and Deepa Rangachari about what we need to consider when treating high-risk subgroups in metastatic non-small cell lung cancer.

With the subgroup data in mind, let's shift gears and explore how these findings influence our real-world decision-making. Melina, given the complexities of managing brain metastases—including the need for local therapies like stereotactic radiosurgery or whole-brain radiation, as well as the impact of corticosteroid use—how do you approach sequencing systemic therapy and local treatment?

Dr. Marmarelis:
So thankfully, we now have a lot of tools to be able to offer more precise treatment of brain metastases, and we are more and more avoiding radiation to the whole brain. Sometimes though, we need to utilize whole-brain radiation to get better control of the CNS. And so it really starts with a conversation with my radiation oncology colleagues about what type of radiation a patient is going to need for CNS control. And then my part of that conversation is, what systemic therapy am I thinking about using? Does it have any CNS activity? And based on those two things, we come up with the timing of the radiation versus the systemic therapy.

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In general, for whole-brain radiation, I do try to get that in before starting systemic therapy to minimize the effects that systemic therapy could have on the increasing toxicity from whole-brain radiation. But that's certainly the minority of patients that we're using whole-brain radiation for.

When we're using stereotactic or Gamma Knife radiation, which is much more precise, then I think it's perfectly reasonable to fold it in between cycles of chemoimmunotherapy, for example. But again, it's a conversation with my radiation oncology colleagues about the risk of the systemic therapy worsening the side effects from radiation.

And in terms of steroids, I think about it a little bit, but I also am cognizant that it's most important to reduce the edema post-radiation because patients can get very symptomatic from that. And short courses of steroids don't have a large effect on overall outcomes when it comes to treating with immunotherapy, so I'm not as dogmatic about stopping the steroids if I'm starting immunotherapy.

Dr. Turck:
And if we take a look at one more high-risk subgroup, Deepa, for patients with low or absent PD-L1 expression and high disease burden, chemoimmunotherapy remains a cornerstone for rapid cytoreduction. Dual immunotherapy, on the other hand, may offer longer-term benefit but less predictable early control. So what tips the scale when you're deciding between these two approaches?

Dr. Rangachari:
In general, when I'm thinking about chemoimmunotherapy versus combination immunotherapy strategies, I'm often asking myself, "What is pushing me to favor a chemotherapy-sparing regimen in a given case?" Because I'm balancing that against the reality that while chemotherapy has some unpleasant, socially unacceptable, and unfavorable toxicities, the corollary to that is that the toxicities that we see in patients who get chemotherapy tend to be far more predictable and time-limited. If you give somebody a platinum doublet, they have fatigue and nausea predictably for perhaps seven to 10 days out of the 21-day course. That is not pleasant, but we know that there are ways that we can prevent it and curtail it, and, with time, those things will generally abate.

With checkpoint inhibitor toxicities, we can be faced with a difficult ability to predict onset of toxicity. We know that when we combine checkpoint inhibitors, the likelihood of significant immune-related adverse events is substantially higher, and once the toxicity commences, the patient may be left with lifelong effects. For example, in the case of endocrinopathies, there's lifelong dependence on thyroid replacement, which is not the end of the world, but it is a consequence that we shouldn't overlook.

Dr. Turck:
In our final moments here, Melina, let's bring all this together. Considering factors like histology, disease distribution, performance status, and patient preferences, how do you integrate all these variables to select the most appropriate treatment strategy for high-risk patients?

Dr. Marmarelis:
Well, I think this is where the nuance comes in and seeing the patient in front of you. I think there are a lot of different factors at play here—certainly, the performance status of the patient. How active are they? How likely are they to bounce back from chemotherapy or immunotherapy side effects? What would long-term steroids do to a patient's comorbid conditions like diabetes if they were to get a more moderate or severe side effect from immunotherapy?

And then as Deepa was talking about in the beginning, we're really getting very precise about the risk here and the potential for a response from immunotherapy with the molecular subtypes. So when I'm seeing STK11 and KEAP1, I'm worried that patients are not going to respond to just a single immunotherapy, so I'm looking more for dual immunotherapy-type approaches or more advanced clinical trials.

So there are definitely a lot of different factors, including molecular, histology, and performance status, and then I talk with the patient about the different risks and options there.

Dr. Turck:
Great comments for us to think on as we come to the end of today's program. And I want to thank my guests, Drs. Melina Marmarelis and Deepa Rangachari, for joining me to share these key strategies and considerations for treating high-risk subgroups in metastatic non-small cell lung cancer. Melina, Deepa, it was wonderful having you both on the program.

Dr. Marmarelis:
Thanks for a great conversation.

Dr. Rangachari:
Likewise, Charles and Melina. Thanks for a great discussion.

Announcer:

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