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Evidence-Based Care for PD-L1-Negative Non-Small Cell Lung Cancer

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:

This is *Project Oncology* on ReachMD, and I'm Dr. Steve Jackson. Here with me to share their perspectives on how we can use the latest evidence and guideline recommendations to guide treatment decisions in PD-L1 negative non-small cell lung cancer are Drs. Thomas Marron and Apar Kishor Ganti. Dr. Marron is a Professor of Medicine in the Division of Hematology and Medical Oncology and a Professor of Immunology and Immunotherapy at the Icahn School of Medicine at Mount Sinai in New York. Dr. Marron, welcome to the program.

Dr. Marron:

Thank you so much for having me.

Dr. Jackson:

And not only is Dr. Ganti a Professor in the Division of Medical Oncology, but he's also the Dr. and Mrs. D. Leon Research Fund Chair in Internal Medicine at the University of Nebraska Medical Center. Dr. Ganti, it's great to have you with us as well.

Dr. Ganti:

Yeah, thank you for having me. It's a pleasure to be here.

Dr. Jackson:

So let's dive right in, starting with you, Dr. Marron. Trials such as KEYNOTE-189, KEYNOTE-407, and CheckMate 9LA have expanded the evidence base supporting first-line immunotherapy-based treatment for patients with metastatic non-small cell lung cancer without actionable driver alterations. Additionally, the current NCCN and ASCO guidelines include multiple recommended first-line approaches for patients with PD-L1-negative disease. So how do you decide among all of these options in real-world practice, especially when your patients don't closely resemble the patients enrolled in the clinical trials?

Dr. Marron:

Well, I think that is a key point: the patients who are in these clinical trials rarely represent our average patient. Patients without driver mutations are typically smokers with many comorbidities, and so you always have to take that into consideration and realize that responses that we see in real practice are not necessarily going to be those that we see in clinical trials. And I think that one of the important things is to look at real-world data that has followed up these studies. And the way that I look at these is I really do it entirely based on PD-L1 status.

So for PD-L1-high patients, unless they have a very large tumor burden and I want to quickly cytoreduce them with chemotherapy, I will stick with PD-1 blockade alone. We have real-world data showing that in the PD-L1-high patients, you don't actually get an overall survival benefit if you start with PD-1 plus chemo, and so you can get away with just PD-1 alone, watching them closely. And then if patients respond but then eventually progress or if they don't respond at all, which is relatively rare in a very high PD-L1 population, then we can just add on chemotherapy. We start with PD-1 plus chemo, and if they progress on that, then you really are looking at more of either a salvage regimen as a second-line option or clinical trials; they should always be in the forefront of your mind, both in the first-line and second-line setting.

And then finally, for the PD-L1-negative patients, they really do quite poorly in general. However, when we saw the data from CheckMate 227, which was looking at PD-1/CTLA-4 versus chemo, interestingly, the greatest benefit was in those patients that were PD-L1 negative, specifically the squamous cell carcinoma subset. So those are the patients who are classically smokers and have no PD-L1. But it appears that by adding CTLA-4 blockade in those patients, you really can get some significant benefit. And so if I have PD-L1-negative patients, especially if patients don't have too much tumor burden, I will start with PD-1/CTLA-4 alone, which is the CheckMate 227 combo.

If patients have a significant amount of disease though, and I'm worried about waiting a couple of months while we start with PD-1 and CTLA-4 alone, I will do the CheckMate 9LA cocktail, which is a platinum doublet plus PD-1 and CTLA-4. CheckMate 9LA was a study looking at just two cycles of chemotherapy. This is a cocktail that our patients tend to tolerate relatively well.

The last thing I'll say is that in the PD-L1-negative patients, I think in that subset in particular, it's extremely important to look at the mutational profiling because we know that a pretty decent subset of those PD-L1-negative patients have bad prognosticator mutations. And so these include STK11, KEAP1, and SMARCA4. So I think that I'd always put in a plug for a clinical trial in that setting in particular. It's always good to search out any additional or new options that might be available in the front-line setting in the setting of a clinical trial.

Dr. Jackson:

Turning to you now, Dr. Ganti, in patients who may not resemble those enrolled in the major first-line clinical trials, particularly those with ECOG performance status of two or higher, what's your approach to selecting one of the available guideline-supported first-line treatment options?

Dr. Ganti:

That is a great question, and it's something that we routinely see in clinical practice because most of these clinical trials want the best of the best, and our patients that we routinely see in real life hardly resemble those patients who are in the clinical trials. And so it's a big challenge to use the clinical trial data on patients who may not necessarily fit those clinical trial criteria.

Having said that, when I look at patients with performance status two or higher, I tend to divide them into two separate groups. Number one, is the patient's performance status bad because of the underlying cancer? In other words, were they doing fine six months ago or a year ago, and when they were diagnosed with the cancer, their performance status worsened? I think that's a significantly different group from those patients who had bad performance status at baseline, meaning they had a number of comorbid conditions which potentially can affect how you treat these patients.

So my approach is a little bit different based on those two sets of patients that I've just mentioned. So if someone was doing very well and their performance status worsened because of their cancer diagnosis, I tend to use the same regimens that were used in the trial because I feel that if we were able to get the cancer under control, their performance status would improve significantly. And so for those patients, I would not hesitate to use a platinum-doublet with an immunotherapy agent. Especially for PD-L1-negative patients, I would use either a platinum-doublet with immunotherapy or even a doublet-immunotherapy using the CheckMate 227 regimen of ipilimumab and nivolumab.

If, on the other hand, the patient has had a bad performance status due to multiple comorbidities that predated the cancer diagnosis, then I tend to be a little bit more careful with them because we know that these individuals typically do not tolerate treatment very well.

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 Drs. Thomas Marron and Apar Kishor Ganti about applying clinical evidence and guidelines to the real-world treatment of PD-L1-negative non-small cell lung cancer.

Now, a complex scenario involves the management of patients with brain metastases. Data suggests that immunotherapy combinations can have intracranial activity, but local therapies like stereotactic radiosurgery remain essential. So if I stay with you, Dr. Ganti, how do you coordinate systemic and local treatments for patients with brain mets?

Dr. Ganti:

So this is a very common problem that we encounter in clinical practice. And in my practice, my approach is to work very closely with the radiation oncologist in patients who have brain metastases. Typically, we would discuss these patients at the tumor board, or I would call the radiation oncologist about these patients and develop a management plan based on each patient's individual characteristics.

What do I mean by that? So, for example, if I have a patient who has a small asymptomatic four-millimeter brain metastases, then I would start off with systemic therapy using whichever regimen is appropriate in that individual, but I closely monitor the brain

metastases. If I have someone, on the other hand, who's symptomatic, I would reach out to the radiation oncologist to have them treat this patient with stereotactic radiosurgery before I initiate any systemic therapy. I would coordinate this with the radiation oncologist and work very closely with them, especially in symptomatic patients.

Dr. Jackson:

And before we close, I'd like to ask each of you to share one clinical pearl you'd want colleagues to remember when making treatment decisions for patients with PD-L1-negative non-small cell lung cancer. Dr. Marron, let's hear from you first.

Dr. Marron:

When you're looking at patients who are PD-L1 negative, you really have to look at them as a very high-risk population. These are patients where you really should be searching out any clinical trials that are available because I think that there's a variety of next-generation therapies that are being added on to our current standards of care, and those patients probably stand the greatest benefit from those trials.

Dr. Jackson:

Thanks, Dr. Marron. And how about you, Dr. Ganti? What's your clinical pearl?

Dr. Ganti:

Treatment is not necessarily one size fits all. We have to take into account the patient's performance status, other comorbidities, and the presence or absence of other mutations like STK11 and KEAP1, which predict lack of response to immunotherapy. So all of these have to be taken into account when deciding on a treatment regimen for these patients.

Dr. Jackson:

As those clinical pearls bring us to the end of today's program, I want to thank my guests, Drs. Thomas Marron and Apar Kishor Ganti, for joining me to discuss how we can optimize treatment selection and patient management in PD-L1-negative non-small cell lung cancer. Dr. Marron, Dr. Ganti, it was great having you both on the program.

Dr. Marron:

Thanks for having us.

Dr. Ganti:

Thank you for having us.

Announcer:

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