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Keeping Pace in Lung Cancer: Guidelines and the Future Direction of Immunotherapy in NSCLC

Announcer:
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Dr. Socinski:
The upward trajectory of medical knowledge associated with the use of immunotherapy in the management of non-small cell lung cancer has reached a fever pitch. Today I’m joined by Dr. Eddie Garon from UCLA. We’ll be discussing not only the intricacies of current immunotherapeutic choice based on patient PD-L1 status, but we’ll also try to take a glimpse into the future. Where can the use of immunotherapy in non-small cell take us, moving forward? This is CME on ReachMD, and I’m Dr. Mark Socinski. Dr. Garon, welcome to the show.

Dr. Garon:
Thank you very much for having me.

Dr. Socinski:
Dr. Garon, what first-line immunotherapy options are available to us when we have a patient with non-small cell lung cancer that we’ve done comprehensive testing, so we know there’s no driver mutations, and the patient has a PD-L1 status of 50% or higher?

Dr. Garon:
Sure, so first, I think one thing we have to, sort of, evaluate over time is what a driver mutation is, and that is expanding, and for some of those indications, that, I think, is maybe beyond what we’ll talk about today. We still do consider immunotherapy in those situations, like KRAS mutations, certainly perhaps BRAF mutations. But let’s assume that sort of none of the typical driver mutations are present and there is a PD-L1 expression of at least 50%. There are basically 3 monotherapy PD-1 or PD-L1 inhibitors that are approved in that indication. Pembrolizumab was the first to be approved. It was based on the KEYNOTE-024 study. This showed a really impressive median overall survival of 30 months, which really was not something that we were used to seeing. There was, subsequently, KEYNOTE-042 study, which enrolled not only patients at the 50% cut point, but also the 1% cut point. That group, even the patients with 50% or better, did a little worse than the really spectacular results of KEYNOTE-024, and in clinical practice, it’s hard to know what the reality is between those. In the interim, there have been 2 other agents that have been approved in that setting. One is atezolizumab, a PD-L1 inhibitor, and also cemiplimab, which is another CTLA4 inhibitor. One other sort of immunotherapy approach that does not use chemotherapy that is approved in that subset, as well as those with lower PD-L1 expression, is the combination of ipilimumab as well as nivolumab, which also has an approval in that greater than 50%.

That being said, there still is also the possibility of using chemotherapy along with immunotherapy, and although there is currently a cooperative group effort to evaluate which of those approaches is better, this still remains a topic that is hotly debated amongst oncologists in this area.

Dr. Socinski:
Are there patients in your practice that have high expression, greater than 50%, that you use, for instance, KEYNOTE-189 or IMpower150 – the chemo/IO strategy?

Dr. Garon:
So in my own practice, I remember that prior to the approval of the combination of chemotherapy and immunotherapy, I used to say that maybe about 15% of cases would feel like an emergency, and we would need to treat with the combination of chemotherapy and immunotherapy. I would say that I have revised that upward. I think that I use chemoimmunotherapy a little more than I maybe thought I would in patients who have high PD-L1 expression, that being over the 50%. I have, in some cases, done it in younger patients, arguing that I think that there may someday be data that shows that it is better. Obviously, in situations where we think there is an emergent, sort of, approach that we need, there is a larger fusion that we're having trouble with drainage, that there is some organous function that we just feel that we really need to quickly start therapy; those are indications. One other group that I at least consider are those who have not been smokers. That group has a pretty wide confidence interval in the monotherapy studies. The cemiplimab study didn't even include them, but they did do quite well on the KEYNOTE-189 study. And so that is also a group that I have looked at combinations of chemotherapy and immunotherapy. I would feel more confidence in the likelihood of response based on the available data if some of these PD-L1 expression were 90% than if it was 50%. And additionally, although I would not necessarily obtain data on tumor mutation burden specifically for this purpose, I think that somebody who had a higher tumor mutation burden, in that patient I also might feel less obligated to add chemotherapy, whereas somebody who maybe had a lower or light or never-smoking history and had a low tumor mutation burden, that might be a situation where I would also consider chemoimmunotherapy, even in the setting of high PD-L1 expression.

Dr. Socinski:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mark Socinski, and here with me today is Dr. Edward Garon. Today we're focusing on the intricacies of current immunotherapeutic choice based on patient PD-L1 status and providing a glimpse of what the future may hold for the use of immunotherapy in non-small cell lung cancer.

Let's shift gears a little bit and tell us how you manage those patients in which the PD-L1 is between the 1%-49% range.

Dr. Garon:
Pembrolizumab monotherapy is approved in that setting. I and many of my colleagues have been reluctant to do that. I think that many of us have found that may be the case. This is also an area where the combination of ipilimumab and nivolumab is approved, although the data is not as strong, and I have generally looked very hard in this group to give the combination of chemotherapy and a PD-1 or PD-L1 inhibitor. I think the right answer, absolutely, is the combination of chemoimmunotherapy.

Dr. Socinski:
So what about the negative patients, the PD-L1 negative? What's your strategy there?

Dr. Garon:
So I think that is a group where, clearly, chemotherapy and immunotherapy has been my standard approach. One of the most polarizing discussions in the field right now has been the role of ipilimumab and nivolumab in that setting. And that is not part of the approved indication for the combination as part of the CheckMate-227 study, although it is part of the indication for the combination of ipilimumab and nivolumab along with chemotherapy. It's part of the CheckMate 9LA study. I think the reason that it is polarizing is that the study design actually specifically excluded these people from the primary analysis for whether or not the drug combination worked, and therefore the FDA did not approve it. That being said, in many respects, the data there was the most impressive data that was seen as part of the study, and it is something that is available in the NCCN. I personally have been a little reluctant to use it outside of its FDA approval, noting that it's a subset analysis, but I definitely have colleagues that feel very strongly otherwise, based on the strong data in a randomized study as part of the CheckMate 227. What has been your take on that?

Dr. Socinski:
I've kind of continued to stick with histology-based chemo plus IO. Occasionally I'll throw in bevacizumab and use the IMpower150 regimen. Then again, occasionally, you have patients with very borderline renal function, and we can't forget there's an approval for carbo and nab-paclitaxel and atezolizumab, based on IMpower130. So there are lots of options here, and that's what makes it interesting to have these sorts of discussions.

Dr. Garon:
Absolutely.

Dr. Socinski:

Let's kind of turn our attention now to some exciting new data and get some perspective from you.

We recently saw an update of the PACIFIC trial, with now 5 years' survival, which was actually quite exciting. We were kind of leveled off it awhile, with regard to new strategies in stage 3, and certainly we've seen a significant increase in the long-term, you know, 3, 4, 5 years' survival from PACIFIC. Your perspective on that finding?

Dr. Garon:
I agree with you. That's really exciting. I remember that it wasn't very long ago that I described stage 3 disease and stage 4 disease with anecdotes of patients who had apparently been cured. That's not what it feels like in the era of PACIFIC. You have a real number of patients who are doing very well after their chemoimmunotherapy and durvalumab. Although there is clearly some pulmonary toxicity that is seen in the studies, it was not prohibitive. And I would say in practice, although some have questioned whether it's maybe a little bit higher than what would be expected based on the studies, I felt it to be a very reasonable approach that we've been able to give to patients. And I think the most interesting thing to me is I feel differently about locally advanced disease at this point. I don't necessarily view it the way I used to, which is something where we had pretty low expectations for good outcomes.

The initially approved approach was the combination of pemetrexed and carboplatin along with pembrolizumab. In the setting, the approvals are histology-specific, so there was also, with pembrolizumab, an approval along with carboplatin and paclitaxel, or nab-paclitaxel, for squamous. There have been different approaches that different studies have had. Some of them include both histologies. The CheckMate 9LA, that has been the case.

The EMPOWER-Lung 3 looked at the combination of chemotherapy plus a PD-1 inhibitor, and that was one of the most recently presented of these combinations. At ESMO, there was also the POSEIDON study looking at durvalumab and tremelimumab along with chemotherapy that, again, looked across histologies. And there also have now been a few studies looking at PD-1 or PD-L1 inhibitors along with chemotherapy, and the results have generally been consistent across the class.

Dr. Socinski:
I would agree. Certainly has created some enthusiasm about this new strategy, and of course, the exciting thing about the PACIFIC data is that it's overall survival.

Dr. Garon, we're kind of getting at the end of our time. This has certainly been a fascinating conversation. Before we wrap up, can you give us something to share with the audience, your one take-home message?

Dr. Garon:
I think the one take-home message is although there are certainly many gaps in terms of our therapy, every once in a while, I have a chance to step back and marvel about how different my clinic feels from when I started my clinic. I started in 2006. Frontline therapy for everybody was carboplatin and paclitaxel, and the outcomes were generally poor. I think it's just so exciting now to have a clinic that just feels very different than that, to have long-term relationships with many of my patients where I've seen them over years, watched their children grow up, watched them have grandchildren. I just think that it is exciting to have seen this sort of progress and looking forward to continued progress in the years ahead.

Dr. Socinski:
I would echo that, but my clinic goes back to starting in 1989, so you can only imagine the differences that I've seen over my career. But I completely agree with you. I tell anyone who wants to listen to me that we're seeing things in lung cancer we never saw before. And it's really become the poster child for targeted therapies and immunotherapies, and our outcomes are getting better.

Unfortunately, that's all the time we have today, so I want to thank the audience for listening in and thank you, Dr. Garon, for joining me and for sharing your incredibly valuable insights. It was great speaking with you today.

Dr. Garon:
Really nice speaking with you, and thank you very much for having me.

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