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Keeping Pace: The Role of Immunotherapy in the Frontline Setting

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Dr. Socinski:
While advanced non-small cell lung cancer remains incurable, innovations and treatment and new insights into the molecular pathogenesis of the disease have led to the development of treatments that significantly extend overall survival. New scientific and clinical data have emerged rapidly, leading to changes in the standard of care. How will these newer therapeutics be utilized in everyday clinical practice? This is CME on ReachMD, and I’m Dr. Mark Socinski.

Dr. Ramalingam:
And I’m Dr. Suresh Ramalingam.

Dr. Socinski:
Welcome, Ram. So let’s get started. So with ASCO just wrapping up, I’d like to know what kind of caught your eye related to the immune checkpoint inhibitors, specifically in the front-line setting, and how do you think this fits into everyday practice, post-ASCO?

Dr. Ramalingam:
Thanks, Mark. There were some very interesting abstracts related to lung cancer at ASCO. When we think about the sphere of immunotherapies, I want to highlight three key abstracts. All three of them were in the oral session, and I had the privilege of presenting the results for the CheckMate -227 trial. This report was an update where we compared the combination of ipilimumab and nivolumab, a chemotherapy in the front-line therapy for non-small cell lung cancer. At this year’s meeting, we had longer follow-up from the patients enrolled in the trial, and we were able to report that the three-year survival rate was approximately 34% for patients treated with ipilimumab and nivolumab. The number was fairly similar for those with a PD-L1 expression of greater than 1% and a PD-L1 expression less than 1%. We also saw that the duration of response to ipi and nivo was almost 3-fold higher compared to what patients achieved with chemotherapy alone. And finally, the safety profile was very tolerable. Most of the autoimmune adverse events happened in the first six months. So this report confirmed that the combination of ipilimumab and nivolumab is effective as front-line therapy in both PD-L1 high and low patients, and it also coincided with the recent FDA approval of nivo and ipi in the front-line setting for patients with PD-L1-positive disease. And this abstract was followed immediately by the second abstract, which I’m going to talk about, which was the combination of chemotherapy just for two cycles along with nivo and ipi. This was presented by Dr. Martin Reck and colleagues, called the CheckMate -9LA trial. Here, patients with newly diagnosed lung cancer, advanced stage disease, were randomized to either chemo alone in the control group or two cycles of chemo with ipi and nivo, which was subsequently continued after the concurrent phase with chemo. The overall survival endpoint for this trial was met. It was 0.66. The PFS hazard ratio was also very similar. Similar hazard ratios were seen in squamous and non-squamous patients. The benefit was seen regardless of the PD-L1 expression. So, this trial showed that adding those two cycles of chemotherapy to ipi and nivo was associated with overall survival benefit. And interestingly, this

regimen was also approved by the FDA just a few days ago. So, these two studies highlight the potential role of ipi and nivo in the front-line therapy setting. I think the benefit is seen in both the PD-L1 positive and negative patients. In my practice, for patients with PD-L1 expression greater than 50%, I still continue to use pembro, and now we have atezolizumab as an option. For PD-L1 less than 50%, I think ipi/nivo belongs in the conversation as we talk about chemo plus PD-1 innovation as another potential strategy.

Dr. Socinski:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mark Socinski, and I'm joined by Dr. Suresh Ramalingam. We are discussing the recent advances in the treatment for non-small cell lung cancer and how they pertain to everyday clinical practice.

So Rama, I want to ask you, in clinic obviously we all embrace comprehensive molecular testing as a standard of care, and let's assume that we don't diagnosis any sort of oncogenic driver that may take us a couple of weeks to get that. We typically know PD-L1 status initially. I just want to kind of get your thoughts about management of those patients who are above 50% – say 90 to 100% – how you look at that population.

Dr. Ramalingam:
Sure. the PD-L1 greater than 50% population accounts for almost 25 to 30% of our patients who don't have a driver mutation. For them, we have two options now. Pembrolizumab, which has been around for a while, and atezolizumab that has recently been approved. I think these are both effective as monotherapy and belong very nicely in the front-line setting for the high PD-L1 patients. There are a smaller subset of these patients who have more bulky disease, more symptoms at the time of presentation, that I might consider adding chemotherapy with PD-L1 or PD-1 inhibition.

Dr. Socinski:
I think to our listeners, that's an important point. I do find that, probably in my practice – and maybe it's just me – you know, probably half of my patients with strong PD-L1 expression may have very bulky disease, may be very symptomatic. And I think your point – that adding chemotherapy, you know, there've been no direct comparative trials to date, but indirect comparisons – you buy about a 20% higher response rate. And this may be a population that has the need for a higher response rate with bulky disease and lots of disease-related symptoms.

Dr. Ramalingam:
So, Mark, how do you manage the low PD-L1s? I think the high PD-L1s, there is now fairly good consensus across the spectrum. When you have a patient with PD-L1 less than 50%, what's your practice?

Dr. Socinski:
I must say, I think this is a population that I am very reluctant to use immunotherapy alone. I have not, kind of, embraced the KEYNOTE-042 message here. I will treat most of those patients with chemo/IO combinations. One of the issues that I consider is, "Is there a role for anti-VEGF therapy in the use of bevacizumab?" And that would now also be true in those patients who are greater than 50%, that I'm going to use chemotherapy in that combination. Bevacizumab would be an option in that population, too, but I don't know how you feel about that. But certainly the less than 50%, in the negative group of populations, I have, up until the – you know, recent data we have from CheckMate -227 and -9LA, I've used either the KEYNOTE-189 regimen or IMpower150 in the non-squamous, and then the KEYNOTE-407, which is a carboplatin with your choice of taxane with pembrolizumab. I don't know, do you have any differing opinions there, Ram?

Dr. Ramalingam:
No. My approach has been very similar until recently, Mark. The bigger question now is, "How are we going to incorporate the combination of nivo and ipi in our practice?" And based on the data that I've seen – I've been part of some of the clinical trials with nivo and ipi – one of the things that strikes me about this regimen is the fact that the responses are durable and we seem to be able to push more patients into the tail of the curve, where they're alive three, four years later. So for that reason, I think the nivo plus ipi regimen merits consideration in patients with low PD-L1 expression.

Dr. Socinski:
You know, I would echo that, you know, I think we started the conversation here by saying that we still consider this disease for the most part non-curable. However, you know, I think we are, with longer follow-up, beginning to understand that there may be some patients that have a very robust immune response, in which control of disease can happen for a long time. And maybe there are patients who might be cured by that population – by that approach.

Dr. Ramalingam:
Absolutely. And Mark, one question that we will all have to figure out is if we give ipi and nivo, would we give them those two cycles of chemotherapy based on CheckMate -9LA? And here again, it may be a similar approach what we talked about for those symptomatic

disease/high disease burden patients, where those two cycles of chemo may be helpful. I don't know what you think about that.

Dr. Socinski:
Yeah, I don't know. I'm still kind of thinking about this new data and, you know, I was having a conversation with a colleague over the weekend during virtual ASCO, and, you know, the comment that I made was, particularly when you're using a regimen like carboplatin and pemetrexed, it's very easy to give four cycles of this regimen. So I don't know what the advantage is of cutting it, or truncating it at two cycles in this particular setting, because most of us feel that our patients can tolerate four cycles of that particular regimen quite well. Of course, obviously, there are also maintenance considerations with pemetrexed there, too. I'm still struggling after the presentations at ASCO on CheckMate -227 and -9LA, you know, how to incorporate the combination of nivo and ipi into my day-to-day practice. Ram, what are your thoughts?

Dr. Ramalingam:
My feeling is the two features that set apart the ipi/nivo combination are, number one, it has the ability to provide durable, long-term responses. Number two, it is also a regimen that you don't have to give chemo with, which means you can have an additional line of therapy for a patient when they progress on ipi plus nivo. So for patients with lower PD-L1 expression greater than 50%, I would definitely consider ipi/nivo for front-line therapy. Now, if the patient has more disease burden and is very symptomatic, just like we talked about for patients with high PD-L1 expression where we give chemo with immunotherapy even in the low patients, one could consider the 9LA approach of giving two cycles of chemotherapy and then adding ipi/nivo with it and continuing that on. So, that's how I see this in my practice in the upcoming months.

Dr. Socinski:
One of the questions that I wanted to ask you, though, is, getting back to those PD-L1 negative patients, I did get the sense in your presentation that maybe, if I remember correctly, the hazard ratio was a bit more robust for the PD-L1-negative population. And is that in everyday practice today? Do you feel like that's a niche for the nivo/ipi compound?

Dr. Ramalingam:
I do. As you rightly point out, the hazard ratio for the PD-L1 negative patients for overall survival was 0.62 with nivo plus ipi. And it is part of the NCCN recommendations, though the endpoint for PD-L1-negative patients for overall survival was a secondary endpoint of the trial. And therefore, it's not in the FDA label for nivo/ipi combination. Now, the 9LA combination, of course, is approved by the FDA, regardless of the PD-L1 expression. So I think in the PD-L1-negative patients, certainly, nivo plus ipi seems to be very effective and definitely merits consideration.

Dr. Socinski:
Yeah, that's great, Ram. So from my vantage point, I think one of the biggest takeaways from today's – or the recent data – is that there's really a renewed hope for therapies that may have a much bigger impact. And I'm just wondering, where do you think we're going from here moving forward? We've had kind of the – what I refer to as the immune-tsunami over the past three to four years. Where do we go next?

Dr. Ramalingam:
I think we're now in a better place to personalize therapies for lung cancer patients, be it targeted therapies or be it immunotherapy, and figuring out who should get IO/IO combination chemo plus IO and immunotherapy alone. And as a result, our patients are at a greater chance of experiencing long-term survival. I think the next step is going to be, how do we overcome resistance to immunotherapy when that happens? And what can we do to prevent the emergence of resistance? And finally, we still need to look at novel combinations to broaden the percentage of patients who benefit from immunotherapy. Right now, we still see only about a third of the patients derive those durable, long-term benefits.

Dr. Socinski:
Thanks, Ram, that was great. Unfortunately, that's all the time we have for today, so I want to thank our audience for your participation and thank you, Dr. Ramalingam, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Ramalingam:
Thank you for having me, Mark.

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