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Keeping Pace: The Use of Immunotherapy in Mutation-Positive Non-Small Cell Lung Cancer

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Keeping Pace: The Use of Immunotherapy in Mutation-Positive Non-Small Cell Lung Cancer” is provided by Prova Education and is supported by an independent educational grant from Bristol Myers Squibb, Lilly, and Merck.

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Dr. Socinski:
While advanced non-small cell lung cancer remains incurable, advances in treatment and new insights into the molecular pathogenesis of the disease have led to the development of treatments that significantly extend overall survival. Scientific and clinical data is emerging on the role of immunotherapy in mutation-positive non-small cell lung cancer patients, so how will these therapeutics be utilized in everyday clinical practice? This is CME on ReachMD, and I’m Dr. Mark Socinski.

Dr. Lopes:
And I am Dr. Gilberto Lopes.

Dr. Socinski:
So, let’s get started, Gilberto. We just wrapped up ASCO recently, and there were some implications of some new data and emerging information that we saw. The first thing I’d like to kind of talk about is the CheckMate 227 and CheckMate 9LA. These were two recent indications by the FDA based on those two trials, and I’d like you to just, you know, briefly tell us what you thought of it and how are you integrating it into your clinical practice?

Dr. Lopes:
Absolutely. The presentation of both trials and the approval by the FDA definitely brings us more options in our armamentarium, and it’s become a little tricky for many of us to actually know where to slot all of the potential treatments that we have for our patients now. We have clearly made immunotherapy part of our first-line treatment, and we now depend on things like PD-L1 expression as well as, of course, the absence of EGFR mutations and ALK translocations to decide which patients would get immunotherapy with or without chemotherapy in the first line. What these two trials bring to the table is a potential option of using fewer chemotherapy cycles, and that was with the CheckMate 9LA in which patients received chemotherapy for four cycles – which would not be a standard of care now but was when the trial was planned – or got chemotherapy for two cycles with nivolumab and ipilimumab, and that treatment of the immunotherapy was maintained after the four cycles of chemotherapy as well. And the results were clearly significant both clinically and statistically, showing a median of overall survival that improved from about 11 months to about 15 months. And we did also have at ASCO continued follow-up on CheckMate 227 showing the three-year update showing that the overall survival has held around 17.2 months in the median, and we now see survival up to 36 months of 34 percent with nivo plus ipi versus 15 percent with chemotherapy alone, and, of course, these certainly qualify as new standards of care.

What’s difficult is to replace what we have been using with chemotherapy plus immunotherapy in the first line based on KEYNOTE and

IMpower studies, suggesting that this is our standard of care. So, who are those patients that we might consider using just two cycles of chemo or just ipi/nivo for patients is the big question. For us, it has been mostly patients that would have contraindications to chemo or who would be very strong in their options about not wanting to use chemotherapy. Otherwise, for most patients, we do tend to use chemotherapy plus immunotherapy with a PD-L1 of 0 or 1 to 49 or even more than 50 if patients have symptoms or their preference is to go for something with better response rates.

Dr. Socinski:
Yeah, I agree. I, you know, I've been struggling since this data and the FDA approval, you know, because the control arm on the two CheckMate trials you so elegantly summarized was chemotherapy alone, and none of us are using chemotherapy alone anymore. As you pointed out, the new standard is chemoimmunotherapy, and so I have to admit it's not entirely clear to me how to fit this in. I think this is a great area where it would be nice to have biomarkers to kind of figure out where those patients were.

I also want to get your thought on – there was a trial presented, abstract 9503, I believe, that was a CITYSCAPE trial. We're all looking for what's going to happen after PD-1/PD-L1 inhibition. You know, we talked about CTLA-4 inhibition with the nivo/ipi stuff, but this is an anti-TIGIT tiragolumab plus atezolizumab in this setting. I want to get your perspectives on that trial.

Dr. Lopes:
CITYSCAPE was a very interesting trial building on a phase I trial in preclinical information suggesting that TIGIT is an important checkpoint pathway in the treatment of lung cancer. TIGIT stands for the T cell immunoreceptor with immunoglobulin and ITIM domains, and this is an inhibitory receptor that is expressed on tumor-infiltrating T cells and NK cells. And the idea behind using the monoclonal antibody tiragolumab is that this can block this inhibitory checkpoint and, with that, increase the efficacy of immunotherapy in patients with lung cancer.

CITYSCAPE was designed as a first-line study. It's a randomized – but it's a phase II randomized study with 135 patients. Patients who did not have EGFR mutations or ALK translocations and who did express PD-L1 at the level of at least 1 percent by the 22C3 immunohistochemical assay were randomized to receive tiragolumab and atezolizumab versus atezolizumab and a placebo as would be one of the options in standard of care for at least some patients. And the trial primary endpoints were overall response rate and progression-free survival, and we did see a benefit in both of those endpoints presented by Dr. Melissa Jones and at ASCO this year. The response rate was 16 versus 31 percent favoring the inclusion of the anti-TIGIT monoclonal antibody, and the median progression-free survival improved from 3.58 to 5.42 months, and this was a difference that was statistically significant and brings us to a potential new treatment.

Of course these need to be confirmed in a larger phase III trial, and especially the difference between the response and the outcomes for patients with PD-L1 between 1 and 49 versus those with 50 percent and above needs to be looked into in more detail because the differences were quite clear with the response rates of 24 versus 66 percent for the combination versus atezolizumab alone for patients with a TPS of 50 percent or greater, and we didn't see very significant differences in the population of patients with 1 to 49. These results are being looked into in a larger phase III trial, and we hope that that will become a standard of care in the near future.

Dr. Socinski:
Yeah, pretty impressive results for the greater than 50 percent PD-L1-positive subgroup, but really underwhelming results for the lesser patients as you pointed out. So obviously, more to come in that area.

Let's transition to a study that you're obviously very familiar with – KEYNOTE-042 – and talk a little bit about the subgroup analysis surrounding KRAS-mutant patients and give us your thoughts there and what the message was.

Dr. Lopes:
I presented the results of KEYNOTE-042 based on KRAS mutations at the ESMO Immuno-Oncology meeting while we could still travel last year. I haven't been in a medical meeting since then. And the interesting thing was that we have come to learn that patients with EGFR and ALK mutations and translocations really don't seem to benefit from immunotherapy, at least as single agents. And we're going to to talk a little bit more about that when we talk about patients who have failed tyrosine kinase inhibitors. But what we wanted to know was what was the relationship between KRAS mutations and, in particular, of the G12C specific KRAS mutation in patients who were treated with pembrolizumab versus chemotherapy in KEYNOTE-042. And what we showed was that patients who did have KRAS mutations actually seemed to benefit more from pembrolizumab versus chemotherapy than patients in the overall study population and that the response rates were quite significant and quite high, in excess of 75 percent for patients who have this specific G12C mutation.

So, KRAS mutations seem to be associated with increased expression of PD-L1 and with increased TMB – tumor mutational burden – so we don't know yet if that's an independent factor or predictive factor for KRAS or if this is because it goes together with those two non-predictive factors. What it does tell us is that patients that have KRAS mutations should not be kept away from getting

immunotherapy, be it as a single agent for patients with PD-L1 expression in excess of 50 percent or in combination with chemotherapy as we usually use for most patients today.

Dr. Socinski:
Now, you mentioned earlier we would get to the EGFR subset of patients. We're not going to address first-line treatment. I think we all agree based on the FLAURA data that osimertinib is the standard of care. But eventually, patients run out of benefit from that agent. What are you doing in the second-line setting? And do you think there's a role for immunotherapy in that setting?

Dr. Lopes:
We do believe there's a role for immunotherapy in that setting, and we do base that determination on the IMpower150 study that you know very well. We did have a subset of patients that was presented at the European Lung meeting last year. Martin Reck presented it if I'm not mistaken –

Dr. Socinski:
Yes.

Dr. Lopes:
– showing that we had about 40 patients or so plus/minus in each one of the three arms in IMpower150. And it does clearly show that response rates, progression-free survival, and quite possibly and probably overall survival seem better, and what to me is fascinating is that the arm that had bevacizumab was the one that we actually saw the difference.

So, I think there is something into VEGF inhibition as we have seen for trials combining tyrosine kinase inhibitors and inhibitors of the VEGF pathways, such as bevacizumab and ramucirumab, and I do believe that there's a role that – for patients who have failed all potential options in EGFR and tyrosine kinase inhibitors, that they should receive chemotherapy plus bevacizumab plus here atezolizumab because that that's the immunotherapy agent that we have data supporting its use.

Dr. Socinski:
Yes, assuming they're eligible for bevacizumab, which not every patient is, but for the most part, I think that it's one of the few trials that included the EGFR mutation-positive patients. And I think it's important to point out that this was after failure of a EGFR TKI in that setting.

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

So, Gilberto, I want to also get your thoughts – we've seen some data on other molecular subsets, specifically what's been kind of in the news, so to speak, lately is the STK11 or KEAP1 mutations. And I just kind of wanted to get your perspective on that. This may or may not be part of a molecular workup that the average community oncologist may do nowadays, but give us your perspective.

Dr. Lopes:
Well, we'll certainly start to hear more and more about KEAP1 and STK11 mutations, as there are targeted agents that are currently in development looking at those two pathways. And in the meantime, these are certainly results that we get when we do broad next-generation sequencing. And a number of colleagues in the community are doing this routinely, and we do see these results, and then we need to know what to do with them in terms of therapy selection. While a few small studies have suggested that these patients have a poor prognosis, I think that as most of these studies have been small and the results relatively heterogeneous, we still have a lot of work to do on these two specific mutations. A small study from four cancer centers at ASCO this year suggested worse prognosis with STK11 mutations in particular, but we did present a subset analysis of KEYNOTE-042 at AACR earlier this year showing that patients with both mutations, when looked into independently, had benefits from receiving pembrolizumab versus chemotherapy. So while the question is far from being settled, I think they should not be used as a way of determining therapy today.

Dr. Socinski:
Yeah I would agree with that, but certainly stay tuned because I think we'll be better in the future at really defining who are the patients that really get really good benefit from our current treatment options, but we also know that there are patients that with current treatments don't reap as great of benefits. So we need new strategies for these sorts of patients.

Well, this has certainly been a valuable conversation, and before we wrap up, Dr. Lopes, can you share with our audience the one take-home message you want them to remember from our discussion?

Dr. Lopes:
Lung cancer treatment, especially in the metastatic setting, has changed a lot from the time I was in training a few years ago – I'm not going to say how many – and it is clear that we do have to select our patients based on molecular factors, and it is clear that

immunotherapy is here to stay, and we certainly have to make sure that patients who are appropriate and eligible get access to these new treatments.

Dr. Socinski:
And from my vantage point, I think one of the biggest takeaways from today is that lung cancer really has become the poster child for both targeted therapy as well as immunotherapy. So, it's a very complex disease, and comprehensive molecular testing as well as immunotherapy considerations are a part of our everyday management decisions for these patients. Unfortunately, that's all the time we have for today, so I want to thank our audience for your participation, and thank you, Dr. Lopes, for joining me and for sharing all your valuable insights. It was great speaking with you today.

Dr. Lopes:
Thank you, Mark. Always great to speak to you, too.

Announcer:
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