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Keeping Pace with Immunotherapy Advances in Non-Small Cell Lung Cancer: Global Perspectives

Announcer:

Welcome to CME on ReachMD. This activity, entitled "Keeping Pace with Immunotherapy Advances in Non-Small Cell Lung Cancer: Global Perspectives" is provided by AGILE and is supported by an independent educational grant from Merck.

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Dr. Patel:

Anti-PD-1 or PD-L1 therapy, such as pembrolizumab, nivolumab, atezolizumab and durvalumab, have become the standard of care for many nonsquamous non-small cell lung cancer patients either in first line and/or in subsequent lines of therapy, but how do we select the best candidates for immunotherapy, and which biomarkers have shown clinical value to help us inform when making these decisions?

This is CME on ReachMD, and I'm Dr. Jyoti Patel. Joining me to discuss these issues are Dr. Gilberto Lopes and Dr. Kai He. Dr. Lopes, Dr. He, welcome to you both.

Dr. Lopes:

Thank you for having me on today's program.

Dr. He:

Thank you for having me.

Dr. Patel:

To get us started, Dr. Lopes, what factors do we take into consideration in selecting first-line therapies for our patients? What patient factors, what biomarkers? How do we put this together to optimize treatment?

Dr. Lopes:

Immunotherapy, and especially combinations of immunotherapy with chemotherapy, have become the main options we have for the treatment of most patients with nonsquamous non-small cell lung cancer who do not have driver mutations, so that's the first factor we put in consideration. If patients have EGFR mutations, ALK translocations, ROS1 translocations, we usually do not start with immunotherapy or chemotherapy/immunotherapy, and we would use a specific tyrosine kinase inhibitor. For certain other mutations, we tend to prefer starting TKI as well, such as patients with a BRAF mutation. And for most other patients, we would consider using immunotherapy alone or chemotherapy with immunotherapy.

PD-L1 becomes an important biomarker. Those patients who have PD-L1 greater than 50% have the opportunity or the option of receiving immunotherapy alone or also with the addition of chemotherapy. We have emerging biomarkers, such as tumor mutational burden, and we also have clinical characteristics that we take in consideration. If patients have already taken a tyrosine kinase inhibitor, such as osimertinib, sometimes we would be worried about starting immunotherapy based on the high risk of development of

pneumonitis in some of these patients, and we also take in consideration treatments that patients might have received before in the adjuvant setting or in the setting of treatment of locally advanced disease.

So, often, the first time we meet a patient, we go over the data that we have, and more often than not, that usually includes having imaging studies showing that patient has metastatic disease and also a particular, specific histologic diagnosis, but we don't necessarily have next generation sequencing (NGS) results at our first visit for most patients. For these patients, we tend to make an assessment of how aggressive disease is and how symptomatic the patients are so that we can make a determination if we need to start treatment right away or if we have time to wait for NGS results.

Dr. Patel:

So let's dig a little bit deeper into that discussion that addresses which immunotherapy agents alone or in combination should be utilized in the first-line setting of patients with advanced lung cancer. Turning to you now, Dr. He, how do you choose between those different regimens and options?

Dr. He:

The first-line treatment of metastatic nonsquamous non-small cell lung cancer has been greatly changed in the last several years. We have single-agent immunotherapy and also have immunotherapy combined with chemotherapy, and there's multiple clinical trials that offer multiple options. We can start from the clinical trial KEYNOTE-189 with a platinum agent plus pemetrexed with or without pembrolizumab. It clearly showed in the patients, regardless of PD-L1 expression level, that have chemotherapy plus pembrolizumab have superior clinical outcome compared to chemotherapy alone, so this offers a great option for patients who have a good performance status and can tolerate chemo.

On the other side, there's KEYNOTE-024 and KEYNOTE-042. In the general clinical practice, we usually—when people have a high PD-L1—that means more than 50%—in my institution, we tend to use pembrolizumab itself. For PD-L1 less than that, we usually turn to the regimen of KEYNOTE-189 as chemotherapy plus pembrolizumab.

There is other option also available. For example, for clinical trial IMpower150, for that particular trial, there's combination of carboplatin plus paclitaxel plus atezolizumab plus bevacizumab. In that 4-drug combination, we usually reserve those offerings for people who have robust performance status and also, based on the trial subgroup analysis, those trials including the patients who have actionable mutation in EGFR and ALK.

In the end of last year, based on IMpower130, this anti-PD-L1 plus carboplatin plus a protein-bound paclitaxel. In that clinical trial, the combination of anti-PD-L1 and chemotherapy have a better outcome than chemotherapy alone.

Currently, there's a CheckMate 227 trial that was nivolumab plus ipilimumab compared with chemotherapy. In that trial, they meet their primary endpoint in PD-L1 more than 1%. Currently, this regimen is still being reviewed by FDA.

There's other options and clinical trials ongoing—for example, MYSTIC trial including durvalumab with or without tremelimumab versus chemotherapy.

Dr. Patel:

For those just joining us, this CME on ReachMD. I'm Dr. Jyoti Patel, and I'm joined by Drs. Gilberto Lopes and Kai He to discuss best practices for selecting which patients with non-small cell lung cancer would benefit from immunotherapy.

So, Dr. Lopes, now that we have a clear understanding of the relationship between the presence or absence of driver mutations, PD-L1 status, and other patient factors that go into selecting the most appropriate first-line therapies, there are a number of emerging biomarkers that we're incorporating into our practice. Let's turn our attention to the concept of tumor mutational burden, or TMB. What is it and how can we use it? And how do we integrate it into our treatment decisions?

Dr. Lopes:

As Dr. Patel mentioned, TMB, tumor mutational burden, is one of the main, maybe most important emerging biomarkers we have in our armamentarium. Tumor mutational burden has a few issues in terms of what thresholds we use, what the correct number would be, if we report number of mutations per megabase or the total number of mutations per genome, and these are just some of the issues that we're trying to solve and trying to actually validate for clinical practice use. It's not currently something that we do use in most of our algorithms by the NCCN, the National Comprehensive Cancer Centers Network, but it is certainly something that we do get results for.

A higher TMB is associated with immunogenic tumor microenvironment. Those patients probably have increased expression of tumor-specific and new antigens that can be targeted by activating immune cells, and that's likely why those patients have better outcomes, increased response rates, progression-free survival, and maybe overall survival than patients that have low TMB. Drawbacks include difficulties related to the sample quantity. We need more tumor tissue to be able to determine it. It also increases turnaround time for

our tests. And most importantly, we still do not have a universally accepted standard way of testing for TMB. And because of those reasons, we still don't use TMB in most of our algorithms to select therapy, but that may change in the future.

Dr. Patel:

So, if we look a little bit more at this relationship between tumor mutational burden in metastatic non-small cell lung cancer and efficacy of immunotherapies, what do we really know about efficacy across a number of agents, Dr. He?

Dr. He:

Almost each agent we are currently using has been studied with their particular relationship correlation with TMB. It starts with, early on, I think, Dr. Rizvi and his colleagues in 2015, 2016, they started efficacy of pembrolizumab with tumor mutation burden. It clearly showed a response in correlation with a higher TMB. Most recently for pembrolizumab, KEYNOTE-158 data they reported last year at ASCO 2019. In 2017, Dr. Carbone and his colleagues published the outcome for CheckMate 026. That's nivolumab versus chemotherapy in the first-line setting.

Follow-up to those studies, there are several other studies using nivolumab or nivolumab plus ipilimumab, particular on the CheckMate 227. That's the first phase III study in non-small cell lung cancer to combine TMB as a coprimary endpoint.

Beyond that, most recently in the MYSTIC study, durvalumab +/- anti-CTLA4, that study also strongly suggests that utility of blood-based TMB measurement can correlate with better outcome.

Dr. Patel:

Unfortunately, as our time is drawing to an end, perhaps you two could each offer thoughts on what are the key take-home messages that we should consider when we're thinking about first-line immunotherapy for patients with advanced non-small cell lung cancer. Dr. He, let's hear your takeaways first.

Dr. He:

I think, most importantly, immunotherapy by itself or by combination becomes mainstay or standard of care of first-line stage IV non-small cell lung cancer. Chemotherapy is not standard of care anymore. Chemotherapy is only reserved for some particular group of patients. Secondly, how we optimize all the combinations, how we use all the biomarkers to optimize the outcome, and how we manage for most of our patients that will eventually progress over first-line immunotherapy, how we improve outcome of those particular groups of patients remains to be a challenge.

Dr. Patel:

That's great. Thank you, Dr. He. Dr. Lopes, anything else to add?

Dr. Lopes:

Just that we still have a number of questions we need answers for and that we will reach it by participating in clinical research, so always encouraging everybody out there to participate in our clinical trials.

Dr. Patel:

Well, with those comments in mind, I want to thank my guests, Dr. Gilberto Lopes and Dr. Kai He, for helping us better understand use of first-line immunotherapy in patients with advanced non-small cell lung cancer. Dr. Lopes, Dr. He, it was really great speaking with both of you today. Thank you.

Dr. Lopes:

Thank you, Dr. Patel.

Dr. He:

Thank you.

Announcer:

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