Transcript Details

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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Current and Future Role of Immuno-Oncologic Agents in Early-Stage, Locally Advanced, and Metastatic NSCLC

[Transcript has been edited for clarity.]

Announcer:
Welcome to CME on ReachMD. This activity, entitled "The Current and Future Role of Immuno-Oncologic Agents in Early-Stage, Locally Advanced, and Metastatic NSCLC" is provided by Prova Education.

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[CHAPTER 1]

Dr. Bruno:
Immuno-oncologic agents have changed the treatment landscape in non-small cell lung cancer. Are you aware of the options currently available for your patients with early-stage non-small cell lung cancer, as well as emerging therapies for patients with advanced disease?

This is CME on ReachMD, and I'm Dr. Debora Bruno. Here with me today, we have Dr. Gilberto Lopes and Dr. Solange Peters.

Dr. Lopes:
Welcome, everybody.

Dr. Peters:
It's a great pleasure to be with you today and to be able to discuss these very important topics. Thank you for having me today.

Dr. Bruno:
So let's get started. Dr. Peters, can you set the stage for this chapterized course by discussing the treatment of early-stage non-small cell lung cancer, as outlined in the NCCN Guidelines?

Dr Peters:
Immunotherapy is now recommended for eligible patients with early stage non-small cell lung cancer in a curative intent strategy combined with surgery. First of all, adjuvant treatment now includes immunotherapy and chemotherapy; previously, adjuvant treatment just included chemotherapy. The IMpower010 trial assessed atezolizumab in the adjuvant setting, in patients with stage 1B to stage 3A non-small cell lung cancer, after complete resection. In that trial, patients received adjuvant chemotherapy, at least 1 cycle, and they were randomized to 1 year of atezolizumab versus observation. A benefit in disease-free survival was observed with atezolizumab in patients with stage 2 and stage 3A non-small cell lung cancer and PD-L1-positive disease. The NCCN Guidelines for Non-Small Cell Lung Cancer recommend adjuvant therapy with chemotherapy followed by atezolizumab for eligible patients with completely resected stage 2 and 3A non-small cell lung cancer with PD-L1-positive disease.

In Europe, the Agency has looked at the related benefit in each PD-L1 subgroup and decided that the benefit was really driven by the

high PD-L1 subgroup, leading to the approval of adjuvant atezolizumab in Europe for patients with stage 2 and 3A non-small cell lung cancer, but only those with more than 50% PD-L1. This is about EU. This is adjuvant. In the adjuvant setting, we still have lots of trials ongoing. We have another positive trial – the PEARLS, or so-called KEYNOTE-091, which is showing again a benefit of DFS [disease-free survival] in patients who received adjuvant chemotherapy followed by pembrolizumab and had stage 1B to stage 3A non-small cell lung cancer, but this time in the ITT [intent-to-treat] population, meaning stage 1B to stage 3A and regardless of PD-L1. But still in US and in Europe, it hasn't led to any current recommendation or approval of adjuvant pembrolizumab. It will probably follow very soon. Again, many trials to come.

If you look at the other strategy, we also have a very interesting, neoadjuvant trial, the CheckMate 816, where 3 cycles of preoperative chemotherapy plus nivolumab were compared to 3 cycle of preoperative chemotherapy followed by surgery. And the treatment ends at surgery, so a very short induction and a short treatment, right. In this trial, a benefit of disease-free survival was observed in all patients from stage 1B to stage 3, and regardless of the PD-L1 expression. Importantly too, the complete response – the pathological complete response – was going from 2% in the control arm to more than 20% in the experimental arm. So a very high magnitude of benefit, which is now recommended in the NCCN Guidelines for Non-Small Cell Lung Cancer and approved by FDA, but we are still waiting for approval in Europe. And of course, again, many trials to come in the neoadjuvant, perioperative, and adjuvant setting.

Dr. Bruno:
Thank you, Dr. Peters. Now, Dr. Lopes, can you discuss some of the key endpoints for recent clinical trials in the adjuvant and neoadjuvant setting for early-stage non-small cell lung cancer?

Dr. Lopes:
Absolutely. Adjuvant chemotherapy followed by osimertinib is recommended in the NCCN Guidelines for patients with completely resected stage 1B to 3A non-small cell lung cancer and certain EGFR mutations, including exon 19 deletions or L858R. However, one of the most impressive and most important clinical advances has been the use of immunotherapy in the neoadjuvant and the adjuvant setting for non-small cell lung cancer. IMpower010 set a new standard of adjuvant atezolizumab after adjuvant treatment with chemotherapy, and the endpoints included disease-free survival and overall survival. In the neoadjuvant trials, we have a smaller number of patients – at least for the trials that we have available up to today – and the clinical endpoints include pathological complete response and disease-free survival.

Dr. Bruno:
Okay, thank you so much, Dr. Lopes. Could you explain to us the important findings from IMpower 010 adjuvant trial, looking at atezolizumab for 1 year, given to patients with resectable, early-stage non-small cell lung cancer, after undergoing 4 cycles of platinum-based chemotherapy in the adjuvant setting?

Dr. Lopes:
At the moment of publication at The Lancet and the current presentations that we had, the disease free survival benefit is mature, and we have seen a benefit favoring the use of adjuvant atezolizumab for certain patients with completely resected stage 2 to 3A non-small cell lung cancer. That benefit is clinically significant with a hazard ratio about 0.8, and what is interesting is first to take a look at the subsets as well, and that's where we still have a little controversy of which patients benefit the most. And in IMpower010, it seemed to be that patients with PD-L1 of 50% or greater are the ones that benefited the most, with a hazard ratio that's highly positive. And for those patients with PD-L1 of less than 1%, we didn't see a benefit. The big question today is how much did those patients that have PD-L1 expressions between 1% and 49% actually benefit from atezolizumab in the adjuvant setting? To contrast that, we have data from a KEYNOTE-091 study [PEARLS] with pembrolizumab, in which the benefit actually seemed to be in patients with a PD-L1 between 1% and 49%. So is this a real clinically important characteristic of these drugs, or is this just because of the luck in the draw in the trials themselves? And I think that this is an important discussion as we move forward.

Dr. Bruno:
Thank you, Dr. Lopes. We also have the recent approval of nivolumab in the neoadjuvant setting, when given for 3 cycles in combination with platinum-based chemotherapy prior to surgical resection in patients with, again, early-stage non-small cell lung cancer. Can you describe the very important findings from CheckMate 816?

Dr. Lopes:
The arm that received preoperative nivolumab in addition to chemotherapy had a much higher pathologic complete response, and pathologic response in general, in certain levels that we really hadn't seen with chemotherapy alone, and it is very heartening to see that these patients seemed to have better disease-free survival when receiving nivolumab as well. And that brings us a new area of research and clinical use of these drugs in which patients that have non-small cell lung cancer that is potentially resectable, up to and to usually single station, low volume disease, we now have the option of giving chemotherapy and immunotherapy as a neoadjuvant

approach as well. The results in terms of both pathologic response, complete response, and disease-free survival seem to favor that kind of approach. Now, is that going to be better than doing surgery first and then chemotherapy and then immunotherapy in the adjuvant setting? And the honest answer right now is that we don't know.

Dr. Bruno:
Thank you. So I guess we can conclude that adjuvant atezolizumab has really demonstrated an improvement in disease-free survival, when compared to best supportive care, in patients with stage 2 to 3A tumors after adjuvant platinum chemotherapy in patients who also express PD-L1 in their tumors. It has decreased the chance of recurrence or death by 34% for patients with stage 2 to 3A non-small cell lung cancer with PD-L1 expression. And also, that 3 cycles of neoadjuvant nivolumab in combination with a platinum doublet led to superior rates of pathologic complete response and also decreased the risk for progression, disease recurrence, and death by 37% in patients with resectable tumors measuring 4 centimeters or greater and/or nodal involvement regardless of the PD-L1 expression. So these 2 approaches are currently recommended by NCCN Guidelines for Non-Small Cell Lung Cancer. The 2 drugs are approved by the FDA currently in these settings and have slowly been incorporated into daily practice.

Dr. Lopes:
Without a doubt.

Dr. Bruno:
Thank you. In Chapter 2, we'll be discussing treatments based on established biomarkers as well as emerging therapies in non-small cell lung cancer. Stay tuned.

[CHAPTER 2]

Dr. Bruno:
Welcome back. We were just discussing the treatment of early-stage non-small cell lung cancer, and now we're going to discuss immuno-oncologic treatments based on established biomarkers as well as emerging therapies in non-small cell lung cancer. Dr. Peters, can you talk about HER2, which is an established biomarker in metastatic non-small cell lung cancer, in the current era?

Dr. Peters:
HER2 is a biomarker well known from the breast cancer colleagues, right? Where they look at amplification of HER2 using immunohistochemistry or FISH analysis. In lung cancer, this is completely different. We also look at HER2 [ERBB2], but currently we don't look at expression or amplification. By the way, they are not very well correlated in non-small cell lung cancer. The third way to modify HER2 is the mutation, which, again, is not correlated with expression and amplification. We look at insertions in the exon 20 of the HER2 gene, because in lung cancer, this is what we call a driver. So it leads to all the characteristics and parameters of the malignant phenotype of the cancer cell. So this is where, in lung cancer, HER2 mutations are a very interesting target, usually found in never-smokers, in adenocarcinoma, and really has led to many potential treatment options in this specific disease entity. Keep in mind HER2 mutations are quite rare. They're between 1% and 3% of non-small cell lung cancer. We have been trying treatment with classical EGFR tyrosine kinase inhibitors, such as dacomitinib and afatinib, which are, I would say, ErbB family blockers and also a HER2 blocker; however, they have very poor response rates of less than 10%. We've been looking at new drugs like poziotinib, which is extremely toxic. The FDA has recently stated that poziotinib cannot be approved in its current state. We've been looking at many agents but they have difficulties in administration or unsatisfactory response rates.

Today, we have a new subsequent therapy agent, fam-trastuzumab deruxtecan-nxki, which is a moiety of a HER2 monoclonal antibody. Fam-trastuzumab deruxtecan is similar to the trastuzumab used in breast cancer. Fam-trastuzumab binds to the HER2 receptor, which is mutated in lung cancer, and a very strong component of chemotherapy is the deruxtecan. And this antibody-drug conjugate has led, in HER2-mutated metastatic non-small cell lung cancer, to a response rate which is about 55%. The toxicity profile is perfectly manageable, with a specific caution to be given to potential inflammatory lung disease, but we have been learning how to use it, and of course we will learn more by treating more patients. Interestingly, this treatment has been evaluated today in the second-line setting after the usual platinum-based chemotherapy plus/minus IO [immunotherapy], and in the future, we hope we can also use it frontline. Based on the initial trial design, fam-trastuzumab deruxtecan is recommended as a second-line option in the NCCN Guidelines for Non-Small Cell Lung Cancer for patients with HER2 mutated metastatic non-small cell lung cancer.

Dr. Bruno:
Thank you. Now, Dr. Lopes, can you please discuss some emerging targets for non-small cell lung cancer, focusing specifically on immunotherapies and antibody drug conjugates?

[Except for a new anti-HER2 agent, none of these agents are currently recommended in the NCCN Guidelines for Non-Small Cell Lung Cancer.]

Dr. Lopes:
In immunotherapy, we have a number of clinical trials that are moving forward. We have classically used CTLA-4, PD-1, and PD-L1 as our main targets, but we have new, emerging targets and their corresponding agents. For instance, we have an anti-LAG-3 that has been approved in melanoma that is currently being tested in lung cancer. We also have some anti-TIGIT agents that unfortunately have had some negative data, so we don't know how many of these new agents are going to be moving forward. We also have new studies looking at checkpoint inhibitors that are beyond the usual lymphocytes or antigen-presenting cells but also look to macrophage function and so on. So there's a wealth of new agents in the immunotherapy realm that will be coming forward to clinical trials and hopefully eventually to the clinic. It's also very exciting to see the development of antibody-drug conjugates [ADCs] in lung cancer as well. We had Dr. Peters discussing anti-HER2 therapies that we have been using in breast cancer for quite some time, and now we have approved agents in the US for anti-HER2 therapy in metastatic non-small cell lung cancer, and we have 2 other emerging targets that are worth mentioning. One is HER3 and the other one is Trop2.

So HER3 has become one of the very hopeful avenues for us to be able to overcome resistance to EGFR mutant-specific treatments, such as osimertinib that is currently recommended as a first-line therapy option for eligible patients with certain EGFR mutations and metastatic non-small cell lung cancer. Patritumab deruxtecan seems to be active with a response rate somewhere between 35% and 40% for patients that have received osimertinib as a first-line agent and then had disease progression, and this is an agent that will likely start to see more data coming forward in the near future. The other target that we're very excited about is Trop2. Trop2 is expressed in about two-thirds of adenocarcinomas, three-quarters of squamous cell carcinomas, and a little bit less for neuroendocrine tumors. But we are now seeing the development of antibody conjugates using Trop2 as the target. We see response rates and we have large randomized trials that are ongoing and hopefully will show us an established role, eventually, for these combinations of antibody and drug conjugates.

Dr. Bruno:
Thank you, Dr. Lopes. One of the interesting features of some of the antibody-drug conjugates – specifically the ones targeting Trop2 – is the ability to work on patients without actionable genomic alterations, except for KRAS mutations. It's interesting to see activity in patients without EGFR mutations or ALK rearrangements both for datopotamab deruxtecan and trastuzumab govitecan. Are you enthusiastic about the potential activity of those drugs for those specific patients with metastatic non-small cell lung cancer?

[These new agents are not approved for non-small cell lung cancer.]

Dr. Lopes:
Absolutely. It's a very attractive way of creating new drugs, in which you really target the cancer by using the specific monoclonal antibodies and having a payload. That if we were to give SN-38 or the other agents that we are using as the actual chemotherapy attached to these antibody-drug conjugates, these are drugs that have so much toxicity that if we use them in a more classic way, as we use docetaxel and other chemotherapy agents, their toxicity would be so much that we wouldn't be able to have a lot of activity. So these are very exciting drugs, and we're looking forward to seeing them actively used in the clinic.

Dr. Bruno:
So, Dr. Lopes, datopotamab deruxtecan is really advancing in terms of demonstrating great response in phase 1 trials, now moving on to phase 3 trials. We actually have a phase 3 trial currently open that is involving patients after initial chemotherapy and immunotherapy and randomizing them to docetaxel or datopotamab deruxtecan.

What do you know, or what can you share with us in terms of preliminary results from those studies?

Dr. Lopes:
What we know about TROPION-Lung02 trial is that we have seen preliminary data showing an overall response rate in the nearly 40% range for the triplet therapy with median follow-up of about 6 to 7 months. And for patients who receive the triplet therapy of datopotamab deruxtecan plus pembrolizumab plus platinum chemotherapy, there's a disease control rate of 84%. So this is very, very promising early data that we hope to see confirmed and we hope to see extended as the clinical trial matures and more data are presented.

Dr. Bruno:
Thank you. In Chapter 3, we'll be discussing regional considerations in the treatment of non-small cell lung cancer. Stay tuned.

[CHAPTER 3]

Dr. Bruno:
So for those of you who are just tuning in, you're listening to CME on ReachMD. I'm Dr. Debora Bruno, and here with me today are Drs. Gilberto Lopes and Solange Peters. We are discussing the current and future roles of immuno-oncologic agents in early-stage, locally

advanced, and metastatic non-small cell lung cancer.

Welcome back. After discussing immuno-oncologic treatments for established biomarkers and emerging agents in non-small cell lung cancer, let's now talk a bit about global considerations when it comes to treating non-small cell lung cancer.

Dr. Peters, what are some regional considerations when diagnosing and treating non-small cell lung cancer patients?

Dr. Peters:
Thinking about oncogene addictions and, beyond that, biomarkers including PD-L1, there are probably 2 challenges today that the community is facing. And I'm in Switzerland. Many colleagues are in the US. Maybe we do feel that biomarker testing is not easily available unless we work in academic settings. It's important to keep in mind that even in our countries, but even more importantly, across countries and across continents, the availability today for this molecular characterization is very poor. For the European Society for Medical Oncology, we just have performed a survey to see what is the accessibility to this biomarkers assessment. And what we observe is, first of all, the accessibility is pretty poor in some countries, particularly for NGS – next-generation sequencing – and more importantly, very often they are not reimbursed, meaning that it's only reserved to out-of-pocket payment, which of course makes the accessibility limited and also probably inequal by nature. So the first thing we can improve is to make sure that biomarker testing is available, which is needed to make treatment decisions, wherever we work in Europe, starting in our countries but also maybe in other countries.

The second interesting question is when should we perform these tests? In the academic setting, we have accessibility, for example, to early diagnosis, biomarkers, and NGS. And I think today, the emergence of new, neoadjuvant, adjuvant treatment in oncogene addiction and also in unmutated non-small cell lung cancer is raising the question about reflex testing. Should we test at the first biopsy, even in early disease? Should we do NGS in all patients with non-small cell lung cancer before surgery, for example? These kind of questions reflect testing in all patients. Of course, NGS testing in all stages of non-small cell lung cancer is only possible in a wealthy environment. So a lot of these questions need quality data to move forward and also reimbursement coverage for all of these accessibility purposes.

Dr. Bruno:
Yes, it's certainly interesting and to a certain extent alarming to see disparities when it comes to diagnosing and testing patients with non-small cell lung cancer. We currently have a vast array of actionable genomic alterations – actually, now we have 11 for populations of non-small cell lung cancers that harbor genomic alterations that we can target with FDA-approved medications. And in order to identify those patients, we certainly need to do biomarker testing for eligible patients with non-small cell lung cancer, and currently the best way to do so is by using next-generation sequencing platforms.

Recently we have seen data within the United States that is alarming. A retrospective study from the US Oncology Network Community Practices documented that less than 50% of patients with advanced or metastatic non-small cell lung cancer undergoing therapy between 2018 and 2020 were actually being tested for the 5 biomarkers that were recommended at that time in order to make best decisions when it comes to first-line therapy. Our group has demonstrated, too, that less than 50% of the patients underwent NGS testing prior to first-line therapy in a retrospective analysis of the Flatiron dataset looking at approximately 15,000 patients with advanced or metastatic non-small cell lung cancer from 2017 through 2020.

We also found racial disparities when it comes to NGS testing. A specific study reported that 36.6% of the patients of White race underwent NGS testing compared to 29% of the patients of Black race. This is certainly very concerning.

Dr. Lopes, what do you see as major challenges when it comes to comprehensive biomarker testing in patients with non-small cell lung cancer? Not only within the US, but also globally?

Dr. Lopes:
We have now been doing genomic testing for more than a decade, and it's become even more important, as we have a larger number of targets and specific therapies that we can use to improve the quality and length of life of our patients. When we look outside of the US, the situation's even worse than what we are sharing here today. We looked at data for Brazil a few years ago, showing that fewer than 20% of patients were getting tested for EGFR mutations alone, and the main reason that happened specifically in the public sector was because patients did not have access to biomarker testing. Even if they had been tested, they did not have access to specific therapies that would block the EGFR mutation. We also have seen that relative access to biomarker testing is decreasing, not just in Brazil, but in a number of countries in Latin America and around the world, and this is a gap that continues to grow, especially as we now have more targets and more therapies, as mentioned.

We also have biological differences. It's well known that Asian patients tend to have EGFR mutation rates in the 40% to 50% range. What we sometimes forget in this country is that Hispanics have a prevalence of about 25% of EGFR mutations, and Blacks about half of what we see in Whites, so just around 5% to 8%. So there are disparities in how we are testing patients, but there's also biological

differences in the prevalence of mutations that we see in different populations. We, without a doubt, need to continue working on making genomic testing more widespread, and access to medications also has to improve, especially outside of the US.

Dr. Bruno:
Thank you for your input. Well, this has been an excellent conversation, very dynamic. To summarize, we now have the ability to use immunotherapy in the neoadjuvant and adjuvant settings for patients with early-stage non-small cell lung cancer with the recent approvals of nivolumab and atezolizumab, respectively, in those specific settings. We are very excited to see new immuno-oncologic agents coming down the pipeline targeting other alterations such as HER3 and Trop2 as Dr. Lopes has discussed. Dr. Peters really explained well the role of trastuzumab deruxtecan currently approved for treatment of patients with HER2 mutation-positive metastatic non-small cell lung cancer following first-line therapy.

And we also discussed here the concerns when it comes to performing broad, comprehensive, genomic testing for patients with advanced non-small cell lung cancer, not only in the US, but also globally.

So today we discussed several biomarkers and immuno-oncologic agents. It's important to understand that this is not an inclusive list; other targeted agents and immunotherapies are recommended in the NCCN Guidelines for Non-Small Cell Lung Cancer.

When we speak about targeting LAG-3, TIGIT, HER3, and Trop2, we want to make sure that the audience understands that those are upcoming potential treatments and strategies, which are not approved by the FDA and not recommended by NCCN Guidelines for Non-Small Cell Lung Cancer.

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

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