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Panel Discussion: A Focus on Emerging Treatment Options in Non-Small Cell Lung Cancer

Narrator:
Welcome to Project Oncology on ReachMD. This activity, Panel Discussion: A Focus on Emerging Treatment Options in Non-Small Cell Lung Cancer is provided by Prova Education and supported by an educational grant from Merck. Your experts joining us today are Dr. Edward Garon, Director of Thoracic Oncology at the David Geffen School of Medicine at UCLA in Los Angeles, California and Blanca Ledezma, Nurse Practitioner at UCLA Hematology/Oncology in Santa Monica, California. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Mackey:
Lung cancer is, by far, the leading cause of cancer death among both men and women with non-small cell lung cancer being the most common type of lung cancer, at approximately 85%. During our panel discussion today, I will be speaking with two clinical experts about emerging treatment options for non-small cell cancer and the adverse events we need to be aware of prior to their use. Oncologist, Dr. Edward Garon and I will focus on the newer immune-modifying therapies and how to utilize them, while Nurse Practitioner, Blanca Ledezma, will share insights about these agents' known side effects, and how to minimize them for our patients. This is ReachMD. I am your host, Dr. Amy Mackey. Dr. Garon and Blanca, welcome to the program.

Dr. Garon:
Thank you.

Ms. Ledezma:
Thank you.

Dr. Mackey:
Dr. Garon, let's start with your perspectives on treatment selection. So, let's take a scenario of a patient whose newly diagnosed non-small cell lung cancer shows a high expression of PD-L1, such as 50% staining. How would you select treatments for this patient and would it differ if the patient's cancer has 40% staining, or 25% staining?

Dr. Garon:
Sure. So, this is an area that has really very rapidly changed. Up until very recently, almost all patients with metastatic non-small cell lung cancer received cytotoxic chemotherapy. Over the last decade, we have seen that patients whose tumors harbor a mutation in the epidermal growth factor receptor gene, or rearrangement involving the anaplastic lymphoma kinase, or ALK gene, have been treated well with agents besides chemotherapy, targeted agents, against those particular genomic abnormalities. However, within the last year, we have now seen data that indicates that for patients with very high degrees of staining, staining in at least half of the cells for PD-L1, that those patients do better with respect to both progression-free survival, as well as overall survival, if they receive pembrolizumab which is a PD-1 inhibitor, as opposed to standard cytotoxic chemotherapy. And so, I think that in patients who do have staining for PD-L1 at that level, it is a very clear choice to choose pembrolizumab. It is not only associated with an improvement in progression-free survival, but even though the study allowed patients to cross over to pembrolizumab if they were originally assigned to the chemotherapy arm, there was still an advantage with respect to overall survival with the patients who were randomized to pembrolizumab.

The second part of the question is a question that I get asked very frequently from practitioners, what about if the patient is, for instance, 40% or 25% positive for PD-L1? And I would really, in a patient who can tolerate chemotherapy, caution providers against going to frontline single-agent pembrolizumab or any other PD-1 or PD-L1 inhibitor, in that setting. When we looked at pembrolizumab as a single agent we actually did find a significant and clear difference between patients who have this high level of staining, staining in at least half of their cells for PD-L1, versus the rest of the patients. And, of course, the rest of the patients do include patients who have staining at the 40% level, at the 25% level. And that group of patients clearly does less well than the group who has staining in at least half of the cells. Further, the study that I mentioned before was the KEYNOTE-024 study, looking at pembrolizumab, there also was a study that was quite similar in design, the CheckMate 026 study. This study used nivolumab which has generally looked very similar in clinical trials to pembrolizumab and took a less highly selective patient population, and in that population there was no advantage seen for nivolumab over standard chemotherapy. And numerically in fact, standard chemotherapy, with respect to progression-free survival, appeared to do better. And therefore, I think that in this group who does have this high level of staining, staining at least half of their cells, clearly pembrolizumab has demonstrated superiority over other standard therapies. However, in the group of patients who does not have that, chemotherapy is still the standard of care.

Dr. Mackey:
So then, what about the patient who has already received platinum-based chemotherapies? How do you choose which PD-1 or PD-L1 inhibitor to use in this case?

Dr. Garon:
Well, at the time of this taping, there are basically 3 agents that are approved. So, pembrolizumab which is the agent I mentioned which is approved in the frontline setting, and, again, in the second-line setting is approved only in patients who have staining for PD-L1. The threshold is somewhat different. Rather than the 50% threshold, the 1% threshold is used, in part, of course, because this is a more difficult situation from the perspective of the comparator, which would be chemotherapy. There are two other agents that are approved: nivolumab and atezolizumab. Both of those are approved without any requirement for positive biomarker staining. So, nivolumab was the initial agent that was approved. It was approved for squamous cell carcinoma, initially, and then non-squamous, non-small cell lung cancer. And atezolizumab is the most recent agent that is approved. It is a PD-L1 inhibitor, meaning that rather than targeting PD-1, it targets the ligand PD-L1. However, these agents are both quite similar, in general, in clinical trials. The antibodies are felt to be acting mainly by inhibiting the interaction between PD-1 and PD-L1, leading to fairly similar activity between the two classes of drugs. The real differences are the biomarker requirement for pembrolizumab, but also the schedule. Nivolumab is given every 2 weeks while pembrolizumab and atezolizumab is given every 3 weeks. And, at this point, I would argue that there really is no great data outside of that threshold for PD-L1 expression, which is a requirement for pembrolizumab, to choose amongst these three agents.

Dr. Mackey:
Let's take another clinical example in which a patient with an EGFR mutation, or an ALK gene rearrangement has exhausted appropriate oncogene-directed therapies. Would this patient go to chemotherapy or start a PD-1 or PD-L1 inhibitor?

Dr. Garon:
So, as I mentioned, the initial group of non-small cell lung cancers that were metastatic that sort of stopped having their frontline therapy be traditional cytotoxic chemotherapy were these genomic alterations; these mutations in EGFR, in gene rearrangements involving the ALK gene. These patients actually were excluded from the frontline study looking at pembrolizumab, for instance, that led to the approval of pembrolizumab in the frontline setting. Their role, in general, has not been particularly well-defined for the PD-1 inhibitors. Certainly, the most common of these which are mutations in EGFR, it has been documented that there are certainly patients with these mutations that do respond to PD-1 or PD-L1 inhibitors. However, the data is also clear that the rate of response for these agents is lower than what is seen with patients who are wild type for EGFR and ALK, or who do not have mutations in EGFR or gene rearrangements involving ALK. I would argue that the data really supports that the response rate and progression-free survival clearly is more likely to be longer and better in patients who receive standard cytotoxic chemotherapy, as opposed to a PD-1 or PD-L1 inhibitor.

Dr. Mackey:
I'm going to turn our discussion now to Blanca, an oncology nurse practitioner, to discuss adverse events experienced by some patients receiving immunotherapies and how these adverse events can be managed.

One of the side effects of immunotherapy is diarrhea or immune mediated colitis. How do you educate patients that diarrhea associated with their immunotherapy treatment is different from diarrhea you might see with other therapies? And, how is it treated?

Ms. Ledezma:
So, oftentimes when patients have received other therapies, such as cytotoxic therapies, chemotherapy, as a result they have had diarrhea that they've managed themselves with anti-diarrheals, adequate hydration, and not reported symptoms until their next treatment

visit, which may not be for an additional 3 weeks from their last therapy, which was appropriate with their chemotherapy treatment. However, it's important that patients understand and be educated that not only patients, family members, caregivers, understand that this is a different treatment but it is an immunotherapy, that there are immune-mediated possible side effects. And, as a result, that these immune-mediated side effects that they have this basic concept they can cause inflammation in their colon and if they have that basic understanding, that they need to understand that early reporting of symptoms is essential. So that not only early reporting of symptoms, but that we also document their baseline. What is their baseline bowel movements to have? Are they having 1 bowel movement per day as their baseline? Oftentimes, our patients are on opioids and they require laxatives to achieve bowel movements, and, as a result, they may have 1 to 2 bowel movements per week, with the use of laxatives. And if they're having a deviation from their baseline where they're having 4 to 5 bowel movements per day with no use of laxatives, then they're having quite a bit of a deviation from their baseline. So, educating patients that early intervention, reporting of symptoms, will be essential and not waiting until their next visit is important. And, how do we treat? How do we manage? Anti-diarrheals are important but not only with anti-diarrheals. You may have to withhold treatment and if it's a grade 3, and also may have to implement corticosteroids such as 1 to 2 mg of prednisone per kg of prednisone or its equivalent, to manage these patients' immune-mediated colitis. And, at times, despite doing early intervention, patients being forthcoming with symptoms, that we cannot control the diarrhea with corticosteroids, that they are steroid-refractory, and we may have to use more immunosuppressive therapies such as infliximab. So, again, the key would be to educate patients, early intervention, symptom reporting, and withhold treatment if necessary, and use of corticosteroids.

Dr. Mackey:
Great. Let's talk about lung complications. How do you differentiate immune-mediated pneumonitis versus disease progression, and how should we manage this?

Ms. Ledezma:
So, it can be quite tricky with our patient population, giving that at baseline they can have shortness of breath and cough to begin with. And establishing a baseline will be essential, and after we establish the baseline we want to know, are they having a great deviation from the baseline? Are they having quite a bit of dyspnea on exertion, walking from the bathroom to their bedroom, when previously they were able to walk around the block with no symptoms? Are now they are requiring continuous oxygen use where previously their oxygen use was just on an intermittent basis? So, these would be red flags that we would want to image these patients to rule out treatment-induced pneumonitis. And if, in fact, it is suspected or it is found, that we do treat these patients with corticosteroids. And, of course, we also want to rule out other potential factors such as infection, and/or pulmonary embolism, or disease progression.

Dr. Mackey:
So Blanca, is fatigue a normal side effect for patients to experience, and if so, how much should they expect, and are there ways to address this?

Ms. Ledezma:
Certainly. So, again, education is important and letting them know that some level of fatigue is normal, but excessive fatigue is not. Especially for those patients that had previous chemotherapy. They may expect more fatigue. So, establishing their baseline will be essential and documenting their baseline and letting them know, this is your baseline, this is the level of fatigue that is normal. And if they have a sudden deviation from their baseline, where they were working part-time and having a nap midday, and suddenly they're not working any further, that they're having to spend the majority of time in bed, then that's a great deviation from their baseline. Having profound fatigue, then we want to investigate further. So, again, educating patients that we want to know these symptoms and that they must communicate to us, not only when we're in clinic, but somehow electronically, or via phone, or some other method that works for them and us. And then further investigate and determine is it some potential endocrinopathy? Is it a thyroid dysfunction? Are they having a hypothyroid? Do we want to check their labs to ensure that it's not related to treatment? And, again, having that baseline will be essential, not only to establish their baseline level of functioning, but to establish their baseline labs, and know that there is a deviation from their labs. And if its hypophysitis and you find that they're adrenally insufficient, that we can replace their cortisol; if it's hypothyroid that we can replace that as well. But again, establishing not only a baseline from their level of functioning but as far as their labs and where their baseline is as well. And early reporting, educating patients, and symptom reporting, so that we can intervene as early as possible.

Dr. Mackey:
And how commonly do you see rash and pruritus develop in patients? And how do you treat that?

Ms. Ledezma:
So, rash and pruritus is probably more common than the immune-mediated toxicities that we see. And so, it's not as detrimental as the other immune-mediated effects that can occur, but, again, these patients have lost quite a bit of autonomy, that we want to arm them and give them as many tools as possible to regain their autonomy and independence, that we want to educate them as to how they can

manage these side effects. So, we can tell them to use rich emollients to moisturize their skin should they have pruritus, that they can use antihistamines to help with the pruritus, that if they have problems in areas to use topical hydrocortisone or corticosteroids. And, of course, with the fact that they have to have the understanding that they must keep us informed of these side effects, should they become a severe rash or pruritus, that we want to know about it, should we have to intervene with oral corticosteroids.

Dr. Mackey:
Lastly, let's focus on the complication of immune-mediated hepatitis. How do you address this?

Ms. Ledezma:
So, immune-mediated hepatitis, it will be essential having the baseline labs; knowing the patient's baseline, and monitoring their labs throughout their treatment. I know at times that we get busy in clinic and when we're in the infusion center, because we're rushed, that we may be tempted to treat these patients without having these critical lab results. It is essential and it is key that we do have these labs so that we monitor these liver function tests because we don't want to dose these patients should there be an increase in their liver enzymes, and if you suspect that there is an immune-mediated hepatitis. But we implement measures so that if we draw labs a day before, so that we're not rushed the day of treatment, and that, and if we do suspect that there is an immune-mediated hepatitis, that we do treat it with corticosteroids and we do taper slowly. But we also have to rule out other factors such as disease progression. These patients are followed by other practitioners; that it's not related to medication, but, again, early intervention will be key. And a big component or a big thing to note is with all of these immune-mediated reactions, is that the median time to onset is 1.3 to 3.7 months; however, it can occur from days to months after, and one thing that is important for us to note is that even after patients come off of therapy, that we have to continue to monitor these patients for these immune-mediated possible side effects; that even after they've started on other therapies, that we do continue to monitor them for these possible toxicities, and that we do continue to do early intervention and appropriate management for these possible immune-mediated reactions.

Dr. Mackey:
Yes, that's great. Absolutely. With that, I'd like to thank my guests, Dr. Edward Garon and Blanca Ledezma, for joining me to discuss Updated Treatment Approaches and the Associated Side Effect Considerations for Patients with Non-Small Cell Lung Cancer.

Dr. Mackey:
I am your host, Dr. Amy Mackey, for ReachMD. To access this and other oncology content, visit us at ReachMD.com where you can Be A Part of the Knowledge.

Narrator:
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