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Highlights from the 13th International Congress of the Society for Melanoma Research: A Focus on Checkpoint Inhibition

Narrator:

Welcome to CME on ReachMD. This segment, Highlights from the 13th International Congress of the Society for Melanoma Research, a Focus on Checkpoint Inhibition, is sponsored by Prova Education. Your host is Dr. Barry Mennen who welcomes Dr. Michael Postow, medical oncologist at Memorial Sloan-Kettering Cancer Center in New York, New York. Dr. Mennen has no relationship reported. Dr. Postow receives consulting fees from Novartis and Bristol-Myers Squibb, and has contracted research with Bristol-Myers Squibb, Array BioPharma, Infinity Pharmaceuticals, Inc., and Novartis. This activity is supported by an independent educational grant from Merck.

Dr. Mennen:
This is CME on ReachMD and I am Dr. Barry Mennen. With me today is Dr. Michael Postow, who joins our program to bring us major updates on the use of immunotherapy in melanoma, as presented at the 13th International Congress of the Society for Melanoma Research that took place recently in Boston, Massachusetts. Dr. Postow, welcome to ReachMD.

Dr. Postow:
Thank you very much. I appreciate being here.

Dr. Mennen:
Dr. Postow, to begin our discussion, immunotherapy has become an integral treatment for melanoma, if not other cancers. Can you explain why there's such great enthusiasm in this field now?

Dr. Postow:
Absolutely. So, immune therapy has been a really interesting area of research for many, many, many decades, and trying to understand how to harness the power of the immune system to control cancer has been something that researchers have tried for many, many, many years. Unfortunately, throughout history, it has been very difficult to get the reproducible benefits in terms of high response rate to our current agents and improvements in overall survival that we are currently seeing now with a number of diseases and with a number of different immune therapy approaches. And so, for years, it's been tested through a number of approaches and it's been a little unclear in terms of why that hadn't been as successful as we would have hoped it to be. However, recently we're really seeing, with a number of different immune therapy strategies, improvements that we haven't seen before. And there are a number of reasons as to why that may be the case that we're now seeing these improvements and I'm happy to talk about some of those specifically. But immune therapy really isn't new. It's just now, really for the first time in many diseases, showing us benefits that we've always been hoping to see.

Dr. Mennen:
Now, from your point of view, what were the major updates in immunotherapy and targeted therapy presented at this year's SMR meeting?

Dr. Postow:
So, at this year's Society for Melanoma Research Meeting, the major updates in targeted therapy included the updates from the Phase III Columbus study which was a Phase III study for patients with BRAF-mutant melanoma that tested a new BRAF and MEK inhibitor combination, encorafenib which is the BRAF inhibitor and binimetinib which is the MEK inhibitor, and it tested it against vemurafenib, a

BRAF inhibitor alone, and also included in that trial was a third arm of encorafenib alone. So, it was a 3-arm study: encorafenib and binimetinib, encorafenib alone, and binimetinib alone. And the study really showed improvements in progression-free survival for encorafenib and binimetinib, compared to vemurafenib alone as the control, and also compared to encorafenib alone. So, this is now the third in class BRAF and MEK inhibitor combination. We already have dabrafenib and trametinib FDA approved. We also have vemurafenib and cobimetinib FDA approved. It is hopeful that encorafenib and binimetinib will be added as a third BRAF and MEK inhibitor combination, and based upon this Phase III study, which was positive for the primary endpoint of progression-free survival, that we are encouraged now that we do have another BRAF and MEK inhibitor combination, hopefully moving forward for patients with BRAF-mutant melanoma. And that's, I think, the major targeted therapy approach for our patients that we can take home from the Society for Melanoma Research Meeting.

As far as immune therapy, there have been additional data that have also been presented at the Society for Melanoma Research Meeting and I think the big updates in immune therapy for this meeting were trying to understand immune checkpoint blockade with drugs such as ipilimumab and nivolumab as well as with pembrolizumab in particular subgroups of patients, particularly those that had high LDH. And we know that high LDH, which is lactate dehydrogenase, is a marker of poor prognosis in patients with advanced melanoma. We know this from many, many years in melanoma research. And patients with high LDH remain a group of higher risks for treatment-related progression as well as death. We saw some data suggesting that even in patients with high LDH there can be benefit from drugs such as pembrolizumab single agent as well as from ipilimumab and nivolumab given in combination. And unfortunately, the responses and benefit in patients with high LDH is not quite as good as patients with low LDH. There can still be benefits in the high LDH group, and so we can't use LDH as a stratification factor for selecting patients for treatment, but it is encouraging that patients can benefit regardless of their LDH.

Dr. Mennen:
Now, what about the broader current state of research in melanoma? What has this year's Congress identified as some of the most important questions to be addressed in ongoing trials?

Dr. Postow:
So, I think, in terms of the bigger questions in melanoma, in general, we have major questions about who benefits from immune therapy and who doesn't benefit from immune therapy. So, we had some interesting conversations about some different theories in terms of how that may be involved and some new and interesting information in that area. But the other information that's come up further is new targets in melanoma and, particularly, in some subtypes of melanoma where we don't have really effective targets, and so there -- as one example of that -- we had a symposium yesterday for uveal melanoma, and some updates today on uveal melanoma. And uveal melanoma is a type of melanoma that comes from the eye, and unfortunately, despite all the big advances we've seen in patients with melanoma, patients with uveal metastatic melanoma remain an area of unmet need. So, there were some updates on some new approaches in uveal melanoma particularly with one drug called IMCgp100 that showed there were some responses in patients with metastatic uveal melanoma which, it's a small group of patients, it's really hard to draw any major conclusions about this, but even the presence of some responses in a small group of patients is very encouraging in a disease where it is very, very difficult to get responses, even with some of the new agents that we're very excited about in melanoma. So, that's just an example of a new target, a new drug, for an unmet patient population where we just haven't yet gotten to the advances that we would like to see and that data were presented earlier today at the Late-Breaking Clinical Updates Plenary Session.

Dr. Mennen:
Let's focus on checkpoint inhibition. Can you explain the mechanism of action of the new immune checkpoint inhibitors and how that differs from targeted therapy against oncogenic signaling pathways such as via BRAF and MEK inhibition?

Dr. Postow:
Absolutely. So, I'm happy to discuss why immune checkpoint inhibition is a different mechanism of helping destroy tumors from targeted therapy. And targeted therapy, I specifically mean in melanoma, we're usually talking about BRAF and MEK inhibition. So, I'll start by discussing targeted therapy and then I will explain how immune therapy is entirely different from that. So, targeted therapy is a more of a traditional method of treating cancer patients where we identify an oncogene, which is an abnormal protein in a tumor cell, and these abnormal proteins are causing too much excitation of these pathways within the cell, and the targeted therapy drugs, such as BRAF inhibitors and MEK inhibitors, and combinations of the two, go specifically to these excited pathways within tumor cells and shut them down, to hopefully stop the tumor cells from growing and try to kill the tumor cells directly. So, it's specific therapy that goes right to the tumor and disables the pathways within the tumor that are overly excited and causing the tumor cells to grow too much. That's targeted therapy; specific targets and specific molecules that inhibit those targets. Immune checkpoint inhibition is an immune therapy approach that specifically enhances the body's own immune system to fight tumors better. So, immune checkpoint inhibition does not target the tumors directly at all. Targeted therapy targets the tumors directly, but immune therapy enhances the body's own immune system. So

how does it do that? Well, the immune system is normally regulated by a number of checks and balances to prevent too much immune activation. And so, in patients with cancer, we believe that there are too many restraints on the immune system and that the immune system is checked, or unable to move forward and kill tumors. And so immune checkpoint inhibitors, such as those that target CTLA-4, or PD-1, or PD-L1, they block these negative signals in the immune system and by blocking the negative; it helps the immune system fight tumors more strongly. So, you can think about it as taking the breaks off of your car and you're going to be preventing the stoppage of the immune response, and by preventing the breaking, or preventing the stopping of the immune response, the immune response is allowed to destroy tumors better. So, immune checkpoint inhibition enhances the immune system through this mechanism and targeted therapy directly kills tumor cells by disabling the oncogenic signaling pathways that are overly excited in certain types of tumors, including melanoma.

Dr. Mennen:
What clinical considerations help you decide whether a patient should be treated with a PD-1 agent, as a single drug, or in combination with an agent that blocks CTLA-4?

Dr. Postow:
One of the main questions in the field is whether patients with advanced metastatic melanoma should be treated with a single-agent PD-1 inhibitor or PD-1 in combination with a CTLA-4 inhibitor such as ipilimumab. The clinical considerations that go through my mind in terms of which patients should be treated with which are the following. We know that single-agent PD-1 is a very, very well-tolerated approach because it has a very low rate of side effects, very few patients need to have steroids to manage their side effects. When you combine PD-1 with a CTLA-4 inhibiting agent, unfortunately the toxicity from that combination approach is increased with that particular combination; however, with that increase in side effects, there also is an increase in short-term efficacy endpoints such as progression-free survival and objective response rate, compared to the single agent PD-1 and CTLA-4 by themselves. So, when I'm thinking about the combination immune therapy approach for a patient, it's a more aggressive approach, it has a little bit of a higher immediate benefit for these patients, and I'm trying to look at my patient and understand, is this someone that could withstand the greater toxicity of combination PD-1 and CTLA-4 blockade, and is this someone that really needs that more aggressive approach against their melanoma. So, if I have a patient who has really, really aggressive melanoma that's making them symptomatic or causing problems, and I think their comorbidities, and other general health status is such that I could give them the more aggressive approach, then that's a patient I would think about for combination immune checkpoint blockade with PD-1 and CTLA-4 together. If I have a different patient that may have some medical comorbidities, and/or may have some very minimal metastatic melanoma, like a very small lung nodule, or maybe just one lymph node that's involved with melanoma, and one small lung nodule, or a couple of tiny skin metastases, that may be a patient I think about for single-agent PD-1 alone, knowing that if a single-agent PD-1 doesn't work by itself, we may have a chance to get a subsequent benefit from giving that patient a CTLA-4 blocking antibody such as ipilimumab in a sequence. And, in fact, there were some updated data from Society for Melanoma Research at this meeting showing that the CTLA-4 blocking antibody, ipilimumab, has benefit in some patients after they progressed on single-agent PD-1 as a first approach. So, it's really about what kind of patient am I dealing with, what kind of disease biology am I dealing with, aggressive or not aggressive, and what the patient's comorbidities are and their ability to tolerate the side effects?

Dr. Mennen:
Now, the biomarker PD-L1 has come under the spotlight lately in immunotherapy. Can you please talk about the value of this and other biomarkers in melanoma treatment such as whether they assist in selecting patients for immunotherapy?

Dr. Postow:
Absolutely. So, in an ideal world, we would know before we treated patients whether or not we should give them 1 drug, 2 drugs, or maybe an alternative approach altogether; however, we don't have any biomarkers just as of yet, for immune therapy agents to select patients for one treatment approach versus another. PD-L1, or programmed death ligand 1, is a protein that can be expressed by many different cells, including tumor cells, and it has been studied in patients getting PD-1 or PD-L1 agents, and it has been studied in patients getting PD-1 in combination with CTLA-4, to try to see, is the presence of this protein, PD-L1, associated with benefit from immune therapy agents such that that would affect our treatment choice for our patients? And the data for PD-1 and PD-L1 efficacy by this biomarker, PD-L1, does differ a bit between different tumors. So, the experience in melanoma is not quite the same as the experience in nonsmall cell lung cancer and may not be quite the experience in some other tumors as well. So, I'll specifically speak about melanoma when I talk about this, that PD-L1 as a biomarker, in my opinion, can't be used to select patients for single-agent PD-1 treatment or for the combination of PD-1 and CTLA-4 blockade together. And that is because patients will have higher response rates with the combination of CTLA-4 and PD-1 blockade compared to single-agent PD-1, regardless of the PD-L1 status of the patient. Progression-free survival differs a little bit in this context, based upon PD-L1 status, but I think, for purposes of broad-picture appreciation of this biomarker, in patients with metastatic melanoma, PD-L1 cannot be used to select patients for one treatment regimen

over another because even patients with PD-L1-negative tumors, they don't have the biomarker at all, they can absolutely still benefit from PD-1 as a single agent, and they can absolutely still benefit from PD-1 and CTLA-4 in combination. So, I think we need more research. It remains a research test in melanoma. It is an important biomarker for research and for trying to understand how we can move forward as a field, but it's not yet ready for clinical application.

Dr. Mennen:
Now, before we wrap up, is there anything you would like to add or reiterate concerning checkpoint inhibition in melanoma?

Dr. Postow:
So, I think, we're making incredible strides with checkpoint inhibition in melanoma. We've seen improvements in overall survival with CTLA-4 blockade alone, with PD-1 blockade alone. We've seen improved responses and progression-free survival when we combine these agents. I think as we move forward, I think, we have a long way to go because despite the improvements that we're having, it doesn't yet help every patient, and so we're going to need to continue to enroll into additional clinical trials so we can learn about triplet combinations, we can learn more about why some patients are not responding to checkpoint inhibitors, and we can also learn about how to manage some of the side effects that come along with this treatment, because unfortunately, some patients can have some significant side effects that, despite their benefits that they're having for their cancers, they need to be well supported during their experience with these side effects. But this is all a very important area of research. We don't know if immune therapy with checkpoint blockade is better than targeted therapy yet for patients with BRAF-mutant melanoma. I don't think this is something that we have to think about these necessarily as competitors. These are all great treatments. We just need to really continue to learn how to use them appropriately and I'm hoping ongoing clinical trials will continue to clarify that for us.

Dr. Mennen:
Dr. Postow, thank you so much for joining us today and sharing your insights on immunotherapy from the 13th International Congress of the Society for Melanoma Research.

Dr. Postow:
Thank you very much. It's a pleasure to be here with you.

Dr. Mennen:
I'm Dr. Barry Mennen, inviting our audience to access this and other CME Expert Interviews on ReachMD where you can be part of the knowledge. Thank you for listening.

Narrator:
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