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Emerging Trends in the Sequencing and Combination of Therapies for Advanced Melanoma

Narrator:

Welcome to CME on ReachMD. This segment: **Emerging Trends in the Sequencing and Combination of Therapies for Advanced Melanoma**, is provided by Vindico Medical Education and is supported by an educational grant from Merck and Company, Incorporated. The activity chair and moderator for today's program is Dr. Sanjiv S. Agarwala, Professor of Medicine at Temple University School of Medicine and Chief - Oncology and Hematology at St. Luke's Cancer Center in Bethlehem, Pennsylvania. Dr. Agarwala is joined today by two expert colleagues: Dr. Steven O'Day, Director of the Los Angeles Skin Cancer Institute and Director of Clinical Research at the Beverly Hills Cancer Institute, Beverly Hills, California, and Dr. Merrick Ross, Professor of Surgery and Chief of the Melanoma Section at the University of Texas MD Anderson Cancer Center in Houston, Texas.

Prior to beginning the activity, please be sure to review the faculty's financial disclosures. Please review the learning objectives for this activity.

Upon successful completion of this educational activity, participants should be better able to describe the mechanisms of action as well as the clinical safety and efficacy profiles of new and emerging therapies for the treatment of advanced melanoma and evaluate the use of biomarkers to guide clinical decision-making for advanced melanoma.

This video is being delivered with a novel E-learning environment that has been designed to support learning and reflection over time. As the learner reacts to the information being provided within this educational activity, key points of emphasis will appear to the right of the video. In this learning stream, the learner will see educator notes, reflective prompts and poll questions that provide additional context at the right moments throughout the activity. We have provided an online step-by-step resource that outlines educational prompts and customized application to make it most relevant for each learner. Below this video there is a searchable library of additional related resources that have been curated by the faculty to provide related information and help answer any questions that arise over the course of the activity. We offer you an innovative learning experience that is engaging and designed to impact positive patient outcomes.

Here is your activity chair and moderator, Dr. Sanjiv S. Agarwala.

Dr. Agarwala:

Melanoma is the sixth most common cancer in the United States, and the number of melanoma cases diagnosed annually is increasing faster than for any other cancer. The medical management of melanoma has changed dramatically since the first description as a disease entity. In this educational activity, leading oncologists will discuss the mechanisms of action, clinical safety and efficacy profiles of new as well as emerging therapies and the use of biomarkers to select regimens and will review evidence-based clinical trial data supporting the medical treatment of advanced melanoma.

So, I'd like to welcome my colleagues, Dr. Steven O'Day and Dr. Merrick Ross, experts in melanoma, to join us today. So, let's start by talking about what is the latest and greatest in melanoma treatment, and let's start with you, Steve. Please explain to us what is checkpoint signaling, immune checkpoint signaling, what does it mean to us?

Dr. O'Day:

So, there's really been a revolution in the immune oncology, and it's centered around the T cell and these very important checkpoints, and we've now identified two very important checkpoints which now are therapeutic targets, which have revolutionized the treatment of melanoma. The first is CTLA4, which is an early checkpoint at the time point of antigen recognition, and a later checkpoint, PD-1, has been identified, which is really more located at T cells that are in the microenvironment. And I think the clinical efficacy, the toxicity and the kinetics of the responses of these checkpoints really relate to early and late and where they are located in terms of where the T cells are in the tissues.

Dr. Agarwala:

Great. So, Merrick, in terms of the current status of monotherapy with these agents that Steve has talked about, can you give us an update on that?

Dr. Ross:

Well, sure. So, the first monoclonal antibody that was developed against anti-CTLA4 is the drug ipilimumab, and this was studied in a prospective randomized fashion that showed for the first time an overall survival benefit in these advanced patients with melanoma. The previous drugs that have been approved for melanoma have not really shown an overall survival improvement in patients. So, the interesting thing with this particular drug is that there's a pretty significant tail of the curve, where the survival rates have leveled off at a certain period of time. And while this is very encouraging, we have some improvements related to that overall survival benefit with the anti-PD-1 drugs, so the second class of drugs that were studied is also monoclonal antibodies against the PD-1 receptor.

And two drugs have been approved by the FDA, both pembrolizumab and nivolumab. We have some long-term survival data related to the anti-PD-1 drugs, and significant improvement compared to ipilimumab alone. So, at the present time, in terms of monotherapy, we probably would not start with ipilimumab at this point in time, but the anti-PD-1 drugs are the drugs that we would use. It's interesting because the anti-PD-1 drugs have been tested in both patients that have failed ipilimumab as well as in the first-line scenario with patients with advanced melanoma, and in both of those situations, the anti-PD-1 drugs have been very effective.

Dr. Agarwala:

So, Steve, very exciting data with monotherapy with these immune agents, as Merrick discussed, but for the BRAF-positive patient, we have some interesting data using a BRAF/MEK combinations that was also updated at ASCO this year, wasn't it? Can you talk about that?

Dr. O'Day:

So, at ASCO this year the combination BRAF/MEK data was updated with 3-year followup, and it was impressive survival data of almost 44% in the combination. Now, we knew that the combination appeared better than single-agent BRAF inhibitor therapy, but we hadn't seen longer followup, and so this is quite exciting data that the combination targeted therapies can also produce longer-term survival in a subgroup of patients, which really puts it back in front and center with decision-making in term of immunotherapy and combination targeted therapy.

Dr. Agarwala:

Right, so it's kind of nice that a BRAF-positive patient has a choice now, and clinicians, of course, have to help make that choice. So, there was also updated data from AACR recently looking at the combination of ipilimumab and nivolumab. I'm going to talk about this later as well, but can you let us know what that showed and how impressive that was, and that makes it feel a little confusing, doesn't it?

Dr. O'Day:

So, we talked a little bit about the combination or the individual monotherapy for the immune therapies, CTLA4 and PD-1 blockade, but obviously, there's an intense interest in combining them with synergistic effect from these checkpoints. And we've seen data over the last several years Phase I, and now we saw at ASCO AACR this year updated data with 2-year survival in a randomized Phase II trial with the combination showing almost 65% 2-year landmark survival, which is the best that we've seen, so very exciting data. So, clearly, combination immunotherapy is leading to really impressive 2-year survivals now that we're hopeful will be persisted over time.

Dr. Ross:

So, Steve, what about the fact that the ipilimumab data in that particular Phase II trial showed that the ipilimumab patients actually did pretty good compared to the previous monotherapy that had been published?

Dr. O'Day:

Yes, so in that randomized Phase II trial, there was, obviously, patients had access to both drugs, and so there clearly was crossover that was likely leading to improved survival in the ipilimumab monotherapy arm, so it's more of a sequence.

Dr. Agarwala:

So, it's really kind of interesting that both these combinations, BRAF combinations, BRAF/MEK and immunotherapy combinations, work well in certain patients. And, Merrick, there was some data looking at specific subsets in the COMBI-d trial, which apparently showed that if you looked at the right subset of patients, if you will, they did really, really well, like the 60% numbers that you quoted in the combination immunotherapy. It looked like you could do that with BRAF/MEK as well, correct?

Dr. Ross:

Yes, so these trials are large enough now that you could look at some of the stratified subsets and, particularly, the patients who have low LDH and relatively small volume of disease in terms of number of sites that are involved at the distant metastatic level, that when you look at those specific subsets when you're looking at the BRAF/MEK combination, the survival rates are pretty impressive. And there's actually some plateauing of the curves, which suggests that some of these responses may be very durable.

One of the original criticisms of the BRAF/MEK data was that the development of resistance that could occur early and people were concerned that there wasn't going to be a plateau, but it appears that for some of the earlier or lower-risk patients, that there looks like a very nice survival benefit. But I'm sure there are patients very similar within the immunotherapy groups that you could see very similar effects where lower volumes of disease would have better outcomes.

Dr. O'Day:

So, traditionally, I think we have been targeting the BRAF/MEK treatments to the worst actors in terms of the metastatic melanoma. What the data in this subgroup is showing is obviously that the best group is the more limited LDH low volume, but of course...

Dr. Agarwala:

They do a little bit of both, right?

Dr. O'Day:

But immunotherapy does well, very well with those patients.

Dr. Agarwala:

I tell you what, let's take polling question number 1, because let's see what people think about this. So, regarding front-line therapy for the BRAF-positive patient, which is the true statement here?

A) All patients should get BRAF-targeted therapy, or

B) All patients should receive immunotherapy.

So, let's see what people think about that. So, Steve, let me start with you here. What will you pick in this? Will you pick an A or a B, or you don't know?

Dr. O'Day:

Well, the real answer is we don't know, and that there's now a randomized trial, an**intergroup* 10:24** that's really going to address – a very important trial, try and address which we should start with. Having said that, I think the immune data right now is very impressive with combination, and the kinetics of the immune response is getting better and better with combination -- at a price because there's increased toxicity. So, the patients that are competing for each study, each of the types of approaches, BRAF/MEK or immune treatments, is getting very comparable, so we can use immunotherapy even in more aggressive disease. So, the truth is we don't know for sure. We still, I'm still impressed with the durability of the immune data, particularly the combination. I'm hopeful that is going to be the best regimen.

Dr. Ross:

So, Steve, as best we can tell, whether the patient's BRAF positive or BRAF wild type doesn't really affect their response to immune therapy. Is that correct?

Dr. O'Day:

That's a very important point, absolutely. So, right now, whether you're BRAF mutated or not, you seem to have comparable immune

responses, so I think there's truly a choice that clinicians have in the first-line setting in BRAF-mutated patients.

Dr. Ross:

So, given the really impressive survival data with the lower-risk patients that are metastatic with the BRAF/MEK combination -- and that's really impressive -- but what about the patient who presents with really advanced, galloping, wildly progressive disease and they're BRAF-positive? How do you decide which to choose first?

Dr. O'Day:

Well, I think traditionally we have used BRAF/MEK combination therapy in those patients because the kinetics of the response is so rapid, literally within a few days, that if patients are in danger of having significant complications of their disease from symptoms, it clearly merits using the BRAF/MEK treatments up front. Having said that, I think the kinetics of response to the immune treatments now in combination are getting much better and that distinction of who needs it for sure and who doesn't is disappearing, so I think we...

Dr. Agarwala:

The gap is narrowing though, isn't it?

Dr. O'Day:

It's narrowing, exactly.

Dr. Agarwala:

That's why the randomized trial you mentioned could be very helpful.

Dr. O'Day:

Yes.

Dr. Agarwala:

So, I think we've always struggled with the biomarker question, correct? So, we know that BRAF is a great biomarker, not because it tells you what to do, it tells you what not to do, because if you don't have BRAF mutation, don't use BRAF-targeted therapy. In immunotherapy we don't really have that, right? So, Steve, can you discuss with us a little bit the randomized Phase III trial that is being presented and updated at ASCO this year that looked at the combination of ipi and nivo together versus ipi versus nivo, what that showed, and was there a biomarker story there to tell?

Dr. O'Day:

So, like you said, molecular markers directed at the tumor, like BRAF, are very good. They're both sensitive and specific in terms of their ability to dictate treatment. Unfortunately, the immune system is a more complex system that has multiple cells and is inducible, and so it's much more difficult to find reliable biomarkers. Having said all that, in the large randomized Phase III trial with combination CTLA4 and PD-1 blockade versus PD-1 or CTLA4 monotherapy, it has been looked at, PD-L1, which is expressed on tumors, has been reasonably predictive, even though it's an inducible marker. Although it doesn't help us pick whether to use immunotherapy or not like BRAF does, it may help us understand who needs the combination and who not based on recent update of that data by a Dr. Wolchok showing that patients with 5% or more staining of PD-L1 had very comparable progression-free survivals as those that received the combination, suggesting there may be a subgroup. Having said that, PFS is just one endpoint. And if you really look at the staining of 5% or less across response rate or durability of the response, numerically there still favors treating combination in everyone. So, I think it's impressive that a single marker, an inducible marker, on a tumor could help us really be quite predictive of who needs combination, and the preliminary data is provocative, and I think I'm just not quite ready to use it as primetime yet.

Dr. Agarwala:

Merrick, would you agree with that? Is that something that are you doing it now yet?

Dr. Ross:

It's very difficult to use because there's more than one assay, and the thresholds for each assay calling positive versus negative are also not consistent. One assay uses a 5% threshold. The other one uses a 1% threshold. So, if you looked at the same patient population and looked at 5 versus 1, the percentages of positivity are much different, so I think that makes it very difficult for the clinician to decide how to use that biomarker in clinical decision-making. And I think until we get more data that is more predictive, I think we really can't use it yet.

Dr. O'Day:

But I think there are other assays that are being looked at. This is one assay. Obviously, the degree of T cell infiltration into tumor, immune signatures, genetic profiles are being looked at. I think we're going to get there. I think we are making progress. And this immune resistance inflammatory state of the tumor, which can be very, hopefully will be, predictive of who needs more aggressive combinations and who needs monotherapy. I think we're going to get there in the future. We're just not quite there yet.

Dr. Ross:

So, it's possible we may be able to develop an immune score, so to speak, that would include things like mutational status, like how many mutations there are within the tumor, the PD-L1 expression on the tumor, and also T cell infiltration and, actually, the characterization of that T cell.

Dr. O'Day:

The ratios of effect are in suppressors.

Dr. Agarwala:

Let's get to the next poll question here. So, let's ask: When choosing first-line immunotherapy for patients with metastatic melanoma, PD-L1 staining of the tumor is useful, yes, no, or maybe? So, I guess in melanoma, it's not as clearcut as is might be in some other tumors where I think even there it's a bit controversial, but it's much more widely used in other cancers.

In melanoma, Merrick, are your clinicians, are you sending PD-L1 staining when you make decisions? And let's look at both the BRAF-positive and the BRAF wild type patient looking at the data that Steve talked about in the combination. And we know one of the issues we really haven't talked about, but it's true, is that when you combine these 2 drugs, the toxicity goes up quite a bit. So, how do we make that choice? They're all available to us right now in the clinic. How do you decide, Merrick?

Dr. Ross:

So, right now we're not really using it as a decision in terms of therapy, that we're using it as part of clinical trials where we're looking at biomarker discovery and evaluating the relevancy of these particular biomarkers, so I think, from a clinical decision-making perspective, it's very difficult to use them at this point in time. So, we get them, but not to the point where we actually decide this therapy versus that therapy.

Dr. Agarwala:

So, you get it just to kind of find out what it is but don't make decisions based on that?

Dr. Ross:

But it's usually just for data gathering for future evaluation so we can make better-informed decisions. But I do think it's an interesting process now that we have some long-term survival with the BRAF/MEK therapies, that it would be interesting to see what the long-term impact in terms of prediction for the patients that are BRAF-positive but they have certain levels of PD-L1 expression, that that expression may actually tilt the decision towards one therapy versus the other. So, if they have fairly significant disease and they're BRAF-positive, what if their PD-L1 expression is really low? Would that influence you or influence you to use BRAF/MEK combination as opposed to...

Dr. O'Day:

Yes, there's no question that PD-L1 expression enriches for response even with monotherapy, the higher level of expression, the higher the problem is. Even in PD-L1 negative patients there is a subset of those that have nice, durable responses, so it's not really... Since the endpoint is long-term survival with these immune therapies, we don't want to not offer life-saving long-term treatment to a subset of patients. But I think where we're hoping it's going to help us is deciding where the low-hanging fruit is. What patients really will achieve long-term survival with just monotherapy with much less toxicity and which really do require... I think, regarding that question, I think the data from ASCO, the updated data from the large, randomized, 3-arm study is encouraging, that maybe we will be able to help pick out a subset of patients that needs less or more.

Dr. Ross:

But the thing that's really confusing it, though, is that the data of the ipi/nivo that used the 5% cutoff, so a lot of those patients that would

be considered PD-L1-negative, using the other assay would be PD-L1-positive.

Dr. O'Day:

Correct.

Dr. Ross:

So, calling things PD-L1-negative isn't necessarily consistent across all patients.

Dr. Agarwala:

That's a very good point. And good news, I guess, is that we're studying this more, and even in the ongoing randomized trial, for example, we're collecting PD-L1 staining to learn more. But I think the points are well taken. The assays are very different, and maybe we'll never know for sure, but I think it's all about personalizing care and figuring out the right treatment for the right patient. And multiple factors will come into play in that, right? So, some really good things going on in melanoma right now, but we can't just sit on our laurels. We have to keep on making progress.

So, Merrick, tell us about some of the exciting new things going on in terms of emerging therapies for melanoma that you're excited about.

Dr. Ross:

Well, this is certainly a very exciting time, and the previous data that we talked about has been a great foundation for future endeavors that would combine immune therapies that would either help stimulate or reverse the inhibition that may be present in terms of T-cell activation. Probably the most important thing in all these therapies is the interaction between the antigen-presenting cells and the T cells, and there are a variety of receptors that will control or dictate how the T cell gets activated, yes or no. And obviously, the checkpoint receptors are very important for that, but there are several other co-inhibitory and co-stimulatory receptors that can be activated or blocked that may either enhance or reduce the activity of the T cell, particularly in the context of an antigen-presenting cell that has the important tumor antigens that have been loaded and primed. So, there are other things to combine with the checkpoint-blocking agents that would improve the overall response rate, and hopefully the overall survival, because clearly we're not where we want to be. We want to cure as many patients as possible or provide long-term survival in as many patients as possible.

Another concept that can be combined with the checkpoint-blocking agents, and that's called oncolytic immunotherapy. So something that we can inject into the tumor that could affect what we call the cancer immune cycle, and that cancer immune cycle may be the ablation of the tumor with some sort of agent that would expose relevant tumor antigens that could be exposed to the T cells that are present or that may be circulated towards the inflammatory response that occurs when a tumor is killed in a very necrotic or inflammatory way.

One of those drugs that can do that is called TVEC (talimogene laherparepvec), which I don't want to say again because it took me 6 months to figure out how to say it to begin with. So, this has been approved as monotherapy recently by the FDA. And it's an interesting drug because it is a herpes simplex virus type 1 that's been modified, and it's been modified in a way that it only really replicates within tumor cells, and when it replicates, it makes something called GM-CSF, which can promote antigen presentation and maturation of the dendritic cells that are resident in the area of the tumor. So, the presenting of those cells or the antigens in a very inflammatory way can actually enhance the immune response and actually may be synergistic with the checkpoint-blocking agents.

So, interestingly enough, there is a trial that's ongoing now that was initially part of a Phase Ib combination of TVEC combined with pembrolizumab and, obviously, it has to be for the subset of patients that have metastatic disease that's accessible to be injected, so like metastasis in the subcutaneous tissue or the skin or in lymph nodes, in addition to having visceral metastases. So, these patients can be offered these intralesional therapies. And based on the Phase Ib data, it's a very safe combination, and probably safer than ipi/nivo, for example. So, we're trying to look for combinations that may be just as effective without the toxicity that's inherent with the checkpoint-blocking agents combination. And the preliminary data is very, very, very encouraging, that we are seeing response rates in the initial Phase Ib part of the trial that are higher than what you would see with either drug given independently. And now there's a Phase III component to this. It's actually going to be a registration trial where patients will be randomized to pembrolizumab alone as single agent versus the combination of TVEC with pembrolizumab.

Dr. Agarwala:

So, Steve, this is kind of a nice way to make that tumor your ally, if you will, use that injectable tumor. And this concept of combining intralesional therapies with other immunotherapies is being done with other agents as well, correct? I mean, it's...

Dr. O'Day:

Absolutely. This is sort of a new frontier. I think with the CTLA4 and PD-1 blockade, we now have very active T cells circulating both in the peripheral immune system and at the microenvironment. But clearly, even with that activation, a large percentage of tumors are not responding, and so that the idea of really going back to the tumor now that the immune system has been really activated and injecting these tumors with oncolytic viruses -- this virus, this herpes simplex virus; we have coxsackie viruses and other viruses that are both oncolytic to the tumor but then also bleed the tumor, so to speak, and allow it to release its neoantigens -- I think is very powerful, and it may be just what the immune system needs to see that tumor a little better and then generate this very powerful, durable immune response. And so the preliminary synergy looks great without a lot of toxicity, which is really what we're trying to achieve in terms of quality of life for patients.

Dr. Ross:

So, Steve, how do you view the toxicity of single-agent checkpoint-blocking agents like pembrolizumab or nivolumab versus the combination of the two? How do you decide from a toxicity profile whether the patient would be eligible for this combination, given the already long discussion that we had about the biomarker where we can't yet exactly predict who is likely to need the combination versus monotherapy?

Dr. O'Day:

Well, I think with PD-1 monotherapy, the serious immune-related toxicities are much lower. They're in the 10 to 15% range. When you combine CTLA4 and PD-1 blockade, you're now in the 50-plus percent range, so much less with PD-1. However, with PD-1 monotherapy, of course, you are committing to a longer duration of therapy, and there may be low-level immune toxicities that persist that are somewhat underappreciated, I think, over months to years that these patients are on these drugs. But the idea would be that these oncolytic viruses seem to add very little toxicity to PD-1 monotherapy as opposed to ipilimumab, which seems to add quite a bit. And so to the extent that these oncolytic virus PD-1 combinations lead to efficacy that's comparable, obviously it's a win-win for the patient. Now, like you said, not all patients have injectable lesions, so it's a subgroup that may benefit, but certainly, it's very encouraging.

Dr. Agarwala:

One size does not fit all. So, an exciting time in melanoma. So, I'd really like to thank my colleagues, Dr. Ross and Dr. O'Day, for sharing their insights on emerging trends in the sequencing and combination of therapies for advanced melanoma.

Please take a moment to take the post-activity test to receive CME credit. I'm Dr. Sanjiv Agarwala. Thank you for joining us.

Narrator:

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