Post-SMR 2015 Congress: Advances in the Management of Metastatic Melanoma

Introduction

Mario Sznol, MD: Welcome to this continuing medical education (CME) program titled, “Advances in the Management of Metastatic Melanoma.” This CME activity is supported by an independent educational grant from Genentech Inc., and is provided by AcademicCME. I am Mario Sznol. I’m a professor of internal medicine and a co-director of the Yale SPORE in Skin Cancer at the Yale Cancer Center in New Haven, Connecticut. I’m joined today by my colleague, Dr. Jeffrey Weber. He’s the deputy director of the Laura and Isaac Perlmutter Cancer Center at the NYU Langone Medical Center in New York, New York. So, welcome everybody. Dr. Weber, I thought we’d start with a brief review of the treatments for metastatic melanoma.

New Advances

Jeffrey S. Weber, MD: Over the past five years, there have been a large number of new drugs for metastatic melanoma. And after a drought of 10-15 years, we now have seven new drugs available, plus additional ones in combination—meaning those drugs both individually and as combination therapy. Things are looking up for patients with melanoma. We now have a whole series of immunotherapeutic drugs, the so-called checkpoint inhibitors, which can be used individually or in combination. That would be ipilimumab—the first drug that ever showed prolonged survival on a randomized trial that was approved in 2011 by the US Food and Drug Administration (FDA) for both first- and second-line melanoma—and the programmed cell death protein 1 (PD-1) drugs. Regarding the PD-1 drugs, pembrolizumab was the first to be approved in September 2014 for metastatic disease, and soon thereafter, nivolumab, the other PD-1 antibody, was approved. Then the combination of those immunotherapies, nivolumab plus ipilimumab, was approved a couple of months ago, so now we have technically four different regimens and three different drugs that are approved and therapeutic. We also have four different targeted therapies and another combination of one of those pairs. We have dabrafenib, vemurafenib, trametinib, and cobimetinib, so respectively, two BRAF inhibitors and two MEK inhibitors. We also have one approved BRAF plus MEK inhibitor combination, so I think we’re doing extremely well. And we now have a second combination of vemurafenib and cobimetinib, so there’s a wealth of options that fall into the immunotherapeutic category or the targeted category, with the targeted drugs directed against melanomas that harbor a BRAF mutation—a mutation in the BRAF gene—for patients with metastatic melanoma today.
Ipilimumab and Nivolumab

Dr. Mario Sznol: Jeff, that’s an excellent summary, and it is an exciting time. Our patients are doing much better with all of these options. Let’s talk a bit about what’s new for the treatment of metastatic melanoma based on findings at recent meetings. The most recent meeting was the Society for Melanoma Research (SMR) 2015 International Congress in San Francisco. We presented long-term survival data for the combination of ipilimumab and nivolumab. These data were based on a phase 1 trial that started in 2009, so we had quite a number of years of follow-up. From the first three cohorts of patients who were treated, the overall survival rate in two years was approximately 79%, and the three-year survival rate was 68%, which I think is unprecedented. When looking at all 94 of the patients in this trial who received the combination of ipilimumab and nivolumab, the two-year survival rate was 73%, which I think is an amazing number. The survival data for the randomized trial are not yet available, but the data from this study would seem to predict that the overall survival rates in that randomized trial will be remarkable, and the median survival may exceed three to four years. There were data also presented at the meeting for pembrolizumab in combination with ipilimumab by Georgina Long. Jeff, do you want to comment on those data?  

Dr. Jeffrey Weber: Before I comment on Georgina’s excellent data, I would say it’s extraordinarily important that if one looks at all 94 patients in the trial you just discussed, there was a median survival of approximately 43 months, which is fantastic. Those are the best data I’ve ever seen. Consider that five to eight years ago, patients were being treated with chemotherapeutic regimens with a median survival of anywhere between 8-12 months. Today, we’re talking about a fair-sized phase 1/2 experience with a median survival of 43 months, and that reflects several of the cohorts where we would agree that they didn’t get the optimal assertive therapy. I predict that we’re looking at a nearly four-year median survival for the CheckMate 067 and 069 cohorts of patients who received both ipilimumab and nivolumab. It’s not just a one-trick pony, because one can look at pembrolizumab, the other PD-1 antibody, with ipilimumab and also see very impressive data. Georgina Long presented the initial results with the KEYNOTE 029 study, which was a study where patients received pembrolizumab at the approved dose, 2 mg/kg every three weeks, and the patients then received ipilimumab at a dose smaller than the approved dose of 3 mg/kg. In this trial, it was given at 1 mg/kg, and over two-thirds of the patients were given all four doses of both drugs in the first 12 weeks. There was a fair incidence of grade 3/4 treatment-related adverse events (AEs), about one in three or 36%, but the response rate was 56%, which is equivalent to what has been seen both in the study you described, your study, the 004 study, and the larger randomized phase 2 069 and phase 3 067 studies. I have a feeling if one could lower the dose of ipilimumab, one could probably increase the tolerability and make things better for patients by maintaining the response rate. Of course, the problem with the pembrolizumab plus ipilimumab data are that the follow-up is going to be a lot shorter than the most mature data from your own trial that you just described. That’s going to be what everyone has to either match or beat in the future.
Dr. Mario Sznol: I think you’re right, Jeff. In the data set that Dr Long presented, it looked like a slightly better group of patients—a group with a lower percentage of patients with lactate dehydrogenase (LDH)—but nevertheless the data were striking. The overall response rate was very similar to 067 and 069 for ipilimumab and nivolumab. If one can give a lower dose of ipilimumab and a higher dose of an anti-PD-1, one may get the same benefit with a lower toxicity rate. As you know with ipilimumab and nivolumab, the rate of grade 3/4 AEs is in the range of approximately 50%-55%. Although toxicity is manageable—there was one death in the randomized trial—we would certainly want a regimen that is better tolerated.

Dr. Jeffrey Weber: Of course, toxicity is always going to be the issue as people think about the approved ipilimumab-plus-nivolumab regimen. There was an interesting abstract presented at the meeting where a quality-of-life assessment was made in patients receiving either ipilimumab alone, nivolumab alone, or the combination in 067. In that study, the combination clearly showed major improvement in efficacy and benefits in quality of life compared to ipilimumab. And while the quality of life is probably fairly similar, the efficacy is so vastly superior both in response to the VMS, one doesn’t give up any significant decrement to quality of life, but one gains a lot of efficacy by going with the combination, certainly vs ipilimumab alone. The question of course is, what is one’s quality of life going to be with nivolumab alone? When extrapolating from long-term experience with both nivolumab alone and pembrolizumab alone, it appears that the median survival is going to be in the 30-32-month range. If the data you cited from the 004 study with the combination holds up, it looks like there will be a major increment in survival, which must be balanced with the decrement in quality of life over the first 12 weeks caused by increased toxicity. I predict that there ultimately will be enough improvement in survival rate with the combination that will justify its more widespread use. We certainly agree that it’s justified with respect to ipilimumab, which was the primary endpoint of the 067 trial. Comparing it to nivolumab shows that it wasn’t powered that well. I think we’re ultimately going to find that even when compared to nivolumab, it’s better to receive the combination.3

Targeted Therapies

Dr. Mario Sznol: Later, we’ll talk about possible predictive factors that might allow us to select between nivolumab alone and the combination. For right now, let’s move on to the targeted therapies. Data were presented for dabrafenib and trametinib and for vemurafenib and cobimetinib. What can you say about the efficacy of those combinations compared to each other individually and their overall activity (for example, median survival and two-year survival rate for those regimens)?

Dr. Jeffrey Weber: Well, the regimens of cobimetinib plus vemurafenib vs dabrafenib plus trametinib appear to have an amazingly equivalent progression-free survival (PFS) and survival record. When looking at the most mature data, which tend to be the dabrafenib plus trametinib data because that went through its initial trials somewhat earlier than vemurafenib and cobimetinib, we see a 25-month median survival. That was in the Combi-B study, the Combi-D study, and the initial phase 1, which was called the 113220 study that I took part in. When looking across three studies of approximately 600-800 patients, the
equivalent medians were 25.0, 25.1, and 25.6 months. It doesn’t get any more consistent than that; it’s truly amazing.

When looking at either dabrafenib alone or vemurafenib alone, there are consistent hits of 18 months in the frontline. This is phenomenally consistent data that confirmed the benefit of using the combination. When looking at the early data from vemurafenib plus cobimetinib, it’s probably going to be about the same with two-year survival rates of slightly over 50%. So we’re talking 50%-60% two-year survival rates. These are very impressive and interesting data in patients treated frontline who were BRAF-mutated. One question this raises is, if single-agent pembrolizumab survival in either BRAF-mutated or wild-type patients gives us 30+ months, and the median survival in the upfront-treated mutated patients with the combination of vemurafenib plus trametinib or vemurafenib plus cobimetinib, one does the math and decides which regimen one would rather be on. This would suggest that perhaps we should be starting first with immunotherapy. That will be compared in a large randomized trial through the cooperative groups where patients will randomly be allocated to first get targeted MEK immunotherapy or vice versa. Giving the numbers a superficial assessment, there’s a strong argument to be made for using immunotherapy first.  

Dr. Mario Szol: I agree with that, Jeff. Even in BRAF-mutated patients, immunotherapy is likely to be more effective, but we know that there are subsets of patients who will need targeted therapies first. There are patients who have brain metastases and require steroids, even at the initiation of treatment, so for those patients, one may want to use targeted therapies first. There are groups of patients who have very high tumor volumes and very rapidly progressive disease. Even though we do see rapid responses with several of the immunotherapy regimens, patients still might need a targeted therapy first, because even in those patients, immunotherapy won’t work fast enough to turn them around. In the vast majority of patients that I see with BRAF mutations, I would start with an immunotherapy. The randomized trial data will tell us more, and clearly there are clinical factors that determine which agents we use first.

LDH Levels and Survival Rates

Dr. Jeffrey Weber: I absolutely agree with you, although interestingly, with Georgina Long’s other presentation from SMR, she looked at how patients receiving dabrafenib plus trametinib could be stratified by their predictive and prognostic factors in terms of survival. She had a very interesting slide showing PFS and also a slide showing overall survival where it was assessed by LDH—whether it was normal, one to two times normal, or two or more times normal—and by number of disease sites. One could stratify and clearly separate the curves very nicely if one had a normal LDH vs LDH that was one to two times normal vs LDH more than twice normal, implying that the disease burden is literally a negative predictive factor based on the LDH for targeted therapy. Interestingly, when looking at patients with normal LDH, which can broadly vary in terms of disease burden, we broke it down by number of disease sites—greater than or equal to three sites vs less than three sites, and one to two vs three or more sites. Even then, we saw clear separation with patients with the fewer number of disease sites doing better. So it would appear that with
Cooperative Oncology Group normal LDH between LDH, that if presentation therapies remains high though rates LDH response rates were those who received immunotherapy prognostic feature even among patients who very exciting. better survival even in the high LDH group, we can see not on suggest that LDH is still a poor prognostic feature even among patients who receive immunotherapy. So if one looks at the 067 data, the patients who had the highest response rates were those who had normal LDH, and there was a decrement in response rates with increasingly higher LDH levels. Even though patients can do very well with immunotherapy with high LDH and maybe even better than with targeted therapies, LDH that remains high is a poor prognostic feature. We need to understand why and develop better therapies for those patients.

Dr. Jeffrey Weber: Georgina’s work and presentation were very interesting in the sense that if one looked at survival rates, patients with above-normal LDH did worse than those with normal LDH. And in patients with normal LDH, those with one to two sites did better than those with three or more sites. But even within the high LDH between one and two times normal group, if a patient had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, that was considered better than if the patient had an ECOG of 1. So one can slice-and-dice by LDH, number of disease sites, and performance status to get a gut feeling for the patients who are going to do poorly. I would think someone with a high LDH, unless they had fast growing disease, might be an interesting candidate, even if they’re BRAF-mutated, for a combination of immunotherapy.

Combining Immune Therapies and Targeted Therapies

Dr. Mario Sznol: Georgina’s work was very important; it was a very nice analysis. Obviously, our phase 1 trial was too small to look at all these factors. But when looking at hundreds of patients treated with the combination, in 067 and 069, before we had the randomized study, we could do a similar analysis and see whether the patients who fit in the same categories do as well or better with immunotherapies than they do with targeted therapy. So I’m looking forward to seeing that analysis in the future. Let’s talk about the next step in the development of these agents, which is the combination of immune therapies and targeted therapies. Did you see any data at SMR, probably the data presented by Hamid et al., that suggested there was a role for combining these two classes of agents?

Dr. Jeffrey Weber: So this was an early study, and I say early because it combined vemurafenib, a BRAF inhibitor with an anti-PD-1 drug, atezolizumab. That’s one of the reasons why they were combined together in particular. Again, we already knew the BRAF plus MEK inhibitors combination would be superior to BRAF alone, so I think that that was one of the issues with this trial being done and how it was
just BRAF alone and BRAF plus MEK. And the MEK inhibitor has theoretical issues with suppressing T-cell proliferation and activation. Being a Monday morning quarterback is easy in retrospect in terms of whether it was an ill-founded concern, but nonetheless, Dr. Omid Hamid presented very early results from this study with approximately 19 patients enrolled who were naïve to all BRAF inhibitor and immunotherapy treatment. The confirmed objective response rate was 76% with three complete responses (CRs) and ten partial responses (PRs). That’s not bad, and the median PFS was about 12 months, which is what one would expect from essentially putting the two types of drugs together—one of which would have a seven-month median PFS, and then about five months for the programmed death-ligand 1 (PD-L1) drug alone. But duration of response was long as expected—20.9 months, which is impressive. It was an interesting study in that they did a lead-in with just a BRAF drug because of the data that the BRAF drug can induce the lymphocytic infiltrate into the tumor, and the resulting tumor destruction can change a so-called cold tumor into a more hot, or inflammatory, tumor type microenvironment. Again, small numbers. Only 19 patients with no surprises in terms of toxicity from what one would expect from either drug alone. AEs were easily manageable and reversible, though interestingly, there were no grade 4 AEs at all. But I like the idea of the PD-L1 drug with the BRAF drug either alone or in combination with the run-in. I might do a four-week run-in, continue it maybe for four more weeks, and then quit, because there are data suggesting that the longer one gives the BRAF and MEK drugs, the greater the chances of losing that lymphocytic infiltrate and the cold tumor that becomes hot will start cooling off. At the end of their abstract, they point out that vemurafenib/cobimetinib plus atezolizumab is now being evaluated, so I think that’s the ultimate goal. It turns out that it’s an urban legend that the MEK inhibitor doesn’t have any obvious documented negative effects on T-cell activation.  

Dr. Mario Sznol: And certainly not on effect on memory T cells, which are doing the heavy lifting at the beginning of treatment. I think the data are exciting because the response rates, even in a small cohort, were higher than one would expect. When combining the BRAF and MEK inhibitors such as vemurafenib, cobimetinib, dabrafenib, and trametinib, the response rates of those agents are very high. They’re going to be in the 70%-90% range, depending on how one selects patients. It’s going to be very difficult to tell whether the response rate is increased by adding an anti-PD-L1 or an anti-PD-L1 plus ipilimumab, or whatever additional immune therapy is decided at that point. The real questions are whether these combined immune therapy-targeted therapy combinations will ultimately lead to a higher overall survival, and whether a larger group of patients can be put into complete remission and remain maintained without treatment for a long period of time. Would you agree that is one of the goals of putting these two types of therapies together?

Dr. Jeffrey Weber: Absolutely, I agree, Mario. We’re victims of our own success. Everything now is about combinations. We now have seven individual agents and three combination regimens that we know work very well. The median survival rates would be measured in multiple years. We’re talking about nearly four years of the data you presented. How does one evaluate a new regimen? First, you’re now into triple, if not quadruple, regimens. And the
ipilimumab plus nivolumab plus drug X is obviously a triple combination. What’s the endpoint? If one’s endpoint is prolongation of median survival, one would be doing this until retirement. One needs surrogate endpoints—PFS would be an acceptable endpoint, and a response rate of a certain duration would be the other surrogate endpoint—but it’s going to make the trials more expensive, difficult to do, bigger, and longer lasting, which of course is an expense.

**Dr. Mario Sznol:** I think if we’re looking at three-year survival rates of 60% or more with just one modality, such as immunotherapy, it’s going to take a lot of patients to show an improvement by combining immune therapies with targeted therapies. It’ll be very difficult to do those randomized studies.

**Dr. Jeffrey Weber:** Yes, the cooperative groups studied ipilimumab plus nivolumab first followed by dabrafenib plus trametinib or dabrafenib plus trametinib first followed by ipilimumab plus nivolumab. Half of the investigators will be retired by the time we get an answer to the question of which regimen is superior, so I think it’s going to be very difficult.

**Dr. Mario Sznol:** Yes, it’s going to be very difficult to reach those endpoints. But we’ll see. That’s why we do randomized studies.

**Dr. Jeffrey Weber:** But we desperately need surrogate endpoints that can be reached more quickly than the classic endpoint of overall survival.

**Dr. Mario Sznol:** My favorite would be a complete remission at some point in time that doesn’t require any additional treatment beyond that time. I would love to be able to treat patients for a year, achieve a complete remission, and then not have to give them any further treatment. That would be ideal. Maybe even shorter periods of time are possible if we figure out a way to combine these agents to achieve that goal.

**Dr. Jeffrey Weber:** I like that.

### Mucosal and Uveal Melanoma

**Dr. Mario Sznol:** Jeff, you know there are subsets of patients with melanoma who are very difficult to treat. Patients with uveal melanoma and those with mucosal melanoma. There were data presented at SMR that suggested for patients with mucosal melanoma, there’s hope. Maybe you want to describe the Larkin data?

**Dr. Jeffrey Weber:** Sure, James Larkin presented very interesting data at SMR where a large number of patients treated with multiple nivolumab trials were assessed to determine which ones actually had primary mucosal melanoma. I was shocked, because approximately 10%, or 86, of the 889 patients had mucosal disease. I always think of mucosal melanoma as approximately 3%-5% of all melanomas. This is a selected group of patients who went on trials, but they’re not that selected. I was quite impressed at how common mucosal melanoma was. The punchline of this very nice retrospective assessment was that there was significant benefit to receiving nivolumab in those who had mucosal melanoma, even though the benefit is probably not quite as high in those with mucosal than in those with cutaneous melanoma. If one looks at the standard parameters, PFS was three months for mucosal melanoma, but 5.1 months for the group as a whole, which reflects predominantly 90% for cutaneous melanoma. If one looks at the overall response rate for these 889 patients,
there was 35+% response rate and 23.3% for the patients with mucosal melanoma. Nonetheless, approximately 5%-6% for each group had CRs. The durations were long—22 months for the overall population. It wasn’t reached, and it was probably a bit more than that for the patients with mucosal melanoma. So a patient can have a long duration of response, which is the hallmark of the use of checkpoint inhibition. As expected, if someone were PD-L1 positive, they did well in either group, whether they had mucosal melanoma or not. And response rate was a bit less—45% vs 51% in the PD-L1 positive group. And we all know that PD-L1 positivity is simply a way to select for patients who are going to have a higher response rate, as opposed to a way to select only for those who are going to benefit. So these were very interesting data, and they certainly confirm my gut feeling from having treated hundreds of these patients that it is appropriate to treat patients with mucosal melanoma with immunotherapeutic agents and that they will benefit compared to the controlled groups on chemotherapy, for example. I always assumed that patients with mucosal melanoma had a very low mutational burden. In fact, there is an interesting abstract at this meeting suggesting that’s not the case. They looked at a modest number of patients with mucosal melanoma and found that they had a large number of single nucleotide variants in the tumor compared to the normal tissue. So maybe that’s one of the reasons why these patients can do well on immunotherapy.

**Dr. Mario Sznol:** Jeff, we’ll have to look at our data. We’ve also sequenced patients with mucosal melanoma, and it hasn’t been our experience that they have a large number of mutations. So it needs to be confirmed, but it is very interesting. Like you, I also would have assumed that mucosal melanomas, which are not unexposed lesions, would have a low number of mutations. For a high number of mutations, there has to be a biological reason for that, and I don’t think we have that. The other interesting part of this is that mucosal melanomas have relatively lower rates of PD-L1 expression. We already know that in the PD-L1 low group, ipilimumab and nivolumab in combination can provide higher response rates. Although not at this meeting, another analysis that has been done from the 067 and 069 data suggests that the combination of ipilimumab and nivolumab can give even higher response rates in patients with mucosal melanoma. In my practice, I tend to offer patients with mucosal melanoma the combination rather than an anti-PD-1 alone.

**Dr. Jeffrey Weber:** I agree with you, and in my own anecdotal experience, the patients with mucosal melanoma who got the combo did very well. So you can argue if this is urban legend or based on fact, but as a practicing investigational clinician, you have to play the cards you’re dealt and often have to make choices based on limited or even bad data. Based on the limited data we have, I absolutely agree with you that if I had a patient with mucosal disease with something other than a trivial metastatic disease, I would treat them if I could with nivolumab and ipilimumab.

**Dr. Mario Sznol:** It’s also important to remember that the small percentage of these patients who progress on the immunotherapy combination might have mutations in CKIP. In fact, some have mutations in BRAF and could be treated with targeted therapies. My experience with CKIP inhibitors has been very good. There weren’t any data addressing CKIP inhibitors in patients who have CKIP mutations for mucosal
melanoma at the recent meetings. There is another group of patients, Jeff, who are very difficult to treat, and they are patients with metastatic melanoma from a uveal primary. I was disappointed from the randomized trial data presented by Dr. Carvajal. That was a randomized study comparing a MEK inhibitor, selumetinib, in combination with dacarbazine vs dacarbazine alone. That was based on promising preliminary data generated from a smaller trial, but the larger randomized study seemed to show no effect of the selumetinib on the response rate or PFS.

**Dr. Jeffrey Weber:** I agree. It’s a classic example of the difference between a limited institution phase 2 and a multi-institutional phase 3 study. You can paraphrase my friend Will by saying that there’s many a slip betwixt tongue and lip. This is a classic phenomenon of moving from a phase 2 to a phase 3 study. Selumetinib is a modestly reactive MEK inhibitor. I’m not sure that this is going to prove in any way to be an effective strategy from the GNAQ- and GNA11-mutated uveal melanomas. A colleague has been involved in assembling all of the patients with uveal melanoma treated on- or off-protocol with PD-1 and PD-L1 antibodies, and they’ve only come up with a handful of responders out of nearly 100 patients. It’s a very dismal scenario to be treating metastatic uveal melanoma with systemic therapy.

**Dr. Mario Sznol:** There’s a small experience with ipilimumab also, and it’s not very promising. There is activity, and we’ve observed a very good response with ipilimumab followed by anti-PD-1 in a patient with large metastatic lesions in the liver. But it’s rare, and we still don’t know the activity of the combination of ipilimumab and nivolumab, although I believe a phase 2 trial of metastatic ocular melanoma is ongoing.

**Dr. Jeffrey Weber:** It’s a tough nut to crack, and I think that treating patients with acral lentiginous mucosal and uveal melanomas is one of the major frontiers in melanoma treatment and research, particularly for uveal melanoma. Once it is a systemic disease beyond the liver, we just don’t have any truly effective therapies.

**IDO Inhibitors**

**Dr. Mario Sznol:** I agree. Let’s turn to new therapies. There are many new agents out there and many new types of immune therapies. There were two abstracts or two presentations at SMR that covered combinations of anti-PD-1—in this case, pembrolizumab with two unique agents, T-VEC and indoleamine 2,3-dioxygenase (IDO) inhibitors. Maybe you could go over the data that were presented for these new therapeutic regimens?

**Dr. Jeffrey Weber:** Georgina Long and Omid Hamid’s data were very early. It’s about the earliest one can report interpretable data—once you get 20 patients with some confirmed response. The MASTERKEY-265 study was a phase 1 trial of T-VEC, whose real name is talimogene laherparepvec, combined with pembrolizumab in unresectable patients with stage IIIb-IIIc N4 disease. The patients were treated to a significant degree. More than half of them had stage IIIb and M1a disease, because it’s a trial where one must directly inject this engineered herpes virus that has just been FDA-approved. It’s the eighth individual drug approved for metastatic melanoma in the last five years. In this trial, they had relatively brief follow-ups and a small number of patients, 21. It wasn’t particularly toxic. They had no
dose-limiting toxicities (DLTs), and they had relatively modest overall AEs. The AEs would be from the pembrolizumab plus the small contribution of things like pyrexia, chills, and fatigue contributed by the direct injection of T-VEC. But they had an unconfirmed response rate of 56%, which is pretty good. It’s likely to be better, even with small numbers of patients on pembrolizumab alone. And it appears the T-VEC added something to the activity of the pembrolizumab, and they had a couple of CRs. Admittedly, this is a select group with most having stage IIIb, IIIc, and stage IV M1a and M1b disease where there will be a fairly high response rate compared to pembrolizumab alone. But if more patients are added and the difference in response rate goes up, the idea that one can prime the immune response by a tumor-destroying stimulus such as an oncolytic virus will hold up, and I think this is something worth pursuing. I like the idea. I think this is ultimately an appropriate use for a directly injected oncolytic virus.  

Dr. Mario Sznol: We’ll have to wait to see what the results of the randomized trial show. It’s important to remember that with pembrolizumab in a frontline setting, the response rate is approximately 40% or a bit higher. In the small cohort of 20 patients, the difference between a promising result and an unpromising result might be a response in one patient.

Dr. Jeffrey Weber: We’re victims of our own success. With any doublet or triplet, there could be a 90% response rate if the number of patients is in the 20 range, which is where one would do early reporting to get a good feel for where it’s going. It might not be statistically significantly different than one drug alone; it’s very difficult.

Dr. Mario Sznol: Jeff, are you set up in your clinic as a medical oncologist to give direct injections of this agent, or do you refer out to your surgeons to do that?

Dr. Jeffrey Weber: Well, NYU is an interesting place. The two existing medical oncologists who see melanoma are Anna Pavlick, the senior one, and Melissa Wilson, the more junior, both of who are very good. They both do their own injections and punch biopsies. The surgeons taught, validated, and qualified them to do punch biopsies and injections, so they do them both. I appreciate the idea, though it depends on how busy I am. I have become a very busy investigational oncologist, so I don’t think I’m going to have time to stick needles in lesions. I’ve done that lots in my time, so I don’t need to do any more. But they do it right there in the clinic.

Dr. Mario Sznol: That’s interesting. I myself have the same concern that in a busy clinic, it’s very difficult to organize to do injections of individual lesions. But if it works, we’ll obviously make the time, because the most important thing is efficacy. Let’s next discuss the other agents. The other data presented were of a very interesting agent, an IDO inhibitor. IDOs deplete tryptophan, and there are a variety of ways in which it tryptophan can inhibit T-cell function within the tumor microenvironment. It’s induced by interferon gamma. T cells that are active in the tumor microenvironment can make interferon gamma, which can induce IDO, so it’s very reasonable to believe that the presence of IDO in the tumor could be a negative feedback regulator of T-cell function. There are preliminary data presented with this agent, epacadostat, in combination with pembrolizumab; the response rates were very
interesting. Do you want to comment on that aspect?

**Dr. Jeffrey Weber:** Epacadostat, or the IDO inhibitor otherwise known as INCBO24360, is very interesting oral drug. I presented an abstract at the European Society for Medical Oncology Congress showing that combining this drug with ipilimumab resulted in a 30% response rate in a modest cohort in the 20s. Once again, this is a small study showing promising early results, and now with pembrolizumab, this looks equally promising. This time, there were patients with melanoma, kidney cancer, lung cancer, bladder, and triple-negative breast cancer treated on a phase 1/2 trial, and the combination was very well tolerated. The treatment-related AEs didn’t seem to be very much higher than pembrolizumab alone, although the grade 3/4 treatment related AEs were 13%; one would expect 8%-9%. And the one patient who did discontinue for treatment-related AE had alterations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which were seen in the initial trials of this drug alone and in the trials of this drug with ipilimumab. But in the 18 patients with melanoma, there was a 56% response rate and an additional bunch of patients for a disease control rate of 78%.

We’re talking three CRs of 18 patients, which isn’t bad because with pembrolizumab alone, one very rarely sees CRs. This is very impressive, and in the 16 patients who had never been treated—and there were a couple of others who had—we’re talking a very impressive 63% response rate. Patients were stained for PD-L1, and PD-L1-negative and PD-L1-positive patients clearly had responses. Everyone was ongoing at the time of the presentation data, so it sounds like a high response rate and a good duration of response. It’s very likely going to be higher even though the numbers were small with pembrolizumab alone. This looks very promising. If it were up to me, I’d go straight to the phase 3 study, and that’s what I believe the companies developing these drugs are going to do. I think it’s very promising; I like the idea. 10

**Dr. Mario Sznol:** Biologically, it makes a lot of sense, and we’ll have to wait for the phase 3 trials, but certainly the range of activity is very similar to ipilimumab and nivolumab. If this combination does turn out to be more active than pembrolizumab, it will challenge the ipilimumab plus nivolumab combination and may even be a preferred choice if the toxicity turns out to be more tolerable.

**Dr. Jeffrey Weber:** You may be right, but I’d be very careful, because there must be 50 combinations of nivolumab, ipilimumab, tocilizumab, and bertilimumab with other immunologic agents, and they all seem to have a 50% response rate. The duration of response, median survival, and the tail of the curve will help us to know for sure. I would hate for people to want to switch away from using ipilimumab plus nivolumab to, for example, nivolumab or pembrolizumab plus epacadostat simply on the basis of response rate without knowing duration and the tail on the curve, so it’s going to be a while before we can make conclusions.

**Dr. Mario Sznol:** I agree completely with you. Response rate is a good endpoint—not the only endpoint, but a good endpoint. Clearly, survival, median survival, and durable CRs may be an important endpoint for these agents. Jeff, I think we’ve covered most of the other topics that were presented that addressed metastatic melanoma at the meeting. Did you have any other presentations or abstracts that you saw that were interesting at the meeting?
**Tumor-infiltrating Lymphocytes**

**Dr. Jeffrey Weber:** There were a couple of interesting little ones. There was an interesting sideline on PD-L1 and tumor-infiltrating lymphocytes in sentinel lymph nodes, showing that sentinel lymph nodes had high PD-L1 expression and very often had significant infiltrate T cells from CD4 and CD8 cells. And if a patient had a high number of cells, they did better, which the investigators were looking at to justify the use of PD-1 blockade as an adjuvant outside of the existence of a tumor microenvironment post-surgery. The irony is that I’ve already published on the pilot use of PD-1 antibodies as adjuvant therapy in resected stage IV melanoma, so I’m fully on board. But they provided the theoretical basis to further justify doing large adjuvant trials of PD-1 antibodies, and the BMS 23A trial was an adjuvant trial of nivolumab vs ipilimumab in stage 3 and 4 resected disease. It accrued 880 patients faster than any trial, probably in the history of any trial in the history of melanoma adjuvant trials.  

**Dr. Mario Sznol:** Yes, it’s amazing that the trial closed before we could even open it. We’re very anxiously awaiting those results, because ipilimumab is an active agent in the adjuvant setting, but at the 10 mg/kg dose approved by the FDA, it’s relatively toxic for this population of patients. If anti-PD-1 was active in this setting, and it should be more active than ipilimumab and less toxic, it would be the winner in the adjuvant setting.

**Dr. Jeffrey Weber:** I have done a number of immunotherapy adjuvant trials in the last 10-15 years, usually as pilots, usually with correlative markers. The best data that I’ve seen came with the combination of ipilimumab plus nivolumab. The best published data I’ve seen came with nivolumab alone, and I would have high hopes for the eventual approval of nivolumab as an adjuvant regimen. I’m sure, unfortunately, that it will be a bit of time—probably not until the end of 2017. There’s also an ongoing pembrolizumab vs interferon trial through the cooperative groups, and that’s a trial that I think will also be a very good trial to watch. The other abstracts that you asked about—a lot of them are related to things that would be of interest to practicing physicians, perhaps more for information than anything else. There were a couple of abstracts that talked about the mutational landscape of melanoma, and it confirmed that there are a very large number of BRAF-mutated patients and the usual 10%-15% NRAS mutations, but I was impressed to see that neurofibromatosis type 1 (NF1) mutants were quite common, between 15%-20%, which is more than NRAS. But the tough nut to crack is going to be improving patients who are triple wildtype—BRAF negative, NRAS negative, and NF1 negative. And coming up with a target for those patients is going to be very difficult, because in the category of approximately a quarter of patients not mutated in BRAF or NRAS or NF1, there could be any one of 50 different mutations that may be a driver. So coming up with a targeted strategy for those patients is going to be very difficult.

**Dr. Mario Sznol:** We’ll have to hope that when we give those patients immune therapy, they go into a complete remission and never require another treatment. There is certainly a lot of room for research in that area if they progress from the checkpoint inhibitors.

**Dr. Jeffrey Weber:** And there was a similar study with a patient-derived xenograft and cell line study. They had a slightly higher rate of
NRAS mutations and a slightly higher rate of BRAF mutations, but they saw a significant proportion of NF1-mutated samples. But they saw a lot of telomerase reverse transcriptase (TERT) promoter mutations. It suggested that it is yet another target, as well as the NF1-mutated target, in patients with metastatic melanoma.

**Dr. Mario Sznol:** I guess we could cover two other topics before we finish. What are your thoughts on treatment of patients with NRAS mutation?

**NRAS Mutation**

**Dr. Jeffrey Weber:** The other urban legend is that the NRAS-mutated population would be more immunologically responsive. I’m not sure that those data have been found in subsequent studies, and it would seem unlikely that that was the case. MEK inhibitors alone are not going to be terribly useful in this population. But I like the idea of the MEK-CDK4 combination, and we have heard about early data from those trials. This is very promising and clearly needs to be perused aggressively.

**Dr. Mario Sznol:** I agree the MEK and CDK4 inhibitor is probably the best home for the NRAS-mutant patients who don’t respond to immune therapies. What do you think about biomarkers predicting response to immune therapies at this point?

**Dr. Jeffrey Weber:** The only data that anyone has that are particularly useful are regarding the use of PD-L1 staining. I was at the Society of Immunotherapy of Cancer meeting just south of Washington DC in November, and they had a debate. I wasn’t up on the stage debating; I was one of the rebuttal witnesses. I made the point that it’s a marker that is detected by immunohistochemistry, meaning it’s open to great interpretation and not easily quantitated. It has a kinetic relationship over time in that it can wax and wane in individual tumors. It has a relationship from tumor to tumor; for example, a lung metastases may be positive, but a liver metastases may be negative. And it requires tissue to detect, so it makes about the worst possible predictive marker that one could ever use in a clinical trial setting. Ultimately, we’re going to have some amalgamation of tumor and peripheral blood markers that will serve to tell us who not to treat, because ultimately a predictive marker isn’t so much to predict who is going to respond but rather identify those patients who will not respond. We know if there is an active tumor, and we know the patients who are going to respond, so we want to filter out the patients who are not going to respond and allow them to potentially get the benefit of another therapy and not waste their and society’s time and money using a drug that is going to be toxic and not successful. I love the reviews by Antoni Ribas, MD, PhD and Tom Gajewski, MD, PhD this past year where they essentially define the sort of tumor that is going to respond to immune therapy, that so-called hot tumor that’s PD-L1-positive and has a vigorous CD8 T-cell infiltrate. That’s probably about one-third of patients, and I think that accounts for the majority of patients who respond to PD-1 blockade alone. Then you have the possibilities: the negative patients who are negative for PD-L1 and T-cell infiltrate. They have very cold tumors, and they’re not going to respond to immunotherapy.

**Dr. Mario Sznol:** I’m not 100% sure, because I think that in the 067 trial, the ipilimumab-nivolumab combination was superior to nivolumab alone and ipilimumab alone in patients who had PD-L1 staining less than 5%
and even in those who had PD-L1 staining less than 1%.

**Dr. Jeffrey Weber:** When I said immunotherapy, I meant a single immunotherapeutic agent. If we have the ability, which I think we do with ipilimumab plus nivolumab to drive T cells into a cold tumor, I think that you’re going to see that, and that may account for the increasing success of that rate.

**Dr. Mario Sznol:** And there are other agents that might do that, such as bevacizumab. Going back and looking at bevacizumab and melanoma in this setting might be interesting at some point in the future. I think we’ve covered the whole gamut of the relevant abstracts in the treatment of metastatic melanoma from SMR and from some of the prior meetings. Do you have any additional comments, or at this point should we close?

**References**

November 18-21 2015; San Francisco, California. Abstract.


