Creating Clarity in Metastatic Melanoma:
Optimizing Treatment and Improving Outcomes

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INTRODUCER Allow me to introduce your speakers this evening. Dr. Anthony Olszanski and Amanda Viereck. Dr. Olszanski is the director of the Phase 1 Developmental Therapeutics Program, the director of the Medical Oncology Melanoma Program, and the vice chair of the Department of Hematology/Oncology at Fox Chase Cancer Center. Ms. Viereck is a medical oncology physician assistant at Fox Chase Cancer Center. Her specialties include colorectal cancer, lung cancer, lung metastasis, and melanoma. Please join me now in welcoming them both to the stage.

[APPLAUSE]

MS. VIERECK Thank you.

DR. OLSZANSKI All right. Well, it's great to be here. Amanda and I are both from Fox Chase. And we're hopefully going to really help you understand a little bit about how we deal with metastatic melanoma, but I think it's important to recognize that what we go over isn't necessarily what the practice pattern is across the United States, or even across the world, and there are differences. So keeping that in mind, we're going to go ahead and get started and jump right into this.

So, we really plan on doing a couple things here, and I hope that you can interpret the implications of the treatment of the clinical pathologic features of melanoma. It's so important to really gauge the risks of a patient. We often don't understand the risks to the patient 'til we really take a good look at the pathologic report. We're going to interpret the clinical data that's been coming out regarding the mechanistic activity and efficacy and even the safety of the new and emerging drugs that are approved for metastatic melanoma, which is, in fact, probably the fastest, most rapidly growing sector in oncology over the last few years in immuno-oncology. We're going to talk about devising strategies for integrating contemporary standard of care management for metastatic melanoma, and then finally formulating plans for enhancing collaboration and communication within a really multidisciplinary teamwork. And I think that's going to be important.

So let's get to the talk now, the evolution of melanoma and the treatment of metastatic melanoma. You know, what's happened over the last decade or two is really phenomenal. Back prior to 2011, when I treated patients with melanoma, it was not exactly the most favored oncologic diagnosis that a patient can have, meaning its survival was only on the order of about 8 months. We had chemotherapy and we knew one thing from chemotherapy – no controlled randomized clinical trial ever showed a survival advantage. In fact, we had no drug that showed a survival advantage. You can see what's happened really over the course of the time since 2011 and onward, we've had this amazing plethora of drugs that have now been approved in the metastatic setting, which you can

see highlighted there in blue. Most of these do focus around immunotherapy, but we even have targeted therapies that are now focusing on metastatic melanoma.

What's remarkable as well is that in the green boxes, which isn't really our focus today in talking, is the treatment for the adjuvant therapy as well. And so you can see we have a lot of therapies that come up, so much so that recently the company that likes to make interferon announced that they're no longer going to be making interferon. And I think if there's one potential message that is really monumental for patients with melanoma at all, it's that interferon, which was a reasonable and valid therapy for patients with stage III, is no longer even going to be available because we've moved so far away. And that's really wonderful.

We have an amazing impact of the current therapies. If you look at the historical overall survival Kaplan-Meier curve, you can see that we really didn't do very well. You can see that only about 25% of patients were actually alive in 1 year—25% alive in 1 year. Keeping that number in mind, last week or two weeks ago in *The New England Journal of Medicine*, there was an update of the 5-year overall survival for patients with metastatic melanoma treated with two checkpoint inhibitors—PD1 plus CTLA-4—and the median overall survival was not reached at 5 years. The median overall survival has not been reached at 5 years. That is astounding. We went from something where only 25% of our patients were alive at 1 year and now we've gone so far.

But you can see on the righthand side of this curve what has actually happened in the world of melanoma. Not only did chemotherapy really not work, but as soon as we started developing these immunotherapies as well as the

target therapies, we saw a new and interesting phenomenon. And that was that the tail of the curve seemed to be flattening out, suggesting maybe for the first time that for some patients we might be applying a cure to them. That we might be actually getting rid of the melanoma so totally, that it's not coming back in those patients, and they're dying of other causes. And that's truly, truly remarkable.

So we're going to start talking about some clinical cases, and we're going to walk you through some clinical cases, and through each one of these clinical cases, we're going to focus on just a few different things. So this one is going to focus a little bit on pathologic features and immunotherapy potential. So Amanda, why don't you take us away with case number 1?

MS. VIERECK Sure. So case number 1, we have a 50-year-old male with melanoma first noticed on his right neck. We have a depth of over 6.5 mm, which is pretty deep. That's well into the dermal layer into the subcutaneous tissue, with ulceration noted. We also have a mitoses of about 12, and we'll go over what some of these mean on the next slide as well. No lymphovascular invasion was noted for him, luckily. In our standard follow-up, we do an MRI of the brain, which showed no evidence of metastatic disease. We also do a PET scan to see if there's any other distant tumors that we might not initially see. So we did see a right neck lymph node that was avid, as well as a right axillary tail node. Because of this, the final stage was a stage IIIC, initially.

DR. OLSZANSKI So IIIC, that's not a particularly good category to be in, but it's still not metastatic, so it's better than metastatic. We're going to talk a

little bit about that pathology report, and I want to sort of emphasize how important it is to really focus on that pathology report so that we can imply or give information to the patient. Amanda, talk a little bit to us about what some of the higher risks and better risk factors might be.

MS. VIERECK Right. So, there's a couple different factors that we look at that, you know, higher risk versus lower risk. Positive nodes are one of the most important things that tell us how aggressive this is and how quickly this is moving. This is one of the most important findings, and it is a higher risk if there are any positive nodes. Ulceration of the tissue is another one. This is showing increased cell proliferation into that epidermal layer, so that is a more aggressive sign as well. The depth – anything over 0.8 mm is considered a higher risk category. Lower than that is lower risk, but anything above that is a higher risk and we need to pay closer attention. The mitotic figures – essentially, if there's more mitoses than 1 per mm^2, looking under the microscope, that is considered a high-risk feature, and should also be taken very seriously. Lymphovascular invasion, that's pretty self-explanatory. If there's anything spreading into the lymph nodes or the vascular area surrounding the tumor, that is also a higher risk.

Some better prognoses are regression, and sometimes we see this if we're doing a repeat biopsy of a certain area. Sometimes on clinical trials we do this pretty often to see if the drug is doing anything to the tumor itself, and sometimes we do see regression of that tumor tissue. We also sometimes see tumor-infiltrating lymphocytes, which essentially means that the body's immune

system is starting to fight against those cancer cells, and we can see that under the microscope. So those are some better things that we can see.

DR. OLSZANSKI So just to go over this mitotic risk – when the pathologist is looking at these patients' tissue under the microscope, they really have to look carefully for things that are looking like dividing cells. And so, if you look at the three arrows up here, these are dividing cells, cells that are stuck in some form of mitotic disfigurement as they're trying to divide. Now, it's common for cells to divide. That's normal. But we consider a good-risk category zero mitoses, not finding anything, or one. Anything above one is actually considered to be a higher risk mitotic figure, but it's really not a dichotomous variable. It's not either zero or one or higher; it's really a continuous variable. So I've seen patients who have had mitotic rates of 40 or 45, and that's really shockingly worrisome for patients, because that's really saying that their melanoma is very aggressively trying to grow.

MS. VIERECK All right. So first question, we're going to try to make this a little bit more interactive while we go through the cases, we have this 50-year-old male with a newly diagnosed stage III melanoma, *BRAF* status right now is unknown. What is the next best plan of treatment? Number 1, a complete lymphadenectomy. Number 2, *BRAF*-targeted therapy. Number 3, observation alone, 4, immunotherapy, or 5, TVEC. [MUSIC]

DR. OLSZANSKI So go ahead and try to answer that question there for us.

MS. VIERECK All right, excellent. So we have the majority of the people here are choosing immunotherapy. That is the correct answer.

DR. OLSZANSKI So the answer we think today would be immunotherapy. It wasn't always immunotherapy, and because we are actually showing you patients who are real live patients, we're actually going to go through the history of what they actually did receive. So this patient in October of 2014 had a complete lymph node dissection, which was, by far and away, the standard of care at that time, if you had a positive sentinel lymph node biopsy, and then had radiotherapy to the right neck, and then in 2014, started on pegylated interferon. Pegylated interferon was relatively new at that time, and discontinued after three doses because of secondary to severe toxicities, which was not terribly uncommon.

So, we're going to talk a little bit about the role of complete lymph node dissection because that was such an important step that we've taken all the way up until the publication of a recent trial. Amanda, can you take us through part of the MSLT-II trial?

MS. VIERECK Sure. So this is looking at the MSLT-II trial, which was released in 2017. Essentially, we're looking at a complete lymph node dissection versus observation with ultrasound of the affected area. Essentially what we're seeing here is there is no significant difference in overall survival of the observation group versus the dissection group. However, we are still seeing a pretty big difference in terms of the side effects, meaning that the lymphedema in

the surgical arm is a real risk posed to those undergoing the complete lymph node dissection.

DR. OLSZANSKI So this was a practice-changing trial that got published. And it really switched the standard of care for patients who had positive lymph nodes with the sentinel lymph node biopsy from complete lymph node dissection more and more towards observation. That doesn't mean that there isn't still a role for complete lymph node dissection in some patients, but for most patients, they can avoid that toxicity of lymphedema and just be observed.

So this is our patient, and in 2016, he had recurrence. In fact, his PET scan showed widespread metastatic disease. But let me tell you the story of this, because when you look at this gentleman's abdomen, you can see that that lesion is not exactly subtle, right? So, I asked him, "Sir, when did you think this melanoma was coming back?" And he said, "About 8 months ago, when I was sunbathing, I noticed I had a black nodule on my belly, and I thought to myself, that's probably melanoma." And I said, "Why didn't you come back?" And he goes, "I didn't want any more of that interferon." And I said, "So why did you come back?" And he says, "Well, my wife started complaining when she felt so many of the bumps and lumps underneath my skin that it was making her upset." True story.

MS. VIERECK Yeah. And just to add in – sorry, can you go back to that picture really quick?

DR. OLSZANSKI Absolutely, I love that picture.

MS. VIERECK And not only is this pretty wide, I mean, this gentleman is wide himself, so you can image this would be probably about this big to begin with. Not only is it that wide, but it's also protruding from his abdomen. It's very, very thick, dense tissue underneath there.

DR. OLSZANSKI Yeah, this is the tip of the iceberg. When you felt it, it was really big.

MS. VIERECK Exactly. And, you know, we have listed down that it was widespread to his neck, chest, abdomen, pelvis, but really, the most palpable was obviously this. But he had subcutaneous nodules throughout. There was not really an inch of his body that did not have some type of nodule underneath.

DR. OLSZANSKI Medical term –

MS. VIERECK Yes.

DR. OLSZANSKI Gross. All right, you want to go ahead with the question?

MS. VIERECK Sure. All right, what are the current best options for this patient? This is a 50-year-old male with recurrent and now metastatic melanoma. We know that he is *BRAF*-positive at this point. Is it number 1, high-dose IL-2. Number 2, dacarbazine. Number 3, PD1 and CTLA-4 combination. Number 4, ipilimumab alone; 5, *BRAF* and *MEK* targeted therapy.

DR. OLSZANSKI So if you can go ahead and answer that question for us. [MUSIC] All right, so 27% of the population here choosing a dual checkpoint inhibitor and 70% choosing *BRAF* plus *MEK*.

MS. VIERECK Yeah. And to mention, both of these are correct. It would be very reasonable to go with number 3, the combination immunotherapy. He is naive to any type of immunotherapy agent. Or we know that he has a *BRAF*-positive mutation, so it would be very reasonable to go with this option as well. In this case – oh, I'll let you talk about this a little bit before –

DR. OLSZANSKI All right. So, this is the data that supports the combination of CTLA-4 plus PD1 versus as single agent. So you can see the green on this Kaplan-Meier curve. The green represents ipilimumab at the bottom there. Has an overall response rate of around 19%, somewhere around there. And that overall response rate has been amazingly consistent among clinical trials. But when we add – when we have just a PD1, the response rate is around, I usually say 40 to 45%, that's what we see with nivo. But when we add the two together, nivo plus ipi, we see an at least additive response rate of 58%, which is really outstanding. This is better than anything that we ever had before, except maybe for the BRAF/MEK inhibitors, which is also around at this point in time. But this slide shows you that combination is better than either single agent alone. That doesn't mean that we always go to combination because the toxicity here is also worse. So there are certain times when we will try to avoid this. But in this particular situation, nivo plus ipi was given to this gentleman.

I will also say about this slide, and we'll talk about it maybe a little bit later as well, but again, I'm going to bring to you from that *New England Journal of Medicine* article, that we now have 5-year overall survival data, and 52% of patients are still alive at 5 years. We have not hit median survival. That's really

amazing. So that plateau that you see there at 3 years, we didn't know if that was real. But that's real. It is real. Patients aren't dying.

This talks a little bit about the efficacy of that. I know it's a busy table, and I just want to sort of focus your attention on the second line from the bottom, the duration of response. For those patients who are having a response, how long is that response really going to last? And you can see here that for ipilimumab, that response rate is going to last somewhere around 14 months, and that's really good. That's better than we ever had before with chemotherapy. But with nivolumab, it's 22 months, and now with nivo plus ipi, we still haven't reached that durability of a response. Some of these patients just keep on responding. And it's amazing.

MS. VIERECK It is. So here, you can see a before treatment and after treatment PET scan for this patient. As you can see on the left, and just as a general recall, a PET scan picks up areas of increased metabolic activity, so these areas of white, most of them are these cancer-related nodules. So you see on the left multiple in multiple different organ systems, and on the right, after treatment, essentially not there.

DR. OLSZANSKI Yeah, we couldn't find anything.

MS. VIERECK Right. Yeah. We would consider this a complete response.

DR. OLSZANSKI So that's really amazing. So the question that we then have to ask is, is cure possible? That's not something that I was able to ever say even in my oncology clinic. So this guy actually received 3 years of therapy; he

was started before we really knew what to do. Typical duration is 2 full years, but throughout his treatment, he had continued radiographic responses. So we continued the therapy. After his therapy did discontinue, he stayed stable for a year, and four continuous nodules remained, and so we didn't know, were these actually sites of active disease, was this remaining tumor tissue? So what do you do when you have a question? You try to answer it. So what did we do?

MS. VIERECK So first we took a small biopsy of the area, which showed no viable tumor tissue. And then he underwent surgical resection of those subcutaneous nodules, which again failed to show any viable tumor tissue. They only showed heavily pigmented cells, and that's just absolutely amazing. And we're calling that a complete pathologic response to his therapy.

DR. OLSZANSKI Even this cartoon character is excited.

MS. VIERECK I know.

DR. OLSZANSKI So, pictures really are worth a thousand words. You can see what he was looking like before and then after. This after picture is just before surgery. This is no melanoma in the tissue at all. This is just pigmentation. When you press this, it's very soft. There's no nodularity at all. It was truly an amazing response. So, is cure possible in this case? Well I can tell you that he continues on observation. I just saw him in October and his scans in October were without any apparent disease, and so we're going to continue scanning him and keeping a close eye on him, but it's potentially something that we're not going to have to worry about for a while for him, and so maybe he'll get back on the beach. I mean, what? What am I saying?

So let's go to clinical case number 2. Let's talk about real-world challenges, workup, and vigilance.

MS. VIERECK So case number 2 is a 30-year-old female, very young, initially presented as a stage IIIC melanoma of the right upper extremity. She ended up having a wide local excision and sentinel lymph node biopsy. Her depth was 2.5 mm with 15 mitoses, so high risk; ulcerated, another high-risk sign; no lymphovascular invasion. But two out of the six sentinel lymph nodes were positive. For her workup, the brain MRI was normal, the PET scan did show a worrisome lesion in the right iliac bone. So we underwent biopsy and unfortunately this was positive for metastatic melanoma, which changes her staging to a stage IV. The next-generation sequencing was sent out to find the *BRAF* status.

DR. OLSZANSKI So not a good diagnosis –

MS. VIERECK No.

DR. OLSZANSKI – for a 30-year-old female. So in this 30-year-old female, who is *BRAF* wild type, what's your best first line of treatment? Is it a BRAF/MEK chemotherapy, IL-2 with radiation therapy, combination checkpoint inhibition, or resection of this sole metastatic site? [MUSIC] All right, so this patient is *BRAF* wild type, so we can't really give her BRAF/MEK therapy, so we shouldn't really be thinking about that too much. The combination, however, in this setting really does make a lot of sense. Resection of bony mets usually never makes sense because normally it's just the tip of the iceberg. Bony mets sometimes are not easy to find. So we did not consider that as an option.

So this patient did undergo nivolumab and ipilimumab combination immunotherapy. However, as could happen with some patients, that first patient we presented really had no significant side effects except for some vitiligo, where his skin had some whiter patches and his hair actually turned white as well. But this person had some extra toxicity. So after receiving three doses of dual-agent immunotherapy, she had nausea, vomiting, GERD symptoms, weight loss, early satiety, and anorexia. And this was a little bit unusual for her character.

So Amanda, what are we thinking at this point in time?

MS. VIERECK Yeah, so at this point in time, her symptoms are pretty vague and they could be encompassed by a multitude of different things. So we have lined out here, is this more of a GI viral illness? Is this more related to H pylori? Is this GERD? Is this peptic ulcer disease? Is this something more rare like gastric metastasis or small bowel obstruction? Is this CNS disease? Or gastritis or duodenitis? At this point, we tried ondansetron and tried to manage her symptoms a little bit better but did not have a very good response. The symptoms just kept pushing on and getting worse and worse. So, before it took too much time – I think it was about a week that we had tried this with no improvement – we consulted with the GI team, who recommended an urgent EGD.

DR. OLSZANSKI So I just wanted to point out that even though this patient's on immunotherapy, and even though we're standing up here and we're going to talk about a toxicity, the differential diagnosis really is wide, and you

really do need to sort of capture all of these when you're thinking about a patient and what might be going wrong. So the results of the EGD, Amanda?

MS. VIERECK Yeah, so – and first I want to mention that immunotherapy is a little bit of a wildcard when it comes to toxicity. There are some that are more common than others; however, we're stimulating the immune system, so really it could affect anything anywhere for whatever reason it wants. So we need to be really vigilant and look out for some of these symptoms when they come across and keep that in the back of our minds always that, is this related to the immunotherapy? So the results of this EGD in her stomach showed severe active gastritis consistent with immune checkpoint inhibitor therapy, and also the duodenum, erosive duodenitis. Again, consistent with the immune checkpoint inhibitor therapy.

DR. OLSZANSKI So we're going to get back to you with a question here. What treatment for immune-mediated gastritis would be appropriate in your setting? Would it be a proton pump inhibitor, H pylori prophylaxis, oral steroids at 0.5, high-dose IV steroids at 1 to 2 mg/kg, or reduce the dose of the immunotherapy? It's quiet.

MS. VIERECK Yeah.

DR. OLSZANSKI All right, so most of the audience believing that high-dose IV steroids would be the most appropriate, which I would suggest would be true. I will tell you, however, that this patient actually did get oral steroids when she first called in, because her symptoms sounded more like just a common GI

bug, and we weren't exactly sure, and she got these oral steroids and had no meaningful response at all.

MS. VIERECK None.

DR. OLSZANSKI So, why might that be, Amanda?

MS. VIERECK Sometimes there is so much inflammation from the active gastritis and duodenitis, she is not able to actually absorb any of the medication from an oral standpoint. So we believe that's what was happening at this point, and it was getting worse and worse before the symptoms were actually showing how severe it was getting.

DR. OLSZANSKI So she got admitted, she got IV steroids, high dose, and her symptoms resolved completely. She had no more symptoms at all. And after a taper, a slow taper over about 4 weeks or so, she then resumed treatment.

So then she completed the fourth dose of the ipi/nivo combination, and initiated the single-agent nivolumab, but shortly thereafter developed severe arthralgias and myalgias after just a single dose. So, she was hospitalized again for IV steroids, and again her symptoms resolved with a 1-month taper of steroids. So, one toxicity wasn't enough for this young lady, and we had to hospitalize her again. What is she studying to do, Amanda?

MS. VIERECK She's studying to become a nurse herself.

DR. OLSZANSKI So she's kind of busy.

MS. VIERECK Yeah.

DR. OLSZANSKI She's got two kids to take care of.

MS. VIERECK Young kids, yeah.

DR. OLSZANSKI She's trying to study to be a nurse. So, these hospital admissions weren't exactly in her plans.

We reinitiated single-agent nivolumab at that time, she got two additional doses, and then she started having new symptoms. This time, she complained of significant fatigue, new headaches, mild nausea, and general malaise. You know, you almost think, well, goodness gracious, she's just getting hypochondriac because everything happens to this poor lady. But you really do have to take these seriously, so let's take these seriously and think about what is the most likely diagnosis. Do you think it’s recurrent gastritis, hypophysitis? Does she have now unfortunately brain mets? Is this a viral illness, or is this hypothyroidism? So yeah, everybody's thinking that this most likely is in fact hypophysitis, but 7% of people thought that CNS mets would explain some of these, and they could, and so this patient did in fact get a brain MRI as part of that workup.

So hypophysitis is inflammation of the pituitary gland which sits at the base of the brain, of course as you know, and it causes adrenal insufficiency. It's a primary cause of adrenal insufficiency, and you can get secondary causes as well.

MS. VIERECK And just to add in to that, hypophysitis can present in a very vague and general way. We've had patients – not that we've had a lot of patients that have had hypophysitis, but we've had before patients presenting with just what they thought of as depression and some fatigue, and it really, really

takes a keen eye on our part and a lot of vigilance, as I said, to really catch some of these. So for this question, which diagnostic test should be ordered at this time if we're thinking about hypophysitis? 1, prolactin. Number 2, cortisol and ACTH; 3, TSH; 4, FSH and LH levels; or 5, human gonadotropin level. [MUSIC]

DR. OLSZANSKI All right, wow, that's great. 96%.

MS. VIERECK Excellent.

DR. OLSZANSKI Everybody's joining the crowd here with cortisol and ACTH. It is important to recognize that all of these can change, but you can't actually make the diagnosis with any of these except for the cortisol and the ACTH. So that's what the answer actually is, and this person had a very, very low random cortisol, which was only 0.5, when it should have been 3 to 16. Now, cortisol is one of those hormones in our body which behaves in a circadian rhythm, and so when we get a random, we don't really know where it should be within that range. But she's below the lower limit of normal here. And so it really gives us that setting that she probably has this. She actually ended up getting a 9 am cortisol without steroids on board and an ACTH at that same time, and it proved beyond a shadow of a doubt that she in fact had hypophysitis.

So, talk to us a little bit more about the immune-mediated side effects, Amanda.

MS. VIERECK Sure. As I said a little bit ago, the immune-mediated side effects can go across a wide range of organ systems. Really, it can affect anything, anywhere, anytime. Most commonly, we see dermatitis and fatigue. Those are usually the most common symptoms that we see. However, we can

see, as in this case, it affecting the endocrine system. That can affect the thyroid or the pituitary. The pituitary is much more rare, but we can see this. And really the healthcare providers, as I've been stressing, we must have a heightened sensitivity for this and keep this always in the back of our mind.

DR. OLSZANSKI It's so, so important.

MS. VIERECK Yeah.

DR. OLSZANSKI So let's move directly on to case number 3. We're going to talk a little bit about comorbidities and how they might influence us, and even talk a little bit about new skills that we have to have as providers if we're going to be giving some of the medications that are now available. Amanda?

MS. VIERECK Sure. Case number 3 is in-transit metastasis. This is a 76-year-old female who developed what she thought was a rash in the fall of 2016. Her PCP tried some antibiotics. Did not work, and eventually worsened. This went on for years, as you can see. She eventually, in the beginning of 2018, had a biopsy of one of those lesions, and it showed to be melanoma. Once they developed that diagnosis, she had a PET scan, which did not show a clear primary, mainly because there are so many lesions at this point. Which one started it? It's very hard to say. She did have left inguinal adenopathy that was present on this PET scan. Of note, she has an active history of ulcerative colitis and is on immunosuppression for this. Her *BRAF* status was negative.

DR. OLSZANSKI That's right, yeah. She's also *BRAF* negative. So, not a good combination. We actually had to treat her a number of times for cellulitis and stuff as well. She had a lot of edema in this leg and it was really affecting her

quality of life. So, the significant comorbidity of ulcerative colitis is really a problem here. She has already an autoimmune disease, and we have immunotherapies, which stimulate the immune system. So we're a little worried about that. She required active immunosuppression, and she continued to have intermittent diarrhea and abdominal pain. So, in your opinion, what's the most appropriate recommendation? Would it be topical therapy like topical imiquimod? Would it be PD1 therapy or CTLA-4 therapy, an oncolytic vaccine, or do you tell this lady that we don't really have any reasonable options for her and you give her some palliative care? [MUSIC]

All right, so there's a lot of variation here. Topical imiquimod is not yet FDA approved. It has a relatively low response rate. So, it's sometimes used in melanoma in situ but not in active melanoma disease. And then, the big reason that Amanda and I didn't really think that PD1 therapy or anti–CTLA-4 therapy was really the best thing to do was because of the ulcerative colitis. We could cause a significant flare of that significant comorbidity. So we chose to give her an oncolytic vaccine, believing that we might be able to get away with some therapy for her. So –

MS. VIERECK And just to note as well, if she had a history of ulcerative colitis but it wasn't active and she was not on active immunosuppression, maybe she had a history and was clear for a year, let's just say, we could have tried PD1 therapy. Probably not a combination, it probably would have been too strong. But we could have tried that. But since she was on active immunosuppression with active episodes happening, that was not really

an option for us. So the right answer was 4, the oncolytic therapy. And I think we went through all of this at this point. Yeah.

DR. OLSZANSKI So let me talk very briefly about oncolytic therapy. There's only been one randomized phase 3 trial. There was a 419-patient trial, which randomized patients 2:1 to receive TVEC or GM-CSF—granulocyte-macrophage colony stimulating factor—which was a drug that we actually used a little bit in melanoma back in the day, but there was never any data that really backed it up. Some phase 2 trials, but never any phase 3 trials.

This trial had a very unique endpoint. It was called the durable response rate, which was the percent of patients who had a response over a 6-month period of time, and they used a response based on the old WHO criteria. So they actually took the sum of the products of the perpendicular diameter. So they would take a lesion and look at both of those diameters, and then multiply those and then add that all up. So the duration, the durable response rate here, was 16% for TVEC and 2% for GMCSF. The AE profile was relatively mild: flu-like symptoms, fatigue, chills, fevers, and some pain at the injection site, which you might expect. But this is where this trial really gave us yet another option for these patients. If you look at the Kaplan-Meier curve, you can see that the TVEC curve on top there in blue did better than GM-CSF. But the bigger part of the story was, how well do responses last? And so if you look at the graph that's with all the red and blue bars, that's the—only looking at the patients who actually responded to therapy—and you can see first, that very few patients actually responded to GM-CSF, and of the patients who responded to TVEC, many of

those patients responded for a very long time, which was great to see. Many of those patients with complete responses.

So TVEC is an attenuated herpes simplex virus. We actually take the HSV virus and we change some of the phenotype of it. It's an intra-tumoral or intra-nodal injection, and we give it once every 2 or every 3 weeks. Typically, we do every 3 weeks because there was a trial that was combining it with ipilimumab and there was a trial that was combining it with pembrolizumab, and sometimes we can get away with adding those. Even though that is not something that is sanctioned yet by the FDA because that trial result is still out there and hasn't been fully reported. But there is some interesting and intriguing data.

So this brings up the need for possibly having some new techniques under our belt. So, Amanda?

MS. VIERECK Sure. So, this is me. So, medications like this that need to be injected via procedures call for new skills to be learned. In this case, and a couple other "trials" that we had on site that were injectables as well, called for us to be able to use ultrasound guidance for some of these injections. For this patient in our case, it wasn't really necessary, because the lesions were very easily seen. But we have some other patients with a little bit deeper masses and nodes that really could utilize the ultrasound machine. So, Tony and I went down to bother the ultrasound techs in our hospital. We brought some chicken breasts and some grapes and we learned ultrasound-guided techniques.

DR. OLSZANSKI You know, I thought it was a very odd day when everybody was talking about you in the office when you came in with a fresh package of Perdue.

MS. VIERECK Yeah.

DR. OLSZANSKI So this is actually a video demonstration. Amanda, walk us through what's actually going on here.

MS. VIERECK Sure. So, I will note that the ultrasound machine that we are using is older than I am, so we are not able to take a video on the actual machine itself. So we had one of the medical students there with us that day recording this on a cell phone so that we could utilize this later on.

So, we are seeing this needle coming through, ultrasound-guided, into a lymph node right there. And I think that's pretty self-explanatory. We were able to administer these medications directly into the tumor sites this way. And we're seeing a very good response in that.

DR. OLSZANSKI It is kinda cool. So this is the before picture; this is what her leg looked like. And after TVEC, which was initiated in 2017 and completed just a little under a year later after 15 injections, she's 78 years old and she's got a beautiful leg. Beautiful leg. And I'm a guy, I'm allowed to say that.

Clinical case number 4. Let's talk about multidisciplinary review and the importance of that critical deliberation and treatment evolution.

MS. VIERECK Yeah. So case number 4 is a 47-year-old female diagnosed with a stage IIIC melanoma of her right heel. At this point in time, the *BRAF* status is unknown. She has a depth of 2.5 mm, mitotic rate of 14,

ulcerated, so we already have a couple high-risk factors. Sentinel lymph nodes were two out of the three, and she also had a couple satellite lesions noted. So stage IIIC, as I had mentioned. She did have melanoma in one out of the 10 lymph nodes. No extranodal extension. And this was found through the superficial lymph node dissection.

At that time, our best course was ipilimumab adjuvant, so this was initiated. However, after two doses, her LFTs jumped to 13.5, the upper limits of normal. That is not a typo. So, she had really significant autoimmune hepatitis. Luckily, this resolved with giving high-dose steroids, but we did not re-challenge due to the severity.

DR. OLSZANSKI So in her workup, she actually did quite well after this. She presented 1.5 years later, however, with multiple new nodules, which were biopsy-proven in-transit melanoma. A PET scan showed only these lesions occurring on her right leg, and her brain MRI was negative for disease. So we did discuss her at Tumor Board, which is a critical step in the evolution of these patients because they're really complex. So we discussed limb perfusion and limb infusion procedures. We discussed possibly putting her on a PD-L1 or PD1 inhibitor with or without investigational drugs, and we even discussed, because she had injectable lesions, giving her TVEC. Amanda?

MS. VIERECK Sure. The patient ended up undergoing an isolated limb infusion with our surgical team and did have a very good response to that. However, 8 months later, new lesions of that same right leg. There were three

very small erythematous nodules at the right thigh. We biopsied all three, and all positive for melanoma. At this time, the tissue was sent for the genomic testing.

DR. OLSZANSKI So just to make sure you understand, isolated limb infusion is not FDA recommended, but it is on the NCCN guidelines as an option for patients, and it is a surgical technique. In this lady with her right leg, she basically got a tourniquet placed over top of the thigh here, and then surgically they put in two catheters. One of the catheters infuses mitomycin C, high doses, and it's limited to the leg here because of that tourniquet, right? So it's not actually going systemically. And then the other catheter, after it dwells about 90 minutes, takes that chemotherapy back out of the leg. That's a limb infusion and that's what she got. A limb perfusion puts the patient through basically what looks like an oxygenator that's ex vivo. So the blood would come out of her body and then go back into the body. Those are the differences really from the procedure. But otherwise, that's exactly what she got. And this has a very high response rate when you can isolate it. Now the problem is, that if you have lesions that are too high, and your tourniquet can't get above all those lesions, then you can't actually use this technique. And that doesn't matter if it's the arm or the leg. But it is a reasonable thing and sometimes those responses can be long-lasting. And so that's what we chose for her at that time.

But, she's failed that, so what treatment options to you feel are next? Would it be repeating that limb infusion, putting her on a CTLA-4 therapy, injection therapy on a clinical trial, a PD1 therapy, or maybe a BRAF/MEK inhibitor? [MUSIC] All right. So a number of people want to inject on a clinical

trial. And 32% want a PD1 therapy. Reasonable things to think about. So the possible answers here are actually a lot of different things. You could consider a repeat limb infusion, but this patient had actually some poor healing around her heel where the melanoma actually started, and she had a lot of pain and some discoloration of her leg as well. So we didn't think that that was in her best interest. She couldn't get CTLA-4 inhibitor again because of that LFT problem that she had, and she had no measurable disease for clinical trials, so TVEC was considered, but we really thought we had better options. The clinical trials all required measurable disease. So we thought the PD1 was rational despite hepatitis on the CTLA-4 inhibitor, and her genomic results at this time were not back yet, so we couldn't give her a BRAF/MEK inhibitor.

So, Amanda?

MS. VIERECK Yeah, so we decided to put her on nivolumab single agent. And that's given IV once every 4 weeks. Her pathology during this time did come back, or genomic testing I should say, and the *BRAF* was positive. So that gives us a great option for treatment in the future. But she's already on nivo, so we wouldn't change that option, right now at least. She went through five courses of nivo over the course of 5 months, and we didn't really see a big change. Per the radiology and per RECIST criteria, she had stable disease. Nothing was measurably growing, but we didn't see a big clinical change, and we were starting to see the pigmentation getting a little bit darker and a little bit more raised. So that really makes us very suspicious and very concerned. So we considered that clinical progression at that point in time.

DR. OLSZANSKI So we took her off of nivo. So what treatment option do you think would be reasonable at this point in time? Would you continue nivo, for example, or pursue a clinical trial using a PD1 plus an investigational agent? Would you switch to BRAF/MEK, begin TVEC injections, or would you amputate, which is also viable? All right. So most of the audience wanting to switch to BRAF/MEK inhibitor, and some 10% or so wanting to pursue a clinical trial, perhaps. So let's talk a little bit about what we did for her.

MS. VIERECK So both options are correct. We could easily switch to the BRAF and MEK inhibitor at this time, and also option 4, the TVEC, would be rational, but it doesn't have as good of an effect as what we want. So what we did was we pursued a clinical trial using a PD1 plus an investigational agent. Because we did not see progression on her scans, we felt that continuing the PD1 would be beneficial to some effect at least. And this way, we would be able to add in an injectable agent along with that to hopefully boost that efficacy.

DR. OLSZANSKI Part of the idea here is that if we can put an investigational agent or, I should say, an oncolytic virus, into the lesion, and start destroying that lesion, we then expose the immune system to all the antigens, all the protein, of that particular tumor. And that may make it a little bit more likely to pick up that protein and then want to try to attack it. So that was the idea here. But what happened?

MS. VIERECK Yeah, so she ended up undergoing six injections on this clinical trial over 2 months. She received pembrolizumab as well with these injections. No new lesions. But again, no significant response. At first, we did see

a little bit of a lessening of the pigmentation of some of these lesions we were injecting. However, that really started to plateau out, and we started seeing no effect whatsoever. So, discussing with our multidisciplinary team and the patient, we decided to consider this clinical progression once again and pursue another treatment option at this time.

DR. OLSZANSKI So as everybody has recognized here, she is *BRAF* positive, and so we did initiate therapy with dabrafenib and trametinib. And Amanda, maybe take us through why we chose that –

MS. VIERECK Sure.

DR. OLSZANSKI – because there's actually three FDA-approved regimens out there.

MS. VIERECK There are. And they are all good options, but dabrafenib and trametinib specifically has a very – or I shouldn't say very low, but it has a lower pill load per day. So this regimen has five tablets per day, whereas other regimens may have up to 11 tablets per day. So, the more tablets per day can be very confusing to patients and can cause issues that way, with especially timing and things like that. So, this was a reasonable choice for us.

DR. OLSZANSKI So I think it's really important to understand the patients that you have in front of them, you know, if you had me in front of them, you wouldn't want to even give me five tablets a day, right? I wouldn't be able to do that. And our compliance as human beings are particularly challenged when it comes to large tablet loads. If we have an older patient who has a lot of comorbidities and they're already taking a lot of tablets, you then begin to

wonder, how in the world they're going to get food into their stomach? Because all they do is chew tablets all day long. So you really do have to take these into consideration.

Another thing you need to take into consideration is how each regimen sort of stacks up from a side effect profile, because they do have some subtle differences and side effects. Dabrafenib and trametinib, it is a great regimen. However, it's sort of dogged by the resurgence of pyrexia, or fevers, in these patients. And so you have to be really vigilant on the treatment of pyrexia and stop the drug when you have a lot of pyrexia. You can oftentimes restart these patients, re-challenge them with full dose and try to get rid of it, and sometimes you might even need to use a little bit of steroids to try to get rid of it. But you need to know how to manage this kind of stuff. The reason that I don't really use vemurafenib and cobimetinib, which is also another reasonable and rational or proved treatment choice, is primarily because what we learned about birth control. And that is, if you're taking 21 tablets in a 28-day cycle, you forget. Right? That's the problem. And with cobimetinib, it's 21 days of tablets, and then 7 days off. And with the vemurafenib, you're taking it every day for the full 28 days. There's no way you could give somebody like me that complex regimen, because I've got bigger fish to fry.

So, in this particular trial, the BRAF/MEK inhibitors targeted therapy, when we looked at it in patients with metastatic melanoma, dabrafenib plus trametinib had an overall response rate of 64%. This is dual BRAF plus MEK inhibition, and that's compared to single-agent BRAF inhibition with vemurafenib at a 51%.

Duration of response was also better at about 14 months versus about 7 months. And amazingly, the grade 3 adverse events ratio is actually lower when you give the two drugs together than when you give a single agent. And I don't know any other sector in medicine where this is usually true. Most of the time, when we combine two different agents, we get a higher adverse event rate. But in this scenario, we actually get a lower adverse event rate. And some of the science really helps us explain that, because if we have unopposed BRAF inhibition, what we can actually have is upregulation of *MEK*, which is a protein that occurs downstream of *BRAF*. And we think it's that upregulation of *MEK* that can cause the toxicities. So when you hit both, you get better efficacy and less toxicity. And that's a bit amazing.

And then at ASCO just last year, we had updated survival, overall survival 5 years was really respectable at 34% in the first-line setting. And I have a couple of those patients in my practice right now that are just doing really well taking the drug every day. We don't stop it. So you want to talk about her response?

MS. VIERECK Yeah. So, the picture on the left is after her immunotherapy before she starts the BRAF and MEK inhibitors, and you can – it's a little bit hard to see on these pictures, but the thickening of the skin in certain areas, especially just the right to her knee, is a profound difference from the left to the right. On the right, she was on the BRAF and MEK inhibitors for about – how many weeks is that now? It's over 2 months at that point.

DR. OLSZANSKI It's over 2-1/2 months now.

MS. VIERECK Yeah, 2-1/2 months at that point on the picture to the right. And so, it's not a dramatic difference yet, but it's fantastic, and we're moving in the right direction, which is the most important part.

DR. OLSZANSKI So I think maybe the patient's words describe it better than the pictures actually do.

MS. VIERECK Yeah.

DR. OLSZANSKI Because on the picture on the right, she counted 124 nodules—124. She told me that she might be off by one or two. On the picture on the right, she can't actually count any nodule. She just sees the pigmentation. But there's nothing there to feel. So she's really having a great response and just has the pigment right now left. So we're really hoping that she can hold onto this response for a really long time.

MS. VIERECK Yeah. I also remember when she came into clinic for the picture on the right, she said, "I can shave my leg again. Thank you!" Which was really exciting.

DR. OLSZANSKI So let's talk a little about what we hoped that we helped you learn or review at this session. We have had significant advances in the last 5 years in the treatment of melanoma, and as you know, and you'll hear later on in this conference, there's a lot of expansion of immunotherapy into many, many, many diseases. And it's really making great strides in the treatment of melanoma. We still have a long way to go, but now I have patients who I've treated 8 or 9 years ago, and they're alive today, when before they would have been dead. So clearly, we're making big roads. We also recognize how important

the multidisciplinary review is. It's really imperative. You need to be able to talk to your colleagues, surgical colleagues, radiation oncology colleagues, the nurses who are taking care of the patients, the physician assistants, the doctors, whoever might be in the room, because everybody needs to be at the table because these decisions are so complex and so inter-related. Amanda, what else did we come across?

MS. VIERECK Sure, yeah. We talked a lot in the beginning about long-term survival, and that cure is now possible, which is not something that we thought we would be saying just even, what, 5 years ago.

DR. OLSZANSKI Yeah.

MS. VIERECK Definitely not.

DR. OLSZANSKI Didn't think.

MS. VIERECK Yeah, so that is really remarkable. Also adverse event recognition and diagnosis, especially earlier on before symptoms get so severe and proper management with steroid dosing is absolutely critical for these patients. And, you know, communication with the patients is very important, but also with primary care as well. I found personally that having a good communication with primary care office, because sometimes the patients don't think it's related. They think, oh, I have this rash, but the primary care gave me this cream. It's not really working. Well, it's probably from the immunotherapy. So, good communication that way is really helpful for proper diagnosis.

DR. OLSZANSKI And I think it's also important to communicate with the people like the endocrinologist, important to communicate with the people like the

pulmonologist when we're treating the adverse events or even working up the adverse events. It really becomes important.

So ultimately, we're trying to provide multiple treatment options because we're really trying to provide ongoing hope for these patients, and we've seen that in that last case, where she's gone through three or four different types of therapies, and finally we've hit on a therapy that is giving her some meaningful response. We also recognize that there are some new skills that we need to sort of embrace and learn if we want to be able to apply our best foot forward in treating these patients.

And so for Amanda and I, we really felt that that was bringing ultrasound into our clinic, so we've just purchased an ultrasound machine. We're doing punch biopsies because that helps us in making diagnoses faster than sending them off to get a biopsy someplace else. We're actually doing fine-needle aspirates or core biopsies when we need to on clinical trial most oftentimes, because we do a lot of clinical trials. And there's also something to be said about viral vector safety. These are live viruses that we're doing, and we really don't know what the consequences of live virus could be, and so we want to be sure that we're mindful of that, and so our institution has very strict guidelines about how we work with the viruses, how the room is terminally cleaned after we use the virus, and the kind of follow-up we give the patient, because we don't know what environment the patient is going out to, and yet they have a wound that has all this live virus in it. And so those are some really important facets of treating patients today.

MS. VIERECK Yeah. It's also important to mention the management skills and growth opportunities for us as providers. You know, a lot of these patients that are developing these endocrinopathies, especially the thyroid – we are starting thyroid replacement in our office, and of course, we are talking to the endocrine team that's right down the hall, which is very lucky for us, as well as the pulmonology and a lot of other teams that are very easily accessible for us in our hospital. But, you know, we are generally starting a lot of these for these patients, and it's important for us to grow and learn these new skills and these new management opportunities, as well as patient education, which is an absolute must. It is so important for patients to be able to recognize some of these side effects themselves, to be able to communicate that with you.

DR. OLSZANSKI So we've gone through the current treatment paradigms of metastatic melanoma. We've gone through an amazing amount of data that shows just how fortunate we really are to work in the healthcare field today. But I want to leave you with some closing thoughts, and that's: why do we really do this? Why do we really treat patients? And I think it's because of what we share in this room with the people that we love and the people who love us. We really do it for the love that we have in our hearts for the people that we treat. And right now, you're looking at the picture of the husband and wife, of that lady who had all those cutaneous lesions that we treated with TVEC. She not only tolerated the therapy, but now she has her dancing legs back. And her husband and her are so joyful and so happy that we were able to provide that to her. But likewise, Amanda and I are so filled with hope that we can provide this kind of

medicine to patients who didn't have any kind of these medicines before. We want to thank you for your attention tonight, and we welcome any questions you might have. Thank you so much.

MS. VIERECK Thank you.

[APPLAUSE]

DR. OLSZANSKI Any questions? One in the back.

QUESTIONER I live in a rural area and when we have – in regard to oral versus IV prednisone, or I mean, steroids, when would you make that decision of when they would require IV versus oral? At what point would you want to put a person in the hospital to give them IV?

DR. OLSZANSKI That's a great question, and I don't think it has a direct perfect answer. And so, you know, so much of medicine is still the art of medicine. I don't think – and I think that's critical to talk about – we should not be getting rid of the art of medicine. What goes on in your brain as you're thinking about things that might differ from what's on a piece of paper is critical for the best management of a patient. So in a patient like that who's having a lot of GI-related immune event or any kind of other immune event, the choice between oral prednisone or IV prednisone is one that needs to be carefully balanced. I would say the following: If a patient is having GI toxicity, you should usually consider IV therapy first and foremost. And primarily because of what Amanda had said earlier. We think the gut is so inflamed that it's unlikely that you're going to get significant systemic absorption. So we've had some patients on very high doses, 60, 100 mg of oral prednisone, and have not seen any significant result.

I think that it also depends a little bit on the toxicity that we're talking about. So you might be able to give oral prednisone to somebody who has high LFTs, but that's a really scary situation, and they probably require extra management to make sure that their LFTs are going to plateau and then start coming down. I hope that helps.

MS. VIERECK Yeah. And just to add to that, if you're ever in question, there is the CTCAE grading system that is an app that you can download onto your phone, and that can be a little bit more helpful in terms of what would be considered a grade 2 in this type of toxicity, or grade 3 or worse. So that might be helpful if you're ever in question.

QUESTIONER And if you wouldn't mind just reviewing when – what's appropriate re-challenging.

DR. OLSZANSKI So re-challenge – when do you re-challenge, right? So, this is really important, and we talked about a couple cases here where patients had active or potential autoimmune diseases. So, you need to know the literature actually suggests that the PD1 inhibitors can oftentimes safely be given to patients who already have ongoing autoimmune disease. But you also have to be realistic about the fact that these drugs do stimulate the immune system and can potentially heighten that autoimmune disease. So, generally speaking, I will re-challenge anybody that I think is having a good response, because if they're having a good response, they may live. And that generally is better than the alternative of they may die, right?

So the biggest toxicity we sometimes forget is death from melanoma. But that's a real toxicity for a lot of patients. They don't want to die. So I think that we have to take that into consideration. But generally speaking, if somebody has really high LFTs, I'm not re-challenging them because that's a life-threatening event. For most other situations, though, except maybe pneumonitis, I would say. Pneumonitis scares the heck out of me as well. I don't re-challenge. And some neurologic toxicities, which are rare. I don't re-challenge for those as well. But for a lot of the toxicities, I will re-challenge. So if somebody's having a bad rash, some pruritus, I'll often re-challenge in that situation. And oftentimes we find that patients really do tolerate it. You saw the lady that we re-challenged with the gastritis and with the arthralgias. So it is possible, but again, we don't have a magic answer here. It takes a lot of patient education to remember to tell them to call you when things aren't going right. And for us to step in at the appropriate time.

Thank you again so much.

MS. VIERECK Yeah, thank you very much for your time.

[APPLAUSE]

[END]