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Addressing Unmet Needs in Metastatic Uveal Melanoma

Announcer:
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Dr. Orloff:
Hello everyone and thank you for joining us today to discuss addressing the unmet needs in metastatic uveal melanoma. My name is Marlena Orloff, I'm Associate Professor of Medical Oncology at Thomas Jefferson University in Philadelphia, and I'm joined today by my two fellow expert presenters, Dr. Jesse Keller, Assistant Professor at WashU as well as Dr. Gregory Daniels, Professor of Medicine at Moores Cancer Center in San Diego.

So, to get us started, I just wanted to talk through some of the learning objectives that we hope to hit today in our discussion. First being really differentiating uveal from cutaneous melanoma. So, this is really where we often start in the discussion, because often patients, you know, when they present with their disease, it's very important to understand that these two distinct subtypes are managed very differently. Next, we'll go on to explain the importance of something called HLA typing in patients with uveal melanoma, and what that means for their treatment decisions and then go on to explain the mechanism of action of a novel bispecific TCR therapy that is specific to the HLA typing, so we'll be tying all that in. And then talking about interpreting the efficacy and safety of clinical trial data on the use of bispecific TCR therapies in patients with metastatic uveal melanoma.

So, as I mentioned, you know, when we first start talking about how we're going to approach a patient with uveal melanoma, again, really important to understand that this is a distinct subtype. So, this is our first section, two melanomas, two stories why uveal is not cutaneous. So, the origins of melanoma kind of span quite a spectrum. Only listed here are really cutaneous and uveal melanoma, but actually, there's even other subtypes of melanoma, such as mucosal, subungual, acral melanomas. But here, really what I want the take home to be is just really distinguishing cutaneous from uveal. So, we know the cutaneous melanoma originates from melanocytes in the skin. There are other types of skin cancers, but melanoma kind of being the one that we, you know, think of as the most concerning. Uveal melanoma, however, originates from melanocytes in the uveal tract of the eye. So, even though these two cancers, however, are originating from the same type of cell, melanocytes, whether or not they originate from the skin or the uveal tract, can actually really drastically change their biology, and ultimately, the way that we manage these patients. When we talk about uveal melanoma, the uvea is made up of the choroid, the ciliary body, and the iris, as depicted in the diagram.

So again, just to put these two subtypes side by side, cutaneous versus uveal, you can see that the incidence of cutaneous melanoma is much more than it is for uveal. Here you could see, you know, about 23 per 100,000 but uveal being about 4.6 per million. We say, in uveal melanoma, about 2,500 new cases diagnosed annually, whereas, obviously cutaneous, much more. When we look at the pie, you know, that is melanomas, cutaneous makes up about 80-90%, whereas uveal is, we typically say, somewhere around 5%.

Cause of cutaneous melanoma we certainly know that UV radiation, UV damage, plays a role in most, but not all. Uveal melanoma, we don't have a cause, it is unclear about why this originates, at least from a kind of epidemiologic environmental type standpoint. The

mutations that drive the two tumors are distinctly different, so in cutaneous melanoma, we think about things like BRAF, NRAS, NF1, KIT. In uveal melanoma, really different panel here. So GNAQ, GNA11 being kind of the hallmark first initiating mutations, and then we see mutations like BAP1, SF3B1, EIF1AX and some others that aren't listed here that actually, then really affect the behavior of the uveal melanoma.

When we talk about risk prognostication in cutaneous, mostly, we're looking at stage, lymph node involvement, sometimes some other pathologic features, and occasionally a genetic risk profile. Uveal melanoma risk prognostication, because we do not incorporate lymph node involvement, it's really genetic profile and stage. Genetic profile can be determined through RNA-based tests, DNA-based tests, so looking at chromosomes or looking at gene signature profiles.

Important to note here, you know the percent of patients who are metastatic at presentation, probably similar across the board, you know, about 5% but the spreading patterns are also very distinctly different. So again, in cutaneous melanoma, we have concern about it traveling to the lymph nodes as well as other organs. Uveal melanoma, for reasons that we haven't totally ironed out, though there are some clues, the first place it likes to show up, close to about 90 plus percent of patients, is the liver, but certainly it can affect other parts of the body, including lung, bone, other soft tissues.

So again, that was just a summary of why I think it's important to kind of really look at metastatic uveal melanoma as it differs from cutaneous. But now we're going to open it up into a bit of a discussion, talking about some practical considerations when we diagnose metastatic uveal melanoma.

Dr. Daniels:
Yeah, I might start off here because I've got some questions. And it's great having both of you with so much experience with uveal, because, as you said, there's with uveal is it's so different than cutaneous. And so I'm curious, Dr. Orloff, what are your considerations when you diagnose a metastatic uveal melanoma patient?

Dr. Orloff:
So, you know, we are going to certainly get into, I think, a lot of the considerations and here in subsequent slides, so I'll just kind of highlight some of them first. So, you know, to take us back a little bit, so our metastatic uveal melanoma patients, they're often diagnosed through scans. Very few patients have symptoms that really bring about their diagnosis of metastatic disease. Majority of patients are getting either, you know, every 3 month or every 6 month or yearly imaging, notably of their liver, so often MRIs, and we are picking up lesions pretty early.

So, you know, one of the first things, you know, we see when we first are concerned about a patient developing metastatic disease after, you know, their treatment of their eye may have been, you know, months or even years before is, you know, where are the tumors? Are they in the liver? Are they outside of the liver? How quickly are they growing? You know, honestly, things like, where are these patients coming from? So, because metastatic uveal melanoma is a rare diagnosis, often patients are kind of traveling to be seen. There's things like HLA, which we'll talk about. So, a lot of different considerations, and I think, like I said in the subsequent slides, we're going to be going through a lot of them. But I will say here again, comparing it to cutaneous melanoma, where, in many ways, metastatic cutaneous melanoma, there's really a clear first line treatment. You know, most patients getting, you know, immune checkpoint inhibition and some other things, whereas in metastatic uveal melanoma, I think, as we'll discuss, there's a lot of things that we need to consider when deciding, you know, how we're going to, you know, treat after diagnosis.

Dr. Daniels:
Yeah, well, I'll flip it over to Dr. Keller, because he has both an academic and a VA Center. And how do you help your patients navigate through this diagnosis?

Dr. Keller:
Yeah, thank you, Dr. Daniels, that's a very good question. I think Dr. Orloff hit really a bunch of the key points, you know, many times, obviously, this new diagnosis of metastatic uveal melanoma is just an emotionally very difficult finding. But many of these patients, as Dr. Orloff mentioned, have had much prior experience with uveal melanoma, based on the fact that our stratification processes, in terms of the risk of recurrence, are really so very effective and informative. Currently, many patients who develop metastatic disease already have a good sense of their risk for this. Nonetheless, there's a lot of discussion about what this means when this disease spreads. It is a very serious and unfortunately not curable situation, and so there's much discussion about what the options will be, about what this means for their life, and about the next steps, and I know we're going to discuss a lot of that moving forward.

Certainly within the VA setting, we oftentimes, as this is a rare disease, we'll discuss access to clinical trials, which is a key part of the care of patients with metastatic uveal melanoma, particularly as we will find, because maybe 1/2 or more of our patients will not have immediate access to a potentially FDA approved indication in the frontline setting. And so, there's a lot of discussion that goes on, both

about the emotional situation we're in, about what this means for a patient's life, about the kind of unfortunately intensive care that they may require as we proceed through this.

Dr. Orloff:
Jumping here now to treatments, we've started to kind of say, okay, we've diagnosed our patient with metastatic uveal melanoma, you know, what do we do next?

So, you know, interesting kind of in this disease now, there is a bit of a kind of a break point regards to a blood test. So, blood HLA testing that can actually determine if patients are eligible for a certain treatment that is FDA approved systemic therapy for uveal melanoma. So, you know, here again, newly diagnosed patient with metastatic uveal melanoma, we're going to want to look at blood HLA testing, also getting things like comprehensive genomic testing, looking for other mutations that don't necessarily drive treatment the way it does, say, in cutaneous melanoma, and then really discussion and multidisciplinary tumor board.

So again, for patients who are HLA-A201 positive, and we're going to dive more into what HLA is and how you test it, but patients have the option for a drug called tebentafusp, which we'll talk about. But they also have options for other things, there's systemic therapy, other systemic therapies, clinical trials, immune checkpoint inhibitors, liver-directed therapy. But for patients who are HLA-A201 negative, tebentafusp is not an option. This is very much an HLA restricted test. So, for those patients, you know, we consider kind of all the other options.

I started to allude to this a bit ago, thinking about the kind of considerations that that I think about you know, when I first see a patient with metastatic disease, you know, thinking about things like HLA status, site of metastatic disease, how quickly the tumors are growing, the tumor burden, whether or not clinical trials are available, and then kind of what I call logistics.

So, Dr. Daniels, after a diagnosis, how do you discuss available treatment options with your patients?

Dr. Daniels:
Yeah, so thank you. You know, usually, as Dr. Keller mentioned, patients come in with this diagnosis, and they know whether they're high risk or low risk, and have already had some of these discussions ahead of time, because, as you alluded to Marlana, that, you know, some of the patients were watching pretty closely because their gene expression profiles put them at such a high risk. And those patients all actually have already tested them for HLA-A2 and had some discussions with them ahead of time.

But when it happens, we usually jump back into the discussion that uveal melanoma is not cutaneous melanoma, because a lot of times, patients will quickly jump onto social media or start getting advice from different areas, and I think just making sure that they're looking at this from the right perspective. Because, you know, the nice thing about cutaneous these days is the percentage of our patients are curable with metastatic disease. And unfortunately, in 2025, I don't have that expectation yet for uveal melanomas, and so we have to talk about that up front.

And as far as treatment strategies you mentioned, you know, liver profusion, and so there's kind of two general things I think about with patients, and we talk about systemic and what that means, and liver directed therapies and when one might be appropriate, and maybe even considering overlapping these therapies in certain patients. And so, we talk about those types of things. We talk about the approved therapies, of course, you alluded to tebentafusp, that is not for everybody, so it's a minority of patients are HLA-A201 positive that we find, it's maybe about 40%. And so we're also talking about off-label use, or semi off-label, you know, some of these checkpoints were approved with melanoma as part of their label, and so there weren't a lot of uveal melanomas included in their trials that got them approved, but haven't had too much trouble getting some of the checkpoints used in uveal melanoma because of the way the labels are. So it'd be interesting to hear what other people have run up against in their uveal patients.

But how about you, Dr. Keller, again, you're also at a VA, you mentioned trying to find the right place, how do you approach this?

Dr. Keller:
Yeah, you know, within the VA system, as with any healthcare system, in any hospital, the capabilities of a single hospital depend a lot upon the staffing, the location of that hospital, and of course, the VA is broad and spread out over a very large geographic scope, and has a very big responsibility in terms of the care for many millions of veterans. You know, we have the ability, certainly within the VA systems, to provide many of the treatments that have sort of been co-opted into uveal melanoma, such as immune checkpoint inhibitors, in some cases, you know, classic chemotherapy can be given, if that's the right point for the patient. Those kinds of treatments almost certainly can be provided at any VA that has oncology services.

When we talk about some of our newer treatments, such as tebentafusp and some of the more sort of, not necessarily novel, but interventional approaches, such as liver-directed therapy, which can be provided in various different mechanisms, such as chemoembolization or radioembolization or even immunoembolization. These things are, I would say, more variable in terms of their

availability or use at any certain VA. A lot of times what will be performed, or what will be done, is that patients will be sent out into the community through a community care referral, which will allow patients to receive these more advanced or specified treatments at a larger, maybe academic center or tertiary care center.

Certainly, for tebentafusp, which we'll be talking about extensively here, this can be given within the VA system, but very often, because of some of the unique toxicities that can occur, this can be maybe started at an outside facility, and then the patient's care brought back within the VA to continue that treatment.

Dr. Daniels:
Well, maybe Dr. Orloff, after you get a referral for a new patient, how do you integrate them into your practice?

Dr. Orloff:
Yeah, so I should have, I think, as I introduced us, kind of explained, you know, I'm the kind of one non-VA. So, we were fortunate to have both our other experts here very closely affiliated with VAs. I'm not actually affiliated with a VA; however, we do see a number of VA patients. So, I'm in an institution where we're a bit unique in that there are actually three medical oncologists that almost exclusively see uveal melanoma along with interventional radiologists. And once a week, we have a multi-disciplinary conference where we see new patients and as well as old patients, reviewing imaging and discuss treatment options for these patients.

So, when we get a referral for a new patient, whether it's from the VA or whether it's from the community, or whether it's, you know, from another, actually, colleague at an academic center, who maybe is referring for a clinical trial they don't have, we review these patients in a multi-disciplinary conference, reviewing their imaging, like I said, reviewing their past treatments, and then we will see them often that day. Again, if liver directed therapy is part of the plan, we'll see them along with interventional radiology.

And then we'll kind of decide, you know, what maybe is the best treatment course, and if it's a treatment course, you know, that requires them to be, you know, in Philadelphia, you know, we try to make that happen. If it's a treatment that we think they can get locally, at a more community center closer to home, we will try to make that connection often with a referring provider. And if it's a VA patient, very similar, we will often coordinate care with their physician at the VA to try to get them the treatment they need.

Certainly, again, as you heard, if it's a treatment that maybe can't be given within the VA, we would either be able to provide it locally or work with perhaps a medical oncologist that is more local to the patient, but maybe outside of the VA. So, we have close collaboration with many physicians around the country, like I said, VA clinicians included, and it's a great partnership. Often the scans will be ordered within the VA, but then we work very closely to kind of get those imaging to review. And again, you know, whenever we can, we really want patients to be able to get treated as close to home as possible. So that's how we—yep, yep, go ahead.

Dr. Daniels:
I find that true too. As Dr. Keller said, I mean, nice thing about the VA is that, while we can't offer everything, we try to match it with the best place for the patient. So, we have the ability to community care out, support travel, other supportive cares for the patients to navigate this journey, so I'm glad that they've reached out to you.

Dr. Orloff:
Yep, yeah, no, absolutely. Okay, so I think now we're going to dive into that HLA typing that we've been mentioning. So, moving on to the next section, the molecular key HLA typing as a gateway to therapy.

So, what is HLA? So, HLA stands for human leukocyte antigen, and they are proteins that are cell surface molecules that present antigenic peptides to T cells, enabling the immune system to kind of distinguish self from nonself, kind of in a normal setting. But these HLA proteins are also helpful in cancer, because they can present bits of the cancer cell to the immune system.

So, in this case, and we'll talk about the mechanism of action of tebentafusp, but here, as you've heard, HLA typing really driving treatment decisions for patients with metastatic uveal melanoma. So, the drug essentially needs to be able to recognize the HLA, and it was designed to recognize HLA-A201, so I know there's a lot of kind of letters and numbers there, but it really needs to be that HLA-A201. And so, what this kind of HLA type does is, really it predicts the candidacy, or the eligibility of patients to be able to get tebentafusp, but actually other bispecific TCR therapies that target specifically HLA peptide complexes. And, you know, the reason that they picked HLA-A201 is because it's really the most common, certainly if you look kind of across in the Caucasian kind of ethnicity group.

So again, so for patients who are A201 positive, they have option for tebentafusp, patients who are negative should not be offered tebentafusp. Sometimes patients will ask, 'Oh, you tested me and I was negative. Can you test me again?' And I try to explain, like, this is like a blood type, it doesn't change, it's not like other biomarkers that you know may be more dynamic. But if someone's positive, they also have other HLA restricted or unrestricted options. And again, there are some trials, actually, though, that are specifically for HLA-

A201 negative patients. So, you know, it's important to, again, know patients positive/negative, to be able to offer them different therapies.

Next, I think we'll have a bit of a discussion about, you know, how we order and interpret HLA tests.

Dr. Keller:
Yes, Dr. Orloff, I have a question for sure, when you're ordering any kind of HLA typing tests, what are some of the important considerations that you take into account? And how do you typically explain this test and its results to a patient?

Dr. Orloff:
Good question. So, I think there's been a learning curve. So, you know, I remember when we first started ordering HLA, you know, back even when these drugs were in clinical trial, you know, we really had a close partnership with our tissue typing lab. So, HLA was really something that was mostly done kind of in the transplant community, and it wasn't really something that, you know, us solid tumor doctors, you know, were ordering. And fortunately, we had a really close, like I said, relationship with our tissue typing lab and so we would send a sample, and they would actually send a report back, and they were very clear in the report, and they would specifically say, like, patient is positive in all caps for HLA-A201, or patient is negative in all caps for HLA-A201. Kind of since the drug certainly has been FDA approved and lots of folks ordering HLA, they may not be at a center that has a tissue typing lab like that, but there are a number of kind of commercial labs that are able to do it.

It is very important that this is blood HLA. So, there are a number of kind of NGS panels that you can send on a patient's tumor that will also report HLA. But really, this needs to be blood specimen. And again, you not only need that A2, you need kind of that A201, so it's really important that when you're requesting it, to also get high resolution testing.

So again, as I mentioned, our lab, when we do it internally, gives me a very clear sentence and statement, but I've definitely seen HLA reports that are a bit confusing, very long, lots of numbers, and you're like, What is this patient? Are they actually positive or negative? So sometimes interpreting the results can be tricky. There's actually been times where I've gotten a report on a patient, not really sure what it was telling me, and I've sent it to our tissue lab to be like, what is this person's HLA? And that's been helpful.

You know, I think we were saying that about 1/2 of patients are HLA-A201, I think you already heard it's actually probably less than that so it's probably the minority of patients, if we were being honest, somewhere, probably in the 40s percent range of patients being A201, but again, you know, very important to check, important to check early. Often, we're checking this in patients who are high risk, so even before they develop metastatic disease.

And you know, the way that I explain it to the patients is such, you know, like we have a drug that is, you know, approved. But, you know, the way the drug works is, it's kind of like a lock and key, and it needs a certain HLA type, you know, to be able to work. And so, you know, with that, lots of patients want to know their HLA, they want to know kind of, if something were to develop, you know, metastatic disease were to develop, you know, what their options are.

So, I guess Dr. Daniels, are there any differences when you're testing this in patients within the VA population?

Dr. Daniels:
Yeah, you know, I'll just say I concur with everything that you said. It's not really that much different. We have a pretty diverse population here in San Diego, and so we'll screen similarly. And what I do is I order a high-resolution HLA typing. So, if you order HLA-A2 present or not, that doesn't quite get you across the finish line, because they could be A2 present, but there are a couple other alleles. There's the 02 for example. And so, you got to get that high res. And so that's how we order it at our VA.

Dr. Orloff:
Okay, great. And I would say just very briefly, you know, here that, you know we're not going to talk about it today, but you know, there may be other drugs or other approaches in development that will actually be expanded to other HLA types. So you know what I always say now too, and when I'm certainly documenting a person's HLA, you know, not enough to say they're A201 positive or negative, but certainly if they're say, you know, HLA-A25 or some of the other more common ones, important to have that somewhere in the patient record, because there may be other HLA-restricted drugs coming down the pipe that are not specifically to A201.

Dr. Daniels:
Yeah, we put it right in the clinic note.

Dr. Orloff:
Perfect.

Dr. Daniels:

So, it's never lost.

Dr. Orloff:
Yep. All right, so moving on to our next section, so really, talking about how these drugs kind of work. So redirected immunity, how bispecific TCRs, so rewire T cells against metastatic uveal melanoma.

So, Dr. Keller, when you're talking to patients, or even other, say, physicians who are not familiar with tebentafusp, how do you kind of describe it to them? And who in your mind is it really indicated for?

Dr. Keller:
Yeah, thanks so much. Yeah, so, I mean, so tebentafusp is a T cell receptor bispecific that targets GP100 and CD3. But typically, the way I describe it to a patient is very visually, and I tell them that this drug sort of grabs onto a melanoma cell with one arm and then a T cell with the other, and just brings them close into contact to allow these T cells in your immune system to do the job of attacking those cancer cells. And obviously, as we've discussed, this is an agent that is indicated for metastatic uveal melanoma patients who are HLA-A0201, positive. So that HLA testing, which we've discussed and gone over so much, is vitally important for the indication for this agent. This is the only FDA approved drug for patients with metastatic uveal melanoma, and so it's a key part of our discussions with all patients who develop metastatic uveal melanoma during their course with this disease.

Dr. Orloff, in your opinion, what should clinicians consider when determining eligibility for tebentafusp?

Dr. Orloff:
So yeah, so I think the two main things we've said metastatic uveal melanoma, and HLA-A201 positive. But I think as we talk more in a second about kind of the administration of tebentafusp and the side effect profile of tebentafusp, you know, this definitely is a drug that may not be appropriate for everyone for a couple of reasons.

So, it requires weekly treatment, first three doses given in the hospital. So, you know, I don't really like to think about it as patient eligibility, but there are some patients who, you know, may not be able to show up for a weekly therapy, and so that's always a consideration. As part of the side effect profile, as we'll discuss, it could be hard on some folks, something called cytokine release syndrome. So, if someone has significant heart issues or a lot of other comorbidities, sometimes, you know, we get concerned about the administration of tebentafusp, you know, making these patients potentially a more complicated situation. But, I don't think any of it's an absolute contraindication, we just need to be very careful.

Okay, so we heard already kind of about how we explain, you know, the drug to patients, and here is really just a schematic of, kind of, you know, really what this looks like on a deeper level. So, you can see in the middle there that kind of blue globular thing with a little coil on the end, that's really the impact of tebentafusp. And as you heard, it's kind of shaking hands, you know, with the T cell on one side, and shaking hands, you know, with a uveal melanoma cell on the other side. And I think it's important to note that that this T cell can be any T cell, it's not necessarily a cancer-specific or uveal melanoma-specific T cell, because of the way the drug's developed with a high affinity, you know, it's really dragging over almost kind of any T cell and forcing it to engage with the uveal melanoma cell through the presentation of GP100 through the HLA. And so, you know, the way that works is, kind of, once that handshake happens, it engages the T cell, which is the effector cell and hopefully induces a cancer cell death. And then you also get the release of cytokines, which is part of the side effect profile.

So, we heard now how we approach patients with metastatic uveal melanoma, why we do something called HLA testing to determine, you know, whether or not they're eligible for tebentafusp. So now we will take it from the bench to the bedside and make some sense of the data on bispecific TCRs in metastatic uveal melanoma.

So here is just a snapshot from a publication that came out now a number of years ago, looking kind of at the 3-year follow-up of patients who received tebentafusp on the original clinical trial. So, the original clinical trial was a randomized trial of tebentafusp versus the control group, and the control group at that time was able to get one of three things. So either single agent pembrolizumab, PD-1 inhibitor, single agent belimumab, a CTLA4 inhibitor, or decarbazine, which is kind of an old chemotherapy and patients, again, were randomized to get tebentafusp or control. And you know what we saw kind of early on, which ultimately got the drug approved, and which we kind of continue to see now at this extended follow-up, is really kind of a break in the overall survival curves. So again, looking at tebentafusp, you know, outperforming the control group, and that continues over time. So really, just taking a couple of snapshots of this data, we're looking at median overall survival of 21.6 months for tebentafusp versus 16.9 months for the entirety of the control group, not necessarily parsed out on what they got, but the majority of patients in the control group did get single-agent pembrolizumab, with a 3-year overall survive survival rate of 27 with tebentafusp and 18% with the control, and hazard ratio of 0.68.

In the bottom snapshot, you see PFS, you know, and I would say the PFS here isn't much different. So, 3.4 months for tebentafusp and

2.9 for control. You know, what we're not going to show is further slides on this topic, but it seems that patients who, even patients who progress on tebentafusp, when we looked at this, actually have better outcomes than patients who progressed on the control arm, or patients who even had stable disease on the control arm. So, it's this upfront progression with tebentafusp, and then it looks like kind of the curve split a bit, that even if you get progression, these patients still kind of generally do better. And then it's a phenomenon that we see in immunotherapies, you know, whether or not it's the true kind of pseudo progression you see early on, or it just takes a little while for the drug to work. But, certainly, it seemed like any exposure to tebentafusp, even if there was kind of early progression, patients ultimately do better.

So, I alluded already, and we heard already that, you know, because the nature and the way that tebentafusp works and kind of engages the immune system, that there's a concern and a risk, and actually a black box warning for cytokine release syndrome. And this actually concern is why the first three doses, as we'll see, of tebentafusp requires, at minimum, a 16-hour observation, which ultimately ends up being kind of an overnight OBS admission. And so, interestingly though, even though we can see cytokine release syndrome very commonly, it's usually early, and it decreases in severity over subsequent doses.

So, you can see here, 89% of patients really having any grade cytokine release. Important to note very briefly, that grade 1 cytokine release is just fever alone. Grade 2 is often fever plus either kind of hypotension or hypoxia, but responding to like some fluids or just some supplemental O2. And then we're talking about grade 3, you know, when not responding to fluids, you know, needing blood pressure support or needing, you know, even more supplemental oxygen, and then it goes on. So, again, grade 1 really just being fever only, so that's really the bulk of a lot of what the CRS is. We also see quite a bit of rash, and again, that's likely related to the mechanism of drugs. So, you know, I tell patients, GP100 is really in two places, one on the surface of the tumor, or presented on the surface of tumor, and

one in the skin, on the melanocytes in the skin. So, a lot of times, what we see, especially with the first three doses, is the immune system essentially getting dragged to the skin, causing a pretty decent rash, you know, itchy, burny, you know, almost like a bad sunburn. But we really only see it with those first 3 doses. And even when it does happen, it's normally only present for about 24-48 hours.

We can see other things: chills, nausea, like I said, the hypotension which would be part of the cytokine release. And then over time, so if patients are on these drugs for 6 months or more, essentially, I often say to expect to see kind of we call melanocyte-related adverse events. So that's normally hair color changes and skin color changes. So, whitening of the hair, eyebrows, and eyelashes and things like vitiligo is often also what we can see.

And here again, just on the left, just to be complete, is the investigator choice arm, and that we really just pulled out the ones that we commonly see with tebentafusp, there wasn't really overlap. What you're really going to see the investigator choice here is the immune checkpoint inhibitor toxicity.

So I mentioned this already, it is a kind of step-wise, 3-week dose escalation, minimum of 16-hour observation. Patients come in, get 20 mcg, then 30, then 68, and if they do okay, then they will continue with 68 mcg as an outpatient, most of the side effects the patients experience, they experience those within the first three doses.

If patients do run into trouble, so having a persistent grade 2 or a grade 3 CRS or something else going on, you will often kind of give intervening steroid, and then not escalate them, and kind of give them the same dose the following week, often with steroid premedication. Then once they get through that, then you can escalate the dose. So, the inpatient dose escalation, you know, can be a bit nuanced, that I think we'll talk about here in a minute in our discussion.

Dr. Daniels:
Well, that's what's top of my mind. Since you've given so much of this, maybe you can share some pearls about how tebentafusp, you handle the administration and some re-infusion considerations.

Dr. Orloff:
You know, the way that we do it is, you know, we bring patients essentially into the hospital, you know, check labs, make sure they're all good. We start fluids kind of the second that they show up, we find that even just starting 150 CCs an hour fluids, when they show up, seems to kind of like fill the tank, so to speak, and we don't see a whole lot of hypotension subsequently. If patients are on blood pressure medication, sometimes for those first three infusions, we'll also have them hold their blood pressure medicine. It's not an absolute. Some people need them just to be able to, you know, show up without a systolic of 200. But occasionally, I'll have patients hold their blood pressure medication just to make sure we're not running into hypotension issues.

But so, check labs, start IV fluids, and then if they're good to go, we infuse. The infusion itself is pretty anti-climactic, you know, I would

say most patients, if they're going to start having side effects, you know, things like CRS and rash, normally about 6-8 hours after. There are patients that sometimes can experience stuff a bit sooner. Often find those are patients with more advanced and kind of bulky disease. So, patients who have more tumor burden, may sometimes experience their symptoms a little sooner. And, you know, for me, I think the most common thing is rash first, so a little bit of itch, a little bit of tingling, then the fever, then the hypotension, and, you know, then, you know, managing it from there.

So, once they do have a fever, we actually increase our vital sign check, so it should be Q4, but then once they start to have a fever, we start checking Q2 because that's when they can start developing the secondary hypotension. We'll manage them with fluid boluses, and normally that holds them. Certainly, if we're running into trouble, unable to get their blood pressure up, even with fluid, we will give steroids and then by the next morning, most of the side effects have kind of done their thing. Often, they're not feeling so hot, they've had a rough night, they've had fever, they're itchy, they're burny, they just want to get out of the hospital. I tell them they should be good within about 24-48 hours, only to do it all again the following week, and then do it again the following week, but then again by really that third infusion, most patients are not really having much in the way of side effects once they transition outpatient.

So, you know, as I mentioned, the patients that worry me the most are the patients that we're treating with, you know, larger tumor burden. You know, some of those patients, I will actually premedicate with steroids out of the gate. I try not to, if we can help it, but if I'm really concerned they're going to have a bad CRS, you know, I may give them dexamethasone or some sort of steroid pre-med. I don't tend to premedicate with Tylenol or anything like that, because it kind of wears off, right? Like, a lot of the side effects start happening at like that, you know, for me 6-8 hours. So, then I just give them, you know, Tylenol or whatever they need, kind of as the symptoms arise, you know. For the itch and the rash, you know, we do things like Benadryl, Atarax, clobetasol topical. You know, I'm not sure how much of all that helps, but patients, you know, like to have things they can try to see if it helps the rash. But again, gone really often within 2 days from the infusion.

We talked about monitoring. Lab testing, we check it weekly. You know, when they're coming in, sometimes the next day, you know, also get labs kind of day after infusion. You often see a lymphocyte drop, again, probably because they're all getting pulled, you know, to places out of circulation. We're also going to be keeping a close eye on the liver functions, one because they can go up with tebentafusp, but also because, you know, again, in patients that we're treating, most of them do have pretty significant hepatic metastatic disease, so just keeping an eye on things there as we're treating them.

And I think, yep, I think that's about it. But I'm curious, Dr. Keller and Daniels, are there any differences you see within the VA or patients that you're treating, and then getting back to the VA?

Dr. Daniels:
Yeah, I mean, I can start. At our VA, we have given bispecifics, you know, that have CRS risk and so using steroids, and, you know, not for this drug, but others, tocilizumab, so we have protocols in place, and we feel pretty comfortable. I will say, one advantage I feel like I have at the VA is our infusion center is in the hospital on the same floor as where the patients can go for monitoring, and so we can start the infusion in the quote unquote outpatient setting, and then patients can do their overnight observation by just going down the hall and checking into our oncology ward.

But I don't know, how about you, Dr. Keller?

Dr. Keller:
Yeah, I think, you know, as we've kind of discussed before, I think the situation is going to vary VA by VA. And at our VA, we're still working on doing those initial doses of these kinds of agents, and our protocols around that within the hospital. So typically, if we see these patients, they've come back after getting their first three doses or so at a larger center where they can be monitored over that 16-hour window. But in general, I think that, you know, we're going to see the same side effects, the same issues. Sometimes some of our VA patients may have a few more of these comorbidities, that high blood pressure, these other things that are going to impact care and treatment some. But in general, I think the approach is very similar, but probably varies, and I think that there's probably going to be variability based on provider comfort with these drugs, as well as the patient's comfort level and willingness to travel. But I think in general, we see much of the same thing.

Dr. Orloff:
After the patients are being transitioned back into VA care, are there any other adverse events, or what else are you monitoring the patients for at that time?

Dr. Keller:
Yeah, you know, and of course, I'm going to be interested in your thoughts on this too. But what I have found is that, you know, when you look at that graph of how these adverse events occur, it really is this just incredible drop as you get past these first few infusions.

And so, when we're out into, you know, months and months down the road, these adverse events are much more tolerable, much less significant for patients in terms of their quality of life.

You know, we are typically still monitoring blood work on a regular basis to monitor liver enzymes and other organ function. And then what I've found is a lot of times, there is some form or element of persistent skin toxicity that can be present. And so sometimes these patients are having some dry skin or some of that persistent itchy rash that bothers them. I've had some patients who have had some aches and pains that they kind of notice a little bit more around the times of infusion. And so, these are all things that we watch for and monitor.

But typically, the nice thing is that that that risk of the very serious cytokine release syndrome really is, for the most part, gone as we get further and further out from those initial few doses. And so, while there is still an observation period for patients that we are incorporating, it is much more manageable, and patients are doing quite well.

What about you, Dr. Daniels and Dr. Orloff, what are you doing for your patients, both, I would say, as they're out, you know, receiving tebentafusp down the line, what sort of things are we doing for their quality of life? And then, what about patients who are going to require something beyond tebentafusp? And what are our options there? And how are we proceeding with those patients?

Dr. Daniels:
Yeah, okay, I'll jump in. You know, I think, unfortunately, almost every patient is going to need an additional option, as Dr. Orloff showed us the curves, that patients do well with tebentafusp, get a benefit, but most will need another line of therapy. And I think it should be another show unto itself to talk about, you know, those other options, but that's when we bring in the combination checkpoint inhibitors. There's been some recent studies looking at the activity of, you know, the Opdualags, the ipi/nivos, how do you combine them with liver-directed therapies? You know, some interesting things that are still developing.

So, I always also put on the plate clinical trials, so going back to community care referrals, some we can send them across country if needed in the VA system. And so just trying to work with patients to see what works for them for clinical trial opportunities.

I don't know, what do you what do you think Dr. Orloff?

Dr. Orloff:
Yeah, so I'll even take kind of that first question I think that Dr. Keller mentioned, which is just, you know, you know, what are we doing for these patients who may be on the drug for, you know, months or years. You know, I do think sometimes it can be a challenge for these folks, you know, showing up weekly for their treatment, you know, so offering treatment breaks. When we do say that you should be really getting the drug weekly, but it is okay to skip a week here and there. So, you know, patients who are doing well on drug have travel plans, you know, they should be able to kind of skip a week here and there, to be able to do those things, especially again, because hopefully they're feeling pretty well, not having a lot of side effects at that time. And again, you know, really trying, hopefully to get them weekly therapy as close to home as possible, so they're not having to, you know, travel long distances to get subsequent therapy.

But, you know, I think Dr. Daniels, again, very correctly showed, you know, that we're not curing folks necessarily with this. I, you know, didn't necessarily show slides looking at things like overall response rate and stuff like that. But, you know, that's not making the cancer completely go away. We've certainly had patients on these drugs for many years. We see a few of those kind of at that tail of the curve. I think we wanted that tail of the curve to be a bit higher, so most patients will need something else.

There have been studies now showing, though, that there are some patients who are on tebentafusp who are maybe having kind of almost a mixed response, like some stuff stable, and then one little guy is growing or another, something else is growing. And, you know, there have been, there's recently a publication showing that the addition of therapy on top tebentafusp looks kind of both potentially safe, you know, and effective, and then kind of prolonging the time that somebody could be on tebentafusp. So, adding either things like radiation or ablation or liver-directed therapy on top of tebentafusp, you know, is an option for patients. But then certainly, if tebentafusp was just not doing what it needs to do, and you need to kind of pivot to other therapies, you know, certainly things like liver-directed therapies or really clinical trials is also what we're looking for.

Dr. Keller:
And if I might ask one question on that, Dr. Orloff, what is a driver for you in these patients who have this mixed response? We see, I think, very often, patients will have some slow growth, or little areas that grow despite an overwhelming portion of benefits clinically? What is the kind of last straw for you in terms of saying it's

time to switch or time to add on? I know that in the trials, many patients were treated beyond progression on tebentafusp, and so is there some nugget of wisdom, or is it just pure judgment that you could share?

Dr. Orloff:
Yeah, you know, I would say, you know, obviously for trial purpose it was very much based on kind of percent of target lesion and, you know, being able to repeat the scan, and essentially, if they plateaued, keep going. But, you know, I think in real world practice, it's probably more of a gestalt, you know. So, if someone, really, you know, has, say, 10 tumors, you know, and 9 are stable or shrinking, and one's growing, you know, even if that growth outpaces the shrinkage, you know, I may still say, okay, we're going to radiate or ablate that one, you know. Or if they have 10 tumors in the liver, and you know, they've been on drug for a while, no new tumors, no development of extra paddock disease, but say, hey, 8 of those 10 tumors are like 5, 6, 9 mm larger, sometimes that's when I add liver-directed therapy and keep tebentafusp in the background.

You know, I think there's a lot we don't know still about, you know, even the differential effect of tebentafusp in the liver versus tumors outside the liver. You know, the majority of our patients obviously having hepatic disease is their dominant site. And we always know that the liver is a harder nut to crack when it comes to immunotherapy, we learned that from immune checkpoint inhibition. So, you know, there are sometimes where I think, okay, the liver just needs a little kick, maybe, and you know, we've added liver-directed therapy and actually have a prospective clinical trial now, I as well as others, looking at combination of tebentafusp with liver-directed therapy and other things.

So I think, to answer your question, I don't know if it's one, you know, nugget of wisdom; I think it's a little bit of a gut, you know, sometimes, you know, and I think this rule applies honestly for any of my patients where I'm treating and I see some progression, I say, okay, if we stay on the same thing, and I see the same delta of progression at the next scan, like, are we in trouble? You know, or do I still have time to figure something else out? So you know, if I have a patient on tebentafusp, and I look back from scan to scan, and I would not be happy with that delta next time, then I'm going to switch therapy, you know.

But I think we're still learning, you know, about sequence, about combination, and I think over the next months and years, you know, we'll see a lot of potential partners with tebentafusp, or a lot of sequences explored and such that will help us better take care of our patients.

Dr. Daniels:
So Dr. Orloff, you mentioned quality of life, and this is a weekly infusion, and sometimes allowing your patients to skip a week. Any other strategies, looking for those nuggets too?

Dr. Orloff:
Yeah, so I think that's really the bulk of it. You know, is that, because these patients end up feeling kind of pretty well, you know, they're not having nausea, vomiting, you know, they're not having kind of the other, you know, symptoms, you know, we may expect for patients who are on cancer therapy for months or years. We want them to be able to be, you know, living their best lives.

So, you know, being able to get them treatment as close to home as possible, to make it as convenient as possible. So, you know, often if patients are on this therapy for a long time, you know, we have built at least as part of our kind of program policy is that they don't even necessarily need to see like a physician provider. So, you know, it can be a lot for these patients to, you know, maybe travel to one office, see a physician, then travel to the infusion center, wait for their drug, get infused and go. So, we try to make it as kind of seamless for our patients as possible. And so often, you know, if they need a check-in, you know, often one of our APPs, will see these patients chair side, you know, just to check in and say, hey, how things are going. You know, we don't necessarily check labs, you know, weekly, once they're out a little while, you know, so again, really trying to make it as seamless for the patients.

And then again, I think setting expectations. So, you know, it's hard when patients are doing so well on this drug for so long, and you know, feeling well. But again, as we've said, you know, often the tumor will grow. And so, you know, setting those expectations that, you know, we, you know, I think may need, you know, to, you know, do something else at some point in time, you know. But often it's a slower, I would say, runway, you know. I think we certainly have drugs that, once a patient's progressing, you have, like, very little time to make a decision. I think, progression on tebentafusp often there's bit of a runway where you can start to have that conversation. And then also, I think, like I said, the other kind of long-term side effect I always remind patients of, so they're not alarmed, is the graying or whitening of the hair, eyebrows, and eyelashes. And then also sun sensitivity, because of the vitiligo, you know, and the hypopigmentation, so just being, you know, really careful, you know, in the sun as well.

So, you know, I guess we are a number of years out now, it feels like yesterday, you know, when tebentafusp was approved, but we're out now, you know, many years so, Dr. Keller, you know, how has the approval of tebentafusp changed how you provide care to patients with metastatic uveal melanoma? I know, for you know, folks who were in the field for a really long time, it was like, oh my gosh, you know, finally something but, curious how it's, you know, really changed your kind of treatment algorithm for patients?

Dr. Keller:

Yeah, I mean, I think obviously it's been a great benefit to many, many patients. And it's been wonderful to be able to offer something to those patients who qualify that has a known overall survival, you know, benefit and it has been excellent

for many, but obviously there's still many for whom we need to do better. And so, we continue to try and look for new ways to treat this difficult disease. But it's definitely become, for those patients who are eligible, my typical frontline choice for patients. There's always a little discussion, and I'm happy to hear thoughts and back and forth on how we sequence these many treatments. And I think that's probably a talk and a long conversation on and of its own. But in general, for those who are HLA-A0201 positive, this is the frontline pick that we in my clinic are using.

And we incorporate, as you've mentioned, these other older treatments that we've used for years into that treatment paradigm, as we feel necessary, on a personalized basis, but it's been great. You know, obviously, when you look at the data, I believe the median overall survival was about 22 versus 17 months or so in the 3-year overall survival reports that they published. So, it's great to tell patients that we have something that's going to help them, and to be able to offer that to them has been just a wonderful experience for us and for the patients.

What about you, Dr. Daniels, how do you provide continued support for these patients, both on treatment and after therapy?

Dr. Daniels:
Yeah, similarly, we try to look at time toxicity, as Dr. Orloff mentioned, you know, anything we can do to minimize points of contact that really, once you're on the medication for a while and tolerating it, patients do very well. So, we also utilize, at the VA, a nurse practitioner. We have case managers, social work, because this is impacting sometimes, you know, how they're getting along with their job. So, you know, I have less of an option for doing a weekend infusion at the VA, whereas I do at the university practice. So having to, again, just try to manage the time toxicity.

We also don't draw labs every week. And even when we draw a lab, we don't have to wait for the results. We can just keep them rolling because they're getting treated and seen, potentially, on a weekly basis.

And at the VA, we community care to other supporting things as well as, I know the manufacturer has a patient support program that we always alert patients to so.

Well, I think, you know, we've talked about how we coordinate between VA and academic centers. Any other points about initiating care for tebentafusp with the VA you want to talk about, Dr. Orloff?

Dr. Orloff:
Yeah, so I would say, you know, and I think you guys probably have had experience with this too, you know, I think we looked, and I think about almost 3/4 of the patients that we initiate tebentafusp on, we end up transitioning them closer to home. So actually, we had one of our fellows take a look at this, and we looked at distance traveled for the first three doses versus distance traveled, you know, on subsequent doses. And it was something like, you know, 200-500 miles to, like, 10 miles or something. So, you know, because we have a lot of experience, you know, with those induction doses that we talked about, can be a bit more complicated to give, you know, we will, and because we can initiate very quickly, you know, we could initiate two or three patients a week, you know, we have the capacity to do that. So, we will often do the initiation those first three or four, however many doses, they need to be safely transitioned. And about 3/4 of our patients, we transition locally.

So this could be a site that doesn't see uveal melanoma, that never saw a uveal melanoma patient. But, we work very closely with the drug company to kind of reach out to those sites to make them feel comfortable with the administration, because the subsequent administration isn't really complex at all, it's just an infusion. I mean, they should be educated on the on the whole lot of it, but really, in some ways, you know, anyone can do it, as long as there's good communication.

So often, what we'll do is we'll give the first, you know, three or four, however many doses we need to safely transition them, kind of pass the baton in a very coordinated way to a more local medical oncologist. So, this could be someone you know within the VA or close to the patient. And then there's continued communication, so we have kind of a database of all of our patients who've we've referred out, oftentimes, we'll still check in with them at time of scans, maybe not every scan, but every couple of scans. Because again, you know, if things start to progress, you know, they often want us to have a discussion with their local person about, you know, what to do next.

And so, you know, when we're then transitioning these patients and passing the batons, you know, we always also counsel the patients. You know, if they ever need anything, you know, they can always, you know, come back home, you know, as we say, or have their local providers, you know, reach out to us. So, a lot of coordination, but a lot of communication. And I think it's really helped again, talking about quality of life for these patients, it's really helped patients be able to stay on this therapy kind of long term and be able to

still work and be with their families and all of that stuff while still hopefully getting the benefit of the drug.

So, you know, we've talked about, you know, potentially transitioning patients back to the VA. Dr. Daniels and Keller, do you have access to tebentafusp in the VA? And how are you kind of getting, you know, some patients tebentafusp, who are part of the VA system? What does that look like?

Dr. Daniels:
Yeah, so we have access at our VA, like I mentioned earlier, we have protocols for cytokine release syndrome and stuff, so we're pretty comfortable with it. And then collaboration, our academic collaborative center is literally right across the freeway, so we work pretty closely with UC San Diego here in San Diego.

Dr. Keller:
And I would say similarly, here in St. Louis, you know, we have access to Washington University in St. Louis as our typical collaborating academic center. And at our center—and, you know, obviously practice patterns are going to vary, and availability and access methods are going to vary based on the Vas—at our center, typically, patients will be sent out initially, and then, you know, brought back in to care down the road based on preference and availability and so forth. But it's very easy, I think, to collaborate with these centers. The process for getting patients out to what they need, it has become very streamlined, I would say, over the past couple of years. And so I think there's definitely access. The means of access are just going to differ probably by each center.

Dr. Orloff:
Yep. So we've already started to allude to the fact that, you know, number one, potentially more than 1/2 of our patients are HLA-A2 negative, which means tebentafusp is not an option. And then, unfortunately, there's a number of patients who ultimately progress on tebentafusp and need another option. And, you know, what we have here is really just a snapshot of some of kind of the more active clinical trials in metastatic uveal melanoma, and this is in no way kind of complete. There's a lot of things ongoing, but these are kind of what I would consider, kind of the more widely available clinical trials, most of which are actually global, or even in the kind of the randomized, you know, phase 3 phase, you know, which is, you know, really looking to see, you know, is this drug a drug that we could then potentially also get approved and be able to offer patients. So they really span, you know, immunotherapy to targeted therapy, to liver-directed therapy to other types of kind of HLA-restricted cellular therapies to, you know, we call epigenetic therapies.

And so again, I think it's just really important to know and great for our patients that, you know, we do have a lot of clinical trials that are available for folks which hasn't always been the case. I think a lot of us, when we first started giving, or at least for me and I know when I first started giving talks about uveal melanoma, you know, 10 plus years ago, you know, maybe there was one trial, you know, or maybe no trials at all, or maybe it was a lot of just single-center trials, you know, folks trying to do something, but really, you know, lots of new, interesting things for our patients on the horizon.

And so I would say, you know, I think with kind of more and more options, more and more clinical trials, you know, the opportunities again, that you mentioned that we haven't discussed here about adjuvant, even neoadjuvant trials that are coming down the pike. So, treatment of patients even before their eye tumors are radiated or treated, you know, I think it's just really important that patients, you know, are kind of seen at some point in their disease course, you know, by someone at kind of an academic kind of center who understands the landscapes, you know, to kind of be able to set patients on the right trajectory. And then, you know, hopefully the patients that will be able to get kind of care locally, VA, otherwise, you know, and have that kind of close collaboration, you know, with some of these centers that are running these trials. So, you know, the patients kind of have the best shot, you know, an improvement in outcomes.

So I think unless Dr. Daniels or Dr. Keller, you have anything to add, I think that wraps up our program. So again-

Dr. Daniels:
Appreciate it. Thank you.

Dr. Orloff:
Yeah.

Dr. Keller:
Thank you so much.

Dr. Orloff:
Yeah. So, thank you for joining us and hope you got a lot out of it. Thank you.

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