EVOLVING THERAPIES IN THE CLINICAL MANAGEMENT OF MELANOMA

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MODERATOR All right everyone. At least we got a quick little break in there. Everyone got to stretch a little bit, I hope. So, we'll go ahead and get started on our next session. We are delighted to have two talented lecturers today, discussing Evolving Therapies in the Clinical Management of Melanoma. So, we'll get to hear a little bit more about the drugs that Dr. Kiel just talked about as well. Please join me in welcoming Ms. Lisa Kottschade and Dr. Markovic, both of the Mayo Clinic.

MS. KOTTSCHADE Good morning, everyone. Thank you to the committee for inviting us to come talk to you today about melanoma. We have a lot to go through, but there's been a lot going on in melanoma in the last few years, as everybody knows. So, we'll try to get through all these slides, but we'll be very happy to take questions at the end.

So, these are the learning objectives. You guys can check those out. Our financial disclosures, I have some, he does not. We won't talk about any off-label or investigational use.

And this is just kind of what we're going to talk about today, four main topics. We're going to talk about, very quickly, overview of the changes that have come with AJCC Version 8. Updates in stage III management, both in surgery, immunotherapy, and targeted therapy, as well as advances in systemic therapy for metastatic disease. And then, we're going to focus a lot on management of

patients with toxicity. While these drugs have been great and have improved survival, we know that there's a lot of associated toxicity that comes with that. And if we don’t manage that then we can't keep these patients on therapy.

So, I'll start with the updates in staging. So, we went to AJCC Version 8 as of January 1, 2018. Really, the most significant changes were with T1 lesions as well as stage III disease, and then there was also some new subcategory stages added to stage III and stage IV.

So, the changes in the stage I, or T1 lesions – so mitotic rate was removed from T1 tumors. So, you put the mitotic rate in, you take the mitotic rate out and you know you're all singing, do the hokey-pokey and turn yourself about.

So, T1a lesions are now defined as nonulcerative, and they also are thinner lesions, so less than 0.8 mm in thickness. A T1b lesion now is any melanoma with a thickness of 0.8 mm to 1.0, or regardless of the ulceration status or any ulcerated melanoma that's less than 0.8 mm in thickness.

So, the big change in stage III is that the in-transit/satellite/microsatellites has been actually added to all of the N subcategories. There is also a new addition of stage IIID subcategory. And the patients who are actually considered stage IIIa has become very narrowed with everybody else essentially being upstaged with this new version.

So, in stage IV disease, you know as in other diseases, they have stage IVA, stage IVB, we actually have stage IV with M subcategories. There was actually a fourth M subcategory added to account for patients with CNS disease, and I think this was actually a good move on their part. Patients were kind of all

lumped together, but we know in melanoma that patients with CNS involvement really are a category of their own. Additionally, they took out the LDH being part of the staging and added that into all the M categories, either they're elevated or not elevated, knowing that patients with elevated LDH do have a worse prognosis.

So, what are some of these impacts on practice? Are we going to see increases in patients who are unnecessarily undergoing sentinel lymph node biopsies with the lowering of the depth, which is usually – the threshold used to be at 1.0 mm. Will more patients be unnecessarily getting adjuvant therapy? And what do we do with these new IIIA category patients, who really weren't studied in any of the adjuvant trials?

So, now I'll turn it over to Dr. Markovic and he's going to present some updates in management of surgical patients with stage III disease.

DR. MARKOVIC Thank you, Lisa. And thank you, ladies and gentleman for having me come speak to you today. I know you guys were wondering if I actually did something this morning, but here goes.

So, stage III melanoma, for those of you that don't do melanoma all the time, is melanoma metastatic to regional nodes? Like most malignancies, stage III disease is regional metastatic disease. And for us, about 25 years ago, the resection of nodal disease was an operatory decision. Somebody had a deep primary melanoma, they all went to surgery, this was back in the 1980s. Big operations of the skin, big operations of nodes. Don Morton, in the late ’90s developed a technique where he basically injected blue dye in the area of the

tumor. The dye drained to the first lymph node. Melanoma metastasizes in a very anatomically correct way, a predictable way, such that the tumor goes to the most proximal sentinel lymph node, virtually always. So, identification of that node and the presence or absence of melanoma within that node is critically significant in our disease, that's what defines stage III melanoma. The MSLT-1 Study, which was run by Dr. Morton, published about 14 years ago—so, actually maybe not that long ago—basically looked at whether or not sentinel lymph node biopsy is beneficial. This was the original trial that gave us sentinel lymph node biopsies, and there, patients with intermediate thickness melanoma, for us depth of disease is relevant, not size of the tumor and this is millimeters, not centimeters. Patients were randomized to wide local excision of the primary tumor plus observation. Basically, resect the primary lesion, don't go after the nodes versus wide local excision and sentinel lymph node biopsy, and then if the sentinel lymph node biopsy was positive, one would go in and resect the rest of the lymph nodes out of that region, the idea being to fully remove any residual malignancy. These were the days when we had no really effective adjuvant therapy.

So this study was published, a 10-year follow-up disease-free and overall survival, and it basically turned out that the sentinel lymph node biopsy did translate in a prolonged 10-year survival time. So, this was a big thing for us, and sentinel lymph node biopsy became the standard of care.

Now, what came out in the practice of this disease with the use of the sentinel lymph node biopsy, is that the majority of patients in whom we did

sentinel lymph node biopsies, actually had negative additional lymph nodes. So, the question became, was the sentinel lymph node biopsy itself – when that was the only node that had cancer in it – was removal of that sufficient to achieve a therapeutic benefit? So, did you really need to go for completion with adenectomy?

So, that was the origin of the MSLT-2 Study. In sentinel lymph node–positive patients, is completion of lymph node dissection necessary? Almost 2,000 patients were randomized to no further surgery following the sentinel lymph node biopsy, or, what we believe is the standard of care, completion of lymph node dissection. And the results were very interesting. Another *New England Journal of Medicine* paper by the group, now here it's 3-year disease-free survival time, not the 10-year endpoint, and basically, disease-free survival was better in the patients that underwent lymphadenectomy, but overall survival at the 3-year time point did not show a difference. There was more lymphedema, obviously if you took out more lymph nodes, less lymph to flow through. And what seemed to be very relevant to outcome was the presence of nonsentinel lymph node metastasis. So, if a patient had more than just a sentinel lymph node, yet had another node, having that level of metastatic disease, beyond the sentinel lymph node was critically predictive of outcome.

So, here is the summary of the overall survival data. The probability of melanoma-specific survival in this patient cohorts showing that both the observation or the completion of lymphadenectomy really did not show a difference, but a couple of words of caution for all of us that practice in this, is the

size of the lymph nodes in this study is less than 1.0 mm, so this holds true if these are tiny micrometastatic mets in the lymph – in the sentinel lymph node, not if one has a 5.0 mm met in the node. The Breslow thickness in most of these patients, in the primary tumor was an intermediate lesion of less than 3.5 mm, so if you have a melanoma that's 5.0 mm, this probably would not apply.

And one of the continuing questions for us is, do patients that actually relapse do better if they had completion lymphadenectomy early versus late? This study was underpowered for this question and this remains to be seen.

So, in summary today, based on MSLT-2, the practice has changed to the point that a patient with a primary sentinel lymph node biopsy, where the node is positive, with the caveats that I earlier mentioned, does not necessarily need to proceed to completion lymphadenectomy, thereby avoiding the toxicities of further surgery.

So, I'll pass it on to Lisa to tell you how to treat these.

MS. KOTTSCHADE So, luckily over the last, say 5 years, we've actually had some improvements in what we can give these patients post-surgically to try and prevent their recurrence. I show this slide only to show you that up until 2009, but really up until 2015, with the first approval of an immune checkpoint inhibitor therapy for adjuvant therapy, it was interferon, interferon or nothing. So, we have had three new drugs approved, well, a combination of drugs, but you know, ipi was the first back in 2015 with the most recent approval of dabrafenib and trametinib in 2018, and I think the very soon to be approved pembrolizumab, later this year. So, you can look and see that with the ipi, the D/T, and the

pembro, these were all performed in similar patient populations, so, IIIA, IIIB, and IIIC. The nivo study was actually a little bit different patient population. With the CheckMate 238 and the updated results were presented at ASCO this year, but the thing I want to show you is, no IIIA patients were actually on this trial, so it was IIIB, IIIC, and stage IV, which the stage IV was an excellent cohort to have. We had never really had adjuvant therapy for these patients who were surgically resected. The other thing is, they also included acral and mucosal melanomas, which is almost unheard of in most studies.

So, you can see that the primary endpoint, which was relapse-free survival favored the nivolumab arm versus the high-dose ipilimumab arm, which for most of us in the melanoma world was a little bit of a sigh of relief. Trying to give adjuvant ipilimumab at 10 mg/kilo was like throwing gas on the fire.

So, the other thing that was very interesting out of this study, is that both the stage III patients as well as the stage IV patients benefited from this therapy, which was a huge home run in our ballpark.

So, in summary, nivo demonstrated superior efficacy versus high-dose ipi for the patients with stage IIIB and C, as well as stage IV melanoma who were at high risk for recurrence. It showed a statistically significant improvement in the distant metastasis-free survival versus ipi. And they continued to look at the durable clinical benefit of this outcome.

So, the next study that is probably going to lead to the approval of pembrolizumab was the EORTC KEYNOTE-054 study. This was randomizing high-risk, stage III melanoma patients to placebo. Again, these patients with IIIa

disease had to have an intra–lymph node metastasis of greater than 1.0 mm, no prior systemic therapy and kind of the usual no autoimmune disease. You can see that based on the recurrence-free survival curves, there was an improvement in recurrence-free survival for the patients who got treatment.

So, in conclusion, this study is a positive study. It remains blinded for distant metastasis-free survival as well as the overall survival, which will be reported shortly.

And then kind of the final one that got approved in the adjuvant setting was for patients who have a *BRAF* mutation. The combination of dabrafenib and trametinib versus placebo.

So, you can see, I think that is probably the biggest P value I have ever seen in my life for 3-year relapse-free survival. I didn't know you could put that many zeros in a P value. But interestingly enough, even though that 3-year overall survival P value looks good, it actually did not reach statistical significance as outlined by the study. I think they wanted it to be 0.0000019, so it actually didn't reach statistical significance, but I'll take that as an improvement in my book. Any numbers that go up, is good.

So, what are these impacts to practice? So, you know, we need to really figure out what to do with the patients who are IIIa. While nivolumab actually got approved in all stage III patients regardless of their substage, we have to really ask ourselves, is this an appropriate thing for patients who are stage IIIa via AJCC 8? Because really that population hasn't been studied. What do we do for BRAF tissue testing? A lot of times there's not enough tissue to test for BRAF at

this stage, and obviously the other thing is, there's been no direct head-to-head comparison between the *BRAF*-mutated group between targeted therapy versus immunotherapy in the adjuvant setting.

Additionally, what do we do with these patients once they relapse on adjuvant therapy? Literally, if they're, you know, 8 months into their immunotherapy and relapse, what do we do with these patients? We don't really have those answers yet.

And then we also have to consider the risk for lifelong toxicity for patients who are receiving adjuvant immunotherapy. You have a 23-year-old that you've now given hypophysitis to, and she is now secondary adrenal insufficient for the rest of her life. That's a big conversation we really need to be having with our patients up front.

So, I'll turn it back over to Dr. Markovic to present the updates in metastatic disease.

DR. MARKOVIC Thank you. So, the next section of our talk is to talk about metastatic disease. You know, I've been in this for almost 30 years and I can tell you what we refer to as metastatic melanoma therapy, is sort of as the Jurassic period is pre-2011. Since that time, we have had an explosion of new drugs that have been developed. The Burroughs Wellcome Fund identified *BRAF* mutations that are involved in half to a third of all the cases of metastatic melanoma. Actually, it's not all mutations, only the druggable, the targetable mutations fill this criteria, which means these specific mutations that react with the vemurafenib, dabrafenib, and encorafenib, are the ones that can be

therapeutically effective, and then the concurrent MEK inhibitors. The idea of combining these drugs is these are two stops along the same signaling pathway, so they more efficiently block the RAS-RAF-MEK-ERK signaling pathway. We've had vemurafenib and cobimetinib, were the first to be approved. Actually, vemurafenib was, followed by dabrafenib, trametinib, and most recently, I'll mention encorafenib and binimetinib. And, of course the explosion of the immuno-therapeutics with ipilimumab, which was the first modern era immune checkpoint inhibitor that produced a survival advantage in patients with metastatic melanoma. All of this has happened since 2011.

So, just a little bit of an update of what actually happened over the last 12 months in our rapidly developing field. The Columbus trial was the introduction of encorafenib and binimetinib, the third of the combinatorial regimens for BRAF V600E/V600K-mutated melanomas. This was a trial that was done largely in Europe because of the penetration of the use of these agents in the United States. The prior two combinations was almost saturated.

Encorafenib and binimetinib have slightly different pharmacokinetics. The encorafenib is daily and it's got a longer half-life. The binimetinib has a shorter half-life than the other MEK inhibitors, it's almost the reverse. And they have a slightly different toxicity profile.

The results that were eluded to earlier by our first morning speaker came from the COLUMBUS phase 3 study where patients received a combination of enco and bini. Vemurafenib, the first agent that was approved in this field, which

is a BRAF inhibitor, and enco 300 at the lower dose, which is the only dose that could be tolerated in these patients, of BRAF inhibitor, the BRAF inhibitor.

So, it was a somewhat complicated study, but the message is very simple. The combination of the two agents versus vemurafenib, advantage to the dual inhibitor. Dual inhibition versus single inhibition with the same BRAF inhibitor, slightly less but still advantage of the dual inhibitor. Progression-free survival, again, combination versus vemurafenib, advantage to the combination. The combination was superior to all versions. So, basically a recapitulation of the prior combinatorial trials of BRAF and MEK inhibitors, seen yet again, in this third version, which potentially offers us options for treatment, vis-à-vis toxicity. The outcomes are somewhat improved relative to the prior phase 3 clinical trials, but these are not head-to-head comparisons. And the evolution of all therapeutics in advanced melanoma has changed, so that overall survival continues to be a more complicated endpoint for us to study. But these drugs are currently available to you in practice.

The second immunotherapeutic agent that had a lot of advertising but little juice, unfortunately at the end of it, was epacadostat. Now, this is a drug that has a unique mechanism of action where it's whole, sole purpose of function is to block the depletion of tryptophan within the tumor marker environment. The idea being, and this is an idea that's been around since the late ’70s actually, that the microenvironment within the tumor where the tumor lives and the immune cells penetrate, is nutritionally deficient. So, that when the immune cells enter this hostile environment surrounded by cancer cells, they cannot execute their

function because there's no, basically there's no food for the army to do it. So, the idea here was, what if we blocked the ability of one of the critical enzymes that utilizes the nutrients, essential amino acids within the tumor marker environment, thereby allowing resources for the invading immune system to function. So, the inhibitors of IDO were introduced. Epacadostat was the first one to enter clinical testing. This is a phase 1-2 clinical trial, 54 patients, and I emphasize 54 patients. This was a waterfall study showing response to therapy, volume reduction of the tumor, in combination with pembrolizumab, these agents make sense, logically to work with checkpoint inhibitors. Unfortunately, the phase 3 study did not show any difference and I've never seen a slide where somebody would say it's a remarkably negative study, so as Lisa showed you the number of zeros that the one difference had, this is sort of the other example of that.

The trial – overall survival, and again, progression-free survival not different. This put some cold water on the field of inhibitors of metabolism within the tumor. There are a significant number of questions and issues regarding this agent, but I think one of the things that we did, probably incorrectly in this study, is that we went from a phase 1-2 study of 52 patients immediately into a randomized phase 3 clinical trial. Sometimes following the old playbook may actually make sense. So, this is one example of something that we will still hear more about, IDO inhibition, but not potentially with this agent. Lisa?

MS. KOTTSCHADE Thanks. So, we'll go on to management of toxicity. I think we'll start with immunotherapy and, you know, people in the melanoma arena are actually uttering that word, cure, which when I started 13

years ago, you just didn't even use that word anywhere. But we have issues that come along with this. So, you know, the wonderful immune-related adverse events, definition, any adverse event that can come because of activation of the patient's immune system and it can literally occur in any tissue, organ, or system. These are often severe and there have been fatalities reported with this class of agents.

So, how often do we see these immune-related adverse events? This is just some snapshots from early melanoma trials. With these, you can see that with anti–PD-1 alone, any immune-related adverse event was around 70, 73% with nivolumab slightly higher. The combination, though, I turn you to the other side, where – over here where we're at about 95% immune-related adverse events. And the picture at the bottom is actually more telling. Most grade 3-4 toxicity is pretty limited to about 15 to 20%, but when you get those in combination, we're talking over 50% of patients having a severe reaction. That can be a big deal. So, what do we see? I love this photo. I've seen this at a number of talks all over time, but I think it's a really good representation of all the things that we can see. And I know there are other side effects that aren't listed there, but this gives us a good coverage. The most common ones we see involve cutaneous toxicity, GI, liver, the endocrine system, and pulmonary.

These are also a couple of nice pictures that I like to show. It shows you the difference in distribution based on the agent you're using. So, you can see here that the grade 1-2 tend to be distributed across the skin and then GI for the anti–CTLA-4. A little lower with PD-1 and then even lower with PD-L1. But if you'll

see that with the grade 3-4 immune-related adverse events, we tend to see higher numbers of those with the anti–CTLA-4 agents.

So, when do these side effects appear? This is a nice photo by Dr. Weber showing the onset. Rash is usually the first that we see followed by GI, then with the liver toxicity as well as the endocrine.

So, what are some less common side effects that we can see? We have seen patients who have developed type I diabetes, primary adrenal insufficiency, the neurologic ones, those are the ones that I find the really hard ones to do, autoimmune encephalitis. And then we're starting to see this new kind of class of rheumatologic side effects.

So, some clinical pearls in the management of this. With the dermatologic, most frequently seen with ipi and PD-1 blockades, single agents, around 40% up to 60% in combo therapy. They get this kind of diffuse maculopapular rash. But they may also just have pruritus in the absence of rash. Patients can also develop vitiligo. While not life-threatening it can be very psychologically damaging to the patient. I had a guy who actually wanted to – he had a complete response, wanted to quit his therapy because he had vitiligo on his face and he wasn't going to go to his daughter's wedding looking like a patchwork quilt. There's also been cases of Stevens-Johnson syndrome and TEN reported. Up to 30% of patients are going to have the itching with no rash even seen. And for some patients, that's actually worse because then they're wondering why they're clawing their skin off but they don't actually have a rash.

So, how do we manage this? At our facility, we kind of do this based on amount of body surface area involved. For those with 20%, we really try to manage these patients symptomatically, not break out the steroids. Oral antihistamines, I will give, you know, either cetirizine or loratadine. We do the topical agents, so some topical hydrocortisone cream. Sometimes, I'll tell my patients to take a little diphenhydramine at bedtime. We can give hydroxyzine.

As we get to more body surface involved, then we really do need to start thinking about adding the steroids in. We are going to probably have our dermatologic colleagues see these patients and we're going to hold their therapy. For greater than 50% of their BSA involved, we may have to stop therapy. Now, I have had some patients that I've been able to successfully rechallenge after their rash has disappeared, but often times the rash will reoccur, fairly quickly.

What do you need to do to manage vitiligo? Well, literally nothing. It's a self-limiting toxicity. But, again, you need to warn your patients that this is likely permanent. And they also need to be cautioned about sun protection in those areas. I've had patients who have gotten some pretty severe burns. They weren't normal sunscreen users, they kind of tanned easy but then, you know, they had these big patches of vitiligo that have absolutely no protection and then they got burned really bad.

So moving on to GI. So, we can see both diarrhea and colitis. I think this is something that needs to continue to be emphasized. These are actually separate entities even though they often occur together. So, diarrhea literally is an increase in the number, or frequency of stools. And colitis, usually is associated

with diarrhea but includes abdominal pain and imaging or endoscopic findings consistent with inflammation. We tend to see this more commonly with ipilimumab than we did with PD-1. And we also can see very high rates with the combination therapy. So, the colitis that patients get from these drugs, actually shares a very close histologic feature of Crohn's disease. And there actually have been fatal bowel perforations with patients treated with ipilimumab. I think on the adjuvant trial, there was at least two or three patients with a fatal bowel perforation.

I'm not going to go through and belabor this. This is more for your reference. This was an algorithm we created to kind of help us manage this. The one thing I do want to do, or show you, that I don't have in there, is under grade 1, I don't have using the antidiarrheal agents and that's a personal preference and I know a lot of places do still do that. I'm going to show you why in a minute, why I don't do that. But this is a real good flow chart that you can use. We are starting to use a little more vedolizumab as opposed to infliximab. It seems to work a little bit better. We've had a little bit of trouble with insurance companies but we are tending to get that approved. It also has more focused concentration in the bowel as opposed to a systemic immunosuppressive effect.

So, this is why I don't use the antidiarrheal agents. This was a patient of ours who, his wife was a nurse and I have nothing against nurses, I'm a nurse, but they thought they could self-manage his diarrhea. And she started pumping antidiarrheals down him. And this is what happened. He called, he said, “My diarrhea is still there. But now I've got a fever, I don't feel well.” I think this guy

was actually life-flighted to us, put in the ICU. But he literally ended up with sepsis, hypertension and was diagnosed with toxic megacolon. Not that this happens in all cases, but I think this is a real eyeopener for us about not continuing, you know, loperamide if they're not responding. This patient required ICU admission. He did respond to high-dose methylpred and then decompression and actually did recover.

So, moving on to the liver toxicities. Most of the time these are asymptomatic transaminitis. On occasion, I have seen hyperbilirubinemia, but about 30% with combo therapy, less than, probably 15% are grade 3-4. Less than 10% in monotherapy. We see it more with the anti–CTLA-4 then we do with PD-1. There have been a few cases of hepatic failure. I think the biggest thing that we need to remember, especially in melanoma, is that you need to rule out any progressive hepatic involvement by the melanoma.

So, how do we manage this? Again, managed based on numbers. For grade 1, you know, we make sure there's not any other cause. Are they having other hepatotoxic drugs? Are they eating acetaminophen like it's going out of style? These patients I'm usually going to watch and keep going with their treatment. I'm going to increase the frequency by how often I'm checking their LFTs, usually twice weekly. And then if they start to have a trending up, then I may actually start them on some low-dose prednisone. Those patients who are at least five times in the upper limit of normal, I am actually going to hold their therapy and probably start with a little higher-dose prednisone. The question is, what do you do with the patient who comes in who's got liver disease and already

has elevated LFTs? Those are a little bit of a challenge. Those patients I just tend to trend and if they stay in the same range, then I don't worry about it. If they have a sharp spike, then obviously I'm looking for disease progression of the liver, but I'm also concerned that they've got autoimmune hepatitis.

For patients who are not responsive to steroids, and this is not a vast majority, but there are a few. We generally have our liver colleagues take a look at these patients and usually we start them on mycophenolate.

So, endocrine AEs. These are probably the worst to diagnose, the easiest to treat, but these are the ones that are usually lifelong. So, we see thyroid dysfunction in about 15% of patients. I actually think that is a very underreported number. I think this was a number that was reported of patients who actually required treatment. I tend to see it in about 30 to 40% of my patients. Sometimes, you don't have to treat it. But, usually what happens is they go through this acute inflammatory stage. Some can progress to thyrotoxicosis, where they have low TSH, high free T4, and we see this a lot more in combination therapy. It's a lot higher. But these patients are going to usually resolve to kind of a euthyroid state and then probably the vast majority are going to progress to overt hypothyroidism. Very few regain function. Again, just an algorithm to kind of help you decipher where your patient may be at. And they may fly through all four of these categories. Over on the far left, these are the patients to be very cognizant about. Patients who have a normal or slightly depressed TSH and a low free T4, these are the patients that I'm going to worry about actually having a secondary hypothyroidism from hypophysitis that may be not being diagnosed. So, these

patients I'm going to screen and make sure that their a.m. cortisol and their ACTH is normal. And then we may have to begin thyroid replacement on them. Patients in the second column from the left, these are your hyperthyroid patients. Usually, it's a self-limiting. They rebound in 3 to 6 weeks. On occasion, we do have some patients who have the usual symptoms of hyperthyroidism with tachycardia that needs to be treated with a beta-blocker for a period of time, but usually they're going to progress very quickly over into column three. They have the subclinical hypothyroidism. These patients generally we're going to watch. There are a few patients who kind of fall between that 5 and 10 range of their TSH that do need to actually start on treatment because they're symptomatic, but usually we don't begin that until their TSH is greater than 10.

So, continuing on with the endocrine AEs. The hypophysitis, so these patients walk into my office, or call me, and they say, "I feel like I've been hit by a truck. I'm in bed 18 hours a day, I can barely get to the bathroom and my head is killing me." So, sometimes they can have visual changes, hallucinations, sometimes nausea, and vomiting. These are patients who are going to have a low, or undetectable ACTH and a.m. cortisol. And 75% of these patients are going to have an enlargement of the pituitary gland on imaging. It was interesting when we first started diagnosing these cases, all of our radiologists started reading these as mets to the pituitary because they couldn't figure out why the pituitary was enlarged. And then, you know, after we kind of started figuring out what this was all from, then that got better. I will still say, if you're ordering an MRI to look for hypophysitis to make sure to ask for pituitary cuts. I think a lot of

the radiologists in the country have gotten very savvy about that, but in some of the rural areas, they may see one of these a year, so they're not used to just doing them. Always got to make sure that there's no CNS involvement by malignancy as well.

So, how do we manage hypophysitis? So, patients who are already on steroids, you really can't interrogate the pituitary axis. You have to wait till they're off steroids. But the one thing to remember is so say you have a patient who is on high-dose steroids for colitis. And you're dropping them down and then all of a sudden they tell you they feel horrible. We have to worry about secondary adrenal insufficiency in these patients, either from the steroids themselves or because they may have had a masked hypophysitis that when we had already started treatment for the colitis, we just masked. Patients who are not receiving steroids and are symptomatic, we are going to give these patients high-dose steroids. The good news is, if this is their only side effect, the high-dose steroids usually only need to be on board for about 1 to 3 weeks. Okay? We can usually do a pretty rapid taper in other settings and then put them on physiologic replacement. If they're asymptomatic and say you were on clinical trial and you happen to pick up that, you know, they were random, or not randomly, but regularly looking at the a.m. cortisol in that clinical trial, these patients we've just started on physiologic replacement. They're few and far between, but I have seen a few.

And then all of these patients need to be comanaged with their endocrinologist because they need to learn about sick-dose steroids as well as what to do in an emergency.

Additional endocrinopathies, we can see primary adrenal insufficiency. I think I've seen two cases of this. The big difference between this and secondary adrenal insufficiency, these patients are going to have a high ACTH and these patients are going to be critically ill. These patients need to be in the ICU, fluid replacement, electrolytes, and high-dose steroids. Again, reiterating that most of the pituitary and adrenal abnormalities don't resolve. These patients require lifelong physiologic dosing, and they need to be instructed on what to do on those sick days.

So, pneumonitis. This has become more challenging and I think we're seeing more cases than what has been reported in the literature. I know our lung colleagues really are starting to see a lot of these cases. Most of the time these patients can present asymptomatically. You're doing their routine scan, the radiologist calls you and says, "Oh, they have all these interstitial infiltrates, you know, you better see them right away." And you walk in the office expecting to see this sick patient and they're like, "Hey, how's it going? I feel great." So, it happens. But then there's the occasional patient that presents and says, "I have this horrible cough. I can't breathe. I don't have a fever, but I just don't feel well. I might be getting pneumonia." I think the fever is the biggest thing. And a lot of these patients are, unfortunately, treated incorrectly in an emergency room situation. I get calls, "Oh, your patient was treated for pneumonia." I said, "Well

how do you know they had pneumonia?" "Well, they had these infiltrates and they came in and they were short of breath, so we put them on some levofloxacin. You probably should see them back in the office." And, I know in the back of my brain that that's not what's going on. And I'm like, "Were they febrile?" "No." "Was their white count up?" "No. But, you know, looked like pneumonia, smelled like pneumonia, so we treated it."

So, these patients can decompensate very quickly as well. I had a patient who I saw in clinic one day, admitted him to the hospital. He was symptomatic in clinic. I mean, his oxygen saturations were like 88% on room air. Barely short of breath at rest. Put him in the hospital. By the time he got over there and got admitted and they were getting ready to get his steroids on board, he was in the ICU on a BiPAP. So, these patients can definitely decompensate very quickly.

Again, differentials can also include PE, progression of disease, and there are people who do get infected so we really need to use our good skills in assessing these patients to make sure that's not the case.

I just want to show you this picture. This shows the evolutionary process that you might see on scans of somebody who's had pneumonitis. In A, that's the acute inflammatory phase, and B, that's those chronic fibrotic changes you may continue to see on CT scans form there on out. And then in C, for those of us that do a lot of PET scans, you can kind of see the FDG-avidity of those peripheral infiltrates.

So, rheumatologic immune-related adverse events. This is really a new category that's gaining a lot of traction, but it's a very real side effect. And we

used to just say, "Oh, they just have some joint aches," and that kind of thing. But there have been multiple studies published on patients who developed polymyalgia rheumatica, giant cell arteritis, we've seen lupus at our place, we've seen scleroderma. So, these are very real and scary side effects that we can see.

These are not the side effects that will present in the first 12 weeks of treatment. These are patients who have been on treatment for a year, 2 years. Or, I have patients who have been off therapy and then come back to me 2 years later and they're like, "You know, I just have this terrible joint pain. I can't get up in the morning. They hurt, they're hot." You know, but they haven't been on therapy for anything. So, these are things that we need to continue to watch for, even after we stop their immune checkpoint inhibitor therapies. The problem is a lot of these patients are steroid refractory. Steroids just don't seem to help and they can be very chronic. The other thing is, working with our rheumatologic colleagues, the normal autoantibodies that we see for these diseases are usually negative. So, these are kind of de novo rheumatologic conditions, diagnoses made on symptoms alone.

So, what are some of the ongoing challenges with immunotherapy? We still have inconsistent reporting of the immune-related adverse events. Current grading system is still not great. I think a lot of the immune-related adverse events are considerably unreported. And then looking at the toxicity spectrum, very early recognition and referral and treatment. We have to educate our patients to call us.

What are the unknowns? When and if to rechallenge with immune checkpoint inhibitor therapy. I think we're getting a lot better with this, and I think we're becoming a lot more gutsy, but there are still times that I'm like, "Oh, I don't know that I want to give this to this guy again."

How does chronic steroid use impact their overall survival? You know, we believe that it's not a huge factor, but we really need to start doing a deep dive into those patients who have had bad side effects and what their ended up survival was. Are there biomarkers that we can do to help kind of identify patients who are at risk? So, if I had a patient who had a certain biomarker, would I give them dual immune checkpoint inhibitor therapy or start with single-agent PD-1?

So, moving on quickly to some of the clinical pearls in targeted therapy management. As mentioned before, anyone from 40 to 60% of patients with melanoma have a somatic mutation of *BRAF* at V600. First approval came in 2011 with the third-in-class approval just this year. There has been significant improvement in PFS and OS with these combinations versus the BRAF inhibitors alone. One of the most common and most frustrating side effects we see is pyrexia. We see this a lot more with the D/T combination than with the other two, but we do see it in all them across the board. In D/T, we can see this in patients, about 50%. Five percent grade 3-4. Around 15% with the other drugs.

These patients may have severe chills, rigors. They can get hypotension and dehydrated and even renal failure with severe pyrexia. Additionally, patients also may just get the chills and, you know, you tell them to take their temperature and they never have a temp. I don't know if you've ever been an adult with the flu

with the chills and you know how miserable it is, and these patients are pretty darn miserable.

Dermatologic adverse events. We tend to see a little bit different type of rash in these folks. An acneiform type rash. You can see the percentages there. The other thing is, we also can see photosensitivity with vemurafenib. This seems to be a very unique side effect to this drug alone. I tell my story that I had a patient who walked from his house to the mailbox and back, and was completely sunburned. So, these patients really need to be taught about photosensitivity. We have seen SJS and TEN and DRESS syndrome with these agents. And then we're also seeing PPE, so hand-foot syndrome with some of them. It's more common, I see with D/T then with the other ones. And then, obviously recognizing the risk for radiation recall and radiation dermatitis. Patients should not be on these agents while they're getting radiation therapy. We found this out the hard way when we were radiating brain metastases doing whole-brain radiation. Patients were on vemurafenib and they were getting stage II burns on their head.

We can also see secondary malignancies. Squams and the keratoacanthomas are the most common, but we have seen basal cells as well. Second primary melanomas. Interestingly, all of the people that I've had that have developed a second primary melanoma, that melanoma has been BRAF wild-type. So, we're definitely doing something inside there.

Liver toxicity, as with the other drugs, we can see this more common with combo therapy. The one main point I want to drive home here though is, you

need to be very careful. If you have a patient who's been on immune checkpoint inhibitor therapy within the last 3 months, and you switch them to targeted therapy or even vice versa, you can see extreme hepatotoxicity crossover, crossover toxicity in these patients. And one of the trials, I think was actually stopped early because of the severe hepatotoxicity with a combination of targeted and immune checkpoint inhibitor therapy.

Cardiac toxicity, much like in the breast cancer arena, we now have our cardiotoxic drugs. We can see prolonged QTc intervals for patients who are on vemurafenib. There is some theoretical thought that this can happen with encobini, but very low numbers. Cardiomyopathy is more the issue. All of the MEK inhibitors can induce cardiomyopathy. It's a class effective, that drug, and we have seen isolated cases with BRAF inhibitors, but it's not generally a standard.

So, what are some of the other rare side effects, so rhabdomyolysis mostly presents as asymptomatic increases in CPK, but we have our first patient we gave them cobi-combo to ended up in the ICU with rhabdomyolysis. Kind of shooed us off from wanting to do that again any time soon. But it does happen and you just need to be very conscientious about it. We can see the uveitis, we can see pneumonitis, as well. So, if you've had a patient who's had pneumonitis on immune checkpoint inhibitor therapy, you switch them to targeted therapy, you need to be very careful and vice versa. I have had reactivation of that pneumonitis doing that.

Patients can get hyperglycemia. This is mostly common with dabrafenib. And then hemorrhage or DVT and then one that's kind of interesting is

panniculitis. So, we were getting lots of calls from our PET scan guys that your patient has widely metastatic disease with all these new subQ lesions. And we're like, "What?" They had been, you know, complete response, everything else. When we biopsied them and they were developing panniculitis. So, just being cognizant of that, that you can see that on scanning. And these can actually be painful. I've had patients call and they say, "I have these little red sores, kind of right underneath my skin, and they really, really hurt."

So, how do me manage the fevers? You can see here it's all based on how high the fever is. You know, for fevers less than 101, we're usually going to try to cautiously continue these agents. I can tell you that most people progress into the middle category and we need to hold the agent. And then we need to do dose reductions. Most patients, I'm not, I'm finding do not respond to antipyretic agents with ibuprofen and acetaminophen. And I usually have to end up starting them on low-dose steroids. When you rechallenge, I usually try to rechallenge at a lower dose and then I have tried to reescalate in a class of patients, but most of the time when you try to reescalate, the fevers recur.

So, patients who have very complicated fevers, obviously rule out infection. If they haven't recovered or stopped the fever within 3 days of stopping the drug then that's when we're also going to start prednisone. If patients tolerate the rechallenge then I will try to taper their prednisone. Not always does that work and I usually have to keep them on low-dose prednisone throughout the course of their therapy.

So managing the derm side effects, rash, the acneiform rash, we usually manage with minocycline 100 mg BID. If it gets worse, we would have to progress to steroids.

Warning signs on any patients who have rash, with blistering skin, sores on their mouth, peeling, fever, or redness, these are patients that need to be ruled out for SJS.

Photosensitivity, again, like I said, it's very common with vemurafenib. We want to instruct our patients to use good photo protection, cover up – and I'm telling my patients, if you're outside at all, you put on sunscreen. Period. Not the, you know, 10 minute rule that we kind of usually used before.

Secondary cutaneous malignancies, we usually just manage those as per protocol, wide local excisions and continue the agents.

Cardiac toxicity. QTc management. For vemurafenib we're going to repeat those ECGs after we start the drug 2 weeks and then monthly times three and then every 3 months. We're going to hold that vemurafenib for a QTc greater than 500. We can retry them if it goes below that. You're going to also want to make sure that they are not on any other medications that prolong the QTc interval. And then if they recur with prolonged QTc, then we need to discontinue that agent.

The deceased LVEF, we want to get a baseline echo, repeat at 1 month and then every 3 to 4 months while they're on therapy. Again, most patients have an asymptomatic decrease in their left ventricular function, but there are some patients who come in with the classic congestive heart failure signs, so

monitoring for edema, that kind of thing. Shortness of breath. If patients who have been diagnosed with a decreased left ventricular function, we're going to repeat their echos more often once we restart drug.

So, some take-home points. One thing with the targeted agents, which is an advantage over the immune checkpoint inhibitors, most of the side effects will dissipate within a few days of stopping or deceasing their drugs. Again, being very cautious when you're switching patients back and forth between therapies, as well as reminding patients that we need to hold their BRAF and MEK inhibition during any kind of radiation therapy, including stereotactic radiosurgery. We usually hold it for about 24 hours ahead of time and 48 hours after. If they're doing a prolonged course of radiation, then you're going to need to hold it longer.

So, I'll turn it back over to Dr. Markovic.

DR. MARKOVIC All right guys, we're almost done, so, we had 100-plus slides for you this morning. So, I just wanted to bring us close to the end here with a brief look into the future. And I only have one slide because, you know, I could probably spend the rest of next week telling you about how this development is coming about. But I would say, one thing that I would encourage all of you to do, is try and educate yourself as much as you can about immunotherapeutics. Immunotherapeutic cancer, you guys, is something completely different. It dates back to the 1880s and only today do we understand it. The reason for that is that the tumor – and this is a great paper if anybody is interested in looking this up – is the malignancy interacts with the immune system on several different levels. The tumor must be seen by the elements of

the immune system, what are features of the cancer that are different, sentinel dendritic cells that read this information need to educate lymphocytes in a regional lymph node. These lymphocytes need to be able to see those targets from the tumor that the dendritic cell has presented, then enter the blood supply, search throughout the body and identify where the tumor cells are, then penetrate the tumor marker environment and execute a cellulytic kill. So, there's a lot that has to go on in order for the immune system to work. The checkpoint inhibitors work on the point where they mask an off switch on the immune system – on the immune cell, that is engaged by the tumor and it shuts it down. The IDO inhibitor depletes the food supply within that tumor marker environment. So, these are attacks on the interface between the immune system and the tumor. And just to show you that that interface is not homogeneous, these are inter-histochemical slides stained for S100B, which is a melanoma for blue, CD8 light-blue cytotoxic T cells, helper T cells, macrophages, regulatory T cells, the suppressor T cells, and B cells. Three different biopsies of the same tumor, three different scenarios of what goes on. So, one of the things that I've learned from this, and we are studying this very heavily, is that the interaction between the tumor and the immune system is very complex. We got lucky with PD-1 inhibitors. There's a lot here that needs to be learned. The complexity needs to be understood. We need to understand what systemic immune homeostasis is. Would you be surprised if I told you that 90% of the genes that the tumor expresses to defend itself from the invading immune system are exactly the

same genes that the placenta uses to protect the baby from mom's immune system. The same goes for the regulation of the systemic response.

And also, the nice thing about where we are in this time in history, is there's a lot of these molecules can be targeted very, very specifically. Recombinant monoclonal antibody technology allows us to produce to a known target a human monoclonal antibody for less than $50,000, their cost. So, we can interphase more clinical testing at very, very reduced costs. And many labs, including ours, are working on this.

So, again, be aware of the revolution of cancer and therapy. Twenty years from now when JADPRO has their meeting, I would say most of the drugs that you will hear in the session just prior to ours will deal with this problem. So with that, and a great look to the future, I'll pass it back to Lisa to summarize.

MS. KOTTSCHADE So, I just want to kind of summarize what we went through today. You know, with the new AJCC staging, we have now substratified patients in stage III to provide better clarity. We've better subcategorized our stage IV patients to put CNS disease into its own category. Patients with sentinel node–positive disease clearly, apparently do not benefit from complete lymph node dissection. I want to put a caveat on that, in that, in Dr. Markovic's talk, we really have to look at how the primary thickness is, so this is still a very multidisciplinary conversation we need to have with our surgeons. Nivolumab is superior to ipilimumab for adjuvant treatment of high-risk melanoma. Pembro appears to be superior to placebo for the adjuvant treatment and is likely going to lead to its approval, even with the distant metastasis-free

survival and overall survival still immature. Dabrafenib and trametinib are better than placebo for adjuvant treatment of high-risk melanoma for patients who are BRAF mutant. Encorafenib and binimetinib present us with a third-in-class option for treating patients with metastatic disease with a little bit more favorable safety profile. Unfortunately, the addition of epacadostat in combination with pembrolizumab did not inpatient progression-free survival or overall survival in patients with metastatic melanoma. And with that, we'd be happy to take any questions.

I see someone in the back there.

FEMALE Thank you. I was wondering if you could speak to the point of neurotoxicity and neuritis with the immunotherapy treatments as far as even myasthenia-like side effects. I didn't see that in the presentation. I was wondering if you could speak briefly to that point.

MS. KOTTSCHADE Yes, sorry. I probably have missed some of the neuro side effects and some of the other side effects. We have seen myasthenia-like side effects. We treat them the same way that you would treat somebody with regular MG. They're very uncommon but they definitely have been reported in the literature. I think we've had one case at our place, of a patient who presented that way. But they present pretty classically like a patient with myasthenia gravis would.

DR. MARKOVIC Let me just add to that. You know, don't be afraid to use IVIG in these patients. You know, myasthenia, at least for the cases that we've seen, is an immunoglobulin-mediated toxicity. The benefit of treatment

against cancer is cell-mediated immunity. So, IVIG uniquely depletes the hormonal – the humeral aspect of this and really has never shown to impact, even in preclinical studies, the antitumor effect of the T cells. So, I would say be aggressive and treat as a de novo myasthenia.

FEMALE I was just going to say that I have a patient on a phase 1 clinical trial and even though we tell them don't take anything additional, he came in one month for his monthly check and he had grade 3 liver functions, and they'd been normal all along. So, we asked him what he was doing and he said, well he went to an herbalist and she looked into his eyes and told him he needed all these herbs and he now had grade 3 liver toxicity. So, you know, we immediately took him off. He did recover well, but they think these herbs are so okay because they're natural. So, that's another thing just to be cognizant of, you know, if you see something like that happen to your patient.

MS. KOTTSCHADE Yeah. That's a really tough thing, because a lot of patients are looking for the natural way to fix their cancer and to feel better and to manage any side effects, so absolutely. Herbals and any over-the-counter medicine needs to be in the differential if your patients are coming in with hepatotoxicity.

FEMALE Good morning. So, in our practice, we've been seeing rises in amylase and lipase that are clinically silent. And we tend to watch them and watch them and they'll hit the 200s and then when they hit 600 we hold the drug. Do you have any guidance?

MS. KOTTSCHADE Don't check your amylase and lipase unless they're symptomatic.

FEMALE Thank you.

DR. MARKOVIC Yeah.

MS. KOTTSCHADE Literally. I mean, we've talked with our GI colleagues and they said that there are so many – you know, I know a lot of the clinical trials require that and made you hold dose based on that or whatnot. But there are cases of fulminant pancreatitis, sometimes we've picked up pancreatitis on imaging alone, but we routinely do not check that for that very reason. Because it causes a lot of concern about do I hold it, do I not? Unless they're symptomatic and have a symptomatically or radiographically diagnosed pancreatitis, we don't check them. Mm-hmm.

FEMALE A question about autoimmune diseases and is – how you – is that a contraindication to receiving like adjuvant treatment?

MS. KOTTSCHADE It's not a complete contraindication. It is a consideration. So, the ones that I have found that we have tried to treat, that have not done well, are people with MS, psoriasis. I have successfully treated patients with IBD. I think it depends on how active the autoimmune disease is. If they are on biologic modifiers for their autoimmune disease, then that would not probably be a candidate. I would give adjuvant or metastatic therapy to, unless I could stop that. That's a really great question, but yes. It's not a – still continues to be a contraindication for most of the clinical trials, so that's why there's not a lot of data out there, but there have been, I think, at least two retrospective

studies that have looked at this issue, and probably a third of those patients had kind of either worsening, or reactivation of a previously quiet autoimmune event, but there have been plenty of patients who have been successfully treated with that. So, I think that needs to be taken on an individual basis and working closely with that patient's rheumatologist as well. Good question.

Okay. I think I'm getting that we're done so, thanks everybody.

DR. MARKOVIC Okay.

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