

Managing Side Effects of Cancer Patients Treated With Immunotherapy

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INTRODUCER Welcome back everyone. Our next session is a topic that is at the top of our minds in our field, managing the side effects experienced by patients treated with immunotherapy. Please welcome our two wonderful speakers Ms. Brianna Hoffner of the University of Colorado Cancer Center, and Ms. Laura Zitella of Stanford Healthcare.

LAURA ZITELLA Thank you very much. Brianna and I are really excited to be here with you today. We have been speaking on immunotherapy quite often this year, and it is a topic we really enjoy, and we are happy to be able to share some of our experiences and some of the things that we have learned taking care of patients who are being treated with immunotherapy.

To get started, these are our learning objectives listed here for your review, but basically what we wanted to do was discuss the most common and uncommon side effects of immunotherapy, go through a few case studies, and answer some common clinical questions that we often get from other providers who are just starting to take care of patients being treated with immunotherapy. These are the disclosures.

We are going to start with a little pathophysiology. This is the cancer immuno-editing hypothesis. This hypothesis has been around for years. It has fallen out of favor and fallen back into favor, and now this is something that we

feel really holds true. What this hypothesis tells us is initially when cancer cells develop in the body, they have neoantigens, so novel antigens that allow the immune system to recognize them and destroy those cells. The immune system recognizes the tumor cells and no cancer is detectable, but unfortunately, what happens is that over time there is a lot of pressure on those tumor cells, and their whole goal is to survive. So the tumor cells stop expressing new antigens or develop other ways to evade detection by the immune system, and then you start seeing the growth of tumor cells that can evade the immune system, and that is the escape phase where now you have a clinically detectable cancer. The whole point of immunotherapy is to somehow reintroduce and reeducate the immune system in order to fight the cancer cells.

This slide depicts our immune checkpoint inhibitors, which are going to be the focus of our discussion today. This depicts the CTLA-4 pathway and the PD-1 pathway. These are pathways that are associated with tolerance. By inhibiting these pathways, we can remove tolerance, release the brakes on the immune system, and activate the immune system against those cancer cells. At the same time, if we activate the immune system so that you lose tolerance, sometimes normal cells, which should have tolerance to the immune system, suddenly become targets of the immune system. This is the focus of our discussion today. We want to talk to you about those immune-related adverse events when you lose tolerance to your normal tissue.

Checkpoint inhibitors are an exciting new category of drugs, and the reason is because they are nonspecific. These drugs are going to work for a wide

variety of tumor types because they are activating your own immune system to fight the cancer and are not specific against any certain disease. In fact, the diseases which were initially studied are ones that historically have been difficult to treat and not very responsive to chemotherapy or other treatments, like metastatic melanoma or metastatic renal cancer. It is really exciting that we have a new tool to treat some of these really difficult-to-treat metastatic diseases.

These are the FDA approvals. This slide Brianna and I have used for the past year, and we have revised it probably 15 times. We have seen so many new approvals this year, which has been extraordinarily exciting, but it has been really hard to keep the slide up to date, so we put the date on it every time we update it.

This is a picture I hope many of you are familiar with. This picture illustrates that any tissue in your body can be the target of the immune system. You can develop an autoimmune disorder in any tissue. Of course the most common are rash and itching, fevers, chills, diarrhea, and colitis. We are going to talk a little bit about the fact that most patients who are treated with immunotherapy are going to develop some adverse event, but it is usually mild to moderate, and of those, rash and diarrhea are really the most common. However, there are other side effects we need to know about so we can detect them early and intervene early for our patients. I have listed here hepatitis and endocrinopathies are relatively common, and then I have listed some rare ones. This list is growing, because as we have started more patients with immunotherapy we have recognized additional side effects. For example, just

this year in the *New England Journal of Medicine*, they reported on a case of fulminant myocarditis, and that is not something that was seen in the initial clinical trials, but it is something we now know can happen very rarely, but we need to be aware that it is possible.

This is the timing of immune-related adverse events. As you can imagine, it takes some time to engage the immune system and activate the immune system. For that reason, we don't necessarily see the side effects immediately. It would not happen a day or two after the drug usually. Usually it requires weeks. With single-agent immunotherapy, on average, the side effects occur about 4 to 10 weeks after the initiation of the drug. CTLA-4 inhibitors tend to have more severe side effects, and they tend to occur earlier. Likewise, combination immunotherapy, CTLA-4 inhibitors, and a PD-1 or PD-L1, is depicted here in this second graph where, with combination therapy, we are seeing more severe side effects and they are happening much earlier.

There is a lot of controversy on how we should screen our patients for side effects, and there really is no consensus. We have listed here some useful tests that you should obtain when treating a patient with immunotherapy, but we know there are many organizations that are working on coming up with consensus guidelines. This year the European Society for Medical Oncology released some consensus guidelines, and we are expecting later this year NCCN and ASCO are going to produce some guidelines.

The management approach to immune-related adverse events in a very simplified version is that for mild to moderate—meaning a grade 1 or 2 side

effect—you generally would treat with supportive care. For a severe side effect, a grade 3 or 4, you treat with steroids. Pretty simple, pretty straightforward. The only exception to this would be hypothyroidism or other endocrinopathies, where you may be able to treat the patient with hormone replacement and you don't necessarily need to use steroids. Endocrinopathies is something that is a little bit different. If you develop type 1 diabetes, you are not going to treat that with steroids; you need to treat that with insulin. That would be the exception to this rule, but otherwise it is generally pretty straightforward, supportive care for mild to moderate and steroids for severe.

This is the management approach for steroid-refractory disease. Fortunately, most of the side effects do respond to steroids, and it is very, very rare that it is steroid refractory. It is more frequent that as you taper the steroid, the symptom will occur and you need to reinitiate steroids. That happens a little more commonly, but it is pretty infrequent that the side effects are refractory to steroids. If they are, the two major drugs that are used are infliximab and mycophenolate mofetil, which are two other immunosuppressive agents. Infliximab is the one that is most used, with the exception of hepatitis, and it is hepatotoxic, so it should not be used for autoimmune hepatitis. You should use mycophenolate mofetil in that situation.

Then we often get the question about when we should reconsider starting immunotherapy. If you need to hold immunotherapy in response to a severe side effect of the immunotherapy, patients can be rechallenged. In general, our approach is that if the side effect resolves and the steroid dose is reduced to less

than 10 mg per day of prednisone, or the equivalent, and the patient is not on any other immunosuppressive drugs, then it is okay to restart the immunotherapy. Keep in mind what we have seen in our practice is that patients may continue to benefit from the immunotherapy long after you have discontinued it. So, if you discontinue the drug in response to an adverse event, but you have managed to activate the immune system, they may continue to have a clinical benefit in terms of tumor response even after you have stopped the drug. It is something to keep in mind, and to reassure the patient that it is okay that the drug is still on hold, because they may still be achieving some benefit from it. Again the exceptions to this are endocrinopathies. Endocrinopathies that are controlled by hormone replacement therapy do not require you to hold the drug, nor do they require the use of steroids.

One brief comment on the management of side effects and steroids, because this is something that is often overlooked. If patients are going to be on high-dose steroids, there is a risk of gastritis, and it is really helpful to use an H2 blocker for GI prophylaxis, like famotidine or ranitidine. Being on steroids, they can develop thrush, so good oral care with clotrimazole troches. Another important thing to remember that is often overlooked is that if a patient is on a dose of prednisone, more than 20 mg a day for more than 4 weeks, so if they are on a prolonged taper, they really need to have PCP prophylaxis against *Pneumocystis jirovecii* pneumonia. The most common prophylaxis is listed here, but there are other drugs that work as well like atovaquone or inhaled pentamidine, or dapsone, but this is the easiest approach.

Brianna is going to take over and lead us in our first case study of the day.

BRIANNA HOFFNER Yes, thank you. We are going to start with patient JL. JL is a 65-year-old male who is a nonsmoker. He was diagnosed with stage IV adenocarcinoma of the lung, and you can see here that he has several metastatic sites. On the right hand side of your screen, you can see his imaging there giving you a picture of his right infrahilar mass. We checked his molecular status, which we should do with all of our patients at this point. He was actually sort of pan-negative. There were no actionable mutations in those molecular testing results, and in addition, he was PD-L1 negative. His past medical history—we are going to come to that in just a second. What we are going to do is we are going to start him on pembrolizumab, carboplatin, and pemetrexed combination. This is one of the only areas where we have a first-line indication for the PD-1 without PD-L1 positivity. This patient was PD-L1 negative as we saw in the prior slide, but this therapy is approved in that setting.

As we think about starting him on a combination of chemotherapy and immunotherapy, we need to do a really good baseline history. He has a history of arthritis, and we know that we can see some arthralgias and myalgias with immunotherapy, so make sure you ask the patient what his symptoms are like at baseline, so we are not falsely attributing things to the immunotherapy as we go along. Another point here, with his hypothyroidism, we do get the question as to whether a preexisting thyroid condition will predispose patients to an endocrinopathy on therapy, and the answer to that question is not that we know of. We do have to give patients that bit of education.

JL was started on treatment. He got his first 4 cycles; tolerated it very well. No irAEs, and then he had scans done at week 12 that showed a 35% decrease in disease burden. He presents for cycle 5. At this point, he is on pembrolizumab only, because with this indication, they get the chemo and pembro combination for the first 4 cycles and then they go to the flat dosing of pembro at 200 mg every 3 weeks. However, he presents to this visit complaining of increased fatigue, urinary hesitancy, and dyspnea on exertion. Your differentials in a lung cancer patient with those symptoms are quite broad, so we get some labs, and there are a few things that are important here. First, if you are looking at his hemoglobin on 09/04, it was 9.1, and on 09/25 it is 7.8, so we have had a precipitous drop in hemoglobin. Then, when we look at his creatinine, we can see that it went from 1.1 to 4.0, so a significant increase there. For his TSH, it was not checked on 09/04. We don't check thyroid function tests at every time point. We only check those every 12 weeks. But you can see that on 09/25, it was within normal range. What do we have here? Always start by identifying what the issues are, grading them, and then you go from there. We have a grade 3 anemia, and this could be an anemia of chronic disease. This patient has a lot of chronic diseases, so is this related to his lung cancer, his thyroid dysfunction, or his kidney dysfunction? Or he could have an iron deficiency anemia secondary to blood loss or insufficient dietary iron. For the creatinine, he could have a nephritis related to immunotherapy; nephrotoxicity from the chemotherapy is certainly a possibility. Dehydration is something that we see in a lot of our patients that often complicates our clinical picture when we are trying to work up renal dysfunction.

Other drug injury—always remember to ask whether they started any other medications—and then his hypertension, which can certainly cause renal dysfunction. We need a little bit more information, so we added on a few labs to include the reticulocyte count and the iron studies. You can see here that his reticulocyte count is 0.9%. His MCV is 82, so it is within normal range. Then when we look at his iron studies, one thing you will often see when you look at iron studies is that the serum iron may be a little bit low. That is not reflective of the total body iron stores since much of your iron is stored in your red blood cells and in your liver in the form of ferritin, and you can see that his ferritin looks fine. So his iron studies are okay. The onus is on us to be able to interpret these labs appropriately.

Anemia. Looking at anemia in the setting of MCV and reticulocyte index, we have an algorithm here. We have a patient who had a hemoglobin of less than 13 as a male, a reticulocyte index of less than 2, his MCV was 82, so between 80 and 100, so this is a hypoproliferative normocytic anemia. There are a lot of causes for normocytic anemia you can see here. This does not give us the full answer, but when we look at the causes of normocytic anemia—anemia of chronic disease—blood loss, which is not likely in this patient, iron deficiency anemia—we looked at his iron labs and those looked good—bone marrow disorders, the rest of his CBC looked fine. There was nothing about his platelets or his white cells that would have indicated a bone marrow disorder. Bone marrow suppression drugs like chemotherapy, and then low levels of hormones such as EPO with chronic kidney disease, but he has an acute kidney injury,

thyroid hormone, but we know that his thyroid is replaced appropriately right now, or hypogonadism. So we believe that this hypoproliferative, normocytic anemia—since we have ruled out all those causes that we just discussed—is related to the chemotherapy. It is a hard thing because we don't necessarily absolutely know, but we have to do really good investigative work to come to the best answer possible. We do know that there was a 12.9% incidence of grade 3 anemia with carboplatin and pemetrexed, so this is a reasonable differential.

Coming back to that increased creatinine on the patient: you are generally never going to be lucky enough to have just one immune-related adverse event that you are dealing with on a patient. It is always multiple things. So we get some urine and we find that there is a FENa greater than 1% indicating a renal or a post-renal cause. The urine culture is negative; however, we do see new protein and a little bit of blood in the urine, as well as a few other abnormalities. When we think about nephritis, this is a rare side effect that occurs in just about 2% of patients, but the most typical clinical presentation is a rise in creatinine with mild proteinuria or pyuria. The median time to onset is 2 to 3 months with ipi, and 3 to 10 months with a PD-1 and PD-L1 drugs. Again, as holds true with everything, a little bit sooner if you combine those two agents. The majority of patients will recover renal function with steroids, but the recovery can take weeks.

Our conclusion here is that JL has a grade 3 anemia related to chemotherapy that will recover in time off of chemotherapy, and a grade 3 nephritis related to the pembrolizumab for which we will treat him with 1 mg/kg of

prednisone and check serial creatinines. His renal function recovered after 4 weeks and the steroids were tapered over 8 weeks. You don't want to taper too quickly because you can always get a rebound phenomenon. He was prophylaxed, as Laura had discussed on a previous slide, and then the pembrolizumab was actually discontinued for this patient. Interestingly, in the approval study for this indication, the acute kidney injury was the most common cause of discontinuation of pembrolizumab, which I thought was interesting given that nephritis was not entirely common.

Laura will now talk to us about HT.

LAURA ZITELLA HT is also someone who unfortunately has multiple side effects to her immunotherapy. She is a 62-year-old female diagnosed in 2016 with stage III colorectal cancer. She underwent surgical resection and adjuvant FOLFOX. Unfortunately, she developed liver metastasis, but it was a single met, so it was resected and rebiopsied and was shown to be MSI high. After the liver metastasis resection, she was treated with FOLFIRI plus bevacizumab and 10 months of maintenance bev plus 5-FU. Unfortunately, there was progressive disease in the liver and also new pulmonary nodules, and so she started nivolumab, fixed dosing, 240 mg IV over 60 minutes every 2 weeks. On week 5 she called the clinic and she was complaining of an itchy rash, so it was not very surprising. These are pictures of what the rash looked like, and then I also have a reminder here about how you grade a rash. Just like with burn patients, we use the rule of nines to estimate the body surface area. In this particular patient, the rash covered the chest and the upper arms. It was

considered about 10% to 30% of the BSA, so it was a grade 2. For grade 2 dermatitis, you don't necessarily need to start steroids unless her supportive care does not work. This patient was treated with supportive care measures and it wasn't effective, so we started prednisone 0.5 mg—a lower dose of prednisone, 0.5 mg/kg per day—and also hydroxyzine for pruritus. One of the things we have learned about pruritus, you probably all know, it is such a hard side effect to treat. And topical medications like topical diphenhydramine and Sarna lotion are really not effective, so you do need to have some systemic medication in order to manage pruritus, and hydroxyzine is a very good one. We delayed nivolumab until the rash resolved 1 week later, and then the prednisone was tapered over 4 weeks. It was restarted week 8 when the prednisone dose was 10 mg per day, and the rash had resolved—those were appropriate criteria for restarting the immunotherapy—and the steroids were discontinued week 9. Unfortunately, 3 weeks later, she presented again, and this time she had elevated liver function tests. This represented a grade 2 elevation in the ALT and the AST, and grade 1 elevation in the T bili. Of course, in a patient like this, part of your differential is the possibility of progressive liver metastasis. We always rule out infectious hepatitis too, but I have to say in my practice, I have never diagnosed an infectious hepatitis in this setting, but we always rule that out. This patient had stable liver mets, so we did not think that the elevation in the liver function tests was related to metastasis and made the diagnosis of autoimmune hepatitis. We held the immunotherapy and restarted the prednisone at a low dose, and the liver function tests normalized in 3 days. This is pretty typical in my experience.

Autoimmune hepatitis responds really well to steroids, and you will see a response pretty quickly. We rechecked the labs after 2 days of steroids, and you can see that the labs improved. The T bili normalized, and the AST and ALT went to a grade 1, so we started tapering the steroids about 10 to 20 mg per week and continued to monitor serial liver function tests. On week 15, the prednisone had been tapered down to 10, so again we restarted the immunotherapy, but she presented on week 20 with fatigue and cold intolerance, and so we checked a TSH and free T4, and her antithyroglobulin and antithyroid peroxidase antibodies were positive. These were consistent with an autoimmune hypothyroidism. In this situation, as I mentioned earlier, you don't necessarily need to hold the immunotherapy and you don't need to treat with steroids, but you do need to treat with thyroid hormone. This is usually a permanent, lifelong side effect, so they will need lifelong hormone replacement therapy. For that reason, usually in this situation—although we might initiate the thyroid hormone—we usually refer them back to their primary care provider or to an endocrine specialist so that it can be followed lifelong. In conclusion, this is a patient who unfortunately had three irAEs. They all were very easily managed with standard therapy for irAEs. She had a grade 2 dermatitis, a grade 2 hepatitis, a grade 2 hypothyroidism, and due to early recognition by the advanced practitioner and appropriate management, the patient was able to stay on therapy.

Brianna is going to talk to us about the other immune-related adverse events that we did not cover in our case studies.

BRIANNA HOFFNER We are going to go through a few highlights, starting with autoimmune hyperthyroidism. Certainly our patient had hypothyroidism, but it is important to remember that they can also become hyperthyroid. What the data has really shown us is oftentimes patients who we diagnosed with hypothyroidism have previously been hyperthyroid and we missed that time period. They go up and they burn out and they come down. If you catch them in that hyperthyroid time period, they can actually be quite sick depending on how significant it is. I have had patients that have presented in AFib RVR, thyroid storm, really looking sick; get your endocrine colleagues involved to help you with that. We find that the radioactive iodine uptake is not terribly accurate, especially if the patient has had a recent CT scan with contrast. You should check the labs that Laura just discussed with the antithyroglobulin and the antithyroid peroxidase, and this is generally self-limiting. The thyroid will burn out.

Hypophysitis is inflammation of the pituitary gland. We didn't talk too much about this before we started using these immunotherapeutic agents more in the last 5, 6, 7 years. The pituitary is small, located in the brain, and it is responsible for a lot of different hormones, ACTH, FSH, TSH, LH, prolactin, and cortisol. If you have a patient who presents with hypophysitis, you can see here some of the common symptoms, but I can tell you anecdotally that they can look really sick. On one of our very first immunotherapy trials, I had a patient who developed hypophysitis, and she came in, we had not yet seen it, and I admitted her for sepsis. She looked horrible. And then counterintuitively, we gave her steroids

and she was fine. Keep in mind that these patients can be sick. The workup would involve evaluation of all the hormones that are released by the pituitary gland. You can get an MRI with pituitary cuts to see whether there is any inflammation there, and you can see the pre- and post-imaging on the slide. The treatment is high-dose steroids for critical illness, and then replacing the hormones that have been knocked out.

Diarrhea or colitis; we talk a lot about this. Just to give you a few highlights here that I would like to point out: the idea that it is possible to have colitis without diarrhea; I think that we didn't fully realize or appreciate. It's those very rare cases where you have a patient who has C diff and doesn't have diarrhea and it just doesn't make sense; we can see that here as well. In your workup, always rule out infectious causes. You can get a CT scan of the abdomen. You can see that white area is the thickening of the bowel, the dark part is the inside of the bowel, and so that is characteristic of colitis. We have looked at studies with budesonide to see if giving budesonide could prevent this from occurring. Those phase 2 studies were negative. That did not seem to help. However, there may be a role for budesonide in the treatment. That's an evolving story with more to come. Then, if you have diarrhea or colitis with one checkpoint inhibitor, it does not mean you cannot get another. If you have a patient who had a grade 3 colitis on ipilimumab, that doesn't mean that they can't get a PD-1 inhibitor.

Pneumonitis, this is just inflammation of the lining of the lungs, and it occurs not terribly frequently, but 1% to 2% of patients treated with PD-1 and/or CTLA-4. We saw that the time to onset interestingly was a bit earlier with nivo

versus pembro symptoms. These are the common symptoms. I've had patients who come in completely asymptomatic.; they look fabulous. At the scan time point, you look at their imaging and it is a rip-roaring pneumonitis. I have others who have come in sick with a cough, sometimes fever, looking like something is wrong. Again, make sure it is not an infectious cause; do the appropriate workup. The slide that Laura showed you about the baseline testing you should do for patients on immunotherapy—one of the things that was included there was a chest x-ray. The reason that we recommend that is because if your patient develops respiratory symptoms, it is much easier to get a chest x-ray versus a chest CT in the moment. And if you have a baseline to compare to, that's going to be enormously helpful to you in making a good diagnosis. You have got to diagnose early, because if you let it go too long, it can lead to irreversible lung disease.

Other irAEs: diabetes mellitus. This is not great when it happens. You probably won't miss it when it happens. Usually, they present in DKA. The GAD65 antibodies is something that we have recently identified as a test that we can send to differentiate the case. GAD65 antibodies would be positive in autoimmune diabetes. Treatment is with insulin therapy; again, get your endocrine team involved early. My experience: I have had a few patients develop this, and they have been really brittle diabetics, and they have all needed insulin pumps. So you are going to need some help there. Or mucosa; we forget about that. We are really good with the education with chemotherapy, but immunotherapy not as much. So you can get a whole host of different issues.

And if you have a patient who has head and neck cancer who is on immunotherapy who presents with dry mouth, your ability to differentiate whether the dry mouth is related to their prior chemotherapy, radiation therapy, and surgery, versus their current immunotherapy, is really hard. So what are your tools? That's the question we all need to ask ourselves and be aware of. Your tools here are things like an ANA, SSA/SSB screen—Sjogren's syndrome A and Sjogren's syndrome B antibodies. Know the tests that you need to do to make the right diagnosis.

Pancreatic: we can see pancreatitis, but we also have seen a lot of asymptomatic elevation in amylase and lipase. We are not sure how to interpret that at this time. A lot of our clinical trials require that we test it every time point, and these labs come back very elevated, and the patient feels fine and their imaging is okay, and then you're sort of in a pickle of what to do. So that is really an evolving story.

Neurologic side effects: patients can get neuropathies with immunotherapies. Again, I think that we forget that. We really have put that into the chemotherapy box, but it can happen on immunotherapy, so make sure you are asking those questions in your review of systems.

And then the really severe things: the myasthenia gravis and the Guillain-Barre syndrome, those are really horrific. I have had a couple of Guillain-Barre syndrome patients. They have been very difficult to manage. Steroids have not been sufficient; we have had to give IVIG and some other treatment modalities. So that is, again, a situation when you are relying on your specialty services.

Arthritis and arthralgia: we have reported that in about 5% of patients. I wonder if we underreport that a little bit. I have found that it seems to be more common in my experience. This is something that you can manage really well on low-dose steroids. 10 mg or even 5 mg of prednisone daily can make a huge difference for those joint aches and pains, and it does not affect the efficacy of their immunotherapy. Please keep that in mind as a management tool.

Hematologic toxicities: we touched on that in the case study. This is an area that is going to become more and more difficult for us as we are combining immunotherapy with so many different chemotherapies. We have trials looking at FOLFOX plus immunotherapy. We already have an approval along with the chemo plus IO, so we need to know how to work up anemia and try to figure out whether it is autoimmune versus related to chemo.

A few emerging reports, Laura mentioned the myocarditis patients; this was published in the *New England Journal of Medicine* in 2016. This was two patients, they were both on combination with PD-1 and CTLA-4. Interesting things about these cases: number one, it occurred for both of them after the first dose, and number two is that they didn't have any sort of characteristics that we know of that would have predisposed them. They both had a little bit of hypertension, but no other cardiac history. That is a really interesting area; obviously, we are talking about it a lot, and more to come on that. On the right-hand side, this is from the *Journal of Immunotherapy of Cancer* from 2017. It is a fascinating article about a lung cancer patient who is treated with PD-1. On imaging, it looked like he had developed new brain mets, so they radiated him.

It still progressed. They took him off trial, resected the brain mets, and actually there was no evidence at all of disease. It was cerebral vasculitis secondary to the PD-1. If you have free time and you want to look at that article, the imaging is really cool, but it's just one of those moments when you are like, "My gosh, anything is possible." We have got to remember that when we take care of these patients.

If they develop an immune-related adverse event, does that mean anything about their overall survival? For those of you who work in lung cancer, you know that with the EGFR TKI drugs, when they develop a rash we tell them, "I know you are uncomfortable, but this is a good sign." And so, we want to have that in immunotherapy. We are not quite there yet. We have a few trials. We have this Moffitt Cancer study of 148 patients treated with nivo plus or minus vaccine. We saw that there is a significant overall survival benefit with rash or vitiligo. No difference with endocrinopathies, colitis, or pneumonitis in that study. Then there is a Mass General study of 154 patients on ipilimumab, which showed a statistically significant overall survival in patients with hypophysitis. There have also been reports of higher response rates in patients who have an immune-related adverse event with nivo given for advanced melanoma. So we are trying, we are gathering the data, we are doing these studies. We don't have the answers for your patients, but you can tell them that this is on its way. In terms of patient education, this is something that we work so hard on, and there are so many resources out there that are fabulous. We could have done an entire talk on that, and we did talk about it, but this is one of the more recent things that

have come out: the NCCN immunotherapy teaching tool. This gives you some side effects monitoring tools, patient checklists, and toxicity information. There is information for providers as well. I would encourage you to go to the website, check it out, and see if there is any piece of it that looks helpful for you.

Moving on to our quality of life, disease response, and patient section of our talk. Quality of life: Laura has humored me in putting this in the talk today, because I think it is really important and, again, an area of emerging interest. Any of you who work in research know that when we have patients on clinical trials, they are always getting those little tablets to do those surveys. The coordinators bring those to do them in the room—the quality of life surveys—and they are like “Where does this information go?” It feels like you never see it again. CheckMate 141 was the study of nivo versus single-agent therapy of investigator’s choice in metastatic head and neck squamous cell carcinoma. We used the EORTC questionnaires there, which is our standardized validated questionnaire that we often use for any sort of quality of life work. What we found was that there were improved or stable quality of life scores following treatment with single-agent nivolumab as compared to chemotherapy. There is also a study of adjuvant ipilimumab in melanoma, and I don’t know how many of you have ever given the 10 mg/kg dose of ipi, but that’s a tough one. In this study, treatment was discontinued in 50% of patients due to drug-related adverse events, and yet our quality of life questionnaires show that there was similar quality of life between the ipi and the placebo groups, so that really doesn’t make any sense, right? This is looking at pembrolizumab and melanoma. This is KEYNOTE-002, and the top,

the blue circles, this is without disease progression. The dotted vertical line is their baseline there, and then the red squares are with disease progression. What you can see here that is important is that patients who had disease progression who were on chemotherapy had a clinically significant decline from baseline versus those that were on pembrolizumab did not have a clinically significant decline. They went down a little bit, but it was not significant in this study. What we see there is the idea that this therapy can afford a good quality of life, and maintain a good quality of life, even in cases where it is not necessarily effective against the disease. Are we answering the question? We are not sure. The validated tools that we have used and always used may not be asking the right questions. In the head and neck study, for example, CheckMate 141, they did not ask any questions about rash or itching. We told you at the beginning of our talk that is one of the most common things that we see with immunotherapies. If they had asked those questions, would our results have been different? I am not sure, but I think that we are going to need to look at different tools and different modalities to evaluate quality of life. A lot more research is needed in this setting to understand what this means for our patients.

LAURA ZITELLA We are going to move from the side effects profile to talk a little bit about the response to immunotherapy and how we educate our patients about what to expect about response and then answer some common questions.

The responses to immune checkpoint inhibitors are different from chemotherapy, and the reason that they are different is because you are using

the immune system. And in order to have an effective tumor response, you have to engage the immune system, and that takes time. We know that the median time to response is 8 to 12 weeks. It's really important to try to refrain from imaging your patients too soon, and we recommend that we image patients at an interval of 12 weeks. The reason is, if you image too soon, you might not see a response, and that makes the interval scan worrisome to the patient, and you don't know how to interpret it, and you will probably go ahead and continue therapy anyway. So we are trying not to image quite as often with patients who are on immunotherapies. The pattern of response is really different. We are talking about a group of patients with widely advanced cancer, very metastatic, few treatment options, and our goal is control, quality of life, and clinical benefit. With immune checkpoint inhibitors, what we see sometimes is that patients will just have stable disease for a long period of time, and that may be your best clinical response. Or you will have stable disease for a really long period of time, and then you will see a response. Or you see an initial response, and then all of a sudden it plateaus and it is controlled for a long period of time. You can also see initial progressive disease because the tumor will grow a little bit in the time that it takes to engage the immune system to start fighting the tumor. Then lastly, there is this concept of pseudoprogression. This is the one that is the most difficult to interpret. You can only prove pseudoprogression in retrospect. Pseudoprogression is a term that refers to when you get imaging and it looks like the patient has had mild progression, but actually the increased size of the tumor isn't from the tumor; it's from the T-cell infiltrate, so there is actually immune

activation. The checkpoint inhibitors are working. It looks like progression, but it is not. The tumor is smaller, but it looks larger because of that T-cell infiltrate. For this reason, if you get a scan and there is progression, often clinicians will continue to treat as long as the patient is having clinical benefit. You have to repeat the scans 4 weeks later in order to prove that it's truly progression, unless it is widely progressive and they are not doing well and you need to change therapy. Disease progression in general should be confirmed with a repeat scan 4 weeks later.

Then there is some data that was published recently looking at the studies that were done, and in some of these studies, patients were treated beyond progression in the study for some reason. They looked at a subset of patients. The example I put here was the CheckMate 025 study that looked at renal cell carcinoma patients treated with nivolumab. About half of them who had progressive disease were treated beyond progression, and of the patients that were treated beyond progression compared to the ones that weren't, you can see here the median overall survival was 28 months versus 15 months. That's almost double. There is a signal that is emerging from the literature that patients may have benefit if they are treated beyond progression. This makes it really difficult and challenging for us as clinicians to understand how long to continue this therapy because on the one hand, we don't want to continue futile therapy in patients, but on the other hand, if patients are having a clinical benefit, then treating beyond progression does make sense and many clinicians will continue to do that as long as the patient is doing well.

The other big question is whether or not patients with preexisting autoimmune disorders can be candidates for immunotherapy. We didn't know the answer to this question because in the clinical trials, anyone who had a preexisting autoimmune disease was excluded from the trial. Now there has been some data looking at patients with preexisting autoimmune disease, and it suggests that they can be safely treated. The group of patients in the study actually had very active autoimmune disease. You can see here they were actually on treatment for their autoimmune disease. So in this group of patients that had a very high risk of having adverse events, about 30% to 40% developed a de novo—so unrelated to their autoimmune disease—immune-related adverse effect. About 30% to 40% had an exacerbation of their preexisting autoimmune disease, almost half had no autoimmune disease flares or immune-related adverse events, and about 20% to 30% had an objective response. In all of these patients who either had a flare of their disease or an immune-related adverse event, they were able to be managed with the appropriate treatment. This is really reassuring data for those of us that are interested in treating patients who have a preexisting autoimmune disorder.

Some other common questions that were asked were “What should I do if the prednisone is not effective?” Steroids are the mainstay of immune-related adverse events, so the first thing we would ask is, “Is it adequately dosed?” Maybe you need to go up on the dose. Maybe they are on 0.5 mg/kg and they need to go to 1 mg/kg or 2 mg/kg. Then if you've tried that and still no effect, then many of these patients are sick enough to require hospitalization, and infliximab

and mycophenolate mofetil are the two agents that are most commonly used for steroid-refractory immune-related adverse events, except for hepatitis where you don't use infliximab. Then we are often asked, "Should we premedicate the infusions with steroids?" And this is really not recommended. The incidents of infusion reactions is actually pretty low with immune checkpoint inhibitors, even though they are monoclonal antibodies. They are engineered differently, so the infusion rate is very low, and we don't recommend routinely premedicating. "Should we modify doses?" This is another area where immunotherapy is really different from chemotherapy. When patients have side effects with chemotherapy, we might continue the chemo and dose reduce them 20%, so this is never done with immunotherapy. You never dose reduce. If they are having side effects, you have to either hold the drug until the side effects resolve or discontinue it completely. You always give full dose; you never give modified doses. The most important question—and this comes up most often with patients—is, "If I am treated with steroids for an immune-related adverse event, is it counteracting the effect of my immunotherapy?" There is data that looks at a group of patients that had an adverse effect to immunotherapy, treated with steroids, and those that didn't, and they had the same rate of response, the same overall survival. At this point, we do not feel that steroids limit the effectiveness. It is really important to initiate steroids early when you need to because the immune activation does not turn off, and the side effect can get really severe if you don't try to bring the immune system back down to an acceptable level with the steroids.

Future directions: there are over 3,000 ongoing immunotherapy trials. This particular area, as you all know, has revolutionized cancer, especially in the past couple of years. We just had two approvals this year for CAR T-cell therapy. We have many, many new monoclonal antibodies, so it is a really exciting area of research. We continue to look at new targets. We are looking at combination therapy, so can you combine immunotherapies? Can you combine immunotherapy with chemotherapy? And if you do, how should they be sequenced? How long should patients be on these drugs? If they are working, do you continue it lifelong in a patient that has metastatic disease? When can you stop? There are a lot of questions to be answered. The major research questions we think are what is the immune response doing that leads to tumor rejection? And what is the immune response doing that it stops rejecting the tumor and it starts growing again? If we can understand those questions, then we can target our therapies based on the mechanism of action. There is a lot of basic science that's also being done in these areas as well.

James Allison is pictured here, and he is an immunotherapy pioneer that discovered CTLA-4, and as in his words, we still have unfinished business with cancer.

Thank you so much for your attention today. We would be very happy to take any questions.

QUESTIONER I have a question. What is your tolerance for transient rise of hyperglycemia? And how do you treat a diabetic when you have to put him on steroids for hyperglycemia?

BRIANNA HOFFNER Great, great question. This is another time when I make sure I am working very closely with my endocrine colleagues. When we are putting someone on steroids, we usually have to adjust their insulin and so I do ask endocrine [specialists] how they would like me to do that. In terms of what I would tolerate for a rise, for a fasting glucose, any time we are getting up into the 200s, I start getting a little bit nervous. As we mentioned, the type 1 diabetes that occurs with the immune checkpoint inhibitors that we have see so far is often they come in DKA, so it is pretty profound. But if they are starting to have a rise, I would check them more frequently. You can use the GAD65 antibody test to help differentiate, as well, if you believe this is evolving immune-related diabetes.

LAURA ZITELLA If you don't think it is immune-related diabetes and you are just administering steroids to someone who has preexisting diabetes, I agree with Brianna, my threshold is 200. Anything over 200 I think you should treat, and then it depends on the patient. I personally will try to treat with oral hypoglycemics first, and if we can't achieve control, then we will go to insulin therapy. But I also work really closely with our endocrine specialists to help manage the patient long term. This is something that is really common. I'm glad that you brought up that question because diabetes is so prevalent, and it's something that, in your clinical practice, you are probably seeing a lot among patients who are on steroids.

QUESTIONER I have a question for you. First of all, thank you so much for your presentation. That was really good information. My first question

is, you mentioned that after a CT scan that thyroid function may be inaccurate. How long after a CT scan should you wait?

BRIANNA HOFFNER Great question. Funny you ask it because we were asking each other that question before we came up here. Yes. It's not the thyroid function; it's the radioactive uptake test that you can use to evaluate the thyroid. That test becomes inaccurate when they have the contrast from a CT scan in their system. It's not that the CT scan actually affects the thyroid function. But I don't know what that interval is that you have to do between contrast dye and the radioactive uptake.

LAURA ZITELLA But it is so unusual to do a thyroid scan, so you are probably not going to be getting a thyroid uptake scan. If you're just asking about checking a serum, TSH and T4, CT scans don't affect that, so you can check the serum, TSH and T4.

QUESTIONER My second question is, the type 1 diabetes, is that reversible or not?

BRIANNA HOFFNER I have never seen it reversed.

LAURA ZITELLA The endocrinopathies generally don't reverse.

QUESTIONER Since its irreversible, do you stop the immunotherapy or do you continue? I mean, they already got it.

LAURA ZITELLA Yes, the damage is done, so I think it's a clinical decision based on the other options the patient might have and how they were doing in terms of their disease response on the immunotherapy. Often times we do discontinue because it's hard. Like I said, the patients that I've had who have

developed this have been brittle diabetics. They have been on pumps, and trying to get things managed has been a difficult thing, so we have discontinued for that reason in many of these patients. But I don't think that we have a hard-and-fast rule at this time.

QUESTIONER In the patients who had pseudoprogression in the early studies, was there any difference on the imaging on PET scans versus CT scans, as far as the pseudoprogression?

LAURA ZITELLA No, because as you know, the PET scan, the way that it works is there is a radioactive isotope attached to glucose, and so glucose is taken up by any highly metabolic cell. If you have inflammation, its taken up; if you have malignancy, its taken up. So that didn't help differentiate. But that's an excellent question, thank you.

QUESTIONER I do have a question in regards to the myasthenia gravis. We have seen that in our practice, and it was a kind of insidious onset. This was a young woman in her 40s with melanoma that only had one dose of high-dose ipi and started out with GI disturbance. We had to try to manage that, and she was not steroid responsive, so then it was Remicade. And for months she continued to have reactivation of her symptoms. And then all of a sudden started complaining of blurry vision, and then called up and she couldn't speak. She had such dysarthria, like cranial nerve 12 dysfunction. So she saw neurology, and they started her on Mestinon, which did absolutely nothing. I am curious, in your practice, with these people—you said you've had a couple with myasthenia gravis—and this is long after the therapy was given, what your

experience was in management, because she still continued to struggle. Now she is being given rituximab.

LAURA ZITELLA That's really interesting. I could have given you the exact same story for my patient. We followed the same progression. I have had two patients actually. In addition, we give the IVIG; I'm sure you've done that as well. One of them got a little bit better for a period of time, and then concurrently he got much worse. He started having visual disturbances, and his melanoma exploded. Then the other patient we got him to a stable state where he was quite debilitated but functional, and then he stayed there. We never got him back to baseline.

QUESTIONER It's really important, now that we are seeing this, these symptoms just don't go away. They keep coming back and that's what, with the immunotherapy, we are learning going forward. We just didn't know this going into it and now we are seeing this long term.

LAURA ZITELLA Yes, absolutely. Thank you.

QUESTIONER Thanks for a wonderful talk. My question is what has been your experience with managing vaccines like flu shots, and others, pneumonia, that kind of thing?

LAURA ZITELLA I'm giving them. That's an excellent question. Usually vaccines require B-cell response in order to exert its effect, and so far we haven't seen any issues. I don't know of any data to guide us there, but we are giving vaccines freely.

BRIANNA HOFFNER We are giving the vaccines as well. They are not live vaccines; the flu shot, for example, is not live. They had that nasal mist until this year, and that one was actually contraindicated, but with the flu shot it has been fine. Most of the protocols originally were written in such a way that we could not give those vaccines, and they have mostly been amended to allow them. So I think that's becoming more of our standard of practice.

LAURA ZITELLA Thank you again for your attention; we really appreciate it. I hope you have a great rest of the conference.

BRIANNA HOFFNER Thank you.

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