Beth Eaby-Sandy: I have to tell you, Marianne is absolutely, in my opinion, the national leading expert in this. She was the only nurse on the NCCN guideline IO toxicity panel. She was the only nurse representative. She is absolutely the expert on this, so I think if you have any questions or cases ... Because we're short on time, what we may do is save any case studies, write them down if you have any, we may save them for our panel discussion at the end of today. She could talk forever about it, so we're going to try to keep it to a half an hour.

Marianne Davies: But I'm not allowed to, so ... Thank you, Beth, for that introduction. I really, really am passionate about the management of toxicities for immunotherapy. And so, we're going to go right through those. You've seen them a million times. We're going to talk about strategies to mitigate. We do have a first question. The strongest data to correlate immune-related adverse events with survival advantage is, in patients with non-small cell lung cancer receiving nivolumab and non-small cell lung cancer receiving pembrolizumab, in patients with melanoma, who experienced pneumonitis, but not skin rash, or patients with melanoma who experienced colitis, but not skin rash, and then unsure.

It's not letting me click. Sorry. Is everybody done?

Beth Eaby-Sandy: You have to wait for the music to be done.

Marianne Davies: Oh, I have to wait for the music. All right. We're across the board, and so we're going to be answering that question for you, hopefully, as we go along. All right. Next question.

Beth Eaby-Sandy: A patient with small cell lung cancer is receiving the combo of ipilimumab and nivolumab in the second line setting, after failure of platinum-based chemotherapy in the first-line setting. She develops worsening diarrhea with mucus in her stools and significant abdominal pain. IV steroids do not improve her symptoms and she's admitted to the hospital for IV hydration and symptom management. She's given a dose of infliximab and finally improves. She is labeled as having a grade three colitis, requiring one dose of infliximab. According to the NCCN guidelines, you should: Permanently discontinue the immunotherapy, consider restarting the PD-1 inhibitor, but not the anti CTLA-4 drug once the symptoms resolve, consider restarting both the PD-1 inhibitor and the anti CTLA-4 drug once symptoms resolve, consider restarting both the PD-1 inhibitor and the anti CTLA-4 drug, but only after a long steroid taper and all symptoms have resolved. Or, you're unsure.

Sounds like a boards question.

Marianne Davies: All right. Everybody voted? Okay. All right.

Beth Eaby-Sandy: All right.

Marianne Davies: Great.

Beth Eaby-Sandy: Yeah.

Marianne Davies: This is certainly an area of ongoing discussion at the NCCN meetings. We meet every six months and update everything. This is certainly something we discuss quite a bit. Going back to what we discussed before, do immune-related adverse events correlate with response to treatment? In the

melanoma arena, we did see that skin toxicities actually did respond, correlate with response. However, none of the other toxicities. Colitis, pneumonitis did not in the melanoma population.

We see some data in non-small cell lung cancer that really does support that if you develop an irAE, imAE, that it does show response to immune checkpoint inhibitors, and there are at least three studies that have really looked at this, that have demonstrated significant improvement and overall survival in patients that develop an immune-related adverse event. Really exciting. We're also seeing the same benefit in head and neck. Because these approvals are coming through for so many other diseases, we don't have enough data yet, but there's a lot of retrospective analysis being looked at across tumor types to really see who benefits best.

The most common irAEs, particularly in the lung population, are pneumonitis, colitis, dermatitis, hepatitis, nephritis, the endocrinopathies, and then there are some others. We're just going to highlight a few here today. She told me not to talk fast, but this is where I have to talk fast, because we're running out of time.

Beth Eaby-Sandy: We're okay. We're not that bad yet.

Marianne Davies: In general, the management, this is a very basic algorithm for how we manage immune toxicities. In general, grade one, those are mild toxicities that you might see in either laboratory abnormalities or maybe diagnostic imaging, patients tend to be non-symptomatic. The treatment is really more supportive therapy, increased monitoring. If the patient has worsening toxicity, not resolving, then you begin to ... You up regulate your management strategy, so you treat them as a grade two, or grade three or four.

In general, grade two are mild symptoms, maybe very mild influence on ADLs. You might consider delaying treatments. Consider corticosteroids at the lower dose of 0.5 to 1 milligram per kilogram per day. If symptoms persist for more than five to seven days ... I want you to keep that in mind, the five to seven days. Then, you're going to increase, escalate your management for these patients. If it doesn't resolve in five to seven days, or if it's worsening, you treat as a grade three to four. In general for grade two, you can resume your immune checkpoint inhibition if you have decreased to a grade one or less.

In general, across the toxicities, grade three or four, you're going to permanently discontinue the immune checkpoint inhibition, except for the endocrinopathies of the skin, and also there's a little variation too, with colitis, that we'll talk about. You escalate your steroids. It's going to be 1 to 2 mgs per kg per day. Consider hospitalization. In all cases of steroids ... These are not methylprednisolone dose packs, you're going to start at your higher dose, and then you're going to taper over a minimum of at least four weeks. We do know that there are other ... Particularly hepatitis and pulmonary, which oftentimes will require longer taper, six to eight weeks in some cases. You can just expect for those toxicities to need a longer taper. If a patient does have resistance, or they're refractory to the steroids, then you can consider a secondary alternative immunosuppressive agent, such as infliximab, depending on the toxicity.

This was a retrospective analysis that my colleague Emily Duffield and I did, where we really looked at what is the onset of the toxicity by sight. Dermatologic, GI, endocrine, I'm not going to go into all of these.

Beth Eaby-Sandy: Remember, you can zoom in on your iPads, if you want to look closer at one or another.

Marianne Davies: You can zoom in. The point of this is that some of the toxicities can occur as early as the first day, second day. They can occur after many, many months of therapy, even after the discontinuation of the therapy. There's been reports of up to a year after completion of immune checkpoint inhibition, where some toxicities have occurred. In general, when we look at the median onset across them, it's about at the three month mark that we see most of the toxicities. Again, that's a generalization, but you can zoom in on that. The point is, You need to be aware of these toxicities at any point of therapy, even after the discontinuation of the therapy.

Our first case that we're going to start with is pneumonitis. We have the CTCAE criteria on the top to help guide you. If you don't have it already as a downloadable app, then I would suggest that you do that because this is really what guides any of the guidelines that we use. Whether it's the NCCN guidelines, ASCO, ESMO, everybody uses this as a grading criteria. We're going to use case studies to really describe this.

This particular patient, 71 year old female, locally advanced non-small cell lung cancer. She was on a radiation oncology study, just to keep that in mind. She was getting pembrolizumab after her radiation. Okay? Her last dose when she comes into you, it was on the 27th of August. She comes in, has a CT scan prior to your visit with her, so on September 13th, which does show that she's got interval development of large areas of ground glass opacity. The reason we've got two scans ... Two images here. This is a little bit higher up in the lungs. If you zoom in on this, you will see that the patient has got some ground glass opacities, really speaking to point number three here.

When you go down lower in the scan, you can see this other hazy area. That's the area that the patient had radiation to. Okay? It's really important to know where was the area of radiation for a patient, to help you distinguish where there's a new area of ground glass opacity to help you rule out or rule in pneumonitis. It's really important to look at this area of the upper scan here for this patient.

Beth Eaby-Sandy: I think there's always a lot of question of what's radiation pneumonitis and what's pneumonitis from the immunotherapy. I think this case really delineated that well. She was due for her last treatment on study on the 13th. We're going to talk a little bit about her case, but as you can see, this is by no means in her radiation portal. Her radiation portal would have been like this. That radiation damage looks very different from these GGOs right here that have appeared, those ground glass opacities that have appeared on her CAT scan in the opposite lung that was radiated.

I think it was pretty clear to us that this was likely a result of the drug, but we'll keep going with her case study. You'll see what happened.

Marianne Davies: Again, she's got significance on her CT scan. In retrospect, there may have been some haziness on a prior scan, but this patient was non-symptomatic when they came in. If I go back, if I can, well ... That's all right. We'll keep going forward. Non-symptomatic. That really puts her at a grade one. She has diagnostic changes only. I'm going to, just for interest of time, answer some of these questions.

Beth Eaby-Sandy: Mm-hmm (affirmative).

Marianne Davies: Based on NCCN guidelines, how would we manage this? Well, we're going to take an opportunity to look at the difference between NCCN and ASCO guidelines in particular, because that might be helpful for you, in terms of how you're managing your patients. When we look at the rates of pneumonitis by package insert, these are across all diseases. This is what's reported collectively. You can see that it's a low percentage of patients of any grade, but we do also know, through clinical trials, that these can progress very rapidly if they're left unmanaged. It is important to certainly be reporting.

2.5 for atezolizumab, the highest rate is the combination of the ipilimumab and the nivolumab at 6%, and particularly of interest is the higher dose of the ipilimumab. Dosing does matter. This is, again, I said across tumor types. However, in non-small cell lung cancer, if you pull out that cohort, they demonstrate higher levels of pneumonitis of, say, the melanoma population, renal cell carcinoma population, and upwards as high as 13%, or a little bit higher than that across our patients in particular, at high risk, and a higher rate, also. Over 4% of patients that are going to have a grade three or four. You need to be more in tune. The patients in non-small cell lung cancer also, which isn't on the slide, is that these patients tend to decompensate much more rapidly than patients with other diagnoses as well, because their compromised pulmonary status.

If we take a look at the NCCN guidelines, by grade one, it's only diagnostic criteria. It suggests considering holding the immune checkpoint therapy, and then reassessing in one to two weeks. What's really important is to assess your patient's pulse oximetry at resting and with ambulation. Before they even start therapy, you should know what their exercise tolerance is, how far they can walk, what their oxygen capacity is. For grade one, we can consider holding but if they had resolution of symptoms, then you could consider going on.

For grade two, where they're more symptomatic, they've got some subtle symptoms and influence on their ADLs, you would hold the immunotherapy in all cases of immune checkpoint therapy. You want to rule out other causes, because in most cases, they're diagnosed with some exclusion. You want to rule out any infectious cause and consider doing an infectious workup if there is an indication for that, and then consult with your pulmonologist and also your infectious disease folks.

Things I want to point out to you is that if a patient does have a more progressive pneumonitis, you want to be assessing them every few days. Monitor every three to seven days. If your intervention is not impacting that patient, you want to escalate your intervention for that patient. I'm not sure how many folks are bringing in their patients every three to seven days, but it is highly recommended, based on many discussions, certainly at the NCCN, and many reports of patient visits to the emergency room, as well.

Again, if no improvement in 48 to 72 hours on steroid therapy, it's recommended that you escalate to grade three management. For these patients, the dosing is methylprednisolone, 1 to 2 milligrams per kilogram per day, and consideration of adding an antibiotic as well, if you're iffy about whether they have an infection, as well.

For grade three to four toxicity, it's permanently discontinued. The immune checkpoint inhibition, same monitoring consideration we talked about. If they're not responding to the immunosuppressant at 1 to 2 milligrams per kilogram, you can consider increasing the dose to 2 to 4, but there's not a lot of data to support that. There is more data that actually supports adding another immunosuppressant agent, such as infliximab. I would suggest, if you think that a patient is at high risk for progressing, put the order in for the infliximab right away, because it often can take a couple of days

to get it approved by insurance companies. If you at least get it approved, you've got it in your bag that you can start to use that if you need to, knowing that these patients can escalate very quickly.

Other considerations are perhaps mycophenolate and also IVIg can be used as an additional immunosuppressant. In most guidelines, we are going to continue the steroid dosing, even though we're adding the secondary immunosuppressant agent, and only when that patient starts to respond, do you begin to wean off the steroids and the immunosuppressant agents.

This is a slight difference, the ASCO guidelines. What I'm going to highlight for you here is that they are saying to, again, hold the immune checkpoint therapy at grade one. The other, NCCN, says consider holding it. ASCO's saying no, we definitely want you to hold it at grade one. Other than that, the guidelines are very similar. I will say that NCCN and ASCO worked very, very closely together on these guidelines, and we also ... They were released on the same day because they wanted the messaging to be very clear across for all providers.

The other thing ASCO adds is that a percentage of lung parenchyma that's involved in the pneumonitis. One is more based on symptoms. ASCO includes that percentage of lung parenchyma. Less than 25% is grade one. 25 to 50% of the lung is grade two, and more than 50% of the lung is a consideration for grade three. You need to use symptoms, as well as your objective data, when you're doing the grading here.

This patient, her last dose was held. The decision was made to hold.

Beth Eaby-Sandy: Right. I didn't feel comfortable on the 13th of September, looking at that scan, even though she had no symptoms. I could not believe she didn't have any shortness of breath. I just said I don't think we should give you one more dose of this. I'm afraid of what could happen.

Marianne Davies: Right.

Beth Eaby-Sandy: Lo and behold, look how much worse that is.

Marianne Davies: Fortunately, Beth ordered a follow up scan at that one month interval, which is part of the guidelines. You can see, despite ... She now had some symptoms, though. You can see the worsening when you look at the GGOs now in that left lung, and you can also see that it's even further down into the lower part of the lung. Started on steroids, so I started on-

Beth Eaby-Sandy: She did not start on steroids, obviously, on September 13th because she was grade one and we don't ... When they're not symptomatic, we don't give steroids. Without steroids and without more immunotherapy, it clearly got worse. These things are not going to get better on their own, generally.

Marianne Davies: In general. This patient was started on her steroids. Because she was hemodynamically stable, it was oral. 60 milligrams of the slow taper, decreasing by 10 milligrams every five days. Again, she had improvement in her symptoms. It was discussed at tumor board, and really felt that it was ... A bronch was not needed. Occasionally, a bronchoscopy might be recommended, if you're really not completely clear on the ideology, if you think there's an infectious component, or perhaps

lymphangitic spread of disease, but it's not mandated for all of our patients. Because of this, the patient's going to start on her steroids and should get another scan in a month.

This is ... Just to highlight that not all immune check therapies have the same level of the pneumonitis. This was brought up in the previous lecture, but you can see the patient's ... The specific study that got durvalumab had higher rates of the pneumonitis that were reported than the others. Know that those patients are going to be at higher risk.

Pearls for managing of pneumonitis, they need a CT scan to evaluate for the pneumonitis. Baseline pulse oximetry at rest and ambulation is critically important. For us, as providers, it's the cheapest thing to do and you can monitor that serial over time. Shortness of breath, dry cough, hypoxia. Patients might have other symptoms, but those are the classics. Manage with high dose prednisone and then you go from there if you need to add an additional immunosuppressant agent. Close, close follow-up is really critically important. The patients that have fatalities were those that you sent out for a week, two weeks, and told them to come back. That's where the fatalities mostly were seen.

Beth Eaby-Sandy: And they couldn't breathe, and they thought that was normal.

Marianne Davies: Right. Colitis is the next one. What I will point out, on the CTCA criteria here, is this is the algorithm for colitis, but there is another one, a grading system, for diarrhea. You really need to use both of those in conjunction to help answer some of these questions. We're going to take another patient, a 52 year old female-

Beth Eaby-Sandy: We're doing very well on time, by the way.

Marianne Davies: Are we? Okay.

Beth Eaby-Sandy: Yeah. We can ...

Marianne Davies: Am I talking too fast?

Beth Eaby-Sandy: No, but we're just doing well on time, so we can dive into these a little.

Marianne Davies: Okay. 52 year old female, stage three, non-small cell lung cancer on durvalumab, post concurrent chemo rads. This patient comes in and, of course, this is probably going on for a few days, but they never call you ahead of time, had six to seven, had a grainy, non-formed stools, variant in size. It was not dark or coffee colored at all, but she did have one that was blood streaked, and some that, when she comes in on that particular day, are mucusy. She had taken loperamide twice, but it didn't appear to have any effect. She's got some mild abdominal discomfort that occurs, cramping right before she's going to have a bowel movement, and then also some associated decrease in her appetite and some associated vomiting. She's been trying to maintain her oral fluid intake.

She subsequently had a CT scan, abdominal CT scan, on the 14th of June, which showed pancolitis. This can be from a variety of different reasons. Again, we have to rule out other causes. Your differential diagnosis here is, is this infectious? Is this a secondary to an antibiotic therapy this patient might have been on? Or is this secondary to immunotherapy? Based on this, what grade of colitis would you say ... Or diarrhea this patient has?

Beth Eaby-Sandy: I think at this particular point in time, it was probably grade two. It's going ... As you'll see, it's going to progress in the case study. How would you manage her at this point in time?

Marianne Davies: Based on the fact that ... We typically ... I don't know if I would have had the abdominal CT scan already, would have treated her symptomatically at the time, held her immune checkpoint inhibition, send off some stool cultures. I don't have the rest of her history here. Had she been on antibiotics? Had she been in the hospital? What level of workup do we need to do for that would be the next question.

Beth Eaby-Sandy: Question for you, she had not been on antibiotics. In your ... If somebody had not been on antibiotics, had not been in the hospital, do you still send the C. Diff when they have pretty much no ...

Marianne Davies: I just treat them as what's probably most likely going to be immune checkpoint inhibition.

Beth Eaby-Sandy: Yeah. It's hard for me, because it's like, okay, and they are having a lot of stools. Sometimes it's easy to send the *C. diff*, but it is highly unlikely to be C. Diff with no pre-extenuating circumstances.

Marianne Davies: Highly unlikely. Exactly.

Beth Eaby-Sandy: Her abdominal CT was routine that day. I agree with you, I'm not sure I would have necessarily gotten it. By the time that colitis is showing up on a CAT scan, it's bad news.

Marianne Davies: Right. Then, I would ... The criteria for colitis here ... Again, you have to put it together with the diarrhea one. It's the number of stools, but then the other associated symptoms. She's obviously got diagnostic confirmation that she's got the colitis, and she also has the number of stools. I would dive a little deeper into her abdominal discomfort, level of discomfort.

Beth Eaby-Sandy: Yeah.

Marianne Davies: She's hovering a grade three, probably is where she is.

Beth Eaby-Sandy: She's hovering grade three. That's okay. She'll get to it.

Marianne Davies: All right. When we look at the work up, the ASCO really does a nice job of giving you the workup of what you need to do. Again, you want to rule out other cause, as if you have the luxury of time. Other tests that are recommended, and the GI folks are recommending, is also doing the lactoferrin and calprotectin levels to see if there's actually disease activity or to see if this is more immune related. Not all organizations actually run these tests. Do you do those at your ...

Beth Eaby-Sandy: The doctor I work with did one a few weeks ago. I was like, "Wow, you're so on top of things."

But when we got the result back, it was abnormal. I ended up emailing the GI doctor, but then the GI doctor said that it wasn't helpful because we didn't have a baseline lactoferrin. Then it was like,

all right, what do you want from me? I'm just trying to figure out other ways to diagnose it. Since we didn't have a baseline, even though it was elevated, she was like, "I can't make for sure."

Certainly if people have underlying irritable bowel syndrome, ulcerative colitis, they're going to have elevated levels of these. This is what I've learned from a GI doctor recently.

Marianne Davies: Exactly.

Beth Eaby-Sandy: If you want to comment, because I know you've done them.

Marianne Davies: Yeah, we've done them. The calprotectin often has to get sent out, by the way. Not every facility has that. Again, that's something that's not going to come back right in time. We don't routinely do that as baseline. We may begin to see this as a recommendation in the future.

Beth Eaby-Sandy: Oh, I said for sure I'm not doing a baseline on every single IO patient. That would be completely ridiculous.

Marianne Davies: Yeah. Well, the percentage of occurrence of colitis is so low in lung cancer anyways, so that cost benefit ratio probably doesn't warrant doing that. Here's the diagnostic work up. I'm not going to go into details for that, but essentially, if you hadn't done a CAT scan, you might have considered it absolutely if they have abdominal discomfort.

The other little caveat, as far as the diagnostic thing that I would say to you, is that the number of stools is not always the indicator and don't use that. A lot of times, patients are on opioids, and so they've got opioid induced constipation. If they go from not having a bowel movement, let's say every three to four days, and all of a sudden go to having two or three a day, you're going to be at a grade one. However, for that patient, it could be a more severe colitis process that's going on. You need to obviously know your patients' baseline.

Beth Eaby-Sandy: Can you comment on colonoscopy in this setting, especially with this patient with inflamed bowel?

Marianne Davies: Mm-hmm (affirmative). It used to be when we first did the trials that we were recommending everybody go to GI and get a colonoscopy. We don't routinely do it. It's in the guidelines, we'll say consider doing a colonoscopy, but if you've got a very inflamed colon already that you can see on the CAT scan, we would not want to send somebody for colonoscopy because then there's going to be a risk of perforation. Again, if you've already got your diagnostics to support, then we would not do it.

Beth Eaby-Sandy: Yeah. Our endoscopists have been less likely to want to scope someone with an already inflamed bowel, just for fear of complications.

Marianne Davies: Absolutely.

Beth Eaby-Sandy: While it would be nice to completely confirm it ...

Marianne Davies: If you didn't have that, there's some other things that are going to come out in the future.

Beth Eaby-Sandy: I think if it's low grade and you're questioning it, then send them for the colonoscopy and get the biopsies to determine it. I had to do that in one patient, where she was kind of having symptoms, but not hard core. I wasn't sure if I should hold the immunotherapy. I'm like, "Let's go get a colonoscopy."

When they did it, it was not colitis. That confirmed to me, okay, I feel confident continuing my immunotherapy.

Marianne Davies: Future studies are really looking at do you do the colonoscopy if you don't have a CT scan that shows ... If the CT scan looks good, you do the colonoscopy, the patient's still having diarrhea. What they're now looking at is the gut microbiome, so really looking at the biota there to see do you have adequate microbiome, or is that what's contributing to the diarrhea as well, and then the lovely procedure of doing fecal transplants has been suggested. That's being done at several larger facilities right now to help relieve these things. That's not totally into the guidelines at this point. A lot of research being done on that right now.

Guidelines for management. If a patient has grade one, you can continue your immune checkpoint therapy. If they have increase in their grade two, you should really hold therapy. Where both of the sets of guidelines break out is if a patient is on combination therapy with CTLA-4 and a PD-L1 or PD-1 inhibitor, versus if they're just on one or the other. In most cases, if they're on dual therapy or CTLA-4, that usually is the culprit.

If a patient does have grade three toxicity, you're going to permanently discontinue the CTLA-4 agent. If they have resolution of the toxicity at grade three, you can consider adding ... Restarting or re-challenging that patient with a PD-L1 or a PD-1 inhibitor. All right? That's where it breaks out from some of the other guidelines. That's the big difference with the colitis, is that CTLA-4 is out the door and then the others can be considered to restarting, if they recover after their steroid therapy.

It's a little bit easier to read, I think, the NCCN guidelines, but I'm biased. For grade one, in general, you're going to use some just oral therapies, as far as loperamide or diphenoxylate atropine to suppress the diarrhea. Hydration and close monitoring. For grade two, you're going to hold and start steroids. If no response in two to three days, you're going to escalate increase your dosing, and consider adding that infliximab. You're going to pre-certify that ahead of time, so you can assure that you have that flexibility of giving it. At grade three, you're going to discontinue CTLA-4 and consider re-challenge of the anti PD-1 therapy. Again, we already discussed the workup.

For this patient, this is the bi-package insert, the occurrences of any grade toxicity. Again, you can see that the higher dose of the ipilimumab really is what is the biggest risk for developing the colitis. This patient comes in and she has a workup. It's negative. She's got the pancolitis. She gets IV therapy and started on prednisone at 80 milligrams once daily, and to be followed up. I don't know if you-

Beth Eaby-Sandy: I know. Don't read the whole thing. I was copying and pasting notes, I think.

Marianne Davies: Again, the patient comes back. She's got a decrease in her level of her number of stools, but still a little bit mucusy. However ... Five mucusy stools, but she's also got 10 to 12 now, despite starting her prednisone. If we come down here, you'll see that when she came in, she was given IV steroids at this point at this visit because she didn't have improvement after two to three days. She was also prescribed budesonide as an alternative, as an additional. That's a locally-acting immunosuppressant to decrease-

Beth Eaby-Sandy: And the insurance didn't cover it.

Marianne Davies: But ... Yep, we're going to get to that in the next one. The patient was instructed to come back then. At this time, Beth put in the order to pre-certify her for the infliximab. She comes back later, she's still having all the loose stools again. What we do find out is that she had never started on the budesonide because her insurance company wasn't going to approve it. Because she wasn't having resolution of the symptoms, she then began her infliximab at that particular time.

Beth Eaby-Sandy: I think a lot of these patients would probably be admitted by now. The interesting thing with this patient is, and I laugh about this, but she just ate her way through it. I don't know how. I remember walking in the room that day, and she was eating those packs of cheese crackers, just chomping them down. I'm like, "Hey!"

I think that kept her out of the hospital, because she literally ate and drank fluids. She never really became severely dehydrated. While she was uncomfortable and in pain, she really did not want to go in the hospital, so we kept her outpatient. I think that may even be the minority of cases. A lot of these patients would have been admitted by this time.

Marianne Davies: Yeah, yeah. Likely, they're going to have other associated symptoms as well.

Beth Eaby-Sandy: Yeah.

Marianne Davies: You're likely doing to be dehydrated and really need that. Pearls, make sure you discuss those bowel habits ad nauseum with your patients, so that you understand what their baseline is. Take into consideration high risk patients, as well. Colonoscopy is the gold standard, however used less and less frequently. Abdominal CT scan may be indicative. If you have any suspicion that the patient's unstable, again, every two to three days monitor them and then consider hospitalization for these patients.

Dermatitis ... We are going to go over a little bit, just so that you know.

Beth Eaby-Sandy: You have 15 more minutes.

Marianne Davies: Okay.

Beth Eaby-Sandy: You're pretty good.

Marianne Davies: For rash, the way that the CTCA qualifies it, and again, this is not ... These were based on people getting chemotherapy. That's how these guidelines were developed. They don't necessarily reflect the picture we're seeing for patients that get immune checkpoint inhibition. The next version is

going to incorporate some of those. In general, rash less than 10% of the body surface area that's affected, that's a grade one. 10 to 30 is a grade two, greater than 30% is a grade three. We do note that, again, the biggest culprit for dermatitis is going to be that combination higher dose ipilimumab with the nivolumab, but we do see it with other checkpoint therapies, as well.

Fortunately, the ... This is another example of the ASCO really providing a little bit more detail to how we're grading those toxicities. For grade two, they're actually describing it as not only body surface area of 10 to 30%, but also having associated symptoms is an and/or. Do you have systemic symptoms? Do you have lymphadenopathy? Do you have any facial swelling? IS there mucosal involvement? You can zoom in on that on your iPad and send that to yourself. That's clearly those contributing factors, are what's really going to guide your management, not just body surface area.

In general, for grade one, you're just going to do symptomatic care. Grade two, you're going to hold your immune checkpoint inhibition and topical steroids, which are medium to high potency topical steroids, to the area of distribution that's involved. You can consider starting on the steroid at 0.5 to 1 milligram per kilogram per day. At grade three, if you've got any skin ... Whether it's the distribution of greater than 30% BSA, or skin sloughing, or ulceration, or erythema, epidermal detachment, any mucosal membrane detachment, again, you're going to hold, you're going to consult with your infectious disease physicians, your dermatologist. You're going to escalate your dosing of your steroid here, and you're also going to escalate the potency of your topicals. That's going to be a high potency topical steroids. Emollients application are critically important across the board.

Grade four is when you have blistering and sloughing. In that case, you're permanently going to discontinue the immune checkpoint inhibition. Up until then, you might consider re-challenging that patient when you've had resolution of the symptoms. This is just a more simplistic version of going through the rash, as far as the NCCN version. Again, more supportive care, topical steroids for up to grade two, and you can restart when that resolves. Grade four definitely is permanently discontinue.

Certain cases, these are life-threatening complications that can occur. Bullous dermatitis. These are urgent need for evaluation by dermatology. Steven Johnson Syndrome, as well. For the bullous dermatitis, if it's a grade one, meaning it's a small distribution of boli that are formed, blistering that's formed, non life-threatening, you're going to use high potency steroids. You can consider immune therapy re-challenge if that resolves. Again, initiate oral steroids at grade two.

For any level of the Steven Johnsons, you're going to permanently discontinue. If a grade three or four of the bullous, you're going to permanently discontinue checkpoint inhibition. Here's some examples of Beth's patients. This patient, I'm understanding, was five days after having one dose?

Beth Eaby-Sandy: Yeah. No, he was on his third dose of pembrolizumab. He's a head and neck cancer patient. On a Thursday, he called our office and said, "I'm having a little bit of blistering here and there. It's not bad. It doesn't hurt. It doesn't itch."

It was on a Thursday. Okay, well, maybe come in tomorrow, and we should take a look, or if it's itching, topicals. We didn't make a big deal of it. He didn't call back on Friday, because he had a routine appointment on Monday. That's what he looked like on Monday. That's just one screen shot of him. I can tell you, that his back and legs were covered in ... You can zoom into his armpit there. They were covered in blistering ulceration. It was unbelievable, in a matter of five days, that this occurred. He was

immediately admitted to the hospital, and he actually went to the ICU for a short time for derm to get this under control, especially because of how fast this ulcerated his body.

Obviously, we permanently discontinued. He had a dramatic response to pembrolizumab, and we often see that with these dramatic responses. The two photographs that are on the right are a Steven Johnson Syndrome in a patient of mine. Again, I just picked some body parts. The middle one is her hand. This is literally what it looked like. Her skin just started peeling off in, I would say, 70% of her body. Just areas of skin started peeling off. You see this red, raw, weeping areas. She was also admitted to the ICU, and she lived, but some of these patients do not. They're so at risk for infection. We had to lay her almost like a burn patient on top of chucks, because we didn't want her sticking to things and putting Telfa pads on the areas that were part of the bed. Aggressive immunosuppressive therapy with derm being all over that.

Marianne Davies: And infectious control.

Beth Eaby-Sandy: Yeah.

Marianne Davies: The other point I want to just make is if you have patients that are developing these in any mucosal involvement, not only infectious disease and dermatologic consultation, but you want to make sure that you involve ophthalmology, because they can begin to have ulcerations in their eyes. GI, because they can have endoscopic ulcerations and sloughing. For females, gynecology as well. Urology, because you can have sloughing in the bladder. These patients can have a lot of internal detriment, as well. It's not just the ... The dermatology's just not going to cut it. Infectious disease. You really need all of those other consultative services to assist you in identifying what the impact is.

Beth Eaby-Sandy: Reminder that they're rare. They're less than 1%. 0.1, 0.2%. We're using a lot of immunotherapies. You're going to see it at some point.

Marianne Davies: It's just sometimes some of the other subtle areas of mucosal involvement, patients aren't reporting those symptoms. Just to raise your awareness that the skin may not be something that's just externally that you're seeing all the time, that the other mucosal areas can be involved. All right, we have minutes, right?

Beth Eaby-Sandy: Five, yeah.

Marianne Davies: Okay, here we go. Endocrinopathy is the most common irAE. Hypothyroidism is the most common, 10 to 20% across. Typically, patients will start with a hyperthyroid picture with a drop in their TSH that you'll notice. Oftentimes, after that hyperthyroid phase, they will convert. Their thyroid will burn out and they will become hypothyroid. Important to check TSH levels at baseline prior to the start of therapy and then check their T4 as well, when you're checking the TSH at regular intervals.

We check it about ... Depending on what cycle they're on, but certainly no more than once a month. No more than that, unless the patient becomes symptomatic. Treatment is levothyroxine for the TSH of over 10 and/or symptomatic. Hyperthyroidism, as I said, in most cases, that thyroid toxicosis is actually going to result in the hypo. If the patient is tachycardic, you can consider beta blockers for management.

The NCCN guidelines really break it down for you, in terms of looking at the TSH. If it's early on, if it's less than 10, you can continue immune checkpoint therapy. If it is elevated with normal T4 or slightly higher, you're going to consider levothyroxine. Hypothyroidism, again, the same. The endocrinopathies, unless they're completely life-threatening, are the ones that you can continue on immune checkpoint inhibition, as long as the patient is stable. They are going to require hormone replacement for the rest of their life, and patients need to be educated about that. They're never going to recover their thyroid function at the end. That's just one of the key points for there, that they need to be ... They've got complete failure of the thyroid, and so you need to start them at what their lifetime dosing would be.

We bump up dosing. We don't start at the lowest, lowest dose of levothyroxine because we know they've got total failure. As long as they tolerate it, that's [crosstalk].

Beth Eaby-Sandy: That's a really good point, actually.

Marianne Davies: Yeah, so ...

Beth Eaby-Sandy: We're so used to starting at the lowest dose of levothyroxine, but once you've destroyed it, it's gone.

Marianne Davies: It's gone. You need full ...

Beth Eaby-Sandy: Maybe a little bit ...

Marianne Davies: Full replacement.

Beth Eaby-Sandy: Yeah.

Marianne Davies: Which is 1.6 micrograms per kilogram, or something like that. I have to look up the exact dosing. It's in the NCCN guidelines, I just don't recall it right now. Adrenal insufficiency ... Is that right? Okay.

Beth Eaby-Sandy: The pharmacist in the room is like, "Yes, it's right."

Marianne Davies: I'm so used to rattling it off. Adrenal insufficiency can occur, as well as hypophysitis, so inflammation of the pituitary. Patients do need an MRI to diagnose this with pituitary or sella cuts, is how it's referred to. Make sure you order that with your radiologist, if they're specifically looking for that. Type 1 diabetes is very rare, less than 1% of the patients, but patients should be getting their blood glucose monitored with each of their treatments.

As far as treatment for adrenal insufficiency, the one line item I really want to point out to you is that, again, these patients are going to require lifetime hormone replacement if they have a full failure. They're going to need steroid replacement. You can either do hydrocortisone or prednisone, in addition to fludrocortisone, at the lowest possible dose. Patients need to have stress dosing if they have another subsequent infection, or if they're going to go on to surgery, so patients need to be educated about that.

The key thing is that you want to start ... Oftentimes with adrenal insufficiency, if you've got hypophysitis as well, you've got multiple hormones that are disregulated and you want to start corticosteroids first. You want to start that first. The other hormones start the next day. Do not start ... If you start the hormones first, before starting the steroid, you risk putting that person into adrenal crisis. All right, that's the one key point for that, I just want to make sure that you leave here with.

Hypophysitis, again, if patients have a hypophysitis central process, you're going to want to do the full panel of endocrine labs because they might also have gonadal dysfunction. They can have ovarian failure. A lot of the additional, subsequent things that we often don't evaluate for, so make sure you're doing the full panel of the endocrine labs. Pearls for management, these can occur. They're the most common, with the thyroid being the most common. You want to get that at baseline. Again, very, very rare for the others, less than 1% of the population. Mostly looking for the thyroid.

Other things that can occur ... I'm not sure how far along we are.

Beth Eaby-Sandy: Yeah.

Marianne Davies: Hepatitis, elevation in your transaminase is nephritis. Neuromuscular toxicities, and then obviously other organs can be involved, as well. Again, most of the cases, this is less than 5% of the population but just be aware. It becomes a little bit more complicated when you're looking at combination chemotherapy and immune checkpoint inhibition to ferret out which one might be the contributor. That's where your diagnostic differential is going to come in.

The more general symptoms, nausea, diarrhea, arthralgias, fatigue, just want to point out that we really do think that true immune-mediated arthralgias are under reported because people think they're just getting old and achy. It really can become more problematic and I would engage with your rheumatologist, in terms of managing that and assessing patients for that risk.

A couple of underlying questions to ask. I think I already addressed the question of solid organ transplant earlier, but some of the other things to consider for other autoimmune diseases, again, it's that shared decision making with your patient. It's that balance. If you've got another underlying autoimmune disease, are you willing to risk the flare of that process for the ability to get immune checkpoint inhibition. That's some of the key things to just keep in mind.

Re-challenge. This is another thing to consider. Rates of recurrent irAEs are about 55%. On the graph on the right hand side, you can see out of the patients that were studied that had recurrent ... The characteristics of those, about 20% have recurrent pneumonitis after they're re-challenged. Hepatitis, colitis, 60%. Arthralgia, 83% of those patients have recurrence. 43% of patients that are re-challenged ... Again, these are small numbers, but just know that is a risk, specifically looking at patients with colitis. It's really, again, a very higher rate about, again, 55% of those patients. Know it's a risk and be on the alert, that potential assessment.

Again, clinical pearls. We have to really be cognizant of how we educate our patients about these toxicities, the rate of occurrence, the timing, et cetera. We can just expect that it's going to be involved ... Our patients are almost across the board with diagnoses. They're going to be on immune checkpoint inhibition at some point. We need to continue to have a better understanding of the

mechanism of how these toxicities develop and different management strategies beyond just the steroids at this time. And then, predictors of IREs is really important.

Beth Eaby-Sandy: All right, let's vote on our two because we're standing between you and lunch. The strongest data to correlate immune-related adverse events, with a survival advantage, is in patients with non-small cell lung cancer receiving nivolumab, patients with non-small cell cancer receiving pembrolizumab, patients with melanoma who experience pneumonitis, but not skin rash, or patients with melanoma who experience colitis, but not skin rash.

Marianne Davies: Even if you don't know, please do vote again just to try to collect all our [crosstalk].

Beth Eaby-Sandy: Okay. Yes. The answer is the nivolumab. Interestingly, melanoma was correlated with skin rash, so that's why that one wasn't correct. The most data that we have was actually the patients with nivolumab that were having any kind of immune-related adverse event. That's where the majority of our data falls. We did get some improvement.

Marianne Davies: Some improvement there.

Beth Eaby-Sandy: A patient with small cell lung cancer's receiving combination of ipi and nivolumab in the second line setting. She develops worsening diarrhea with mucus in her stools, and significant abdominal pain. IV steroids do not improve her symptoms. She's admitted to the hospital for IV hydration, symptom management. She's given a dose of infliximab, and it finally improves. She's labeled as having grade three colitis that required one dose of infliximab.

According to NCCN, you should permanently discontinue the immunotherapy, considering restarting a PD-1 inhibitor, but not the anti CTLA-4 drug once the symptoms resolve, consider restarting both the PD-1 inhibitor and the anti CTLA-4 drug once symptoms resolve, consider restarting both but only after a long steroid taper and all symptoms have resolved, or you're still unsure.

Okay, good. Yes. We would only ... Marianne, we would only restart the PD-1, right?

Marianne Davies: Exactly. The PD-1 is the only one, so that is the correct answer. I think that was our last question.