BASAL CELL CARCINOMA AND MELANOMA

WENDY H. VOGEL, MSN, FNP, AOCNP It's my pleasure to introduce our next session. The Management of Skin Cancers Basal Cell Carcinoma and Melanoma. Please welcome our speakers, Ms. Brianna Hoffner from the University of Colorado Cancer Center and Dr. Daniel Siegel of the SUNY Downstate Medical Center. Thank you.

MS. HOFFNER Good morning. Thank you so much for having us. It's great to be here.

DR. SIEGEL Hello everybody. It's a pleasure to be here. Learning objectives: we want to increase your understanding of mechanisms of action on immunotherapy and treatment of melanoma and treatment of advanced basal cell. We've got new skill sets for you to apply and manage the adverse events. So, we will also discuss the pivotal role in the expertise of the advanced practitioner, which Brianna will do and we will take it away.

Now, I have served on Speaker's Bureau for Genentech, the producers of vismodegib, and for Novartis that makes sonidegib, and I've participated in other advisory boards, and Brianna has nothing to disclose.

MS. HOFFNER Unfortunately, no.

DR. SIEGEL And we have nothing to hide, so let's get into it. A basal cell cancer diagnosis, it's important to make a diagnosis, because if you make that diagnosis early, you won't be dealing with advanced disease. But again, it's the classic rodent ulcer; central ulceration; rolled borders; radial blood vessels; pretty distinctive pink to gray lesions; non-healing ulcers; non-healing

red scaly areas; the shaving cut that hasn't healed since World War II, you know. And why is it important? We're discussing advanced disease here, and advanced disease all starts out as one aberrant cell. And again, patients might have multiple primary tumors that may respond to therapy, and you may be challenged at times for using a drug that is costly, so do as I do in this regard: if you're thinking of using a hedgehog inhibitor, strip the patient down, mark and count up the other basal cells. It's a lot easier to justify to ensure that you've treated the index tumor and 75 others. It amortizes the cost.

And again, just a little clinical review: this is from a slide from the talk I gave two years ago in Orlando. It covers a lot more basics, because we won't spend time with the basics. We have little time today, so we're going to try and truck along here.

MS. HOFFNER We're going to keep moving.

DR. SIEGEL Advanced basal cell is a neologism invented by Genentech, because before that, we had other less than scientific but descriptive terms. We talked about gigundos, honkers, train wrecks, people crawled out from under a rock. Brianna and I were just talking about one who crawled out from his motorcycle but --

MS. HOFFNER Yes.

DR. SIEGEL -- the big lesion on an arm. Again, these are the biggies that we used to look at and say, you know, I can do it, I'm the macho Mohs surgeon, but again, was it the best thing for the patient? Before the advent of hedgehog inhibitors it was, but not anymore. Now again, NCCN Guidelines,

the Bible for everybody, suspicious lesions, you biopsy them. The high-risk ones, the ones we're concerned about, they're the ones that are more likely after procedures to treat them, such as standard excision -- if you get a positive margin, you want to either go back and do Mohs, you consider adjuvant RT and if that fails you have another -- a number of choices, none of which are great, except the hedgehog pathway inhibitors. If you do Mohs or radiation and you don't get it all, the same thing. You ultimately wind up at a hedgehog pathway inhibitor.

And, again, high-risk lesions; what makes them high risk? Large size, bigger than 20 millimeters, the size in low-risk areas bigger than 20 millimeters, but high-risk areas, the central face, around the eyes, the ears, the T-zone, small tumors, bigger than 6 millimeters are high risk. Poorly defined borders, recurrences, because recurrences in basal cell are always interesting. You never know where they go and you know that certain things don't happen, like cartilage invasion is uncommon, except if they had prior treatment and someone has breached the perichondrium and you now have a conduit for tumor tracking. And of course, aggressive growth patterns. Instead of having this expanse cell balloon-like growth, you have little tendrils meandering along, single cell strands that if you don't get them all out, it comes back again. You know, follow-up for recurrences, frequent, every 6 to 12 months; and again if it's local, you go to the primary treatment path once again. In metastatic disease, it can be surgery or RT, but more often than not, it will wind up these days with a hedgehog inhibitor, but keep in mind, metastatic disease is real rare.

So drugs for basal cell pre-January of 2012. We had cisplatin and 5-FU, it was mediocre at best. Superficial basal cells could be treated topically with 5-FU with imiquimod, photodynamic therapy, vigorous cryotherapy, you know, lower cure rates, and, again, nothing was wonderful, and 85% of these patients were disease free at five years from that particular lesion, but 15% had the adventures of multiple recurrences. So systemic therapy, what works, this is sort of fun mechanistically.

But, again, first we'll say there's money in bugs and I mean insects, specifically fruit flies, America's favorite research tool. High school students to Nobel prize winners. You can ask questions like, "How do eggs grow bodies?" You know, what came first, the chicken or the egg? So hedgehog mutants result in abnormally shaped embryos, and this is where the term hedgehog comes in, as we'll see in some photos later on. Basically, some of the mutants have little hairy-like structures on the tummy that look like little hedgehogs on there. And again, the hedgehog segment polarity gene is the one that influences normal development of the structures and there are denticles, not testicles, on there, and just again, rough bits on the outside of the larvae.

In the 1970s, a couple of researchers isolated mutations in the genes that controlled the development of the segmented anterior/posterior body axis of the fly. And again, the parallel, why this is important is this plays a role in developing the human embryo and in the development of basal cell carcinoma and the result in the discovery of genes, involved in the development of segmentation. They got a Nobel prize for that, and the Drosophila hedgehog gene was identified as one

of several important genes that played a role. Now here we have on the top, the cartoon showing what the tummy of the larvae looks like. In Panel B, you see this like scanning the M of the normal one, and in C you take a look, it looks kind of bristly there. It gives the sense of looking at a hedgehog, which are cute little critters on there. So there are multiple flavors of the hedgehog gene.

Of interest today is Sonic Hedgehog, which can be made from certain perspectives to look just like the character and it was actually named after the character Sonic the Hedgehog by one of the scientists involved, after seeing one of his kid's comic books.

We will explain the pathway very simply. We'll start out with a cell schematically. For a cell we will use a cell phone and other common structures on there. So here we have the cell, and we have the patched protein up there, and here we have smoothened. And what would happen is patched is inhibitory to its smoothened and nothing happens; there's no smoothened-enabled signal transduction and nothing goes on. And of course what happens now if we have the hedgehog ligand bind to patched? Well, the inhibition goes away and then the smoothened migrates up to the cell membrane. You get single transduction. You wind up getting target gene expression.

So now you say one thing -- some people will often say, but Doc, is it natural? Now interestingly, it's not natural, but it's modeled on nature. Nature has its own hedgehog pathway inhibitor cyclopamine, and cyclopamine is found in the California corn lily, also known as the California False Hellebore or the Western False Hellebore, and this is veratrum californicum; it is, according to the

California agricultural people, a weed on there. That's a nasty poison that inhibits the hedgehog pathway. It causes birth defects in both animals, such as sheep, and it can do the same in humans. You can wind up getting nasty things. It is a nasty toxin. You can't treat with it because there's not a therapeutic window. But drum roll, oral hedgehog pathway inhibitors do have a use that outweighs the risks.

So here we have that circumstance we just showed you, and lo and behold, here is our hedgehog pathway inhibitor, it binds to smoothened on there. When it binds to smoothened on there, transduction stops, there's no target gene expression, and nothing happens, and that's how these drugs now work. Vismodegib was first to market, sonidegib came to market shortly after -- four years after. The phase II study that got it to market was the one from the *New England Journal of Medicine*. And it's important to remember this got to market with only phase II studies. It was so good, the results were so dramatic, the government didn't insist on phase III studies, something I know is common in the oncology world, very uncommon in the derm world. It is rare for us in dermatology to have something that comes to market without extensive phase III studies.

And again the bottom line is the patients were treated 150 milligrams, one capsule a day, until either the disease progressed or you had intolerable toxicity, and it made it to market on that study.

Adverse events are common. When I sit with patients I say, you will get muscle spasms. You will lose your hair. Your taste will be altered and may even

go away. Everybody wants to lose weight, most of my patients haven't. It seems the older ones do and the other ones are less frequent in terms of adverse events. You can also get constipation, arthralgias, diarrhea, and ageusia. I'm always fascinated that one drug gives you both constipation and diarrhea. The amenorrhea may be irreversible, but outside of the basal cell nevus syndrome population, you're probably not treating a lot of patients for whom that is an issue. Some patients develop hyponatremia, hypokalemia, and azotemia. The important takeaway here is that when patients wind up having those, I tell them diarrhea, nausea, vomiting, you have that, get yourself to your primary doc, my office, or a walk-in clinic, and we give them an index card and I write down electrolytes and BUN, nothing really to follow otherwise on there.

The spasms are interesting. Some describe them as cramping, little pulls or twitches on there. Pickle juice works for some. Pickle juice is essentially Gatorade with salt. Massage can help, but that's costly unless you have a willing family member. A Valium is very effective. You might want to use Flexeril first for all the issues of controlled substances. But again, drug holidays. You know, if you have the patient take a break for one month or six weeks, often the symptoms go away, and they may be less troublesome after they come back. No specific labs to follow for vismodegib, though sonidegib does recommend a variety of labs that are in their label and again, telling the patients if they get diarrhea or vomiting worse than what they might think is a normal URI or GI problem, then let the provider know to check electrolytes and BUN.

Now these are some pictures from that seminal *New England Journal of Medicine* study. Baseline to 20 weeks on that case and again, baseline to 24 weeks -- pretty impressive results. Big tumor, no tumor or tiny tumor, or residual crusting, but really dramatic responses. Nothing drug-wise was doing that. As I mentioned, vismo first, sonidegib 2015, and others are coming along. We have a variety of drugs out there.

Now what's new, we'll cover some of ASCI. Well, they had the data that came out of the MIKIE study that we were involved in, looking at a couple of different regimens to cut down side effects. One was three months of daily treatment, followed by alternating placebo, essentially a holiday for two months, followed by another course. And the other regimen was 24 weeks treatment, then eight-week on/off courses and primary objectives looking at percent reduction from baseline at the end of treatment. Both worked well. Neither one really was much better than the other, though A had a numerically better outcome and the safety profiles were comparable. No surprises. It was STEVIE looking at analysis in 1,215 patients in the real-world setting. Again, these patients were treated the same way, 150 a day until progression occurred. The primary objective here was safety. These patients were followed for 12 months after the last dose of drug, and looking at 165 sites, 36 countries, a big study, your average patient was 72 years of age, interestingly mostly men and at the time of analysis, a third of them still were on the study, and lo and behold, basically it showed that they had many complete and durable responses.

Out of my alma mater Albany Med, Jeff Ross's group did some genetic sequencing of metastatic basal cell and squamous cell cancers, and they found high mutational loads -- no surprise on there. They found more cell cycle dysregulation and squamous cells that were metastatic and more hedgehog pathway alterations in metastatic basal cell. Again, another study looked at sonidegib when it came out. This drug, when it was in trials, was looked at with two doses, 200 milligrams and 800 milligrams a day. This was a 30-month follow-up study on both doses. Looked at median duration of exposure of about 11 months, and the overall response rate was about 56% interestingly at the lower dose, but then the higher dose may have had to do with compliance is my suspicion on there and again, similar responses regardless of histology, and again the 200 milligram patients had a more favorable safety profile and again, the reactions, which seemed to be common to the class of drugs with the spasms, alopecia, and dysgeusia, again durable responses were demonstrated here. There was resistance demonstrated in a French case series of 207 patients. Nicole Seguin Bassett performed that one; 10 centers. They had primary resistance in 10 patients, 18% had secondary resistance. It's not a surprise, but again, this is oncology; it makes things interesting. So when some things come along, we just find the way around it, and we can discuss that in the Q and A. And now I'm happy to turn it over to Brianna.

MS. HOFFNER Thank you. All right. So melanoma, the incidence of melanoma is rising. This is one of the few cancers that that's true for. It's rising especially fast among young women, which has spurred a lot of conversation

about tanning beds, but probably it's multifactorial. So survival by stage here. You can see that really stage 4 disease has the worst survival rates; however, the 2C, there's really a blip there. Probably the reason for that is that 2C disease as you know if you're familiar with the staging of melanoma, includes in-transit disease, and so that in-transit probably is really behaving more in a metastatic fashion, and that's likely why there is such a significant dip in the 2C population.

So in treating melanoma, we have a lot of different targets and we've really been leading the way in the immune therapy conversations. But we also have the targeted therapies and our hope, of course -- if you have two things that work, why not combine them, so we are working towards that goal as well. So oncolytic immunotherapies and checkpoint inhibitors, such as the CTLA-4s and PD-1s, cytokines, they still have a place, like IL-2, and then targeted therapies, and we'll talk more about all of those.

So immune checkpoints in melanoma: this graphic is a great graphic from Dr. Chansky, but he is going to talk to you guys next about immunotherapy in general, so I'm not going to belabor this point just to see where these checkpoint inhibitors are working. Where is that CTLA-4 and where is that anti-PD-1 working. So there's a central immunity with the CTLA-4s and then more peripheral with the PD-1s. And again, this is looking at the mechanism of action, but I'm going to let them talk about that in the next presentation.

So T-VEC, which is an oncolytic immune therapy. This was really a new thing. T-VEC got approval just last year in October of 2015. So T-VEC is an attenuated live herpetic virus, and it's an intra-lesional therapy. This is something

that is important for us to know about as advanced practice providers, because we can administer this treatment. That is within our scope, and a lot of institutions as they are rolling this out are trying to figure out the best way to do that, and often times we are the most capable of reading through the protocols and taking the time to inject these patients and treat them. So we will talk a little bit more about this, but essentially the way this works is you inject the live attenuated virus directly into the lesions that cause the cells to lyse, which causes this immunogenic response. We've seen that they can get a response, not just at the site that you inject but also in other lesions.

For example, I had a patient who probably had about a hundred in-transit metastases on her leg. We treated eight of them, because there is only a certain volume you can inject, and they all resolved. So it's not just the treated lesions that this can have efficacy.

So approved immunotherapies, and then T-VEC on the bottom. But look at this, you know if you look in the last five years, we have made so much progress and that's really kind of the point that I want to drive home. We had the ipi and then the pembro, nivo, and then the combination most recently as I mentioned the T-VEC, which is not actually an immunotherapy really.

So survival in the first-line setting. You guys have all seen this slide. It's an old slide. This is from the *New England Journal of Medicine* in 2011. The only reason I put it up here is to point out that in 2011, ipi was a real game changer. This was our first immunotherapy, our first checkpoint inhibitor immune therapy, and it was significantly better than decarbazine in terms of overall survival. The

other thing that we learned from ipilimumab, which was a really important lesson, is that the immune therapies are durable. Patients who respond continue to respond, right? Because our question with these initial trials was what's going to happen long-term, but these patients continued to be responders.

So that was great, but we felt like we could do better, and so then we had nivo. This is from the *New England Journal of Medicine* article in 2015. This is nivo versus decarbazine. So you remember those curves that I showed you with the ipi versus decarbazine, and this is even better, right? The nivo made an enormous difference. The hazard ratio of 0.42 is just remarkable. That's the hazard ratio for death.

So we looked at the pembrolizumab, anti-PD-1 versus ipilimumab, the anti-CTLA-4, and we saw that the pembro has a higher efficacy than the ipi, so again this theme of just building. You know, we've got something good, let's find something better, and that's why we combine them. So the CTLA-4 plus PD-1 versus single-agent PD-1 -- and this is a conversation that's still sort of ongoing, not just in the melanoma world, but in other malignancies as well, as you guys know. And so we found that the combination probably works more quickly and may have higher efficacy, especially in patients who are PDL-1 negative; however, there is a lot more toxicity with that as well, so it's something to consider.

So speaking of toxicity, immune-related adverse events. I'm just going to go through this briefly with you guys. So immune-related adverse events or immune-mediated adverse events is anything ending in "itis" because itis just

means inflammation. We are upregulating your immune system with these drugs, and therefore you can have inflammation anywhere. These are the common ones I have listed, which you've probably all seen, but there is a lot of very uncommon things for us to keep in mind as we treat these patients.

So colitis, this is more common with the anti-CTLA-4 therapies than it is with the PD-1; however, if you combine PD-1 and CTLA-4, the incidence again sort of increases there as you can see. The management of colitis is based on the grade and how significant it is. This grading is the CTCAE grading. So you can see that if a patient is grade 2 or higher, that you are going to need to intervene. You're going to hold immunotherapy starting at grade 2, and you would permanently discontinue immunotherapy likely for a grade 3 or 4, depending on presentation.

Hepatitis is less common than colitis, but something to be very aware of -- about 2 to 9% of patients. The clinical pearl that I would give here is that if you see a patient and they have elevated liver enzymes, make sure you bring them back within 48 hours, because you never know where you're catching them in that curve, and things can change very quickly. If they come in AST, ALT of 500, start them on their steroids, bring them back in 48 hours. You want those numbers to be going down. If they're not going down, you may need to do higher-dose steroids, IV steroids, or something else.

So we talked about this, mycophenolate may be useful in patients who have the persistent hepatotoxicity so, again, something to keep in mind. It's not just your standard steroids; there are a few other modalities.

Dermatitis. So we're pretty good at this. We got really good at this with the ipilimumab. It's more common again with the ipi than it is with PD-1, but again the combination of PD-1 and CTLA-4 bumps that up above just the single-agent PD-1. This is usually your earliest toxicity for patients on immune therapy. There is kinetics of toxicity, and the rash is generally what you're going to see first. So for management, it just again depends on the grade. You should use topical steroids, educating patients not to take long hot showers, baths, things like that. And then if it is severe, you need to use IV steroids or oral steroids. Antibiotics have not really been helpful with rash, just so you know. This is more of a macular rash, generally. It's not that papular rash that we've seen with some of the other drugs that can improve with antibiotics.

So endocrinopathy. This is an interesting one because generally this is a toxicity that does not resolve. I tell patients that I'm putting on immune therapies that we can treat everything; we can take care of it. The one thing that might not turn around or likely won't turn around is an endocrinopathy, such as hypothyroidism, hyperthyroidism, etc.

Hypophysitis is an interesting thing because it's not something what we were really that familiar with as providers, or didn't have to be as familiar with as providers, prior to the start of using these immunotherapies for our patients. So hypophysitis is just inflammation of the pituitary gland. It can be very difficult to identify and to treat. I want you to know that I admitted my first hypophysitis patient that I ever saw for sepsis. They were not septic, obviously, but they can be profoundly ill. You know, that patient was slumped over in the chair, not really

talking, their words weren't that clear, they looked horrible. And then of course just a little bit of steroid and they were fine. But you can do an MRI with pituitary cuts. You can check their hormone levels, and you can work with your friends in endocrine to make sure that you're doing the diagnostic work-up appropriately.

So surveillance. Clinical trials have generally recommended that you check thyroid function tests every 12 weeks for patients on immunotherapies, although there is some variation in practice there, but the point is to make sure that you're checking them regularly. Time to onset of endocrine toxicity tends to be much later. This is usually the last one that you see. So rash first, endocrine last. It's not always the case, but something to keep in mind.

Management is hormone replacement or something like methimazole for a hyperthyroidism. The hypothyroid is more common than hyperthyroidism. We do not think that a pre-existing thyroid disorder puts patients at a higher risk of developing an endocrinopathy.

There is a lot of other immune-related adverse events, seriously, anything [ending] in "itis." I've been telling people recently that we've been seeing some plantar fasciitis. I've had three or four patients that have had that. You can get some weird neuro-toxicities like Guillain-Barré or myasthenia gravis that can be very severe. You can get neuropathies with these drugs. They're all immune mediated. You have to keep that in mind in your management, but work with your consulting services and with your colleagues in other practices to make sure that you're diagnosing these things correctly and working it up.

And so you should always rule out all other causes of an adverse event before just assuming that it's immune in nature. However, steroids are going to be your backbone of care, and then there are other things such as infliximab or mycophenolate that you can use to mediate these reactions.

Targeted therapies. So vemurafenib versus decarbazine. Again, the point here is just to show you what we had before and where we went. So these are the plots showing you that with vemurafenib, the response rate was nearly 50%. That's a single-agent vemurafenib versus decarbazine of about 5%, so this was a remarkable change. This is from 2011 as well. It was a good year in melanoma. So then we wanted to combine BRAF and MEK. This is one of the few examples in medicine where combining two agents is actually less toxic than a single agent. Any of you who have given a single-agent MEK inhibitor know that it can be a real nightmare. Same with single-agent BRAF, but when you put them together, patients really do tend to tolerate it better. And we see that the overall survival and response rates are better.

So BRAF mutations occur in about 50% of melanomas. They do portend a more aggressive melanoma. The BRAF inhibitor single agent has about a 50% response rate as we discussed; however, the problem is that we see an acquired resistance. With single-agent BRAF inhibition, about six months is the median time to resistance.

So the adverse events -- the rash that you see with BRAF inhibitors is also generally more macular in nature. Cardiac, here this is important. You can get a QTC prolongation, so the BRAF inhibitors and the MEK inhibitors have different

cardiac toxicities, but they can both be cardiotoxic, so make sure that you're checking EKGs on these drugs. Uveitis is something that we don't often see. You can also see that of course with immune therapy since it's an itis. And they'll come in, they'll say, you know, my vision is a little blurry, I have a spot in my vision. Work with your friends in ophthalmology though to diagnose that. You can do steroid eye drops for treatment, and it generally resolves.

So AE management as we just discussed. Other things that they get are the arthralgias. Those are a bit difficult to manage. NSAIDs or narcotics can be helpful. Stretching, heat, things like that. And then hepatic toxicity. Just make sure you're monitoring the liver function tests; otherwise, we talked about those.

So MEK inhibitors, they have a lower single-agent overall response rate of about 25%, so use these in combination. Similar side effects to BRAF, but also you can get a retinal vein occlusion, so that's an emergency if your patient comes in and can't see. If they really have an acute loss of vision in an eye, make sure you take that very seriously and get them to ophthalmology though emergently.

So for cardiac, for MEK inhibitors, it's a cardiomyopathy that you can see, so you're checking EKGs. On the BRAF inhibitors and MEK inhibitors, you need to monitor echos.

So we talked a little bit about the AE management here. The diarrhea and the fevers are two other things that I should mention with the MEK inhibitors. Those can be hard. Patients have been so well trained about fevers that they often present to the emergency room; however, we see this with this drug commonly. So make sure you educate them that this can happen. If they're not

neutropenic, which you would not expect on these agents, it's not the same medical emergency. They can take antipyretics.

So BRAF plus MEK, as we discussed, is more effective. The median time of response with combination is about 10.5 months, as we noted the resistance with single-agent BRAF is about six months. So these work better and they last longer. And, as I said, the side effect profile is better.

So we wanted to cruise through the introduction to basal cell melanoma so we can get to the cases and really get to some of the issues that we see in practice and talk about this with you guys and leave some time for questions.

So our first case is our melanoma case. So we have a 58-year-old female with stage 4 melanoma with metastasis to the liver and bone. And so we have decided to initiate her on the ipilimumab plus nivolumab. So one thing that I want to note here is that the dosing of the nivolumab is different when you use it in combination. You guys are familiar with dosing as a single agent. Recently nivolumab went to a flat dosing rather than weight-based dosing. However, in the combination you use it as weight-based dosing when you're giving it with the ipilimumab. So she gets her first three cycles, and then on August 27, she presents to an outside hospital complaining of fever, cough, and shortness of breath. So this is always the case, right? We would love to see these patients at our treating facility so that we can evaluate them, because we know the patients, we know these drugs. We always feel like we're the experts. But it's hard to get to the facilities. A lot of our patients live far away, so very often you're having these conversations with emergency room physicians from outside hospitals.

So your patient -- their vital signs are okay, the heart rate is maybe a little elevated. Maybe a little elevation in respiratory rate. Oxygen is sort of borderline. Temperature is sort of borderline. There is nothing here that particularly stands out at you as alarming. The chest x-ray, which you guys can probably all read after your radiology session yesterday, shows a right middle lobe pneumonia, and so this patient is started on Augmentin every 12 hours by the emergency room clinician. So three days later she's back in your office. Good news, you got your hands on the patient but still doesn't look good. She has low-grade fever, a cough, and now she has diarrhea, which started on August 29. So this is the thing, this is the reason that we have this case in here, because this is really hard. You guys, this one is complicated. You would like to think that we're going to have one thing at a time to manage. We're never that lucky. So the patient now respiratory-wise has issues and GI-wise has issues. She denies sick contacts, no dietary changes. She is having eight loose bowel movements a day, not having any relief with Imodium, and the cough is making it difficult to sleep at night, so really this patient is looking kind of punky.

So this is from the common terminology criteria for adverse events. The CTCAE. There is an app for that. If you guys don't have it on your phone, it's free, you should. It makes it much easier to understand these toxicities and understand your management of these toxicities. So if you look at the definitions for diarrhea, an increase of four to six stools per day over baseline is grade 2, and grade 3 is an increase of greater than or equal to seven stools per day over baseline. And then under pulmonary for cough, you have for a grade 2

symptomatic and narcotic medication indicator, a grade 3 symptomatic and significantly interfering with sleep or ADL. So this is why it's important to use the CTCAE and really ask your patient these questions. So she told you she can't sleep because of this cough, right? So according to that, she has grade 3 diarrhea, because she's having eight bowel movements a day, so that's over -- it's seven or more above her baseline. She generally has one bowel movement a day, and then she has a grade 3 cough because this is interfering with her sleep.

So now that we've graded them and figured out what's going on, we don't know what the cause is, right? What are our differentials here? So that emergency room clinician put her on antibiotics. So does she have diarrhea because she's on antibiotics? A lot of people get diarrhea on Augmentin, right? Or does she have an infectious diarrhea, right? We can't forget that these patients can get *C. diff*, even though they're not getting hospital treatments, they still are at risk for those infections, or is this a colitis related to immunotherapy. And then with the cough, you know the clinician in the outside emergency room felt like that x-ray looked infectious, so it could be infectious. It could be inflammatory or it could be irritation, so you really have a wide differential.

So you need better imaging at that point, and that's when you would order a CT scan of the chest and the pelvis, abdomen, and pelvis. So this is her CT scan of her chest. You can see that she has bilateral patchy infiltrates. This is a very characteristic pattern that you see with a pneumonitis. Then the abdominal CT scan [is] very profound. You can see that there's really significant thickening of the lumen of the bowel there. Can you guys all sort of appreciate that? So you

can see this is the lining of the bowel and so that is much thicker. You shouldn't really be able to see the two sides of the bowel. It's usually just one line around the bowel, so she's got a lot of inflammation there.

So we believe then that she has a grade 3 colitis and a grade 3 pneumonitis. So what would we do about that? We would initiate steroids at a milligram per kilogram of Solu-Medrol or the equivalent. The reason we're going to do IV steroids initially is because she has this very significant colitis, so her ability to absorb anything is really diminished, right? If you give her oral prednisone, she's going to poop it out, she's not going to absorb it. So start with the IV steroids so that you get some activity, and you can always transition to an oral steroid once the patient is feeling a bit better. Taper slowly. [If] you give her a week of a mg per kg of steroid and then you take her off, all these things are going to rebound. These are grade 3 adverse events. She has two immune-related adverse events, and so you want to treat it appropriately. You're going to taper it slowly. Consider antibiotic prophylaxis because she's already got something going on in her lungs, so she's at significant risk to develop a secondary infection, and now I'm telling you that we're going to put her on high-dose steroids for a prolonged period of time. So those of you who work in bone marrow transplant, for example, you know that we always prophylax. Don't forget to do it with our solid patients who we're putting on these long-term steroid doses. And we're going to have to discontinue her immune therapy due to the grade 3 adverse events.

DR. SIEGEL Thank you, Brianna. The next case is an example of treating the patient, not necessarily treating the disease, but doing what is best for the patient here. 98-year-old white female, yes 98 is correct, presents with a basal cell that had been excised from her nose eight years before presentation to my office in August of 2013. The patient was well oriented and communicative. She had her two younger sisters who live with her accompany her, and the surgeon who did the original surgery told her that the margins were positive, but she didn't think it would be a problem, so she shouldn't bother coming back in her lifetime there. A year later she had bleeding along the suture line. She had one more surgery and she got radiation therapy over the subsequent three years. A past history was notable for other non-melanoma skin cancers. She had a pacemaker for decades. She had a history of congestive heart failure. Medications included warfarin, but my practice seems everyone is on warfarin and folic acid and atenolol. She's also on digoxin.

Over the preceding five years, she became reclusive, as the appearance of the lesion and the associated fragrance deferred visitors. Family visits became quite infrequent. The only people who got to see her during that time were her sisters and her nephew who is a dermatologist. Everyone else would speak to her by phone or would drop off the map. She was referred to me by her nephew who is a dermatologist in a state a few states away because her primary derm was not comfortable giving her a hedgehog inhibitor due to her age. And I was the closest person he knew to her who would see her and treat her despite the age. That was interesting.

The patient lives, as you can see, in New York City in Queens. My office is on Long Island in Smithtown. It's about 40, 45 minutes by car away from that, and if one looks, you would find that within a four-mile radius of her home, there were 48 dermatologists. Between her home and my office, there's probably about another 75, but nobody would touch her.

So here she is on August 29. Now again, from my perspective, you know, this is a nice basal cell, it's surgically manageable, but again, she doesn't want surgery, and this is what she's been sitting with for five years now. And so we take a close look at this and one of the markers to look at, she has alar retraction. The alar is pulling away, which could be a sign of scarring from a prior procedure or the tumor infiltrating and causing contraction on there. She's got some tropin in the lower lid starting out, she has no nodes, and if you palpate it, it's bigger than it looks. So again, this was one that you might call a honker or the new terminology, an advanced basal cell. We had an extensive discussion -- age and cardiac history might preclude surgery; it might not, again if you're a cowboy. And removal of the nose will result in a loss of valve function. No nose, you don't have pressure against the lungs as you exhale. The lungs collapse, fill with fluid, and, you know, it could do the patient in.

In any event, she didn't want surgery. So we had more discussion. She already had maximal radiation to the area, so she left with lots of info. I took the vismodegib brochures, the only drug market at the time, and as I do with all my patients, I started a hedgehog inhibitor. I highlighted things, I pointed things out. I try to educate the patient to cut down on the Saturday night 11 o'clock phone call.

Again, a few phone calls over the next few weeks to talk to the patient and her sisters.

She came back in October to see me, the reason being that she was starting to bleed more. She agrees to start vismo that day. We obtained a confirmatory biopsy to show that indeed this was a basal cell, not a squamous cell cancer. Despite one's clinical certainty, often you have to do this to make insurers happy. We found infiltrative basal cell cancer. No surprise there.

Well, she begins treatment about two weeks after the visit. Here is what she looked like on October 7, not much change in the two -- just a lot of blood and hemorrhagic crusting on there. And again, you know, pretty much an interesting tumor. It's pretty extensive. And we get a phone call in mid-December. She's starting to lose weight as her appetite is going away because food just doesn't taste as well and her sisters were concerned. She had been getting fragile over the past few years. There were concerns. So hair loss was not a concern, though it was happening. She had no muscle spasms, which was uncommon. I expected to hear about that. Almost everybody does. She was the first patient I treated who didn't have the spasms, and we all agree, no difficulties. Take a drug holiday. It's an easy drug to say take a holiday on. Unlike melanoma, basal cell cancer is slow growing. We have more flexibility, so we take a drug holiday, and she comes back in January.

She had a wonderful holiday season, hung out with family and friends. She had her 99th birthday in early January and she was eating again. She feels

good, but no desire to go back on the drug. On exam, she had some focal crusting, no palpable tumor.

There she is on January 13th. She was missing a bunch of her hair, hence the cap that someone knitted for her. Pretty good result. Again, the alar retraction might have gotten worse as the tumor healed in. As the scar -- the area healed in following tumor ablation on there. But just again, comparative before and after, a pretty darn good response. Now remember, she didn't start this until about October 20. So you think, October to November, December, so 2-1/2 months. Pretty impressive response, and this is what patients typically do when they're responders on there. Pretty good response on there. She was doing well and she passed away a few months later. Probably cardiac causes, not related to drug. The family was overjoyed. I got presents from various family members that they were able to hang out with her, see her, other than communicating by phone or Skype without the video on -- they were able to hang out with their aunt and it was wonderful, they were all happy. And again, she had that long interlude that we had shortened up. Again, an example of the fact that age is not a limitation and it's reasonable.

And I did point out in the beginning what was so important, that she was fully competent and with it. Because if someone came in and she was out of it, if she were obtunded, I would think, why are we doing this? But in this case, the patient was involved in the decision. She wanted to try it, and it was a success story. Thank you.

MS. HOFFNER All right. So we left time for questions. We said we would leave five minutes. So, what questions do you guys have for us?

FEMALE 1 My question was about your presentation, and both were wonderful; thank you. So suppose your patient has, you know, a side effect level three with the diarrhea, but she admits she didn't take anything for it, which I can't believe often happens, but it does. So what would you do then? Would you insist she hold it a few days and say she treat it and resume, or what would you do if they just hadn't treated the side effect?

MS. HOFFNER Well, once you get to a grade 3 toxicity, the treatments, your first steps when they're at grade 1 of course, as you guys know, is dietary modifications. So you cut out everything fun, no alcohol, no caffeine, no dairy -- there goes the ice cream, no spicy. You know, it's a nightmare. And they can generally get better with that and Imodium, as you know. You're right, we get a lot of patients who have a grade 3 colitis. They are still eating all of those things. They haven't touched Imodium. And then it's a question of what you do, but because they do have a grade 3 toxicity, they're really at risk of a bowel perforation, which can be a sentinel event for them, so I would discontinue the immune therapy and treat it as a grade 3 toxicity. And this is where it's important for us as APPs to make sure we educate patients well; to tell them, let us know early, because we can intervene and we can help you. But if it gets to a point of being a toxicity that would take you off treatment, we have to do the safe thing for you.

FEMALE 1 And you would never resume it two months later? Okay, thanks.

FEMALE 2 Thank you for that excellent presentation. In your case 1, is there a particular prophylactic antibiotic that you would recommend, particularly in light of her ongoing diarrhea?

MS. HOFFNER A good question. A lot of times we'll do just the standard Bactrim three times a week dosing, because that way you're not not getting as many of the GI toxicities, not hitting their marrow with the Bactrim, things like that. So usually that's okay. Sometimes we'll put patients on like a Levaquin dosing, depending [on] how tenuous they look. But you're right; the thing about that is, that you have the potential to make the diarrhea worse. If the diarrhea is truly just entirely related to the immune-mediated adverse event, then the antibiotic isn't going to make much of a difference. So depending [on] how they respond to antibiotic therapy. But it's a good point and a good question. You really can get down a rabbit hole with treating one thing and running into more problems with another.

FEMALE 3 Hi, just a quick question. So we've been doing the dual ipi/nivo, and so we'll see after cycle two or three, we've been seeing grade 3 colitis or grade 3 hepatitis. And what we've tried to do after giving a significant break with steroids and after tapering off of steroids is coming back in with single-agent nivo. What are your thoughts on that?

MS. HOFFNER That's a really good question and a really good point. About the toxicities with combo therapy versus single agent, because they are

much less with single agent. So, I think that the answer to that question is that we don't know; however, you guys are not the only ones doing that, trying to come back to a single agent after having a significant toxicity with the dual blockade. So I think that with very close monitoring my opinion is that with very close monitoring, that's reasonable. I have seen that work. I have seen that be successful with patients, but it's something you have to be very careful [with]. Once you know that they have this immunogenic potential, they are always at risk for developing other IRAEs. Hopefully we'll get more information on that as we have those combinations in use longer.

FEMALE 4 I just wanted to point out -- and thank you, that was an excellent presentation -- that both companies that make those drugs have little pocket cards. We have patients that come from a long distance like you do, so it's really important to give them that little card with your number on it so the ER doc from outside can call you. Because many of them are not knowledgeable. I personally had a patient who ended up with a colostomy because she kept reporting to an outside ER. It was too far for her to come to us. The outside ER did not call us, and she ended up with a perforation and colectomy, colostomy, and then subsequently a stroke because of this situation. So, if we can really get patients to carry their pocket card with our number, it gives all the information about how they should be treated, if they have grade 3 AEs, particularly the colitis issue.

MS. HOFFNER Absolutely. So the BMS drugs do have the pocket cards. BMS came out with that with the ipi, and it was something that was very

helpful, and so they did that again with the nivo. I can tell you that all of the companies, all of the manufacturers of these drugs are looking at what we can do better for patient education and for patient materials that they can have with them. You know, we've talked about all kinds of different things like a fob on your keychain and a bracelet and the cards, and I've gone to a bunch of different meetings. It's been impressive. I can tell you that there are a lot of non-branded initiatives to get better at these immune-related adverse events and people understanding immune therapies, so a lot of the nonprofit organizations are coming together with the support of drug companies of course to make guidelines and information [so] that hopefully we have less of these issues down the line, and also initiatives to educate community physicians who are or are not in oncology and emergency room clinicians.

All right, I think our time is up. Thank you guys, this has been really fun. I appreciate it.

[END]