MANAGEMENT OF SIDE EFFECTS FOR PATIENTS RECEIVING MULTIMODALITY THERAPY IN THORACIC ONCOLOGY

Marianne Davies, DNP, ACNP, AOCNP®, Yale University School of Nursing & Medicine
Beth Eaby-Sandy, MSN, CRNP, Abramson Cancer Center, Hospital of the University of Pennsylvania

INTRODUCER Welcome back everyone. My name is Carolyn Grande and I am a nurse practitioner from the Abramson Cancer Center. I am also the Chair of the Education Committee for APSHO and serve on the planning group for this conference. Before we begin, may I remind you to please silence your cell phones for our next lecture? We are delighted to have our next speakers join us. Please welcome Ms. Marianne Davies of the Yale University School of Nursing and Medicine, and Ms. Beth Eaby-Sandy of the Abramson Cancer Center, as they discuss the Management of Side Effects for Patients Receiving Multimodality Therapy in Thoracic Oncology.

MS. DAVIES Thank you all for joining us and we are happy to be here for the second to last session for today. Beth and I are going to be discussing management of side effects of patients receiving multimodality treatment in thoracic oncology, but in order for us to set the scene, we are actually going to be giving you a little background on the state of affairs in terms of lung cancer right now. Our learning objectives are to identify strategies to mitigate adverse events of checkpoint inhibitors in particular, evaluate emerging data regarding the management of AEs, EGFR and ALK inhibitors. Then, also we

will begin to have a discussion about formulating plans to mitigate AEs associated with radiotherapy. These are our financial disclosures.

MS. EABY-SANDY I am just going to do a brief overview of lung cancer. Then we are going to talk about locally advanced non–small cell lung cancer, because there is a little bit that has changed in that field. The scope of the problem, I probably don't have to tell most of you, lung cancer is the second most commonly diagnosed cancer in men, next to prostate cancer, and the second most common in women next to breast cancer. However, if you take in the death rate and the perspective, lung cancer per year kills 154,000 people. That's more than breast, prostate, and colon combined annually. As you can imagine it is a common cancer, the second most commonly diagnosed, but it is also very deadly. Because of that reason our patients are on treatment constantly. It is not like they are having treatment breaks frequently. They are on treatment for metastatic disease almost all of the time.

Histology matters in lung cancer. We used to see that it was 50/50 between adenocarcinoma and squamous cell carcinoma, but when we talk about non–small cell lung cancer, adenocarcinoma is by far the most common type in the United States at 62%, followed by about 20% squamous. Small cell is that very aggressive type that makes up about 13% and that number is shrinking, then 5% is a mixture of everything else. But that does guide our therapy, based upon the histology. If you look at the stages in survival, you can see most people, unfortunately, are diagnosed at a distant stage, so 57% will have metastatic disease, but then another 22% will have what is called regional, but that is stage

III, which is also very aggressive and only has about a 15% 5-year survival rate. So, 79% of these are usually going to be advanced and require life-long treatment. Let's pause and talk about stage III for just a minute. What is stage III lung cancer? Stage III lung cancer means you have a tumor on one side of your chest and the lymph nodes have spread into the mediastinum, or the centralized area. Not the hilar nodes, which are adjacent to the tumor, but they have spread into that middle or mediastinal area of the chest. A stage IIIA means that they are on the ipsilateral side, or the same side, of the tumor. Contralateral is a stage IIIB, which means that the mediastinal nodes on the other side of the mediastinum; it's crossed over the mediastinum is a stage IIIB. Then there is a new stage IIIC, which is a satellite nodule in a different lobe of the same lung. There are various other things that can make you a stage III when we look into tumor size, but that's in general what we are seeing. Like I was saying the 5-year survival rate is not great, even with treatment for stage III lung cancer. I took a look at some of the hallmark studies; the CALGB 39801 was an old study with paclitaxel and carboplatin plus radiation, a common regiment that we use. Across studies it is anywhere between 4% and 19%. The reason I put 5-year survival rates is these are kind of the cure rates. In lung cancer, if you can go 5 years without your cancer coming back, we generally consider that a cure rate. It is rare that it would come back after that. The other common regimen seen in locally advanced disease, or stage III, is etoposide, cisplatin, and radiation. This is given day 1 though 5 with cisplatin on day 8 again. That had a little bit better survival depending on the study that you looked at, somewhere between 15% and one

looking at even 29% 5-year survival rate. A large meta-analysis looking at all the stage IV chemo-radiation studies for lung cancer said it was about 15% average 5-year survival rate. Therefore, unfortunately, 85% of these people are going to die of their disease and have recurrence. About 30% of patients are diagnosed in this stage. The standard of care is chemoradiation. You can do surgery, however, that is a little bit decreased now since I have been doing lung cancer for 15 years. We used to operate more on these patients, but the morbidity and mortality associated with pretty large surgeries for stage III lung cancer has somewhat gone by the wayside, especially because concurrent chemoradiation gives them just about as good, and sometimes better, survival rates than what we have seen surgically, so a lot of these patients will go to chemoradiation. Unfortunately, the median progression-free survival, so how long does it take your cancer to come back? Eight to 10 months after treatment. That's obviously terrible. I showed the three common regimens that we tend to use, some of which I have already talked about.

Now there is new data of adding immunotherapy. Let's talk about that. This is a trial of durvalumab, post-chemoradiation. These patients had chemoradiation with one of those regimens that I talked about, platinum plus another drug, concurrent with radiation, and for those patients who did not progress, and most don't, it is a very poor prognosis if your cancer grows while on chemoradiation. For those of those who did not progress, they were randomized to either get durvalumab at 10 mg/kg every 2 weeks for 12 months, versus placebo. What we found here was that not only was there a significant

improvement in the progression-free survival, so if you look you will see the progression-free survival, significant improvement over placebo. Then overall survival came out very recently showing that we are saving more lives than not and actually the median has not been reached. You see NR means not reached. The median survival about 28 months for the placebo arm, but the overall survival not reached yet. That's really encouraging to me, meaning that by giving this for a year after chemoradiation it appears that we are definitely saving lives. We will really look out for that 5-year survival rate when that comes out. We significantly prolonged progression. You can see 16 months versus around 6 months.

What are the toxicities from chemoradiation? I think you guys know these pretty well. Not much has changed in this is the past 15 years, except I would say there is probably less esophagitis. Would you agree, Marianne?

MS. DAVIES I think with more focused radiation and SBRT that we will see less of that.

MS. EABY-SANDY Yes, and proton radiation as well, which we do at Penn. I think we see definitely less esophagitis and less skin burns as well. The pancytopenias, we are really not going to change that. Chemotherapy is going to do its thing. Nausea, fatigue, radiation pneumonitis, but again they vary depending on what radiation technique the patient is getting, the patient themselves and what their comorbidities are, and what is the concurrent chemoradiation regimen you used. So, it's interesting, when that durvalumab study came out, we were all "Oh my goodness, we are going give everyone

pneumonitis." Marianne is going to talk about the side effects of immunotherapy, but one of them is inflammation of the lungs, pneumonitis, that is induced the immunotherapy. So we thought, okay, you just blasted somebody's lungs with radiation, damaged them, and now we are going to give them immunotherapy. We very much awaited this toxicity data, and as you can see here, it really wasn't much different from the placebo arm. You can see all grade of pneumonitis in the durvalumab arm was 33.9%, versus 24.8%, but if you look at severe, grade 3 or 4, meaning I had to discontinue the durvalumab, was 3.4% versus 2.6%, so not a huge difference. We were not significantly causing harm to these patients by giving them the immunotherapy.

So, our management strategies again haven't changed much for everything else, esophagitis, supportive care, unfortunately, most of the pharmacologic stuff doesn't work very well. I could yammer on about magic mouthwash, but ya'll know, especially with lung cancer patients, it's really hard to get something topical. They are getting radiated here, not here. So, to get something topical down to that esophagus is really difficult. Obviously the pancytopenias, we are not going to change much either. We can't give growth support, GCSF, for patients who are on radiation because there is an interaction there, especially for lung radiation, so we can't give supportive drugs to keep the white count up. Skin burns, mostly topical preps, but like I said, those have been less with the newer radiation techniques that we have. Nausea is a whole other ball game, and there is a lot of good medication right now to prevent CINV and just being on top of that and using the proper prophylaxis. Then radiation

pneumonitis, just know what to look for. I am going to do a slide on pneumonitis when we talk about the targeted therapies. I am going to switch over to Marianne now to give you an overview of advanced non–small cell lung cancer.

MS. DAVIES As Beth introduced, the histology is the first thing that we look at with non–small cell lung cancer, and that's what we are focusing on today, but also molecular driver mutations are of critical importance for our patients. We are going to highlight what those mutations are. Standardly, they have been *EGFR, ALK, ROS, BRAF*, and now we are monitoring patients for PD-L1 expression, and all of those really should be reflex testing in most facilities. In the past, our considerations were that we should always consider doing molecular testing, particularly in patients who are never smokers and those with mixed histologies, but you will see as we go on that we probably need to think about doing these by reflex in all of our patients. This is a fairly recent slide of all of the driver mutations that we have in non–small cell lung cancer, and you can see that the largest driver is *KRAS*. Unfortunately, at this particular time, we do not have targeted therapies to *KRAS*, and 36% of our patients do not have an identifiable oncogenic driver. *EGFR* was one of the first ones that we identified, that makes up about 17%, followed by *ALK*, and then there are several others that make up the platform for molecular drivers for this population.

We will start with *EGFR. EGFR* makes up about 20% of our lung cancers. It occurs more in men than in women, more common in Asians than Caucasians, more common in never smokers. That's why we target the never smokers always when it comes to looking at molecular drivers. The thing, as I suggested earlier, if

we only targeted people that were women and never smokers, we would miss about 57% of the patients that potentially could have this as an oncogenic driver. In patients with *EGFR*-mutant non–small cell lung cancer, first- and second-generation EGFR TKIs are superior to platinum-based chemotherapy doublets. Platinum-based chemotherapy doublets really were the standard of care for more than 15 years, until I had the *EGFR* as the identified driver. This study is one of our second generations. This is of afatinib, and you can see that over cisplatin-based doublet, almost doubling the progression-free survival. We have multiple studies looking at several of these targeted therapies that demonstrated similar results. The unfortunate thing is that these oncogenic mutational-driven cancers, once we diagnose and identify it, after the first- and second-generation TKI, there is the development of clinical resistance to that EGFR TKI. That typically occurs at about the 1-year mark. So, as soon as somebody is diagnosed and we begin to treat them, already we need to begin to think about what our second-line treatment is going to be for that patient. Our current practice now, in many cases, is to rebiopsy patients, and that might be either tissue biopsy, or it may be liquid biopsy, to look at these mechanisms of resistance. The most common mechanism of resistance for *EGFR*-driven lung cancer is T790 mutation. That makes up about 60% of those drivers of the mutation. That begins to be where we target our development of our next generation of therapies. Osimertinib is a third-generation EGFR inhibitor and that specifically targets that T790 mutation. When we look at progression-free survival and overall survival against standard EGFR TKI, you can see superiority in that third-line TKI inhibitor. So, again we

are expanding our palate for what treatment options we have for our patients. When we are looking at acquired resistance now to third-line therapy, because again we get a certain length of opportunity to treat patients even with a third line, now we are beginning to look at additional mechanisms of acquire resistance. Again, this requires either additional serum, liquid biopsy or tissue biopsy to look at it. There are a few mechanisms that actually pop out at us. One is the MET mechanism. It is an acquired resistance. They didn't have it as a primary driver of their lung cancer, but they are developing it as a secondary mechanism. We also see that. Although, it looks small in here, we actually do see that that's one of the higher acquired mechanisms of resistance.

In summary, for initial therapy for nonsquamous non–small cell lung cancer, with *EGFR* mutations, osimertinib is our first-line therapy, followed by erlotinib, afatinib, gefitinib, dacomitinib. We look for progression at the T790. We test for that. We test for other acquired resistant mechanisms, and, again, begin to think about what our next line is. Right now, looking at also combinations of therapy and what is the appropriate sequencing. Some of the discussion now revolves around the thought that maybe we should start with the osimertinib in the first-line setting for so many practitioners I think have actually gone down that path.

Now, let's look at the *ALK* mutations. This is an ever evolving field as you will hear shortly. Crizotinib was the very first one that was approved; however, it did not really have good penetration in the blood-brain barrier and brain metastases are one of the most common mechanisms of progression of disease

for *ALK*-driven non–small cell lung cancers. This was followed by second generation, so ceritinib, alectinib, brigatinib, and now we have third-generation lorlatinib, and others that are in clinical trials. Currently, right now, crizotinib, ceritinib, and alectinib are approved in first line or later therapies and brigatinib approved in second-line therapy. As of yesterday, the FDA has now granted approval to lorlatinib in second-line and later therapies. We are constantly in this race to keep up with our treatments.

This gives you an idea of improvement with our second-line treatment with alectinib over crizotinib. The reason there is such a significant improvement with alectinib over crizotinib for the *ALK*-driven cancers is because there is significant improvement in control in the CNS. Those patients treated with crizotinib have a fourfold increase in CNS progression versus the alectinib. There is improvement in overall survival given that line of therapy. There are other mutations. We have got *ROS1* gene rearrangements; crizotinib is now approved in the treatment for those rearrangements, as is ceritinib. I am not sure, I didn't read the FDA approval really closely to see if lorlatinib was actually approved in this, but I am assuming that it would have received that approval, because it is an ALK and a ROS targeted TKI. For *BRAF V600A* mutation dabrafenib and trametinib are approved therapies. MET exon 14 makes up about 3% of non–small cell lung cancers and crizotinib is the approved recommended therapy in that line. RET inhibitors. There are a few. These are just two of the ones in trials right now. There are certainly other targets that are involved in non–small cell lung cancer, such as HER2 and the NTRK fusions. Again, the field continues to grow. This is

my attempt at providing a summary of the mutations. The ones that are in bold are those that have approved agents right now. Those that are in just regular text are those that you might be able to consider in off label or compassionate use in some cases, and some of the ones in italics are actually in emerging therapies that are in clinical trials right now. Again, this is not just one disease, even within the context of lung cancer, within non–small cell lung cancer there is certainly a huge range of different cancers that we are treating with different targets.

In general, for those that don't have actionable mutations, adenocarcinoma is the first-line treatment in the NCCN guidelines, is pembrolizumab, an immune checkpoint inhibitor or for patients that perhaps don't qualify for just single agent, if they don't have an appropriate PD-L1 expression of 50% they can get combination chemotherapy and immune checkpoint therapy with carboplatin or cisplatin, pemetrexed, and pembrolizumab. Also, recommended in the NCCN is carboplatin, paclitaxel, bevacizumab, in an appropriate patient population along with atezolizumab. In the squamous cell population, pembro is also approved, as is combination chemotherapy and pembrolizumab, and for patients that are not immune checkpoint inhibitor candidates, then chemotherapy doublets really remain the standard of care.

In the second-line therapy, again systemic immune checkpoint therapy. This really lays out the foundation for all of our patients that don't have a driver mutation that's initially identified. In those patients that do have a driver mutation; however, if they do have progression of disease, they are candidates. If there is not a second- or third-line TKI that is in the lineup then they would be candidates

for immune checkpoint inhibitor therapy, or a doublet systemic chemotherapy. This is just an example of one of the approvals for KEYNOTE-24 for pembrolizumab, which really just did demonstrate in the initial report out in terms of improvement of overall survival over chemotherapy. This really extended out to the 2 years. This was an update in analysis that was done by Julie Bramer. This was what led to the approval. Next lines we are looking at, as I mentioned, is combination TKIs, but we are also looking at when we look at immune checkpoint therapy is combinations such as nivolumab, and ipilimumab over chemotherapy and a study that was just published this year by Matt Hellmann in the *New England Journal of Medicine* demonstrated that there is a significant improvement in progression-free survival, as well as duration of response for patients with non–small cell lung cancer, treated with doublet immune checkpoint inhibitor. At this point, it is not yet FDA approved in terms of that combination.

Just a really quick summary as far as the immune checkpoint inhibitors that are approved for non–small cell lung cancer: We have got nivolumab in both of the dosing schedules, whether it's every 2 weeks or every 4 weeks. We have pembrolizumab in the first-line setting and second-line setting. There is some consideration for PD-L1 testing. Atezolizumab and, as Beth already explained, the one that's approved for stage III, is the durvalumab.

Moving on to toxicity management.

MS. EABY-SANDY We wanted to make this more the bulk of the talk, and talking about how we manage toxicities. I am going to talk about the targeted therapies. We will start off by talking about EGFR inhibitor rash. We

know this is the most common toxicity we see with EGFR inhibitors, but I do think it's interesting because now with osimertinib being available in the first-line setting we have seen significantly less rash with this drug. You wouldn't go generally to another first-generation EGFR inhibitor in the second line. So, I've seen less rash in my population of patients. It tends to be on the face and chest, but it can be on other parts of the body. It can range anywhere from very mild to pretty severe. It is often described as a papulopustular eruption because it tends to be acne-like in the way that it forms. Why does it happen? We don't necessarily know exactly, but what we do know is the epidermis, that layer underneath the first layer of your skin, really relies on epidermal growth factor in a large way. What ends up happening is, when you inhibit epidermal growth factor, you are going to have negative effects on the epidermis. The epidermis is responsible for holding fluid and basically hydrating your skin. That's why it gets so dehydrated. The epidermis becomes very thin because EGFR is being inhibited, so you end up with very dry skin, thin flaky skin, and then we also thing there is a recruitment of the immune system, and that's where you get the pustular reaction, due to the inhibition of epidermal growth factor. We think that's generally why it occurs and why we have the symptoms. Now I put cetuximab and panitumumab in here. They are not approved in lung cancer. Cetuximab sometimes can be used, but it does not have an FDA approval, but I put some of the incidences in here, just to give you an idea that they do vary pretty significantly sometimes between drugs. The pink ones are the more recent ones. As a matter of fact dacomitinib was just within weeks, has been approved in lung

cancer, another EGFR inhibitor, so it is a pretty crowded field, but if you look over in that grade 3 or 4 incident column you can see osimertinib, which is the one we generally are using first line, only 0.5% of people have a severe rash with that. That probably has the best outcome when we talk about toxicity from rash, and that's been pretty nice. There is a meta-analysis looking at EGFR rash and clinical benefit. This was published in 2013, so this was before osimertinib was getting most of its play. This was generally taking into account the other drugs which were causing significant rash. And rash did play a significant indicator as far as response. We do know that is true in lung cancer, with the EGFR inhibitors, if you have an *EGFR* mutation, you are taking an EGFR inhibitor, and you get a bad rash, that tends to correlate with response, which was all the more reason that we wanted to make certain we were treating it well. However, that really does not apply with osimertinib. I want to make that clear. Osimertinib has such a less amount of rash, and basically better results in the first-line setting than those other drugs. I want to be clear, even while this does correlate, it does not really correlate with the osimertinib as much, because this meta-analysis looked at that before osimertinib was in the first-line setting.

Can you do preventative measures? Yes. There was a study. Now, this is panitumumab patients which has a higher rate of grade 3-4 rash than the usual ones that we use, but this did show an improvement in colorectal patients, if you preemptively gave them doxycycline and topical hydrocortisone cream. I will say the study you had to put topical hydrocortisone cream all over your body, so the compliance was iffy on that study, and that was difficult. It was a very select

population. I'm thinking of the tube I would prescribe, that would get my arm. So, this is not overly real world, and I can't say that I've done this with most of my EGFR, but what I will say is I was part of a paper that was recently published for osimertinib and we do not recommend preemptive treatment because the rash is so minimal that we don't think there is any need for prevention.

Other suggestions for prevention of the obvious, use creams without dyes or fragrances, use SPF sunscreen when you are going to be out in the sun, or even if you are not going to be in direct sunlight, but you are going to be out and about, use something like that, protective clothing. Erlotinib or afatinib are recommended to take on an empty stomach because that's going to give you a more regulated absorption, as opposed with food, which would speed up the absorption and give you more significant toxicities. The other drugs can be taken with or without food and not effect rash. Avoid, obviously, very hot showers, direct sunlight or extreme temperatures. The MASCC recommendations for treatment state that – there are some topicals listed up there. You may not know some of these, and MASCC is a multinational organization, so we chose topicals that are available all around the world. Fluocinonide is a higher potency topical steroid, so I wouldn't recommend a whole lot of use of that on the face, but it is topical and can be helpful for the rash. The systemic would be doxycycline or minocycline, so the antibiotics patients will ask how long should I remain on them? There is safety data that you can remain on these drugs for a significant period of time, months and months, but a lot of time the rash will wax and wane, so if they are on the antibiotics for a month and the rash improves they can cut

out the antibiotics and see how the rash is doing. You can use a retinoid, which is recommended there, but I don't usually prescribe that. If it gets to that point I am going to refer them to dermatology.

Just some pictures of rash: This is a mild to moderate rash. The patient just has it around her nose and her chin. It was bothersome, but not severe. For her, she was on erlotinib. We continued it and prescribed some topical clindamycin to dry up the pustules some, encouraged her to moisturize. This is a patient with a grade 3 rash initially, that you can see on the left, and you can see he wasn't shaving anymore. With men, you know it's bad when they can't even shave their face. We treated him with oral doxycycline and topicals, and you see he did improve. This was only a week later, so he did have improvement with that. That is something that is reasonable to treat a grade 2 or 3 rash that way. This is a patient with a severe grade 3-4 rash. She claims she wasn't in the sun, but you can kind of see the sunglasses line, but what I will say about this, is she may not have been. What we tend to see is the rash from – this drug-induced rash tends to be worse in patients where they have had prior sun exposure. So it looks like she probably had a lot of prior sun exposure there and the rash. We have also seen this with men who wore V-neck T-shirts a lot of their life. They are on these EGFR inhibitors and then they get the rash just in that V area where obviously they have had sun exposure over time. For this patient we held drug, treated her with topicals doxycycline, and then we restarted at a lower dose. Obviously, be sure she is using sunscreen. Has anyone seen trichomegaly? So, curling of the eyelashes, this is pretty significant, this is a woman, and she had

just trimmed them. This is usually a longer-term side effect after being on the drugs for many months. We recommend trimming them carefully, but if they are curling in, really try to consult ophthalmology and see what they might think, because this can certainly develop into blepharitis, conjunctivitis, infections, scratching of the cornea, so just an annoying side effect.

Paronychias. Paronychias can be on the fingers or the toes. This is inflammation around the nail beds. It is not bacterial usually, although you can culture it, if there is a bacterial component you can treat it, but generally it's not. It is usually inflammatory due to the inhibition of epidermal growth factor in this area. Usually treatments, you can do diluted vinegar soak, only a tiny bit of vinegar per water. There is also bleach soaks, again, a very, very small amount of bleach to a very large amount of water. I would recommend looking at the MASCC Skin Toxicity Study Group paper on this if you want the exact ratios, but again, you can culture it, topical steroids or even cauterization with silver nitrate, but for a lot of these cases, I have sent them to dermatology or podiatry to consider a partial nail avulsion. That's what it ends up with a lot of times because you don't necessarily want to hold drug, and that's not something that's going to resolve quickly from holding drug, especially the patients need the EGFR inhibitors. I will say as much as I said osimertinib doesn't cause as much rash, doesn't cause as much rash, this is something that osimertinib causes just as much, if not more than the other EGFR inhibitors. Paronychia is a real thing that we still struggle with.

MS. DAVIES I think it's worth making sure you send them to the dermatologist because the other consideration is that some people wind up holding their drug and you have less compliance with medication adherence when they have these types of really painful side effects. If they can't get their shoes on, they can't walk, they might stop taking their drugs.

MS. EABY-SANDY Yeah, loose fitting shoes or flip flops are better, but we all know how that goes in the Northeast in the winter, not the shoes of choice. Fissuring and cracking, again really dry skin can occur from this, so you want to use thick moisturizing creams, but really super gluing these fissures together is really the best thing, but that's actually recommended in our MASCC paper, using a super glue to glue these cracks and fissures together so they don't get infected. Scalp rash can be difficult to manage. This was actually a patient on osimertinib, so while she didn't have much of a rash anywhere else, she did have issues with her scalp and dry scalp. Selenium-based shampoos or moisturizing shampoos, and then there are some prescription shampoos as well. Then, pruritus and psoriasis, itching and dry skin can become really bad. This is again an osimertinib patient. Antihistamines, topical moisturizers, and I put a question for aprepitant and pregabalin, which have a little bit of anecdotal data that's been published in looking at this, but I can't say that I have ever used either to treat this.

Diarrhea is the second most common side effect of EGFR inhibitors, and I just put incidences up there. Again, it varies over the drugs, but if you look at osimertinib, only 2.2% grade 3-4 as compared with some of the other drugs that

approved now in lung cancer. Incidents wise, they probably all are around 50 to 60%, other than dacomitinib or afatinib which have a higher rate. Loperamide, diphenoxylate atropine, hydration, electrolyte repletion, or dose reductions which often happen with afatinib. I can say we dose reduce for diarrhea every once in a while, but I don't dose reduce too often for diarrhea with these drugs. Usually it's pretty manageable. Side effects can vary from drug to drug, especially the incidents. Dacomitinib was just approved this month. It does have superiority over gefitinib in the first-line setting, but again, there is no head-to-head with osimertinib, which is the drug we are most commonly using, which also appears to be least toxic. Afatinib has some post hoc analysis looking at using 30 mg as opposed to 40 mg; 40 mg is the dose that was approved in the first-line setting, but it appears that the pharmacokinetics are really the same between 30 and 40, and 30 seems to be much better tolerated for this drug.

MS. DAVIES Some people will start at 30 and escalate up to 40.

MS. EABY-SANDY I think that was interesting, that the pharmacokinetics were the same. Moving on to *ALK/ROS1*. This is again, not a ton of patients. *ALK* is only about maybe 5 to 7%, and *ROS1* is 1%, but I chose these drugs individually because these have different side effects. As opposed to the EGFR inhibitors where it's rash, diarrhea, rash, diarrhea, these drugs have different side effects depending on the drug. The one weird thing with crizotinib, and this was the standard of care for years and years, so you may still have patients on it, is these visual changes where in the first 3 months they are taking

the drug they have a hard time going from light to dark. At night, especially, in a light room, and then you walk into a dark room and flip the light switch on, the images just trail all back and forth. I have heard a lot of descriptions of it which seem odd. It is not an injury to your eye, or any eye problems. We just recommend not driving at night because that can be difficult when it's dark and you have headlights coming at you. You can see the rest of the warnings. I am going to talk a little bit about some of these, but this is pneumonitis. Pneumonitis or ILD. We talked briefly about this. I want to make a clarification, pneumonitis from the TKIs is much worse usually. This is a permanent discontinuation, whether it is an EGFR inhibitor, an ALK inhibitor, the oral tyrosine kinase inhibitor, this is severe and it is a permanent discontinuation. It's not I-Os where you can treat it and rechallenge. We do not rechallenge with these drugs. This is a patient with a CT scan before starting crizotinib on the left hand side. You can see only 2 weeks later significant bilateral pneumonitis from crizotinib. This had to stop and never give again. It can be severe. Obviously, acute onset shortness of breath needs to be worked up with a CT scan right away.

MS. DAVIES Some consideration for that too is that if you are thinking about them moving on to second-line therapy with an immune checkpoint inhibitor, that would be a significant risk factor for that patient.

MS. EABY-SANDY That's a good point. Ceritinib was the second drug approved. I put these in order of their approval. Ceritinib was the second drug approved, but I can't say that I use it a whole lot anymore in my practice either. The most common adverse events were pretty significant. Those are

pretty significant GI toxicities. I will say there is recent data to support a significantly lower dose, 450 mg daily instead of the 750 mg, on an empty stomach, and there is less GI toxicity with it. But due to the toxicity, this drug didn't get a whole lot of play. Alectinib is the drug we are generally using in the first-line setting, due to superiority that Marianne mentioned earlier. The one thing that is a little bit different about alectinib is CPK levels can be elevated and that can also manifest with myalgias, significant myalgias in some patients. Just be aware of it. We do routinely check CPKs on these patients, though sometimes they are elevated and there are no myalgias. It kind of all depends, but you have to follow your institutional guidelines on if you are going to dose reduce, which I have had to do in the past for this. Brigatinib, I was about to say is the newest one, but as of yesterday lorlatinib is the newest, but brigatinib was recently approved in the past year or two. The one good thing about this, I think it's the only one that's one pill once a day. That's helpful. But the ILD rate, or interstitial lung disease rate or pneumonitis rate, is much higher with this one than the other ones. However, this is one, unlike the rest, that you actually can manage it and retreat, and dose reduce, as opposed to the other TKIs. This is the only drug that has a higher rate of ILD, but it's usually not as severe and usually you can dose reduce, treat with prednisone, dose reduce, if they recover. That's why there is a run-in of 90 mg daily. If the patient tolerates that you go up to 180, but if they develop ILD and that 90 mg cohort, then you are going to hold drug and dose reduce. Lorlatinib was approved yesterday. I didn't get a chance to put a slide in, in the past 24 hours on it. The only thing I will say about lorlatinib is that it tends

to have the same side effects as the other ALK inhibitors, which is a little bit of nausea, a little bit of GI toxicity, a little bit of edema, but the one thing that is specific to it is hypercholesterolemia, so we have seen some elevated cholesterol levels in these patients. That is one thing we check on study with them as opposed to the other drugs.

Conclusions: Alectinib is superior to crizotinib in the first-line settings and toxicities significantly vary as opposed to the EGFR inhibitors. You have to know drug to drug.

Real quickly BRAF, BRAF is a thing in lung cancer too, not just you melanoma folks. We have this in lung cancer as well. It is pretty rare. Only 1%, but again, the main thing I'll highlight, I have a whole bunch of stuff on there, is the fever. The fever is weird with this. Patients get it, but if you hold drug, and it's a high fever, 102, 103, and I often will do an infectious workup the first time, but usually it's going to be negative. Hold drug, and usually you can restart them at the same dose. Sometimes they will get a fever again, and then you hold it, and restart them at the same dose. You don't always have to dose reduce for fever. That's the one thing I will say about this.

Long laundry list here of other drugs with other toxicities, but for the most part there is a little bit of cardiotoxicity with some of the ALK inhibitors that you may want to check and echo at baseline, or even an EKG, but for the most part, these drugs are generally well tolerated, especially the second and third generations. So, conclusions: Several targeted therapies are approved in lung cancer. They generally have different toxicity profiles, so you have to check the

package insert or really be knowledgeable of the drug. There is more and more to come, literally, as we know, dacomitinib and lorlatinib are just in the past weeks, and most of the toxicities are predicted, so they should be manageable because we should know they are going to happen and educate patients about them.

MS. DAVIES Now we are on the fast track, and management of toxicities of those immune checkpoint inhibitors, which have become the mainstay for all of us. So, as we know, immune checkpoint inhibitors promote T-cell activity, but that activation really cannot be confined to anti-tumor effects alone. That amplification of the immune system can lead to unrestrained T-cell attack on any organ system. The first key in terms of managing patients is that we want to make sure that we are ruling out any other cause for these toxicities. My colleague, Emily and I did a meta-analysis of several of the earlier studies. This was published about a year and a half ago now and it's already out dated, but looked at several different combinations of therapies and looked at each of the toxicities, and looked at the range. This is not, and I'm sure you can read this very clearly all the way in the back, but looked at each of the toxicities to see when was the median onset, based on drug, based on combination, and what was that span. What we know from these therapies is that the median onset is about 5 to 12 weeks across the checkpoint inhibitors; however, it can occur within days. It can occur even within hours. We have had some cases of recorded acute pneumonitis, or pericarditis, within even hours. They also can occur after months of treatment or even after discontinuation of treatment. It may

effect one organ, or it may effect multiple organs, and at this time we don't have any biomarkers to help us identified what patient is going to be at risk for which of the organ systems that are going to be affected, or in what sequence. So, that's where a lot of the work on looking at immune-mediated adverse events really is going at this time. The incidents and severity is higher in anti-CTLA4 agents over those with PD-1 or PD-L1 agents. There is some suggestion that there is a dose dependency. We do know that there is also some suggestion that there is a cumulative effect with anti-CTLA4 agents that we don't tend to see with the anti–PD-1 or anti–PD-L1 agents. There is also an increase with the combination of the immune checkpoint inhibitors. One thing I want to point out, we are talking about in lung cancer anti–PD-1 and anti–PD-L1, but there are several other checkpoints that are currently under investigation. We are beginning to see in clinical trials, phase 1/phase 2 trials at this point, combinations of using those other checkpoints, so I am sure at that point we will begin to see even another kind of picture of the presentation of these immune checkpoint adverse events. When we look at the treatment-related side effects, in terms of combination, I just wanted to point this out. This was also published by Hellmann this year in the *New England Journal of Medicine*. This is looking at the treatment side effects of combination drug, the darker colors on both sides are grade 1/grade 2, so we can see that most often times, the toxicities are fairly well tolerated, and then the lighter colors on each are the ones that experience grade 3-4 toxicity. This was combination of nivolumab and ipi, and this is nivolumab as a single agent. You

can see that there is just an increased risk of that treatment-related side effect in the combination therapy.

We are going to do it by organ system as best we can. We can't cover every single organ system, but in patients with lung cancer, they do experience a slightly higher rate of pneumonitis as an immune-mediated toxicity over some of the other organ diseases that we see, slightly higher rates than patients with melanoma, renal cell carcinoma, and others that are treated with immune checkpoint inhibitors. Keys to getting patients ready to be on treatment, in terms of prevention, smoking cessation is really important. Patients do tolerate treatment and have less risk of pneumonitis if they stop smoking, if the receive the appropriate vaccinations. Those that are at risk are those that have received prior chest radiation, those that have COPD, and I should certainly add, those that have been on a TKI and have had any experience of pneumonitis, so a drug-induced pneumonitis, would increase a patient's risk of developing pneumonitis due to an immune checkpoint inhibitor. Presentation is typically dyspnea, shortness of breath at rest, a dry nonproductive cough, so any change in the respiratory status. Tachypnea, tachycardia, very infrequently patients may develop a chest pain, but typically what we will see is a change in their oxygen requirements, so if it is somebody who is oxygen dependent, they might have to turn up their level of oxygen support. They might have an increased need with any type of exercise, or even in the evening. The really easy thing to ask patients is, can you walk as far as you used to be able to walk, can you climb the stairs the way you used to be able to, do you need to take more frequent breaks in

order to accomplish the same task? Then, monitoring their oxygen saturation is a very quick and cheap way to monitor their status. Other things on physical exam, measuring heart rate, again the oxygen saturation, getting a diagnostic imaging, CT scan is really the standard tool. Some people will do x-rays, but you really can't typically get a good picture of a pneumonitis, or the level of pneumonitis, or lung involvement, in order to grade it, by just doing an x-ray. Typically, you will see interstitial infiltrates, ground glass opacities. Important when you are ordering your CT scans, typically we will inform the radiologist if they are not familiar with immune checkpoint inhibitors, that we are looking for drug-induced pneumonitis or we are trying to make sure that we are ruling out other causes, so is there a risk for pulmonary embolus, is there progression of disease, is there is lymphangitic spread of disease or pneumonia or effusions? You want to make sure you are really painting that picture for the radiologist so they can give you the best feedback possible. In terms of laboratory assessment, if a patient does have an infectious appearance, you can continue to do an infectious workup if you're worried about an infectious pneumonia, but typically these patients done always have that. For consultation, pulmonary and infectious disease can be very helpful in managing the toxicity. The important thing, what we are doing, is we are going to grade the toxicity. In general standards, if the patient has less than 25% of the lung involved, that's considered a grade 1 or mild. These patients might have very subtle symptoms or maybe not any symptoms at all. They may just have some diagnostic changes that were picked up on the restaging scans. In those cases we can continue on with immune checkpoint therapy. For grade 2,

where there is 25 to 50% of the lung involved, or the patient has become more symptomatic, the recommendation is to hold the immune checkpoint inhibitor. If the patient is more hemodynamically unstable we will begin steroids with methylprednisolone at 1 to 2 mg/kg per day until the patient has stabilized. Once they have gone to a grade 1 or resolved, then we begin to taper that steroid over a month. For grade 3-4 where there is more than 50% of the lung involved, then that is going to be considered grounds for permanent discontinuation. The patient should also have an infectious workup and be followed with a pulmonologist. If a patient does not have recovery of symptoms or improvement in symptoms in 24 to 48 hours, we raise it or escalate the treatment to the next level of immunosuppression. That would be infliximab at 5 mg/kg and the second dose can be given in 14 days if that is necessary.

Dermatologic toxicities are the second most common. When you look at melanoma, derm tends to occur more frequently in melanoma and pneumonitis kind of third in line in terms of the toxicities, but it is a little different in lung. Prevention is just as with the TKIs, sunscreen, moisturizer, instructing patients to wear sunglasses. Risk factors are if they have an underlying dermatologic condition such as psoriasis or eczema. Presentation, often times the first presentation is significant pruritus. Patients might say that they feel like they are crawling out of their skin, even if they don't have any demonstration of a rash, but they then will develop a macular papular rash. If it does progress, patients have progressed to 10, so toxic epidermal necrolysis, or Stevens-Johnson syndrome, such as the patients in some of these pictures in the bottom. You want to rule out

other causes, such as cellulitis, contact dermatitis, allergies, sun exposure, radiation recall, other drug reaction, or maybe it's going to be a flare of that underlying autoimmune disease. Again, physical examination of the skin is important, and in general no diagnostic imaging is done. In terms of lab work, occasionally the rash might be a little bit concerning and questionable enough where it is not so clear that it is due to the immune checkpoint inhibitor, in which case a dermatologist can be very helpful and oftentimes biopsy the rash to really clarify the etiology of that rash. Right now, our grading is based on the MASCC guidelines for grading and it's really not the best tool for grading a dermatologic toxicity from and immune checkpoint inhibitor. Right now we use the body surface area, so grade 1 is less than 10%, grade 2 is 10 to 30%, grade 3-4 is greater than 30% body surface area, but what I will say is that a rash can be significantly toxic to a patient and it might only be in a 10 to 15% area of the body. You can actually develop sloughing of the skin such as is suggestive of Stevens-Johnson's type syndrome, and again it might be a small body area. So BSA is not the best tool. You really need in combination to look at the severity of the rash or the skin disorder, and also the percentage of the body that's involved. But for the tool that we have right now, for what we are using, we continue on with the immune checkpoint inhibitor at grade 1, and using topical steroids and moisturizers. For a grade 2, we would do a higher potency topical steroid, plus/minus oral prednisone, and grade 3-4 we would hold the immune checkpoint inhibitor, treat topically and also treat systemically with the methylprednisolone. Other considerations, again as I mentioned, a derm consult is quite helpful in

identifying the etiology and the management. In most cases, these patients, if their rash resolves we can go on to successfully treat them, unless they have had the Stevens-Johnson syndrome. It tends to kind of wax and wane through the course of their treatment and it might not recur at all.

Gastrointestinal toxicity, diarrhea, and colitis: The one thing I would like to point out and raise awareness in terms of the colitis, colitis does not always mean that the patient has a significant increase in the number of stools that they have per day. Think about our lung cancer patients, that might be on high doses of opioids, they might have chronic constipation, and so an onset of colitis for them might just mean they are now going every other day, or maybe just once a day, but if it is associated with abdominal cramping, discomfort, or even spasm or pain, or associated nausea, that could be what colitis looks like for that patient. We know in the preliminary studies actually that the diarrhea unfortunately was kind of under reported in terms of its significance. Again, monitoring the volume is going to be important. If it is less than – what we are still using is the old criteria, which is not immune related, but for now that's what we have, so less than four stools per day considering holding the immune checkpoint inhibitor, treating with loperamide. If it is moderate, we are going to hold, initiate steroids. If they are refractory they will start on a secondary immunosuppressive agent. Grade 3, this is one thing that's a little different, some of the other grade 3s we permanently discontinue, for GI toxicity we hold and consider resuming if there is resolution of symptoms. Grade 4 is permanently discontinuing and starting steroids. GI consult can be extremely helpful in helping to manage patients.

Endocrine toxicities, the thyroid, can be significantly affecting. Patients have vague symptoms, fatigue, sluggishness, weight loss, or weight gain. Many patients may present with asymptomatic hypothyroid syndrome, so if a TSH is less than 10, we just continue to monitor their thyroid functions. They might not need supplementation. If the TSH is greater than 10, we continue, but we introduce levothyroxine. Again, in most of these cases, what we are doing is targeting. We want to get our level to a T4 of mid-range. That's the lab that you are chasing. Central hypothyroidism is a secondary hypothyroidism due to dysfunction of the pituitary. We can continue the immune checkpoint inhibitor after we treat hypophysitis. Additional labs are around managing or assessing the hypophysitis in these cases. You can see that in most cases, we don't have to discontinue the immune checkpoint inhibitor because we are going to manage with hormone replacement.

Adrenal insufficiency is infrequent, but it can be life threatening if it is not identified correctly, so monitoring the appropriate lab values to assess for adrenal function is important, including doing a morning cortisol stimulation test. One key to adrenal insufficiency is that if you successfully manage these patients with hormone replacement, they can successfully rechallenge on the immune checkpoint inhibitor. The key is you want to start the corticosteroid hormone replacement, prior to any other hormone replacements, so prior to their initiation of levothyroxine replacement. You want to make sure you are avoiding adrenal crisis. Typically patients will need hydrocortisone or prednisone in the dosing that's going to mimic natural secretion, so higher dose in the morning, and lower

dose in the evening, as well as fluticasone replacement. Hypophysitis, again we are going to introduce the hormone replacement as necessary depending on the organ dysfunction that the patient is exhibiting. If you have successful treatment, you can go on to rechallenge these patients. There are many other organ systems that can be involved, I wish we had time to go through every single one of them, but in most cases, hepatic, renal, in most of those cases they tend to be slight elevations in the lab function, so you want to make sure you are assessing, holding hepatotoxic drugs, limiting nephrotoxic drugs, managing that toxicity. If they are in lower grades, we can usually go on to successfully rechallenge. Goals, refractory, IRAEs can occur, so the goal if you have no improvement in the toxicity after you have initiated methylprednisolone therapy, a secondary immunosuppressive agent might be necessary. Infliximab is the most common. It is contraindicated in patients that have hepatic involvement, or hepatitis. It can reactivate HBV, and also TB, so you want to make sure you test for TB. It does require preauthorization, which can be a lengthy process in some cases. Mycophenolate is a second immunosuppression agent that might be necessary. Other things that have been used are things like cyclosporin, IVIg particularly in the neurotoxicities that have developed.

Guiding principles: Corticosteroids really are the main stay of treatment for these patients. Use of the corticosteroid has not been shown to reduce antitumor effect, and that's important when we are educating our patients. Sometimes steroid taper might require more than 4 weeks, so keep that in mind. I have a patient who had pneumonitis that has actually been on about a year of a steroid

taper. We just can't get him any lower than 12 mg per day of prednisone. We need, if they are going to be on long-term steroid prophylaxis against pneumocystis, and also fungal infections, it is going to be important, proton pump inhibitor to prevent gastritis, and then just keep in mind if they are on long-term steroid use, prevention of osteoporosis. I have already talked about the infliximab risks. Just keep in mind also as there are more and more approvals for immune checkpoint inhibitors, that there are special considerations for patients that have either had an organ transplant in the past or stem cell transplant or maybe going to that in the future, that there is a risk of losing graft with stimulation of the immune system with T-cell activity. You have got to go down that path really cautiously. There are several resources that are available to help support you in managing your patients. Right now the NCCN, SITC, and ASCO have had a significant coordination of efforts in developing guidelines that are free and accessible to you. AIM with immunotherapy was just launched 2 weeks ago, and all of these organizations are here and you can get that information while you are here, many of which are available online to help support you in following algorithms for managing these toxicities, and keeping your patients safely on therapy.

MS. EABY-SANDY Marianne was the only nurse on the NCCN guideline panel for the management of immune-related toxicities.

MS. DAVIES Any questions? I don't know how much time we have. We are on a tight schedule, but I understand that there is really something fun to look forward to before the next one too. Beth and I are happy to

stay for any questions. If anybody has anything, we will be out in the back. Thank you.

[END]