First-Line Therapy for Non–Small Cell Lung Cancer: State-of-the-Art Targeted Therapy and Immunotherapy Approaches

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RASHEDA PERSINGER-ADAMS Good evening, my name is Rasheda Persinger-Adams. Welcome to our CE-certified symposium, "First Line Therapy for Metastatic Non–Small Cell Lung Cancer: State of the Art Targeted Therapy and Immunotherapy Approaches." This symposium is certified by the Annenberg Center for Health Sciences at Eisenhower.

Allow me to introduce your two speakers for this evening: Dr. Joshua Bauml and Ms. Christina Knepley. Dr. Bauml is an Assistant Professor of Medicine at the Perelman School of Medicine at the University of Pennsylvania and the Co-Deputy Director of Clinical Research for the airways program at the Abramson Cancer Center. His research is on improving outcomes for patients with lung and head and neck cancers by performing translational analysis surrounding biomarkers and doing advanced registry work.

Ms. Knepley is an oncology nurse practitioner for thoracic and head and neck malignancies at the Abramson Cancer Center Hospital at the University of Pennsylvania.

Please help me welcome them here tonight.

DR. JOSHUA BAUML Thanks so much, and thank you all for coming this evening. It's great to see so many faces out in the audience. So I'm really

excited to be here today with Christina to talk about how we manage non–small cell lung cancer. Over the last 2 years, it seems that our paradigm has changed about every 6 weeks, but now it's been steady for a bit, so these slides are up to date as of at least yesterday, right? So by tomorrow, I don't know, but it's good right now. And one of the nice parts about this talk is that we're going to talk about the updates from the therapeutic landscape in terms of trial data, but we're also going to talk about patient experience, how patients actually react when they receive these agents, and one of the nice experiences that I have as a clinician is I get to work with Christina, and we work together and collaborate on how we can take care of the patients. So she's going to be able to talk about some of the toxicities and how we manage those, which is basically what happens in our practice anyway, and so it's good to let her talk about her expertise, and I can talk about mine, and we can work together, and we also have an opportunity at the end to answer any questions that you guys may have about the data presented or about anything else about lung cancer, okay? So without any further ado, welcome, I already did that, good. Disclosures, these are mine and Christina's financial disclosures.

This activity will discuss some things that may or may not be FDA approved, you should consult your prescribing information to make sure that everything is appropriate.

So the learning objectives: What are we going to talk about tonight? We're going to talk about how we use biomarkers to guide the treatment of metastatic non–small cell lung cancer. We're going to talk about the clinical data supporting

first-line management using immune checkpoint inhibitors. We're going to talk first-line treatment plans and how that affects patient outcomes, and we're going to talk about how we manage adverse events because they happen; they happen in clinic, they happen frequently, and we need to figure out what to do with them.

So lung cancer is a major problem, and there are two types of lung cancer: There is non–small cell and small cell. Non–small cell represents the vast majority of lung cancers, and literally the reason this originated was that years ago, pathologists looked under a microscope, said these cells are small; these cells, not so much; and here's where we are at this time. Among non–small cell, we have adenocarcinoma, squamous cell, large cell, and other. Adenocarcinoma is the most common subtype of non–small cell lung cancer. It is present both in smokers but also among never and light smokers; this is the type of lung cancer they tend to get. It's more common in women than men. This is one that more likely occurs in young persons, typically found in the outer areas of the lung. It may grow slower, but sometimes it grows quickly. Squamous cell carcinoma tends to be central, very frequently associated with smoking. If someone has a diagnosis of squamous cell lung cancer, and they are never a smoker, I doubt that pathologic diagnosis, and we really need go back to the biopsy to see whether it is accurate.

Looking at biomarkers, this is a very complicated field. In adenocarcinoma, this pie chart over here represents the different subgroups of molecular targets that exist for adenocarcinoma of the lung, and you can see those ever-shrinking pieces of the pie, and what that means is that each of those

represents a subtype of lung cancer where the treatment and outcomes are markedly different. Now the big ones we know about. We know about *EGFR*, we know about *KRAS*, we know about *ALK*, but there are more and more of them. At this time, there are FDA-approved treatments on the basis of *EGFR* mutation, *ALK* fusion, *ROS1* fusion, *BRAF V600E* status, also *NTRK* and PD-L1 also guides treatment. So if you have a patient with nonsquamous non–small cell lung cancer who comes into your clinic, I don't know, maybe if there was a question about this topic, you would have to test them for these at minimum, and often there are different ways we can do that testing. In squamous cell, it's a bit more complicated. There are not molecular targets that are associated with specific response patterns, but PD-L1 testing is critical in this patient population as well. We still do the full testing as I described before in squamous if we doubt the diagnosis. A young, never smoker comes into your office, and the biopsy shows squamous disease, remember that a biopsy is usually a tiny needle going into something the size of a softball, okay? And so it might get at something that's not representative of the full picture, but still that mutation or molecular alteration would be there.

What are liquid biopsies? This is something that's becoming more and more prevalent. Liquid biopsies utilize circulating tumor DNA to identify molecular alterations. This is the same technology that is currently used in obstetrics where you can draw a blood test on a pregnant woman and identify DNA from the fetus. It's the same idea in patients who have a cancer diagnosis. The circulating DNA in their body is largely coming from the tumor that's rapidly dividing. This can be

a very valuable tool if your initial biopsy is not adequate to do molecular testing if it's too small. The key thing about liquid biopsies that you need to remember is that a positive test, you can act on, it's reliable. A negative test is basically useless. This is the opposite of a D-dimer, okay? So if you have a D-dimer that's positive, it's a useless test, but a negative one can rule out a clot. In this setting, a positive test is very useful; a negative test is not reliable because the sensitivity of the assay is only about 70 to 80%.

So let's talk about types of testing that are done, starting with things like PCR, IHC, FISH. These are individual gene tests. So they can test for *EGFR* or *BRAF* or *KRAS*, and this is how we used to do this testing. We would say, "Does the lung cancer have an *EGFR* mutation? No? Okay. Do they have *KRAS*? No? Okay." And you keep going down the line, but each time you do one of those tests, you use a little bit of tumor and a little bit of time, and our patients with lung cancer don't have a lot of both of those things, and so as a result, we've really moved away from things like PCR and IHC and FISH because we now use something called next-generation sequencing, and with this testing, we're able to, at one time off of a small sample, get a lot of information off of hundreds, sometimes thousands of genes. But we're now taking this a step even further than this. So DNA-based NGS – there are many commercial vendors that do this sort of sequencing. They are very good at identifying mutations, things like *EGFR* mutation, *BRAF* mutation. They're not so good at identifying fusions or translocations, things like *ALK, ROS1*, and *BRAF*, and that's due to the nature of the way those genes stick together. So what many centers including Penn is now

doing is doing a DNA-based NGS as well as an RNA-based NGS. This is sometimes called a multiplex PCR or Archer assay to identify fusions, and this has a much higher sensitivity for identifying things like *RET, NTRK*, and this is becoming more and more important as we learn about different molecular drivers.

So let's talk a little bit about our current therapeutic targets. I'm going to talk about immunotherapy in the second half here, but just remember, we do always have to check for PD-L1. So *EGFR*, epidermal growth factor receptor, is tyrosine kinase activated on cells, and sensitizing mutations can be seen in about 10 to 15% in caucasians, much higher in East Asians. The two most common mutations that are seen in adenocarcinoma of the lung are an exon 19 deletion and a point mutation in exon 21 called the L858R. There are rarer mutations. It's important that when you see a mutation that spits out on your NGS report to make sure that it's one of the sensitizing mutations. You can see here that about 85 to 90% of the time, it's going to be one of those top two; that's an easy answer. But if you find rarer mutations, and specifically on exon 20 insertions, those are not cases where we would use TKIs, and someone who doesn't have one of these alterations at all should not be given one of these treatments because they just tend not to work for those people. So these are the drugs that are FDA approved for the treatment of *EGFR*-mutant lung cancer as well as their indications.

I'd like to talk about the FLAURA trial. This is really what guides my current management of *EGFR*-mutant non–small cell lung cancer. Patients with

untreated sensitizing mutations in *EGFR* were randomized to osimertinib or a standard EGFR TKI, which was the investigator's choice of gefitinib or erlotinib; these were standard of care before this trial, and this is what we saw: We saw that there was a marked improvement in progression-free survival with the use of osimertinib, and we also just recently at ESMO saw that there was an improvement in overall survival with the use of osimertinib. And so this is a big deal, this changed the landscape for me, and the other reason it changed it is the safety. Osimertinib was better tolerated than gefitinib or erlotinib. There was a lower rate of fail/adverse events; similar rate of severe adverse events, but if you look at the rate of rash, it was much lower with osimertinib than with gefitinib or erlotinib, and so we'll talk about rash, but we have sometimes actually changed people who were stable on gefitinib or erlotinib to osimertinib because they were suffering so much from the rash. Taking a look here at the slide, you can see the rate of rash here, of severe rash, 7% versus 1%, but you can see that rash or acne is a most common cause of adverse events on this trial, just maybe calling your attention to that.

ALK and *ROS1* are other alterations that are seen. *ALK* is a fusion, as is *ROS1*. So if you do an NGS assay, and it says this patient has an *ALK* mutation, that is not a patient who gets targeted therapies. *ALK* mutations are not sensitizing; *ALK* fusions and translocations are. It's important to remember that these tend to occur in never or light smokers. These are the drugs that are currently FDA approved for the treatment of *ALK*-translocated non–small cell lung cancer. At this point, most of our therapy is based around the ALEX study.

This study randomized patients to alectinib or crizotinib, which was previously the standard of care for *ALK* translocated non–small cell lung cancer, and this what we saw: A marked improvement in progression-free survival with alectinib, and this to me was really remarkable because up until alectinib, every TKI was associated with a response of around a year, and then they would progress. But the duration of response, if you look at progression-free survival up here, at 2 years, you're still not at the median, so this is remarkable efficacy. And the other benefit of alectinib over crizotinib, and we actually see that similarly with osimertinib, is that both osimertinib and alectinib have excellent ability to penetrate the blood-brain barrier, and so they have efficacy against CNS metastases. Taking a look at the safety, you can see that in terms of all-grade adverse events, pretty similar incidents, but if you look at the grade 3 to 5 adverse events, there was a lower rate with alectinib than there was with crizotinib. I think both of these are relatively well-tolerated drugs, but in this study, they did find improved outcomes in terms of safety for alectinib.

So just a quick word about *BRAF* and *NTRK*: *BRAF*, and this is specifically *BRAF V600E*, so unlike in melanoma where many *BRAF* mutations are sensitizing to BRAF inhibitors, in *BRAF*-mutant lung cancer, it is only *V600E* that should be clinically targeted, and dabrafenib and trametinib are FDA approved in this setting. For *NTRK*, we now have two drugs for the management of *NTRK* fusion cancers. This occurs less than 1%, and we have two drugs in this space—just showing how exciting this field is.

There are emerging targets. So for *MET* exon 14 skipping mutations, we have crizotinib available, tepotinib and capmatinib that are in development. For *RET* fusion non–small cell lung cancer, we now have – there's cabozantinib and vandetanib, which are approved but have very limited efficacy and substantial toxicity. These new drugs, pralsetinib and selpercatinib, I promise, I'm not making up these names, they are very effective against *RET* fusion non–small cell lung cancer – RET fusion cancers in general, and they have much better tolerability than the old agents.

For *HER2* mutant, we have multiple agents. TMB, I'm going to skip for many reasons at this time.

So in summary, this is a really complicated field for targeted therapies. It is very possible that you will have a patient who comes in for a diagnosis of lung cancer, the type of lung cancer you've never seen, and that's okay. You always can reach out for help and say, "Look, I haven't seen this before. What do we expect with one of these drugs?" Reach out to colleagues at other institutions to work as a community to figure out how we can best take care of these patients. Chemotherapy does still work for these patients, but immunotherapy tends not to. With that, I will hand things off to Christina for the next step.

CHRISTINA KNEPLEY So I wanna go through some of the case studies that Dr. Bauml and I have seen with the targeted therapy. So normally whenever a patient starts, they see me about 2 weeks after they initially start the medication, and I normally reinforce education, go over the most common side effects. I encourage a patient diary for some of them. Us, at Penn, are lucky

enough that we have wonderful triage nurses that can call and check in on patients or take their phone calls if they have any questions, and again, patient education. Some of the side effects can include pneumonitis, colitis, dermatitis, hepatitis, a lot of ’itis's. So we're going to go through the first case study. I will be asking some questions, so I encourage audience participation.

So we have a 56-year-old female with exon 19 deletion and brain mets. She recently started osimertinib 80 mg about 2 weeks ago. She calls in reporting a new rash on her face and chest that looks like teenage acne that started about 2 days ago. So some of the general recommendations I would recommend for anyone who starts this, even before the rash would appear, moisturize the skin, sun protection out in the sun, long sleeves, hat, gloves if needed, avoid very hot showers with washing dishes and showering. We use a grading system; it's very helpful in the management of it: grade 1, less than 10; grade 2, 10 to 30, sometimes can be associated pruritus; and then there's the management to the side. Okay, so she called triage, you might message triage, "I would like a little bit more information," any additional symptoms for them to ask, itching, pruritus, or tenderness. So the likely cause of the rash? Yeah, the *EGFR*, and then what grade would anyone – what would you grade this rash at? So I would do a 2. So the management for that would be I typically would start with a topical clindamycin and then a topical steroid for the redness. Okay, so you start her on the meds, she calls back 2 days later, a little bit improvement, but now she has some tenderness in the areas of her rash and it spread a little bit farther down her chest. She also reports that her fingernails are hurting, they look like they

split, and her scalp is very itchy, and she had a little bit of diarrhea before starting, but now it's worsened over the last week. So paronychia can happen with these medications. Patient education. Again, avoid hot water when washing the dishes specifically, trim the nails. Sometimes I recommend water and vinegar soaks before starting any medication. You could do topical steroids or antibiotics, and if it's really bad, I would start systemic antibiotics. Scalp: Moisturizing shampoos, and I recommend the dandruff shampoos over the counter, or else you can do a prescription if it's needed. The same with the fissures: Basically avoid hot water is what I'm getting at, thick moisturization, and we sometimes recommend doing something like Krazy Glue if they're really bad. Okay, so she earlier complained of diarrhea; you can sometimes manage it well with over-the-counter like Imodium, and you can add a prescription if needed. It's really important to educate about hydration, and then again, the grading system is very helpful in how you would manage the side effects. Okay, so she called earlier in the case study and said it had gotten more tender and was spreading, so that's when I would add an oral antibiotic, normally twice a day. Sometimes if they've been on it for a long time, patients take it once a day, and it seems to manage, but that's up to their discretion and after we talked about our recommendations. She can use Imodium as needed, and she returns and is saying she's feeling well, and her scans show that she's responding nice to therapy.

All right, second case study: A 39-year-old female with *ALK* translocation non–small cell lung cancer. She was recently started on lorlatinib after progressing on alectinib. We've also added atorvastatin to her regimen, and

she's coming in complaining of shortness of breath. So pneumonitis can be a side effect of the TKIs. It's rare, but it can be fatal. If confirmed, you would not use that drug again. Normally, it shows up with acute onset shortness of breath, normally a workup would be a chest CT with contrast. And then an important side note – Dr. Bauml briefly discussed brigatinib. In particular, it's associated with a specific pulmonary event that is not pneumonitis. So that's an exception to the rule, and if there is a pulmonary event, brigatinib, if it's mild to moderate, you would continue escalating the dose; you start at 90, and then you would increase over a week, and then you would continue, and you watch the side effects.

Now we're going back to the case study. Okay, so you ordered a CT with contrast, and it shows no evidence of pneumonitis for this patient. Her shortness of breath resolved. As we learned, she's a 39-year-old patient, she's a little bit young. It didn't show any pneumonia or anything concerning. She just had a little bit of anxiety and ended up feeling better. She is noted though to have elevated LDL at her toxicity visit, so hypercholesterolemia is one of – it's a unique toxicity with lorlatinib. You monitor her labs, you hold treatment anything that's higher than a grade 3 or higher. It's okay to restart at a lower dose after she's a grade 2 or less, and again, we started her initially on atorvastatin, and you would always want to do a statin as a concurrent agent.

Patient education is key. I spend most of my visit educating patients on when to call and the side effects that they should be made aware of. Brigatinib is associated with a pulmonary event that's not pneumonitis, and hypercholesterolemia is a unique toxicity seen in lorlatinib.

DR. JOSHUA BAUML Great, thanks. So now I often say as a physician at Penn that if I give a talk and don't say the word immunotherapy, I get fired, so I said it, and I'm going to say immunotherapy a couple times now. So those patients who don't have these molecular targets, what do we give them? In lung cancer, we give them immunotherapy, and so we gotta figure out exactly how we're going to use that drug. So this was the first study that planted the role of platinum doublet chemotherapy in non–small cell lung cancer. So it's important to note patients with *EGFR* or *ALK* aberrations were not allowed on this trial because immunotherapy does not work in that setting, so it's absolutely essential that if you have a patient who is coming in, it doesn't matter what their PD-L1 is. If they don't have molecular data back, you have to be very hesitant about starting them on treatment, and specifically starting them on immunotherapy because if you start them on immunotherapy, sometimes you're unable to safely administer the targeted therapy, so it's absolutely essential that you be aware of that before you start treatment.

But in KEYNOTE-024, patients with greater than 50% PD-L1 were randomized to pembrolizumab or a platinum doublet, and you can see a very large improvement in progression-free survival as well as an improvement in overall survival, and based upon this, this drug was FDA approved for patients with greater than 50% PD-L1.

Now as with everything in oncology, greater than 50% is only a third of patients; could we help more patients by lowering the threshold? So KEYNOTE-042 looked at patients who were greater than 1% PD-L1 positive, again

randomized to pembrolizumab or a platinum doublet. And, you know, you first look at this, and you say, "Oh, the intention-to-treat is positive." But then you have to remember, the last slide that I showed you said that those patients who are greater than 50%, which is 50% of these people by the way, we know those guys already benefited from pembrolizumab. So the real question is, what about that 1 to 49%? Did they gain any benefit from the use of pembrolizumab over chemotherapy? And the answer is no. Okay? And so even though this study led to an FDA approval for patients who have PD-L1 greater than or equal to 1%, I personally do not recommend pembrolizumab monotherapy for these patients who are 1 to 49 because we know there is no benefit over chemotherapy, and you actually can see that in the early parts of this survival curve, pembrolizumab was actually worse, and so this is an issue that we need to be aware of. So what do we do for patients who are less than 50%? It turns out we have options.

So KEYNOTE-189 was a study that randomized patients, again excluding molecular drivers, to either carboplatin or cisplatin with pemetrexed with a placebo, or platinum with pemetrexed and pembrolizumab. After four cycles, they went onto maintenance pemetrexed and pembrolizumab or pemetrexed and placebo, and these were the results: We see an improvement in overall survival, and it's important to know there's an overall survival benefit here seen regardless of PD-L1 status, so even for those patients who are PD-L1 0, the addition of pembrolizumab led to an improvement in overall survival over platinum doublet. So this really makes it very straightforward for any patient who does not have a molecular driver and has adenocarcinoma, platinum, pemetrexed with

pembrolizumab is a reasonable approach. Toxicity? The addition of pembrolizumab was not associated with a substantial increase in the severe adverse events. There was a greater incidence of discontinuation due to adverse events because you're introducing a whole new type of drug, so you've got immune-mediated adverse events, which we need to be aware of, and Christina is going to talk about it in a bit.

KEYNOTE-407 was the same exact study but in squamous. So in squamous, we tend not to use pemetrexed; we use taxanes. This study randomized patients to carboplatin and paclitaxel, either nanoparticle albumin-bound or solvent-based with pembrolizumab or a placebo. After that, after four cycles, pembrolizumab or placebo maintenance—and I may sound like a broken record—but the results were the same. We see an improvement in overall survival with the addition of pembrolizumab regardless of PD-L1 status. And so based on this for a patient with squamous disease, regardless of their PD-L1 status, we can give them a combination of platinum, taxane, and pembrolizumab. I would say that for those patients who have greater than 50% PD-L1, we have two options. We can still give them pembrolizumab monotherapy, or we can give them histology appropriate chemoimmunotherapy. Taking a look at the toxicity, again, the addition of pembrolizumab was not associated with a marked increase in the toxicity. Looking at the grade 3 or higher adverse events, 69.8% versus 68.2%, but there was a higher rate of discontinuation on pembro because you've got a whole different class of adverse events. There were no new safety signals

that were noted in either of these chemoimmunotherapy studies with adding pembrolizumab.

IMpower150: Now I always say as an oncologist, and I'm sure that you guys experience this as well, we need to be able to say impossible words very quickly, and this study really tests that. So IMpower150 randomized patients to carboplatin, paclitaxel, bevacizumab, atezolizumab; or carboplatin, paclitaxel, atezolizumab; or carboplatin, paclitaxel, bevacizumab, and the last one was the standard-of-care arm. Interestingly, this study did allow patients with *EGFR* or *ALK* alterations provided they had failed a TKI before. So what you steal for a patient with molecular target, you use it, but this study did allow patients with molecular alterations. You can see that there was an improvement in overall survival with the use of the quadruplet regimen, and this is now FDA approved. It's uptake is a bit, you know – it's based on toxicity, how we choose between this regimen and the KEYNOTE-189 regimen. We have difficulty in terms of the hair loss and neuropathy associated with the paclitaxel in this regimen, so that has been a limiting factor, but for those patients who have *EGFR* mutation or *ALK* who have failed TKIs, this is the only regimen that has any data, and so it's something we discuss with our patients. Taking a look at the toxicity, the addition of atezolizumab similar to the addition of pembrolizumab was not associated with a substantial increase in toxicity. In fact, if you look at the rate of treatment-related adverse events, the quadruplet comes in a little bit below the triplet, but that's not statistically significant.

So CheckMate 227 is a study that kept changing its design as it was going on, so it is very, very confusing. What I'm going to say is I'm going to focus on its initial design. What they did was they randomized patients who had metastatic non–small cell lung cancer. If they were PD-L1 greater than 1%, they were given the options on randomization of nivolumab, which is a PD-1 inhibitor, and ipilimumab, which is a CTLA-4 inhibitor, or chemotherapy standard platinum doublet, or nivolumab monotherapy. And if they were PD-L1 negative, they were randomized to nivolumab and ipilimumab, histology-appropriate chemotherapy, or chemoimmunotherapy using nivolumab. They then did a subsequent analysis looking at tumor mutation burden. We're not going to focus on that because that was a bit of a rollercoaster because last year there was positive data, and more recently, there's been negative data. I'm going to focus on the most recent data that is most likely to lead to subsequent approvals in this space, in my estimation. So this was the most recently presented data as a function of the initial randomization, looking at patients who are PD-L1 greater than or equal to 1%, the use of nivolumab and ipilimumab was associated with an overall survival benefit over chemotherapy. Okay? If you look at the PD-L1 negative, similarly, there was an improvement in overall survival with nivolumab and ipilimumab over chemotherapy, and this is pretty interesting. This is a chemo-free regimen, but we need to remember that ipilimumab is not as easy to administer as the PD-1 and PD-L1 inhibitors, so if you look at the incidents of total adverse events here, in nivolumab and ipilimumab as opposed to chemotherapy, 32.8% versus 36%, it's pretty similar incidents, it's just a matter of which toxicities you wanna go with.

And the other barrier here is that first of all, this is not FDA approved at this time, but maybe in the future. This is a comparison to chemotherapy, and the ground has moved under our feet. We're no longer using platinum doublet chemotherapy as our reference population, so how do we know how to apply these data to more modern regimens?

So in summary, immunotherapy has completely changed the landscape for the management of every patient with metastatic non–small cell lung cancer that doesn't have a molecular driver. We now have multiple FDA-approved PD-1 and PD-L1 inhibitors for the management of non–small cell lung cancer, but it's really, really important to remember the adverse events because they're very different than what we see in targeted therapy, and they are very different from what we see with chemotherapy. So with that, I'll hand it over to Christina.

CHRISTINA KNEPLEY Okay, so we're going to go through some case studies for the immunotherapy. Okay, immunotherapy toxicity is real. We're not as concerned with the traditional chemo side effects like nausea and vomiting, I would say is one of the biggest ones, but it can get a little bit confusing when we're giving it along with chemotherapy. Any words that ends in ’itis, it can happen. There's a lovely chart right there, and you can see.

All right, Case Study 1: A 65-year-old male with stage IV non–small cell lung cancer, PD-L1 90%, has been on pembrolizumab for 9 months. He presents for his routine treatment with increased shortness of breath, changes in his baseline cough. He reports that sometimes his shortness of breath is so severe that he has to stop to catch his breath. His vital signs are here. It's important to

note that his pulse-ox is 90%, but he does not require oxygen, and his normal baseline is 95 to 100. What are some differentials that you guys would think of? [Inaudible response from participant.] Anything else? Infection-wise maybe? Pneumonia, yep. Okay. Should any testing be ordered? A CT? Okay, so a CT with IV contrast. When I first started, I would always text Dr. Bauml and I would be like, "I think there's something wrong. I'm going to order a CT scan." And then he would always say, "Okay, just make sure you do a PE rule out because we're going to give them contrast anyway, and then also a walking and resting pulse-ox." Okay, so you get the CT scan done, it shows diffuse ground-glass opacities in both lungs, his walking pulse-ox drops down to 85%, but quickly returns to 90% after stopping. So, pneumonitis? Again, important to grade because it helps with the management and determines if we should hold or continue the drug later. Many phases of pneumonitis; it's a nice chart to look at. So we saw in this patient particularly had ground-glass opacities. Management? Grade 1, increase monitoring; grade 2, you should withhold it and start on a steroid; grade 3 or 4, you would definitely discontinue it; and specifically a grade 4, and they would never get that again. So we saw pneumonitis on his scan, he was started on prednisone 1 mg/kg daily. He feels better almost immediately. Normally when we get CT scans, we can order them as stat. Again, we have radiology in our building. They go downstairs, they come back up, I would start them on treatment on their steroids. I send them home, but I give them very strict instructions that once they start on the steroid, if they're not feeling better even within a couple hours into the next day depending on the time, they need to call our office

immediately. I keep them on the high dose for about a week, and then if they're feeling better, you taper over about a 4-week period. Then he comes into the office during one of his visits, he's almost done with his steroids, and he asked, "Can I go back on my treatment?" I'm actually going to ask Dr. Bauml, he loves talking about graphs.

DR. JOSHUA BAUML So this is interesting, so the re-exposure is major issue – everyone can hear me, yeah? So, you know, when someone is having an excellent response, this guy was having an excellent response, you don't want to take it away and never give it back because you're worried that the cancer will grow. So this was an interesting study where they looked at what happened when you re-exposed patients to immunotherapy who had responded to steroids and were doing better. What they found was that the rate of immune-mediated adverse event recurrence depends on what the adverse event is. So it turns out that for pneumonitis, which is over here all the way on the left, you can see that the rate of recurrence is actually really low, and there was a subsequent study that found that the rate of recurrence of pneumonitis when you re-expose them is only about 25%. So you have a 75% chance that it's never going to come back, so the answer is usually to re-expose them, but you can see that there is higher incidents for things like arthritis and myositis, and so this was a recent paper that was just in *JCO* this last week, which looked at what do we do in terms of rechallenge? And while initially the recommendations were for grade 4, you stop. Generally speaking, our approach is that you would think about it. So we had a patient who had like a Stevens-Johnson syndrome reaction. That

patient is not getting PD-1 inhibition again. Okay? That's done, that door has closed, right? Because the risk/benefit doesn't play out. But in contrast, if you have someone who has colitis, which was relatively mild and was responsive to steroids, then, yeah, you should try again because even though it's about a 50/50 shot of it recurring, that is a 50/50 shot of it not recurring too, and they can have a prolonged response to treatment. In pneumonitis, specifically, I nearly always try to re-expose unless they were really, really sick and in the ICU, and I'm worried about them dying, but it has to get to a very high level before I don't want to re-expose.

CHRISTINA KNEPLEY Okay, second case study. So we have a 56-year-old female with stage III non–small cell lung cancer. She recently was treated with concurrent chemorad, and then she has been on nivolumab for 9 weeks. She reports baseline bowel movements two to three daily, and she presents in clinic with abdominal pain, increase in bowel movements now four to five and some blood and mucus. Oh, and one thing that I've been meaning to say, is that no matter how well you know the patient, I always do a very detailed review of systems before I start any immunotherapy because even if they have a cough or anything, it could be a little bit different, and that's one of the key things I like to ask our patients. Okay, so what are your differentials that you would think besides that one? [Inaudible response from participant.] C. diff infection potentially? Okay, so she's having abdominal pain, mucus and blood in her stool. What would you grade her? Again, grading is very helpful for further management, so we graded her as a 2, we said that she has colitis, grade 2. She

has increased bowel movements along with some abdominal pain and blood and mucus in her stool, so we would hold her treatment and start her on 1 mg/kg daily. Her symptoms are improving; the slides are supposed to kinda bump in, but they didn't do it. So would you order a CT scan? Yeah, so if her symptoms are improving, I technically don't always order a CT scan. I think it's kind of provider or practice specific. If they're not improving, I would order one of the abdomen and pelvis, and if they continue to get worse, that's definitely when you would do an inpatient admission; hopefully, there's a direct bed admission; if not, they'll have to sit in the ER, which people are not happy about, start IV fluids, IV steroids, and consult GI. And this patient was a research patient, so we made the team aware as well, and there would probably be discussion if she would continue to be on the trial or not.

So in summary, educate, prednisone 1 mg/kg taper over 4 to 6 weeks, and then if there's also adrenal insufficiency, which you would not use steroids for, but I would then consult endocrine. And then we did have a patient with Stevens-Johnson, we did an urgent consult, and they saw him the same day.

DR. JOSHUA BAUML So in summary, for the management at this time of metastatic lung cancer, if you have a patient with a molecular target, you want to use a targeted therapy. Resistance is a major issue. We didn't really get into the weeds on that today, but that is something that comes up, and chemotherapy is really the best approach in that setting because immunotherapy tends not to work as well for those patients. Immune checkpoint inhibitors have changed the landscape for all other people, though it's absolutely essential to talk

to your patients, educate them, engage with them to make sure we manage immune-mediated adverse events as well as adverse events from targeted therapies. We want to remember the specific adverse events that are associated with the drug that you're starting, and this can be really hard because you think about *ALK*-translocated non–small cell lung cancer, that's 3% of lung cancers, and in some of your practices, you might have one person with *ALK*, you might have two. Some larger practices, you'll have many, but it's difficult to keep track as the drugs keep changing, so it's just best to go back, look at what the drug is associated with so you can make sure to manage the side effects appropriately.

In terms of immune-mediated adverse events, the general rule, 1 mg/kg of steroids, hold the drug, is a general approach for everything except the endocrine adverse events, and we always involve appropriate specialties when we need help, so if I have a patient who has hypophysitis, I'm not going to manage that by myself, right? You need to have a pituitary, and there's a whole group of doctors who have spent their whole lives thinking about endocrine and hormones; I'm going to ask them for help, and it's important to involve the teams as needed.

All right, so we have time to answer some questions. So what questions do you guys have? Yes?

FEMALE I was just curious for severe pneumonitis, if they're in the ICU getting supportive care and on high-dose steroids, how long would you let them go like that before you would consider starting the infliximab?

DR. JOSHUA BAUML Starting what?

FEMALE The infliximab?

DR. JOSHUA BAUML Oh, yeah, yeah, so non-steroid medicines?

FEMALE Yeah.

DR. JOSHUA BAUML Generally, it's based on clinical picture. We would expect within about a day or two that you would see improvement. So if you're seeing someone who's in the ICU and they're declining, I'd be pretty quick to start a nonsteroidal anti-inflammatory drug in that setting because, I mean, it's really a matter of life and death.

MALE Is there any evidence that the immune-mediated adverse effect/burden correlates with response of the cancer?

DR. JOSHUA BAUML Yeah, that's a great question, and actually there is. Patients who have immune-mediated adverse events tend to have a higher response rate, longer progression-free survival; they just do better. And that's actually something reassuring to tell your patients because often, because of all the excitement about immunotherapy, patients don't want to stop it, I find, and they get very upset when I say "We're holding it." But I say, "Look, you know, the patients who had this on trial, they all stopped it, and they did better." So it's just indicative the immune system is hyperactive. Other questions? Yeah?

FEMALE So is it your practice with lorlatinib [inaudible] a statin, given the high incidence of hypercholesterolemia, or are you waiting until -- [cross-talk]?

DR. JOSHUA BAUML It's six of one, half-dozen of the other because if you don't start it on the first day, you're going to get the lipid panel when you

see them at the first assessment, and it's going to be high. The rate of hypercholesterolemia is very high with this drug.

FEMALE So you (indiscernible/inaudible).

DR. JOSHUA BAUML We tend to, yeah. But you do have to monitor CKs in that setting.

FEMALE When you rechallenge a patient after an immune-mediated event, do you see typically that the grade of the ’itis is the same or worse when you rechallenge?

DR. JOSHUA BAUML So it gets even more complicated than that. It may not even be the same immune-mediated adverse event. It can switch. So it's not always as severe though if you had a patient who is very, very sick, that's just when we get a little bit hesitant about it, like when we were talking with the Stevens-Johnson, it's just, the risk; you have to calculate the risk/benefit and talk with the patient about that.

FEMALE Hi.

DR. JOSHUA BAUML Hi.

FEMALE I'm just wondering how you treat or do you treat patients with known immune-mediated diseases with immunotherapy, and how do you manage that?

DR. JOSHUA BAUML So that's a fantastic question because patients with autoimmune disease were excluded from all of these trials, and so what do we do? So there was a really good series that was done from Dana-Farber and Sloan Kettering as a shared experience to describe the outcomes of patients with

autoimmune diseases who are treated with immune checkpoint inhibitors. They found that the rate of flare was actually not that high; it was only about 20 to 25%, so I tend to look at what is their autoimmune condition? How uncontrolled is it? If I have a patient who comes in and they have discoid lupus, and they've never received systemic therapy for it, that's a very different picture than a patient who has rheumatoid arthritis that's actively on DMARD agents, so you have to talk with their rheumatologist and balance it together. I don't like to continue their immunosuppressant drugs while we give things like PD-1 inhibitors, that doesn't make any sense to me. But we just work with a rheumatologist. We've had patients who we had to stop because we gave them one dose and their rheumatoid arthritis came back roaring, and we've had patients who have done fine, so you just have to monitor it closely. Really the only group that is a really hard stop on immunotherapy are recipients of solid organ transplants. That group is a nonstarter because if you give that patient a checkpoint inhibitor, there's a very high concern for organ rejection, and that's, you know, if you have a patient who has a heart transplant, it's not compatible with life. But we actually did have a patient who I saw as a second opinion who had a kidney transplant, and he had cutaneous squamous cell carcinoma, and the response rate to PD-1 blockade in cutaneous squamous cell carcinoma is over 50%. He had a very widely metastatic disease, and he said, "Look, my kidney might reject, and I'm not going back on dialysis, so I would die in that setting." He said, "But if I don't do this, I'm going to die." And so we had a very long talk about it, and I think he got treatment locally, but I think he proceeded with checkpoint blockade. But you

just have to have a discussion about it. Other questions? Fantastic. Thanks so much everyone.

[END]