Alice Shaw: Hello. I'm Dr. Alice Shaw, a medical oncologist at the Massachusetts General Hospital Cancer Center. I'd like to welcome you to Improving Outcomes for Patients with Non–Small Cell Lung Cancer: A Six-Part Virtual Tumor Board Integrating Best Practices and Emerging Evidence to Enhance Care, brought to you by the publishers of *The ASCO Post* and Harborside Medical Education.

Alice Shaw: Today we'll focus on the newest diagnostic and therapeutic paradigms in the field of non–small cell lung cancer. For decades the mainstay of therapy for metastatic non–small cell lung cancer, was platinum-based chemotherapy. For over a decade, genetic alterations and targeted therapies have become part of the treatment schema, with new targets and treatments discovered and approved rapidly.

Alice Shaw: Most recently, immunotherapy has become part of the treatment paradigm for non–small cell lung cancer as first-line monotherapy, first-line treatment in combination with chemotherapy, and second-line therapy. Immunotherapy has even transformed the treatment paradigm in locally advanced disease.

Alice Shaw: Included in each tumor board discussion will be one to two case studies illustrating key aspects of the topic at hand. Here to discuss new diagnostic and paradigms for non–small cell lung cancer, are two expert clinicians from Massachusetts General Hospital. Can you please introduce yourselves?

Lecia Sequist: I'm Lecia Sequist. I'm a medical oncologist at Mass General. I focus on lung cancer and I do research on EGFR lung cancer as well as novel methods of early cancer detection.

Justin Gainor: My name's Justin Gainor. I'm also a medical oncologist in the Center for Thoracic Cancers at Massachusetts General Hospital. My area of focus is on cancer immunotherapy and I'm an active investigator studying new immunotherapies in trying to identify novel biomarkers of response in resistance to immunotherapy.

Alice Shaw: Here are our financial disclosures.

Alice Shaw: In this module, we'll discuss the management of checkpoint inhibitor–associated immune-related adverse events in the treatment of non–small cell lung cancer using a case study of a 63-year-old female patient. The learning objectives for this module are to evaluate best practices and interpret the clinical significance of emerging data regarding prevention and management of immune-related adverse events, to plan strategies to incorporate best practices and emerging data into practice, and to apply best practices and emerging data to manage immune-related adverse events effectively.

Alice Shaw: Let's turn now to our case. This is AO, a 63-year-old female, former 20 pack/year smoker with a remote history of multiple sclerosis who initially presented three years ago with a right leg pain, and she was found to have a right lower

extremity DVT, and started on anticoagulation. PE protocol chest CT was performed, and revealed a large right pleural effusion as well as right middle lobe and right upper lobe lung nodules.

Alice Shaw: She underwent right-sided thoracentesis with cytology demonstrating poorly differentiated adenocarcinoma consistent with lung origin. Molecular testing was positive for a KRAS mutation, as well as a P53 mutation. The remainder of her staging scans at that time were negative. She underwent right VATS with talc pleurodesis, and then started on first-line carboplatin/pemetrexed—this was before KEYNOTE-189—and she received four cycles of the combination before transitioning to maintenance pemetrexed. She responded well to chemotherapy, but after seven months, the scan showed worsening disease in the chest. At this point, we discussed second-line options including docetaxel or PD-1/PD-L1 inhibitors.

Alice Shaw: So Dr. Gainor, this patient did have a history of multiple sclerosis. She had had one, maybe two episodes many, many years ago. This was not an active issue for her now. You recently published a paper in *JCO* on the safety of checkpoint inhibitors in patients with non–small cell lung cancer and preexisting autoimmune disorders, and I believe your series did include patients with neurologic conditions such as multiple sclerosis. So could you summarize what you found, and how would you feel offering this patient a checkpoint inhibitor?

Justin Gainor: Sure. Well, as you know, all of the clinical trials of PD-1 and PD-L1 inhibitors that really established them as standard of care in non–small cell lung cancer excluded patients with baseline autoimmune conditions. So this patient really isn't captured by any of those studies. And so that was really the impetus for us investigating this now in the real-world setting where now these drugs are approved, what do we actually do with the patient in front of us just like this, who has a history of an autoimmune condition, but it was years ago, not necessarily on any therapy for it right now. How should we treat them? And so we looked at over 50 patients with baseline autoimmune conditions. This included things like neurological conditions like MS. This included rheumatological conditions that was actually, the dominant part of the population were patients with rheumatologic conditions, as well as gastrointestinal autoimmune conditions, namely IBD, so Crohn's and ulcerative colitis.

Justin Gainor: And so what we observed was that about 50% of patients will do fine with their PD-1 or PD-L1 inhibitor, despite having a baseline autoimmune condition. But in the remaining 50%, they'll either have a flare in their baseline autoimmune condition, defined as an exacerbation in their baseline symptoms, or they'll develop a new immune-related adverse event. Now, I should caution that in this series, this relied on clinicians already feeling comfortable trying these drugs in patients with baseline autoimmune conditions. So there may be a selection bias here and that these were more mild autoimmune conditions, and I think that's reflected in the fact that only 20% of patients in this patient population were actually on some form of disease-modifying therapy. So as we think about this,

that's an important consideration. And so when I'm seeing a patient in front of me where there is this history, I want to know what was the history of this autoimmune problem? Are you currently having any active symptoms? Are you on any therapies for it?

Justin Gainor: And the trend that we've seen in, I think this is borne out in melanoma as well, is it looks like the rheumatological conditions are more likely to flare, whereas gastrointestinal and neurological conditions are less likely to flare, and that's what we observed in our series.

Alice Shaw: And in your series, those 20% who may have already been on some type of immunosuppression for their baseline condition, were those the patients that were more likely to declare?

Justin Gainor: They're more likely. So patients who enter the therapy already having some symptoms are more likely to experience an exacerbation of that.

Alice Shaw: So this patient who really has no symptoms of her MS, and in fact, has never been on any medications for the MS, would you feel comfortable prescribing her a checkpoint inhibitor?

Justin Gainor: I'd say, after a long conversation with her. I think this is one of those times where you really have to counsel a patient a lot, and really go through this is what you know toxicity might look like, because even though immune-related adverse events, severe immune-related adverse events are not particularly common, when they happen, they can be quite severe and even fatal. So we want the patient fully understanding what could happen.

Alice Shaw: And Dr. Sequist, in your experience, are there some patients who you would absolutely say, "Nope, you cannot go on a checkpoint inhibitor," other than patients, for example, who may have active autoimmune conditions actively requiring treatment? Are there other patients? So, would you consider a transplant patient for checkpoint inhibitor therapy?

Lecia Sequist: I think it depends on the situation. I might be hesitant to take someone who is on a disease-modifying agent for their underlying disease, or has a significant medical issue like transplant like HIV and put them on front line, especially if you know there are going to be multiple lines of therapy, but if you have someone, your patient had already progressed on frontline chemotherapy, you're getting into salvage options, and there I think, when it comes specifically to transplant, you might consider the type of transplant, and whether there's an alternative option. I think we had a case we were all talking about in clinic recently of a kidney transplant patient where in case that transplant fails, you always have the backup option of dialysis, whereas, for example, a heart transplant patient, you really don't have many other options. So it may depend a bit on that, and also what scenario they are in for other treatment options.

Alice Shaw: So it is a bit of a risk benefit analysis. I think we can counsel them with regards to the risk. I'm wondering about the potential benefit here, and Justin, maybe you can speak to this. This patient, of course, is second line, her molecular mutations were P53 and KRAS, and I'm wondering if you can comment on whether those mutations make you feel more inclined to proceed with immunotherapy or less inclined?

Justin Gainor: Yeah, I think that's a great question. So as part of your risk benefit analysis, I think you want to have a better sense of what is the likely benefit in this patient, and some of the things that we've talked about during these modules, one, has been PD-L1 expression. So I'd want to know what this patient's PD-L1 score was, even though in the second-line space, it's less relevant for a patient like this, I think it has some bearing. We think about clinical factors, smoker, neversmoker, or things like that. And then certain molecular alterations. In prior modules, we've talked about EGFR mutations being associated with worse outcomes with PD-1 inhibitors. In KRAS, the significance of KRAS actually depends on the comutations.

Alice Shaw: The context.

Justin Gainor: The context. It really matters, and I think this is where we're starting to get more and more data and it does look like the comutation, so other mutations present along with KRAS, actually make a big difference. And Dr. Skoulidis recently published several papers now looking at defining KRAS mutations by their comutations, and it looks like KRAS plus P53 as in this patient, is one defined subgroup, versus KRAS plus LKB1 or STK11, and it looks like that latter group actually has much diminished responsiveness to PD-1 pathway blockade versus the KRAS P53, which seems much more active. So in this patient, I would be cautiously optimistic that they may derive benefit from a PD-1 blockade.

Alice Shaw: So we had the same thoughts as we were sort of thinking about options for these patients. We went back to her cytology specimen to see if we could do PD-L1 testing, but actually it had been depleted because of the molecular testing. So she basically is PD-L1 unknown. But we did note her KRAS and P53 mutations and felt like, again, considering risks, benefits for her, that there was a pretty significant chance of benefit, especially in the second-line setting. And of course, we counseled her about the potential risk in terms of her MS and she considered her options and actually ended up opting to proceed with nivolumab. So she did two cycles of nivolumab, and actually really had no side effects, none to speak of, and also no neurologic symptoms to suggest any worsening or exacerbation of her MS. And her first scans showed significant improvement in those lung nodules, although she did actually have some mildly enlarged hilar lymph nodes that we thought were likely reactive.

Alice Shaw: Actually Justin, I was going to ask you if you see that a lot in these patients who may be responding where some lymph nodes, almost like a mixed response in a way. She clearly had improvement in her disease with those nodules regressing,

but some of the lymph nodes nearby looked slightly enlarged. Would that be concerning to you, or would you think that's consistent with a response?

Justin Gainor: I agree with you that anecdotally, we've certainly seen more mixed responses in patients receiving checkpoint inhibitors. So it wouldn't give me tremendous pause and say we have to stop therapy. I think I'd want to push ahead. I might get an earlier scan just to reassure myself in terms of subsequent imaging.

Lecia Sequist: She also felt really well, and these were fairly mild changes in her lymph nodes, so we felt comfortable continuing. So she continued on nivolumab, and at cycle number four, we actually noted for the first time that she had an elevated creatinine. So her creatinine had been usually around 1, and now was about 2.24. So we reviewed her medications, we actually gave her some hydration in case she was a little bit under with her fluids, and her creatinine really did not budge. We did end up holding the nivolumab, and one week later, we rechecked her creatinine, and it was still almost identical at 2.2. And at this point, we referred her to nephrology for a possible autoimmune nephritis, and the plan actually that we came up with was to start prednisone steroids if there was no improvements, or if worsening, but in fact for this patient, her creatinine steadily improved over the next six weeks and did return to normal after about two months off of nivolumab. So she stayed off drugs, and her creatinine function improved.

Alice Shaw: So I don't know if either of you want to speak to the adverse events such as nephritis that we can see with checkpoint inhibitors, and I would say in particular for her with the autoimmune nephritis, are there key features in terms of diagnosis and management, that we should discuss?

Lecia Sequist: Justin, I think, is seeing more cases of these than I, so I will just say one brief thing, and then let him fill in the rest. But many of the autoimmune kidney problems are a little bit occult in that they may not present with the classic dirty urine, and the sediment may not necessarily be helpful. I think for many of these autoimmune complications, it's really helpful to have a staff of other specialists that are well versed, or at least interested in learning about immune therapy, because one of the big problems that we've seen with patients, cancer patients on immune therapy is presenting to a local emergency room, and people not picking up on the fact that this is a complication of their immune therapy. For example, they may come in with diarrhea and not be started on steroids because autoimmune colitis is not necessarily in the differential. So having a well versed team of medical specialists is important.

Justin Gainor: I would echo the sentiments that having a multidisciplinary team is really important. And I think at Mass General, we've done this both on the outpatient side and on the inpatient side where we've identified a series of experts in each of the subspecialties, as well as we've established a severe immunotherapy toxicity inpatient service where it's staffed by clinicians with particular expertise in immunotherapy or interest, and that enables us to connect with the right consulting clinicians. But also, it served as a useful framework to then study

these events and understand what is the biology, how does it differ, because things like nephritis, it's not very common. So if you look across studies of PD-1/PD-L1 inhibitors, it's less than 1% having significant nephritis. So these are relatively rare, and I think these are episodes where you really have to put on your internist's cap again and really think about-- it's really excluding other things, taking careful medication history, making sure that there's nothing, no new exposures. I think it's ruling out obstructive uropathy, it's assessing volume status, making sure that it's not hypovolemia. Certainly sounds like the fact that it persisted on repeat checks over time, that this was likely immune mediated.

Alice Shaw: And her workup is not entirely clear. I think the nephrologist had looked at the urine sediment and had assessed all the things you were saying and was not clear. And so I'm wondering what would be a cardinal feature of autoimmune nephritis, and for example, biopsy. Was that what you would consider the best way to sort of confirm a diagnosis of autoimmune nephritis?

Justin Gainor: So you're right in that if you look at all of the guidelines—and I would encourage people to actually look at various sets of guidelines that have recently been released—so ASCO, NCCN, ESMO, have each released guidelines managing autoimmune toxicities from checkpoint inhibitors, so they're useful guides. You'll notice that almost all of them include renal biopsy, but delving into the literature, there aren't huge pathologic case series on exactly what we would see, and my personal experience has been that our nephrologists have been wary about pursuing a renal biopsy in that it is a procedure with risk, and if they see improvement over time, they're even more likely to give empiric courses of steroids than jump straight to a biopsy.

Alice Shaw: Right. So she actually kind of recovered spontaneously without the need for steroids, and so we ended up actually, once her creatinine had normalized, we ended up restarting Nivolumab, and she did continue on nivolumab for about another two months, creatinine remained fine. Scan showed ongoing response, those lymph nodes that had looked a little reactive, either were about stable or got a little bit smaller. So it looked like she was responding well and now tolerating the drug well. But then she did develop some progressive shortness of breath and mild cough. Her oxygen levels were fine. We ended up getting a PE protocol chest CT, which did not show any PE, but did show bilateral ground glass opacities that looked concerning for either a typical pneumonia or a drug-related pneumonitis ILD. So what would you do next, Lecia, for our patients in this situation?

Lecia Sequist: So I would stop the nivolumab, and after this, the second suspected immune-related toxicity, I would probably be wary about restarting it. With pneumonitis, you really want to start prednisone or some sort of steroid medicine unless it's really extremely asymptomatic grade 1 x-ray findings only, but this patient was coughing and had a little bit of hypoxemia. So you want to start high-dose steroids, probably 60 mg of prednisone, and you don't want to do a rapid taper like we sometimes do for COPD flares. With pneumonitis, sometimes tapering

over three to four or even more weeks it’s necessary so that patients don't have flareups as you step down with each prednisone taper dose.

Justin Gainor: I think this actually brings up a good point that the question about to rechallenge or not, even after the nephritis, we're still learning here about when you can rechallenge, when can't you. In one recent retrospective analysis, it looked like among people who have to hold a checkpoint inhibitor for some sort of irAE, looks like about 50% of them will be fine on rechallenge, 50% will develop either a new immune-related adverse event, or a flare of the old one, and it's about 50/50 of those. So 25% flare, 25% new irAE, 50% fine. So unfortunately, it seems like this patient potentially falls into that category of developing a new adverse event.

Lecia Sequist: It's really hard when patients have had a dramatic response.

Justin Gainor: Of course.

Lecia Sequist: As many of the patients with immune-related adverse events have, that they feel very emotionally engaged in continuing the treatment, and even sometimes with life-threatening side effects, want to keep taking it.

Alice Shaw: So we did discontinue the nivolumab for her. We did treat with empiric steroids briefly, but I ended up on prednisone, as you said, at 60 mg a day to start for presumed pneumonitis.

Alice Shaw: If we can just back up a little bit, maybe, Justin, speak a little bit about the clinical trial experience with pneumonitis, with single-agent checkpoint inhibitors. Maybe a little bit about how common it is, timeframe of developments, this sort of the range of severity, and again, I know you mentioned that there are these now standardized kind of algorithms or sort of guidelines for physicians.

Justin Gainor: Yeah, so some general themes. So the frequency is relatively low, so 3 to 5% of patients will develop pneumonitis. Most of it is grade 1, which, as Lecia alluded to, is asymptomatic. It's just pattern on chest CT, but about 2 to 3% of people will actually be symptomatic, and that's at least grade 2 if you're starting to have symptoms. What we've come to recognize is that if you use combination checkpoint inhibitor, so for example, nivo/ipi, the frequency more or less doubles, and it can occur earlier. So the more immune therapies you use, the higher the chances, and the sooner they can occur. They can really occur at any point. If you look at the largest series of pneumonitis, which looked at two different institutions, it was anywhere from nine days to 19 months. But if we look at our clinical trial experience in some of the CheckMate 057, it was about seven months was the median time to onset.

Justin Gainor: So it just emphasizes that you need to be vigilant, and then just because a patient's tolerating therapy for months and months, even years, doesn't mean

that they can't develop an immune-mediated event. And so, as I already alluded to the terms of working it up, we're treating patients with lung cancer, and we've all seen they have comorbidities, COPD, they can get viral infections. I do think taking a careful history, making sure that there's, this is not just their COPD, that this is something else taking a good infectious history. Chest CT is really important. Viral panel is part of my standard workup.

Alice Shaw: How about bronchoscopy?

Justin Gainor: And bronchoscopy, I would say, is plus or minus. And I think it's important here to distinguish pneumonitis from other immune-related adverse events, say for example, colitis. In colitis, when we biopsy, we're looking for pathologic changes associated with an inflammatory disease state. By contrast, the rule of bronchoscopy is often to rule out other things. It's to rule out infection, and we have a paucity of data on what would a blind biopsy on bronchoscopy would actually look like in the setting of pneumonitis. It's also complicated by the fact that there's this sweet spot for when you can actually perform a bronchoscopy on someone clinically. In the most severe cases of pneumonitis, those patients are too sick to actually have a bronchoscopy because it may push them towards intubation. So it's really the lower amounts of oxygen requirements where we're doing them. So in a patient who is clinically stable, low amounts of supplemental O2 requirement, I do think it's useful. It's on the guidelines, but really, their principal use is ruling out infection.

Alice Shaw: So after about one week of dosing with prednisone at 60 mg, she noted significant improvement in her breathing and cough, I think otherwise we probably might've pursued further workup. And then we were able to slowly wean the prednisone down over about four to six weeks. And when she got to about 20 mg of prednisone, she was feeling fine. We obtained new restaging scans at that point, which showed that the ground glass opacities had nearly resolved and there was no evidence of disease, kept her off of nivolumab, and eventually weaned her prednisone down to off. And she remained off steroids and off nivolumab for about three months. But then at this point, three months in, she now had recurrent shortness of breath and cough, and another CT at this point showed yet again these ground glass, this resurgence of the ground glass opacities. No evidence of disease, but just the ground glass opacities.

Alice Shaw: So just thinking a little bit about this case, it's interesting, she's actually been off nivolumab now for a number of months, and we're seeing this flare up in the pneumonitis again, and this is something that you guys would expect to see in patients who have been on a checkpoint inhibitor?

Lecia Sequist: It is definitely something that I've seen in patients, not always with pneumonitis, but having their autoimmune side effects flare up, even months after they stopped exposure.

Justin Gainor: One of the things that we like to talk about and emphasize is the potential for durability of responses to checkpoint inhibitors. That can actually be a double-

edge sword in that that durability also applies to immune-mediated adverse events. And so it's not unusual for you to see some flair, especially as you're trying to taper steroids, and sometimes even after you've completed--

Alice Shaw: She had been off steroids entirely for about three months. Unfortunately, we had to put her back on steroids. She was symptomatic again with the shortness of breath and cough, but she responded fine to that again with pretty rapid resolution in her symptoms, and we were able to taper the prednisone again. So as of today, she's remained actually off steroids now and off nivolumab, and her last dose of nivolumab was almost two years ago, and so that's pretty remarkable. But just last week, we got a CAT scan of the chest, and now we're beginning to see some likely progression of disease. This is a long time after her initial dosing with nivolumab, and even a long time after her last episode of pneumonitis. So how would you feel about rechallenging this patient with nivolumab given her history?

Lecia Sequist: I would be nervous given history of multiple breakthroughs of side effects require multiple steroid courses. I would probably not retreat her.

Alice Shaw: How about you, Justin?

Lecia Sequist: I would say the same. I think it was the nephritis, and now multiple episodes of pneumonitis that was symptomatic. Probably would not rechallenge.

Speaker 20: What do you think about differences between PD-1 versus PD-L1 inhibitors in terms of the risk of pneumonitis in this patient? As you were saying, Lecia, she's very emotionally attached to this idea of immunotherapy. Her disease has been under really good control, and despite the complications, there's still been no cancer, and so she's very motivated to try and stay on an immunotherapy, and one of her questions was possibly switching the immune therapy. Any role for doing that?

Justin Gainor: I think we've all heard anecdotes of people trying to switch therapies. Several years ago, there was a big emphasis on the differences between PD-1 versus PD-L1 inhibitors. Theoretically, there was, one of the purported benefits of a PD-L1 inhibitor was that you're not blocking PD-L2, whereas PD-1 inhibitors do, and PDL-1, PDL-2 is thought to play a role in immune tolerance in the lungs. But we've certainly seen pneumonitis with PD-L1 inhibitors as well, and it looks like on the whole, there's not a substantial difference there. So it would give me pause to even try a PD-L1 inhibitor as well in this patient.

Alice Shaw: And Lecia, you had mentioned this a little bit earlier about how some of our patients who have actually had some dramatic responses to immunotherapy are the ones who also have had some of the toxicities. Is there a clear correlation between these immune-related adverse events and efficacy, especially response or durability of response to checkpoint inhibitors?

Lecia Sequist: I believe that there is a correlation, and particularly that people with autoimmune side effects are the ones that are often likely to have the long-term durable responses, even once you stop treatment.

Alice Shaw: Does that correlation hold up for PD-L1 expression as well, meaning if you have higher levels of PD-L1, do you feel that that could be a potential indicator that you could be at higher risk for these irAEs?

Justin Gainor: It's a great question. I think it's a challenging analysis to do. One of the reasons why is if you have high PD-L1 expression, you're more likely to respond, your exposure to PD-1 inhibitors is likely to be longer. And so to get at that question, and I think you're starting to see people do landmark analyses, looking at trying to control it as much as possible, so looking at immune-related adverse events within the first 12 weeks of therapy. So trying to get at that question, and it does look like if you have more irAEs, you have a higher response rate even within those 12 weeks, teasing apart based on PD-L1 status. I'm not aware of that data yet.

Alice Shaw: So I think I also feel the same concern about rechallenging her with a checkpoint inhibitor. So in fact, what we've talked about is considering some KRAS-directed strategies, perhaps. She does have the KRAS mutation. If I recall, her KRAS mutation is G12C, so we are considering some trials. I don't know, Dr. Gainor, if you want to speak to this, being one of the leaders of the Stand Up to Cancer and Lung Cancer Dream Team, which has focused on KRAS, if you want to talk about any efforts, potential trials, for example, this patient could consider.

Justin Gainor: Sure. As you all know, that people have tried targeting KRAS for decades, and just by knowing about this oncogenic driver for a long time, those efforts have fallen short. And in some of the recent efforts, there was some initial enthusiasm about MEK inhibitors, so targeting downstream, and based on some promising phase II data. But unfortunately, the confirmatory phase III study—this is selumetinib—fell short. It was a negative study. More recently, and I think particularly relevant for this patient, is that she has a KRAS G12C mutation. G12C happens to be the most common codon mutation in non–small cell lung cancer. And recently, Kevan Shokat has identified that there's a unique binding pocket there for allosteric inhibition of KRAS, specifically of KRAS G12C. And so there are some very promising preclinical data saying that you can actually target KRAS G12C, and the hope is that in the subsequent years, we'll actually start seeing these agents enter the clinic.

Alice Shaw: So to summarize and highlight features of this case, immune-related adverse events, irAEs, are common in patients treated with checkpoint inhibitors, including PD-1/PD-L1 inhibitor monotherapy, and any organ may be affected, but irAEs most commonly involve the skin, gastrointestinal tract, endocrine glands, and liver, and then some of the sites that are less common, but we discussed today, include the lung, kidney, heart, and brain, among others. And in general, treatment of moderate to severe irAEs involves holding the checkpoint inhibitor and administrating corticosteroids, which we did for this

patient. And finally, Justin, just to reinforce your point that there are specific guidelines and algorithms that have been developed. These are available to all physicians for the management of irAEs.

Alice Shaw: Thank you both for joining me today. We hope you enjoyed this discussion. Be sure to check out the other modules in this virtual tumor board series on Improving Outcomes for Patients with Non–Small Cell Lung Cancer. For more information please visit educate.ASCOpost.com.