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 highlight best practices and emerging data on combining cytotoxic chemotherapy and immunotherapy for patients with non–small cell lung cancer and apply them to a case study of a 71-year-old male patient. The learning objectives for this module are to evaluate best practices and interpret the clinical significance of emerging data regarding the combination of cytotoxic chemotherapy and immunotherapy, to plan strategies to incorporate best practices and emerging data into practice, and to apply best practices and emerging data to treat patients safely and effectively with combination therapy.

Alice Shaw: Dr. Gainor, before we begin with the first case study, I'm wondering if you can provide the rationale for combining chemotherapy with immunotherapy. I ask this because I think, before we had the results of some of these trials, I think

there was some skepticism about whether or not chemo and immunotherapy would really be beneficial for patients.

Justin Gainor: You're right. I think there was a lot of skepticism, myself included, that there was concern that by ... we're constantly telling our patients when they're getting chemotherapy that this is immunosuppressive. They have to call us for fevers that you have to watch out. There was concern that the additional chemotherapy could actually be antagonistic and actually reduce the efficacy of checkpoint inhibitors, especially because if we think about the agents that we're commonly giving together with chemotherapy, things like corticosteroids, for antiemetic prophylaxis, are also things that are also immunosuppressive. I think there is just a viable concern in the field initially.

Justin Gainor: On the other hand, though, others made the argument that there could actually be synergy there. That by giving chemotherapy we could lead to increased cancer antigen release, and that could indeed prime these tumors and make them more likely to respond to checkpoint blockade. Some in the middle thought it was maybe just additive, even if there's not this priming, at least you're giving two effective therapies that given together you may find the patients who don't respond to one but respond to the other, and you ensure that more people get access to both effective therapies.

Alice Shaw: Okay. We'll hear more about the actual data in just a minute. But Dr. Sequist, before we go to the case, is your experience nowadays that outside of the patients who have PD-L1, that most of your patients with metastatic non–small cell lung cancer are receiving a combination of chemotherapy and immunotherapy, and have you encountered any issues at all with insurance for these combinations?

Lecia Sequist: Yeah, absolutely. In the last two or three years, it's been a complete change where we were looking for those very specific patients with high PD-L1 and everyone else would start with chemo. Now, everyone starts with some sort of immunotherapy except for a few exceptions. I think the insurance companies at least in my experience have really been appraised of the latest data, and I haven't had too many troubles with getting insurance coverage.

Alice Shaw: Great. So, let's turn to the case. This is my patient WS, he is a very long-term patient of mine, now 71 years old, he's a former 30 pack/year smoker, and has multiple medical problems. He was diagnosed with stage IIB non–small cell lung cancer about five years ago and underwent left pneumonectomy at the time with pathologies showing poorly differentiated carcinoma and he had seven of 13 nodes positive for malignancy. At this time, he underwent four cycles of cisplatin/docetaxel as adjuvant therapy and then was under active surveillance.

Alice Shaw: Now, during active surveillance he developed two FDG-avid lung nodules, and this is in the remaining right lung, and this is separated in time by about one year. Neither of these were accessible by bronchoscopy, he was considered high risk for a CT-guided biopsy being status post pneumonectomy. And since there

was no other evidence of disease, he underwent empiric stereotactic body radiotherapy, or SBRT, to each nodule.

Alice Shaw: Now, in March of this year, WS developed progressive dysphagia and weight loss. Endoscopy and EUS demonstrated severe obstruction of his esophagus, likely due to an infiltrating esophageal wall mass with extensive malignant-appearing lymphadenopathy. Biopsy showed a poorly differentiated carcinoma, TTF1 positive, similar in appearance to the original diagnostic specimen, also evidence of focal glandular differentiation. His PD-L1 testing showed high positivity at 8%, and his molecular testing only showed a P53 mutation, but nothing targetable.

Alice Shaw: PET-CT at this time showed extensive FDG-avid disease with FDG-avid nodules in the left pneumonectomy space, bilateral mediastinal adenopathy including extensive paraesophageal lymphadenopathy that was causing the esophageal obstruction. He also had diffuse bone and liver metastasis. Fortunately his brain MRI was negative.

Alice Shaw: Dr. Gainor, and you may remember him, he was very symptomatic when he recurred, we actually had to hospitalize him for symptom management and also had to place a feeding tube as he was unable to take virtually any PO. But up until that point, he actually had a reasonably normal functional status, performance status was 1. What options would you consider for him, taking into account his histology, likely adenocarcinoma given the glandular formation, his extensive tumor burden and his high PD-L1 expression?

Justin Gainor: I think there are several potential options here. One would be single-agent pembrolizumab, this would be based on KEYNOTE-24, where we know that among patients who are treatment naive, who have PD-L1 expression 50% or greater that pembro was superior to platinum-doublet chemotherapy with respect to both progression-free survival and overall survival. That would be an option.

Alice Shaw: And response rate.

Justin Gainor: And response rate. Right. A response rate would be around 43% with monotherapy. More recently, we've seen data from KEYNOTE-189, which compared platinum pemetrexed plus pembro versus platinum pemetrexed. This enrolled patients regardless of PD-L1 status, but I think as we'll get into it, it is important to look at the subgroups of this study. But in the intention to treat population, the addition of pembrolizumab resulted in improvements in progression-free survival as well as overall survival. Importantly, in overall survival, it is positive across all subgroups including the high PD-L1 expressors.

Justin Gainor: I think the question mark in this patient is would we treat this patient with pembro monotherapy or should we pursue the triplet? In my practice, there are a couple of things that point me in one direction or the other. I think if we look

at the data, it's hard, and one can choose any endpoint to argue one way or the other. If you are a hazard ratio person, you may say that the triplet is favored because it just showed a more impressive hazard ratio. But if you look at 12-month progression-free survival, it looks pretty comparable between the two.

Justin Gainor: What I've generally done is I take into account what's the patient disease burden? How symptomatic are they? What are their preferences? Do they want to try to avoid chemotherapy or not? In this particular patient, it really seems like you have one shot on goal that he's really symptomatic, and I would argue that in order to get a higher response rate, improve things symptomatically, I would treat with the triplet first.

Alice Shaw: That was probably our major consideration as well that the response rate is higher, has been shown to be higher with the triplets, I think in the 60% range, and as you said, this patient had really extensive disease and I felt like he needed to have the best shot at a good response. But before talking more about him, Dr. Sequist, what if his histology had been squamous cell, and not nonsquamous cell, would you be comfortable offering him carboplatin, paclitaxel, or not paclitaxel with pembrolizumab based on the KEYNOTE-407 study?

Lecia Sequist: Yes, we have a very analogous set of data now in squamous than we do in nonsquamous where we still have the KEYNOTE-24 suggesting that pembrolizumab monotherapy can be very active compared to chemotherapy in patients with PD-L1 level greater than 50%. But at ASCO this year, we saw the KEYNOTE-407 study where they randomized squamous-based chemotherapy with either carbo/taxel, or carbo/nab-paclitaxel with or without pembrolizumab in frontline patients with squamous cell. Again, we saw a PFS benefit and an OS benefit, response rate benefit. So very analogous to KEYNOTE-189. I have already started treating squamous patients frontline with that regimen.

Alice Shaw: With the triplet?

Lecia Sequist: Hm-mm-hmm (affirmative).

Alice Shaw: Now, kind of another hypothetical situation. This patient had high PD-L1, but Justin, what if this patient actually had a PD-L1 of 0%? How would that change your recommendation for first-line therapy? Or would it change it?

Justin Gainor: I would still treat with the triplet being carbo/pemetrexed/pembrolizumab, that is again based on KEYNOTE-189. And there when I say across the different PD-L1 subgroups, they broke things down to 50% and above, 1% to 49%, and less than 1%. Even in the less than 1% subgroup, there was an improvement in survival with the addition of pembrolizumab to chemotherapy. I would still treat this patient with the triplet.

Alice Shaw: This is someone who you might pursue TMB testing to find out tumor mutational burden? Would that impact your clinical decision making at all? If he had 0% PD-L1.

Justin Gainor: If he had 0% PD-L1 staining, recently at ASCO, this past year, Dr. Borghaei and colleagues presented an update to the CheckMate 227 study, complicated study designed in that there are multiple arms in that study. But by and large you can think about the arms as either nivolumab monotherapy, nivo plus ipi, nivo plus chemo, or platinum-doublet chemotherapy, and there are stratifications in that study for both PD-L1 expression with a 1% cut point, or TMB.

Justin Gainor: Dr. Borghaei presented some interesting data that among the subgroup who were both PD-L1 low and TMB low, they seemed not to derive benefit with the additional PD-1 to platinum-doublet chemotherapy. As we'll discuss in another module, TMB right now I don't think is fully ready for prime time. There are still issues regarding standardization of reporting. Where that fits in the current landscape I think is still a matter of debate. So for this particular patient, I wouldn't necessarily use the TMB to impact my decision making, particularly since one of the problems with TMB is the turnaround time. It sounds like this patient is quite ill, he needs to get started on therapy quickly. I don't think we have the two weeks or so to get that data back.

Alice Shaw: As the patient had rapidly progressive disease, and was sort of increasing in terms of his disease-related symptoms, we did recommend proceeding with the triplets of carboplatin, pemetrexed, and pembrolizumab. I'm wondering if you can just reveal sort of the practicalities of this triplet regimen, Dr. Sequist. Could you reveal how we give this regimen, the transition to maintenance, what is maintenance, how long do we continue maintenance after a patient has completed the triplets?

Lecia Sequist: It's an every-three-week regimen; it's fairly easy for patients to take. It's your standard doses of carboplatin and pemetrexed, and then you just layer the pembro 200 milligrams on top of that. Patients have tolerated it fairly well, and the way that the study was set up was to give four cycles of the triplet and then transition to a pembrolizumab-pemetrexed maintenance.

Alice Shaw: Do you ever do six cycles of the triplet if a patient is doing great?

Lecia Sequist: I don't know if I've been in that situation. I probably would because that was sort of the same way that I approached chemotherapy doublet, was that most patients would get four and then go to maintenance, but some patients, if they were doing very well, go to six. I would not push it beyond six. But certainly the trial focused on four cycles. Then there's this separate question about how long to continue the pembrolizumab maintenance. There was never a study in the past that limited the amount of pemetrexed chemo maintenance, but several of the initial studies for immunotherapy were set up to either give one or two years and then some of them were indefinitely. I think there's still a lot of debate out there about how long to give the immunotherapy maintenance.

Alice Shaw: Because in KEYNOTE-189 they stopped after 35 cycles, two years basically, of the pembrolizumab, although I believe you could've continued pemetrexed as you were saying, I guess, you could go beyond that. But I don't know if, Dr. Gainor, is there any more data on sort of the optimal duration of immunotherapy in this setting?

Justin Gainor: I agree with Dr. Sequist. Right now we still don't know. Many of the treatment durations have been quite arbitrary, one, two years, then the best data that we have so far is the CheckMate 153 study. This study was not initially designed to actually look at this question, no, so I think that's an important caveat that this was a community-based study of close to 10,000 patients receiving nivolumab. Then, it was subsequently amended to try to get at this question and patients were then, who were still on therapy after a year, they could've either had an ongoing response, ongoing stable disease, or had progressed but were driving ongoing clinical benefit. So those patients were also included.

Justin Gainor: They were randomized to either discontinue nivolumab, or continue beyond that one-year mark. In this post hoc exploratory analysis, it did look like continuing the nivolumab beyond one year was associated with improved progression-free survival compared to stopping at one year. I would say before I saw that data, I was routinely stopping after a careful discussion with my patient, but I think it's caused me to rethink that. It still doesn't tell us one year versus two years, or any more, but I think in the absence of a clear toxicity that's limiting your dosing, I have a conversation with my patient and I'd say most of the time now I'm continuing it.

Lecia Sequist: In our practice, we have seen some patients though who have very late toxicity, meaning that they were on checkpoint inhibitor for two, two and a half years with almost no toxicity, then all of a sudden, out of the blue, get a very serious life-threatening toxicity.

Justin Gainor: Right.

Lecia Sequist: Unclear if the continued therapy exacerbated that or if that would've happened even if they had stopped.

Justin Gainor: Exactly. I think there's also some rationale behind stopping, which is that these are immune checkpoints, and that if you continue to try to inhibit them, could you be pushing T cells more towards that exhaustion phenotype. I think, this is a ... we're in a whole new world here in terms of how these therapies work, and we can't always take the same paradigms that we've used for chemotherapy and apply them to immunotherapy.

Alice Shaw: Speaking of toxicity, Lecia, I think it's important maybe for us to discuss now that carboplatin, pemetrexed, and pembrolizumab are ... it's such a widely used regimen maybe to discuss just for a minute or so the toxicities of the triplet

regimen. Can you comment on some of the common toxicities that were reported in the study and what you've seen in practice as well?

Justin Gainor: The top three adverse events in the study were nausea, fatigue, and anemia. Those were the top three. But by and large, the addition of pembrolizumab, if you look at the toxicity table, didn't add a substantial amount of toxicity, and I would say that in my clinical practice that's born out as well. That overall it seems quite similar to just platinum/pemetrexed with the important caveat of two things. One is that there was a higher frequency of acute kidney injury in the triplet-containing arm; it's around 5% versus less than 1%. Then the second thing is the need to watch for these immune-mediated adverse events, which is certainly different than what we would experience with platinum/pemetrexed.

Alice Shaw: Were those episodes of nephritis that we're seeing with the triplet, were those reversible, do you recall?

Justin Gainor: I don't think they actually went into a great bit of detail in the manuscript, I think one of the challenges in interpreting that is also we know that pemetrexed can also cause renal insufficiency. We know that patients who were receiving the triplet did better than those who were receiving platinum/pemetrexed. Dose exposure over time can also be playing a role. We don't know.

Alice Shaw: Right. Any other toxicities, I guess, as you were saying, Lecia, sort of a typical toxicities of immunotherapy still have to be aware of those as these patients go on the triplet regimen, so the hypothyroidism, other common?

Lecia Sequist: Fatigue and itching can be fairly common, but not serious, side effects.

Alice Shaw: This patient tolerated his first cycle of the treatment very well, I was actually very nervous because he was quite sick at the time, he did have actually nausea and fatigue, the expected side effects from the chemo-immunotherapy regimen, and he was able to go on and receive cycle number two. Actually after cycle number two, he started to note an improvement in his dysphagia and also some bone pain that he had had. We obtained scans after that cycle number two, and he had marked improvement in his lymphadenopathy that had been causing the obstruction, and also improvement in his liver metastasis.

Alice Shaw: Pretty nice response, it was fairly rapid. We saw it radiologically as well. Dr. Gainor, would you say this is pretty typical for what you see with the triplet regimen?

Justin Gainor: It is. As you alluded to earlier, it is a higher response rate with the triplet regimen, around 60% among people who have high PD-L1 expression. This would be pretty similar to what I would expect.

Alice Shaw: What about durability? What should I tell my patient about how long to expect this response to last?

Justin Gainor: We don't know yet. I think this speaks to one of the challenges that we all face in the clinic now, which is that so many of these studies are coming out so quickly and they're coming out after the first analysis, and we don't have that long-term follow-up. I think that that's one of the challenges, is that we don't know ... the duration of response high PD-L1 expressors has not been reached in KEYNOTE-189, has not been reached in KEYNOTE-24 with immunotherapy. I think both patients and us alike are dealing with that uncertainty and I think that can be hard when it comes to prognostication.

Alice Shaw: So this patient went on to receive cycle number three of the triplet regimen, and at that point actually he had developed a quite significant fatigue and anemia, so we ended up switching him just a little bit early to maintenance pemetrexed and pembrolizumab. He's actually done much better on the maintenance regimen; he's now at six months. Has no pain at all, and also his dysphagia had already improved and then resolved and so no feeding tube needed at this point anymore either. He's really done fantastic.

Alice Shaw: But I want to spin the story a little bit just to discuss a possible situation that we've run into. Dr. Sequist, what if this patient had had a typical EGFR mutation? Just to think about two different scenarios, if you had a patient who was newly diagnosed metastatic non–small cell lung cancer who had both an EGFR mutation and high PD-L1 expression, what would be your recommended choice of treatment for them?

Lecia Sequist: When you have that scenario, it think that the EGFR mutation trumps the high PD-L1 expression. We know that patients with an EGFR mutation can have a very long and durable response with frontline TKI. Actually the KEYNOTE-189 study that we've been discussing specifically excluded EGFR patients. So we don't have any evidence directly at how they would do with frontline triplet. There was a study that was done, a similar-type study looking at chemo-immunotherapy in the frontline, and this is the IMpower150 study. It did allow both EGFR and ALK patients to enroll.

Lecia Sequist: They were supposed to have been pretreated with one or more TKIs. The majority of them were. Although some did get it in the frontline setting. This was a regimen of carboplatin, paclitaxel, bevacizumab, and atezolizumab, so a quadruplet regimen. But they had a prespecified plan in their analysis to look at the wild-type patients, the majority of the participants, and then separately to also look at outcomes among the EGFR and ALK group. That study found positive PFS and OS benefit for the whole study, as well as for specifically the mutant-positive group.

Alice Shaw: So that takes me to the second situation, which you just answered, which is what if the patient had EGFR, failed all the available EGFR TKIs, now would you consider chemotherapy immunotherapy? It sounds like you're saying yes based on the IMpower regimen, but what do you think about the KEYNOTE-189 regimen, even though as you said they excluded EGFR patients? Would you consider carboplatin/pem/pembrolizumab in an EGFR patient after EGFR TKIs?

Lecia Sequist: This is a question that we get a lot nowadays from the community oncologists. One because a quadruplet regimen isn't FDA approved yet, although it probably will be in the future. But it can difficult to access a quadruplet regimen at the current time. And the carbo/pem/pembro is so well tolerated, we know that EGFR patients do well with carbo/pemetrexed, and it's very appealing to think about giving the carbo/pem/pembro. I think it's an individualized, it's a case-by-case decision that we have to make.

Lecia Sequist: Maybe one other consideration for EGFR patients is the excellent CNS control that osimertinib affords. In some patients, especially patients with a history of CNS metastasis, I do get nervous about stopping the osimertinib. But more directly, we just don't have evidence for carbo/pem/pembro, but probably it will work well in EGFR patients if we extrapolate from IMpower150.

Alice Shaw: What do you think, Dr. Gainor, about the KEYNOTE-189 versus IMpower150 for EGFR or ALK patients who have failed available TKIs?

Justin Gainor: Yeah. With the caveat that technically EGFR and ALK were not included in KEYNOTE-189, but for me there's something attractive about the carbo/pem/pembro. As a chemotherapy backbone, we tend to like pemetrexed in that it doesn't cause alopecia, like a taxane-containing regimen would. I point to the neversmoking subgroup in KEYNOTE-189. That subgroup, even though it doesn't include EGFR an ALK patients, that subgroup did derive benefit and there was an improvement with carbo/pem/pembro in KEYNOTE-189. Acknowledging that this is an extrapolation, I have used that in my own head to justify pursuing that.

Justin Gainor: I would add one other thing to Dr. Sequist's point about patients who have both EGFR and PD-L1 high and yet are treatment naive. I would point to also a recent small trial by Eddie Garon and colleagues where they tried looking at high PD-L1 expressors who were EGFR positive who were TKI naive. In that study, they didn't see any responses among confirmed EGFR-mutant patients despite having high PD-L1 expression. I think that teaches us that PD-L1 expression is a less reliable biomarker among EGFR-positive patients.

Alice Shaw: Although, you have a series as well where you have neversmokers who have high PD-L1, and you looked at their responsiveness to checkpoint inhibitors, and what did you find from your study?

Justin Gainor: We looked at high PD-L1 expressors, and here PD-L1 positivity was defined as 50% above. EGFR represented a smaller subset. But we did see a response rate of about 30% among never or light smokers with high PD-L1 expression versus a response rate of about 40% in the smoking population. Importantly though while the response rates were somewhat even, the durability of that response was less in the light or neversmokers. There was a significant detriment in duration of response. Now, we don't really fully understand that right now, but one could hypothesize that there's a less diverse neoantigen landscape that

that's more subject to immunoediting among never or light smokers. But I think that warrants validation in larger subsets.

Alice Shaw: Back to what Dr. Sequist was saying, we had a patient with a targetable alteration, EGFR, ALK, or ROS, but also high PD-L1; we're still going to go forward and have their first-line therapy be the appropriate TKI.

Justin Gainor: Correct.

Alice Shaw: Just a last question about this case, what should I talk to this patient about his next-line option? He's responding to carboplatin/pemetrexed/pembrolizumab, we hope this response will be durable. What would you say would be his next-line options?

Justin Gainor: Fortunately, this is where I think is one of the greatest unmet needs in thoracic oncology is right now, in that we have good first-line therapies for patients who don't have targetable alterations with the triplet chemo/IO combinations. But then after that, when patients progress, our options get much more limited. In the absence of a clinical trial, I think then we're back to docetaxel plus or minus ramucirumab, which is admittedly response rates 7% to 33%. So we clearly need more clinical trials in that space.

Alice Shaw: Let's see if this patient, he's very, of course, optimistic about immunotherapies now that he's had this wonderful response. My guess is when the time does come where he has some more progression, he has progression of disease, he may very well opt for a trial of immunotherapy strategy rather than the standard docetaxel-type regimen.

Alice Shaw: To summarize this module and this case in particular, based on KEYNOTE-189, the combination of carboplatin, pemetrexed, and pembrolizumab, is a standard first-line treatment option for patients with advanced nonsquamous non–small cell lung cancer. For those patients with high PD-L1, meaning TPS of 50% or higher, single-agent pembrolizumab or the triplet regimen are both standard options, and important factors as you outlined, Justin, to consider include tumor burden, performance status, comorbidities, and of course patient preference.

Alice Shaw: Other chemotherapy immunotherapy combinations have also shown superiority to chemotherapy alone, including carboplatin/paclitaxel or nab-paclitaxel, pembrolizumab for squamous cell carcinoma, that's the KEYNOTE-407 study we discussed. Also, Lecia, the IMpower150 regimen you mentioned of carboplatin/paclitaxel/bevacizumab and atezolizumab in nonsquamous non–small cell lung cancer.

Alice Shaw: Finally, combined chemotherapy immunotherapy may even be superior to chemotherapy alone in patients with oncogene-driven non–small cell lung cancer after they have failed prior TKI therapy.

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.