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 strategies and best practices for choosing optimal first-line and subsequent therapies for patients with metastatic non–small cell lung cancer using two case studies, a 64-year-old male patient, and a 66-year-old male patient. The learning objectives for this module are to evaluate best practices and interpret the clinical significance of emerging data regarding first- and subsequent line treatment for metastatic non–small cell lung cancer, to plan strategies to incorporate best practices and emerging data into practice, and to apply best practices and emerging data to treat patients with metastatic non–small cell lung cancer safely and effectively.

Alice Shaw: So our first case is MO, who is a 64-year-old male with a remote light smoking history about 10 pack/years. He first presented to his PCP with a two-week

history of right upper quadrant pain. Abdominal ultrasound revealed a partially cystic, partially solid mass, possibly arising from the right kidney. Abdominal CT demonstrated a right adrenal mass measuring 5.7 x 3.4 cm. He underwent right adrenalectomy, with pathology demonstrating a poorly differentiated high-grade carcinoma.

Alice Shaw: Many of the cells had a squamoid morphology leading to the final diagnosis of adenosquamous carcinoma. PD-L1 testing was done on the specimen and showed positivity in over 95% of the tumor cells. He underwent chest CT, which reveled extensive bilateral mediastinal lymphadenopathy, with the largest nodes in the right paratracheal region and AP window. But essentially confluent lymphadenopathy from the precarinal nodes to the subcarinal node, and even extending into the right hilum. He had a staging brain MRI, which showed a 1.2 cm right thalamic lesion, consistent with metastasis. He was asymptomatic from this. Molecular testing was submitted and unfortunately revealed no targetable alterations. Now the patient had recovered well from the adrenalectomy, and he actually was even working full time. He had mild dyspnea on exertion, but otherwise he felt quite well. So Dr. Gainor, for this patient, with newly diagnosed metastatic non–small cell lung cancer and high PD-L1, what are his optimal treatment options at this point? Maybe you can review the landscape of the current therapies for these patients.

Justin Gainor: So this is a PD-L1-positive patient. By positive, I mean 50% or greater PD-L1 expression. In these patients, there are a multitude of treatment options. The first would be pembrolizumab monotherapy, and that is based on KEYNOTE-24. This was a randomized phase III study comparing pembro versus platinum doublet chemotherapy. This was in patients with PD-L1 expression in 50% or greater of cells. That study was positive for both progression-free and overall survival.

Justin Gainor: In addition to KEYNOTE-24, which really established the role of PD-L1 monotherapy in first-line management of these patients, we've recently seen data from the chemo plus IO studies. Really, there are a number of studies looking at in the nonsquam population and in the squamous population. So in the nonsquamous population, I think the most pivotal study was KEYNOTE-189, which compared carboplatin pembrolizumab and pemetrexed versus carbo/pemetrexed. There is also an option to use cisplatin in that study, but that study was positive with respect to both progression-free survival and overall survival.

Alice Shaw: And across all etiology.

Justin Gainor: Exactly, so that study was open to all PD-L1 subgroups, and if you look at the high expressors, the PD-L1 greater than 50%, there was certainly a benefit to the chemo plus IO in that study, but again the comparison was chemotherapy alone. So we don't have the chemo plus IO versus IO.

Alice Shaw: Right, in the high PD-L1.

Justin Gainor: In the high PD-L1 expressors, and so we're left with cross-draw comparisons, and really trying to, it really depends which endpoint you look at; you can make arguments one way or the other, choosing between monotherapy versus combination therapy for those patients. I should also mention that in squam patients, we saw a very similar trend, where in the KEYNOTE-407 study, which compared chemotherapy plus pembrolizumab versus chemotherapy alone, and here is more histology-driven chemotherapy that was given. It was either carboplatin plus either paclitaxel or nab-paclitaxel, and in that study again we saw that the addition of pembrolizumab resulted in improvements in PFS as well as overall survival.

Alice Shaw: And again–

Justin Gainor: And overall survival is across all PD-L1 subgroups. So in this patient, the considerations I would make are one, what's his disease burden? Sounds like this patient does have a relatively heavy disease burden, so how much do we need? Are we in need of inducing a rapid response? How symptomatic are they? And the histology are going to play a role, and I also think we can't forget about the patient's untreated brain metastasis as well.

Alice Shaw: What about other possible combinations of chemotherapy and immunotherapy? They've also been studied in the first-line setting. Can you speak to any of those?

Justin Gainor: Right.

Alice Shaw: And whether or not, you might consider those?

Justin Gainor: Yeah, so, good point. In the nonsquamous setting, IMpower150 looked at the quadruplet regimen of carboplatin, paclitaxel, bevacizumab plus atezolizumab, so chemotherapy plus IO plus VEGF versus chemo plus VEGF. And in that study, it was also positive for progression-free survival; I would say that the progression-free survival was pretty comparable to what was seen in the KEYNOTE-189, although the overall survival, in terms of magnitude, acknowledging cross-trial comparisons, seemed less, had a less effect size than was seen in KEYNOTE-189. Nonetheless, if one is considering that regimen, you have to think about, is this patient a bevacizumab candidate? This particular patient has an untreated brain metastasis that we know of, which would be a contraindication to bevacizumab up front.

Justin Gainor: In the squamous setting, I would direct you to IMpower131, which was a study that looked at carboplatin/taxane plus atezolizumab versus carboplatin/taxane, and in that study, we again saw an improvement in progression-free survival, but importantly, there is no difference in overall survival in that study.

Alice Shaw: I think you bring up an important point about this patient, which is that he had an untreated, an asymptomatic brain metastasis, and I'm wondering, Dr.

Sequist, what are your thoughts for a patient like this, and treatment with immunotherapy? Do you feel like you have to treat the brain metastasis first, for example, with stereotactic radiosurgery, or do you feel comfortable proceeding with immunotherapy or chemo-immunotherapy combination?

Lecia Sequist: Well we're so used to thinking about the blood-brain barrier, and do drugs cross the blood-brain barrier? We have to remember with immunotherapy, these are really drugs, the drugs themselves probably don't cross the barrier, but importantly, if the immune system is activated to attack the cancer, the immune cells can cross the blood-brain barrier. So I've had a lot of questions about, does the drug get into the brain, and it's really more do the T cells get into the brain? And I think that there has been several series looking at responses in the brain; if the patient responds below the brain, they're likely to respond in the brain as well, so it has to do with what is the likelihood of response to immunotherapy?

Lecia Sequist: In my practice, I would treat small asymptomatic mets, especially with chemo IO and see if there was a response before jumping to radiation, but this patient's metastasis is in a crucial part of the brain, and also a little bit larger just to base line size, so I might worry about leaving it untreated in this patient.

Alice Shaw: There's also data, not just from lung, but also melanoma about using checkpoint inhibitors for untreated metastases, is that right?

Justin Gainor: Yeah, so recently in the *New England Journal Medicine*, there was a study, it was close to 100 patients, treated with nivolumab and ipilimumab with melanoma, and all these patients had untreated brain mets, and it did look like the intracranial disease control was fairly comparable to the extracranial disease control. And I think studies like that are important, because it also gives us insights into toxicities, and in that study they showed that around a third of patients had some treatment-related CNS adverse event, but in terms of grade 3 or 4 adverse events, it was less than 10%.

Justin Gainor: So I think it does show that these drugs can have activity in the central nervous system, but I agree with Lecia that, for this particular patient, I might think about treating that thalamic brain met first.

Alice Shaw: So we did think about it and in fact refer this patient to see a radiation oncologist who actually felt concerned about doing SRS to this lesion given its location potentially causing radial necrosis, and in fact being familiar with the data on the activity of checkpoint inhibitors, and of course knowing this patient's very high PD-L1 status, actually refer them back to me to consider systemic therapy despite that untreated brain metastasis.

Alice Shaw: So I had a long discussion with this patient about treatment options, of course, and the challenge and trying to treat this untreated brain metastasis the risks, but also a long discussion about systemic options, which I outlined as a single-agent pembrolizumab or possibly combination chemotherapy with

pembrolizumab. This patient as I mentioned, was not very symptomatic, some dyspnea on exertion, but otherwise felt quite well, and also was working as I said full time. And he really felt strongly that he wanted to try single-agent pembrolizumab and not have the side effects that come with the chemotherapy.

Alice Shaw: So in fact, he opted to proceed with first-line pembrolizumab, and actually tolerated the pembrolizumab quite well. Lecia, I don't know if you want to speak to tolerability in your experience with single-agent pembro?

Lecia Sequist: Yes, single-agent immunotherapy is very tolerable; the most common side effect patients have is no side effects all, and the most common side effect that we need to manage is often thyroid toxicity, which is fairly easy to manage and often doesn't cause a lot of symptomatic problems for patients. It's only about 10 or 15% of patients that will have more serious side effects that could potentially cause life-threatening complications, or even complications that need to be managed, such as colitis or pneumonitis, or you can really see inflammation with any organ, I think we're going to talk about that in a future module. But you have eyes peeled for any sort of toxicity; luckily most patients don't have much.

Alice Shaw: So he did do really well, we also monitored really closely for any emerging neurologic symptoms given the untreated brain metastasis, and obtained our first set of scans after two doses of pembrolizumab, and he of course was thrilled, because his first brain MRI showed near complete response in the thalamic lesion, and his chest CT also showed a really significant reduction in the lymphadenopathy. And so he continues actually today on pembrolizumab; he's at about six months at this point, doing well, actually really no toxicities, certainly no evidence of autoimmune toxicities, and has continued to work and maintain his active lifestyle through all of this.

Alice Shaw: So Dr. Gainor, what are your thoughts about this patient and when might he develop progression? What do the trials suggest about that? And what is known about mechanisms of resistance to pembrolizumab?

Justin Gainor: Great questions. So in the trials, so in KEYNOTE-24, the median progression-free survival was a little over 10 months. But what we don't have right now, has not been reached, is the duration of response, which is where this patient would fall into; so we really don't know, and I think we eagerly await updated data from KEYNOTE-24 to help guide those conversations with our patients. In terms of mechanisms of resistance to PD-L1 inhibitors, I would use the same paradigm of thinking that we use in targeted therapies, where we think about intrinsic resistance, and then acquired resistance to therapy.

Justin Gainor: Unfortunately our majority of patients progressing on PD-L1 inhibitors will have intrinsic resistance; they just never respond to begin with. And I think the spectrum there could be completely different, they may not, for example, they may not have the right new antigens, or they may not have PD-L1 expression;

there may be multiple mediators there. In terms of acquired resistance though, I think we're just now starting to scratch the surface, and there I think we can look to our melanoma colleagues and some of the work that they've been doing. And right now I think there are three mechanisms that have been put out there.

Justin Gainor: The first is escape mutations and interferon gamma signaling, and that's been described in melanoma, interferon gammas, of course, are very important in driving an immune response; the second is loss of the target antigen expression. This is particularly relevant if you're thinking about autologous-cellular therapy where the surface target may be lost. And then lastly, genetic mutations in beta-2-macroglobulin, and this makes a lot of intuitive sense because beta-2-m stabilizes HLA. So this is one place where you can have a single mutation suddenly prevent you from expressing the antigen that's being recognized by the immune system.

Justin Gainor: So in a series published by Yale, Scott Gettinger and colleagues, it looked like beta-2-m mutations were relatively infrequent in lung or less frequent than what's been seen in melanoma, about one out of 13 patients. But that's the largest series we have right now, so I think we need to, in the coming years, start understanding acquired resistance much better and really pursue in the same way we're doing for targeted therapies.

Alice Shaw: So do you think routinely providers should be, for example, rebiopsying patients when they fail on a checkpoint inhibitor, or are we not quite there yet to know what to look for?

Justin Gainor: I don't think we know what to look for yet. Of course, all of us at a big academic institution, this is part of our research mission, and so–

Alice Shaw: But in the community?

Justin Gainor: But in the community I don't think it should be a standard of care, because we don't know what to do with that information just yet. But I think in an academic setting, we're not going to know what the next treatment should be until we start understanding what's at the other end of resistance to PD-L1.

Alice Shaw: And so if you were to see a patient, let’s say in the future, this patient does progress on pembrolizumab, and they're coming, and of course we know they have standard options like chemotherapy, but say this patient wants to continue pursuing immunotherapies, and we've all heard about many of the immunotherapy combinations that are being explored in patients post-PD-L1. Are there any you feel particularly excited about right now?

Justin Gainor: Sorry, I think it's still early days, and I think this could be several modules in of itself. But I think the types of combinations that I'm intrigued by are those that are trying to cause cold tumors to become hot; I think that's a framework that

right now we haven't met with a lot of success for that, but there are some promising strategies, and so if we think to the cancer community cycle and the ways that we can try to stimulate an immune response; I think people are taking various steps to try to inflame tumors, ranging from personalized new antigen vaccines, to stimulators of innate immune system, to oncolytic viruses.

Justin Gainor: Right now, most of our data comes from very small phase I/phase II studies of expansion cohorts with very small numbers of patients, so I think we have to still be a little skeptical about the early findings. One intriguing piece of data came out within the last six months of an IL-15 superagonist, and that drug actually showed responses in three out of 11 patients who were previously resistant to PD-L1. So it may seem like a low response rate, but I think that's encouraging, and so hopefully we'll begin to see more and more data like that.

Alice Shaw: Hopefully when this patient does need another therapy, there'll be lots more data to inform our choice of combination. Great, so let's move to the second case. This is SL, who is a 66-year-old male, he is a commercial fisherman, and has an 80 pack/year smoking history. And I first met him about four years ago, when he was diagnosed with bulky unresectable stage 3A non–small cell lung cancer, adenocarcinoma histology. And at that time, our testing was performed and was negative for any targetable lesions.

Alice Shaw: He was treated at the time with EP 50/50, with concurrent radiation to 66 Gy, and his first scans after chemoradiation did show a decrease in the size of the primary lesion as well as the lymphadenopathy. Now this was well before the PACIFIC trial, which we already spoke about in an earlier module, so he did not receive any consolidation therapy, he just moved into active surveillance. About eight months after completing definitive chemoradiation, SL developed seizure activity and was admitted to the hospital. Brain imaging at the time revealed a new 1.8-cm right superior frontal gyrus lesion. He actually underwent neurosurgical resection of the lesion, followed by radiation to the resection cavity.

Alice Shaw: As he was recovering from surgery, he developed worsening upper gastric pain, anorexia, nausea, and weight loss. And we performed restaging scans of his body, which showed stable disease in the chest, but extensive new disease in the abdomen, including multiple peritoneal implants, enlarged in necrotic mesenteric nodes in the upper abdomen, ulceration of the stomach itself, which is adjacent to a large pancreatic tail mass. And an EGD was performed, which confirmed a large, about 10 cm malignant-appearing ulcerated gastric mass, as well as multiple large malignant perigastric and retroperitoneal nodes.

Alice Shaw: So Dr. Sequist, if you were meeting this patient today, what therapy would you consider recommending for him, and remember this is recurrence lung adenocarcinoma, extensive tumor burden, he had no known oncogenic drivers in his specimen, and I should state that he also, because it was four years ago, at that time, PD-L1 testing was not done, so he's PD-L1 unknown.

Lecia Sequist: But good performance status?

Alice Shaw: Good performance status, except quite symptomatic from the abdominal progression.

Lecia Sequist: So he seems like a really good candidate to consider triplet therapy with carboplatin, pemetrexed, and pembrolizumab. We know that the triplet therapy has a higher response rate than chemotherapy alone and that it also works across the spectrum of PD-L1 expressions, so even though we don't, even if he's zero, this is a good option for him.

Alice Shaw: So now at the time, the triplet regimen, KEYNOTE-189 had not been presented or published, and so at the time I actually offered him combination chemotherapy platinum pemetrexed, which he had not received, or actually single-agent nivolumab. And he was a platinum candidate as I mentioned, pretty good functional status despite the escalating symptoms, but he had only less than a year prior finished EP 50/50. And he really did not want to proceed with chemotherapy again, so instead, he opted to proceed with single-agent nivolumab.

Alice Shaw: So Dr. Gainor, this is essentially a second-line patient, having failed EP 50/50 less than a year ago, and I'm wondering if you can review the data on checkpoint inhibitors in the second-line setting, and of course speak to the importance of PD-L1 testing as well.

Justin Gainor: So in the second-line setting, we actually have five positive randomized studies. And in all of these studies, the comparison arm was docetaxel, so these were all patients previously treated with platinum doublet, and they were randomized to either PD-1 or PD-L1, versus docetaxel. Interestingly, many of these studies did not meet their endpoint of progression-free survival, but they were all positive for overall survival. And they were positive regardless of PD-L1 expression status, so even if someone was negative for PD-L1 expression, there's still an overall survival improvement compared to docetaxel.

Justin Gainor: Now, all of these studies differed a bit in terms of the diagnostic antibody that was used to gauge PD-L1 expression. One of these studies, KEYNOTE-10, actually only enrolled patients who were greater than 1%, for PD-L1 expression, whereas four others—CheckMate-017 and -057, POPLAR, and OAK—all of those studies enrolled patients regardless of PD-L1 expression. So the standard of care in someone who received platinum doublet first would be PD-1 or a PD-L1 inhibitor.

Justin Gainor: And in the United States, there are three approved agents. There's nivolumab, atezolizumab, which are approved regardless of PD-L1 expression, and pembrolizumab is approved if PD-L1 scores are greater than 1%. And so more importantly, the cut point in the second-line pembrolizumab is different than

first line. Here PD-L1 score of 1% and above was sufficient, providing overall survival benefit.

Alice Shaw: So this patient did go ahead with nivolumab at the time we were doing the every-two-week dosing of nivolumab, and it was really quite remarkable because after two weeks from starting nivolumab, he noted an improvement in his abdominal symptoms and we could tell sort of objectively, because he was requiring less pain medications. Still had some symptoms, but overall very improved. And by four weeks, so now after just two doses of nivolumab, his pain had completely resolved, and he was entirely off pain medications.

Alice Shaw: Early satiety had improved and he was actually back to eating normally, so really quite a remarkable turnaround. Actually, Lecia, very reminiscent of some of our patients with targets who go on to targeted therapies. And in fact first restaging scans, which we obtained after about six weeks of three doses, confirmed the response, and in fact, when we performed the repeat endoscopy at six months, the ulceration had completely resolved. And so he did well on nivolumab for the next nine months, but then at that point, he started to develop recurrent abdominal pain, periumbilical right lower quadrant, and abdominal imaging at this time showed an enlarging small bowel metastasis.

Alice Shaw: We could not easily biopsy this; there were no other active sites of disease in his body, so I guess we would say this looks like a case of oligoprogression on checkpoint inhibitor. And I'm wondering what your experience has been with this, and how do you approach patients who have oligoprogression?

Lecia Sequist: Well, oligoprogression is a relatively new term that we've thinking about in lung cancer. It first came to the forefront with patients on targeted therapies who had prolonged responses to their therapy, and then seemed to be progressing in only one spot, probably due to a single clone that came up with a resistance mechanism.

Lecia Sequist: The experience with targeted therapy patients is that, if you get rid of that clone through some sort of locally ablated mechanism, either surgery or radiation, then they can continue on the rest, the rest of their disease can continue to do quite well, and that strategy has been transplanted into the immune therapy world. And there isn't a prospective trial looking at this yet, that's very hard to do, but certainly, many anecdotal reports have patients who have done quite well with some sort of locally ablative therapy. And there's even thought that if you use radiation, maybe you'll induce the abscopal effect, and that can be helpful overall.

Alice Shaw: And what've you seen? Just seeing in your practice? What have you done for these patients?

Justin Gainor: I completely agree. I think you want to think about local therapy in the setting of oligoprogression. And oligoprogression can actually be quite common in

patients with acquired resistance to PD-1. In one recent retrospective study of about 26 patients with acquired resistance, that is, initial response followed by progression to PD-1, 88% of those patients had progression in one or two sites, so I think it does speak to that there may be a few areas where progression is concentrated and that we might think about local therapies.

Justin Gainor: Now we don't have data though on what the benefits to those therapies are yet, but I think it makes intuitive sense, and it aligns with what we've done with other treatment paradigms, namely, targeted therapy.

Alice Shaw: So I have to say this was a pretty tough case for me, because this is somewhat data free in a way. There's a lot of anecdotal experience, and we of course are extrapolating a bit from the targeted therapy experience, but also this patient had what really seemed like a peritoneal implant, which we often worry that's a site of disease that we're seeing, but there may be other tiny little implants that we aren't just seeing yet. So this is fairly challenging for both me as his provider and of course the patient.

Alice Shaw: But ultimately, because he was symptomatic from this, he did opt to undergo small bowel resection, and this peritoneal implant was resected fully, and pathology showed poorly differentiated carcinoma with necrosis, and actually we did do PD-L1 testing on the specimen—remember we didn't have it a diagnosis—and his PD-L1 was 50%. So in fact he continued on nivolumab, recovered fine, and continued on nivolumab, and actually he remains on nivolumab today 18 months later, and he's actually thrilled that he opted to do the surgery and now be able to maximize his time on the nivolumab.

Alice Shaw: Now at some point, Dr. Gainor, we know he will have more multifocal progression, and we'll likely need to switch therapies, and you briefly talked before about therapies post-PD-1, and you know therapy strategies post-PD-1, but what about just a standard strategy for this patient in terms of chemotherapy or chemobiologic therapy? What would you consider for him?

Justin Gainor: So one option would be, so this is a patient who got a platinum doublet, but he got it in combination with radiation, and now he's gotten a PD-1 inhibitor. I think we'd have to see what his performance status was like at the time of progression. Sounds like you had offered him a platinum doublet before, and if you wanted to be very, very aggressive, and he had a very good performance status that could be entertained.

Alice Shaw: Platinum pemetrexed.

Justin Gainor: Platinum pemetrexed would certainly be one option, and in a nonsquamous patient, I would certainly want to make sure he got pemetrexed at some point. Alternatively, if one was pursuing single-agent cytotoxic chemotherapy, one could do either docetaxel plus or minus ramucirumab. And we know that there, the addition of ramucirumab certainly increases response rates to docetaxel,

and we do have a randomized phase III study, in which it also improves survival, but I will say, treating these patients, sometimes patients just aren't eligible to receive ramucirumab, particularly when it's given with every-three-week docetaxel, that can be a bit more challenging.

Alice Shaw: His performance status has really remained excellent on the nivolumab, so hopefully were he to develop progression in the future, we likely would consider a platinum kind of combination with pemetrexed, and then maybe reserve docetaxel, as you said, with ramucirumab, for down the road. My experience with the combination of docetaxel/ramucirumab has also been somewhat challenging at times, because of the toxicity; Dr. Sequist, I don't know if you want to speak to that at all.

Lecia Sequist: Yeah, well, the way the regimen is approved, you have to give every-three-week docetaxel, which can be really toxic, can cause a lot of neutropenia. A lot of times, when you're giving single-agent docetaxel, at least our practice is, we like to break it up into a weekly lower dose, snippets for better tolerability, and so with ramucirumab it can be tough.

Alice Shaw: So to summarize the cases that we just discussed, for patients with newly diagnosed metastatic non–small cell lung cancer like our first case, with high PD-L1, with TPS 50% or higher, standard first-line therapy is pembrolizumab. For patients with newly diagnosed metastatic non–small cell lung cancer with a TPS of less than 50%, standard first-line therapy is platinum doublet plus pembrolizumab. And standard second-line options after failure of platinum doublet chemotherapy and immunotherapy do include docetaxel plus or minus ramucirumab. And finally just to Justin's point, there are numerous immunotherapy strategies under development for patients who have failed prior checkpoint inhibitors.

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.