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 best practice and emerging data in the management of patients with locally advanced non–small cell lung cancer and apply this knowledge to a case study of a 52-year-old female patient. The learning objectives for this module are to evaluate best practices and interpret the clinical significance of emerging data regarding safe and effective treatment of patients with locally advanced disease, 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.

Alice Shaw: So before we start, Dr. Sequist, I'm wondering whether or not you can provide maybe some historical context for the treatment of locally advanced, unresectable non–small cell lung cancer. And many of us remember using

consolidation therapy after chemo/radiation. And of course there are negative studies that then followed. And now, up until recently, we weren't using it. So maybe you can give us an overview of the field.

Lecia Sequist: Sure. It has changed a lot over the decades where we went from sequential chemo/radiation to combined. And then some of the best outcomes in the 1990s were with the EP 50/50 regimen, the SWOG regimen they called it at that time, which included EP 50/50 with concurrent radiation, and then outback chemotherapy or consolidation of sorts with a taxane. And that was the standard for many years until a randomized study showed that the taxane was actually adding toxicity without necessarily improving outcomes. And so from that point in the early 2000s, then the consolidation chemo was dropped. After pemetrexed was introduced for advanced lung cancer, it was then tested in the locally advanced setting with concurrent chemo/radiation cisplatin/pemetrexed. And that was shown to be equally as effective as the SWOG regimen, the older SWOG regimen, with easier schedule and easier tolerability. And so–

Alice Shaw: And that included consolidation pemetrexed.

Lecia Sequist: It did include consolidation pemetrexed, three cycles, without real evidence base of why they were doing it and no arm that looked at a pemetrexed regimen without the consolidation. But the study, the ProtecT study, that's how it was designed. And so until immune therapy came out, that was the standard at least for adenocarcinoma.

Alice Shaw: And Dr. Gainor, maybe you can provide some rationale for thinking about combining a checkpoint inhibitor or using, incorporating a checkpoint inhibitor into a regimen for locally advanced disease, and particularly after a patient completes definitive chemo/radiation. Really maybe explain again in broad terms why was there this interest in using checkpoint inhibitors.

Justin Gainor: Yeah. So I think the first thing is, one, this is an unmet need. Now we know that despite giving chemo and radiation concurrently that the vast majority of patients will actually recur of their disease. So we know that we need to do better. And so a lot of preclinical work has gone into what are the effects of radiation and chemotherapy on the immune microenvironment. And there are really three potential ways by which chemo and radiation may augment the effects of checkpoint blockade. The first is just via tumor antigen release. And this is something that applies to both.

Justin Gainor: The next is with respect to radiation, it can really lead to a release of DAMPs, or damage associated molecular patterns, which may produce a more inflammatory microenvironment.

Justin Gainor: And then, lastly, the third thing would be recruitment of cytokines, so producing more chemo-attractive cytokines that, again, lead to a more favorable immune microenvironment. So those three things together, the thought is that with

chemo and radiation it may prime the immune system and make these tumors more likely to respond.

Alice Shaw: So with that background, let's turn to our case. This is JT who is a previously health 52-year-old female, never smoker, working full time as a lawyer. And for about one year, she had a nagging cough. And then the cough worsened over about a few month period prompting her to see her primary care physician. At that time chest X-rays showed patchy opacities in the right middle lobe, possibly consistent with pneumonia. However, a follow-up chest CT demonstrated the 3-cm right hilar mass with an endobronchial component obstructing the right middle lobe bronchus. There was also associated subcarinal lymphadenopathy measuring about 1.9 cm. Staging PET showed intense FDG uptake of the right perihilar mass, the subcarinal lymphadenopathy, and also a left but not enlarged paratracheal lymph node. And there was no other distant FDG uptake. Her brain MRI was negative. The patient underwent a bronchoscopy and EBUS as well as mediastinoscopy. And pathology of the right hilar mass was positive for adenocarcinoma. The level 7 as well as 4L nodes were also positive for adenocarcinoma. And PD-L1 testing was done on her specimen and showed a TPS of 20%.

Alice Shaw: So she was diagnosed with a T1cN3M0 or stage 3B non–small cell lung cancer and she was started on definitive chemo/radiation. So Dr. Sequist, you already briefly alluded to some of the regimens that we use, but I'm wondering if you can, for this case in particular given what you've heard now about this patient, what you would recommend as the standard chemo/radiation for her.

Lecia Sequist: Yeah, it sounds like she got the optimal treatment, cisplatin/pemetrexed. Since the histology is adenocarcinoma, you want to do that with concurring chemo/radiation. There've been a lot of studies in the radiation oncology literature looking at the dose of radiation and they've shown that actually going higher than 60 Gy is not necessarily more beneficial. But I think you have to really work with your local experts and see what they recommend. This patient sounds like she had a contralateral mediastinal lymph node so I'm sure they really wanted to make sure that the mediastinum was sterilized.

Alice Shaw: So you would go ahead with cisplatin/pemetrexed combined with radiation, a definitive course of radiation.

Lecia Sequist: That's right.

Alice Shaw: And this is of course based on the PROCLAIM study. And we talked about this already but that study did happen to include a little bit of outback pemetrexed prior to the PACIFIC trial. Would you have done this for this patient?

Lecia Sequist: It sounds like this patient is young and very fit, probably had a great performance status and could tolerate outback chemo. I have found actually in my practice when I've tried to give such patients who seem up front like they

would be able to tolerate consolidation cycles, those consolidation cycles are tougher than you think. And I usually don't get through three of them. I say, "Let's try three," and we end up dropping it after one or two. So I would say my enthusiasm for outback chemo, even single-agent pemetrexed, is lukewarm.

Alice Shaw: And Dr. Gainor, again, before PACIFIC, would you have offered a patient like this potentially consolidation with pemetrexed?

Justin Gainor: So I would've offered a young patient, but I would've entered the course saying, with the expectation that many of our patients don't make it beyond, the most important part of your care is the concurrent chemo and radiation, and let's just see how you do.

Alice Shaw: So this patient did receive concurrent cisplatin pemetrexed with radiation to the right hilar mass and the right mediastinum, and received a total of three cycles of chemotherapy with radiation to 66 Gy in 33 fractions. Now, at the time she was diagnosed, in addition to having the PD-L1 testing, her tumor tissue was also submitted for multiplex molecular testing. And I'm wondering, Dr. Sequist, if you maybe can speak to the guidelines for molecular testing in a patient like this with locally advanced disease. Are you routinely testing these patients for actionable drivers?

Lecia Sequist: For a patient with stage III disease, I am routinely testing them, not necessarily because I think it's going to affect the recommendations, at least not for chemo/radiation, but because they have such a high chance of recurrence and you want to know about the driver mutation, if it's there, immediately at the time of recurrence. The official guidelines only recommend testing in advanced-stage disease, so this is certainly an area of controversy.

Alice Shaw: And, Dr. Gainor, if we knew this patient did have an EGFR mutation or ALK rearrangement, would you consider ... how would you think about a TKI as induction therapy? And is there data to support that?

Justin Gainor: Yeah, so it's a good question. And part of the challenge is finding these patients before they begin their induction therapy, so actually doing the molecular testing and then actually being able to enroll them in a clinical trial to actually get the data of how beneficial induction therapy is, has been very challenging. And I think Lecia can probably speak to this, having run one of those studies, that it's been challenging actually getting all of that done before a patient can actually get started. I don't know, maybe you can ...

Lecia Sequist: I think that's true. So we ran a study out of Mass General that was single arm. But the RTOG has actually tried to run a randomized trial in this setting and they've really struggled. For the patients that we were able to identify with an EGFR mutation before they started on their combined therapy, as part of this trial we gave them induction EGFR TKI. And I think the results were very successful for a small, single-arm study. Many of the patients who were not

operable because of the size or the central location of their tumor, actually had sufficient shrinkage that they became operable. For those, like this patient, with a contralateral lymph node, you probably wouldn't convert them to being operable but it looks like there is promise as far as operability and also pathologic response seen on surgery for stage III patients who receive induction TKI.

Alice Shaw: So interestingly this patient, her NGS testing did come back actually during her third week of chemo/radiation. And she did not have EGFR or ALK. But she turned out to have ROS1 rearrangement, which we confirmed both by the NGS as well as by FISH. So let's just keep that in mind that this is a patient with locally advanced ROS1-rearranged lung cancer. So she completed her full course of chemo/radiation. And I would say overall she tolerated therapy quite well, had the expected esophagitis and some nausea, well controlled with medical management. And we obtained a restaging CT, which showed persistent obstruction of the right middle lobe by this central mass, but it was somewhat smaller and there was a decrease in the subcarinal lymphadenopathy with no new disease.

Alice Shaw: So, Dr. Gainor, for this patient and for patients in general who have now completed a definitive course of chemo/RT, again in this setting we likely might have considered consolidation pemetrexed in the old days. We might even have considered just surveillance, again in the old days. But maybe now you can tell us a little about the PACIFIC trial and how that's impacted our management.

Justin Gainor: Yeah, I would say that the PACIFIC study has changed our standard of care for this setting. So the PACIFIC study was a randomized phase III study. Patients were randomized 2:1 to either durvalumab, a PD-L1 inhibitor, versus placebo. And the PD-L1 inhibitor was delivered every two weeks up to a year.

Alice Shaw: And this was independent of PD-L1 status.

Justin Gainor: This is independent of PD-L1 status. So patients submitted archival specimens but there was no entry criteria what the PD-L1 score had to be. And there were co-primary endpoints. We have the first, which was progression-free survival. And this was a very positive study with an improvement in progression-free survival compared to placebo. And so the medium PFS in the durva arm is 16.8 months versus 5.6 in the placebo arm.

Alice Shaw: And I believe that was starting from the end of chemo/radiation.

Justin Gainor: Exactly. I think that's an important point is that I think we're going to be seeing more studies in the next few years looking at this consolidation or even adding PD-1 inhibitors to concurrent therapy. And I think we have to be comparing apples to apples. And in this study, PACIFIC, PFS was measured from the time of randomization that was after chemo/radiation. So you're also selecting out a subgroup there because the people who had primary progression aren't

included in this study. So I think that's an important point. So, yeah, it was a positive study with respect to progression-free survival. And we know, at least by press release, that it was a study also positive for overall survival. So I think it defines our new standard of care.

Alice Shaw: And maybe you can speak a little bit to what we eluded to earlier about PD-L1 staining. They had shown their subgroup analyses and which subgroups were deriving benefit. And it appeared that actually most, although not all, but most subgroups derived benefit from consolidation durvalumab. And maybe you can comment on the subgroups defined by PD-L1 status.

Justin Gainor: Right. So first, about a little over a third of patients actually didn't have enough tissue for PD-L1 testing. So that's the first point. The second is that since this was a study using durvalumab, there was a different cut point used to define PD-L1 expression. In this study it was 25% and higher was defined as PD-L1 expression. It did look like there was a trend towards improved benefit in that group. But the PD-L1 negative patients and those with unknown status also benefited. So I would say that consolidation durvalumab is indicated regardless of PD-L1 expression.

Alice Shaw: So no selection--

Justin Gainor: No selection.

Alice Shaw: --based on PD-L1 expression.

Justin Gainor: Right. At least in the United States.

Alice Shaw: One notable exception in the forest plot that was presented and published in terms of the subgroups was of course the EGFR-mutant subgroup of patients. And it was small. I believe it was a total of 43 patients. But they showed that that EGFR-mutant subgroup appeared to derive quite a bit less benefit, maybe no benefit from using durvalumab as consolidation. Although I think what was interesting is that the neversmoking or nonsmoking population though within the PACIFIC trial did appear to derive quite significant benefits from durvalumab. And so I'm wondering what both of you may think about that data.

Lecia Sequist: It does go along with what we've seen using single-agent checkpoint inhibitors in metastatic patients. That EGFR tends to recurrently be a subgroup of patients that don't benefit. But I think that it, to me, it was a little confusing that the neversmokers benefited and the EGFR mutation patients didn't. It was such a small group. I think we need more information, to be honest.

Alice Shaw: What are your thoughts, Dr. Gainor?

Justin Gainor: Yeah, I agree. I think it's a small subgroup. And here, in contrast to the metastatic setting where there's always a comparator arm, an active treatment

like docetaxel, here the comparator was placebo. And so it may be that, even though it's less common for a neversmoker to respond, there are still responses in some patients, especially when you're comparing it against placebo. I think we need more. We need to look at the next wave of studies and focus in on that subgroup.

Alice Shaw: So this patient did not have EGFR. She had ROS1. But Dr. Sequist, as an expert in EGFR-mutant lung cancer, what are you recommending these days for your patients with locally advanced unresectable EGFR-mutant lung cancer? Are you following the data that we just talked about in PACIFIC and not going forward with durvalumab, or are you considering durvalumab given the data is still pretty early?

Lecia Sequist: Yeah. It is tough because I would say the PACIFIC data and durvalumab represents the biggest improvement in the care of stage III patients that we've had in 20 years. And to see a new therapy that actually brings, at least by press release we've heard there's a survival benefit. That is really a sea change. I think the concern, for me, we talked about in the last module a little bit, toxicity between even sequential use separated in time between an IO and a TKI. So with EGFR patients I do worry about their risk of recurrence. And if I've recently given them durvalumab and then if they recur shortly after and you want to give a TKI, you are bringing in a lot of unnecessary excess toxicity potentially. But of course at the time that you're considering giving the durvalumab they haven't recurred and you're hoping to give them the best chance of not recurring.

Alice Shaw: Almost, at least at this point, a case-by-case assessment.

Lecia Sequist: It is a case-by-case assessment. And I think looking at their risk of recurrence and also other factors as far as their risk of pneumonitis, maybe how much radiation exposure they had received with their chemo/radiation.

Alice Shaw: And Dr. Gainor, she actually had ROS1 and I'm wondering what do you do now for your locally advanced unresectable ALK- or ROS1-positive lung cancer patients? Do you offer them durvalumab? Would you offer this patient durvalumab now that she's completed chemo/radiation?

Justin Gainor: Yeah. I feel similar to Lecia in that it's hard to be dogmatic about this given the lack of data. I think it's a case-by-case conversation with the patient. If a patient is really looking at this degree of PFS benefit and saying, "I want to do everything possible to try to improve my chances of this cancer coming back," in the absence of concerns I would have about toxicity, I do think it would be reasonable to proceed. Especially because, even though we know this patient has a targetable genetic alteration, all of our data is in the stage IV setting. And we don't know post-concurrent chemo/radiation. Crizotinib doesn't look like it's going to be curative in that setting. We don't know. And so I think I would go with the data that we have, which would be PACIFIC.

Alice Shaw: So this patient thought about her options of pursuing durvalumab versus even considering consolidation pemetrexed or surveillance. And again this patient, being a very otherwise healthy and active young patient, opted actually to proceed with durvalumab, and really because of this data suggesting an improvement in overall survival that we've heard about. So she had done well with chemo/radiation, as I mentioned, and she was scheduled to start durvalumab about two weeks after the end of her radiation. But at this time, when she came in, she noted she had more fatigue and in fact we ended up postponing the durvalumab for actually another three weeks. So Dr. Gainor, maybe you can speak to this issue, which is when can most patients proceed with consolidation durvalumab, and is the timing important?

Justin Gainor: In PACIFIC, the initial protocol was that patients had to be randomized within 14 days of completing radiation. So that meant there was no consolidation allowed in PACIFIC. One can imagine the logistical challenges of enrolling a patient on a clinical trial within 14 days of completing radiation. And so that was acknowledged in the study through a protocol amendment where it was then moved to 42 days. And I think that was far easier. But nonetheless, they did an exploratory subgroup analysis where they looked at outcomes of patients who started within 14 days versus 42 days. And it did look like there was a trend towards better outcomes in patients who were started within 14 days. Now, that's confounded by a number of things.

Alice Shaw: Selection bias.

Justin Gainor: I think it is. Those patients are more likely to be healthier. They may have had a lower volume of disease that gets radiated. I think there are a number of things that may explain better outcomes in that group. But nonetheless, I would say that, all things equal, if a patient can get started earlier, I would start them earlier. But you have to look at the patient in front of you and see. You're talking about a year of therapy. And so if they're already having significant fatigue, I think patient may be best served by just waiting an extra week or two.

Alice Shaw: And we've been asked a few times over the last even few months about patients who may actually have completed chemo/radiation, their oncologists are interested in still squeezing in some outback or consolidation chemo before durvalumab. Dr. Sequist, what do you think about that approach?

Lecia Sequist: I wouldn't recommend it because we've had randomized trials in the past that have showed there really isn't a benefit to the outback chemotherapy. And the most recent study, the ProtecT study we spoke about, that included it. There was no comparison there to a similar arm that didn't include it. So I think the sum of the data does not support giving outback chemo. And given the time constraints that were implicit in PACIFIC, I would push forward with durva instead of chemo.

Alice Shaw: I think that makes the most sense to move from chemo/radiation, allow recovery, and move to durvalumab.

Justin Gainor: Right.

Alice Shaw: So maybe one of you can briefly just explain the schedule of durvalumab, the duration of treatment, and maybe just a brief word on side effects.

Lecia Sequist: Sure. It's given every two weeks for a year. And both in the trial and in my experience in clinic, it's been very well tolerated. I think there was some concern among all of us when we heard about the design of PACIFIC that maybe these patients who had just had chest radiation would have quite high rates of pneumonitis, and that hasn't borne out at all. The rate of pneumonitis on PACIFIC was fairly low. And patients still have the expected autoimmune side effects, commonly have thyroid problems, fatigue, itching.

Alice Shaw: I think it was surprising about the pneumonitis risk. That was a major concern. And maybe Dr. Gainor you can speak to that a little bit. There wasn't a really huge difference between the two arms. Is that right?

Justin Gainor: Right. That's right. So the rates were in the 30 to 40% range. But of course that includes radiation-related pneumonitis. So on a numerical level there was about a 9% difference between the durva and the placebo arm. But if you look at grade 3/4, there really wasn't a real difference there. So we're not seeing a huge safety signal. In our own institutional experience I would say that that bears out as well in that we haven't seen a large safety signal with adding PD-1 inhibitors in patients receiving chest radiotherapy.

Lecia Sequist: Do you think that has to do with PD-1 versus PD-L1?

Justin Gainor: I don't think so. That is part of I think the rationale why the PD-L1 inhibitors were the first studied post-chemo/radiation in that early-on there was the theoretical benefit of PD-L1 inhibitors, that there'd be lower rates of pneumonitis. And the reason for that theory was that PD-L2 plays a role in immune tolerance in the lungs. So a PD-1 inhibitor's going to also engage that interaction, whereas PD-L1 inhibitors won't. But I would say that overall it doesn't look like there's substantial differences between PD-1 and PD-L1 inhibitors. And recently in ASCO, Solange Peters and colleagues actually presented some early data looking at concurrent chemo/radiation with nivolumab, a PD-1 inhibitor. And it didn't seem like there was a high rate of pneumonitis in that group too.

Alice Shaw: And so do you feel durvalumab is the only checkpoint inhibitor to use in this setting of consolidation therapy given the PACIFIC trial? Or, again, a number of questions from oncologists has been, "Can we use a different PD-1 or PD-L1 inhibitor as consolidation?" What are your thoughts on that?

Justin Gainor: I would go where we have the data, which is durvalumab. That's the drug that's been approved in this setting and that's what I would do.

Alice Shaw: And then the other common question that we hear about is for a patient who's been on durvalumab now and then unfortunately has a recurrence, what would be your first-line therapy? Do we know yet the optimal first-line therapy?

Justin Gainor: I don't think we do. But I would approach it the same way as I would in someone who progressed after getting chemo/radiation, using the same framework, which is how soon afterwards, what was their initial response, what was their tolerability? If someone progressed while they were receiving durva, I wouldn't go down the immunotherapy route of further treatment. Whereas if someone completed their one year of therapy and then recurred two years later, you might reassess, do I pursue PD-1 or not? I think it's more of an open question and one where we frankly don't have the data yet.

Alice Shaw: And then last question to both of you. Again, this patient was ROS1 and we've really focused on durvalumab as her consolidation therapy. And, in fact, she did go ahead and receive durvalumab. But I think some oncologists might have considered using crizotinib for her as consolidation. And so any thoughts on that?

Lecia Sequist: I think that's a data-free zone. It theoretically makes sense, but even among the more common EGFR mutation we don't have definitive data that adjuvant therapy helps with early-stage patients. So if I were the patient, I actually might lean towards trying something like that. But I would be really remiss about giving it to a patient. I think there's not a lot of data.

Alice Shaw: Dr. Gainor?

Justin Gainor: I would echo those sentiments. Right now we don't have any definitive data. We know that in the EGFR space it looks like certainly disease-free survival can be improved with the TKI. But in terms of that translating into overall survival, we don't have that yet. We can look to other disease areas like melanoma, BRAF. In that setting, adjuvant BRAF plus MEK, there's benefit there. But right now we just don't have the data in lung and specifically in a rare subset like ROS1.

Alice Shaw: And, again, she's a never smoker. And that never smoking subset did derive significant benefit from durvalumab. So the data does really support using durva.

Justin Gainor: Durva, right.

Alice Shaw: So to summarize, the PACIFIC trial has established durvalumab consolidation as the new standard of care for patients with locally advanced unresectable non–small cell lung cancer. And just to reiterate the data, compared to placebo durva improved progression-free survival, as you mentioned Dr. Gainor, from 5.6 to 16.8 months. Also improved response rate from 16% to about 28%, duration of response and, as we mentioned, in a press release we've heard that durva also improved overall survival. All subgroups of patients benefited from durvalumab

consolidation with the possible exception of EGFR mutation-positive patients. But we acknowledged that that was a smaller subset. And finally, durva is general relatively well tolerated, and pneumonitis of any grade can be seen in roughly about a third of the patients.

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.