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 be discussing the treatment and management of patients with ALK-positive non–small cell lung cancer and applying that knowledge to a case study of a 40-year-old female patient. The learning objectives for this module are to evaluate best practices and interpret the clinical significance of emerging data regarding the management of ALK-positive non–small cell lung cancer, to plan strategies to incorporate best practices and emerging data into clinical practice, and to apply best practices and emerging data to treat patients with ALK-positive non–small cell lung cancer safely and effectively.

Alice Shaw: So GL is a 40-year-old woman, neversmoker, who was evaluated at a local hospital after a motor vehicle accident and incidentally found to have a 3.7-cm left lower lobe mass. Further workup included a PET scan, which demonstrated

that the left lower lobe mass was FDG-avid, and there was associated FDG-avid left hilar and subcarinal lymphadenopathy. There was no evidence of distant metastasis, and brain MRI was also negative. She underwent bronchoscopy and mediastinoscopy, and sampling of the subcarinal node demonstrated adenocarcinoma, well differentiated with mucinous features. She was diagnosed with T2aN2M0 were stage IIIA non–small cell lung cancer.

Alice Shaw: The patient received neoadjuvant chemotherapy with radiation therapy, followed by VATS lobectomy and mediastinal dissection. The surgical specimen showed a 2.9-cm residual adenocarcinoma predominately acinar pattern with evidence of treatment effect. Carcinoma was present in one level 7 lymph node with the remaining 15 nodes negative. She then received four cycles of consolidation chemotherapy with carboplatin and pemetrexed.

Alice Shaw: The patient then started on active surveillance with serial scans. One year after completing chemotherapy she developed headaches and neck pain. Brain MRI was obtained and unfortunately revealed multiple brain metastases, the largest measuring 10 mm. Restaging FDG-PET showed avid mediastinal and left hilar lymphadenopathy, and she was diagnosed with metastatic, recurrent non–small lung cancer and now referred to our hospital. Now we obtained her prior pathology specimen, and we performed molecular testing, our SNaPshot analysis, and EGFR and ROS1 were both negative, but ALK IHC was positive. And we confirmed ALK positivity using our next-generation sequencing assay, which revealed a HIP1-ALK rearrangement.

Alice Shaw: So, Dr. Sequist, before we turn to a discussion on treatment options for metastatic ALK-positive lung cancer, I'm wondering if you can provide some background on this molecular subset of non–small cell lung cancer. How common are these ALK rearrangements? Is this a typical ALK-positive patient you might see in the clinic? And what is the general sort of overall prognosis these days for patients with metastatic ALK-positive lung cancer?

Lecia Sequist: Sure. Rearrangements involving ALK are the second most common driver mutation that we see in lung cancer, and so it is really important to test all lung cancer patients now that we have a wide range of treatments available for them.

Lecia Sequist: And this patient is the textbook example of what you would expect for an ALK patient. She's a neversmoker, she's young, only 40 years old, and ALK has a much higher incidence among neversmokers compared to smokers with lung cancer and also tends to segregate into the younger population, and has a slight gender predominance in males. So she's really the type of ALK patient you would expect to see, and it's always good news to deliver the news that you have an ALK translocation because it does have a better prognosis than some other types of lung cancer. Median survivals nowadays with the number of ALK-effective drugs that are on the market is between four and five years.

Alice Shaw: Yeah, I think it's notable that in PROFILE 1014, which was the first-line study of crizotinib versus chemotherapy, now conducted a number of years ago, that median overall survival for that study came in at exactly what you said: four to five years. And I think back then there were even fewer options for ALK-targeted therapies as there are now. So, I think the outlook is very good now and hopefully will continue to improve.

Lecia Sequist: Absolutely.

Alice Shaw: And Dr. Gainor, this patient did receive prior chemotherapy, but she was completely TKI-naive, so not received any ALK inhibitors at all at this point. And so, maybe you could briefly provide sort of a summary of treatment options for patients like this who have newly diagnosed or recurrent metastatic ALK-positive lung cancer.

Justin Gainor: Yeah, I think there are two points: One is that the patient is TKI-naive, and the second also is brain metastases, and I think those are two things we want to keep in mind. Currently, in the United States, there are three ALK inhibitors that are approved for first-line use in ALK-positive lung cancer. The first agent approved was crizotinib, and you already alluded to PROFILE 1014, which was the first randomized phase III study in patients with TKI-naive ALK-positive lung cancer. And there the comparator arm was chemotherapy, and crizotinib was superior to platinum doublet chemotherapy, and that really was the first ALK inhibitor where we were using in newly diagnosed patients.

Justin Gainor: More recently, there have been a series of second-generation ALK inhibitors to enter the clinic that are more potent and more selective for ALK. We have two of these agents that are approved for patients who are TKI-naive: that's ceritinib and alectinib. Ceritinib was approved on the basis of ASCEND-4, where again the comparator arm was chemotherapy. And then, alectinib, which we now have two studies in the frontline space: the J-ALEX study, which was conducted in Japan, and the global ALEX study. And these studies are important to know because here we actually have a comparison of TKI versus TKI. So alectinib was compared against crizotinib, and in the global ALEX study showed a significant improvement in progression-free survival, which was the primary endpoint of this study. And so, based on the global ALEX study, which also showed not just improvements and progression-free survival but also significant improvements in intracranial responses and cumulative incidents of brain metastases with alectinib, that has become our standard of care, which is first-line alectinib.

Justin Gainor: We have received press releases saying there's a fourth ALK inhibitor which may enter the first-line space; this is brigatinib, which, in a randomized phase III study, is being compared against crizotinib; this is the ALTA-1L study. And we've heard from our press release that this was a positive study, but we're waiting on that data.

Alice Shaw: Dr. Gainor had mentioned alectinib's activity, particularly in the CNS. We've seen that in the ALEX study as well as in the earlier phase I and II studies of

alectinib, and we know that alectinib is not a substrate of P-gp, one of the major drug efflux pumps that may limit exposure of these drugs in the brain. And so I'm wondering, for this patient, what are your thoughts because she's symptomatic from the brain metastases? We, of course, started dexamethasone for her. Do you feel, given the availability of these brain penetrable drugs like alectinib, that she requires radiation therapy prior to starting a drug like alectinib?

Lecia Sequist: Not necessarily; especially, it would be a good sign if she had some symptomatic improvement on the Decadron. These drugs work so well; alectinib is a prime example, also, in the EGFR world, ceritinib is another example of a TKI that works so well in the CNS that we often can get away with avoiding radiation. And that's something we'd like to do because these patients also, as we just mentioned, have a longer survival and so more time accumulated to be able to have negative side effects from radiation if you give it early on—things like seizures from radiation, necrosis. So trying to avoid radiation is definitely a top priority for patients with a targetable mutation because of their long expected survival. And now with drugs that get into the CNS, we often can get away with doing that.

Alice Shaw: Dr. Gainor, would you also be comfortable with treating a patient like this, with the symptomatic brain metastases with a drug like alectinib?

Justin Gainor: I would. In the global ALEX study among patients with measurable CNS metastases, the intracranial response rate was over 80%, so I would feel comfortable treating this patient with first-line alectinib.

Alice Shaw: We just put together a series, in fact, from our own institution looking at patients with ALK-positive lung cancer with either symptomatic brain metastases or large brain metastases, defined as 1 cm or greater. And in fact, the intracranial response rate was as high for those patients as it was for patients who were completely asymptomatic from their brain metastases, so I would agree that we're pretty comfortable using these drugs and holding off on radiation.

Alice Shaw: So we did talk to the patient about different options, of course, discussed radiation, but also talked about starting on a brain-penetrable ALK inhibitor and specifically, alectinib. And this is for the reasons you mentioned, Justin, about the data from the ALEX trials. And the patient did opt to proceed with alectinib at the standard dose, 600 mg, twice a day. And a question, Dr. Sequist, for you. So, we had done testing on her sample from diagnosis, and that's where we saw the ALK rearrangement. Do you feel that she should have another biopsy at this point to confirm the ALK rearrangement?

Lecia Sequist: Prior to starting the alectinib? I think it depends a little bit on the length of time it's been since her primary diagnosis and whether the pattern of disease is different. If you have someone who has a surgery, and you have a recurrence on the suture line, that's a very clinically suggestive picture that it's the same

cancer. If it is the same cancer, we know that their driver mutations should be present in every cell, so sometimes doing repeat testing is not necessarily indicated. But if you had someone who had had multiple stage I cancers resected in the past, and now they seem to have a distance recurrence, those types of diseases could be molecularly heterogeneous, so I think it depends a little bit on the clinical scenario.

Alice Shaw: In her case, we thought about it, but her relapse was within a year of her initial diagnosis. It was in the mediastinum but also with brain metastases. We felt fairly confident it was likely the same cancer as before, so again, we started her on the alectinib. And one question, Justin, kind of a practical question is the dosing of alectinib. You refer to the ALEX studies. One of them is a Japanese study called J-ALEX, and the second study was a global ALEX study, and they used two different doses of alectinib, which is very confusing. I think to many providers, the global ALEX study used the standard 600 mg twice a day dose that this patient went on, but in J-ALEX, they actually used a 300 mg twice a day dose. So just wondering if you can comment on those two different doses, and what should we all be using when we prescribe alectinib?

Justin Gainor: Right, so in the J-ALEX study they used a dose of 300 mg twice daily, and this was really due to Japanese restrictions on sodium lauryl sulfate, which is in the formulation. And so, it wasn't doses above 300 weren't explored, there aren't toxicity issues there. It was really just a restriction on the formulation. In the global ALEX study, 600 mg BID was used. I should also point out that that too is not even the MTD of alectinib. And looking at cross-trial comparisons of exposure, it looks like we should be treating patients in the United States with 600 mg BID, especially in a patient where we want to ensure good exposure in the brain. I would say that that's crucial in this patient, and so I would feel comfortable with that.

Alice Shaw: Right, you bring up a good point that I think the reason we all favor the 600 dose is because when they've done the pharmacokinetic studies across, like you said, populations of patients, it seems like the 600 mg dose ensures that the most patients are achieving sort of adequate drug levels and adequate ALK inhibition.

Alice Shaw: So this patient went on to alectinib at 600 mg twice a day and did well. She had muscle aches in the beginning, probably for about a month, and also though during this time, developed grade 3 transaminitis. So, Dr. Sequist, what has your experience been like with alectinib and side effects? Have you found that alectinib is a tolerable drug or have you encountered certain side effects that have been problematic?

Lecia Sequist: It is very tolerable. A lot of the patients that I've treated have been on crizotinib previously, and so they also have their own interpatient comparator. And most patients in that scenario find alectinib easier to tolerate than crizotinib. It has less lower extremity DML, which can be really bothersome, especially when patients are on crizotinib for a long time. So, it is fairly tolerable, but it is

important to monitor the LFTs because that is one of the more common laboratory side effects that you see.

Alice Shaw: Right, and I would say also that the GI side effects seem to be quite a bit better with alectinib than crizotinib; particularly there's really very little nausea or vomiting with alectinib, which has been nice, and really no diarrhea, but I've seen more constipation with alectinib than crizotinib. So I would agree that tolerability seems quite good with alectinib, but there are certain things to monitor, including the liver function tests, as well as the creatine phosphokinase since the muscle enzymes can also be increased with the alectinib.

Alice Shaw: So this patient was on for about six weeks, and we obtained her first restaging scans and were very happy to see that her brain MRI and her chest CT showed significant improvements. All the brain lesions responded, the edema that was associated with the brain lesions had resolved, and the chest CT also showed a significant improvement in the lymphadenopathy; also, no new disease. So, Dr. Gainor, is this a typical response, would you say for some newly diagnosed patient starting on alectinib, and so quick, at six weeks? Seeing such a good response?

Justin Gainor: I would say, yes. We know that when you use a highly effective targeted therapy in a genetically defined subtype of patients, you see responses very early. And we know with alectinib, based on the global ALEX study, that most patients will experience a response, both extracranially, as well as intracranially.

Alice Shaw: And durability-wise, I think what we've all seen with alectinib is that these responses tend to be quite durable. Certainly in the ALEX studies, the median duration of response was quite long, exceeding 20, 25 months, and potentially even longer on the update of the ALEX trial.

Alice Shaw: So, this patient continued on alectinib almost two years, actually, and had ongoing response in the brain and body during this time. But then right about two years, she had a brain MRI, just a surveillance brain MRI, that unfortunately showed some mild enlargements of several of the brain lesions which had previously responded to the alectinib. These were all very small, probably less than 5 mm, and she did not have any symptoms. So what do you think about this now, this situation where she's actually relapsing just in the brain on alectinib, which already is brain penetrable? What would you recommend for her next steps? Dr. Gainor, if you want to start.

Justin Gainor: So, in my mind, it matters a bit what the progression in the brain looks like. Is this one isolated site of disease? Is it multiple sites? Is the patient symptomatic? If it's one site or even two sites, where you're thinking that this is more of an oligoprogression, you might think about some sort of local therapy, be it surgical resection or focused radiation. If a patient's having more diffuse progression in the CNS, then we have to think about either more extensive forms of radiation, like whole-brain radiation. But I think to Dr. Sequist's point, these patients are

living longer and longer and so we're wary of the potential for neurocognitive effects down the road.

Justin Gainor: So, it also makes me think about potential other systemic therapy options. Right now, we do have data using a third-generation ALK inhibitor that's still investigational at this point, and this is lorlatinib. This was a drug that was specifically designed to be more CNS penetrant as well as be able to overcome known ALK resistance mutations. And then, in a phase I/II study, which you're very aware of, this drug has shown very promising activity in patients after one, two, and even three prior ALK inhibitors, with the response rates of 30 to 40% after second-generation ALK inhibitors, including responses in the CNS. So if the patient was able to pursue a clinical trial, that's something that I would certainly want to pursue in this patient.

Alice Shaw: So if this patient weren't able to pursue a trial of lorlatinib or access it, what about alectinib and dose-escalating alectinib since you've actually published on that approach. Would you consider that for this patient?

Justin Gainor: I would. I would. I think it speaks to the point we raised earlier, which is that 600 twice daily is not the MTD of alectinib, and doses even 900 mg BID have been explored, and have been found to be safe and effective. So, the paper that you're alluding to is work we did together looking at a patient with leptomeningeal disease and brain parenchymal disease, and in that setting we were able to re-induce responses with alectinib at a higher dose. So that's something that I would certainly entertain in someone whose tolerating a dose of 600 twice daily well, and if they didn't have clinical trial access.

Alice Shaw: So we did discuss it with the patient and seriously considered it. I think the patient herself was concerned because she'd had the transaminitis in the past and was worried about dose escalating her alectinib and now running into liver issues again. Before we turn to what we actually did end up doing for her, I was wondering, Dr. Sequist, what are your thoughts about liquid biopsy at this point. This patient is developing resistance, but right now it's only in the brain. Any rule for liquid biopsy?

Lecia Sequist: Well, when the amount of active disease is small, and often when it's confined to the brain, we don't see any findings on a plasma test looking for circulating tumor DNA. Just the shedding is very low or it may not be able to get into mainstream circulation. But in general, if the patient was having more of a systemic progression, liquid biopsies can be helpful in patients with ALK because what you're really looking for at the time of drug resistance is whether you can find an ALK mutation, trying to determine whether the tumor is still dependent on ALK or whether it's developed an ALK independent mechanism of resistance.

Lecia Sequist: And so, those point mutations in ALK are fairly detectable on plasma tests.

Alice Shaw: Yep. So we didn't actually do liquid biopsy for her because it was CNS only, but I think you're right, if she'd had more extensive progression we likely would have offered liquid biopsy testing to try and identify specific ALK resistant mutations.

Alice Shaw: Now, when we talked with the patient, she had multiple brain lesions. We talked about options, and as I mentioned, we didn't want to try and increase alectinib, so in fact we did go to the third-generation inhibitor, lorlatinib. And as Dr. Gainor mentioned, this is a more potent and brain-penetrable TKI than the second-generation class. And in fact, lorlatinib has FDA breakthrough therapy designation now for ALK-positive lung cancer, and we expected to be approved any day now.

Alice Shaw: Dr. Gainor, you've already talked about lorlatinib's activity, especially in the brain. I'm wondering if you can speak to side effects, tolerability of lorlatinib. It is a very different drug than the other ALK inhibitors.

Justin Gainor: You're right. It is a very selective ALK inhibitor. Some more unusual side effects that distinguish it from other ALK inhibitors, we tend to see elevations in cholesterol, so it is important to monitor patients' cholesterol triglycerides on therapy. And many of our patients will require cholesterol therapy. We also see edema; this is something that's been seen with other ALK inhibitors, most notably, crizotinib. And then, a third thing that somewhat distinguishes it from others is that there can be neurological side effects with the drug, mild, cognitive disturbances. It tends to improve with dose holding and resolve, and it also improves with dose reductions. I think it's important to recognize in our patients and take the necessary steps if you do see it emerge, which is hold and then dose reduce.

Alice Shaw: And I know, Dr. Sequist, you've had a few patients on lorlatinib with these neurocognitive side effects. I'm wondering if you also could just elaborate a little bit more about how patients describe these side effects, and how are they impacting their function.

Lecia Sequist: I think it can vary from patient to patient and sometimes it's actually the patient's spouse or caregiver that notices it more than the patient themselves. Sometimes it can be more neurocognitive and sometimes more almost personality: irritability, concentration. Patients with underlying psychiatric disorders also, we've noticed that they may potentially have some trouble or some recurrence of their underlying disease too while they're on lorlatinib. It's just something new for us to get used to as this drug comes to market.

Alice Shaw: Right. And the standard dose is 100 mg. That will be the standard dose once the drug is approved, given once a day. As you're both pointing out, though, this drug is unique in these neurocognitive and mood side effects, but I think it's important when I counsel my patients, just to let them know that these side effects are reversible. They do resolve once the drug is held. And, I would say, every patient that I've treated has been able to tolerate lorlatinib once the drug is dose reduced appropriately. So these are definitely something to be aware of.

They can be really disruptive to patients in terms of their work and their family life, but I think as long as doctors and the patients also are kind of proactive about these side effects, they can generally be managed.

Alice Shaw: So this patient was on lorlatinib, on for about six weeks. And again, we obtained our first set of scans and had a really nice response in the brain to lorlatinib. Her body was still stable on lorlatinib, and really just reported mild grade 1 side effects. And she specifically had some mild forgetfulness; she would occasionally feel like she's forgotten something and also felt like her speech was a little bit slowed at times, but overall, was functioning very well. And Justin, as you were referring to, her cholesterol did increase. That's pretty uniform for most patients on lorlatinib, and we started her on a statin, and her cholesterol was well controlled after that.

Alice Shaw: So just maybe in the final few minutes, I'm wondering if we could speak a little bit to what happens after lorlatinib. It's our third-generation, probably the most potent and brain penetrant ALK inhibitor, and yet we have patients who are beginning to relapse on lorlatinib. What are our options for those patients? Dr. Gainor, do you want to start?

Justin Gainor: So, I would reference work that you've done as a leader in this field. It does look like as patients move from first- to second- to third-generation ALK inhibitors, it does look like there's progressive ALK independence post a third-generation ALK inhibitor. There may still be a subset that is highly ALK dependent. I think you've shown that trying to understand the molecular landscape of patients as they move from each ALK inhibitor is important and has treatment implications.

Justin Gainor: I think it also points us to the need for combination therapies. We know that moving from one inhibitor to the other can also, at some point, lead to resistance. And trying to understand that, and trying to co-op that by using combinations. Various combinations are now either being explored preclinically or starting to enter the clinic. Combinations looking at ALK and the MAP kinase pathway is one notable example.

Alice Shaw: And Dr. Sequist, you've worked in the EGFR now for many, many years, and I'm wondering if we can learn in the ALK field, at least some of the sort of lessons you've learned in EGFR, specifically with regard to these combination therapies. How successful have combinations been for your patients on EGFR inhibitors, and what are sort of the exciting combinations that are coming?

Lecia Sequist: Well, I think the combination therapies, at least in EGFR, have been most successful when they are targeted at the appropriate resistance mechanism. And that's one of the tricky things is that sometimes a new resistance mechanism is discovered and we don't yet have a good drug that hits it. But I think with some of the second and third generation of these TKIs, the fact that they're becoming more and more specific and having less off-target toxicities does allow us to combine them more easily than some of the first-generation drugs.

Alice Shaw: You mentioned the EGFR/MET combinations that have looked quite good.

Lecia Sequist: Absolutely.

Alice Shaw: For ALK we'll also have some ALK/MET combinations. Also, as Justin, you said, ALK/MAP kinase combinations, so I think a lot of hope for the future in terms of patients, even if they relapse on a drug like lorlatinib.

Lecia Sequist: And I think something that was old, and is now new again, is also thinking about combinations of chemotherapy with TKI. We saw it this past ASCO, a Japanese study looking at frontline chemotherapy with an EGFR inhibitor actually did better than the EGFR inhibitor alone.

Lecia Sequist: And so, for our patients with acquired resistance, whether they are EGFR, ALK, or what have you, it does make sense to think about, again, an older question of whether we should continue the TKI along with introducing chemotherapy, and what might be the possible benefits and detriments there.

Alice Shaw: To summarize, ALK rearrangement confers sensitivity to ALK inhibitors with responses lasting months and now, in some cases, years. At the present time for ALK-positive lung cancer, first-line treatment is alectinib, but there are ongoing trials of other next-generation ALK inhibitors as first-line therapy and specifically, brigatinib, which Justin, you already discussed. And also, lorlatinib is also being studied as first-line therapy in a head-to-head trial with crizotinib. Lorlatinib is a third-generation, kind of our latest generation of ALK inhibitors. It has documented activity after first- and second-generation ALK inhibitors, and it will be approved very soon, so it's an important drug for oncologists to be aware of.

Alice Shaw: And then, finally, just to highlight, I think, one important aspect of ALK-positive lung cancer, sort of is shown in this case, which is that the CNS, the central nervous system, is a very common site of spread in ALK-positive lung cancer. And fortunately, CNS disease can often be controlled using these very brain-penetrable ALK inhibitors, such as alectinib and lorlatinib, and often times, we can either postpone or even sometimes prevent the need to proceed with radiation 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.