Molecular Profiling, Precision Medicine, and Targeted Therapies for the Treatment of *ALK* Positive NSCLC

Alice T. Shaw, MD, PhD: Hello, and welcome to this educational activity entitled, *Molecular Profiling, Precision Medicine, and Targeted Therapies for the Treatment of* ALK-*positive Non–Small Cell Lung Cancer*.

My name is Alice Shaw, and I'm Director of the Center for Thoracic Cancers at Massachusetts General Hospital, and Professor of Medicine at Harvard Medical School in Boston, Massachusetts, and it's my honor to be hosting this educational activity today.

Here's a disclaimer and disclosure, indicating that I may be discussing off-label use of approved agents or agents that are in development.

Here are my financial disclosures.

Today we'll be reviewing *ALK* rearrangements, the significance of molecular and genetic testing in non–small cell lung cancer, current and emerging treatment options for *ALK*-positive non–small cell lung cancer, recognition and management of adverse events associated with treatments, and finally, I'll end with several clinical case scenarios.

Here are the learning objectives for this activity.

So let's move to the first topic of understanding *ALK* rearrangements.

By way of background, *ALK* rearrangements were first discovered in non–small cell lung cancer about 11 years ago by a group in Japan led by Dr. Hiro Mano, and this was published in a seminal paper in *Nature* where Dr. Mano's group reported the discovery of a novel *EML4-ALK* fusion in a small subset of patients with non–small cell lung cancer. *EML4-ALK* results from a chromosomal inversion on chromosome 2p that leads to fusion of a portion of the *EML4* gene to a portion of the *ALK* gene, which includes the tyrosine kinase domain of ALK. This fusion of *ALK* to another partner gene leads to the aberrant expression and constitutive activation of the ALK tyrosine kinase, and this drives transformation of cells into cancer.

After that seminal publication, we've now learned that there are a variety of different *ALK* rearrangements, with EML4 being the most common partner gene. There are a variety of other partner genes, as well, and, overall, these *ALK* rearrangements can be identified in about 3% to 7% of our patients with lung adenocarcinoma.

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Early on after the discovery of *ALK* rearrangements in non–small cell lung cancer, we began studying patients with this newly identified molecular subtype of lung cancer, and we found early on that patients with *ALK*-rearranged—or so-called *ALK*-positive—non–small cell lung cancer have some characteristic clinicopathologic features.

As shown here in the pie chart on the left, most patients who have *ALK*-rearranged lung cancer are never-smokers or have a minimal smoking history. It's a small minority of patients, less than 10%, who have a more significant smoking history, so *ALK*-positive lung cancer is a disease of never-smokers.

We also observed that patients with *ALK*-positive lung cancer tend to be younger, on average, than other patients with different types of lung cancer. At our institution, the average age of patients with advanced *ALK*-positive lung cancer is about 50 years old, and that's about 15 years younger than the average patient with a non–*ALK*-driven lung cancer.

Most *ALK*-positive lung cancers have adenocarcinoma histology, and within the different types of adenocarcinoma, *ALK*-positive cancers can be associated with solid growth pattern, and sometimes with abundant signet ring cells, which is shown in this example of an H&E-stained tumor from an *ALK*-positive patient.

Shown here on the bottom two right panels are the two FDA-approved tests for diagnosing *ALK* rearrangements. One is immunohistochemistry, which is shown in the middle panel, and the other is the ALK fluorescence in situ hybridization (FISH) assay, which is shown on the right, and I'll be talking more about these assays in just a minute.

But just really to highlight that, again, with the presence of an *ALK* rearrangement, this now leads to expression of ALK when it normally is never expressed in the lung, and this can be detected using various immunohistochemistry assays, as shown here.

Now let's move to the second portion of this activity, which focuses on the significance of molecular and genetic testing in non–small cell lung cancer.

Shown here are the guidelines issued by the National Comprehensive Cancer Network (NCCN®); there are a variety of other guidelines, which are very similar. Here what I wanted to emphasize is that for patients who are diagnosed with advanced non–small cell lung cancer, in particular nonsquamous cell lung cancer, the recommendation is to perform molecular testing for a number of validated targets, including *ALK*

rearrangements, and ideally these tests should be conducted as part of broader or multiplex molecular testing.

I would note that even for patients with advanced squamous cell lung cancer, we do also consider molecular testing, including the same drivers—*EGFR*, *ALK*, and others—because rarely do we identify patients even with squamous cell carcinoma who do harbor one of these targets, in particular patients with squamous cell and either a light- or never-smoking history, those patients definitely should undergo molecular testing.

Now there are a number of guidelines, as I mentioned, that have been established for molecular testing in non–small cell lung cancer. Shown here are guidelines from the International Association for the Study of Lung Cancer (IASLC), and I wanted to really emphasize here that the recommendation is that multiple slides be cut from the formalin-fixed paraffin-embedded tissue block to establish the diagnosis and also to perform molecular testing, so that you don't need to return to cut more slides in the future, which really can waste the tissue.

Focusing in on testing for *ALK* specifically, shown here is the first US Food & Drug Administration (FDA)-approved test for *ALK* rearrangements, and here for this assay there are red and green probes that are flanking the highly conserved translocation breakpoints within *ALK*. And in the setting of a rearrangement, these probes are now separated, leading to a splitting of the red and green signals, as shown on the left panel, the panel labeled A.

We also can see as a positive sign if there are isolated red signals, that's shown here in panel B. Here, for a positive assay, what we're looking for is the percentage of split signals or isolated red signals. If the percentage is 15% or greater that is considered a positive assay, if the percentage is less than 15%, then that is considered negative for *ALK* rearrangements.

Now, ALK FISH can be technically challenging to perform and to interpret, so many labs, including ours, have actually moved to ALK immunohistochemistry. The Ventana ALK immunohistochemistry (IHC) assay using the D5F3 antibody is an FDA-approved test or the companion diagnostic for using ALK inhibitors, and shown here is an example of how ALK IHC can be incorporated into screening patients for *ALK* rearrangements.

In this particular algorithm, a positive *ALK* IHC result is confirmed using a second assay, the FISH assay. In my institution, we typically do secondary confirmation with FISH, or

more commonly now we're using next-generation sequencing. However, I would note that a positive *ALK* IHC result is sufficient to proceed with treatment with an ALK inhibitor.

Now let's move to the meat of this educational activity, which focused on current and emerging treatment options for patients with advanced *ALK*-positive non–small cell lung cancer.

This slide summarizes what had been our traditional approach to patients with advanced *ALK*-positive lung cancer, and this approach is something that we had been doing up until about 1 year ago. And up until then we had been using ALK inhibitors sequentially, often starting with our first-generation ALK/ROS/MET inhibitor crizotinib, at the time of progression moving to a second-generation inhibitor which is more potent and has broader activity than crizotinib, and these second-generation inhibitors include ceritinib, alectinib, brigatinib, and ensartinib, and then at progression on a second-generation ALK inhibitor we just started moving now to our latest third-generation ALK inhibitors such as lorlatinib.

So today, I'll spend some time talking about the data that led to this treatment strategy, but I think a lot of what we'll focus on is really what is the best first-line therapy. In fact, we do have data now showing that crizotinib in particular really is not our best first-line therapy, but probably a second-generation ALK inhibitor, such as alectinib, is preferred.

So what is our best first-line therapy? Several years ago, to establish ALK inhibitors as the standard first-line therapy for patients with advanced *ALK*-positive lung cancer, this large, randomized, phase 3 study was conducted; this was PROFILE 1014. This was a study for newly diagnosed advanced *ALK*-positive lung cancer. They were randomized to receive either first-line crizotinib, the first-generation ALK inhibitor, at standard dosing versus platinum/pemetrexed chemotherapy as first-line therapy. The primary endpoint of this study was progression-free survival (PFS).

This study easily met its primary endpoint showing that crizotinib was significantly superior to platinum/pemetrexed chemotherapy as first-line treatment for patients with *ALK*-positive lung cancer.

Here you can see that the median PFS with crizotinib was close to 11 months as opposed to 7 months with standard chemotherapy, and this really led to the global adoption of crizotinib, the first-generation ALK inhibitor, as a standard first-line therapy for patients with *ALK*-positive lung cancer.

Now, since then we had the development of multiple new second-generation inhibitors, which as I mentioned are more potent than crizotinib, many of them overcome the most common crizotinib resistance mutations, and many of them are also much more brain-penetrable than crizotinib. These drugs were shown to be active in patients who failed crizotinib and so were approved initially in that setting, but the key question that we started to address was whether or not these second-generation more potent and brain-penetrable drugs should be used as first-line therapy.

So now, we have some data on these second-generation inhibitors as first-line therapy in patients with *ALK*-positive lung cancer. Shown here is probably the most important study to date which is the Global ALEX study, which, again, focused on patients with advanced *ALK*-positive lung cancer, newly-diagnosed. These patients were randomized to receive either first-line alectinib at the standard dose of 600 mg twice a day or to receive the standard crizotinib at its standard dose of 250 mg twice a day.

This slide shows the primary endpoint of the ALEX study, which was investigator-assessed PFS. This study was markedly positive in favor of alectinib as first-line therapy. The median PFS with alectinib actually was not reached at the time of the data cutoff; however, the median PFS with crizotinib was 11 months, which is about what we would expect from previous studies. The hazard ratio for progression-free survival was 0.47, so heavily favoring alectinib, with a highly statistically significant *P* value.

I should note that PFS as assessed by the independent review committee also very favorable in favor of alectinib, hazard ratio of 0.50 and a median PFS with alectinib as assessed by the independent review committee was close to 26 months.

Now one of the very important secondary endpoints within the ALEX study was time to CNS progression. As I mentioned earlier, these second-generation drugs, and in particular, alectinib can penetrate the blood-brain barrier, achieve high levels in the brain, and had already shown a CNS activity in patients who had previously failed crizotinib, and so we wanted to focus on how active these drugs would be in the first-line setting.

Here we performed a competing risk analysis with CNS progression, non-CNS progression, and death as competing events, and here we looked at the time to CNS progression and showed that alectinib significantly delayed the time to CNS progression, with a cause-specific hazard ratio of 0.16; again, highly statistically significant.

Shown on the right are the cumulative incidence rates of CNS progression in those patients treated with first-line alectinib versus first-line crizotinib. Again, I think this just emphasizes the point that alectinib is very active in the brain and had a much lower rate of CNS progression compared to crizotinib.

Shown here are the intracranial response rates that were observed in the ALEX study in patients who received first-line alectinib versus first-line crizotinib. As expected, the response rates in the CNS with alectinib were much higher at 81% compared to crizotinib at 50%, and I think, notably, the duration of intracranial response was much longer with alectinib at 17.3 months as compared to only 5.5 months with crizotinib. Therefore, alectinib is clearly much, much more active in the CNS compared to crizotinib.

More recently at the American Society of Clinical Oncology 2018 meeting, we presented updated data on the Global ALEX study; here we had an additional 9 months of follow-up. PFS continues to be significantly superior for those patients who received first-line alectinib compared to first-line crizotinib. We do have a median PFS at this updated time point of close to 35 months with alectinib as compared to about 11 months with crizotinib; so, again, really markedly prolonged frontline PFS with a more potent second-generation inhibitor, alectinib. This study helped to establish alectinib as the standard first-line therapy for patients with advanced *ALK*-positive lung cancer.

On this next slide, I've also shown you data from another randomized study of alectinib versus crizotinib in Japanese patients. This was a very similar study as the Global ALEX study, but conducted only in Japan, so we refer to it as the J-ALEX study, and this provides additional support for the superiority of alectinib as first-line therapy over crizotinib.

I would make a note that in the J-ALEX study, patients received first-line alectinib at a dose of 300 mg twice a day, and that is the approved dose in Japan. However, outside of Japan the standard dose, the one that we use in the United States and anywhere outside of Japan, is the 600 mg twice-a-day dosing.

And I also wanted to mention additional data supporting the first-line use of second-generation inhibitors, and the data I'm going to show you now is with a different a different second-generation inhibitor, this is using the drug ceritinib; it was really the first of the second-generation inhibitors tested in patients with crizotinib resistance. This drug then was tested in this large, phase 3 study, the ASCEND-4 study, where first-line

ceritinib was compared head-to-head with standard platinum/pemetrexed chemotherapy.

So shown here is the study design of this ASCEND-4 trial where patients were randomized 1:1 to receive either first-line ceritinib or standard chemotherapy, and, again, the primary endpoint in this study was PFS.

And I think, not surprising to most of us, ceritinib was able to easily beat chemotherapy in this head-to-head trial with the median PFS with first-line ceritinib of 16.6 months as compared to only 8.1 months with chemotherapy.

Now, again, just note that the comparator in this ASCEND-4 trial is chemotherapy, not crizotinib, so this is a separate trial, obviously, compared to ALEX and J-ALEX, but also it does not use the same comparator as ALEX or J-ALEX. Nevertheless, this trial was very exciting in showing that frontline ceritinib was able to confer a prolonged frontline PFS coming at close to 17 months.

Now here this slide summarizes the data that we have on ALK inhibitors in the first-line setting—crizotinib in PROFILE 1014, ceritinib in ASCEND-4, and now alectinib in two randomized trials, J-ALEX and ALEX—and compares the efficacy data seen across these 4 studies. And what I've highlighted here in the red box is the median PFS seen with each of these ALK inhibitors as first-line therapy, and just to review with crizotinib we had a median PFS of close to 11 months, with ceritinib a median PFS of about 16.5 months, and in both J-ALEX and ALEX we had a very long frontline median PFS of greater than 25 months. Again, just to remind you that the updated ALEX study was even longer in terms of frontline PFS of about 35 months.

You can also see on this slide the PFS in patients with brain metastases at baseline, and I think here you can also pretty clearly see that the PFS in patients with brain metastases was prolonged in patients who received alectinib as part of the ALEX studies.

Finally, the bottom row here compares the response rates across these 4 trials. They're very high with first- and second-generation inhibitors, perhaps with a suggestion that the response rate in J-ALEX was even higher at 92%. These are all separate trials so I would say that cross-trial comparisons are somewhat limited, but very high response rates across the board.

Now I do want to just briefly mention another second-generation inhibitor, brigatinib. This was originally tested primarily in the setting of *ALK*-positive disease that failed crizotinib, and this is also an FDA-approved drug for *ALK*-positive disease post-crizotinib, and that was based on data from the phase 2 ALTA trial.

Two different dosing regimens of brigatinib were studied in patients who had failed on prior crizotinib, and we saw that brigatinib is highly active in patients who have failed crizotinib, with a response rate in the 50% range approximately and with a prolonged median PFS, as well; again, this is one of the standard options for patients who have failed prior crizotinib.

Brigatinib has now also completed a phase 3 study, a head-to-head comparison of brigatinib versus crizotinib as first-line therapy, and we're all eagerly awaiting those results, which should be presented at an upcoming congress.

So we've talked a lot about first- and primarily second-generation ALK inhibitors, focusing on using second-generation inhibitors as first-line therapy.

Now that we have more and more patients on second-generation drugs, the question really is what do we do for those patients when they relapse due to resistance? And, fortunately, we do now have a better understanding of resistance to second-generation ALK inhibitors and we have a very good treatment option for patients who have failed or are refractory to second-generation inhibitors, and I'm going to focus now on the third-generation inhibitor lorlatinib.

Lorlatinib is a third-generation ALK and ROS1 small molecule tyrosine kinase inhibitor, it has a very unique structure compared to the other ALK and ROS1 inhibitors. It has this very large macrocyclic structure and it was specifically designed to overcome known resistance mutations that can confer resistance to ALK inhibitors, and to penetrate the blood-brain barrier, and that's why this drug is referred to as third-generation.

Shown here in the table on the right is some preclinical in vitro data examining the activity of first-, second-, and third-generation ALK inhibitors against different resistant models, each of which harbors a different resistance mutation. These ALK inhibitors have differing levels of activity depending on the presence of an ALK-resistance mutation, and as you can see in the column highlighted by the yellow box under lorlatinib, lorlatinib does appear to retain the greatest potency against all of the known single ALK-resistance mutations.

Now lorlatinib has already completed both phase 1 and phase 2 testing, and based on the results, lorlatinib was granted FDA Breakthrough Therapy designation for *ALK*-positive lung cancer previously treated with ALK inhibitors, and we're anticipating that lorlatinib may receive FDA approval in the next few months.

I wanted to show you some of the data supporting the efficacy of lorlatinib in previously treated *ALK*-positive disease. This shows you two of the expansion cohorts within the phase 2 study of lorlatinib, and here the focus is really on patients who have failed 2 or more ALK inhibitors—typically, for example, crizotinib and second-generation ALK inhibitors, sometimes even more than one second-generation ALK inhibitor.

What you can see here summarized in the table and the waterfall plots is that lorlatinib does have activity in this patient population, with a confirmed response rate of about 40%, and, notably, the confirmed intracranial response rate in these patients was 48%; so a very high response rate even in the CNS of patients who have failed a prior second-generation inhibitor. Here at this particular time point for this study, we did not yet have a median duration of response, but we did have a median PFS of about 7 months.

Now this slide highlights, I think, an important aspect of lorlatinib's clinical activity, which is its ability to penetrate the CNS and induce CNS responses. As part of the phase 1 study, we did actually measure the concentrations of lorlatinib in the cerebrospinal fluid (CSF) for patients, and we were able to show that the CSF levels were very close to plasma levels, about 75% of the level of plasma level, so patients are able to achieve high drug levels in the brain.

And as shown on the right here, we focused on intracranial activity specifically in patients in the phase 1 study showing the sort of depth of responses in CNS target lesions in *ALK*-positive disease, many of whom had failed one or two prior ALK inhibitors. So a very important, I think, feature of lorlatinib, that it can actually treat a CNS progression in patients who have failed prior ALK inhibitors, including alectinib.

Now, I do want to mention that after a patient fails a second-generation inhibitor such as alectinib, in some cases we can make use of another second-generation inhibitor such as brigatinib; however, it seems with the limited data we have so far that using one second-generation inhibitor after another may have less activity than moving from a second-generation inhibitor to a more potent drug like lorlatinib.

Shown here is an example of some of the clinical data that we've accumulated so far, focusing on the activity of brigatinib after failure of alectinib, so one second-generation inhibitor after another, and we saw that the response rate was about 17%, with a median PFS of 4.4 months. When we've looked at these patients' tumors more carefully, there is a suggestion that those patients who will respond to brigatinib after alectinib are those that have acquired specific brigatinib-sensitive mutations, and it's only a small percentage of patients, roughly about 15% or so, who have those mutations.

So there can be some activity of a second-generation inhibitor after another second-generation inhibitor, but typically, I think the standard approach will be to move from one second-generation inhibitor to a third-generation more potent inhibitor such as lorlatinib.

So just to summarize what we've talked about so far, and also summarized NCCN Guidelines, first-line therapy now based on all of the clinical trial data we have so far really is, I think, the preferred first-line therapy has changed from crizotinib to alectinib based on the ALEX and J-ALEX studies, showing that significantly superior PFS with alectinib and also significant intracranial activity with alectinib. Crizotinib and ceritinib in the United States are also approved as first-line therapy, but, again, our preferred first-line therapy is alectinib.

After patients fail on crizotinib, I mentioned earlier that a standard approach is to move them on to a more potent second-generation inhibitor, and that can be ceritinib, alectinib, or brigatinib. And now what's actually rapidly evolving is what to do after patients progress on a second-generation inhibitor such as alectinib or ceritinib, and soon we will have as a standard option in the United States the third-generation inhibitor lorlatinib for these patients who fail prior alectinib or ceritinib.

Now, I think it's important to review the adverse events that are associated with these different ALK inhibitors. As I mentioned, these ALK inhibitors can be very active for patients, patients can remain on these ALK inhibitors sometimes for several years or more, so it's very important to understand and know how to manage these adverse events appropriately.

Let's start with alectinib, and shown here on this slide are the common adverse events that have been reported with alectinib in the ALEX study.

The most common side effects that we see with alectinib are fatigue, myalgias, edema, and constipation. Nausea and vomiting are notably uncommon with alectinib, and also I

would note that on occasion we can have an increase in liver function levels, transaminases in particular; however, it's not very common with alectinib overall, only about 15% of our patients have an increase in transaminases, but it is something that we need to watch as patients are starting on alectinib.

Another side effect that I would mention with alectinib, which does bother a number of patients, is increased weight. It's reported in about 10% of patients, however, I would say in real-life practice, the majority of patients do experience some increase in weight, so this is something that patients should be counseled about.

Ceritinib is notably more difficult due to gastrointestinal (GI) side effects. As you can see here from the ASCEND-4 trial, GI side effects are extremely common with ceritinib—85% of patients who received ceritinib in this study experienced diarrhea, 5% actually had grade 3 or 4 diarrhea, so very significant diarrhea. A majority of patients do experience nausea and vomiting—66% to 69% of patients had nausea and vomiting again; a small proportion even with grade 3 or 4.

I would also note that with ceritinib, we do see a significantly higher rate of increased transaminases compared to, for example, alectinib. The rate of all-grade alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase was 53% to 60%, and with a proportion of those being grade 3 or 4, so significant transaminitis.

Ceritinib does come with additional and more significant side effects so that patients do need to be very closely monitored and treated to manage these side effects effectively.

From the phase 2 ALTA study of brigatinib, there are a number of side effects, including GI side effects. I would say that GI side effects are a little more common with brigatinib than alectinib, but not as common as with ceritinib.

I think the side effect that's most important to note with brigatinib—there are actually two that are most important to note. The first one is what we call early pulmonary toxicity, and some of that's captured here in this dyspnea row. However, this early pulmonary toxicity is quite unique with brigatinib where patients can experience shortness of breath, cough, even hypoxia after their very first dose of brigatinib. And it seems to be, fortunately, only seen in a few percentage of patients, but it can be very significant where patients develop severe shortness of breath and hypoxia, and it can even be life-threatening. So this is a toxicity that all oncologists should be aware of if they're going to prescribe brigatinib.

For that reason, the dosing of brigatinib is what we call a step-up dosing, meaning that patients should be started first on 90 mg, which is half the normal dose once a day. If they tolerate the 90 mg dose for 1 week without any respiratory symptoms or other toxicities, they can then be escalated to the standard dose of 180 mg once daily.

The other unique side effect I want to mention with brigatinib, because it's not seen with the other ALK inhibitors, is hypertension. We do see hypertension in about 20% or so of patients treated with brigatinib; in this particular study 6% of the patients actually had grade 3 or higher hypertension. Again, this is something that requires close monitoring, and patients may require treatment with antihypertensives and on occasion some patients will have very significant hypertension that may even require dose reduction or dose discontinuation.

This table summarizes the adverse events that we saw in the phase 1/2 study of lorlatinib. I would say the most common one that we see—and, again, really uniquely with lorlatinib—is hyperlipidemia, so both increased cholesterol as well as increased triglycerides are very common in patients treated with lorlatinib. Almost all patients will develop these adverse events, and the majority of them will require treatment with a cholesterol-lowering agent such as statin therapy.

Other common side effects with lorlatinib include edema, peripheral neuropathy, increased weight, and neurocognitive and mood effects. I do want to mention these for a moment, because, again, these are very uniquely associated with lorlatinib and not with other ALK inhibitors.

Patients often report that they may feel more forgetful, that they may feel like they can't multitask, or they may feel that their speech is not as fluent, that they're stumbling on words more frequently, and sometimes those are very mild and patients aren't really bothered. But if they are more significant, patients will respond to dose interruption, which resolves those side effects completely, and typically patients can do well on a lower dose either one or two dose levels down.

I also want to mention the mood disturbance that can occur with lorlatinib. Some patients will report that they feel like their mood is more labile, in general they describe it as feeling like emotions are intensified, and some patients will feel more irritable. It's a minority of patients; however, it is something to be aware of because, again, this can become bothersome and it is fully reversible, it responds to dose hold and dose reduction.

I would also note that like alectinib, lorlatinib has very few GI side effects, so, fortunately, no nausea or vomiting, very rarely do we see diarrhea. However, constipation is quite common on lorlatinib as it is with alectinib, so another important side effect to be aware of, as these patients stay on these drugs chronically.

Finally, I'm just going to remind everyone of some of the adverse events that have been reported with crizotinib. We aren't using crizotinib in *ALK*-positive lung cancer as much, since alectinib has become the preferred first-line therapy; however, some patients can benefit from crizotinib for many months, even sometimes years, and so you may even have patients who are continuing on crizotinib now. Again, it's important to recognize the adverse events with crizotinib.

I would say the most common one to be aware of is visual disturbance. This tends to be mild, grade 1, and typically only triggered when there's a change from dark to light. There are also GI side effects with crizotinib—nausea, vomiting, diarrhea, and sometimes constipation. We are aware of liver toxicity that can be seen with crizotinib, primarily increased transaminases. That typically occurs in the first few months of treatment, so requires close monitoring during that time.

Overall, crizotinib is relatively well tolerated, but I would say it does have, again, some distinct side effects such as visual disturbance, and is probably viewed as somewhat more difficult than the newer second-generation and third-generation drugs such as alectinib and lorlatinib.

This slide is a nice summary of the most common adverse reactions that have been reported across first- and second-generation ALK inhibitors. We don't have lorlatinib on here because it's not yet FDA-approved, but this slide just highlights some of the common adverse reactions that can be seen across these ALK inhibitors, and also highlights the more unique ones or the ones that you really need to focus on for particular ALK inhibitors, such as brigatinib and cough, for example, or crizotinib and visual disturbance.

Now in the final section, let's move to clinical case scenarios. I think these will very nicely illustrate some of the findings and results that we've already talked about. These are real patients in my own practice, and so I hope that these will be illustrative of the optimal management of *ALK*-positive disease, at least as of today.

Molecular Profiling, Precision Medicine, and Targeted Therapies for the Treatment of *ALK* Positive NSCLC

Our first case is a patient who I followed for many years. She was 46 years old at the time of diagnosis, a never-smoker, and she had had a stage T2N0 non–small cell lung cancer, a lung adenocarcinoma that had been fully resected with a lobectomy.

After lobectomy, she underwent 4 cycles of adjuvant chemotherapy with cisplatin/docetaxel—this was a number of years ago—and then, unfortunately, 2 years after completing her adjuvant therapy, she relapsed with multifocal lung nodules, and this was biopsy-proven to be recurrence.

Now, this was a number of years ago and so we were only testing for 2 markers at that time, *EGFR* and *ALK*. She was *EGFR* wild-type but found to be positive for *ALK* rearrangement by FISH, and she was started on the phase 1 study of crizotinib at 250 mg twice daily, the standard dose.

Shown here on this slide is her response after 7 weeks of crizotinib. You can see that typical for *ALK*-positive disease, she had a very rapid and dramatic improvement once she started on the targeted therapy. She had a near complete response by RECIST.

However, after about 2 years, we started to note some mild progression again in her lungs on computed tomography. She was not symptomatic so we actually continued her on crizotinib for about another 10 months or so. In addition, we were following surveillance brain magnetic resonance imaging (MRI), which I typically do in *ALK*-positive disease, brain MRIs remain negative. However, we ultimately discontinued her from crizotinib after almost 3 years because she started to develop respiratory symptoms, including some hemoptysis, and this went along with her continued progression on chest computed tomography.

These images illustrate her response and then progression to crizotinib. As you can see in the chest film on the far right, all of those tumors had initially responded to crizotinib very quickly, but with time, they gradually grew back.

An appropriate next treatment for this patient would be any second-generation inhibitor.

After she relapsed on crizotinib, we performed a biopsy to confirm the recurrence, we also performed molecular testing and we identified a secondary resistance mutation, and we moved her on to the second-generation inhibitor ceritinib, which actually was the only one available at that time. She did receive what is now the standard dose of ceritinib, which is 450 mg once daily with food, and this patient had another nice response to this second-generation inhibitor. Her symptoms improved quickly and she

achieved a RECIST-confirmed partial response again, with a near-complete response coming in at about 70% tumor reduction.

Now this patient was followed monthly in the clinic, she did experience some of the typical side effects of ceritinib, intermittent diarrhea with some cramping and some rare episodes of nausea. After 5 months on ceritinib also developed asymptomatic transaminitis, and I wanted to highlight this because this can be seen with any of the ALK inhibitors, but I have seen it more commonly and the clinical trial data suggests that it is more common with ceritinib.

For this patient, both her AST and ALT bumped up to 10 times the upper limit of normal. Her total bilirubin remained normal, though. We withheld her ceritinib and her ALT continued to climb for the next few days, peaking at 30 times the upper limit of normal. Bilirubin remained normal. We ruled out other potential etiologies for her. Altered liver function tests, they were all negative. There were no other medications other than ceritinib to explain the abnormal liver function test results.

This is an important case because, again, we do see this not uncommonly with ceritinib, and I would say that the answer to this is that this patient's liver function test results fully normalized, she had no residual abnormalities in her labs at all, we had no other etiologies for the liver dysfunction. We did resume ceritinib but this was dose-reduced to the next dose level down at 300 mg a day. This patient was able to continue on ceritinib. She did not have any further bumps in her liver function tests.

Let's move on to a different case. This is a 40-year-old patient of mine, never-smoker, diagnosed with stage IIIA non–small cell lung cancer; this was lung adenocarcinoma. She underwent induction chemoradiation followed by VATS lobectomy and mediastinal dissection. She then went on to receive 4 cycles of a consolidation chemotherapy at a local hospital near her.

One year after completing chemotherapy, unfortunately she developed headaches and neck pain. A brain MRI was obtained that demonstrated multiple brain metastases, with the largest measuring 10 mm. She also underwent a positron emission tomography scan at that time which also showed a recurrence in the body with fluorodeoxyglucose-avid mediastinal and left hilar lymphadenopathy.

Now, this patient underwent molecular testing of her tumor when she relapsed and now had stage IV disease, and molecular testing demonstrated an *ALK* rearrangement.

So this is now basically a frontline patient in need of treatment, so which of the following treatment regimens would be most appropriate?

Now, in this case of a patient with—it's not newly diagnosed—but it's recurrent metastatic non–small cell lung cancer with an *ALK* rearrangement, I think the most appropriate therapy for first-line use for her would be alectinib based on the ALEX and J-ALEX data.

This patient was started on standard alectinib 600 mg twice a day. She did very well on this but the typical myalgias developed the first month, which then subsided after another month or so of treatment. Her first scans at 6 weeks showed a significant response in the brain lesions, as well as complete resolution of the intrathoracic lymphadenopathy. This patient now continues on alectinib after about 18 months with ongoing response.

Shown here is the patient's intracranial response to alectinib. On the left is shown an axial image from her brain MRI highlighting the different brain metastases and the marked edema that this patient had at the time she relapsed prior to going onto alectinib. Once she started on alectinib she underwent a repeat brain MRI, shown on the right, and here you can see that she's had a dramatic response to treatment with alectinib, and with resolution of the edema, and all that's really left is a small cystic lesion at that site of the dominant brain lesion; so a really marked response and one that's fairly typical for alectinib in the brain.

To summarize, here are some key takeaways from our activity today. First, all patients with metastatic nonsquamous non–small cell lung cancer should have multiplex testing, that includes testing for *ALK* rearrangements. And I would note that, again, if the patient has an unusual histology such as squamous cell and they're a younger never-smoker, that is also a patient who should undergo testing for the presence of an oncogenic driver such as *ALK*.

Standard first-line therapy for metastatic *ALK*-rearranged non–small cell lung cancer is now alectinib, and I would also want to highlight that the third-generation ALK inhibitor lorlatinib has demonstrated clinical activity in patients treated with prior ALK inhibitors, including alectinib, and lorlatinib is anticipated to gain FDA approval for this indication.

Finally, there are some common side effects among the ALK inhibitors, but each drug does have its own unique safety profile, and oncologists should be aware of the unique adverse events that can occur with each of the ALK inhibitors.

Thank you so much for participating in this activity today.

References

Ahn M, Camidge DR, Tiseo M, et al. Brigatinib in crizotinib-refractory ALK+ NSCLC: updated efficacy and safety results from ALTA, a randomized phase 2 trial. *J Thorac Oncol*. 2017;12:S1755-S1756.

Besse B, Solomon BJ, Felip E, et al. Lorlatinib in patients (Pts) with previously treated ALK$^+$ advanced non-small cell lung cancer (NSCLC): updated efficacy and safety. *J Clin Oncol*. 2018;36: abstract 9032.

Camidge DR, Peers S, Mok T, et al. Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC) vs crizotinib (CZ) in untreated advanced ALK+ NSCLC. *J Clin Oncol*. 2018;36: abstract 9043.

Ettinger DS, Wood DE, Aisner DL, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Non-Small Cell Lung Cancer. Version 6.2018. © 2018 National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Gainor JF, Dardaei L, Yoda S, et al. Molecular mechanisms of resistance to first- and second-generation ALK inhibitors in ALK-rearranged lung cancer. *Cancer Discov.* 2016;6:1118-1133.

Hida T, Nokihara H, Kondo M,et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* 2017;390:29-39.

Johnson TW, Richardson PF, Bailey S, et al. Discovery of (10R)-7-amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2H-8,4-(metheno)pyrazolo[4,3-h][2,5,11]-benzoxadiazacyclotetradecine-3-carbonitrile (PF-06463922), a macrocyclic inhibitor of anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) with preclinical brain exposure and broad-spectrum potency against ALK-resistant mutations. *J Med Chem*. 2014;57:4720-4744.

Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol*. 2017;35:2490-2498.

Lin JJ, Zhu VW, Schoenfeld AJ, et al. Brigatinib in patients with alectinib-refractory ALK-positive non-small cell lung cancer: a retrospective study. *J Thorac Oncol*. 2018 Jun 20. pii: S1556-0864(18)30714-7. doi: 10.1016/j.jtho.2018.06.005. [Epub ahead of print]

Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. *N Engl J Med*. 2017; 377:829-838.

Shaw AT, Solomon B, Kenudson MM. Crizotinib and testing for ALK. *J Natl Compr Canc Netw*. 2011;9:1335-1341.

Shaw AT, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive advanced *ALK*-positive non-small cell lung cancer (NSCLC): primary results of the global phase III ALEX study. *J Clin Oncol*. 2017;35: abstract LBA9008.

Shaw AT, Ou SHI, Felip E, et al. Efficacy and safety of lorlatinib in patients (pts) with ALK+ non-small cell lung cancer (NSCLC) with one or more prior ALK tyrosine kinase inhibitor (TKI): a phase I/II study. *J Clin Oncol*. 2017;35: abstract 9006.

Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 2007;448:561-567.

Solomon BJ, Mok T, Kim D-W, et al. First-line crizotinib versus chemotherapy in *ALK*-positive lung cancer. *N Engl J Med*. 2014;371:2167-2177.

Solomon BJ, Shaw A, Ou S, et al. Phase 2 study of lorlatinib in patients with advanced ALK+/ROS1+ non-small-cell lung cancer. *J Thorac Oncol*. 2017;12:S1756.

Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet* 2017;389:917-929.

Tsao MS, Hirsch FR, Yatabe Y, eds. *IASLC Atlas of ALK Testing in Lung Cancer*. Aurora, Colorado: International Association for the Study of Lung Cancer; 2013. https://www.iaslc.org/sites/default/files/wysiwyg-assets/alk_atlas_final_lo-res_09.23.13.pdf.