Improving the Quality of Care for Patients Harboring *ALK*+ NSCLC

AXIS: Welcome to our educational activity, *Improving the Quality of Care for Patients Harboring ALK+ Non–Small Cell Lung Cancer*. Our faculty presenter is Dr. D. Ross Camidge, Director of Thoracic Oncology at the University of Colorado Cancer Center.

D. Ross Camidge, MD, PhD: So [here are the] disclaimers and disclosures—we'll be talking about some off-label and some research data.

Here are my disclosures and conflicts of interest.

We're going to talk a little bit about molecular testing in non–small cell lung cancer and update you in terms of what you should and shouldn't be doing. And then we're going to focus on an example with regard to *ALK*-positive lung cancer. There are now many different options, and we're going to focus on first-line options and how you might decide among these.

Here we go. Improving the quality of care for patients finding and treating *ALK*-positive non–small cell lung cancer from first line to beyond.

We're going to talk about what is ALK; why does it matter? And figuring out what you're going to start with and where do you go to next?

What is *ALK*-rearranged lung cancer?

ALK stands for anaplastic lymphoma kinase. As its name suggests, it was originally discovered as a gene in lymphoma back in the 1990s, and in 2007 it was found to be an oncogenic driver in a subset of non–small cell lung cancer. And because non–small cell lung cancer is much more common, it became much more relevant.

So *ALK* is involved normally in the development of the gut and nervous system, and then it's silenced by having its promoter silenced very early in embryogenesis. It's turned on again and functions as an oncogene when a gene rearrangement places the promotor of some other gene active in that tissue and a little 5' portion of that gene in front of it. The 5' portion of the partner gene acts as a multimerisation motif. So EML4, which is the most common one, is a structural protein, and it acts to bring together the ALK domains which then start signal.

And you can find it in lots of different ways: with immunohistochemistry because ALK is not normally expressed in adult tissues in most tissues or FISH is routinely used. But we're going to be nudging you toward next-generation sequencing because really it's about multiplex testing rather than trying to remember to not check individual boxes for molecular testing.

How common is *ALK*? Well, in the French series where they really increased national screening of lung cancer up—when I say that I mean national screening of molecular drivers in cases of lung cancer—very rapidly. They started this in 2008, and by 2010 they were testing 80% of the diagnoses of lung cancer in the country. Here we can see *ALK* running about 5%. If you look in never smokers, it's up to about 14%. So depending on what your denominator is, you can make it more common.

Now, testing for it. You can see in the NCCN Guidelines, if you have anything other than squamous cancer, you should do testing, which is part of a broad molecular profile. And that is so that you can pick up what are 7 and, as of Friday, 8 molecularly specific aberrations in non–small cell lung cancer, which now have an FDA-approved therapy. They are—in no particular order—*EGFR*, *ALK*, *ROS1*, *BRAF*, *NTRK*, *MET* exon 14 skip mutations, *RET* gene rearrangements, and *EGFR* exon 20 insertions. You should also do PD-L1 testing.

If you have squamous cancer, they recommend the same thing. They say consider testing. Now why do they say consider testing? Well particularly if you have an atypical squamous—so under the microscope it's called squamous, but it's a never smoker, or it's a very small sample, and you can't rule out adenosquamous. Honestly, if the patient has had a 60-pack year smoking history and horrid emphysema, you know, and there's a risk of repeat biopsy to get tissue because you don't have enough, you might want to think about it because the yield is going to be pretty low. But generally speaking, at least in my practice, unless there's a good reason not to, I'm going to be testing all non–small cell lung cancer histologies.

Now, interesting enough, if you look at how frequently we are doing that broad molecular panel, as the NCCN suggests, well you can see this was a survey that came out in 2020. In your opinion, what percentage of patients with lung cancer are molecularly tested in your country? Less than 50%—61% of people around the world were saying less than 50% of cases were tested, and that was 51% in the United States. Of course, we all believe we're doing better. Because if you ask the question what about the people in your clinic—whose numbers dropped to 36% and 10%—it's always the other guys who are doing it wrong.

One of the things in terms of the multiplex testing, there are 2…well, 3 main reasons for doing multiplex testing, as opposed to single-gene testing. First one is pragmatic. I just listed eight molecularly specific subtypes of non–small cell lung cancer that you need to be testing for. You're looking after lots of different cancers. How are you going to remember to check each different box? So by doing multiplex screening and having the sample sent out only once to confirm that those eight are actually in that panel, you don't have to worry about it going forward.

Second is you do individual tests, you blow through the tissue quite a lot because each one needs an individual negative control. There's better tissue utilization. And the third reason, which I think is important, is the health economics. We showed more than a decade ago now or nearly a decade ago now but the health economics in the era of personalized medicine are slightly different. Used to be cost of drug benefit from drug, but now you have to factor in the cost of the screening. If you operate on the right-hand side of this curve when the frequency of what you're looking at is fairly common, cost of the screening isn't very much. You know, you get a pretty high positivity rate. If you're looking at something that's only present in 1%, you blow a lot of money before you get your first positive.

So how do we operate on the right-hand side of the curve? Well sure, you can play around with the cost of various things, and you can try and clinically enrich, but really the sensible thing is to try and get a higher hit rate but by looking for multiple different things that are relevant. So multiplex testing has a health economic advantage. And indeed, once you get past about 4 analytes, next-generation sequencing is cheaper. And so now, as I said, there are eight analytes, so we are way past that tipping point. So if you're still doing single-gene testing, you need to sit down with whoever your pathologists are and have a discussion about that.

So what does lung cancer look like? As I said, there are seven—and this slide is really out of date as of Friday—eight molecularly specific FDA licenses, and you tend to look for these in that major initial first-line treatment decision. Everything else is lumped together and has a conversation about immunotherapy or chemoimmunotherapy.

As I said, nobody is perfect; nobody is knocking it out of the park. Again, if you look around the world, the number of people still doing single-gene testing when this survey was done nearly a year ago, 43% of people—33% of people in the United States—are still doing single-gene testing. So, we could improve even given the skills we already have.

Well why does it matter? Because ALK is highly targetable. In the first-line setting, we have alectinib, brigatinib, and lorlatinib, all preferred by the NCCN. Ceritinib is licensed but not usually recommended. Crizotinib is really yesterday's paradigm. We'll go into some of the subsequent therapy in a minute.

Given all of these drugs are licensed in the first-line setting, how do we choose among them? Well, a lot of them have done head-to-head studies at least against crizotinib. That was the kid to beat. So ceritinib just went against platinum-based chemo, but you don't really need to know about that. We're going to focus on the ALEX studies. which were alectinib versus crizotinib; that was done in most of the world. J-ALEX was just done in Japan. ALTA-1L was brigatinib versus crizotinib. And then in 2020, we had two studies—one ensartinib versus crizotinib, which is not currently licensed in the United States; and then, the new kid on the block, lorlatinib versus crizotinib, which is technically what's called a third-generation drug, and I'll show you that. This is really shaking up our thinking.

These are data from the ALEX study (alectinib versus crizotinib), the ALTA-1L study (brigatinib versus crizotinib), and the CROWN study (lorlatinib versus crizotinib) lined up. And they're lined up by the degree of follow-up, so you can at least try and compare like with like. There are subtle differences. Progression-free survival as assessed by the investigator, whereas assessed by an independent radiology review committee. But here's the headline. The ALEX study and the ALTA-1L study, essentially, had the same result.

These drugs may have looked different in the post-crizotinib setting. But in the first-line setting, they both reduce the risk for progression or death (PFS) by about 50%. Whereas in the CROWN study, PFS was reduced by nearly 70%, hazard ratio of 0.28. So, based on this, you would think this should be a no-brainer—we should absolutely be using lorlatinib as our first-line treatment choice. But I'm going to challenge that thought for you because among a bad prognosis non–small cell lung cancer, ALK is really a very different beasty.

Now, when people started to look at these different studies, they started to say well there were subtle differences in the design of study, what was the diagnostic views, were you allowed prior chemotherapy, what's the rate of brain metastases? None of those differences matter. Because if you look at the control arm, the crizotinib arm, it really performed pretty similarly give or take a month or two. Generally speaking, these are genuine results that we can look at.

So, the usual idea in oncology is you give your best drug first. And I've just told you lorlatinib has the best hazard ratio versus crizotinib, so it should be an obvious choice. But what if that PFS isn't king anymore? What if overall survival matters, but then how do we assess overall survival and other factors and such, which might mess up our decision making about that? Are there other factors to consider including shared decision making with the patient about their preferences and goals given that we might be now entering the field in ALK of a personalized approach, taking into consideration these more minor differences deciding on the best drug for an individual patient.

Shared decision making, as you know, is sitting down with the patient and having them be a part of the decision-making process taking into account cost, side effects, convenience—all of that actually is perfectly set in these first-line decision makings in ALK. And here's where I'm going. So in terms of the 'you have to use your best drug first,' this was a really interesting study.

So, this is over 100 outpatients in a single center. And this is their overall survival. So overall survival in lung cancer 20 years ago was about 10 months for Stage IV disease. Here, the overall survival is 81 months; that's the median. I mean just think about it—these people are now routinely surviving over a decade with Stage IV disease. This isn't your grandmother's non–small cell lung cancer anymore. But look at the figure on the left-hand side. This is overall survival by year of diagnosis bracketed into 3 different groups. Now, it didn't make any difference—that's the headline—but why do those groupings matter?

Because the black line represents survival before there was any licensed ALK inhibitor. The blue line represents when only crizotinib was available, and the green line represents one of these next-generation inhibitors that are available. And there's no difference. What does this tell you? Well it might be telling you that this is a forgiving disease, and that you can play catchup later. The patients just have to stay in the game. So the idea that you've got to give your first drug first, your best drug first because you don't have a second chance may not be true.

If that's the case, the only thing that's going to decide on whether to use lorlatinib, which has a license in the second- and third-line setting upfront, or to keep it for later depends on, for example, any evidence that overall survival matters. Well, there's zero evidence that sequence matters among these drugs. The clue that overall survival is sometimes positive in a study is confounded. If you look at the study designs, which I said didn't make any difference, the only difference that matters is whether crossover was allowed.

For some countries around the world where these studies are heavily recruited, if you didn't allow crossover, what you were really talking about was you were denying access to the drug at any point in somebody's treatment journey. So there's difference between, you know, if you allow crossover and there's still an overall survival advantage, that tells you sequence matters. If you don't allow crossover and overall survival is positive, you can't tell if that is sequence versus just getting access to the drug in the first place.

So let me illustrate that. So ALEX, alectinib versus crizotinib, there's the 2-year overall survival. I'm going to focus on 2 years because that allows me to compare studies—73%, 65% overall survival and that difference eventually became statistically significant.

This is the ALTA-1L study, brigatinib versus crizotinib. No difference in overall survival. Oh my goodness, brigatinib must be a terrible drug. But no. Look on the right-hand side at the 2-year overall survival—yes, they're the same, but they're the same as the experimental arm in the ALEX study. So, in ALEX where there was no crossover allowed and in ALTA-1L where crossover was allowed, when you allow crossover, you can bring both arms up to the same level.

Think I'm just making this up? Well remember this is ALEX, alectinib versus crizotinib. Do you remember I said there was a Japanese study, J-ALEX, which was also alectinib versus crizotinib? But in J-ALEX, crossover was allowed. On the bottom left, there was no overall survival difference. So it's not the drugs; it's the study design that can mislead you into thinking that overall survival is really a surrogate for sequence mattering, and we really don't have that.

So, if sequence doesn't matter, then do we still have to go on PFS being the single best thing? Or can we look at some of these other factors—convenience, cost, safety, tolerability—and where do we go next?

Well, I'm going to illustrate that with a case study. Here is a 45-year-old woman, never smoker again, presents with cough, pain in her left hip. She has Stage IV disease, including bone metastases and a brain metastasis, and she has EML4-*ALK*–positive lung cancer. What should her first treatment be?

We discussed irradiating the brain and the bone metastases. And I think you can certainly have a conversation about that traditional model. But in *ALK*-positive lung cancer, I'm going to

illustrate that this drug works incredibly well and incredibly quickly, including in the brain and in the bone.

Here are many of these drugs showing response rates in the brain of…if you look in the middle column where it says iORR, that's intracranial response rate, crizotinib's not very good, but all of the others are running 50% to 80% response rate in the brain and prolonged control in the brain. The joke is that you could actually get somebody on a pill, and they'd be responding in the brain before they got their first appointment with the radiation oncologist. So at least for some of these newer drugs, you don't have to reach for radiation therapy, especially whole brain. That's the thing to put off if someone's going to live for 10 years.

What about some of the other factors? Well convenience and cost. Alectinib is eight pills a day—four in the morning/four in the evening. That's either good if you want to have multiple flexibility in dosing, or bad if you can't take pills. Brigatinib is one pill once a day; lorlatinib is one pill once a day. There are different drug-drug interactions, so alectinib is probably the cleanest. Here are difference in cost, but it all depends on who exactly is doing the paying.

What about safety and tolerability? Honestly, this is the thing that I think is mostly shaking up the idea of let's go for the drug with the slightly longest PFS.

How do you assess safety and tolerability across studies? You can look at the grade 3 or greater adverse event rate, but we have to recognize that not all grade 3 events are the same significance. A grade 3 laboratory abnormality may be different from grade 3 diarrhea. We also have to recognize that if people are staying on these drugs for years, the PFS for some of these things are running 2 to 3 years. But even low-grade toxicities will matter. You can look at the dose reduction rate of what might seem like a way of integrating that altogether, but that's based on the rules in the study. The study may say if you have a grade 3 CPK elevation, you maybe have no symptoms; you have to dose reduce. Because in the real world, you might ignore that. And then finally, there's quality of life, and when you look at that, you have to figure out what's an effect on the cancer versus what's a side effect of the drug.

These are the side effects from the first-line studies. If you look in the top row, there is a range of different side effects. Some of them are class effects. Liver function test abnormalities usually which are not that significant, some gastrointestinal disturbance. There aren't any that really leap out as a sort of very low quality with the exception of ceritinib, and that really has got quite a lot of nausea and vomiting, a lot of diarrhea. But then that's not the drug we're using. You can

see that actually having an 80% dose reduction rate. But look over in the red box here. The dose reduction rate in the clinical study for the experimental arm was 19% with alectinib.

It was 24% in another alectinib study. Lorlatinib was 21%, ensartinib 24%. And brigatinib, I think, stands out as having the highest dose reduction rates—29% in the first time they presented the data going up to 38% with longer follow-up. That doesn't sound very good. But then you have to look at what the dose reductions are for. Mostly they're for amylase, lipase, and blood CPK elevation, none of which were symptomatic. And there was an interesting study at the World Congress on Lung Cancer in 2020 that said in the real world—once brigatinib was out there and being used as a licensed drug—people were ignoring these laboratory abnormalities. In the real world, the dose rate was only 15%.

What about quality of life? As I said, it gets a little difficult. But let's look here in terms of trying to compare like with like. ALTA-1L brigatinib versus crizotinib, CROWN lorlatinib versus crizotinib. This is where we start to pull apart the idea that it's not just about PFS and all these drugs are the same. This is the time to worsening of PFS. Now some of this you would say, well you don't control the cancer on crizotinib, so that curve is going to go down. But the median time on crizotinib is usually running about 9 months, and the curve was separating before that. So it was in the suggestion that there was a cumulative side effect of crizotinib dragging down the quality of life, which at least the brigatinib wasn't doing, and then there's an effect on the cancer.

Look on the right-hand side with lorlatinib, those curves don't separate really until people are progressing on the crizotinib. Suggesting that while lorlatinib might be giving with one hand good efficacy, it's probably taking away with the other one in terms of some of its side effects. And indeed, lorlatinib is an elephant in the room for the side effects. So about 80% of patients will have to go on a statin or a triglyceride-lowering agent. There's significant peripheral neuropathy and a weight increase. Something like 20% of patients will increase their body weight by 20%. So that is a celebrity diet in reverse, and it's usually from hyperphagia.

Perhaps the thing that really scares people is that the drug has higher cognitive function effects and make people have memory issues and alter their speech patterns and alter their sleep and give them visual or auditory hallucinations and can alter their mood such that they become incredibly irritable. Indeed, in the current label for the second or third line, if you lumped all these things together, 54% of patients had some kind of a CNS effect on lorlatinib. Now, that means 46% didn't—we have to remember that this is a good drug in some people. But also that these

side effects are usually dose related and highly reversible. However, it does make people pause for thought about jumping onto this as a first-line drug when maybe you can play catchup later.

Let's talk a little bit about playing catchup later. So these are data for lorlatinib data (in the green box) when used after these other next-generation inhibitors—so its current label, which is second or third line. You can see it's got about a 40% response rate and about a 6 month PFS. Look at some of the other drugs, though, initially they seem disappointing—25% response rate and lower PFS for ensartinib, ceritinib, and then the first case series of brigatinib used in the second-line setting after a next-generation drug. But later brigatinib studies showed much higher response rates.

Honestly, what is this telling you? It is not telling you that this gives 40% benefit to everybody. Well, it's telling you that there's a proportion of people who are still addicted to ALK when they progress on a next-generation inhibitor, and some of these drugs still work on those mechanisms of resistance. Through mechanism of resistance that works on the drug you choose, and they do well. The PFS is a composite of those who are progressing on your new drug and those who are benefiting. You look at the duration of response. The durations of response are actually all pretty good with these drugs.

Let's talk a little bit about mechanisms of resistance. Well, you can get on-target resistance mechanisms, so *ALK* mutations that prevent some but not all of these drugs binding, and the spectrum of mutations you get changes depending on which drug you're progressing on. You can see here that G1202R doesn't come up that often post-crizotinib but is a bit of a problem child because it's not hit by ceritinib, alectinib, or brigatinib, although it is hit by lorlatinib. But really the elephant in the room or what I want you to hold onto is just like the best drugs—like brigatinib or lorlatinib used in the second-line setting post a next-generation inhibitor only about 40% response rate. What that's really telling you is nearly 50% of people are developing a second driver. So it has nothing to do with ALK; ALK is still suppressed, and some other driver is going on. So changing ALK inhibitors may not do anything.

We saw a clue from this from some nice data from the initial lorlatinib study. If you could perform a biopsy before the patients went on lorlatinib after they progressed on a next-generation ALK inhibitor and you could find a mutation in *ALK*, they had something like a 60% response rate; and if you didn't, it was a 26% response rate. Equally, your PFS, if you found a mutation, was 11 months, and it was 5 months if you didn't. Now, what you can take from this is hey, if you're only going to give lorlatinib you don't need to do this. However, we are starting to identify some

of the second drivers, and so conceivably we may even be in the deciding position where we do a biopsy to say this is your best or next best treatment. The other thing to take home is you still have a 26% response rate even if you don't have a mutation, so clearly the mutation testing isn't perfect.

As I said, if you find a specific mutation, you can look up tables like this one to tell you which drugs will work, so you don't always have to go onto lorlatinib, although it has the broader spectrum of coverage.

But as I mentioned, there are second drivers. *MET* is definitely developing a role as best supporting actor as a mechanism of acquired resistance across multiple different oncogenes. Often it's by *MET* amplification, but also *MET* mutations and *MET* fusions can be mechanisms of acquired resistance in ALK. So if you perform a repeat biopsy and you found an *ALK* mutation, you're going to go for another ALK inhibitor. If you found *MET* amplification, you probably want to add in a MET inhibitor, and that's a whole different story.

The other things you can do, if you get to chemotherapy, is know that all of the gene rearranged subtypes of lung cancer—*ALK*, *ROS*, *RET*, *NTRK*—have exaggerated sensitivity to pemetrexed. We don't quite know why; this has been known for over a decade. And so if you're going to choose a chemo, which would probably be carboplatin and pemetrexed, there's not a lot of data that immunotherapy works in ALK. So probably the big debate is carbo/pem alone or carbo/pem and keeping the ALK tyrosine kinase inhibitor (TKI) going. Nobody knows, but the assumption is if you had disease in the brain that was being controlled on the TKI, it might be a little foolish to stop it.

So what does managing ALK look like from the extra CNS perspective? Well, if you have progression outside the brain—even sometimes inside the brain—on your initial ALK inhibitor, as on the left-hand side, first thing you're going to ask is it oligoprogression, an isolated area? Zap it with focused radiation and stay on the drug. Let's say you can't do that. In an ideal world, you would repeat a biopsy and reanalyze with the same broad-spectrum multigene testing that you had before. If you found an ALK-dominant mechanism of resistance, an ALK mutation, that's great. You'll look up one of those tables and select your best, cheapest, best tolerated, whatever ALK inhibitor in the green box.

If you find something else, which is a second driver, that you can identify and you can act on it let's say MET, you can talk about off-trial or in-trial (if you can get access to one) adding in

another agent to work on that second pathway. But if you don't find a resistance mechanism or you find a resistance mechanism that you can't act on, well sure you can try another next-line ALK inhibitor. Remember there was a 20% response rate to lorlatinib even if you didn't find a mutation, but you should almost expect it not to work, and therefore have a close eye on your patients. If you get to the point where that's not working, then it's really about pemetrexed-based chemotherapy with the debate being do you keep the TKI going.

In the CNS, it's similar. So if there is disease progression in the brain, the first thing you want to ask is whether you can zap it with radiotherapy, stereotactic radiation surgery, and stay on the drug. You're not going to be able to perform a repeat biopsy on that, although people are talking about sampling the CNS. Where are you going to go? Well you can try another next-generation inhibitor. Lorlatinib is really good at getting into the brain. Or are you doing other fancy things like adding in bevacizumab, if you're adding in temozolomide—these are all works in progress. We don't really have a good plan for that.

To summarize, let's talk about molecular testing. Single genes, nah; FISH, nah. You want to be on next-generation sequencing. All you have to do is sit down with your provider and say what panel are you doing? Does it include all the things that are currently licensed? Thank you very much. First-line *ALK*-positive non–small cell lung cancer—you're going to start with a next-generation TKI. You could choose alectinib or brigatinib or lorlatinib. I think because of the side effects with lorlatinib, even though its PFS is likely to be longer, that's really not a surrogate for overall survival. And I think a lot of people are still sticking with the alectinib or the brigatinib.

At progression, ideally, you would perform a repeat biopsy and reanalyze and choose either another ALK inhibitor or a rational combination or something else based on the result. It's not a perfect world. Sometimes you have access to that, and sometimes you don't. If you have to shoot from the hip, you're just going to try and go for a broader spectrum ALK inhibitor. But if you don't know, you should go into it almost expecting it not to work. Remember something like 50% of cases will have a second driver and have either a repeat biopsy planned ahead or be ready to jump in with pemetrexed-based chemotherapy. You've always got local radiotherapy to fall back on, and we've already mentioned that chemotherapy should be pemetrexed based.

AXIS: Thank you, Dr. Camidge, for that excellent presentation and for your dedication to continuing professional education. For our attendees today, thank you for your participation.

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