



Dr. D. Ross Camidge on One Size Doesn't Fit All: ALK Gene Rearrangements, ALK Inhibitors, and the Future of Lung Cancer

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Dr. West: Welcome everyone. My name is Dr. Jack West. I'm a medical oncologist at Swedish Cancer Institute in Seattle, Washington. I'm also the President and CEO of GRACE, the Global Resource for Advancing Cancer Education.

Today we're very honored to have Dr. Ross Camidge, medical oncologist and lung cancer expert at the University of Colorado Health Care Center in Denver, specifically Aurora, Colorado. Dr. Camidge will be talking about some really rapidly evolving work on what's called the EML4-ALK translocation and how that fits into the context of tailoring molecular therapies for lung cancer. Thanks for joining us, Ross.

Dr. Camidge: You are very welcome. I'm delighted for those of you who are watching, you can see a picture of me which my mother is very proud of.

So for those of you who are wondering, I do actually have a British accent; it's not fake. It's the genuine article.

I'm going to give you something to set the scene. I've entitled it "One Size Doesn't Fit All," and it's really about breaking down the idea of lung cancer as one disease into multiple different diseases.

So here's our historical background. Lung cancer essentially for about the last 40 years the only distinction that was made was between something that was called small cell lung cancer and everything else, which together was called non-small cell lung cancer, which if you think about it is a admission of failure. It actually defines what the disease isn't as opposed to what the disease is. That whole lumping everything together reached a plateau, at least for those people with advanced disease, and by advanced disease, I mostly mean people who have fluid around the lungs (pleural effusion which has cancer cells within it), or cancer which has spread outside of the lungs.

That advanced disease in the late 1990s had reached a plateau in the center that whatever chemotherapy you gave and you can see on the graph four different combination chemotherapies, it didn't really make that much difference what you got. They all did equally well, or if you're a pessimist equally badly.

That same logic extended even in the early 2000s when we started to get what were called targeted therapies. Now many of you will have heard of drugs like Iressa, which is also called gefitinib, and Tarceva, which is also called erlotinib, and they had something called the EGFR. The epidermal growth factor receptor is expressed on many lung cancers and when people first started to develop these drugs, they said let's give them to everybody. They seem to be expressed in everybody; maybe they'll work in everybody.

And when they did that, this was the pivotal study which was run through Canada. It was called the BR21, and it was with people with advanced lung cancer who had been through one type of chemotherapy or two, and then they were randomized to receive Tarceva, a tablet, or a placebo tablet. The little picture is what's called progression-free survival. That's the time it takes for the cancer to grow after you start the treatment. Really, when you look at hundreds of people there was a marginal difference. It was about two weeks in terms of how long it took for the cancer to grow on average and the survival was slightly better than that. But it was enough when you look at all of those people together to say that this was statistically significant and it was enough to get the drug a license.

Now what most people who were using these drugs actually found was that two or four weeks or whatever difference wasn't actually what you saw in patients because the patients aren't averages—they're individuals. What you really saw was some people did amazingly well and some people had no benefit at all and together that averaged out to this rather unimpressive figure. However, because it was in enough people, it was enough to get the drug a license.

So this is an example of what I mean by those dramatic responses. This is a CT scan through somebody's chest. The left-hand figure, the black is the air in the lungs and the fluffy white stuff where the red arrow is pointing is the cancer in the lungs. This is somebody who I put on Tarceva and literally within a few weeks they came off oxygen, they put on nearly 40 pounds in weight. You can see it's a much bigger person—it's the same person—on the scan on the right-hand side; a really dramatic response to Tarceva. It turned out that these people tended to have a specific mutation in their EGFR. It wasn't enough that the protein was there, but it had to be turned on. Although, if you give the drug to everybody, the averages are marginally beneficial, it was clear that some people were getting these dramatic responses.

So the story of the EGFR in lung cancer was the beginning of breaking through that one size fits all. Tarceva was licensed in 2004 in

everybody. But at that same time, these mutations were found in about 10%-15% of the population. Retrospectively, they were the people who seemed to have the most dramatic responses. But it took nearly another five years from when the drug was licensed to show prospectively that if you selected people who just had that mutation, that the drug Tarceva or its relative Iressa was so good that it was actually better than chemotherapy in the first-line setting. So suddenly you go from having a drug that you want to give to everybody to actually nailing it down to a very small proportion of people who really benefit. Sometimes when Dr. West and I would be at meetings people would say well that's the exception, that's the one thing that disproves the rule. But really everything else is non-small cell lung cancer and everything else is the same. The really exciting thing is just in the last year that that model certainly was shattered because we got the second example.

The second example relates to this drug which is called PS02341066. I can tell you actually now it has a name; it's called crizotinib and this maybe the first time that name has officially been used because it was officially announced this week. But I'm going to call it 1066 for short.

1066 is a tablet and it was developed to hit two particular molecules. Now this has nothing to do with lung cancer at this point. Its designed to hit a molecule called c-MET, which has been involved in lots of different cancers including gastric cancer, esophageal cancer, kidney cancer and a small proportion of lung cancer. And another molecule that maybe two years ago most of us in lung cancer had never even heard of called ALK. ALK stands for anaplastic lymphoma kinase because this was a molecule that was abnormal in hematological malignancies, in lymphomas and in rare brain tumors. But it wasn't reported in lung cancer.

So when this study, this is called a phase I study, so Pfizer who makes the drug, said we have a drug and it hits c-MET and ALK, and we think its going to be important in these rare cancers. What we have to do is find out the right dose to give. So in a phase I study, you have all people with all different types of cancers who are eligible and they can go on and each new group of people that goes on gets a higher dose of the drug because you try to find the highest tolerable dose of the drug. There are these little step-ups that you can see going in this slide.

The striking thing about this study was that Pfizer from the get-go decided that their drug wasn't going to work in everybody. They had learned from the Tarceva model. They said its going to work in a small group of people that we think we can test in the laboratory (they had lots of little cells growing in petri dishes from different types of cancers). It was clear that their drug worked amazingly well in some cells and did

absolutely nothing in others. They felt that some of these were driven by c-MET and some of them were driven by ALK because the drug hit both. They always decided once they found out what they called the RP2D, recommended phase II dose, the dose that they felt was tolerable and they wanted to take forward, that they would pause the study and deliberately add in people whose tumors they felt on the basis of a test done on the tumor that was driven by either c-MET or ALK. Now the striking thing was that when the study started in 2006, as I said ALK was a new and reported in some very rare cancers including types of lymphoma, but after the study was started in 2007, ALK changes were actually reported in lung cancer. So it's a real example of people being nimble enough to change to emerging data. So this is what an ALK positive test looks like. It's very subtle. It's actually a break in chromosomes. The chromosomes are the long bits of DNA where all the genes sit inside somebody's nucleus. If you look at them what happens in an ALK-positive patient is that there is a break in the chromosome and red and green dots which are normally right next to each other suddenly get separated. That's because the bit in the middle which is gray in my example gets flipped around. The blue blobs on the slide are actually cancer cells. You can see in the two white arrows show that a red and a green blob are separated. Right next to them within the same cell because of course we have two copies of a chromosome—one from our mother and one from our father—you can see that the red and green dots are right next to each other and actually appear yellow because they are so close.

The test is very subtle. In a positive patient what you see is the separation of the red and green dots. This test is called a break-apart test. That test was developed in combination with the University of Colorado and Massachusetts General Hospital to try and detect patients who were ALK-positive. So the Phase I study is going on, they find the right dose; they plan to enrich with people with all different types of cancers that they done some kind of test that says your cancer is driven by c-MET or ALK. Somewhere along the way they say, by the way ALK is present in a much more common cancer, lung cancer and so we started to screen patients. People sometimes get put off by the idea that it's only present in between 3% and 4% of lung cancer. But lung cancer is unfortunately very common; so 3-4% of a large number is still a large number.

What was striking whilst the study was going on is, first of all that the drug was relatively well tolerated. This isn't chemotherapy. It's a tablet which is much more like a key than a lock. It goes in and interferes with the function of one or two different molecules — c-MET and ALK. Now those molecules, even though they're mostly involved in how we develop from a few cells up into a fully grown adult, have very little role

in the adult person, so when you take these drugs their side effects are mild. They cause some nausea, and that nausea tended to get easier when you took the tablets twice a day in a divided dose as opposed to once a day. They also tended to be easier if you took the tablets on a full stomach as opposed to an empty stomach.

They can cause some diarrhea and some constipation, just seems to depend on how people are wired.

It has a slightly quirky side effect in the sense that it can interfere with how we see things. It's very subtle, but it's really related to how people adjust to dark and light. Most people report it as you go from a dark room and you turn on the light switch and what happens is you see just that sort of flashbulb effect. Or you see the ghostly image of your hand — just for a fraction of a second longer. It's more prominent really at the edges of your vision than in the middle. It doesn't get any worse, it doesn't interfere with people driving or watching TV. It's more a curiosity.

The very first time it was reported was actually from a patient in New Zealand who was driving along a country lane with trees in it and the sunlight was sort of on and off and on and off and they thought the sun was hanging around into the darkness a bit longer because the study went on in America, Australia and Korea at the time.

The only other slightly more serious side effect is in rare individuals the blood test of how the liver work can be abnormal. That's probably what you might call idiosyncratic: we're all put together differently and its just how some people handle the drug, but it seems very rare.

At this point in time, the data I'm going to show you is on the first 50 patients with lung cancer who were ALK-positive who got the drug. Now there are plenty of people who don't have ALK-positive lung cancer who have different types of cancer, but are still being evaluated. What I'm doing is honing down on that little enriched group of people who had ALK-positive lung cancer.

And this slide which is called a waterfall plot is really one of the most dramatic that most people have seen in lung cancer. In the waterfall plot, each one of those bars is an individual person. What you do is you take the measurement of their tumor before they go on study and then you look at how much it shrinks or grows at the maximum; then you plot it. So if it shrinks a lot you plot a long bar down; if it grows and never shrinks, you plot a bar upwards.

What you can see is that nearly all of the 50 patients, their bars were going down. There's a formal grading system for how much it shrinks, whether its called a partial response (PR) or whether its called just stabilization (SD). You can see that most people are in the partial response category.

You can see that some people even on the far right are nearly down to 100%, i.e. their cancers have almost completely disappeared. When you look at it all together, nearly 2/3 of people have very dramatic shrinkages and at least 90% of people have either shrinkage or stabilization.

Sometimes they like to report something called the median progression-free survival, which is how long it takes for 50% of the people to start to grow again. We don't know that data because nearly 75% of people who started on the drug are still on it.

That doesn't mean it lasts forever. There are some people who have clearly started on the drug and their disease has progressed even after an initial response. But we don't yet know the full length of time it takes.

If we go back to the Tarceva example with those people who are exquisitely sensitive with the EGFR mutations, we know that it ranges from a year to multiple years that some people could stay on the drug. I suspect it may well be the same with the ALK-positive patients who are on the ALK inhibitor.

I want to show you some real examples. This is one of the first patients treated who was treated at Massachusetts General Hospital and you can see the fluffiness in the scans on the left-hand side which is fluffiness in the black is the cancer within the lungs. Here after two cycles, so that's eight weeks of treatment with the ALK-inhibitor, their scans have completely normalized.

This is a different type of scan. This is what's called an FLT-PET scan. This is a patient from Australia. The red blob is actually the backbone and on the FLT-PET as opposed to a normal PET it also lights up your bones. It doesn't mean there's cancer there. It's just how it lights it up. But cancer in this example is the fluffy green blob on the bottom right of the top slide and that has rapidly disappeared within four weeks.

The key word is "rapid" here. So the patients who go on this drug, who are wired in the right way will feel better within days. So their earlier scans are really done about a month. But this is a real world example and I had a patient who flies in from Minnesota to be treated and he had terrible disease which was surrounding his heart and he was in a lot of

pain. When I saw him on the Friday morning, he was on Dilaudid a very powerful opiate painkiller and he started the treatment on the Friday and I asked him to email me over the weekend and on Sunday he said I have the funny visual changes and on Sunday afternoon he came off his Dilaudid. So the responses can be dramatic.

I have another patient who is the coach of his daughter's soccer team and he had been coaching from the sidelines because he couldn't run around and he couldn't shout very much and within pretty much 10 days of starting on the drug he was back to doing sprints up and down the field.

So for those people the cancer is perceived to be addicted to this particular pathway. When you interrupt it with this drug, the cancer dies away rapidly.

Now, where does this mean this is going? Well, the Phase I study which is where the drug is initially only available, was only available in a small number of centers around the world which was the University of California-Irvine, University of Chicago, University of Colorado, Mass General, Dana Farber, Beth Israel in Boston, Memorial Sloan Kettering in New York, Seoul National University in Korea, and Peter McCallum in Melbourne, Australia.

What has now happened is because of these very encouraging results the sponsoring company, Pfizer is leading straight from this Phase I, this very early study directly to a Phase III study, which they hope if positive will actually get the drug licensed and be freely available. That said, the Phase III study is going to be very widely available both nationally and internationally.

But in order to prove it works, the Food & Drug Administration was very explicit. They said you have to compare it to something. It's not enough to say that people responded dramatically. It's not enough to say they respond rapidly. It is not enough to say that most people are still on the drug. You have to prove it's better than what is already out there.

So this study which will be called PROFILE 1007 will be its official name, and its official name is A8081007, and code number for finding it on clinicaltrials.gov is on the slide, is a randomized study for people after they've received one line of chemotherapy -- so what's called the second-line setting. Why the second-line setting? Because it's recognized it'll take the general community a little while to get used to doing the testing, because it only works if your tumor is ALK-positive, to get used to doing the testing. So they may have already started

treatment. So when the test results come back you want to have something that they go on that is their Plan B.

In this study, if your cancer is ALK-positive, then you are randomized to receive the ALK-inhibitor 1066 or your doctor's choice of two licensed second-line treatments, which is either Alimta or Taxotere.

The study has a companion study. This is actually a very nice thing done by Pfizer. This is a companion study which says we think this drug is so important that although we have to prove it works otherwise nobody's ever going to get access to it in the future unless we can get it approved and licensed in a properly designed registration study. We think everyone should have access to this drug one way or another. If you go into the Phase III study and you are randomized to receive the chemotherapy, if the chemotherapy works stick with it. But if the chemotherapy stops working, you can still get access to 1066 in what would be the third-line setting for you. There you would go into this Phase II, you might like to call it a "catch man's" study to catch all those people who have either been randomized to chemotherapy in the Phase III study, or if for whatever reason they have been through too much chemotherapy already and are not eligible for the Phase III study. This study is there for them.

The key thing is if you are in the second-line setting though and you are eligible for the randomized study, you have to go into that. Although that seems like a tough thing because everybody believes something new must be better, I think it's perfectly reasonable to say you have to prove it. But this is very nice because it means you do get two shots on target so you'll either get it in the Phase III study or within the Phase II study. Again, that would be in all of the centers where the Phase III study is open.

So the Phase I study as I said is for those centers which don't yet have the Phase II and Phase III studies will remain open so they're still allowing patients who are ALK-positive to go onto the Phase I study. For example at the University of Colorado, I'm still putting patients on the Phase I study because our Phase II and Phase III studies are not yet open, but we expect them to be open in a few months time. Those are the other centers where the Phase I study is still open.

Once those centers have the ALK lung Phase II and III studies open, however, they will close to putting anymore ALK lung patients on the Phase I study, although they will still be open to patients who may have ALK-driven tumors which have nothing to do with lung cancer or MET-driven tumors which have nothing to do with lung cancer because those

enriched cohorts are still going on and we still have yet to see the signals made arrive from that.

So this is the other thing that you want to know. You say “okay, this sounds wonderful if you’re ALK-positive. But how do I know if I’m ALK-positive?” ALK-positive patients if you look at all lung cancers together is only about 3%-4% of the population, so it sounds a little bit like going to Vegas and playing the long bets. But there are certain features which are more associated with being ALK-positive than others and that’s what I’m going to describe now.

One small technical point, the test that break-apart probe tells you that the ALK gene is broken, the most common thing that breaks it is it forms a fusion with something called EML4, and that’s why some people call this EML4 ALK. Technically that’s incorrect because the test looks for an ALK gene rearrangement. The most common rearrangement may well be EML4, but if you’re a purist, slightly anal retentive like I am, you would call it an ALK gene rearrangement.

So this if you look at those 50-odd patients who’d gone on, what did they tend to have in common? Most but not all of them had never smoked, but you can see that some of them were smokers, so its not an absolute; its not black and white, its just less common if you’re a smoker. Most but not all of them had adenocarcinoma but again its not black and white. So I think what it says is these are not a substitute for testing. They may be what your physician or you yourself might use to try to decide if you should go somewhere and try to get ALK tested, but really my advice would be particularly for people who have adenocarcinoma that they should get tested. The histology is probably a stronger thing than the smoking status.

On a side note, people have noted that it tends to be more common in men than women, but I think as our data set gets larger that maybe reviewed. Also, again, since its not absolute, its not anything you can use to decide who to screen or not. Similarly, the age of people they tend to be a little bit younger than the average lung cancer patient but the age range is very wide. My oldest patient is in his middle 70s who has an ALK gene rearrangement; the youngest is 21. Again, its not anything which you can put an absolute cutoff on. I go back to the idea that almost everyone should at least think about being tested.

There is one thing which seems slightly more absolute and that’s the idea of additional molecular tests which can be performed nearer to home. So at the University of Colorado we’ve been performing routine molecular testing since early 2008 looking for things called EGFR mutations which I’ve described; and also things called KRAS mutations.

Then since 2007 we've been looking at c-MET and ALK partly in association with the study.

What became clear is that most of the people who were ALK-positive which is the green dots on the left-hand side of the slide compared to the people who were ALK-negative on the right-hand side of the curve, first of all this emphasizes the smoking point. So the more years you've smoked, the higher your dot up is and you can see most of the green dots are right down on the bottom. So very few of them have smoked apart from the lady on the far right-hand side of the green dots who smoked for about three years.

But the other thing you can see is that most of the people do not have EGFR mutations, and they do not have KRAS mutations. So they seem to be almost mutually exclusive. I say almost because its not absolute and there is no particular reason why you can't have both apart from the fact that most cancers usually have one dominant driver in this setting and if one is setting the cancer off and running you may not necessarily need to have another one. So being what's called "wild type" which means not having a mutation, wild type goes back to the original terms from using fruit flies in genetics, being wild type EGFR and KRAS seems to be one of the strongest predictors for driving you to get tested for other things. If you can get your doctor to test your tumor for EGFR and KRAS mutations in an appropriate way and it is negative for both of those, I would strongly suggest that you try to find some way of getting tested for ALK.

So this is where we are now. We've started to break through that wall the idea that lung cancer is just one disease and its not. We already had the EGFR mutants as an example and then suddenly we have a second example which within two years of the gene being discovered in lung cancer, we're already seeing dramatic responses because of some aspects of serendipity where a drug was perfectly matched with a particular test. Again, when you have the second example, people start to say "well, hold on, maybe there are other things lurking within that yellow blob, within that box of everything else being the same." There may be treatments that if you tailor them perfectly you can get the kind of dramatic responses. So where are we going now?

The answer is that people have picked up on the idea of molecularly-defined lung cancer and trying to find specific treatments within something called the Lung Cancer Mutation Consortium. If you're wondering where the Obama stimulus money went, this is at least one place where it did. So nearly \$5 million came from the stimulus package to support this consortium which consists of 13 major cancer treatment centers involved with treating lung cancer and their plan is to

look for at least nine different mutations or genetic changes in a thousand patients with adenocarcinoma over the next two years. The centers that are involved contained within the box in there, its coordinated through the University of Colorado, but essentially the centers are scattered throughout the country ranging from the East Coast, Texas, through to California.

The more exciting thing is the plan that with all of these patients who get all of these mutations checked is that eventually that same infrastructure in the consortium will have specific drugs to catch each of those types. The paradigm for that is the ALK. So anyone who finds an ALK patient will be putting them into those Phase II or Phase III studies. What they hope is if you have an EGFR mutation there will be an EGFR mutation specific study. If you have a KRAS mutation, there will be a KRAS mutation study and so on and so forth for the other six different mutations and gene changes that they're looking for.

So, in summary, I would say categorically that I don't think lung cancer is one disease. I think it is multiple different diseases on the molecular level. I would say that molecular profiling has already led the way showing clear benefit for choosing those who are going to benefit from the EGFR inhibitors like Tarceva. I would say that the crizotinib, Pfizer's new drug 1066 has already shown a very strong signal in another molecularly-defined subpopulation of lung cancer, the ALK-positive patients and that large national and international studies are now ongoing in what is essentially a newly defined subtype of lung cancer to prove that this drug works.

Those patients tend to have adenocarcinoma. They tend to have little in the way of a smoking history. And I think importantly they tend to not have these other driving mutations. I would say quite categorically if this is you, if you can get your doctor to show that you don't have an EGFR or KRAS mutation, you should go get tested. I think this principle of doing the molecular testing and then matching the drugs to these tests results is slowly starting to happen in many centers. I know that Dr. West is already doing this for the EGFR inhibitors in Seattle. I think the Lung Cancer Mutation Consortium is now taking this to its logical extension in exploring the potential of this really exciting new direction of breaking down "not one size fits all" and try to get personalized medicine really into the clinic in a real way.

These are all real people who have benefitted from the ALK inhibitor. So the lady on the top she's called IIA, she was the very first patient in Colorado. She's actually standing next to Dr. Garcia, who helped develop the FISH test. So she's actually looking at a picture of her own cancer cells which we saw in one of the earlier slides. Troy, who is

carrying his daughter on his shoulders. This is a great example of somebody with stage IV lung cancer who's doing a fun run. Then Ellen who is smiling from the TV advert all of the patients do so well they want to tell their story. Ellen just got engaged. So congratulations to Ellen.

Dr. West: Actually in the local Seattle media market there was a feature about Andy, who you've treated and has done spectacularly as well.

Dr. Camidge: Yeah, he's the soccer coach I talked about.

Dr. West: Exactly. That's pretty good if you can go back to coaching soccer and being as active as that.

One question that came in was about the feasibility of 1066 in say, in an older or marginal performance status patient. Is this at all like certain kinds of chemotherapy in which performance status or age other than its association with the ALK translocation would be prohibitive at all?

Dr. Camidge: So I'm relatively opinionated on this matter. So, apologies to those who have a different opinion from me. I think the idea of choosing treatment on the basis of somebody's age is fundamentally wrong. I think what drives success is whether you know what drives the cancer. So here the important thing is whether your tumor is ALK-positive or not. Whether you're 8 or 80 and because the drug is so relatively well tolerated whether you're fit or not, really makes very little difference. As the example I gave you of somebody who was really very unwell and had been admitted to hospital with severe pericarditis, swelling around the heart, and was on very powerful pain killers, his performance status as they call it was pretty poor. And he literally rolled out of his bed and walked within a few days of starting on the drug. I think the other example I gave you is my oldest patient is 78 and again age is no barrier to benefitting from this. It's all about whether your tumor is wired in this way.

Dr. West: Great. Another question I had is, have there been patients who have had to come off because of toxicity issues, whether it's liver function tests or anything else; or thus far has it really only been due to progression of the underlying disease?

Dr. Camidge: The liver function test is really the only thing which has made people come off the treatment. What we've done there is we have reduced the dose of the drug. So there a couple of examples of patients who've done that. Remember the data set is relatively small. At least one of my patients even though they felt completely well, their blood tests were going out of control. We held the drug for a week or so. Their blood tests came back to normal which fitted with it being an effect of the drug

and then we put them back on a reduced dose. The blood tests of how their liver worked have been completely fine since then and their disease remains under control. Its one of these things that there is a level which has an activity against the bad gene in the cancer and that level may be lower than the level at which people have bad side effects who are sensitive to it in their liver. So if you can get into that sweet spot, you can keep their disease under control without causing problems.

So, no, most people who come off the drug come off it because their drug stops working. That's the sting in the tail, its clearly not going to last forever in everybody.

Dr. West: A question came in about how did the folks at the Lung Cancer Mutation Consortium arrive at the target of nine mutations to test for?

Dr. Camidge: That's a really good question. There's nothing magical about it. It's partly that this is an evolving field. When you write to Mr. Obama and you say, "Please can I have 5 million?", you have to put something down on paper. At that point in time, the mutations that people could think of that they felt were well enough characterized that you could define what the test was and that had at least a reasonable possibility of there being a potential drug to catch those patients just happened to be nine. I guess if we were to submit the same thing in two years time, it wouldn't be nine; it might be 15 or 20; it constantly changes and evolves.

Dr. West: Another question came in about some of the practicalities like how much tissue is required? Is there any reason to think it would be problematic to test a tumor that has already been exposed to and shrunk on prior chemotherapy?

Dr. Camidge: Mostly we believe this is something that happens early on in the development of the cancer. As long as you have a specimen of your cancer even if it was from when your cancer was cut out and then it came back or your original biopsy even if you've been through lots of different chemotherapies, that original biopsy is still valid. So you don't always need a fresh biopsy. That's the first thing.

The second thing is how much tissue is required? The answer is not very much. The tests, there are a number of different tests but the only definitive test is this test which actually looks at the cells, looks at the red and green dots and that's called the FISH test, which stands for fluorescent in situ hybridization. As you can see can actually be done on a very small number of cells. So you don't need a big chunk, just I think 3 or 4 slides is all that is required.

The one caveat to that is that if your biopsy comes from bone as opposed to anywhere else, the techniques that they use to dissolve the bone unfortunately mess up the test. So, people who have bone only biopsies may need to have another bit of their cancer biopsied.

Dr. West: Another question on the practical aspect is how do patients go about getting tested if they aren't already at a place that is doing this fairly regularly?

Dr. Camidge: There are number of private firms which are talking about doing the ALK testing. Here it's difficult to be certain to know what to recommend. In the proposed studies which are the only way you can get access to the drug at present, they are not accepting testing from outside private firms. They think the test, you can see how close together those red and green dots are, how subtle this test is and they feel it all has to be done within a central place. At the moment you have to go to one of the centers which are doing one of trials and there they send off the testing to a central place. Some of the bigger centers, University of Colorado and Mass General and I believe Vanderbilt as well, are trying to get their local labs accredited and that should be perfectly feasible given that they helped to develop the test in the first place. There is the potential in that setting that you can arrange for your oncologist to send the specimen to some of these pathology labs. The testing won't automatically be free because you're sending from the outside. If you come to one of the doctors at one of these places the testing is usually free. But that's the way to do it.

Dr. West: Otherwise you need to go someplace that is running these trials which are rolling out worldwide right now.

Dr. Camidge: Yeah. What we've done with some patients is they've flown in to see us, carrying their tumor block, which is a little bit of the tumor embedded in wax with them. Sometimes we talk through but in case there are other trials that they're appropriate for and then send the test off and it takes one or two weeks to come back. Andy, the patient who's been on your Seattle news station, actually got his tumor sent to Mass General. Its amazing these things are flying around the country. When the test came back and then he came to us because we were the nearest center with the study.

The big worry the guide in the community until we know how good they are at doing this test is not the worry about them doing a test that comes back positive. The real worry is that they will inappropriately tell you that your negative you miss out on the opportunity. I think what one can do locally is you can say I can get the EGFR sent. I can get the

KRAS sent off. And if you're "wild type" of both of those, you're really enriching the chances that you're going to be positive. And that's time to say now where can I send my tumor to be tested or where can I physically go to talk to these people and bring the tumor along with me.

Dr. West: Again, on the practical aspects, is it possible to do testing from cytology, from a bronchial lavage or a fine needle aspiration or do you need to have enough from a core biopsy?

Dr. Camidge: It doesn't have to be a core biopsy. Bronchial lavage is probably a little challenging because they've probably used all the cells up in the test. So when they do the bronchial lavage they usually stain the cells which makes it, not impossible, but it makes it slightly harder to do the test. If they've drained fluid off and sometimes they spin that down and form what's called a cell pellet and then they embed that in wax and you can take little slices of that off. Purely from a bronchial lavage, hard to say, but I'd say unlikely. I think sometimes we have to embrace the idea that if we're going to make this a more personalized choices, we do need suck up the idea of having another biopsy just so we can get the right material for making these calls.

Dr. West: Well, thank you so much for taking the time. It was a great presentation and I think people got a lot out of it. I really appreciate your help today.

Dr. Camidge: My pleasure.