ALK Inhibition: From Biology to FDA-Approved Cancer Therapy, Part 2

by Dr. D. Ross Camidge

Dr. West:
Hello and welcome. My name is Dr. Jack West, and I'm a medical oncologist in Seattle, Washington, and the Founder and CEO of GRACE, the Global Resource for Advancing Cancer Education. This is the second part of a program done in partnership with the LUNGevity Foundation, covering the topic of ALK inhibition from basic science to FDA-approved anticancer therapy for patients whose tumors have an ALK rearrangement.

In part one, which is available as a separate podcast, Dr. Ben Solomon from the Peter MacCallum Cancer Centre in Melbourne Australia covered the initial discovery of ALK rearrangements in the lab, as well as the early development of the ALK inhibitor crizotinib and the subsequent clinical research that led to it now becoming commercially available as XALKORI.

The second part of the presentation was by Dr. Ross Camidge, a medical oncologist and the Director of the Thoracic Oncology Program at the University of Colorado in Denver. Just over 18 months ago, Dr. Camidge did a tremendous presentation for us back when this was still a very early story, and he's remained a pivotal part of the story since that time. His presentation focuses on a range of implications of crizotinib in terms of screening and considerations for potentially valuable treatments after crizotinib. Here's Dr. Camidge:

Dr. Camidge:
Thanks very much. I've entitled my sort of part two of this double act "Adventures in the Screening Trade" – if anyone knows what that's a reference to, I'll explain that at the end. And then partly because crizotinib is not a cure, we have to recognize that we have to plan for what happens when the crizotinib stops working, and really to look at what we're going to do in terms of life beyond crizotinib.

These are my disclosures. I've advised a number of different drug companies who are trying to develop compounds that work in ALK-positive lung cancer, and I'm an investigator on most of the crizotinib studies.

Let me start by talking about screening for ALK patients. So these are all ALK-positive patients. And how do we find them? They're all individual, they're all different. The only thing that they happen to have in common is they're unfortunate enough to have the same molecular abnormality in a cancer that they didn't ask for.

And what I'm going to briefly comment on is the different techniques. And I'm only going to comment on it briefly, because with crizotinib being licensed, it's licensed in conjunction with a test. It's only for people who have proven to be ALK-positive, and the actual licensing language says you have to be proven ALK-positive by an FDA-approved test, and there is currently only one FDA-approved test, and that's the FISH test that Ben showed you earlier.

So in terms of the real world, knowing about these other tests at the moment isn't going to make any difference, but just in terms of looking to the future, other techniques, immunohistochemistry, which is a way of looking at the protein, RT-PCR which is a way of amplifying specific bits of DNA, and various other tests – I think will come and they probably will become FDA-approved tests in the future, but at the moment I wouldn't worry about it if people weren't asked specific tests about FISH testing. We can cover those later.

What I really want to talk about is something which is the idea as to who to screen given that you can only give crizotinib to somebody who's proven to be ALK-positive. I've got on record as saying therefore if you want to treat everybody who's potentially treatable, i.e. you have to catch everybody who's ALK-positive, the only way to do that, unless you can define a group who has a zero percent change of being positive, is to screen everybody. However, some may say that it's a relatively naïve approach because it's clearly recognized that the odds of being ALK-positive vary depending on several different factors. There are groups that have a much higher chance of being ALK-positive, and groups which have a much lower chance of being ALK-positive. And increasingly when you recognize that those factors exist, the cost effectiveness of screening for ALK is starting to be discussed.

And although cost effectiveness is not as sexy as a new understanding or a new treatment for cancer, it's the real world. And unless we understand cost effectiveness, we'll always be simply the recipients of those decisions and not an active participant. So if you'll indulge me, I'm going to talk a little bit about cost effectiveness. And the key thing to understand about cost effectiveness is it depends on the perspective you're adopting. So if you're the person who's holding the purse strings, it's easy to understand the perspective. You're trying to decide if it's appropriate for you individually to pay, let's say, about $1000 to screen your tumor to see if it's ALK-positive. And you might be able to look up based on the factors that you know about yourself, whether you're a smoker, how old you are, what type of lung cancer you have, down the microscope, your individual odds of being positive. And you can imagine yourself as a bit like being in Vegas and you're standing at the gaming tables; you can decide individually whether you want to place the bet of $1000 knowing that you have a 1% or a 10% or a 50% chance of winning, and knowing that if you win you will win access to the drug and decide whether that's a bet that you wish to make.

But we don't all hold the purse strings for all of our healthcare, and indeed in many places it's the government or large insurance firms such as Kaiser or Medicare who are actually holding most of the purse strings. And therefore the perspective is not of an individual, but of society, and there the calculation is done rather differently because what the societal view will do is it has to take into account the cost of all of those people who you pay for screening, but who actually have a negative result. And all of those negative costs have to be added to the overall cost of the one person who then turns out to be positive and actually gets treated. Let me try to illustrate that in the next slide.

So here's a worked example. At the moment, the FISH test does cost about $1000; sometimes it's slightly more than that. But let's imagine only one in a hundred people is positive. So from a societal perspective, it's going to cost you $100,000 just to find one positive – $1000 for Mrs. Jones who is positive, plus the cost of the other 99 people you've screened who are negative. What that actually means is we're talking about the cost of the drug, which crizotinib is being put on the market at something like $9600 a month, but even at those prices, and the screening costing $1000 a person, when the frequency of the abnormality you're looking at, ALK positivity, is relatively low in the screened population, so about 5% or less, the overall costs are actually hugely dominated by the screening and not the cost of the drug, which is hard to get your head around. Really, $10,000 a month is the big deal, the cost of the drug? Well no, if you have to pay

$100,000 to find that one person who's even treated with the drug in the first place. So the screening particularly at low frequencies as a marker can have a huge impact on the cost effectiveness. And that's why there's going to be a real push from some people to adopt what you might call enrichment policies.

And let me show you what I mean by enrichment policy. We had published about this time last year that you could introduce a series of filters when you're essentially sitting in the clinic of the physician to increase the hit rate of ALK-positive screening in the patient you had in front of you. So you could screen everybody who had advanced non-small cell lung cancer, NSCLC in this slide. But if you only screen those with adenocarcinoma, a specific type of lung cancer down the microscope, you would catch most of the ALK-positive people, so your hit rate would go up. If you only took the people with adenocarcinoma who were never smokers, again you'd be screening a smaller population, but most of the ALK populations would be concentrated in that group, and again your hit rate would go up. And the most extreme filter was if they had lung cancer, adenocarcinoma, never smokers, and were negative on two other molecular tests, which tended to be different diseases.

And you can see if you look at the second in column, and the fourth in column, that as you go down each column the savings of enrichment are two-fold. First of all, you end up screening absolutely fewer people. So if you just screened adenocarcinoma, never smokers, who are EGFR and KRAS negative, you only end up screening 2% of the lung cancer population. And the second screening, the second saving, is that when you screen those people, your hit rate in that group is much higher. So there's a real push to say what about identifying these factors that can enrich people who are positive for the marker you're interested in? The analogy you can sometimes use is there's a certain number of fish, if you excuse the expression of the word "fish" in two contexts here, a certain number of fish in a pond, and what you do is you scoop out a whole bunch of water and throw it away, and now when you drop your line in the water your chances of actually catching a fish go up because most of them are left behind.

However, there is a cost associated with this enrichment policy, and if I go back to my fishing analogy, sometimes when you scoop that water out and throw it away, some fishes are lost in that group as well because each of these enrichment steps is not perfect. Although they may capture most of the people who are ALK-positive, they will miss some. And if you look in the two right-hand columns here in this worked example, there are 16 lung cancer cases out of initial 1000. If you only screened adenocarcinomas, you'd capture 14 of them, but you'd miss two of them. If you only screened adenocarcinoma, never-smokers, you'd miss half of the ALK-positive cases. So these are the costs of enrichment, is actually these non-screened cases, these true missed positives. And we don't really have a way of calculating that, but it's something we have to think about.

Therefore when we're talking about who to screen, we have to recognize that the push for enrichment strategies only screening some members of the lung cancer population may be an economic necessity when we're thinking about screening for rare diseases that are down in the kind of 1% to 5% frequency. But we also have to recognize that any enrichment leaves people behind. Now that may seem like a kind of terrible Sophie's Choice to make here, but there are alternative ways, and one way is simply to reduce the cost of the screening test per person, so it's not $1000 per person per test. But if it was $100 or $50, you could screen a lot more people cost effectively. Or the other way to do it is you're not just screening for one abnormality for $1000, but you're screening for 50 different abnormalities. You could screen for EGFR, and KRAS, and BRAF, and many other molecular abnormalities at the same time, and those kind of multiplex

assays, which will bring down the cost of testing because your hit rate will go up because you will have a 30% hit rate, but it'll be for 10 different abnormalities. That will come in the future.

All right. Let's move on to the more traditional things that physicians talk about, and new drugs.

So what happens when crizotinib stops working? Well there are other ALK inhibitors out there. Crizotinib is the only licensed one, and as you heard it's only licensed in the U.S., and it's the only one that's licensed specifically for ALK. But another drug, pemetrexed, it's also called Alimta, which is an intravenous chemotherapy, actually has very increased activity in ALK-positive lung cancer, and it's actually been a licensed treatment in general since about 2004. And then two other classes of drugs are starting to be explored within clinical trials. Something called heat shock protein-90 inhibitors, HSP-90 inhibitors, are starting to show evidence of increased activity in ALK-positive lung cancer. And then beyond crizotinib, many other ALK inhibitors are starting to be developed.

Well, I'll deal with pemetrexed first. Well what do we know about it? Well it's very much an evolving data set, but we do know that ALK-positive patients who have been treated with Alimta compared to sort of average ALK-negative patients have a much longer time before their cancer starts to grow, and that's called progression-free survival, and a much higher response rate than these other groups. In a recent series, the response rate was 40% as opposed to 14%.

But you have to put your hand up and say these are all relatively small series. The only reassuring thing is that the first series, which we published early in the year from Colorado, was fairly convincingly replicated by a completely independent group coming out of South Korea. So the fact that two completely independent groups in two different parts of the world are seeing a very similar thing does make you feel like it may be a genuine phenomenon.

The other thing to take out from this message is I don't think anyone is saying that Alimta only works in ALK-positive cancer, simply that the people who are super-responders to this drug tend to be more concentrated amongst the ALK-positive group.

And I can show that if I just take one figure from the first of these papers. So this is like the waterfall plot that Ben showed, only now we're not looking at the response of the cancer, we're looking at the time it takes for the cancer to grow, and that's the progression-free survival measured in months on the horizontal axis. Again, each of those lines is an individual patient treated with Alimta, either Alimta on its own, or Alimta combined with some other drugs in a combination therapy.

We split that into four groups. The first group was EGFR-mutant lung cancer, and the second was KRAS lung cancer, the third was ALK-positive lung cancer, and the third was a group that we called triple-negative for all of those three markers. And I think you can see a couple of things here. Firstly, that in the ALK-positive group there are more people with longer bars, so more people tend to do better, but it's not everybody. There are some people who don't do that well on Alimta. The other thing that's clear is that there are some people with very long bars in some of the other groups as well, particularly in the KRAS-mutant group. So some people just being ALK-positive isn't the only group who's benefitting. But the ALK-positive group tends to concentrate these people who are doing very well on Alimta.

The other thing to take in from this figure is that all of the people in this study had, even if they were ALK-positive, had not seen crizotinib. They were crizotinib-naive.

So what is the significance of this pemetrexed, or Alimta, which is its trade name, significance? Well, three things stand out. Firstly, if you're doing very well on pemetrexed, and nobody has tested your tumor, I would at least think about being tested for whether the tumor is ALK-positive. But as you've seen, that is not a guarantee. You could, for example, have one of these other molecular abnormalities.

The second thing is if you're ALK-positive and you're on crizotinib, and it stops working, and you've never seen Pemetrexed, then to at least think about getting onto Pemetrexed has another line of defense. Now every one of those studies had actually gone the other way around. They had had Pemetrexed and then gone to crizotinib. We have very limited data on the other way around, and we don't fully know whether being resistant to crizotinib is going to affect your outcomes with Pemetrexed. What I can tell you is at least of the two patients I've treated in that scenario, both of them have responded.

Finally, if you are in a country where you know that you're ALK-positive, but you don't have access to crizotinib, then at least knowing that Pemetrexed is a drug that you might have significant activity with means that maybe it's where you'd want to go.

All right. Now let's talk about some of the newer drugs, so some of the new ALK inhibitors that are in development. Well there's a long list, and it's always out of date as people develop new drugs, and as they move through from just being in the laboratory into clinical trials. What I can tell you is although some of these clinical trials have started, there is not yet any information available on how they're doing that's available within the public domain, and we'll just have to wait and see with regard to that.

But you may ask yourself if crizotinib is looking so good, and Ben's slides show that it's really very efficacious and pretty well tolerated, why do we need any new ALK inhibitors? Well you can raise a couple of reasons. Firstly, even though crizotinib seems pretty well tolerated, no drug is completely clean. You heard that crizotinib has activity against Met and possibly some other molecules in the human body, and maybe a slightly cleaner ALK inhibitor or at least one that hits ALK and some other things, they have a different, and for some people, more preferable side effect profile. Crizotinib is a tablet that's pretty easy to take, but it is given twice a day, and maybe some of these new drugs might only be given once a day. These seem relatively small reasons, and I think most people are interested in new ALK inhibitors because of their potential to work when the crizotinib stops working.

And when crizotinib stops working it really stops working in one of two ways because people's cancers either grow within the brain and that raises the possibility, I'll show you, that maybe the crizotinib isn't penetrating into the brain very well, and maybe some of these newer drugs will – a greater percentage will get into the brain. Or even if the same percentage gets in, if the drug is more potent it will still be able to have activity. Or because when people's cancers originally shrink in their body and then start to grow despite the crizotinib still being there, the actual biology of the cancer may have changed, and maybe some of these new drugs may have activity in that new biology when the crizotinib is no longer working, and that's called acquired resistance.

So let's take a look at some of those. I'd like to look at the brain as an example. So this is a case from Beth Israel Hospital in Boston, treated by Daniel Costa. He's an excellent physician there. A young man who had excellent control of his disease with the crizotinib, but started to develop some deposits in the brain, and then the MRI scan, you can see on the right-hand side, these are the little white deposits in the brain that are shown with very small black arrows. What they did in the young man was they were able to take a blood sample and a sample of the fluid around the

brain, what's called the cerebrospinal fluid, or CSF, about 5 hours after he took the standard crizotinib. And what they showed is that compared to the levels in the blood, less than 0.3% was getting into the brain, raising the possibility that these levels were actually just too low to work on the ALK-positive cancer cells within the brain.

Now that sounds a little worrying, but we've got to take a few words of warning here. Firstly, this is only a single patient and we're all different. Secondly, the so-called barrier between the blood and the brain can vary both between individuals and depending on what's happened in an individual. So if you've had a radiotherapy or a very heavy burden of disease in the brain, maybe the barrier's not as intact and maybe more will get through. But it does raise the possibility that if the brain might be an Achilles' heel when it comes to crizotinib, we should at least think about scanning people's brains before they start and certainly keeping an eye on it when they're on the therapy.

Let's talk about change in the underlying biology. So this is a different scenario. This is where your cancer initially responded and then started to grow despite the crizotinib still being there. And this is one of my patients, and if you look at the top left-hand panel, this is their initial PET scan. And all those big white blobs are heavy deposits of the ALK-positive cancer in the liver and around the kidneys, shown by the blue arrows. In July 2009, she went on the crizotinib, and you can see over the next two panels on the top level, everything disappeared. She had a complete response. Then about 9 months later, no we're in the bottom left-hand panel, at about April 2010, suddenly with close surveillance, a little dot appears and that was a PET-positive dot in her right adrenal gland. And we biopsied and showed that it was cancer, and that was logged as progression in the graph that Ben showed with people taking about 10 months to progress, she would be one of those cases.

But what we decided because all of the rest of her disease, all the heavy stuff in the scan above her was still very much under control, we were allowed to treat that one deposit and keep the crizotinib going. We treat it with something called SBRT, stereotactic body radiation therapy, which has trade names like Gamma-Knife, and Cyber-Knife. And so we zapped that, kept the crizotinib going, and then a few months went by and another little dot turned up. We did exactly the same thing, zapped it and kept the crizotinib going, and we repeated that several times, extending the overall duration of disease control to nearly double that from when the cancer first started to progress.

But apart from the fact that you can use radiotherapy to zap these little lesions, what I really want you to take home is that even in that last panel, in the bottom right-hand side, compare that to the top left-hand side, most of her disease is still really well under control. All of the cancer hadn't got stopped, just some of it.

And we're starting to realize how the cancer got stopped, and one way is that the ALK molecule develops an additional mutation, which means that the crizotinib is not as active in those cancer cells anymore. Several different crizotinib-resistant mutations have been described, and most of the ones can be generated in the laboratory, and they're not all the same. Some of them are more resistant to the drug than others. Indeed, some of them can even coexist together. One of the first cases, two were described in the same patient. And in the deep end they also coexist with something called second drivers, so these are completely separate molecules, separate from ALK, which are also stepping up to the plate to drive the cancer cell. And the only one that's actually been described in a patient is not surprisingly something we heard about in other lung cancers, something called EGFR, epidermal growth factor receptor, signaling – this one not because it has a mutation, it just seems to be driving harder.

So cancers can squirm out of control from the drug, the crizotinib in different ways. They can alter the target for the drug, get extra mutations in the ALK, or they can bring up a friend who would have helped them drive the cancer cells despite the crizotinib still being there. But what we still don't know is how frequently does each mechanism occur, and are we talking about 50% get mutations, or 10%, or 5%? How often do the second drivers occur, and what are the different second drivers? It's still very much a work in progress.

But let me talk about another class of drugs which may have activity in this resistance, I think, and that's the HSP-90 inhibitors. What's a heat shock protein? Well essentially it's a car seat for these abnormal proteins. So in my picture, the giraffe is the EML4-ALK fusion protein. It's a little fragile, it's a little vulnerable because it's an unusual protein that doesn't exist in nature, and in order to get it to mature properly you've got to protect it. And a heat shock protein is called a chaperone, and it wraps around these proteins and keeps them safe.

If you come in with a heat shock protein-90 inhibitor, the 90 is a particular molecule, it does the equivalent of throwing the giraffe out of the car seat, and it's an unhappy molecule and it doesn't hang around as much. These drugs are only available in clinical trials. I've given the names of a couple there, STA-9090, and IPI-504, and they're mostly intravenous. But in the lab, they seem to disrupt these fusion proteins whether there's a resistance mutation there or not because they just disrupt the whole molecule. And that offers a lot of promise as a potential way of treating crizotinib-resistant disease, but there is both promise and some concern over that when we see the clinical data.

And two groups, and I'm going to show you data from one group here, have published some studies of these HSP-90 inhibitors in patients. The first thing to note is another waterfall plot is time of response of the tumor. If you look at the far right-hand side, the red bar's going down – that's ALK-positive patients all responding to the drug. Great. That's exactly what we want it to do. But the key thing is all of those ALK-positive patients, just like in my Alimta study, are crizotinib-naïve. What's a little more sobering is the patients who had failed crizotinib and then went onto the study are unfortunately the two yellow bars where the axis is on the left-hand side, and they're not responding to the drug.

Now that's different from what we're seeing in the lab where people who have resistance mutations are responding to HSP-90 inhibitor, at least their cells are. But these patients on the left-hand side, I don't know that they have an ALK mutation. They've just stopped responding to the crizotinib. They may have one of these second drivers, and if that second driver doesn't care whether HSP-90 is there or not, then maybe it won't respond. And it brings up the idea that if molecularly profiling your patient to say you're ALK-positive in the first place is important, potentially molecularly profiling you when the crizotinib stops working to figure out your mechanism resistance and direct you to the right drug may be equally important.

So I think I'm now on the summary slides. This is regard to where do we go beyond crizotinib. Well crizotinib and pemetrexed are both licensed therapies with activity in ALK-positive lung cancer. Crizotinib is specific to ALK; pemetrexed just seems to be having an increased activity in ALK. It's unclear whether resistance to one will affect resistance to the other, and I think that's a work in progress.

In terms of crizotinib developing acquired resistance, partly it sits through the drug penetrating into the brain, and partly through changes in the biology of the cancer. ALK mutations and other

second drivers are now starting to be described, although we still don't know the frequency with which each occurs.

The next generation of ALK inhibitors and drugs called HSP-90 inhibitors may have activity against some of the resistance mutations that are being described, but it's unclear if these drugs will penetrate into the brain. And it's unclear how much these drugs will have resistance through means other than these ALK mutations and the frequency with which these different mechanisms will occur. And at least in theory, when there's two drivers you may require drugs in combination, or a much broader approach such as chemotherapy.

I wanted to end with just a couple of pictures. So we talked a lot about people, and it's sometimes nice just to put faces to names. And these are many of the people who are involved in the development of crizotinib. And on the far left, this somebody who you'd never see a picture of. This is Keith Wilner from Pfizer. And he was really the sort of gentle genius of this who helped to shepherd it along and really get a drug from the very earlier studies all the way through to licensing, and he was a fantastic guy to work with.

Next in, you can see Dr. Solomon, then Dr. Ignatius Ou, who is our colleague from University of California. Irvine, who'd shown you the PET scan earlier, myself, and finally on the right-hand side is Dr. Alice Shaw from Massachusetts General Hospital, who's just been fantastic to work with, and has really helped to lead a lot of developments in this field with a very large group of ALK-positive patients at Massachusetts General.

I think my last slide is to explain where my title "Adventures in the Screening Trade" comes from. It's about a book from "Adventures in the Screen Trade" by William Goldman, who is the screenwriter for "Butch Cassidy and the Sundance Kid." And since Ben and I have done a little double act here, I've shown that picture and I'll be happy to have pictures at this point. You can decide which one of us is Butch and who is Sundance.

Dr. West:
Thanks very much. We'll end this program here, with our next and last podcast in this series covering the question and answer session from this activity with Drs. Solomon and Camidge.

Thanks again to LUNGevity Foundation for their co-sponsorship with GRACE to make this activity possible.

ALK Inhibition: From Biology to Approved Therapy for Advanced Non-Small Cell Lung Cancer, Part 2

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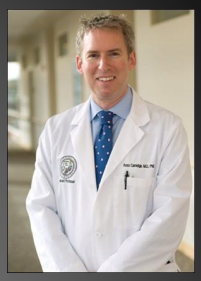
ALK Inhibition (Part 2)
Adventures in the screening trade
…and life beyond crizotinib



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Disclosures

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- **Research Funding:**
  - **2010: Eli-Lilly (Translational)**

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Techniques for detecting ALK gene rearrangements:

Technique	Fusion partner specific	Reference
DNA: break apart FISH probe	NO	Kwak et al, NEJM 2010
DNA: dual fusion FISH probes	YES	Varella-Garcia et al, ASCO 2010
RNA: RT-PCR	YES	Kwak et al, NEJM 2010; Danenberg et al, ASCO 2010
Protein: IHC	NO	Kwak et al, NEJM 2010

Currently FISH is only technique used as entry criterion for crizotinib trials and only FDA approved test = gold standard

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Who to screen?

- Drug only given to proven ALK+ patients
- To catch everyone potentially treatable = screen everyone

- But odds of a positive vary depending on several factors
- Increasingly, the cost-effectiveness of screening is being discussed

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Cost-effectiveness depends on perspective

- If a patient is paying for the screening – give them the odds and the cost of the test and let them decide?
  - *A 'bet' of $1000 with individually calculable odds for a win (positive screen result), and a known prize (access to drug)*
- BUT if insurance/government/etc (society) is paying – the calculation is different.
- All the costs from those who are negative on screening get added to the overall cost of each positive patient that eventually gets treated


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'Cost-effectiveness' - example

- If test is only positive in 1% of those screened and the screening test costs $1000/person
- From societal perspective -
  it costs $100,000 to find each positive person
  ($1000 for the one positive plus the cost of 99 negatives)
- If the drug costs even $10,000/month, at these prices, when frequency is low in screened population (e.g. 5% or less), the screening costs actually dominate over the cost of the drug in the overall cost-effectiveness calculation!

  = push for enrichment policies


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The 'savings' of enrichment: fewer screens, higher hit rate

Screening Criteria	Predicted proportion of ALK positives	Literature comparators	Percentage of total initial population screened	Predicted number of ALK+ cases found per 1000 Initial NSCLC cases	Predicted number of ALK+ cases missed per 1000 Initial NSCLC cases
Advanced NSCLC	1.6%[1,2]	2.6%[8]	100%	16	0
Advanced stage adenocarcinoma	3.7%[2,3]	3.8%[2]	39%	14	2
Advanced stage adenocarcinoma /Never smokers	13.7%[2,4]	13%[9], 9.9%[10]	5.80%	8	8
Advanced stage adenocarcinoma /Never smokers /EGFR and KRAS wildtype	35.9%[5,6,7]	33%[9], 48%[11]	2.00%	7	9

1: Solomon et al, 2009; 2: Weickhardt and Camidge, 2011; 3 Owonikoko et al, 2007; 4: Ramalingham et al, 2011; 5: Girard et al, 2011; 6: Reily et al, 2008; 7: Kris et al, 2011; 8: Doebele et al, submitted; 9: Shaw et al, 2009; 10: Yi et al, 2011; 11: Camidge et al, 2010

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Atherley and Camidge, Submitted

The 'cost' of enrichment: 'non-screened' missed positives

Screening Criteria	Predicted proportion of ALK positives	Literature comparators	Percentage of total initial population screened	Predicted number of ALK+ cases found per 1000 Initial NSCLC cases	Predicted number of ALK+ cases missed per 1000 Initial NSCLC cases
Advanced NSCLC	1.6%[1,2]	2.6%[8]	100%	16	0
Advanced stage adenocarcinoma	3.7%[2,3]	3.8%[2]	39%	14	2
Advanced stage adenocarcinoma /Never smokers	13.7%[2,4]	13%[9], 9.9%[10]	5.80%	8	8
Advanced stage adenocarcinoma /Never smokers /EGFR and KRAS wildtype	35.9%[5,6,7]	33%[9], 48%[11]	2.00%	7	9

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Atherley and Camidge, Submitted

Who to screen, summary

- Enrichment strategies may be an economic necessity in screening for rare diseases
- But enrichment leaves people behind

- Alternatively, the cost of screening per person has to be dramatically reduced from approx. $1000/person/test
- Or screens have to be multiplexed

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Other ALK "Inhibitors" in lung cancer beyond crizotinib

- Pemetrexed (Alimta) –Increased activity in ALK+ NSCLC: FDA licensed in NSCLC August 19th 2004
- HSP90 inhibitors – Increased activity in ALK+ NSCLC
- Newer specific ALK inhibitors

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Pemetrexed (Alimta)

- ALK patients on alimta (compared to 'average ALK negative' patients) have:
  - Longer time before cancer grows
  - Higher response rate
- All small series, but replicated in different centers
- ALK negative cancesr can also have good responses to pemetrexed – it just seems super-responders are more concentrated among the ALK+ group

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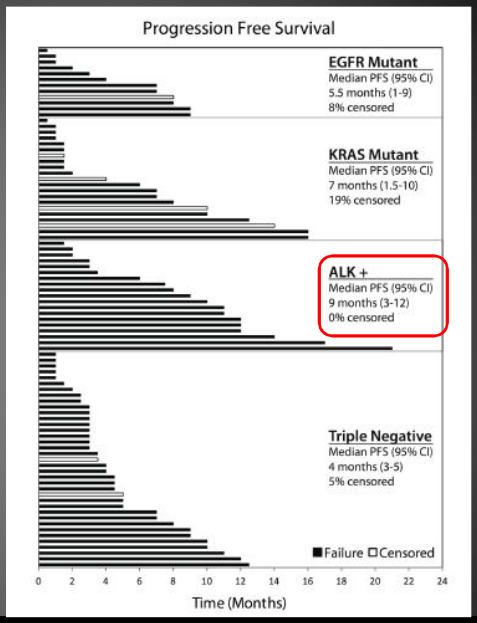
Camidge et al, JTO 2011
Lee et al, JTO 2011

Pemetrexed (Alimta)

NB Mixed mono and combination therapy

All patients were crizotinib naive



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Camidge et al, JTO 2011

Possible pemetrexed significance

- If doing very well on pemetrexed consider being ALK tested
- If ALK+ and crizotinib stops working consider going onto pemetrexed (Note everyone was crizotinib naïve in studies to date)
- If known to be ALK+, but no access to crizotinib consider trying pemetrexed

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New ALK inhibitors in development

Table 4. Anaplastic lymphoma kinase inhibitors currently in development.

Drug	Company	Phase of testing	Status	Clinicaltrials.gov ID
Crizotinib (PF-023341066)	Pfizer	Phase II/III	Open	NCT00585195, NCT00932893, NCT01154140 and NCT00932451
ASP-3026	Astellas	Phase I	Open	NCT01284192
XL228	Elexis	Phase I	Completed	NCT00526838
LDK378	Novartis	Phase I	Open	NCT01283516
AP-26113	Ariad	Preclinical		
CH5424802	Chugai	Preclinical		
CEP-37440	Cephalon	Preclinical		

Data taken from [101].

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Weickhardt and Camidge, Clin Invest 2011

Why do we need new ALK inhibitors?

- Different side-effect profile
- More convenient regimen

Patients eventually progress on crizotinib:

- Brain penetration of new drugs +/- higher potency
- Action against biological changes in tumor causing acquired resistance

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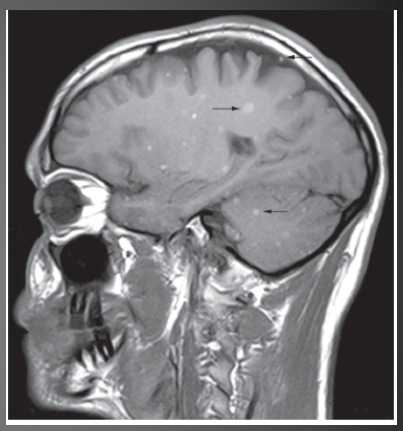
Progression within brain

•29 y/o male with ALK+ NSCLC
•Systemic (body) control but brain progression

•Blood and cerebrospinal fluid (CSF) sampling 5 hours after taking 250mg crizotinib

<0.3% gets into brain)
?too low to work on ALK



•Caveats: One patient, blood brain 'barrierness' may vary
•**However, baseline brain scan and some kind of routine brain surveillance on crizotinib may need to be considered**

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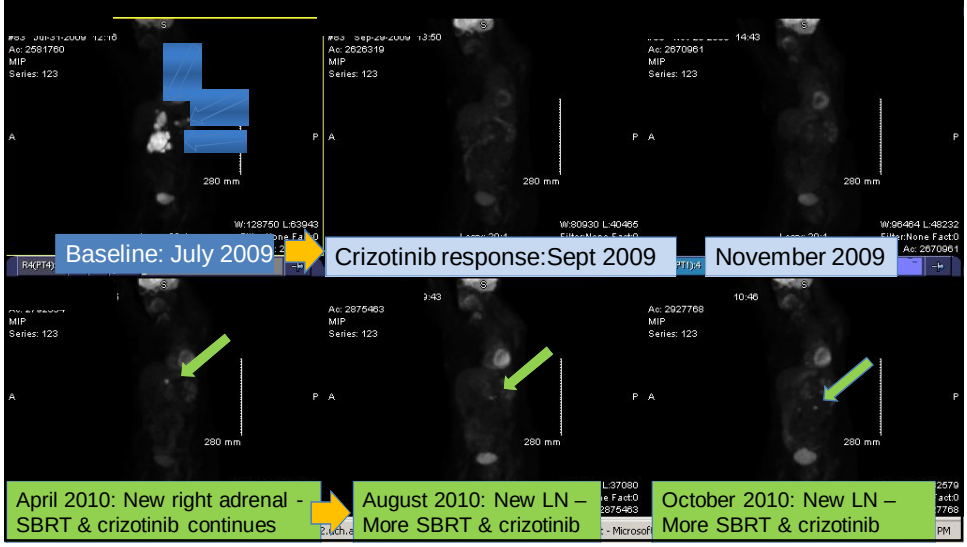
Costa et al, JCO 2011

Natural selection of resistant clones while most disease still controlled by crizotinib



Crizotinib resistance mutations in ALK

- Selected out while on therapy – make ALK more resistant to crizotinib
- Multiple different ones - some are more resistant than others
- Different mutations may co-exist together and with ‘second drivers’ in molecules other than ALK (e.g. increased EGFR signaling)
- How often each mechanism occurs still unknown

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Choi et al, NEJM 2010; Sasaki et al, CCR 2010; Sasaki et al, Cancer Research 2011

HSP90: A car-seat for fusion proteins

HSP90 inhibitor *(upsets giraffe from car-seat)*

Several drugs all only in trials e.g.STA9090 or IPI-504. (most usually given IV)

In lab- seem to work on ALK fusions regardless of whether Crizotinib resistance mutation present or not

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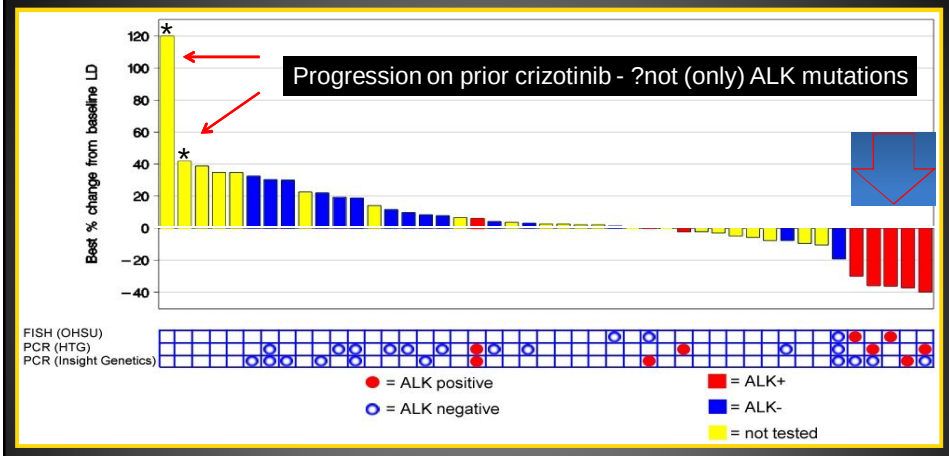
Sasaki et al, CCR 2010;
Katayama et al, PNAS 2011

ALK Rearrangement and HSP90 Inhibitors (STA 9090)



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Wong et al, ASCO 2011

Sequist et al, JCO 2011

Anti-ALK therapy in NSCLC summary 1

- Crizotinib and pemetrexed are licensed therapies with activity in ALK+ NSCLC: unclear whether mechanisms of resistance will overlap or not
- Crizotinib acquired resistance partly through probable drug penetration issues (brain) and partly through ALK mutations and possible second drivers (e.g. EGFR) – frequency of each is unknown

Anti-ALK therapy in NSCLC summary 2

- 2nd generation ALK inhibitors and HSP90 inhibitors may have activity against (some) resistance mutations
- Brain penetration unclear for each drug
- Activity when resistance through other means unknown and frequency of different resistance mechanisms is unknown
- Second driver scenarios will likely require drug combinations or broader approaches like chemo

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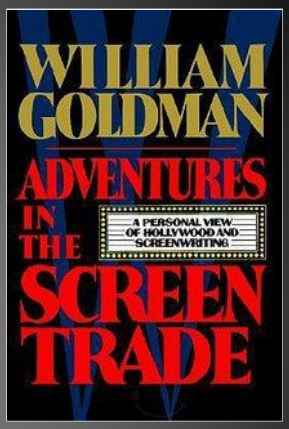
Left to right: Keith Wilner (Pfizer), Ben Solomon (Peter Mac), Ignatius Ou (UC Irvine), Ross Camidge (U Colorado), Alice Shaw (MGH)

ALK double act



Questions?

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