



**Question and Answer Session**  
**with Drs. Ben Solomon and Ross Camidge on ALK Inhibition,**  
**from Biology to FDA-Approved NSCLC Therapy**  
with Dr. H. Jack West

**Dr. West:**

Hi, this is Jack West, Seattle-based medical oncologist and Founder and CEO of GRACE, the Global Resource for Advancing Cancer Education. Our recent live webinar in the series by GRACE in partnership with the LUNGeivity Foundation featured Drs. Ben Solomon, from the Peter MacCallum Cancer Centre in Melbourne, Australia, and Dr. Ross Camidge, from the University of Colorado in Denver. They covered a wide range of topics, covered in separate presentations podcasts, on the biology of EML4-ALK rearrangements, early clinical experience with the ALK inhibitor XALKORI (which also known its scientific name of crizotinib), which patients are most appropriate to screen for EML4-ALK, and some alternative treatment possibilities for ALK-positive patients that look promising, either if they are unable to receive XALKORI or if they experience progression on it.

Here is the question and answer session that followed their presentations, with both faculty members participating.

Somebody had asked about ground glass findings on a CT scan in someone with what otherwise appears to be a stable disease. Do you ever see infiltrates in this as a potential side effect like interstitial lung disease, and in EGFR inhibitor therapy, or do you think this is unrelated to the treatment itself?

**Dr. Solomon:**

So I might start, Jack. So pneumonitis has been described as a very uncommon side effect of crizotinib. I've not seen it in patients treated with crizotinib on its own; I've seen it in a clinical trial where crizotinib was given in combination with another drug and it was a little bit uncertain which was responsible. But certainly in the Phase I study, there's been probably less than a handful of reports of pneumonitis, these infiltrates as a result of crizotinib. The message would be if a patient is developing shortness of breath that seems out of context with other things, it's something that should be looked for and it's important to look for other causes such as atypical infections, but it's certainly on the list of possible side effects.

**Dr. West:**

Another question -- so the implication would be we've seen some data that there's almost complete mutual exclusivity between the EGFR mutation and an ALK rearrangement. If you knew someone has an EGFR mutation or for that matter a KRAS mutation, how much or how little will that dissuade you from screening? I'll start with Ross, and then the question of if you had somebody who had responded well for months on an EGFR inhibitor, even if they hadn't been tested, would that dampen your enthusiasm for testing?

**Dr. Camidge:**

It's an excellent question. I think it's slightly different from EGFR and KRAS. First of all, the data about them being almost mutually exclusive was based on very small series, and I think as we see larger series we can see that occasional overlaps do occur, but they are rare. I think if

somebody had an EGFR mutation, I would be tempted to put them on an EGFR inhibitor upfront. If they had a KRAS mutation, given that they aren't necessarily very good treatments for KRAS, I would think fairly hard about testing them for ALK. And I have to come clean here, that we don't sort of carry back who we test one or other for; we do a sort of multiplex assay, and if you walk through the door in Colorado you're going to get EGFR, and KRAS, and ALK, and a whole bunch of other stuff done rather than just doing one, waiting for it to be negative, and then the other, and then the other.

**Dr. West:**

Another question about crizotinib serving as a Met inhibitor: do you have any insights about its promise in that setting? Or a profile of the type of patients who have Met over-expression for whom crizotinib could be a very relevant treatment? Is this another group of patients who are predominantly squamous, or non-squamous, and with little or no smoking history, are there any demographic characteristics that go with Met over-expression? What proportion of the patients are we talking about there?

**Dr. Solomon:**

So I guess a challenge for us has been to work out what really makes a tumor dependent on Met, and we sort of initially started off thinking that mutations in Met, which have been described somewhere between 2% and 5% of lung cancers, would be the things that made tumors dependent and we put patients on crizotinib and they'd respond. But it turned out really hard to find mutations in Met, at least in our experience. And since then, some data's emerged that really questions whether some of the previously described mutations are really biologically important. But what we have found and what, again, Ignatius Ou, from California, has published is that there are uncommon lung cancers that have Met amplification and have high levels of Met amplification, and those tumors can potentially be reliant on Met and can respond to crizotinib. And we've also seen that in tumors from other sites such as the esophagus or the stomach that have Met amplification and that they can respond to crizotinib. Ross, did you want to sort of expand on that?

**Dr. Camidge:**

Clearly there are people who do respond. Even with Met gene amplification, it's a continuous variable. It's not positive or negative; you can have two copies, five copies, ten copies, and we're still trying to figure out where the relevant cut-point is. Because we're still figuring that bit out, it's harder to answer Jack's other question as to what exactly are the characteristics of someone who has a Met-driven cancer because we don't know what a Met-driven cancer looks like yet.

**Dr. West:**

So another question that comes up, very appropriate, is we don't at this point have evidence that overall survival is significantly improved in a Phase III setting, although the retrospective data certainly suggests that. Do you have any sense of if you know someone has an ALK rearrangement, what is the optimal time to start them on crizotinib? Is it first-line, or because the studies have largely been in the second-line and later setting that this would be reserved for after that setting?

**Dr. Camidge:**

So we do know within the Phase I study that there were a small number of patients who were naive to all other treatments and went on – our true first-line patients, and their response rate was certainly as good as everybody else's. In fact, it was slightly higher, but that may just be a fluke of the very small numbers involved. We know by analogy from the EGFR-mutant population that people tend to do better and preserve their quality of life when they get on the right drug as soon as possible. Is it a disaster if you find out you're ALK-positive after you've had your first line of

chemotherapy and go on crizotinib second-line? No. So I think in the future as people know this, they will be tempted to go on the more specific targeted drug, which tend to be better tolerated as soon as they know that, but that's a work in progress.

**Dr. West:**

Okay. Great. And thanks to Dr. Solomon who has to slip off and get to clinic. But thank you for taking the time today.

**Dr. Solomon:**

Yeah. Absolutely. So Ross, you brought up the case of a few patients who have really occult brain disease that develops in the central nervous system while on crizotinib. Have you taken to and would you recommend surveillance screening with a head MRI in asymptomatic patients who are on crizotinib, or potentially an EGFR inhibitor for a prolonged period of time?

**Dr. Camidge:**

Yes, and my practice is changing. I can tell you what I do and I have no idea if it's right or not, but I can only tell you it's what I do. Somebody I know has brain metastases, then I have fairly regular surveillance of the brain. At the same time I do body scans, or occasionally alternating with the body scans. In somebody who doesn't have deposits in the brain, or they just had a scan at some point in the past and then it was clear, if I then find that they have a specific malignant abnormality and they go on one of those drugs that you've described, either crizotinib or erlotinib, what I've now started to do is to do at least a once a year annual MRI of the brain just to keep an eye on it, and not wait for people to present with symptoms. So I have started to change my practice because I am worried that this is an area that is not necessarily well treated by some of these drugs, and I also tend to feel that if we wait until someone presents with symptoms from damage to their brain, that's not always going to be reversible.

**Dr. West:**

Yeah. Absolutely. This is a very relevant question that someone has asked about. We have seen, and I'm sure you have patients who have responded to a re-challenge to an EGFR inhibitor after developing acquired resistance. Has it been seen before with crizotinib? Have there been patients who have developed resistance, been treated with another approach, and then gone back onto crizotinib and then shown a response?

**Dr. Camidge:**

The short answer is that data set doesn't exist for the very simple reason that the only access that the crizotinib was in a clinical trial, and if you came off the clinical trial but you stopped the drug, then you couldn't get back on because you'd been treated with crizotinib. However, now that crizotinib is licensed, I think we will be able to generate that data set. If I had to guess, I think absolutely. There will be a re-challenge phenomenon, and what I mean by that is you respond to crizotinib, you stop responding, then you are taken off the drug and you do other stuff. Other stuff that's not specifically directed against ALK, which may be some kind of chemotherapy, radiotherapy, or a break from treatment, and then you go back onto an ALK inhibitor. And I think the cancer will have unlearned some of the mechanisms of being ALK-resistant, and you'll get a partial response. So I think it will happen, but the data set is yet to be generated.

**Dr. West:**

Thank you. We know in the EGFR setting that patients who have an EGFR mutation have a remarkable response very often, if not always, but that there can still be a benefit for the patients who don't have an EGFR-driven cancer. They don't have an activating EGFR mutation. Can you speak to what we know or what is in development for studying crizotinib in a broader population?

**Dr. Camidge:**

That's a very good question. It touches on a number of different things. One is what is the true benefit of an EGFR-TKI and an EGFR overall population. But let's just touch on some of the issues related to the crizotinib. So first is crizotinib doesn't just work in ALK-positive lung cancer. We've already seen the example of Met-driven lung cancer that responds to crizotinib, so an ALK-negative – unless you've looked at Met it may be one explanation for those who do well.

The second thing is no test is perfect, and the way of saying somebody is positive for ALK is using this so-called FISH test, which counts the proportion of cells which show a particular abnormality. And there are people who are pretty close to the borderline, and you could imagine that there are some people who are just missed positives because the person doing the counting counts a few too many cells, few of them, than they should have done. And therefore, they will probably respond to crizotinib because they're a false negative.

Now that's a slightly different scenario from saying this is a genuine benefit of the drug in a group of people who are sort of wild types in their abnormality. And I think EGFR is a very different thing because EGFR expression is actually very common in lung cancer, whereas ALK expression is fantastically rare apart from those tumors which are ALK-driven.

**Dr. West:**

Great. Well thank you very much for taking the time today. Another great presentation. I was very happy to have a tandem presentation, especially one that covers about 12, 14 time zones and is truly international, especially with your origin. So thanks. Thanks so much for this.

I hope and I fully expect that we'll be able to have you back every couple of years telling about the next exciting breakthrough with the new drug, and targeting a new population. But I also think as you and I have had some conversations, this leads to new challenges in how to reach targets and do clinical trials on smaller and smaller populations, who hopefully will become engaged as they have a very big potential gain from it. But anyway, thank you so much for today, and also for your great work on the subject that got us here.

**Dr. Camidge:**

My pleasure. Thanks very much, Jack.

**Dr. West:**

That's the end of our program. Thanks again to the LUNGeVity Foundation for their ongoing partnership with GRACE, making this series of webinars possible.

I hope this activity has been helpful.