

ALK Inhibition: From Biology to FDA-Approved Cancer Therapy, Part 1

By Dr. Ben Solomon

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. Together, we're partnering with the LUNGeVity Foundation to bring you a program featuring two leading lung cancer experts. This is also a truly international effort, allowing us to live up to the "Global" in our name, because the first speaker will be Dr. Ben Solomon, who's a medical oncologist and lung cancer expert at the Peter MacCallum Cancer Centre in Melbourne, Australia, to be followed by Dr. Ross Camidge, who hails from the U.K. originally, and he is a medical oncologist and the Director of the Thoracic Oncology Program at the University of Colorado in Denver.

Now, both of them have been part of the whole evolving story of ALK inhibition, really from the earliest reports of it as a potentially relevant target in lung cancer, followed by its early testing, and then very recently its FDA approval and commercial availability. This agent and pathway has in many ways been unique in development for lung cancer in that it is for a very targeted population, and that has raised a whole range of new issues and challenges. So this has been a very interesting story, and the rest I'll leave to our guest faculty to tell. With that, I'll turn it over to Dr. Ben Solomon.

Dr. Solomon:

Thanks, Jack. It's a real pleasure to chat with you and Ross, and with the other folks out there. And it's a very civilized time of the day, nine o'clock in Melbourne, so looking forward to starting.

So just firstly my disclosures, which are these

I thought we'd start off firstly by talking a little bit about the biology of ALK in lung cancer -- the full name is anaplastic lymphoma kinase. It belongs to an important family of proteins called tyrosine kinases, and these tyrosine kinases are important molecular switches in normal cells where they turn on and off to regulate various important processes in cells. But these kinases can also become abnormally activated in cancers. If you like, the switch becomes locked in an "On" position and causes cancers to grow and proliferate.

And now ALK, or anaplastic lymphoma kinase, gets its name because it was originally identified in an uncommon lymphoma called anaplastic large cell lymphoma, and it was found that in this tumor is a particular gene rearrangement called the translocation, which results in a fusion of ALK with another protein called NPM, which results in its abnormal activation. And since then, ALK has been identified as being activated in a number of other tumors, mostly uncommon tumors such as diffuse large B-cell lymphomas, a tumor type called an inflammatory myofibroblastic tumor, and in some childhood neuroblastomas. But its role in a common tumor, in a non-small cell lung cancer was not identified until just four years ago, 2007, when another ALK fusion called EML4-ALK was identified, which seems to be present in about 3% to 5% of lung cancers.

It turns out that in the case of lung cancer, ALK gene rearrangements usually arise due to fusion, which forms as a result of a rearrangement which occurs on chromosome 2. Now the way this occurs is that a part of chromosome 2 flips on itself in a process called an inversion, and that results in the formation of a new protein, which contains ALK partnered with or bound to another protein, or part of another protein called EML4, and now ALK isn't normally even expressed in the lung, but in the context of this fusion you get abnormal expression of ALK.

And not just expression, you get activation of ALK and you get initiation of these various downstream signaling pathways, which cause cells to grow and proliferate, and really cause really what we call a driver in terms of making a cell a cancer. And because of this it's a logical target to treat cancers, and it turns out that in the lab, if you block ALK cells in mouse models, you cause tumors to regress.

So the other point to make still on the biology is EML4 is the usual partner with ALK. Very occasionally you can get other genes that are involved, which occur much less commonly. And different variants that we've identified, which have different portions of the EML4 gene involved, but it's really not clear whether these different variants behave differently in tumors. And they certainly all seem to be sensitive to ALK inhibition.

So if we move, then, to the effects of crizotinib with ALK gene rearrangements, crizotinib is a small molecule, it's a tablet which is designed to inhibit tyrosine kinases, and it turns out that it was actually designed to inhibit a tyrosine kinase called Met or c-MET, but it happens also to have activity against ALK.

There was a phase I study which was started, I think, late in 2006, that Ross and I were involved with, which involved three continents and eight different centers, so really a multinational effort. And the study involved what we call a traditional Phase I portion where we try to work out what the right dose of the drug to use is, and from this part of the study we worked out that the right dose seemed to be 250 milligrams, given twice daily.

But a really exciting bit of this study is it didn't stop there; it had a second part, which was designed right from the beginning to look at the activity of this drug in a cohort of patients who had the presence of the target that the drug was directed at. So initially we thought this would be patients with Met activation, but in 2007 after the study had begun, the ALK gene rearrangements were identified. And in the course of the dose escalation we had two patients with ALK gene rearrangements that had great responses, so a lot of the effort in the second part of the study was directed towards identifying patients with ALK gene rearrangements. And it turned out that almost all the patients were patients who had tumors with ALK rearranged lung cancers. So the way we identify these patients was with a test called the FISH, or Fluorescence In Situ Hybridization, and Ross will talk in the second part of this presentation about the different ways to identify ALK gene rearrangements in tumors. But in this particular study we used this test called FISH, where you can see these red and green dots on the slide. Those identify cells which have rearranged ALK genes. And we used this test to identify patients for the study, and we calculated that for the first 82 patients on the study we needed to screen over 1500 patients to identify the first 82 patients for the study.

Ross recently updated results from this study at ASCO earlier this year, and these are the characteristics of the first 119 patients now that we put on the study. They tended to be younger, have a younger age than the typical patient with non-small cell lung cancer, so the median age of patients that were enrolled in this study was 51, whereas the median age of

patients with non-small cell lung cancer in general was around 70. But importantly, there was a pretty wide age range ranging from 21 to 79, so certainly age shouldn't limit screening for ALK.

And similarly, patients tended to be never smokers, but we did identify patients who had smoked in the past. And tumors tended to be of adenocarcinoma histology. And importantly, a lot of the patients that had entered on this study had a number of different lines of prior treatment, many patients having even more than four lines of prior treatment.

So what were the results of the study? Well this plot is a plot that we call a waterfall plot, and what it shows is really that the majority of patients treated on the study had shrinkage of their tumors. So each of the bars on this plot represents an individual patient, and what the bar shows is the maximal change in size of tumor on the study, and the numbers on the Y axis are the percentage change, and anything below the horizontal axis indicates a shrinkage. So as you can see, the majority of the patients did have some degree of shrinkage, and in many patients this was – there was considerable shrinkage and there are criteria to determine what we call the response rate, which is more than a 30% shrinkage of tumors. And the response rate in this study was 61%.

It turns out that the responses were pretty rapid. This is a PET scan from the patient of one of our colleagues -- Ignatius Ou in California -- and this is a PET scan done after two weeks of treatment, which shows almost completely disappearance of uptake of FDG in the tumors. And suddenly it's what patients tell us -- you start on a patient on crizotinib, and you see them a week or so later and they tell you that within days they feel their symptoms improving. And this is very characteristic of two other ALK gene-dependent tumors such as tumors with EGFR mutations where patients treated with EGFR inhibitors like erlotinib described very similar effects.

And when you look at the time that the disease is controlled by the drug, the data for this is still maturing, but it seems that the median progression-free survival is 10 months. So what this means is that tumors can eventually become resistant to treatment with crizotinib, but the median time that crizotinib maintains disease control seems to be in the order of 10 months; however, this data is still maturing.

A second study, a phase II study called Profile 1005 has been conducted following the phase I study, which shows very similar results in terms of response rate, as you can see, from the waterfall plot. And very similar response rate and duration of disease control.

On the basis of these two studies, the FDA approved crizotinib, which is now known as XALKORI, for the treatment of patients with advanced lung cancer with ALK gene rearrangements.

From a global perspective, I think it's important to know that this approval is still only within the U.S. and that the regulatory authorities outside the U.S. have yet to approve crizotinib. I think, though, it really for us was very exciting. Well it was exciting from a number of perspectives -- it was exciting to find a new treatment that seemed to be very effective in this subset of patients, but it was also exciting to see how quickly things were able to move forward from identification of the gene in 2007 to approval in less than four years later in 2011. And this really happened with the happy coincidence that a drug which happened to inhibit ALK in clinical trials in 2006.

It is important to point out that there are some ongoing studies, which will really define the base for crizotinib in lung cancer treatment. There are two phase III trials; the trial on the top of this

slide, Profile 1007, which compares crizotinib to standard second-line chemotherapy, which will usually be pemetrexed. And this study will hopefully complete accrual at the end of the year; and there's another study, the Profile 1014 study, which is a first-line study. And these studies will define the place of crizotinib in lung cancer treatment -- so they're important studies.

We are getting some data about how crizotinib impacts on lung cancer symptoms and quality of life. It's important to point out that patients with ALK gene rearrangements have very similar symptoms to other patients with lung cancer. They have very similar incidence of symptoms such as pain, cough, shortness of breath, or fatigue. And some of the data that's emerging from the phase II study and the Profile 1005 study is that crizotinib seems to improve global quality of life.

This graph shows an improvement in quality of life from baseline seen at the second cycle, and seems to be maintained through treatment. And the probably the reason it does this is that it improves symptoms such as cough, shortness of breath, and pain. So this is nice data to show that not only does it cause responses in tumors, but it improves symptoms and quality of life. The other thing which we're really getting now quite a good picture of is what the typical side effects associated with crizotinib treatment are.

There are a number of side effects which seem to occur commonly, and these are shown in this graph from both the phase I study and the phase II study. Visual symptoms tend to be very common, and I'll talk about those in some detail in the next slide. But there are some other symptoms such as nausea and vomiting which occur frequently, but interestingly tends to be relatively mild for most patients, but is really significantly impacted by whether you take the pill on an empty stomach or just after you've eaten. If you take the pill after you've eaten, it seems to reduce the amount of nausea that you get. Some patients get loose bowel motions, diarrhea, edema is another common side effect, which refers to swelling, particularly of the ankles. It tends to be mild, and seems to be a class effect of MET inhibitors, so probably not related to the ALK inhibition.

If we talk a little bit more about the visual side effects, the visual side effects tend to occur in association with a dark to light transition, so they tend to be seen first thing in the morning when a patient wakes up and opens their eyes. These tend to last from a few seconds to a few minutes. And we've tried to get a bit of a handle through a questionnaire that we've asked patients and the visual side effects tend to come in three main groups, and the first is shimmering, flashing, or trailing lights, and I've got a great picture from a patient of Ross's, which illustrates this. The second is streamers, or strings, or floating lights, usually at the peripheries of images. And the third is overlapping shadows or afterimages. And interestingly we don't fully understand why this occurs, and they're not associated with abnormal findings on eye exams.

So this image is from a patient of Ross's, which really very nicely shows these trails of light which occur in the peripheries of vision, and is seen under conditions of low light. And the next image is from a patient of mine which shows the effect that this patient experiences when he's looking at the lamp and then shifts his gaze to the left. He sees overlapping shadows and particularly enhancement of the edge of the lamp with the lines that he's shown afterwards.

But importantly when we ask patients whether these visual disturbances seem to affect their ability to do the things they need to do, it doesn't seem to be the case, and it seems to be something that is mild and interestingly seems to get less prominent as treatment goes on.

And so at this point, I'll thank Ross for this slide. So this week is the equivalent of our Super Bowl, the Australian Rules Football Grand Final, so I'll take this opportunity to hand ball onto Ross to continue the presentation.

Dr. West:

Thanks very much. That'll end this podcast, but we'll next turn to Dr. Ross Camidge for the second part of the program, as he addresses some of the new questions that have now emerged around ALK testing, including the feasibility and who to test.

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



Global
Resource for
Advancing
Cancer
Education



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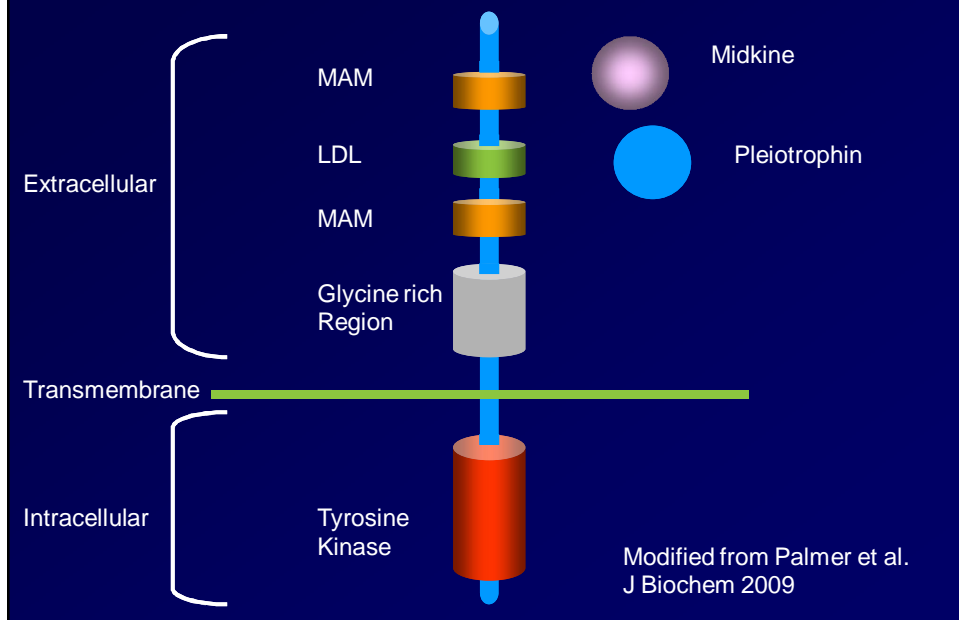


Disclosures

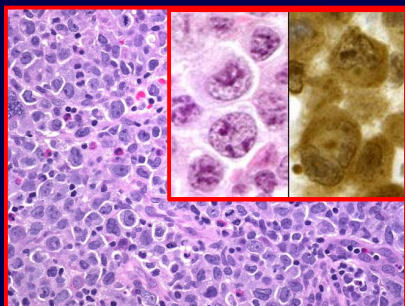
- Ben Solomon has consulted for and received research funding from Pfizer

ALK gene rearrangements in NSCLC

Human Anaplastic Lymphoma Kinase (ALK)

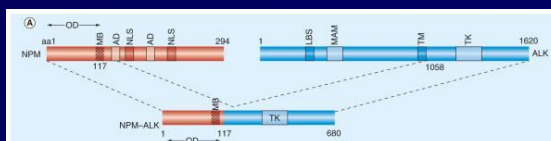


Anaplastic Lymphoma Kinase



t(2;5) NPM-ALK

Anaplastic
Large Cell
Lymphoma



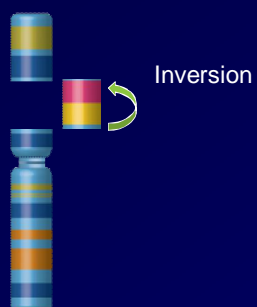
ALK alterations in Cancer

Tumour Type	ALK alteration	Frequency
Anaplastic Large Cell Lymphoma	ALK fusion	60-80%
Diffuse Large B cell Lymphoma	ALK fusion	Rare
Inflammatory Myofibroblastic tumour	ALK Fusion	50-60%
Neuroblastoma	Point Mutation and/or amplification	6-8%, 4%
Non-Small Cell Lung Cancer	ALK Fusion (usually EML4-ALK)	3-5%

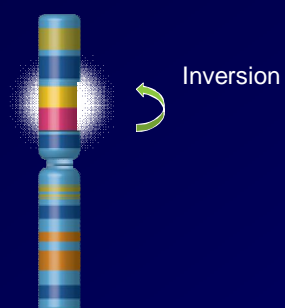
ALK Gene Rearrangements



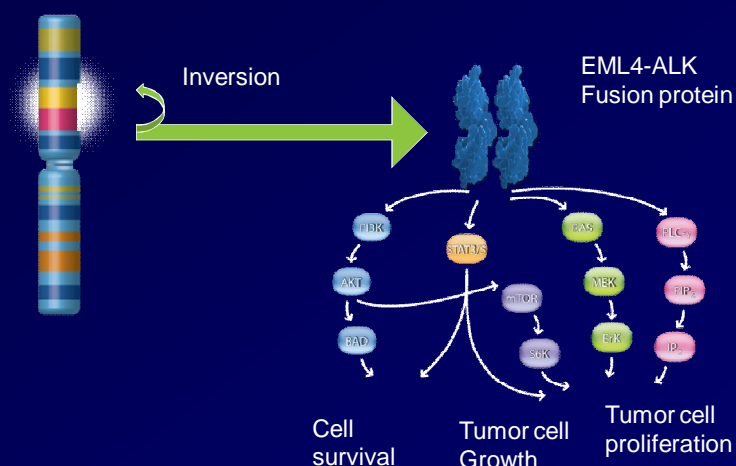
ALK Gene Rearrangements



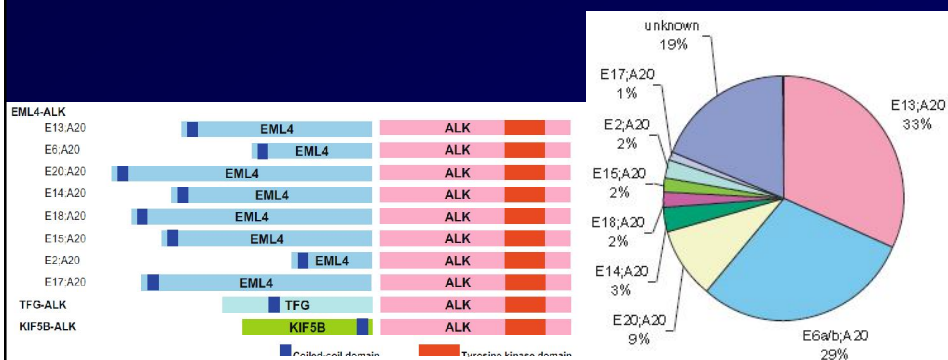
ALK Gene Rearrangements



ALK Gene Rearrangements



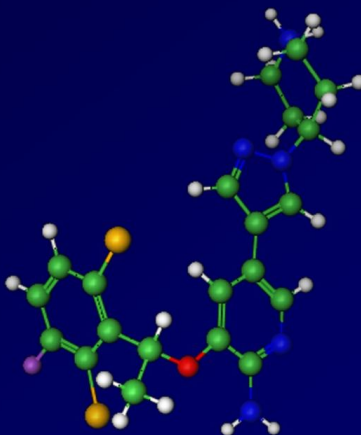
ALK Gene rearrangements in NSCLC: Variants



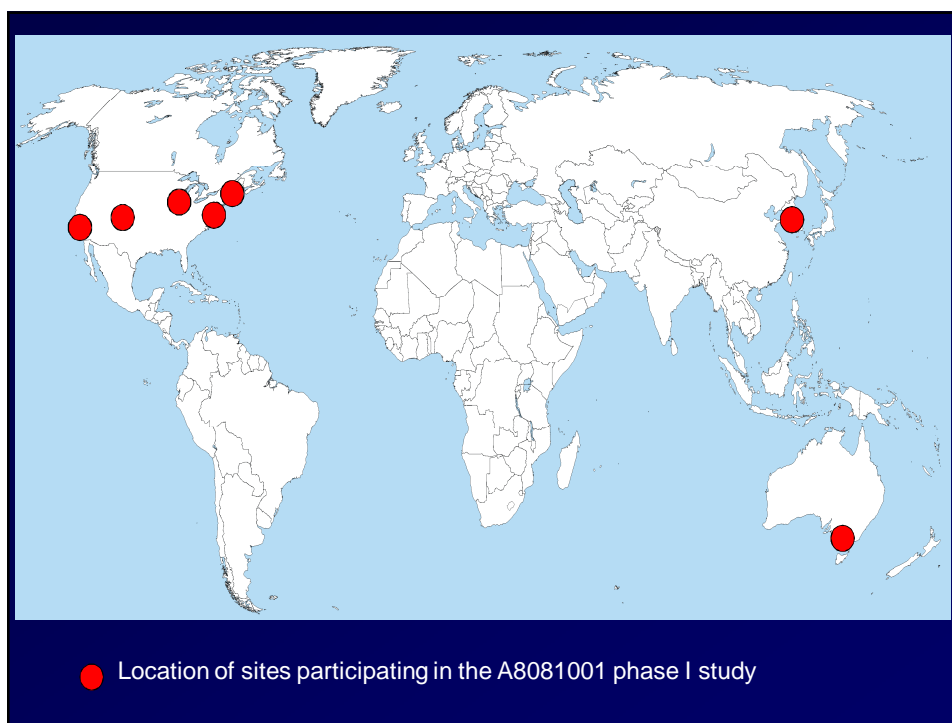
Sasaki et. al., 2010

Efficacy of Crizotinib in NSCLC with ALK gene rearrangements

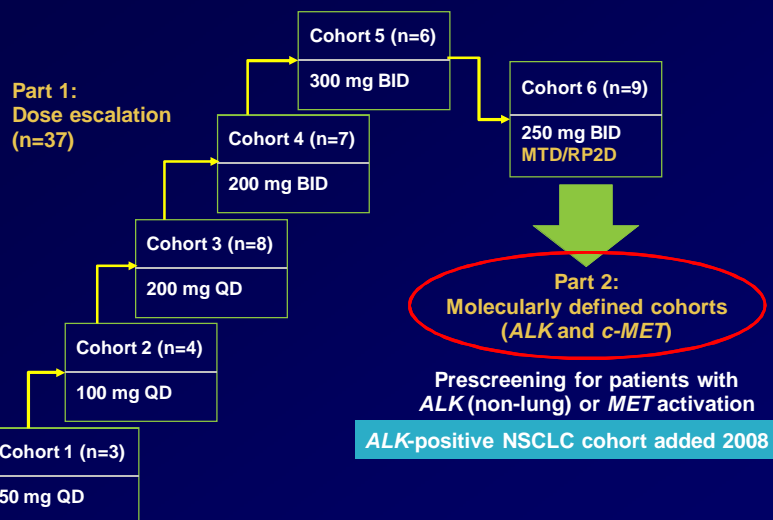
Crizotinib (Xalkori, PF02341066) First-in-human ALK inhibitor



Oral inhibitor of ALK and MET tyrosine kinases



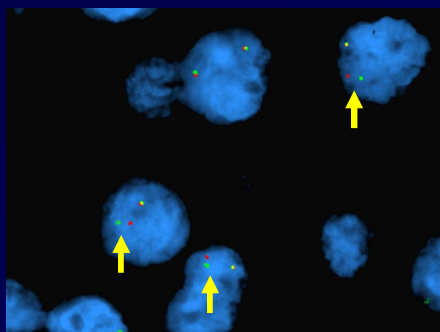
Crizotinib: First-in-Human/Patient Trial



BID, twice daily; QD, once daily; MTD, maximum tolerated dose; RP2D, randomized phase 2 dose

Modified from Tan et al. J Clin Oncol 2010;28:15S abstract 2596

Screening for ALK Gene Rearrangements for the phase I clinical Trial

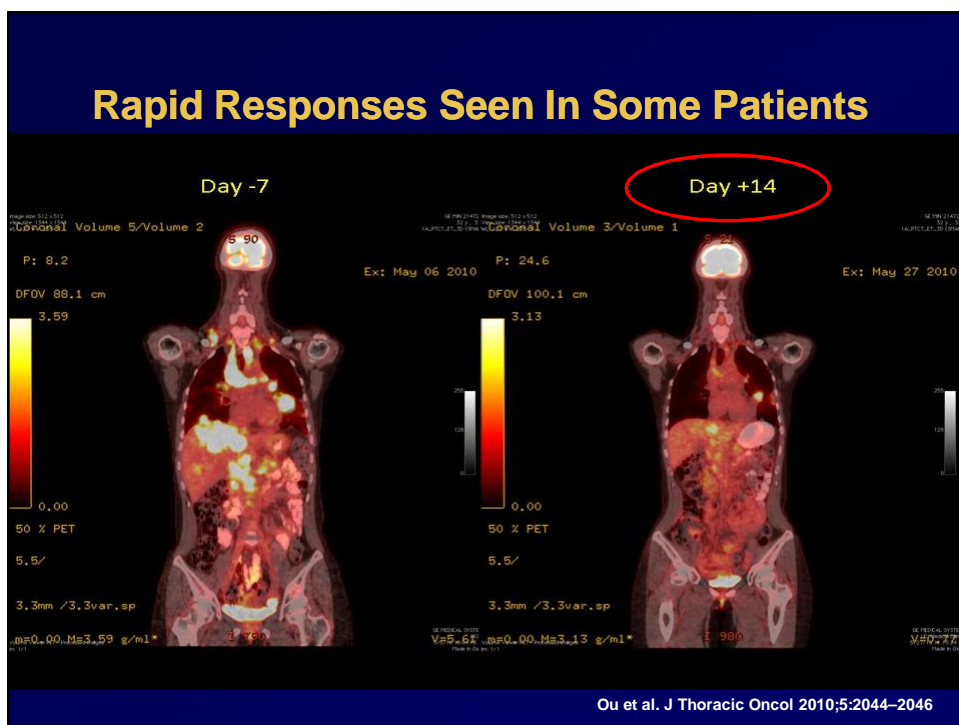
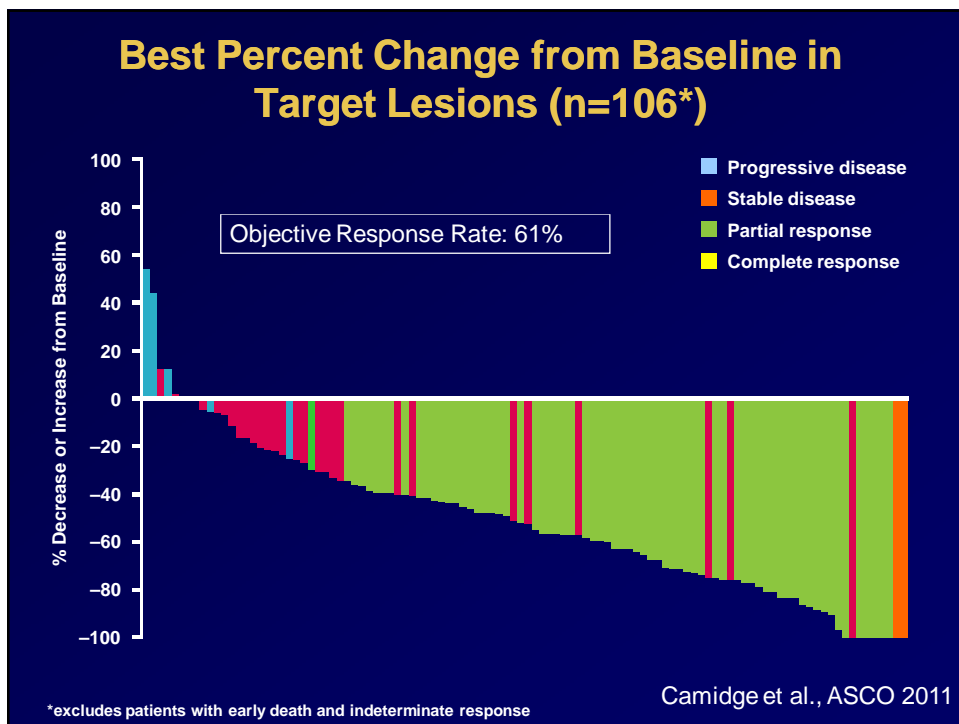


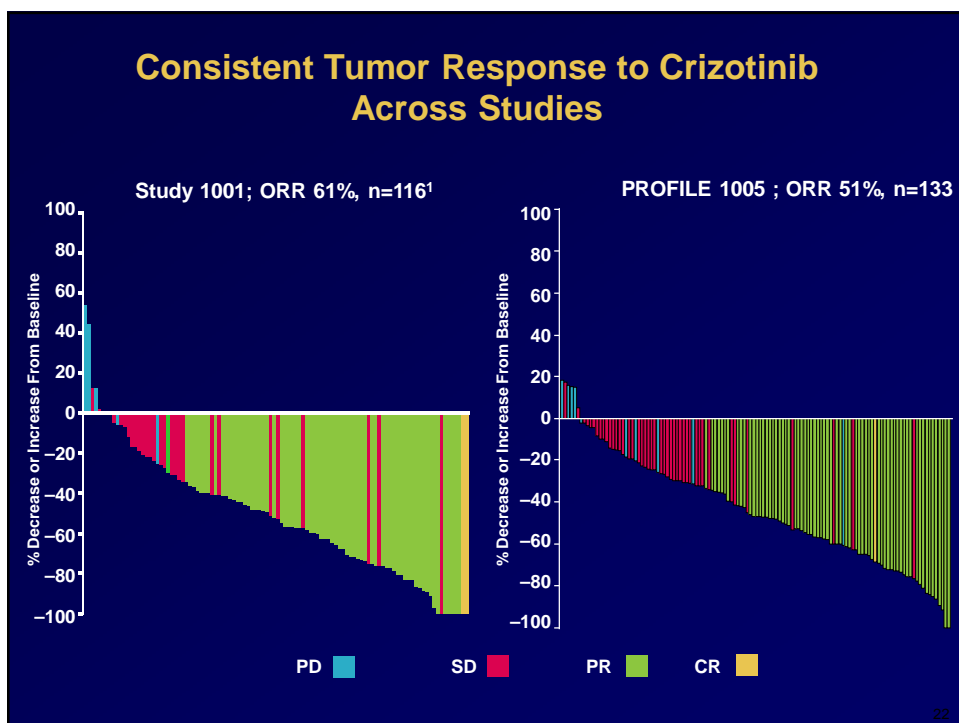
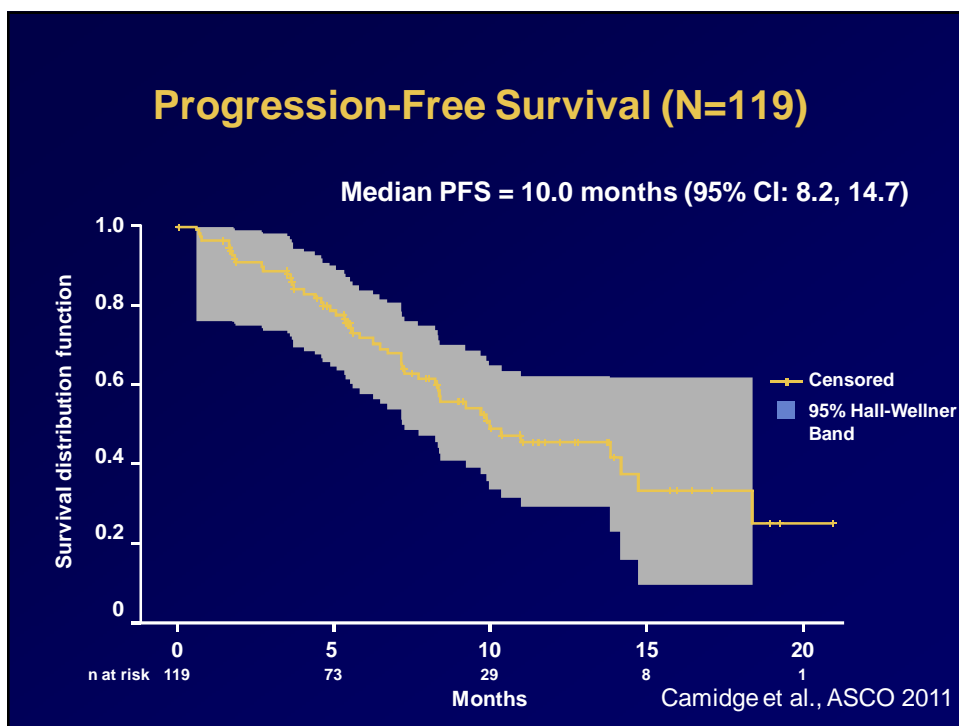
ALK FISH
(Companion Diagnostic)

Over **1500** patients screened to find the first 82 patients for the clinical trial

Baseline Characteristics (N=119)

Characteristics		N=119
Age, yrs	Median	51
	Range	21–79
Gender, n (%)	Male / Female	59 (50) / 60 (50)
Race, n (%)	White	74 (62)
	Asian	34 (29)
	Other	11 (9)
Smoking status, n (%)	Never smoker	86 (72)
	Former/current smoker	32 (27) / 1 (1)
Histology, n (%)	Adenocarcinoma	116 (97)
	Other	3 (3)
ECOG PS, n (%)	0	41 (34)
	1	63 (53)
	≥2	15 (13)
Prior systemic regimens, n (%)	0	16 (13)
(advanced/metastatic disease)	1	36 (30)
	2	24 (20)
	3	17 (14)
	≥4	26 (22)





Robust and Durable Efficacy

	Study 1001 ¹ N=116	Study 1005 ² N=133
Best overall response		
Complete response	2	1
Partial response	69	67
Stable disease	31	45
Progressive disease	6	10
Other [†]	8	10
Objective response (CR+PR) rate	61% (95% CI: 52%, 70%)	51% (95% CI: 42%, 60%)
Duration of response	48 weeks (median)	7-42 weeks (range)
Duration of treatment, median	32 weeks	22 weeks
Median PFS	10.0 months (95% CI: 8.2, 14.7)	Not mature

Study 1001 - Independent Radiology Review ORR (n=105) 52% (95% CI: 42%, 62%), as assessed by RECIST version 1.0

Study 1005 from 60-day clinical data update - Independent Radiology Review ORR (n=105) 41.9% (95% CI: 32.3%, 51.9%), as assessed by RECIST version 1.1

[†]Including "indeterminate" and "early death"

1. Camidge R et al. Presented at 2011 ASCO; Abstract 2501

2. Riely GJ et al. Presented at WCLC on July 6, 2011; Abstract 1618

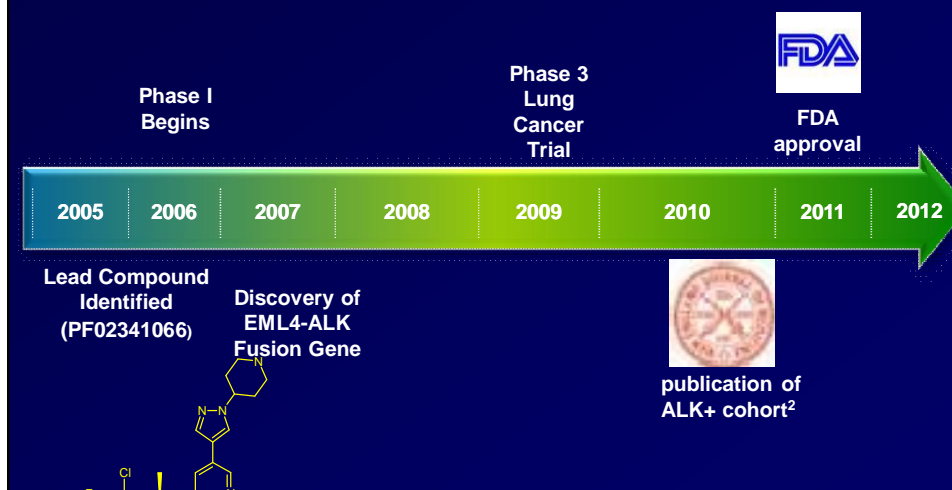
23

US FDA approval – August 2011

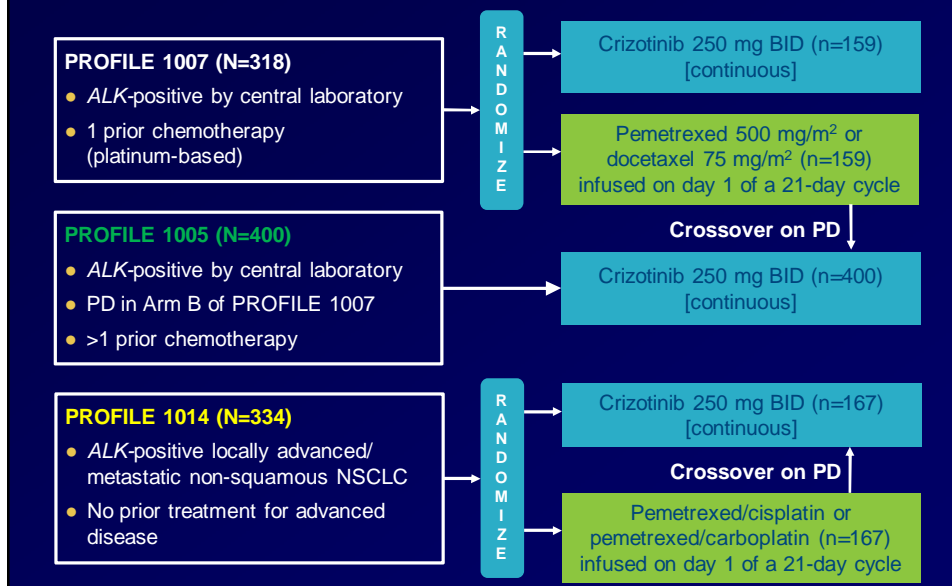


XALKORI is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

TIMELINE: Rapid development from target identification to FDA approved therapy



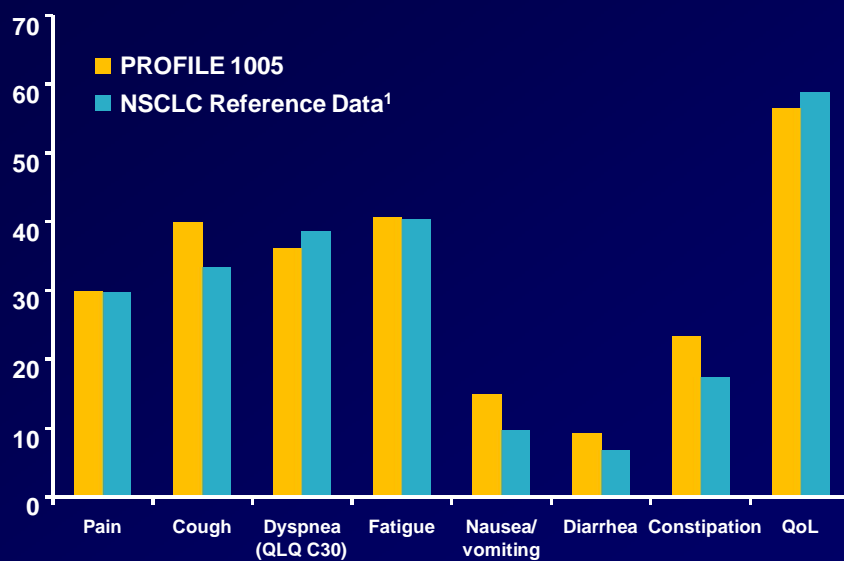
Ongoing Crizotinib PROFILE Program



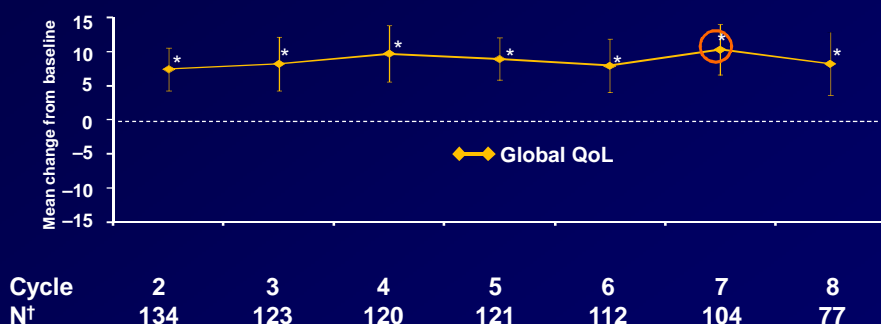
How does crizotinib impact on lung cancer symptoms and Quality of Life?

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Mean Baseline Scores of Select Items of the EORTC QLQ-C30 and QLQ LC13

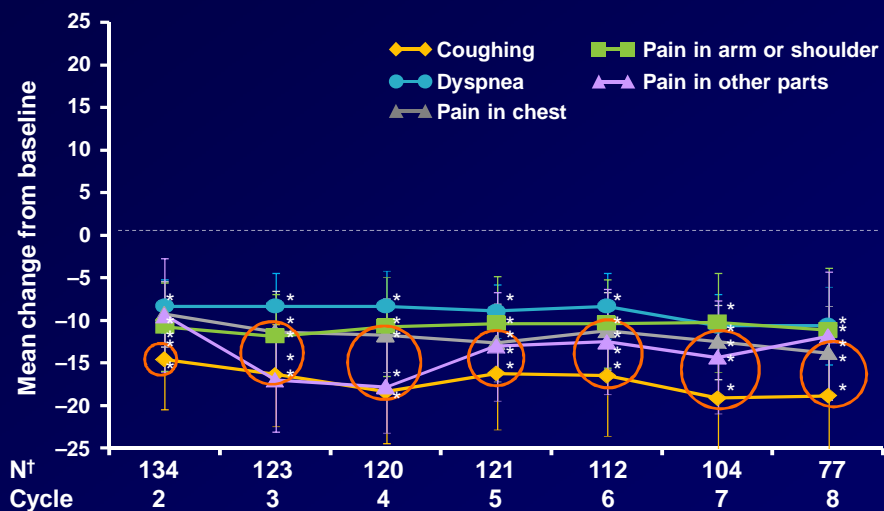


Mean Change from Baseline: Global Quality of Life QoL (QLQ-C30)



Clinically meaningful differences (≥ 10 point mean change); *Significant ≤ 0.05 (confidence interval) not adjusted for multiplicity; †N=patients completing at least 1 question at each cycle; completion rates vary by domain/symptom; † scores = improved QoL or more symptoms

Mean Change from Baseline: Select Symptom Domains (QLQ-LC13)



Clinically meaningful differences (≥ 10 point mean change); *Significant ≤ 0.05 (confidence interval) not adjusted for multiplicity; †N=patients completing at least 1 question at each cycle; completion rates vary by domain/symptom; † scores = less symptoms

What are the major side-effects seen in patients treated with crizotinib?

Most Common Treatment-Related AEs (All Grades)

Adverse event	Study 1001 ¹ N=119 n (%)	Study 1005 ² N=136 n (%)
Visual effects*	74 (62)	80 (59)
Nausea	58 (49)	78 (57)
Diarrhea	51 (43)	58 (43)
Vomiting	42 (35)	59 (43)
Edema**	33 (28)	39 (29)
Constipation	32 (27)	37 (27)
Decreased appetite	20 (17)	30 (22)
Fatigue	17 (14)	37 (27)

AE occurring in ≥20% of patients in one arm of the study

*Cluster term including visual impairment, photopsia, vision blurred, vitreous floaters and diplopia.

**Cluster term including localized edema, edema and edema peripheral.

1. Camidge R et al. Presented at 2011 ASCO; Abstract 2501
2. Riely GJ et al. Presented at WCLC on July 6, 2011; Abstract 1618

Visual Side-effects

Typically associated with dark-to-light transitions.
Last seconds to a few minutes.

1. Shimmering, flashing, or trailing lights (64-75%)
2. Streamers, strings, or floaters (50-75%)
3. Overlapping shadows or after-images (55-69%)

Not associated with abnormal findings on
ophthalmologic examinations.

Characteristic Visual Effects With Crizotinib

- 'Trails' from lights in peripheral vision in low light conditions (eg dawn and dusk)



- At edges of vision in low light conditions:
 - Image persistence
 - Flashes of light, which do not appear to be connected to a real light source
 - Flipped registration from high contrast images (e.g. stripes)

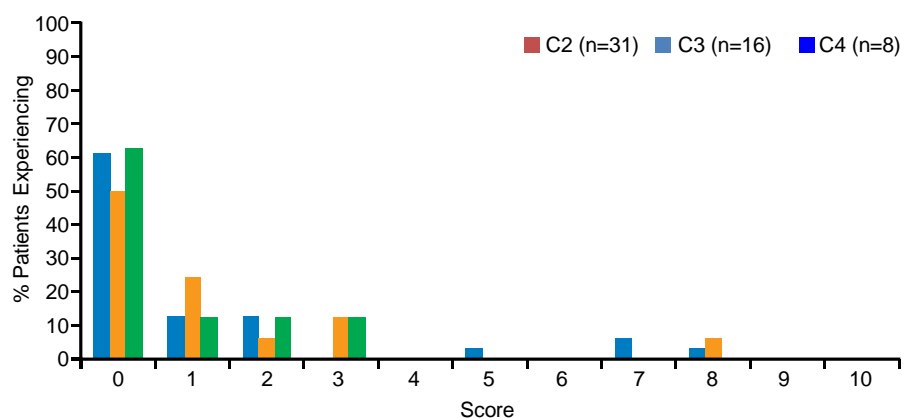
Overlapping shadows and after images



Patient illustration of effect observed when focusing first on lamp and then shifting gaze to left. A series of overlapping shadows or after images are seen particularly at the trailing edge of the lamp.

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Impact of Visual Disturbances on ADLs



During the past three weeks, how much did visual disturbances affect your ability to do your regular daily activities?

Scale of 0 to 10 with 0= No Effect and 10= Completely prevented from conducting daily activities

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