

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



Global
Resource for
Advancing
Cancer
Education



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



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Disclosures

- **Advisory Role: Ad Hoc Advisory Boards/Consultations (most recent contact last 3 years):**
 - 2011: Ariad, Chugai, Novartis, Synta
 - 2010: Pfizer
- **Research Funding:**
 - 2010: Eli-Lilly (Translational)



Lung Cancer Patients See Amazing Results In Clinical Study
Experimental Drug Could Help One In 20 Lung Cancer Patients

ONLY ON Q13 FOX: Redmond Man Claims Experimental Cancer Pill Delivered Him Miraculous Results
Redmond Man's Lung Cancer Disappears With Revolutionary Therapy

Woman 'cancer-free' after taking new lung cancer drug in Colorado
Drug in clinical trials at University of Colorado Cancer Center

Video: Lung Cancer Patients See Amazing Results In Clinical Study

Video: Cancer Pill Original story: Cancer Pill Original Story 10/19/10

Video: Clinical trials at CU Cancer Center has helped Lindsay Gomes battle

August 18, 2010

Finding ALK positive patients

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

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

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

'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

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

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

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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

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

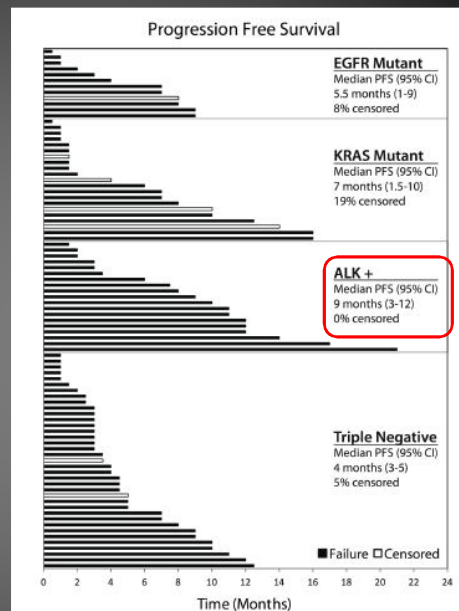
Pemetrexed (Alimta)

- 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 cancer can also have good responses to pemetrexed – it just seems super-responders are more concentrated among the ALK+ group

Pemetrexed (Alimta)

NB Mixed mono
and
combination
therapy

All patients were
crizotinib naive



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

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].

Why do we need new ALK inhibitors?

- Different side-effect profile
- More convenient regimen

Patients eventually progress on crizotinib:

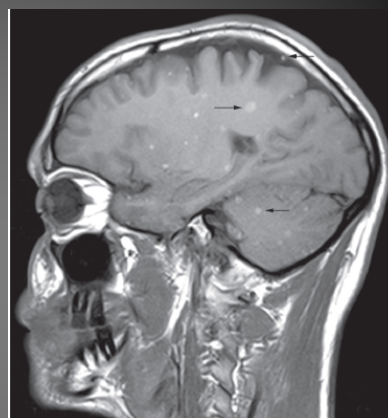
- Brain penetration of new drugs +/- higher potency
- Action against biological changes in tumor causing acquired resistance

Progression within brain

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

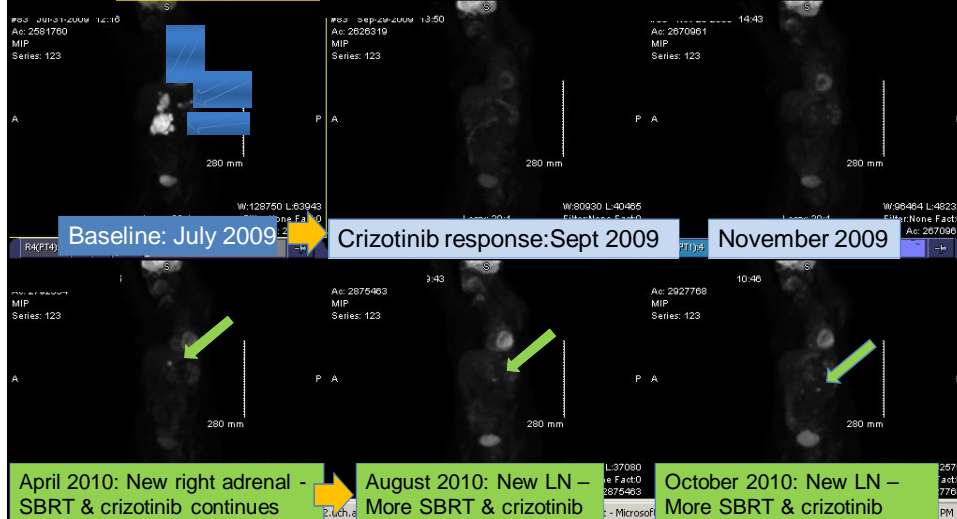
- Blood and cerebrospinal fluid (CSF) sampling 5 hours after taking 250mg crizotinib

<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

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

HSP90: A car-seat for fusion proteins

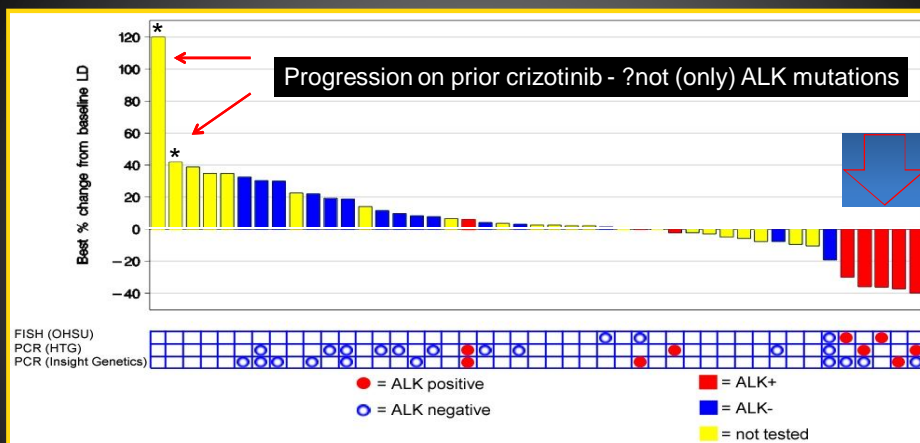


HSP90 inhibitor
(upsets giraffe from car-seat)

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**

ALK Rearrangement and HSP90 Inhibitors (STA 9090)



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

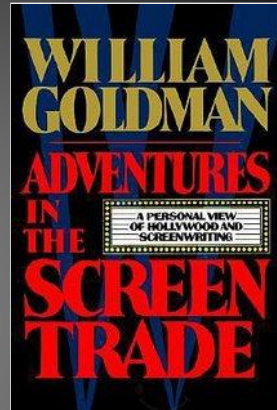


University of Colorado
Anschutz Medical Campus

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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Global
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LUNGevity
Find it. Treat it. Live.