Advances in Targeted Therapies for Lung Cancer

Alice T. Shaw, MD PhD
March 11, 2016
Overview

• Introduction to Lung Cancer
• First Generation Targeted Therapies
• Second Generation Targeted Therapies
• Evolution of Resistance
• Summary and Future Directions
Overview

- Introduction to Lung Cancer
- First Generation Targeted Therapies
- Second Generation Targeted Therapies
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Lung Cancer is the Leading Cause of Cancer Deaths Worldwide

**INCIDENCE**

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Male</th>
<th>Female</th>
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<tbody>
<tr>
<td>Lung</td>
<td>1.825</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>1.677</td>
<td></td>
</tr>
<tr>
<td>Colorectum</td>
<td>1.361</td>
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<tr>
<td>Prostate</td>
<td>1.112</td>
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<tr>
<td>Stomach</td>
<td>0.952</td>
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<tr>
<td>Liver</td>
<td>0.782</td>
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<tr>
<td>Cervix</td>
<td>0.528</td>
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<tr>
<td>Oesophagus</td>
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<tr>
<td>Bladder</td>
<td>0.430</td>
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<td>Other</td>
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**MORTALITY**

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<thead>
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<th>Cancer Type</th>
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<th>Female</th>
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<tr>
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<tr>
<td>Breast</td>
<td>0.522</td>
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<td>0.694</td>
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<tr>
<td>Prostate</td>
<td>0.307</td>
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<tr>
<td>Stomach</td>
<td>0.723</td>
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<tr>
<td>Liver</td>
<td>0.746</td>
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<tr>
<td>Cervix</td>
<td>0.266</td>
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<td>Oesophagus</td>
<td>0.400</td>
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<tr>
<td>Bladder</td>
<td>0.165</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2.789</td>
<td></td>
</tr>
</tbody>
</table>

WHO IARC, January 2014
Lung Cancer Occurs in Never Smokers

Lung Cancer Is Often Diagnosed at an Advanced Incurable Stage

Stage at Diagnosis
- Localized: 15%
- Regional: 22%
- Metastatic: 57%

5-Yr Relative Survival
- Localized: 54%
- Regional: 27%
- Metastatic: 4%

2004-2010, SEER Cancer Statistics Review
Standard Chemotherapy Provides Modest Benefit in Lung Cancer

Overall survival ~12 mos

PFS ~5 mos

Scaglitti et al., JCO 26(21): 3543-3551, 2008
Limited Benefit of Second-Line Chemotherapy

Overall survival ~8 mos

Hanna et al., JCO 22(9): 1589-1597, 2004
A New View of Lung Cancer

HISTOLOGIC SUBTYPES
- Small cell
- Large cell
- Squamous cell carcinoma
- Adenocarcinoma

MOLECULAR SUBTYPES
Molecular Classification of Lung Cancer

Oncogenic Drivers

- KRAS
- EGFR
- ALK
- PIK3CA
- HER2
- BRAF
- ROS
- MET
- AKT
- NTRK1
- MEK1
- FGFR
- Unknown
Oncogenic Drivers Confer Sensitivity to Targeted Therapies: Oncogene Addiction

ROS1+ NSCLC

Pre-Treatment

Crizotinib x 8 weeks
Impact of Matching Targets and Targeted Therapies: Improved Survival
Overview

• Introduction to Lung Cancer
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  • Second Generation Targeted Therapies
  • Evolution of Resistance
• Summary and Future Directions
Clinical Activity of an EGFR Inhibitor Leads to Discovery of Oncogenic EGFR Mutations

Typical clinical features:
- Never or light smoking history
- Female
- Asian descent
- Adenocarcinoma

Baseline

After 6 weeks of gefitinib

Lynch et al., NEJM 350: 2129-39, 2004
Mutant EGFR is Effectively Inhibited by Gefitinib and Other EGFR Inhibitors

Lynch et al., NEJM 350: 2129-39, 2004
EGFR Inhibitors are Effective in Patients Harboring Mutant EGFR But Not Wildtype EGFR

Odds ratio >1 implies greater chance of response on gefitinib

Mok et al., NEJM 361:947-57, 2009
EGFR Inhibitors are Standard First-Line Therapies for Patients with Sensitizing EGFR Mutations

<table>
<thead>
<tr>
<th>Country</th>
<th>Trial</th>
<th>Agent</th>
<th>RR (%)</th>
<th>Median PFS (mo)</th>
<th>Median OS (mo)</th>
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<tr>
<td></td>
<td></td>
<td>TKI</td>
<td>Chemo</td>
<td>TKI</td>
<td>Chemo</td>
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<tr>
<td>IPASS Mut +</td>
<td>gefitinib</td>
<td>71.2</td>
<td>47.3</td>
<td>9.5</td>
<td>6.3</td>
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<tr>
<td>First-SIGNAL Mut +</td>
<td>gefitinib</td>
<td>84.6</td>
<td>37.5</td>
<td>8.4</td>
<td>6.7</td>
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<td>WJTOG</td>
<td>gefitinib</td>
<td>62.1</td>
<td>32.2</td>
<td>9.2</td>
<td>6.3</td>
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<td>NEJ002</td>
<td>gefitinib</td>
<td>73.7</td>
<td>30.7</td>
<td>10.8</td>
<td>5.4</td>
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<td>OPTIMAL</td>
<td>erlotinib</td>
<td>83</td>
<td>36</td>
<td>13.7</td>
<td>4.6</td>
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<tr>
<td>EURTAC</td>
<td>erlotinib</td>
<td>58</td>
<td>15</td>
<td>9.7</td>
<td>5.2</td>
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<tr>
<td>LUX-Lung 3</td>
<td>afatinib</td>
<td>56.1</td>
<td>22.6</td>
<td>11.1</td>
<td>6.9</td>
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<tr>
<td>LUX-Lung 6</td>
<td>afatinib</td>
<td>66.9</td>
<td>23.0</td>
<td>11.0</td>
<td>5.6</td>
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</table>
Identification of the transforming
EML4–ALK fusion gene in non-small-cell
lung cancer

Manabu Soda¹,², Young Lim Choi¹, Munehiro Enomoto¹,², Shuji Takada¹, Yoshihiro Yamashita¹, Shunpei Ishikawa⁵,
Shin-ichiro Fujiwara¹, Hideki Watanabe¹, Kentaro Kurashina¹, Hisashi Hatanaka¹, Masashi Bando², Shoji Ohno²,
Yuichi Ishikawa⁶, Hiroyuki Aburatani⁵,⁷, Toshiro Niki³, Yasunori Sohara⁴, Yukihiro Sugiyama² & Hiroyuki Mano¹,⁷
Crizotinib Was Initially Developed to Target a Different Kinase CMET

Co-crystal structure of crizotinib (PF-02341066) bound to c-MET
Crizotinib Inhibits Multiple Kinase Targets Including ALK

<table>
<thead>
<tr>
<th>Kinase</th>
<th>$IC_{50}$ (nM) mean*</th>
<th>Selectivity ratio</th>
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<tbody>
<tr>
<td>c-MET</td>
<td>8</td>
<td>–</td>
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<tr>
<td>ALK</td>
<td>40-60</td>
<td>5-8X</td>
</tr>
<tr>
<td>ROS</td>
<td>60</td>
<td>7X</td>
</tr>
<tr>
<td>RON</td>
<td>80</td>
<td>10X</td>
</tr>
<tr>
<td>Axl</td>
<td>294</td>
<td>34X</td>
</tr>
<tr>
<td></td>
<td>322</td>
<td>37X</td>
</tr>
<tr>
<td>Tie-2</td>
<td>448</td>
<td>52X</td>
</tr>
<tr>
<td>Trk A</td>
<td>580</td>
<td>67X</td>
</tr>
<tr>
<td>Trk B</td>
<td>399</td>
<td>46X</td>
</tr>
<tr>
<td>Abl</td>
<td>1,159</td>
<td>166X</td>
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<tr>
<td>IRK</td>
<td>2,887</td>
<td>334X</td>
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<td>Lck</td>
<td>2,741</td>
<td>283X</td>
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<tr>
<td>Sky</td>
<td>$&gt;10,000$</td>
<td>$&gt;1,000X$</td>
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<tr>
<td>VEGFR2</td>
<td>$&gt;10,000$</td>
<td>$&gt;1,000X$</td>
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<tr>
<td>PDGFRβ</td>
<td>$&gt;10,000$</td>
<td>$&gt;1,000X$</td>
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</table>

Study Design of Phase 1 Trial of Crizotinib

Part 1: Dose escalation

Cohort 1 (n=3)
50 mg QD

Cohort 2 (n=4)
100 mg QD

Cohort 3 (n=8)
200 mg QD
1 DLT: grade 3 ALT elevation

Cohort 4 (n=7)
200 mg BID

Cohort 5 (n=6)
300 mg BID
2 DLTs: grade 3 fatigue

Part 2: Dose expansion
Molecularly enriched cohorts (c-MET, ALK in ALCL, IMT)

Cohort 6 (n=9)
250 mg BID
MTD/RP2D

9/2006

Kwak et al. NEJM 363:1693-1703, 2010
The Key: Finding the Right Patient

 Patients screened: 1500
ALK-positive patients: 82

ALK break-apart FISH assay
[Courtesy John Iafrate, Massachusetts General Hospital]

Kwak et al. NEJM 363:1693-1703, 2010
Clinical and Diagnostic Features of ALK-Rearranged Lung Cancer

- Smoking history
  - ≤10 pyrs
  - >10 pyrs

- Neversmokers

- No. of Patients vs. Age

- Adenocarcinoma
- ALK IHC (FDA approved)
- ALK FISH (FDA approved)
ALK Rearrangement Confers Marked Sensitivity to Crizotinib

Pre-Treatment

Crizotinib x 12 weeks
Activity of Crizotinib Established in a Molecularly Defined Subset of NSCLC

ORR = 60.8%* in 143 evaluable patients
(133 evaluable patients shown)
Median response duration = 49.1 wks
Median PFS = 9.7 mos

Camidge et al., Lancet Onc 13(10): 1011-9, 2012
Crizotinib is a Standard Therapy for Patients with Metastatic ALK+ NSCLC

<table>
<thead>
<tr>
<th>Phase</th>
<th>PROFILE 1001&lt;sup&gt;1&lt;/sup&gt; (N=143)</th>
<th>PROFILE 1005&lt;sup&gt;2&lt;/sup&gt; (N=259)</th>
<th>PROFILE 1007&lt;sup&gt;3&lt;/sup&gt; (N=172)</th>
<th>PROFILE 1014&lt;sup&gt;4&lt;/sup&gt; (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Line of therapy</td>
<td>Any line</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line and beyond</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line</td>
</tr>
<tr>
<td>Response rate</td>
<td>61%</td>
<td>60%</td>
<td>65%</td>
<td>74%</td>
</tr>
<tr>
<td>PFS, median (mos)</td>
<td>9.7</td>
<td>8.1</td>
<td>7.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Survival probability at 12 mos</td>
<td>75%</td>
<td>NA</td>
<td>70%</td>
<td>84%</td>
</tr>
</tbody>
</table>

<sup>1</sup>Camidge et al., Lancet Onc 13(10): 1011-9, 2012  
<sup>2</sup>Kim et al., ASCO 2012  
<sup>3</sup>Shaw et al., NEJM 368(25): 2385-94, 2013  
<sup>4</sup>Solomon et al., NEJM 371(23): 2167-77, 2014
Matching Targets with Targeted Therapies in Advanced Lung Cancer

Metastatic or incurable lung cancer

MOLECULAR TESTING

All patients with advanced disease

Multiplex genetic testing preferred

Targets

EGFR
- erlotinib
- gefitinib
- afatinib

ROS1
- crizotinib

MET
- crizotinib

BRAF
- dabrafenib
- trametinib

NTRK1
- entrectinib
- LOXO-101

ALK
- crizotinib

1L
Overview

- Introduction to Lung Cancer
- First Generation Targeted Therapies
- **Second Generation Targeted Therapies**
- Evolution of Resistance
- Summary and Future Directions
Almost All Patients Develop Resistance to Targeted Therapies Over Time

Baseline  
After 8 weeks of crizotinib  
After 34 months of crizotinib
Mechanisms of Resistance to 1st Generation EGFR Inhibitors

The 3rd Generation Inhibitor AZD9291 (Osimertinib) Is A T790M Mutant-Selective EGFR Inhibitor

<table>
<thead>
<tr>
<th></th>
<th>H1975 (T790M/L858R)</th>
<th>PC-9 VanR (ex19del/T790M)</th>
<th>PC-9 (ex19del)</th>
<th>Calu 3 (WT)</th>
<th>NCI-H2073 (WT)</th>
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<tbody>
<tr>
<td>AZD9291</td>
<td>11 (6, 19)</td>
<td>40 (30, 54)</td>
<td>8 (7, 9)</td>
<td>650 (457, 924)</td>
<td>461 (230, 924)</td>
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<tr>
<td>Dacomitinib</td>
<td>335 (265, 424)</td>
<td>531 (465, 607)</td>
<td>0.4 (0.3, 1)</td>
<td>65 (37, 116)</td>
<td>54 (ND)</td>
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<tr>
<td>Afatinib</td>
<td>483 (403, 579)</td>
<td>679 (532, 868)</td>
<td>0.8 (0.7, 0.9)</td>
<td>71 (35, 144)</td>
<td>30 (9, 99)</td>
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<tr>
<td>Gefitinib</td>
<td>6962 (6304, 7688)</td>
<td>4232 (1998, 8965)</td>
<td>23 (20, 25)</td>
<td>1933 (1299, 2876)</td>
<td>200 (41, 974)</td>
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<tr>
<td>Erlotinib</td>
<td>6165 (5392, 7050)</td>
<td>5778 (4766, 7029)</td>
<td>28 (22, 36)</td>
<td>4101 (2732, 6156)</td>
<td>692 (193, 2478)</td>
</tr>
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</table>

Cross et al., Canc Discovery 4: 1046-61, 2014
Osimertinib Binds to EGFR T790M Via Cys797

Cross et al., Canc Discovery 4: 1046-61, 2014
**Third Generation EGFR T790M Inhibitors Can Overcome T790M-Mediated Resistance**

AZD9291

- Confirmed ORR in patients with centrally tested T790M+ tumours was **61%** (78/127; 95% CI 52%, 70%)
- Disease control rate (CR+PR+SD) was **95%** (121/127; 95% CI 90%, 98%)
- Median PFS **9.6 mos** (95% CI 8.3 – NR)

Yang et al., ESMO 2014
Janne et al., NEJM 2015
Sequential EGFR Inhibitor Therapy in Patients Who Relapse due to T790M

1L 
Erlotinib, gefitinib, or afatinib

2L 
Osimertinib (or other 3rd gen EGFR TKI)

PD

Rebiopsy
T790M
Multiple Secondary ALK Mutations Can Mediate Resistance to Crizotinib

Modified from Lovly and Pao, Sci Transl Med 4(120): 120ps2, 2012
Less Than 30% of Crizotinib-Resistant Tumors Harbor Secondary ALK Resistance Mutations
# Next Generation ALK Inhibitors

<table>
<thead>
<tr>
<th>ALK TKI</th>
<th>ROS1 activity</th>
<th>Status</th>
<th>Ongoing Studies</th>
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<tbody>
<tr>
<td>Ceritinib</td>
<td>Yes</td>
<td>FDA Approved (4-29-2014)</td>
<td>Phase 3 (vs chemo)</td>
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<tr>
<td>Alectinib</td>
<td>No</td>
<td>Approved in Japan (7-4-2014)</td>
<td>Phase 3 (vs crizotinib)</td>
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<td></td>
<td></td>
<td>FDA Approved (12-11-15)</td>
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<tr>
<td>Brigatinib</td>
<td>Yes</td>
<td>Investigational FDA Breakthrough Therapy</td>
<td>Phase 2 (90 vs 180 mg)</td>
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<tr>
<td>X-396</td>
<td>Yes</td>
<td>Investigational</td>
<td>Phase 1/2</td>
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<td>Entrectinib</td>
<td>Yes</td>
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<td>Phase 2</td>
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<tr>
<td>CEP-37440</td>
<td>Unk</td>
<td>Investigational</td>
<td>Phase 1</td>
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<tr>
<td>Lorlatinib</td>
<td>Yes</td>
<td>Investigational</td>
<td>Phase 2</td>
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First and Next Generation ALK Inhibitors

Crizotinib

Ceritinib

Brigatinib

X-396

Alectinib

Lorlatinib

Next Generation ALK Inhibitors Can Induce Rapid Responses in Crizotinib-Resistant Patients

Baseline

After 3.5 weeks of ceritinib

Shaw et al., NEJM 370(13): 1189-97, 2014
Next Generation ALK Inhibitors Induce Durable Responses in Most Crizotinib-Resistant, ALK+ NSCLC Patients

Ou et al., ASCO 2015

Global Phase 2 Study of Alectinib

Systemic BOR:  
- PD (n=22)  
- SD (n=35)  
- PR (n=61)

Objective Response Rate: 50%
Median Duration of Response: 11.2 mos
Next Generation Inhibitors are Active Against Tumors Without ALK Resistance Mutations

<table>
<thead>
<tr>
<th>Best % response</th>
<th>22 26 32 34 43 44 45 48 49 49 49 51 52 58 59 60 60 63 63 85</th>
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<tr>
<td>PFS on LDK378 (wks)</td>
<td>19 71 12 8 36 49 18 29 30 41 31 23 12 18 71 77 21 42 61 39</td>
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<tr>
<td>ALK FISH</td>
<td>+ + + + + + + + + + + + + + + + + + + + +</td>
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<tr>
<td>ALK amplification</td>
<td>- - - - - - - - - + - - - - + - - - - - - - -</td>
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<tr>
<td>ALK mutation</td>
<td>- - - - - - - + - - - - + + + - - + - - + - -</td>
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</tbody>
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Modified from Shaw et al., NEJM 370(13): 1189-97, 2014
Current Treatment Strategy for Metastatic ALK+ NSCLC

1L
- Crizotinib

2L
- Ceritinib, alectinib, brigatinib, others

PD
Acquired Resistance to Next Generation ALK Inhibitors
Shifting Profile of ALK Resistance Mutations Depending on the ALK Inhibitor

Post-crizotinib

Post-ceritinib

Amplification
L1196M
G1269A
G1202R
C1156Y
S1206Y
1151Tins
L1152R
F1174V
No mutation

G1202R
F1174C/V
Other ALK mutations
Shifting Profile of ALK Resistance Mutations Depending on the ALK Inhibitor

Post-crizotinib

- L1196M
- G1269A
- Other ALK mutations
- G1202R
- C1156Y
- S1206Y
- I1171T/N/S
- 1151Tins
- L1152R
- F1174V
- No mutation

Post-alectinib

- G1202R
- I1171T/N/S
Lorlatinib is a Highly Potent, CNS Penetrant ALK/ROS1 TKI

Johnson et al., J Med Chem 57: 4720-4, 2014

<table>
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<tr>
<th></th>
<th>crizotinib</th>
<th>PF-06463922</th>
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<tbody>
<tr>
<td>ALK WT NIH3T3 IC50 (nM)</td>
<td>80</td>
<td>1.3</td>
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<tr>
<td>ALK L1196M NIH3T3 IC50 (nM)</td>
<td>843</td>
<td>21</td>
</tr>
<tr>
<td>ALK G1202R NIH3T3 IC50 (nM)</td>
<td>1148</td>
<td>77</td>
</tr>
<tr>
<td>ROS1-CD74 IC50 (nM)</td>
<td>11</td>
<td>0.24</td>
</tr>
<tr>
<td>MDR BA/AB</td>
<td>45</td>
<td>1.5</td>
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</table>
Clinical Activity of Lorlatinib in ALK- and ROS1-Rearranged NSCLC

PD occurred in 14 patients: new lesions (n=8), non-target lesions (n=2), both new and non-target lesions (n=4).

PD=progressive disease; R=ROS1+; ROS1=c-ros oncogene 1; TKI=tyrosine kinase inhibitor
Lorlatinib Can Overcome the ALK G1202R Resistance Mutation

Patient 1: ALK⁺ NSCLC
Previously treated with crizotinib and ceritinib
Local molecular testing after ceritinib with ALK G1202R
Started lorlatinib at 75 mg QD
Dose reduced to 50 mg QD
Ongoing at >12 months

Patient 2: ALK⁺ NSCLC
Previously treated with crizotinib and brigatinib
Local molecular testing after brigatinib with ALK G1202R
Started lorlatinib at 200 mg QD
Dose reduced to 100 mg QD
Ongoing at >8 months

Shaw et al., ASCO 2015
Current Treatment Strategy for Metastatic ALK+ NSCLC

1L: Crizotinib

2L: Ceritinib, alectinib, brigatinib, others

PD

3L: Lorlatinib

G1202R

I1171

F1174

No ALK mutation

Combo therapy

Rebiopsy
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Serial Biopsies Reveal Dynamic Populations of Different Tumor Clones

<table>
<thead>
<tr>
<th>Histology</th>
<th>Adeno</th>
<th>Adeno</th>
<th>Adeno</th>
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<tbody>
<tr>
<td>Genotype</td>
<td>L858R</td>
<td>L858R</td>
<td>L858R</td>
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<td></td>
<td>TP53</td>
<td>TP53</td>
<td>TP53</td>
</tr>
<tr>
<td>EGFR TKI status</td>
<td>Sensitive</td>
<td>Resistant</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Tumor Burden</td>
<td></td>
<td></td>
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<tr>
<td>Treatment</td>
<td>Chemo</td>
<td>Erlotinib</td>
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<tr>
<td>Timeline</td>
<td>2007</td>
<td>2008</td>
<td>2009</td>
</tr>
</tbody>
</table>

Sequist et al, Sci Transl Med 2011
**Heterogeneity of Resistance Mechanisms Discovered at Autopsy**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Normal Liver</th>
<th>Diaphragm Tumor</th>
<th>Lung Tumor</th>
<th>Liver Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological Features</td>
<td>Normal Tissue</td>
<td>Adenocarcinoma</td>
<td>SCLC</td>
<td>SCLC</td>
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<td>Number of Reads</td>
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<td>350,864,233</td>
<td>388,189,232</td>
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<tr>
<td>Average Coverage</td>
<td>146</td>
<td>287</td>
<td>319</td>
<td>253</td>
</tr>
<tr>
<td>Primary EGFR Mutation</td>
<td>WT</td>
<td>L858R</td>
<td>L858R</td>
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<tr>
<td>Secondary EGFR Mutation</td>
<td>WT</td>
<td>T790M</td>
<td>WT</td>
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<td>PIK3CA Status</td>
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<td>WT</td>
<td>E545K</td>
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<tr>
<td>TP53 Status</td>
<td>WT</td>
<td>WT/Δ154-163</td>
<td>-/Δ154-163</td>
<td>-/Δ154-163</td>
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<td>RB1 status</td>
<td>WT</td>
<td>WT</td>
<td>-/-</td>
<td>-/-</td>
</tr>
</tbody>
</table>

Longitudinal Evolution of Resistance in ALK+ NSCLC

- Crizotinib
- Ceritinib
- Lorlatinib

Variants:
- S1206Y
- G1202R
- C1156Y
- C1156Y + L1198F
Structural Basis for ALK L1198F-Mediated Resistance to Lorlatinib and Sensitivity to Crizotinib

Shaw et al., NEJM 2015 Dec 23
The Selective Pressure of Each ALK Inhibitor Shapes the Longitudinal Evolution of Resistance

prior to crizotinib

No ALK mutation

ALK C1156Y

ALK C1156Y/L1198F

ALK C1156Y/I1171S

crizotinib resistant

lorlatinib

No L1198F

crizotinib resensitization

lorlatinib resistant
Summary

- All patients with newly diagnosed metastatic lung cancer should undergo multiplex molecular testing.
- For patients with oncogene-addicted lung cancers, targeted therapies have transformed the natural history of disease.
- Essentially all patients will develop resistance to targeted therapies over time.
- There are new and emerging treatment strategies for patients who relapse on targeted therapies; these will be most effective when tailored based on the underlying resistance mechanism.
ALK-based combos

PF3922

AP26113

cabo

RXDX

ceritinib

crizotinib

EGFR-based combos

Aafatinib+cetuximab

EGF816

CO-1686

AZD9291

ALK

ROS1

RET

EGFR

Adapted from Nature 513: S8-9, 2014
Future Directions

● Liquid biopsies (ie blood-based assays of circulating tumor DNA) to allow noninvasive, dynamic monitoring of response and resistance in real time

● Combinations of ALK inhibitors and other targeted agents to overcome resistance due to off-target mechanisms

● Upfront drug combinations, possibly in an intercalated manner, to prevent the emergence of resistant clones

● Multimodality treatment regimens involving targeted therapies, local therapies like radiation, and even immune or vaccine-based strategies
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