TARGETING ALK SEQUENCING OF AGENTS

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Disclosures Slide

Advisory Boards: Eli Lilly, Roche, Genentech, Boehringer-Ingelheim, Astra-Zeneca, Pfizer, MSD, Clovis, Pierre Fabre, Bristol-Myers-Squibb, Novartis

Symposia: Eli Lilly, Roche, Pfizer, Astra-Zeneca, Boehringer-Ingelheim, Novartis
Current Treatment Strategy for ALK+ Patients

Crizotinib

Isolated CNS PD

CNS local Tx

PD

Ceritinib or alectinib*

PD

CT

*Available in Japan and US, not in EU

Hazard ratio for progression or death in the crizotinib group, 0.45 (95% CI, 0.35–0.60)

No identification AR mechanism ~25%

ALK amplification ~6–16%

ALK target alteration ~28–49%

ALK mutations ~22–33%

- L1196M
- G1202R
- S1206Y
- G1269A
- 1151Tins
- Others

Increased EGFR signalling ~30–35%

Change in driver mutations ~5%

KIT amplification ~10%
Impact of the Current Strategy on ALK+ Patients OS

OS for patients treated with sequential crizotinib and ceritinib

Impact of 2nd generation ALK inhibitor on patients outcome after resistance to crizotinib

- Median OS: 34.7 months (28.5-NR)
- Median OS: 19.6 months (12.2-28.5)
- Median OS: 15.3 months (11.1-22.5)

Log rank: p<0.0001

Gainor, CCR 2015; Duruisseaux M, WCLC 2015
How to Improve the Current Strategy?

- How to optimize the selection of second- and subsequent treatment lines if crizotinib is used in frontline setting?
- Should crizotinib remain the first-line treatment or should we use next-generation, more potent ALK inhibitors in frontline treatment?
- Which role for cytotoxic chemotherapy in ALK+ patients?
- Is there a room for treatment combinations?
Many Factors Have to Be Taken into Account to Define the Best Sequence

- Comparative activity of next-generation ALK inhibitors
  - For ALK TKI naïve patients and in post-crizotinib setting
  - According to resistance mechanisms (resistance mutations)
  - According to ALK fusion variants
  - In central nervous system
  - Role of 3rd generation ALK inhibitors (lorlatinib …)

- Role of other treatments beside ALK TKIs
  - Role of pemetrexed-based chemotherapy and maintenance pemetrexed
  - HSP90 inhibitors
  - Treatment of resistance consecutive to bypass activation
  - Room for brain radiotherapy

- Brain metastases present at baseline or during the disease course
How to optimize the selection of second- and subsequent treatment lines if crizotinib is used in frontline setting?
# ALK Inhibitors after Crizotinib Failure

## Systemic Efficacy and Tolerance

<table>
<thead>
<tr>
<th></th>
<th>Alectinib NP28673 (n=138)*</th>
<th>Alectinib NP28761 (n=87)*</th>
<th>Brigatinib (n=71)*</th>
<th>Ceritinib ASCEND-1 (prior ALKi) (n=163)**</th>
<th>Ceritinib ASCEND-2* (n=140)**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>n=122</td>
<td>n=69</td>
<td>n=70</td>
<td>n=163</td>
<td>n=140</td>
</tr>
<tr>
<td><strong>ORR, %</strong></td>
<td>50</td>
<td>51</td>
<td>71</td>
<td>56</td>
<td>39</td>
</tr>
<tr>
<td><strong>DCR, %</strong></td>
<td>79</td>
<td>80</td>
<td>87</td>
<td>74</td>
<td>77</td>
</tr>
<tr>
<td><strong>mDoR, mos</strong></td>
<td>11.2</td>
<td>13.5</td>
<td>9.3</td>
<td>8.3</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>mPFS, mos</strong></td>
<td>8.9</td>
<td>8.1</td>
<td>13.4</td>
<td>6.9</td>
<td>5.7</td>
</tr>
<tr>
<td><strong>Toxicity issues</strong></td>
<td>Very few</td>
<td>Dyspnea</td>
<td>Gl (QoL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORR: objective response rate; DCR: disease control rate; mDoR: median duration of response; mPFS: median progression-free survival

*By IRC; **By investigator

| Ou, JCO 2016; Shaw, Lancet Oncol 2016; Camidge, ASCO 2015; Kim, Lancet Oncol 2016; Mok, ASCO 2015 |
CNS Metastases are a Difficult Problem in ALK+ Patients

- Increasing proportion of brain mets as patients fail increasing line of treatment
  - Cumulative incidence: 23.8, 45.5, and 58.4 % at 1, 2 and 3 yrs/diagnosis
- Control of CNS disease becomes crucial with the improvement of systemic disease control
- Importance of local treatments (WBRT, stereotactic RT, surgery)
  - Late toxicity of WBRT is of concern
- Variable CNS penetration of ALK TKIs
- Assessing ALKi in brain mets depends on several parameters
  - Symptomatic vs asymptomatic brain mets
  - Untreated lesions vs pretreated with previous WBRT
  - Crizotinib pretreated vs crizotinib naïve brain mets
  - Measurable lesions vs non-measurable lesions

Plasma/CSF level of Alectinib

**Graph:**
- Linear equation: $y = 1.685x - 2.567$
- Correlation coefficient: $r^2 = 0.75$
# ALK Inhibitors After Crizotinib Failure

## CNS activity

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (n=60)</th>
<th>Alectinib (n=138)</th>
<th>Brigatinib* (n=15)</th>
<th>Brigatinib* (n=33)</th>
<th>Ceritinib ASCEND-2 Measurable (n=20)</th>
<th>Ceritinib ASCEND-1 Measurable and non-measurable (n=75)</th>
<th>Ceritinib ASCEND-1 Measurable (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS ORR, %</td>
<td>64</td>
<td>43</td>
<td>53</td>
<td>33</td>
<td>45</td>
<td>19</td>
<td>36</td>
</tr>
<tr>
<td>CR, %</td>
<td>22</td>
<td>27</td>
<td>7</td>
<td>33</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>CNS DCR, %</td>
<td>80</td>
<td>86</td>
<td>87</td>
<td>88</td>
<td>80</td>
<td>65</td>
<td>61</td>
</tr>
<tr>
<td>CNS mDoR, months</td>
<td>10.8</td>
<td>11.1</td>
<td>18.9**</td>
<td></td>
<td>–</td>
<td>6.9</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*8% patients with CNS mets at baseline were crizotinib-naïve; **n=16

ORR: objective response rate; CR: complete response; DCR: disease control rate; mDoR: median duration of response

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**EUROPEAN LUNG CANCER CONFERENCE 2016**

Gadgeel, WCLC 2015; Camidge, ASCO 2015; Kim, Lancet Oncol 2016; Mok, ASCO 2015
Acquired Resistance to Crizotinib
### Which Next-Generation ALKi to Select for Post-Crizotinib Systemic Progression?

<table>
<thead>
<tr>
<th></th>
<th>L1196M</th>
<th>G1269A/S</th>
<th>C1156Y</th>
<th>R1275Q</th>
<th>S1206Y</th>
<th>I1171T</th>
<th>V1180L</th>
<th>F1174V/L</th>
<th>D1203N</th>
<th>G1202R</th>
<th>Other kinases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ROS1, MET</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>ROS1, IGF1R</td>
</tr>
<tr>
<td>Alectinib</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>RET</td>
</tr>
<tr>
<td>Brigatinib</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>EGFR</td>
</tr>
</tbody>
</table>

**N-terminal αC-helix**

- G1123S
- 1151Tins
- C1156Y
- I1171T/N5
- F1174C/L4
- V1180L

**Gate-keeper**

- L1196M
- G1202R
- D1203N
- S1206Y
- G1269A

**ATP-binding pocket**

- Solvent front

PF-06463922 Appears as the Most Potent Inhibitor Against All Clinically-Relevant ALK-Resistant Mutants

Zou HY et al. Cancer Cell 2015; 28:70–81
Phase 1 Study of PF-06463922 in Patients with Advanced NSCLC with Specific Molecular Alterations

Overall ORR, n (%)

<table>
<thead>
<tr>
<th>Molecular Alteration</th>
<th>Overall ORR, n (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior ALK TKI</td>
<td>11 (32) [17–51]</td>
</tr>
<tr>
<td>1 prior ALK TKI</td>
<td></td>
</tr>
<tr>
<td>≥2 prior ALK TKI</td>
<td></td>
</tr>
</tbody>
</table>

Overall ORR (including unconfirmed PRs), n (%), [95% CI]

<table>
<thead>
<tr>
<th>Molecular Alteration</th>
<th>Overall ORR (including unconfirmed PRs), n (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior ALK TKI</td>
<td>15 (44) [27–62]</td>
</tr>
<tr>
<td>1 prior ALK TKI</td>
<td></td>
</tr>
<tr>
<td>≥2 prior ALK TKI</td>
<td></td>
</tr>
</tbody>
</table>
Importance of Repeated Biopsy on Treatment Sequencing in ALK+ Patients

A Timeline of Treatment

B Effect of Therapy

E Clonal Progression

Shaw, NEJM 2015
Activity of Ceritinib Seems Partially Independent from Resistance Mutation Subtype

Shaw, NEJM 2014; Gainor, CCR 2015
Clinical Benefit of Next-Generation ALKi is Beyond That Expected from Re-biopsy Series

- Some crizotinib failures due to PK causes?
- Underestimation of resistance mutation frequency?
- Tumor heterogeneity?
- Activity on some bypass (IGF-1R)?
- Chemotherapy between crizotinib and NG ALKi?

Doebele, JTO 2014
How to Optimize Post—Crizotinib Treatments Sequence?

- **Crizotinib**
  - NGS ALK
    - C1156Y
    - I1171T
    - G1202R
  - NGS

- **Ceritinib**
  - No mutation
    - ALKi 2nd G
      - Not ceritinib
        - Not alectinib
      - Not alectinib
    - Lorlatinib

- **CT/Pemetrexed**

**NGS / multiplex ddPCR**

- Ceritinib
  - 1151Tins
  - L1152R
  - C1156Y
  - F1174C/V
  - G1202R
- Alectinib
  - I1171N/S/T
  - V1180L*
  - G1202R
- Lorlatinib
  - No mutation
  - C1156Y

**PFS**

- 3
- 6
- 9
- 12
- 15
- 18
- 21
- 24
- 27
- 30
- 33
- 36

**Months**
Should crizotinib remain the first-line treatment or should we use next-generation ALK inhibitors in frontline treatment?
Two Different Strategies

- **"Interventional" approach**
  - Start with crizotinib and adaptation of subsequent treatments to mechanisms of resistance
  - Next-generation ALKi are able to overcome resistance to crizotinib in most cases
  - **Hypothesis:** $\text{PFS}_{\text{crizo} / 1\text{st line}} + \text{PFS}_{\text{ALKi} 2\text{nd G} / 2\text{nd line}} > \text{PFS}_{\text{ALKi} 2\text{nd G} / 1\text{st line}}$
  - Risk: rapid emergence of brain metastases, shorter disease control duration

- **"Preventive" approach**
  - To obtain deeper and longer responses with NG ALKi more potent than crizotinib
  - To prevent or delay emergence of resistances
  - More penetrable-brain blood barrier ALKi would delay or prevent CNS metastases
  - **Hypothesis:** $\text{PFS}_{\text{ALKi} 2\text{nd G} / 1\text{st line}} > \text{PFS}_{\text{crizo} / 1\text{st line}} + \text{PFS}_{\text{ALKi} 2\text{nd G} / 2\text{nd line}}$
  - Risk: strategy leading to highly resistant disease with cross-resistance to other ALKi
"Interventional" vs "Preventive" Strategy

- **Crizotinib**
  - Median PFS: 11 months

- **Next-G ALKi**
  - Median PFS: 17-18 months
  - Gainor, CCR 2014; adapted from Shaw, ECC 2015

- **Crizotinib** + **Ceritinib**
  - Median PFS: 17.4 months

- **Next-G ALKi**
  - Median PFS: > 24 months
Intracranial TTP\textsuperscript{a} by IRR in Patients with/without Brain Metastases at Baseline (Profile 1014)

<table>
<thead>
<tr>
<th>Pretreated brain metastases present</th>
<th>Brain metastases absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib (n = 39)</td>
<td>Chemotherapy (n = 40)</td>
</tr>
<tr>
<td>Events, no. (%)</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Median, months</td>
<td>15.7</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.45 (0.19 to 1.07)</td>
</tr>
<tr>
<td>Crizotinib (n = 132)</td>
<td>Chemotherapy (n = 131)</td>
</tr>
<tr>
<td>Events, no. (%)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Median, months</td>
<td>NR</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.69 (0.33 to 1.45)</td>
</tr>
</tbody>
</table>

NR, not yet reached
\( ^a \)Time from randomization to first documentation of intracranial tumor progression
\( ^b \)2-sided log-rank test
# ALK TKIs Activity in ALK+, Crizotinib-Naïve Patients

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib Profile 1014</th>
<th>Crizotinib Profile 1007</th>
<th>Ceritinib Ascend 1</th>
<th>Ceritinib Ascend 2</th>
<th>Alectinib AF-001 JP</th>
<th>Brigatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>III</td>
<td>III</td>
<td>I</td>
<td>II</td>
<td>I/II</td>
<td>I</td>
</tr>
<tr>
<td>Countries</td>
<td>Global</td>
<td>Global</td>
<td>Global</td>
<td>Global</td>
<td>Japan</td>
<td>USA/Spain</td>
</tr>
<tr>
<td>ALK fusion diagnosis</td>
<td>FISH (central)</td>
<td>FISH (central)</td>
<td>FISH (local)</td>
<td>FISH (central)</td>
<td>IHC + FISH (central)</td>
<td>FISH (local)</td>
</tr>
<tr>
<td>Treatment line</td>
<td>1</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
<td>≥1</td>
</tr>
<tr>
<td>Patients</td>
<td>172</td>
<td>173</td>
<td>83</td>
<td>124</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>ORR</td>
<td>74%</td>
<td>65%</td>
<td>72%</td>
<td>64%</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>10.9</td>
<td>7.7</td>
<td>18.4</td>
<td>11.1</td>
<td>27.7</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

**Countries:** Global, Japan, USA/Spain

**ALK fusion diagnosis:** FISH (central), FISH (local)

**Treatment line:** 1, ≥1

**Patients:** 172, 173, 83, 124, 46, 8

**ORR:** 74%, 65%, 72%, 64%, 94%, 100%

**Median PFS, mos:** 10.9, 7.7, 18.4, 11.1, 27.7, Not reached

References: Solomon, NEJM 2014; Shaw, NEJM 2013; Ou, JCO 2016; Seto, Lancet Oncol 2013; Camidge, ASCO 2015; Kim, Lancet Oncol 2016; Mok, ASCO 2015
ASCEND IV
Ceritinib First-Line Phase III Trial

**Phase III**

**ASCEND IV**

1. Stage IIIB/IV NSCLC
2. ALK+ by central laboratory IHC
3. Treatment-naive chemotherapy or ALK inhibitor

n=348

Randomise

Chemotherapy (INV choice):
- PEM 500 mg/m$^2$ + cisplatin 75 mg/m$^2$
- PEM 500 mg/m$^2$ + carboplatin

LDK378 750 mg/day
ALEX Alectinib First-Line Phase III Trial

Stage IV NSCLC
ALK+ by IHC central testing
Treatment-naive
PS 0-2
Measurable disease
Stable, untreated brain metastases allowed

Primary Endpoints
- Progression free survival by investigator
- Secondary Endpoints
  - PFS by independent review
  - Time to CNS progression
  - ORR, DoR
  - OS
  - PROs

Safety

Chugai’s ALK Inhibitor “Alecensa®” Trial Stopped Early for Benefit
- Demonstrates Statistically Significant Improvement in PFS in a Japanese Phase III Head to Head Study with Crizotinib -

Alectinib
600 mg BID
N=143

Crizotinib
250 mg BID
N=143

No crossover

Accrual completed
ALK Master Protocol in Advanced Lung Adenocarcinoma

Pls: Alice Shaw, Shakun Malik

Ariad- AP26113 (brigatinib)
Ignyta- RXDX-101
Novartis - Ceritinib
Pfizer- PF-06463922 (lортatinib)
Roche/Chugai - Alectinib
Tesaro - TSR-011
Xcovery-X-396
## Which Room for Cytotoxic Chemotherapy? Pemetrexed Activity in ALK+ NSCLC Patients

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin-pemetrexed 1\textsuperscript{st} line</th>
<th>Pemetrexed 2\textsuperscript{nd} line</th>
<th>Docetaxel 2\textsuperscript{nd} line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>ALK+</td>
<td>ALK+</td>
<td>ALK+</td>
</tr>
<tr>
<td>ORR</td>
<td>45%</td>
<td>29%</td>
<td>7%</td>
</tr>
<tr>
<td>ORR</td>
<td>23%</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>7.0</td>
<td>5.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>

- All ALK+ patients will receive chemotherapy at one point of their disease course
- Platinum-pemetrexed combinations seem the most active regimen
  - Positioning of chemotherapy should be early enough to allow administration of platinum-based regimen
- Role of maintenance pemetrexed should be addressed by ASCEND IV phase III trial
- Role in case of two successive ALK TKI failures, multiple asymptomatic brain metastases, between two ALK TKIs treatments?

*References: Solomon, NEJM 2014; Shaw, NEJM 2013; Sequist, JCO 2013; Hanna, JCO 2004*
ALKi in Combination with Other Agents

- ALKi + pemetrexed-based chemotherapy
- ALKi + HSP90 inhibitors
  - Phase I crizotinib + ganetespib: RP2D C 250 mg BID, G 150 mg/m² D1-8 q3 wks, ORR: 8/12 (67%)
- ALKi + TKI addressing bypass mechanisms of resistance
- ALKi + IOs

Riely G, ASCO 2015; Beckman R, PNAS 2012
Targeting ALK: Sequencing of Agents

- Current standard approach with crizotinib followed by 2\textsuperscript{nd} generation ALKi provides an unprecedented survival duration for ALK+ NSCLC pts.

- This "interventional" strategy is supported by some points:
  - Crizotinib provides a median PFS of 10 months with a good safety profile.
  - A majority of crizotinib-resistant pts respond to next-generation ALKi.
  - Some next-generation ALKi resistances are sensitive to other ALK TKIs.
  - Repeated biopsies and/or cfDNA can be useful to select the ALKi most likely to be active.

- Issues of CNS involvement, CT positioning.
Targeting ALK: Sequencing of Agents

- The "preventive" strategy remains to be validated yet
  - Importance to prevent or delay CNS metastases
  - ALEX phase III results should be available at the end of 2016
    - Alectinib might be used in first-line treatment
  - The answer might only be provided by trials like ALK Master Protocol (cross over)
  - Optimizing treatment sequences will anyway need a repeated knowledge of successive resistance mechanisms
    - Impact of cfDNA remains to be assessed in this setting
Acknowledgments

- Alexis CORTOT, Lille University Hospital, France