ESMO PRECEPTORSHIP ON

NEW treatment options for ALK+ NSCLC

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DISCLOSURE OF INTEREST

Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

Honoraria: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

Clinical trials research: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo

Travel, Accommodations, Expenses: AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer
ALK GENE REARRANGEMENTS IN NSCLC

- Found in 3-7% of NSCLC
- Typically adenocarcinoma histology
- Younger patients (median age ~50 years)
- Often never or light smokers
- At least 15 EML4-ALK variants have been described in lung cancers.
Diagnostics of ALK translocations

IHC

FISH
Break apart:
Orange:red/green fusion normal
Red: ALK 3’break
Zytovision

NGS

ALK
Reads marked in ALK to pair with region of EML4

EML4
Reads marked in EML4 to pair with region in ALK

Images courtesy of A. Scheel and R. Büttner, Cologne.
CHALLENGES TO PRECISION MEDICINE IN NSCLC

Timing of molecular testing

- At diagnosis
- Therapeutic monitoring?
- At relapse

Potential role of liquid biopsy

Treatment Landscape in ALK+ NSCLC Is Evolving

**US milestones**
- **EML4-ALK** identified as driver oncogene in NSCLC
- Crizotinib regular approval (any line) 2011
- Crizotinib accelerated approval (post-crizotinib) 2013
- Ceritinib accelerated approval (post-crizotinib) 2014
- Alectinib 1L approval 2017
- Lorlatinib conditional approval (post-2G +/- crizotinib) 2019

**EU milestones**
- Crizotinib conditional approval (≥2L) 2012
- Ceritinib conditional approval (post-crizotinib) 2015
- Alectinib 1L approval 2017
- Brigatinib accelerated approval (post-crizotinib) 2019
- Lorlatinib conditional approval (post-2G +/- crizotinib) 2018

**PLATINUM DOUBLETs**
- Crizotinib 1L label extension 2015

**ALK-TARGETED AGENTS**
- Crizotinib accelerated approval (any line of therapy) 2011
- Ceritinib accelerated approval (post-crizotinib) 2014
- Alectinib 1L approval 2017
- Lorlatinib conditional approval (post-2G +/- crizotinib) 2019

1L, first line; 2L, second line; 2G, second generation; ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; NSCLC, non–small cell lung cancer.
ALK: 1L Treatment is changing

**Crizotinib**

**Ceritinib**
C Soria et al. *lancet* 2017

**Alectinib**
Peters S et al, *NEJM* 2017

**Brigatinib**
Camidge et al. *NEJM* 2018

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (months)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib (n=172)</td>
<td>10.9</td>
<td>0.45 (0.36–0.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chemotherapy (n=171)</td>
<td>7.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Medical History

- 59 year-old female patient, non smoker
- No past history
- No exposition to asbestos

  - 1st symptom: visual disturbance
  - Eye fund: right choroid lesion

- CT scan: right pulmonary mass + lymph nodes + liver metastases
Lung Cancer Staging

T4 N3 (bilat) M1c (lung, brain, liver)
stage IV

L.Mezquita  D.Planchard et al, Gustave Roussy
Molecular testing found ALK positivity (IHC and FISH), EGFR-, BRAF-, HER2-, ROS1- and PDL1+ (10%)

- **March 2016**
  - PS 2 (abdominal pain)
  - CRIZOTINIB 250mg bid
  - Close interval follow-up with MRI

- **Front-line therapy:**
  - Clinical benefit: ↓ Symptoms (PS0)
  - Partial response after 2 months
# Summary of crizotinib trials in ALK+ NSCLC

<table>
<thead>
<tr>
<th></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><strong>Phase</strong></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Line of therapy</strong></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><strong>Response rate</strong></td>
<td>61%</td>
<td>60%</td>
<td>65%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>PFS, median (mos)</strong></td>
<td>9.7</td>
<td>8.1</td>
<td>7.7</td>
<td>10.9</td>
</tr>
<tr>
<td><strong>Survival probability at 12 mos</strong></td>
<td>75%</td>
<td>NA</td>
<td>70%</td>
<td>84%</td>
</tr>
</tbody>
</table>

Crizotinib as a standard treatment first line ALK+ NSCLC
... after 10 months crizotinib

- **Nov 2016**

- **Symptoms +++**
  - Abdominal pain

- **Body CT scan**
  - Liver progression +++

D. Planchard et al, Gustave Roussy
Unmet need for 2-3\textsuperscript{nd}-generation ALK inhibitors that:
Have activity against crizotinib-resistance mutations

<table>
<thead>
<tr>
<th>ALK TKI</th>
<th>ADDITIONAL TARGETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{st} generation</td>
<td>Crizotinib</td>
</tr>
<tr>
<td>2\textsuperscript{nd} generation</td>
<td>Alectinib</td>
</tr>
<tr>
<td></td>
<td>Brigatinib</td>
</tr>
<tr>
<td></td>
<td>Ceritinib</td>
</tr>
<tr>
<td></td>
<td>Ensartinib</td>
</tr>
<tr>
<td></td>
<td>Entrectinib</td>
</tr>
<tr>
<td>3\textsuperscript{rd} generation</td>
<td>Lorlatinib</td>
</tr>
</tbody>
</table>

Timeline of FDA accelerated approvals
2\textsuperscript{nd} generation ALK-TKI in crizotinib-refractory NSCLC

<table>
<thead>
<tr>
<th>Design/Assessment</th>
<th>Ceritinib Phase 1/2</th>
<th>Alectinib Phase 2</th>
<th>Brigatinib Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>6.9M (5.6-8.7)</td>
<td>8.9M (5.6-11.3)</td>
<td>15.6M (11.1-NR)</td>
</tr>
<tr>
<td>ORR</td>
<td>56% (49-64)</td>
<td>50% (41-59)</td>
<td>55% (44-66)</td>
</tr>
<tr>
<td>IC ORR</td>
<td>36%</td>
<td>57%</td>
<td>67%</td>
</tr>
<tr>
<td>Duration of Response</td>
<td>8.3M</td>
<td>11.2M</td>
<td>14.8M</td>
</tr>
</tbody>
</table>

Developing the optimal treatment sequence

Next-generation ALK inhibitor vs chemotherapy post-crizotinib

- **ASCEND-5** (NCT01828112): Phase 3, advanced NSCLC (n = 231): ceritinib vs docetaxel/pemetrexed (primary endpoint: PFS)
- **ALUR** (NCT02604342): Phase 3, advanced NSCLC (n = 120): alectinib vs docetaxel/pemetrexed (primary endpoint: PFS)
Phase III ASCEND-5 study
Kaplan-Meier Plots of PFS (BIRC)

<table>
<thead>
<tr>
<th>No. of patients at risk Ceritinib Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceritinib  115  116</td>
</tr>
<tr>
<td>Chemo  116  45</td>
</tr>
<tr>
<td>Censoring times</td>
</tr>
<tr>
<td>0 2 4 6 8 10 12 14 16 18 20 22 24</td>
</tr>
</tbody>
</table>

| Events, n (%) | 83 (72.2) | 89 (76.7) |
| Median (95% CI), months | 5.4 (4.1, 6.9) | 1.6 (1.4, 2.8) |
| HR (95% CI) | 0.49 (0.36, 0.67) |
| Log-rank p-value | <0.001 |

Giorgio Scagliotti et al, ESMO 2016; Shaw AT et al, Lancet onco 2017
ALUR trial
Primary endpoint: PFS (investigator-assessed)

At data cut-off (26.01.17), median follow-up was 6.5 months with alectinib and 5.8 months with chemotherapy.

Median time on treatment was 20 weeks (range: 0.4–62.1) in the alectinib arm and 6 weeks (range: 1.9–47.1) in the chemotherapy arm.

HR=0.15 [95% CI: 0.08–0.29]; p<0.001

Alectinib* Median 9.6 months [95% CI: 6.9–12.2]

Chemotherapy‡ Median 1.4 months [95% CI: 1.3–1.6]

Silvia Novello et al ESMO 2017, annals of onco 2018
... after 10 months of crizotinib

- **Dec 2016**

- Symptoms +++
  - Abdominal pain

- Body CT scan
  - Multifocal liver progression +++

- **Our proposal:**
  - Rebiopsy: MATCH-R protocol (NGS, CGH, WES)
  - 2nd line before we get results of molecular testing: **CERITINIB**
... after 6 months ceritinib

- **Good tolerance**
- **Partial response (55%)**

- **PET scan**
  - Liver PD ++++

- **Biopsy:**
  - Adenocarcinoma IHC ALK +++
  - *ALKG1202R resistance mutation*
Distinct profiles of ALK resistance mutations after failure of a second generation ALK TKI

- Crizotinib, N=55
- Ceritinib, N=24
- Alectinib, N=46
- Brigatinib, N=7

Legend:
- L1196M/Q
- G1269A
- C1156Y
- G1202R
- I1171T/N/S
- S1206Y
- E1210K
- F1174C
- V1180L
- G1202del
- ≥2 ALK mutations
- ALK WT (ALK-independent)

Updated from Gainor et al., Cancer Discov 6: 1118-33, 2016
### Lorlatinib Covers the Broadest Range of ALK Resistance Mutations

Secondary mutations in the ALK kinase domain can induce resistance to first- and second-generation ALK TKIs\(^1\)

Lorlatinib has broad-spectrum potency against most known ALK resistance mutations, including ALK G1202R\(^{1,2}\)

<table>
<thead>
<tr>
<th>Mutation status</th>
<th>Crizotinib</th>
<th>Ceritinib</th>
<th>Alectinib</th>
<th>Brigatinib</th>
<th>Lorlatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML4-ALK</td>
<td>38.6</td>
<td>4.9</td>
<td>11.4</td>
<td>10.7</td>
<td>2.3</td>
</tr>
<tr>
<td>C1156Y</td>
<td>61.9</td>
<td>5.3</td>
<td>11.6</td>
<td>4.5</td>
<td>4.6</td>
</tr>
<tr>
<td>I1171N</td>
<td>130.1</td>
<td>8.2</td>
<td>397.7</td>
<td>26.1</td>
<td>49.0</td>
</tr>
<tr>
<td>I1171S</td>
<td>94.1</td>
<td>3.8</td>
<td>177.0</td>
<td>17.8</td>
<td>30.4</td>
</tr>
<tr>
<td>I1171T</td>
<td>51.4</td>
<td>1.7</td>
<td>33.6</td>
<td>6.1</td>
<td>11.5</td>
</tr>
<tr>
<td>F1174C</td>
<td>115.0</td>
<td>38.0(^a)</td>
<td>27.0</td>
<td>18.0</td>
<td>8.0</td>
</tr>
<tr>
<td>L1196M</td>
<td>339.0</td>
<td>9.3</td>
<td>117.6</td>
<td>26.5</td>
<td>34.0</td>
</tr>
<tr>
<td>L1198F</td>
<td>0.4</td>
<td>196.2</td>
<td>42.3</td>
<td>13.9</td>
<td>14.8</td>
</tr>
<tr>
<td><strong>G1202R</strong></td>
<td>381.6</td>
<td>124.4</td>
<td>706.6</td>
<td>129.5</td>
<td>49.9</td>
</tr>
<tr>
<td>G1202del</td>
<td>58.4</td>
<td>50.1</td>
<td>58.8</td>
<td>95.8</td>
<td>5.2</td>
</tr>
<tr>
<td>D1203N</td>
<td>116.3</td>
<td>35.3</td>
<td>27.9</td>
<td>34.6</td>
<td>11.1</td>
</tr>
<tr>
<td>E1210K</td>
<td>42.8</td>
<td>5.8</td>
<td>31.6</td>
<td>24.0</td>
<td>1.7</td>
</tr>
<tr>
<td>G1269A</td>
<td>117.0</td>
<td>0.4</td>
<td>25.0</td>
<td>ND</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Note: **IC\(_{50}\)\,<50\,nM** | **IC\(_{50}\)\,>50–<200\,nM** | **IC\(_{50}\)\,\geq200\,nM**

IC\(_{50}\), half-maximal inhibitory concentration; ND, not done.

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**ALK positive crizo-resistant NSCLC stage IV**

Primary resistance to Ceritinib

- **March 2017**
  - PS 1 (abdominal pain +++ liver)

- **Our options:**
  - Expanded access to Brigatinib
  - Expanded access to Lorlatinib *(not available)*
  - Platinum-based chemo

- **After 6 weeks Brigatinib:**
  - Hospitalization for clinical deterioration
  - *CT scan:*
    - Multifocal liver progression
    - Infradiaphragmatic nodal PD

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D. Planchard et al, Gustave Roussy
Are second generation ALK inhibitors active after failure of a prior second generation inhibitor?
Limited efficacy of second generation ALK TKIs after alectinib

<table>
<thead>
<tr>
<th></th>
<th>Hida et al., 2018 (ASCEND-9)(^1)</th>
<th>Yoshida et al., 2018</th>
<th>Lin et al., 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK TKI</td>
<td>ceritinib</td>
<td>ceritinib</td>
<td>brigatinib</td>
</tr>
<tr>
<td>Country</td>
<td>Japan</td>
<td>Japan</td>
<td>US</td>
</tr>
<tr>
<td>No. of patients</td>
<td>20</td>
<td>9</td>
<td>22</td>
</tr>
<tr>
<td>Median f/u</td>
<td>11.6 mos</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ORR</td>
<td>25%</td>
<td>16%(^*)</td>
<td>17%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>3.7 mos (1.9-5.3)</td>
<td>N/A</td>
<td>4.4 mos (1.8-5.6)</td>
</tr>
<tr>
<td>Intracranial ORR</td>
<td>N/A</td>
<td>N/A</td>
<td>1 of 4 (25%)</td>
</tr>
</tbody>
</table>

\(^1\)Hida et al., Cancer Sci 109:2863-72, 2018; \(^2\)Yoshida et al., In Vivo 32:158—90, 2018; \(^3\)Lin et al., J Thorac Oncol 13:1530-38, 2018
Lorlatinib is a 3nd-Generation Potent, Selective, CNS-Penetrant ALK/ROS1 TKI

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib</th>
<th>Lorlatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK WT NIH3T3 IC₅₀ (nM)</td>
<td>80</td>
<td>1.5</td>
</tr>
<tr>
<td>ALK L1196M NIH3T3 IC₅₀ (nM)</td>
<td>843</td>
<td>21</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>
</tr>
<tr>
<td>CSF or free brain: free plasma (rodent)</td>
<td>–</td>
<td>0.23–0.33</td>
</tr>
<tr>
<td>Log D</td>
<td>2.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase; CSF, cerebrospinal fluid; D, distribution coefficient; IC₅₀, half-maximal inhibitory concentration; MDR, multidrug-resistant transporter; nM, nanomolar; ROS1, c-ros oncogene 1; WT, wild-type

## Phase 1/2 Study of Lorlatinib: Design and Patient Populations

### Cohort and Mutation Lines of therapy

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mutation Lines of therapy</th>
<th>N=275 (Phase 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP1</td>
<td>Lorlatinib 100 mg QD PO(^a)</td>
<td></td>
</tr>
<tr>
<td>EXP2</td>
<td>Crizotinib</td>
<td>Lorlatinib 100 mg QD PO(^a)</td>
</tr>
<tr>
<td>EXP3A</td>
<td>Crizotinib</td>
<td>CT</td>
</tr>
<tr>
<td>EXP3B</td>
<td>Non-crizotinib ALK-TKI</td>
<td>± CT</td>
</tr>
<tr>
<td>EXP4</td>
<td>ALK-TKI(^b) ALK-TKI(^b)</td>
<td>± CT</td>
</tr>
<tr>
<td>EXP5</td>
<td>ALK-TKI(^b) ALK-TKI(^b)</td>
<td>± CT</td>
</tr>
<tr>
<td>EXP6</td>
<td>ROS1+</td>
<td>Lorlatinib 100 mg QD PO(^a)</td>
</tr>
</tbody>
</table>

\(^a\) Any pretreatment

\(^b\) ALK-TKI: ALK-tyrosine kinase inhibitors
Efficacy Lorlatinib in ALK+ Pts Previously Treated with Crizotinib ± Chemotherapy (EXP2–3A)

<table>
<thead>
<tr>
<th></th>
<th>EXP2+3A (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n/N (%)</td>
<td>41/59 (69)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(56, 81)</td>
</tr>
<tr>
<td>IC ORR, n/N (%)</td>
<td>25/37 (68)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(50, 82)</td>
</tr>
<tr>
<td>Median DOR, mo (95% CI)</td>
<td>NR</td>
</tr>
<tr>
<td>(11.1, NR)</td>
<td></td>
</tr>
<tr>
<td>DOR ≥6 mo, n⁰/n (%)</td>
<td>20/41 (49)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>NR</td>
</tr>
<tr>
<td>(12.5, NR)</td>
<td></td>
</tr>
</tbody>
</table>

- 37 patients (63%) had brain metastases at baseline.

ORR: 72.9% (update ASCO19)

ORR: 70.3% (update ASCO 19)

CI, confidence interval; CT, chemotherapy; DOR, duration of response; mo, months; NR, not reached.

Updated Efficacy and Safety: B.Besse et al, ASCO 2019

Benjamin J. Solomon et al, WCLC 2017; lancet onco 2018
Efficacy Lorlatinib in ALK+ Pts Previously Treated with Prior Non-crizotinib ALK TKI ± CT (EXP3B)

**Overall**

**ORR: 42.9%** (update ASCO19)

<table>
<thead>
<tr>
<th>ORR, n/N (%)</th>
<th>9/27 (33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% CI)</td>
<td>(16, 54)</td>
</tr>
</tbody>
</table>

IC ORR, n/N (%) | 5/12 (42) |
| (95% CI)       | (15, 72)  |

Median PFS, mo | 5.5 |
| (95% CI)       | (2.9, 9.0) |

---

**IC ORR: 46.2% (19.2–74.9)**

**Update ASCO19**

*Updated Efficacy and Safety: B.Besse et al, ASCO 2019*


---

* Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.

* Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, reversion to normal node size (<10 mm) prevented the percent change from baseline from reaching –100%. Some patients with a total change from baseline of ~100% are shown as partial responses due to the inclusion of non-target lesions in the summary.
Efficacy Lorlatinib in ALK+ Pts Previously Treated with ≥2 Prior ALK TKIs ± CT (EXP 4-5)

- 83 patients (75%) had brain metastases at baseline.

**EXP4–5: ≥2 prior ALK TKIs ± chemo (n=111)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N/N (%) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n/N (%)</td>
<td>43/111 (39) (30, 49)</td>
</tr>
<tr>
<td>IC ORR, n/N (%)</td>
<td>40/83 (48) (37, 59)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>6.9 (5.4, 9.5)</td>
</tr>
</tbody>
</table>

**Overall**

- ORR: 39.6%
- Update ASCO19

**Intracranial**

- ORR: 48.1%
- Update ASCO19

---

CI, confidence interval; CT, chemotherapy; DOR, duration of response; mo, months; NR, not reached.

*Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.*

*Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, inversion to normal node size (>10 mm) prevented the percent change from baseline from reaching −100%. Some patients with a total change from baseline of −100% are shown as partial responses due to the inclusion of non-target lesions in the summary.*

---

Updated Efficacy and Safety: B.Besse et al, ASCO 2019

Benjamin J. Solomon et al, WCLC 2017; lancet onco 2018
### Best Response in Patients Harboring the ALK G1202R Mutation

**EXP2–5**

Patients with multiple ALK mutations are detected in either cfDNA or tumor tissue (archival or de novo) analysis sets.

#### Table: ALK Mutation Analysis

<table>
<thead>
<tr>
<th>ALK Mutation</th>
<th>No.</th>
<th>ORR (95% CI), %</th>
<th>Median DOR, Months (95% CI)</th>
<th>Median PFS, Months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1202R/del</td>
<td>28</td>
<td>57 (37 to 76)</td>
<td>7 (6.1 to 24.4)</td>
<td>8.2 (5.6 to 25.6)</td>
</tr>
</tbody>
</table>

**ORR: 57% (37 to 76)**

![Graph showing best overall response]

- **Complete response**
- **Partial response**
- **Stable/No response**
- **Objective progression**

#### Additional Information:

- Patients with multiple ALK mutations
- Objective progression

---

*Detected in either cfDNA or tumor tissue (archival or de novo) analysis sets

Shaw et al, JCO 2019
ORR in Previously Treated Patients With ALK+ NSCLC Harboring the Most Frequent ALK Mutations in cfDNA (EXP2–5)

ALK Kinase Domain Mutations Detected in cfDNA of Previously Treated Patients With ALK+ NSCLC (EXP2–5)

Updated Efficacy and Safety: B.Besse et al, ASCO 2019
ALK resistance mutations in tumor tissue predict response to lorlatinib after a 2nd gen ALK TKI

Shaw et al, JCO 2019

- Tumor ALK mutation positive (n = 29)
  - Median PFS: 11.0 months (95% CI, 6.9 to NR)
- Tumor ALK mutation negative (n = 81)
  - Median PFS: 5.4 months (95% CI, 3.9 to 6.9)
  - HR: 0.47 (95% CI, 0.27 to 0.83)
The 3\textsuperscript{rd} Generation ALK/ROS1 TKI Lorlatinib has become a standard therapy after 2\textsuperscript{nd} Generation TKIs
ALK positive crizo-resistant NSCLC stage IV
Primary resistance to Ceritinib & Brigatinib

- **May 2017**
  - PS 2 (abdominal pain +++ liver)
  - Admitted in the hospital
  - *Blood for “liquid biopsy”*
    - ALK-EML v3 by RT-PCR
    - ALK G1202R mutation

- **Our options:**
  - ✔ Expanded access to Lorlatinib
  - ✔ Platinum-based chemo
  - ✔ Immunotherapy (+/- Chemo)

D. Planchard et al, Gustave Roussy
ctDNA monitoring during treatment

D. Planchard et al, Gustave Roussy, L. Friboulet team at Gustave Roussy; G. Recondo et al, CCR 2019
4 months of Lorlatinib...

Tissu biopsy + Plasma sample

D. Planchard et al, Gustave Roussy
Emergence of 2 mutations ALK - G1202R and F1174L

Unpublished data: do not post

D.Planchard et al, Gustave Roussy, L.Friboulet team at Gustave Roussy
MATCH-R program

Patients with + biomarker tumor exposed to a targeted therapy and an initial response

In vitro patient Cell lines

Mouse xenograft models

Tumor biopsy
Whole-exome sequencing
RNAseq
CGH

PI JC. Soria-F. André and B. Besse at Gustave Roussy
Efficacy of ALK inhibitors on the novel G1202R/F1174L mutations

D.Planchard et al, Gustave Roussy, L.Friboulet team at Gustave Roussy; G.Recondo et al, CCR 2019
Acquired Resistance Mutations to ALK Inhibitors Identified by Single Circulating Tumor Cell Sequencing

Isolation of single CTCs by FACS

Detection of ALK compound mutations in two single CTCs among 12

<table>
<thead>
<tr>
<th>ALK</th>
<th>Mutation</th>
<th>VAF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>T1151M</td>
<td>100%</td>
</tr>
<tr>
<td>ALK</td>
<td>F1174C</td>
<td>31%</td>
</tr>
<tr>
<td>ALK</td>
<td>F1174L</td>
<td>9%</td>
</tr>
<tr>
<td>ALK</td>
<td>G1202R</td>
<td>29%</td>
</tr>
</tbody>
</table>

Number of sorted CTCs (cell sorting)
Percentage of tumor cells in the biopsy
VAF (%) of the SNV
Not mutated
Low coverage

E.Pailler et al, CCR 2019
MTB Decision: CDDP + Pemetrexed...

D. Planchard et al, Gustave Roussy
Emergence of G1202R and S1206F mutations

cDNA monitoring during treatment

D. Planchard et al, Gustave Roussy, L. Friboulet team at Gustave Roussy; G. Recondo et al, CCR 2019
MTB decision: IO...

Lorlatinib  CDDP-PEM  C3 PEM maintenance  IO (PD1 inhibitor)

D. Planchard et al, Gustave Roussy
IMMUNOTARGET cohort, *fusion*+ subgroup

Outcomes in ALK/ROS1/RET + population

<table>
<thead>
<tr>
<th>Driver</th>
<th>N</th>
<th>ORR</th>
<th>mPFS (m)</th>
<th>mOS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALK</td>
<td>23</td>
<td>0</td>
<td>2.5</td>
<td>17</td>
</tr>
<tr>
<td>RET</td>
<td>16</td>
<td>6%</td>
<td>2.1</td>
<td>21.3</td>
</tr>
<tr>
<td>ROS1</td>
<td>7</td>
<td>17%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

PFS by N# line

Patients with ALK, ROS1 or RET mutation

\[ p = 0.47 \]
ALK fusion

EGFR+/ALK+
ORR ALK+: 0/6

EGFR+/ALK+ arm (ATLANTIC Trial)
ORR ALK+ : 0/15

Gainor CCR 2016, Garassino Lancet Oncol 2018
CheckMate 370 (Nivolumab + Crizotinib): Closed Early due to toxicities

- 13 patients enrolled on study
- PR in 5/13 (38%) patients and SD in 2 (15%)
- 5 patients (38%) developed severe hepatic toxicities

Spigel et al, JTO 2018
Increased Hepatotoxicity Associated with Sequential Immune Checkpoint Inhibitor and Crizotinib Therapy

Among the 11 patients treated with an ICI followed by crizotinib, five (cumulative incidence 45.5%) experienced development of a grade 3 or 4 increase in alanine transaminase level and four (cumulative incidence 36.4%) experienced development of a grade 3 or 4 increase in aspartate transaminase level.

Jessica J. Lin et al, JTO 2019
Oncologist against Cancer
Clonal evolution of resistance to sequential ALK targeted therapies

Alice T. Shaw et al NEJM 2016 Satoshi Yoda et al, cancer discovery 2018
Developing the optimal treatment sequence
Next-generation ALK inhibitor as 1st-line treatment

- **PFS1:** 11 m
  - Crizotinib

- **PFS2:** 5.4 m
  - Ceritinib
  - Alectinib

≥ PFS1 + PFS2?

Next generation ALK inhibitor
- Ceritinib
- Alectinib...
ASCEND-4: Phase 3 - Primary Endpoint: PFS by BIRC

Ceritinib Demonstrated an Estimated 45% Risk Reduction Vs Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib (N=189)</th>
<th>Chemotherapy (N=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>89 (47.1)</td>
<td>113 (60.4)</td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td><strong>16.6</strong> (12.6, 27.2)</td>
<td><strong>8.1</strong> (5.8, 11.1)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.55 (0.42, 0.73)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Gilberto de Castro et al, IASLC 2016; JC Soria et al Lancet 2017
Ceritinib Achieved Better PFS in Patients Without and With BM

**Brain metastases at baseline: No**

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib (N=130)</th>
<th>Chemotherapy (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>54 (41.5)</td>
<td>72 (57.6)</td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td><strong>26.3</strong> (15.4, 27.7)</td>
<td>8.3 (6.0, 13.7)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td><strong>0.48</strong> (0.33, 0.69)</td>
<td>1.00 (0.70, 1.40)</td>
</tr>
</tbody>
</table>

**Brain metastases at baseline: Yes**

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib (N=59)</th>
<th>Chemotherapy (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>35 (59.3)</td>
<td>41 (66.1)</td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td><strong>10.7</strong> (8.1, 16.4)</td>
<td>6.7 (4.1, 10.6)</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI) = **0.70** (0.44, 1.12)

Gustave Roussy

ALEX: Progression-Free Survival at Primary Analysis (by Independent Review Committee)

- Median follow up time: alectinib 17.6 months; crizotinib 18.6 months
- Alectinib mPFS = 25.7 months
- Crizotinib mPFS = 10.4 months
- Hazard ratio for disease progression or death: 0.50 (95% CI: 0.36-0.70)
  \( P < 0.0001 \) (log-rank test)
ALEX: Primary and Final Analyses of PFS (by Investigator)

**Primary Analysis**
Median follow-up, **18.6 months**

- **Alectinib (n=152)**
  - Median PFS, months (95% CI): 34.8 (17.7-NE)
  - HR (95% CI): 0.43 (0.32–0.58)
  - Log-rank P value: <0.0001

- **Crizotinib (n=151)**
  - Median PFS, months: 10.9 (9.1-12.9)
  - HR (95% CI): 0.47 (0.34–0.65)
  - Log-rank P value: <0.001

**Final Analysis**
Median follow-up, **37.8 months**

- **Alectinib (n=152)**
  - Median PFS, months (95% CI): 34.8 (17.7-NE)

- **Crizotinib (n=151)**
  - Median PFS, months: 10.9 (9.1-12.9)

---

NE, not evaluable; NR, not reported; PFS, progression-free survival.
ALEX: PFS by Baseline Brain Metastases Status (by Investigator)

### Primary Analysis

**Patients with CNS metastases at baseline**

- **Alectinib (n=64)**
- **Crizotinib (n=58)**

**Patients without CNS metastases at baseline**

- **Alectinib (n=88)**
- **Crizotinib (n=93)**

<table>
<thead>
<tr>
<th></th>
<th>Patients with baseline CNS metastases</th>
<th>Patients without baseline CNS metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alectinib (n=64)</td>
<td>Crizotinib (n=58)</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>25.4</td>
<td>7.4</td>
</tr>
<tr>
<td>HR</td>
<td>0.37</td>
<td>0.46</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.23-0.58</td>
<td>0.31-0.68</td>
</tr>
</tbody>
</table>

### Final Analysis

<table>
<thead>
<tr>
<th></th>
<th>Alectinib (n=88)</th>
<th>Crizotinib (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months</td>
<td>38.6</td>
<td>14.8</td>
</tr>
<tr>
<td>HR</td>
<td>0.51</td>
<td>0.46</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.33-0.80</td>
<td>0.31-0.68</td>
</tr>
</tbody>
</table>

---

*All patients with CNS metastases at baseline, irrespective of radiotherapy.

CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PFS, progression-free survival.

ALEX: PFS HR by Subgroups at Primary Analysis (by Investigator)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/No. of Patients</th>
<th>HR for Disease Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>164/303</td>
<td>0.48 (0.35–0.66)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>125/233</td>
<td>0.48 (0.34–0.70)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>39/70</td>
<td>0.45 (0.24–0.87)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>91/171</td>
<td>0.39 (0.25–0.60)</td>
</tr>
<tr>
<td>Male</td>
<td>73/132</td>
<td>0.61 (0.38–0.98)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>72/138</td>
<td>0.46 (0.28–0.75)</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>92/165</td>
<td>0.49 (0.32–0.75)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active smoker</td>
<td>12/17</td>
<td>1.16 (0.35–3.90)</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>103/190</td>
<td>0.44 (0.29–0.66)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>49/96</td>
<td>0.42 (0.23–0.77)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44/97</td>
<td>0.40 (0.21–0.77)</td>
</tr>
<tr>
<td>1</td>
<td>105/186</td>
<td>0.48 (0.32–0.71)</td>
</tr>
<tr>
<td>2</td>
<td>15/20</td>
<td>0.74 (0.25–2.15)</td>
</tr>
<tr>
<td>CNS metastases at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>78/122</td>
<td>0.40 (0.25–0.64)</td>
</tr>
<tr>
<td>No</td>
<td>86/181</td>
<td>0.51 (0.33–0.80)</td>
</tr>
<tr>
<td>Previous brain radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>26/47</td>
<td>0.33 (0.14–0.74)</td>
</tr>
<tr>
<td>No</td>
<td>138/256</td>
<td>0.52 (0.36–0.73)</td>
</tr>
</tbody>
</table>

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival.

ALESIA (phase III trial in Asian pts) – PFS (investigator)

- Alectinib (n=125)
- Crizotinib (n=62)
- Censored

**Graph:**
- Progression-free survival (%)
- Time (months)
- Median PFS: Alectinib 11.1 months, Crizotinib NE
- HR: 0.22 (95% CI 0.13–0.38)

**Table:**
- Patients with event, n (%): 26 (20.8) vs 37 (59.7)
- Median PFS, months: Alectinib NE, Crizotinib 11.1 (95% CI 20.3–NE 9.1–13.0)
- P-value (log-rank test): P<0.0001

Primary data cut-off: 31 May, 2018
Median duration of follow up (alectinib vs crizotinib): 16.2 vs 15.0 months
The p-values presented for the efficacy endpoints are descriptive only
NE, not estimable

# ALESIA PFS by investigator – Subgroup analysis

<table>
<thead>
<tr>
<th>Baseline risk factors</th>
<th>Alectinib (n=125)</th>
<th>Crizotinib (n=62)</th>
<th>Alectinib better</th>
<th>Crizotinib better</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td><strong>187</strong></td>
<td><strong>62</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>125</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median</strong> (months)</td>
<td>NE</td>
<td>11.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.24</td>
<td>(0.14–0.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age group, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>166</td>
<td>52</td>
<td>0.24</td>
<td>(0.14–0.42)</td>
</tr>
<tr>
<td>≥65</td>
<td>21</td>
<td>10</td>
<td>0.21</td>
<td>(0.04–1.08)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>89</td>
<td>28</td>
<td>0.35</td>
<td>(0.16–0.78)</td>
</tr>
<tr>
<td>Male</td>
<td>98</td>
<td>34</td>
<td>0.17</td>
<td>(0.09–0.34)</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active smoker</td>
<td>7</td>
<td>3</td>
<td>&lt;0.01</td>
<td>(0.00–NE)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>129</td>
<td>45</td>
<td>0.30</td>
<td>(0.16–0.55)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>51</td>
<td>14</td>
<td>0.15</td>
<td>(0.06–0.41)</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>26</td>
<td>8</td>
<td>0.40</td>
<td>(0.10–1.62)</td>
</tr>
<tr>
<td>1</td>
<td>156</td>
<td>53</td>
<td>0.20</td>
<td>(0.11–0.36)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>1</td>
<td>&lt;0.01</td>
<td>(0.00–NE)</td>
</tr>
<tr>
<td><strong>CNS mets at baseline (IRC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67</td>
<td>23</td>
<td>0.11</td>
<td>(0.05–0.28)</td>
</tr>
<tr>
<td>No</td>
<td>120</td>
<td>39</td>
<td>0.34</td>
<td>(0.18–0.85)</td>
</tr>
<tr>
<td><strong>Prior brain radiation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>5</td>
<td>0.13</td>
<td>(0.02–0.70)</td>
</tr>
<tr>
<td>No</td>
<td>174</td>
<td>57</td>
<td>0.25</td>
<td>(0.14–0.43)</td>
</tr>
</tbody>
</table>

Zhou C et al, lancet Respir Med 2019

Mets, metastases
ALTA-1L, Primary Endpoint: BIRC-Assessed PFS

- Brigatinib met the prespecified threshold for statistical superiority vs crizotinib

Investigator-assessed median PFS was NR (95% CI, NR–NR) in the brigatinib arm and 9.2 months (95% CI, 7.4–12.9 months) in the crizotinib arm (HR, 0.45 [95% CI, 0.30–0.68]; log-rank P=0.0001)

1-year OS probability: brigatinib, 85% (95% CI, 76–91%); crizotinib, 86% (77–91%)

D Ross Camidge et al, IASCL 2018; DR Camidge et al, NEJM 2018
### Intracranial PFS

**Patients With Any Brain Metastases at Baseline**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. (%) Patients With Events</th>
<th>Median Intracranial PFS (95% CI)</th>
<th>1-Year PFS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brigatinib (n=43)</td>
<td>11 (26)</td>
<td>NR (11.0–NR)</td>
<td>67 (47–80)</td>
</tr>
<tr>
<td>Crizotinib (n=47)</td>
<td>26 (55)</td>
<td>0</td>
<td>21 (6–42)</td>
</tr>
<tr>
<td></td>
<td>2 (4)</td>
<td>5.6 months (4.1–9.2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. (%) Patients With Events</th>
<th>Median Intracranial PFS (95% CI)</th>
<th>1-Year PFS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brigatinib (n=94)</td>
<td>2 (2)</td>
<td>9 (10)</td>
<td>NR (NR)</td>
</tr>
<tr>
<td>Crizotinib (n=91)</td>
<td>7 (8)</td>
<td>4 (4)</td>
<td>NR (NR)</td>
</tr>
</tbody>
</table>

- Intracranial PFS was significantly improved with brigatinib compared with crizotinib in the ITT population (HR, 0.42; 95% CI. 0.24–0.70; P=0.0006 by log-rank test)

**HR: 0.27**

**Patients Without Brain Metastases at Baseline**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. (%) Patients With Events</th>
<th>Median Intracranial PFS (95% CI)</th>
<th>1-Year PFS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brigatinib (n=91)</td>
<td>75</td>
<td>NR (NR)</td>
<td>NR (NR)</td>
</tr>
<tr>
<td>Crizotinib (n=76)</td>
<td>65</td>
<td>15</td>
<td>42 (18–80)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. (%) Patients With Events</th>
<th>Median Intracranial PFS (95% CI)</th>
<th>1-Year PFS, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brigatinib (n=94)</td>
<td>2 (2)</td>
<td>9 (10)</td>
<td>NR (NR)</td>
</tr>
<tr>
<td>Crizotinib (n=91)</td>
<td>7 (8)</td>
<td>4 (4)</td>
<td>NR (NR)</td>
</tr>
</tbody>
</table>

HR for intracranial progression or death, 0.96 (95% CI, 0.42–2.22), P=0.9274 by log-rank test
Efficacy in EXP1 (Lorlatinib): ALK+, treatment-naïve patients

<table>
<thead>
<tr>
<th></th>
<th>EXP1 (n=30)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n/N (%) (95% CI)</td>
<td>27/30 (90)</td>
<td>(74, 98)</td>
<td></td>
</tr>
<tr>
<td>IC ORR, n/N (%) (95% CI)</td>
<td>6/8 (75)</td>
<td>(35, 97)</td>
<td></td>
</tr>
<tr>
<td>Median DOR, mo (95% CI)</td>
<td>NR</td>
<td>(10.2, NR)</td>
<td></td>
</tr>
<tr>
<td>DOR ≥6 mo, n²/n (%)</td>
<td>16/27 (59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>NR</td>
<td>(11.4, NR)</td>
<td></td>
</tr>
</tbody>
</table>

A total of eight patients (27%) had brain metastases at baseline.

ORR: 90%  IC-ORR 75%

Treatment with lorlatinib in treatment-naïve patients gave impressive ORR (90%) and IC ORR (75%). The CROWN trial of crizotinib vs lorlatinib will further address lorlatinib in the first line relative to current standard of care.

CROWN: Phase 3, Randomized, Open-label Study of Lorlatinib vs Crizotinib in 1L ALK+ NSCLC (NCT03052608)

**Primary endpoint:** Blinded independent central review (BICR)–assessed PFS

**Key secondary endpoints:** OS, PFS (Investigator), ORR by BICR and Investigator (per RECIST v1.1), intracranial objective response (BICR), intracranial time to progression, duration of response (BICR), time to tumor response (BICR), clinical benefit response (BICR), PFS2 (Investigator)

### Eligibility Criteria
- Locally advanced or metastatic ALK+ NSCLC
- At least 1 extracranial measurable target lesion (not previously irradiated)
- No prior systemic therapy for NSCLC
- ECOG PS 0-2
- Asymptomatic, untreated brain metastases were allowed

N=280

### Treatment
- Lorlatinib 100 mg qd
- Crizotinib 250 mg bid

**Recruiting**

**Primary Completion Date:** December 31, 2020

1L, first line; ALK, anaplastic lymphoma kinase; bid, twice per day; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; qd, every day.

[https://clinicaltrials.gov/ct2/show/NCT03052608](https://clinicaltrials.gov/ct2/show/NCT03052608)
exAlt3: Phase 3, Randomized, Open-label Study of Ensartinib vs Crizotinib in 1L ALK+ NSCLC (NCT02767804)

- Stage IIIIB or IV ALK+ NSCLC
  - By FDA-approved assay performed centrally
- At least 1 extracranial measurable target lesion (not previously irradiated)
- ≤1 prior chemotherapy regimen for metastatic disease
- ECOG PS 0-2
- Asymptomatic, untreated brain metastases were allowed

N=290

R 1:1

Ensartinib 225 mg qd

Crizotinib 250 mg bid

• PD
• Unacceptable toxicity

Primary endpoint: PFS by independent radiology review (per RECIST v1.1)

Key secondary endpoints: OS, ORR (independent radiology review and Investigator), PFS (Investigator), time to response (independent radiology review), duration of response (independent radiology review and Investigator)

Active Primary Completion Date: November 4, 218

1L, first line; ALK, anaplastic lymphoma kinase; bid, twice per day; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; qd, every day.

https://clinicaltrials.gov/ct2/show/NCT03052608
# Available and Emerging ALK Inhibitors in First-Line: Overview of Phase 3 Study Designs

<table>
<thead>
<tr>
<th>Study</th>
<th>ALK Testing</th>
<th>Prior Therapy</th>
<th>CNS Metastases</th>
<th>Primary Endpoint</th>
<th>CNS Imaging Assessment</th>
<th>Crossover</th>
<th>Stratification</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROFILE 1014[^1,2]</td>
<td>FISH; central</td>
<td>Treatment naïve</td>
<td>26% vs 27%</td>
<td>IRC PFS</td>
<td>CT or MRI</td>
<td>Allowed</td>
<td>ECOG PS ≤1 vs 2; presence vs absence of CNS metastases; Asian vs non-Asian</td>
</tr>
<tr>
<td>ASCEND-4[^3]</td>
<td>IHC; central</td>
<td>Treatment naïve</td>
<td>31% vs 33%</td>
<td>IRC PFS</td>
<td>CT or MRI</td>
<td>Allowed</td>
<td>WHO PS, CNS metastases, adjuvant chemotherapy</td>
</tr>
<tr>
<td>ALEX[^4]</td>
<td>IHC; central</td>
<td>Treatment naïve</td>
<td>42% vs 38%</td>
<td>IA PFS</td>
<td>CT or MRI</td>
<td>Not allowed</td>
<td>ECOG PS ≤1 vs 2, Asian vs non-Asian, presence vs absence of CNS metastases</td>
</tr>
<tr>
<td>eXalt3[^5]</td>
<td>IHC, FISH, or RT-PCR; central</td>
<td>≤1 prior chemotherapy</td>
<td>14% vs 28%</td>
<td>IRC PFS</td>
<td>Not specified</td>
<td>Allowed</td>
<td>ECOG PS ≤1 vs 2, prior chemotherapy, clinical stage (IIIB/IV vs postoperative recurrent)</td>
</tr>
<tr>
<td>J-ALEX[^7]</td>
<td>IHC; central</td>
<td>Treatment naïve</td>
<td>35% vs 37%</td>
<td>IA PFS</td>
<td>MRI</td>
<td>Not allowed</td>
<td>ECOG PS ≤1 vs 2, presence vs absence of CNS metastases</td>
</tr>
<tr>
<td>ALTA-1L[^9]</td>
<td>IHC, central</td>
<td>≤1 prior chemotherapy</td>
<td>29% vs 30%</td>
<td>IRC PFS</td>
<td>MRI</td>
<td>Allowed</td>
<td>Presence vs absence of CNS metastases, prior chemotherapy</td>
</tr>
<tr>
<td>CROWN[^11]</td>
<td>FISH or IHC; not specified</td>
<td>Treatment naïve</td>
<td>NA</td>
<td>IRC PFS</td>
<td>Not specified</td>
<td>Not allowed</td>
<td>Presence vs absence of CNS metastases; Asian vs non-Asian</td>
</tr>
</tbody>
</table>

**Notes:**
- ALK, anaplastic lymphoma kinase; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group; FISH, fluorescent in situ hybridization; IA, investigator assessed; IHC, immunohistochemistry; IRC, independent review committee; PS, performance status; WHO, World Health Organization.
## Safety profiles

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib(^1)</th>
<th>Ceritinib(^2)</th>
<th>Alectinib(^3)</th>
<th>Brigatinib(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3+ AEs in ≥5% of patients</td>
<td>↑ AST/ALT 14% ↓ ANC 11%</td>
<td>↑ ALT 31% ↑ GGT 29% ↑ ALP 29% ↑ AST 17% Diarrhea 5% Vomiting 5%</td>
<td>↑ ALT 5% ↑ AST 5% Anaemia 5%</td>
<td>↑ CPK 16% ↑ Lipase 13% Hypertension 10% ↑ Amylase 5%</td>
</tr>
<tr>
<td>Any Grade AE → Dose Reduction</td>
<td>21%</td>
<td>(80%)*</td>
<td>16%</td>
<td>29%</td>
</tr>
<tr>
<td>Any Grade AE → Treatment Discontinuation</td>
<td>12%</td>
<td>5%</td>
<td>11%</td>
<td>12%</td>
</tr>
</tbody>
</table>

ASCEND-8\(^5\): 450mg (fed) vs. 750mg (fasted)

**Equivalent efficacy**

**Less GI toxicity**

---

Best sequence?
Best sequence?

You don’t manage only ONE line
It is a MARATHON
Updated Results from PROFILE 1014: Final Primary OS Analysis (ITT Population)

Median follow-up ~46 months in both arms

HR 0.760 (95%CI: 0.548, 1.053); \( a \)P=0.0978

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=172)</th>
<th>Chemotherapy (N=171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>71 (41.3)</td>
<td>81 (47.4)</td>
</tr>
<tr>
<td>Median OS (95% CI), months</td>
<td>NR (45.8, NR)</td>
<td>47.5 (32.2, NR)</td>
</tr>
</tbody>
</table>

4 year OS rate
Crizo: 56.6%
Chemo: 49.1%

T.Mok et al, ASCO 2017, B.J Solomon et al, JCO 2018
Impact of Subsequent Therapy on OS: ALK TKI versus Treatment Other Than ALK TKI

No. at risk

Crizotinib followed by any ALK TKI
57 57 57 57 50 45 42 40 33 25 16 8 3 1 0
Crizotinib followed by any follow-up therapy other than ALK TKI
37 36 30 22 19 16 13 9 5 3 2 1 0 0 0
Chemotherapy followed by any ALK TKI
145 136 123 113 97 86 79 70 60 43 30 20 10 1 0
Chemotherapy followed by any follow-up therapy other than ALK TKI
3 2 2 1 1 1 1 1 1 1 1 1 1 0 0

T.Mok et al, ASCO 2017, B.J Solomon et al, JCO 2018
ALK patients: outstanding OS (French EAP)

EAP CLINALK

N=318
Crizo → next gen. TKIs.
OS = 7.5 years
Secondary endpoint: OS

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib (N=151)</th>
<th>Alectinib (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n (%)</td>
<td>40 (27)</td>
<td>35 (23)</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (NR)</td>
<td>NR (NR)</td>
</tr>
<tr>
<td>HR (95% CI) P-value (log-rank test)</td>
<td>0.76 (0.48–1.20)</td>
<td>P=0.24</td>
</tr>
</tbody>
</table>

Peters S et al, NEJM 2017
Stage IV lung carcinoma with ALK translocation

Crizotinib [I, A; MCBS 4]
Alectinib [I, A; MCBS 4]
Certitnib [I, B; MCBS 4]
Brigatinib [I, B]a

Disease progression

Oligoprogression

Local treatment (surgery or RT) and continue targeted systemic treatment

Systemic progression

Systemic progression

Re-biopsy recommended (not mandatory for decision)

Alectinib [I, A; MCBS 4]
Certitnib [I, A; MCBS 4]

Systemic progression

Platinum-based ChT (see Figure 2)
In selected cases, alternative new generation ALK TKIs if available (lorlatinib, brigatinib) [II, B]a
Carboplatin/paclitaxel/bevacizumab/atezolizumab [III, B]a

D. Planchard et al, annals of onco 2018
Brigatinib – 3001: Phase 3, Open-label, Multicenter International Study

**Primary endpoint:** PFS per RECIST 1.1 as assessed by BIRC

**Secondary endpoints:**
- time to intracranial progression by BIRC
- ORR by BIRC
- intracranial ORR (iORR) by BIRC (modified RECIST v1.1)
- time to response by BIRC
- intracranial duration of response by BIRC (iDOR)

**Statistical considerations:** ~246 total patients (164 events) to detect an improvement in median PFS from 9 to 15 months (HR=0.60)

**IA at 70% PFS events**

**Locally advanced or metastatic ALK+ NSCLC**
- Disease progression on crizotinib
- 0-2 lines prior chemotherapy

(N=246)

**Arm A:**
- Alunbrig™ 90 mg → 180 mg qd

**Arm B:**
- Alecensa® 600 mg po bid with food

Stratified by:
- Brain metastases at baseline
- Best response to prior crizotinib (CR/PR vs SD/PD/other)

Disease assessment q8w (including brain MRI for all patients)

ALK, anaplastic lymphoma kinase; bid, twice per day; BIRC, blinded independent review committee; IA, interim analysis; NSCLC, non–small cell lung cancer; po, by mouth; qd, every day; q8w, every 8 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.
Biomarker integration in the management of patients with ALK-NSCLC, post crizotinib

Gonzalo Recondo et al, nature reviews 2018
Biomarker integration in the management of patients with ALK-NSCLC, 2\textsuperscript{nd} or 3\textsuperscript{rd} generation

Resistance mutations in ALK KD with next-generation ALK TKIs

- Alectinib:
  - V1180L
  - I1171T/N/S
  - Ceritinib
  - Brigatinib
  - Lorlatinib

- Ceritinib:
  - F1174L/C/V
  - C1156Y
  - Alectinib
  - Brigatinib
  - Lorlatinib

- Brigatinib:
  - E1210K + S1203N
  - E1210K + S1206C
  - Lorlatinib

- Any second-generation:
  - G1202R
  - Lorlatinib

- Lorlatinib:
  - C1156Y + L1198F
  - Crizotinib

Gonzalo Recondo et al, nature reviews 2018
THANK YOU!

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