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April 28, 2018
Edgardo S. Santos, M.D., FACP
EGFR & ALK: Where Are We Now?

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Speakers Bureau: Genentech, Pfizer, Novartis, Merck, Celgene, Amgen, AstraZeneca, Lilly, Takeda, Boehringer-Ingelheim

The speaker will directly disclose the use of products for which are not labeled (e.g., off label use) or if the product is still investigational.
Survival with the five most frequent oncogenic drivers

<table>
<thead>
<tr>
<th>Altered Gene</th>
<th>N</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR (sensitizing)</td>
<td>140</td>
<td>4.0 years (2.7 to 5.4)</td>
</tr>
<tr>
<td>EGFR (other)</td>
<td>50</td>
<td>3.3 years (2.2 to 6.2)</td>
</tr>
<tr>
<td>ALK</td>
<td>73</td>
<td>4.3 years (3.0 to NA)</td>
</tr>
<tr>
<td>KRAS</td>
<td>231</td>
<td>2.4 years (1.9 to 3.6)</td>
</tr>
<tr>
<td>Drivers in Two Genes</td>
<td>32</td>
<td>2.0 years (1.6 to 4.6)</td>
</tr>
</tbody>
</table>

Kris and Johnson; JAMA 2014
What’s New From ASCO 2017, ESMO 2017, WCLC 2017, ELCC 2018?
EGFR MUTANT TUMORS
Activating mutations in the EGFR kinase domain confer therapeutic vulnerability to EGFR TKIs

The prevalence of EGFR mut. lung adenocarcinoma varies between different countries.

Different types of EGFR TKIs have been developed:

1st gen. (erlotinib, gefitinib)
- 4-Anilino-quinazoline
  - reversible, non covalent binding

2nd gen. (afatinib, dacomitinib)
- Anilino-quinazoline
  - covalent, irreversible binding

3rd gen. (osimertinib)
- Mono-anilino-pyrimidine
  - covalent, irreversible binding

Midha et al, Am J Cancer Res 2015

Wang et al, Oncotargets and Therapy 2016
Is There A Controversy? Yes or No

SHOULD OSIMERTINIB BE THE FIRST LINE THERAPY IN EGFR SENSITIVE MUTATION?

- **Osimertinib** > Gefitinib/Erlotinib (FLAURA study; phase III)
- Afatinib vs Osimertinib? (no data)
- Afatinib > Gefitinib (LUX-Lung 7; phase IIb)
- Dacomitinib > Gefitinib (ARCHER 1050; phase III trial)

"Sequence vs No Sequence" .... The question?

THIS IS NOW!!! APRIL 28, 2018
April 18, 2018

US FDA approves Osimertinib as 1st-line treatment for EGFR-mutated non-small cell lung cancer

First line use of Osimertinib offers potential new standard of care; Osimertinib delivered unprecedented median progression-free survival of 18.9 months versus 10.2 months compared with current standard of care

AstraZeneca today announced that the US Food and Drug Administration (FDA) has approved Osimertinib for the 1st-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations, (exon 19 deletions or exon 21 L858R mutations), as detected by an FDA-approved test. The approval is based on results from the Phase III FLAURA trial, which were presented at the European Society of Medical Oncology 2017 Congress and published in the New England Journal of Medicine.
OSIMERTINIB VS STANDARD-OF-CARE EGFR-TKI AS FIRST-LINE TREATMENT IN PATIENTS WITH EGFRm ADVANCED NSCLC: FLAURA

Ramalingam SS¹, Reungwetwattana T², Chewaskulyong B³, Dechaphunkul A⁴, Lee KH⁵, Imamura F⁶, Nogami N⁷, Ohe Y⁸, Cheng Y⁹, Cho BC¹⁰, Cho EK¹¹, Vansteenkiste J¹², Voon PJ¹³, Zhou C¹⁴, Gray JE¹⁵, Hodge R¹⁶, Rukazenkov Y¹⁶, Soria JC¹⁷

¹Emory University, Winship Cancer Institute, Atlanta, GA, USA; ²Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; ³Oncology Unit, Department of Medicine, Chiang Mai University, Chiang Mai, Thailand; ⁴Prince of Songkla University, Songkhla, Hat-Yai, Thailand; ⁵Division of Medical Oncology, Chungbuk National University College of Medicine, Chungbuk National University College of Medicine, Cheongju, Korea; ⁶Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan; ⁷Department of Thoracic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; ⁸Department of Internal Medicine, National Cancer Center Hospital, Tokyo, Japan; ⁹Jilin Provincial Cancer Hospital, Changchun, China; ¹⁰Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; ¹¹Division of Hematology and Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea; ¹²University Hospital KU Leuven, Leuven, Belgium; ¹³Hospital Unum Sarawak, Kuching, Malaysia; ¹⁴Pulmonary Hospital of Tongji University, Shanghai, China; ¹⁵Department of Thoracic Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; ¹⁶AstraZeneca, Cambridge, United Kingdom; ¹⁷Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France

Presented by SS Ramalingam at the European Society of Medical Oncology Congress 2017
FLAURA DOUBLE-BLIND STUDY DESIGN

**Patients with locally advanced or metastatic NSCLC**
- Key inclusion criteria
  - ≥18 years*
  - WHO performance status 0 / 1
  - Exon 19 deletion / L858R (enrolment by local\* or central\† EGFR testing)
  - No prior systemic anti-cancer / EGFR-TKI therapy
  - Stable CNS metastases allowed

**Stratification by mutation status**
- (Exon 19 deletion / L858R) and race
  - (Asian / non-Asian)

**Osimertinib**
- (80 mg p.o. qd)
- (n=279)

**Randomised 1:1**

**EGFR-TKI SoC**
- Gefitinib (250 mg p.o. qd) or
- Erlotinib (150 mg p.o. qd)
- (n=277)

**RECIST 1.1 assessment every 6 weeks\‡ until objective progressive disease**

Crossover was allowed for patients in the SoC arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

**Endpoints**
- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

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*FLAURA data cut-off: 12 June 2017; NCT02296125
\*250 years in Japan; \†With central laboratory assessment performed for sensitivity; \‡Assays EGFR Mutation Test (Roche Molecular Systems). \§Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; \‡Every 12 weeks after 18 months CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; p.o., orally; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; qd, once daily; SoC, standard-of-care; TKI, tyrosine kinase inhibitor; WHO, World Health Organization*
PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)

Median PFS, months (95% CI)
- Osimertinib: 18.9 (15.2, 21.4)
- SoC: 10.2 (9.6, 11.1)

HR 0.46
(95% CI 0.37, 0.57)
p<0.0001
PFS* IN PATIENTS WITH AND WITHOUT CNS METASTASES AT STUDY ENTRY

With CNS metastases (n=116)

- Median PFS, months (95% CI)
  - Osimertinib: 15.2 (12.1, 24.4)
  - SoC: 9.6 (7.0, 12.4)

- HR 0.47
  - (95% CI 0.30, 0.74)
  - p=0.0009

Without CNS metastases (n=440)

- Median PFS, months (95% CI)
  - Osimertinib: 19.1 (15.2, 23.5)
  - SoC: 10.9 (9.6, 12.3)

- HR 0.46
  - (95% CI 0.36, 0.59)
  - p<0.0001

CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

FLAURA data cut-off: 12 June 2017
Tick marks indicate censored data; *By investigator assessment
CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PFS, progression-free survival; SoC, standard-of-care
## Drug Exposure in the Brain

<table>
<thead>
<tr>
<th></th>
<th>Osimertinib</th>
<th>Gefitinib</th>
<th>Rociletinib</th>
<th>Afatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>25</td>
<td>6.25</td>
<td>100</td>
<td>7.5</td>
</tr>
<tr>
<td>Plasma $C_{\text{max}}$ (µmol/L)</td>
<td>0.82</td>
<td>0.82</td>
<td>3.32</td>
<td>0.14</td>
</tr>
<tr>
<td>Brain $C_{\text{max}}$ (µmol/L)</td>
<td>2.78</td>
<td>0.17</td>
<td>BLQ</td>
<td>BLQ</td>
</tr>
<tr>
<td>Brain/plasma $C_{\text{max}}$ ratio</td>
<td>3.41</td>
<td>0.21</td>
<td>&lt;0.08</td>
<td>&lt;0.36</td>
</tr>
</tbody>
</table>

NOTE: Doses equivalent to clinical doses or reported previously.

Abbreviation: BLQ, below limit of quantification (rociletinib 0.25 µmol/L, afatinib 0.05 µmol/L); $C_{\text{max}}$, maximum plasma concentration.

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![PET images of drug exposure in the brain](image_url)

OVERALL SURVIVAL INTERIM ANALYSIS

141 deaths in 556 patients at DCO: 25% maturity; osimertinib: 58 deaths (21%), SoC: 83 deaths (30%)

HR 0.63
(95% CI 0.45, 0.88)
p=0.0068†

†A p-value of <0.0015 was required for statistical significance at current maturity

Median overall survival
- Osimertinib: Not reached
- SoC: Not reached

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>No. at risk Osimertinib</th>
<th>No. at risk SoC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>279</td>
<td>277</td>
</tr>
<tr>
<td>3</td>
<td>276</td>
<td>263</td>
</tr>
<tr>
<td>6</td>
<td>269</td>
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<td>18</td>
<td>154</td>
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<td>21</td>
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<tr>
<td>27</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
So, based on the FLAURA study.....

Should the winner take it all?
Molecular mechanisms of acquired resistance to 1st and 2nd gen. TKIs: in about 60% of cases EGFR T790M resistance mutation.

Yu et al., Clin Cancer Res 2013
Optimal sequence for EGFR mutation?

First generation TKI (10 months) → Osimertinib for T790M (10 months) → OS?

Second generation TKI (14-16 months) → Chemo (5 months) → Osimertinib for T790M (10 months) → OS?

Osimertinib (19 months) → Chemo (5 months)
3rd gen. EGFR-TKI as 1st line therapy are superior to 1st gen. inhibitors

Initial biopsy

EGFR del 19 L858R

Erlotinib, Gefitinib (8-10m)

T790M

Osimertinib (8-10m)

Osimerinib (18.9m)

PD: rebiopsy

FLAURA
Phase III
Osimertinib vs. Standard EGFR-TKI

Median PFS, months (95%KI)
18.9 (15.2; 21.4)
10.2 (9.6; 11.1)

HR 0.46
(95%KI 0.37; 0.57)
p<0.0001

Soria et al, NEJM 2018
Sequential therapy in EGFRmut NSCLC: increasingly molecularly guided

1\textsuperscript{st} gen. EGFR-TKI
PFS: 10 m

T790M+
Osimertinib
PFS: 10 m

T790M-
Chemo
PFS: 5 m

2\textsuperscript{nd} gen. EGFR-TKI
PFS: 14.7 m (dacom.)

T790M+
Osimertinib
PFS: 10 m

T790M-
Chemo
PFS: 5 m

alternatively: 1\textsuperscript{st} gen. EGFR TKI + bevacizumab:
\textit{T790M+}: PFS 16 m / \textit{T790M-}: PFS 10 m

Osimertinib PFS: 19 m

PD: rebiopsy

EGFR C797S
EGFR G724S
hl MET amp.
HER2 amp.
KRAS Mut

Targeted therapies
Chemo-therapy

OS ?
Genetic alterations associated with Acquired Resistance to Osimertinib

Target-dependent

- C797S
- G724S
- L718Q
- G796S/R/D
- L792F/H/Y

Target-independent

- MET amplification
- HER2 amplification
- EGFR amplification
- KRAS amplification
- KRAS\textsuperscript{G12S}
- BRAF\textsuperscript{V600E}
- MEK\textsubscript{1}\textsuperscript{G128V}
- JAK\textsubscript{2}\textsuperscript{V617F}
- ERBB2 exon 20 insertion
- FGFR3-TACC3 fusions
- small cell transformation
Arguments for 3rd gen. inhibitor 1st line

- PFS superior to 1st and 2nd gen. TKI
- Treatment option for all pts. (not only in T790M+)
- Toxicity profile better
- Evidence also for brain mets

> final OS analysis of FLAURA might underline these arguments

PD: rebiopsy
The Case for Using Osimertinib as 1st Line Tx

- Superior PFS
- Favorable OS trend (cross-over allowed)
- CNS activity
- Better tolerance
- Overcome key resistance mechanisms

Suresh Ramalingam. Is PFS Still a Relevant Endpoint for 1st Line TKI? European Lung Cancer Congress, April 11-14, 2018
APPLE Trial under EORTC

Randomized, open-label, multicenter, 3-arms, phase II study in advanced, G-mutant and EGFR TKI naïve NSCLC patients, to evaluate the best strategy of sequencing gefitinib and osimertinib treatment.
What about uncommon EGFR mutations and EGFR exon 20 insertion mutations?

<table>
<thead>
<tr>
<th>EGFR mutation</th>
<th>Approximate frequency (%)</th>
<th>EGFR TKI [in vitro sensitivity and expected overall response rate (ORR)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1st generation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gefitinib 250 mg</td>
</tr>
<tr>
<td>Sensitizing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion</td>
<td>45.0</td>
<td>++++ (ORR &gt;70%)</td>
</tr>
<tr>
<td>L858R</td>
<td>35.0</td>
<td>++++ (ORR &gt;80%)</td>
</tr>
<tr>
<td>G719X</td>
<td>3.0</td>
<td>+++ (ORR &gt;55%)</td>
</tr>
<tr>
<td>L861Q</td>
<td>3.0</td>
<td>++ (ORR &gt;55%)</td>
</tr>
<tr>
<td>S768I</td>
<td>&lt;1.5</td>
<td>+ (ORR &gt;45%)</td>
</tr>
<tr>
<td>Exon 18 indel/E709X</td>
<td>&lt;0.5</td>
<td>++ (ORR &gt;55%)</td>
</tr>
<tr>
<td>Exon 19 insertion</td>
<td>&lt;0.5</td>
<td>++ (ORR &gt;55%)</td>
</tr>
<tr>
<td>A763_Y764insFQEA</td>
<td>&lt;0.5</td>
<td>++ (ORR &gt;55%)</td>
</tr>
<tr>
<td>Exon 18–25 duplication (EGFR-KDD)</td>
<td>&lt;0.5</td>
<td>++ (ORR &gt;55%)</td>
</tr>
<tr>
<td>Rearrangement (EGFR-RAD51)</td>
<td>&lt;0.5</td>
<td>++ (ORR &gt;55%)</td>
</tr>
<tr>
<td>Insensitizing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 20 insertion</td>
<td>&gt;7.0</td>
<td>- (ORR &lt;5%)</td>
</tr>
<tr>
<td>T790M inherited</td>
<td>&lt;1.0</td>
<td>- (ORR ~0%)</td>
</tr>
<tr>
<td>Others</td>
<td>&gt;2.0</td>
<td>? (ORR ?)</td>
</tr>
<tr>
<td>Acquired resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T790M + sens.</td>
<td>&gt;50.0 (1st/2nd gen. TKI)</td>
<td>- (ORR ~0%)</td>
</tr>
<tr>
<td>C797X + T790M + sens.</td>
<td>&lt;50.0 (osimertinib)</td>
<td>- (ORR &lt;0%)</td>
</tr>
</tbody>
</table>

++++, maximum inhibition; ++++, moderate inhibition; ++, adequate inhibition; +, minimal inhibition; -, no significant inhibition beyond the therapeutic window of wild-type EGFR; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ?, unknown; sens, sensitizing mutation; gen., generation.
# Uncommon EGFR mutations: afatinib 1\textsuperscript{st} line indication extended (Jan 2018)

<table>
<thead>
<tr>
<th>EGFR Mutation</th>
<th>Number of Afatinib Treated Patients (N = 32)</th>
<th>Number of Confirmed Responses (N=21)</th>
<th>Duration of Response (months) (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S768I</td>
<td>1</td>
<td>1</td>
<td>37.3</td>
</tr>
<tr>
<td>S768I and G719X</td>
<td>5</td>
<td>4</td>
<td>4.1, 13.2, 15.2, 29.5+</td>
</tr>
<tr>
<td>S768I and L858R</td>
<td>2</td>
<td>1</td>
<td>34.5+</td>
</tr>
<tr>
<td>G719X</td>
<td>8</td>
<td>6</td>
<td>5.7+, 8.1, 9.6, 23.5+, 25.2, 31.8+</td>
</tr>
<tr>
<td>G719X and L861Q</td>
<td>3</td>
<td>2</td>
<td>2.8+, 6.8</td>
</tr>
<tr>
<td>L861Q</td>
<td>12</td>
<td>7</td>
<td>2.8, 4.0, 4.1, 8.3+, 12.9, 15.2, 20.6</td>
</tr>
<tr>
<td>L861Q and Del 19</td>
<td>1</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

+ response ongoing at time of censoring

**Subset analysis LUX lung 2,3,6 (32pts):**

- **ORR:** 66%
- **DOR > 12m:** 52%
EGFR exon 20 insertion mutations: no therapeutic efficacy of 1st and 2nd gen. EGFR-TKIs > poziotinib induces partial response in 73% (8/11)

Elamin et al., WCLC 2017 abstract ID 10369
ALK Translocation Present
Controversy

SHOULD ALECTINIB BE THE **UNDISPUTABLE** FIRST LINE THERAPY IN ALK MUTANT LUNG CANCERS?

Crizotinib vs Alectinib (ALEX study)

Resurrection of Ceritinib

Brigatinib given unprecedented results in crizotinib-naïve pts

The question here **IS NOT** Sequence vs No Sequence....

**IT IS**: WHAT SHOULD BE THE SEQUENCE?

THIS IS NOW!!! APRIL 28, 2018
Alectinib vs crizotinib in treatment-naïve advanced ALK+ NSCLC: primary results of the global phase III ALEX study (LBA9008)

Alice Shaw¹, Solange Peters², Tony Mok³, Shirish M. Gadgeel⁴, Jin Seok Ahn⁵, Sai-Hong Ignatius Ou⁶, Maurice Perol⁷, Rafał Dziadzioṣko⁸, Dong-Wan Kim⁹, Rafael Rosell¹⁰, Ali Zeaiter¹¹, Ting Liu¹¹, Sophie Golding¹¹, Bogdana Balas¹¹, Johannes Noe¹¹, Peter N. Morcos¹², and D. Ross Camidge¹³ on behalf of the ALEX investigators

1. Massachusetts General Hospital, Boston, MA, USA; 2. Lausanne University Hospital, Switzerland; 3. Chinese University of Hong Kong, Hong Kong; 4. Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; 5. Sungkyunkwan University School of Medicine, Seoul, South Korea; 6. Chao Family Comprehensive Cancer Center, University of California, Irvine School of Medicine, Orange, CA, USA; 7. Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France; 8. Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; 9. Seoul National University Hospital, Seoul, South Korea; 10. Catalan Institute of Oncology, Barcelona, Spain; 11. F. Hoffmann-La Roche Ltd, Basel, Switzerland; 12. Roche Innovation Center, New York, USA; 13. University of Colorado, Denver, CO, USA
Study design

KEY ELIGIBILITY
- Advanced or metastatic ALK+ NSCLC
- ALK+ by central IHC testing
- Treatment-naive
- ECOG PS 0–2
- Measurable disease
- Asymptomatic brain metastases allowed

ENDPOINTS
- Primary
  - PFS (RECIST 1.1), by investigator review
- Secondary
  - PFS by IRC
  - Time to CNS progression
  - ORR, DOR
  - OS
  - Safety and tolerability
  - Patient-reported outcomes

Alectinib
600 mg BID PO

NO CROSSOVER per protocol

Crizotinib
250 mg BID PO

RANDOMIZE
N=286

Stratification factors:
- ECOG PS (0/1 vs 2)
- Race (Asian vs non-Asian)
- Brain metastases (present vs absent)

ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PO, by mouth; PFS, progression-free survival; IRC, independent review committee; CNS, central nervous system; ORR, objective response rate; DOR, duration of response; OS, overall survival

Presented by: Alice T. Shaw

Presented By Alice Shaw at 2017 ASCO Annual Meeting
Primary endpoint: PFS, investigator-assessed

<table>
<thead>
<tr>
<th>Months</th>
<th>Crizotinib</th>
<th>Alectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>151</td>
<td>152</td>
</tr>
<tr>
<td>3</td>
<td>132</td>
<td>135</td>
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<tr>
<td>6</td>
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<td>3</td>
</tr>
<tr>
<td>30</td>
<td></td>
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</tr>
</tbody>
</table>

Progression-free Survival (%)

<table>
<thead>
<tr>
<th>Crizotinib (N=151)</th>
<th>Alectinib (N=152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n (%)</td>
<td>102 (68)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.1 (9.1–13.1)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.47 (0.34–0.65)</td>
</tr>
<tr>
<td>P-value (log-rank test)</td>
<td>P &lt; 0.0001</td>
</tr>
</tbody>
</table>

Presented by: Alice T. Shaw
PFS: analysis by subgroups*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of events/ No. of patients</th>
<th>Hazard ratio (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</td>
<td>125/233</td>
<td>0.48 (0.34–0.70)</td>
</tr>
<tr>
<td>≥65</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>Ethnicity</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 (0.32–0.76)</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>Non-smoker</td>
<td>103/190</td>
<td>0.44 (0.29–0.66)</td>
</tr>
<tr>
<td>Past smoker</td>
<td>49/96</td>
<td>0.42 (0.23–0.77)</td>
</tr>
<tr>
<td>ECOG PS</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 (0.25–2.16)</td>
</tr>
<tr>
<td>CNS Mets 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>86/161</td>
<td>0.51 (0.33–0.80)</td>
</tr>
<tr>
<td>Prior 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>

*Investigator assessment
**PFS by baseline CNS metastases status**

**Patients with CNS metastases at baseline**

- **Alectinib (N=64)**: 7.4 months (6.6–9.6)
- **Crizotinib (N=58)**: NR (9.2–NR)

**Patients without CNS metastases at baseline**

- **Alectinib (N=88)**: 14.8 months (10.8–20.3)
- **Crizotinib (N=93)**: NR

**HR 0.40**

(95% CI 0.25–0.64)

**HR 0.51**

(95% CI 0.33–0.80)

*Investigator assessment*
Secondary endpoint: OS

- Patients with events, n (%): Crizotinib (N=151) 40 (27), Alectinib (N=152) 35 (23)
- Median OS, months: NR (Crizotinib), NR (Alectinib)
- HR: 0.76 (95% CI: 0.48–1.20), P-value (log-rank test): P=0.24

No. at Risk
- Crizotinib: 151, 141, 127, 115, 103, 95, 73, 33, 13, 1
- Alectinib: 152, 142, 131, 127, 119, 107, 87, 51, 24, 5
Summary

- This is the first global randomized phase III study to compare next-versus first-generation ALK inhibitors in previously untreated, advanced ALK+ NSCLC

- Compared to crizotinib, alectinib:
  - significantly prolonged PFS
    - HR 0.47, 95% CI 0.34-0.65; p<0.0001
  - significantly delayed time to CNS progression
  - significantly improved intracranial ORR and DOR
  - had a more favorable AE profile
Despite these impressive results....

There are other Marvel Avengers....

Brigatinib

Lorlatinib

Ceritinib
Different Potential Sequence Scenarios of ALK Inhibitors Treatment:
PFS1 + PFS2 (PROFILE 1014 + ALTA)

(CRIZOTINIB)  (BRIGATINIB)

Profile 1014 (Phase 3)
Crizotinib
Median PFS = 10.9 m

ALTA (Phase 2)
Brigatinib
Median PFS = 16.7 m

Total PFS = 27.6 months!! (> 25.7 months)

SCENARIO # 1

PROFILE 1014 (Phase 3)
Crizotinib
Median PFS = 10.9 m

ALTA (Phase 2)
Brigatinib
Median PFS = 16.7 m
Caution! Post-Crizotinib PFS drop-off from Ph2 to Ph3

<table>
<thead>
<tr>
<th>ALK TKI</th>
<th>Ceritinib</th>
<th>Alectinib</th>
<th>Brigatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>6.9 months$^1$</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Phase 2</td>
<td>7.2 months$^2$</td>
<td>8.4 months$^4$</td>
<td>16.7 months$^6$</td>
</tr>
<tr>
<td>Phase 3</td>
<td>5.4 months$^3$</td>
<td>7.1 months$^5$</td>
<td>??? No trial</td>
</tr>
</tbody>
</table>

2. Crino et al, JCO 2016; 34: 2866-2873  
5. Novello et al, ESMO 2017
Phase 1/2 Trial of Brigatinib PFS in ALK+ NSCLC Patients

For patients with prior crizotinib who received 90 mg → 180 mg qd (n=25):
- Median PFS was 16.3 months (95% CI, 9.2–28.1 months)
- Kaplan-Meier (KM) probability of PFS was 62% at 1 year and 38% at 2 years

Lyudmila A Bazhenova et al: ESMO 2017 Madrid Poster 1344
PFS1 + PFS2 (PROFILE 1014 + ALTA)

PROFILE 1014 (Phase 3)
Crizotinib
Median PFS = 10.9 m

ALTA (Phase 2)
Brigatinib
Median PFS = 16.7 m

Total PFS = 27.6 months!!

Total PFS = 34.2 months??????

ALTA (Phase 1)
Brigatinib
Median PFS = 34.2 m

SCENARIO # 2
PFS model of 2G ALK TKI as first-line versus subsequent line of treatment

<table>
<thead>
<tr>
<th></th>
<th>Ceritinib</th>
<th>Alectinib</th>
<th>Brigatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-naive</td>
<td>16.8m</td>
<td>25.7m</td>
<td>(34.2m)</td>
</tr>
<tr>
<td>Post-crizotinib</td>
<td>5.4m – 7.4m</td>
<td>7.1m – 8.4m</td>
<td>16.7m</td>
</tr>
</tbody>
</table>
Current Sequence of ALK-TKI

Before ALEX:
- Crizotinib 11M
- Alectinib 9M

After ALEX:
- Alectinib 26M
- Ceritinib
- Brigatinib (Lorlatinib)

TKI or Chemo?
The Case for Using Alectinib as 1st Line Tx

- Superior PFS
- CNS activity
- Better tolerance
- Overcome key resistance mechanisms
## Brigatinib: better PFS than that of Alectinib

### Next 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>

*revised chart of Shirish M, et al. Curr. Treat Options in Oncol 2017 18:36*
**Lorlatinib: TKI-naive**

Results of ALEX

<table>
<thead>
<tr>
<th></th>
<th>Crizotinib</th>
<th>Alectinib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>75.5%</td>
<td>83%</td>
</tr>
<tr>
<td><strong>IC ORR</strong></td>
<td>29%</td>
<td>53%</td>
</tr>
<tr>
<td><strong>mPFS</strong></td>
<td>10.4M</td>
<td>25.7M</td>
</tr>
</tbody>
</table>

PFS1 + PFS2 + PFS3 (PROFILE1014 + ALTA + Lorlatinib Phase 2) OR PFS1 + PFS2 (ALEX + Lorlatinib Phase 2)

PROFILE 1014 (Phase 3)
Crizotinib
Median PFS = 10.9 m

ALTA (Phase 2)
Brigatinib
Median PFS = 16.7 m

Lorlatinib Phase 2
Median PFS = 6.9 m

3.3 months advantage in PFS when sequencing from crizotinib

Total PFS = 34.5 months!!

ALEX (Phase 3)
Alectinib
Median PFS = 25.7 m

Lorlatinib Phase 2
Median PFS = 5.5 m

Total PFS = 31.2 months!

3.3 months advantage in PFS when sequencing from crizotinib

SCENARIO # 3

SCENARIO # 4

Coming Up Soon…. Challenges
A Future Paradigm or Wishful Thinking?

PFS1 + PFS2 (Brigatinib Phase 1 + Lorlatinib Phase 2)

Total PFS = 39.7 months!!??

SCENARIO # 5

Brigatinib (Phase 1) (N = 8)
Median PFS = 34.2 m

Lorlatinib Phase 2
Median PFS = 5.5m

Coming Up Soon…. Challenges
Genetic diagnosis is needed!!!

Will the Choice of 1st Line ALKi TKI Impact on Patterns of Progression & Mechanism of Resistance?

A. Crizotinib-resistant specimens
   \( N = 55 \)

B. Ceritinib-resistant specimens
   \( N = 24 \)

C. Alectinib-resistant specimens
   \( N = 17 \)

- G1202R
- I1171T
- V1180L
- L1196M

Lorlatinib
Ceritinib/
Brigatinib/Lorlatinib
Chemo? Other TKI?
Ceritinib/
Brigatinib/Lorlatinib

Justin F. Gainor et al. Cancer Discov 2016;6:1118-1133
The Art of Precision Medicine

A Timeline of Treatment

B Effect of Therapy

Resensitization to Crizotinib by the Lorlatinib ALK Resistance Mutation L1198F

Shaw et al.
NEJM 2016
Plasma ALK mutation kinetics during treatment. The figure illustrates the change in allelic fraction of EML4-ALK and ALK mutations during sequential treatment with next-generation ALK inhibitors for A) MGH987 and C) MGH989; B) ALK fusion and mutation kinetics prior to and after ablation of an oligometastasis. The x axis depicts days from initial plasma collection, whereas the y axis reports allelic fraction. Criz, crizotinib; Chemo/A, chemotherapy + alectinib; lorlat, lorlatinib.
Currently recruiting

- crizotinib vs brigatinib
- crizotinib vs lorlatinib
- crizotinib vs ensartanib

**Will translational research from these studies help to define the future algorithm for selection and sequencing of ALK TKIs?**

- **ALK Master Protocol is due to open 2018 in US**

Focus on ALK positive patients who have progressed on a next generation ALKi; on PD will have biopsy and ALK mutation status (tissue or liquid biopsy) will be used for ALK TKI selection
Efficacy and Updated Safety of Ceritinib (450 mg or 600 mg) With Low-Fat Meal vs 750 mg Fasted in ALK+ Metastatic NSCLC


Affiliations: 1Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; 2Masaryk Memorial Cancer Institute, Czech Republic; 3Centro di Riferimento Oncologico-IRCC, Aviano, Italy; 4Seoul National University Hospital, Seoul, Republic of Korea; 5State Pavlov Medical University, St Petersburg, Russia; 6Az. Osp. Univ.Maggiore della Carità, Italy; 7Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; 8The Clatterbridge Centre NHS Foundation Trust, Liverpool, United Kingdom; 9Ottawa Hospital Cancer Centre, Ottawa, Canada; 10Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 11Songklanagarind Hospital, Prince of Songkla University, Songkhla, Thailand; 12A.S.S.T. Papa Giovanni XXIII, Italy; 13Novartis Pharma AG, Basel, Switzerland; 14Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; 15Medical University of Gdansk, Poland
## Inclusion criteria

- Stage IIIB/IV ALK+ NSCLC
- Treatment-naive* (efficacy analysis) or previously treated with ≥ 1 systemic therapy (PK analysis included both)
- ALK+ status was assessed by Ventana IHC (treatment-naive) or FDA approved FISH (previously treated)
- WHO PS 0-2
- Neurologically stable brain metastases (symptomatic or not)

### Randomization is stratified by:
- Brain metastases – presence/absence
- Prior treatment (applicable only for PK analysis part) – prior crizotinib/crizotinib naive but treated with other systemic therapy/treatment-naive with ALK+ by IHC

*R Prior adjuvant or neo adjuvant therapy allowed if relapse occurred >12 months after chemotherapy

# Patients may continue to receive treatment with ceritinib following disease progression, including cases of isolated brain progression if, in the opinion of the investigator, continued treatment provides clinical benefit

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**ASCEND-8: Phase 1, Randomized, Global, Open-label, Parallel Design Study (NCT02299505)**

- **Ceritinib 450 mg/day with low-fat meal**
- **Ceritinib 600 mg/day with low-fat meal**
- **Ceritinib 750 mg/day under fasted conditions**

Ceritinib may be continued until unacceptable toxicity, disease progression, withdrawal of consent or at the discretion of the investigator.
## DOR and PFS by BIRC Assessment

<table>
<thead>
<tr>
<th>DOR</th>
<th>Ceritinib 450 mg fed (N = 32)</th>
<th>Ceritinib 600 mg fed (N = 30)</th>
<th>Ceritinib 750 mg fasted (N = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>6 (18.8)</td>
<td>6 (20.0)</td>
<td>11 (39.3)</td>
</tr>
<tr>
<td>Patients censored, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing without event or death</td>
<td>26 (81.2)</td>
<td>24 (80)</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td></td>
<td>23 (71.9)</td>
<td>22 (73.3)</td>
<td>17 (60.7)</td>
</tr>
<tr>
<td>Median duration of response, months (95% CI)</td>
<td>16.4 (7.1-16.4)</td>
<td>NE (6.9-NE)</td>
<td>10.4 (7.1-NE)</td>
</tr>
<tr>
<td>Estimated 12-month DOR rate, % (95% CI)</td>
<td>74.6 (48.4-88.8)</td>
<td>72.5 (47.6-87.0)</td>
<td>42.5 (18.1-65.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PFS</th>
<th>Ceritinib 450 mg fed (N = 41)</th>
<th>Ceritinib 600 mg fed (N = 40)</th>
<th>Ceritinib 750 mg fasted (N = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>12 (29.3)</td>
<td>13 (32.5)</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>Patients censored, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing without event or death</td>
<td>better 29 (70.7)</td>
<td>27 (67.5)</td>
<td>23 (57.5)</td>
</tr>
<tr>
<td></td>
<td>26 (63.4)</td>
<td>23 (57.5)</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td>Median progression-free survival, months (95% CI)</td>
<td>better 17.6 (8.5-NE)</td>
<td>NE (8.3-NE)</td>
<td>10.9 (6.3-NE)</td>
</tr>
<tr>
<td>Estimated 15-month PFS rate, % (95% CI)</td>
<td>66.4 (46.5-80.4)</td>
<td>58.0 (35.9-74.8)</td>
<td>41.0 (19.6-61.5)</td>
</tr>
</tbody>
</table>

^Efficacy-analysis set
**Take home message....**

- Osimertinib met its primary endpoint PFS over Gefitinib/Erlotinib; OS is immature, but *promising*.

- Osimertinib is approved for 1\textsuperscript{st} Line Therapy for sensitive EGFR mutations.

- Osimertinib: very active on CNS metastases & favorable toxicity profile.

- ALEX places Alectinib as the optimal first line ALK TKI choice
  - With CNS metastases
  - Without CNS metastases; relatively “neuroprotective”; delays emergence resistance mutation relative to crizotinib
  - OS is immature
  - PD on crizotinib is salvagable
Take home message....

- Mutational analysis **will be necessary** for TKI ALK inhibitor selection after PFS1.

- Best TKI ALKi sequence is not yet determined.

- ASCEND-8 data suggest that ceritinib at dose of 450 mg with food could be a potential new treatment regimen for managing GI AEs with similar efficacy as 750 mg fasted dose in treatment-naïve patients with ALK-rearranged advanced NSCLC.

- Brigatinib and Lorlatinib have shown **promising** PFS1 in crizotinib naive patients.

- How to treat EGFR and ALK mutant patients is a physician’s decision based on his/her experience; today, there are not correct or wrong choices....

*Just More Therapeutic Options for Our Lung Cancer Patients*
For any question, email Dr. Santos: esantos@brrh.com

Or contact Teri Valls, Meeting Planner at: tvalls@meccinc.com