A Phase IIIb open-label, single-arm study of afatinib in EGFR TKI-naïve patients with EGFRm+ NSCLC: An interim analysis

Yi-Long Wu,1 Haiyan Tu,1 Jifeng Feng,2 Meiqi Shi,2 Jun Zhao,3 Yuyan Wang,3 Jianhua Chang,4 Jialei Wang,4 Ying Cheng,5 Jing Zhu,5 Eng-Huat Tan,6 Kai Li,7 Yiping Zhang,8 Victor Lee,9 Cheng-Ta Yang,10 Wu-Chou Su,11 Chi Leung Lam,12 BJ Srinivasa,13 Senthil Rajappa,14 Ching-Liang Ho,15 Kwok Chi Lam,16 Yi Hu,17 Shailesh Arjun Bondarde,18 Xiaoqing Liu,19 Jean Fan,20 David Kuo,21 Yu Wang,21 Kaimin Pang,22 Caicun Zhou23

1Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China; 2Jiangsu Provincial Tumor Hospital, Nanjing, Jiangsu, China; 3Beijing Cancer Hospital, Beijing, China; 4Fudan University Shanghai Cancer Center, Shanghai, China; 5Division of Thoracic Oncology, Jilin Province Cancer Hospital, Changchun, China; 6Department of Medical Oncology, National Cancer Centre, Singapore; 7Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; 8First Zhejiang Cancer Hospital, Hangzhou, China; 9Department of Clinical Oncology, The University of Hong Kong, Queen Mary Hospital, Hong Kong; 10Chang-Gung Memorial Hospital, Linkou, Taipei, Taiwan; 11National Cheng Kung University Hospital, Tainan, Taiwan; 12Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong; 13HCG Hospital, Bangalore, India; 14Basavataramak Indo American Cancer Hospital & Research Institute, Hyderabad, India; 15Tri-Service General Hospital, Taipei, Taiwan; 16Prince of Wales Hospital, Shatin, New Territories, Hong Kong; 17Department of Oncology, Chinese PLA General Hospital, Beijing, China; 18Shatabdi Superspeciality Hospital, Mumbai Naka, Nashik, Maharashtra, India; 19307th Hospital of PLA, Beijing, China; 20Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; 21Boehringer Ingelheim (China) Investment Co., Ltd, Shanghai, China; 22Boehringer Ingelheim Singapore Pte Ltd, Singapore; 23Shanghai Pulmonary Hospital, Tongji University, Shanghai, China

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Introduction

- Afatinib, an irreversible second-generation ErbB family blocker, is approved in many countries for the first-line treatment of patients with advanced *EGFR* mutation-positive (*EGFRm*) NSCLC.

- Data from the Phase III LUX-Lung (LL) 3 and LL6 trials and Phase IIb LL7 trial suggest that afatinib may offer more favorable clinical outcomes over standard platinum-based chemotherapy and first-generation reversible *EGFR* tyrosine kinase inhibitors (TKIs), for treatment-naïve patients with advanced *EGFRm* NSCLC\(^1\)\(^{-3}\).

- In a pre-specified analysis of Del19+ patients from LL3 and LL6, afatinib significantly prolonged overall survival (OS) versus chemotherapy\(^4\).

- Here, we present an interim analysis of a large Phase IIIb open-label study of afatinib in a broad Asian population of *EGFR* TKI-naïve patients with *EGFRm* NSCLC, in a setting similar to real-world practice.
Introduction (cont’d)

**LL3 (Global) and LL6 (China, South Korea and Thailand)**

- First-line afatinib significantly improved PFS versus platinum-doublet chemotherapy in patients with *EGFRm*+ NSCLC (independent review):
  - LL3: 11.1 vs 6.9 months, HR=0.58; p<0.001\(^1\)
  - LL6: 11.0 vs 5.6 months, HR=0.28; p<0.0001\(^2\)

**LL7 Global**

- First-line afatinib significantly improved PFS and TTF versus gefitinib in patients with advanced *EGFRm*+ NSCLC,\(^3\) with a non-significant trend towards improved OS with afatinib versus gefitinib\(^5\)
  - PFS (independent review): 11.0 vs 10.9 months, HR=0.73; p=0.017\(^3\)
  - TTF: 13.7 vs 11.5 months, HR=0.73; p=0.0073\(^3\)

HR, hazard ratio; PFS, progression-free survival; TTF, time to treatment failure
Methods

- Study objective: To evaluate the safety of afatinib in patients with locally advanced or metastatic NSCLC harboring EGFR mutation(s) who have never been treated with an EGFR TKI.

**Phase IIIb**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Primary endpoint</th>
<th>Other endpoints</th>
<th>ClinicalTrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced EGFRm+ NSCLC not previously treated with an EGFR TKI; ECOG PS 0–2; Patients with asymptomatic brain metastases* were eligible</td>
<td>Safety assessment; number of SAEs</td>
<td>TTSP,† PFS, TRAEs</td>
<td>NCT01953913</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group Performance Status; SAEs, serious adverse events; TRAEs, treatment-related adverse events; TTSP, time to symptomatic progression; *For at least 4 weeks on stable doses of medication; †Time from first administration of afatinib to the date of first documented clinically significant symptomatic progression that required a change in or stopping of anti-cancer treatment, according to the investigator’s assessment. Safety was assessed by intensity and incidence of AEs according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; Clinical symptomatic progression was assessed by the investigator; Radiological assessments were performed at the investigators’ discretion.
Baseline characteristics

- As of 13 February 2017, data were available for 479 patients

- China (n=351; 73%)
- India (n=50; 10%)
- Taiwan (n=29; 6%)
- Hong Kong (n=25; 5%)
- Singapore (n=24; 5%)
Baseline characteristics (cont’d)

**Age at baseline, years**
- Min. 27
- Median 59
- Max. 82

- <65 years: 26.3%
- ≥65 years: 73.7%

**Gender**
- Female: 52.4%
- Male: 47.6%

**EGFR mutation type**
- Common (Del19 and/or L858R)*: 86.0%
- Uncommon: 14.0%

**Tumor histology**
- Adenocarcinoma: 96.0%
- Squamous: 1.5%
- Other: 2.5%

Data are %
*With or without an uncommon EGFR mutation*
Baseline characteristics (cont’d)

19.2% of patients had asymptomatic brain metastases

Number of lines of prior chemotherapy

- 0 lines: 19.8%
- 1 line: 78.1%
- 2 lines: 2.1%

Smoking history

- Never smoked: 69.3%
- Currently smokes: 10.2%
- Ex-smoker: 25.3%

19.2% of patients had asymptomatic brain metastases.
Safety and tolerability

Dose modifications

• Dose reductions to afatinib 30 mg were required by 24.8% of patients
  – 6.1% had further reductions to afatinib 20 mg

• SAEs were reported in 115 (24.0%) patients
  – Grade 3, 9.0%; Grade 4, 3.1% of patients
  – 13 (2.7%) patients had malignant neoplasm progression as a SAE
  – 37 (7.7%) patients died; due mainly to either malignant neoplasm progression (2.5%) or respiratory disorders (2.7%)

• Afatinib-related SAEs were reported in 29 (6.1%) patients
  – The deaths of 2 (0.4%) patients were considered afatinib-related:
    1 (0.2%) patient with dyspnea and 1 (0.2%) with respiratory failure
Safety and tolerability (cont’d)

Percentage of patients with SAEs* (≥1%)

*Most common SAEs excluding malignant neoplasm progression; †Included afatinib-related SAEs in ≥1% of patients; ‡All grades also includes AEs of Grades 1 and 2
Safety and tolerability (cont’d)

- Grade ≥3 afatinib-related AEs occurred in 122 (25.5%) patients; diarrhea (10.4%) and rash/acne (7.9%) were the most common.
- 18 (3.8%) patients discontinued treatment due to afatinib-related AEs.

Most frequently reported Grade ≥3 afatinib-related AEs

- Diarrhea: 10.4%
- Rash/Acne*: 7.9%
- Stomatitis*: 3.3%
- Paronychia*: 2.5%
- Increased ALT: 0.6%

*Grouped term; ALT, alanine aminotransferase
Efficacy

- Median TTSP (15.3 months [95% CI: 13.4–17.5]) was 3 months longer than PFS (12.1 months [95% CI: 10.8–13.7])

Analysis of TTSP

- Number at risk: 479 405 352 308 271 227 187 161 147 127 111 86 58 23 19 10 10 5 2 0 0

CI, confidence interval
Efficacy (cont’d)

Analysis of PFS

Time since start of treatment (months)

Number at risk: 479 391 335 278 252 202 169 144 126 109 82 64 36 16 13 10 8 3 1 0 0

Estimated PFS probability

Afatinib 40 mg

25th  Median  75th

5.75   12.05   22.20
Efficacy (cont’d)

TTSP subgroup analyses*
• Median TTSP was longer in patients with:
  – Common versus uncommon *EGFR* mutations
  – Elderly patients: ≥65 years versus <65 years

PFS subgroup analyses
• Median PFS was longer in patients with:
  – Common versus uncommon *EGFR* mutations
  – Elderly patients: ≥65 years versus <65 years
  – Lower ECOG PS: ECOG PS 0 vs ECOG PS 1 vs ECOG PS 2
    (ECOG PS 2: 10.6 months [95% CI: 6.4–15.5])

*No significant difference in median TTSP by ECOG PS
## TTSP and PFS subgroup analyses

<table>
<thead>
<tr>
<th></th>
<th>Common</th>
<th>Uncommon</th>
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<tbody>
<tr>
<td><strong>By EGFR mutation type</strong></td>
<td></td>
<td></td>
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<tr>
<td>Median TTSP, months [95% CI]</td>
<td>15.8 [13.8–18.2]</td>
<td>10.0 [7.3–22.1]</td>
</tr>
<tr>
<td>Median PFS, months [95% CI]</td>
<td>12.6 [10.9–13.9]</td>
<td>9.1 [5.6–13.6]</td>
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<tr>
<td><strong>By Age</strong></td>
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<tr>
<td>&lt;65 years</td>
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<tr>
<td>Median TTSP, months [95% CI]</td>
<td>14.3 [12.4–16.9]</td>
<td>18.5 [13.4–21.9]</td>
</tr>
<tr>
<td>Median PFS, months [95% CI]</td>
<td>11.3 [10.1–13.7]</td>
<td>13.5 [10.8–17.3]</td>
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<tr>
<td>≥65 years</td>
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<td><strong>By ECOG PS</strong></td>
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<tr>
<td>ECOG PS 0</td>
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</tr>
<tr>
<td>Median TTSP, months [95% CI]</td>
<td>16.2 [13.0–22.1]</td>
<td>15.3 [12.4–17.5]</td>
</tr>
<tr>
<td>ECOG PS 1</td>
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</table>
Key findings and conclusions

Safety and tolerability
• The safety data of afatinib from this interim analysis of a large-scale Asian population of EGFR TKI-naïve, EGFRm+ NSCLC patients are consistent with those of the LL3, 6, and 7 studies
• Dose reduction rates were lower in this interim analysis (25%) versus 52%, 28% and 39% in the LL3, 6 and 7 trials,\(^1\)\(^3\) respectively, confirming that in real-world practice most afatinib-related AEs are manageable, and result in few treatment discontinuations

Efficacy
• Median TTSP was longer than median PFS of afatinib in EGFR TKI-naïve patients with EGFRm+ NSCLC, which suggests that afatinib treatment may be continued beyond progression, reflecting real-world clinical practice and treatment guidelines
• Afatinib demonstrated encouraging TTSP and PFS in patients with common and uncommon EGFR mutations, and also encouraging TTSP and PFS given this study included EGFR TKI-naïve patients with/without prior chemotherapy
• Data from larger Asian patient populations will be evaluated in further analyses of this trial
References


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