Interim analysis from a Phase IIIb, open-label study of afatinib in EGFR TKI-naïve patients with \textit{EGFR} mutation-positive (\textit{EGFR}\textsubscript{m+}) NSCLC

Filippo de Marinis,\textsuperscript{1} Konstantin K. Laktionov,\textsuperscript{2} Artem Poltoratskiy,\textsuperscript{3} Inna Egorova,\textsuperscript{4} Maximilian Hochmair,\textsuperscript{5} Antonio Passaro,\textsuperscript{1} Maria Rita Migliorino,\textsuperscript{6} Giulio Metro,\textsuperscript{7} Maya Gottfried,\textsuperscript{8} Daphne Tsoi,\textsuperscript{9} Gyula Ostoros,\textsuperscript{10} Simona Rizzato,\textsuperscript{11} Guzel Z. Mukhametshina,\textsuperscript{12} Michael Schumacher,\textsuperscript{13} Silvia Novello,\textsuperscript{14} Rafal Dziadziuszko,\textsuperscript{15} Wenbo Tang,\textsuperscript{16} Laura Clementi,\textsuperscript{17} Agnieszka Cseh,\textsuperscript{18} Dariusz Kowalski\textsuperscript{19}

\textsuperscript{1}Division of Thoracic Oncology, European Institute of Oncology, Milan, Italy; \textsuperscript{2}Carcinogenesis Institute of N.N Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences, Moscow, Russia; \textsuperscript{3}Department of Preclinical and Clinical Trials, Petrov Research Institute of Oncology, St Petersburg, Russia; \textsuperscript{4}Thoracic Department, Clinical Oncology Dispensary, St Petersburg, Russia; \textsuperscript{5}Department of Internal Medicine and Pneumology, Krankenhaus Nord, Klinik Floridsdorf, Vienna; \textsuperscript{6}Department of Oncological Pneumology, San Camillo-Forlanini Hospital, Rome, Italy; \textsuperscript{7}Department of Medical Oncology, Santa Maria della Misericordia Hospital, Perugia, Italy; \textsuperscript{8}Department of Oncology, Tel Aviv University, Tel Aviv, Israel; \textsuperscript{9}Department of Oncology, St John of God Murdoch Hospital, Murdoch, WA, Australia; \textsuperscript{10}Department of Tumor Biology, National Korányi Institute for Pulmonology, Budapest, Hungary; \textsuperscript{11}Department of Oncology, Azienda Sanitaria-Universitaria Integrata, Udine, Italy; \textsuperscript{12}State Healthcare Institute Republican Clinical Oncological Center, Ministry of Health of the Republic of Tatarstan, Kazan, Russia; \textsuperscript{13}Thoracic Centre, Ordensklinikum Elisabethinen, Linz, Austria; \textsuperscript{14}Oncology Department, University of Turin, Turin, Italy; \textsuperscript{15}Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; \textsuperscript{16}Statistics, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA; \textsuperscript{17}Clinical Operations, Boehringer Ingelheim Italia S.p.A., Milan, Italy; \textsuperscript{18}Department of Medical Affairs, Boehringer Ingelheim RCV GmbH & Co. KG, Vienna, Austria; \textsuperscript{19}Department of Lung Cancer and Thoracic Oncology, Oncology Centre and Institute, Warsaw, Poland

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Introduction

- Afatinib, an irreversible ErbB family blocker, demonstrated significantly improved efficacy outcomes and a manageable safety profile in patients with EGFRm+ NSCLC when compared with platinum-doublet chemotherapy in Phase III clinical trials\(^1,2\)

**LUX-Lung 3 (Global) and 6 (China, South Korea, and Thailand)**

- Median PFS with first-line afatinib versus platinum-doublet chemotherapy in patients with EGFRm+ NSCLC with common and uncommon mutations:
  - LUX-Lung 3: 11.1 vs 6.9 months, HR=0.58; p=0.001\(^1\)
  - LUX Lung 6: 11.0 vs 5.6 months, HR=0.28; p<0.0001\(^2\)

- These findings led to the approval of afatinib in many countries for the first-line treatment of patients with EGFRm+ NSCLC\(^3,4\)

- As RCTs are conducted in highly controlled settings, with strict inclusion criteria, it is important to support findings of afatinib efficacy and tolerability with real-world studies of broader patient populations

*EGFRm+*, epidermal growth factor receptor mutation-positive; HR, hazard ratio; PFS, progression-free survival; RCT, randomized controlled trial
Objectives

• The aim of this prospective study, 1200.55 (NCT01853826), was to evaluate the efficacy and safety of afatinib in EGFRm+ NSCLC, in a patient population similar to real-world practice
# Methods

## Global, prospective, open-label, single-arm, multicenter, Phase IIIb study

| Key inclusion criteria | • Locally advanced or metastatic *EGFRm*+ NSCLC  
| • EGFR TKI-naïve  
| • ECOG PS 0–2  
| • Patients with asymptomatic brain metastases were permitted* |
|---|---|
| Key exclusion criteria | • Prior EGFR TKI treatment |
| Treatment | • Afatinib 40 mg/day until disease progression or other withdrawal criteria were met  
| • Dose reduction in 10-mg decrements to a minimum of 20 mg/day was permitted |
| Primary endpoint† | • Safety assessment (AEs measured descriptively) |
| Further endpoints | • TTSP  
| | • PFS |

*Previously treated, with SD for ≥4 weeks on stable doses of medication; †Disease assessments and AEs recorded at baseline and every 28 days during treatment; All patients who received ≥1 dose of afatinib (treated set) were included in safety and efficacy analyses AE, adverse event; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTSP, time to symptomatic progression
Baseline characteristics

Interim analysis
Data cut-off: April 2018

N=479 patients enrolled and treated

Gender
- 314 (66%)
- 165 (34%)

Race
- Caucasian 465 (97%)
- Other 4 (<1%)
- Asian 10 (2%)

Age
- Min 25
- Median 65
- Max 89
- ≥65 years 241 (50%)
- <65 years 238 (50%)

Percentages may not total 100% due to rounding
Baseline characteristics (cont’d)

The study population included patients who are sometimes not eligible for RCTs.

**Line of therapy**
- 1st: 374 (78%)
- 2nd: 81 (17%)
- ≥3rd: 24 (5%)

**Brain metastases**
- No: 395 (83%)
- Yes: 83 (17%)

**ECOG PS**
- 0: 171 (36%)
- 1: 271 (57%)
- 2: 36 (8%)

Percentages may not total 100% due to rounding

*Missing (n=1)
Baseline characteristics (cont’d)

**EGFR mutation type***

<table>
<thead>
<tr>
<th>EGFR Mutation Type</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ex20ins</td>
<td>37 (8)</td>
</tr>
<tr>
<td>G719S/A/C</td>
<td>12 (3)</td>
</tr>
<tr>
<td>T790M</td>
<td>12 (3)</td>
</tr>
<tr>
<td>L861Q</td>
<td>10 (2)</td>
</tr>
<tr>
<td>S768I</td>
<td>9 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (4)</td>
</tr>
</tbody>
</table>

Percentages may not total 100% due to rounding

†Uncommon *EGFR* mutations with/without common mutations (uncommon mutations only, n=62); ‡Del19 or L858R mutations only (i.e., no uncommon mutations); §Patients can appear in more than one mutation category
Efficacy

- Overall efficacy outcomes were encouraging in this broad patient population (Figures 1 and 2)

Figure 1. Median TTSP and PFS (N=479)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>TTSP Median (95% CI)</th>
<th>PFS Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14.9 (13.8–17.6)</td>
<td>13.4 (11.8–14.5)</td>
</tr>
</tbody>
</table>

Cl, confidence interval
Efficacy (cont’d)

Figure 2. Best tumor response

<table>
<thead>
<tr>
<th>Best tumor response (N=479)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>25 (5)</td>
</tr>
<tr>
<td>PR</td>
<td>193 (40)</td>
</tr>
<tr>
<td>SD</td>
<td>193 (40)</td>
</tr>
<tr>
<td>PD</td>
<td>34 (7)</td>
</tr>
<tr>
<td>NE</td>
<td>23 (5)</td>
</tr>
</tbody>
</table>

ORR 46% (n=218)

DCR 86% (n=411)
Efficacy (cont’d)

- Clinical benefit was demonstrated across a range of subgroups (Figure 3).
- As also observed in the LUX-Lung trials, prolonged efficacy was seen in patients with ECOG PS 0/1, and in patients with Del19+ NSCLC.
- The lower efficacy in the uncommon mutation subgroup may be due to the relatively high proportion of exon 20 insertions in this group.
- Outcomes according to specific type of uncommon EGFR mutation type will be further evaluated.

Figure 3. Median TTSP and PFS by patient subgroup

- Afatinib demonstrated efficacy in hard-to-treat patient subgroups, including those sometimes excluded from clinical trials.

*Missing n=1; †Del19 or L858R mutations only (i.e., no uncommon mutations); ‡Uncommon EGFR mutations with/without common mutations.
Safety

- AEs were predictable and manageable, and were consistent with results of RCTs\textsuperscript{1,2,5}
  - 462 (96\%) patients had at least one DRAE (Table 1), most commonly diarrhea and rash
  - These were also the most common AEs leading to dose reduction, but led to few discontinuations (Figure 4)

*Percentage of overall population (N=479). DRAE, drug-related adverse event
Safety (cont’d)

Figure 4. Most common AEs leading to dose reduction and DRAEs leading to treatment discontinuation

All other DRAEs leading to treatment discontinuation: <1% each
### Safety (cont’d)

#### Table 1. Summary of AEs

<table>
<thead>
<tr>
<th></th>
<th>All grades, n (%)</th>
<th>Grade ≥3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>478 (&gt;99)</td>
<td>315 (66)</td>
</tr>
<tr>
<td>Any SAE†</td>
<td>202 (42)</td>
<td>171 (36)</td>
</tr>
<tr>
<td>AE leading to dose reduction</td>
<td>258 (54)</td>
<td>156 (33)</td>
</tr>
<tr>
<td>Any DRAE</td>
<td>462 (96)</td>
<td>210 (44)</td>
</tr>
<tr>
<td>DRAE leading to treatment discontinuation</td>
<td>37 (8)</td>
<td>26 (5)</td>
</tr>
</tbody>
</table>

**DRAEs in ≥10% of patients**

<table>
<thead>
<tr>
<th></th>
<th>All grades, n (%)</th>
<th>Grade ≥3, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>416 (87)</td>
<td>77 (16)</td>
</tr>
<tr>
<td>Rash</td>
<td>246 (51)</td>
<td>51 (11)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>142 (30)</td>
<td>17 (4)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>87 (18)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>79 (16)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>67 (14)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Skin fissures</td>
<td>51 (11)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>50 (10)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>50 (10)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Dermatitis acneiform</td>
<td>49 (10)</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

†DR SAEs n=39 (8%), most commonly diarrhea n=15 (3%), dehydration n=6 (1%), vomiting n=5 (1%), all others n<4 (<1%) each. DR SAE, drug-related serious adverse event; SAE, serious adverse event.
Key findings and conclusions

- Interim efficacy and safety results with afatinib in this near ‘real-world’ patient population with \( \text{EGFR}^\text{m+} \) NSCLC are consistent with findings from the pivotal LUX-Lung trials\(^1,2,5\)
  
  - TTSP/PFS were longer for patients with ECOG PS 0/1 vs 2, and for patients with Del19 or L858R mutations versus those with uncommon mutations. TTSP/PFS were longer for patients with common mutations regardless of ECOG PS

  - Diarrhea and rash were the most common DRAEs. Both were generally manageable with dose reduction and led to few treatment discontinuations

- Importantly, afatinib also demonstrated clinical benefit in patients who are sometimes excluded from clinical trials, such as those with ECOG PS 2, asymptomatic brain metastases, NSCLC harboring uncommon EGFR mutations, and those who received \( \geq 1 \) previous line of therapy
References

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• All author disclosure statements can be found in the published abstract.

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