AFATINIB FOLLOWED BY OSIMERTINIB IN REAL-WORLD PATIENTS WITH EGFR MUTATION-POSITIVE NSCLC: AN OBSERVATIONAL STUDY

Maximilian J. Hochmair,1 Alessandro Morabito,2 Desiree Hao,3 Cheng-Ta Yang,4 Ross A. Soo,5 James C-H Yang,6 Rasim Gucalp,7 Balazs Halmos,7 Lara Wang,8 Amanda Golembesky,9 Angela Märten,9 Tanja Cufer10

1Department of Respiratory and Critical Care Medicine, and Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Otto Wagner Hospital, Vienna, Austria; 2Thoracic Medical Oncology, Istituto Nazionale Tumori, “Fondazione G.Pascale”-IRCCS, 80131 Napoli, Italy; 3Tom Baker Cancer Center, Cummings School of Medicine, University of Calgary, Calgary, Alberta, Canada; 4Department of Thoracic Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan; 5Department of Haematology-Oncology, National University Hospital, Singapore; 6Department of Oncology, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan; 7Department of Oncology, Montefiore/Albert Einstein Cancer Center, Bronx, New York, USA; 8Boehringer Ingelheim Taiwan Limited, Taiwan; 9Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; 10University Clinic Golnik, University of Ljubljana, Ljubliana, Slovenia
Disclosure slide

MJH reports personal fees from Speakers honorarium Boehringer Ingelheim, AstraZeneca, and Roche
AMo has received honoraria from Boehringer Ingelheim, Roche, AstraZeneca, Pfizer, MSD, and
Bristol Myers Squibb
DH reports research funding and consultancy from Boehringer Ingelheim and Astra Zeneca.
RAS reports grants and personal fees from Astra Zeneca, personal fees from BMS, Boehringer
Ingelheim, Celgene, Lilly, Merck, Novartis, Pfizer, Roche, Taiho, and Ignyta
JC-HY reports personal fees from Boehringer Ingelheim, Eli Lilly, Roche/Genentech, Chugai, Astellas,
MSD, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, Bristol Myers
Squibb, Ono Pharmaceuticals, Daiichi Sankyo, AstraZeneca, Hansoh Pharmaceuticals, and Takeda
Pharmaceuticals
BH reports grants and personal fees from Boehringer Ingelheim, Astra Zeneca, Pfizer, Novartis and
Takeda, personal fees from Genentech/Roche, and grants from Merck
LW, AG and AMä report employment with Boehringer Ingelheim
TC reports consultancy and honoraria from AstraZeneca, Roche, Pfizer, MSD, Bristol Myers Squibb,
and Boehringer Ingelheim
EGFR mutation-positive NSCLC: choice of first-line treatments

First-generation EGFR TKIs
- Erlotinib
- Gefitinib

Second-generation EGFR TKIs
- Afatinib
- Dacomitinib

Third-generation EGFR TKIs
- Osimertinib

TKI, tyrosine kinase inhibitor
Choice of treatment strategy: availability of subsequent treatment options is a key consideration

Regardless of which first-line TKI is chosen, acquired resistance is inevitable.

Emergence of the T790M mutation is the main molecular resistance mechanism to gefitinib, erlotinib and afatinib (present in ~50–70% of tumors at the time of acquired resistance).

Osimertinib is the only globally approved T790M inhibitor.

Treatment with sequential EGFR TKIs, with osimertinib reserved as a second-line option, may therefore maximize time on targeted drugs.
Medical and electronic health records of consecutive patients treated in a real-world practice were retrospectively reviewed.

Patients with *EGFR*-mutated (Del19/L858R) TKI-naïve advanced NSCLC who were treated first-line with afatinib, developed T790M, and received second-line osimertinib treatment.

**Primary outcome:** time on treatment

**Study limitations:** (1) exclusion of patients who died on first-line afatinib; (2) under-representation of patients who had a long-term response to afatinib.
GioTag study: inclusion criteria

Medical and electronic health records of consecutive patients who met the following criteria were retrospectively reviewed between December 28, 2017 and May 31, 2018

- Had EGFR-mutated (Del19/L858R) TKI-naïve advanced NSCLC, were treated first-line with afatinib, developed the T790M mutation and received second-line osimertinib treatment
- Aged ≥18 years
- Provided written informed consent where required
- Patients could have received osimertinib as part of a compassionate use or expanded access program
- Inclusion was restricted to patients who initiated osimertinib treatment ≥10 months prior to enrollment to avoid early censoring and ensure mature data
- A maximum of 15 patients were enrolled per site

Patients were excluded if they had:
- Received any other first- or second-line treatments
- Active brain metastases at the start of either afatinib or osimertinib therapy
- Been treated within a clinical trial
GioTag: 204 patients across 10 countries

204 patients (Austria, Canada, Israel, Italy, Japan, Singapore, Slovenia, Spain, Taiwan and the United States) received first-line afatinib.

Patients discontinued due to:
- Progressive disease (n=190)
- AE/ADR (n=10)
- Other/no data (n=4)

At the time of the analysis, 106 patients had discontinued osimertinib, due to:
- Progressive disease (n=98)
- AE/ADR (n=2)
- Death (n=4)

All 204 patients acquired the T790M mutation and received second-line osimertinib.

ADR, adverse drug reaction; AE, adverse event
Patient characteristics were typical of a first-line *EGFRm*+ NSCLC population

<table>
<thead>
<tr>
<th></th>
<th>At start of afatinib therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>110 (53.9)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>60.0 (30–86)</td>
</tr>
<tr>
<td>Median weight, kg (range)</td>
<td>70.2 (37–116)</td>
</tr>
<tr>
<td>Median BMI, kg/m² (range)</td>
<td>25.3 (15.0–45.2)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>50 (24.5)</td>
</tr>
<tr>
<td>Non-Asian</td>
<td>138 (67.6)</td>
</tr>
<tr>
<td>Stage IV disease, n (%)</td>
<td>197 (96.6)</td>
</tr>
<tr>
<td><em>EGFR</em> mutation, n (%)</td>
<td></td>
</tr>
<tr>
<td>Del19</td>
<td>150 (73.5)</td>
</tr>
<tr>
<td>L858R</td>
<td>53 (26.0)</td>
</tr>
<tr>
<td>Del19 + L858R</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>ECOG PS 0 / 1 / ≥2, n (%)</td>
<td>43 (21.1) / 110 (53.9) / 31 (15.2)</td>
</tr>
<tr>
<td>Presence of brain metastases, n (%)</td>
<td>21 (10.3)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status
Sequential afatinib and osimertinib provided sustained clinical benefit in real-world clinical practice.

Overall median time on treatment: 27.6 months (90% CI: 25.9–31.3)

CI, confidence interval
Clinical benefit of sequential treatment was seen across patient subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Median time on treatment, months (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>27.6 (25.9–31.3)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Non-Asian (n=138)</td>
<td>27.6 (24.5–29.2)</td>
</tr>
<tr>
<td>Asian (n=50)</td>
<td>46.7 (26.8–NR)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;65 years (n=133)</td>
<td>27.6 (26.3–30.3)</td>
</tr>
<tr>
<td>≥65 years (n=71)</td>
<td>27.6 (19.9–44.5)</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td></td>
</tr>
<tr>
<td>Del19 (n=150)</td>
<td>30.3 (27.6–44.5)</td>
</tr>
<tr>
<td>L858R (n=53)</td>
<td>19.1 (16.8–25.1)</td>
</tr>
<tr>
<td>Presence of brain metastases</td>
<td></td>
</tr>
<tr>
<td>Yes (n=21)</td>
<td>19.4 (16.0–NR)</td>
</tr>
<tr>
<td>No (n=183)</td>
<td>28.4 (26.7–32.0)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0/1 (n=153)</td>
<td>31.3 (27.6–44.5)</td>
</tr>
<tr>
<td>≥2 (n=31)</td>
<td>22.2 (16.0–27.0)</td>
</tr>
</tbody>
</table>
Prolonged treatment duration in Asian patients

Median time on treatment: 46.7 months
Prolonged benefit in patients with Del19-positive disease

• Approximately 75% of patients had Del19-positive disease
• This high proportion likely reflects the higher frequency of T790M acquired resistance in Del19-positive versus L858R-positive tumors
  • ~75% of patients with Del19-positive disease may acquire T790M resistance\(^1\)\(^-\)\(^4\)

Median time on treatment
Del19: 30.3 months (90% CI: 27.6–44.5)
L858R: 19.1 months (90% CI: 16.8–25.1)

Benefit was particularly notable in Del19 patients with ECOG PS 0/1

Median time on treatment: 36.4 months (90% CI: 29.2–46.7)
Overall survival: 2-year and 2.5-year landmark analysis showed encouraging results

<table>
<thead>
<tr>
<th>Total number of events</th>
<th>63</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year survival rate (maturity)</td>
<td>79% (50%)</td>
</tr>
<tr>
<td>2.5-year survival rate (maturity)</td>
<td>69% (37%)</td>
</tr>
</tbody>
</table>
Overall survival: further encouraging results in patients with ECOG PS 0/1
Our results demonstrate the feasibility of sequential afatinib and osimertinib therapy in patients with EGFR mutation-positive NSCLC who acquire T790M.

With median time on treatment of 27.6 months in a real-world setting, notably prolonged in Asian patients and those with Del19-positive disease, sequential therapy appears feasible and potentially effective.

While prospective studies are needed to fully determine the optimum treatment strategy, this sequential approach might offer sustained clinical benefit, while avoiding chemotherapy.
Acknowledgments

• We thank all patients and their families, and investigators and staff at all clinical sites, for their valuable participation in these studies
• This work was supported by Boehringer Ingelheim
• Contract Research Organization support was executed by Parexel
• Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Jane Saunders of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the development of this oral presentation

†These materials are for personal use only and may not be reproduced without written permission of the authors and the appropriate copyright permissions.