Afatinib followed by osimertinib in patients with EGFR mutation-positive (EGFRm+) advanced NSCLC: updated data from the GioTag real-world study

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Introduction

- **EGFR TKIs in NSCLC**
  - EGFR TKIs are first-line treatment of choice for patients with *EGFRm+* NSCLC
  - Three generations of EGFR TKI are now widely available

<table>
<thead>
<tr>
<th>First-generation EGFR TKIs</th>
<th>gefitinib</th>
<th>erlotinib</th>
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<tbody>
<tr>
<td>Second-generation EGFR TKIs</td>
<td>afatinib</td>
<td>dacomitinib</td>
</tr>
<tr>
<td>Third-generation EGFR TKI</td>
<td>osimertinib</td>
<td></td>
</tr>
</tbody>
</table>

- Second- (afatinib and dacomitinib)\(^{1,2}\) and third-generation (osimertinib)\(^3\) EGFR TKIs have demonstrated superior PFS over first-generation EGFR TKIs
- However, the best first-line treatment choice and treatment sequence to maximise OS for patients with *EGFRm+* NSCLC is currently unknown

*EGFRm+, EGFR mutation-positive; TKI, tyrosine kinase inhibitor*
**Introduction (cont’d)**

**Acquired resistance to EGFR TKIs**
- The gatekeeper EGFR T790M mutation is a common resistance mechanism to first- and second-generation EGFR TKIs\(^4\)
- Multiple mechanisms for resistance to osimertinib are reported, but no putative resistance mechanism has been detected in ~60% of cases\(^5,6\)

*Afatinib*

<table>
<thead>
<tr>
<th>T790M-positive acquired resistance in around 60–75% of cases (more common in Del19- than L858R-positive tumours),(^7) facilitating second-line treatment with osimertinib(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour cells with activating EGFR mutation</td>
</tr>
<tr>
<td>Afatinib treatment</td>
</tr>
<tr>
<td>Acquired resistance</td>
</tr>
<tr>
<td>Osimertinib</td>
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</table>

*Osimertinib*

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<tr>
<th>Heterogeneous resistance mechanisms(^5,6): no clear targeted treatments post osimertinib but some agents have shown promise in early phase trials(^8,9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C797S (7% of tumours)(^5)</td>
</tr>
<tr>
<td>MET amplification (15%)(^5)</td>
</tr>
<tr>
<td>Histological transformation (19%)(^6)</td>
</tr>
<tr>
<td>No putative mechanism of resistance (~60%)(^5)</td>
</tr>
</tbody>
</table>

\(\text{T790M cells can be present in small numbers prior to treatment and can also emerge during treatment}\(^10\)
**Introduction (cont’d)**

**Rationale for sequential afatinib and osimertinib**

- Most patients progressing on afatinib will be eligible for second-line treatment with osimertinib
- Osimertinib has shown first- and second-line (against T790M) activity\(^3,11\)
- There is currently no standard targeted treatment for patients progressing on osimertinib

**Hypothesis:** Clinical outcomes with B > A???

### Diagram

<table>
<thead>
<tr>
<th>A</th>
<th>1(^{st})-line osimertinib (FLAURA)(^3)</th>
<th>No standard targeted 2(^{nd})-line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS: 18.9 months</td>
<td>PFS: ???</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>1(^{st})-line afatinib (LUX-Lung 3, 6, 7)(^1,12,13)</th>
<th>T790M</th>
<th>2(^{nd})-line osimertinib (AURA3)(^11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS: 11.0–11.1 months</td>
<td>PFS: 10.1 months</td>
<td></td>
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</tbody>
</table>
The GioTag study: original analysis

- GioTag is a global observational study assessing clinical outcomes in patients treated with first-line afatinib and second-line osimertinib after detection of T790M.
Introduction (cont’d)

• In the original analysis of the GioTag study, promising TTF was reported in patients treated with afatinib and sequential osimertinib in everyday clinical practice.\(^{14}\)

• Outcomes were particularly promising in Asian patients and patients with tumours harbouring a Del19 mutation

<table>
<thead>
<tr>
<th>Overall n=204</th>
<th>Median TTF: 27.6 months (90% CI: 25.9–31.3)</th>
</tr>
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<tbody>
<tr>
<td>Del19 74% (n=150)</td>
<td>Median TTF: 30.3 months (90% CI: 27.6–44.5)</td>
</tr>
<tr>
<td>Asians 25% (n=50)</td>
<td>Median TTF: 46.7 months (90% CI: 26.8–NR)</td>
</tr>
</tbody>
</table>

• However, in the original analysis of GioTag, OS data were immature

CI, confidence interval; NR, not reached; TTF, time to treatment failure
Objective

- To conduct an updated analysis of OS and TTF of patients treated in the GioTag study
Methods

• The GioTag study is a global observational study across 10 countries (Austria, Canada, Israel, Italy, Japan, Singapore, Slovenia, Spain, Taiwan and the USA)\textsuperscript{14}
• A maximum of 15 consecutive patients were enrolled from each site

The first global, observational study to evaluate outcomes of patients who received first-line afatinib followed by osimertinib (NCT03370770)

• Medical charts (62%) and electronic health records (38%) of consecutive patients treated in real-world practice were retrospectively reviewed

• Patients had $EGFRm+$ (Del19/L858R) TKI-naïve advanced NSCLC and were treated with first-line afatinib, developed T790M-mediated acquired resistance, and received second-line osimertinib treatment

• Primary outcome: TTF
• Exploratory outcome: OS
Methods (cont’d)

• This interim updated analysis (database lock April 2019) was performed when 42% of patients had experienced an OS event. TTF was also reanalysed.
• Updated data were collected from available electronic health records from 94 patients (all from the USA).
• Final analysis, incorporating manual chart reviews from an additional 29 patients, is anticipated in early 2020.
Results

Patients
- Baseline characteristics of the GioTag patients have been described previously\textsuperscript{14}
- Patients who are often excluded from clinical trials e.g. those with ECOG PS of $\geq 2$, or those with brain metastases, were included
- Patients had diverse ethnicity; most patients were Caucasian, but the study included Asians and African Americans
- At the start of afatinib treatment, 74% of patients had $EGFR$ Del19-positive tumours
Results (cont’d)

*One patient was excluded from the updated analysis due to reports of conflicting data.

- 203 patients treated with first-line afatinib and second-line osimertinib*
- 15% of patients had ECOG PS of ≥2
- 10% had stable brain metastases
- 59% Caucasian
- 25% Asian
- 9% African American
- 5% Other
- 3% No data

*One patient was excluded from the updated analysis due to reports of conflicting data.
Results (cont’d)

Overall survival
- Median follow-up was 30.3 months (interquartile range 24.0–36.8)
- In this broad patient population, median OS was almost 3.5 years
- 80% of patients were still alive after 2 years
- In patients who received the approved 40 mg/day dose of afatinib, median OS was 45.3 months (90% CI 37.6–47.6)

OS: overall dataset
Results (cont’d)

OS: patients with Del19-positive tumours

- Median OS was almost 4 years in patients with Del19-positive tumours
- In patients with Del19-positive tumours who received afatinib 40 mg/day, median OS was 45.7 months (90% CI 45.3–47.6)
Results (cont’d)

Time to treatment failure
• Median TTF was similar to that reported for the original analysis

TTF: overall dataset

TTF: patients with Del19-positive tumours
Results (cont’d)

Treatment with osimertinib

- Median TTF: 15.6 months (90% CI: 13.8–17.1) with second-line osimertinib
- Median treatment exposure: 16.2 months (range 0.1–27.4) with first-line osimertinib in FLAURA³

- Of note, prior treatment with afatinib did not appear to preclude prolonged TTF with second-line osimertinib (15.6 months)
- In the FLAURA trial, median exposure to osimertinib in a first-line setting was 16.2 months³
Key findings and conclusions

• In this updated analysis of GioTag, median OS was almost 3.5 years, and the 2-year OS rate was 80%
• In patients with Del19-positive tumours, median OS was almost 4 years
• Overall, the median TTF was 28.1 months
• Median TTF with osimertinib was 15.6 months, indicating that substantial clinical benefit with osimertinib can be achieved in a second-line setting following afatinib
• These data, along with high rate of emergence of T790M in patients treated with afatinib, especially in patients with Del19-positive disease (~75%), indicate that sequential afatinib followed by osimertinib is potentially a feasible therapeutic strategy
• Prospective data are required to evaluate the OS of patients treated with different EGFR TKIs, and sequential regimens, in patients with EGFRm+ NSCLC
References

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