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 \textit{EGFRm+} NSCLC
• Three generations of EGFR TKI are now widely available

\textit{EGFRm+}, \textit{EGFR} mutation-positive; TKI, tyrosine kinase inhibitor
Introduction (cont’d)

- Second- (afatinib and dacomitinib)\textsuperscript{1,2} and third-generation (osimertinib)\textsuperscript{3} EGFR TKIs have shown superior progression-free survival over first-generation EGFR TKIs
- Both dacomitinib and osimertinib have demonstrated significant OS benefit over first-generation EGFR TKIs;\textsuperscript{4,5} afatinib demonstrated a trend towards improved OS versus gefitinib\textsuperscript{6}
- However, second- and third-generation EGFR TKIs have never been directly compared in prospective trials

**Acquired resistance to EGFR TKIs**

- The gatekeeper EGFR T790M mutation is a common resistance mechanism to first- and second-generation EGFR TKIs\textsuperscript{7}
- Multiple mechanisms for resistance to osimertinib are reported but no putative resistance mechanism has been detected in ~60% of cases\textsuperscript{8,9}

OS, overall survival
Afatinib

T790M-positive acquired resistance in around 60–75% of cases (more common in Del19- than L858R-positive tumors),

facilitating second-line treatment with osimertinib

Osimeinib

Heterogeneous resistance mechanisms:

no clear targeted treatments post osimertinib but some agents have shown promise in early phase trials

C797S (7% of tumors)

MET amplification (15%)

Histological transformation (19%)

No putative mechanism of resistance (~60%)

*T790M cells can be present in small numbers prior to treatment and can also emerge during treatment
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
- There is no standard targeted treatment for patients progressing on osimertinib

**Hypothesis:** Clinical outcomes with B > A???
Introduction (cont’d)

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

![Diagram showing treatment sequence: First-line afatinib → Second-line osimertinib → Median OS: Not reached, 2 year OS: 79%]

• In the original analysis of the GioTag study, promising TTF was reported in patients treated with afatinib and sequential osimertinib in everyday clinical practice\(^\text{17}\)

• Outcomes were particularly promising in Asian patients and patients with tumors harboring a Del19 mutation

TTF, time to treatment failure
• However, in the original analysis of GioTag, OS data were immature.

**Median time to treatment failure:**

- Overall, n=204: 27.6 months (90% CI: 25.9–31.3)
- Del19, 74% (n=150): 30.3 months (90% CI: 27.6–44.5)
- Asians, 25% (n=50): 46.7 months (90% CI: 26.8–NR)

**CI**, confidence interval.
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{17}

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

• Patients had \textit{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: time to treatment failure

• Exploratory outcome: overall survival
• This interim updated analysis (database lock April 2019) was performed when 42% of patients had experienced an OS event. TTF was also reanalyzed.

• 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{17}
- Patients who are often excluded from clinical trials, e.g. those with ECOG PS of ≥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 tumors

ECOG PS, Eastern Cooperative Oncology Group performance status
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.
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
• Four in five 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)
Results (cont’d)

OS: overall dataset

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

OS: patients with Del19-positive tumors

<table>
<thead>
<tr>
<th>Afatinib followed by osimertinib</th>
<th>Del19 (N=149)</th>
<th>L858R (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>58</td>
<td>27</td>
</tr>
<tr>
<td>Median OS, months (90% CI)</td>
<td>45.7 (45.3–51.5)</td>
<td>35.2 (32.0–39.1)</td>
</tr>
</tbody>
</table>

Patients at risk

149 149 145 141 119 82 50 18 4 1 1
Results (cont’d)

Time to treatment failure

TTF: overall dataset

- Median TTF was similar to that reported for the original analysis
Results (cont’d)

Time to treatment failure

TTF: patients with Del19-positive tumors

<table>
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</thead>
<tbody>
<tr>
<td>Events</td>
<td>92</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Median TTF, months (90% CI)</td>
<td>30.6 (27.6–32.0)</td>
<td>21.1 (16.8–26.3)</td>
<td></td>
</tr>
</tbody>
</table>
Results (cont’d)

OS and TTF overall and in patients receiving afatinib 40 mg/day

- In patients who received the approved dose of afatinib (40 mg/day), OS (median 45.3 months; 90% CI 37.6–47.6) and TTF (median 28.1 months; 90% CI 26.8–30.6) were comparable to the overall population.
Results (cont’d)

Treatment with osimertinib

- Of note, prior treatment with afatinib did not appear to preclude prolonged TTF with second-line osimertinib (15.6 months)
- Median time from osimertinib discontinuation to death was 8 months
- In the FLAURA trial, median exposure to osimertinib in a first-line setting was 16.2 months

**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 FLAURA

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3. FLAURA trial reference
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 tumors, median OS was almost 4 years.
- Overall, the median TTF was 28.1 months.
- TTF and OS outcomes were similar in patients who received the approved starting dose of afatinib (40 mg/day) and in the overall dataset.
- These data, along with high rate of emergence of T790M in patients treated with afatinib, especially in patients with Del19-positive disease (~75%),\(^1\) 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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