Making the case for EGFR TKI sequencing in *EGFR* mutation-positive NSCLC: a GioTag study US patient analysis

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Aim: To assess time-to-treatment failure (TTF) in US patients with epidermal growth factor receptor (*EGFR*) mutation-positive non-small-cell lung cancer (NSCLC) who received sequential afatinib–osimertinib treatment in the global, observational GioTag study. **Patients & methods:** Patients had *EGFR* T790M mutation-positive disease after first-line afatinib and subsequently received osimertinib. The primary outcome was TTF. **Results:** In 129 patients at US centers, median TTF was 28.4 months (90% CI: 27.0–34.1). Median overall survival was 47.6 months (90% CI: 35.5–51.5). **Conclusion:** Sequential afatinib–osimertinib in this US-treated population was associated with long median TTF and represents an effective, evidence-based treatment option for US patients with *EGFR* mutation-positive NSCLC not presenting with active brain metastases or *de novo* T790M. **Clinical Trial Registration:** NCT03370770 (ClinicalTrials.gov)

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Treatment with an *EGFR* tyrosine kinase inhibitor (TKI) is the evidence-based standard of care for patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC), based on reports of prolonged progression-free survival (PFS) and improved tolerability with *EGFR* TKIs relative to chemotherapy [1–6]. In the US, three generations of *EGFR* TKI are available: the reversible first-generation TKIs erlotinib [7] and gefitinib [8], the irreversible second-generation ErbB family blockers dacomitinib [9] and afatinib [10] and the irreversible third-generation, *EGFR* wild-type sparing TKI osimertinib [11]. Several large randomized controlled studies have demonstrated improved efficacy outcomes with the second- [12–14] and third-generation TKIs [15,16] and also more favorable tolerability with osimertinib [16], compared with the first-generation agents in *EGFR* mutation-positive NSCLC. Indeed, the dramatic improvement in PFS reported with osimertinib compared with gefitinib and erlotinib in the Phase III FLAURA study [16], as well as its activity against the *EGFR* T790M resistance mutation [17] and its ability to cross the blood–brain barrier [18–20], has distinguished osimertinib from the first-generation TKIs. Consequently, osimertinib has been rapidly adopted as a preferred first-line treatment for *EGFR* mutation-positive NSCLC; however, there are no prospective data comparing outcomes with osimertinib and second-generation TKIs and very few patients present with *de novo* T790M (when direct sequencing techniques are used) [21–23] or CNS metastases [24].

With all of the *EGFR* TKIs, acquired resistance to first-line treatment is inevitable, necessitating second-line treatment options. The most common mechanism of resistance to first- and second-generation *EGFR* TKIs is the emergence of T790M (reported in ~60 of all patients and up to ~75% of patients with *EGFR* Del19 mutations using techniques including liquid biopsy digital droplet [dd] PCR) [25–28]. As shown by the AURA studies, osimertinib is a suitable treatment option for patients progressing with an *EGFR* T790M after first-line *EGFR*

TKI therapy [17,25,29] and has been approved by regulatory authorities in this setting [11]. Conversely, resistance mechanisms to first-line osimertinib appear to be heterogeneous and include *MET*, *EGFR* and *KRAS* amplification, *KRAS* or *PIK3CA* mutations, *EGFR* C797S mutation and small-cell transformation [30–32]. Due to the genomic complexity of tumors with *EGFR* mutation-positive NSCLC following first-line osimertinib, no standard targeted second-line treatment has been identified [30,31] and at present is likely to be chemotherapy based or an experimental therapy [33]. There is rationale, therefore, for investigating sequential *EGFR* TKI treatment in patients with *EGFR* mutation-positive NSCLC, reserving osimertinib for second-line use and thereby prolonging chemotherapy-free treatment.

Data on the cumulative benefit of sequential *EGFR* TKIs in patients with *EGFR* mutation-positive NSCLC are limited [17,25,29,34]. Assessing outcomes in a ‘real-world’ treatment setting, the global GioTag study investigated use of osimertinib in patients who develop *EGFR* T790M-positive disease after first-line afatinib [35]. In the primary analysis (database lock: May 2018), median time-to-treatment failure (TTF, defined as time from start of afatinib to discontinuation of osimertinib, or death) was 27.6 months (90% CI: 25.9, 31.3) and was 30.3 months (90% CI: 27.6–44.5) in patients with *EGFR* Del19 mutation-positive NSCLC [35]. An interim analysis from a later data snapshot (April 2019) has also been reported [36]. These real-world data indicate that sequential afatinib–osimertinib is an attractive treatment option for patients with T790M-acquired resistance and effectively prolongs the overall chemotherapy-free treatment period. Further, these data complement previous findings from the randomized clinical trial setting that provided rationale for further investigation of sequential afatinib–osimertinib treatment [34]. In a pooled analysis of patients with *EGFR* Del19/L858R mutation-positive NSCLC from the Phase III LUX-Lung 3 (afatinib vs cisplatin plus pemetrexed) and 6 (afatinib vs cisplatin plus gemcitabine) and Phase IIb LUX-Lung 7 (afatinib vs gefitinib) studies, 37 patients received osimertinib as $\geq$ second-line treatment and the 3-year overall survival (OS) rate in these patients was $\sim$ 90%.

To ensure maximal survival benefit for individual patients treated in real-world clinical practice, it is important to confirm treatment outcomes in different patient subgroups. In the primary GioTag analysis, TTF was particularly encouraging in patients with tumors harboring an *EGFR* Del19 activating mutation and also in Asian patients [35]. Here, we report a subgroup analysis of patients from the GioTag study who were treated in the US, aiming to provide further insight into the outcomes associated with sequential afatinib–osimertinib treatment in US clinical practice.

Materials & methods

Study design & patients

The GioTag study (ClinicalTrials.gov: NCT03370770) has previously been reported in detail [35]. This was a global observational study in which medical and electronic health records of consecutive patients treated in everyday clinical practice were reviewed. A maximum of 15 patients were enrolled per site. Patients had advanced/metastatic NSCLC harboring common *EGFR* mutations (Del19/L858R) and had acquired an *EGFR* T790M mutation after first-line afatinib; they then received second-line osimertinib. Patients with active baseline brain metastases were excluded. Patients had stopped first-line afatinib and started osimertinib treatment $\geq$ 10 months prior to enrollment to avoid early censoring and to ensure data maturity. The study was conducted in compliance with the principles of the Declaration of Helsinki, in accordance with the International Conference on Harmonization, Harmonized Tripartite Guideline for Good Clinical Practice, Good Epidemiological Practice, Guidelines for Good Pharmacoepidemiology Practice and relevant sponsor Standard Operating Procedures. All patients provided written, informed consent where required.

Outcomes & statistics

The primary outcome was time on treatment, reported here as TTF (time from the start of afatinib to the discontinuation of osimertinib or death). TTF and OS were estimated using Kaplan–Meier methodology.

Data for this US subgroup analysis were sourced from medical and electronic records of consecutive patients treated at US treatment centers between 28 December 2017 and 31 May 2018 (database lock: 31 May 2018). Data were supplied by Cardinal Health (OH, US), Montefiore/Albert Einstein Cancer Center and Cancer Alliance of Nebraska.

Table 1. Baseline demographics, disease characteristics and treatment starting dose in patients from US centers.

Characteristic	At start of afatinib therapy (n = 129)	At start of osimertinib therapy (n = 129)
Median age, years (range)	60 (52–66)	
Age:		
– <65 years	91 (70.5)	
– ≥65 years	38 (29.5)	
Male, n (%)	64 (49.6)	
Race:		
– White	81 (62.8)	
– Black or African American	18 (14.0)	
– Asian	19 (14.7)	
– Other†	11 (8.5)	
Mutation type:		
– Del19 only	91 (70.5)	
– L858R only	37 (28.7)	
– Del19+L858R	1 (0.8)	
Disease stage:		
– IIIB	1 (0.8)	
– IV	128 (99.2)	
Brain metastases	7 (5.4)	
ECOG PS:‡		
– 0	26 (20.2)	16 (12.4)
– 1	74 (57.4)	56 (43.4)
– 2	28 (21.7)	55 (42.6)§
Afatinib starting dose/day:		
– 40 mg	108 (83.7)	
– 30 mg	12 (9.3)	
– 20 mg	8 (6.2)	
– 10 mg	1 (0.8)	
Osimertinib starting dose/day:		
– 80 mg		126 (97.7)
– 60 mg		2 (1.6)
– 40 mg		1 (0.8)

Data represented as n (%), unless otherwise stated.
†Includes Native American or Alaska native (n = 2 [1.6%]), Native Hawaiian or other Pacific Islander (n = 1 [0.8%]), no data (n = 1 [0.8%]), other (n = 7 [5.4%]).
‡Data were unavailable for one patient.
§Two (1.6%) patients had ECOG PS 3.
ECOG PS: Eastern Cooperative Oncology Group performance status.

Results

Patients

A total of 129 patients from US centers were included in the analysis. Patient baseline characteristics at the start of afatinib and osimertinib therapy are summarized in Table 1. Median age at the start of afatinib treatment was 60 years (range: 52–66), 64 (49.6%) patients were male and 28 (21.7%) patients had Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2. At the start of osimertinib treatment, 57 (44.2%) patients had ECOG PS ≥2. Baseline *EGFR* Del19 mutations (n = 92; 71.3%) were more common than L858R mutations (n = 37; 28.7%). The main reason for discontinuation of afatinib was disease progression (in 125 [96.9%] patients) and four (3.1%) patients discontinued due to adverse events (AEs). Three patients (2.3%) had afatinib dose interruptions.

In total, 58 (50.0%) patients had discontinued osimertinib at the time of data collection. This was due to progressive disease in 54 (41.9%) patients, one (0.8%) patient discontinued due to AEs and three (2.3%) discontinued for other reasons. No dose interruptions occurred during osimertinib treatment.

Time-to-treatment failure

TTF is summarized in Table 2. Overall median TTF for sequential afatinib and osimertinib was 28.4 months (90% CI: 27.0–34.1; Figure 1). Median time on afatinib was 11.3 months (90% CI: 10.3–12.0) and on osimertinib was 15.0 months (90% CI: 13.4–16.4). Median time between the end of afatinib treatment and the start of osimertinib treatment was 22 days (range: 1–284).

In subgroups according to patient baseline and disease characteristics, long median TTF was reported in patients with *EGFR* Del19-positive disease (30.3 months), patients with ECOG PS 0/1 (32.7 months) and patients aged ≥65 years (34.1 months; Table 2). Encouraging median TTF was also reported for patients aged <65 years old

Table 2. Median TTF[†] overall and by treatment in patients from US centers.

Patient group	Overall median TTF (90% CI)	Median TTF on afatinib (90% CI)	Median TTF on osimertinib (90% CI)
All patients (n = 129)	28.4 (27.0–34.1)	11.3 (10.3–12.0)	15.0 (13.4–16.4)
<65 years (n = 91)	28.4 (27.0–32.7)	11.1 (10.2–11.9)	15.9 (14.3–17.1)
≥65 years (n = 38)	34.1 (19.9–44.5)	12.2 (9.2–13.1)	12.3 (5.7–NR)
Del19 only (n = 91)	30.3 (28.1–NR)	12.0 (11.4–13.1)	15.9 (13.8–17.6)
L858R only (n = 37)	24.7 (14.7–27.0)	10.0 (9.0–10.3)	8.6 (5.1–14.6)
ECOG PS 0/1 (n = 100)	32.7 (28.4–NR)	11.8 (10.4–12.2)	15.9 (14.6–17.6)
ECOG PS ≥2 (n = 28)	22.6 (16.0–27.6)	10.0 (7.1–10.9)	11.1 (4.6–14.3)

[†] Kaplan–Meier analysis, medians shown in months.

ECOG PS: Eastern Cooperative Oncology Group performance status; NR: Not reached; TTF: Time-to-treatment failure.

Figure 1. Overall TTF with sequential afatinib and osimertinib in US patients from the GioTag study.
TTF: Time-to-treatment failure.

(28.4 months) and patients with ECOG PS ≥2 (22.6 months). Median TTF is not reported for patients with baseline brain metastases due to the small sample size (n = 7), but TTF for individual patients is shown in Figure 2.

Overall survival

Among all patients, the Kaplan–Meier estimate of 2-year OS was 85% (data maturity, 35%). Median OS was 47.6 months (90% CI: 35.5–51.5; Figure 3).

Discussion

This subgroup analysis of the GioTag study indicates that sequential afatinib and osimertinib represents a highly effective and evidence-based treatment option for patients with *EGFR* mutation-positive NSCLC in the US. This

Figure 2. TTF for patients with brain metastases at baseline. Arrows denote that treatment was still ongoing at data cut-off.
TTF: Time-to-treatment failure.

Figure 3. OS with sequential afatinib and osimertinib in US patients from the GioTag study.
OS: Overall survival; US: United States.

regimen was associated with encouraging TTF in US patients overall, as well as across several subgroups, including those with *EGFR* Del19-positive disease and ECOG PS 0/1. Findings were generally consistent with the global primary GioTag analysis [35].

In this US subgroup analysis of GioTag, median TTF in patients with *EGFR* Del19 mutation-positive NSCLC was numerically longer than in all US patients (30.3 and 28.4 months, respectively). Prolonged efficacy with afatinib

in patients with Del19-positive disease has also been reported in randomized controlled trials. In LUX-Lung 3, for example, OS was significantly improved with afatinib versus chemotherapy in patients with Del19-positive tumors (median 33.3 vs 21.1 months; $p = 0.0015$) [37]. This improvement was observed despite limited use of second-line osimertinib at the time. As the emergence of T790M is more common in *EGFR* Del19 (up to 75% of cases) than L858R mutation-positive disease [25,27,28,38–40], sequential afatinib–osimertinib may be considered a particularly attractive treatment option for many patients with Del19-positive NSCLC.

Our findings also add to a growing body of real-world evidence demonstrating favorable outcomes with sequential afatinib–osimertinib treatment [27,35]. The GioTag study reported outcomes in patients who may have been excluded from randomized controlled studies, such as those with poor performance status [41]. Almost a quarter of the patients treated at US centers had ECOG PS ≥ 2 , in whom median TTF was 22.6 months, suggesting that such patients with typically poor prognosis could benefit from sequential afatinib–osimertinib. In addition, the long TTF (median 34.1 months) seen in patients aged ≥ 65 years suggests that older age did not have a detrimental effect on treatment outcome. In this real-world study, median time on osimertinib was 15.0 months. This was longer than median PFS seen in the AURA3 clinical trial (11.0 months by independent central review) [29]. Disease progression determined by investigator assessment was the primary reason for treatment discontinuation in the GioTag study and it is possible that this long duration reflects the absence of specific disease assessment methodologies (constraints or requirements) that would normally be stipulated in clinical trial study designs. By comparison, in the clinical trial setting of AURA3, disease progression was determined by investigator assessments according to Response Evaluation Criteria in Solid Tumors, version 1.1 and also with a sensitivity analysis of PFS by blinded independent central review.

There are several limitations of the GioTag study, which have been reported in detail [35]. Two key limitations include the retrospective nature of the study and the lack of a comparator arm limiting interpretation of results. Notably, although methodological efforts were implemented to minimize the potential for selection bias (e.g., including only consecutive eligible patients from sites and limiting enrollment to a maximum of 15 patients per site), patients who died on afatinib or who were unfit or unwilling for second-line therapy were excluded. Conversely, as patients were required to have started second-line osimertinib ≥ 10 months prior to data collection and afatinib was only approved in the US in the second half of 2013 [10], patients who derived long-term benefit from first-line afatinib may be underrepresented. In addition, data on AEs, cumulative incidence of brain metastases during treatment and patterns of disease progression (e.g., incidence of oligo-progressive disease or receipt of loco-regional treatment) were not collected for analysis. As there were only seven patients with baseline brain metastases, it was also not possible to conduct meaningful time-to-event analysis for this small subgroup.

Despite the growing body of clinical trial and real-world data on the five *EGFR* TKIs, the optimal sequence of TKI treatment for the individual patient warrants further investigation. There are several factors for consideration in *EGFR* TKI sequencing. First, data indicate that sequential afatinib–osimertinib is a feasible therapeutic strategy for many patients [34,35], especially those with *EGFR* Del19-positive disease, among whom techniques such as liquid biopsy ddPCR have detected high T790M emergence rates [25,27,38–40]. However, reserving osimertinib for second-line use will mean that some patients (i.e., those whose tumors accrue T790M-independent mechanisms of resistance) might never have the opportunity to benefit from the favorable efficacy and tolerability associated with osimertinib. Second, the recently reported OS benefit with osimertinib versus first-generation *EGFR* TKIs (median: 38.6 months [95% CI: 34.5–41.8] vs 31.8 months [95% CI: 26.6–36.0]; hazard ratio: 0.80 [95% CI: 0.64–1.00]; $p = 0.046$) provides compelling evidence for the use of osimertinib in the first-line setting [16,42]. However, data from the ARCHER 1050 [15] and LUX-Lung 7 [13] clinical trials have demonstrated improved outcomes with the second-generation *EGFR* TKIs, dacomitinib and afatinib, respectively, versus the first-generation *EGFR* TKIs, suggesting that the benefit of osimertinib over second-generation *EGFR* TKIs may be less than that seen with first-generation *EGFR* TKIs. In addition, given the heterogeneity of resistance mechanisms to osimertinib [31] and current lack of targeted treatment options following its failure [33], sequential afatinib and osimertinib may offer a highly effective treatment option for some patients, such as those with *EGFR* Del19-positive disease, given the high emergence rate of T790M [25,27,38–40]. As demonstrated in the primary and US GioTag analyses [35], for some patients this sequence would yield close to 3 years of targeted therapy, delaying the need for conventional chemotherapy. A final consideration is cost-effectiveness. Although the cost-effectiveness of sequential afatinib–osimertinib has not been assessed, a recent analysis suggested that osimertinib is not a cost-effective first-line therapy for *EGFR* mutation-positive NSCLC when compared with first- or second-generation TKIs [43]. However, it is important to note that

further clinical trials and molecular studies are needed to resolve the outstanding questions over the optimal first-line EGFR TKI treatment strategy and identify patients for whom sequential therapy may be most appropriate.

Although the optimal first-line EGFR TKI remains under debate, investigation into novel treatment strategies is ongoing. Recent reports from Phase I trials have demonstrated preliminary antitumor activity with JNJ-61186372 (a bispecific antibody to EGFR and MET) [44] and U3-1402 (an antibody–drug conjugate targeting HER3) [45] in patients whose disease has progressed after a third-generation TKI. Further data suggest consideration should be given to first-line EGFR TKI combination therapy, including antiangiogenic [46,47] or chemotherapeutic agents [48–50] as the combination partners. The Phase III RELAY trial investigating erlotinib plus the VEGFR2 antagonist ramucirumab [46] and the Phase III NEJ026 study investigating erlotinib plus the anti-VEGF monoclonal antibody bevacizumab [47] have demonstrated encouraging efficacy improvements compared with EGFR TKI monotherapy treatment. More data are awaited from these and other ongoing EGFR TKI combination studies [48–50], including the AfaBev-CS study investigating afatinib in combination with bevacizumab [51].

Conclusion

Analysis of patient data from the GioTag study demonstrated a median TTF of 28.4 months in US patients treated with sequential afatinib–osimertinib in real-world clinical practice. Furthermore, encouraging TTF was reported across a broad range of subgroups, including those with Del19-positive disease and ECOG PS 0/1.

Our results demonstrate the feasibility of sequential afatinib and osimertinib for patients in the US with *EGFR* mutation-positive NSCLC not initially presenting with *de novo* brain metastases or *EGFR* T790M-mutated disease.

Summary points

- For patients with *EGFR* mutation-positive non-small-cell lung cancer, second-generation (afatinib and dacomitinib) and third-generation (osimertinib) EGFR tyrosine kinase inhibitors (TKIs) have been shown to be superior to first-generation EGFR TKIs in the first-line setting.
- Resistance is inevitable to all of the EGFR TKIs; however, there is a lack of validated, targeted therapeutic options following first-line osimertinib.
- The global, observational GioTag study assessed first-line afatinib followed by osimertinib in patients who developed the T790M mutation following afatinib therapy; this analysis looks at outcomes in the subgroup of patients from the US.
- Overall, in 129 patients treated at US centers, the median time-to-treatment failure was 28.4 months (90% CI: 27.0–34.1) and encouraging time-to-treatment failure was seen across patient subgroups, particularly those with Del19-positive disease ($n = 91$; median: 30.3 months) and Eastern Cooperative Oncology Group performance status 0/1 ($n = 100$; median: 32.7 months).
- In these real-world patients in US clinical practice, median overall survival was 47.6 months.
- Consistent with the overall study population, sequential afatinib–osimertinib therapy is an effective, evidence-based treatment strategy in US clinical practice.

Supplementary data

An infographic accompanies this article and is included at the end of the references section in the PDF version. To view or download this infographic in your browser, please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0188

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Data sharing statement

The datasets generated and analyzed during the study are available from B Feinberg on reasonable request.

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THE GIOTAG STUDY: FOCUS ON PATIENTS IN THE USA

Afatinib followed by osimertinib for *EGFR*m+ NSCLC

WHAT IS THE GIOTAG STUDY?

*EGFR*m+ = with an *EGFR* mutation
NSCLC = non-small-cell lung cancer

1. Hochmair MJ, et al. *Future Oncol.* 2018; 14; 2861–74

A global study¹

Looking at medical records of patients with *EGFR*m+ advanced NSCLC

Specifically patients who received **afatinib** followed by **osimertinib**

WHY AFATINIB FOLLOWED BY OSIMERTINIB?

Patients normally receive an *EGFR* TKI as their first treatment and popular choices include:

1

osimertinib

or

afatinib

1

Eventually this **first treatment** will stop working and a **second treatment** will be needed

Osimertinib is a highly effective first treatment², but the second treatment would likely have to be³:

chemotherapy or an experimental therapy

Afatinib is also an effective first treatment⁴, and if a mutation called ***EGFR* T790M** is present in the tumor when afatinib stops working, then

EGFR T790M

2

osimertinib is an effective second treatment²

2. U.S. Food and Drug Administration. 2020. Tagrisso® (osimertinib). Highlights of prescribing information (revised 05/2020); 3. Planchard D, et al. *Clin. Cancer Res.* 2019; 25:2058–63; 4. U.S. Food and Drug Administration. 2019. GILOTRIF® (afatinib). Highlights of prescribing information (revised 10/2019)

Researchers wanted to see how long patients who received **afatinib** and then **osimertinib** stayed on treatment

WHAT WERE THE GLOBAL RESULTS?

204
patients¹

Recruited from
10 countries

Median time on
afatinib + osimertinib
27.6 months

1. Hochmair MJ, et al. *Future Oncol.* 2018; 14; 2861–74

WHY FOCUS ON US PATIENTS?

Treatments can have different results in different groups of patients

It is useful for US doctors to see the results for a group of patients similar to those they will treat

WHAT WERE THE US RESULTS?

129
patients

Total median time on
afatinib + osimertinib
28.4 months
(over 2 years)

Median survival time
for US patients
47.6 months
(nearly 4 years)

ECOG PS = Eastern Cooperative Oncology Group performance status

Median time on afatinib + osimertinib was encouraging in different patient groups, including:

patients who had tumors with a specific type of mutation called ***EGFR* Del19**,
30.3 months

patients with **good** general health status (ECOG PS 0 or 1),
32.7 months

and also patients with **poor** general health status (ECOG PS 2+) **22.6 months**

WHAT DOES THIS MEAN FOR PATIENTS WITH *EGFR*m+ NSCLC?

It is already known that if **afatinib** stops working and the **T790M mutation** is present, then **osimertinib** is a highly effective second treatment option²

2. U.S. Food and Drug Administration. 2020. Tagrisso® (osimertinib). Highlights of prescribing information (revised 05/2020)

US patients receiving afatinib and then osimertinib in this context, could stay on treatment for around 28 months (**over 2 years**) before having to consider other options like chemotherapy, and could achieve long-term survival (**nearly 4 years**)

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