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Sequential afatinib and osimertinib in patients with *EGFR* mutation-positive NSCLC and acquired T790M: A global non-interventional study (UpSwinG)

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ABSTRACT

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are standard of care for *EGFR* mutation-positive non-small cell lung cancer (NSCLC). However, optimal sequence of treatment has yet to be defined. Overall survival (OS) is influenced by the availability/use of subsequent therapy after first-line treatment. Emergence of T790M is the main mechanism of resistance to afatinib and second-line osimertinib could be a treatment option in this instance.

Methods: In this non-interventional, global study (NCT04179890), existing medical/electronic records were identified for consecutive EGFR TKI-naïve patients with *EGFR* mutation-positive NSCLC (Del19 or L858R) treated with first-line afatinib and second-line osimertinib in regular clinical practice (n = 191; all T790M-positive). The primary objective was time to treatment failure (TTF). Key secondary objectives were OS and objective response rate (ORR).

Results: At the start of afatinib treatment, median age (range) was 62 years (34–88). Fifty-five percent of patients were female and 67% were Asian. ECOG PS (0/1/≥2) was 31%/57%/12%. Fourteen percent of patients had brain metastases. At the start of osimertinib treatment, ECOG PS (0/1/≥2) was 25%/61%/14% and 14% had brain metastases (rising to 29% at the end of osimertinib treatment). The source of biopsy material (solid/liquid) was 86%/3% at the start of afatinib and 54%/33% at start of osimertinib. Mutations were mainly detected with PCR methods. Overall, median TTF was 27.7 months (95% CI: 24.0–30.2) and median OS was 36.5 months (95% CI: 32.9–41.8). ORR with afatinib and osimertinib was 74% and 45%. TTF, OS and ORR were generally consistent across subgroups.

Conclusion: Sequential afatinib and osimertinib demonstrated encouraging activity in patients with *EGFR* mutation-positive NSCLC and acquired T790M. Activity was observed across all subgroups, including patients

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with poor ECOG PS or brain metastases. ECOG PS and incidence of brain metastases remained stable prior to, and after, afatinib treatment.

1. Introduction

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are standard of care for the first-line treatment for patients with *EGFR* mutation-positive non-small cell lung cancer (NSCLC) [1]. Currently, three generations of EGFR TKI are available for use and have differences in mechanism of action [1]. First-generation EGFR TKIs (erlotinib and gefitinib) reversibly inhibit EGFR, while second-generation EGFR TKIs (afatinib and gefitinib) act as irreversible ErbB family blockers. The third-generation EGFR TKI, osimertinib, irreversibly blocks mutated EGFR, including the gatekeeper resistance mutation, T790M, but is wild-type sparing. Seminal randomized trials have demonstrated significant clinical benefit with second- and third-generation EGFR TKIs versus first-generation EGFR TKIs [2–7]. However, to date, no head-to-head data exist that have directly compared second- and third-generation EGFR TKIs. Therefore, first-line treatment of choice, in terms of which EGFR TKI to use in which patient, has not been unequivocally defined.

Notwithstanding the limitations of cross-trial comparisons, the best median progression-free survival (PFS) achieved to date with an EGFR TKI is 17.7 months with osimertinib in the phase III FLAURA trial [6]. Osimertinib also demonstrated significant overall survival (OS) advantage over gefitinib/erlotinib in this study [7], thus positioning it as a recommended first-line treatment option. However, OS is highly influenced by the availability and implementation of subsequent treatment options beyond acquired resistance. This may explain, in part, the observation that osimertinib does not improve OS versus gefitinib/erlotinib in Asia and, in particular Japan, which has well-resourced healthcare and high rates of subsequent therapy [8].

Emergence of the T790M mutation is the predominant molecular resistance mechanism to first- and second-generation EGFR TKIs, including afatinib. While the detection rate of T790M has varied across studies (largely due to differences in detection methodologies), it appears to be present in up to 50–75% of tumors at the time of acquired resistance, with the likelihood being highest in patients with Del19-positive disease [9–11]. Therefore, in principle, the majority of patients treated with first-line afatinib could receive second-line osimertinib, which has demonstrated strong activity in this setting [12].

Here we describe the findings of a real-world, non-interventional, global, multi-center study (UpSwinG: Real World study on TKI activity in Uncommon mutations and Sequencing Giotrif®). The study utilized pre-existing data collected from the medical records of consecutive patients treated with EGFR TKIs and comprised two cohorts. Cohort 1 included patients with tumors harboring uncommon or compound *EGFR* mutations who received first- or second-line EGFR TKI treatment. Cohort 2 included patients with common *EGFR* mutations treated with sequential afatinib and osimertinib. The results from Cohort 2 are reported here.

2. Materials and methods

2.1. Study design

UpSwinG was a non-interventional, global, multi-center study (NCT04179890) conducted across nine countries (United Kingdom, Taiwan, South Korea, Japan, France, Germany, Austria, Spain, Italy). Medical and electronic health records of consecutive patients treated in a real-world practice setting who met the following criteria were retrospectively reviewed between November 2019 and July 2020: aged $\geq$ 18 years with *EGFR* mutation-positive (Del19 or L858R), TKI-naïve, advanced NSCLC treated with first-line afatinib and, following detection of T790M, second-line osimertinib. Patients with active brain metastases or treated as part of a clinical were excluded (treatment with osimertinib within an expanded access/compassionate use program was permitted). Patients who participated in the GioTag study were also excluded. *EGFR* mutation detection (activating mutations and T790M) was undertaken locally using different methodologies as per standard care. Information on methodology used and source of material (biopsy, cytology, blood) prior to first-line and second-line treatment was collected. To avoid early censoring, patients must have started osimertinib treatment at least 10 months prior to data entry but did not need to still be on treatment. A maximum of 15 patients were enrolled per site.

The study was undertaken in compliance with the principles laid down in the Declaration of Helsinki, in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline for Good Clinical Practice, Good Epidemiological Practice and Good Pharmacoepidemiology Practice, and relevant local regulations. Informed and privacy consent signatures were obtained depending on local regulations.

2.2. Outcomes & assessments

The primary outcome was time to treatment failure (TTF), defined as the time from the first dose of afatinib to the last dose of osimertinib, or death by any cause. Secondary objectives were OS, time on treatment with first- and second-line treatment, overall response rate (ORR), and description of methodology and the material (liquid vs tissue) used for mutation detection.

2.3. Statistical analyses

Prespecified subgroup analysis of outcome was planned according to: *EGFR* mutation type (Del19 or L858R); Eastern Cooperative Oncology Group performance status (ECOG PS); ethnicity; presence or absence of brain metastasis; starting dose of afatinib. The target recruitment was 200 patients with an estimated censoring rate of 10%. TTF and OS were estimated using the Kaplan–Meier method. Medians and two-sided 95% confidence intervals (CIs) were calculated using Greenwood's variance estimate. For patients still on treatment, TTF was censored at the date of data collection. Subgroup analyses were limited to descriptive statistics.

3. Results

3.1. Patients

Between December 17, 2019 and January 19, 2021, a total of 207 patients were enrolled across 44 sites in $\geq$ 9 countries and 191 were eligible for analysis (Supplemental Table 1). Two sites In Korea enrolled more than 15 patients in order to achieve the overall recruitment goal. Of the 16 ineligible patients, eight did not receive first-line afatinib or second-line osimertinib, four did not start osimertinib $\geq$ 10 months prior to data entry, two had active brain metastases at start of afatinib therapy, one did not have a common *EGFR* mutation, and one was treated within a clinical trial. Most patients with known ethnicity were either Asian (67.0%) or Caucasian (31.3%; Table 1). The frequency of Del19 and L858R mutations was 70.7% and 29.3%, respectively. At the start of afatinib therapy, median age was 62 years (range, 34–88) and 12.0% of patients with known ECOG PS had a score of $\geq$ 2 (Table 1). A total of 13.8% of patients had brain metastases. At the start of osimertinib therapy, ECOG PS was known in 153 patients. ECOG PS score was 0, 1 and $\geq$ 2 in 24.8%, 61.4% and 13.7% respectively. The frequency of brain metastases was 14.1% at the start of osimertinib therapy and 29.3% at

Table 1
Baseline characteristics.

	Patients (n = 191)
Median age, years (range)	62 (34–88)
Female, n (%)	106 (55.5)
BMI, n (%)	
Underweight	12 (6.3)
Normal	74 (38.7)
Overweight/obese	48 (25.1)
Unknown	57 (29.8)
Smoking status, n (%)	
Never	121 (63.4)
Previous	52 (27.2)
Current	12 (6.3)
Unknown	6 (3.1)
Ethnicity, n (%)	
Caucasian	55 (28.8)
Asian	118 (61.8)
Other	3 (1.6)
Unknown/Not collected	15 (7.9)
Stage, n (%)	
IIIB/C	15 (7.9)
IV	176 (92.1)
Histology, n (%)	
Adenocarcinoma	186 (97.4)
Squamous	3 (1.6)
Mixed	1 (0.5)
Not otherwise specified	1 (0.5)
Metastases, n (%)	
None	20 (10.5)
Adrenal	19 (9.9)
Bones	91 (47.6)
Brain	26 (13.6)
Liver	27 (14.1)
Lung contralateral	50 (26.2)
Lung ipsilateral	40 (20.9)
Lymph nodes	32 (16.8)
Pleura	66 (34.6)
Spine	5 (2.6)
Other	13 (6.8)
Unknown	2 (1.0)
ECOG PS, n (%)	
0	49 (25.7)
1	90 (47.1)
≥ 2	19 (9.9)
Unknown	33 (17.3)
Mutation type, n (%)	
Del19	135 (70.7)
L858R	56 (29.3)
Treatment lines, n (%)	
2	120 (62.8)
3	33 (17.3)
4	18 (9.4)
5	11 (5.8)
6	4 (2.1)
7	4 (2.1)
8	0
9	1 (0.5)

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group.

the end of osimertinib treatment.

Prior to afatinib treatment, *EGFR* mutational analysis was undertaken on tissue or liquid biopsies in 83.8% and 3.1% of cases, respectively (Table 2). Mutations were mainly detected (63.9% of cases) with polymerase chain reaction (PCR)-based techniques. Sequencing was undertaken in 7.9% of cases and Next-Generation Sequencing in 4.2% of cases (Table 2). Prior to treatment with osimertinib, tissue or liquid biopsies were undertaken in 48.7% and 29.8% of cases, respectively (Table 2). PCR-based techniques were used in 63.4% of cases; next-generation sequencing was used in 6.8% of cases. Disregarding one patient whose second biopsy was Del19 negative, all patients still had a detectable common *EGFR* mutation after afatinib treatment. In some cases, other genetic aberrations were detected. Prior to initiation of afatinib, two patients had an *ALK* rearrangement, one patient had *MET* amplification and six patients had other mutations (not specified). Prior to osimertinib treatment, three patients had an *ALK* rearrangement, one patient had *MET* amplification, one patient had a *ROS1* translocation and three patients had other mutations (not specified).

3.2. Clinical outcomes

After a median observation period of 30.0 months (interquartile range [IQR]: 22.4–39.8), the median duration of treatment with afatinib and osimertinib was 15.1 months (95% CI: 13.5–16.7) and 9.5 months (95% CI: 8.3–11.2), respectively. Thirty patients remained on osimertinib at data cut-off. Of the patients who discontinued osimertinib, 71 (44.1%) received at least one further line of therapy (Supplemental Table 2). In almost all cases, subsequent therapy was chemotherapy or a chemotherapy-based combination.

The median time from end of osimertinib treatment to death was 5.0 months (95% CI: 4.2–6.5). Overall, median TTF was 27.7 months (95% CI: 24.0–30.2; Fig. 1A, Table 3). TTF was largely consistent across patient subgroups (Table 3).

Median OS was 36.5 months (95% CI: 32.9–41.8; Fig. 1B, Table 3). OS was also generally consistent across subgroups. OS was longest in Asian patients (42.3 months), especially Asian patients with a Del19 mutation (43.8 months).

The ORR with afatinib was 73.6% (Table 3); median duration of response (DoR) was 9 months (IQR: 3–17). The disease control rate (DCR) was 100%. Of 178 evaluable patients, 3 (1.7%) had a complete response (CR), 128 (71.9%) had a partial response (PR) and 47 (26.4%) had stable disease (SD). In patient subgroups the ORR ranged between 67.3% (non-Asian patients) and 91.3% (brain metastases present; Table 3).

The ORR with osimertinib was 45.2% (Table 3); median DoR was 6 months (IQR: 2–10). The DCR was 86.7%. Of 166 evaluable patients, two (1.2%) had a CR, 73 (44.0%) had a PR, 69 (41.6%) had SD and 22 (13.3%) had progressive disease. ORR with osimertinib was consistent across subgroups (Table 3).

In this study, most patients (81.7%) received the approved afatinib starting dose of 40 mg. After a median observation period of 27.5 months (IQR: 23.6–30.1), the median duration of treatment with afatinib and osimertinib was 15.3 months (95% CI: 13.6–16.7) and 9.3 months (95% CI: 8.1–11.1), respectively. TTF, OS and ORR outcomes in patients who received the approved dose of afatinib are shown in Supplemental Table 3 and Supplemental Fig. 1.

4. Discussion

This study demonstrated promising activity of sequential afatinib and osimertinib in patients with *EGFR* mutation-positive NSCLC and acquired T790M. In the 191 patients assessed, all of whom were treated in a 'real-world' clinical practice setting, median TTF was over two years and median OS was over three years. Given the real-world setting, the observation of comparable ORRs with first-line afatinib in this study and prospective trials was encouraging [3,13,14]. Moreover, response rate was largely consistent across subgroups, including patients with poor prognostic features such as ECOG PS ≥ 2 and brain metastases. Accordingly, TTF in these subgroups was either comparable, or only slightly lower than in the overall dataset.

Overall, our findings suggest that a sequential EGFR TKI approach could be considered in everyday clinical practice, given that osimertinib has demonstrated strong activity in a second-line setting with a favorable tolerability profile, reflecting its EGFR wild-type sparing mechanism of action. In the phase III AURA3 trial, osimertinib conferred significantly improved PFS (median 10.1 vs 4.4 months; HR, 0.30; 95% CI: 0.23–0.41) and response rate (71% vs 31%) versus chemotherapy in T790M-positive NSCLC patients after disease progression with first-line

Table 2
Approaches for the detection of mutations.

	Prior to afatinib (n = 191)	Prior to osimertinib (n = 191)
Biologic sample(s) used for mutation testing, *n* (%)		
Tissue, histological sample (solid biopsy)	160 (83.8)	93 (48.7)
Cytological sample	19 (9.9)	18 (9.4)
Blood (liquid biopsy)	6 (3.1)	57 (29.8)
Other	2 (1.0)	7 (3.7)
Unknown	6 (3.1)	19 (9.9)
Methodology used for mutation testing, *n* (%)		
Amplification Refractory Mutation System (ARMS)	4 (2.1)	3 (1.6)
Qiagen	1 (0.5)	0
Roche	1 (0.5)	1 (0.5)
Unknown	2 (1.0)	2 (1.0)
PCR-based techniques	122 (63.9)	121 (63.4)
ddPCR	39 (20.4)	46 (24.1)
PCR clamping	41 (21.5)	41 (21.5)
Real-time PCR	17 (8.9)	12 (6.3)
Targeted PCR	11 (5.8)	12 (6.3)
PCR (COBAS)	11 (5.8)	9 (4.7)
PCR (type not specified)	2 (1.0)	1 (0.5)
Fragment analysis	1 (0.5)	0
Sequencing	15 (7.9)	2 (1.0)
Sanger sequencing	7 (3.7)	0
Pyrosequencing	3 (1.6)	0
Other	1 (0.5)	0
Unknown	4 (2.1)	2 (1.0)
Next-Generation Sequencing (NGS)	8 (4.2)	13 (6.8)
Targeted NGS	6 (3.1)	5 (2.6)
Whole-genome sequencing	1 (0.5)	8 (4.2)
Other	1 (0.5)	1 (0.5)
Unknown	41 (21.5)	51 (26.7)

Abbreviations: PCR, polymerase chain reaction.

EGFR-TKI therapy [12]. There was no significant difference in OS (median 26.8 vs 22.5 months; HR, 0.87; 95% CI: 0.67–1.12) which probably reflects high crossover [15]. In contrast to first- and second-generation EGFR TKIs, there does not appear to be a predominant mechanism of resistance to first-line osimertinib. Indeed, resistance mechanisms are highly heterogeneous, encompassing both EGFR-dependent and EGFR-independent mechanisms [16]. Consequently, at present, no targeted treatment options have been approved for use post osimertinib; most patients who receive subsequent therapy are given platinum-doublet chemotherapy [17]. Therefore, it is possible that reserving osimertinib for second-line use, rather than using as first-line treatment, could help maximize time on targeted treatment and defer the need for more toxic chemotherapy regimens. The observation in the current study that ECOG PS and presence of brain metastases were largely stable before and after first-line treatment suggest that most patients probably remain sufficiently fit to receive subsequent osimertinib after afatinib.

The data presented herein substantiate previous studies, most notably the recent global, non-interventional GioTag study (NCT03370770). Like the current study, GioTag was undertaken in a real-world clinical setting and assessed outcomes in 203 EGFR TKI-naïve patients with *EGFR* mutation-positive NSCLC who received sequential afatinib and (after detection of T790M) osimertinib [18]. In these patients, median TTF was 27.7 months and median OS was 37.6 months, with particularly encouraging results in Asian patients (median TTF 37.1 months; median OS 44.8 months) [19]. Other studies have also demonstrated the potential benefits of sequential EGFR TKI treatment [10,20–22]. One of these studies indicated that sequential treatment with afatinib and osimertinib was more efficacious than sequential erlotinib/gefitinib and osimertinib [21]. However, these real-world studies do not substitute for prospective trials, and head-to-head studies are required to directly compare regimens, with OS as the key endpoint. Several such studies are ongoing; for example, the phase II trial, Heat-on-Beat, is comparing initial treatment with afatinib versus osimertinib in Japanese patients with *EGFR* mutation-positive NSCLC [23]. In addition, an ongoing randomized open-label phase IV study in Germany is comparing first-line afatinib followed by osimertinib versus first-line osimertinib in patients with *EGFR* mutation-positive NSCLC (NCT04413201). A similar study is comparing dacomitinib followed by osimertinib/chemotherapy versus osimertinib followed by dacomitinib/chemotherapy (NCT03810807).

Given the current lack of prospective data comparing second- and third-generation EGFR TKIs, first-line treatment of choice for *EGFR* mutation-positive remains open to debate, particularly in Asian patients where reserving osimertinib for second-line use does appear to be a valid strategy. Of note, in the Asian sub-analysis of FLAURA, there was no evidence of OS benefit with osimertinib over gefitinib/erlotinib (median OS 37.1 vs 35.8 months, respectively; HR, 1.0; 95% CI: 0.75–1.32) [24]. Also, in a Japanese sub-analysis of FLAURA, OS was actually lower in the osimertinib arm than the comparator arm (median OS 39.3 months vs not reached, respectively; HR, 1.39; 95% CI: 0.83–2.34) [24].These findings could reflect high rates of subsequent therapy in Asian, and particularly Japanese, patients where sequential use of EGFR TKIs following failure of erlotinib/gefitinib was common [24]. Based on all these observations, and the encouraging data presented herein, it may be hypothesized that sequential afatinib and osimertinib could be particularly effective in countries with well-resourced healthcare systems that are geared towards high rates of subsequent therapy. The type of mutation (Del19 vs. L858R) may also impact the strategy.

When considering the possibility of sequential EGFR TKI regimens in real-world clinical practice, it is important that efficient molecular diagnosis services are available so that mechanisms of acquired resistance (particularly detection of T790M) can be identified. For this reason, one of the predefined objectives of this study was to describe the methodology and material used for mutation detection. Prior to treatment with afatinib, most activating mutations were detected based on tissue biopsy and PCR-based assays. Following acquired resistance to afatinib, the most common source for rebiopsy material was still tumor tissue, but nearly a third of patients underwent liquid biopsy to detect T790M. The implementation of liquid biopsies is important as not all patients will be eligible for, or consent to, a second tissue biopsy. Also, sensitive liquid biopsies may detect sub-clonal T790M mutations that may be missed by tissue biopsy. The availability of sensitive T790M assays is also an important factor when considering sequential EGFR TKI therapy. Our data indicate that the current uptake of highly sensitive techniques, like next-generation sequencing, remains quite low in real-world practice. Detection rates of T790M following afatinib vary from study to study and this, at least in part, may reflect differences in methodology. It may be that combination of liquid biopsy in conjunction with sensitive assays will help maximize the identification of patients who could benefit from sequential afatinib and osimertinib in everyday practice. For example, a cohort study (n = 67) that utilized liquid biopsy and a droplet-digital PCR assay (with a more sensitive detection threshold than several commercially available assays) detected T790M in 73% of patients with acquired resistance to afatinib [10]. Further improvements in mutation detection technologies will increase the feasibility of sequential EGFR TKI in the future. Nevertheless, regardless of technological developments, a proportion of patients will fail afatinib treatment due to T790M-independent mechanisms and will therefore be ineligible for second-line osimertinib. Despite recent promising developments with, for example, immunotherapy-based combinations, treatment options for these patients remains an unmet need [25]. Currently, this is a potential drawback of embarking on a sequential strategy at the outset of treatment.

While this study provides important insights into the activity of sequential afatinib and osimertinib in a real-world setting, it has several limitations inherent of a retrospective study. Clearly, there was potential for selection bias, as the study was largely restricted to sites using

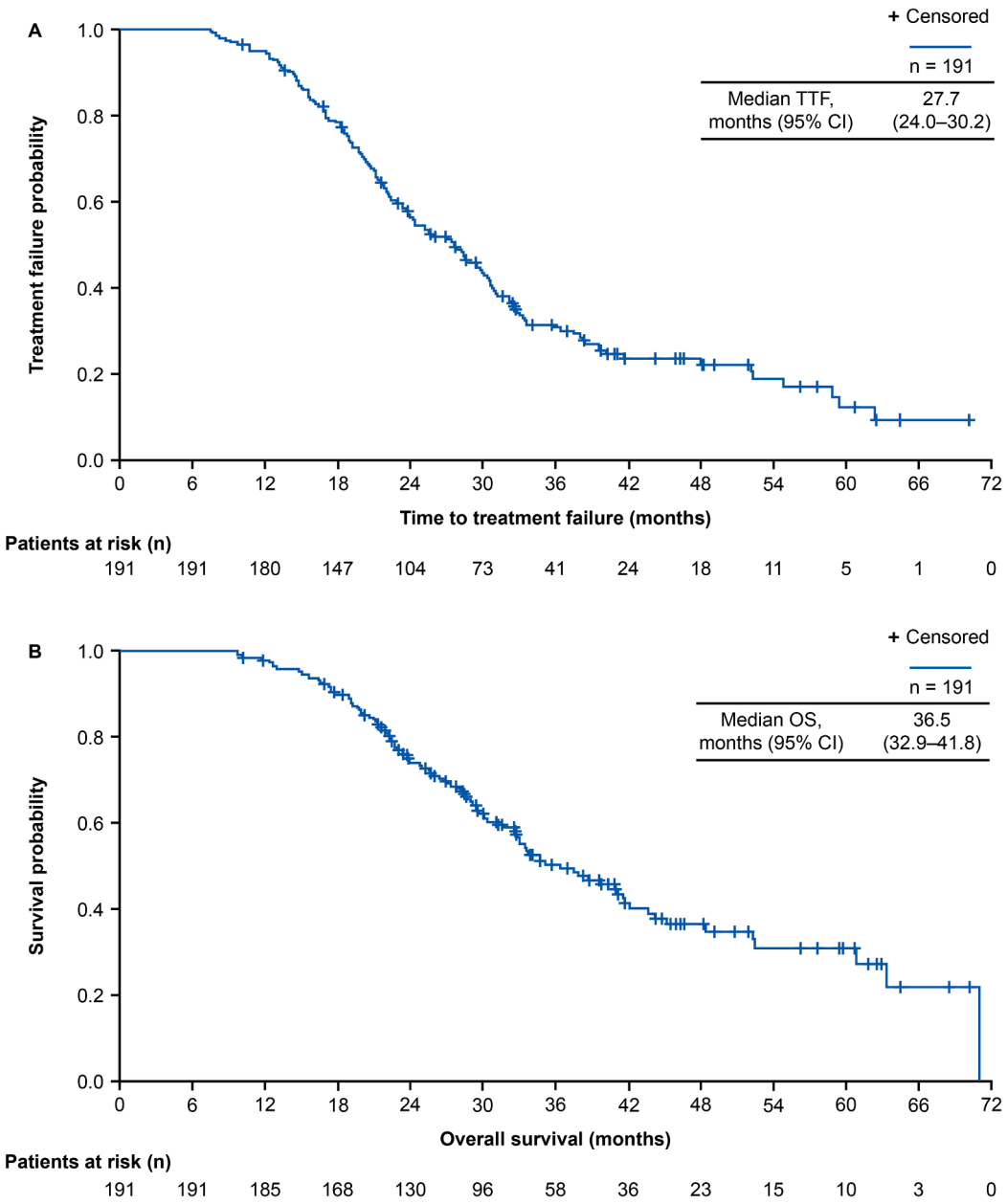

Fig. 1. TTF (A) and OS (B) in patients receiving sequential afatinib and osimertinib. Abbreviations: CI, confidence interval; OS, overall survival; TTF, time to treatment failure.

afatinib on a regular basis that also had access to osimertinib for the treatment of T790M-positive tumors. Although osimertinib was approved in most regions at the time of data analysis, it had only been available for a maximum of two to three years, thus limiting the number of sites and patients eligible for the study. Also, there is potential for prevalence-incidence bias as patients who die on afatinib could not be included. Conversely, patients with long-term benefit from afatinib had a lower likelihood of being included in the study. Finally, this study could not include patients with brain only progression on afatinib, where T790M status testing is usually unobtainable, or progression at other sites for which tissue sampling was clinically or technically impossible. Together, these factors may influence the generalizability of the results to all patients treated with first-line afatinib in real-world clinical practice. However, several steps were undertaken to minimize the potential for selection bias. For instance, to avoid differential center influence on study results, a maximum of 15 consecutive patients per site were enrolled. Furthermore, patients must have initiated osimertinib treatment at least 10 months prior to data entry to avoid early censoring. The other main limitation of the study was the lack of a comparator group, thus limiting the interpretability of the results. Also, all patients included in the study had T790M-mediated acquired resistance prior to receiving osimertinib. Accordingly, the data are not generalizable to all patients treated with first-line afatinib as no information was collected for T790M-negative patients. Finally, all data analyses were exploratory with no formal testing for statistical significance.

In conclusion, the results of the UpSwinG study provide further real-world evidence that sequential afatinib and osimertinib confers encouraging activity in patients with *EGFR* mutation-positive NSCLC and acquired T790M. Reserving osimertinib for second-line use after afatinib could be an option, especially in Asian patients and/or patients with a Del19 activating *EGFR* mutation. Prospective data comparing different sequential regimens in patients with *EGFR*-mutation positive NSCLC are required.

Table 3
Time to treatment failure, overall survival and overall response rate in patient subgroups.

	Median TTF, months (95% CI)	Median OS, months (95% CI)	ORR, %	
			Afatinib	Osimertinib
All patients	27.7 (24.0–30.2)	36.5 (32.9–41.8)	73.6	45.2
Mutation type				
Del19	28.6 (24.5–31.2)	38.0 (33.1–44.4)	74.0	47.1
L858R	22.1 (19.8–30.4)	33.1 (24.9–41.8)	72.7	40.4
Ethnicity				
Asian	28.8 (22.4–31.2)	42.3 (33.2–63.5)	79.3	48.0
Non-Asian	25.5 (22.1–28.6)	31.3 (27.2–38.0)	67.3	36.0
Brain metastases present				
No	28.4 (24.3–30.8)	37.6 (33.1–42.3)	71.2	45.8
Yes	21.4 (19.2–30.9)	29.6 (22.4–NR)	91.3	41.7
ECOG PS				
<2	28.5 (24.0–30.9)	39.8 (32.9–45.2)	77.9	47.9
≥2	29.6 (20.5–32.3)	33.1 (21.8–37.6)	70.6	40.0
Asian and Del19	29.7 (23.0–33.0)	43.8 (33.2–71.1)		

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reached; ORR, objective response rate; OS, overall survival; TTF, time to treatment failure.

Data sharing statement

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

CRediT authorship contribution statement

Sanjay Popat: Conception/design, Provision of study material or patients, Collection and/or assembly of data, Data analysis and interpretation, Manuscript writing. **Hyun Ae Jung:** Provision of study material or patients, Collection and/or assembly of data, Data analysis and interpretation. **Shin Yup Lee:** Provision of study material or patients, Collection and/or assembly of data. **Maximilian J. Hochmair:** Conception/design, Provision of study material or patients, Collection and/or assembly of data, Data analysis and interpretation, Manuscript writing. **Seung Hyeun Lee:** Provision of study material or patients, Collection and/or assembly of data. **Carles Escriu:** Provision of study material or patients. **Min Ki Lee:** Provision of study material or patients. **Maria R Migliorino:** Provision of study material or patients. **Yong Chul Lee:** Provision of study material or patients, Manuscript writing. **Nicolas Girard:** Provision of study material or patients, Data analysis and interpretation, Manuscript writing. **Hasan Daoud:** Conception/design, Manuscript writing. **Angela Märten:** Conception/design, Data analysis and interpretation, Manuscript writing. **Satoru Miura:** Conception/design, Provision of study material or patients, Data analysis and interpretation. All authors provided final approval of manuscript. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

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Declaration of Competing Interest

Sanjay Popat: AstraZeneca, Roche, Boehringer Ingelheim, Pfizer, Novartis, Takeda, BMS, MSD, EMD Serono, Bayer, Blueprint, Daiichi Sankyo, Guardant Health, Janssen, GSK, BeiGene, Incyte, Eli Lilly, Amgen, Seattle Genetics (C/A), AstraZeneca, Roche, Boehringer Ingelheim, Clovis, Celgene, Novartis, Takeda, Ariad, BMS, MSD, Daiichi Sankyo, Guardant Health, Janssen, Epizyme, GSK, Mirati, Trizel, Turning Point Therapeutics (RF); **Maximilian J. Hochmair:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Roche (H), Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Novartis, Roche (C/A); **Carles Escriu:** Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca (C/A), Bristol-Myers Squibb, Pfizer (Other – lecture fees); **Nicolas Girard:** AstraZeneca (E, immediate family member), Roche, Lilly, Boehringer Ingelheim, AstraZeneca, Novartis, Pfizer, Bristol-Myers Squibb, Merck Sharp & Dohme, Takeda, GlaxoSmithKline, AbbVie, Pharmamar, Janssen, Sanofi (C/A), Roche, AstraZeneca, Bristol-Myers Squibb, MSD Oncology (Other - travel, accommodations, expenses), Roche, AstraZeneca, Boehringer Ingelheim (RF); **Hasan Daoud:** Boehringer Ingelheim International GmbH (E); **Angela Märten:** Boehringer Ingelheim (E); **Satoru Miura:** Chugai Pharma, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Lilly, Daiichi Sankyo (C/A), Chugai Pharma, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Lilly, Daiichi Sankyo, Taiho Pharma, Ono Pharma, Bristol-Myers Squibb, Novartis, AbbVie, Kyowa Hakko Kirin, Pfizer, Nippon Kayaku (Other - speaker's bureau). The other authors indicated no financial relationships.

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Appendix A. Supplementary data

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