ACTA ONCOLOGICA
2023, VOL. 62, NO. 12, 1854–1861
https://doi.org/10.1080/0284186X.2023.2274481

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Treatment outcomes of non-small cell lung cancers treated with EGFR tyrosine kinase inhibitors: a real-world cohort study

Otto Manninen[a], Laura Puuniemi[a,b], Sanna Iivanainen[a], Martti Arffman[c], Riitta Kaarteenaho[b] and Jussi P. Koivunen[a]

[a]Research Unit of Cancer and Translation Medicine, Cancer Center, Medical Research Center (MRC) Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland; [b]Research Unit of Biomedicine and Internal Medicine, Center of Internal Medicine and Respiratory Medicine, Medical Research Center (MRC) Oulu, Oulu University Hospital, and University of Oulu, Oulu, Finland; [c]Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland

ABSTRACT

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) are a standard of care treatment options in non-small cell lung cancer (NSCLC). The present study investigated real-world EGFR TKI use and patient outcomes in NSCLC.

Material and methods: We collected all the patients who had reimbursement for EGFR TKIs in Finland 2011–2020 and had data available at Finnish Cancer Registry. Survival and time-on-treatment (ToT) were analyzed from the first EGFR TKI purchase and patients were stratified according to the TKIs.

Results: Whole patient cohort consisted of 1498 individuals who were treated with erlotinib ($n = 998$), afatinib ($n = 258$), or gefitinib ($n = 238$). In the *EGFR* mutant cohort (all gefitinib users and afatinib users with non-squamous histology; $n = 466$), survival was comparable to registrational trials while patients treated with afatinib had improved survival (HR 0.67 CI 95% 0.53–0.85) and longer ToT (13.9 vs 11.9 months, NS) compared to those treated with gefitinib. Females treated with afatinib had improved survival (HR 0.61 CI 95% 0.44–0.83) and longer ToT (15.1 vs 12.5 months, NS) compared to gefitinib while similar was not observed in males. Later line osimertinib treatment was applied for 78 patients. Approximately 20% of the individuals treated with previous gefitinib or afatinib had later line osimertinib treatment. Efficacy analysis of osimertinib treated showed similar ToT and survival regardless of the first line EGFR TKI.

Conclusions: *EGFR* mutants treated with afatinib have improved outcomes compared to gefitinib while later-line osimertinib was applied only for around 20% of the individuals. The study further highlights the good real-world performance of EGFR TKIs and sheds light on therapy sequencing.

ARTICLE HISTORY
Received 25 April 2023
Accepted 19 October 2023

KEYWORDS
EGFR TKIs; nSCLC; EGFR mutant; RWE

Background

Targeted therapy directed at the epidermal growth factor receptor (EGFR) is one of the treatment options for non-small cell lung cancer (NSCLC). EGFR tyrosine kinase inhibitors (TKIs) were initially used in the treatment of NSCLCs without molecular selection [1,2]. Later, molecular characterization has led to the identification of *EGFR* mutated NSCLC in which EGFR TKIs yield a superior response rate, progression-free survival (PFS), and quality-of-life scores when compared to chemotherapy [3–5]. Recent studies with mutation specific EGFR TKI osimertinib have shown that the agent improves PFS and overall survival (OS) compared to the 1st generation TKIs (gefitinib and erlotinib) in the first-line setting and chemotherapy in acquired T790M + resistance mutation patients [6–9].

EGFR TKIs are generally well tolerated and permanent treatment discontinuations because of treatment related adverse events (TRAEs) are rare. Acneiform rash is the most frequent TRAE (approximately 50 to 80%) of EGFR TKIs. The frequency and severity of the rash are higher with the 1st and 2nd generation TKIs compared to the 3rd generation TKI osimertinib [6,10]. Good tolerability of osimertinib has been the main reason why it is considered the treatment of choice in the first-line setting. However, osimertinib has not formally been compared to 2nd generation TKIs such as afatinib or dacomitinib.

We have previously shown that combining data from nationwide registries can be used to investigate treatment outcomes of EGFR TKIs in NSCLC [11,12]. However, the treatment landscape of EGFR TKIs is ever-changing with the use of novel drugs. Unanswered clinically relevant issues remain, such as the optimal therapy sequencing and real-world therapy access. Since our previous studies [11,12], the number of afatinib treated has increased markedly and osimertinib

CONTACT Jussi P. Koivunen jussi.koivunen@ppshp.fi Research Unit of Cancer and Translation Medicine, Cancer Center, Medical Research Center (MRC) Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland

Supplemental data for this article can be accessed online at https://doi.org/10.1080/0284186X.2023.2274481.

treatment in *EGFR* T790M + resistance setting has become available.

The current study was initiated to investigate the real-world EGFR TKI use and performance in non-small cell lung cancer. We specifically aimed to explore the usability of drug reimbursement and purchase registry data in the generation of cohort and to study treatment outcomes according to different TKIs and patient subgroups.

Materials and methods

Cohort

We collected data on patients who had received special reimbursement for EGFR TKIs (gefitinib, erlotinib, afatinib, and/or osimertinib) in the Special Reimbursement Register of the Social Insurance Institution (SII) of Finland in 2011–20. The *EGFR* mutational status is not registered in any of the used registries and is not available. Therefore, indirect methods were used to separate patients from *EGFR* mutant cohort. During the study period, TKIs were reimbursed according to the following criteria: 1) gefitinib: the presence of activating *EGFR* mutations; 2) afatinib: the presence of activating *EGFR* mutations or 2nd or later treatment in squamous cell carcinoma; 3) erlotinib: 2nd or later line treatment or presence of activating *EGFR* mutations; 4) osimertinib: the presence of *EGFR* T790M. Using personal identity codes, we linked data for the patients from the Prescription database of SII (EGFR TKIs), Finnish Cancer Registry (FCR), and the Causes of Death Statistics of Statistics Finland from 2011 until the end of June 2021. Pseudonymization was carried out by Findata (the data permit authority for the social and healthcare sector which activities are based on the Act on the Secondary Use of Health and Social Data (552/2019)) before the data analysis and all the analysis was done using secure portal platform Kapseli (Findata-provided secure operating environment for the processing of data on individuals).

Outcomes

Survival was analyzed from the 1st EGFR TKI purchase date to death or end-of follow-up and death counted as an event. Survival for the osimertinib treated was analyzed from the first osimertinib or EGFR TKI purchase date to death or end-of follow-up and death counted as an event. The time-on-treatment (ToT) was analyzed from the date of the 1st EGFR TKI or osimertinib purchase to the last purchase date plus days on the treatment according to the number of tablets in the last purchase; treatment discontinuation before 30.6.2021 was counted as an event. However, a gap of 10 days between purchases was allowed to account for a continuation of the treatment.

Statistics

Survival was studied using the Kaplan–Meier analyses with log-rank tests to compare survival differences. Cox regression models were used to conduct univariate and multivariate analyses for survival. In a multivariate setting, proportional hazard models were used to adjust for sex, tumor histology (adenocarcinoma or other), later line osimertinib use, and/or the selected first-line EGFR TKI. The results are reported with a 95% confidence level. IBM SPSS Statistics 25.0.0.0 for Windows was applied for statistical analysis.

Permits

Data collection was carried out according to national legislation and under a permit from Findata (THL/6637/14.05.00/2021). Informed consent was not required due to the registered nature of the study.

Results

Patients

All the patients who had received reimbursement for EGFR TKIs (gefitinib, erlotinib, afatinib, osimertinib) in NSCLC in Finland 2011-20 were identified from the national reimbursement registry. Indication of use or mutational status are not gathered in the reimbursement registry and, therefore, this data is not available. The final analysis was carried out on patients ($n = 1498$) who had EGFR TKI reimbursement, had purchases of EGFR TKIs, and had data available in FCR.

Patient demographics are presented in Table 1. In brief, erlotinib was the most common TKI used ($n = 998$, 66.6%), followed by afatinib ($n = 258$, 17.2%), and gefitinib ($n = 238$, 15.9%). We also generated an *EGFR* mutant cohort which consisted of 1) all gefitinib-treated patients and 2) a subgroup of afatinib-treated patients without squamous cell histology. With squamous cell histology excluded, the afatinib cohort size was 228 patients and the whole *EGFR* mutant cohort was altogether 466 patients. Osimertinib was the first TKI in four patients and these were excluded from further analysis, while later line osimertinib was present in 78 patients (5.2%) (Table 1). None of the afatinib treated with

Table 1. Demographics.

	n (%)
All	1498 (100)
Sex	
Female	787 (52.5)
Male	711 (47.5)
Stage	
Local	68 (4.5)
Advanced	1020 (68.1)
Unknown	410 (27.4)
Histology	
Adenocarcinoma	1103 (73.6)
Squamous cell carcinoma	129 (8.6)
Other/unknown	266 (17.8)
First EGFR TKI	
Gefitinib	238 (15.9)
Erlotinib	998 (66.6)
Afatinib	258 (17.2)
Osimertinib	4 (0.3)
Later line Osimertinib	78 (5.2)
First EGFR TKI gefitinib	14 (0.9)
First EGFR TKI erlotinib	27 (1.8)
First EGFR TKI afatinib	37 (2.5)
Median follow-up time (time-on-treatment)	4.8 mo
Median follow-up time (survival)	10.7 mo

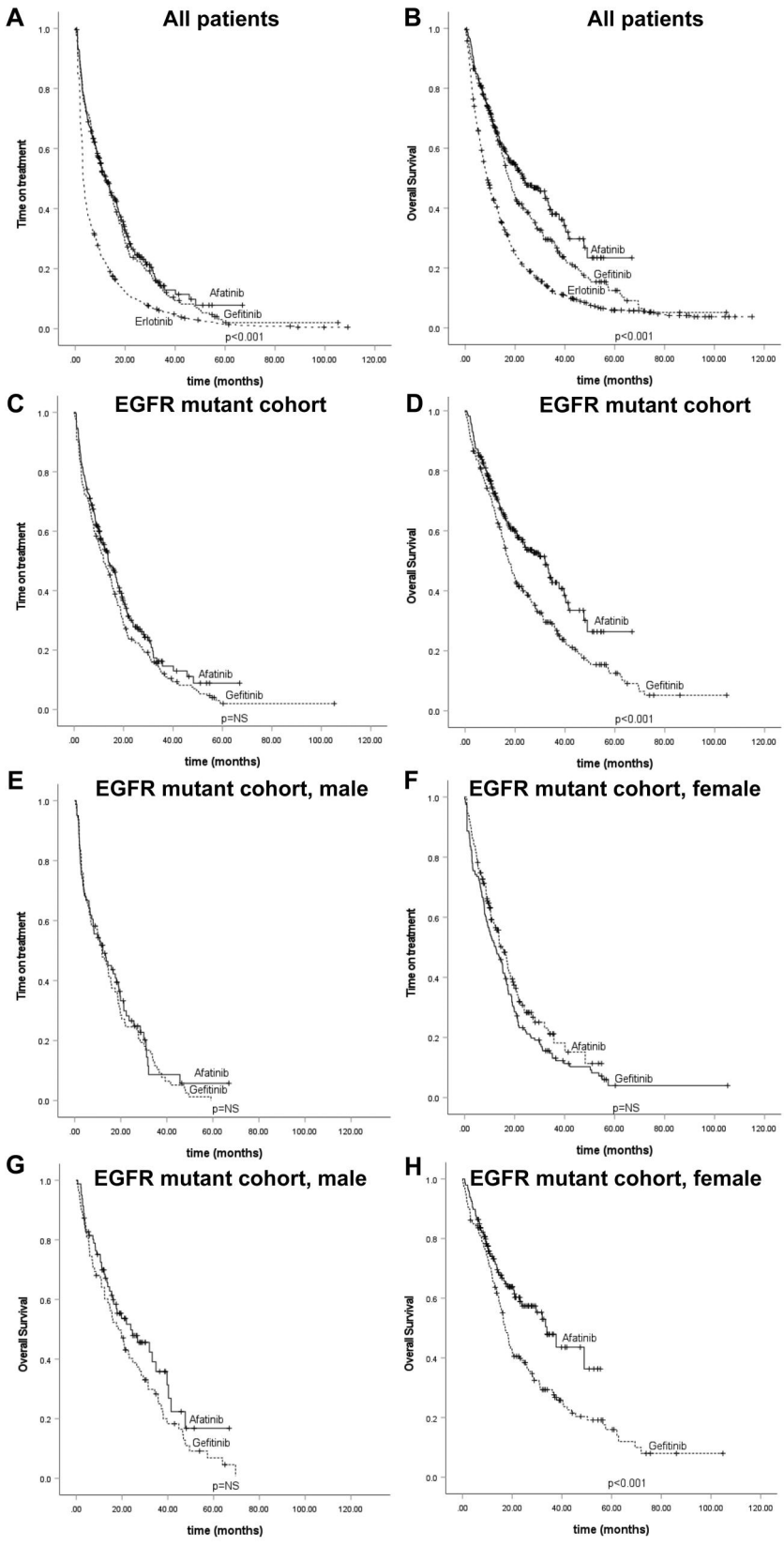

Figure 1. Kaplan-Meier analysis for time-on-treatment and overall survival. A) Time-on-treatment in the whole cohort. B) Overall survival of the whole cohort. C) Time-on-treatment in the *EGFR* mutant cohort D) overall survival in the *EGFR* mutant cohort. E) Time-on-treatment in the *EGFR* mutant cohort for males. F) Time-on-treatment in the *EGFR* mutant cohort for females. G) Overall survival in the *EGFR* mutant cohort for males. H) Overall survival in the *EGFR* mutant cohort for females. The survival endpoints were calculated from the date of the first EGFR TKI purchase and stratified according to the first purchased TKI. Crosses mark censored events.

squamous cell histology had later-line osimertinib treatment present (not shown).

Time-on-treatment and survival according to the selected first EGFR TKI in the whole cohort

We analyzed the survival measures according to the first EGFR TKI purchased. For the whole cohort, the median follow-up for time-on-treatment (ToT) treatment, a surrogate marker for progression-free survival, was 4.8 months, and for survival, 10.7 months. Next, we analyzed the cohort for ToT according to the first EGFR TKI purchased. In Kaplan-Meier analysis, afatinib and gefitinib had very similar ToTs (median of 12.2 vs. 11.9 months) while ToT for erlotinib was significantly shorter (median of 3.2 months, $p < 0.001$) (Figure 1A, Table 2). In univariate analysis for ToT, HR for afatinib was 0.462 (CI 95% 0.391–0.717) and gefitinib 0.573 (CI 95% 0.495–0.664) compared to erlotinib. In multivariate analysis, including sex, histology, and later line osimertinib, treatment duration benefit for afatinib (HR 0.519 CI 95% 0.437–0.616) and gefitinib (HR 0.617 CI 95% 0.531–0.717) retained (Table 2). Even though the use of osimertinib in the later line is a time-dependent factor, we felt that it behaves more as a baseline factor (describes *EGFR* mutation) and was included in the models.

Kaplan-Meier analysis for overall survival showed that patients treated with afatinib had the best survival followed by gefitinib, and erlotinib ($p < 0.001$) (Figure 1B). In univariate analysis for overall survival, HR for afatinib was 0.459 (CI 95% 0.318–0.478) and gefitinib 0.620 (CI 95% 0.530–0.724) compared to erlotinib. In multivariate analysis for overall survival including sex, histology, and later line osimertinib, the survival benefit for afatinib (HR 0.492 CI 95% 0.400–0.605) and gefitinib (HR 0.693 CI 95% 0.581–0.801) retained (Table 2).

Table 2. Univariate and multivariate analysis for time-on-treatment for the first TKI and survival in the whole cohort.

	Univariate		Multivariate	
	HR	CI (95%)	HR	CI (95%)
Time-on-treatment				
Sex				
Female vs. Male	0.753	0.677–0.838	0.818	0.734–0.911
Histology				
Adenocarcinoma vs. other	0.688	0.609–0.778	0.830	0.732–0.942
First TKI				
Gefitinib vs. Erlotinib	0.573	0.495–0.664	0.617	0.531–0.717
Afatinib vs. Erlotinib	0.462	0.391–0.717	0.519	0.437–0.616
2nd line osimertinib				
Yes vs. No	0.525	0.415–0.663	0.606	0.479–0.768
Survival				
Sex				
Female vs. Male	0.737	0.658–0.825	0.790	0.705–0.868
Histology				
Adenocarcinoma vs. other	0.681	0.599–0.774	0.837	0.734–0.954
First TKI				
Gefitinib vs. Erlotinib	0.620	0.530–0.724	0.693	0.590–0.814
Afatinib vs. Erlotinib	0.459	0.318–0.478	0.492	0.400–0.605
2nd line osimertinib				
Yes vs. No	0.153	0.100–0.231	0.182	0.119–0.279

We also carried out analysis for ToT and overall survival for the erlotinib users according to time of therapy initiation. There was an improved ToT and survival based on the treatment initiation (<2015 vs ≥2015), however, the difference was small (HR 0.950; 0.925) suggesting that time division could not truly divide erlotinib users for EGFR wild-type and mutants (Supplementary Table 1).

Time-on-treatment and survival according to the selected first EGFR TKI in EGFR mutants

We focused further analysis on the *EGFR* mutant cohort consisting of gefitinib and afatinib treated without squamous cell histology. In the ToT analysis, patients treated with afatinib had non-significantly longer treatment duration than gefitinib treated (median of 13.9 vs. 11.9 months, HR 0.845 CI 95% 0.688–1.037) but the difference was non-significant (Figure 1C, Table 3). In the survival analysis, afatinib showed increased survival benefit compared to gefitinib (Figure 1D, Table 3). In a multivariate analysis including sex, and later line osimertinib, survival benefit for afatinib (HR 0.771 CI 95% 0.604–0.984) was retained (Table 3). Even though the use of osimertinib in the later line is a time-dependent factor, we felt that it behaves more as a baseline factor (describes T790M resistance related to a more indolent disease course) and was included in the models.

We also carried out time-on-treatment and survival analysis according to the patient's sex. In females, the survival was improved (HR 0.606 CI 95% 0.442–0.832) and longer ToT was observed (15.1 vs. 12.5 months, HR 0.806 CI 95% 0.621–1.046) in afatinib treated compared to gefitinib (Table 4, Figure 1F, 1H). In contrast, a similar difference was not observed in males (OS HR 0.756 CI 95% 0.518–1.104, ToT HR 0.930 CI 95% 0.665–1.209) (Table 4. Figure 1(E, G)

Later line osimertinib treatment

Second or later line osimertinib reimbursement based on the presence of T790M was received in Finland on 1 February 2019. In our cohort, 78 patients had received osimertinib

Table 3. Univariate and multivariate analysis for time-on-treatment for the first TKI and survival in the EGFR mutant cohort.

	Univariate		Multivariate	
	HR	CI (95%)	HR	CI (95%)
Time-on-treatment				
Sex				
Female vs. Male	0.863	0.701–1.063	0.852	0.691–1.049
First TKI				
Afatinib vs. Gefitinib	0.845	0.688–1.037	0.857	0.697–1.055
2nd line osimertinib				
Yes vs. No	0.828	0.611–1.122	0.842	0.619–1.147
Survival				
Sex				
Female vs. Male	0.827	0.654–1.046	0.756	0.597–0.956
First TKI				
Afatinib vs. Gefitinib	0.669	0.526–0.853	0.771	0.604–0.984
2nd line osimertinib				
Yes vs. No	0.198	0.111–0.353	0.204	0.114–0.366

Table 4. Univariate analysis for time-on-treatment and survival according to gender in the EGFR mutant cohort.

	Univariate	
	HR	CI (95%)
Time-on-treatment		
Afatinib vs. Gefitinib	0.845	0.688–1.037
Females		
Afatinib vs. Gefitinib	0.806	0.621–1.046
Males		
Afatinib vs. Gefitinib	0.930	0.665–1.299
Survival		
Afatinib vs. Gefitinib	0.669	0.526–0.853
Females		
Afatinib vs. Gefitinib	0.606	0.442–0.832
Males		
Afatinib vs. Gefitinib	0.756	0.518–1.104

after previous TKI treatment (Table 1). To characterize the estimated percentages of EGFR TKI treated who received osimertinib in the later line setting, we limited the analysis to the patients who had previous EGFR TKI discontinued between 1.1.2019 and 31.6.2021 ($n = 62$, 80.8% of all osimertinib users). Of the gefitinib, erlotinib, and afatinib treated, 20.2%, 16.0%, and 19.2% received osimertinib as a later line treatment, respectively.

Among all the osimertinib users, the median ToT on osimertinib was 13.8 months (95% CI 11.0–16.6). The median survival from the first osimertinib purchase was not reached and the estimated mean survival was 20.8 months (95% CI 18.2–23.5) (Figure 2A–B). Overall survival analysis from the

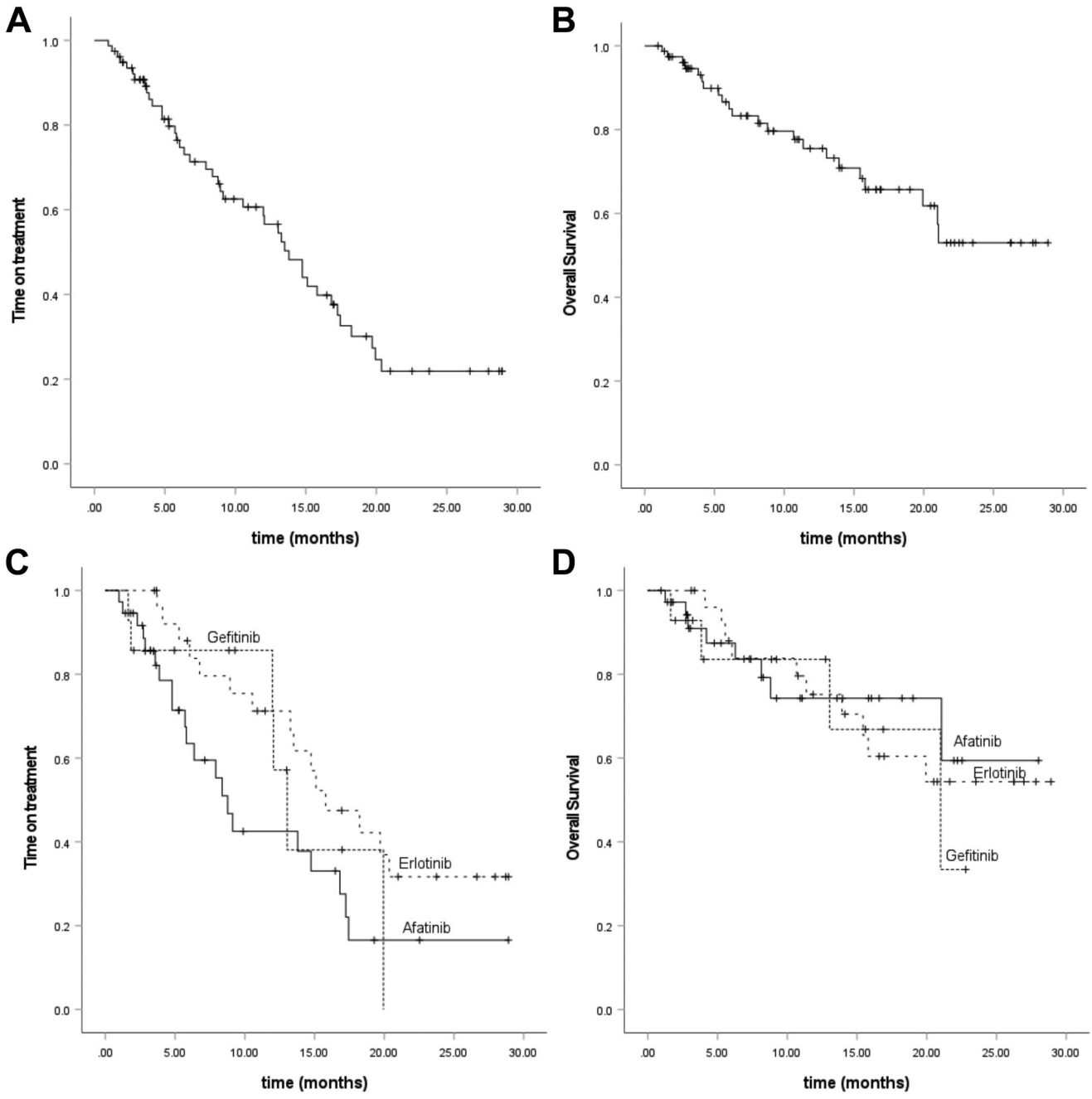

Figure 2. Kaplan-Meier analysis for overall survival and time on treatment for osimertinib treated. A) Time-on-treatment with osimertinib. B) Overall survival on osimertinib C) time-on-treatment with osimertinib according to the first EGFR TKI. D) Overall survival according to the first EGFR TKI. The survival endpoints were calculated from the first date of later line osimertinib purchase. Crosses mark censored events.

first EGFR TKI purchase showed a median survival of 63.9 months (95% CI 45.1–82.8) (not shown).

Next, we analyzed the survival and treatment duration according to the selected first line TKI. Longer osimertinib ToT was observed with erlotinib pre-treated (15.8 months 95% CI 10.9–20.7) compared to afatinib (8.8 months 95% CI 6.9–10.6) but this was not statistically significant. The overall survival from the first osimertinib purchase did not differ according to the first selected EGFR TKI (Figure 2(C–D)).

Discussion

In this study, we investigated the use of EGFR TKIs and treatment outcomes in RWE settings using a large nationwide cohort. We were able to show that the outcomes in the *EGFR* mutant population were better for afatinib than gefitinib treated patients which was presumably driven by the improved survival of females. Furthermore, excellent outcomes were observed among the later line osimertinib treated patients.

Due to national legislation changes in Finland, most of the retrospective studies require a permit from the Finnish Social and Health Data Permit Authority, Findata. With a single permit, Findata can grant access to various nationwide registries maintained by different national authorities and combine data with personal identity codes, while the final analysis is done with anonymized data in a secure portal (Kapseli). The current study is one of the first to test the feasibility of the system to study cancer drug use. We were able to show that the new system is feasible for studying EGFR TKIs in the RWE setting. Such studies enable verification of drug performance in real-world setting, comparison of different drugs that have not been evaluated in randomized studies and studying outcomes over the entire length of care pathways using a larger patient pool.

The main focus of this study was to investigate EGFR TKI RWE outcomes in the *EGFR* mutant population. Even though EGFR TKIs were previously used in *EGFR* mutation non-selected populations, the current use is exclusively limited to *EGFR* mutant patients. Since the national reimbursement registry does not collect data on *EGFR* mutations, varying indications for reimbursements need to be taken into consideration to artificially generate mutational data. Gefitinib is reimbursed only when *EGFR* mutations are present, and this represents a true *EGFR* mutant population. Afatinib, however, is reimbursed in two different indications and purchase of the drug does not characterize a sole *EGFR* mutant population. Since the other indication for afatinib requires squamous cell histology, which is usually mutually exclusive with *EGFR* mutations, we do believe that using a squamous cell histology exclusion criterion, a true *EGFR* mutant population was generated. This was further supported by the observation that none of the patients treated with afatinib in squamous cell histology had later line osimertinib treatment. Using the available data, *EGFR* mutant and *EGFR* wild type populations cannot be artificially separated among the erlotinib users. The outcomes in different *EGFR* mutations vary, but since this data is lacking in our cohort, it cannot be further studied.

According to the results, RWE performance of gefitinib and afatinib was favorable. mTOT was 13.9 and 11.9 months for afatinib and gefitinib users which was similar to PFS observed in the LUX-lung 7 trial (11.0 and 10.9 months). Furthermore, the median OS also followed closely to the ones observed in LUX-lung 7 (26 and 23 months vs. 27.9 and 24.5 months) [13]. The findings suggest that the performance of EGFR TKIs in real world setting follows very closely the results observed in randomized trials.

When comparing the first line EGFR TKI treatments, the survival of afatinib treated was superior to gefitinib. Since the tolerability of afatinib is worse compared to gefitinib, one could speculate that afatinib is more frequently selected over gefitinib to good performance status patients. However, we also observed that mToT was longer in afatinib treated, and that the survival benefit was retained in multivariate analysis which suggests that there is a true treatment benefit with afatinib over gefitinib. Afatinib has been shown to outperform gefitinib in a randomized trial using PFS as a performance measure [13]. Furthermore, another second-generation EGFR TKI, dacomitinib, has shown improved PFS and OS compared to gefitinib [14,15].

Another interesting observation in our study is that afatinib is more efficient in females. We did not observe any difference in survival of gefitinib treated according to gender. A similar phenomenon has been observed in subgroup analysis of two randomized trials comparing second-generation TKIs afatinib or dacomitinib to gefitinib [13,14]. We do not have an explanation for the observed gender driven outcome difference, but it may represent a true finding since this has also been observed in previous trials.

Our study included a small cohort of second or later-line osimertinib treated patients. Considering that the presence of T790M mediated resistance is shown to be present in about half of the patients [16], only about 20% of the patients received osimertinib therapy. There are numerous reasons which could explain the observation, such as the infeasibility of a second tumor biopsy or decline in performance status. This observation implies that osimertinib as the first-line therapy would be preferred if it is considered superior to the first or second generation TKIs. Outcomes of osimertinib treated were comparable to registrational trials with mTOT and mean OS of 13.1 and 20.8 months (AURA3 mPFS and mOS of 10.1 and 26.8 months in osimertinib treated) [8,9]. Furthermore, median survival from the first TKI purchase to the survival event surpassed the mOS of first line osimertinib trial FLAURA (63.9 vs. 36.8 months) [7]. This could be explained by 1) the patient selection in RWE setting such as a higher likelihood of better performance status patients to receive later line therapy, 2) osimertinib reimbursement occurring during the study period and increased probability of selecting slowly progressing patients to the therapy who progressed before the reimbursement, and/or by 3) improved outcomes of afatinib therapy sequence. Since the

2nd generation TKIs have not been compared in a randomized fashion to osimertinib, it is still unclear whether the first-line 2nd generation TKI and later line osimertinib sequence compared to the first-line osimertinib could result in non-inferior or even improved survival. Some retrospective studies have investigated first-line afatinib and osimertinib and have not been able to establish the superiority of osimertinib [17,18].

Our study had some obvious limitations. The retrospective nature possesses confounding factors compared to prospective randomized trials. Furthermore, due to the registry nature of the base data, some potentially important stratification or confounding factors such as specific mutational status, performance score, or a true line of therapy were missing. Our study was based on drug purchases only, but it is likely that the purchased oncological drugs were used with a very high frequency. The number of the second or later line osimertinib users was limited and, therefore, caution is needed when interpreting these results. During the study period, the first line osimertinib was not reimbursed and it couldn't be compared to other EGFR TKIs in that indication.

In conclusion, the current study evaluated RWE use of EGFR TKIs and treatment outcomes in NSCLC. We were able to show using national drug reimbursement and purchase registries as a source data and combining this to other registries, that an RWE cohort can be generated. The main findings of the study were that afatinib outperforms gefitinib in *EGFR* mutants especially in females and outcomes of the second or later line osimertinib were excellent.

Ethics approval and consent to participate

All Data collection was carried out according to national legislation and under a permit from the Findata (THL/6637/14.05.22/2021). Pseudonymization was carried out before data analysis. Informed consent was not required due to the register nature of the study.

Consent for publication

All the authors have read and approved the final version of the manuscript.

Author's contributions

OM, SI, MA, and JPK designed and coordinated the work. OM, MA, SI, and JPK, carried out statistical analysis. All the authors participated in analysis and interpretation of the data, and drafted, read, and approved the final version of the manuscript.

Disclosure statement

OM reports personal fees from MSD outside the submitted work. LP and MA declare no conflict of interest. SI reports personal fees from MSD, personal fees and grants from Roche, personal fees from BMS, personal fees and grants from AstraZeneca, personal fees from Novartis, personal fees from Takeda, personal fees from Janssen, personal fees from Eisai all outside the submitted work. RK reports consulting, lecture, and advisory board fees from Boehringer Ingelheim, virtual congress costs from Roche and Novartis, an advisory board fee from MSD, outside the submitted work. JPK reports grants and personal fees from Roche, grants and personal fees from AstraZeneca, personal fees from Janssen, personal fees from BMS, personal fees from Merck, personal fees from Amgen, personal fees from Novartis, personal fees from Merck KgA, personal fees from Sanofi all outside the submitted work. JPK is a part-time employee of Faron Pharmaceuticals.

Funding

This work was supported by the University of Oulu, Oulu University Hospital, and Boehringer-Ingelheim. This work was also supported by Oulun Yliopisto;Oulun Yliopistollinen Sairaala.

ORCID

Laura Puuniemi http://orcid.org/0000-0001-5319-4580
Sanna Iivanainen http://orcid.org/0000-0003-1075-1134
Jussi P. Koivunen http://orcid.org/0000-0001-6425-1640

Data availability statement

Owing to data protection legislation in Finland, individual-level data on the study subjects cannot be released.

References

[1] Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet. 2008;372(9652):1809–1818. doi:10.1016/S0140-6736(08)61758-4.

[2] Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non–small-cell lung cancer. N Engl J Med. 2005;353(2):123–132. doi:10.1056/NEJMoa050753.

[3] Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380–2388. doi:10.1056/NEJMoa0909530.

[4] Zhou C, Wu Y-L, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735–742. doi:10.1016/S1470-2045(11)70184-X.

[5] Yang JC-H, Wu Y-L, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol. 2015;16(2):141–151. doi:10.1016/S1470-2045(14)71173-8.

[6] Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. N Engl J Med. 2018;378(2):113–125. doi:10.1056/NEJMoa1713137.

[7] Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med. 2020;382(1):41–50. doi:10.1056/NEJMoa1913662.

[8] Wu Y-L, Mok TSK, Han J-Y, et al. Overall survival (OS) from the AURA3 phase III study: osimertinib vs platinum-pemetrexed (plt-pem) in patients (pts) with EGFR T790M advanced non-small cell lung cancer (NSCLC) and progression on a prior EGFR-tyrosine kinase inhibitor (TKI). Annals of Oncology. 2019;30:ix158. doi:10.1093/annonc/mdz437.001.

[9] Mok TS, Wu Y-L, Ahn M-J, et al. Osimertinib or platinum–pemetrexed in EGFR T790M–positive lung cancer. N Engl J Med. 2017;376(7):629–640. doi:10.1056/NEJMoa1612674.

[10] Shah RR, Shah DR. Safety and tolerability of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in oncology. Drug Saf. 2019;42(2):181–198. doi:10.1007/s40264-018-0772-x.

[11] Alanen V, Iivanainen S, Arffman M, et al. Tetracyclines increase the survival of NSCLC patients treated with EGFR TKIs: a retrospective nationwide registry study. ESMO Open. 2020;5(5):e000864. doi:10.1136/esmoopen-2020-000864.

[12] Alanen V, Iivanainen S, Arffman M, et al. Purchase of prophylactic topical corticosteroids is associated with improved survival in NSCLCs treated with EGFR TKI: real-world cohort study. Acta Oncol. 2021;60(9):1100–1105. doi:10.1080/0284186X.2021.1937309.

[13] Park K, Tan E-H, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 2016;17(5):577–589. doi:10.1016/S1470-2045(16)30033-X.

[14] Wu Y-L, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(11):1454–1466. doi:10.1016/S1470-2045(17)30608-3.

[15] Mok TS, Cheng Y, Zhou X, et al. Updated overall survival in a randomized study comparing dacomitinib with gefitinib as First-Line treatment in patients with advanced non-small-cell lung cancer and EGFR-activating mutations. Drugs. 2021;81(2):257–266. doi:10.1007/s40265-020-01441-6.

[16] Wagener-Ryczek S, Heydt C, Süptitz J, et al. Mutational spectrum of acquired resistance to reversible versus irreversible EGFR tyrosine kinase inhibitors. BMC Cancer. 2020;20(1):408. doi:10.1186/s12885-020-06920-3.

[17] Huang Y-H, Hsu K-H, Tseng J-S, et al. The difference in clinical outcomes between osimertinib and afatinib for first-line treatment in patients with advanced and recurrent EGFR-mutant non-small cell lung cancer in Taiwan. Target Oncol. 2022;17(3):295–306. doi:10.1007/s11523-022-00878-x.

[18] Ito K, Morise M, Wakuda K, et al. A multicenter cohort study of osimertinib compared with afatinib as first-line treatment for EGFR-mutated non-small-cell lung cancer from practical dataset: CJLSG1903. ESMO Open. 2021;6(3):100115. doi:10.1016/j.esmoop.2021.100115.