research article

Real-world outcomes, treatment patterns and T790M testing rates in non-small cell lung cancer patients treated with first-line first- or second-generation epidermal growth factor receptor tyrosine kinase inhibitors from the Slovenian cohort of the REFLECT study

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Radiol Oncol 2022; 56(3): 371-379.

Received 31 01 2022
Accepted 07 04 2022

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Disclosure. NT: honoraria (self) from MSD, Boehringer Ingelheim, Roche, Pfizer, AstraZeneca; honoraria (institution) from MSD, Boehringer Ingelheim, Roche, Pfizer, AstraZeneca; RD: consulting fees from Krka, Novartis, Roche; honoraria (self) from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Roche, Sanofi Aventis, Takeda; honoraria (institution) from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Novartis, Roche, Sanofi Aventis, Takeda; support for attendings meetings or travel, Merck Sharp & Dohme, Roche; NE: honoraria (self) from AstraZeneca, Chiesi, Pfizer, Roche, Boehringer Ingelheim, Merck Sharp & Dohme, Amgen, Eli Lilly, Novartis, Sapio, GSK, Krka; honoraria (institution) from AstraZeneca, Chiesi, Pfizer, Roche, Boehringer Ingelheim, Sapio, Merck Sharp & Dohme, Amgen, Eli Lilly, Novartis, GSK, Krka; IO: Honoraria (self) from AstraZeneca, Chiesi, Pfizer, Roche, Boehringer Ingelheim, Merck Sharp & Dohme, Amgen, Eli Lilly, Novartis, Sapio, GSK; honoraria (institution) from AstraZeneca, Chiesi, Pfizer, Roche, Boehringer Ingelheim, Sapio, Merck Sharp & Dohme, Amgen, Eli Lilly, Novartis, GSK; MU: honoraria (self) from AstraZeneca, Boehringer Ingelheim, BMS, Roche, Eli Lily, MSD, Lek, Krka, Novartis, TEVA, Pfizer; DV: honoraria (self) from AstraZeneca, Chiesi, Pfizer, Roche, Boehringer Ingelheim, Merck Sharp & Dohme, Amgen, Eli Lilly, Novartis, Sapio, GSK; honoraria (institution): AstraZeneca, Chiesi, Pfizer, Roche, Boehringer Ingelheim, Sapio, Merck Sharp & Dohme, Amgen, Eli Lilly, Novartis, GSK; TJ: employee of AstraZeneca; UJ: honoraria (self) from AstraZeneca, Boehringer Ingelheim, MSD, Roche, Pfizer; honoraria (institution) from AstraZeneca, Boehringer Ingelheim, MSD, Roche, Pfizer, Novartis, BMS

Background. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective treatments for EGFR mutation-positive (EGFRm) non-small cell lung cancer (NSCLC). However, routine clinical practice is different between countries/institutions.

Patients and methods. The REFLECT study (NCT04031898) is a retrospective medical chart review that explored real-life treatment and outcomes of EGFRm NSCLC patients receiving first-line (1L) first-/second-generation (1G/2G) EGFR TKIs in 8 countries. This study included adult patients with documented advanced/metastatic EGFRm NSCLC with 1L 1G/2G EGFR TKIs initiated between Jan 2015 – Jun 2018. We reviewed data on clinical characteristics, treatments, EGFR/T790M testing patterns, and survival outcomes. Here, we report data from 120 medical charts in 3 study sites from Slovenia.

Results. The Slovenian cohort (median age 70 years, 74% females) received 37% erlotinib, 32% afatinib, 31% gefitinib. At the time of data collection, 94 (78%) discontinuations of 1L TKI, and 89 (74%) progression events on 1L treatment were reported. Among patients progressing on 1L, 73 (82%) were tested for T790M mutation yielding 50 (68%) positive results, and 62 (85%) received 2L treatment. 82% of patients received osimertinib. Attrition rate between 1L and 2L was 10%. The median (95% CI) real-world progression free survival on 1L EGFR TKIs was 15.6 (12.6, 19.2) months; median overall survival (95% CI) was 28.9 (25.0, 34.3) months.

Conclusions. This real-world study provides valuable information about 1G/2G EGFR TKIs treatment outcomes and attrition rates in Slovenian EGFRm NSCLC patients. The reduced attrition rate and improved survival outcomes emphasize the importance of 1L treatment decision.

Key words: real-world study; non-small cell lung cancer; epidermal growth factor receptor; T790M testing, attrition

Introduction

Lung cancer remains a major public health challenge worldwide, due to its diagnosis in advanced stages and high rate of mortality.[1,2] The discovery of sensitizing mutations to epidermal growth factor receptor (EGFR) has changed the treatment paradigm for lung cancer and has allowed for improved outcomes in patients with tumours harboring such actionable mutations.[3,4] Tyrosine kinase inhibitors (TKIs) targeting EGFR have proven efficacy for the treatment of EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) and are the treatment of choice when this sensitizing mutation is found.[1] Several generations of EGFR TKIs have been developed and have become gradually available – from the first-generation erlotinib and gefitinib, to second-generation afatinib and dacomitinib, and third-generation osimertinib.[5]

Initial treatment recommendations for metastatic EGFRm NSCLC relied on first- and second-generation (1G/2G) EGFR TKIs, but despite promising initial responses to these therapies, the disease inevitably develops resistance and the progression requires treatment change.[6] In approximately half of cases, the resistance is mediated by the EGFR secondary mutation T790M[1,7], which is targeted by osimertinib in exon 20.[8] Based on AURA3 study results, the standard of care is now testing for the T790M mutation in all patients whose disease has progressed on 1G/2G EGFR TKIs and treatment with osimertinib when the T790M resistance mutation is identified.[1,7,8] Based on the FLAURA study results, which showed significant survival benefit with osimertinib versus comparator EGFR TKIs, osimertinib received approval by the European Medicines Agency in 2018 and became the preferred first-line (1L) treatment option in advanced or metastatic EGFRm NSCLC.[1,9]

The implementation of testing and treatment recommendations in clinical practice is not always a simple process. Access to new methods of molecular testing and novel therapies may be affected by lengthy local approvals and reimbursement processes, particularly in Central Eastern Europe (CEE).[10,11] Among countries in this region, Slovenia benefits from having a long tradition in cancer care and one of the oldest population-based cancer registries in Europe.[12,13] The advantage of having implemented a national cancer registry consists in the objective evaluation of the burden of disease and trends over time and is in direct conjunction with adequate setting and resource allocation at institutional level.[12,14]

In Slovenia, the molecular testing of EGFRm is reflex and it was partially covered by pharmaceutical companies until July 2020, when it became fully reimbursed by the public health system.[15] However, the reimbursement of innovative anti-cancer therapies is still not optimal, and it exceeds 2 years.[16] For example, the newly approved osimertinib as 1L therapy was reimbursed only in October 2020.

In addition to patient and tumour characteristics, the treatment decisions in real-world (RW) practice are driven by clinical and cost-effectiveness, safety, and availability of treatments.[17] As shown by the recent RW experience with 1L 1G/2G EGFR TKIs, the efficacy and safety of these agents proven in registration trials usually translate in real-life practice; yet, the testing rates of the resistance mutation T790M are not optimal.[18-26] To what extent the same findings apply in the Slovenian population is unknown. For this reason, Slovenia participated in this multinational medical chart review with the overarching goals of understanding the outcomes of EGFRm NSCLC patients initiated on 1L 1G/2G EGFR TKIs, treatment and T790M testing patterns, and attrition rates in various locations from Europe and Israel.[27] Here we present the results of the Slovenian patients included in this study.

Patients and methods

Study design and participants

The retrospective medical chart review "Real-world treatment patterns, clinical outcomes, and EGFR / T790M testing practices in EGFR-mutated advanced non–small cell lung cancer patients receiving First-Line EGFR TKI Therapy" (REFLECT, ClinicalTrials.gov: NCT04031898) was conducted in 7 European countries and Israel. Overall, medical chart review and data collection were carried out in 49 clinical centres from May to December 2019, and 3 comprehensive cancer care centres in Slovenia participated in this study. In Slovenia, data abstraction was conducted from October to December 2019.

The study design has been reported elsewhere.[27] Briefly, eligible patients for this study were ≥ 18 years of age with a confirmed diagnosis of locally advanced or metastatic EGFRm NSCLC who initiated 1L therapy with a 1G/2G EGFR TKI (afatinib, gefitinib or erlotinib) between January 1, 2015 and June 30, 2018. At the time of medical chart review, patients could have been alive or deceased, provided that the date of last follow-up or death was known. Patients were identified in the chrono-

logical order of initiating 1L EGFR TKIs within the study period of interest (i.e., starting with January 1, 2015) and enrolled consecutively in the electronic data collection form until the site's quota was reached. Patients enrolled in a clinical trial for experimental treatments related to EGFRm NSCLC and patients receiving systemic treatment for their locally advanced or metastatic NSCLC prior to the 1L EGFR TKIs were excluded.

In each participating country, the Institutional Review Boards (IRBs) or Ethics Committees (ECs) approved the protocol and study conduct. This medical chart review did not require informed, written consent from patients who were alive at the time of data collection unless the local IRBs/ECs required otherwise. In Slovenia, the Agency for Medicinal Products and Medical Devices (JAZMP) and the National Medical Ethics Committee (KME) approved the study, and an informed consent waiver was granted.

Outcomes and definitions

The primary outcome included progression events during treatment with 1L EGFR TKIs and time to progression, defined as time from initiation of 1L 1G/2G EGFR TKI therapy until the earliest sign of progression or death prior to start of a new therapy line or start of a new therapy line. Progression was defined as radiological progression according to any imaging method, start of new therapy line, death, or other record indicative of progression, such as documented evaluation of the clinician. To differentiate this primary outcome from the progression free survival (PFS) reported in randomized clinical trials, we use the term "real-world PFS" (rwPFS).

The secondary outcomes of this study included attrition rates and T790M testing rates among patients progressing on 1L 1G/2G EGFR TKIs, types of treatments received in subsequent lines, incidence of central nervous system (CNS) metastases and leptomeningeal disease (LMD) and time to their development, overall survival (OS) from the start of 1L EGFR TKI therapy, and OS from first diagnosis of CNS metastases and/or LMD to the date of death from any cause, with patients last known to be alive censored at the date of last available follow-up.

Data collection

Patient- and disease-specific data were obtained from the patient's medical records and registered by participating investigators in an electronic case report form. Each patient's case was allocated an anonymized, encrypted identifier. Data were collected from the time of initial NSCLC diagnosis until death or the last available follow-up at the time of the patient's inclusion in the study.

TABLE 1. Clinical characteristics at the time of initial NSCLC diagnosis

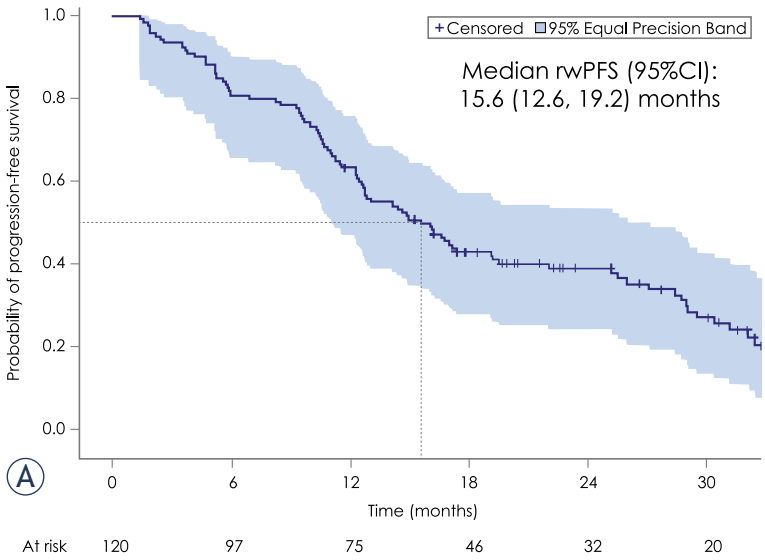
Characteristic	N = 120 n (%)
Smoking history	
Current smoker	7 (6)
Former smoker	33 (28)
Never smoker	76 (63)
Unknown	4 (3)
ECOG performance status	
0	28 (23)
1	62 (52)
2	22 (18)
3	6 (5)
4	1 (1)
Unknown	1 (1)
Stage at initial diagnosis	
Early stage (I-II)	13 (11)
Limited regional (IIIA)	4 (3)
Locally advanced (IIIB)	0
Metastatic (IV)	103 (86)
Site of distant metastases	
Adrenal	12 (10)
Bone	54 (45)
Brain	33 (28)
Liver	19 (16)
Lung	60 (50)
Lymph nodes	60 (50)
Peritoneal	2 (2)
Pleura	38 (32)
Skin/soft tissue	3 (3)
Other*	10 (8)

* Other sites of distant metastases included: bone marrow, eye, kidney, spleen, and pericardium.

ECOG=Eastern Cooperative Oncology Group

Statistical analysis

Sample size was based on the feasibility information received from each country, taking into ac-



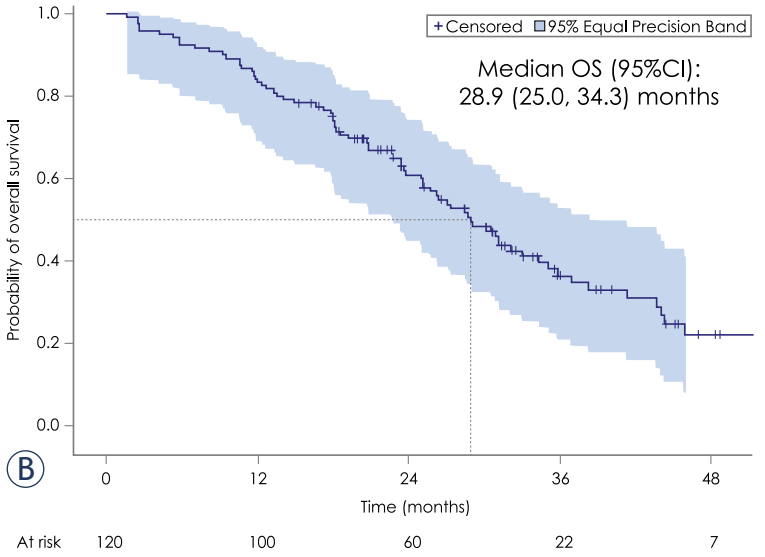


FIGURE 1. (A) Kaplan-Meier curves for median real-world progression free survival on first-line (1L) epidermal growth factor (EGFR) tyrosine kinase inhibitors (TKIs) therapy. **(B)** Kaplan-Meier curves for median overall survival from start of 1L EGFR TKI therapy. Censored patients are indicated with a cross.

CI = confidence interval; OS = overall survival; rwPFS = real-world progression-free survival

count the volume of potentially eligible patients treated with 1L EGFR TKIs in the period of interest for the study. It was anticipated that each participating physician would contribute with 5–30 case records to the study and each country would collect data from 50–180 medical records.

This study had no formal statistical hypothesis; descriptive statistics were used to assess the demographic and clinical characteristics, treatment patterns, and attrition rate. Kaplan-Meier estimators were used to describe median PFS and OS with 95% confidence interval (95% CIs). All analyses were performed in the full analysis set. The stratified OS analysis required > 20 number of events and a level of maturity of > 50%. The study was not powered for group comparisons.

Results

In total, 120 medical charts were included in this medical chart review from 3 study sites in Slovenia. The sites participating in the REFLECT study were also the only centres where lung cancer is being treated in Slovenia: 1 national cancer centre and 2 university hospitals.

Demographic, clinical and EGFR mutation characteristics at baseline

The median age (range) of patients was 70 (33–93) years, the majority were female (74%) and had never smoked (63%). At the initial diagnosis of NSCLC, adenocarcinoma was the predominant histological subtype (99%), and the majority of patients (86%) had metastatic stage. Most patients (75%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. The most frequent sites of metastases at the time of initial diagnosis were lung and lymph nodes (50% each), bone (45%), pleura (32%), and brain (28%) (Table 1). The median (range) follow-up time was 24.3 (1.6–57.7) months.

EGFR mutation status was determined from tissue biopsy (75%) or cytology specimens (25%). The specimen was extracted from the primary tumour in most cases (73%). In 2% of patients, the biopsy site was unknown. The most frequent EGFR mutation was exon 19 deletion (58%) followed by exon 21 L858R point mutation (28%); uncommon mutations (15%) included G719X, L861Q, S768I, T790M, and exon 20 insertions.

First-line EGFR TKI therapy, progression and survival

The 1L EGFR TKI therapies initiated during the period of interest for the study had a balanced distribution: 37% of patients received erlotinib, 32% gefitinib and 31% afatinib. At the time of data collection, 94 patients (78%) discontinued 1L EGFR TKIs due to progression events or toxicities. Toxicities occurred in 9 cases (8%), with 5 of them (4%) not

starting any further treatment line. A number of 26 patients (22%) continued 1L treatment.

In total, 89 progression events per protocol were reported: 47 radiological progression events (39%), 22 clinical progression events (18%), 16 deaths (13%) and 4 cases (3%) with start of a new therapy line without documented progression.

Median (95% CI) rwPFS was 15.6 (12.6, 19.2) months (Figure 1A). Estimated probabilities for rwPFS (95% CI) at 12, 24 and 36 months were 63% (54%, 71%), 39% (30%, 48%) and 18%% (10%, 28%), respectively. Median (95% CI) OS from start of 1L EGFR TKI was 28.9 (25.0, 34.3) months (Figure 1B). Estimated probabilities for OS (95% CI) at 12, 24 and 36 months were 83% (75%, 89%), 61% (51%, 69%) and 36% (27%, 46%), respectively.

T790M mutation testing and osimertinib treatment

Of the 89 patients with progression events on 1L EGFR TKI therapy, 73 (82%) were tested for the T790M mutation at any time. Of the 73 patients tested for T790M mutation, the mutation was identified in 50 patients (68%) and the test was negative for 23 patients (32%). Of the 73 patients with disease progression on 1L EGFR TKIs who were tested for the T790M mutation, 62 (85%) received second-line (2L) treatment. In these patients, the 2L included osimertinib (84%), chemotherapy (15%) or targeted therapy (1%).

Among the rest of the 16 patients with progression on 1L EGFR TKI therapy who were not tested for T790M mutation, 4 patients (25%) received 2L treatment, with either chemotherapy or osimertinib (50% each).

Testing for the T790M mutation was performed by using liquid biopsy in most cases (77%), followed by tissue biopsy (14%) or cytology specimen (9%). Most tests (97%) were based on Cobas® EGFR mutation test (Roche). The mean time (standard deviation) between the initiation of 1L EGFR TKIs and T790M testing was 14.4 (9.0) months.

Second and subsequent therapy lines

Of the 89 patients with disease progression on 1L EGFR TKIs, 66 (74%) initiated 2L treatment. In the Slovenian cohort of patients, 16 (13%) patients who discontinued 1L died before receiving 2L treatment, while 12 (10%) patients alive of the time of 1L discontinuation did not receive any further line. The 2L treatments included osimertinib (82%), chemotherapy (17%) and other targeted therapy (1%). At the time of data collection 18 patients (28%) were still receiving 2L treatment (Figure 2).

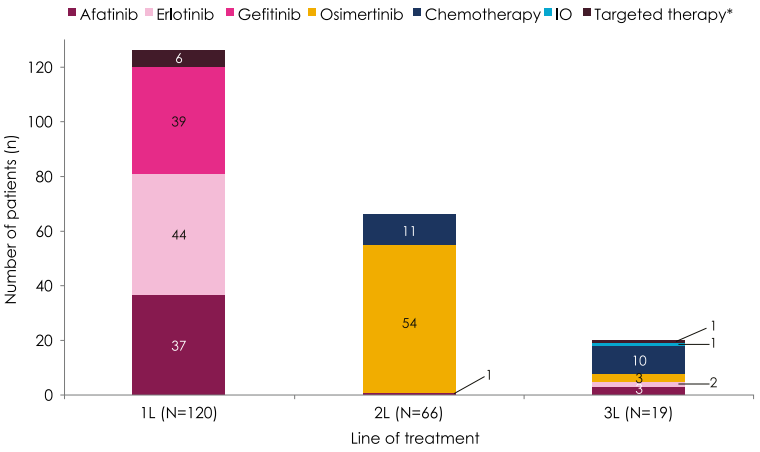


FIGURE 2. Treatment patterns patients in with locally advanced or metastatic epidermal growth factor receptor mutated (EGFRm) non-small cell lung cancer (NSCLC) treated with first-line (1L) first-/second-generation (1G/2G) EGFR tyrosine kinase inhibitors (TKIs). Note that multiple treatments could have been administered at each line of treatment.

* Targeted therapy besides afatinib, erlotinib, gefitinib and osimertinib (1L: not specified; 3L: crizotinib); 2L = second-line; 3L =third-line; IO = immuno-oncology

Of the 48 patients discontinuing 2L, 19 (40%) received third-line (3L) treatment, which consisted of chemotherapy (53%), targeted therapy (26%), osimertinib (16%), or immuno-oncological therapy (5%) (Figure 2). At the end of data collection, 1 patient (5%) was still on 3L treatment. Attrition rates on 1L, 2L, and 3L treatment are shown in Figure 3.

Of the 18 patients discontinuing 3L, 5 (28%) received fourth-line (4L) treatment, which consisted of targeted therapy (60%) or osimertinib (40%). All patients discontinued 4L, with one case of death being registered, while the remaining 4 patients received the fifth-line of treatment (5L), which consisted of targeted therapy (50%), chemotherapy (25%), and osimertinib (25%) (Figure 2). All patients discontinued 5L treatment.

Central nervous system metastases

The medical charts of 46 patients (38%) recorded the presence of central nervous system (CNS) metastases: in 33 cases (28%) these were present at the start of 1L EGFR TKIs, and in 13 cases (11%) the CNS metastases developed after the start of 1L treatment. In all cases (100%), an imaging examination (computed tomography or magnetic resonance imaging scan) was used for the diagnosis of the CNS metastases, and in 2 cases (4%) tissue biopsy was also performed. Patients with CNS metastases

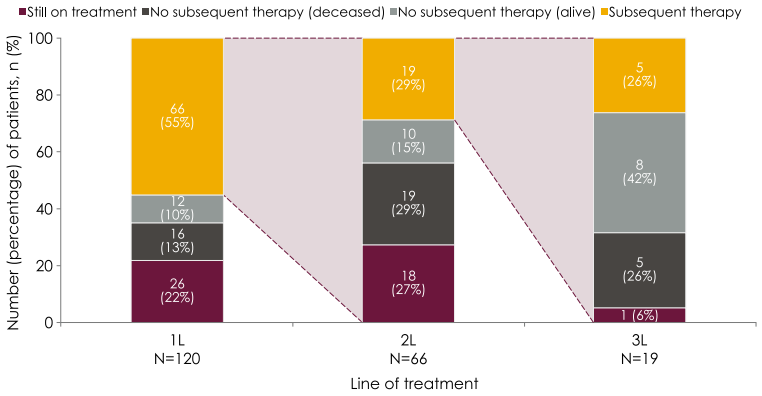


FIGURE 3. Attrition rates at first-line (1L), second-line (2L) and third-line (3L) in patients with locally advanced or metastatic epidermal growth factor receptor mutated (EGFRm) non-small cell lung cancer (NSCLC).

had a median age (range) of 67.5 (33.0–87.0) years and most (70%) were female. Treatments applied for CNS metastases included whole brain radiation therapy (63%), targeted therapy (63%), stereotactic radiosurgery (11%) and surgical resection (9%); in 4% of cases no treatment was provided.

The median (range) time from the initiation of 1L EGFR TKIs to CNS metastases diagnosed during 1L or later lines treatment was 19.8 (7.7, 34.6) months. The median (95% CI) OS in patients with CNS metastases at the start of 1L EGFR TKIs was 24.3 (18.4, 41.5) months, with 24 events reported. In the group of patients with CNS metastases developed during treatment, the number of events was too small to allow reporting of OS.

Leptomeningeal disease

Leptomeningeal disease (LMD) was reported in 4 patients: for 1 patient before and for 3 after the start of 1L EGFR TKI therapy. In all patients the diagnosis relied on imaging examinations only. The median (range) time from the initiation of 1L EGFR TKIs to LMD diagnosed during treatment was 19.6 (4.5, 28.7) months. The number of events was too small to allow reporting of OS.

Discussion

This is the first comprehensive analysis of the outcomes, treatment patterns, and testing rates in metastatic EGFRm NSCLC patients who received 1L 1G/2G EGFR TKI therapy in Slovenia over 3.5 years, from 2015 to 2018. This is a nationally representative dataset for our clinical practice because all 3 large-volume centers from Slovenia that ensure an integrated oncology care of lung cancer patients, with national coverage, participated in the REFLECT study.

Considering the real-life setting, the unselected population of patients with EGFRm NSCLC and the relatively equal distribution of 1G/2G EGFR TKIs (37% erlotinib, 32% afatinib, 31% gefitinib), our findings indicate positive treatment outcomes with 1L EGFR TKIs with a median rwPFS of 15.6 months. In the overall cohort from the REFLECT study (n=896), the median rwPFS was 13.0 (95% CI 12.3, 14.1) months and more patients received afatinib (45%).[27] In clinical trials of 1G/2G EGFR TKI therapy, the acquired resistance developed after a median of 9.2–14.7 months of targeted treatment.[6] Other European RW studies that partially overlap with the limits of the data collection set for the REFLECT study, but with a different distribution of the 1G/2G EGFR TKI therapies have shown PFS ranging from 7.6 to 11.0 months.[18-20,22,26] The enhanced rwPFS outcomes observed in the Slovenian cohort may be the result of more standardized and homogenous cancer care across centers, including established pathways for EGFR and T790M mutation testing, as well as effective control policies. Furthermore, in many cases the treatment may have continued beyond radiological progression, a common approach in patients with genetic actionable alterations.[1] Another observational study specifically exploring the continuation of EGFR TKIs beyond radiological progression showed that patients continued treatment without clinical deterioration for a median of 5.1 months and had a median PFS of 15.3 months.[28]

The median OS from the start of the 1L 1G/2G EGFR TKI therapy was 28.9 months in the Slovenian cohort and 26.2 (95% CI 23.6, 28.4) months in the overall REFLECT study cohort.[27] In general, the median OS reported in RW studies with 1L 1G/2G EGFR TKIs varies greatly, due to timelines set for the analysis, factors related to the healthcare system and access to EGFR TKIs, patient characteristics and data quality. Our findings are in line with those of other reports and are relevant for the period under study, when third-generation EGFR TKI osimertinib was not yet approved as 1L treatment.[18,20,22,24,26] Following osimertinib 1L approval and subsequent market entries, more data on the effectiveness of osimertinib in various geographies are awaited.

Upon progression on 1L 1G/2G EGFR TKIs, Slovenian national guidelines for the treatment of NSCLC, in accordance with European guidelines, recommend testing for resistance mutation

T790M and, in patients with positive test results initiation of osimertinib.[1,29] In this cohort, 82% of patients were tested for the presence of T790M upon progression on 1L; the resistance mutation was identified in two-thirds (68%) of these patients, thereby providing an opportunity for treatment that is effective against disease with T790M mutation. Expressed at the level of the overall Slovenian cohort (42%), this positive rate of T790M is in line with other RW data from European cohorts.[21,23,30,31] Additionally, in most patients (n=66) receiving 2L treatment in our cohort, post-progression treatment consisted of osimertinib (82%), preponderantly in patients with the T790M mutation. These results support a unified approach to T790M testing and subsequent treatment at the national level, consistent with guidelines recommendations.[1,29] In current local practice, when a clinical progression is suspected (even before radiologic progression), an active search with minimally invasive liquid biopsy for the presence of resistance T790M mutation is begun. This approach allows for early initiation of 2L systemic therapy with the goal of improving patient outcomes.

Over the course of the lung cancer disease, many patients develop CNS metastases, which confer a poor prognosis and present additional treatment challenges.[32] CNS metastases are often identified in patients with adenocarcinoma and molecular alterations, and their incidence is significantly correlated with the presence of EGFR-activating mutations.[1,33,34] In this cohort, 38% of patients had CNS metastases, most of them present at the time of diagnosis of the metastatic stage of lung cancer (28%). In a local retrospective analysis exploring the cumulative incidence of brain metastases in 629 patients with adenocarcinomas tested for EGFRm, those with the EGFR activating mutation had a longer time to CNS progression (25.9 vs. 11.9 months, p=0.002).[35] In this REFLECT study cohort, the time to CNS progression was 19.8 months, with a median OS of 24.3 months in patients with CNS metastases at the start of 1L 1G/2G EGFR TKI therapy. The difference may be due to advances in radiological techniques used to identify CNS metastases, as well as practice changes. The dynamic landscape of technology, improved local control and reduced morbidity are reflected in the current management of CNS metastases as stereotactic radiosurgery has become the foremost treatment modality in patients with "limited" intracranial disease.[36]

REFLECT was primarily a study of attrition rates between treatment lines. In this cohort, of the 78 patients who started 1L 1G/2G EGFR TKIs and were alive at the time of treatment discontinuation, 12 (15%) did not receive 2L treatment. The trend of not receiving further treatment was sustained in subsequent lines, although the number of patients alive at the time of treatment discontinuation progressively decreased. The rate of patients not receiving 2L treatment after the 1L EGFR TKIs was initially reported in clinical trials and it was approximately 35%, whereas in RW studies the rate varies more widely (10–62%).[25,37,38] Although the REFLECT study did not explore the reasons why patients did not receive further treatment lines, data reported in the literature suggest various causes, including lack of genetic testing, low T790M mutation rate, poor performance status and even patient's preference not to receive the next line of treatment, which would be chemotherapy in many cases.[37] In our cohort we noticed that 18% patients progressing on 1L EGFR TKI were not tested for presence of T790M mutation. The rationale behind the lack of T790M testing at progression was not investigated, but such finding might be explained by rapid deterioration of clinical status followed by death on 1L EGFR TKI, presence of exon 20 insertion, which is associated with limited efficacy of common EGFR TKIs and unfavorable prognosis or poor performance status at the time of disease progression rendering patient ineligible for any further systemic therapy.[37,39,40] Hence, the true T790M positivity rate and proportion of patients eligible for targeted 2L may be different in real-life. Beyond possible differences in healthcare setting and availability of effective treatment options, exploring locally in more depth the reasons behind attrition rates is crucial to further improve patient outcomes.

The real-life character of this study confers both strengths and limitations. With a minimal set of inclusion and exclusion criteria, and a representative dataset for Slovenia, this study allowed for building RW evidence on 1L 1G/2G EGFR TKI therapy at the national level based on a 3.5-year data review (2015–2018). The fact that data collection relied entirely on information existing in patients' records, which sometimes have insufficient or missing data, is a key limitation in such designs. Nevertheless, Slovenia benefited from the participation of all 3 of the country's institutions in which lung cancer is treated. As a result, data availability was very good, with minimal cases of unknown information in patients' histories. In general, secondary data collection may be subject to selection bias, including of sites and patients. To reduce site selection bi-

as and potential patients' spreading between sites, all 3 Slovenian comprehensive cancer centers were included in the study. To reduce patient selection bias, the ethics review package submitted has requested an informed consent waiver, which was granted by the National Ethics Committee. Thus, all medical records of eligible patients were considered, irrespective of the vital status at the time of data collection and patients were enrolled consecutively in the electronic data collection form in the chronological order of starting the 1L 1G/2G EGFR TKI therapy. In contrast to clinical trials design, disease progression was not confirmed through a standardized, objective method, and the study definition reflects the RW situation (start of a new line of therapy or any other records indicative of progression, besides radiological tests). Finally, the study was not powered to compare the individual 1G/2G EGFR TKIs, and therefore outcomes could not be further characterized by molecule.

Conclusions

This real-world study, performed in a representative dataset for Slovenian clinical practice, provides insights into the effectiveness of 1G/2G EGFR TKIs and T790M testing patterns in EGFRm NSCLC patients receiving routine care. The survival outcomes and reduced attrition rate reported in this real-life setting from our country are encouraging. Newer 1L treatment options require follow-up studies to reflect the dynamic changes in clinical practice.

Acknowledgments

Medical writing support was provided by Ana Maria Iordan (MD, MSc) of MedInteractiv (Bucharest, Romania) and funded by AstraZeneca in accordance with Good Publication Practice (GPP3) guidelines. Statistical analyses were provided by Planimeter Inc (Budapest, Hungary) and were funded by AstraZeneca. The REFLECT study (NCT04031898) was funded by AstraZeneca.

Authorship: NT, RD, NE, IO, MU, DV, UJ have been involved in the acquisition and interpretation of data, critical revision of the article and approved the final version to be submitted. TJ has been involved in the interpretation of data, critical revision of the article, supervision and approved the final version to be submitted.

References

1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [published correction appears in *Ann Oncol* 2019; **30**: 863-70]. *Ann Oncol* 2018; **29(Suppl 4):** iv192-237. doi: 10.1093/annonc/mdy275
2. World Health Organization. International Agency for Research on Cancer (IARC). GLOBOCAN 2020. Cancer today. Lung. [internet]. [cited 2021 Feb 16]. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/15-Lung-fact-sheet.pdf
3. Carcereny E, Morán T, Capdevila L, Cros S, Vilà L, de Los Llanos Gil M, et al. The epidermal growth factor receptor (EGRF) in lung cancer. *Transl Respir Med* 2015; **3:** 1. doi: 10.1186/s40247-015-0013-z
4. Gelatti ACZ, Drilon A, Santini FC. Optimizing the sequencing of tyrosine kinase inhibitors (TKIs) in epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC). *Lung Cancer* 2019; **137:** 113-22. doi: 10.1016/j.lungcan.2019.09.017
5. Vansteenkiste J, Wauters E. Tyrosine kinase inhibition of EGFR: a successful history of targeted therapy for NSCLC since 20 years. *Ann Oncol* 2018; **29(Suppl 1):** i1-i2. doi: 10.1093/annonc/mdx724
6. Westover D, Zugazagoitia J, Cho BC, Lovly CM, Paz-Ares L. Mechanisms of acquired resistance to first- and second-generation EGFR tyrosine kinase inhibitors. *Ann Oncol* 2018; **29(Suppl 1):** i10-i19. doi: 10.1093/annonc/mdx703
7. Santoni-Rugiu E, Melchior LC, Urbanska EM, Jakobsen JN, Stricker K, Grauslund M, et al. Intrinsic resistance to EGFR-tyrosine kinase inhibitors in EGFR-mutant non-small cell lung cancer: differences and similarities with acquired resistance. *Cancers* 2019; **11:** 923. doi: 10.3390/cancers11070923
8. Mok TS, Wu Y-L, Ahn M-J, Kim HR, Ramalingam SS, Shepherd FA, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med* 2017; **376:** 629-40. doi: 10.1056/NEJMoa1612674
9. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018; **378:** 113-25. doi: 10.1056/NEJMoa1713137
10. Cufer T, Ciuleanu TE, Berzinec P, Galffy G, Jakopovic M, Jassem J, et al. Access to novel drugs for non-small cell lung cancer in Central and Southeastern Europe: a Central European Cooperative Oncology Group analysis. *Oncologist* 2020; **25:** e598-601. doi: 10.1634/theoncologist.2019-0523
11. Ryska A, Berzinec P, Brcic L, Cufer T, Dziadziuszko R, Gottfried M, et al. NSCLC molecular testing in Central and Eastern European countries. *BMC Cancer* 2018; **18:** 269. doi: 10.1186/s12885-018-4023-4
12. Zadnik V, Primic Zakelj M, Lokar K, Jarm K, Ivanus U, Zagar T. Cancer burden in Slovenia with the time trends analysis. *Radiol Oncol* 2017; **51:** 47-55. doi: 10.1515/raon-2017-0008
13. Zwitter M, Čufer T, Vrankar M, Kern I, Štupnik T, Rozman A, et al. Lung cancer in Slovenia. *J Thorac Oncol* 2019; **14:** 1327-31. doi: 10.1016/j.jtho.2019.02.025
14. Zanetti R, Sacchetto L, Coebergh JW, Rosso S. To accelerate cancer prevention in Europe: challenges for cancer registries. *Eur J Cancer* 2018; **104:** 151-9. doi: 10.1016/j.ejca.2018.09.001
15. Thunissen E, Weynand B, Udovicic-Gagula D, Brcic L, Szolkowska M, Hofman P, et al. Lung cancer biomarker testing: perspective from Europe. *Transl Lung Cancer Res* 2020; **9:** 887-897. doi: 10.21037/tlcr.2020.04.07
16. Janzic U, Knez L, Janzic A, Cufer T. Time to access to novel anticancer drugs and the correlation with ESMO-magnitude of clinical benefit scale in Slovenia. *Expert Rev Pharmacoecon Outcomes Res* 2019; **19:** 717-23. doi: 10.1080/14737167.2019.1702879
17. Hirsh V, Singh J. Optimal sequencing strategies in the treatment of EGFR mutation-positive non-small cell lung cancer: clinical benefits and cost-effectiveness. *Am J Health Syst Pharm* 2020; **77:** 1466-76. doi: 10.1093/ajhp/zxaa197
18. Leduc C, Merlio JP, Besse B, Blons H, Debieuvre D, Bringuier PP, et al. Clinical and molecular characteristics of non-small-cell lung cancer (NSCLC) harboring EGFR mutation: results of the nationwide French Cooperative Thoracic Intergroup (IFCT) program. *Ann Oncol* 2017; **28:** 2715-24. doi: 10.1093/annonc/mdx404

19. Syrigos KN, Georgoulias V, Zarogoulidis K, Makrantonakis P, Charpidou A, Christodoulou C. Epidemiological characteristics, EGFR status and management patterns of advanced non-small cell lung cancer patients: the Greek REASON observational registry study. *Anticancer Res* 2018; **38:** 3735-44. doi: 10.21873/anticanres.12654

20. Schuette W, Schirmacher P, Eberhardt WEE, Dietel M, Zirrgiebel U, Muehlenhoff L, et al. Treatment decisions, clinical outcomes, and pharmacoeconomics in the treatment of patients with EGFR mutated stage III/IV NSCLC in Germany: an observational study. *BMC Cancer* 2018; **18:** 135. doi: 10.1186/s12885-018-4032-3

21. Reale ML, Chiari R, Tiseo M, Vitiello F, Barbieri F, Cortinovis D, et al. Be-TeaM: an Italian real-world observational study on second-line therapy for EGFR-mutated NSCLC patients. *Lung Cancer* 2020; **140:** 71-9. doi: 10.1016/j.lungcan.2019.12.006

22. Pluzanski A, Krzakowski M, Kowalski D, Dziadziuszko R. Real-world clinical outcomes of first-generation and second-generation epidermal growth factor receptor tyrosine kinase inhibitors in a large cohort of European non-small-cell lung cancer patients. *ESMO Open* 2020; **5:** e001011. doi: 10.1136/esmoopen-2020-001011

23. Pereira I, Gaspar C, Pina M, Azevedo I, Rodrigues A. Real-world T790M mutation frequency and impact of rebiopsy in patients with EGFR-mutated advanced non-small cell lung cancer. *Cureus* 2020; **12:** e12128. doi: 10.7759/cureus.12128

24. Gijtenbeek RGP, Damhuis RAM, Groen HJM, van der Wekken AJ, van Geffen WH. Nationwide real-world cohort study of first-line tyrosine kinase inhibitor treatment in epidermal growth factor receptor-mutated non-small-cell lung cancer. *Clin Lung Cancer* 2020; **21:** e647-53. doi: 10.1016/j.cllc.2020.05.019

25. Chiang AC, Fernandes AW, Pavilack M, Wu JW, Laliberté F, Duh MS, et al. EGFR mutation testing and treatment decisions in patients progressing on first- or second-generation epidermal growth factor receptor tyrosine kinase inhibitors. *BMC Cancer* 2020; **20:** 356. doi: 10.1186/s12885-020-06826-0

26. Cuppens K, Lodewyckx L, Demedts I, Decoster L, Colinet B, Deschepper K, et al. Real-world treatment patterns, epidermal growth factor receptor (EGFR) testing and outcomes in EGFR-mutated advanced non-small cell lung cancer patients in Belgium: results from the REVEAL study. *Drugs Real World Outcomes* 2021; **8:** 141-52. doi: 10.1007/s40801-021-00243-w

27. Addeo A, Hochmair M, Janzic U, Dudnik E, Charpidou A, Płużański A, et al. Treatment patterns, testing practices, and outcomes in the pre-FLAURA era for patients with EGFR mutation-positive advanced NSCLC: a retrospective chart review (REFLECT). *Ther Adv Med Oncol* 2021; **13:** 1-11. doi: 10.1177/17588359211059874

28. Goto Y, Tanai C, Yoh K, Hosomi Y, Sakai H, Kato T, et al. Continuing EGFR-TKI beyond radiological progression in patients with advanced or recurrent, EGFR mutation-positive non-small-cell lung cancer: an observational study. *ESMO Open* 2017; **2:** e000214. doi: 10.1136/esmoopen-2017-000214

29. Unk M, Mohorčič K, Osrajnik I, Čufer T. Lung cancer – Slovenian clinical practice guidelines in systemic treatment 2017. [Slovenian]. *Onkologija* 2017; **21:** 52-62.

30. Minari R, Mazzaschi G, Bordi P, Gnetti L, Alberti G, Altimari A, et al. Detection of EGFR-activating and T790M mutations using liquid biopsy in patients with EGFR-mutated non-small-cell lung cancer whose disease has progressed during treatment with first- and second-generation tyrosine kinase inhibitors: a multicenter real-life retrospective study. *Clin Lung Cancer* 2020; **21:** e464-73. doi: 10.1016/j.cllc.2020.02.021

31. Dal Maso A, Lorenzi M, Roca E, Pilotto S, Macerelli M, Polo V, et al. Clinical features and progression pattern of acquired T790M-positive compared with T790M-negative EGFR mutant non-small-cell lung cancer: catching tumor and clinical heterogeneity over time through liquid biopsy. *Clin Lung Cancer* 2020; **21:** 1-14.e3. doi: 10.1016/j.cllc.2019.07.009

32. Owen S, Souhami L. The management of brain metastases in non-small cell lung cancer. *Front Oncol* 2014; **4:** 248. doi: 10.3389/fonc.2014.00248

33. Page S, Milner-Watts C, Perna M, Janzic U, Vidal N, Kaudeer N, et al. Systemic treatment of brain metastases in non-small cell lung cancer. *Eur J Cancer* 2020; **132:** 187-98. doi: 10.1016/j.ejca.2020.03.006

34. Li L, Luo S, Lin H, Yang H, Chen H, Liao Z, et al. Correlation between EGFR mutation status and the incidence of brain metastases in patients with non-small cell lung cancer. *J Thorac Dis* 2017; **9:** 2510-20. doi: 10.21037/jtd.2017.07.57

35. Stanic K, Zwitter M, Hitij NT, Kern I, Sadikov A, Cufer T. Brain metastases in lung adenocarcinoma: impact of EGFR mutation status on incidence and survival. *Radiol Oncol* 2014; **48:** 173-83. doi: 10.2478/raon-2014-0016

36. Shinde A, Akhavan D, Sedrak M, Glaser S, Amini A. Shifting paradigms: whole brain radiation therapy versus stereotactic radiosurgery for brain metastases. *CNS Oncol* 2019; **8:** CNS27. doi: 10.2217/cns-2018-0016

37. Roeper J, Kurz S, Grohé C, Griesinger F. Optimizing therapy sequence to prevent patient attrition in EGFR mutation-positive advanced or metastatic NSCLC. *Future Oncol* 2021; **17:** 471-86. doi: 10.2217/fon-2020-0854

38. Nadler E, Pavilack M, Espirito JL, Clark J, Fernandes A. Observational study of treatment patterns in patients with epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer after first-line EGFR-tyrosine kinase inhibitors. *Adv Ther* 2020; **37:** 946-54. doi: 10.1007/s12325-020-01221-4

39. Wang F, Li C, Wu Q, Lu H. EGFR exon 20 insertion mutations in non-small cell lung cancer. *Transl Cancer Res* 2020; **9:** 2982-91. doi: 10.21037/tcr.2020.03.10

40. Remon J, Hendriks LEL, Cardona AF, Besse B. EGFR exon 20 insertions in advanced non-small cell lung cancer: a new history begins. *Cancer Treat Rev* 2020; **90:** 102105. doi: 10.1016/j.ctrv.2020.102105

41. Dent RAG, Cole P. In vitro maturation of monocytes in squamous carcinoma of the lung. *Br J Cancer* 1981; **43:** 486-95. doi: 10.1038/bjc.1981.71

42. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355:** i4919. doi: 10.1136/bmj.i4919

43. Chapman S, Nakielny R. *A guide to radiological procedures.* London: Bailliere Tindall; 1986.

44. Evans R, Alexander P. Mechanisms of extracellular killing of nucleated mammalian cells by macrophages. In: Nelson DS, editor. *Immunobiology of macrophage.* New York: Academic Press; 1976. p. 45-74.