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ORIGINAL RESEARCH ARTICLE

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

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Abstract

Background Treatment of patients with epidermal growth factor receptor-mutated (EGFRm) non-small cell lung cancer (NSCLC) continues to evolve expeditiously.

Objectives This retrospective study investigated real-world treatment patterns and EGFR mutation testing in patients with EGFRm advanced NSCLC in Belgium.

Methods Data were extracted from medical records of adults diagnosed with EGFRm locally advanced/metastatic NSCLC between 1 September 2015 and 31 December 2017. Patients were followed retrospectively from diagnosis until 1 September 2018, end of clinical activity or death. Data on demographics, patient outcomes and disease characteristics, treatment patterns and EGFR mutation testing at diagnosis and progression were analyzed descriptively.

Results A total of 141 patients were enrolled. At diagnosis, median age was 69 years, 63.1% were female, 88.7% had metastatic disease, 94.3% had adenocarcinoma histology, 76.6% had ECOG 0/1, 70.9% had common EGFR mutations and 29.1% had only rare mutations. In first line, 73.8% of patients received first/second-generation EGFR–tyrosine kinase inhibitors (1G/2G EGFR-TKIs), while 21.9% received other systemic treatments. Among 61 patients progressing on and discontinuing a first 1G/2G EGFR-TKI, 45 (73.8%) received subsequent systemic treatment while 16 (26.2%) did not; 20 (32.8%) received osimertinib. Among 65 patients progressing on a first 1G/2G EGFR-TKI, 47 (72.3%) were tested for T790M, of whom 25 (53.2%) were positive.

Conclusion These real-world data from Belgium show that a substantial fraction of patients with EGFRm NSCLC do not receive 1G/2G EGFR-TKIs in first line and do not receive subsequent systemic treatment after progression on 1G/2G EGFR-TKIs. Only a third receive osimertinib upon progression on 1G/2G EGFR-TKIs. These observations should be considered in first-line treatment decisions.

Trial Registration ClinicalTrials.gov: NCT03761901—December 3, 2018

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Key Points

Over 20% of epidermal growth factor receptor-mutated (EGFRm) advanced non-small cell lung cancer (NSCLC) patients did not receive European Society for Medical Oncology (ESMO) standard of care in first line (first/second-generation EGFR–tyrosine kinase inhibitors [EGFR-TKIs]).

After progression on a first EGFR-TKI, nearly 30% of patients were not tested for T790M, 26% did not receive subsequent systemic treatment for NSCLC and only a third were treated with osimertinib.

These results are in line with other real-world data and should be considered when choosing first-line treatment.

1 Introduction

For about a decade, epidermal growth factor receptor–tyrosine kinase inhibitors of the first and second generation (1G/2G EGFR-TKIs; e.g., gefitinib, erlotinib, afatinib) have been the standard first-line (1L) treatment for EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) patients [1, 2]. Approximately 10%–20% of Caucasian patients with NSCLC harbor EGFR mutations [3–5]. Most are in-frame deletions in exon 19 (~ 40–60%), or exon 21 mutations resulting in L858R substitutions (~ 30–45%), so-called 'common mutations' [5]. 1G/2G EGFR-TKIs were approved based on superior progression-free survival (PFS) versus chemotherapy in randomized trials [6–12]. However, most patients develop resistance to these EGFR-TKIs and progress after 9–13 months [6–12]. The most common resistance mechanism—occurring in ~ 50–60% of patients—is a secondary EGFR mutation causing a T790M substitution [13–15]. The third-generation EGFR-TKI osimertinib potently and selectively inhibits both EGFR-activating mutations and EGFR-T790M [13]. A randomized trial (AURA3) showed significantly improved PFS in patients with EGFR-T790M advanced NSCLC treated with osimertinib versus platinum-pemetrexed chemotherapy in second line (2L) after progression on a 1G/2G EGFR-TKI [16]. Recently, another randomized trial (FLAURA) demonstrated that treatment-naïve patients with EGFRm advanced NSCLC receiving osimertinib had a significantly longer median PFS and overall survival (OS) than patients receiving gefitinib or erlotinib [17, 18].

Current guidelines for EGFRm advanced NSCLC by the European Society for Medical Oncology (ESMO) recommend 1L treatment with an EGFR-TKI as standard of care and consider osimertinib as the preferred option [2, 19]. In patients progressing on a 1G/2G EGFR-TKI due to T790M, osimertinib is recommended as 2L treatment; in T790M-negative patients, chemotherapy is recommended [2, 19]. Hence, detection of a targetable EGFR mutation at diagnosis and T790M at progression is required to guide treatment decisions [2, 19]. Molecular testing poses challenges, however. Waiting times may be long (problematic if progression is fast); hard-to-reach lesions make tissue biopsies difficult, possibly resulting in suboptimal samples, re-biopsies and multiple molecular tests; liquid biopsies allow easy repeat sampling, but are characterized by lower sensitivity compared with tests on tissue biopsies [20–23]. Understanding EGFR-TKI use and outcomes in real-world clinical practice is important but data are limited. In REVEAL (REtrospective, obserVational study to describe the treatment patterns and outcomes of Epidermal Growth Factor Receptor mutant [EGFRm] locally Advanced or metastatic Non-Small-Cell Lung Cancer [NSCLC] patients in Belgium), we investigated real-world treatment patterns, demographics, disease characteristics, EGFR mutation/T790M testing and clinical outcomes in patients with EGFRm advanced NSCLC to evaluate the need and impact of (future) novel therapies.

2 Methods

2.1 Study Design and Patients

This retrospective, observational study used data from medical records of 141 patients diagnosed with EGFRm advanced NSCLC in 17 selected centers in Belgium (3–15 patients per center, a mix of academic, larger and smaller general and peripheral centers). Investigators were asked to include all EGFRm locally advanced/metastatic patients within their patient files eligible within the diagnosis window.

Male or female patients ≥ 18 years old were eligible if they were diagnosed between 1 September 2015 and 31 December 2017 with EGFRm locally advanced or metastatic NSCLC (radiologically or pathologically confirmed) not amenable to curative surgery or chemoradiotherapy. At study initiation, ESMO guidelines considered 1G/2G EGFR-TKIs as the standard 1L treatment, while osimertinib was only recommended in patients progressing on 1G/2G EGFR-TKIs due to T790M [24]. Osimertinib as 2L treatment has been reimbursed in Belgium since December 2016 and was available under a medical need program before this (from August 2016).

Patients were excluded if no follow-up data were available after diagnosis or if they refused to have their data collected. Depending on the centers' ethics committees' requirements,

patients either signed an informed consent form, received an information letter with the opportunity to object to the use of their medical information or were not specifically informed about the use of their medical records for this study. Patients were retrospectively followed from the date of diagnosis until a pre-specified cut-off date (1 September 2018), end of clinical activity or death, whichever came first. The cut-off date allowed for a theoretical minimal follow-up of 8 months for each patient, but the observation period could last from 1 day (e.g., in case of death shortly after diagnosis) up to 3 years.

The study (ClinicalTrials.gov identifier: NCT03761901) was performed in accordance with the Declaration of Helsinki, Good Clinical Practice and Good Pharmacoepidemiology Practice guidelines and laws and regulations governing medical practice in Belgium. The study protocol and other study-related documents were submitted or notified to each center's ethics committee.

2.2 Objectives

Primary objectives were to evaluate demographic characteristics at diagnosis; NSCLC disease characteristics, treatment patterns and patient outcomes (in terms of reason for treatment discontinuation, lost to follow-up and death) in 1L, 2L and third-line (3L); the proportion of patients receiving subsequent systemic treatment after progression; and EGFR mutation testing at diagnosis and progression on 1G/2G EGFR-TKIs. Secondary objectives were to evaluate PFS, time to treatment discontinuation (TDT) and time to start of subsequent treatment (TST) in 1L, 2L and 3L; and OS for all patients and by receipt (or not) of osimertinib.

2.3 Data Collection

Pseudonymized patient data were collected through medical record review and encoded in electronic case report forms (eCRFs) by site study personnel. Collected demographic data included age, sex, race and history of smoking. Data on disease characteristics were cancer stage and histology at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status [25], sites of metastasis, details on brain/leptomeningeal metastases and local ablative therapy at diagnosis and after progression. Data on treatment patterns included treatment received in each line, progression after each treatment and duration of treatment beyond progression (i.e., time between progression on a line and discontinuation of that line or death). In 1L, information on receipt of best supportive care/no systemic treatment was collected to understand how many patients were not treated at all. In 2L/3L, analysis on receipt of best supportive care was not of interest but for practical reasons (related to eCRF set-up), this information was recorded only if a T790M test was performed for that patient in the respective line.

The proportion of patients receiving subsequent systemic treatment after progression was calculated for patients progressing on a 1G/2G EGFR-TKI if it was the first EGFR-TKI on which they progressed. To evaluate EGFR mutation testing at diagnosis, we collected the type of mutation, biopsy type, molecular testing location (in-house or external laboratory) and calculated the time between diagnosis and receipt of a first positive EGFR test result (time to result, TTR) (if the result was received on the day of or after diagnosis), between receipt of a first positive EGFR test result and 1L treatment start (if the test was performed before 1L treatment started and the result was received on the day of or after diagnosis) and between diagnosis and 1L treatment start. Similar variables were collected and calculated to evaluate T790M testing after progression on a 1G/2G EGFR-TKI (being the first EGFR-TKI on which the patient progressed). For TTR after progression, the first positive test was considered in T790M-positive patients and the last negative test in T790M-negative patients. Time intervals were not calculated if one or more dates to perform the calculations were incomplete. Information on testing methodology and T790M testing platform were not obtained in the study.

PFS was defined as the time between the start of 1L/2L/3L treatment and progression in the respective lines or death. TDT was defined as the time between the start of 1L/2L/3L treatment and discontinuation of the respective lines or death. OS was defined as the time between the start of 1L treatment and death. The TST analysis is not reported here because TST has limited clinical relevance and statistical limitations and a high degree of censoring around the median complicated interpretation.

2.4 Statistical Analyses

Data (pooled across centers) were analyzed descriptively and results were reported using summary statistics: mean values with standard deviations and median values with ranges for continuous variables and relative frequencies and proportions for categorical variables. Median PFS, TDT and OS were calculated with 95% confidence intervals (CIs) using Kaplan-Meier statistics. PFS, TDT and OS were not calculated if the number of events was < 20. Missing data were not imputed, except for three patients with partial dates of diagnosis (to avoid excluding these patients from the analysis set) for whom a missing day was imputed with day 15. There were no formal sample size or power calculations. The aim was to enroll ~ 200 patients.

Demographics, disease characteristics and EGFR testing patterns at diagnosis were analyzed on the 'all enrolled' analysis set, including all enrolled patients. Treatment patterns and patient outcomes were analyzed on the 'all treated'

analysis set, including all enrolled patients who received at least one treatment of any type (including best supportive care). Secondary outcomes were analyzed on the 'efficacy' analysis set, including all enrolled patients who received at least one systemic treatment. Disease characteristics and T790M testing patterns after progression on 1L/2L/3L were analyzed on the 'all treated patients with progression' set, including all treated patients with at least one progression in 1L, 2L or 3L. Some analyses on patients with progression (ECOG performance status, location of progression, brain metastases, treatment beyond progression) were only performed on patients receiving systemic treatment.

SAS version 9.4 was used for all analyses.

3 Results

3.1 Patients and Disease Characteristics

All 141 enrolled patients were included in the 'all enrolled' and 'all treated' analysis sets; 135 (95.7%) received at least one line of systemic treatment ('efficacy' analysis set) and 76 (53.9%) had at least one progression in a treatment line ('all treated patients with progression' set).

The patients' median age was 69 years and 51.1% never smoked; most were female (63.1%), Caucasian (95.0%), with metastatic (88.7%), non-squamous cell carcinoma or adenocarcinoma (94.3%) and had an ECOG performance status of 0 or 1 (76.6%, data missing for 14.9% of patients) (Table 1). At diagnosis, brain metastases were detected in 33 (23.4%) patients (Table 1); 11 were symptomatic and 14 were treated with radiotherapy. An additional eight (5.7%) patients developed brain/leptomeningeal metastases during 1L treatment (Table 1); five were symptomatic, six were treated with radiotherapy and one with surgery and radiotherapy. Of the 125 (73.6%) metastatic patients, 92 had only non-brain metastases, of whom 18 received local ablative therapy.

During the observation period, 58/141 (41.1%) patients had a progression in 1L, 36/77 (46.8%) in 2L and 14/36 (38.9%) in 3L (Fig. 1). Among patients progressing on their treatment and receiving a subsequent systemic treatment, 19/45 (42.2%) had brain/leptomeningeal metastases at the start of or during 2L treatment and 10/24 (41.7%) at the start of or during 3L. Among 45 patients who progressed on 1L treatment and received a systemic 2L treatment, 12 (26.7%) had an ECOG performance status of 0, 18 (40.0%) had status 1 and 6 (13.3%) had status 2 (data missing for nine [20.0%] patients). Among 24 patients progressing in 2L and receiving a systemic 3L treatment, four (16.7%) had status 0, six (25.0%) had status 1, five (20.8%) had status 2 and one (4.2%) had status 3 (data missing for eight [33.3%] patients).

Table 1 Patient characteristics at diagnosis

Characteristic	'All enrolled' analysis set $N = 141$
Age, years	
Mean (SD)	69 (11.0)
Median (range)	69 (43–91)
Sex	
Female	89 (63.1)
Male	52 (36.9)
Race	
Asian	6 (4.3)
Black	1 (0.7)
Caucasian	134 (95.0)
History of smoking	
Current	12 (8.5)
Former	55 (39.0)
Never	72 (51.1)
Missing	2 (1.4)
Cancer stage	
Metastatic	125 (88.7)
Locally advanced	16 (11.3)
Histology	
Non-squamous cell carcinoma or adenocarcinoma	133 (94.3)
Squamous cell carcinoma	4 (2.8)
Large cells	2 (1.4)
Undifferentiated[a]	2 (1.4)
ECOG performance status	
0	45 (31.9)
1	63 (44.7)
2	9 (6.4)
3	1 (0.7)
4	2 (1.4)
Unknown	21 (14.9)
Brain/leptomeningeal metastases	
At diagnosis	33 (23.4)
During 1L	8 (5.7)

Numbers are *n* (%) except for age

1L first-line treatment (including systemic or best supportive care), *ECOG* Eastern Cooperative Oncology Group, *N* total number of patients enrolled in the study, *SD* standard deviation

[a]Non-small cell lung cancer histology not otherwise specified

3.2 Treatment Patterns

Of the 141 enrolled patients, 135 received a systemic treatment in 1L and six received best supportive care only, 73 were treated systemically in 2L and 32 in 3L. At the end of the observation window, 58 (41.1%) patients had an ongoing systemic treatment (32 in 1L, 18 in 2L and 8 in 3L) and 69 (48.9%) had discontinued all systemic treatment up to 3L (Fig. 1).

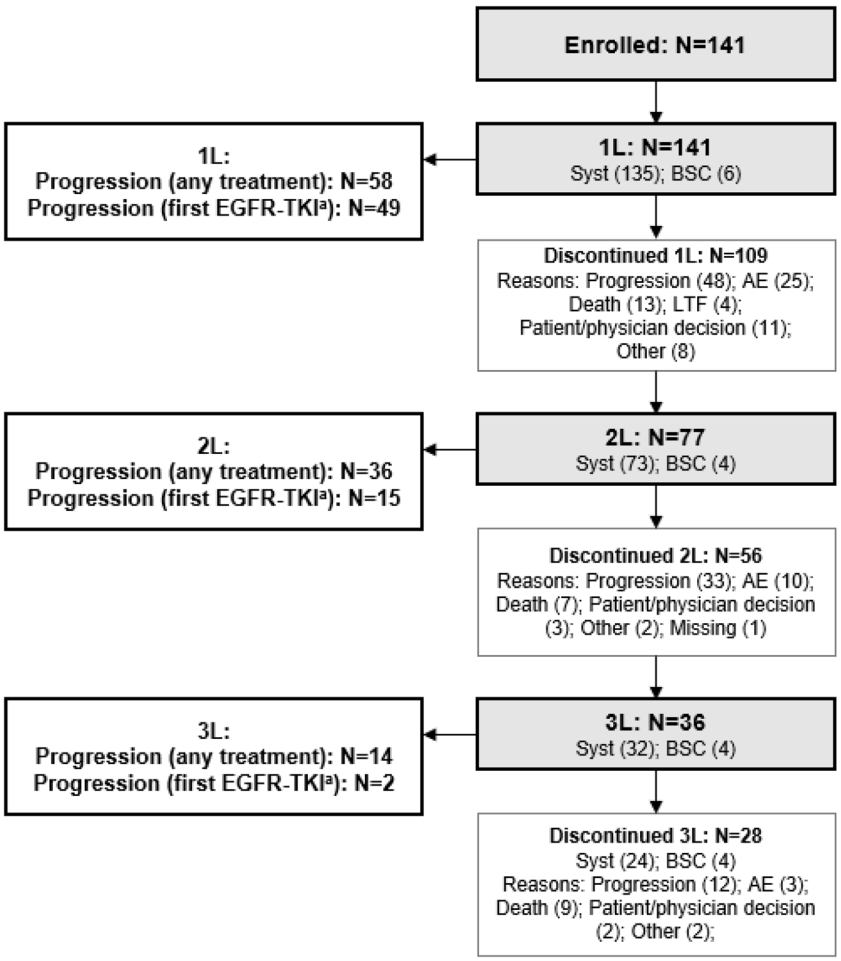

Fig. 1 Patient flow diagram. Patients who received best supportive care (no systemic treatment) in 2L or 3L after discontinuing 1L or 2L, respectively, were only reported in the 2L or 3L patient population if they had a T790M test done after progression in 1L or 2L, respectively. [a]Only considers progressions on an EGFR-TKI (first/second-generation) if it was the first time the patient progressed on an EGFR-TKI (i.e., a progression in 2L or 3L was only counted if the patient received no prior EGFR-TKI or received a prior EGFR-TKI on which the patient did not progress). *1L* first-line treatment, *2L* second-line treatment, *3L* third-line treatment, *AE* adverse event, *BSC* patients receiving best supportive care or no systemic treatment for non-small cell lung cancer, *EGFR-TKI* epidermal growth factor receptor-tyrosine kinase inhibitor, *LTF* lost to follow-up, *N* number of patients in the indicated population/category, *Syst* patients receiving systemic treatment

Table 2 Treatment patterns by line

Treatment type	1L *N* = 141	2L *N* = 77	3L *N* = 36	1L in patients with common mutations *N* = 100
First/second-generation EGFR-TKI	104 (73.8)	29 (37.7)	4 (11.1)	84 (84.0)
Afatinib	26 (18.4)	5 (6.5)	0 (0.0)	17 (17.0)
Erlotinib	27 (19.1)	11 (14.3)	1 (2.8)	24 (24.0)
Gefitinib	51 (36.2)	13 (16.9)	3 (8.3)	43 (43.0)
Chemotherapy	25 (17.7)	16 (20.8)	18 (50.0)	11 (11.0)
Immunotherapy[a]	3 (2.1)	6 (7.8)	4 (11.1)	1 (1.0)
Osimertinib[b]	0 (0.0)	18 (23.4)	4 (11.1)	0 (0.0)
Other[c]	3 (2.1)	4 (5.2)	2 (5.6)	1 (1.0)
Best supportive care	6 (4.3)	4 (5.2)	4 (11.1)	3 (3.0)

Numbers are *n* (%)

[a]Nivolumab, pembrolizumab

[b]One patient received osimertinib after an adverse event on an EGFR-TKI and one after progression on chemotherapy (de novo T790M)

[c]Crizotinib (2 patients in 1L, 1 in 3L), erlotinib + chemotherapy (1 in 2L), lorlatinib (1 in 2L), osimertinib + trastuzumab (1 in 2L), study medication ASP8372 (1 in 1L), trastuzumab (1 in 2L), ipilimumab (1 in 3L)

1L first-line treatment, *2L* second-line treatment, *3L* third-line treatment, *EGFR-TKI* epidermal growth factor receptor-tyrosine kinase inhibitor, *N* number of treated patients in each line (including those receiving only best supportive care)

Most patients (73.8%) received a 1G/2G EGFR-TKI in 1L (of whom 80.8% had a common EGFR mutation), 17.7% received chemotherapy, 2.1% received immunotherapy and 2.1% received other systemic treatments; no patients were treated with osimertinib in 1L (Table 2). In 2L and 3L, 1G/2G EGFR-TKI use decreased (37.7% and 11.1%, respectively) and other treatment types increased (Table 2). Twenty-two patients (15.6%) received osimertinib in 2L or 3L (Table 2). Sixteen patients (11.3% of the total population) received their first 1G/2G EGFR-TKI in 2L.

To better understand why 26.2% of the patients were not treated with 1G/2G EGFR-TKIs in 1L, we assessed their EGFR mutation status. Of 25 patients treated with chemotherapy in 1L, 11 had common EGFR mutations and 14 had rare mutations (6 exon 20 insertions). Of the three patients receiving immunotherapy and three receiving other systemic treatments, one each had a common EGFR mutation, while the remaining had rare mutations (Table 2).

Among the 58, 36 and 14 patients who progressed in 1L, 2L and 3L, respectively, 40 (69.0%), 19 (52.8%) and 2 (14.3%) continued their treatment beyond progression. However, only three (7.5%) patients in 1L and none in the other lines continued their treatment for >3 months; 29 (72.5%) patients in 1L, 15 (78.9%) in 2L and both patients in 3L continued for < 1 month; eight (20.0%) patients in 1L and four (21.1%) in 2L continued for 1–3 months.

3.3 Treatment After First Progression on a 1G/2G EGFR-TKI

Across treatment lines, 66 patients progressed on a 1G/2G EGFR-TKI (49 in 1L, 15 in 2L, 2 in 3L; considering the first EGFR-TKI on which they progressed) (Fig. 1, Table 3). For five of these 66 patients, treatment was ongoing at the end of the observation window. Among the remaining 61 patients who progressed on and discontinued EGFR-TKI treatment, 45 (73.8%) received a subsequent systemic treatment for NSCLC and 16 (26.2%) did not. Detailed results by treatment line are provided in Table 3. Of the 45 patients who received a subsequent systemic treatment, 20 received osimertinib (i.e., 32.8% of the 61 patients who progressed on/discontinued EGFR-TKI treatment).

When considering progression on any treatment in 1L, 2L and 3L, 81.8%, 68.6% and 61.5%, respectively, received a subsequent systemic treatment for NSCLC (Table 3).

3.4 EGFR Mutation Testing at Diagnosis

At diagnosis, a total of 158 EGFR mutation tests were performed on the 141 enrolled patients. For most patients (125 [88.7%]), a single test provided a final positive result; 15 (10.6%) patients had two tests and one (0.7%) had three tests. Most samples used for testing were tumor tissue specimens (75.3%), followed by cytology (16.5%) and liquid biopsy (8.2%) specimens (Table 4). When considering only the final positive tests, the proportion of tumor tissue samples was 80.1%.

The most frequently identified mutations were exon 19 deletions (41.1% of patients) and exon 21 L858R substitutions (29.8%). A surprisingly large proportion of patients (29.1%) harbored rare EGFR mutations only, mostly G719X substitutions, followed by exon 20 insertions and S768I substitutions (Table 4).

For 18/141 patients, EGFR mutation testing (providing the first positive result) was done before the diagnosis of advanced NSCLC (i.e., at an earlier disease stage). For the remaining 123, it was performed after the diagnosis date. The median TTR was 15 (calendar) days. Another 9 days (median) were calculated between the first positive test and 1L treatment start. This resulted in a median of 20 days

Table 3 Proportion of patients receiving a subsequent systemic treatment after progression

Parameter	First progression on EGFR-TKI[a]				Progression on any treatment		
	Across lines	1L	2L	3L	1L	2L	3L
Patients with progression	66	49	15	2	58	36	14
Current treatment ongoing	5	3	1	1	3	1	1
Current treatment discontinued	61	46	14	1	55	35	13
Subsequent systemic treatment[b]	45 (73.8)	36 (78.3)	8 (57.1)	1 (100.0)	45 (81.8)	24 (68.6)	8 (61.5)
No subsequent systemic treatment[b]	16 (26.2)	10 (21.7)	6 (42.9)	0 (0.0)	10 (18.2)	11 (31.4)	5 (38.5)

Numbers are *n* or *n* (%)

1L first-line treatment, *2L* second-line treatment, *3L* third-line treatment, *EGFR-TKI* epidermal growth factor receptor-tyrosine kinase inhibitor

[a]Only considers progressions on an EGFR-TKI (first/second-generation) if it was the first time the patient progressed on an EGFR-TKI (i.e., a progression in 2L or 3L was only counted if the patient received no prior EGFR-TKI or received a prior EGFR-TKI on which the patient did not progress)

[b]Percentages calculated relative to the number of patients who progressed and discontinued their treatment

Table 4 EGFR mutation testing results at diagnosis and after first progression on an EGFR-TKI

Parameter	At diagnosis (1L)	After first progression on EGFR-TKI[a] (at 2L/3L)
Test performed	*N* = 141	*N* = 65
Yes	141 (100)	47 (72.3)
No	0 (0.0)	16 (24.6)
Unknown	0 (0.0)	2 (3.1)
Test positive	*N* = 141	*N′* = 47
Yes	141 (100)	25 (53.2)
No	0 (0.0)	22 (46.8)
Biopsy type	*N″* = 158	*N″* = 66
Tumor	119 (75.3)	30 (45.5)
Primary tumor	92 (58.2)	16 (24.2)
Metastasis	27 (17.1)	14 (21.2)
Liquid	13 (8.2)	25 (37.9)
Cytology[b]	26 (16.5)	10 (15.2)
Urine	0 (0.0)	0 (0.0)
Cerebrospinal fluid	0 (0.0)	1 (1.5)
Testing location	*N″* = 158	*N″* = 66
External	75 (47.5)	36 (54.5)
In-house	83 (52.5)	30 (45.5)
Type of EGFR mutation detected[c]	*N* = 141	
Common mutation only	96 (68.1)	
Common and rare mutation	4 (2.8)	
Rare mutation only	41 (29.1)	
No EGFR mutation detected[d]	3 (2.1)	
Non-informative[d]	5 (3.5)	
Exon 19 deletion	58 (41.1)	
Exon 21 L858R	42 (29.8)	NA
G719X	17 (12.1)	
Exon 20 insertion	15 (10.6)	
S768I	6 (4.3)	
T790M	3 (2.1)	
E709X	2 (1.4)	
L861Q	0 (0.0)	
C797X	0 (0.0)	
Other	11 (7.8)	

Numbers are *n* (%)

1L first-line treatment, *2L* second-line treatment, *3L* third-line treatment, *EGFR(-TKI)* epidermal growth factor receptor(-tyrosine kinase inhibitor), *N* total number of patients enrolled in the study or progressing on an EGFR-TKI, *N'* total number of patients progressing on an EGFR-TKI and having a T790M test done, *N''* total number of tests performed, *NA* not applicable

[a]Only considers progressions on an EGFR-TKI (first/second-generation) if it was the first time the patient progressed on an EGFR-TKI (i.e., a progression in 2L or 3L was only counted if the patient received no prior EGFR-TKI or received a prior EGFR-TKI on which the patient did not progress)

[b]Cytology samples collected through endobronchial ultrasound-guided transbronchial needle aspiration

Table 4 (continued)

[c]Percentages calculated relative to the total number of patients (*N* = 141). Note that the sum of all mutations is higher than the total number of patients because a patient can have more than one mutation; multiple tests from the same patient were counted once if the same mutation was detected in the different tests but if different tests from the same patient identified different mutations, all were included

[d]Patients with uninformative or negative tests were retested and had a final positive result (also included in this table)

between diagnosis and 1L treatment start. Median TTR was similar for in-house and external testing (Table 5).

3.5 EGFR T790M Testing After Progression

T790M testing was analyzed on 65 of the 66 patients who progressed on a 1G/2G EGFR-TKI. One patient was excluded because of an incomplete date of progression. Of these 65 patients, 47 (72.3%) had a T790M test performed, of whom 25 (53.2%) were positive (in 2L, 3L or both). In total, 66 tests were performed (on the 47 patients); in 2L, 26 (70.3%) patients had one test done, ten (27.0%) had two tests and one (2.7%) had four tests; in 3L, ten (76.9%) patients had one test and three (23.1%) had two tests. Samples used for testing were tumor tissue specimens (45.5%), followed by liquid (37.9%) and cytology (15.2%) specimens (Table 4). The initial EGFR mutation was detected in 72.7% of all tests. For the 25 patients with a final positive T790M test, the initial EGFR mutation was detected in 84.0% of patients (52.0% had exon 19 deletions, 36.0% L858R mutations and 12.0% exon 20 insertions).

For the 47 patients with progression on a 1G/2G EGFR-TKI and tested for T790M, the median time between disease progression and receipt of the test result was ~ 17 days for 2L and 3L. An additional 12 days (median) in both lines were calculated between receiving the final test result and 2L/3L treatment start. This led to a total median time of ~ 28 days between progression and 2L/3L treatment start (Table 5).

3.6 Clinical Outcomes

The number of patients who discontinued on each line and reasons for discontinuation are provided in Fig. 1. During the observation window, 62 patients (27 in 1L, 18 in 2L and 17 in 3L) died, of whom six (1L), four (2L) and three (3L) died while receiving systemic treatment. No deaths were treatment-related.

For the secondary endpoints, we only present the analyses for all treatment types and/or treatment with 1G/2G EGFR-TKIs, because in most other cases, analyses were not performed due to a low number of events or are not shown because interpretation is of limited clinical relevance. The

Table 5 EGFR mutation testing time intervals at diagnosis and after first progression on an EGFR-TKI

Time intervals	At diagnosis (1L)		After first progression on EGFR-TKI[a]			
			At 2L		At 3L	
	N	Median (min, max), days	*N*	Median (min, max), days	*N*	Median (min, max), days
From diagnosis/progression to test result						
Overall	123	15.0 (1.0, 365.0)	36	16.5 (1.0, 270.0)	11	17.0 (1.0, 30.0)
External	58	14.5 (1.0, 92.0)	22	22.5 (1.0, 270.0)	7	11.0 (1.0, 30.0)
In-house	65	15.0 (1.0, 365.0)	14	15.5 (7.0, 187.0)	4	21.5 (17.0, 30.0)
From test result to start of treatment						
Overall	98	9.0 (1.0, 393.0)	29	12.0 (2.0, 215.0)	9	12.0 (3.0, 50.0)
External	49	9.0 (1.0, 62.0)	18	11.5 (4.0, 54.0)	6	21.5 (3.0, 50.0)
In-house	49	8.0 (1.0, 393.0)	11	12.0 (2.0, 215.0)	3	10.0 (10.0, 12.0)
From diagnosis/progression to start of treatment						
Overall	140	20.0 (1.0, 408.0)	37	28.0 (5.0, 226.0)	12	27.5 (2.0, 62.0)
External	69	21.0 (3.0, 102.0)	22	29.5 (5.0, 191.0)	8	26.5 (2.0, 62.0)
In-house	71	18.0 (1.0, 408.0)	15	26.0 (8.0, 226.0)	4	28.0 (26.0, 34.0)

1L first-line treatment, *2L* second-line treatment, *3L* third-line treatment, *EGFR-TKI* epidermal growth factor receptor-tyrosine kinase inhibitor, *min* minimum, *max* maximum, *N* total number of patients eligible for the analysis (with the necessary data available to calculate time intervals)

[a]Only considers progressions on an EGFR-TKI (first/second-generation) if it was the first time the patient progressed on an EGFR-TKI (i.e., a progression in 2L or 3L was only counted if the patient received no prior EGFR-TKI or received a prior EGFR-TKI on which the patient did not progress)

median PFS between 1L treatment start and progression (or death) was 7.5 months (95% CI 5.5–9.7) across treatment types and 7.6 months (95% CI 6.5–11.8) for 1G/2G EGFR-TKI-treated patients. Median PFS in 2L was 6.3 months (95% CI 4.6–8.2) across treatments. The median TDT after 1G/2G EGFR-TKI treatment was 8.8 months (95% CI 6.8–14.3) in 1L and 5.1 months (95% CI 4.0–12.2) in 2L. PFS and TDT analyses could not be performed for 3L EGFR-TKI treatment. The median OS from 1L treatment start was 27.4 months (95% CI 20.5 to not reached). The sub-analysis in patients receiving osimertinib was not performed because the number of events was too low.

4 Discussion

In this retrospective, real-world evidence study in Belgium, demographic and disease characteristics were comparable to those in typical EGFRm advanced NSCLC populations seen in other European countries (i.e., mean age 69 years, mostly women, approximately 50% never-smokers, mostly adenocarcinomas, metastatic disease and ECOG status 0/1) [9, 26, 27]. In line with published literature [28, 29], nearly 25% of patients had brain/leptomeningeal metastases at diagnosis. This may have been underestimated since brain scans were not performed systematically in all centers.

While most patients in this study were treated with 1G/2G EGFR-TKIs in 1L (per ESMO recommendations at the time of the study [24]), ~ 22% received another systemic treatment (mostly chemotherapy). A potential explanation is the larger-than-expected proportion of patients with only rare EGFR mutations (~ 29%, versus 10–20% as previously published [5, 30, 31]). The sensitivity of rare EGFR mutations to 1G/2G EGFR-TKIs is more heterogeneous than that of common mutations, with some (e.g., exon 20 insertions) showing no or little response to currently available EGFR-TKIs [30]. However, among the 31 patients receiving a systemic treatment other than EGFR-TKIs in 1L, 13 had common mutations and were expected to be treated with an EGFR-TKI. Another possible reason for the relatively high proportion of patients receiving chemotherapy in 1L is that chemotherapy might have been initiated while waiting for the EGFR mutation testing result due to fear of rapid disease progression and clinical decline, particularly if results were delayed. We currently have no clear explanation for the larger-than-expected proportion of patients with only rare mutations, but one potential contributing factor might be the relatively high number of large academic centers involved in this study, possibly causing bias towards more challenging cases with rare mutations. Other than this, the EGFR mutation testing results at diagnosis were in line with expectations, with exon 19 deletions and L858R substitutions being most common [5, 26].

Of patients who progressed on and discontinued 1G/2G EGFR-TKI treatment, 26% did not receive a subsequent systemic treatment. This approximates the 32% not receiving subsequent treatment after discontinuing 1L 1G EGFR-TKI treatment in the control arm of the randomized FLAURA

study [17]. Several recent real-world evidence studies also found sizable proportions of patients not receiving subsequent treatment after progression (e.g., 25% [32]) or after discontinuation (regardless of progression; e.g., 30–62% [33–36]) of EGFR-TKI treatment. In our study, one third of the patients progressing on (and discontinuing) a 1G/2G EGFR-TKI received osimertinib as next-line treatment. Likewise, 31% of patients treated with a 1G EGFR-TKI in 1L in FLAURA received osimertinib in 2L [17], and comparable percentages were reported in real-world evidence studies (25–32%) [32, 35–37]. The observation that a substantial proportion of patients progressing on a 1G/2G EGFR-TKI do not receive subsequent treatment and only one third receives osimertinib should be taken into account when deciding on 1L treatments for these patients. Maximizing benefits in terms of PFS, OS and toxicity should be a priority and might depend on this decision.

Reasons for the high proportion of patients not receiving a subsequent treatment in real-world evidence studies included rapid deterioration of the performance status, death and lack of T790M testing [32, 36, 37]. In our study, T790M testing rates after progression were relatively high (~ 72%). Moreover, in approximately a quarter to a third of the patients, two tests or more were performed to obtain a result. Interestingly, liquid biopsies seemed well integrated in the testing algorithm, especially after progression. The fact that only 84% of initial mutations were found in the T790M positive tests is probably related to this. Sorber et al. observed that in 7% of T790M-positive liquid biopsy samples the original EGFR-activating mutation could not be detected, mostly due to technical failures [38]. Furthermore, one external lab in our study only measured T790M mutations and not the initial mutation in their liquid biopsy assay. The T790M positivity rate (53%) in this study was similar to previously published results (50–60%) [13–15]. Although testing rates are reassuring, they indicate that nearly 30% of patients are not tested after progression (likely due to death, unwillingness to be re-biopsied or treated further, difficult-to-reach biopsy sites, complications and insufficient amounts of tissue to analyze) [21–23].

TTR for EGFR mutation testing was clinically acceptable and corresponded to that recommended in expert consensus guidelines (i.e., test results available within 2 weeks of receiving the sample in the testing laboratory) [19, 39–41]. However, ranges for TTR were large, meaning that in some hospitals or for some patients, waiting times could have been longer than recommended. This might lead to the initiation of alternative 1L treatments (e.g., chemotherapy or immunotherapy) before having obtained the testing result, which would be unfavorable for EGFRm patients, considering the demonstrated inferiority of these other treatments in this population [6–12, 42]. Moreover, considering the attrition of patients towards next lines, this might decrease chances for patients to receive the most appropriate subsequent therapy.

The median OS (27 months) was comparable to results seen with 1G/2G EGFR-TKIs in clinical trials and real-world studies (21–35 months) [17, 32, 34, 37, 43–46]. The median PFS for patients receiving 1L 1G/2G EGFR-TKIs in our study (7.6 months) was lower than that observed in clinical trials (9–13 months) [6–12, 27] and in some real-world studies (9–19 months) [32, 45, 47–51]. The inclusion of patients with a higher ECOG performance status (versus clinical trials) and the large proportion of patients with rare EGFR mutations might have contributed to this. Moreover, the evaluation of progression was based on radiological assessment, clinical judgement or other methods used in clinical practice and not necessarily on Response Evaluation Criteria In Solid Tumors (standard method used in prospective studies). Comparison of progression-related outcomes with clinical trial data is therefore difficult. In addition, duration of follow-up differed between patients depending on the time of diagnosis and could have been limited for some patients, potentially influencing this and other outcomes. Additional limitations of our study include its retrospective and descriptive nature and the small number of patients for some sub-analyses. Generalizability may also be limited because the study was performed in a relatively large proportion of larger academic centers with expertise in EGFRm NSCLC treatment.

5 Conclusion

The results from this real-world evidence study in Belgium highlight that although most EGFRm advanced NSCLC patients received 1G/2G EGFR-TKIs in 1L, 22% received other treatments. Twenty-six percent of patients did not receive a subsequent systemic treatment for NSCLC after progressing on and discontinuing 1G/2G EGFR-TKI treatment. Seventy-two percent of patients progressing on a 1G/2G EGFR-TKI were tested for T790M, leaving nearly 30% untested. Approximately half of the tested patients were T790M-positive. Finally, only one third of patients progressing on and discontinuing a 1G/2G EGFR-TKI were treated with osimertinib. These observations should be considered when deciding on 1L treatments, which should optimize benefits for patients in terms of PFS, OS and toxicity. The T790M testing rates, frequent use of liquid biopsies for EGFR mutation testing (especially at progression) and TTRs that were in line with (inter)national guidelines indicate that EGFR mutation testing has been optimized in Belgium within a relatively short timeframe despite the existing hurdles to perform (re-)biopsies.

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Declarations

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Conflict of interest L. Lodewyckx is an employee of AstraZeneca. All other authors and/or their institutions received study fees and/or non-financial support from AstraZeneca during the conduct of the study and for advisory boards. In addition, outside the submitted work, K. Cuppens received personal fees and non-financial support from Bristol-Myers-Squibb, Hoffman-La Roche, Merck-Sharp-Dohme, Pfizer and Boehringer-Ingelheim and personal fees from Merck-Serono; I. Demedts received a grant and personal fees from AstraZeneca; L. Decoster received travel grants from Hoffman-La Roche, Merck-Sharp-Dohme and a study grant from Boehringer-Ingelheim; K. Deschepper received personal fees from AstraZeneca, Hoffman-La Roche, Merck-Sharp-Dohme, Boehringer-Ingelheim and Bristol-Myers-Squibb; D. Galdermans received personal fees from Hoffman-La Roche, Merck-Sharp-Dohme, Boehringer-Ingelheim and Chiesi; A. Janssens received non-financial support from Hoffman-La Roche; B. Colinet received personal fees and non-financial support from Bristol-Myers-Squibb, Hoffman-La Roche, Merck-Sharp-Dohme, Pfizer, Boehringer-Ingelheim and Bayer.

Ethics approval The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice and Good Pharmacoepidemiology Practice guidelines and laws and regulations governing medical practice in Belgium. The study protocol and other study-related documents were submitted or notified to each center's ethics committee. Approval was granted by each ethics committee.

Consent Depending on the centers' ethics committees' requirements, patients either signed an informed consent form, received an information letter with the opportunity to object to the use of their medical information or were not specifically informed about the use of their medical records for this study.

Availability of data and material The datasets used in the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

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