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ORIGINAL RESEARCH ARTICLE

European and US Real-World Treatment Patterns in Patients with Epidermal Growth Factor Receptor Mutation-Positive Non-Small Cell Lung Cancer: A Retrospective Medical Record Review

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Abstract

Background Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the preferred first-line (1L) therapy for EGFR mutation-positive (EGFRm) advanced/metastatic non-small cell lung cancer (NSCLC).

Objective Our objective was to describe real-world treatment patterns and T790M testing practices in patients with 1L disease progression (Europe/USA) following treatment with first- or second-generation EGFR-TKIs.

Methods This was a retrospective, non-interventional medical record review of patients with EGFRm locally advanced/metastatic NSCLC from routine clinical practice (EGFR-TKI initiation: 1 January 2015 to 31 December 2017; follow-up: last available medical record). Endpoints were demographic/clinical characteristics, incidence of central nervous system (CNS) metastases/leptomeningeal disease, second-line (2L) treatment, T790M mutation testing, and osimertinib treatment prevalence.

Results Among 469 patients, 73% ($n = 341/469$) progressed on 1L EGFR-TKI treatment. Of those who progressed, 74% ($n = 252/341$) were tested for T790M, with 50% ($n = 126/252$) testing positive; 75% ($n = 94/126$) of T790M-positive patients received osimertinib (mostly 2L). Of the patients with progression, 24% ($n = 83/341$) did not receive 2L treatment, and 88% ($n = 73/83$) of these patients died. At diagnosis of advanced disease, 9% of patients ($n = 41$) had CNS metastases; at EGFR-TKI initiation, 14% of patients ($n = 68$) had CNS metastases. Over the study period, 11% of patients ($n = 42$) developed CNS metastases not detected at NSCLC diagnosis.

Conclusions Rates of resistance mutation testing and subsequent utilization of recommended 2L therapies could be improved. As more targeted therapies are developed, it will be crucial to improve the molecular testing rates to ensure patients receive appropriate, effective, and timely treatment.

1 Introduction

Epidermal growth factor receptor (EGFR) mutations account for up to 14% of European and up to 24% of US-based non-small cell lung cancer (NSCLC) cases [1]. The most commonly reported EGFR mutations include deletions in exon 19 (45% occurrence) and a point mutation in exon 21 (L858R; 40–45% occurrence) [2]. At the time of this study, first-generation (1G; erlotinib and gefitinib) and second-generation (2G; afatinib) EGFR-tyrosine kinase inhibitors (EGFR-TKIs) were the preferred first-line (1L) therapy for

Key Points

In this retrospective, non-interventional medical record review of patients in Europe and the USA with epidermal growth factor receptor (EGFR) mutation-positive advanced non-small cell lung cancer (NSCLC), 73% progressed on first-line EGFR-tyrosine kinase inhibitor (TKI) therapy, and 24% of patients with disease progression did not receive second-line treatment.

Rates of resistance mutation testing could be improved, as 26% of patients with disease progression were not tested for T790M and 25% of T790M-positive patients did not receive osimertinib at second or later line.

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patients with EGFR mutation-positive (EGFRm) advanced or metastatic NSCLC [3, 4]. These treatments have been shown to improve outcomes, tolerability, and quality of life compared with platinum-based chemotherapy in the 1L setting [3]. Most patients with EGFRm advanced or metastatic NSCLC will develop resistance to EGFR-TKIs, with progression of disease occurring after a median of 8–16 months [5–7]; EGFR T790M resistance mutations are observed in 50% of patients [8].

Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFR-TKI-sensitizing and EGFR T790M resistance mutations and has demonstrated efficacy in NSCLC central nervous system (CNS) metastases [9–14]. In November 2015, osimertinib received accelerated approval from the US FDA and the European Medicines Agency for use as a second-line (2L) treatment for patients who had previously received 1G/2G EGFR-TKIs. In 2016, from the phase III AURA3 study in patients with T790M-positive advanced NSCLC, the median duration of progression-free survival (PFS) was significantly longer with osimertinib than with platinum plus pemetrexed chemotherapy [13]. In 2017, and on the basis of AURA3, osimertinib was granted full marketing authorization by the European Commission and approval by the FDA [15]. In 2018, on the basis of the phase III FLAURA efficacy and safety data [10, 14], osimertinib was approved as a 1L treatment for patients with metastatic NSCLC whose tumors have EGFR-TKI sensitizing mutations (exon 19 deletion or L858R) [16, 17]. In the final FLAURA results, patients with EGFRm NSCLC who had received osimertinib had a median overall survival (OS) of 38.6 months (95% confidence interval [CI] 34.5–41.8) compared with patients who received a comparator EGFR-TKI (median OS 31.8 months; 95% CI 26.6–36.0; $P = 0.046$) [14].

1L treatment for patients with EGFRm locally advanced or metastatic NSCLC is well defined and, at the time of this study, several recommended treatment options were available for patients who progressed on a 1G/2G EGFR-TKI (e.g., platinum doublet chemotherapy, osimertinib) [3, 4]. However, data concerning real-world treatment patterns after progression are lacking, so this study reviewed real-world data from that patient population in Europe and the USA and assessed T790M testing practices.

2 Methods

2.1 Study Design and Data Source

This study was a retrospective, non-interventional, medical record review of patients with EGFRm advanced or metastatic NSCLC from routine practice settings in France, Germany, the UK, and the USA. The study investigated treatment sequencing and attrition patterns of patients with NSCLC treated with a 1L regimen containing a 1G/2G EGFR-TKI (gefitinib, erlotinib, or afatinib). The first date on which a patient initiated an EGFR-TKI as 1L treatment for EGFRm locally advanced or metastatic NSCLC was defined as the overall study index date. The index date had to occur within a 3-year period from 1 January 2015 to 31 December 2017 (study entry window), which allowed sufficient follow-up time after treatment with a 1G/2G EGFR-TKI to determine progression, while also predating the approval of osimertinib in the 1L setting. The follow-up period was the time between study index date and last available medical record.

The data were obtained from physician-led review of medical records through the use of a web-based electronic data collection form (eDCF). Participating physicians, or delegated clinical research staff, completed the eDCF for patient records that met the study inclusion criteria using a secure web-access link. Progression was noted from retrospective comments in patient notes (computed tomography [CT] scan, magnetic resonance imaging [MRI], bone scan, other imaging studies), histopathology, or other evidence from patient notes deemed by the clinician to be indicative of progression and was not independently verified. CNS metastases were diagnosed using imaging, spinal tap, or neurologic exams and leptomeningeal disease (LM) diagnosed using cerebrospinal fluid cytology, tissue, or imaging.

2.2 Study Population

2.2.1 Physicians

Participating physicians had a caseload in the past year of four or more patients with EGFRm NSCLC; had ≥2 years' experience in medical practice managing the treatment of oncology patients; were responsible for making treatment decisions for patients with NSCLC under their care; and spent at least 60% of their time conducting patient care, as judged by the participating physician.

2.2.2 Patients

Included adult patients were aged ≥ 18 years at first diagnosis of confirmed locally advanced unresectable or metastatic NSCLC, had a laboratory-confirmed EGFR mutation (e.g., exon 19 deletion, L858R mutation), and received the EGFR-TKIs gefitinib, erlotinib, or afatinib as monotherapy or in combination with other treatments as 1L treatment. Patients could have been alive or deceased at the time of medical record abstraction. Patients were excluded if they had previously enrolled in an interventional clinical trial for an experimental treatment related to EGFRm NSCLC or received any systemic therapy for locally advanced or metastatic

NSCLC prior to 1L EGFR-TKI treatment. Patients were also excluded if they had missing or unknown data on any of the following key study dates: initial NSCLC diagnosis; first diagnosis of, or progression to, locally advanced or metastatic NSCLC; 1L EGFR-TKI initiation for locally advanced or metastatic disease; or death or last available follow-up.

2.3 Objectives

The study objectives were to describe patient demographics, baseline disease characteristics, 1L and 2L treatment patterns, and T790M test results in patients with EGFRm NSCLC who had received a 1G/2G EGFR-TKIs for locally advanced or metastatic disease. In addition, information on CNS metastases and LM disease was collected.

2.4 Standard Protocol Approvals, Registration, and Patient Consents

This study was conducted in accordance with local standards in the USA, the UK, France, and Germany. The study was performed in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization, and good clinical practice. Patient consent was not required because of the retrospective nature of the study.

2.5 Endpoints

Study measures and endpoints included baseline patient demographics and clinical characteristics; incidence of CNS metastases and LM disease; 1L EGFR-TKI treatment; 2L treatment after 1L progression; incidence and results of T790M testing; and the proportion of patients receiving osimertinib treatment, including line of therapy in which it was initiated.

2.6 Statistical Methods

The study aimed to include data from 175 patients from the USA, 100 from the UK, and 75 each from France and Germany. These numbers were considered sufficient to provide an acceptable level of precision for summary statistics with respect to a range of values. All analyses were summarized descriptively through the tabular display of mean, median, range and standard deviations (SDs) of continuous variables of interest and frequency distributions for categorical variables, with data pooled across all countries. Given the exploratory and descriptive nature of the study, no formal study hypotheses are presented. All analyses were conducted using SAS statistical software (version 9.4, Cary, NC, USA; SAS Institute Inc; 2012).

3 Results

3.1 Physicians

A total of 115 physicians participated in the study: USA (55 [48%]), UK (21 [18%]), Germany (23 [20%]), and France (16 [14%]). Their medical specialty was medical/clinical oncologist (81%), pulmonologist (16%), and internal medicine specializing in oncology (3%; Germany only). The mean ± SD number of patients with EGFRm locally advanced or metastatic NSCLC treated by each physician in the past year was 38 ± 24; the median number of years in practice was 15 (range 5–28).

3.2 Baseline Patient Demographics and Disease Characteristics

Overall, 469 patient records were reviewed in the study: USA (202 [43%]), UK (109 [23%]), France (84 [18%]), and Germany (74 [16%]). Median age at study index date was 62 (range 34–91) years, 65% of patients were aged ≤ 65 years, and 57% were male (Table 1). Most patients tested positive for exon 19 deletion (n = 357 [76%]), whereas 25% tested positive for L858R mutation and 2% for other mutations. The median follow-up from index date to last available medical record was 19.8 (range 0.3–50.3) months. The incidence of CNS metastases and LM disease at baseline and throughout the study is shown in Table 2.

3.3 First-Line Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor Treatment and Second-Line Treatment After First-Line Progression

The majority of patients (n = 436/469 [93%]) received 1L 1G/2G EGFR-TKI treatment as a monotherapy: afatinib 39%, erlotinib 35%, gefitinib 20%. The remaining patients (7%) received 1L 1G/2G EGFR-TKIs in combination with monoclonal antibodies or chemotherapy. Combination treatment was given either as dual, triple, or quadruple therapy.

Overall, 258/341 patients (76%) who progressed on 1L therapy received subsequent 2L treatment (Table 3). Of the 341 patients who progressed on 1L treatment, 83 (24%) did not receive a 2L therapy, and 73 (88%) of these 83 patients died (Fig. 1 in the electronic supplementary material [ESM]).

Osimertinib-containing regimens were the most common 2L therapies initiated (n = 109/258 [42%]), followed by 1G/2G EGFR-TKI-containing regimens (13%) and platinum doublet chemotherapy (10%).

Table 1 Baseline patient demographics and disease characteristics

Characteristic	Patients ($N = 469$)
Country	
USA	202 (43)
UK	109 (23)
France	84 (18)
Germany	74 (16)
Age at index date[a], years, median (minimum–maximum)	62.0 (34.0–91.0)
31–50	52 (11)
51–65	251 (54)
66–75	123 (26)
> 75	43 (9)
Sex	
Male	265 (57)
Female	204 (43)
Race	
Caucasian	281 (60)
African/Black	44 (9)
Asian	39 (8)
Middle Eastern	11 (2)
Indian subcontinent	7 (2)
Unknown/don't know	87 (18)
Smoking status at initial NSCLC diagnosis	
Current smoker	53 (11)
Former smoker	232 (50)
Never smoker	180 (38)
Unknown	4 (1)
Stage at initial NSCLC diagnosis	
Early (stage IA, IB, IIA, IIB)	11 (2)
Limited regional (stage IIIA)	27 (6)
Locally advanced (stage IIIB)	68 (14)
Metastatic (stage IV)	350 (75)
Unknown	13 (3)
ECOG PS at first diagnosis of locally advanced/metastatic NSCLC	
0	74 (16)
1	257 (55)
2	121 (26)
3	16 (3)
4	1 (< 1)
EGFR mutation type	
Exon 19 deletion	357 (76)
L858R mutation	117 (25)
Others[b]	8 (2)

Data are presented as *n* (%) unless otherwise indicated

ECOG Eastern Cooperative Oncology Group, *EGFR* epidermal growth factor receptor, *NSCLC* non-small cell lung cancer, *PS* performance status, *TKI* tyrosine kinase inhibitor

[a]Index date defined as first date on which a patient newly initiated a first-/second-generation EGFR-TKI as first-line treatment for EGFR-mutated locally advanced or metastatic NSCLC

[b]Other mutations included exon 21 deletion ($n = 4$), T790M ($n = 2$), and exon 20 deletion ($n = 2$)

Table 2 Incidence of central nervous system metastases and leptomeningeal disease at baseline and throughout study period

Incidence	Present	Absent	Not known
CNS metastases			
Initial diagnosis EGFRm advanced/metastatic NSCLC	41 (9)	360 (77)	68 (14)
Index date	64 (14)	393 (84)	12 (3)
Developed during study period	11 (42)	–	–
LM disease			
Initial diagnosis EGFRm advanced/metastatic NSCLC	4 (< 1)	69 (15)	396 (84)
Index date	4 (< 1)	69 (15)	396 (84)
Developed during study period	6 (1)	–	–

Data are presented as *n* (%)

CNS central nervous system, *EGFRm* epidermal growth factor receptor mutation, *LM* leptomeningeal, NSCLC non-small cell lung cancer

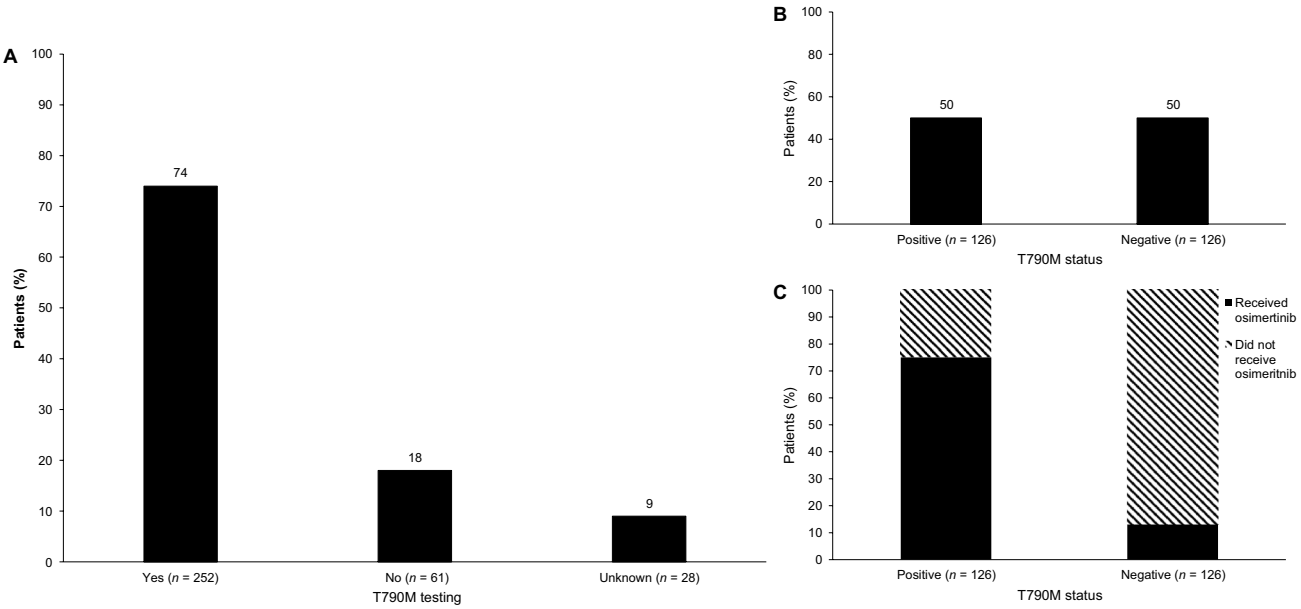

Fig. 1 Incidence of T790M mutational testing and status in patients with locally advanced or metastatic non-small cell lung cancer who progressed on first-line epidermal growth factor receptor tyrosine kinase inhibitors. **A** T790M testing rates. **B** T790M status in patients who were tested. **C** Receipt of osimertinib by T790M status

3.4 T790M Mutation Testing

Of the 341 patients who progressed on 1L treatment, 252 (74%) were tested for T790M, with 126 patients (50%) testing positive (Fig. 1A–C; Fig. 1 in the ESM). In total, 320 patients (68%) were tested for T790M. The most commonly used test was the cobas® EGFR mutation test ($n = 63/320$ [20%]), followed by the Guardant360® ($n = 36/320$ [11%]); however, in 141 patients who were tested (44%), the test type was unknown, and other test types were used in the remainder of patients. Of the 126 patients whose tumor tested as T790M positive, 94 (75%) subsequently received osimertinib (Fig. 1C; Fig. 1 in the ESM). Median time to next treatment was 13.3 months (range 12.4–14.0) in patients whose tumors were T790M tested and 17.8 months (range 15.0–33.4) in patients who had no record of a test.

3.5 Osimertinib Treatment and Line of Therapy

Overall, 111/469 patients (24%) received osimertinib (any treatment line). The majority of these received 2L osimertinib ($n = 109$).

Table 3 Overview of second-line treatments

Treatment regimen	Patients with T790M	Patients without T790M	All patients[a]
Second-line treatment regimen	118	107	258
Osimertinib-containing regimen[b]	93 (79)	11 (11)	109 (42)
Pembrolizumab	0	11 (11)	16 (6)
Carboplatin + pemetrexed	0	13 (13)	15 (6)
Cisplatin + pemetrexed	0	7 (7)	12 (5)
Erlotinib	0	6 (6)	10 (4)
Afatinib	0	0	7 (3)
Nivolumab	0	0	7 (3)
Bevacizumab + erlotinib	0	0	6 (2)
Gefitinib	0	0	6 (2)
Afatinib + bevacizumab	0	0	5 (2)
Other regimens recorded in < 5 patients	25 (21)	59 (57)	65 (25)
Duration of second-line treatment (months)			
Mean	5.5 ± 3.6	5.1 ± 4.0	5 ± 3.6
Median (minimum–maximum)	5.5 (0.03–20.3)	3.9 (0.4–24.8)	4.5 (0.03–24.8)

Data are presented as n (%) or mean ± standard deviation unless otherwise indicated

[a]Includes 21 patients who were not tested for T790M and 12 with T790M status unknown

[b]Osimertinib was given alone as well as in combination with other agents, e.g., osimertinib + vincristine

4 Discussion

Data from this study demonstrated that nearly three-quarters ($n = 341/469$ [73%]) of patients progressed during the study period while receiving 1L 1G/2G EGFR-TKI therapy. In total, 83 patients (24%) did not receive 2L treatment, and 73 (88%) of those died after disease progression. A significant proportion of the patients who progressed did not get tested for the T790M resistance mutation that could have informed subsequent treatment choice; approximately one-quarter of patients who had tumors that were T790M positive did not go on to receive osimertinib.

During the study period, osimertinib was approved as a 2L treatment option for patients who had previously received 1G/2G EGFR-TKIs, with 24% of all patients evaluated here receiving osimertinib at 2L or later. However, the reasons why patients did not receive 2L therapy or were not tested for T790M were not captured in the eDCF, although some patients may have had disease progression prior to the approval of osimertinib in the 2L. Roeper et al. [18] reported a similar percentage (30% of 112 patients with EGFRm NSCLC) who did not receive 2L therapy in a real-world German study; the most commonly reported reason for not receiving treatment was poor performance status (PS), most frequently due to CNS metastases, fast progression, and death [18].

Roeper et al. [18] also noted that a lack of T790M testing was a factor in patients not receiving 2L treatment. In a real-world US study, only 19% of 246 patients were tested for T790M, and more than two-thirds had no record of receiving subsequent therapy [19]. In a recent study, rapid T790M testing in the clinical practice setting was feasible, with a median of 16 days between discontinuing afatinib and initiation of osimertinib; all patients were tested for T790M prior to osimertinib treatment [20]. For the patients in this study who did not receive osimertinib despite a positive T790M test, factors such as rapid deterioration of PS or patient's decision not to treat could have prohibited further therapy. These factors are concerning, given osimertinib's effectiveness in patients with CNS metastases (e.g., ability to cross the blood–brain barrier) and in patients with T790M. In the present study, 341 patients progressed on 1L EGFR-TKI treatment, with 74% tested for the T790M mutation, possibly reflecting real-life testing challenges (e.g., obtaining sufficient tissue samples, sensitivity of liquid biopsy analysis, patients dying prior to testing), and it was not possible to determine what type of sample/test was used. Of those who were tested, 50% tested positive, which is consistent with the literature [8, 21]. Reimbursements for osimertinib in the 2L setting were available by November 2015 in the USA [22], October 2016 in the UK [23], June 2017 in France [24], and April 2017 in Germany (retracted from market but still reimbursed) [25], suggesting that T790M testing may not have been common practice for some countries when patients were receiving treatment. It is also interesting to note the distribution of patients whose tumor tested positive for exon 19 deletion versus L858R at baseline, although it is not clear what factors were driving this.

Since this study was initiated, on the basis of the FLAURA study [10, 14], the osimertinib indication was expanded to include 1L treatment in patients with metastatic NSCLC whose tumors have EGFR-TKI-sensitizing mutations [16, 17]. The FLAURA study demonstrated that patients with previously untreated EGFRm locally advanced NSCLC had a significantly longer median PFS with osimertinib versus comparator EGFR-TKIs [10]. Following this update, future studies could examine real-world treatment patterns and mutation testing practices following 1L osimertinib treatment.

CNS metastases frequently occur in patients with NSCLC and are associated with a poor prognosis and a high economic burden [26, 27]. In this study, there was a trend for the incidence of CNS metastases to increase between diagnosis and initiation of 1L EGFR-TKI treatment. In addition, 11% of patients who did not have CNS metastases prior to 1L treatment initiation went on to develop CNS metastases. However, the percentage of patients developing CNS metastases was lower than that reported in the literature, which may be due to the relatively short follow-up period, asymptomatic CNS metastases not being diagnosed because routine brain imaging may not have occurred, or the diagnosis of CNS metastases not being captured in patient notes. The number of patients with LM disease did not increase between diagnosis and the start of 1L EGFR-TKI treatment, but a small percentage of patients went on to develop LM disease thereafter. 1L osimertinib was shown to significantly reduce the risk of CNS progression by 52% versus comparator EGFR-TKIs in the FLAURA study (hazard ratio 0.48; $P = 0.014$) [12]. In the phase I BLOOM study (NCT02228369), osimertinib (160 mg once daily) demonstrated a clinically meaningful LM objective response rate (62%; 95% CI 45–78) and a duration of response of 15.2 months (95% CI 7.5–17.5) by blinded independent central review, in patients with EGFRm NSCLC and cytologically confirmed LM disease who had progressed on 1G/2G EGFR-TKIs [28]. These data demonstrate that, for patients with CNS metastases, early treatment intervention with osimertinib could reduce the risk of CNS progression.

A key limitation of this study was its retrospective nature, meaning data were more likely to be missing than with a prospective clinical study, and a potential existed for selection bias by physicians for patient inclusion in the study overall (e.g., patients more likely to be alive or with better outcomes at the time of data abstraction); it is possible that patients who died early on in the treatment sequence were less likely to be included than patients who had survived. This is more likely to apply to patients who were treated earlier on in the calendar years of inclusion and whose notes may not have been easily accessible. In addition, as access to EGFR-TKIs will differ by country, and reimbursement for osimertinib in the 2L setting became available at different times during the study period for each country, it is challenging to evaluate what effect this had on treatment choice, particularly in the 2L. These data should only be considered in the context of the country in which the data were gathered and are not necessarily globally applicable. More of the included patients were from the USA than from the individual European countries. In addition, progression was determined based on clinical deterioration or radiological progression using a CT scan, MRI, bone scan, or other imaging techniques assessed by individual physician assessment rather than a stringent response measure, e.g., Response Evaluation Criteria in Solid Tumors (RECIST). As such, routine brain imaging may not have been standard between the countries of study.

Real-world evidence studies provide valuable insights into real-world treatment practices and molecular testing and its importance, particularly for understanding acquired resistance in subsequent treatment lines for this patient population. In addition, as more acquired resistance pathways are identified and targeted therapies are further developed, efficient and accurate molecular testing is increasingly needed. Insights from this study will be particularly important for countries where osimertinib is only approved in the 2L setting.

5 Conclusions

This study demonstrated that one-quarter of patients with EGFRm locally advanced or metastatic NSCLC progressing after 1L EGFR-TKI treatment did not receive 2L therapy. In addition, only 74% of patients who progressed after 1L treatment were tested for T790M at any point after diagnosis. The reasons for the lack of 2L treatment and mutation testing may include poor underlying health status and death, resulting in the poor 1L–2L attrition and molecular testing at progression. It is important that patients receive the best available treatment at 1L. Further real-world studies are required to understand how rates of resistance mutation testing and utilization of treatment recommendations could be improved. Testing rates and subsequent treatment decisions may be revisited with the increasing use of osimertinib as a 1L treatment. Additionally, further improvement in EGFRm NSCLC molecular testing rates to identify effective therapies is critical to improving patient outcomes.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-021-00261-8.

Declarations

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Conflicts of interest Riyaz Shah has received fees for honoraria and has served on advisory councils/committees for AstraZeneca and Roche. Nicolas Girard has served on advisory councils/committees for AstraZeneca, Boehringer Ingelheim, Pfizer, and Roche and has received consultancy fees and other fees from AstraZeneca, Boehringer Ingelheim, Pfizer, and Roche. Saurabh P. Nagar and Keith L. Davis are employees of RTI Health Solutions, which received contract research funding from AstraZeneca for the conduct of this study. Frank Griesinger has served on advisory councils/committees for AstraZeneca, Boehringer Ingelheim, Pfizer, and Roche and has received fees for honoraria and research funding from AstraZeneca, Boehringer Ingelheim, Pfizer, and Roche. Julia Roeper has no conflicts of interest that are directly relevant to the content of this article. Parisa Karimi, Ning Yu, and Aliki Taylor are employees of AstraZeneca and own stocks or shares in AstraZeneca. William Sawyer is a contract employee of AstraZeneca. Josephine Feliciano has received research funding from AstraZeneca, Bristol Myers Squibb, and Pfizer and has received consultancy fees from AstraZeneca, Bristol Myers Squibb, Eli Lilly and Company, Genentech, and Takeda.

Availability of data and material Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Ethical approval This study was conducted in accordance with local standards in the USA, UK, France, and Germany. The study was performed in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization, and good clinical practice.

Consent Not applicable.

Author contributions Conception and design: Saurabh P. Nagar, Keith L. Davis, William Sawyer, and Aliki Taylor. Data analysis and interpretation, manuscript writing, and final approval of manuscript: all authors. All authors agree to be accountable for all aspects of the work.

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