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ORIGINAL RESEARCH ARTICLE

Retrospective Analysis of Real-World Management of *EGFR*-Mutated Advanced NSCLC, After First-Line EGFR-TKI Treatment: US Treatment Patterns, Attrition, and Survival Data

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Abstract

Background and Objectives Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are standard-of-care first-line (1L) treatment for *EGFR* mutation-positive advanced/metastatic non-small cell lung cancer. In 2015, osimertinib, a third-generation EGFR-TKI, received US accelerated approval for second-line (2L) *EGFR* T790M-positive non-small cell lung cancer treatment. The objective of this US study was to characterize treatment patterns, attrition, and survival in *EGFR* mutation-positive non-small cell lung cancer, after 1L first-/second-generation EGFR-TKI treatment.

Methods We retrospectively analyzed 1029 patients diagnosed with stage IIIB/IV non-small cell lung cancer from 1 January, 2011 to 31 December, 2018 using the US electronic medical record CancerLinQ Discovery® database. Demographic/disease characteristics, *EGFR* mutations, treatments, and death dates were collected.

Results From 1 January, 2011 to 31 December, 2014 (< 2015 cohort), 519 patients received 1L EGFR-TKIs and 510 between 1 January, 2015 and 31 December, 2018 (≥ 2015 cohort). Median follow-up from advanced diagnosis was 19.8 months (interquartile range: 9.9–33.4 months). Twenty-eight percent of patients (288/1029) died without receiving 2L, and 52% (539/1029) initiated 2L with 35% (186/539) receiving osimertinib; in the < 2015 and ≥ 2015 cohorts, the same proportion initiated 2L (52%; 272/519 vs 267/510, respectively). Median overall survival from advanced diagnosis for patients initially diagnosed with stage I–IIIA disease was 43.3 months (95% confidence interval 30.9–73.7), vs 26.4 months (95% confidence interval 24.4–28.1) for stage IIIB–IV; all-cause mortality hazard ratio: 1.56 (95% confidence interval 1.2–2.0; $p = 0.001$).

Conclusions We identified disease stage, performance status, and central nervous system metastasis as survival predictors, highlighting the importance of optimal 1L treatment selection. Over a quarter of patients died before initiating 2L; half progressed after 1L and received 2L, of whom a third received 2L osimertinib.

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Key Points

This retrospective real-world US study aimed to characterize treatment patterns, attrition, and survival in patients with *EGFR* mutation-positive advanced non-small cell lung cancer, after receiving first-line treatment with first-generation or second-generation epidermal growth factor receptor-tyrosine kinase inhibitors.

Between 2011 and 2018, 28% of all patients who received first-/second-generation epidermal growth factor receptor-tyrosine kinase inhibitors in the first line died before receiving second-line treatment and 52% of patients initiated second-line treatment; of the patients who received second line, 35% received second-line osimertinib.

Disease stage at initial diagnosis, performance status, and central nervous system metastasis were identified as predictors of survival, highlighting the importance of optimal first-line treatment selection.

1 Introduction

In 2021, it is estimated that there were 235,760 new lung cancer cases in the US [1]. Yearly decreases in lung cancer mortality rates have been attributed to reductions in smoking, early diagnosis, and improvements in treatment; however, overall survival (OS) remains poor, mainly owing to the late stage of disease at identification. Annual percent change in incidence from 2007 to 2017 is − 2.1% and 50.8% of cases are diagnosed at the metastatic stage [1–3]. Non-small cell lung cancer (NSCLC) accounts for approximately 80–90% of all lung cancers, and sensitizing mutations in epidermal growth factor receptor (*EGFR*) are found in approximately 24% of US patients with NSCLC [4, 5]. The most commonly reported *EGFR* mutations are deletions in exon 19 (ex19del) and a point mutation in exon 21 (L858R) [6].

Prior to April 2018, US guidelines recommended that patients with *EGFR* mutation-positive (*EGFR*m) advanced NSCLC initiate treatment with the EGFR-tyrosine kinase inhibitors (EGFR-TKIs) erlotinib or gefitinib (first-generation), or afatinib (second-generation) as first-line (1L) therapy [7]. However, most tumors will acquire resistance to EGFR-TKIs, with the *EGFR* T790M resistance mutation occurring in ~ 50% of patients [8]. In patients whose tumors progress and acquire the *EGFR* T790M mutation, treatment with osimertinib is recommended in the second-line (2L) setting [7].

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, the US Food and Drug Administration granted accelerated approval of osimertinib for the 2L treatment of patients who had previously received first-generation or second-generation EGFR-TKIs, with full market approval granted in 2017 on the basis of the phase III AURA3 study. In AURA3, median progression-free survival was significantly longer with 2L osimertinib vs platinum-pemetrexed chemotherapy (10.1 months vs. 4.4 months; hazard ratio [HR]: 0.30; 95% confidence interval [CI] 0.23–0.41; $p < 0.001$) in patients with T790M-positive NSCLC [14]. Subsequently, in April 2018, the Food and Drug Administration approved osimertinib for the 1L treatment of patients with *EGFR* ex19del/L858R-positive metastatic NSCLC [15]. As not all patients with *EGFR*m NSCLC receive 2L treatment following 1L first-generation or second-generation EGFR-TKIs, it is important to optimize 1L treatment [16–20].

Real-world evidence on the use of EGFR-TKIs in patients with *EGFR*m NSCLC is important in order to understand treatment and sequencing patterns, and survival outside the setting of clinical studies, to optimize treatment strategies in clinical practice [19, 21]. This retrospective real-world US study using data from electronic health records (EHRs) was designed to investigate temporal trends in treatment patterns from the time of diagnosis to 1L EGFR-TKI treatment and subsequent treatments, including duration of 1L and 2L treatment, to better understand patient attrition. The impact of clinical features on outcomes, including OS, in clinical practice was also an objective. The CancerLinQ Discovery® (CLQD) database includes demographically diverse, longitudinal EHR data from medical oncology organizations; treatment, sequencing, attrition, and survival data were collected for patients with *EGFR*m advanced NSCLC treated with 1L first-generation or second-generation EGFR-TKIs.

2 Methods

2.1 Study Design and Data Source

Data were obtained from 47 participating US oncology organizations including academic sites, integrated healthcare systems, and independent private practices. The de-identified patient-level data were obtained from EHRs or underlying data warehouses as structured data, and augmented through technology-assisted human abstraction of unstructured notes and scanned documents (e.g., curated data), including diagnosis, anatomic pathology, imaging, surgery, medications, radiotherapy, and molecular pathology [22]. Patients were

followed up from the date of the advanced NSCLC diagnosis (index date; 1 January, 2011 to 31 December, 2018) until the date of death, or the last available clinical activity record by the data cut-off (31 December, 2019), whichever came first.

2.2 Study Population

Adult patients (≥ 18 years of age at index) with diagnosed *EGFR*m advanced (stage IIIB/IV) NSCLC that started 1L first-generation or second-generation EGFR-TKIs for advanced disease were included. The *EGFR* mutational status was confirmed using clinician notes and/or laboratory testing reports. Staging was derived from four sources: stage group variable in the CLQD database; tumor, node and metastases-derived stage group; metastatic diagnosis or tumor imaging; and radiotherapy of the brain (Stage IV). Central nervous system metastases were ascertained in two ways: through *International Classification of Diseases* codes 9/10, and evidence from EHRs, including imaging reports and clinician notes in the same way that staging was derived. Eligible patients had to have received at least one first-generation or second-generation EGFR-TKI (specifically erlotinib, gefitinib, or afatinib or combinations of these therapies) as a 1L treatment. First line was defined as initiation of EGFR-TKI with no previous systemic treatment; subsequent systemic anti-cancer treatment was considered 2L. Patients were also required to have at least two documented clinical activity dates (e.g., visit date, start of therapy date, lab test date, vital assessment date, any diagnoses date) on or after diagnosis. Patient data were divided into two calendar cohorts: those who started 1L treatment from 1 January, 2011 to 31 December, 2014 (before osimertinib accelerated approval date, referred to as the < 2015 cohort) vs 1 January, 2015 to 31 December, 2018 (referred to as the ≥ 2015 cohort).

2.3 Standard Protocol Approvals, Registration, and Patient Consents

Institutional review board approval was not sought as the CLQD database is a secondary source of data, consisting only of collected de-identified data; no patient-identifiable information was included in the analytical dataset. Patient consent was not required for this retrospective study as personal health information was not needed.

2.4 Objectives and Endpoints

The following treatment patterns were assessed: 1L EGFR-TKI treatment and subsequent treatments for *EGFR*m advanced NSCLC, time between diagnosis and 1L treatment, and duration of 1L and 2L treatment. Most baseline (pre-EGFR-TKI treatment) patient demographic and clinical characteristics were collected at the index date; sites of metastases were collected at any time prior to the index date. Overall survival was defined as the duration between the index date and the date of the last follow-up by data cut-off or death, whichever occurred first. Patient vital status was determined using structured and/or curated EHR data, as well as via a third-party commercial database (obituarydata.com). The relationship between OS and the following baseline characteristics was examined: Eastern Cooperative Oncology Group (ECOG) performance status at the index date, disease stage at initial diagnosis, *EGFR* mutation status, and by calendar cohort (< 2015 vs ≥ 2015).

2.5 Statistical Methods

Baseline characteristics and distribution of treatment patterns were summarized using descriptive statistics; mean (standard deviation) and median values (interquartile range [IQR]) for continuous data, and relative frequencies and proportions for categorical data. Overall survival was estimated by the Kaplan–Meier method and stratified by age at index, presence of CNS metastases, ECOG performance score at index, and *EGFR* mutation status. Following an assessment of proportional hazards assumption (through examining the model fit in Schoenfeld residual plots [23]), multivariate Cox proportional hazards models were used to analyze OS from the index date, adjusted for baseline characteristics; adjusted HRs are presented with 95% CIs. No formal assessment of confounding or missing data was planned and missing values were treated as a separate category in the multivariable analyses.

3 Results

3.1 Patients

Of the 71,726 patients with lung cancer who had curated data identified in the CLQD database, 1912 had a record of *EGFR*m NSCLC. Within this group of 1912 patients, 1029 initiated 1L first-generation or second-generation EGFR-TKIs from 2011 and were identified for this study (Fig. 1). The median duration of follow-up from the index date to the last medical record by data cut-off/death was 19.8 months (IQR 9.9–33.4).

The median age at initial NSCLC diagnosis was 65 years (IQR 57–75) and at the index date was 66 years (IQR 57–76); of 1029 eligible patients, 69% ($n = 707/1029$) of patients were female and 34% ($n = 346/1029$) were former or current smokers (Table 1). At initial diagnosis, 80% ($n = 821/1029$) of patients had late-stage disease (IIIB–IV) and 90% ($n = 921/1029$) had adenocarcinoma; CNS metastases were present in 32% ($n = 325/1029$) of patients at

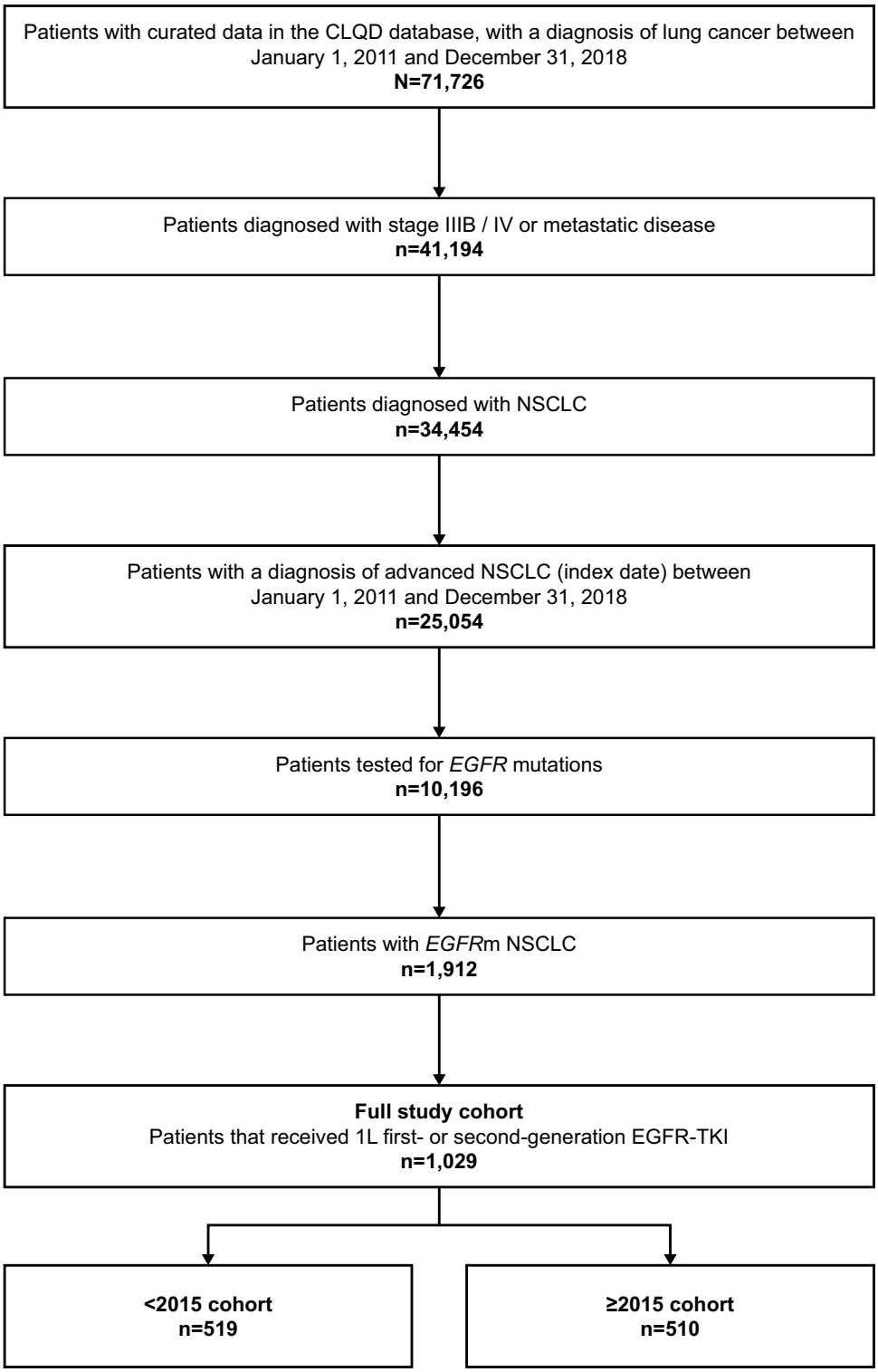

Fig. 1 Summary of patient selection. *1L* first-line, *CLQD* CancerLinQ Discovery®, *EGFR* epidermal growth factor receptor, *EGFRm* epidermal growth factor mutation-positive, *EGFR-TKI* epidermal growth factor receptor-tyrosine kinase inhibitor, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer

baseline and in 47% ($n = 480/1029$) of patients at any time during the study period. Ex19del was confirmed in 32% of patients ($n = 334/1029$), L858R deletion was confirmed in 12% ($n = 120/1029$), and *EGFR* mutation type was unknown in 54% ($n = 553/1029$); the remaining 2% of patients ($n = 22/1029$) had other *EGFR* mutations, including T790M, L861Q, S768I, Exon 20 Insertion, or G719X.

Table 1 Patient demographics and clinical characteristics

	1 January, 2011 to 31 December, 2014 cohort ($n=519$)	1 January, 2015 to 31 December, 2018 cohort ($n=510$)	All patients ($N=1029$)
Sex, *n* (%)			
Male	155 (30)	167 (33)	322 (31)
Female	364 (70)	343 (67)	707 (69)
Age at initial diagnosis, years, median (IQR)	64 (56–74)	67 (58–76)	65 (57–75)
Age at index, years, median (IQR)	64 (56–74)	67 (59–77)	66 (57–76)
Race, *n* (%)			
White	318 (61)	293 (56)	611 (59)
Asian	64 (12)	94 (18)	158 (15)
Black/African American	63 (12)	49 (10)	112 (11)
Other[a]	46 (9)	42 (8)	88 (9)
Unknown/not documented	28 (5)	32 (6)	60 (6)
Smoking status, *n* (%)[b]			
Current/former	168 (32)	178 (35)	346 (34)
Never	334 (64)	327 (64)	661 (64)
Unknown/not documented	17 (3)	5 (1)	22 (2)
Disease stage at initial diagnosis, *n* (%)			
Stage I	23 (4)	29 (6)	52 (5)
Stage II	11 (2)	12 (2)	23 (2)
Stage III	20 (4)	33 (7)	53 (5)
Stage IIIB	11 (2)	13 (3)	24 (2)
Stage IV	412 (79)	385 (76)	797 (78)
Missing data	42 (8)	38 (8)	80 (8)
Histology at initial diagnosis, *n* (%)			
Adenocarcinoma	460 (89)	461 (90)	921 (90)
Large cell carcinoma	2 (< 1)	4 (1)	6 (1)
Other non-small cell carcinoma	37 (7)	28 (5)	65 (6)
Other types	0	1 (< 1)	1 (< 1)
Squamous cell	6 (1)	5 (1)	11 (1)
Missing data	14 (3)	11 (2)	25 (2)
CNS metastases, *n* (%)			
CNS metastases at baseline	168 (32)	157 (31)	325 (32)
CNS developed later[c]	70 (13)	85 (17)	155 (15)
No CNS metastases reported	281 (54)	268 (53)	549 (53)
EGFR mutation, *n* (%)[d]			
Ex19del positive	180 (35)	154 (30)	334 (32)
L858R positive	56 (11)	64 (13)	120 (12)
Other	8 (2)	14 (3)	22 (2)
Unknown	275 (53)	278 (55)	553 (54)
EGFR T790M status, *n* (%)[d]			
Positive	28 (5)	29 (6)	57 (6)
Negative	11 (2)	42 (8)	53 (5)
Unknown/indeterminate	1 (< 1)	3 (1)	4 (< 1)
Missing data	479 (92)	436 (85)	915 (89)
ECOG performance status at initial diagnosis, *n* (%)			
0/1	141 (27)	196 (38)	337 (33)
≥ 2	34 (7)	32 (6)	66 (6)
Missing data	344 (66)	282 (55)	626 (61)

Table 1 (continued)

	1 January, 2011 to 31 December, 2014 cohort ($n=519$)	1 January, 2015 to 31 December, 2018 cohort ($n=510$)	All patients ($N=1029$)
ECOG performance status at index, *n* (%)			
0/1	163 (31)	218 (43)	381 (37)
≥2	34 (7)	43 (8)	77 (7)
Missing data	322 (62)	249 (49)	571 (55)

ECOG European Cooperative Oncology Group, *Ex19del* exon 19 deletion, *IQR* interquartile range

[a]American Indian or Alaska Native are included in the other races group

[b]Closest to index date

[c]After index or with unknown date

[d]From the first successful *EGFR* test, which can be before or after index

3.2 Treatment Patterns and Attrition

3.2.1 First-Line Treatment

Overall, 1L EGFR-TKI treatment was initiated by 519 patients from 1 January, 2011 to 31 December, 2014 (<2015 cohort) and by 510 patients from 1 January, 2015 to 31 December, 2018 (≥2015 cohort). Treatment patterns are summarized in Table 2.

The median time between the index date and start of 1L treatment was 0.9 months (IQR 0.4–1.6), and median 1L treatment duration was 11.0 months (IQR 4.6–19.4). The most frequently prescribed 1L EGFR-TKI was erlotinib (77%, $n=791/1029$), followed by afatinib (13%,

Table 2 Summary of treatment lines with treatment durations

	1 January, 2011 to 31 December, 2014 cohort ($n=519$)	1 January, 2015 to 31 December, 2018 cohort ($n=510$)	All patients ($N=1029$)
Time from index to start of 1L treatment, months, median (IQR)	1.0 (0.5, 2.0)	0.8 (0.2, 1.3)	0.9 (0.4, 1.6)
1L EGFR-TKI treatment[a], months, median (IQR)	11.2 (4.8–22.1)	10.6 (4.3–17.7)	11.0 (4.6–19.4)
1L treatment received, *n* (%)[b]			
Erlotinib	444 (86)	347 (68)	791 (77)
Afatinib	34 (7)	99 (19)	133 (13)
Gefitinib	1 (<1)	14 (3)	15 (1)
Other EGFR-TKI-based therapy	40 (8)	50 (10)	90 (9)
2L treatment			
2L treatment[a], months, median (IQR)	6.1 (3.1–11.2)	6.4 (3.3–11.7)	6.2 (3.2–11.5)
Received any 2L treatment, *n* (%)	272 (52)	267 (52)	539 (52)
2L treatment received, *n* (%)[c]			
Osimertinib (third-generation EGFR-TKI)	38 (14)	148 (55)	186 (35)
Platinum-based chemotherapy	66 (24)	35 (13)	101 (19)
First-/second-generation EGFR-TKI	69 (25)	26 (10)	95 (18)
Anti-VEGF-based therapy	49 (18)	15 (6)	64 (12)
PD-1/PD-L1-based therapy	13 (5)	34 (13)	47 (9)
Other chemotherapy	25 (9)	5 (2)	30 (6)
Other therapy	12 (4)	4 (2)	16 (3)

1L first line, *2L* second line, *EGFR-TKI* epidermal growth factor receptor-tyrosine kinase inhibitor, *IQR* interquartile range, *VEGF* vascular endothelial growth factor

[a]First and last date of treatment or death, whichever occurred first

[b]Percentages calculated against cohort totals

[c]Percentages calculated against the total number of patients who received any 2L treatment

$n = 133/1029$), other EGFR-TKI-based treatment (9%, $n = 90/1029$) and gefitinib (1%, $n = 15/1029$). Twenty percent of patients ($n = 202/1029$) were continuing to receive their 1L first-generation or second-generation EGFR-TKI at the data cut-off.

3.2.2 Second-Line and Later Lines of Treatment

In total, 827 patients discontinued 1L treatment, and of these patients, 65% ($n = 539/827$) initiated 2L treatment; patient disposition by 1L progression is summarized in Fig. 2. The median duration of 2L treatment was 6.2 months (IQR 3.2–11.5) (Table 2). The same proportion of the ≥ 2015 cohort (52%; $n = 267/510$) received any 2L treatment compared with the < 2015 cohort (52%; $n = 272/519$) (Table 2). Overall, osimertinib was the most frequent 2L treatment (35%; $n = 186/539$). First-generation and second-generation EGFR-TKIs were the most common 2L treatments < 2015 (25%; $n = 69/272$), while osimertinib was the most common ≥ 2015 (55%; $n = 148/267$). Only 10% of patients ($n = 26/267$) receiving 2L treatment ≥ 2015 initiated first-generation or second-generation EGFR-TKIs. Other ≥ 2015 treatments included: platinum-based chemotherapy (13%; $n = 35/267$), anti-PD-1/PD-L1-based therapy (13%; $n = 34/267$), anti-vascular endothelial growth factor-based therapy (6%; $n = 15/267$), other chemotherapy (2%; $n = 5/267$), and other therapy (1%; $n = 4/267$).

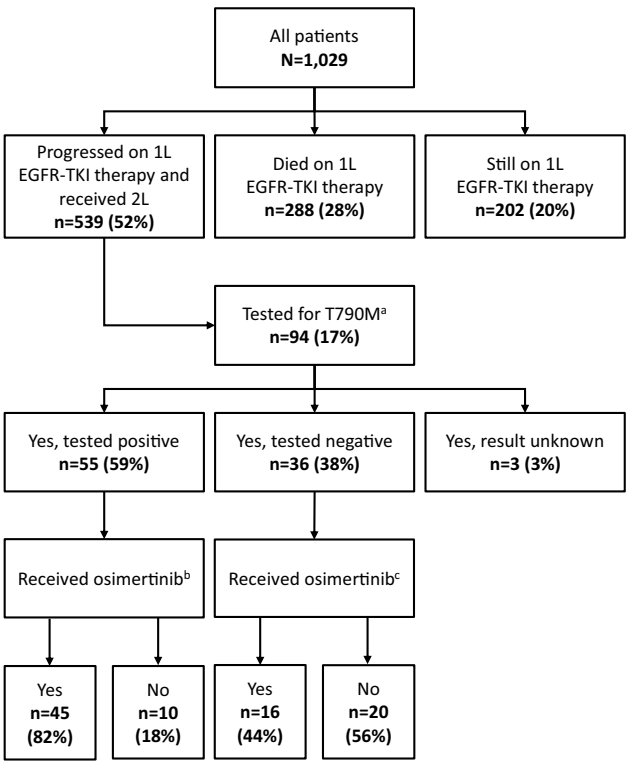

Fig. 2 Patient disposition by first-line (1L) progression. [a]Calculated as the proportion of patients who progressed on 1L epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment. [b]Receipt of osimertinib as a second-line (2L) or later treatment; calculated as the proportion of patients who tested positive for T790M. [c]Receipt of osimertinib as a 2L or later treatment; calculated as the proportion of patients who tested negative for T790M

Overall, 25% of patients ($n = 258/1029$) initiated third-line treatment; anti-PD-1/PD-L1-based therapies were the most common third-line treatments (26%; $n = 66/258$). Of the total study population, 12% of patients ($n = 125/1029$) initiated fourth-line or later-line treatment. In all treatment lines after 1L, osimertinib was received by 45% of patients ($n = 244/539$), equating to 24% of the entire study population ($n = 244/1029$).

3.2.3 T790M Testing

Because of the limitations of using EHRs and retrospective data collection, only 12% of patients ($n = 123/1029$) had available *EGFR* T790M test results; of the patients who received 2L treatment, only 17% ($n = 94/539$) had a record of a T790M mutation test at any time (Fig. 2): 59% ($n = 55/94$) had tumors that were T790M positive. Of these, 82% ($n = 45/55$) received osimertinib at any line and 58% ($n = 32/55$) were alive at the end of the study period. Of the 38% of patients ($n = 36/94$) whose tumors were T790M-negative, 44% ($n = 16/36$) received osimertinib at any line and 56% ($n = 20/36$) were alive at the end of the study period. Three patients received a T790M test but their results were unknown. Of the patients who had no record of 2L treatment, 6% ($n = 29/490$) had T790M testing: 21% ($n = 6/29$) had tumors that were T790M positive, and one was alive at the last follow-up. Of the remaining patients, 76% ($n = 22/29$) had tumors that were T790M negative, and 3% ($n = 1/29$) had an unknown result; eight were alive at the last follow-up.

3.3 Survival and Mortality

Survival outcomes were analyzed in all 1029 patients, as summarized in Fig. 3; overall, median OS was 27.2 months (95% CI 25.9–30.0). Median OS was 24.7 months (95% CI 22.5–27.2) and 13.0 months (95% CI 8.8–20.6) in those with an ECOG score of 0–1 and ≥ 2 at the index date, respectively (HR for all-cause mortality: 1.91 [95% CI 1.4–2.6; $p < 0.001$]; Fig. 4A). In patients with early-stage disease (I–IIIA) at initial diagnosis, median OS from index was 43.3 months (95% CI 30.9–73.7), compared with 26.4 months (95% CI 24.4–28.1) for late-stage disease (IIIB–IV) [HR 1.56 (95% CI 1.2–2.0; $p = 0.001$); Fig. 4B]. Patients with confirmed ex19del or L858R mutations had a median OS of 30.5 months (95% CI 27.6–37.1) and 29.6 months (95% CI 25.1–36.0) respectively (Fig. 4C). The median OS for patients initiating a 1L

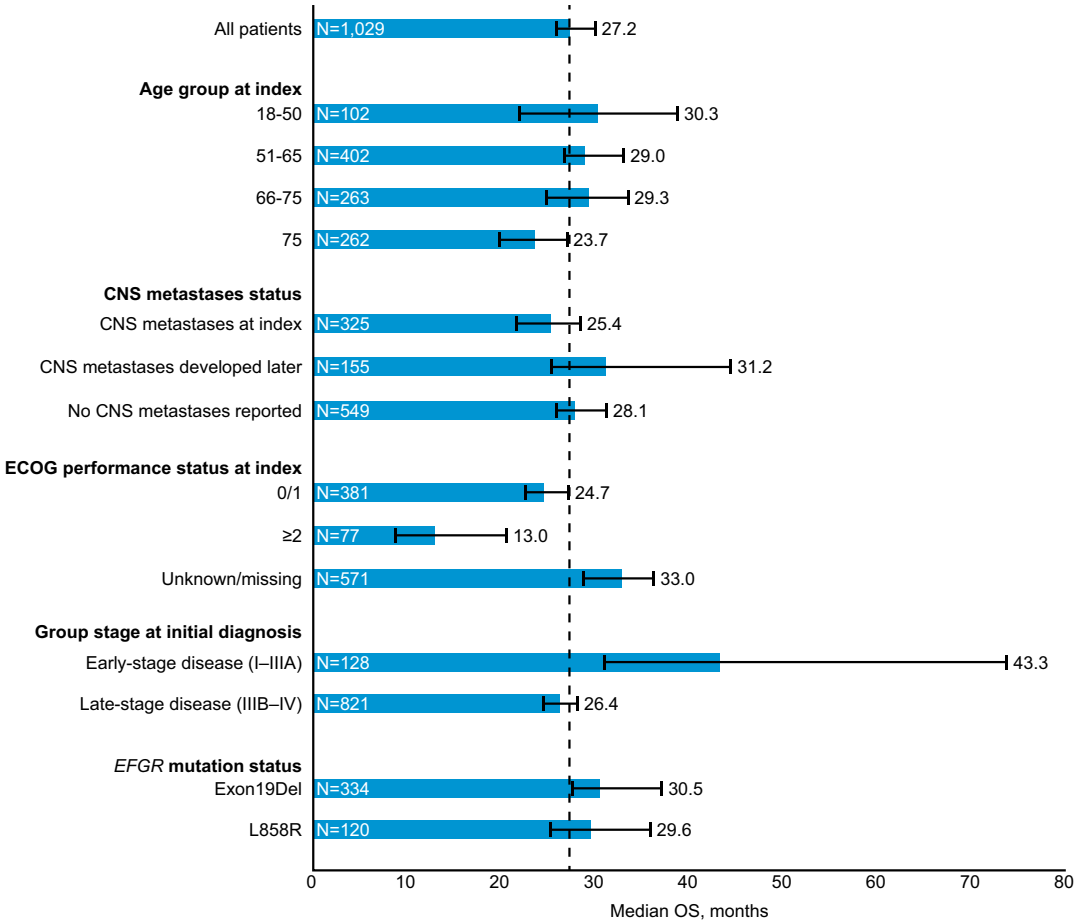

Fig. 3 Overall survival from the index date to the last follow-up. *CNS* central nervous system, *ECOG* European Cooperative Oncology Group, *EGFR* epidermal growth factor receptor, *Ex19del* exon 19 deletion, *OS* overall survival

EGFR-TKI < 2015 was 28.3 months (95% CI 25.5–31.3) and 26.4 months for ≥ 2015 (95% CI 24.7–30.3; Fig. 4D).

Of the 1029 patients receiving 1L EGFR-TKI treatment, 288 (28%) died without receiving 2L treatment; a further 320 patients (31%) died after receiving 2L treatment. The mortality rate of patients who did not receive 2L treatment was the same as that of patients who did initiate 2L treatment (59%; $n = 288/490$ vs 59%; $n = 320/539$, respectively). Median OS from the start of 2L treatment was longer in patients who received 2L osimertinib ($n = 186$; 28.9 months [95% CI 21.7–37.6]) than in patients who received other treatments at 2L ($n = 353$; 13 months [95% CI 11.8–15.4]).

The risk of all-cause mortality was significantly increased by unknown/indeterminate mutation status (HR vs EGFR-TKI sensitizing mutations: 1.44; 95% CI 1.19–1.75; $p < 0.001$). The risk of all-cause mortality was significantly reduced by never being a smoker (HR 0.50; 95% CI 0.36–0.69; $p < 0.001$) and having no reported CNS metastases (HR 0.80; 95% CI 0.66–0.96; $p = 0.017$). See Table 1 of the Electronic Supplementary Material for OS for all multivariable analyses.

4 Discussion

From this retrospective longitudinal study using the US CLQD database, we reviewed key treatment patterns and survival outcomes in patients with NSCLC in a real-world setting. Between 2011 and 2018, approximately a quarter of patients (28%) died without receiving 2L treatment after a median follow-up period of 19.8 months. This is consistent with previous data showing that a clinically significant proportion of patients (30%) die prior to initiating 2L treatment [16, 17, 19, 20]. In this study, approximately half of patients who received 1L EGFR-TKIs went on to receive 2L therapies. In comparison, other real-world evidence studies have estimated that only 12–37% of patients with *EGFR*m NSCLC receive 2L treatments [17, 19, 20]. However, these studies assessed patients over a shorter time period, and may have been impacted by treatment approvals and guideline changes during this time. Our data therefore demonstrate the importance of optimal 1L treatment selection to improve outcomes for patients with *EGFR*m NSCLC.

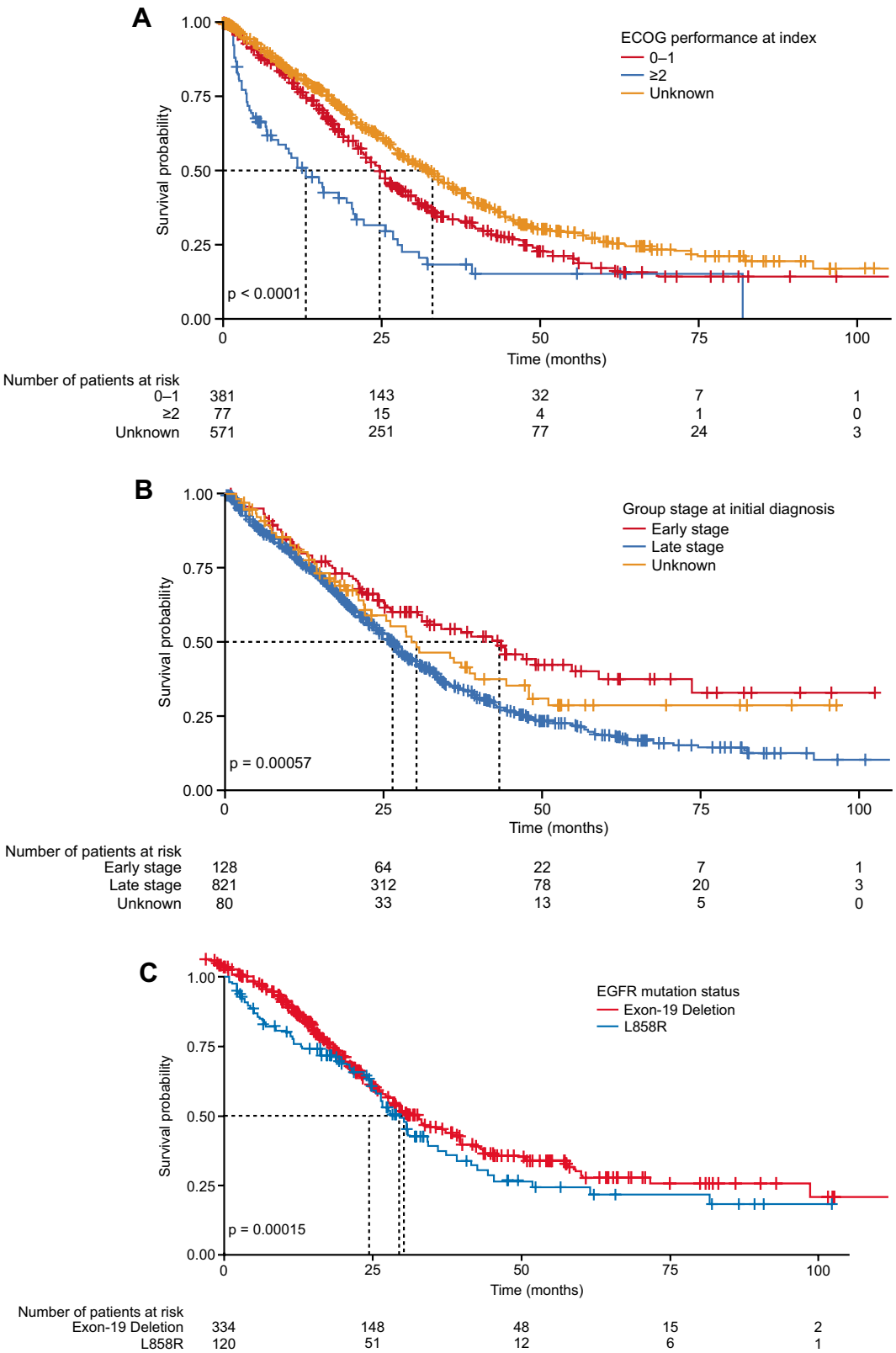

Fig. 4 Kaplan–Meier estimates of overall survival from the index date to the last follow-up (months) by **A** European Cooperative Oncology Group performance status at index, **B** stage at diagnosis, **C** epidermal growth factor receptor (EGFR) mutation detail, and **D** cohort (< 2015 and ≥ 2015)

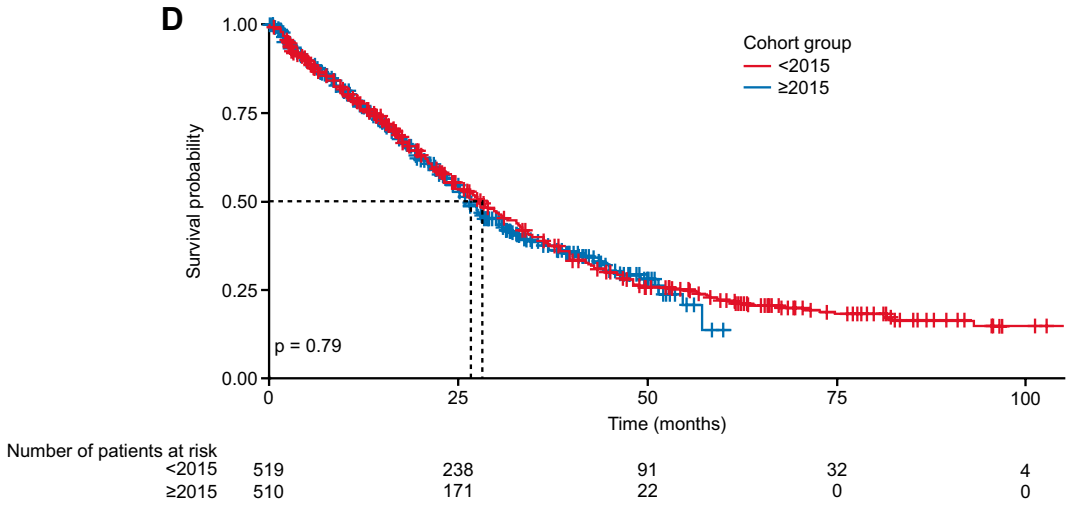

Fig. 4 (continued)

The median OS from index to the last follow-up in this real-world study was 27.2 months (95% CI 25.9–30.0), which is in line with clinical trials of first-generation or second-generation EGFR-TKIs (18.8–34.1 months) [24–31], supporting the use of these US EHR data in calculating OS. In addition, EHR data from the Flatiron dataset in the US reported similar median OS between treatment groups in patients diagnosed with *EGFR*m advanced NSCLC after May 2013 (23.1 months, 20.7 months, and 19.3 months for erlotinib, afatinib, and chemotherapy, respectively) [32]. The OS results here are consistent with known mortality risk factors, including lower OS among patients with CNS metastases and higher ECOG scores [33, 34]. As would be expected, age and advanced disease stage were also associated with shorter OS, as well as unknown mutation type. Comparatively, there was no significant difference in OS between patients initiating 1L EGFR-TKI treatment < 2015 or ≥ 2015, despite increases in available treatment options. This may have been influenced, in part, by a delay in clinical uptake of 2L osimertinib following its approval in November 2015, and therefore OS data for the ≥ 2015 cohort may have been diluted by historical treatment patterns. Any comparison of a retrospective collection of OS data and prospective clinical trial data must recognize the more stringent inclusion and exclusion criteria for prospective randomized studies along with the evolving treatment and biomarker testing landscape occurring over time.

The main strength of this study was the use of the CLQD database to analyze data from a large population of patients with lung cancer, using real-world information from EHRs. The large size of the database helped to ensure that estimates measured had relatively high precision. Conversely, a limitation of the study was missing information owing to the differences of reporting patient data from individual subscribing practices, in particular, the incomplete molecular data including the missing information relating to T790M mutational status, and months from initial diagnosis to the *EGFR*m and T790M test. This was because of molecular testing results being appended to the EHRs and therefore only assessed via curation; it is likely that many patients receiving osimertinib were T790M positive, but we do not have record of their test or results in the CLQD database. This is likely to affect the results from the patients in the ≥ 2015 cohort, as T790M testing was not standard of care prior to the approval of osimertinib in 2015. The ECOG performance status was also missing for over half of the patients. Not all patients in the CLQD database have curated data and because this analysis required curated variables, patients without curated data were excluded. This is not likely to impact the internal validity of the results; however, they may not be generalizable to all patients with *EGFR*m NSCLC. Furthermore, the CLQD dataset used in this analysis contains EHR data from 47 medical oncology organizations in the US, but may not be representative of the entire country, as it is a convenience sample of practices that have chosen to participate in the CancerLinQ network and the retrospective collection of data may have the potential for reporting bias. The collection of data also does not account for physician adherence to clinical guidelines and recommendations, and the impact this has on treatment decisions; we also focused on patients who received 1L treatment, whereas some patients with lung cancer may receive supportive care only. Furthermore, this analysis only reports on the proportion of patients who received first-/second-generation EGFR-TKIs as a 1L treatment and therefore, this selected population does not represent all patients with EGFRm NSCLC. Finally, as some patients

were followed up until the last available clinical activity record, it is not possible to accurately determine the proportion of patients continuing treatment at the data cut-off.

5 Conclusions

This retrospective real-world US study in patients with *EGFR*m advanced NSCLC, identified through the CLQD database, has further characterized 1L and 2L treatment patterns and patient attrition and survival. Findings indicated that, between 2011 and 2018, many patients with *EGFR*m advanced NSCLC died prior to initiating 2L therapy; therefore, treatment optimization for this patient population should incorporate the most effective agents early on in the course of treatment with the most effective EGFR-TKI therapy initiated at 1L. In addition, age, advanced disease at initial diagnosis, and unknown mutation type were associated with shorter OS. Further real-world evidence is needed to identify those patients who are most at risk of not receiving 2L therapy and what barriers exist for the use of third-generation agents in the 1L setting.

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Declarations

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Conflict of interest J. Nieva reports ownership of stock/shares for Cansera, Epic Sciences, and Quantgene and has received honoraria from AstraZeneca, Fujirebio, Genentech, Western Oncolytics, Takeda, and Amgen. J. Nieva has received research grants/funds from Genentech and Merck & Co. K. Reckamp received personal fees for consulting from Amgen, AstraZeneca, Blueprint, Boehringer Ingelheim, Calithera, Euclises, Genentech, Guardant, Janssen, Lilly, Merck KGA, Precision Health, Seattle Genetics, Takeda, and Tesaro. K. Reckamp received (institution) research grants/funds from AbbVie, Acea, Adaptimmune, Boehringer Ingelheim, Bristol Myers Squibb, Genentech, GlaxoSmithKline, Guardant, Janssen, Loxo Oncology, Molecular Partners, Seattle Genetics, Spectrum, Takeda, Xcovery, and Zeno. D. Potter was an employee of AstraZeneca when this research was conducted. D. Potter joined ASCO and CancerLinQ after participating in this study. This study and related conclusions reflect the independent work of study authors and do not necessarily represent the views of ASCO or CancerLinQ. A. Taylor and P. Sun are employees of AstraZeneca and report ownership of stocks/shares. Medical writing support for the development of this article, under the direction of the authors, was provided by Preeyah Purang, BSc and Gemma White, MSc, of Ashfield MedComms UK, an Ashfield Health company, and was funded by AstraZeneca.

Ethics approval Institutional review board approval was not sought as the CLQD database is a secondary source of data, consisting only of collected de-identified data; no patient-identifiable information was included in the analytical dataset.

Consent to participate Patient consent was not required for this retrospective study as personal health information was not needed.

Consent for publication Not applicable.

Availability of data and material Data underlying the findings described in this article may be obtained on request in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/submission/disclosure.

Code availability Not applicable.

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