ORIGINAL ARTICLE

Changing Treatment and Metastatic Disease Patterns in Patients with EGFR Mutated NSCLC: An Academic Thoracic Medical Investigator's Consortium Registry Analysis

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ABSTRACT

Introduction: Osimertinib is now a standard first-line (1L) therapy for EGFR-mutated (EGFRm) advanced NSCLC. We aimed to characterize patterns of therapy and longitudinal risk of brain and liver metastasis in a cohort of EGFRm NSCLC.

Methods: Patients with metastatic EGFRm NSCLC who received 1L systemic therapy at sites within the Academic Thoracic Medical Investigator's Consortium were included; demographic and clinical data including treatment patterns were described. Analyses of overall survival, time to next treatment, and incident brain and liver metastasis were performed using the Kaplan-Meier method, Cox regression,

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and cumulative incidence functions on patients who started 1L therapy in 2015 or later.

Results: The full cohort included 1132 patients and the mean age of the participants was 63.4 years; among the participants, 53% were White individuals, 68% were female individuals, and 67% were nonsmokers. Among the participants, 830 patients received 1L systemic therapy in 2015 or later. The predominant first EGFR–tyrosine kinase inhibitor was erlotinib (65%) before 2018 and osimertinib (81%) after 2018. The median time to the next treatment after the start of 1L therapy was 13.9 months overall and the longest in patients receiving 1L osimertinib (28 months). In the post-2015 cohort, the baseline prevalence of brain metastasis (BM) was 54% and among patients without baseline brain metastasis, the probability of incident BM at 12, 24, and 48 months was 8%, 22%, and 44%, respectively. Development of an on-treatment brain metastasis among patients without baseline brain metastasis was associated with a 3.2 times higher risk of death.

Conclusion: Even in a contemporary era with prevalent osimertinib use, the baseline and longitudinal risk of BM development was high. The ongoing risk of developing BM, together with the associated survival detriment, argues for routine surveillance of the brain through magnetic resonance imaging for patients with EGFRm NSCLC, which is not currently included in the guidelines.

Keywords: EGFR NSCLC; Practice patterns; Brain metastasis; Guidelines

Introduction

NSCLC is the leading cause of cancer-related death worldwide. Outcomes with NSCLC are improving in part owing to therapies targeted against specific alterations, including EGFR mutations which have been shown to occur in 15% to 30% of patients overall and upwards of 50% in those identifying as Asian or Pacific Islander (PI).[1–3] The most common EGFR alterations are L858R and exon 19 deletion (e19del), comprising about 90% of EGFR-mutated (EGFRm) NSCLC.[4]

For patients with EGFRm metastatic NSCLC (mNSCLC), tyrosine kinase inhibitors (TKIs) have become the standard of care for first-line (1L) treatment over chemotherapy alone given their improved efficacy and safety.[5–9] The United States Food and Drug Administration approved erlotinib, afatinib, and gefitinib for the 1L setting in EGFRm NSCLC in 2013, 2013, and 2015, respectively. Each subsequent generation of EGFR-TKI has reported increasing efficacy in clinical trials.[10,11] The third-generation TKI osimertinib was approved by the Food and Drug Administration in the second-line (2L) setting for T790M mutation-positive NSCLC in 2015 and then in the 1L setting in 2018 on the basis of improvements in progression-free survival and overall survival (OS) compared with first-generation TKIs erlotinib or gefitinib.[12,13] Importantly, osimertinib has better central nervous system activity than earlier-generation TKIs.[14–16]

After improved survival from TKI therapy, there has been increasing focus on treatment and prevention of brain metastases, which are more prevalent in patients with EGFRm mNSCLC; approximately 10% to 15% of patients with EGFRm mNSCLC have brain metastases at diagnosis and 50% of patients develop brain metastases within five years of diagnosis.[17–22] National Comprehensive Cancer Network guidelines recommend a brain magnetic resonance imaging (MRI) scan at the time of diagnosis.[23]

An accurate understanding of patient characteristics, treatment patterns, comutations, resistance mechanisms, and their associations with clinical outcomes will help to inform future treatment selection and tailoring in the rapidly changing treatment landscape of EGFRm mNSCLC. In this analysis, we describe treatment patterns over time, baseline and on-treatment comutations, and clinical outcomes including the development of brain and liver metastases in a multi-institutional cohort of patients with EGFRm NSCLC.

Materials and Methods

Study Sample

We included patients with mNSCLC harboring a sensitizing EGFR mutation who received 1L systemic therapy before 2021 at one of 12 academic cancer centers (11 in the United States, one in Canada) participating in the Academic Thoracic Medical Investigator's Consortium (ATOMIC) Driver Mutation Registry.[24] Local Institutional Review Board's approval was obtained at each site with a waiver of consent because of the study's retrospective nature. The study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. Demographics, genotypes, clinical characteristics, treatment records, and clinical outcomes were retrospectively abstracted from the electronic medical records by trained staff using a standardized digital form. Data were abstracted from 2018 to 2021 and the last recorded patient activity was March 31, 2021. Patients without documented treatment in the metastatic setting were excluded. Analyses of follow-up time including OS, time to next treatment, and

incident brain and liver metastasis were performed in a subset of patients who started 1L therapy on or after January 1, 2015 (hereinafter, "2015+ cohort") to reflect a more contemporary population treated in the osimertinib era (after the first approval of osimertinib in 2015).

Study Measures

Patient characteristics recorded included year of 1L therapy initiation, age at start of 1L therapy, sex (male, female, or other/unknown), race (White, Asian or PI, Black, or other race), ethnicity (non-Hispanic or Hispanic), and smoking status (current, former, or none).

Baseline EGFR mutations were defined as the first recorded EGFR alteration(s) for each patient and categorized as e19del alone, L858R alone, compound with e19del or L858R, or other EGFR alteration. Comutations were defined as alterations in non-EGFR genes and classified by pathogenicity (pathogenic versus non-pathogenic or indeterminate) using the VarSome database and expert opinion when pathogenicity was still unclear (Supplementary Table 1**)**. When patients harbored both non-pathogenic and pathogenic variants of the same gene in the same sample, the alteration for the gene was characterized as pathogenic.

EGFR alterations and comutations were detected using next-generation sequencing (NGS) or polymerase chain reaction on tissue, plasma, or urine samples. Baseline comutations were defined as those detected from one year before 60 days after the start of 1L therapy. Pre-TKI, on TKI1, and on TKI2 comutations were defined similarly with respect to initiation of TKIs (Supplementary Fig. 1; Supplementary Table 1).

Treatment records included systemic agent names with start and end dates. End dates that were missing were assumed to indicate ongoing treatment at the time of data cutoff. Lines of therapy were determined from individual treatments to reflect changes in clinical status using a set of rules we previously described.[25,26] For time-to-next therapy analyses, lines of therapy were placed into different categories depending on the line in question. In the analysis of time from initiation of 1L to initiation of 2L, lines were classified as osimertinib-, erlotinib-, afatinib-, gefitinib-containing, or chemotherapy/immunotherapy; meanwhile, in the analysis of time from initiation of 2L to initiation of third-line treatment, erlotinib-, afatinib-, and gefitinib-containing were grouped into "Other EGFR TKI" (Supplementary Table 1). Subjects who received TKIs other than those listed and did not fall into any of the above-mentioned groups were excluded from the time to next treatment (TTNT) or death analysis. Separately from lines of therapy that included any type of systemic therapy, EGFR TKIs were also ordered (on TKI 1, on TKI 2, etc.) and used for treatment pattern and comutation analyses.

The presence of brain and liver metastases was determined for baseline (from 60 days before initiation of 1L therapy) and subsequent scans. Cross-sectional imaging (MRI, computed tomography [CT], or positron emission tomography CT scans of the abdomen/pelvis, chest, spine, or skull base to mid-thigh) was used to determine the presence of liver metastases; MRI or CT of the brain was used for determining brain metastases.

Statistical Analysis

Patient demographics, clinical characteristics, and baseline sensitizing EGFR mutations were summarized using counts with proportions and mean values with standard deviations for the full and 2015+ cohorts. For the full cohort, pie charts were created to show the distribution of baseline EGFR sensitizing mutations, and a heatmap of comutations detected at baseline and new mutations detected on TKI 1 and TKI2 was created to describe the emergence of new variants in EGFR and non-EGFR genes over the course of targeted therapy. Treatment patterns, both by overall line of therapy and order of EGFR TKI, were shown using alluvial plots. These were stratified by date of 1L therapy before or after January 1, 2018, to capture change in practice patterns after approval of 1L osimertinib.

For the 2015+ cohort, the cumulative incidence of brain metastasis at 12, 24, 36, and 48 months after the start of 1L therapy was estimated using the cumulative incidence function among patients with a negative baseline brain scan. Time to incident brain metastasis was calculated from the start of 1L therapy until the first detection of brain metastases, with death considered as a competing event. Patients without detection of brain metastases or death were censored at the date of the last recorded patient activity. Estimation of the incidence of liver metastases was performed in the same manner. The Kaplan-Meier method was used to estimate the distribution of OS and the TTNT. OS was defined as the time from the start of 1L therapy until death; patients alive at last recorded patient activity were censored at that time. OS was examined for the overall cohort and stratified by baseline sensitizing EGFR mutation and baseline brain/liver metastasis. OS stratified by time-varying brain/liver metastasis was examined using extended Kaplan-Meier and Cox regression. Time to next treatment was defined as the time from the start of treatment until the start of the next line of therapy or death; patients without a record of initiating subsequent therapy or death were censored at the date of the last recorded patient activity. Median follow-up time was estimated using the reverse Kaplan-Meier method defined as the

time from the start of 1L therapy until the date of last patient activity recorded for patients without observed death; patients with observed death were censored at the time of death. For OS and TTNT, comparisons were performed over key variables (EGFR mutation type, pathogenic *TP53, PIK3CA* comutation, and type of therapy).

Data analysis was performed from October 2022 to September 2023 using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) with *survival* version 3.5.6 and *cmprsk* version 2.2.11 packages.[27,28]

Results

Patient Characteristics

Among 1187 patients in the ATOMIC Driver Mutation Registry with EGFRm mNSCLC, 1132 patients received systemic therapy for metastatic disease and were included in the full cohort; 830 patients received 1L systemic therapy in 2015 or later (Supplementary Fig. 2). Among 1132 patients in the full cohort, the mean age was 63.4 years, 53% identified as White and 29% as Asian/PI, 68% were female individuals, and 67% had no history of smoking. Baseline brain scans were recorded for 619 patients (55%), of whom 320 (52%) had brain metastases at baseline. Baseline body cross-sectional imaging was recorded for 851 patients (75%), of whom 120 had liver metastases (14%) **(**Table 1**)**.

Treatment Patterns

Treatment patterns over time are shown in Figure 1, stratified by 1L treatment beginning before or after 2018. Of the 805 patients who began 1L therapy before January 1, 2018, 12.3% (n = 99) received chemotherapy alone as 1L treatment and targeted therapy as 2L. Among 327 patients who began therapy on or after January 1, 2018, this proportion fell to 2.75% (n = 9). Of the 787 patients who began 1L therapy before January 1, 2018, and received at least one TKI across any line of therapy, 64.5% (n = 508) received erlotinib and 9.15% (n = 72) received simertinib as their first TKI. Among the 309 patients who began therapy on or after January 1, 2018, and received at least one TKI across any line of therapy, these proportions were 7.44% (n = 23) and 80.6% (n = 249), respectively.

Baseline Sensitizing EGFR Alterations

Figure 2 and Supplementary table 2 depict the baseline EGFR-sensitizing mutations in the complete cohort. Of the 1120 patients with a recorded type of EGFR alteration, the most common sensitizing EGFR alterations were e19del alone (51%, n = 571) and L585R alone (30%, n =342). Compound EGFR mutations were observed in 44 patients with e19del (3.9%) and 41 patients with L858R (3.7%). Other EGFR alterations were observed in 124 patients (11%), and among these patients, 26 had exon 20 insertions (21%).

Baseline and On-Treatment Comutations and On-Treatment EGFR Mutations

Baseline NGS testing (defined as one year before 60 days after the start of 1L therapy) was available for 580 patients (51%). Pre-TKI NGS testing (defined as one year before 60 days after the start of the first EGFR TKI) was recorded for 649 patients (57%).

Among the 649 patients with pre-TKI NGS available, the distribution of EGFR comutations pre-TKI, on TKI1 (n = 318, 49%), and on TKI2 (n = 132, 20.3%) are depicted in Figure 3. TP53 was the most common comutation (n = 168, 25.9%) and was mostly present at baseline (n = 158, 24.3%), followed by PIK3CA (n = 36, 5.5%) also mostly present at baseline (n = 35, 5.4%). Notably, 62 patients (10%) had T790M present at baseline. EGFR T790M was most commonly detected on TKI1 (i.e., during receipt of first TKI) (n = 173 out of 318, 54.4%), with 172 of these found among patients receiving an earlier generation TKI and only 1 in a patient receiving osimertinib. During the TKI2 period, EGFR C797S was the most common comutation (n = 22 out of 132, 16.7%), with all instances appearing among patients who received earlier generation TKIs.

2015+ Cohort

Baseline characteristics were similar in the nested cohort of 830 patients who initiated 1L therapy on or after January 1, 2015 (Supplementary Table 3).

Incidence of Brain and Liver Metastases

A total of 481 patients out of 830 patients (58%) had a baseline brain scan, and among these patients with a baseline scan, 262 patients (54%) had brain metastases at baseline. Among 219 (46%) patients in the 2015+ cohort with negative brain scans at baseline, the probability of incident brain metastasis was 8% (95% confidence interval [CI]: 5%–13%) at 12 months after the start of 1L therapy, 22% (95% CI: 16%–29%) at 24 months, 33% (95% CI: 25%–42%) at 36 months, and 44% (95% CI: 34%–54%) at 48 months (Fig. 4*A*). Among patients classified as having no brain metastasis at the start of first-line therapy, 90% had an MRI to determine brain metastasis status. 10% of the patients classified as having no brain metastasis had CT as their only scan to determine this classification.

Among 645 patients (78%) with baseline cross-sectional body imaging, 93 patients (14%) had liver metastases at baseline. Among 552 patients (85%) in the 2015+ cohort without detection of liver metastases on

Table 1. Baseline Cohort Characteristics (Total Cohort)

Characteristic	N = 1,132
Year of front-line therapy, n (%)	
<2015	302 (27%)
2015-2017	503 (44%)
>2017	327 (29%)
Age at start of front-line therapy, Mean (SD)	63.4 (12.1)
Age at start of front-line therapy, n (%)	
<65	619 (55%)
65 +	513 (45%)
Sex, n (%)	
Female	773 (68%)
Male	358 (32%)
Other/Unknown	1 (<0.1%)
Race, n (%)	
White	603 (53%)
Asian/PI	327 (29%)
Black	95 (8.4%)
Other	107 (9.5%)
Ethnicity, n (%)	
Non-Hispanic	1,055 (95%)
Hispanic	53 (4.8%)
Missing	24
Smoking status, n (%)	
Currently or formerly smoked	377 (33%)
No smoking history[a]	755 (67%)
Baseline brain metastasis, n (%)	
Baseline brain met	320 (28%)
Baseline brain met-free (confirmed negative)	299 (26%)
No baseline brain scan available	513 (45%)
Baseline liver metastasis, n (%)	
Baseline liver met	120 (11%)
Baseline liver met-free (negative on ab/pelvic, skull base to mid-thigh, chest, spine scans)	731 (65%)
No baseline scan available	281 (25%)
Baseline sensitizing alteration, n (%)	
Exon 19 deletion	614 (55%)
L858R	381 (34%)
Other[b]	124 (11%)
Missing	13
Baseline sensitizing alteration (compounds), n (%)	
Compound Exon 19 deletion[c]	33 (2.9%)
Compound L858R[d]	31 (2.8%)
Exon 19 deletion	581 (52%)
L858R	350 (31%)
Other[b]	124 (11%)
Missing	13
NGS test available at baseline, n (%)	
Baseline NGS test	649 (57%)
No Baseline NGS test	483 (43%)
Front-line therapy, n (%)	
Targeted therapy-containing	953 (84%)
Afatinib-containing	100
Erlotinib-containing	445
Gefitinib-containing	106
Osimertinib-containing	293
Other targeted therapy-containing regimen[e]	9
Chemotherapy	161 (14%)
Chemo-immunotherapy	10 (0.9%)
Immunotherapy[f]	8 (0.7%)

[a]Includes n = with unknown smoking status.
[b]e20ins (n = 27), G719X (n = 23), L861Q (n = 12), T790M (n = 9), G719A (n = 5), L861Q + T790M (n = 3), S768I (n = 3), G719A + T790M (n = 2), G719S + S768I (n = 2), G719X + S768I (n = 2), Glu709_Thr710delinsAsp (n = 2), L861R (n = 2), T790M + e20ins (n = 2), A1076A (n = 1), A289T + G719X (n = 1), A647T (n = 1), A702T (n = 1), A864V (n = 1), E709A + G719A (n = 1), E709K + E719C + G709K + G719C + G719X (n = 1), E709K + G719X + K714N (n = 1), E865* (n = 1), Exon 18 (non-canonical) + S720Y (n = 1), G709A + G719X (n = 1), G719C (n = 1), G719S (n = 1), G719X + S768I + T274T (n = 1), G719X + T790M (n = 1), G719X + V769M (n = 1), G779F (n = 1), G863S (n = 1), K754T + L833V + T790M (n = 1), K757R (n = 1), L369I + T790M (n = 1), L778R (n = 1), L858Q (n = 1), L861Q + S768I (n = 1), R108T (n = 1), R149W + e25rearrangement (n = 1), R831H (n = 1), S768I + e20ins (n = 1), V774L (n = 1), e21_NOS (n = 1).
[c]T790M (n = 12), G724S (n = 2), S752F (n = 2), S768I (n = 2), A750P + G724S (n = 1), A955T (n = 1), D587D + K327Q (n = 1), D612D (n = 1), F856L (n = 1), G239V + T790M (n = 1), G719A (n = 1), G719S + R108K (n = 1), K949N (n = 1), L718V (n = 1), M2461 (n = 1), P644P (n = 1), S306L (n = 1), V674I (n = 1), Y163C (n = 1).
[d]T790M (n = 11), S768I (n = 2), A871G (n = 1), E545E (n = 1), G719X + T790M (n = 1), G729A (n = 1), G901A + V834L (n = 1), L279H + L718Q (n = 1), L62R (n = 1), L718V (n = 1), L747V (n = 1), L792F (n = 1), L792H (n = 1), L833V (n = 1), R108K (n = 1), R776H (n = 1), T39T (n = 1), V292L (n = 1), V834L (n = 1), e21_NOS (n = 1).
[e]Crizotinib (n = 4), Amivantamab (n = 1), Cetuximab + Docetaxel + Gemcitabine (n = 1), Icotinib (n = 1), Tesevatinib (n = 1), Trastuzumab + Platinum + Pemetrexed (n = 1)
[f]Includes Crizotinib (n = 4), Cetuximab, docetaxel, gemcitabine (n = 1), Icotinib (n = 1), Tesevatinib (n = 1), Trastuzumab, platinum, pemetrexed (n = 1), Amivantamab (n = 1).

negative cross-sectional body imaging at baseline, the probability of incident liver metastasis was 8% (95% CI: 6%–11%) at 12 months after the start of 1L therapy, 18% (95% CI: 14%–22%) at 24 months, 25% (95% CI: 20%–29%) at 36 months, and 30% (95% CI: 24%–36%) at 48 months. We did not see a difference in the cumulative incidence of brain or liver metastases by the type of treatment received in 1L (TKI versus chemotherapy etc.).

Time to Next Treatment or Death

A total of 733 patients out of 830 patients (88%) were treated with 1L targeted therapy (alone or in combination with chemotherapy/immunotherapy), and 97 patients (12%) received 1L chemotherapy/immunotherapy without targeted therapy. Among patients treated with 1L targeted therapy, the most common 1L targeted agent was osimertinib (n = 291, 40%), followed by erlotinib (n = 261, 36%), afatinib (n = 93, 13%), and gefitinib (n = 80, 11%).

After excluding 8 patients who received a less common targeted agent, the median TTNT after the start of

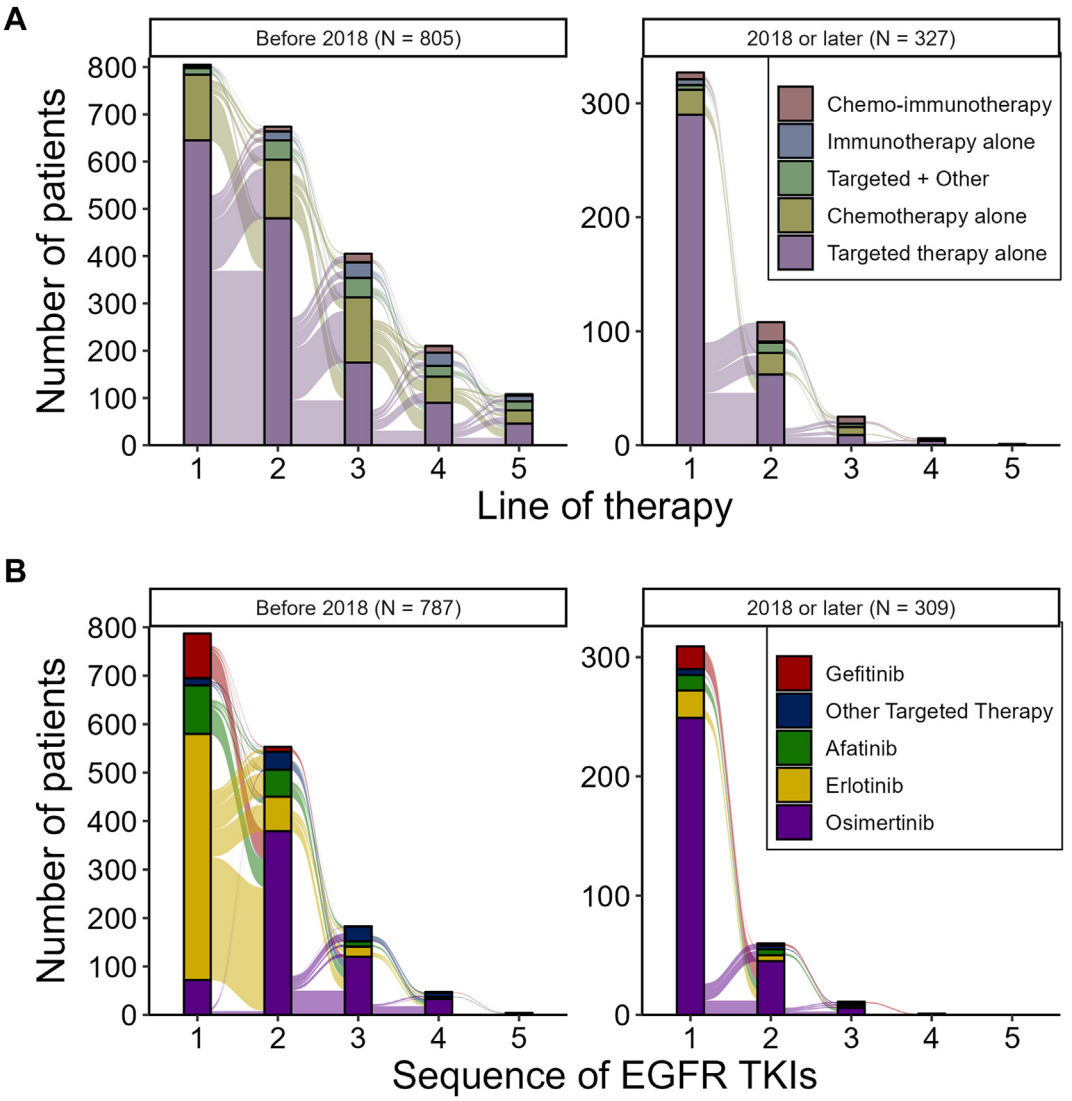

Figure 1. Treatment patterns stratified by the start of 1L therapy before or after 2018 by *(A)* line of therapy and *(B)* order of EGFR-directed targeted therapy. 1L, first-line.

1L therapy was 13.9 months (95% CI: 13.1–15.1) overall and longest in patients receiving 1L osimertinib at 28 months (95% CI: 20.0–not evaluable [NE]). The median TTNT of other EGFR-TKIs as 1L was 13.4 months (95% CI: 12.0–14.6) for erlotinib, 12.6 months (95% CI: 9.6–16.4) for afatinib, and 14.3 months (95% CI: 11.5–17.9) for gefitinib. Median TTNT for 1L chemotherapy/immunotherapy was 4.6 months (95% CI: 3.9–8.1) (Fig. 5*A*). Of patients who received 1L TKI, 19 patients (2.3%) had chemotherapy added to their 1L TKI as 2L therapy.

A total of 518 out of 830 patients (62%) were treated with 2L therapy, and among these, 400 patients (48%) were treated with a targeted agent (alone or in combination with chemotherapy/immunotherapy). The most common 2L targeted agent was osimertinib (n = 310, 60%), 83 patients (16%) received erlotinib, afatinib, or gefitinib, and 118 patients (23%) received 2L chemotherapy and/or immunotherapy without targeted therapy. Excluding 7 patients who received a less common targeted agent, the median TTNT for 2L therapy was 14.0 months (95% CI: 12.2–18.0) overall, 20.5 months (95% CI: 16.2–29.4) for osimertinib, 9.2 months (95% CI: 7.5–12.9) for other EGFR TKIs, and 9.0 months (95% CI: 6.2–10.5) for chemotherapy/immunotherapy (Fig. 5*B*).

OS

With a median follow-up of 25.3 months (95% CI: 23.2–27.1), the estimated median OS was 35.4 months (95% CI: 32.7–37.9) (Supplementary Fig. 3*A*). Patients with EGFR e19del had higher median OS (38.7 months, 95% CI: 35.9–46.3) than patients with L585R (33.9 months, 95% CI: 27.9–38.0) or other baseline EGFR alterations (28.3 months, 95% CI: 23.1–37.7)

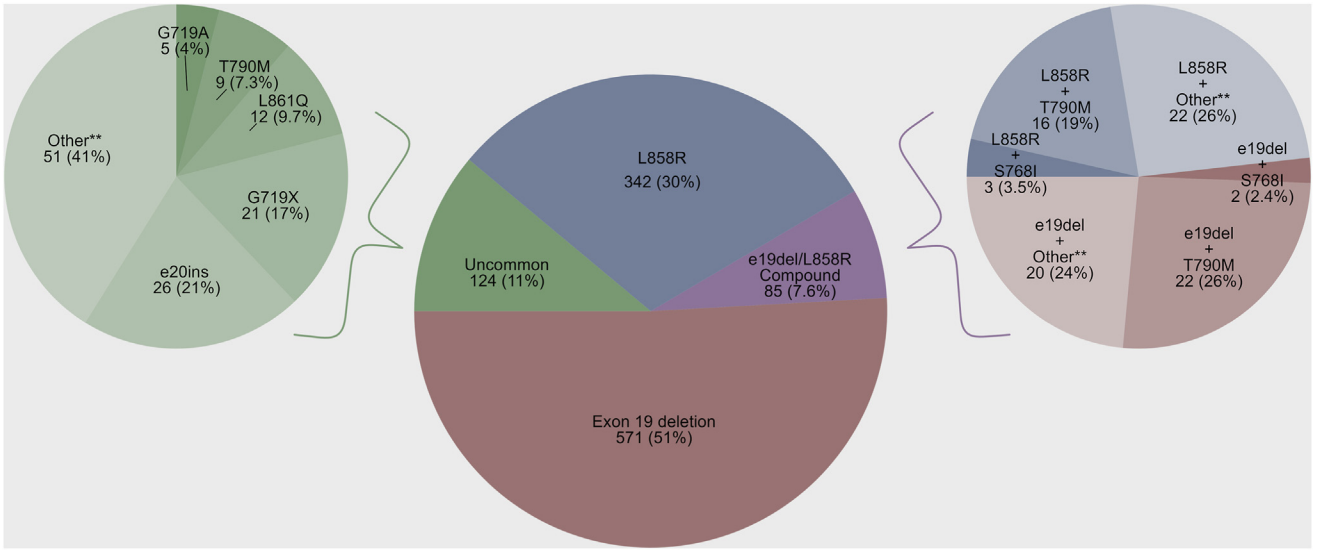

Figure 2. Distribution of baseline EGFR sensitizing alterations (total cohort).

(Supplementary Fig. 3*B*). OS among patients with baseline BM was 27.9 months (95% CI: 23.7–34.4). Among patients with a confirmed negative brain scan at baseline, OS was 38 months (95% CI: 33.2–58.4). Among patients with no baseline scan available, the median OS was 41 months (95% CI: 35.8–NE) (Supplementary Fig. 3*C*). Among patients with baseline LM, OS was 25 months (95% CI: 21.1–27.5). Among patients with a

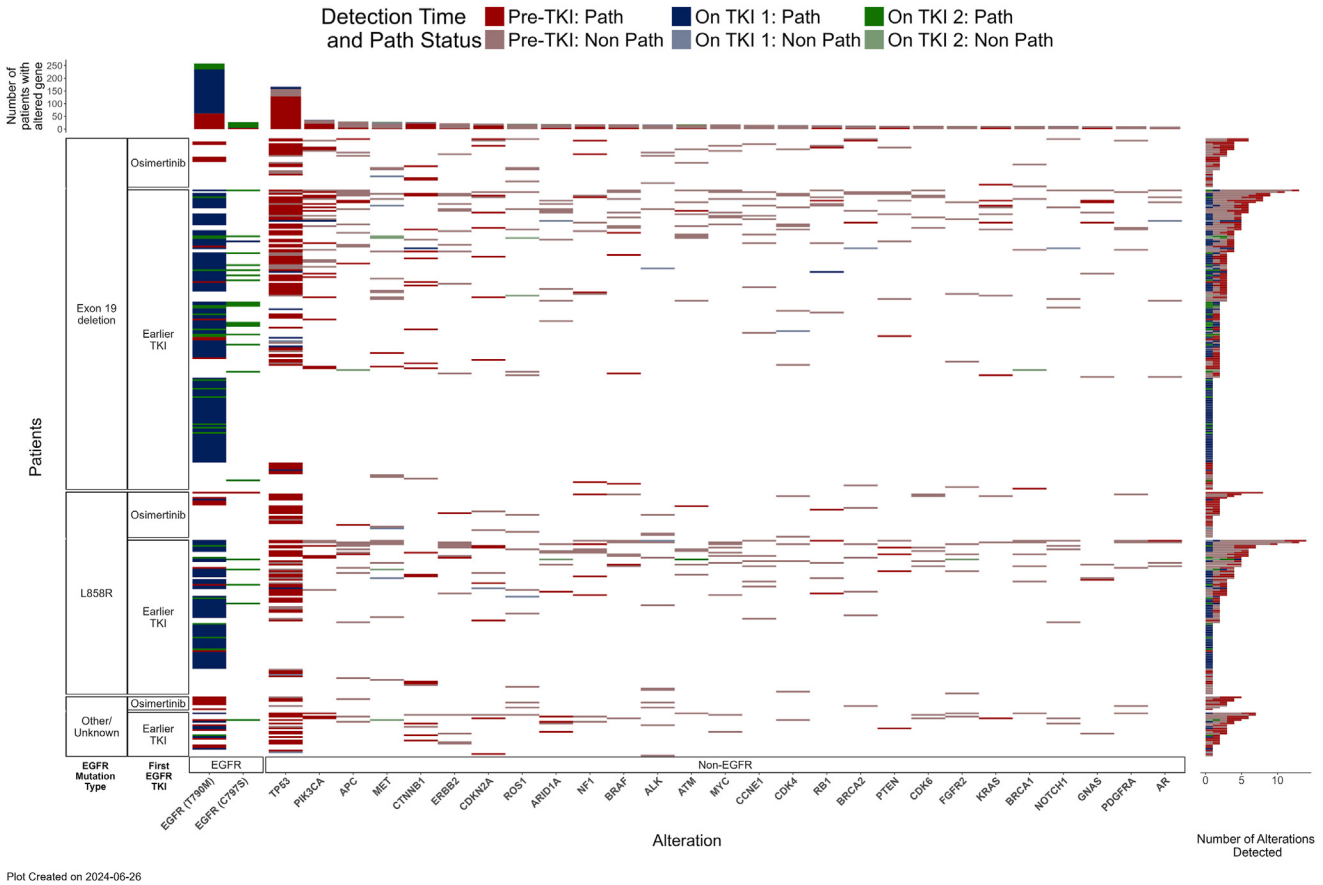

Figure 3. Distribution of comutations detected during baseline, on TKI1, and on TKI2 (total cohort). TKI, tyrosine kinase inhibitor.

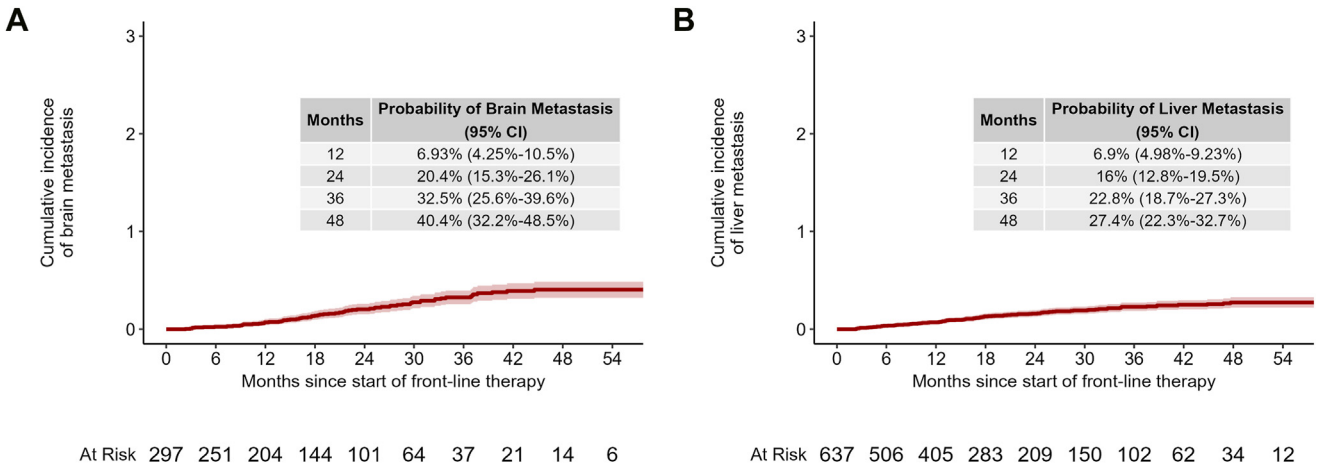

Figure 4. Cumulative incidence of *(A)* brain metastasis and *(B)* liver metastasis probabilities at 12, 24, 36, or 48 months after the start of front-line therapy (2015+ cohort).

confirmed negative scan for liver metastasis at baseline, OS was 39.4 months (95% CI: 36.1–45). Among patients with no baseline scan available, the median OS was 33.8 months (95% CI: 31.1–NE) (Supplementary Fig. 3*D*). Using a Cox regression with incident brain metastasis modeled as a time-varying covariate, brain metastasis developed after baseline was associated with a 120% higher risk of death (hazard ratio = 3.2, 95% CI: 2.1–4.9) compared with no brain metastasis. Extended Kaplan-Meier curves reported that both patients with baseline brain metastasis and post-baseline brain metastasis had worse survival than those without brain metastasis (Supplementary Fig. 3*E*). Similar associations can be seen with liver metastasis (hazard ratio = 4.2, 95% CI: 3.0-5.8) (Supplementary Fig. 3*F*).

Among 473 patients with NGS testing at baseline, 97 (21%) and 15 (3.2%) patients had pathogenic variants of *TP53* and *PIK3CA*, respectively. Fewer patients had pathogenic variants of *RB1* (n = 2, 0.4%) or *ERBB2* (n = 4, 0.8%). OS and TTNT did not appear to meaningfully differ by detection of these pathogenic comutations (Supplementary Fig. 4*A–D*).

Discussion

In this retrospective cohort of patients with EGFRm mNSCLC from multiple institutions across North America, we describe treatment patterns over time, tumor mutation profiles, risk of incident brain and liver metastases, TTNT, and OS. As expected, 1L TKI therapy, and in particular 1L osimertinib, became more common after 2018, on the basis of studies showing superior efficacy of first-line osimertinib compared with earlier generation TKIs.[12,29] Though treatment sequencing was heterogeneous

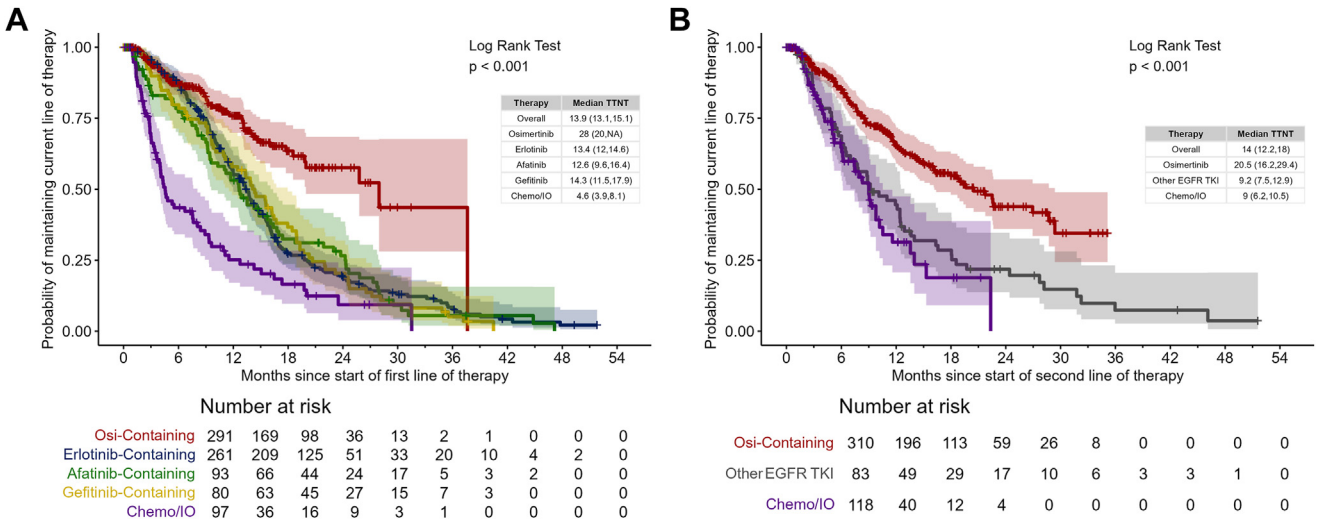

Figure 5. Time to next line of therapy or death for A) first-line or B) second-line therapy (2015+ cohort). 2015+, on or after January 1, 2015.

in our cohort of patients spanning over two decades, a consistent signal was seen for longer TTNT with osimertinib across 1L and 2L compared with earlier generation TKIs and chemotherapy/immunotherapy, underscoring the potency and tolerability of this agent.

Although recent and ongoing trials including FLAURA2 and MARIPOSA are expected to expand frontline treatment options beyond osimertinib monotherapy to combination approaches,[30–32] these regimens carry increased toxicity, and it remains unknown which patients will benefit most from intensified upfront treatment. Notably, TTNT after 1L osimertinib in our cohort (28 months) was markedly better than progression-free survival reported in MARIPOSA and FLAURA2; this may be due to treatment beyond progression (for instance, after local therapy for oligoprogression, which was not recorded in our cohort). Nevertheless, these results emphasize that many patients in a real-world setting derive prolonged benefit from frontline osimertinib monotherapy.

In our study, emergent T790M was typically observed during treatment with earlier generation EGFR TKIs, consistent with other studies that have described this resistance mechanism in up to 50% of EGFRm mNSCLC progressed on earlier EGFR TKIs.[33–35] Interestingly, baseline T790M was also reported in 62 patients in this cohort (10% of 649 patients); other studies that have reported highly variable rates of baseline (i.e., de novo) T790M mutations in EGFRm mNSCLC ranging from less than 1% to as high as 17%.[36–38] Comutations in *TP53* and *PIK3CA* genes were not found to be associated with worse survival in our cohort, in contrast to prior studies showing worse outcomes with these co-alterations,[39–42] though small numbers may have limited our ability to detect these differences.

Brain metastases were common in this cohort and more prevalent at baseline (54% of the cohort with baseline imaging) than previously reported (15%) in EGFRm NSCLC.[21,22,43,44] Over half of patients with baseline brain scans had brain metastases at baseline and the cumulative incidence of new brain metastases in patients without baseline brain metastases increased steadily over time, with a cumulative incidence of 44% at 4 years after the start of 1L therapy. Interestingly, no difference in brain metastasis incidence by treatment type was detected in this cohort, possibly owing to sample size limitations. Importantly, brain metastases both at baseline and developing on-treatment were associated with considerably worse OS. The ongoing risk of developing brain metastases, together with the associated survival detriment, makes a compelling case for routine surveillance brain MRIs for patients with EGFRm NSCLC, which are not currently included in guidelines.

A few studies have investigated surveillance brain imaging in patients with EGFR wild-type NSCLC. Yokoi et al.[45] performed frequent follow-up brain CTs every two to six months in patients with resected NSCLC and found that most patients with central nervous system relapse had asymptomatic disease when brain metastases were discovered. Another study advocated for the use of biannual MRI to detect small (<30 mm) brain metastases, providing patients with earlier detection and opportunity for locally ablative procedures such as stereotactic radiosurgery.[46] Nevertheless, an observational study found that regular follow-up MRI every three to six months was not associated with a survival advantage over usual care.[47] Notably, the analysis did not adjust for any confounders of MRI interval frequency such as the presence of brain metastases at baseline. Given the higher risk of brain metastases in EGFRm mNSCLC, a mutation-specific recommendation for a higher frequency of brain imaging may also be reasonable.[48,49] Ultimately, well-designed observational studies or randomized studies will be needed to determine the benefit, cost-effectiveness, and optimal frequency of brain imaging, especially amongst those harboring EGFR mutations. In clinical practice, ATOMIC members advocate for performing surveillance brain MRIs in this patient population every 6 to 12 months.

This retrospective electronic medical record-based study has limitations. First, there were a relatively small number of TKI NGS samples available, which limited our ability to detect emergent alterations. Nevertheless, overall, missing data was low (≤1%) for variables used in covariate analyses. Second, the ATOMIC registry consists of only academic centers, so generalizability may be limited. Finally, our decision to restrict time-to-event analyses to a nested cohort of patients who started 1L in 2015 or later was made post-hoc and stemmed from an observation wherein patients diagnosed in earlier years had longer than expected survival. We suspect this was because patients diagnosed in earlier years had to survive long enough to be tested for an EGFR mutation to be identified by each institution's abstraction methods and be included in the ATOMIC registry. In addition, patients would have met eligibility for inclusion in the cohort after the start of follow-up (i.e., at the start of 1L therapy), resulting in immortal time bias.[50] Restricting time-to-event analyses to the 2015+ cohort was thought sufficient to remove this bias given the approval of osimertinib for the 2L setting in 2015 and the establishment of routine EGFR testing. In addition, the period of this cohort and the rapidly changing treatment patterns also made it difficult to estimate the effects of specific treatments on OS. Another limitation of this real-world data analysis is that 5% of our cohort with brain imaging at baseline only had a CT scan

performed without MRI. Nevertheless, we felt that this was a low proportion of our cohort and likely would not impact our overall results. Lastly, although surveillance frequency was not standardized given the multi-center retrospective nature of this study, many academic centers have similar practice patterns for routine surveillance imaging.

In this large multi-institutional cohort of over a thousand patients with EGFRm mNSCLC treated with systemic therapy over the past two decades, we observed (1) a predictable practice pattern shift over time to first-line osimertinib, (2) superior time on treatment with osimertinib administered in any line of therapy compared with earlier generation TKIs, and (3) a high risk of brain metastases both at baseline and on-treatment, which supports the utility of longitudinal surveillance imaging of the brain in EGFRm mNSCLC.

CRediT Authorship Contribution Statement

Margaret Stalker: Writing - original draft, Writing - review & editing, Formal analysis.

Connor B. Grady: Data curation, Formal analysis, Writing - review & editing.

Alex Watts: Data curation, Formal analysis, Writing - review & editing, Visualization.

Wei-Ting Hwang: Methodology, Validation, Supervision.

Krishna Chandrasekhara: Writing - review & editing.

Fangdi Sun: Writing - review & editing.

Geoffrey Liu: Writing - review & editing.

Devalben Patel: Writing - review & editing.

Jorge Nieva: Writing - review & editing.

Amanda Herrmann: Writing - review & editing.

Kristen Marrone: Writing - review & editing.

Vincent Lam: Writing - review & editing.

Vamsi Velcheti: Writing - review & editing.

Stephen Liu: Writing - review & editing.

Gabriela Liliana Bravo Montenegro: Writing - review & editing.

William Tompkins: Writing - review & editing.

Tejas Patil: Writing - review & editing.

Jared Weiss: Writing - review & editing.

Kelsey Leigh Miller: Writing - review & editing.

William Schwartzman: Writing - review & editing.

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Khvaramze Shaverdashvili: Writing - review & editing.

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Amanda Cass: Writing - review & editing.

Wade Iams: Writing - review & editing.

Dara Aisner: Writing - review & editing.

Charu Aggarwal: Writing - review & editing.

Ross Camidge: Writing - review & editing.

Lova Sun: Conceptualization, Investigation, Supervision, Writing - review & editing.

Melina Marmarelis: Conceptualization, Investigation, Supervision, Writing - review & editing, Funding acquisition.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at [https://doi.org/10.1016/j.jtocrr.2024.100765].

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