ORIGINAL ARTICLE

Characteristics of Long-Term Survivors With EGFR-Mutant Metastatic NSCLC

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Received 10 December 2023; revised 9 March 2024; accepted 24 March 2024
Available online - 26 March 2024

ABSTRACT

Introduction: Characteristics of long-term survivors in EGFR-mutant (EGFRm) NSCLC are not fully understood. This retrospective analysis evaluated a multi-institution cohort of patients with EGFRm NSCLC treated in the pre-osimertinib era and sought to describe characteristics of long-term survivors.

Methods: Clinical characteristics and outcomes were abstracted from the electronic medical records of patients with EGFRm metastatic NSCLC who started first-line therapy before 2015. Demographics and comutations were compared between greater than or equal to 5-year survivors and less than 5-year survivors. Multivariable Cox proportional hazard and logistic regression models were used to evaluate factors associated with survival and the odds of death within 5 years, respectively.

Results: Overall, 133 patients were greater than or equal to 5-year survivors; 127 were less than 5-year survivors. Burden of pathogenic comutations including TP53 and

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Cite this article as: Tompkins W, Grady CB, Hwang W-T, et al. Characteristics of long-term survivors with EGFR-mutant metastatic NSCLC. *JTO Clin Res Rep* 2024;5:100669.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2024.100669

PIK3CA was similar between greater than or equal to 5-year survivors and less than 5-year survivors. Receipt of first-line chemotherapy rather than EGFR tyrosine kinase inhibitor was similar between the groups (22% of <5-y versus 31% of ≥5-y). Baseline brain metastasis and history of smoking were associated with higher odds of death within 5 years (odds ratio = 2.16, $p = 0.029$ and odds ratio = 1.90, $p = 0.046$, respectively). Among patients without baseline brain metastases, cumulative incidence of brain metastases at 5 years was 42.3%. Both baseline and post-baseline brain metastasis were associated with worse overall survival compared with no brain metastasis (hazard ratio = 3.26, $p < 0.001$ and hazard ratio = 4.99, $p < 0.001$, respectively).

Conclusions: Within patients treated for EGFRm metastatic NSCLC before 2015, absence of brain metastasis and nonsmoking status were predictive of 5-year survival. Our findings help to define a subset of patients with EGFRm NSCLC with excellent survival outcomes who may not require intensification of initial therapy.

Keywords: EGFR; EGFR TKI; NSCLC; Next-generation sequencing; Brain metastasis

Introduction

EGFR tyrosine kinase inhibitors (TKIs), such as the third-generation TKI osimertinib, have become standard first-line treatment for patients with metastatic NSCLC (mNSCLC) and a sensitizing EGFR mutation (EGFRm).[1–9] Although outcomes have improved for patients with EGFRm NSCLC, not all patients have a durable response to EGFR TKIs; contemporary trials have focused on strategies to improve outcomes with first-line treatment. Recently, it was reported that the addition of chemotherapy to EGFR TKI in the first-line setting improves progression-free survival.[10,11] The move toward more potent and aggressive first-line treatment options and combinations is understandable in a disease where many patients are unable to receive second-line therapy. Nevertheless, the improvement in progression-free survival in these efforts provided must be weighed against toxicity, patient quality of life, and other costs of treatment intensification.

Personalization and tailoring of treatment in EGFRm NSCLC will require an enhanced understanding of which patients have aggressive disease and will truly benefit from upfront treatment intensification and which patients have equally good outcomes with less intensive and less toxic first-line therapy. A better understanding of determinants of prognosis is also essential to clinical trial design, for instance, in incorporating appropriate stratification factors, to ensure balance across arms. Several observational studies have identified factors such as nonsmoking status, EGFR e19 del, and absence of brain/liver metastasis to be associated with improved survival in EGFRm NSCLC.[12–22] Nevertheless, findings regarding the prognostic significance of age, sex, metastatic site, and line of TKI therapy have been conflicting,[20,21] and the significance of non-EGFR comutations such as *TP53* and *PIK3CA* in the EGFRm population remains incompletely understood. Furthermore, no studies have evaluated the impact of development of brain metastasis at various time points on treatment, and there remains controversy over whether brain metastases are simply a general marker of aggressive disease biology or an independent risk factor for worse survival.[23]

Although platinum-based chemotherapy and earlier generation EGFR TKIs are no longer the contemporary standard of care for first-line treatment of EGFRm mNSCLC, patients treated with these regimens in earlier years now have extended follow-up. Data from long-term survivors treated with earlier generation EGFR TKIs provide an opportunity to identify subgroups with a more indolent natural history and favorable survival outcomes who may be well served by less intensive first-line therapy (e.g., EGFR TKI monotherapy rather than chemotherapy combination). In this retrospective multi-institutional cohort of patients with EGFRm mNSCLC across North America, we sought to describe the clinical, demographic, and genotypic characteristics of long-term survivors with EGFRm mNSCLC[24] treated in the pre-osimertinib era and evaluate impact of comutations and on-treatment development of brain metastasis on survival.

Materials and Methods

Study Population

Clinical characteristics and outcomes were abstracted from the electronic medical records of patients with EGFRm mNSCLC at 12 institutions (11 United States, one Canada) participating in the Academic Thoracic Medical Investigator's Consortium. Data abstraction occurred at member institutions by trained data abstractors using a standardized digital form from 2018 to 2021, and data cutoff was March 31, 2021. Data analysis occurred from November 1, 2022, to June 1, 2023. For this analysis, we included patients with mNSCLC and sensitizing EGFR mutations who started first-line therapy before 2015, before the Food and Drug Administration approval of osimertinib for mNSCLC for T790M (March 30, 2017) or for first-line metastatic disease (April 18, 2018). Greater

than or equal to 5-year survivors were defined as those alive at 5 years after start of first-line therapy. Less than 5-year survivors were defined as those who died within 5 years after start of first-line therapy. Patients were excluded from the primary analysis if their vital status at 5 years could not be ascertained (i.e., no death date and lost to follow-up <5 y from start of first-line therapy), but they were included in sensitivity analyses. In addition to the overall cohort, we also defined a baseline brain scan cohort, which included all patients who had either magnetic resonance imaging or computed tomography (CT) of the brain performed within one year before 60 days after the start of first-line therapy.

Study Measures

Patients' baseline sensitizing EGFR mutation was categorized as exon 19 deletion (e19del), L858R, or other EGFR-sensitizing mutation based on the first available sample where the alteration was detected. Baseline compound EGFR alterations (i.e., additional EGFR alterations) and baseline comutations (i.e., alterations in non-EGFR genes) were defined as alterations detected on next-generation sequencing (NGS) from samples collected within one year before or 60 days after the start of first-line therapy. Comutation pathogenicity (pathogenic versus non-pathogenic or indeterminant) was assigned using the VarSome database,[25] and expert opinion when pathogenicity was still unclear. Baseline liver scans were defined as magnetic resonance imaging, CT, or positron emission tomography–CT scans of the abdomen/pelvis, chest, spine, or skull base to mid-thigh performed within one year before or 60 days after the start of first-line therapy.

Statistical Analysis

Baseline characteristics. Baseline patient characteristics were summarized using medians, interquartile ranges, frequencies, and proportions. Differences in the distribution of baseline characteristics between greater than or equal to 5-year and less than 5-year survivor groups were tested using Wilcoxon ranked sum for continuous variables and Fisher's exact tests for categorical variables. Overall survival (OS) was defined as time from the start of first-line therapy to death or patients were censored at last contact. The distribution of OS was estimated using the Kaplan-Meier method.[26] Median follow-up time was estimated using the reverse Kaplan-Meier method.[27] Baseline comutation burden was summarized as the number of patients with at least one alteration in a non-EGFR gene of the number of patients with baseline NGS and compared between greater than or equal to 5-year and less than 5-year survivor groups using Wilcoxon ranked sum tests.

Survival analyses. To evaluate factors associated with OS, we estimated hazard ratios (HR) for death using a multivariable Cox proportional hazard model including terms for age, sex, race, smoking status, sensitizing EGFR mutation, presence of brain and liver metastasis at baseline, first-line therapy year, and first-line therapy. We also estimated odds ratios (ORs) of death within 5 years after the start of first-line therapy with a multivariable logistic regression model with the same terms. Sensitivity analyses were performed including the following: (1) a complete case survival analysis (both Cox and logistic regressions) including only patients with baseline scans performed allowing ascertainment of brain and liver metastasis status; (2) a sensitivity survival analysis including patients lost to follow-up before 5 years (Cox model censoring patients at last contact; logistic regression classifying patients lost to follow-up before 5-y as <5-y survivors).

Baseline brain scan cohort. Among patients who had a baseline brain scan and no detected baseline brain metastasis, a cumulative incidence function was used to estimate the probability of developing a new brain metastasis from the start of first-line therapy; death was considered as a competing event and patients without events were censored at last contact. The effect of brain metastasis development at baseline and post-baseline (i.e., after the start of first-line therapy) on the distribution of OS was evaluated with a three-level time-dependent variable (baseline brain metastasis, no baseline brain metastasis, post-baseline brain metastasis). Extended Kaplan-Meier curves were plotted by time-dependent brain metastasis status from the start of first-line therapy to death; otherwise, patients were censored at last contact. This descriptive method allowed patients with no baseline brain metastasis who subsequently developed a brain metastasis during follow-up to move across risk sets (i.e., from no baseline brain metastasis to post-baseline brain metastasis) at the time of brain metastasis detection.[28] A multivariable Cox proportional hazard model was used to estimate the association between OS and brain metastasis development as a time-dependent variable adjusted for the same variables as previously mentioned. Adjusted survival probabilities at 5 years were estimated for a hypothetical patient (female sex, <65 y old, White race, non-Hispanic ethnicity, never smoker, EGFR e19 del, started first-line therapy in 2014) with no brain metastasis (at baseline and post-baseline), baseline brain metastasis, or who developed brain metastasis at 1 year, 2 years, 3 years, or

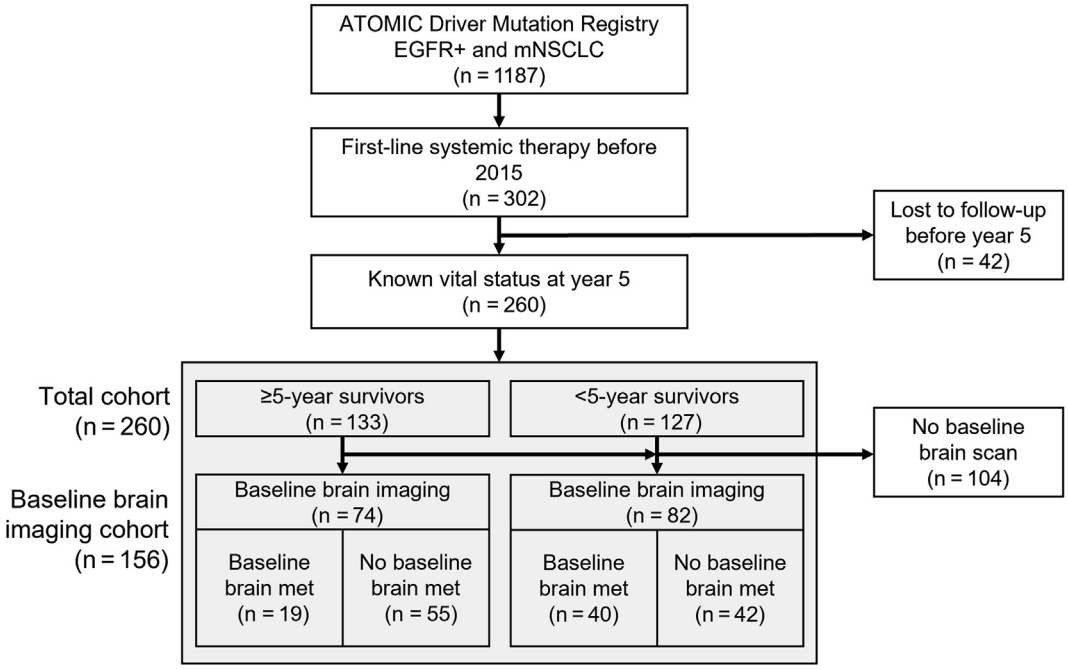

Figure 1. Study sample and analytic cohorts. ATOMIC, Academic Thoracic Medical Investigator's Consortium.

4 years after the start of first-line therapy and by receipt of first-line targeted therapy-containing regimen versus chemotherapy alone.

Analyses were performed in R version 4.2.1 with *survival* version 3.5.6[29] and *cmprsk* version 2.2.11[27,30] packages. Local institutional review board approval was obtained at each site with a waiver of consent due to the retrospective nature of this study.

Results

Patient Demographics

Among 1187 patients with EGFRm mNSCLC in the Academic Thoracic Medical Investigator's Consortium registry, 260 received first-line systemic therapy (either chemotherapy and/or EGFR TKI) before 2015 and had a known vital status 5 years after the start of first-line therapy (Fig. 1). Furthermore, 42 patients who were lost to follow-up before year 5 were excluded. Of the included patients, 133 were greater than or equal to 5-year survivors and 127 were less than 5-year survivors. Clinical characteristics were similar between the greater than or equal to 5-year and less than 5-year survivor groups, with a few notable exceptions (Table 1). Fewer greater than or equal to 5-year survivors had baseline brain metastases compared with less than 5-year survivors (14% versus 31%, Fisher's exact $p = 0.005$). Greater than or equal to 5-year survivors were also enriched in earlier years (31% versus 15% in 2011–2012, Fisher's exact test for all year categories, $p < 0.001$). EGFR TKI-based first-line therapy was the most common (80% of which was erlotinib), whereas 27% of patients overall received chemotherapy alone in the first line, with no significant difference between less than 5-year (22%) and greater than or equal to 5-year (31%) survivors. Furthermore, 78.9% of greater than or equal to 5-year survivors and 47.2% of less than 5-year survivors received subsequent osimertinib. In addition, 97.3% of patients in the total cohort received EGFR TKI at some point in their course (97.0% of ≥5-y survivors and 97.6% of <5-y survivors); treatment patterns of greater than or equal to 5-year survivors and less than 5-year survivors are found in Supplementary Figure 1.

Comutations

Among patients with baseline NGS (n = 100), comutations found in the greater than or equal to 5-year and less than 5-year survivor groups are found in Figure 2. The number of comutations did not differ between greater than or equal to 5-year and less than 5-year survivors (median [interquartile range] 1.5 [0–5] versus 2.0 [0–5] comutations per patient, Wilcoxon ranked sum $p = 0.911$). The frequency of patients with at least one pathogenic comutation was also similar between groups (56% versus 52%, Fisher's exact $p = 0.55$). *TP53* and *PIK3CA* mutations were the most common comutations found in both groups with most categorized as pathogenic; of note, most RB1 comutations found were not considered pathogenic (Fig. 2). Pathogenic *TP53* mutations were numerically lower in greater

Table 1. Baseline Characteristics, Total Cohort

Characteristic	Overall, N = 260	<5-y Survivors, N = 127	≥5-y Survivors, N = 133	*p* Value
Year of first-line therapy, n (%)				<0.001[a]
<2011	40 (15)	9 (7.1)	31 (23)	
2011-2012	60 (23)	19 (15)	41 (31)	
2013	72 (28)	34 (27)	38 (29)	
2014	88 (34)	65 (51)	23 (17)	
Age at start of first-line therapy, mean (SD)	61.3 (10.6)	61.5 (11.1)	61.2 (10.1)	0.86[b]
Age at start of first-line therapy, n (%)				>0.99[a]
<65	162 (62)	79 (62)	83 (62)	
≥65	98 (38)	48 (38)	50 (38)	
Sex, n (%)				0.42[a]
Female	181 (70)	85 (67)	96 (72)	
Male	79 (30)	42 (33)	37 (28)	
Race, n (%)				0.31[a]
White	152 (58)	67 (53)	85 (64)	
Asian/PI	69 (27)	39 (31)	30 (23)	
Black	14 (5.4)	7 (5.5)	7 (5.3)	
Other	25 (9.6)	14 (11)	11 (8.3)	
Ethnicity				0.21[a]
Non-Hispanic	250 (98%)	123 (99%)	127 (96%)	
Hispanic	6 (2.3%)	1 (0.8%)	5 (3.8%)	
Missing	4	3	1	
Smoking status, n (%)				0.50[a]
Never smoker[c]	180 (69)	85 (67)	95 (71)	
Ever smoker	80 (31)	42 (33)	38 (29)	
Prior surgery before metastatic disease, n (%)				0.057[a]
Prior surgery	61 (23)	23 (18)	38 (29)	
No record of prior surgery	199 (77)	104 (82)	95 (71)	
Baseline brain metastasis, n (%)				0.005[a]
Baseline brain met-free (confirmed negative)	97 (37)	42 (33)	55 (42)	
Baseline brain met	59 (23)	40 (31)	19 (14)	
No baseline brain scan	103 (40)	45 (35)	58 (44)	
Missing	1	0	1	
Baseline liver metastasis				0.077[a]
Baseline liver met-free (negative on ab/pelvic, skull base to mid-thigh, chest, spine scans)	176 (68%)	91 (72%)	85 (64%)	
Baseline liver met	34 (13%)	19 (15%)	15 (11%)	
No baseline scan	49 (19%)	17 (13%)	32 (24%)	
Missing	1	0	1	
Baseline sensitizing alteration				0.37[a]
Exon 19 deletion	146 (56%)	66 (52%)	80 (61%)	
L858R	76 (29%)	41 (32%)	35 (27%)	
Other[d]	37 (14%)	20 (16%)	17 (13%)	
Missing	1	0	1	
Baseline sensitizing alteration (compounds)				0.19[a]
Compound exon 19 del	13 (5.0%)	4 (3.1%)	9 (6.8%)	
Compound L858R[e]	17 (6.6%)	6 (4.7%)	11 (8.3%)	
Exon 19 del	133 (51%)	62 (49%)	71 (54%)	
L858R	59 (23%)	35 (28%)	24 (18%)	
Other[d]	37 (14%)	20 (16%)	17 (13%)	
Missing	1	0	1	

(continued)

Table 1. Continued

Characteristic	Overall, N = 260	<5-y Survivors, N = 127	≥5-y Survivors, N = 133	*p* Value
First-line therapy, n (%)				0.12[a]
Chemotherapy	69 (27)	28 (22)	41 (31)	
Targeted therapy containing	191 (73)	99 (78)	92 (69)	
First-line therapy				0.79[a]
Erlotinib	153 (80%)	77 (78%)	76 (83%)	
Gefitinib	23 (12%)	13 (13%)	10 (11%)	
Afatinib	4 (2.1%)	3 (3.0%)	1 (1.1%)	
Other targeted therapy[f]	11 (5.8%)	6 (6.1%)	5 (5.4%)	
Missing	69	28	41	

[a]Fisher's exact test.
[b]Welch two-sample *t* test.
[c]Includes n = 4 with unknown smoking status, all in 5+-year survival group.
[d]Less than 5-year survivors: e20ins (n = 4), G719X (n = 2), E709K+G719X+K714N (n = 1), exon 18 (noncanonical)+Glu709_Thr710delinsAsp+T710* (n = 1), G719A+T790M (n = 1), G719X+S768I+T274T (n = 1), R149W+e25rearrangement (n = 1), V774L (n = 1); greater than or equal to 5-year survivors: T790M (n = 3), E709A+G719A (n = 1), Glu709_Thr710delinsAsp (n = 1), K754T+L833V+T790M (n = 1), L861Q (n = 1), e20ins (n = 1).
[e]Less than 5-year survivors: T790M (n = 3), G729A (n = 1), T39T (n = 1); ≥5-year survivors: T790M (n = 2), E282K+L861Q (n = 1), E545E (n = 1).
[f]Less than 5-year survivors: erlotinib + bevacizumab (n = 2), afatinib + pembrolizumab (n = 1), erlotinib + gemcitabine (n = 1), osimertinib (n = 1), platinum + erlotinib + pemetrexed (n = 1); ≥5-year survivors: erlotinib + bevacizumab (n = 2), cetuximab + docetaxel + gemcitabine (n = 1), erlotinib + pemetrexed (n = 1), erlotinib + vinorelbine (n = 1).
Met, metastasis; PI, Pacific Islander.

than or equal to 5-year survivors when compared with less than 5-year survivors (32.7% versus 45.8%, Fisher's exact $p = 0.22$), but this difference was not statistically significant (Supplementary Table 1). Though infrequent, pathogenic comutations with *PIK3CA* were also found at similar frequency in both survival groups (7.7% versus 8.3%, Fisher's exact $p = >0.99$, Supplementary Table 1).

Overall Survival

With a median follow-up time of 90.8 months (95% confidence interval [CI]: 84.4–98.7 mo; range 2.1–234.2 mo), median OS was 61.2 months (95% CI: 54.8–70.1 mo). Baseline brain metastasis was associated with higher odds of death within 5 years (OR = 2.16, 95% CI: 1.09–4.39, p value = 0.029) and nonsignificant trend toward worse OS (HR = 1.43, 95% CI: 1.00–2.05, p value = 0.052) (Fig. 3). Baseline liver metastasis was associated with worse OS (HR = 1.55, 95% CI: 1.03–2.34, p value = 0.036) but was not associated with odds of death within 5 years (OR = 0.94, 95% CI: 0.40–2.21, $p = 0.89$). Baseline non-e19del or non-L858R (i.e., other) EGFR alterations were associated with both worse OS (HR = 1.93, 95% CI: 1.09–3.42, $p = 0.025$) and higher odds of death within 5 years (OR = 3.09, 95% CI: 1.02–9.88, $p = 0.049$) compared with EGFR e19del. History of smoking was associated with higher odds of death within 5 years (OR = 1.90, 95% CI: 1.02–3.60, p value = 0.046) but was not associated with OS (HR = 1.31, 95% CI: 0.94–1.83, p value = 0.11). Starting first-line therapy before 2011 compared with later years was associated with both lower risk of death and lower odds of death within 5 years. Sensitivity analyses were performed to further investigate whether the effect of year affected other associations with survival and revealed no change in the direction of associations (Supplementary Tables 2 and 3).

Additional sensitivity analyses restricted to patients with complete baseline brain and liver imaging (n = 151) were consistent with the primary analysis, except that baseline brain metastasis was associated with worse OS (HR = 1.69, 95% CI: 1.11–2.56, $p = 0.013$), whereas baseline liver metastasis was not associated with either worse OS or odds of death within 5 years (Supplementary Table 4). Sensitivity models which included patients lost to follow-up within 5 years from the start of first-line therapy in the less than 5-year survivor group were also consistent with the primary analyses, except that baseline brain metastases were associated with worse OS (HR = 1.55, 95% CI: 1.08–2.22, $p = 0.017$) but not odds of death within 5 years (Supplementary Table 5).

Baseline Brain Imaging Cohort

Baseline brain scans were available for 60% of the overall cohort (156 of 260). Characteristics of the baseline brain imaging cohort for greater than or equal to 5-year (n = 74) and less than 5-year survivors (n = 82) are found in Supplementary Table 6. In this cohort, baseline brain metastasis were more common in less than 5-year survivors compared with greater than or equal to 5-year survivors (49% versus 26%, Fisher's exact $p = 0.005$). Among patients without baseline brain metastasis (n = 97), the probability of developing brain metastasis was 7.2% at 12 months (95% CI: 3.2%–13.5%) and 42.3% at 60 months (95% CI: 32.3%–51.9%) after start of first-line therapy (Fig. 4*A*). Baseline

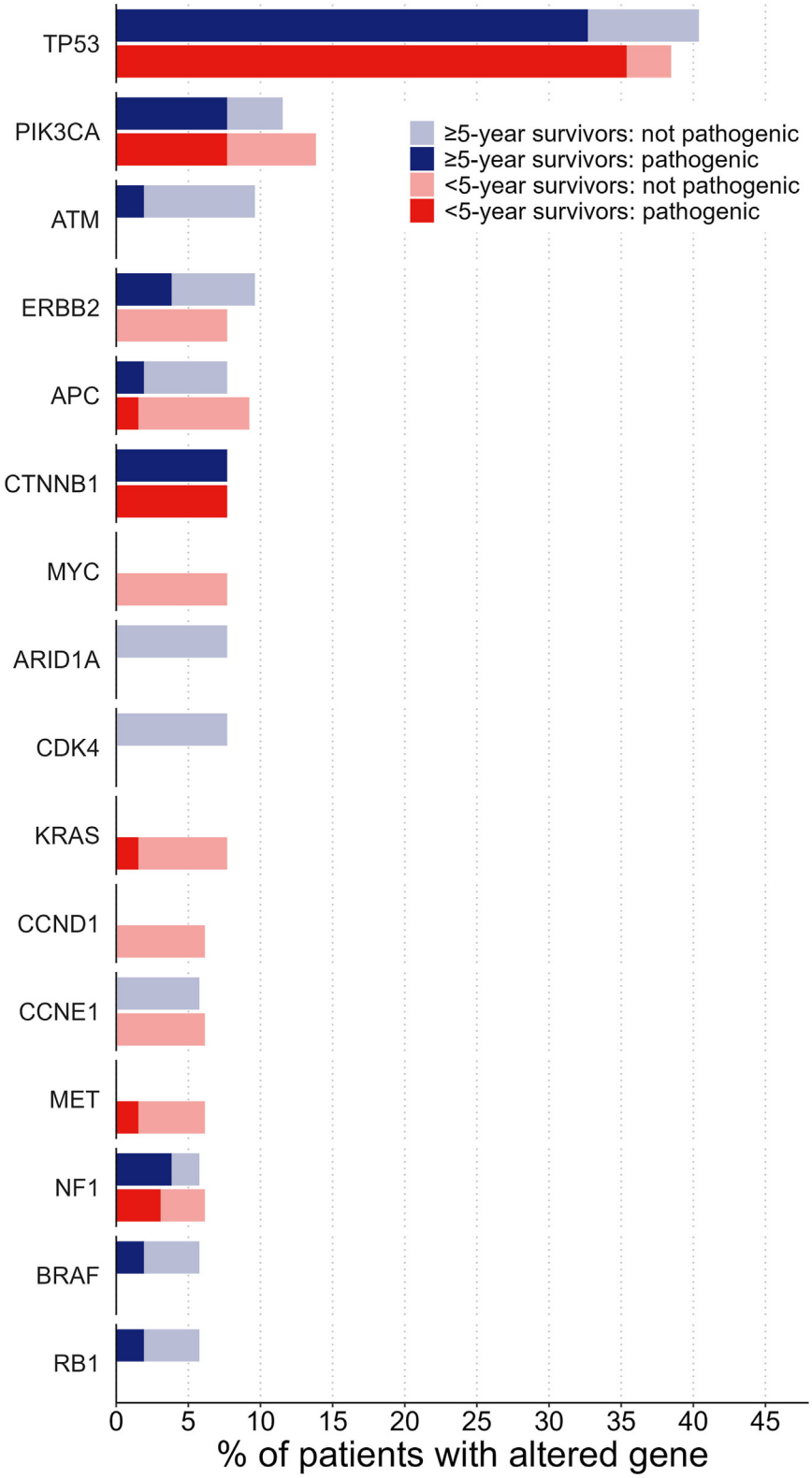

Figure 2. Proportion of patients with non-EGFR alterations by survival group. Includes patients with baseline next-generation sequencing, defined as next-generation sequencing samples collected within 1 year before and 60 days after start of first-line treatment ($\geq$5-y survival group, n = 52; $<$5-y survival group, n = 48). Comutations with greater than 5% prevalence illustrated.

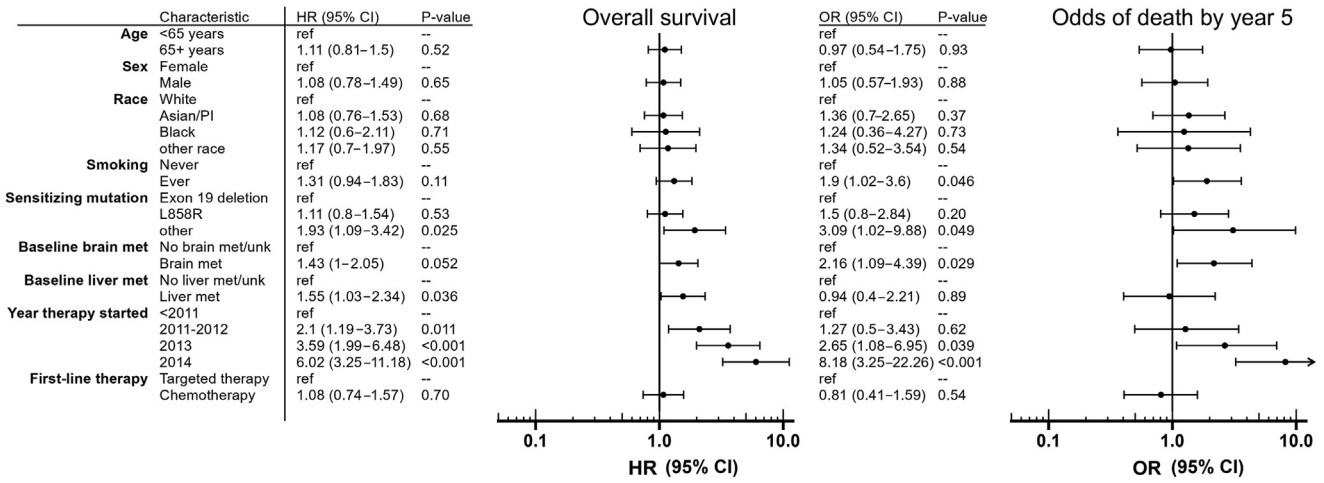

Figure 3. Factors associated with overall survival and odds of death by 5 years after start of frontline therapy. CI, confidence interval; HR, hazard ratio; OR, odds ratio.

and post-baseline (i.e., on treatment) brain metastases were associated with worse unadjusted OS compared with no brain metastasis (Fig. 4*B*). After adjustment for demographic and baseline clinical factors, both baseline and post-baseline brain metastasis were associated with worse OS compared with no brain metastasis (HR = 3.26, 95% CI: 1.94–5.49, $p < 0.001$, and HR = 4.99, 95% CI: 2.98–8.35, $p < 0.001$, respectively, Table 2). The adjusted 5-year OS probability was highest for patients with no brain metastasis and lowest in patients who developed brain metastasis 1 year after the start of first-line therapy. Estimates for 5-year survival probabilities were numerically lower for patients who received chemotherapy alone in the first-line setting compared with those who received a targeted therapy-containing regimen, regardless of the presence or timing of new brain metastasis (Supplementary Fig. 2).

Discussion

This study sought to identify factors associated with long-term (≥5-y) survival in a large multicenter cohort of patients treated before the osimertinib era, focusing on the impact of brain metastasis—both at baseline and on-treatment—on OS. In this cohort of patients diagnosed with EGFRm mNSCLC before 2015, greater than or

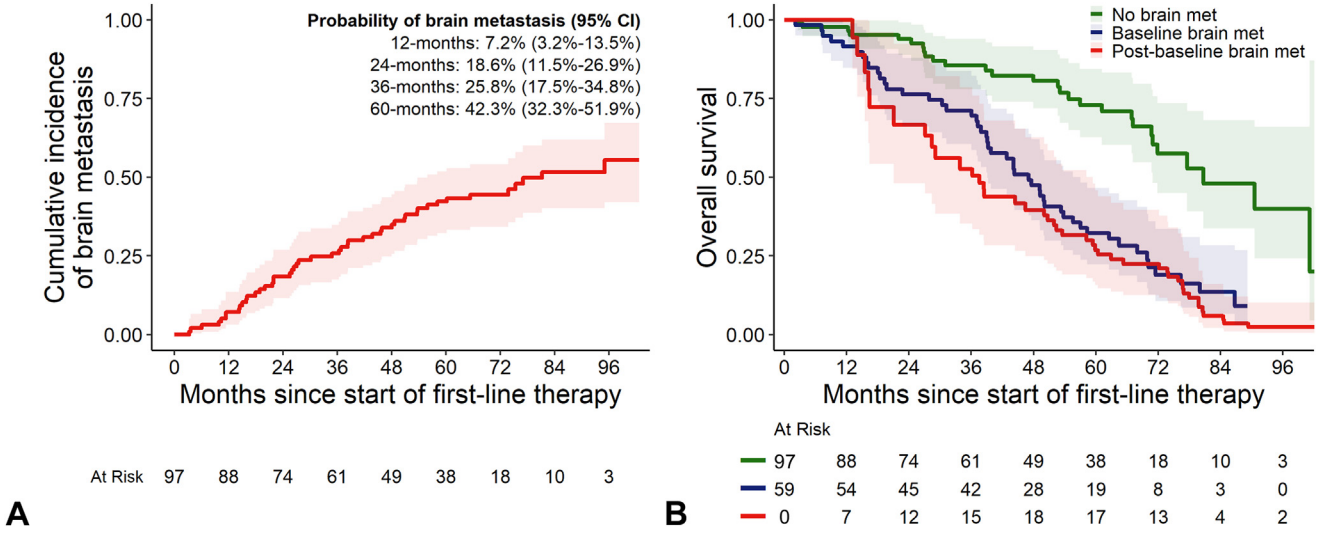

Figure 4. Brain metastases over time. (*A*) Cumulative incidence of brain metastasis over time in patients with baseline imaging and no baseline brain metastasis (n = 97). (*B*) Extended Kaplan-Meier curves of overall survival by time-dependent brain metastasis status. Patients with no baseline brain metastasis who subsequently developed a brain metastasis during follow-up move across risk sets (i.e., from no baseline brain metastasis to post-baseline brain metastasis) at the time of brain metastasis detection.

Table 2. Adjusted HRs for Death Associated With Baseline Brain Metastasis and Post-Baseline Development of Brain Metastasis (Modeled as a Time-Varying Covariate)

Time-Dependent Brain Met Development	Adjusted HR (95% CI)	*p* Value
No brain metastasis	Ref	-
Baseline brain metastasis	3.26 (1.94-5.49)	<0.001
Post-baseline brain metastasis	4.99 (2.98-8.35)	<0.001

Note: Among patients with brain imaging within 365 days before or 60 days after the start of first-line therapy (n = 156). HRs adjusted for age, sex, race, smoking status, baseline sensitizing mutation, year and type of first-line treatment, and baseline liver metastasis.
CI, confidence interval; HR, hazard ratio; met, metastasis; ref, reference.

equal to 5-year survivors were more likely to be nonsmokers and not have baseline brain metastasis. We also found a marked detrimental impact of brain metastases that developed early on treatment. Though baseline brain metastasis may be a marker of more aggressive disease biology in general, it is notable that baseline liver metastasis was associated with worse OS but not lower odds of survival at 5 years, whereas brain metastasis was more strongly associated with lower odds of survival at 5 years. This suggests that brain metastasis may represent an independent risk factor for death before 5 years that is separate from general disease aggressiveness. Both patients with baseline brain metastasis and even more prominently those who developed brain metastasis while on treatment had a lower probability of survival at 5 years (Supplementary Fig. 2). This is not surprising, as on-treatment development of brain metastases implies some degree of treatment failure even in this pre-osimertinib cohort, because earlier generation TKIs do have some central nervous system activity.

In our cohort, receipt of first-line chemotherapy was not associated with worse survival compared with first-line targeted therapy, but 5-year–adjusted survival estimates stratified by timing of brain metastasis development did favor first-line targeted therapy. Formal testing for the interaction of first-line therapy and presence or timing of new brain metastasis was not pursued due to sample size limitations. Prior studies of earlier generation EGFR TKIs have also failed to reveal survival benefit of first-line TKI,[20] with one large Japanese cohort actually revealing higher 5-year survival in patients treated with first-line chemotherapy compared with first-line EGFR TKI.[21] This is a clear contrast to prospective trial data revealing survival advantage with first-line osimertinib,[10] although studies comparing earlier generation EGFR TKIs to chemotherapy also failed to reveal an OS advantage.[31] As in these trials, high rates of crossover to later-line osimertinib, which occurred in 56.5% of patients treated with first-line chemotherapy and 66.0% of patients treated with first-line EGFR TKI, likely contributed to the absence of survival difference in our cohort.[32] Nevertheless, this also suggests that there may be a subset of patients who have excellent survival with sequencing of less potent treatments and may not need upfront treatment intensification.

Among patients with NGS testing at baseline, we did not find an association between comutation burden and greater than or equal to 5-year survival. In addition, baseline comutation with pathogenic *TP53* or *PIK3CA* alterations was not associated with greater than or equal to 5-year survival. Several studies have investigated the prognostic and predictive role of *TP53* in *EGFR*m NSCLC and have mostly found that it is associated with poor response to TKI and worse survival.[33–36] These studies have varied on their categorization of TP53 alteration (pathogenic, exon location, etc.) and are generally much larger than our sample size with NGS testing. Nevertheless, our findings emphasize the need for better characterization of the predictive potential of *TP53* mutations including mutational subtypes, particularly if this factor will be used to decide whether to intensify first-line therapy.

There are important limitations of this retrospective study. Notably, the apparent protective effect of diagnosis in early years likely reflects ascertainment bias wherein patients diagnosed in earlier years who had poor survival were less likely to be captured in the data set. A bias in testing patterns in earlier years, wherein nonsmoking East Asian females with better prognoses were tested for EGFR mutations more often, may have also contributed to this early year protective effect. Exclusion of patients with unknown vital status at year 5 was necessary to accurately distinguish greater than or equal to 5-year versus less than 5-year survivors in our primary analysis but likely contributed to the long observed median OS in our cohort (including a higher than previously reported[20,21] proportion of greater than or equal to 5-y survivors). We undertook a sensitivity analysis to address possible selection bias introduced by this exclusion and revealed that results were similar (Supplementary Table 5). Cumulative incidence of brain metastases was subject to heterogeneous real-world central nervous system monitoring practices; thus, we restricted our risk set to those with negative brain metastases at baseline. Finally, because osimertinib is now standard first-line therapy for patients with EGFRm NSCLC, generalizability of these findings to contemporary treatment is unclear. Nevertheless, these

findings add to a body of evidence suggesting that there are clinical factors that predict less aggressive disease biology and favorable prognosis regardless of treatment strategy, which may help to identify patients who may not need maximally intensive upfront therapy.

In this multicenter study of 260 patients with EGFRm mNSCLC treated in the pre-osimertinib era, never-smoking status and absence of brain metastases were associated with survival beyond 5 years, whereas previously reported factors including age, sex, comutations, and type of first-line therapy were not associated with long-term survival. These findings help to define a subset of patients with excellent survival outcomes even in the absence of maximally potent upfront therapy. As the first-line treatment landscape for EGFRm mNSCLC continues to evolve with novel agents and combination strategies, these data may help to inform personalized treatment selection and tailor first-line treatment strategies to optimize survival and toxicity.

CRediT Authorship Contribution Statement

William Tompkins: Conceptualization, Investigation, Data curation, Writing, Project administration.

Connor Grady: Methodology, Software, Data curation, Validation, Formal analysis, Investigation, Project administration.

Wei-Ting Hwang: Methodology, Software, Formal analysis.

Krishna Chandrasekhara: Investigation, Data curation.

Caroline McCoach: Supervision, Data curation, Writing—reviewing and editing.

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D. Ross Camidge: Conceptualization, Supervision, Data curation, Writing—reviewing and editing.

Melina Marmarelis: Conceptualization, Methodology, Investigation, Writing—original draft, Data curation, Writing—reviewing and editing, Supervision, Project administration.

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Disclosure

Dr. McCoach reports working as an employee at Genentech. Dr. G. Liu reports receiving institutional grants from NCI, CIHR, CCSRI, AstraZeneca, Takeda, Boehringer Ingelheim, AMGEN, EMD Serono, Pfizer, and Bayer; receiving personal honoraria from AstraZeneca, Pfizer, EMD Serono, and Takeda; and participating on the Data Safety Monitoring Board/Advisory Board for AstraZeneca, Pfizer, EMD Serono, Merck, AbbVie, Jazz, Takeda, Anheart, Roche, Bristol-Myers Squibb, Novartis, and Lilly. Dr. Nieva reports receiving institutional grants from Genentech and Merck; receiving consulting fees from ANP Technologies, Aadi Biosciences, AstraZeneca, BioAtla, G1 Therapeutics, Genentech, Mindmed, Naveris, and Sanofi; receiving travel support from AstraZeneca; having a patent planned with Cansera; participating on the Data Safety Monitoring Board/Advisory Board for Kalivir; and having stock in Amgen, Novartis, Johnson & Johnson, and Cansera. Dr. Marrone reports receiving grants from Mirati Therapeutics and Bristol-Myers

Squibb; receiving consulting fees from Daiichi Sankyo, Regeneron, Janssen, Mirati, Amgen, and AstraZeneca; receiving honoraria from Merck, Regeneron, Bristol-Myers Squibb, and AstraZeneca; and participating on the Data Safety Monitoring Board/Advisory Board for Puma. Dr. Lam reports receiving grants from Bristol-Myers Squibb, Merck, SeaGen, and AstraZeneca; receiving consulting fees from SeaGen, Bristol-Myers Squibb, AstraZeneca, Guardant Health, Takeda, and Anheart Therapeutics; and participating on the Data Safety Monitoring Board/Advisory Board for Iovance Therapeutics. Dr. Velcheti reports receiving consulting fees from Bristol-Myers Squibb, Merck, OnCOC4, AstraZeneca, Roche, Novocure, Takeda, Taiho, and Regeneron. Dr. S. Liu reports receiving institutional grants from AbbVie, Alkermes, AstraZeneca, Elevation Oncology, Ellipses, Genentech, Gilead, Merck, Merus, Nuvalent, OSE Immunotherapeutics, Puma, RAPT, and Turning Point Therapeutics; receiving consulting fees from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Catalyst, Daiichi Sankyo, Elevation Oncology, Genentech/Roche, Gilead, Guardant Health, Janssen, Jazz Pharmaceuticals, Merck, Merus, Mirati, Novartis, Pfizer, RAPT, Regeneron, Revolution Medicines, Sanofi, and Takeda; and participating on a Data Safety Monitoring Board/Advisory Board for Candel Therapeutics. Dr. Patil reports receiving research funding from EMD Serono, Janssen, and Gilead; receiving consulting fees from AstraZeneca, Biocept, Boehringer Ingelheim, Bristol-Myers Squibb, Bicara, Caris, Daiichi, Guardant Health, Guidepoint, EMD Serono, Janssen, Jazz Pharmaceuticals, Mirati Therapeutics, Natera, Pfizer, Sanofi, Regeneron, Roche/Genentech, and Takeda; and participating on the Data Safety Monitoring Board/Advisory Board for Elevation Oncology. Dr. Weiss reports receiving institutional grants from AstraZeneca, G1, Loxo/Lilly, Mirati, SDP, BI, and PDS; receiving consulting fees from AZD, EMD Serono, Genentech, G1, Jounce, AbbVie, Nanobiotix, Merck, Sanofi, Gilead, PDS, and AMGEN; participating on a Data Safety Monitoring Board or Advisory Board for Jounce and Beigene; having a leadership or fiduciary role for Cancergrace; and having stock/stock options for Nektar, Vesselon, Achilles, Nuvalent, Lyell, En Fuego, and Vertex. Dr. Dowell reports receiving consulting fees from Takeda, Catalyst, Beigene, and Janssen. Dr. Villaruz reports receiving consulting fees from Sanofi, Gilead, Johnson & Johnson, EMD Serono, Daiichi Sankyo, AstraZeneca, and Janssen. Dr. Cass reports receiving honoraria from OncLive, Medscape, and PharmacyTimes; and participating on the Data Safety Monitoring Board/Advisory Board for G1 Therapeutics, Takeda, and Regeneron. Dr. Iams reports receiving consulting fees from OncLive, Clinical Care Options, Chardan, Cello Health, and Curio Science; and participating on the Data Safety Monitoring Board/Advisory Board for Genentech, Mirati, Outcomes Insights, Jazz Pharmaceuticals, G1 Therapeutics, Takeda, AstraZeneca, Sanofi, Janssen, Amgen, Bristol Myers Squibb, and NovoCure. Dr. Aisner reports receiving consulting fees from Merus, Genentech, Bayer, AbbVie, and AstraZeneca; receiving support for attending meetings from AstraZeneca; and serving as Chair of Board for Genomics Organization for Academic Laboratories. Dr. Aggarwal reportsreceiving consulting fees from Genentech, Lilly, Merck, AstraZeneca, Daiichi Sankyo, Sanofi/Regeneron, Pfizer, Janssen, Boehringer-Ingelheim, Takeda, Arcus Biosciences, Mirati Therapeutics, Gilead Sciences, Novocure, AbbVie, and Jazz Pharmaceuticals; receiving speaking fees from AstraZeneca and Roche/Genentech; and receiving research funding from Merck Sharp & Dohme, AstraZeneca/MedImmune, Daiichi Sankyo, Loxo@Lilly, and Candel Therapeutics. Dr. Camidge reports receiving honoraria for consulting from AbbVie, Anheart, Beigene, Eli Lilly, Immunocore, Janssen, Prelude, Seattle Genetics, Valence, Appolomics, AstraZeneca/Daiichi, Dizal, EMD Serono, Elevation, Hengrui, Hummingbird, Medtronic, Mersana, Mirati, Nalo Therapeutics, Onkure, Regeneron, Roche, Sanofi, Takeda, Theseus, and Xcovery. Dr. Marmarelis reports receiving research funding from Eli Lilly, AstraZeneca, and Merck; receiving consulting fees from AstraZeneca, Novocure, Boehringer Ingelheim, Janssen, Takeda, Blueprint Pharmaceuticals, Bayer, Bristol Myers Squibb, Ikena, and Regeneron; receiving honoraria from Thermo Fisher; and having stock in Merck and Johnson & Johnson. Dr. Sun reports receiving honoraria from Bayer and participating on the Data Safety Monitoring Board/Advisory Board for Seagen, Sanofi Genzyme, and Regeneron. The remaining authors declare no conflict of interest.

Acknowledgments

Funding is provided by AstraZeneca and LUNGevity.

Alex Watts, MS, helped with this research study in the following capacities: Methodology, Software, Formal Analysis.

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.2024.100669].

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