Impact of EGFR mutation and ALK rearrangement on the outcomes of non–small cell lung cancer patients with brain metastasis

Suresh K. Balasubramanian, Mayur Sharma, Vyshak A. Venur, Philipp Schmitt, Rupesh Kotecha, Samuel T. Chao, John H. Suh, Lilyana Angelov, Alireza M. Mohammadi, Michael A. Vogelbaum, Gene H. Barnett, Xuefei Jia, Nathan A. Pennell, and Manmeet S. Ahluwalia

Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, Ohio (S.K.B., M.S., S.T.C., J.H.S., L.A., M.A.V., G.H.B., M.S.A.); Cleveland Clinic, Cleveland, Ohio (V.A.V.); Research Volunteer, Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, Ohio (P.S.); Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio (R.K., S.T.C., J.H.S., L.A., A.M.M., M.A.V., G.H.B., N.A.P., M.S.A.); Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland Clinic, Cleveland, Ohio (S.T.C., J.H.S.); Department of Neurosurgery, Neurological Institute, Cleveland Clinic, Cleveland, Ohio (L.A., A.M.M., M.A.V., G.H.B.); Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio (X.J.); Department of Hematology/Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio (N.A.P., M.S.A.)

Corresponding Author: Manmeet Singh Ahluwalia, M.D., Professor, Cleveland Clinic Lerner College of Medicine, Director, Brain Metastases Research Program. Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Taussig Cancer Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk CA5, Cleveland, OH 44195 (ahluwam@ccf.org).

Abstract

Background. The impact of activating alterations in non–small cell lung cancer (NSCLC) (epidermal growth factor receptor [*EGFR*] mutation/anaplastic lymphoma kinase [*ALK*] translocation) in prognosticating patients with brain metastasis (BM) is not well defined. This study was sought to identify this impact in NSCLC patients with BM accounting for the known validated variables.

Methods. Among 1078 NSCLC-BM patients diagnosed/treated between January 1, 2000 and December 31, 2015, three hundred and forty-eight with known *EGFR*/*ALK* status were analyzed. Overall survival (OS) and intracranial progression-free survival (PFS) were measured from the time of BM.

Results. Ninety-one patients had either *ALK* (*n* = 23) alterations or *EGFR* (*n* = 68) mutation and 257 were wild type (WT; negative actionable mutations/alterations). Median age of *EGFR*/*ALK*+ NSCLC BM patients was 60 years (range 29.8–82.6 y) and ~50% (*n* = 44) had Karnofsky performance status (KPS) score >80. Median number of BM was 2 (1 to ≥99). The median OS for the ALK/*EGFR*+ NSCLC BM was 19.9 versus 10.1 months for the WT (*P* = 0.028). The number of BM in the *EGFR*/*ALK*+ group did not impact OS (BM = 1 with 21.1 months vs 2–3 with 19.1 months and >3 with 23.7 months, *P* = 0.74), whereas fewer BM in the WT cohort had significantly better OS (BM = 1 with 13.8 mo, 2–3 with 11.0 mo and >3 with 8.1 mo; *P* = 0.006) with the adjustment of age, KPS, symptoms from BM and synchronicity.

Conclusions. Number of BM does not impact outcomes in the EGFR/*ALK*+ NSCLC patients, implying that targeted therapy along with surgery and/or radiation may improve OS irrespective of the number of BM. Number of BM, extracranial metastasis (ECM), and KPS independently affected OS/PFS in WT NSCLC BM, which was consistent with the known literature.

Key Points

1. Number of brain metastases does not impact outcomes in EGFR/*ALK*+ NSCLC patients.

2. Known BM prognostic variables affected OS/PFS in wild-type NSCLC BM only.

Importance of the Study

The disease-specific graded prognostic assessment (DS-GPA) tool for NSCLC BM includes age, KPS, ECM, and number of BM. There is a paucity of literature in addressing the role of activating mutation/rearrangement status in NSCLC BM. Our study found significant prognostic differences between EGFR/ALK+ and WT patient cohorts with respect to these prognostic variables. The number of BM affected OS/PFS only in the WT cohort but had no impact in the EGFR and ALK positive patients. Recently, Sperduto et al revised their original DS-GPA scale to include genetic and molecular data, called Lung-molGPA, and interestingly, number of BM is still a prognostic factor in this patient cohort; however, no statistically significant correlation is demonstrated in their study. Results of our study provide insight into this interaction between the number of BM and genetic alterations and its overall impact on survival.

Brain metastasis (BM) is a serious neurological sequela of systemic malignancies that affects quality of life and overall survival (OS) in this patient population. BM is the most common malignant brain tumor and the incidence rate varies from 8.3 to 14.3 per 100000 based on population registry analysis.[1,2] More than 50% of brain metastases occur in lung cancer patients,[3] followed by those with diagnoses of breast cancer, melanoma, renal cancer, colorectal cancer, and cancer of unknown primary.[4,5] BM is associated with a median survival that ranges from 3 to 48 months based on the type of cancer, known subtype, and the treatment modality.[6–9] Given this wide variation in median survival among patients with BM, various models have been postulated to help predict prognosis in these patients.[10] Recursive partitioning analysis, one of the early prognostic indices, did not consider the site of primary malignancy causing BM as a factor affecting survival in patients with BM.[11] To address this limitation, a new disease-specific graded prognostic assessment (DS-GPA) tool was suggested that categorized patients based on primary malignancies.[12] For lung cancer patients with brain metastases, age, performance status, extracranial metastases (ECM), and number of brain metastases were reported as significant factors that impact OS. According to this DS-GPA scale, patients with multiple BM (≥4) have inferior outcomes compared with single or limited BM (≤3) in patients with non–small cell lung cancer (NSCLC).[6] More recently, this scale has been updated to include molecular markers in patients with NSCLC.[13] However, there is a paucity of studies evaluating the role of driver mutations/alterations in NSCLC patients with BM.[13]

The incidence of tumor associated epidermal growth factor receptor (_EGFR_) mutation and anaplastic lymphoma kinase (_ALK_) rearrangement varies from 10% (in the USA) to 35% (in East Asia) and 5–7%, respectively, in patients with NSCLC.[14–18] The aim of our study was to evaluate the prognostic significance of different patient, tumor, and treatment characteristics in NSCLC patients with BM, for whom molecular profiling data were available. We also evaluated the impact of these alterations (_EGFR_ mutation and _ALK_ rearrangement) on outcomes of NSCLC BM patients, especially with respect to variables that were prognostic in the DS-GPA scale, such as number of BM.

Materials and Methods

Clinical Data and Treatment Characteristics

Following approval of the institutional review board at the Cleveland Clinic, patients with NSCLC BM and known mutational/rearrangement status treated between 2000 and 2015 were included in this retrospective study. Demographics, clinical characteristics (Karnofsky performance status [KPS], symptoms), tumor characteristics (presence/absence of ECM, number of BM, and synchronicity of BM with primary tumor), and treatment characteristics (radiation techniques, surgery, chemotherapy, targeted therapy, and temporal relationship to the local treatment for BM) were collected in an online database (REDCap). Patients with negative _EGFR_ mutation and _ALK_ rearrangement were labeled as wild type (WT) for the analysis.

Stereotactic radiosurgery (SRS) was delivered through Gamma Knife (Elekta Instruments). All patients underwent brain MRI (T1-weighted with gadolinium contrast) for evaluating the number of metastases and planning for SRS. Since 2007, the Gamma Knife model has been upgraded from Model B to Model C to Model 4C and Perfexion. The dose prescribed to the peripheral margin was typically chosen based on the maximum dimension for each lesion according to the Radiation Therapy Oncology Group 90-05 protocol.[19] Whole brain radiation therapy (WBRT) was usually given at 30–37.5 Gy in 10–15 fractions. Erlotinib, gefitinib, and afatinib were the small-molecule tyrosine kinase inhibitors (TKIs) used in treating patients with _EGFR_ mutation, whereas crizotinib and ceritinib were the TKIs used in patients with _ALK_ rearrangement.

Mutational Analysis

EGFR mutation was tested using real-time PCR, and _ALK_ rearrangement was tested using interphase fluorescence in situ hybridization (FISH). For _EGFR_ mutation, real-time PCR was used to evaluate specific mutations, deletions, and insertions in the tyrosine kinase domain of the _EGFR_ gene. Eight reactions using 30 primers were used to target specific regions of exons 18–21 as well as WT sequence. FISH for the _ALK_ gene (2p23) involving a dual color, break-apart probe—consisting of a mixture of 2 FISH DNA probes hybridizing to the centromeric and telomeric sides on the _ALK_ (2p23) gene (Abbott Molecular)—was used to detect the presence of a translocation involving _ALK_ (2p23).

Outcome Variables and Endpoints

The primary outcome was OS, while the secondary outcome was progression-free survival (PFS). For the purpose of this study, intracranial progression-free survival was referred to as

PFS. OS and PFS were calculated from the time of first brain metastasis. Radiographic data, including CT and MRI scans, were reviewed to determine intracranial patterns of failure. Local failures were diagnosed with a range of modalities, including serial imaging, MR perfusion to evaluate cerebral blood volume within the treated lesion, 2-fluoro-2-deoxy-D-glucose avidity via PET, and surgical pathology, as determined by the treating physician. Recurrence and response after treatment were assessed by the treating physicians using established criteria.[20] In case of disagreement or if imaging was not clear, serial imaging follow-up was ordered or multidisciplinary tumor board review was used to identify local failures. Similarly, radiation necrosis was diagnosed using an institutional algorithm.[21] Date of death was identified using electronic health records or an online database (Social Security Death Index). The date of last follow-up was considered for survival analysis if date of death was not available.

Statistical Analysis

Categorical data were analyzed as frequency counts and percentages, whereas measured data were evaluated using medians and ranges. Time-to-event data were summarized using Kaplan–Meier estimates and analyzed using log-rank tests and Cox proportional hazards models. Univariable and multivariable analyses were performed for variables such as clinical factors and mutational status of patients. A two-tailed *P*-value of <0.05 was considered significant. All analyses were performed using SAS v9.4.

Results

Patient Demographics

A total of 1078 patients treated at our institution from 2000 to 2015 for NSCLC BM were reviewed. Of these, 348 patients with known molecular mutational/rearrangement status were identified and included in our analysis. Patient characteristics are listed in Table 1. Among 348 patients, 91 (26%) were positive for a mutation/rearrangement (68 [75%] had an activating mutation in the EGFR and 23 [25%] had *ALK* rearrangement) and 257 (74%) were WT (no known identifiable actionable mutations). There were more smokers in the WT cohort (*P* < 0.001), whereas there was an equal distribution of smokers and nonsmokers in the *EGFR*/*ALK*+ cohort. Fifty percent (44/91) in the *EGFR*/*ALK*+ cohort had KPS > 80. Median number of BM was 2 (1–99) and the majority of patients had a single metastasis in both groups (37% in the EGFR/*ALK*+ and 46% in the WT cohort). There was a significant difference in terms of presence of ECM (71% of *EGFR*/*ALK*+ cohort vs 59% of WT, *P* = 0.04), symptoms from BM (63% of *EGFR*/*ALK*+ cohort vs 72% of WT, *P* = 0.36), and synchronicity in relation to the diagnosis of primary tumor between the 2 groups (57% of *EGFR*/*ALK*+ cohort vs 62% of WT, *P* < 0.001).

Treatment Characteristics

Thirty-three percent of patients in the EGFR/ALK+ group and 39% of patients in the WT cohort were treated with SRS ± surgery as an upfront treatment. Whereas WBRT ± surgery was used as an upfront treatment in 43% of patients in the EGFR/ALK+ group and 50% of patients in the WT cohort. Fifteen patients (17%) in the *EGFR*/*ALK*+ cohort received a combination of SRS plus WBRT compared with 6% in the WT cohort (*P* < 0.005) (Table 1). Thirty-three percent of patients in the *EGFR*/*ALK*+ cohort received targeted treatment after the diagnosis of brain metastases as first-line therapy compared with none in the WT group (Table 1). Seventeen percent of patients received some form of targeted therapy before the diagnosis of BM in the *EGFR*/*ALK*+ groups. In the *EGFR*+ group alone, most patients (79%) received targeted therapy in the first-line setting, whereas only one fifth (21%) received it at disease progression. In contrast, half of the patients (50%) in the ALK+ group received targeted therapy in the first-line setting and the remainder at disease progression. There were 6 patients in the *EGFR*+ group who received targeted therapy before the diagnosis of BM and this therapy was continued after diagnosis of BM along with local treatment for BM. Four patients in the *ALK*+ group (17%) and one in the *EGFR*+ group (1%) did not receive any targeted therapy, due to either rapid progression of systemic disease or patient's choice of palliative care (Table 1).

Progression-Free Survival and Overall Survival

On univariate analysis, patients with poor performance status and those with presence of ECM had worse PFS in the *EGFR*/*ALK*+ group and WT group. However, the number of BM (1 BM vs 2–3 BM vs >3 BM) had no impact on PFS in the *EGFR*/*ALK*+ cohort (*P* = 0.78), whereas it was a statistically significant prognostic factor in the WT group (*P* = 0.014; Supplementary Table 1, Fig. 1A, B. The univariate analysis on PFS suggested that patients with a higher number of brain metastases in the WT cohort had a higher risk of disease progression.

The median OS for the ALK and *EGFR* positive NSCLC BM was 19.9 months compared with 10.1 months for the WT cohort (*P* = 0.028). When assessed independently, the median OS for the EGFR+ group was 19.1 months compared with 48.0 months in the ALK+ group (*P* = 0.13). The median OS for the ALK/*EGFR* + group of patients who received targeted therapy after the diagnosis of BM had significantly better OS and PFS compared with the patients who received targeted therapy prior to the diagnosis of BM (hazard ratio [HR], 0.39 [0.22–0.68], *P* = 0.0009, and HR 0.52 [0.30–0.89], *P* = 0.017) respectively). The presence of ECM negatively impacted OS in the WT but not in the *EGFR*/*ALK*+ cohort (Supplementary Table 1A and Fig. 1C, D). ECM was highly correlated with number of BM (*P* = 0.027) in the WT cohort but not in the *EGFR*/*ALK*+ group (*P* = 0.64) (Supplementary Table 1B). Based on the fact that ECM may be a cofounding factor for BM in the WT NSCLC, we designed 2 multivariate analysis models (one excluding ECM and one including ECM) to elucidate a prognostic model for those patients who present with BM alone and for those who present with both BM and ECM.

- **PFS and OS excluding ECM.** On multivariate analysis, the number of brain metastases (1 BM vs 2–3 BM vs >3 BM) had no statistically significant impact on PFS

**Table 1** Patient and treatment characteristics

Clinical Factors	*EGFR*/*ALK*+ NSCLC BM Cohort (*n* = 91)	Wild Type Cohort (*n* = 257)	*P*
Age, y, median (range)	60.0 (29.8,82.6)	60.8 (37.3,92.8)	0.059
Sex *n* (%)			0.57
Male	38 (42)	117 (45)	
Female	53 (58)	142 (55)	
Smoking status *n* (%)			<0.001
Smokers	47 (52)	233 (91)	
Nonsmokers	44 (48)	24 (9)	
KPS *n* (%)			0.90
<70	9 (10)	28 (12)	
70–80	35 (40)	109 (46)	
>80	44 (50)	99 (42)	
No. of brain metastases[#] median (range) and *n* (%)	2.0 (1.00, ≥99[$])	2.0 (1.00, ≥99[$])	0.23
1	34 (37)	118 (46)	
2–3	24 (27)	70 (28)	
>3	33 (36)	66 (26)	
Extracranial metastases (ECM) *n* (%)			0.04
No	26 (29)	104 (41)	
Yes	65 (71)	152 (59)	
Clinical symptoms *n* (%)			0.036
Asymptomatic	33 (37)	68 (28)	
Symptomatic	56 (63)	178 (72)	
Synchronous *n* (%)			<0.001
No	39 (43)	97 (38)	
Yes	52 (57)	160 (62)	
First-line treatment *n* (%)			
SRS ± surgery	30 (33)	98 (39)	0.48
WBRT ± surgery	39 (43)	125 (50)	0.40
WBRT + SRS	15 (17)	16 (5)	0.005
Other	7(7)	18(6)	
TKI, target therapy *n* (%)			0.0001
Yes	45 (33)	0 (0.0)	
No	91(67)	257(100)	
Timing of targeted therapy *n* (%)			
	***ALK*+ (*N* = 23)**	***EGFR*+ (*N* = 68)**	
Before BM diagnosis	4 (17)	11 (17)	
After BM diagnosis	15 (65)	48 (73)	
as first line	7 (47)	38 (79)	
at progression	8 (53)	10 (21)	
Both	0 (0.0)	6 (9)	
Never	4 (17)	1 (1)	

[#]Evaluated by MRI brain with gadolinium contrast.
[$]≥99 denote at least 99 brain metastases, which can be physically counted on MRI brain with contrast.

or OS in the *EGFR*/*ALK*+ cohort, whereas it did in the WT group (Table 2, Fig. 2A–D). In the WT cohort, patients with single BM had significantly longer OS and PFS compared with those with 2–3 or >3 BM. However, there was no significant difference in OS/PFS in patients with 2–3 BM or >3 BM (Table 2, Fig. 2B and D, and Supplementary Table 2). Also, the estimated median survival in patients with a single BM in the WT cohort
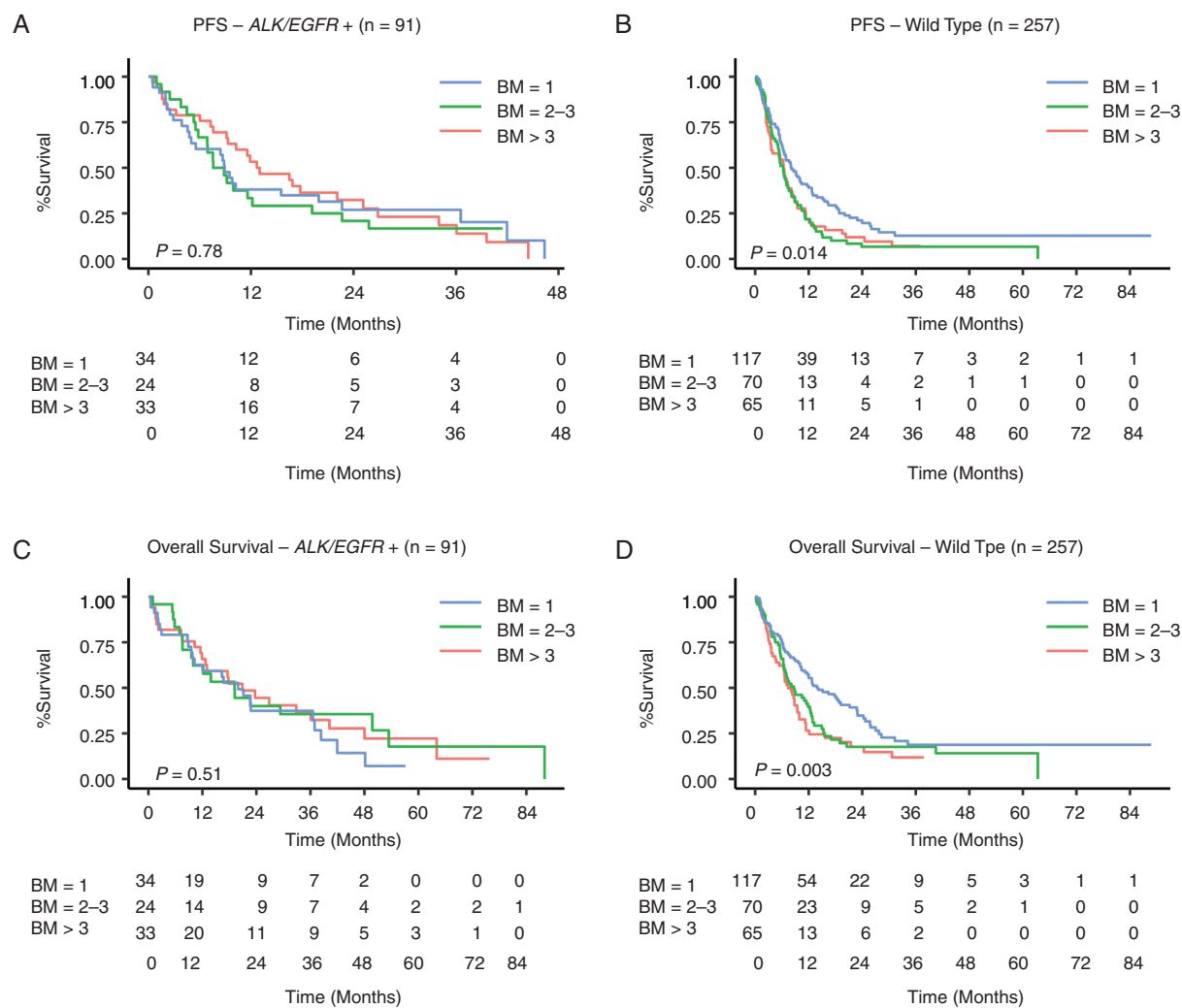
Fig. 1 Univariate analysis showing (A, B) PFS and (C, D) OS in the *EGFR*/*ALK*+ and WT cohorts, respectively.

(Supplementary Table 2) was significantly higher than that of patients with >3 brain metastases (OS: 13.8 mo vs 8.1 mo, respectively, $P = 0.007$); however, no significant difference in OS was observed between 2–3 and >3 brain metastases (11 mo vs 8.1 mo, $P = 0.38$).

- **PFS and OS including ECM.** On multivariate analysis, the number of BM did not impact PFS/OS in patients in the *EGFR*/*ALK*+ cohort but did marginally in the WT group ($P = 0.08$ and 0.06, respectively) (Tables 2 & 3 and Fig. 3A–D). After including ECM in the analysis, the number of BM (single, 2–3, or >3) had no significant impact on PFS/OS in patients in either the *EGFR*/*ALK*+ or WT cohorts. However, there was a trend toward significance ($P = 0.09$) in patients in the WT group with single BM and improved estimated median OS (Supplementary Table 3) which was in contrast to the *EGFR*/*ALK*+ group that retained insignificance regardless of presence or absence of ECM in the model. In the WT cohort, the previously significant impact of number of BM on OS/PFS became less significant after including

ECM in the model. This was attributed to the statistically significant association between the number of BM and presence of ECM in the WT but not in the *EGFR*/*ALK*+ cohort ($P = 0.027$ vs 0.64).

Discussion

BM occurs in up to 40% of patients with systemic cancers based on clinical and autopsy studies.[4,9,22–24] The management of BM has changed dramatically in the past few years and the majority of patients are being treated with SRS as part of multimodality.[7,25–31] The blanket approach of treating >4 BM with WBRT is less common these days. Yamamoto et al[32] reported that SRS without WBRT is suitable for patients with up to 10 BM, and OS in these patients was not different than in those with 2–4 BM. With improvement in radiation techniques along with availability of newer chemotherapeutic agents/targeted therapies that can reach

better concentration in cerebrospinal fluid,[33] it is likely that a higher number of BM would be amenable to treatment.[34] The number of BM is a "moving target" in terms of management strategies and is a matter of contentious debate. In a classical study of 4259 patients,[6] age, KPS, presence of ECM, and number of BM were identified as prognostic markers in patients with NSCLC and small cell lung cancer. However, there is a paucity of literature addressing the activating mutation/rearrangement status of BM and outcomes in patients with NSCLC.[13,35–37]

The results of our study suggest significant prognostic differences between *EGFR*/*ALK*+ and WT patient cohorts with NSCLC and BM. We found that the number of BM affected OS and PFS only in the WT cohort and had no impact in patients with positive actionable activating molecular alterations (*EGFR* and *ALK* respectively). In the WT patient cohort, OS was affected by the presence of ECM and there was a strong correlation between the number of BM and presence of ECM. We also noted significant differences in OS in patients (WT cohort) with single versus 2–3/>3 BM compared with those with 2–3 BM versus >3 BM. We noted that the number of BM only tended to impact OS/PFS after excluding ECM in the model in patients with WT NSCLC BM. This finding can be attributed to the fact that the number of BM and the presence of ECM are correlated, thus reducing the significance of impact of number of BM on OS/PFS after including ECM in the analysis for the WT cohort.

Recently, Sperduto et al[13] revised their original DS-GPA scale to include genetic and molecular data, called Lung-molGPA. This revised scale was based on their earlier multi-institutional retrospective study of 1521 patients with known alteration status in 816 patients (54%).[13] They reported a median survival from first treatment of BM for the *EGFR*/*ALK* negative, *EGFR*+, *ALK*+, *KRAS*+, and unknown mutation status to be 14, 23 (*P* < 0.01), 45

(*P* < 0.001), 12 (*P* = 0.84), and 12 (*P* = 0.12) months, respectively.[13] Interestingly, they described that the number of BM was still a prognostic factor in this patient cohort; however, no statistically significant correlation was demonstrated in their study.[13] Results of our study provide insight into this interaction between the number of BM and genetic alterations and its overall impact on survival. Also, we tested the different DS-GPA variables among patients with positive actionable genetic alterations (*EGFR*/*ALK*) and without it (WT).

In this recently revised prognostic scale,[13] patients with *EGFR*/*ALK*+ lung adenocarcinoma were given higher scores and those with Lung-molGPA scores of 3.5 to 4.0 had a longer median survival (46.8 mo) compared with those with scores of 0–1.0 (6.9 mo), 1.5–2.5 (13.7 mo), and 2.5–3.5 (26.5 mo).[13] Concordantly, we have also identified activating mutational status (*ALK* rearrangement and *EGFR* mutation) as a possible positive prognostic indicator for NSCLC BM (median OS 19.9 mo vs 10.1 months for *EGFR*/*ALK*+ vs WT BM, respectively [*P* = 0.028]). This finding is similar to a median OS of 25.7 months in patients with *EGFR* positive BM compared with 3.8 months in patients with WT NSCLC BM.[37] Interestingly, this study reported increased incidence of synchronous BM in patients with mutation positive NSCLC compared with those with WT. Also, the difference in OS was seen only in patients with synchronous BM compared with those with metachronous BM (14.6 mo *EGFR* MT vs 2.5 mo *EGFR* WT; *P* = 0.2). However, we noted increased incidence of synchronous BM in patients with WT BM compared with the *EGFR*/*ALK*+ group (62% vs 57%, respectively; *P* < 0.05), though there was no impact of this variable on OS/PFS in either of these cohorts. This difference can be attributed to the epidemiological variation in the frequency of mutations/rearrangements (Korean population vs USA population) and smaller sample size in the previous study.[37]

Table 2 Multivariable analysis excluding ECM

PFS	*EGFR*/*ALK*+ NSCLC HR (95% CI)	*P*	Wild Type HR (95% CI)	*P*
Age (<50 vs 50–60 vs >60)	0.83 (0.60, 1.14)	0.24	0.91 (0.73, 1.14)	0.42
KPS (<70 vs 70–80 vs >80)	0.65 (0.43, 1.00)	0.05	0.73 (0.59, 0.92)	0.006
Brain mets (1 vs 2–3 vs >3)	0.92 (0.69, 1.22)	0.56	1.22 (1.02, 1.46)	0.029
Symptomatic	1.11 (0.64, 1.92)	0.71	1.05 (0.74, 1.49)	0.80
Synchronous	0.75 (0.45, 1.24)	0.26	0.79 (0.58, 1.07)	0.12
OS				
Age (<50 vs 50–60 vs >60)	1.28 (0.88, 1.86)	0.20	1.05 (0.84, 1.33)	0.65
KPS (<70 vs 70–80 vs >80)	0.35 (0.22, 0.55)	<0.001	0.70 (0.56, 0.89)	0.004
Brain mets (1 vs 2–3 vs >3)	0.95 (0.69, 1.31)	0.74	1.31 (1.08, 1.59)	0.006
Symptomatic	0.87 (0.48, 1.60)	0.66	0.97 (0.67, 1.40)	0.85
Synchronous	0.69 (0.40, 1.19)	0.18	0.83 (0.60, 1.15)	0.25
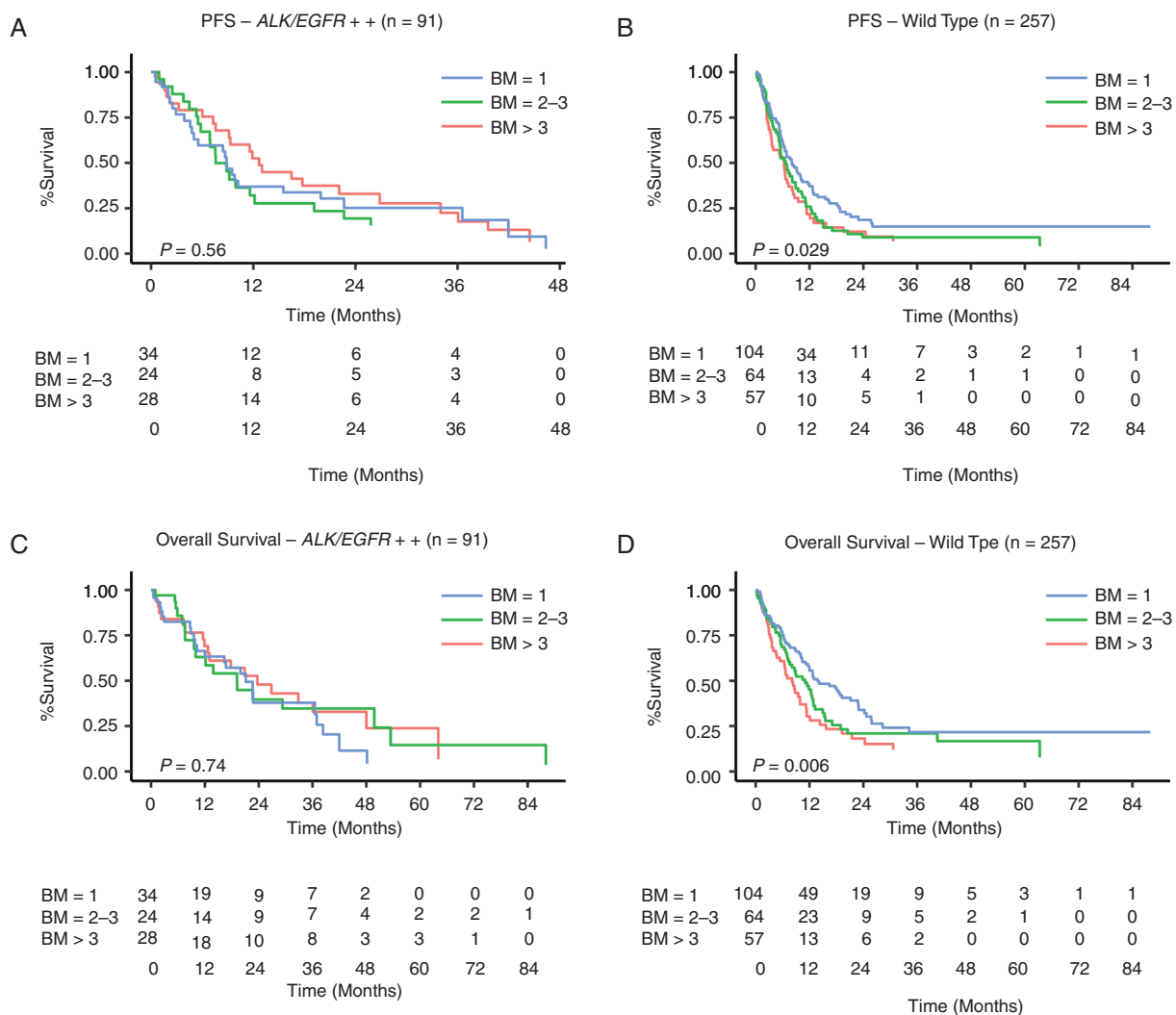
Fig. 2 Multivariate analysis showing (A, B) PFS and (C, D) OS in the *EGFR*/*ALK*+ and WT cohorts, respectively, excluding patients with ECM.

Another study reported improved OS in patients with mutation-positive NSCLC BM compared with those with WT BM (19.9 mo vs 7.1 mo; *P* < .001) in early onset BM.[35] However, no such difference was noted in those with late onset (≥6 mo) BM after diagnosis.[35] Eichler et al[36] identified *EGFR* mutational status as an independent predictor of improved survival in NSCLC patients, with a median PFS of 12.7 months and median OS of 14.5 months.

Yuan et al[35] reported single late onset BM and chemotherapy as positive predictors of survival in patients with WT NSCLC BM and systemic treatment only as a positive predictor in those with mutation-positive BM. In concordance, on multivariate analysis, we found that presence of ECM, KPS, and number of BM (tended toward significance) significantly affected OS/PFS in the WT cohort, whereas only KPS correlated with OS/PFS in the *EGFR*/*ALK*+ cohort. In our study, number of BMs had no correlation with either OS or PFS in the *EGFR*/*ALK*+ cohort (*P* = 0.51 and 0.78

respectively). However, number of BMs showed correlation with both OS and PFS in the WT cohort (*P* = 0.003 and 0.014 respectively). Our study demonstrated prognostic benefit of *EGFR*/*ALK*+ patients with NSCLC BM.

Implications for Revised GPA

Our study, as well as others,[13,38] has shown that mutational status has an impact on the outcome of patients with NSCLC BM. *EGFR*/*ALK*+ NSCLC BM represents a diverse patient population with different prognostic factors and favorable outcome. More importantly, our study shows that the number of BM does not impact OS in *EGFR* and *ALK* positive NSCLC compared with the WT NSCLC brain metastases. Number of BM, presence of ECM, and KPS were independent predictors of OS/PFS in patients with WT NSCLC BM as seen in other studies.
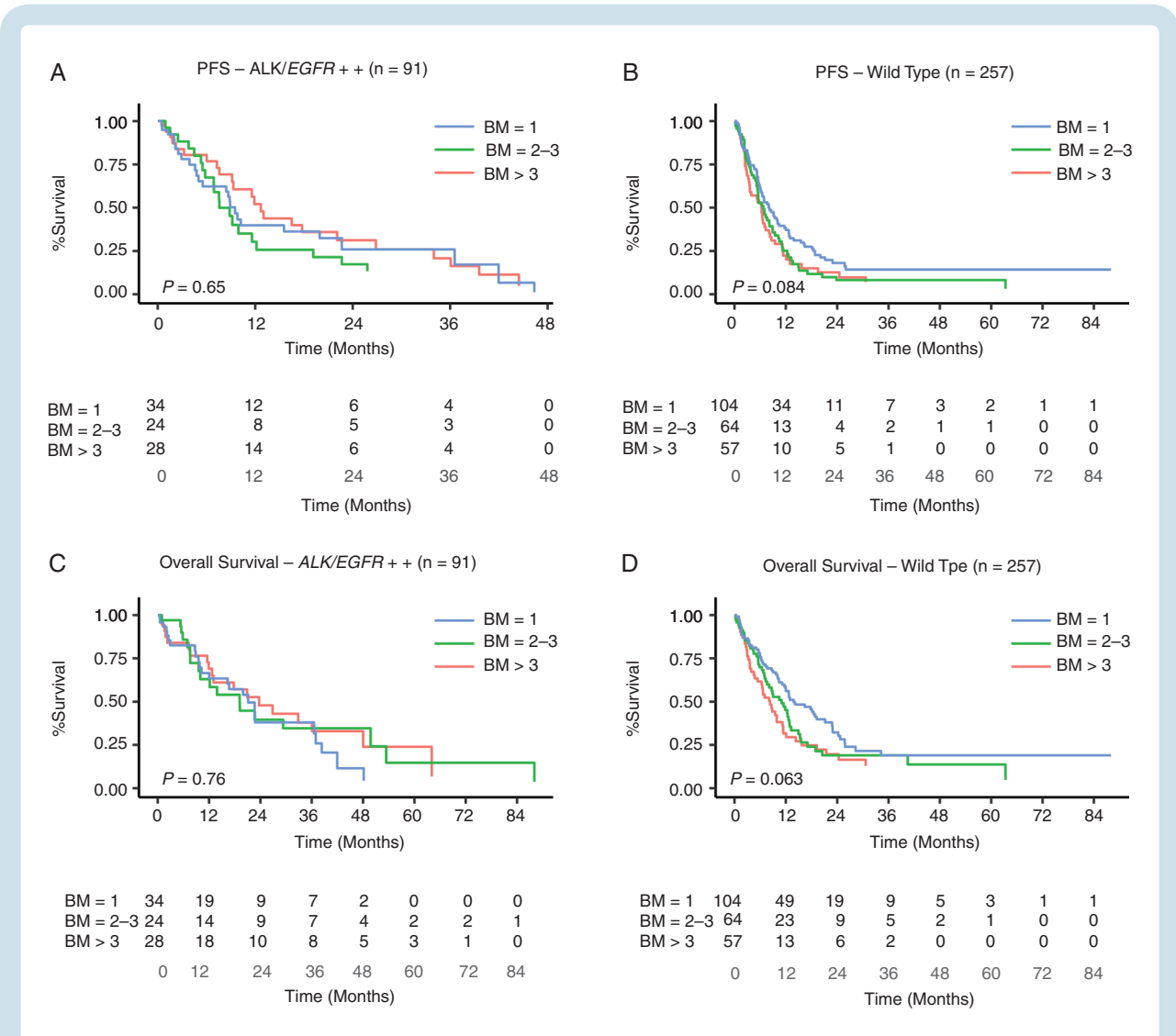
Fig. 3 Multivariate analysis showing (A, B) PFS and (C, D) OS in the EGFR/*ALK*+ and WT cohorts, respectively, including patients with ECM.

Implications for Clinical Management and Role of TKIs

Various studies have shown that patients with *EGFR*/*ALK*+ NSCLC BM treated with TKIs have improved disease control and survival.[38–40] Shaw et al[40] reported that patients with *ALK*+ NSCLC BM, if not treated with an *ALK* inhibitor, crizotinib, had survival similar to those with WT patients, thus demonstrating the importance of *ALK* inhibitors in these patients. Also, Johung et al[38] reported improved outcomes (OS: 49.5 mo and PFS: 11.5 mo) following a combination of radiation therapy (SRS/WBRT) and TKIs in patients with *ALK* rearranged NSCLC. With respect to the timing of targeted therapy, our results are consistent with recently published studies.[13,38,41] In our study, *EGFR*-mutant and *ALK*+ patients who received TKIs prior to diagnosis of BM had significantly worse outcomes compared with those who received TKIs after the diagnosis of BM, which can be attributed to the selection of TKI-resistant niche in the brain along with the possibility of an aggressive disease.

The effect of crizotinib on CNS disease is poorly understood.[42,43] Other TKI agents such as certinib[44] and alectinib[45] have been investigated in patients with crizotinib-resistant ALK+ tumors. Second-generation ALK inhibitors such as brigatinib have been shown to have improved CNS penetration with improved responses in patients with crizotinib treated NSCLC, with the highest intracranial PFS in patients treated with 180 mg once daily.[46] Availability of these second-generation ALK inhibitors made it possible to treat these patients with multiple BMs/ECMs and reduce the disease burden to the level that can be treated with stereotactic radiation, while keeping WBRT as a reserve in these patients.

Results of our study showed that patients with actionable mutations/alterations were likely to respond better to new-generation TKIs with good CSF penetration (second generation) irrespective of number of BMs/ECMs compared

Table 3   Multivariable analysis including ECM

PFS	*EGFR*/*ALK*+ NSCLC HR (95% CI)	*P*	Wild Type HR (95% CI)	*P*
Age (<50 vs **50–60** vs **>60)**	0.81 (0.59, 1.13)	0.21	0.92 (0.74, 1.15)	0.48
KPS (<70 vs **70–80** vs **>80)**	0.59 (0.38, 0.92)	0.02	0.72 (0.58, 0.90)	0.004
Brain mets (1 vs **2–3** vs **>3)**	0.93 (0.70, 1.25)	0.65	1.17 (0.98, 1.41)	0.084
Symptomatic	1.06 (0.60, 1.87)	0.84	1.13 (0.79, 1.61)	0.50
Synchronous	0.72 (0.43, 1.18)	0.19	0.78 (0.57, 1.06)	0.11
ECM (yes/no)	0.51 (0.30, 0.87)	0.014	1.41 (1.03, 1.94)	0.031
OS				
Age (<50 vs **50–60** vs **>60)**	1.28 (0.88, 1.88)	0.20	1.06 (0.84, 1.34)	0.62
KPS (<70 vs **70–80** vs **>80)**	0.35 (0.22, 0.55)	<0.001	0.69 (0.54, 0.87)	0.002
Brain mets (1 vs **2–3** vs **>3)**	0.95 (0.69, 1.31)	0.76	1.20 (0.99, 1.46)	0.063
Symptomatic	0.87 (0.48, 1.60)	0.66	1.09 (0.75, 1.59)	0.65
Synchronous	0.69 (0.40, 1.18)	0.18	0.80 (0.58, 1.11)	0.18
ECM (yes/no)	0.97 (0.54, 1.74)	0.91	1.95 (1.37, 2.77)	<0.001

with those with WT BMs. Therefore number of BMs had impact on prognosis in patients with WT BMs by increasing the burden of CNS disease with increasing number of BMs and dependence on radiation treatment only, till we have chemotherapeutic options available for this cohort of patients. Number of BM has traditionally been considered a bad prognostic factor and patients with a large number of BM were likely to be treated with WBRT, which has long-term deleterious effects; the results of our study challenge this practice in patients with actionable mutations/alterations.

Limitations

The potential limitations of our study include its single institutional retrospective design, non-homogeneous management strategies, lack of randomization, unknown *kras* mutational status, and variability in the extent of follow-up. Though it is known that patients with *ALK*+ NSCLC BM have a more favorable prognosis than those with *EGFR*+ NSCLC BM,[38] we grouped them together, since both of these alterations can be treated with targetable agents and have better prognosis than the wild type. Nevertheless, our results will provide a reference to prognosticate the outcomes based on the mutational status and number of BM in patients with NSCLC. We acknowledge that we have not compared our results with the Lung-molGPA scale as described by Sperduto et al,[13] which is based on number of BM (being a significant negative prognostic factor); however, this would be the focus of our future studies.

Conclusion

The number of BM does not impact OS in *EGFR*/*ALK*+ NSCLC, implying that targeted therapy along with surgery and/or radiation may improve OS regardless of the number of BM, whereas lack of activating actionable molecular alterations negates use of targeted treatment and would convey poor prognosis. Number of BM, presence of ECM, and KPS were independent predictors of OS/PFS in patients with wild type NSCLC BM.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

actionable mutations | ALK | EGFR | NSCLC | number of brain metastases | radiosurgery | targeted therapy | wild type

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