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Article

Title: Lung-molGPA in EGFR-mutated Adenocarcinoma: Prognostic Implications of Molecular Subtypes and Targeted Therapies

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Abstract: EGFR mutations are heterogenous but all carry the same weighting in the Lung-molGPA. The aim of this study was to elucidate the different prognostic implications of molecular subtypes and frontline TKIs in EGFR-mutated lung adenocarcinoma with synchronous brain metastases (BM) using the Lung-molGPA. Medical records were searched in hospital databases from 2011 to 2015. Patients with EGFR-mutated adenocarcinoma and brain metastases who received TKIs were included. The Kaplan-Meier method was used to estimate survival, and multivariate Cox proportional hazard models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). A total of 256 patients were included with a median overall survival (OS) of 17.2 months. In multivariate analysis of OS, only age (≥70 versus <70 years, HR:1.71, 95% CI:1.25-2.35, p<0.001), KPS (<70 versus ≥70, HR:1.71, 95% CI:1.26-2.31, p<0.001), and rare mutations (other versus exon 19 deletions, HR:1.78, 95% CI:1.04-3.05, p=0.037) remained statistically significant. In patients with a Lung-molGPA score ≤2.5, EGFR molecular subtypes had different median OS (exon 19 deletions versus Leu858Arg versus other, 18.8 vs 12.4 vs 12.1 months, p=0.021). In conclusion, different molecular subtypes treated with frontline TKIs have different prognostic implications in the Lung-molGPA. Further prospective studies are warranted to validate these findings.

Keywords: Lung-molGPA; exon 19 deletion; Leu858Arg; rare mutation; prognostic implication

1. Introduction

Brain metastases (BM) are common in patients with lung cancer, with rates of up to 30% at the first diagnosis, and results in shorter overall survival and increased morbidity [1]. The diagnosis-specific graded prognostic assessment (DS-GPA) tool is used to predict median survival. It is calculated using four prognostic factors including age, Karnofsky performance scale (KPS),

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extracranial metastases (ECM) and the number of BM, and the median survival of patients with lung cancer and BM according to the DS-GPA has been reported to range from 3.0 to 14.8 months [2]. Further, 50-60% of patients with EGFR-mutated lung adenocarcinoma develop BM, possibly due to longer survival, inferior CNS penetration of some EGFR-TKIs and/or actual predilection for BM. The Lung-molGPA index is an update of the DS-GPA that incorporates gene alteration data, and it has been shown to have a better prognostic ability [3]. However, whether frontline treatment and molecular subtypes such as exon 19 deletions, exon 21 substitutions (Leu858Arg, L858R), or other rare mutations have different prognostic implications is largely unknown in these patients. Therefore, we conducted this retrospective study of the prognostic implications of molecular subtypes and frontline TKIs on EGFR-mutated patients with BM to investigate this issue.

2. Results

Of the 256 patients with advanced EGFR-mutated lung adenocarcinoma and BM included in this study, 43.7% had exon 19 deletions, 49.2% had Leu858Arg, and 7.0% had other mutations. With regards to frontline treatment, 10.2%, 15.6% and 74.2% of the patients received afatinib, erlotinib or gefitinib, respectively. In addition, 9.4% of the patients received WBRT followed by TKIs as their initial treatment, 37.5% of the patients received WBRT and TKIs, and 53.1% of the patients received TKIs alone. Other baseline characteristics including sex, age, ECM, and number of BM are listed in Table S1. There were significant differences in baseline age ($p<0.001$), KPS ($p<0.001$), ECM ($p<0.001$), number of BM ($p<0.001$), timing of BM ($p<0.001$), EGFR mutation subtypes ($p=0.040$), and timing of WBRT ($p<0.001$) between those with a high (>2.5) and low (≤2.5) Lung-molGPA score, but not in sex ($p=0.766$), or frontline TKIs ($p=0.871$). The median OS was 17.2 months, and patients with Lung-molGPA scores of 1, 1.5-2.0, 2.5-3.0, and 3.5-4.0 had median OS of 4.4, 15.5, 15.5, and 23.7 months, respectively ($p<0.001$, Figure 1a and 1b). The median OS of the patients with exon 19 deletions, Leu858Arg, or rare mutations were 18.1, 16.6, and 12.9 months, respectively ($p=0.104$, Figure 1c), and the patients who received afatinib, gefitinib, or erlotinib had median OS of 25.2, 17.4, and 12.6 months, respectively ($p=0.036$, Figure 1d).

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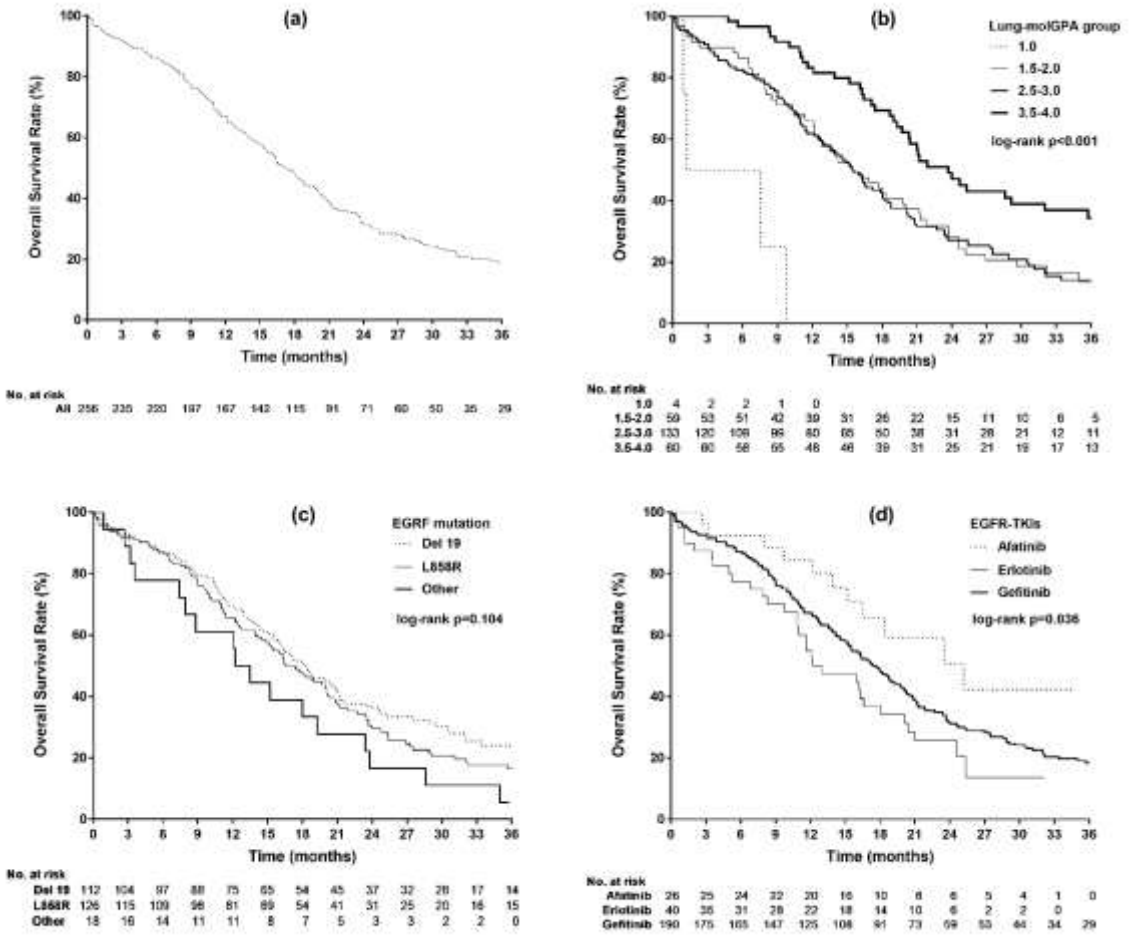

Figure 1. Kaplan-Meier survival outcome curves in patients with advanced EGFR-muted NSCLC with brain metastases. (a) Overall survival in the study cohort. (b) Overall survival grouped by Lung-molGPA score. (c) Overall survival grouped by EGFR molecular subtypes. (d) Overall survival grouped by EGFR-TKIs.

In multivariate analysis of OS, only age (≥70 versus <70 years, HR: 1.71, 95% confidence interval (CI): 1.25-2.35, p<0.001), KPS (<70 versus ≥70, HR: 1.71, 95% CI: 1.26-2.31, p<0.001), and rare mutations (other versus exon 19 deletions, HR: 1.78, 95% CI: 1.04-3.05, p=0.037) remained statistically significant after adjusting for other factors. WBRT followed by TKIs, combination of WBRT and TKIs or TKIs alone were not statistically significant either in crude or adjusted multivariate analysis. Subtypes of molecular alterations such as Leu858Arg had a trend of an inferior OS after adjustment (Leu858Arg versus exon 19 deletions, HR: 1.32, 95% CI: 0.96-1.80, p=0.086) (Table 1).

Table 1. Multivariate analysis of overall survival in the patients with advanced NSCLC.

	Crude		Adjusted*	
Variables	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Sex				
Female	Reference		Reference	
Male	1.13 (0.85-1.51)	0.394	1.11 (0.83-1.50)	0.484
Age (years)				

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<70	Reference		Reference	
≥70	1.73 (1.27-2.35)	<0.001	1.71 (1.25-2.35)	<0.001
KPS				
<70	1.70 (1.28-2.26)	<0.001	1.71 (1.26-2.31)	<0.001
≥70	Reference		Reference	
Extracranial metastases				
Absent	Reference		Reference	
Present	1.04 (0.77-1.42)	0.790	1.18 (0.82-1.69)	0.383
Number of brain metastases				
1-4	Reference		Reference	
>4	1.18 (0.89-1.57)	0.251	1.25 (0.93-1.68)	0.137
Brain metastases timing				
Synchronous	Reference		Reference	
Metachronous	0.93 (0.69-1.24)	0.606	0.79 (0.51-1.20)	0.267
EGFR mutation types				
Del 19	Reference		Reference	
L858R	1.19 (0.89-1.60)	0.244	1.32 (0.96-1.80)	0.086
Other	1.72 (1.02-2.91)	0.042	1.78 (1.04-3.05)	0.037
EGFR-TKIs				
Afatinib	0.57 (0.31-1.05)	0.069	0.61 (0.33-1.16)	0.132
Erlotinib	1.36 (0.92-2.02)	0.119	1.34 (0.89-2.02)	0.161
Gefitinib	Reference		Reference	
RT				
WBRT alone	1.19 (0.74-1.92)	0.474	1.10 (0.64-1.91)	0.731
WBRT+TKI	1.15 (0.85-1.55)	0.377	1.02 (0.68-1.53)	0.927
TKI alone	Reference		Reference	

*Adjusted for sex, age, KPS, extracranial metastases, number of brain metastases, timing of brain metastases, EGFR mutation types, TKIs and timing of RT

*Abbreviations: NSCLC, non-small-cell lung cancer; GPA, graded prognostic assessment; KPS, Karnofsky performance status; Del 19, exon 19 deletions; L858R, Leu858Arg; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors; RT, radiation therapy; WBRT, whole brain radiation therapy.

We then performed multivariate analysis of OS in the patients with a high or low Lung-molGPA score. In the patients with a low Lung-molGPA score, EGFR molecular subtypes had different prognostic implications (Leu858Arg versus exon 19 deletions, HR: 1.85, 95% CI: 1.20-2.84, p=0.005; other versus exon 19 deletions, HR: 2.18, 95% CI: 1.11-4.26, p=0.023) but not frontline TKIs (afatinib versus gefitinib, HR: 0.61, 95% CI: 0.27-1.36, p=0.227; erlotinib versus gefitinib, HR: 1.20, 95% CI: 0.68-2.13, p=0.530) after adjusting for other factors. In the patients with a high Lung-molGPA score, neither molecular subtype nor frontline TKIs had any prognostic implications (Table 2).

Table 2. Multivariate analysis of overall survival in the patients with advanced NSCLC by Lung-molGPA score.

	Crude		**Adjusted***	
Variables	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Lung-molGPA: ≤2.5				
EGFR mutation types				
Del 19	Reference		Reference	
L858R	1.60 (1.05-2.42)	0.028	1.85 (1.20-2.84)	0.005
Other	2.11 (1.09-4.08)	0.026	2.18 (1.11-4.26)	0.023
EGFR-TKIs				
Afatinib	0.62 (0.29-1.35)	0.231	0.61 (0.27-1.36)	0.227
Erlotinib	1.32 (0.76-2.30)	0.328	1.20 (0.68-2.13)	0.530
Gefitinib	Reference		Reference	
Lung-molGPA: >2.5				
EGFR mutation types				

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Del 19	Reference		Reference	
L858R	1.02 (0.66-1.57)	0.943	0.94 (0.60-1.47)	0.781
Other	1.29 (0.54-3.09)	0.562	1.29 (0.52-3.22)	0.581
EGFR-TKIs				
Afatinib	0.48 (0.18-1.32)	0.154	0.46 (0.16-1.35)	0.157
Erlotinib	1.42 (0.82-2.46)	0.208	1.46 (0.82-2.62)	0.200
Gefitinib	Reference		Reference	

*Adjusted for sex, timing of brain metastases, EGFR mutation types, TKIs and timing of RT

Patients with a low Lung-molGPA score with exon 19 deletions, Leu858Arg or other mutations had median OS of 18.8, 12.4, and 12.1 months, respectively (p=0.021), compared to 16.5, 20.4, and 18.0 months, respectively (p=0.839), in those with a high Lung-molGPA score (Figure 2a and 2b). In addition, the patients with a low Lung-molGPA score who received frontline afatinib, gefitinib, erlotinib had median OS of 23.5, 15.5, and 12.2, respectively (p=0.252), compared to >36, 19.0, and 16.3, respectively (p=0.123), in those with a high Lung-molGPA (Figure 2c and 2d). The characteristics of the patients with mutations other than exon 19 deletions and Leu858Arg are listed in Table S2.

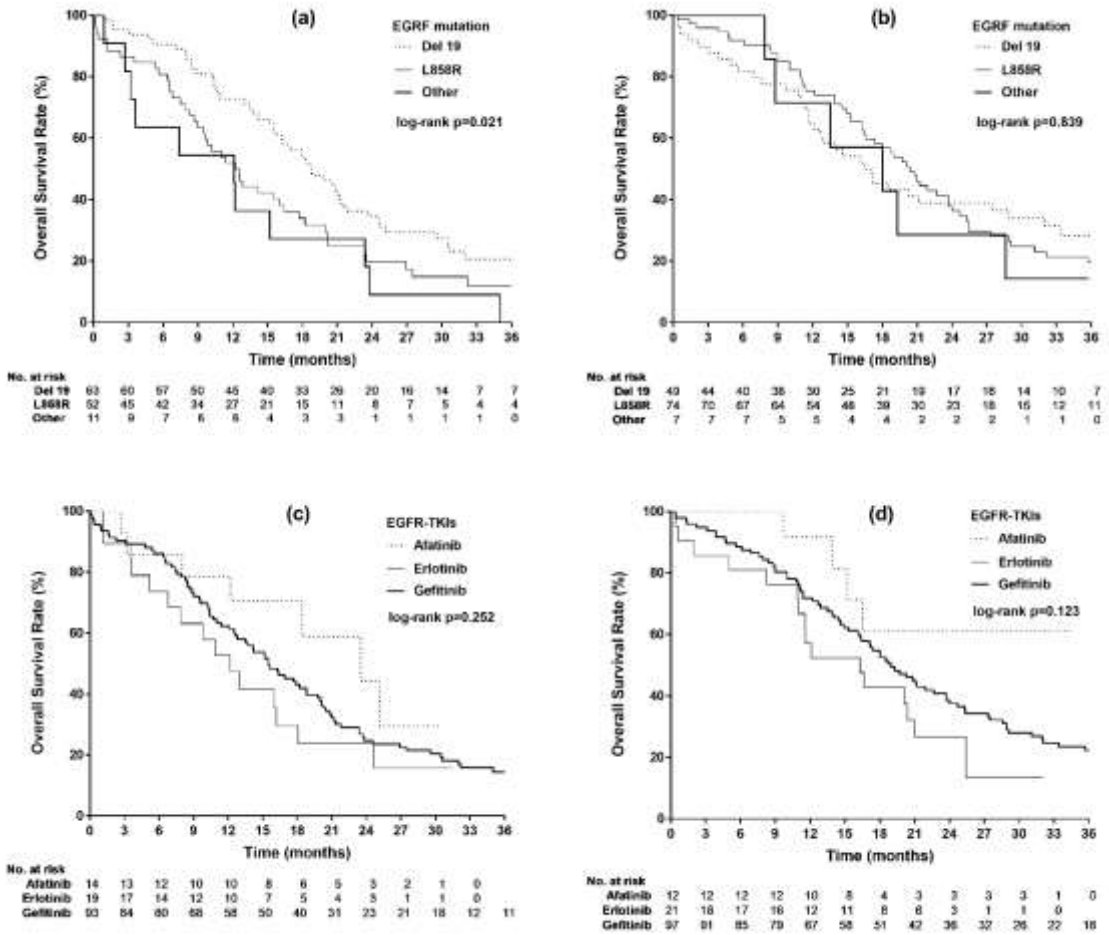

Figure 2. Kaplan-Meier survival outcome curves in patients with advanced EGFR-muted NSCLC with brain metastases grouped by high or low Lung-molGPA score (a) Grouped by EGFR molecular subtypes in patients with a Lung-molGPA score ≤2.5. (b) Grouped by EGFR molecular subtypes in patients with a Lung-molGPA score >2.5. (c) Grouped by EGFR-TKIs in patients with a Lung-molGPA score ≤2.5. (d) Grouped by EGFR-TKIs in patients with a Lung-molGPA score >2.5.

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3. Discussion

This study is the first study to address the prognostic implications of molecular subtypes and frontline TKIs on EGFR-mutated BM stratified by Lung-molGPA score. This cohort further validated the usefulness of the Lung-molGPA index in an East Asian population. The median OS in this EGFR-mutated lung cancer cohort was 17.2 months, which is slightly longer than the OS reported in pure EGFR-mutated or mixed lung cancer studies [3, 5-8]. This may be because all of the patients in this cohort received at least one TKI, which may have provided both systematic and intra-cranial disease control [9,10]. In addition, the number of BM (>4 versus 1-4, HR: 1.25, 95% CI: 0.93-1.68, p=0.137) and ECM (present versus absence, HR: 1.18, 95% CI: 0.82-1.69, p=0.383) did not have prognostic value when TKIs were applied in a frontline setting. Although the updated Lung-molGPA was useful in prognostic stratification in these patients, it could not reflect differences in molecular subtypes or frontline TKI treatment. Patients with other rare mutations had a worse OS after adjusting for other factors and frontline TKIs, which reflects the relatively poor efficacy of first- and second-generation TKIs in patients with these mutations [11]. We further stratified the cohort into those with high (>2.5) and low (≤2.5) Lung-molGPA scores arbitrarily to balance the number of patients, and found different prognostic implications of molecular subtypes and frontline TKI treatment. In the patients with a low Lung-molGPA score, inherent molecular subtypes were more associated with the prognosis, but not the frontline TKI. In addition, the patients with different molecular subtypes had distinct survival benefits with frontline TKIs [12-14]. In those with a high Lung-molGPA score, which deemed to be with better prognosis, frontline TKI and inherent molecular subtypes were not associated with different prognostic implications. It seemed to be that the differences within inherent molecular subtypes were diluted with a high Lung-molGPA score. However, whether this observation can be applied to third generation TKIs or osimertinib is not known. Osimertinib has been reported to show remarkable intra-cranial responses and median survival up to 15.2 months in these patients [15]. Still, osimertinib shows overall survival advantage in patients with exon 19 deletions (HR: 0.68 [0.51-0.90]) over those with Leu858Arg (HR: 1.00 [0.71-1.40]) [16].

Whether palliative radiation to BMs is beneficial in EGFR-mutated lung cancer is under intense debate, with rapid advancements in newer TKIs being able to penetrate the CNS [10,11]. In our cohort, only two patients (1.2%) received stereotactic radiosurgery to BM with restrict reimbursement policy, and the timing to WBRT was not related to prognosis. Thus, it seems reasonable to keep WBRT as a last resort when BM worsen under frontline TKIs, since it is associated with a risk of cognitive dysfunction and could further deteriorate the quality of life in these patients. However, further prospective studies are needed to elucidate this issue. In addition, the survival of patients with other rare EGFR mutations and BM has not been addressed before, since these patient comprise less than 5% of all cases of EGFR-mutated non-small-cell lung carcinoma. In this cohort, 77.8% of the patients were treated with frontline gefitinib, and the median OS was 12.2 months.

There are several limitations to this study. In retrospective studies, assessments of local control and intra-cranial progression-free survival can be unreliable, and thus we chose OS as an alternative but most clinically meaningful endpoint. In addition, different survival outcomes were noted with the different frontline TKIs, but such difference was diminished after multivariable analysis. Our finding should be deemed as hypothesis-generating, and larger prospective study empowered to address this issue is eagerly awaiting. In addition, frontline osimertinib is not available with the reimbursement policy in Taiwan. However, this data could still be valuable as real-world evidence

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since many parts of this world do not have osimertinib for frontline use, partly because of the cost-effectiveness issues.

4. Materials and Methods

We conducted this retrospective hospital-based cohort study at Chang-Gung Memorial Hospital in Taiwan, and it was approved by the Institutional Review Board. A total of 848 patients with EGFR-mutated lung adenocarcinoma were identified from April 2011 to June 2015 in Chang-Gung Research Databases [4]. EGFR mutations were identified by direct DNA sequencing using an amplification refractory mutation system (ARMS, QIAGEN, Hilden, Germany) or competitive allele-specific TaqMan PCR (Cast-PCR, Applied Biosystems, Foster City, CA) with genomic DNA from paraffin-embedded tissue. Patients diagnosed with lung cancer and BM by imaging studies such as CT, MRI or cytology from cerebrospinal fluid were included. Patients with double cancers were excluded from this study. In total, 162 patients were included in this study. Variables including age (<70 versus ≥70 years), sex, KPS (<70 versus ≥70), ECM (presence versus absence), the number of BM (>4 versus 1-4), timing of brain metastases (≤60 [synchronous] versus >60 [metachronous] days after diagnosis), EGFR mutation subtypes (exon 19 deletions versus Leu858Arg versus others), frontline TKIs (afatinib versus erlotinib versus gefitinib), the timing of whole-brain radiation therapy (WBRT, combination versus sequential versus salvage) were collected retrospectively. In Taiwan, gefitinib has been reimbursed by the National Health Insurance Program (NHIP) for the first-line treatment of patients with stage IIIb or IV non-small cell lung cancer with EGFR-activating mutations since June 2011, with erlotinib and afatinib being added in November 2013 and May 2014, respectively. Sequential WBRT was defined as frontline WBRT followed by TKI treatment for 2 weeks and salvage WBRT after 2 months of treatment with frontline TKIs. The primary endpoint was overall survival (OS), which was calculated from the date of lung cancer diagnosis and frontline TKI treatment to death or last follow-up. OS and prognostic factors were evaluated in multivariate analysis. The patients were stratified according to a high or low Lung-molGPA score (>2.5 versus ≤2.5), EGFR mutation subtypes and type of frontline TKI.

Kaplan-Meier curves were used to estimate OS, and the log-rank test was used to compare times to events between groups. Multivariate analyses and stratified analyses were performed using Cox proportional hazards regression models (hazard ratio, HR). All reported p values were two-tailed, and a p value of 0.05 was considered to indicate statistical significance. Adjustments were made for multiple comparisons. All analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC).

5. Conclusions

The Lung-molGPA can predict the prognosis in EGFR-mutated adenocarcinoma, and different molecular subtypes and frontline TKI treatment have distinct prognostic implications in these patients. Further studies are warranted to verify these findings.

Supplementary Materials:

Table 1. Baseline characteristics of the patients with brain metastases and NSCLC by Lung-molGPA score.

	All		molGPA: ≤2.5		molGPA: >2.5		
Variables	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	***P*-value**
Total	256		126		130		
Sex							0.766

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Female	150	(58.6)	75	(59.5)	75	(57.7)	
Male	106	(41.4)	51	(40.5)	55	(42.3)	
Age (years)							<0.001
<70	185	(72.3)	72	(57.1)	113	(86.9)	
≥70	71	(27.7)	54	(42.9)	17	(13.1)	
KPS							<0.001
<70	99	(38.7)	79	(62.7)	20	(15.4)	
≥70	157	(61.3)	47	(37.3)	110	(84.6)	
Extracranial metastases							<0.001
Absent	184	(71.9)	55	(43.6)	129	(99.2)	
Present	72	(28.1)	71	(56.4)	1	(0.8)	
Number of brain metastases							<0.001
1-4	141	(55.1)	49	(38.9)	92	(70.8)	
>4	115	(44.9)	77	(61.1)	38	(29.2)	
Timing of brain metastases							<0.001
Synchronous	162	(63.3)	60	(47.6)	102	(78.5)	
Metachronous	94	(36.7)	66	(52.4)	28	(21.5)	
EGFR mutation types							0.040
Del 19	112	(43.7)	63	(50.0)	49	(37.7)	
L858R	126	(49.2)	52	(41.3)	74	(56.9)	
Other	18	(7.0)	11	(8.7)	7	(5.4)	
EGFR-TKIs							0.871
Afatinib	26	(10.2)	14	(11.1)	12	(9.2)	
Erlotinib	40	(15.6)	19	(15.1)	21	(16.2)	
Gefitinib	190	(74.2)	93	(73.8)	97	(74.6)	
RT							<0.001
WBRT alone	24	(9.4)	8	(6.3)	16	(12.3)	
WBRT+TKI	96	(37.5)	36	(28.6)	60	(46.2)	
TKI alone	136	(53.1)	82	(65.1)	54	(41.5)	

Abbreviations: NSCLC, non-small-cell lung cancer; GPA, graded prognostic assessment; KPS, Karnofsky performance status; Del 19, exon 19 deletions; L858R, Leu858Arg; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors; RT, radiation therapy; WBRT, whole brain radiation therapy.

Table 2. Survival outcomes and Lung-molGPA scores in the patients with rare EGFR mutations.

Sex	Age	TKI	Mutation	BM timing	OS (months)	Dead	molGPA
F	40.9	Gefitinib	G719A + L757M	Metachronous	35	1	3
F	56.2	Gefitinib	Exon 20 ins	Metachronous	7.4	1	1.5
F	57.6	Gefitinib	Exon 20 dup	Synchronous	19.3	1	3.5
F	62.4	Gefitinib	G719X	Synchronous	7.9	1	3
F	69.9	Gefitinib	G719A + exon20 G/A2607	Synchronous	8.8	1	4
F	74.7	Gefitinib	G719A + exon20 G/A2607	Synchronous	12.1	1	1.5
F	76.3	Gefitinib	2485-2502	Metachronous	23.4	1	2.5
M	44.7	Gefitinib	G719X + S768I	Synchronous	28.6	1	3.5
M	53.8	Gefitinib	G719X +L861Q	Synchronous	35.8	0	3.5
M	56.2	Gefitinib	Exon 20 ins	Synchronous	13.5	1	3
M	57.3	Erlotinib	Exon 20 ins	Synchronous	12.2	1	2
M	58.3	Gefitinib	L861Q + exon 20 G/A2607	Synchronous	18	1	3
M	59.9	Gefitinib	G719X	Metachronous	15.2	1	1.5
M	71.7	Gefitinib	L861Q + E866Q	Metachronous	23.8	1	1.5
M	73.6	Erlotinib	Exon 20 dup	Synchronous	3.6	1	2.5
M	77.3	Afatinib	Exon 20 ins	Synchronous	3.2	1	2.5
M	77.9	Afatinib	L861Q	Synchronous	2.7	1	2.5
M	78.5	Gefitinib	Exon 20 dup	Synchronous	0.9	1	1

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