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Efficacy of PD-1/PD-L1 inhibitors in patients with non-small cell lung cancer and brain metastases: A real-world retrospective study in China

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Abstract

Background: There is only limited knowledge of the treatment responses and clinical outcomes of immune checkpoint inhibitors (ICIs) in driver gene-negative non-small cell lung cancer (NSCLC) patients with brain metastases (BM). This study aims to assess the efficacy of immunotherapy in these patients in a real world setting.

Methods: NSCLC-BM patients without driver gene mutations who received ICIs were retrospectively identified between July 2017 and December 2019. The primary observation endpoint was intracranial objective response rate (iORR), and secondary objectives were objective response rate (ORR), intracranial and systemic progression-free survival (iPFS, PFS), and overall survival (OS).

Results: We reviewed 1578 patients with lung cancer and BM. According to the exclusion criteria, 41 patients were finally enrolled. Among these 41 patients, iORR was 36.6% (95% confidence interval [CI] = 21.2%–52.0%), whereas iPFS was 6.8 (95% CI = 3.32–10.35) months. Additionally, ORR, PFS, and OS were 24.4% (95% CI = 10.7%–38.1%), 6.2 (95% CI = 4.57–7.83) months and 13.7 (95% CI = 11.20–16.26) months, respectively. ICIs combined with concurrent radiotherapy group exhibited preferred iORR ($p = 0.030$) compared with no radiotherapy group, and ICIs plus chemotherapy showed improved OS ($p = 0.024$) compared to ICI monotherapy. Moreover, the lines of ICI treatment ≥2 ($p = 0.005$) and derived neutrophil-to-lymphocyte ratio (dNLR) ≥3 ($p = 0.010$) were independently negative factors for OS.

Conclusion: In NSCLC-BMs patients lacking driver genes, ICIs exhibited an effective drug regime. A combination of ICIs with concurrent radiotherapy showed a better intracranial response, whereas ICIs plus chemotherapy were associated with superior OS.

KEYWORDS
brain metastases, efficacy, non-small cell lung cancer, PD-1/PD-L1 inhibitors

INTRODUCTION

Lung cancer is one of the leading malignancies globally and is responsible for the highest cancer-related mortality in China.[1] Non-small cell lung cancer (NSCLC) alone accounts for ~80%–85% of lung cancer cases.[2] Central nervous system (CNS) metastases, including brain metastasis (BM) and leptomeningeal metastasis (LM), are the most frequent sequela of NSCLC. These conditions contribute heavily to dismal prognosis and poor quality of life.[3] Approximately 10%–20% of NSCLC patients have CNS metastases at initial NSCLC diagnosis, whereas ~25%–40% of NSCLC patients develop CNS metastases during cancer progression.[4–6]

Because of the difficulty in crossing the blood–brain barrier (BBB), chemotherapy exhibited limited intracranial antitumor activity.[7] Local treatments, including surgery and

radiotherapy such as stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT), are the principal treatment of brain metastases in NSCLC. However, the resistance to chemotherapy or radiation is still a significant obstacle in treating brain metastases in NSCLC. For NSCLC patients with BM-harboring driver gene mutations, in epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK), tyrosine kinase inhibitors (TKIs) showed superior efficacy against BM as compared to chemotherapy by yielding a higher intracranial objective response rate (iORR) and intracranial progression-free survival (iPFS).[8–10] However, it is still challenging to treat driver gene-negative patients with BM, owing to the lack of effective intracranial antitumor regimens. In summary, the management of brain metastases remains a considerable challenge for physicians, with these bottlenecks restricting the efficacy of traditional therapies.

The immune checkpoint inhibitors (ICIs) targeting anti-programmed death receptor 1 (PD-1) and its ligand (PD-L1) have become the most promising treatment approach for advanced NSCLC patients.[11,12] Briefly, PD-(L)1 inhibitors act against malignancies by inhibiting the tumor immune escape by blocking the interaction of PD-1 expressed on T cells and PD-L1 expressed on tumor cells and, thereby, reactivating antitumor activity mediated by cytotoxic T cells to fight cancer.[13] Several studies have suggested that ICI treatment can show an excellent intracranial response and survival in patients with NSCLC and BM as compared to chemotherapy in the first and second-line setting of NSCLC.[14–19]

Because randomized controlled trials (RCTs) have strict enrollment requirements to guarantee internal stability, it may lose external scalability. In consequence, the results of clinical trials do not entirely mirror real clinical situations.[14,18,20,21] Real-world studies can address the shortcomings of RCTs and further guide follow-up studies to verify further the feasibility of immunotherapy for patients with less selected BM based on clinical practice. Additionally, several treatment strategies including ICI monotherapy, combination with chemotherapy, and antiangiogenesis agents, are

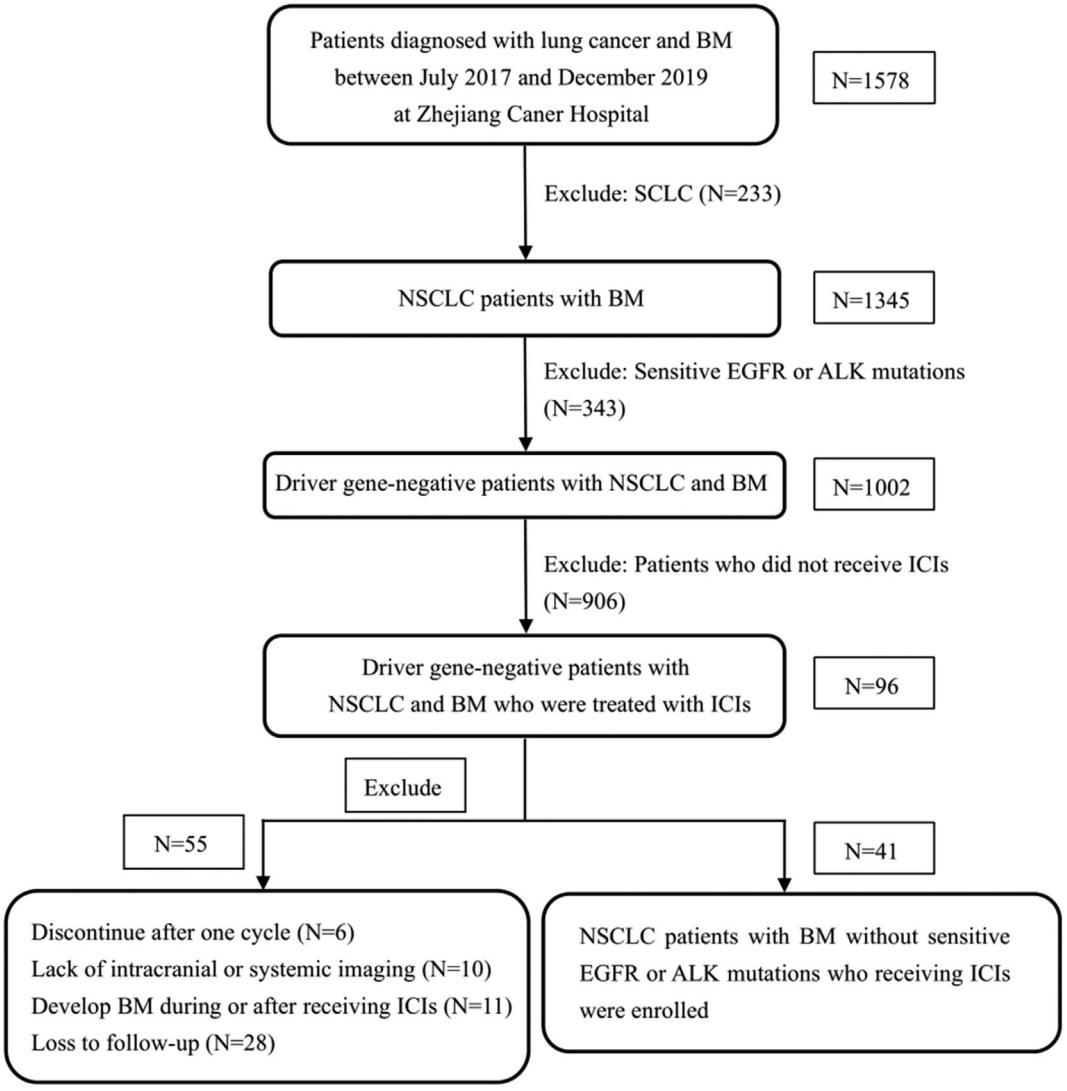

FIGURE 1 Study flowchart. ALK, anaplastic lymphoma kinase; BM, brain metastases; EGFR, epidermal growth factor receptor; ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer; SCLC, small-cell lung cancer

TABLE 1 Characteristics of 41 NSCLC patients with brain metastases

Characteristic	*N* (%)
Age	
Median age (range)	61 (34–78)
≤70 years old	32 (78.0)
>70 years old	9 (21.9)
Sex	
Male	28 (68.2)
Female	13 (31.7)
Smoking history	
Yes	22 (53.6)
No	19 (46.3)
ECOG-PS	
0–1	39 (95.1)
≥2	2 (4.8)
Histological subtype	
Squamous carcinoma	8 (19.5)
Adenocarcinoma	33 (80.4)
Driver gene mutation	
EGFR uncommon mutation	3 (7.3)
KRAS mutation	5 (12.2)
Others	2 (4.8)
Negative or unknown	31 (75.6)
PD-L1 status	
Positive (≥1%)	14 (34.1)
1%–49%	9 (22.0)
≥50%	5 (12.2)
Negative (<1%)	11 (26.8)
Unknown	16 (39.0)
Synchronous BM	
Yes	21 (51.2)
No	20 (48.7)
Number of BM	
<3	21 (51.2)
≥3	20 (48.7)
Number of organs with metastases	
1	20 (48.7)
≥2	21 (51.2)
Symptomatic BM	
With	19 (46.3)
Without	22 (53.6)
Local BM treatment	
Surgery	1 (2.4)
WBRT	15 (36.6)
SRS	12 (29.3)
SRS + WBRT	2 (4.8)
No local treatment	11 (26.8)
Radiotherapy timing	
ICIs with concurrent radiotherapy	10 (24.4)
ICIs with non-concurrent radiotherapy	19 (46.3)
Lines of ICIs treatment	
1	17 (41.5)
≥2	24 (58.5)
Immunotherapy drug	
PD-1 inhibitor	38 (92.6)
PD-L1 inhibitor	3 (7.3)
Immunotherapy regimens	
Monotherapy	18 (43.9)
Pembrolizumab	6 (14.6)
Nivolumab	6 (14.6)
Atezolizumab	3 (7.3)
Sintilimab	3 (7.3)
Combination therapy	23 (56.0)
Immunotherapy plus chemotherapy	14 (34.1)
Pembrolizumab plus pemetrexed	1 (2.4)
Pembrolizumab plus platinum-based chemotherapy	4 (9.8)
Nivolumab plus albumin-bound paclitaxel	1 (2.4)
Nivolumab plus platinum-based chemotherapy	2 (4.9)
Sintilimab plus docetaxel	1 (2.4)
Sintilimab plus platinum-based chemotherapy	5 (12.2%)
Immunotherapy plus antiangiogenic therapy	9 (22.0)
Pembrolizumab plus bevacizumab	2 (4.9)
Pembrolizumab plus anlotinib	5 (12.2)
Nivolumab plus bevacizumab	2 (4.9)
DS-GPA score	
0–1	11 (26.8)
1.5–2.5	23 (56.1)
≥3	7 (17.1)
LDH	
≥ULN	17 (41.4)
<ULN	24 (58.5)
dNLR	
≥3	16 (39.0)
<3	25 (60.9)
LIPI score	
Good (0)	17 (41.4)
Intermediate (1)	15 (36.6)
Poor (2)	9 (22.0)

Note: Synchronous BM was defined as patients were diagnosed with NSCLC and BM at same time. ICIs combine with concurrent radiotherapy was defined as that ICIs was given within 2 weeks before or after of radiotherapy.

Abbreviations: BM, brain metastases; dNLR, derived neutrophil to lymphocyte ratio; DS-GPA, diagnosis-specific graded prognostic assessment; ECOG-PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene; ICIs, immune checkpoint inhibitors; LDH, lactate dehydrogenase; LIPI, lung immune prognostic index; NSCLC, non-small cell lung cancer; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; SRS, stereotactic radiosurgery; ULN, upper limit of normal; WBRT, whole brain radiotherapy.

being investigated in NSCLCs with BM. However, of all the treatment strategies, which one is optimal and most effective remain an unresolved question. Therefore, we retrospectively analyzed the efficacy of PD-1/PD-L1 inhibitors for NSCLC patients lacking driver gene mutation with BM and explored optimal treatment strategies for this specific patient subgroup in a real-world setting.

MATERIALS AND METHODS

Study population

Data of NSCLC patients with BM who started ICIs between July 2017 and December 2019 at Zhejiang Cancer Hospital were retrospectively collected. The patients were followed until December 31, 2020. The enrolled patients met the following selection criteria: (1) histologically confirmed diagnosis of advanced NSCLC; (2) with at least one measurable intracranial and extracranial lesion that was diagnosed by brain magnetic resonance imaging (MRI) or computed tomography (CT) scans before the initiation of anti-PD-1/PD-L1 treatment; (3) treated or untreated BM and active (defined as newly appeared or growing lesions) or not; (4) no prior treatment with PD-1/PD-L1 inhibitor monotherapy or other ICIs; and (5) no sensitive EGFR or ALK driver gene alteration. Patients whose responses cannot be evaluated because of receiving ICIs for less than two cycles or losing follow-up were excluded. The Zhejiang Cancer Hospital Ethics Committee approved this study.

The patient's clinicopathological features, laboratory results, and treatment strategies were recorded. PD-L1 expression in naive treatment tumor biopsy samples was assessed using the Dako 22C3 platform (Agilent). A patient was considered to be PD-L1 positive if ≥1% of tumor cells were stained positive. Moreover, lactate dehydrogenase (LDH) levels, dNLR (defined as absolute neutrophil count/leukocyte count minus total neutrophil count), and lung immune prognostic index (LIPI) scores (calculated by dNLR and LDH levels) within 30 days before the initiation of ICIs treatment were collected.[22] dNLR >3 and LDH greater than the standard upper limit of normal (ULN) were taken as cutoff values. LIPI scores were divided into three groups based on dNLR and LDH level: good, 0 factors; intermediate, 1 factor; poor, two factors. ICIs combined with concurrent radiotherapy were defined as that ICIs were given within 2 weeks before or after radiotherapy. Patients with non-concurrent radiotherapy and ICIs were categorized as those who received radiotherapy and ICIs over 2 weeks apart.[23]

Assessments

The data were collected and analyzed according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Intracranial and extracranial tumor responses for ICIs were based on brain MRI and chest CT scans evaluated every two treatment cycles. Each observation was divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The primary observation endpoint was the iORR. The secondary objectives were intracranial and systemic disease control rate (iDCR, DCR), iPFS, systemic objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). We defined the iORR and the ORR as the proportion of patients with intracranial and systemic complete or partial responses. The iDCR and the DCR refer to the ratio of intracranial and systemic CR, PR, and SD cases, respectively. PFS was calculated from the date of the first immunotherapy administration until PD or death due to any reason. iPFS was calculated from the first immunotherapy administration until BM progressive disease or death because of any cause. OS was defined as starting the immunotherapy to death or the end of the last follow-up day.

Statistical analysis

We applied a Cox proportional hazards regression model to evaluate factors independently associated with OS, PFS, and iPFS. According to their clinical relevance and statistical significance, the variables included in the final multivariate model were evaluated in univariate analysis (cutoff

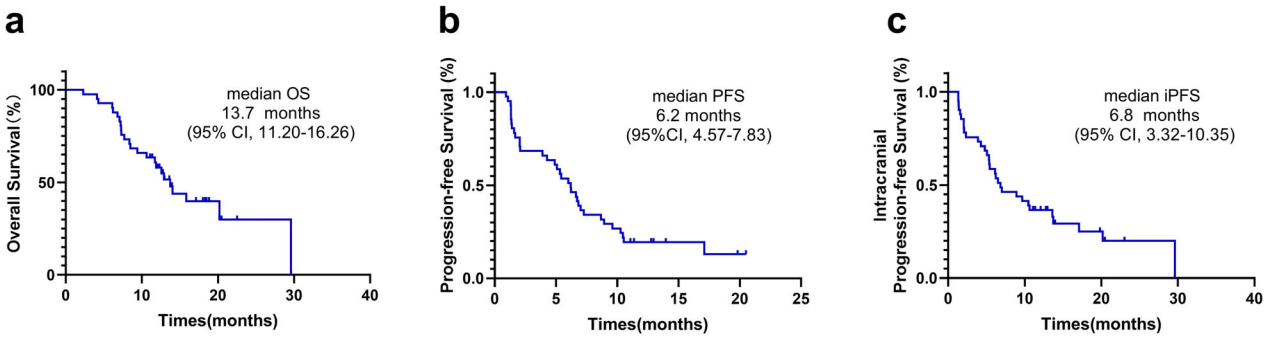

FIGURE 2 Kaplan–Meier analysis for OS (a), PFS (b), and iPFS (c) in all patients with brain metastases ($n = 41$). iPFS, intracranial progression-free survival; OS, overall survival; PFS, progression-free survival

$p = 0.05$). Statistical analyses were performed using SPSS 25.0 (IBM) and GraphPad Prism version 8.0 (GraphPad Software). The distribution of patients' baseline information was summarized using frequency analysis. The OS, PFS, and iPFS were calculated based on the Kaplan–Meier method. The log-rank test was used to compare the differences

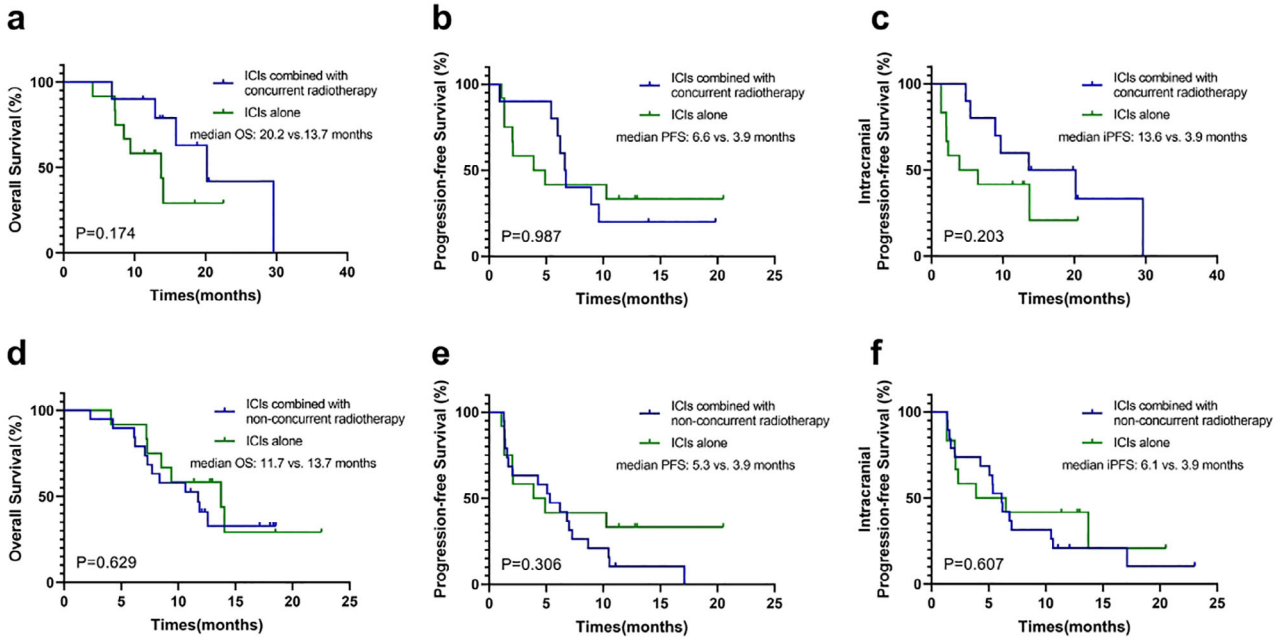

FIGURE 3 Kaplan–Meier analysis for OS (a), PFS (b), and iPFS (c) between patients with brain metastases treated with ICIs combined with concurrent radiotherapy ($n = 10$) and ICIs alone ($n = 11$). Kaplan–Meier analysis in population underwent ICIs combined with non-concurrent radiotherapy ($n = 19$) and ICIs alone (n = 11) for OS (d), PFS (e), and iPFS (f). ICIs, immune checkpoint inhibitors; iPFS, intracranialprogression-free survival; OS, overall survival; PFS, progression-free survival

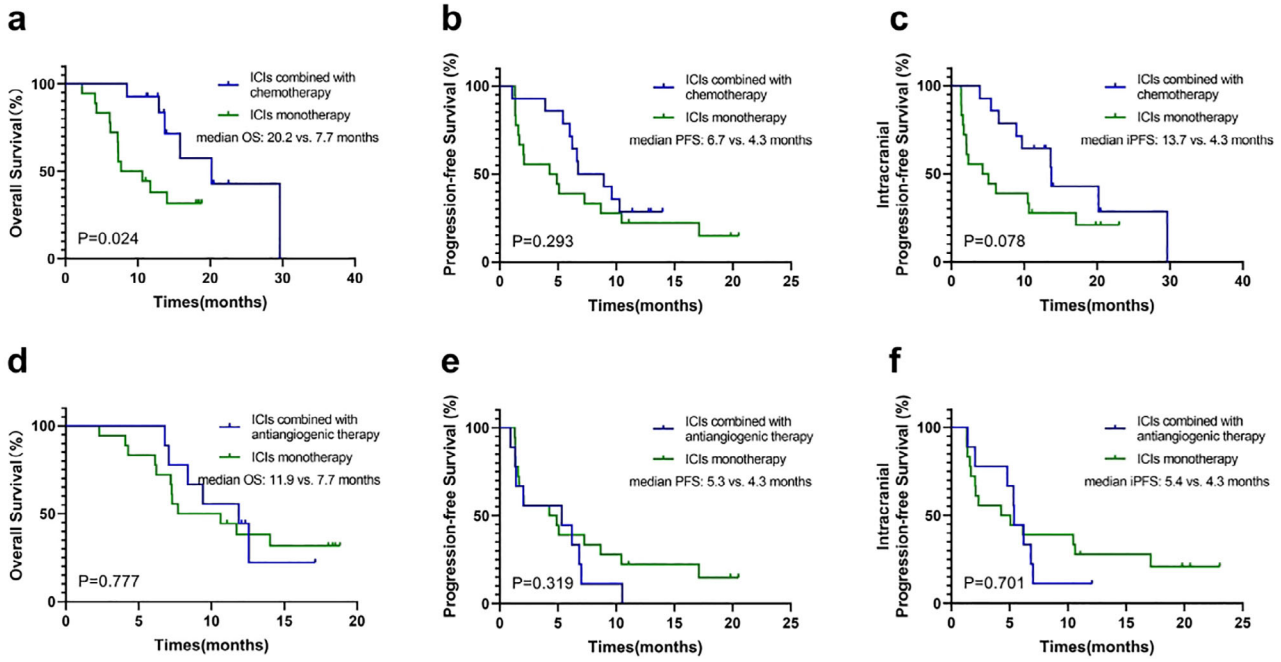

FIGURE 4 Kaplan–Meier analysis for efficacy of immunotherapy combined with chemo or antiangiogenic therapy: OS (a), PFS (b) and iPFS (c) in patients with brain metastases receiving ICIs combined with chemotherapy ($n = 14$) or ICI monotherapy ($n = 18$). OS (d), PFS (e) and iPFS (f) in patients with brain metastases receiving ICI monotherapy ($n = 18$) or ICIs combined with antiangiogenic therapy ($n = 9$). ICIs, immune checkpoint inhibitors; iPFS, intracranial progression-free survival; OS, overall survival; PFS, progression-free survival

between the subgroups for all related factors. Additionally, Fisher's exact test was applied to compare the differences in ORR, DCR, iORR, and iDCR between different treatment strategies. Statistical significance was set at $p < 0.05$.

RESULTS

Baseline population characteristics

Data of 1578 patients with lung cancer and BM at Zhejiang Cancer Hospital were included in this study. According to the exclusion criteria as detailed in methodology, 41 patients were enrolled in this study (Figure 1). The baseline characteristics of these patients are summarized in Table 1. The majority of the patients were younger than 70 years old (<70 years old, 78%), male (68.2%), and 53.6% had a smoking history, with an Eastern Cooperative Oncology Group (ECOG) performance status 0–1 (95.1%), whereas two had PS ≥2. In the BM group, 33 patients have histology adenocarcinoma subtype (80.4%), and 8 (19.5%) showed squamous carcinoma. Fourteen patients (34.1%) had a positive PD-L1 expression, whereas 11 patients (26.8%) were PD-L1-negative. Twenty-two patients (53.6%) had <3 brain lesions, whereas 19 patients (46.3%) had symptomatic BM. More than half of the patients were classified as class 1.5–2.5 (23/41, 56.1%), 26.8% were labeled as class 0–1, and 17.1% were regarded as class ≥3 based on the diagnosis specific-graded prognostic assessment (DS-GPA) score.

Regarding the treatment regimens, 30 (73.2%) patients received local treatment as follows: 12 (29.3%) received SRS, 15 (36.6%) were treated with WBRT, two were administered with WBRT and SRS and only one underwent surgery. Among patients who received radiotherapy, 10 patients (24.4%) were treated with concurrent radiotherapy. Meanwhile, ICIs were administered as the first-line treatment for 18 (43.9%) and second- or later-line therapy for 23 (56.0%). Twenty-three (56.0%) patients received ICI combination therapy: 14 patients (34.1%) received a combination of ICIs and chemotherapy, and nine patients (22.0%) received ICIs and antiangiogenic treatment. The detailed ICIs regimens that were administered in our study are presented in Table 1.

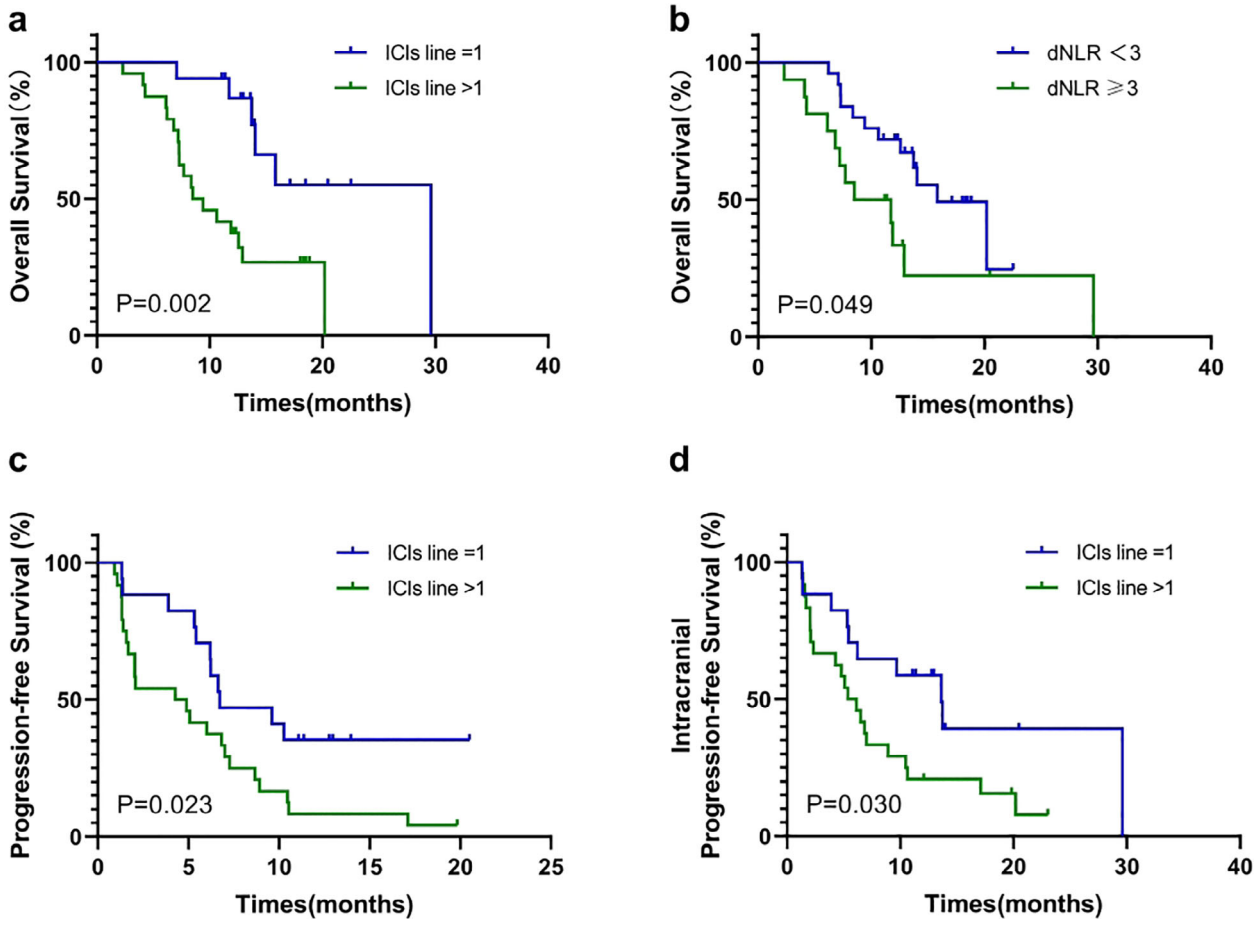

FIGURE 5 Kaplan–Meier analysis for prognostic factors: (a) overall survival stratified according to ICIs line; (b) overall survival stratified according to dNLR; (c) progression-free survival stratified to ICIs line; (d) intracranial progression-free survival stratified to ICIs line. The respective log-rank *p* value for descriptive purposes only. ICIs, immune checkpoint inhibitors

Evaluation of efficacy

Efficacy of immunotherapy

The last follow-up date was December 31, 2020, and the median follow-up time was 18.03 (95% confidence interval [CI] = 12.75–23.31) months. At the last follow-up, 7 (17.1%) patients had continued ICI treatment and 24 (58.5%) had died. Intracranial responses for ICIs were first determined. Five patients (12.2%) achieved CR, 10 (24.4%) experienced PR, 19 (46.3%) showed SD, and seven (17.1%) had disease progression. The iORR was 36.6% (95% CI = 21.2%–52.0%) and the iDCR was 82.9% (95% CI = 70.9%–95.0%). Survival analysis showed that the median iPFS was 6.8 (95% CI = 3.32–10.35) months (Figure 2(c)). For systemic treatment response, the ORR was 24.4% (95% CI = 10.7%–38.1%), and the DCR was 65.9% (95% CI = 50.7%–81.0%). In addition, 11 patients showed heterogeneous treatment responses in extracranial and intracranial lesions. Among these cases,

TABLE 2 Univariate and multivariate survival analyses of OS

	Univariate			Multivariate		
Variables	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age (y)						
≤70 vs. >70	0.81	0.27–2.40	0.704			
Sex						
Female vs. male	1.99	0.86–4.63	0.102			
Smoking history						
Yes vs. no	1.15	0.76–1.74	0.508			
ECOG-PS						
<2 vs. ≥2	0.90	0.12–6.70	0.915			
Histological subtype						
Squamous carcinoma versus adenocarcinoma	1.63	0.48–5.54	0.427			
Synchronous BM						
Yes vs. no	0.82	0.54–1.23	0.335			
Number of BM						
<3 vs. ≥3	2.58	1.09–6.11	0.025	1.91	0.79–4.60	0.149
Number of organs with metastases						
1 vs. ≥2	1.10	0.73–1.67	0.643			
DS-GPA score						
0–1 vs. 1.5–2.5	0.60	0.23–1.53	0.283			
0–1 vs. ≥3	0.66	0.19–2.27	0.511			
Local BM treatment						
Yes vs. no	0.94	0.37–2.40	0.901			
Lines of ICIs treatment						
1 vs. ≥2	4.28	1.57–11.65	0.002	4.46	1.56–12.75	0.005
Immunotherapy regimen						
Monotherapy vs. combination therapy	0.48	0.21–1.12	0.081	0.46	0.18–1.16	0.100
IrAE						
Yes versus no	0.91	0.40–2.07	0.821			
LDH						
≥ULN vs. <ULN	1.21	0.51–2.87	0.658			
dNLR						
≥3 vs. <3	2.27	0.98–5.22	0.049	3.48	1.34–9.03	0.010
LIPI score						
Good vs. intermediate	0.87	0.33–2.29	0.778			
Good vs. poor	1.47	0.53–4.12	0.464			

Abbreviations: BM, brain metastases; CI, confidence interval; dNLR, derived neutrophil to lymphocyte ratio; DS-GPA, diagnosis-specific graded prognostic assessment; ECOG-PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICIs, immune checkpoint inhibitors; IrAE, immune-related adverse events; LDH, lactate dehydrogenase; LIPI, lung immune prognostic index; OS, overall survival; ULN, upper limit of normal.

eight patients who experienced disease progression in the extracranial lesions had a response in the intracranial lesions, whereas the other three had a negative situation. Further analysis showed that the median OS was 13.7 (95% CI = 11.20–16.26) months (Figure 2(a)), and the median PFS was 6.2 (95% CI = 4.57–7.83) months (Figure 2(b)).

Furthermore, seven patients were treated with ICI alone without radiotherapy. Among them, the iORR was 28.6% (95% CI = 16.6%–73.7%) and the ORR was 28.6% (95% CI = 16.6%–73.7%). The median OS, PFS, and iPFS were 11.3 (95% CI = 5.96–16.58) months, 4.9 (95% CI = 0.00–12.16) months, and 2.3 (95%CI = 1.66–3.00) months, respectively. One patient with PD-L1 expression over 50% received ICIs as first-line treatment, and intracranial response reached PR. Additionally, six patients were treated with ICI as second- or later-line treatment. PD-L1 expression status was not determined in three patients, two patients had negative PD-L1 expression and another one had PD-L1 expression of 1%–49%.

TABLE 3 Univariate survival analyses of PFS and iPFS

	Univariate analyses of PFS			Univariate analyses of iPFS		
Variables	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age (y)						
>70 vs. ≤70	0.87	0.38–1.99	0.735	0.97	0.64–1.49	0.903
Sex						
Male vs. female	1.57	0.76–3.25	0.215	1.34	0.92–1.95	0.122
Smoking history						
Yes vs. no	1.06	0.53–2.12	0.875	1.02	0.71–1.46	0.928
ECOG-PS						
<2 vs. ≥2	0.39	0.05–2.90	0.339	1.88	0.25–14.01	0.529
Histological subtype						
Squamous carcinoma vs. adenocarcinoma	1.79	0.74–4.32	0.192	1.39	0.56–3.44	0.471
Synchronous BM						
Yes vs. no	0.94	0.67–1.33	0.741	0.85	0.59–1.21	0.361
Number of BM						
<3 vs. ≥3	1.67	0.85–3.30	0.132	1.58	0.77–3.25	0.210
Number of organs with metastases						
1 vs. ≥2	1.29	0.92–1.82	0.135	1.27	0.88–1.82	0.195
DS-GPA score						
0–1 vs. 1.5–2.5	1.07	0.48–2.37	0.866	1.17	0.50–2.72	0.713
0–1 vs. ≥3	1.05	0.37–2.97	0.922	1.04	0.34–3.18	0.947
Local BM treatment						
Yes vs. no	0.63	0.27–1.46	0.277	0.93	0.40–2.16	0.857
Lines of ICIs treatment						
1 vs. ≥2	2.26	1.09–4.67	0.023	2.34	1.06–5.13	0.030
Immunotherapy regimen						
Monotherapy vs. combination therapy	0.91	0.45–1.81	0.777	0.67	0.33–1.38	0.275
IrAE						
Yes vs. no	0.80	0.41–1.57	0.509	0.77	0.38–1.58	0.472
LDH						
≥ULN vs. <ULN	1.09	0.55–2.16	0.815	1.78	0.83–3.83	0.135
dNLR						
≥3 vs. <3	1.57	0.79–3.15	0.196	1.25	0.60–2.61	0.556
LIPI score						
Good vs. intermediate	1.05	0.49–2.28	0.894	0.90	0.40–2.02	0.800
Good vs. poor	1.48	0.61–3.59	0.388	0.81	0.31–2.14	0.673

Abbreviations: BM, brain metastases; CI, confidence interval; dNLR, derived neutrophil to lymphocyte ratio; DS-GPA, diagnosis-specific graded prognostic assessment; ECOG-PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICIs, immune checkpoint inhibitors; iPFS, intracranial progression-free survival; IrAE, immune-related adverse events; LDH, lactate dehydrogenase; LIPI, lung immune prognostic index; ULN, upper limit of normal; PFS, progression-free survival.

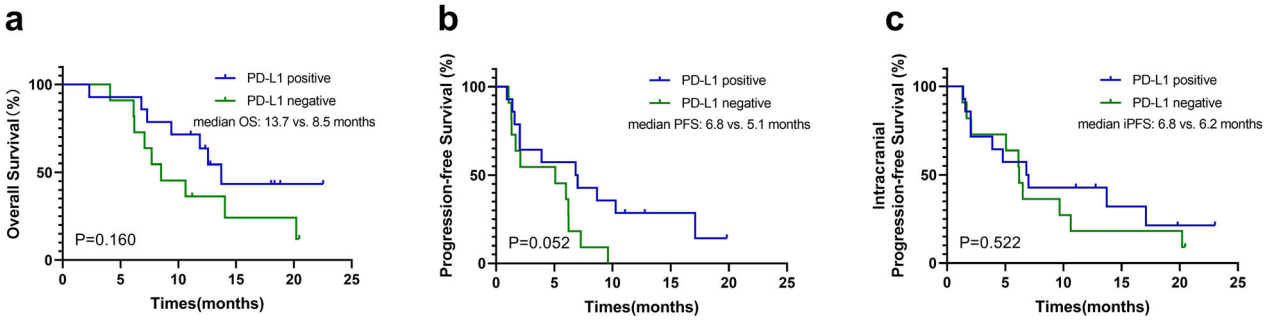

FIGURE 6 Kaplan–Meier analysis for OS (a), PFS (b) and iPFS (c) in population with PD-L1 expression detection ($n = 25$). The respective log-rank p value for descriptive purposes only. OS, overall survival; iPFS, intracranialprogression-free survival; PFS, progression-free survival

Efficacy of combined immunotherapy and radiotherapy

We further analyzed the difference of efficacy among patients receiving ICIs plus concurrent radiotherapy ($n = 10$), ICIs with non-concurrent radiotherapy ($n = 19$), and ICIs alone ($n = 11$). Higher iORR was significantly observed in patients who received ICIs in combination with concurrent radiotherapy over compared to ICIs alone (iORR = 80.0% vs. 25.0%, $p = 0.030$). However, survival benefits (iPFS, PFS, and OS) were not observed for patients who received ICIs combined with concurrent radiotherapy compared to those received ICIs alone (median iPFS = 13.6 vs. 3.9 months, $p = 0.203$; median PFS = 6.6 vs. 3.9 months, $p = 0.987$; median OS = 20.2 vs. 13.7 months, $p = 0.174$) (Figure 3(a)–(c)). ICIs combined with non-concurrent radiotherapy showed similar iORR compared to ICIs alone (iORR = 21.1% vs. 25.0%, $p = 1.000$). There was no statistically significance among iPFS, PFS, or OS benefit (median iPFS = 6.1 vs. 3.9 months, $p = 0.607$; median PFS = 5.3 vs. 3.9 months, $p = 0.306$; median OS = 11.7 vs. 13.7 months, $p = 0.629$) between ICIs combined with non-concurrent radiotherapy or ICIs alone (Figure 3(d)–(f)).

Efficacy of immunotherapy combined with chemo or antiangiogenic therapy

When patients are given ICIs in combination with chemotherapy ($n = 14$) it failed to improve iORR (43.5% vs. 27.8%, $p = 0.300$) and iPFS (median iPFS = 13.7 vs. 4.3 months, $p = 0.078$) (Figure 4(c)) as compared to ICI monotherapy ($n = 18$). Interestingly, remarkable improvement of OS, but not that of ORR or PFS, was observed in the ICIs in combination with chemotherapy group compared to the ICI monotherapy (ORR = 42.9% vs. 16.7%, $p = 0.132$; median OS = 20.2 vs. 7.7 months, $p = 0.024$; median PFS = 6.7 vs. 4.3 months, $p = 0.293$) (Figure 4(a), (b)). However, when ICIs were combined with antiangiogenic therapy ($n = 9$) such combination showed neither systemic nor intracranial clinical benefits as compared to the ICI monotherapy (iORR = 11.1% vs. 27.8%, $p = 0.628$; median iPFS = 5.4 vs. 4.3 months, $p = 0.701$; ORR = 11.1% vs. 16.7%, $p = 1.000$; median OS = 11.9 vs. 7.7 months, $p = 0.777$; median PFS = 5.3 vs. 4.3 months, $p = 0.319$) (Figure 4(d)–(f)).

Univariate and multivariate analysis for prognostic factors for NSCLC-BM

Further, we evaluated the effect of different variables on clinical outcomes using univariate and multivariate Cox model analysis. Univariate analyses of OS revealed that the number of brain lesions ≥3 ($p = 0.025$), the lines of ICI treatment ≥2 ($p = 0.002$, Figure 5(a)), and dNLR ≥3 ($p = 0.049$, Figure 5(b)) were associated with poor survival. On the other hand, further investigation showed that the lines of ICI treatment ≥2 ($p = 0.005$) and dNLR ≥3 ($p = 0.010$) were independent prognostic factors of OS based on multivariate analyses (Table 2). Meanwhile, only the lines of ICI treatment ≥2 served as a negative indicator according to univariate analyses both on PFS ($p = 0.023$, Figure 5c) and iPFS ($p = 0.030$, Figure 5(d)) (Table 3).

Median OS for patients who received ICIs as first-line treatment and second- or later- line treatment were 29.6 (95% CI = NA) months and 8.5 (95% CI = 4.98–12.02) months, respectively. And median PFS were 6.7 (95% CI = 2.21–11.26) months and 4.3 (95% CI = 0.63–7.91) months, respectively. In addition, median iPFS were 6.7 (95% CI = 5.25–8.21) months and 2.3 (95% CI = 0.00–5.69) months, respectively.

With respect to PD-L1 expression status, the median OS, PFS and iPFS were similar between PD-L1-positive patients ($n = 14$) and PD-L1-negative patients ($n = 11$) (median OS = 13.7 vs. 8.5 months, $p = 0.160$; median PFS = 6.8 vs. 5.1 months, $p = 0.052$; median iPFS = 6.8 vs. 6.2 months, $p = 0.522$) (Figure 6(a)–(c)).

DISCUSSION

Here, we analyzed the efficacy and survival of NSCLC patients with BM treated with ICIs in the real-world setting. Forty-one NSCLC patients identified as driver-gene negative were enrolled in our study. For the entire cohort of patients,

immunotherapy exhibited favorable efficacy on the intracranial lesions and OS. We found that combining ICI treatments with concurrent radiotherapy results in a better intracranial response, whereas ICIs combined with chemotherapy was associated with superior OS. In general, ICIs serve as an effective strategy to treat CNS metastases in NSCLC patients without driver gene mutations based on our analysis.

The efficacy of ICIs on NSCLC patients with brain metastasis is a significant concern, but most patients with BM were under-represented in clinical trials. The outcomes of ICIs for less-selected NSCLC patients with BM were determined rarely. In a retrospective study, Hendriks et al.[24] observed the iORR was 27.3% for 255 NSCLC-BM patients treated with ICI monotherapy regardless of PD-L1 expression. A meta-analysis reported by Kim et al.[25] showed that patients treated with ICI monotherapy, but no brain radiotherapy had an iORR of 24%, suggested a similar remission rate of intracranial lesions with extracranial lesions for ICI monotherapy. More recently, one prospective single-arm clinical trial had also evaluated the efficacy of pembrolizumab in 37 NSCLC-BM patients with PD-L1 ≥1% (over 50% received previous local brain therapy), and the iORR was 29.7%.[26] PD-L1 expression is a strong indicator for the efficacy of ICIs. A multicenter retrospective study analyzed NSCLC-BM patients with PD-L1 expression ≥50% treated with pembrolizumab in first-line setting.[27] The iORR was 62.5% in 11 patients who had not received local radiotherapy, indicating tremendous potentials of ICIs for BM in patients with previously untreated NSCLC and high PD-L1 expression. However, Tozuka et al.[28] showed a poor iORR of 13.3% for anti-PD-1/PD-L1 antibody monotherapy in 15 NSCLC patients with active BM. This may be because of the high proportion of patients with PS >2 (38%) and EGFR or ALK mutations (25%) who may have a low response to immunotherapy.[29,30] In addition, Gauvain et al.[31] reported that the iORR of 9% on NSCLC patients with BM treated with nivolumab, which was lower than previous studies of immunotherapy monotherapy. Whereas, it is vital to note that those patients were treated with nivolumab as second- or later-line treatment, and most of their PD-L1 expressions were not determined (12% with PD-L1 overexpression and 76% with unevaluable PD-L1 status). In our small sample size study, seven patients with BM were treated with ICIs monotherapy but not local radiotherapy. Consistently, ICIs showed promising efficacy for the intracranial lesions with an iORR of 28.6% and presented a similar response rate with extracranial lesions. It is worth noting that most patients were treated in a second-line setting with ICIs. Another critical point is the PD-L1 expression, and one patient with PD-L1 ≥50% reached PR for the intracranial response, suggesting preferred outcomes for the patients with PD-L1 high expression. Moreover, our systemic and intracranial survival data (OS of 11.3 months and PFS of 4.9 months) were also consistent with results reported in other series.[32,33] Collecting evidence supports active efficacy of ICIs monotherapy for brain metastases in NSCLC patients without driver gene mutations, especially for patients with previously untreated NSCLC and high PD-L1 expression.[14,16,17,27,34–36]

The optimal therapeutic regimen for the management of the NSCLC-BM remains controversial in the era of immunotherapy. Preclinical research has revealed that radiotherapy may increase immunotherapy sensitivity by increasing the release of tumor antigens, thereby improving antigen presentation and opening the BBB to recruit tumor-infiltrating lymphocytes (TILs).[37–39] Therefore, combining ICIs with radiotherapy may play a synergistic role in treating NSCLC with BM. Consistent with such mechanisms, several studies exhibited preferred intracranial efficacy in a combinational treatment of NSCLC-BM patients with ICIs and radiotherapy.[25,40–43] ICIs combined with concurrent radiotherapy improved iORR, but not survival (iPFS, PFS, and OS) compared to ICIs alone, suggesting that concurrent radiotherapy and ICIs may serve as a potential preferred treatment strategy for the higher rate of lesion response in CNS metastases A meta-analysis revealed that the patients who received combination therapy with ICI and radiotherapy showed better iORR compared to ICI monotherapy.[25] Geier et al.[44] demonstrated that prior radiotherapy along with nivolumab improved iORR (30.0% vs. 6.7%). However, the survival advantage (iPFS, PFS, and OS) was observed in patients treated with concurrent radiotherapy compared to ICIs alone therapy, but did not reach a statistically significant level in their study. The optimal treatment time of radiotherapy with ICIs was discussed by Ahmed et al.[45] They found that delivery of ICIs during or after radiotherapy exhibited superior efficacy on the intracranial lesions, but not OS. Consistently, our study suggested that concurrent radiotherapy plus ICIs was associated with higher intracranial response, but not OS. Therefore, ICIs combined with concurrent radiotherapy may serve as a potential treatment regimen for NSCLC with BM. Further studies need to evaluate the efficacy and safety of this combination in a prospective design.

Platinum-based chemotherapy exerts multiple positive immune-modulatory influences giving a solid rationale for combination treatment with immunotherapy.[46] Immunotherapy combined with chemotherapy has become the standard treatment regimen for patients with metastatic NSCLC based on durable responses and improved survival regardless of PD-L1 expression. In clinical studies of NSCLC, ICIs combined with chemotherapy have yielded positive extracranial outcomes. However, most active or untreated BM patients have been excluded from clinical trials. The intracranial response has not been determined in less-selected patients with BM.[20,47,48] Additionally, a meta-analysis by Yang et al.[49] found that patients with BM who underwent ICIs combined with chemotherapy only experienced superior OS, but not PFS or iPFS than chemotherapy. Sun et al.[47] suggested that ICIs combined with chemotherapy significantly showed superior survival (iPFS, PFS, and OS) than ICI monotherapy. This study found that ICIs combined with chemotherapy group prolonged OS compared with ICI monotherapy group, and baseline characteristics of patients between these two groups were equally. Therefore, ICIs combined with chemotherapy may show a superior survival advantage than ICI monotherapy for less-selected NSCLC patients with BM. The optimal treatment strategies for NSCLC with BM should be further investigated

in prospective large-patient cohorts. In this direction, a single-arm, open-label, phase II clinical trial of immunotherapy combined with chemoradiotherapy in EGFR/ALK-negative NSCLC patients with brain metastases is currently ongoing in our center.

We observed that PD-L1 expression was not associated with survival. Similarly, Takamori et al.[50] examined PD-L1 expression in patients with BM and found no impact on survival, even PD-L1-positive BM group presented a worse brain-specific disease-free survival than the PD-L1-negative BM group ($p < 0.05$). At the same time, another study has identified PD-L1 expression as a survival predictor in BM patients.[51] An unrelated correlation of PD-L1 expression with survival in our study can be attributed to several reasons. First, there was organ heterogeneity for PD-L1 expression in the tested samples, which varied with the treatment process.[52] Our biopsy sites from lung, brain, and lymph node metastasis may have different PD-L1 expression patterns and different predictive values for ICI benefits in NSCLC. Second, PD-L1 is considered an effective predictor for ICI monotherapy, but not for ICI combination treatment.[53] In our study, more than half of the patients received combination treatment, which interfered with the predictive effect of PD-L1 on survival.

Interestingly, we found that the line of ICIs treatment was an independent prognostic factor for OS, PFS, and iPFS in NSCLC patients with BM. At the same time, an apparent survival benefit was observed when immunotherapy was used early. Some analysis reported the independent prognostic value of dNLR, LDH, and LIPI scores in immunotherapy for NSCLC.[22,54] Here, we found that patients with a dNLR ≥3 at baseline showed worse OS than the dNLR <3 subgroup, but LDH and LIPI scores did not affect survival in our cohort. The practical and convenient biomarkers to distinguish NSCLC patients with BM benefiting from immunotherapy still need further exploration.

Our study has several limitations:

1. Its modest sample size and retrospective nature would prevent definitive conclusions. Our cohort was quite heterogeneous regarding local and systemic treatments; perhaps a sensitivity analysis with a large population may have been helpful.
2. There were some biases in patients' treatment strategies, such as different ICI treatment regimens, with or without local therapy.
3. The data on PD-L1 expression was not comprehensive, as discussed above.

Eventually, because of the wide variety of ICIs in our study, the influence of different ICIs on the results cannot be ruled out. But our results suggest that BMs treated with ICIs tend to have clinical benefits.

CONCLUSION

This real-world analysis found that immunotherapy can provide a favorable efficacy for NSCLC patients with BM. Moreover, ICIs combined with concurrent radiotherapy may show better intracranial response, whereas a combination of ICIs and chemotherapy may be associated with favorable survival outcomes.

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CONFLICT OF INTEREST

The authors have declared that no competing interest exists.

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