Original Article

Efficacy and safety of immune checkpoint inhibitors for advanced non-small cell lung cancer with leptomeningeal metastases harboring targetable mutations

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Background: Driver gene-positive non-small cell lung cancer (NSCLC) patients are prone to develop leptomeningeal metastasis (LM), leading to an extremely high mortality. The objective of this study was to assess the efficacy and safety of immune checkpoint inhibitors (ICIs) treatments for patients with NSCLC and LM harboring targetable mutations.

Methods: We retrospectively collected records of patients with NSCLC harboring targetable mutations and prescribed ICIs following the diagnosis of LM at Huashan Hospital, Fudan University. In addition, we reviewed relevant literature and enrolled patients who met the inclusion criteria. Clinical characteristics were statistically analyzed, and the Kaplan-Meier method and log-rank test were employed to assess the median progression-free survival (mPFS) and median overall survival (mOS).

Results: A total of 37 patients with NSCLC harboring targetable mutations who received ICIs after LM diagnosis were included. The median age of the enrolled patients was 54 years (range, 33–70 years), and 62.2% were female. Following ICI administration, the intracranial objective response rate (iORR) and intracranial disease control rate (iDCR) for all enrolled patients were 18.9% and 62.2%, respectively. The mPFS of all patients was 2.5 months [95% confidence interval (CI): 2.166–2.834 months] and the mOS was 5.8 months (95% CI: 5.087–6.513 months). Both univariate and multivariate analyses revealed a significant increase in mOS or individuals who had previously undergone cranial radiation therapy compared to those who had not. Furthermore, different histology molecular types were found to be potentially associated with survival time.

Conclusions: Some patients with NSCLC harboring targetable gene mutations following LM diagnosis may benefit from ICI treatment with relatively good tolerance. However, further screening of the most suitable patient populations for ICIs is required.

Keywords: Leptomeningeal metastases (LM); non-small cell lung cancer (NSCLC); immune checkpoint inhibitors (ICIs)

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Introduction

Leptomeningeal metastases (LM) occur when cancer cells spread to the compartments that contain cerebrospinal fluid (CSF). The incidence of LM from solid tumors has risen due to advancements in systemic treatments for individuals with solid tumors, leading to extended patient survival, along with the refinement of more sensitive detection techniques (1). Non-small cell lung cancer (NSCLC) is a frequent contributor to LM, accounting for 3–5% of cases of advanced NSCLC. The incidence is even higher in specific patient subgroups with targetable mutations due to their extended lifespan resulting from novel molecular treatments (2) and may still be underestimated by virtue of the nonspecific symptoms and signs. Although the use of tyrosine kinase inhibitors (TKIs) has been shown to extend the lifespan of individuals with targetable mutations, the efficacy of TKIs in eradicating micro-metastases is compromised by insufficient TKI levels in the CSF, leading to a higher frequency of LM (3).

In previous retrospective studies (4,5), it was found that LM was more prevalent in individuals with epidermal growth factor receptor (*EGFR*) mutations than in those without *EGFR* mutations. Moreover, LM has been found in approximately 10.3% of cases with anaplastic lymphoma kinase (*ALK*) rearrangements and consistently presents as a late complication (6). Other genetic alterations may potentially yield benefit from targeted therapy, including the fusion of ROS proto-oncogene 1 (*ROS1*); alterations or amplification of Kirsten rat sarcoma virus (*KRAS*) G12C, proto-oncogene B-Raf (*BRAF*) V600E, and mesenchymal-epithelial transition factor (*MET*) exon 14; rearrangement of RET proto-oncogene (*RET*) and neurotrophic tyrosine receptor kinase type 1–3 (*NTRK 1–3*); and insertion mutations of human epidermal growth factor receptor 2 (*HER2*) exon 20 (7,8). However, there is no standard treatment regimen for patients with LM from NSCLC who harbor genomic alterations and have developed resistance to targeted therapy.

The diagnosis and monitoring of LM are challenging, as LM is a severe complication related to an unfavorable prognosis and a diminished quality of life for patients. A diagnostic flowchart, developed by the European Association for Neuro-Oncology-European Society for Medical Oncology (EAN-ESMO) group, includes neurologic symptoms, imaging, and CSF cytology (9,10). Initial clinical manifestations can be subtle, with typical indications comprising headache, nausea, vomiting, impaired vision, neurological impairments, unsteady walking, stupor, and even cerebral herniation (11). Brain and spinal cord magnetic resonance imaging (MRI) are standard methods for evaluating LM. Characteristic MRI findings include linear ependymal enhancement, enhancement of cranial nerve roots, and nodular leptomeningeal enhancement (12,13). The primary diagnostic criterion for LM is detecting tumor cells in the CSF. Although the specificity of CSF cytology methods is high, their quality and sensitivity are low. Huashan Hospital has created a mature platform dedicated to improving the positive rate of CSF cytology by accumulating practical experience and adjusting various procedural details. To optimize results, it is recommended to process recently obtained CSF samples within a 30-minute timeframe. In cases where the initial CSF cytology yields negative results,

Highlight box

Key findings

- In our study, the median age of the enrolled patients was 54 years (range, 33–70 years) and 62.2% were female.
- Following immune checkpoint inhibitor (ICI) administration, the intracranial objective response rate and intracranial disease control rate for all enrolled patients were 18.9% and 62.2%, respectively. The median progression-free survival of all patients was 2.5 months [95% confidence interval (CI): 2.166–2.834 months], and the median overall survival (mOS) was 5.8 months (95% CI: 5.087–6.513 months).
- Both univariate and multivariate analyses revealed a significant increase in mOS for individuals who had previously undergone cranial radiation therapy compared to those who had not (P=0.02). Furthermore, different histology molecular types were found to be potentially associated with survival time.

What is known and what is new?

- Leptomeningeal metastases (LM) were more prevalent in non-small cell lung cancer (NSCLC) individuals harboring targetable gene mutations. Currently, the efficacy of immunotherapy in NSCLC cases harboring targetable mutations is controversial.
- Little data have been reported on the efficacy of ICI therapy in patients with NSCLC and LM, particularly those with targetable gene alterations and a history of failed tyrosine kinase inhibitor therapy. Our study showed the potential role of ICI therapy in these populations.

What is the implication, and what should change now?

- While ICI treatment improved survival in certain patients in our study and produced acceptable adverse events, the use of ICIs in patients with LM from driver gene-positive NSCLC still needs significant advancement. This is especially important due to the limited availability of curative drugs for patients with LM.

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a second lumbar puncture should be considered. Additional immunocytochemical staining of cytokeratin (CK) 7, thyroid transcription factor 1 (TTF1), and CK20 may help to confirm the diagnosis when CSF cytology reports are equivocal, suspicious, or atypical of the CSF.

The prognosis of LM remains poor despite systemic treatment. Immune checkpoint inhibitors (ICIs) have emerged as the preferred initial therapy for patients with driver gene-negative NSCLC regardless of programmed cell death-ligand 1 (PD-L1) expression (14). However, for driver gene-positive patients, platinum-based chemotherapy remains the standard treatment option when TKI therapies prove ineffective (15). Currently, the efficacy of immunotherapy in NSCLC cases harboring targetable mutations is controversial (16). Subgroup analyses from the IMpower150 study (17) indicated that the combination of atezolizumab (PD-L1 antibody), bevacizumab, and chemotherapy improved overall survival (OS) in patients with *EGFR*-mutated NSCLC previously treated with TKIs. However, it is worth noting that this subgroup analysis involved a relatively small number of patients (n=35). In addition, ICIs have demonstrated encouraging efficacy in treating brain metastases from lung cancer, and it has been shown that the immune response can help these immune inhibitory molecules cross the blood-brain barrier (18-20). Unfortunately, there are limited data on the efficacy of ICIs for patients with LM, as these patients are often excluded from clinical trials. The LM population remains an understudied cohort and may have an opportunity for improved outcomes in the era of immunotherapy.

In this retrospective study, we conducted a thorough literature review and collected data from NSCLC patients harboring targetable mutations who were diagnosed with LM and treated with ICIs at Huashan Hospital. The aim of this study was to assess the efficacy and safety of ICI treatment in patients with advanced NSCLC harboring targetable mutations who have been diagnosed with LM. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-477/rc).

Methods

Data collection and patients

Data from patients with NSCLC harboring targetable alterations and diagnosed with LM between January 2018 and May 2022 were collected. All patients were diagnosed and treated at the Department of Oncology, Huashan Hospital, Fudan University. A systematic search of the scholarly works published from January 2017 to May 2022 was carried out on the PubMed, Cochrane, and Embase Library databases with the specified search terms "leptomeningeal metastases", "lung cancer", "immune checkpoint inhibitor", "PD-1/PD-L1 antibody", "nivolumab", "pembrolizumab", "atezolizumab", "avelumab", "sintilimab", and "camrelizumab". We selected clinical studies that specifically investigated individuals with LM harboring targetable mutations treated with ICIs. Only studies with complete and comprehensive clinical information were included. Ultimately, six extensive multicenter series were selected from which 23 patients with NSCLC with targetable driver mutations were included. The flow diagram of patient enrollment is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Huashan Hospital, Fudan University (approval No. 2022-634). Informed consent was taken from all the patients.

Inclusion and exclusion criteria

LM is diagnosed by the detection of tumor cells in the CSF or by the observation of characteristic findings on the MRI of the brain/spinal cord that are accompanied by typical neurological symptoms. In this study, the neuroimaging findings were confirmed by at least two experienced radiologists. Only patients treated with ICI monotherapy or combination therapy after the development of LM were included in the study. ICIs included PD-1 or PD-L1 antibodies such as nivolumab, pembrolizumab, atezolizumab, toripalimab, camrelizumab, and sintilimab. With the integration of molecular testing into advanced NSCLC management, identifying actionable genetic changes has become an essential part of the diagnostic criteria for NSCLC. The alterations that were targeted included deletions in *EGFR* exon 19; mutations in L858R/S768I/L861Q/G719X/T790M, *KRAS* G12C, and *BRAF* V600E; rearrangements in *ALK*, *ROS1*, and *RET*; rearrangements or alterations in *MET* exon 14; fusions in *NTRK* 1–3; and insertion of exon 20 in *HER2* (*ERBB2*). These gene alterations were defined as targetable mutations due to the approval of corresponding targeted therapies for NSCLC by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).

The inclusion and exclusion criteria for the published

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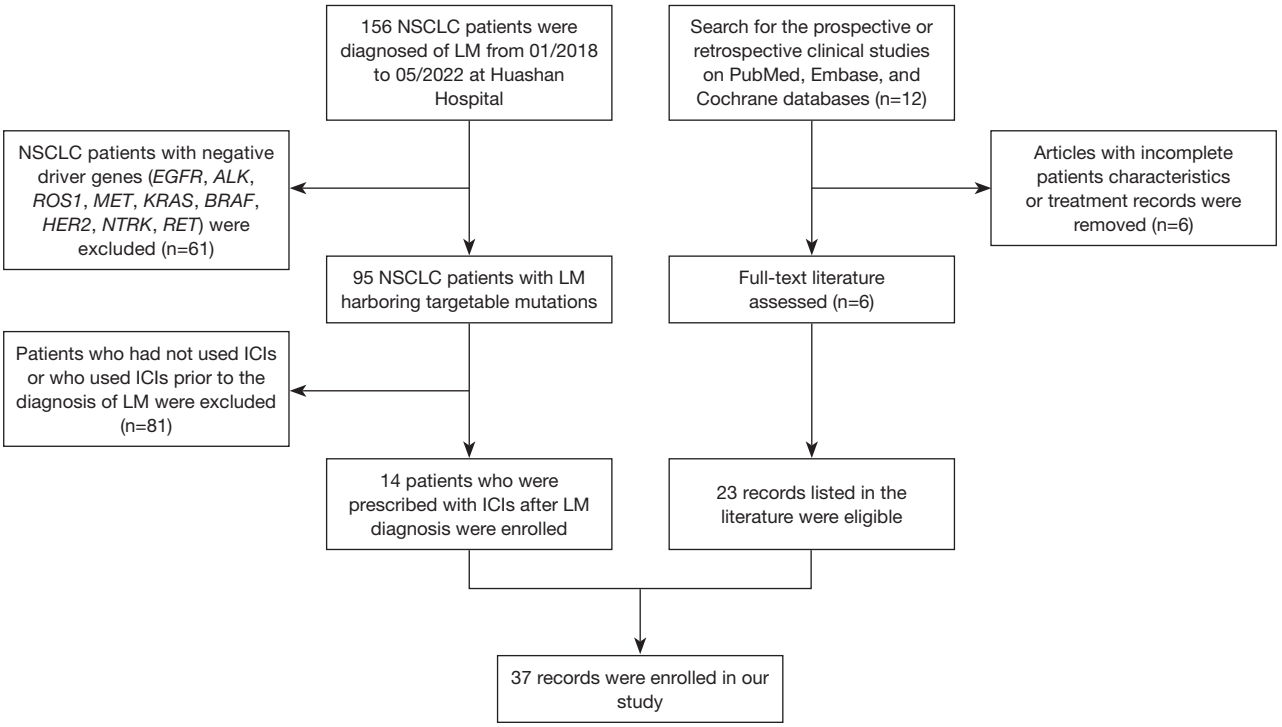

Figure 1 Flow diagram of patient enrollment. NSCLC, non-small cell lung cancer; LM, leptomeningeal metastases; ICI, immune checkpoint inhibitor; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; *ROS1*, ROS proto-oncogene 1; *MET*, mesenchymal-epithelial transition factor; *KRAS*, Kirsten rat sarcoma virus; *BRAF*, proto-oncogene B-Raf; *HER2*, human epidermal growth factor receptor 2; *NTRK*, neurotrophic tyrosine receptor kinase; *RET*, RET proto-oncogene.

series data were identical. Patients diagnosed with NSCLC and LM based on positive CSF analysis and/or imaging before beginning ICI therapy were included in all six prospective studies (14,20-24). Of these patients, those harboring targetable mutations were screened, and those with inadequate data were excluded. We ensured that all enrolled patients had been treated with ICIs after LM diagnosis and administration of standard treatment. These selected studies had the largest and most detailed medical records of patients with NSCLC and LM.

Assessment and statistical analysis

Data on demographics, clinical features, pathology, molecular analysis, treatment strategies, and survival outcomes were obtained retrospectively from the medical records and follow-up. Detailed neurological examinations, cerebrospinal MRI, computed tomography (CT) scans, and CSF tests were performed every 8–10 weeks or when patients complained of new neurological symptoms or signs. Apart from non-measurable lesions such as LM, other lesions were assessed based on the Response Evaluation Criteria in Solid Tumors (version 1.1) (25). For LM, the evaluation followed the Response Assessment in Neuro-Oncology (RANO) LM criteria (26), which involve a comprehensive assessment combining neurological system evaluation, neuroimaging evaluation, and standard CSF cytology, with the outcomes categorized as response, stable disease (SD), or progression. Both intracranial and extracranial conditions were evaluated according to these criteria.

Progression-free survival (PFS) started from the initiation of ICI treatment until the occurrence of progressive disease (PD) or death from any cause. OS was considered to be the time interval from the start of ICI treatment to death for any reason. The main outcomes of the study were the following: intracranial objective response rate (iORR), defined as the proportion of patients who achieved a complete response (CR) or a partial response (PR) with intracranial measurable lesions after treatment or those with LM showing a response; intracranial disease control rate (iDCR), defined as the proportion of patients with objective

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response and those with an SD of intracranial lesions for a certain period; PFS; OS; and adverse events (AEs). We employed the Kaplan-Meier method to compute survival curves and employed the log-rank test to compare variables.

In addition, we used a Cox proportional hazards regression model to assess the potential correlation between the clinical factors we analyzed and survival time. Statistical analyses were performed using SPSS 27.0 (IBM Corp.).

Results

Patient selection and characteristics

A total of 156 patients with stage IV or recurrent metastatic NSCLC were diagnosed with LM between January 2018 and May 2022 at Huashan Hospital, Fudan University. Among them, 95 patients harbored targetable mutations, and 14 patients were treated with ICIs after LM diagnosis. All patients experienced continued disease progression or intolerable side effects during standard treatments, particularly those treated with TKIs. Our literature search further filtered six prospective clinical studies with the largest populations and detailed multicenter records, with a focus on cases of NSCLC with LM. In the literature, 29 out of the 51 patients with NSCLC and LM possessing targetable mutations were treated with ICIs. After excluding six patients with incomplete records, 37 patients were ultimately included. The median follow-up duration after the initial ICI treatment was 10 months.

The characteristics of the 37 patients in our study are summarized in *Table 1*. The median age of the cohort was 54 years (range, 33–70 years), and 23 patients (62.2%) were female. More than half (19/37) of the patients were former or current smokers. During ICI therapy, brain metastases were found in 64.9% (24/37) of the individuals. Only five patients did not show typical neurological symptoms, while the remaining 32 patients did show these symptoms, varying from mild headache to severe neurological symptoms, such as visual disorders, headache, vomiting, facial paralysis, sensory disorders, and unstable walking. Although tumor cells were found in the CSF of 21 patients (56.8%), the patients from our institution had a higher percentage of positive results from CSF cytology at 78.6% (11/14), owing to the higher sensitivity of our CSF cytology diagnostic platform.

The patients harbored different gene subtypes at baseline: 20 (54.1%) harbored *EGFR* mutations, including the more common *EGFR* mutations such as exon 19 deletion or exon 21 L858R point mutation, and the less common *EGFR* mutations such as the exon 18 G719X point mutation. Some of these patients acquired the *EGFR* T790M mutation after first- or second-generation EGFR-TKI therapy. One patient acquired an additional C797S mutation after treatment with a third-generation EGFR-TKI and benefited from the combined treatment with first- and third-generation inhibitors. Furthermore, two patients acquired *MET* exon 14 alterations after developing resistance to EGFR-TKIs, two had *ERBB2* E20 mutations, and seven had *KRAS* mutations. In addition to these driver genes, alteration of the *TP53* gene was the most common combined mutation.

Patients' treatment modalities

The history of radiotherapy (RT) was unavailable for ten patients, while 16 underwent brain RT either before or during their ICI treatments. None of the patients received ICIs as their initial treatment. Most patients opted for ICIs in backline therapy, with a median of fourth treatment lines. In our study, the ICI therapies comprised PD-1 and PD-L1 antibodies as a monotherapy (18/37, 48.6%) or in combination (19/37, 51.4%) with chemotherapy, bevacizumab, anlotinib, or other agents. The most commonly prescribed ICI was nivolumab, taken by 19 patients, followed by pembrolizumab, which eight patients took. Additionally, four patients received camrelizumab, two received toripalimab, and one received sintilimab. Three patients received the PD-L1 antibody atezolizumab. As the patients with LM consistently presented with symptoms of high intracranial pressure, five received ventriculoperitoneal shunt (VPS) surgery to relieve hydrocephalus. The details of LM, PFS, and OS resulting from ICIs for each patient are listed in *Table 2*.

Efficacy of ICI therapy

Seven patients (18.9%) demonstrated PR consisting of intracranial involvement after a comprehensive assessment, which included an evaluation of the combined neurological system, neuroimaging, and CSF cytology. Moreover, 16 patients (43.2%) exhibited stable symptoms of intracranial metastases, while 14 patients (37.8%) experienced PD with deteriorating symptoms after immunotherapy. As a result, the iORR and iDCR for all enrolled patients were 18.9% and 62.2%, respectively. All 14 patients from our institute received at least two

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Table 1 Characteristics of the enrolled patients

Case No.	Age at start of ICI (years)	Gender	Smoking history	ECOG PS score	Histology/molecular status	PD-L1	BM	Symptoms before ICI treatment
1	54	F	N	2	*EGFR*	+	Y	Headache, vomiting
2	59	M	N	2	*EGFR*	–	N	Headache, epileptic seizure
3	56	F	N	2	*EGFR*	–	Y	Headache, blindness
4	70	M	Y	2	*EGFR*	–	Y	Facial paralysis
5	47	F	N	1	*ALK*	+	Y	Headache, neck pain
6	69	F	N	2	*EGFR*	UA	Y	Headache, nausea
7	55	F	N	2	*EGFR*	UA	Y	Headache, vomiting
8	70	M	Y	2	*EGFR, MET*	UA	Y	Visual disturbances
9	50	F	N	2	*ERBB2*	UA	Y	Visual disturbances
10	52	M	N	2	*EGFR*	UA	N	Headache, walking problems
11	33	M	Y	2	*EGFR*	UA	N	Headache, vomiting
12	57	M	Y	2	*EGFR*	UA	Y	Nausea, walking problems
13	65	M	N	2	*EGFR*	UA	Y	Dysarthria, walking problems
14	51	F	N	1	*ALK, MET*	+	Y	Headache, nausea
15	65	F	Y	1	*KRAS*	+	N	Visual disturbances
16	53	M	Y	1	*KRAS*	UA	N	Facial paralysis
17	63	F	UA	1	*KRAS*	+	Y	Headache
18	69	M	Y	1	*ALK*	UA	N	Light headache, vertigo
19	52	F	Y	2	*EGFR*	UA	Y	Blindness, nausea
20	55	F	Y	2	*KRAS*	UA	Y	Headache, nausea
21	51	F	Y	1	*MET*	+	Y	Sensory loss, pain in legs
22	69	F	N	2	*EGFR*	UA	Y	None
23	53	F	Y	1	*BRAF*	+	N	Light headache
24	44	F	N	1	*EGFR*	+	Y	None
25	56	M	Y	1	*EGFR*	+	Y	None
26	38	M	N	1	*EGFR*	UA	N	None
27	34	F	N	2	*EGFR*	+	N	Headache, nausea, vomiting
28	45	M	Y	1	*ERBB2*	–	Y	Headache
29	45	F	N	1	*EGFR*	UA	N	Dizziness, speech disorder
30	66	F	Y	2	*KRAS*	+	N	Visual disorder
31	54	M	Y	2	*KRAS*	UA	Y	Facial paralysis
32	64	F	UA	1	*KRAS*	+	Y	Headache
33	69	M	Y	2	*ALK*	UA	N	Light headache, vertigo
34	52	F	Y	2	*EGFR*	–	Y	Visual disorder, nausea
35	51	F	Y	2	*MET*	+	Y	Sensory loss
36	69	F	N	2	*EGFR*	UA	Y	None
37	54	F	Y	2	*BRAF*	+	N	Light headache

ICI, immune checkpoint inhibitor; F, female; M, male; N, no; Y, yes; UA, unavailable; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; *MET*, mesenchymal-epithelial transition factor; *KRAS*, Kirsten rat sarcoma virus; *BRAF*, proto-oncogene B-Raf; PD-L1, programmed cell death-ligand 1; BM, brain metastasis.

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Table 2 Leptomeningeal metastases details, treatment modalities, neurological symptoms, and survival time from ICI initiation of each patient

Case No.	Type of ICI	Mono/ combined	CSF	MRI	Brain RT	VPS	Brain RT before ICI	Intracranial response	ICI PFS (m)	OS (m)	ICI treatment line	Major AE
1	Nivolumab	Combined	+	Y	N	Y	N	PR	4	9.5	3	Arrhythmia
2	Nivolumab	Combined	+	Y	N	Y	N	PR	2.5	3.5	4	Myelosuppression
3	Nivolumab	Combined	–	Y	Y	N	Y	PR	4	11	4	Encephalitis
4	Camrelizumab	Combined	+	Y	Y	N	Y	PR	7	10	4	Eructation
5	Camrelizumab	Combined	eq	Y	Y	N	Y	SD	6	10+	4	Vomiting
6	Camrelizumab	Combined	+	Y	N	N	N	PD	2	5.5	4	Hypothyroidism
7	Sintilimab	Combined	+	Y	N	Y	N	SD	2	5.5	7	Hypothyroidism
8	Nivolumab	Combined	+	Y	N	N	N	PD	1	4.2	7	UA
9	Toripalimab	Combined	+	N	N	N	N	SD	2	8	2	Encephalitis
10	Nivolumab	Combined	+	Y	N	Y	N	PD	1	3.2	5	Eructation
11	Toripalimab	Combined	+	Y	N	Y	N	SD	2	2	3	Hypothyroidism
12	Nivolumab	Combined	–	Y	Y	N	Y	SD	2	19	3	Encephalitis
13	Atezolizumab	Combined	+	Y	N	N	N	SD	2	6	4	Eructation
14	Camrelizumab	Combined	+	N	Y	N	Y	SD	4	14+	3	Hypothyroidism
15	Pembrolizumab	Mono	–	Y	N	UA	N	SD	7.3	13+	3	UA
16	Nivolumab	Mono	+	Y	N	UA	N	PR	6.4	10.7	2	UA
17	Pembrolizumab	Mono	–	N	Y	UA	Y	SD	6.1	12.9+	2	UA
18	Nivolumab	Mono	+	Y	N	UA	N	PD	2.8	3.7	4	UA
19	Nivolumab	Mono	–	Y	Y	UA	Y	SD	2.5	10.6+	4	UA
20	Nivolumab	Mono	–	Y	Y	UA	Y	PD	2	2	2	UA
21	Pembrolizumab	Mono	+	Y	Y	UA	Y	PD	1.9	2	5	UA
22	Nivolumab	Mono	–	Y	Y	UA	Y	PD	1.7	5.8	7	UA
23	Nivolumab	Mono	+	Y	N	UA	N	PD	0.7	1.9	3	UA
24	Atezolizumab	Combined	+	N	Y	UA	Y	PR	2.8	6.2	UA	UA
25	Pembrolizumab	Combined	–	Y	N	UA	N	SD	2.2	2.1	UA	UA
26	Atezolizumab	Combined	–	Y	N	UA	N	PD	5	5.4	UA	UA
27	Pembrolizumab	Combined	–	N	Y	UA	Y	PD	0.2	3	UA	UA
28	Nivolumab	Combined	+	Y	N	UA	N	PR	0.6	0.8	UA	UA
29	Nivolumab	Combined	+	Y	N	UA	N	SD	4.7	4.8	UA	UA
30	Pembrolizumab	Mono	–	Y	N	UA	N	SD	7	13	UA	UA
31	Nivolumab	Mono	–	Y	N	UA	N	PR	6	11	UA	UA
32	Pembrolizumab	Mono	eq	Y	Y	UA	Y	SD	5.8	13	UA	UA
33	Nivolumab	Mono	+	Y	N	UA	N	PD	2.8	3.7	UA	UA
34	Nivolumab	Mono	–	Y	Y	UA	Y	SD	2.8	11	UA	UA
35	Pembrolizumab	Mono	+	Y	Y	UA	Y	PD	2	2	UA	UA
36	Nivolumab	Mono	UA	Y	Y	UA	Y	PD	2	5.8	UA	UA
37	Nivolumab	Mono	+	Y	N	UA	N	PD	0.5	1.9	UA	UA

ICI, immune checkpoint inhibitor; Mono, monotherapy; Combined, combined therapy; CSF, cerebrospinal fluid; eq, equivocal; MRI, magnetic resonance imaging; Y, yes; N, no; RT, radiotherapy; VPS, ventriculoperitoneal shunt; UA, unavailable; PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; m, months; AE, adverse event.

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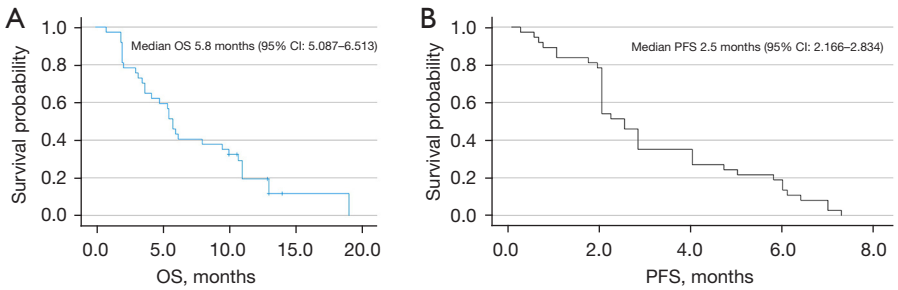

Figure 2 Kaplan-Meier estimates of OS and PFS for all enrolled populations. OS, overall survival; CI, confidence interval; PFS, progression-free survival.

cycles of ICIs and baseline brain MRI imaging. Two patients (patient #5 and patient #7) were excluded due to progression of extracranial lesions (including liver and lymph nodes), while the other 12 patients were excluded due to poor control of LM lesions. Of these, one patient benefited from ICIs with symptom relief and extended PFS (patient #4). Among the seven patients with SD as the best central nervous system response, one experienced PR as the best extracranial response, and two patients did not experience intracranial PD according to MRI but did experience extracranial PD during follow-up.

As shown in *Figure 2*, the median PFS (mPFS) of all included patients was 2.5 months [95% confidence interval (CI): 2.166–2.834 months], and the median overall survival (mOS) was 5.8 months (95% CI: 5.087–6.513 months). Notably, better mPFS and mOS were observed in the subgroup of patients with *KRAS* mutations than in the subgroups with *EGFR* alterations, *ALK* fusion variants, and those with other mutations (such as *BRAF*, *MET*, and *ERBB2*); specifically, the mPFS were 6.1, 2.1, 3.4, and 1.3 months for these subgroups, respectively, while the mOS were 12.9, 5.65, 3.7, and 1.9 months, respectively. The 3-month PFS and OS rates were 48.1% and 75.7%, respectively. Only three patients obtained a PFS exceeding 6 months (3/37), with one experiencing gradual symptomatic improvement. Furthermore, the 6-month OS rate and 12-month OS rate were 43.2% and 16.2%, respectively. Throughout the treatment course, 13 patients had the opportunity to receive subsequent therapy such as chemotherapy, bevacizumab, or anlotinib in combination with or without ICIs or TKIs, along with the best supportive care.

Univariate analysis revealed that a history of cranial radiation therapy was significantly associated with a longer OS (P=0.02) (*Figure 3A*). However, mPFS between the groups that underwent RT or without RT showed no statistical significance (P=0.94) (*Figure 3B*). In addition, different histology molecular types were associated with the PFS and OS. As previously mentioned, patients in the *KRAS* group had the longest OS and PFS among the four genomic groups, as illustrated in the survival curves (*Figure 3C*,*3D*). Meanwhile, monotherapy/combination therapy, age, gender, smoking history, performance status (PS) score, and presence or absence of brain metastasis were not statistically associated with PFS or OS. After adjusting for the other variables, multivariate analysis (*Figure 4*) confirmed the associations between a history of cranial radiation therapy, different genomic groups, and OS.

AEs and safety

AEs of the 14 patients from our institution were recorded in *Table 2*. Eructation, vomiting, myelosuppression, and constipation, were attributable to chemotherapy. The majority of AEs was hypothyroidism, which was determined to be related to immunotherapy. In one patient (patient #3), a post-treatment psychiatric abnormality was assessed by a neurologist, who identified it as autoimmune encephalitis, which was potentially linked to the ICI treatments. Certain AEs, such as interstitial pneumonia, were absent in the examined 14 patients.

Discussion

TKIs are the optimal treatment option for patients with LM harboring targetable gene alterations (21,27). Unfortunately, upon failure of TKI therapies, these patients typically have very few alternative therapeutic options. Although little data have been reported on the efficacy of ICI therapy in patients with NSCLC and LM, particularly

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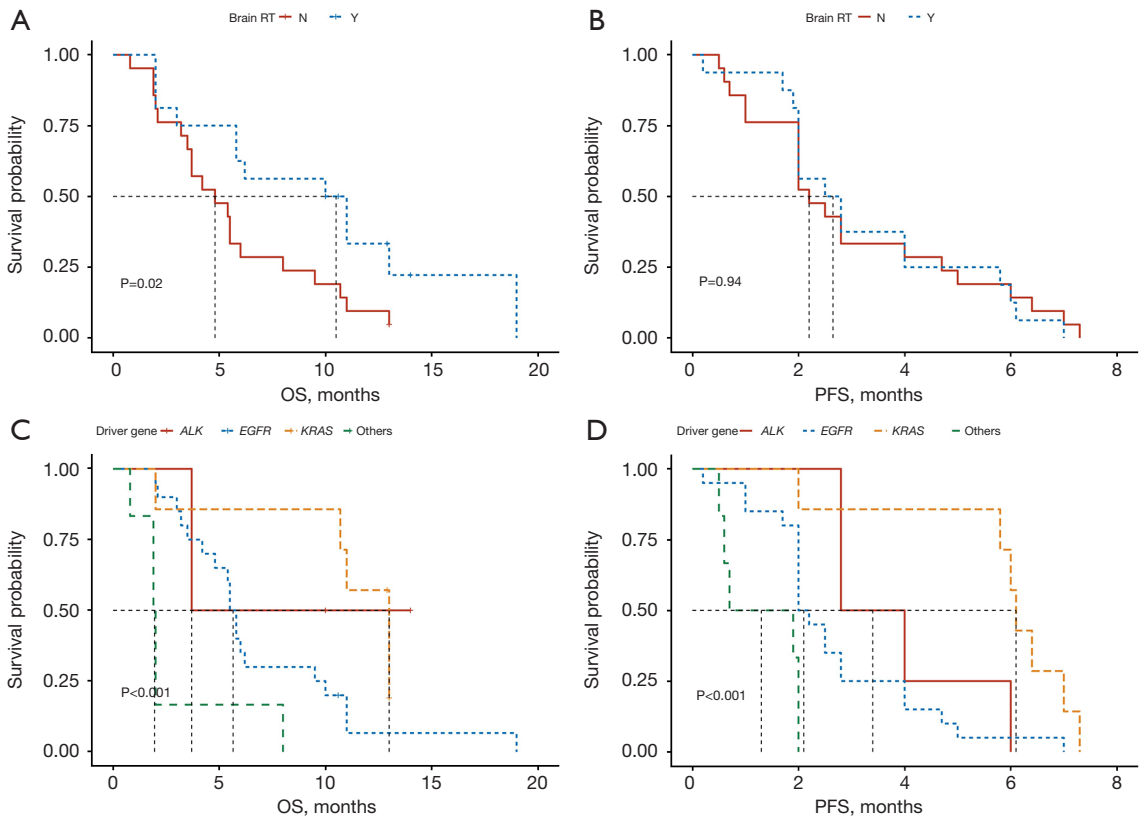

Figure 3 Kaplan-Meier estimates of PFS and OS after the treatment with ICIs. (A) OS of patients with/without RT; (B) PFS of patients with/without RT; (C) OS of different histology molecular subgroups; (D) PFS of different histology molecular subgroups. OS, overall survival; PFS, progression-free survival; RT, radiotherapy; N, no; Y, yes; *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma virus; ICI, immune checkpoint inhibitor.

those with targetable gene alterations and a history of failed TKI therapy, our study showed the potential role of ICI therapy in these populations. In this study, we analyzed 37 cases from multiple centers in detail.

There is currently a lack of agreement regarding the potential benefits of intracranial RT for patients with LM (28,29). Notably, there has been no implementation of randomized clinical trials to evaluate the efficacy and tolerance of RT in LM populations. A retrospective analysis found that NSCLC patients with LM (n=125) had a poor mOS of only 3 months. Furthermore, no therapeutic advantage was observed with whole-brain RT (30), and retrospective studies have failed to reveal any correlation between whole-brain RT and survival in patients with LM (31,32). However, our study found that the mOS of patients with a history of brain RT was longer than that of those lacking such a history.

In recent years, retrospective studies have shown that a combination of radiation with immunotherapy can improve locoregional and distant control by stimulating immune response and result in better survival outcomes (33-35). Radiation appears to boost the immune system by activating T cells, dendritic cells, and other immune cells in the tumor microenvironment (TME), releasing tumor-associated antigens and improving antigen presentation (36,37). In addition, brain RT can potentially disturb the blood-brain barrier, thereby facilitating the entry of additional peripheral effector T cells into the CSF.

Based on our results, we concluded that the clinical response to ICI therapy varies depending on the presence of diverse driver mutations. Regarding these molecular subgroups, *KRAS*-mutated patients with LM appeared to benefit the most from ICI treatment compared to those with *EGFR*-, *ALK*-, *BRAF*-, or *HER2*-mutated tumors. Consistent with the results of the IMMUNOTARGET study (38), patients with *KRAS*-mutated tumors (n=271)

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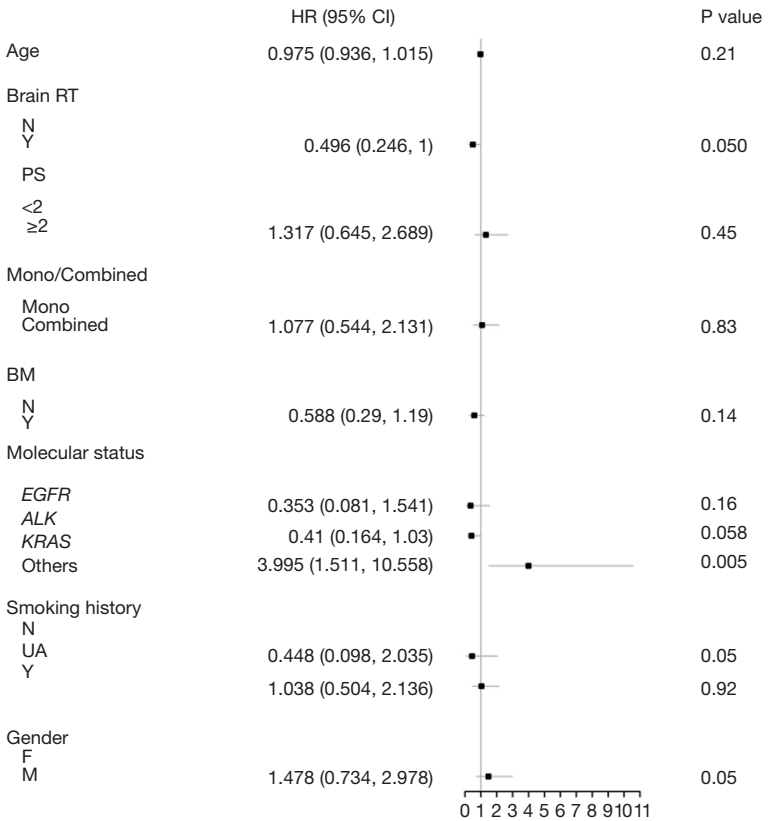

Figure 4 Forest plots of the associations of clinical factors with OS. RT, radiotherapy; N, no; Y, yes; PS, performance status; Mono, monotherapy; Combined, combined therapy; BM, brain metastasis; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; *KRAS*, Kirsten rat sarcoma virus; UA, unavailable; F, female; M, male; HR, hazard ratio; CI, confidence interval; OS, overall survival.

exhibited the highest percentage of PR or CR. The ORR reached 26%, with a mPFS of 3.2 months. This may be attributed to the higher likelihood of PD-1 and PD-L1 expression in *KRAS*-mutated NSCLC (39).

However, due to the limited sample size and missing data, we could not identify a substantial association between the clinical benefits of ICIs in the *KRAS*-mutated group and the degree of PD-L1 expression.

Given the significantly elevated incidence of LM in individuals with NSCLC harboring *EGFR* mutations, exploring the potential advantages of ICI treatment for *EGFR*-mutated patients with LM is imperative. In our restricted cohort, 20 out of 37 patients with LM harbored *EGFR* mutations. Among them, four showed symptomatic relief after ICI treatments (patient #7 might have benefited from VPS surgery), and two achieved a PFS exceeding 5 months (patients #4 and #27 received combined therapy). Despite the ongoing debate regarding the efficacy of immunotherapy in individuals with *EGFR*-mutated NSCLCs, our findings suggest that certain patients, including those with LM, can receive positive clinical results. A greater understanding of these cases may help us to identify patient populations harboring targetable mutations that would benefit from ICI therapy. A recent analysis summarized the impact of various oncogenic drivers of NSCLC on the immune TME and the response to ICIs (37). Further investigations are necessary to uncover the mechanisms responsible for the response to the therapy.

Several studies have confirmed the favorable tolerability of immune monotherapy, immune-combination platinum-containing chemotherapy, immune-combination chemotherapy, and anti-hematopoietic therapy after resistance to *EGFR*-TKI treatment. Additionally, the adverse effect profile was similar to the driver gene-negative NSCLC patients. The ATLANTIC study's results (40) showed that $EGFR^+$ or ALK^+ patients treated with durvalumab monotherapy had a similar adverse effect profile to those of $EGFR^-$ and ALK^- patients. The

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ORIENT-31 (41) and ORIENT-11 (42) studies explored the use of sintilimab in combination with chemotherapy in patients with resistant *EGFR*-mutated and primary driver gene-negative nonsquamous NSCLC. They found that both the efficacy and safety were generally consistent in both studies. In the *EGFR* mutation subgroup analysis of the IMpower150 study, AEs observed in the $EGFR^+$ subgroup treated with atezolizumab combined with chemotherapy and bevacizumab were consistent with those of the overall population. In this study, only AEs from 14 patients at our institute—who were prescribed combination immunotherapy with chemotherapy and antiangiogenic therapy—were recorded. Generally, the treatment was relatively well tolerated, even in patients with poor PS scores. However, special attention is warranted for patients diagnosed with autoimmune encephalitis after ICI therapy, especially in those with intracranial metastases.

As discussed above, although ICI treatment could improve survival in some specific patients in our study and provide acceptable AEs, the application of ICIs in patients with LM from driver gene-positive NSCLC still requires substantial development. This is particularly crucial given the limited availability of curable drugs for patients with LM. Moving forward, an in-depth investigation into the underlying mechanisms and the identification of the most suitable treatment populations is warranted. Ongoing studies on LM are anticipated to provide valuable guidelines, shaping the trajectory of ICI application in this challenging clinical context.

Conclusions

The study found that some NSCLC patients with LM harboring targetable mutations might benefit from immunotherapy and have relatively good tolerance. For patients with LM who are resistant to targeted therapy, PD1/PD-L1 drugs, either alone or in combination, can be tried. However, more research is needed to accurately identify the benefiting population.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Huashan Hospital, Fudan University (approval No. 2022-634). Informed consent was taken from all the patients.

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