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ORIGINAL RESEARCH

Anti-PD1 Therapy Plus Whole-Brain Radiation Therapy May Prolong PFS in Selected Non–Small Cell Lung Cancer Patients with Brain Metastases: A Retrospective Study

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Background: Whole-brain radiotherapy (WBRT) remains an essential modality of treatment for brain metastases (BMs) derived from non-small cell lung cancer (NSCLC) patients and anti-PD-1 therapy has demonstrated intracranial responses in these patients. We aimed to evaluate if the combination of the two treatments could yield additive efficacy.

Methods: A retrospective review of our institution's database was carried out to identify NSCLC patients with BMs who had been treated with anti-PD1 therapy and/or WBRT between 2015 and 2020. Patient characteristics, main outcomes, including progression-free survival (PFS) and overall survival (OS), and factors affecting these outcomes were analyzed. SPSS 24 was used for statistical analysis. Appropriate statistical tests were employed according to the type of data.

Results: Overall, 21 NSCLC BM patients were identified that had received WBRT. Of these, ten had been additionally treated with anti-PD1 therapy within 30 days of WBRT initiation. Median PFS was 3 (95% CI 0.8–5.1) months with WBRT alone versus 11 (95% CI 6.3–15.6) months with combined treatment. Risk of disease progression was 71% lower with the combined approach (HR 0.29, 95% CI 0.11–0.80; p=0.016). A trend toward improved OS was also observed with the combined approach (HR 0.33, 95% CI 0.08–1.12; p=0.107). Concurrent treatment (p=0.028) and male sex (p=0.052) were associated with improved PFS, while OS was associated only with age (p=0.02).

Conclusion: Concurrent WBRT and anti-PD1 therapy may delay progression and improve survival in BM patients with confirmed EGFR- and ALK-negative NSCLC histology. Prospective studies are warranted to validate and elucidate on the additive effect of the two modalities.

Keywords: brain metastasis, BM, whole-brain radiation therapy, WBRT, non–small cell lung cancer, NSCLC, immune checkpoint blockade, ICB, combination, combined therapy

Introduction

Lung cancer is the leading cause of death from cancer in the US.[1] Non–small cell lung carcinoma (NSCLC) constitutes 85% of lung cancer cases.[1,2] A majority of NSCLC cases are diagnosed at an advanced stage (around 60%) with a 5-year survival rate of merely 5%.[1] In general, platinum-based chemotherapy is offered as first-line treatment for advanced-stage NSCLC patients, with a 20% response rate.[3,4] Molecular targeted agents are recommended for NSCLC patients with specific genetic mutations, such as *EGFR* and *ALK* rearrangement, which are present in 10%–15% and 5% of NSCLC

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cases, respectively.[5–7] Prevalence of EGFR$^+$ (up to 30%) and ALK$^+$ NSCLC is higher among Asian populations.[8] However, ALK rearrangement is likely because of the high proportion of never-smokers (30% in Asia versus 10% in US) and younger age of onset in East Asian NSCLC cases.[9] Recently, anti-PD1/PDL1 monoclonal antibodies have also been approved for advanced-stage NSCLC in first/second-line settings, alone or in combination with chemotherapy.[10] Innovative strategies, such as addition of stereotactic ablative radiotherapy (RT) to immunotherapy, are also being pursued, and have demonstrated abscopal responses in metastatic sites and delayed disease progression.[11,12]

Around 40% of NSCLC patients experience brain metastases (BM) during disease progression.[13,14] Depending on the presentation, management of BMs may comprise whole-brain radiation therapy (WBRT) alone, surgical resection with/without stereotactic radiosurgery (SRS)/WBRT, and SRS alone or with/without WBRT.[15–18] A surge in the application of SRS has emerged in recent years.[19] Nonetheless, WBRT alone remains a major component of BM management.[15,19,20] Chemotherapy fails to attack BMs due to selective screening of the blood–brain barrier.[21] On the other hand, molecularly targeted and immunotherapeutic agents have shown intracranial responses in NSCLC BM patients.[22–42] Of the former, gefitinib (87.8%), erlotinib (82.4%), icotinib (67.1%), afatinib (35%), and osimertinib in EGFR$^+$ NSCLC and crizotinib (21%), ceritinib (73%), alectinib (57%), brigatinib (42%–67%), lorlatinib (71%), and ensartinib (64%) in ALK$^+$ NSCLC have shown excellent intracranial responses.[22–33] Molecularly targeted agents have also displayed additive effects in combination with RT compared to RT alone, but these are restricted to a small percentage of NSCLC patients.[43–46] For NSCLC BM patients with no genetic mutations (EGFR$^-$/ALK$^-$), immunotherapeutic agents, such as anti-CTLA4 and anti-PD1/PDL1 mAbs can be an optimal option. In fact, combination of RT and immunotherapeutic agents has demonstrated synergistic responses in BM patients.[47–55] Herein, we present a retrospective review of NSCLC BM patients treated with WBRT alone or WBRT plus anti-PD1 to elucidate on additive effects of additional anti-PD1 therapy.

Methods

Patient Selection

A retrospective review was performed of 21 EGFR- and ALK-negative NSCLC patients with BMs who had been treated at our institution. Ethics approval was obtained from the institutional review board of Shenzhen People's Hospital, Shenzhen, China. Written informed consent for participation was obtained from patients or their guardians in accordance with the Declaration of Helsinki.[56] STROBE guidelines for cohort studies were followed for reporting.[57] The patients had either received WBRT alone or WBRT plus anti-PD1 monoclonal antibodies during 2015–2020. All included patients had developed BMs after being treated with first-line platinum-based chemotherapy at initial lung cancer diagnosis. Patients in the control group had been offered second-line docetaxel chemotherapy for systemic disease and WBRT for BMs. The median dose of WBRT was 30 Gy/10 F for the entire cohort. Anti-PD1 therapy was initiated within 30 days of WBRT induction. A median of six cycles (three to 17) had been received by the patients. Baseline characteristics, eg, age, sex, smoking history, performance status, histopathology of lung cancer, and cancer differentiation, were recorded for the entire cohort.

Follow-Up and End Points

The primary end point was progression-free survival (PFS), defined as time from BM diagnosis to disease progression on clinical and radiological evaluation during follow-up or death following treatment induction. Progression of disease was defined according to RECIST 1.1 criteria, which characterizes new BM occurrence also as disease progression.[58] Overall survival (OS) was the secondary end point and defined as time from BM diagnosis to death. Patients were followed up with clinical evaluation and radiological imaging (CTs and MRIs) obtained at 3-, 6-month, and 1-year intervals.

Statistical Analysis

Statistical analysis was carried out with SPSS 24. Relationships between groups for baseline characteristics were determined with chi–square tests for categorical variables, and Fisher's exact test was used when small cells were encountered using 2×2 contingency tables. For continuous variables, two-tailed *t*-tests were used to examine comparisons. Median OS, PFS, and univariate analyses were performed using the Kaplan–Meier method. Factors with $p<0.25$ on univariate analyses were selected for multivariate analyses. The Cox proportional-hazard model was adopted for calculating HRs and 95% CIs for OS and PFS and to undertake multivariate analyses. $p\leq0.05$ was considered to reflect statistical significance.

Results

Patient Characteristics

Our study looked at 21 patients with three or more BMs derived from confirmed EGFR-negative and ALK-negative stage IV NSCLC. A majority had poorly differentiated adenocarcinoma histopathology, as shown in Table 1. All patients were treated with WBRT between 2015 and 2020. Ten additionally received anti-PD1 antibody treatment initiated within 30 days of WBRT induction. Median age was 56 years and median follow-up 13 months. The cohorts differed significantly only in terms of smoking status (p=0.047). Never-smokers were predominant in the WBRT-alone group. The cohorts showed no significant differences for the other baseline characteristics: age, sex, histopathology, tumor differentiation, number of extracranial metastatic organs, and follow-up duration. Baseline characteristics of the participants are outlined in Table 1.

Progression-Free Survival

Median PFS was 3 (95% CI 0.8–5.1) months with WBRT alone versus 11 (95% CI 6.3–15.6) monthswith combined treatment (Figure 1). Risk of disease progression was 71% lower with the combined approach (HR 0.29, 95% CI 0.11–0.80; p=0.016). Potential predictors of PFS were

Table 1 Baseline characteristics of study participants

Cohorts	Overall	WBRT plus anti-PD1	WBRT alone	*p*
Patients, n	21 (100%)	10 (41%)	11 (59%)	
Age, years	55.6±12.5	59.6±10.04	52.1±13.9	0.187
Median (range)	56 (34–77)	58.5 (44–73)	48 (34–77)	
<60	14 (67%)	6 (43%)	8 (57%)	0.536
≥60	7 (33%)	4 (57%)	3 (43%)	
Sex				
Male Female	15 (71%) 6 (29%)	9 (60%) 1 (17%)	6 (40%) 5 (83%)	0.063
Smoking				
Never Former/current	11 (52%) 10 (48%)	3 (27%) 7 (70%)	8 (73%) 3 (30%)	**0.047***
NSCLC pathology				
Adenocarcinoma Squamous	18 (86%) 3 (14%)	8 (44%) 2 (67%)	10 (56%) 1 (33%)	0.473
Pathology differentiation				
Well Poor	2 (9%) 19 (91%)	1 (50%) 9 (47%)	1 (50%) 10 (53%)	0.944
KPS				
70–80 90–100	12 (57%) 9	7 (58%) 3 (33%)	5 (42%) 6 (67%)	0.253
Metastatic organs, n#				
Brain only Extracranial	11 (57%) 10 (43%)	4 (64%) 6 (60%)	7 (36%) 4 (40%)	0.277
Follow-up	14.3±5.9	15.3±4.3	13.5±7.3	0.516
Median (range)	13 (2–30)	14.5 (9–24)	13 (2–30)	

Notes: *p<0.05. Data presented as means ± SD or n (%), unless indicated otherwise. #Extracranial organs other than primary organ (lung) included liver, bone, and breast.
Abbreviations: WBRT, whole-brain radiotherapy; NSCLC, non–small cell lung carcinoma; KPS, Karnofsky performance status.

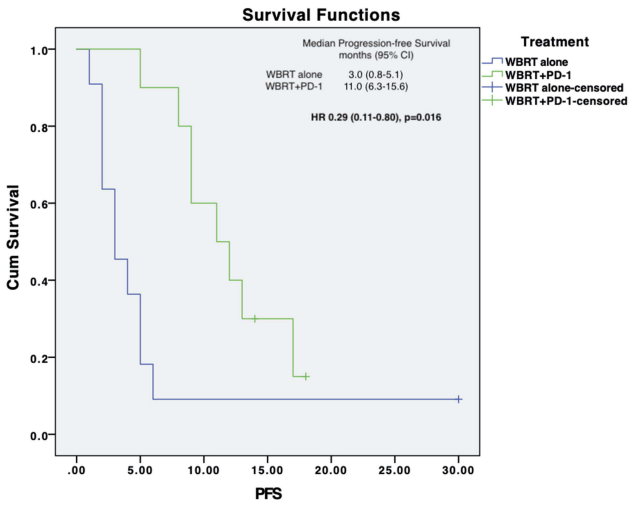

Figure 1 Kaplan–Meier progression-free survival (PFS) curves for WBRT alone (no PD1), and WBRT plus PD1 inhibition therapy (WBRT+PD1).
Abbreviation: Cum, cumulative.

examined: age, sex, smoking history, tumor histopathology and differentiation, KPS score, and existence of extracranial metastatic organs (Tables 2 and 3). With the exception of WBRT plus anti-PD1 treatment (p=0.010), none of the factors investigated was significantly associated with PFS. Three factors that showed close association (p<0.25) with PFS on univariate analyses were selected for multivariate analysis. Of the three factors, treatment type and male sex showed significant prognostic association with PFS on multivariate analyses.

Overall Survival

Median OS was 13 (95% CI 9.9–16.0) months with WBRT alone versus 24 months (95% CI not reached) with WBRT plus anti-PD1 therapy (Figure 2). The risk of death was 67% lower with WBRT plus anti-PD1 therapy than WBRT alone (HR 0.33, 95% CI 0.08–1.12; p=0.107). None of the factors examined on univariate analyses was significantly associated with improved OS (Table 4). Only treatment type was suggestive of prognostic value for OS (p=0.088). Multivariate analyses consisted of predictive factors that showed close association with OS: treatment type, age, sex, and number of metastatic organs. Only age was significantly associated with better OS (p=0.020). There was a suggestion of prognostic association for sex (p=0.073) and treatment type (p=0.070).

Table 2 Univariate analysis of progression-free survival

Factors	Comparators	n	Survival time	
			Median (95% CI)	Significance
Treatment group	WBRT alone WBRT plus anti-PD1	11 10	3 (0.8–5.5) 11 (6.3–15.6)	***p*=0.010***
Age, years	<60 ≥60	14 7	11 (0.0–26.3) 5 (1.3–8.6)	*p*=0.284
Sex	Female Male	6 15	2 (not reached) 9 (2.4–9.5)	***p*=0.060**
Smoking	Never Former/current	11 10	5 (1.7–8.2) 9 (0.0–18.2)	*p*=0.337
NSCLC pathology	Adenocarcinoma Squamous/large cell	3 18	5 (1.8–8.1) 13 (0.0–27.4)	*p*=0.368
Pathology differentiation	Well Poor	2 19	3 (not reached) 6 (2.4–9.5)	*p*=0.351
KPS	≤80 90–100	12 9	5 (0.7–9.2) 6 (0.1–11.8)	*p*=0.745
Metastatic organs, **n**[#]	Brain only Extracranial	12 9	5 (3.9–6.0) 9 (0.7–17.2)	***p*=0.105**

Notes: *p<0.05. Bold font indicates factors with p<0.25 and selected for multivariate analysis. [#]Extracranial organs other than primary organ (lung) included liver, bone, and breast.
Abbreviations: WBRT, whole-brain radiotherapy; NSCLC, non–small cell lung carcinoma; KPS, Karnofsky performance status.

Table 3 Multivariate analysis of progression-free and overall survival

Factors	Comparators	HR (95% CI)	Significance
Predictive factors for PFS			
Treatment group	WBRT plus anti-PD1 WBRT alone	0.29 (0.09–0.87)	***p*=0.028***
Sex	Male Female	0.33 (0.10–1.01)	***p*=0.052***
Metastatic organs[#]	Brain only Extracranial	0.41 (0.14–1.22)	*p*=0.112
Predictive factors for OS			
Treatment group	WBRT plus anti-PD1 WBRT alone	0.23 (0.05–1.12)	*p*=0.070
Age, years	<60 ≥60	0.12 (0.02–0.71)	***p*=0.020***
Sex	Male Female	0.25 (0.05–1.14)	*p*=0.073
Metastatic organs[#]	Brain only Extracranial	0.38 (0.07–1.90)	*p*=0.238

Notes: *$p<0.05$. [#]Extracranial organs other than primary organ (lung) included liver, bone, and breast.
Abbreviations: WBRT, whole-brain radiotherapy; NSCLC, non–small cell lung carcinoma.

Discussion

Advances in systemic therapies, ie, molecularly targeted therapy and immunotherapy, have opened up new therapeutic options for BM patients.[22–42,59,60] Both these systemic treatments have shown intracranial responses and prolonged survival.[22–42] In our study, patients who had received WBRT were also treated with anti-PD1 therapy. In comparison to the cohort with only brain-directed WBRT, these patients showed prolonged PFS and OS.

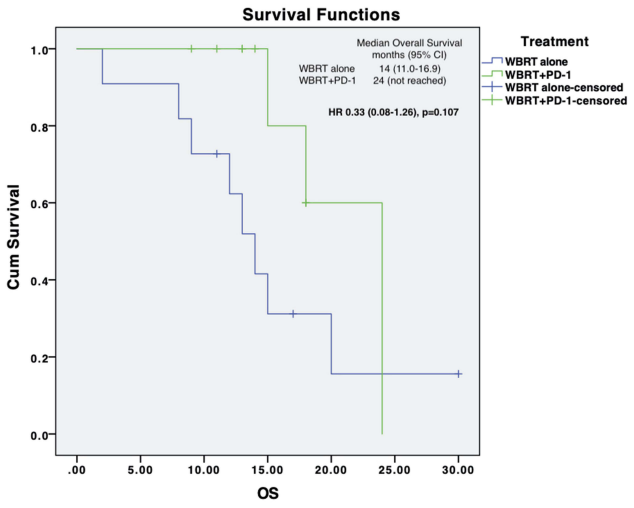

Figure 2 Kaplan–Meier overall survival (OS) curves for WBRT alone (no PD1), and WBRT plus PD1-inhibition therapy (WBRT+PD1).
Abbreviation: Cum, cumulative.

Our results are supported by other studies carried out with similar designs, where adding immunotherapy to RT resulted in a benefit for NSCLC BM patients.[42,47–55,61–64] In patients with a history of RT (brain and extracranial), pembrolizumab significantly improved PFS (HR 0.56, 95% CI 0.34–0.91; *p*=0.019) and OS (HR 0.58, 95% CI 0.36–0.94; *p*=0.026) compared to patients receiving pembrolizumab without RT history.[47] Secondary analysis of a phase III trial also revealed superior PFS (HR 0.38. 95% CI 0.16–0.91; *p*=0.02) and OS (HR 0.74, 95% CI 0.49–1.13; *p*=0.16) with atezolizumab to chemotherapy in which both cohorts had received RT to the brain.[48] A large retrospective study comprising 13,998 NSCLC patients revealed that addition of immunotherapy (n=545) to RT was associated with an improvement in OS (13.1 vs 9.7 months, $p<0.0001$).[49] Unfortunately, no details were provided, and the study was published only as an abstract. In a separate study involving NSCLC, response rates were similar between patients with BMs (20.6%) and without BMs (22.7%) with the use of combined treatment (*p*=0.484). Although PFS (1.7 months vs 2.1, *p*=0.009)

Table 4 Univariate analysis of overall survival

Factors	Comparators	n	Survival time	
			Median (95% CI)	Significance
Treatment group	WBRT alone WBRT plus anti-PD1	11 10	14 (11.0–16.9) 24 (not reached)	***p*=0.088**
Age, years	<60 ≥60	14 7	20 (10.5–29.4) 15 (12.9–17.0)	***p*=0.187**
Sex	Female Male	6 15	13 (5.79–20.2) 18 (not reached)	***p*=0.154**
Smoking	Never Former/current	11 10	24 (9.99–30.0) 18 (10.5–19.4)	*p*=0.668
NSCLC pathology	Adenocarcinoma Squamous/large cell	3 18	Not reached 18 (13.6–22.3)	*p*=0.773
Pathology differentiation	Good Poor	2 19	12 (not reached) 18 (12.5–23.4)	*p*=0.272*
KPS	≤80 90–100	12 9	15 (13.7–16.2) 20 (4.9–35.0)	*p*=0.626
Metastatic organs, n[#]	Brain only Extracranial	11 10	15 (13.8–16.1) 20 (16.1–23.8)	***p*=0.178**

Notes: *$p<0.05$. Bold font used for factors with $p<0.25$ and selected for multivariate analysis. [#]Extracranial organs other than primary organ (lung) included liver, bone, and breast.

Abbreviations: WBRT, whole-brain radiotherapy; NSCLC, non–small cell lung carcinoma; KPS, Karnofsky performance status.

and OS (8.6 months vs 11.4, $p=0.035$) were significantly longer in patients without BMs, there was no association found for BMs on OS on multivariate analysis.[50] In a retrospective matched-cohort study of NSCLC-derived BM patients who had received ICIs within 3 months showed significantly rapid regression of BMs (2.5 vs 3.1 months, $p<0.0001$) and improved CNS complete response (eight of 16 [50%] vs five of 32 [15.6%], $p=0.012$) for concurrent use of ICI and SRS (n=17, BMs 45) compared to SRS alone (n=34, BMs 92).[51] Nonetheless, no survival benefit was exhibited in the form of PFS (HR 2.18, 95% CI 0.72–6.62; $p=0.11$) or OS (HR 0.99, 95% CI 0.39–2.52; $p=0.99$). Likewise, a retrospective study of 85 NSCLC BM patients showed no statistical difference in median survival for an IT group (n=39) and CT group (n=46) — median OS 10 vs 11.6 months, $p=0.23$ — despite significantly superior lesion shrinkage for the IT cohort in a subset of patients with lesion volume >500 mm^3 (90% vs 47.8%, $p=0.001$).[52] In conclusion, in accordance with our study, these studies provide firm support for the use of immune checkpoint inhibitors along with RT.

Several studies that included BM patients with other primary tumor sites, such as melanoma, RCC, and others, in addition to NSCLC, have also shown intracranial responses with/without an improvement in PFS and OS.[42,53,54] An enhanced response rate of 60% was revealed with palliative RT plus durvalumab in a secondary analysis of BM patients (NSCLC, melanoma, RCC).[42] Continuation of PD1-inhibition therapy (median 179 days) after RT in a small subgroup of 25 BM patients who had also received initial PD1-inhibition therapy before RT showed an additional 238 days' improvement in survival.[54] In another retrospective study (n=260), improved median OS was observed with SRS/SRT and ICIs compared to SRS/SRT alone (14.5 vs 12 months).[53] However, this study failed to report any difference in PFS for treatment cohorts (PFS CI 2.3 vs nCI 2.3 vs SRS alone 3.7 months).[53] In a study by Kotecha et al, significant improvement in overall best objective response was observed with concurrent RT compared to SRS alone (67% vs 57%, $p=0.014$).[55]

Our study fails to provide direct proof of an additive effect for the two treatments; therefore, medical literature was explored to gather such evidence in BMs. Two arguments can be given that support the additive effect of RT–ICI combination. Firstly, as outlined in Table 5, several

Table 5 Studies reporting intracranial responses and clinical efficacy of immune checkpoint inhibitors alone or combined with RT in the management of brain metastasis–derived from NSCLC

Studies	Research design	Cancer type	Patients, n	Mutation status	Radiotherapy	Immunotherapy	Sequence of treatment	Intracranial response rate	Median PFS (95% CI)	Median OS (95% CI)	Follow-up
Single-arm studies reporting efficacy of ICI alone or in combination with RT											
Dudnik et al[36]	Retrospective	NSCLC	5	NR	NR	Nivo	NR	2 (40%) CR 1 PR 1	NR	NR	28 weeks
Hellmann et al[37]	Phase I trial	NSCLC	78	NR	NR	Cohort 1-Nivo 3 mg/kg q2w + ipi 1 mg/kg q12w (n=38) Cohort 2 Nivo 3 mg/kg q2 w + ipi 1 mg/kg q6w (n=39)	NR	Cohort 1 18 (47%) (31–64) Cohort 2 15 (38%) (23–55)	Cohort 1 8.1 (5.6–13.6) Cohort 2 3.9 (2.6–13.2)	1-year OS: Cohort 1 NC Cohort 2 69% (52–81)	Cohort 1 12.8 months (IQR 9.3–15.5) Cohort 2 11.8 months (6.7–15.9)
Spigel et al[38]	Phase II trial	NSCLC	13	EGFR (3)	NR	Atez (1,200 mg q3w)	NR	ORR 23% (range 5–54)	2.5 (1.2–4.2)	6.8 (3.2–19.4)	31.1 months
Gauvain et al[39]	Phase II trial	NSCLC	43	None (17) EGFR (3) KRAS (11)	NR	Nivo 3 mg/kg q3w)	NR	ORR 9% (3–23%)	3.9 (2.8–11.1)	7.5 (5.6–NR)	5.7 (2.7–8.4)
Crinò et al[40]	Retrospective	NSCLC	406	NR	NR	Nivo 3 mg/kg q3w)	NR	ORR 68 (17%) CR 4 (1%) PR 64 (16%) SD 96 (23%)	NR	8.6 months (6.4–10.8)	6.1 months (range 0.1–21.9)
Goldberg et al[41]	Phase II trial	NSCLC	18	EGFR (1) KRAS (4) ALK (1)	11 (WBRT 6/ SRS 5)	Pemb (10 mg/kg q2w)	Previous RT	ORR 33% (14–59), CR 4 PR 2	NR	7.7 months (3.5–NR)	6.8 months (IQR 3.1–7.8)

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Table 5 (Continued).

Studies	Research design	Cancer type	Patients, n	Mutation status	Radiotherapy	Immunotherapy	Sequence of treatment	Intracranial response rate	Median PFS (95% CI)	Median OS (95% CI)	Follow-up
Levy et al[42]	Phase II trial	NSCLC, melanoma, RCC	10	NR	10	Durv (10 mg/kg every q2w)	Palliative RT	ORR 60%, CR 2/10, PR 4/10, SD 4/10	NR	NR	15.6 months (range, 2.5–27.6)
Hendriks et al[50]	Retrospective	NSCLC	255	NR	172 (72 with WBRT, 99 with SRT and 2 with WBRT + SBRT)	ICI	RT followed by ICI	ORR 20.6%	1.7 (1.5–2.1)	8.6 months (95% CI 6.8–12.0)	15.8 months
Studies comparing previous/any RT and ICI and absence of RT											
Shaverdian et al[47]	Phase I trial	NSCLC	97	NR	42 (brain and extracranial)	Pemb (2 mg/kg q2w, 10 mg/kg q2/3w	Previous RT Time lapse 9.5 months (range 10–1,060, IQR 4.7–13.5)	NR	4.4 months (2.1–8.6) vs 2.1 (1.6–2.3) HR 0.56 (0.34–0.91), p=0.019	10.7 months (6.5–18.9) vs 5.3 (2.7–7.7 HR 0.58 (0.36–0.94), p=0.026	32.5 months (IQR 29.8–34.1)
Gadgeel et al[48]	Phase III trial	NSCLC	125 IT 61 CT 64	NR	106 IT 5 CT 51	Atez (1,200 mg q3w)	Previous RT	NR	Not reached vs 9.5 (5.8–20.1) HR 0.38 (0.16–0.91), p=0.02 (TTINSBMs)	16 (10.6–20.1) vs 11.9 (7.0–14.1) HR 0.74 (0.49–1.13), p=0.16	28 months
Studies comparing concurrent RT and ICI and RT alone											
Chen et al[53]	Retrospective	NSCLC (157), melanoma (70), RCC (33)	260	NR	260 (SRS/SRT)	Anti-PD1/PDL1 or Anti-CTLA4 mAb (OR concurrent)	Concurrent (within 2 weeks): 28 Before/after SRS/SRT: 51 SRS/SRT alone: 181	NR	2.3 (1–19)/2.3 (1–33)/3.7 (1–52) (CI/non-CI /SRS)	24.7/14.5/12.9 (CI/non-CI/SRS) CI vs non-CI: HR 2.69, p=0.002 CI vs SRS alone: HR 2.40, p=0.006	9.2 months

Shepard et al[51]	Retrospective	NSCLC	51 SRS–ICI 17 SRS 34	NR	51 SRS	Anti-PD1/PDL1	Concurrent (within 3 months)	CNS CR: 8/16 (50%) vs 5/32 (15.6%), p=0.012	HR 2.18 (0.72–6.62), p=0.11	HR 0.99 (0.39–2.52), p=0.99	10–16 months
Singh et al[52]	Retrospective	NSCLC	85 IT 39 CT 46	NR	85 SRS	Anti-PD1/PDL1 or anti-CTLA4 mAb (OR concurrent)	NR	Volume shrinkage in lesions with volume >500 mm^3: 90% vs 47.8%, p=0.001	NR	10 months (8.3–13.2) vs 11.6 months (7.7–15.6), p=0.23	NR
Kotecha et al[55]	Retrospective	NSCLC (99), melanoma (25), RCC (18), others	150 (1,003 BM lesions)	NR	SRS	PD1/PDL1 inhibitors	Concurrent 564 SRS alone 439	Intracranial response: immediate ICI vs nonimmediate ICI 71% vs 53%, p=0.008 Concurrent vs SRS alone: 59% vs 56%, p=0.34 Overall BOR: concurrent 67% vs SRS alone 57%, p=0.014 CR 348 vs 147 PR 181 vs 168 SD 94 vs 81 PD 51 vs 43, p=0.042	NR	30 months (24–38)	>12 months
Patruni et al[49]	Retrospective	NSCLC	13,998	NR	XRT	Immunotherapy	Concurrent 545			13.1 months vs 9.7, p<0.0001	

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Table 5 (Continued).

Studies	Research design	Cancer type	Patients, n	Mutation status	Radiotherapy	Immunotherapy	Sequence of treatment	Intracranial response rate	Median PFS (95% CI)	Median OS (95% CI)	Follow-up
Studies comparing concurrent RT and ICI according to timing of induction											
Pike et al[54]	Retrospective	NSCLC (79), melanoma (48), RCC (10)	137	EGFR 6	RT	Anti-PD1/PDL1 or anti-CTLA4 mAb (OR concurrent)	PD1 followed by RT (59) Discontinued anti-PD1 therapy (34) Continued (25)	NR	NR	Median 309 days vs 415, p=0.18 (additional 238 days) (discontinued vs continued)	NR
Ahmed et al[61]	Retrospective	NSCLC	17	EGFR (2) KRAS (3) Both (1)	SRS/FSRT	Anti-PD1/PDL1	Median 1.6 months before/ after RT	NR	6-month rate of distant brain control: 57% vs 0, p=0.05 (concurrent/ before vs after SRS)	HR 9.2 (1.9–65.3), 0.006 (univariate) (concurrent/ before vs after SRS)	8.7 months (range 1.3–53.4)
Lesueur et al[62]	Retrospective	NSCLC	104 (46 BM patients)	EGFR (2) KRAS (3) Both (1)	RT		6 months before (59) During or after 3 months (45)	NR	1-year PFS: 21.3% vs 12.5%, p=0.90	1-year OS: 55.3% vs 42.2%, p=0.39 (before vs during/after)	15.8 months (12.24-19.4)
Schapira et al[63]	Retrospective	Lung cancer	37 (85 BMs)	NR	SRS	PD1/PDL1 inhibitors	Concurrent vs before/after PD1-pathway inhibitors		1-year LC, 100% vs 72.3%, p=0.016 (concurrent/ after PD1i vs before PD1i) 1-year DBF, 38.5% vs 65.8% vs 100%, p=0.042 (concurrent vs before vs after PD1i)	1-year OS, 87.3% vs 70% vs 0, p=0.008 (concurrent vs before vs after PD1i)	

Koenig et al[64]	Retrospective	NSCLC (45), melanoma (38), RCC (6), Others	97 (580 BMs)	$EGFR^+$ 12 $BRAF^+$ 18	SRS	Anti-PD1/PDL1 or anti-CTLA4 mAb (OR concurrent)	Concurrent: within 4 weeks of SRS Others: within 5 months		Intracranial failure: LF 18 events (12/292 vs 6/206, p=0.224) DIF: 87 events (51/77 vs 36/50, p=0.314) Extracranial failure: 114 events (68/89 vs 46/52, p=0.079) (concurrent vs nonconcurrent)	Concurrent vs nonconcurrent: 48.6% vs 25.4% at 1 year; multivariate HR 0.57, 0.33–0.99; p=0.044	

Abbreviations: NSCLC, non–small cell lung carcinoma; RT, radiotherapy; SRT, stereotactic RT; FSRT, fractionated stereotactic RT; OS, overall survival; PFS, progression-free survival; TTINSBMs, time to incidence of new solitary brain metastases; WBRT, whole-brain RT; SRS, stereotactic radiosurgery; NR, not reported; mAB, monoclonal antibody; IT, immunotherapy; CT, chemotherapy; CNS, central nervous system; CR, complete response; PR, partial response; SD, stable disease; ORR, objective response rate; BOR, best objective response; DBF, distant brain failure; LF, local failure; CI, concurrent immunotherapy; Nivo, nivolumab; Pemb, pembrolizumab; Atez, atezolizumab; RCC, renal cell carcinoma; NC, not calculated.

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studies have reported intracranial activity of ICIs in BMs. As monotherapy, immune checkpoint inhibitors targeted at the PD1/PDL1 checkpoint have reported 9%–33% intracranial response rates in NSCLC BM patients.[36–41] Secondly, close sequencing of ICI with RT has been shown to enhance the additive effect of combined treatment, probably by taking advantage of local damage caused to the blood–brain barrier during RT, thereby providing a window of opportunity for immune checkpoint blockers to cross into the brain and be more effective.[65] Several studies reporting failure of the combined approach in improving outcomes of patients have pointed out the importance of RT–ICI sequencing.[51,53,55] For example, Chen et al found that patients receiving ICIs within 2 weeks (n=28) derived the best survival advantage (24.7 months), which was significantly better than other cohorts of nonconcurrent ICIs (HR 2.40, p=0.006) and SRS/SRT alone (HR 2.69, p=0.002).[53] Similarly, Kotecha et al study found no difference in intracranial response for the treatment difference (59% vs 56%, p=0.34); however, significant intracranial response was observed in patients receiving immediate ICI (71% vs 53%, p=0.008).[55] Alternatively, a longer window between the treatments may cause failure, as reported in Shepard et al (ICI within 3 months of RT).[51] A 14-day window for palliative RT and immunotherapy has been considered safe, and early initiation of immunotherapy after RT may also capitalize on residual and ongoing radiation-induced tumor-antigeni stimulation.[66,67] A concurrent approach is also supported by preclinical evidence to avert acquired resistance to fractionated RT.[68] Several other studies that used combined treatment have also demonstrated the effect of RT–ICI sequencing on outcomes of BM patients.[61–64] In a small cohort of NSCLC BM patients (n=17), delivery of anti-PD1 (nivolumab/durvalumab) before or concurrently (median 21 days before/after RT) with SRS/fractionated stereotactic RT demonstrated significantly improved 6-month distant brain control rate (57% vs 0, p=0.05) compared to patients receiving anti-PD1 after RT at a median 1.6 (range 0.2–4.7) months.[61] Univariate analysis revealed timing was also significantly associated with OS (HR 9.2, 95% CI 1.9–65.3; p=0.006).[61] Concurrent or after PD1-inhibitor induction was associated with higher intracranial 1-year local control (100% vs 72.3%, p=0.016) compared to patients receiving PD1-pathway inhibition before SRS in a retrospective study of 37 lung cancer patients with 85 BM lesions.[63] Moreover, 1-year distal brain failure (p=0.042) and 1-year OS (p=0.008) also showed significant differences for PD1-therapy sequencing, as shown in Table 5. A study involving BM patients of multiple primary sites, however, showed no intracranial failure difference between concurrent (defined as ICI given within 4 weeks of SRS) versus noncurrent (within 5 months).[64] Nonetheless, improved extracranial control and OS was higher in the concurrent group.

Efficacy of ICIs in lung cancer has also been associated with EGFR-mutation status.[69] EGFR wild-type was associated with increased OS compared to EGFR-mutated NSCLC.[69] Our study included only EGFR-negative NSCLC patients for better assessment of combined treatment. Most of these studies contained NSCLC patients that were positive for EGFR, ALK, and KRAS mutations.[38,39,41,54,61,62,64] Inclusion of such patients in treatment/control groups may confound ultimate survival advantage, as molecularly targeted agents aimed at these oncoproteins have shown intracranial responses and improved outcome compared to RT alone.[43–46] Such observations may explain failure of ICI + RT–induced intracranial response translation into PFS and survival advantage.[51,52] In our study, male sex and age were associated with improved PFS and/or OS on univariate/multivariate analyses. However, this could mainly have been due to the revalence of male gender in the anti-PD1 cohort (nine vs one). Likewise, patients aged <60 years were predominant in the entire cohort (14 vs seven). Therefore, these factors may have contributed to the association between these factors and efficacy outcomes.

Our study is limited by the small cohort and retrospective nature of research design. The small cohort limits the reliability of multivariate analysis in our study. Moreover, our study was not powered sufficiently to detect OS advantage, and failure to register OS should be interpreted with caution. Retrospective research studies are prone to recall, observation, and selection biases.[70] Men and smokers were predominant in the combined group, which may limit the efficacy outcomes observed in our study, as smoking is associated with induction of PDL1 expression, which in turn is used as a biomarker to predict response to ICI.[71] No PDL1 expression was assessed for patient selection in our study. Our study is also prone to chronological bias, as participants in the two cohorts were not from the same period. PD1 inhibior–treated patients had been diagnosed more recently. Furthermore, lack of

assessment of safety and adverse events also limits the application of our results.

Conclusion

Our results suggest anti-PD1 therapy as an alternative treatment option in NSCLC BM patients lacking EGFR and ALK mutations. NSCLC BM patients showed a trend toward improved PFS and OS with the combined approach. Further evaluation of WBRT and anti-PD1 therapy combinations are warranted in larger studies.

Data Sharing

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethics approval was obtained from the tthical review board of Shenzhen People's Hospital, Shenzhen, China. All study participants or legal guardians provided informed written consent prior to study enrollment.

Author Contributions

All authors made a significant contribution to the work reported, whether in conception, design, execution, acquisition of data, analysis and interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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