Original Article

Intracranial response pattern, tolerability and biomarkers associated with brain metastases in non-small cell lung cancer treated by tislelizumab plus chemotherapy

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Background: Programmed cell death protein-1/programmed cell death protein-ligand 1 (PD-1/PD-L1) inhibitor and chemotherapy are the standard treatment for advanced non-small cell lung cancer (NSCLC) without sensitizing mutations. However, patients with untreated, symptomatic or recently-irradiated brain metastases (BMs) are mostly excluded from immunochemotherapy trials. This study aims to evaluate the intracranial response pattern, tolerability and biomarkers of tislelizumab plus chemotherapy in NSCLC with untreated, symptomatic or recently-irradiated BM.

Methods: This multicenter, single-arm, phase 2 trial enrolled patients with treatment-naïve, brain-metastasized NSCLC. BM could be untreated or irradiated. Symptomatic or recently-irradiated BMs that were deemed clinically stable were allowed. Patients received tislelizumab (200 mg) plus pemetrexed (500 mg/m^2) and carboplatin (AUC =5) on day 1 every 3 weeks for 4 cycles, followed by maintenance with tislelizumab plus pemetrexed. Primary endpoint was 1-year progression-free survival (PFS) rate. Secondary endpoints included intracranial efficacy and tolerability. PD-L1 expression, tumor mutational burden (TMB) and genomic alterations were evaluated as potential biomarkers.

Results: A total of 36 patients were enrolled, 19.2% had prior brain radiotherapy, 8.3% had symptomatic BMs that required corticosteroids ≤10 mg/d or antiepileptics. Confirmed systemic and intracranial ORR (iORR) was 43.8% and 46.7%, respectively. One-year systematic PFS rate and One-year iPFS rate was 36.8% and 55.8%, respectively. About 41.7% patients had neurological adverse events, 90% patients had concordant intracranial-extracranial responses. No intracranial pseudoprogression or hyperprogression occurred. Patients with prior brain radiation trended towards higher systemic (83.3% *vs.* 34.6%) and iORR (75.0% *vs.* 42.3%). Similar intracranial efficacy was observed in tumors with different PD-L1 and TMB levels, while alterations in cytokine receptors pathway predicted higher iORR (P=0.081), prolonged systematic PFS [hazard ratio (HR) =0.16, P=0.021] and overall survival (OS) (HR =0.71, P=0.029).

Conclusions: Untreated or irradiated BMs in NSCLC follows a conventional response and progression pattern under immunochemotherapy with altered cytokine receptors pathway being a potential biomarker for systemic and intracranial outcomes.

Keywords: Non-small cell lung cancer (NSCLC); brain metastasis (BM); immunochemotherapy; response evaluation; predictive biomarker

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Introduction

Brain metastases (BMs) are present in about 40% of patients with stage IV non-small cell lung cancer (NSCLC) at diagnosis (1). However, in pivotal trials that established anti-programmed cell death protein-1/programmed cell death protein-ligand 1 (PD-1/PD-L1) monotherapy or immunochemotherapy as the standard treatment for advanced NSCLC, patients with baseline BM only accounted for 1.6%-18% in all enrolled cases (2-7). By far, only three trials had specifically probed the intracranial activity of immunotherapy in NSCLC (8-10), while all rejected patients with concurrently- or recently-irradiated BM. Prospective data on the intracranial efficacy and tolerability of immunotherapy in patients with concurrently- or recently-irradiated BMs are lacking (11).

Highlight box

Key findings

- Tislelizumab plus chemotherapy show desirable intracranial efficacy in non-small cell lung cancer (NSCLC). Untreated or irradiated brain metastases in NSCLC follows a conventional response and progression pattern under immunochemotherapy with altered cytokine receptors pathway being a potential biomarker for systemic and intracranial outcomes.

What is known and what is new?

- Data regarding the intracranial response-progression patterns, neurological tolerability and biomarkers of immunochemotherapy for NSCLC with untreated, symptomatic, or recently-irradiated brain metastases are lacking. This study provides the first prospective data supporting tislelizumab plus chemotherapy as a safe and effective first-line treatment for nonsquamous NSCLC with untreated, symptomatic brain metastasis (BM), and as a potential salvage therapy for those with irradiated BM. Altered cytokine receptors pathway could act as a potential biomarker in this population.

What is the implication, and what should change now?

- By showing that intracranial lesions in immunochemotherapy-treated NSCLC share similar response-progression patterns with extracranial sties, this study calls for the inclusion of brain-metastasized NSCLC into future trials on immunochemotherapy.

Predictive biomarkers for systemic and intracranial outcomes in immunotherapy-treated NSCLC also require further study (11-14).

Tislelizumab is a humanized anti-PD-1 monoclonal antibody (McAb) with high PD-1 binding affinity and minimized Fcγ receptor binding on macrophages (15). Tislelizumab plus chemotherapy have been approved for treatment-naïve advanced NSCLC in China based on the RATIONALE-307 and RATIONALE-304 trials (3,16). In the present phase 2 trial (NCT04507217), we intended to further probe the intracranial efficacy, tolerability and biomarkers of tislelizumab plus pemetrexed and carboplatin in patients with NSCLC by allowing untreated, symptomatic, or recently-irradiated BM. Potential biomarkers including PD-L1, tumor mutational burden (TMB) and genomic alterations were evaluated for their correlation with systemic and intracranial outcomes in this population.

Methods

Study design and patients

This is a multicenter, single-arm, phase 2 trial (Trial Registration number NCT04507217). Eligible patients were aged 18 to 75 years old, had histologically or cytologically confirmed stage IV NSCLC, at least one BM confirmed by brain magnetic resonance imaging (MRI), at least one measurable lesion defined by Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1), no previous systemic treatment, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and adequate organ function. BM could be untreated or previously irradiated. Symptomatic BM that could be controlled by corticosteroids ≤10 mg/d, antiepileptics or dehydration treatments (clinically stable) were allowed. Complete eligibility criteria are available in study protocol. This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (as revised in 2013). The study protocol and all amendments were approved by the institutional review board at each

participating site. All patients provided written informed consent before enrollment.

Treatments

Patients received tislelizumab (200 mg) plus pemetrexed (500 mg/m^2) and carboplatin (Area under the curve, AUC =5) intravenously on day 1 every 3 weeks for 4 cycles, and received maintenance treatment with tislelizumab (200 mg) plus pemetrexed (500 mg/m^2) every 3 weeks up to 24 months or until disease progression, unacceptable toxicity, or death. Tumor assessment was performed by radiologic imaging. Systemic responses were assessed based on RECIST v1.1 (17). Intracranial responses were assessed based on the Response Assessment in Neuro-Oncology-Brain Metastases (RANO-BM) criteria (18). Adverse events were monitored throughout the study until 90 days after the last dose, and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Endpoints

Primary endpoint was 1-year progression-free survival (PFS) rate, defined as the proportion of patients who remained progression-free at 1 year after treatment initiation per RECIST v1.1. Secondary endpoints included systemic and intracranial overall response rate (iORR), disease control rate (DCR), median PFS, duration of response (DOR), 1-year intracranial PFS (iPFS) rate, overall survival (OS) and safety. PD-L1 expression, TMB, baseline genomic profiles and clinicopathological features were analyzed for their correlation with systemic and intracranial outcomes.

Biomarker analysis

Tumor tissues (fresh or achieved) were obtained before treatment. Genomic analyses with a next-generation sequencing panel of 425 genes were performed in the central laboratory (Geneseeq Technology Inc., Nanjing, China). Genomic alterations including single base substitutions, short and long insertions/deletions (INDELs), copy-number variants and fusions were assessed. TMB was determined by analyzing somatic mutations including coding base substitution and INDELs per megabase (Mb). The cutoff point for TMB-high (TMB-H) was set at 10 mutations/Mb (19). PD-L1 expression was detected by immunohistochemistry staining with an VENTANA SP263 antibody. PD-L1 expression was evaluated on tumor cells (TCs) as well as on tumor-infiltrating immune cells by certified pathologists. PD-L1 positive status was defined as the presence of membrane staining of any intensity in 1% of TCs or the presence of PD-L1 staining of any intensity in tumor-infiltrating immune cells.

Statistical analysis

The estimated number of enrollment for this study was 35 to allow preliminary evaluation of efficacy and tolerability. Safety analysis was performed in patients who received at least one dose of treatment (Safety set). Systemic efficacy was assessed in patients with at least one post-treatment tumor assessment (RECIST1.1 efficacy analysis set, RECIST1.1 EAS). Intracranial efficacy was assessed in patients with at least one post-treatment intracranial tumor assessment (RANO-BM EAS). Categorical outcomes (ORR, DCR) were presented as percentages and two-sided 95% confidence interval. Time-to-event outcomes (PFS, OS) were estimated using the Kaplan-Meier method. Difference between categorical outcomes were tested using the Chi-squared or Fisher's exact test. Univariate regression analyses were performed to identify potential factors associated with PFS. Statistical significance was defined as a two-sided P value <0.05 or a hazard ratio (HR) excluding 1. Statistical analyses were performed using SPSS (version 24.0.0 for Windows, IBM, New York, USA) and SAS (version 9.4).

Results

Patients

From 15 September 2020 to 30 January 2021, 46 patients from six participating centers were screened. A total of 36 patients were eligible and treated with at least one cycle of treatment (safety set, Figure S1). Baseline characteristics are summarized in *Table 1*. Among them, 29 patients (80.6%) had untreated BM. Seven (19.4%) had prior brain radiotherapy. Median time interval between brain radiotherapy and the initiation of systemic treatment was 1.7 weeks (range, 0.6–3.7). Eleven patients (30.6%) had multiple BM (≥4) and 18 (50.0%) had brain lesions greater than 10mm in diameter (range, 2–24 mm). Three patients (8.3%) required corticosteroids or antiepileptics for BM-related symptoms at baseline. As off data cutoff (30 January 2023), the median follow-up duration was 12.8 months (95% CI: 10.5–15.4).

Table 1 Patient characteristics

Characteristics	Patients (N=36)
Age (years)	58.0 [41–72]
Sex, n (%)	
Male	24 (66.7)
Female	12 (33.3)
ECOG PS	
0	6 (16.7)
1	30 (83.3)
Histological type	
Adenocarcinoma	34 (94.4)
Other	2 (5.6)
Smoking status	
Never	13 (36.1)
Former	14 (38.9)
Current	9 (25.0)
Previous local CNS therapy	
None	29 (80.6)
Stereotactic radiosurgery	6 (16.7)
Whole brain radiotherapy	1 (2.8)
Metastatic sites other than CNS	
None	6 (16.7)
Intrathoracic only	2 (5.6)
Extrathoracic	28 (77.8)
Liver metastases	
Yes	9 (25.0)
no	27 (75.0)
Adrenal gland metastases	
Yes	4 (11.1)
no	32 (88.9)
Bone metastases	
Yes	15 (41.7)
no	21 (58.3)
Number of brain metastases	
1–3	24 (66.7)
≥4	11 (30.6)
Unknown	1 (2.8)
Size of maximal brain lesions	
<5 mm	3 (8.3)
5–10 mm	14 (38.9)
>10 mm	18 (50.0)
Unknown	1 (2.8)

Data are presented as n (%) or median [range]. ECOG PS, Eastern Cooperative Oncology Group performance-status; CNS, central nervous system.

Systemic efficacy

A total of 32 patients had at least one post-treatment tumor assessment and were included in the RECIST1.1 EAS (26 untreated, 6 irradiated). Confirmed systemic ORR was 43.8% (95% CI: 26.4–62.3%). DCR was 90.6% (95% CI: 75.0–98.0%, *Figure 1A*, Figure S2). Median time to response was 1.7 months (95% CI: 1.3–2.7). By the time of data cutoff, responses were ongoing in 5 patients (35.7%, *Figure 1B*). Median DOR was 17.8 months (95% CI: 3.4–not reached). Median PFS was 7.5 months (95% CI: 5.1–18.4, *Figure 2A*). With a median follow-up duration of 12.8 months, 1-year PFS rate in the RECIST1.1 EAS was 36.8% (95% CI: 18.0–55.7%). Eight patients (8/15, 53.3%) had extracranial progression only, 3 patients (3/15, 20.0%) had intracranial progression only, and 4 (4/15, 26.7%) had progression in both intracranial and extracranial lesions. All intracranial progressions were documented in patients without prior brain radiotherapy. A total of 11 deaths (30%) occurred as off data cutoff. The 1-year OS rate was 71.3% (95% CI: 53.1–83.4%, *Figure 2B*).

In subgroup analysis by clinicopathological features (Figure S3), patients with smoking histories had a higher likelihood of systemic response (60.0% *vs.* 16.7%, P=0.028). Prior brain radiotherapy trended towards higher ORR (83.3% *vs.* 34.6%, P=0.064), while baseline liver metastases trended towards lower 1-year PFS rate (16.7% *vs.* 42.2%, P=0.052).

Intracranial response patterns

A total of 30 patients had at least one post-treatment intracranial tumor assessment and were included in the RANO-BM EAS (26 untreated, 4 irradiated). Confirmed iORR was 46.7% (95% CI: 28.3–65.7%) with 4 complete remission (CR) (13.3%) and 10 partial response (PR) (33.3%). Intracranial DCR was 96.7% (95% CI: 82.8–99.9%). Median time to intracranial response was 1.4 months (95% CI: 1.3–2.7). 90% of patients (n=27) had concordant responses in intracranial and extracranial lesions (*Figure 1A*). Dissociated intracranial-extracranial responses were observed in three patients, 2 with PR/stable disease (SD) intracranially and progressive disease (PD) extracranially, 1 with PD intracranially and PR extracranially. No intracranial hyperprogression or pseudoprogression was observed. As off data cutoff, intracranial responses were ongoing in 5 patients (35.7%), 9 patients (30%) had intracranial disease progression or died (*Figure 1B*). 1-year iPFS rate was 55.8% (95% CI: 30.7–75.0%, *Figure 2C*).

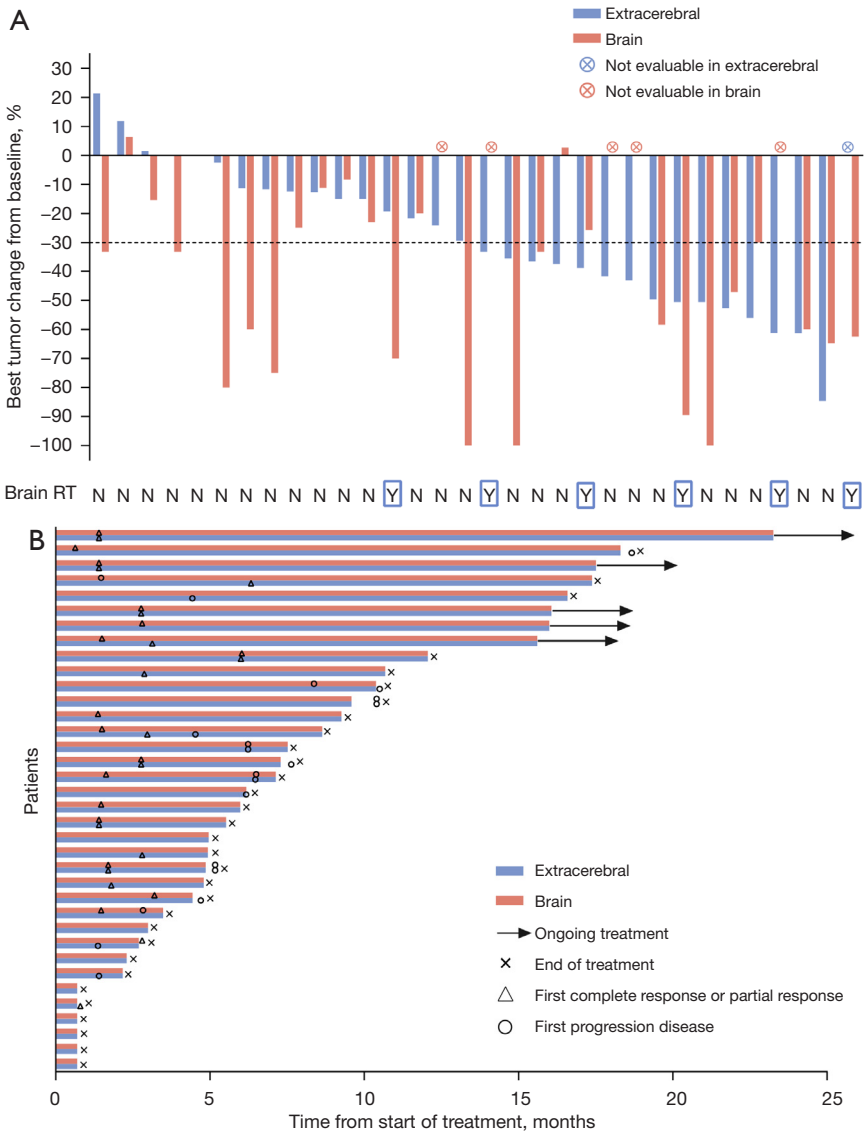

Figure 1 Tumor response characteristics. (A) Best percentage change of intracranial and extracerebral target lesions from baseline in RECIST1.1 efficacy analysis set. Best brain metastasis response assessed by RANO-BM and extracerebral response by RECIST v1.1. Each bar represents an individual patient. One patient was not evaluable for extracerebral response due to the absence of targeted tumor lesions. Five patients were not evaluable for intracranial response (absence of targeted tumor lesions, n=3; lack of post-treatment brain image, n=2); (B) duration of response and progression pattern in brain and extracerebral lesions in safety set. Length of the horizontal bars presents treatment duration. RECIST, Response Evaluation Criteria in Solid Tumors; RANO-BM, Response Assessment in Neuro-Oncology-Brain Metastases; RT, radiotherapy.

Median iPFS was not reached (95% CI: 6.4–NR).

Among patients with prior brain radiotherapy, confirmed systemic ORR and iORR was 83.3% (5/6) and 75% (3/4), respectively. These patients all remained progression-free as off data cutoff. Median time on treatment was 13.4 months (95% CI: 3.8–17.7). Subgroup analysis by clinicopathological features did not identify other factors correlated with differential intracranial outcomes (Figure S3).

Safety

Treatment-related adverse events (TRAEs) of any grade

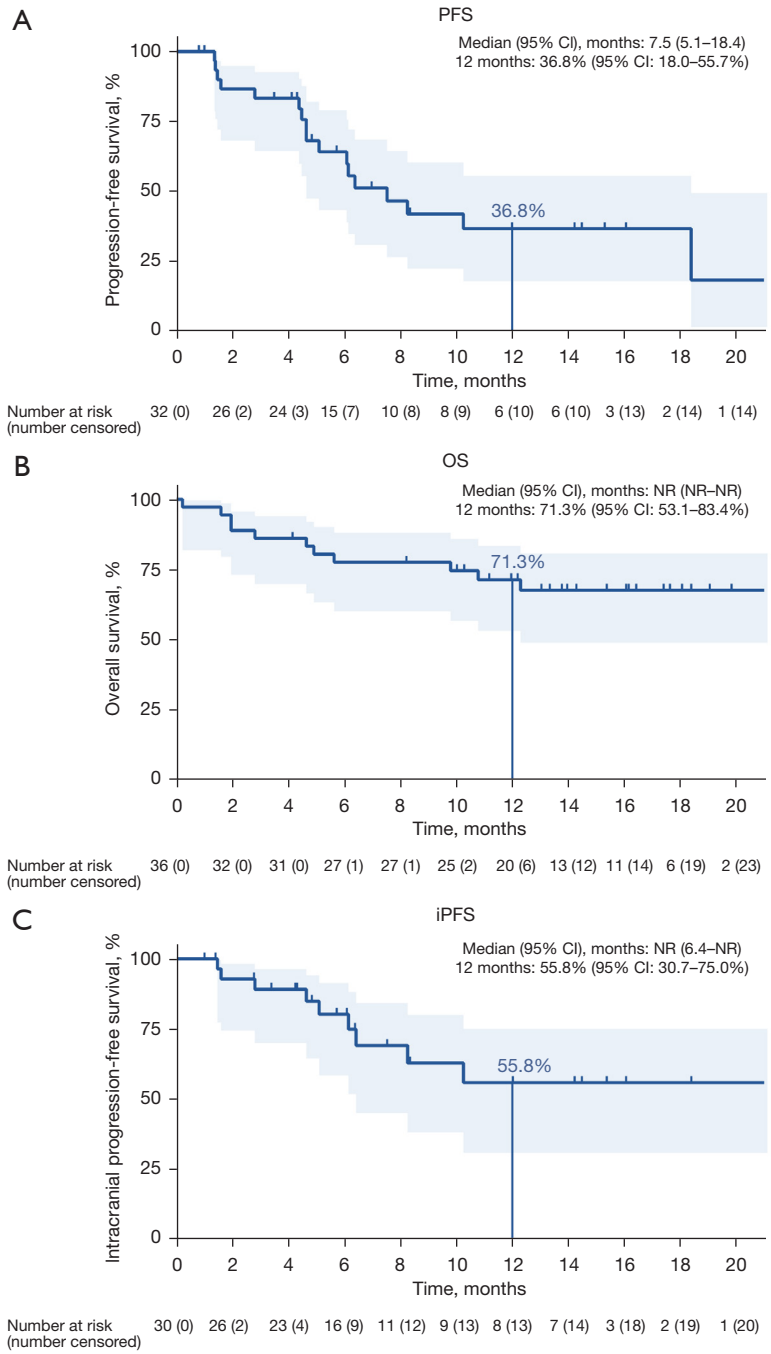

Figure 2 Kaplan-Meier survival curves. (A) Systemic PFS in RECIST1.1 efficacy analysis set (n=32); (B) OS in safety set (n=36); (C) iPFS in RANO-BM efficacy analysis set (n=30). PFS, progression-free survival; OS, overall survival; iPFS, intracranial PFS; RECIST, Response Evaluation Criteria in Solid Tumors; RANO-BM, Response Assessment in Neuro-Oncology-Brain Metastases; CI, confidence interval; NR, not reached.

occurred in 34 (94.4%) patients (*Table 2*). Grade 3 or higher TRAEs occurred in 12 (33.3%) patients. The most common TRAEs (any grade, ≥30%) were anemia (58.3%), leukocytopenia (47.2%), neutropenia (44.4%), elevated aspartate aminotransferase (38.9%) and alanine aminotransferase (36.1%). Neurological adverse events (AEs) regardless of attribution were documented in 15 (41.7%) patients, including insomnia (n=6), dizziness

Table 2 Treatment-related adverse events

Adverse events	Patients (N=36)	
	Any grade	Grade ≥3
Treatment-related adverse events	34 (94.4)	12 (33.3)
Anemia	21 (58.3)	3 (8.3)
White blood cell count decrease	17 (47.2)	2 (5.6)
Neutrophil count decrease	16 (44.4)	5 (13.9)
Alanine aminotransferase increase	13 (36.1)	1 (2.8)
Aspartate aminotransferase increase	14 (38.9)	0 (0)
Platelet count decrease	9 (25.0)	5 (13.9)
Hypoproteinemia	8 (22.2)	1 (2.8)
Decreased appetite	8 (22.2)	0 (0)
Hypocalcemia	7 (19.4)	0 (0)
Peripheral edema	6 (16.7)	0 (0)
Palpebral edema	5 (13.9)	0 (0)
Hyponatremia	5 (13.9)	0 (0)
Hypokalemia	5 (13.9)	0 (0)
Rash	4 (11.1)	0 (0)
Fatigue	4 (11.1)	0 (0)
Immune-related adverse events	5 (13.9)	2 (5.6)
Platelet count decrease	2 (5.6)	2 (5.6)
Rash	2 (5.6)	0

Data are presented as n (%). Treatment-related adverse events of any grade occurring in 10% or more of patients are listed. Immune-related adverse events of any grade occurring in 2 or more of patients are listed.

(n=4), headache (n=2), seizure (n=2) and paresthesia (n=1). All neurological AEs were grade 1 or 2. No neurological AE occurred in patients with prior brain radiotherapy. Five patients (13.9%) experienced 15 immune-related adverse events (irAEs). Grade 3 or higher irAEs occurred in two patients. TRAEs-associated dose interruptions were documented in 12 (33.3%) patients. No TRAEs-associated dose modification was reported. Three (8.3%) patients had TRAEs-associated treatment discontinuation. There was no treatment-related death.

Biomarker analysis

Genomic analysis was performed on tumor tissues from 13 patients. Molecular profiling results of these patients are listed in Figure S4. The median TMB value was 4.2 mutations/Mb. Three patients (3/13, 23.1%) were classified as TMB-high. TMB-high patients trended towards higher systemic response rate (OR =6.52, 95% CI: 0.23–526.48) and prolonged systemic PFS (HR =0.25, 95% CI: 0.03–2.16) in comparison to TMB-low patients. No difference in intracranial outcomes was observed (Figure S5). PD-L1 immunohistochemistry (IHC) staining was performed on 12 patients. Seven (58.3%) patients were PD-L1 positive (TC ≥1%). Similar systemic and intracranial responses were observed in patients with PD-L1 positive (ORR =28.6%, iORR =28.6%) and negative tumors (ORR =20%, iORR =25.0%, Figure S6).

Analysis of baseline mutation profiles identified alterations in cytokine receptors pathway correlated with differential outcomes. Patients with alterations in cytokine receptors pathway (CYSLTR2, KDR, EGFR, FLT1, PGR, IL7R) had higher likelihood of intracranial response (P=0.081, *Figure 3A*) and significantly longer systematic PFS (HR =0.16, 95% CI: 0.03–0.92, P=0.020, *Figure 3B*) than patients without. Validation analysis using the external MSKCC dataset showed that NSCLC patients carrying alterations in this pathway had significantly prolonged OS under immunotherapy (HR =0.71, 95% CI: 0.52–0.97, P=0.029, *Figure 3C*) (20). Exploring tumor microenvironment associated with this pathway using the TCGA-LUAD dataset demonstrated a higher infiltration of M1 macrophages (P<0.0001), CD4+ memory T cells (P=0.001), activated mast cells (P=0.0004) and resting mast cells (P=0.007, *Figure 3D*) in tumors with altered cytokine receptors pathway (21).

Discussion

The present trial investigated the intracranial efficacy, tolerability and biomarkers of tislelizumab plus pemetrexed and carboplatin for advanced nonsquamous NSCLC with BM. Confirmed intracranial responses were observed in 46.7% of patients. The 1-year iPFS rate yielded by PD-1 inhibitor plus chemotherapy in this study is 55.8%, which exceeds the previously reported 33% with anti-PD-1 monotherapy in this population (10).

PD-1/PD-L1 inhibitors plus chemotherapy have been established as the standard first-line treatment for advanced NSCLC without sensitizing mutations (2-7). Recently, the Atezo-Brain and CAP-Brain trial respectively reported durable intracranial responses to immunochemotherapy

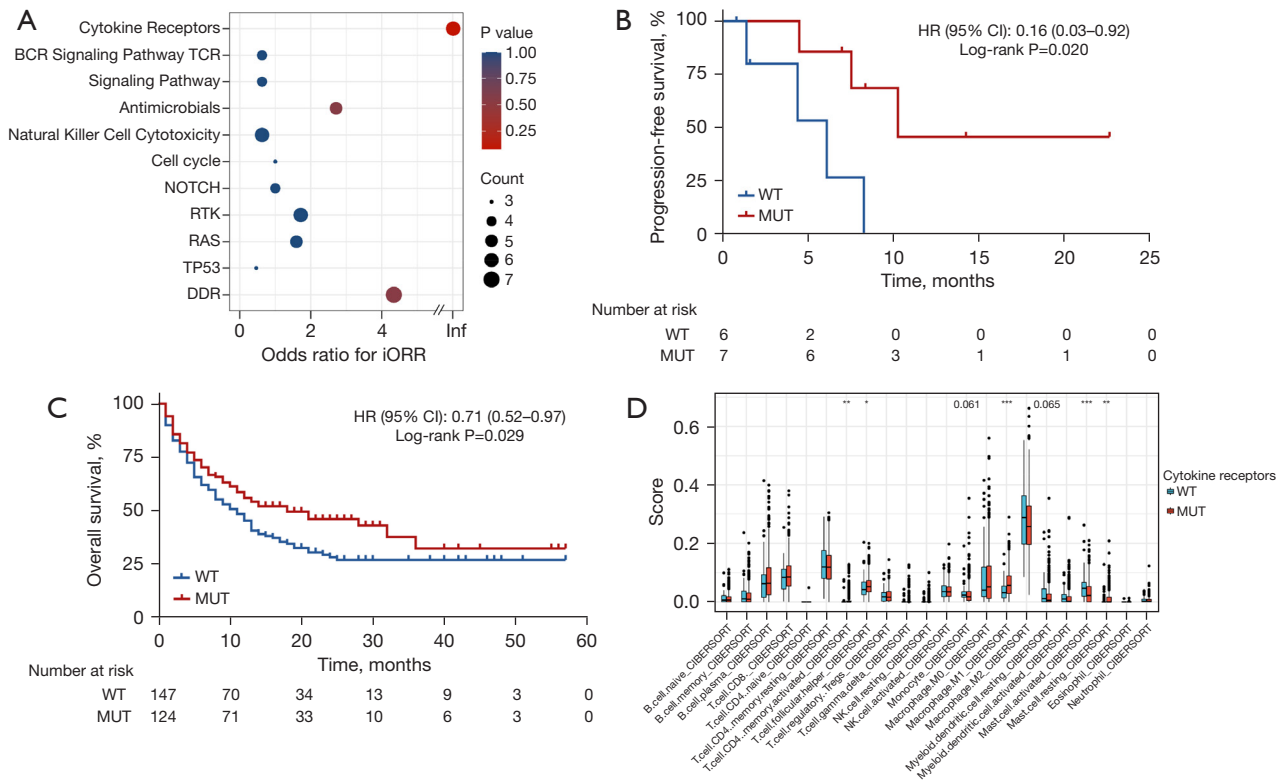

Figure 3 Association of cytokine receptors pathway alterations and clinical outcomes. (A) Likelihood of intracranial objective response rate between patients with altered cytokine receptors pathway versus those without. Statistical analysis was performed using Fisher's exact tests in evaluable patients in the study (n=12); (B) Kaplan-Meier curves of systemic progression-free survival between patients with altered cytokine receptors pathway (MUT, n=7) versus those without (WT, n=6). P value was calculated using a log-rank test; (C) Kaplan-Meier curves of overall survival in immunotherapy-treated non-small cell lung cancer patients with altered cytokine receptors pathway (MUT, n=124) and those without (WT, n=147) in the Memorial Sloan-Kettering Cancer Center cohort; (D) CIBERSORT analyses quantifying the proportion of immune cells in the tumors with altered cytokine receptors pathway and tumors with wildtype genes in the TCGA-LUAD cohort (n=510). *, P<0.05; **, P<0.01; ***, P<0.001 by Wilcoxon rank sum tests. iORR, intracranial objective response rate; HR, hazard ratio; CI, confidence interval; MUT, mutated; WT, wildtype; TCGA-LUAD, The Cancer Genome Atlas-lung adenocarcinoma.

in patients with untreated BM (8,9). In the current trial, about one fifth of the study population had received brain radiotherapy before enrollment. 8.3% required corticosteroids or antiepileptics for neurological symptoms. The median time interval between brain radiotherapy and systemic immunotherapy was 1.7 weeks (range, 0.6–3.7 weeks). Tislelizumab plus pemetrexed and carboplatin led to a confirm ORR of 43.8% and a confirmed iORR of 46.7% (4 CRs, 10 PRs) in this population. The 1-year iPFS rate was 55.8%. All neurological AEs were grade 1 or 2. No neurological AE or radiation necrosis was reported in patients with prior brain radiation. Corroborating with previous studies, this trial further support PD-1 inhibitor plus chemotherapy as a safe and effective first-line treatment for advanced NSCLC with BM. It provides the first prospective data demonstrating that systemic immunochemotherapy following brain radiation within the two-week interval is well tolerated in this population.

In terms of intracranial response characteristics, 90% of patients had concordant intracranial-extracranial tumor responses. Median time to intracranial response (1.4 months) was similar to the median time to systemic response (1.7 months). The intracranial efficacy of tislelizumab plus chemotherapy measured by iORR, iDCR and iPFS was similar to the systemic efficacy reported here and in previous trials (2,3,7). No intracranial pseudoprogression or hyperprogression was observed.

The rate of intracranial pseudoprogression was also low (0.8%) in a previous retrospective study (13). About 53.3% of patients in this study had extracranial progression only, 20% had intracranial progression only. No intracranial progression occurred in patients with prior brain radiotherapy. Taken together, these results indicate that BM in NSCLC follows a conventional response and progression pattern under immunochemotherapy, where an enlarged brain lesion may indicate real disease progression.

In subgroup analysis by clinicopathological features, patients with prior brain radiotherapy trended towards higher systemic (83.3% *vs.* 34.6%) and iORR (75.0% *vs.* 42.3%) in comparison to patients with unirradiated BM. All post-radiotherapy patients remained progression-free by the time of data cutoff. Median time on treatment was 13.4 months. Brain radiotherapy remains a crucial therapeutic strategy for patients with BMs. Recent progress in stereotactic techniques and radiotherapy equipment has provided greater efficacy and better tolerability for patients subjected to brain radiation. Despite the wide application of immunotherapy in advanced NSCLC and the high occurrence of BMs in this population, data on the relationship between immunotherapy and brain radiotherapy are scarce. Evidence from retrospective studies suggests that the combination of brain radiotherapy and systemic immunotherapy is superior to radiotherapy alone in terms of local disease control and overall survival (22-24). Results from the current study further indicate that systemic immunotherapy administered concurrently with or shortly following brain radiotherapy could provide more durable disease control and survival benefits for patients with BM. Nevertheless, the favorable outcomes observed with irradiated patients in this study might be confounded by the fact that patients with oligometastatic brain diseases were more likely to receive prior brain radiotherapy. Meanwhile, whether the short interval between brain radiation and systemic treatment contribute to the efficacy observed in this study is also unknown. Future studies are warranted to validate our findings and to further investigate the relationship, sequence and combination of local radiotherapy and systemic immunotherapy in advanced NSCLC with BMs.

PD-L1 expression and TMB have been validated as predictive biomarkers for systemic efficacy in immunotherapy-treated NSCLC (2,19,20). The NCT02085070 study showed that PD-L1 expression also correlated with intracranial efficacy of anti-PD-1 monotherapy (10). While in this study, similar systemic and intracranial efficacy were observed in patients with PD-L1 positive and negative tumors. The Atezo-Brain and CAP-Brain also reported that PD-L1 level could not predict differential efficacy of immunochemotherapy in NSCLC with BM (8,9). About 23.1% of patients had TMB-high tumors in this study. Consistent with previous reports (6), TMB-high patients here trended towards better systemic outcomes under immunochemotherapy in comparison to TMB-low patients. But similar intracranial outcomes were observed in patients with different TMB levels. Although the power of this analysis is limited by the small sample size, our findings suggest the site-specificity of TMB assessment. A previous study in NSCLC reported that sampling site could affect TMB values, which were higher in metastatic sites than primary tumors (25). Therefore, TMB assessment based on primary lung tumors may not necessarily predict intracranial outcomes in immunotherapy-treated NSCLC. In contrast, our biomarker exploration found that patients with cytokine receptors pathway alterations tended to have higher likelihood of intracranial responses, significantly prolonged PFS and OS in immunotherapy-treated NSCLC, suggesting that this pathway may be a potential biomarker in this population.

Limitations

Limitations of the current trial included its single-arm nature and small sample size. Additionally, only one third of patients provided tumor tissues for biomarker analysis, which could limit the power of our biomarker exploration. Meanwhile, this study recruited patients solely from China, which may undermine the representativeness of the study population. However, given that previous pivotal trials on immunochemotherapy reporting similar results in Asian and Western patients, we assume that results of our study could be extrapolated to Western patients.

Conclusions

Building on the current evidence, this study further provide prospective data on the intracranial response/progression pattern, tolerability and potential biomarkers associated with BM in immunochemotherapy-treated NSCLC. BM in NSCLC follows a conventional response and progression pattern with short time to response and rare incidence of pseudoprogression or hyperprogression. In patients with recently-irradiated BM, systemic immunochemotherapy is well tolerated and trends towards better outcomes compared

with unirradiated patients. PD-L1 and TMB fail to predict intracranial efficacy of immunochemotherapy in NSCLC with BM, while alterations in cytokine receptors pathway may be potential biomarkers in this population. Further studies are warranted to clarify the relationship between local radiation and systemic immunotherapy to determine the optimal treatment sequence for NSCLC with BM.

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Footnote

Trial Protocol: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-687/tp

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-687/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-687/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-687/coif). L.Z. received research fund and support from BeiGene Ltd. and Geneseeq Technology Inc. L.Z. also reports that BeiGene provided the research fund and the investigated drugs, and that Geneseeq Technology offered genomic sequencing analysis. The other authors have no conflicts of interest to declare.

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. This study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (as revised in 2013). The study protocol and all amendments were approved by the institutional review board at each participating site. All patients provided written informed consent before enrollment.

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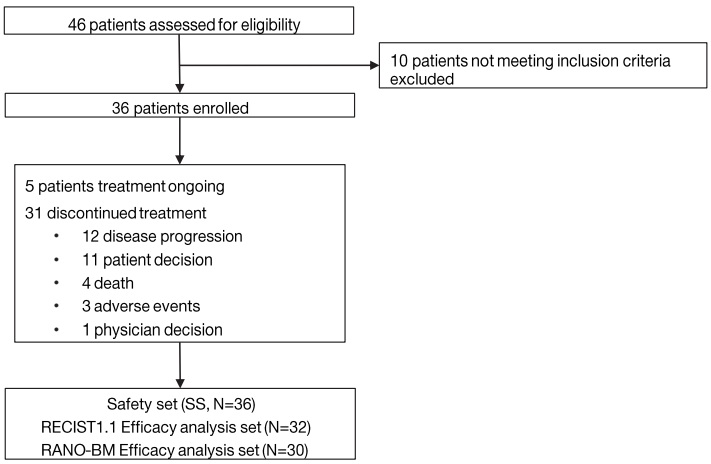

Figure S1 Flow diagram.

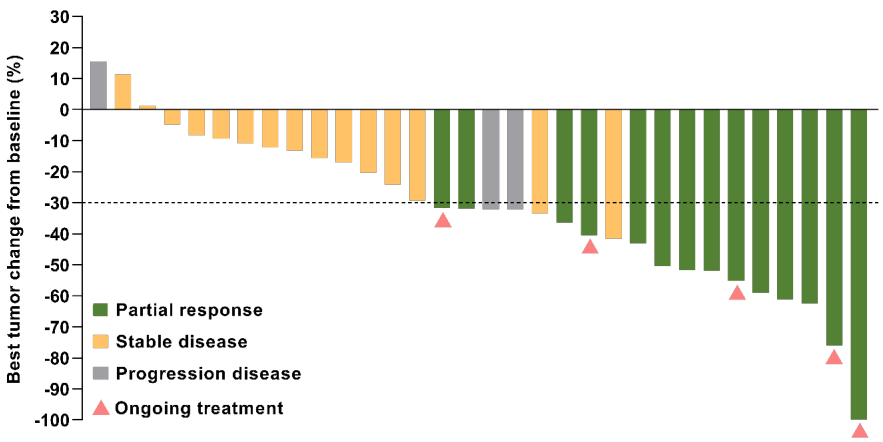

Figure S2 Waterfall plot for best percentage change in sums of diameters of target lesions from baseline in Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 efficacy analysis set (n=32). Best responses were assessed by RECIST v1.1. Each bar represents an individual patient. Two patients had progressive diseases (PD) despite >30% shrinkage of target lesions due to the development of new lesions in brain or liver.

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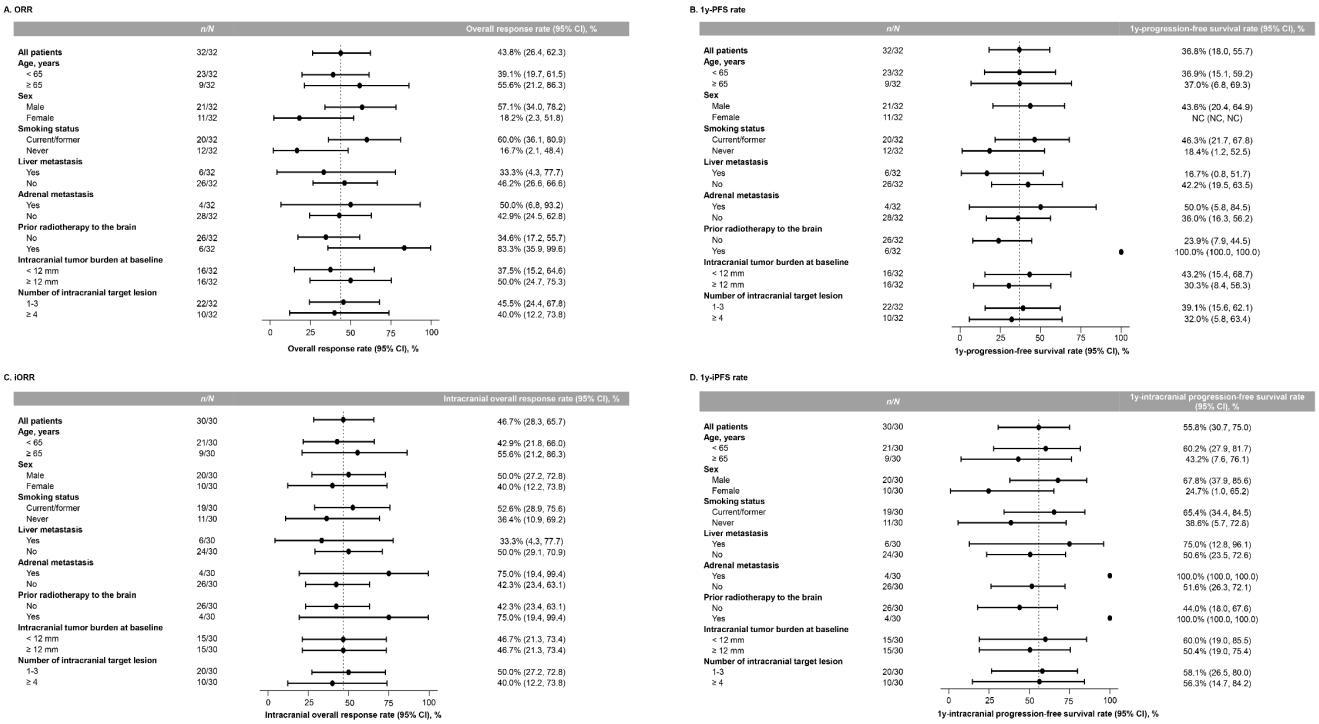

Figure S3 Subgroup analysis for systemic and intracranial efficacy by clinicopathological features. Forest plots show systemic objective response rate (A), 1-year progression-free survival rate (B), intracranial objective response rate (C) and 1-year intracranial PFS rate (D) by clinicopathological features. CI, confidence interval; ORR, objective response rate; PFS, progression-free survival; iORR, intracranial objective response rate; iPFS, intracranial progression-free survival.

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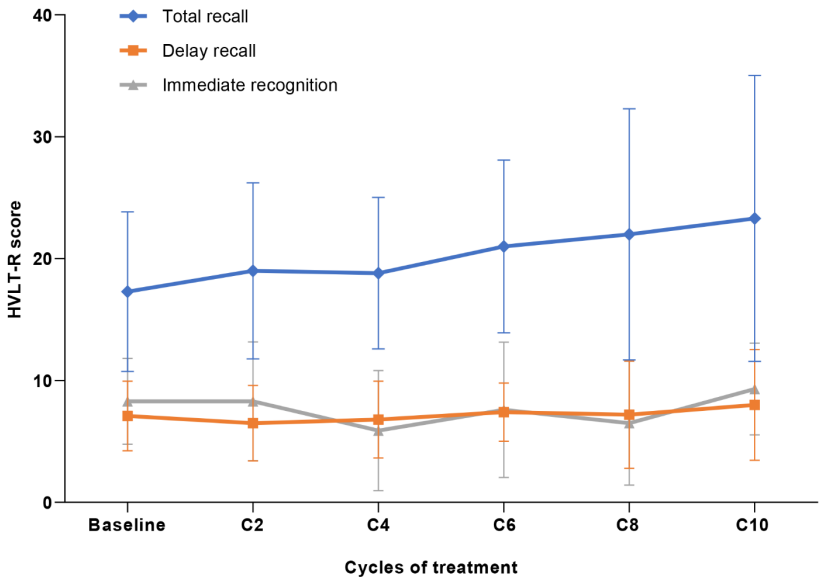

Figure S4 Hopkins Verbal Learning Test-Revised (HVLT-R) Scores. Raw scores were derived from the cognitive assessments. Data were plotted as means plus or minus standard deviations.

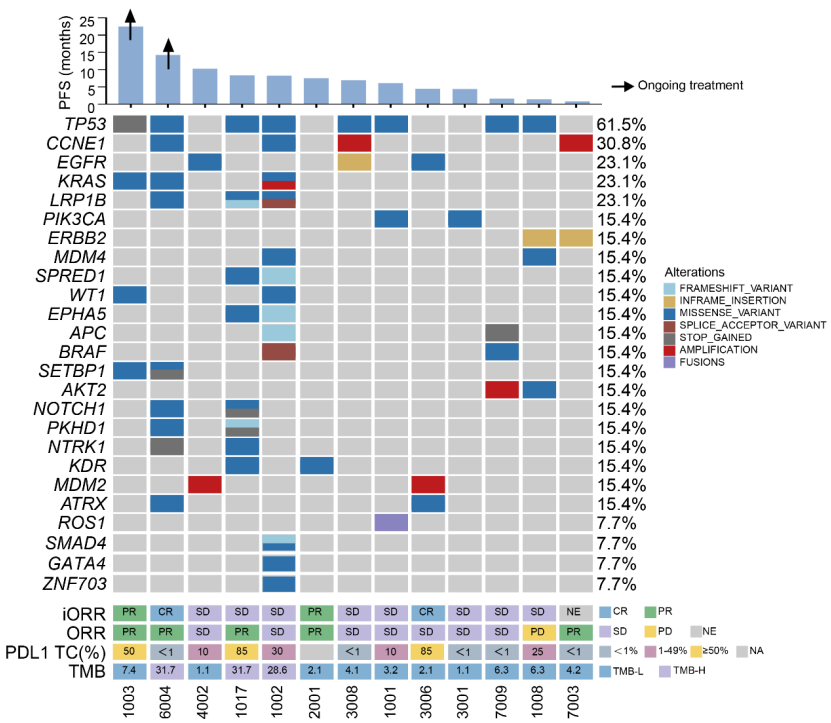

Figure S5 Baseline mutation profiles, PD-L1 and TMB of patients. The heatmap depicts Top 25 mutated genes in this study. Reported frequencies include a composite of missense, nonsense, indel, splice mutations, copy-number variants and fusions for each gene. The top bar chart shows progression-free survival of each patient, and arrow indicates patients are still ongoing treatment. The clinical benefits (intracranial overall response rate, overall response rate), PD-L1 expression and TMB values are annotated in the bottom panel. PD-L1, programmed cell death protein-ligand 1; TMB, tumor mutational burden.

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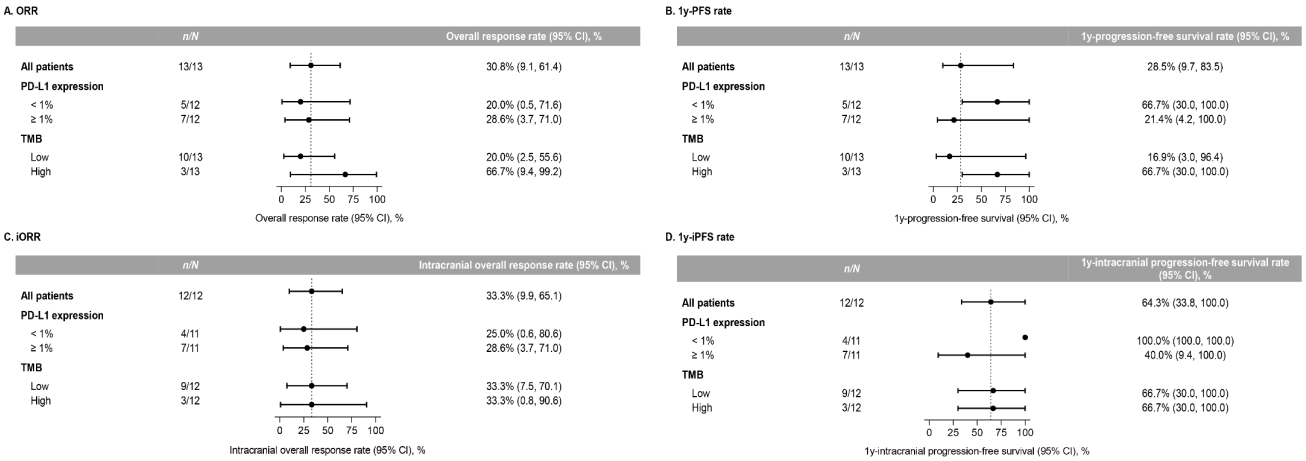

Figure S6 Subgroup analysis for systemic and intracranial efficacy by PD-L1 expression and TMB. Forest plots show systemic objective response rate (A), 1-year PFS rate (B), intracranial objective response rate (C) and 1-year iPFS rate (D) in PD-L1 or TMB subgroups. PD-L1, programmed cell death protein-ligand 1; TMB, tumor mutational burden; CI, confidence interval; ORR, objective response rate; PFS, progression-free survival; iORR, intracranial objective response rate; iPFS, intracranial progression-free survival.

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