Efficacy of pembrolizumab in patients with brain metastasis caused by previously untreated non-small cell lung cancer with high tumor PD-L1 expression

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Efficacy of pembrolizumab in patients with brain metastasis caused by previously untreated non-small cell lung cancer with high tumor PD-L1 expression

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ABSTRACT

Objectives: Pembrolizumab is recommended for patients with previously untreated non-small cell lung cancer (NSCLC) with a programmed death ligand 1 (PD-L1) tumor proportion score (TPS) of ≥1%. The KEYNOTE-024 study described the efficacy of pembrolizumab in patients with previously untreated NSCLC who had a PD-L1 TPS of at least 50 %. However, patients with untreated brain metastasis (BM) were excluded from many clinical trials. Therefore, we assessed the efficacy of pembrolizumab against BM of NSCLC with high tumor PD-L1 expression.

Materials and Methods: We retrospectively reviewed patients who received pembrolizumab as first-line treatment against NSCLC with PD-L1 TPS ≥ 50 % between March 2017 and September 2019. Treatment efficacy was compared between patients with (BM group) and without BM (non-BM group). In addition, the BM group was divided into patients who previously received treatment for BM before pembrolizumab (BM-T group) and those with no prior treatment for BM (BM-not T group).

Results: Eighty-seven patients (23 BM group and 64 non-BM group) were assessable for efficacy. No significant differences in patient characteristics were found between the BM and non-BM groups, but proportion of patients with stage IV at diagnosis was significantly higher in the BM group. Median progression-free survival (PFS) (6.5 months vs. 7.0 months) and overall survival (OS) (21.6 months vs. 24.6 months) did not significantly differ between the two groups. The response rate of BM was 70 %. The BM group was subdivided into 13 patients in the BM-T group and 10 patients in the BM-not T group. No significant differences in patient characteristics were found between the two groups, but maximum diameter of BM and proportion of patients with symptomatic BM were significantly greater in the BM-T group. PFS and OS did not significantly differ between the two groups. The median PFS of BM was 13.6 months in the BM-T group and 18.6 months in the BM-not T group.

Conclusion: Pembrolizumab may be effective for BM caused by previously untreated NSCLC with high PD-L1 tumor expression.

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1. Introduction

Lung cancer is the most common cause of cancer-related death [1]. Non-small cell lung cancer (NSCLC) is the most frequent histological type of lung cancer, accounting for 85 % of all lung cancers [2]. It has been reported that almost 60 % of patients with lung cancer had disseminated disease at diagnosis. Chemotherapy is recommended for patients with metastatic NSCLC. Molecular abnormalities have been discovered in patients with NSCLC over the last decade. At present, molecular and biomarker analyses are recommended in many guidelines when treating patients with metastatic NSCLC [3–5].

It has been reported that brain metastasis (BM) was present in 10 %–20 % of patients with NSCLC at diagnosis, and approximately 20 %–40 % of patients eventually develop BM [6–8]. Although targeted drugs are effective for BM in patients with NSCLC harboring driver mutations, cytotoxic drugs are less likely to penetrate the central nervous system because of the blood–brain barrier [9]. The standard treatment for BM in patients with NSCLC that does not harbor driver mutations is radiotherapy (RT), such as whole-brain RT (WBRT) and stereotactic radiosurgery (SRS). However, the median survival time (MST) of patients treated with WBRT was 4–8 months, and the prognosis of these patients is poor [10–12]. It has also been reported that WBRT increases the risk of cognitive dysfunction [13]. Thus, the development of more effective treatments against BM in patients with NSCLC lacking driver mutations is warranted.

In 2016, the results of the KEYNOTE-024 study comparing pembrolizumab with chemotherapy for patients with previously untreated NSCLC with a programmed death ligand 1 (PD-L1) tumor proportion score of at least 50 % was reported [14]. The median progression-free survival (PFS) was 10.3 months for patients receiving pembrolizumab, versus 6.0 months for those receiving chemotherapy. Pembrolizumab statistically prolonged PFS compared with chemotherapy, and the drug became a standard therapy for patients with previously untreated NSCLC with high tumor PD-L1 expression. However, patients with untreated BM were excluded from this study. In addition, patients with previously treated BM were only included if their metastases were stable more than 4 weeks after treatment. Recently, a review of the efficacy of immune checkpoint inhibitors (ICIs) against BM was reported [15]. The results of retrospective and prospective studies were assessed in this study, and it was suggested that ICIs had activity in patients with BM caused by NSCLC. However, this report did not include studies of patients with BMs of previously untreated NSCLC with high tumor PD-L1 expression. Therefore, the efficacy of pembrolizumab against BM of NSCLC with high PD-L1 tumor expression is unclear.

2. Materials and methods

2.1. Patients

We retrospectively reviewed the medical record data of patients who were treated with first-line treatment between March 2017 and September 2019 at Shizuoka Cancer Center. The recruitment criteria of this study were follows: (1) histological or cytological confirmation of NSCLC; (2) PD-L1 tumor proportion score of ≥50 % using the PD-L1 IHC 22C3 pharmaDx assay; (3) receipt of pembrolizumab as the first-line treatment; (4) tumor did not harbor driver mutations; (5) completion of MRI of the head at the time of diagnosis; and (6) no history of interstitial lung disease, drug-induced interstitial lung disease, and radiation pneumonitis requiring steroid treatment. Patients who did not have stage IV NSCLC at the time of diagnosis were treated with pembrolizumab as a first-line treatment if 6 months had passed since the last date of adjuvant chemotherapy or chemoradiotherapy.

We divided the patients into two groups according to presence of BM. The BM group comprised patients with BM before treatment with pembrolizumab, and patients without BM prior to treatment comprised the non-BM group. To assess the efficacy of treatment against BM, patients who received prior treatment for BM before pembrolizumab therapy comprised the BM-T group, and the remaining patients with BM were categorized into the BM-not T group.

2.2. Evaluation and statistical analysis

We evaluated tumor response to pembrolizumab according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by performing computed tomography of the chest and abdomen, magnetic resonance imaging (MRI) of the head, and bone scintigraphy or positron emission tomography–computed tomography [16]. The response rate of BM (BMRR) was also assessed according to RECIST using MRI. BMs that were ≥10 mm in size in the long axis were designated as target lesions regardless of the prior history of treatment against BM. Although RECIST does not permit evaluations of previously irradiated lesions as target lesions, the lesions treated with radiotherapy were evaluated as target lesions in our study to compare efficacy between radiotherapy plus pembrolizumab and pembrolizumab monotherapy. Therefore, the BMRR of the BM-T group was used as a reference value. The clinical evaluation of progression-free survival (PFS) and overall survival (OS) after the start of pembrolizumab was conducted using the Kaplan–Meier method to assess the time to recurrence or death. PFS of BM was defined as the period from the start of pembrolizumab to the progression of BM or death. We followed patients until March 2020, and patients who did not die or exhibit progression were censored. On the basis of the report by Sperduto et al., we collected the diagnosis-specific Graded Prognostic Assessment score (ds-GPA) [17]. Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria version 5.0 [18]. The log-rank test was used to compare cumulative survival between the groups. All P values were reported as two-sided, and $P < 0.05$ was considered statistically significant. All categorical variables were analyzed using the χ^2 test or the Fisher exact test, as appropriate. All statistical analyses were performed using JMP version 9.0 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Institutional Review Board of Shizuoka Cancer Center.

3. Results

3.1. BM and Non-BM groups

3.1.1. Patient characteristics

Between March 2017 and September 2019, 87 patients with NSCLC and a PD-L1 tumor proportion score of ≥50 % were treated with pembrolizumab as the first-line treatment. Twenty-three patients comprised the BM group, and the non-BM group included 64 patients. No significant differences in age, sex, ECOG performance status, histological type, and smoking history were observed between the BM and non-BM groups, but the former group included a significantly higher proportion of patients with stage IV disease at diagnosis (Table 1). In the BM group, the median number of BMs was three (range, 1 to ≥10), and the median maximum diameter of BMs was 13.6 mm (range, 2.6–60.6 mm). Thirteen patients were treated for BM. Symptoms of BM were found in six patients. Four patients exhibited incomplete hemiplegia, one patient had equilibrium disturbance, and one patient had memory disturbance. Two of the six patients with symptoms of BM were administered systemic steroids to treat brain edema. However, steroid therapy was discontinued at the start of pembrolizumab treatment because their symptoms improved (Table 2).

3.1.2. Efficacy

There was no significant difference in the overall response rate (ORR) between the BM and non-BM groups (57 % vs. 42 %, $P = 0.24$). The BMRR was 70 % in the BM group (Table 3). The median PFS was 6.5 months (95 % confidence interval [CI] = 2.0 months to not reached) in the BM group, compared with 7.0 months (95 % CI = 2.9–15.0 months) in the non-BM group ($P = 0.73$, Fig. 1A). The MST was 21.6 months (95

Table 1
Patient characteristics in the BM and non-BM groups.

	BM Group (n = 23)	Non-BM Group (n = 64)	P Value
Age (years)			
Median	70	70.5	
Range	56 - 81	45 - 87	0.77
≥75 (%)	39	33	0.58
Gender, n (%)			
Male	17 (74)	47 (73)	
Female	6 (26)	17 (27)	0.96
PS at recurrence, n (%)			
0	3 (13)	8 (13)	
1	18 (78)	49 (77)	
2	2 (9)	7 (10)	0.95
Histological type, n (%)			
Adenocarcinoma	16 (70)	44 (69)	
Squamous	4 (17)	12 (19)	
Other	3 (13)	8 (12)	0.99
Stage at treatment, n (%)			
stage IV	19 (83)	35 (55)	
Postoperative or post-chemoradiotherapy recurrence	4 (17)	29 (45)	0.02
PD-L1 expression, n (%)			
50−74 %	5 (22)	23 (36)	
75−100 %	23 (36)	41 (64)	0.21
Smoking Status, n (%)			
Current or Former	21 (91)	56 (88)	
Never	2 (9)	8 (12)	0.62
Number of BM, n			
median	3		
range	1 - ≥10		
Maximum diameter of BM			
median	13.6 mm		
range	2.6–60.6 mm		
Treatment of BM, n (%)	13 (57)		
Symptomatic BM, n (%)	6 (26)		
ds-GPS at the start of pembrolizumab, n (%)			
0 - 1.0	9 (39)		
1.5 - 2.0	9 (39)		
2.5 - 3.0	4 (17)		
3.5 - 4.0	1 (5)		

Abbreviations: PS: performance status, PD-L1: programmed cell death ligand 1, BM: brain metastasis, ds-GPA: diagnosis-specific Graded Prognostic Assessment.

% CI = 8.3–33.2 months) in the BM group, versus 24.6 months (95 % CI = 18.9 months to not reached) in the non-BM group (P = 0.57, Fig. 1B). The median PFS of BM was 18.6 months (95 % CI = 8.3–29.0 months) in the BM group, compared with 23.8 months (95 % CI = 11.9 months to not reached) in the non-BM group (P = 0.62, Fig. 1C).

3.2. BM-T and BM-not t groups

3.2.1. Patient characteristics

In total, 13 and 10 patients were grouped into the BM-T and BM-not T groups. No significant differences in patient characteristics were found between the two groups, but the maximum diameter of BM and the proportion of patients with symptomatic BM were significantly greater in the BM-T group.

3.2.2. Efficacy

There were no significant differences in ORR and BMRR between the two groups (Table 4). ORR was 54 % in the BM-T group, versus 60 % in the BM-not T group (P = 0.77). BMRR was 77 % in the BM-T group, compared with 60 % in the BM-not T group (P = 0.21). In the BM-not T group, all responses of BM were complete responses. Five patients displayed improvement of symptoms caused by BM, and the condition of one patient with incomplete hemiplegia remained unchanged. The median PFS was 6.5 months (95 % CI = 0.5 months to not reached) in the BM-T group, versus 5.3 months (95 % CI = 0.4–10.8 months) in the non-BM group (P = 0.47, Fig. 2A). The MST was not reached (95 %

Table 2
Patient characteristics in the BM-T and BM-not T groups.

	BM-T Group (n = 13)	BM-not T Group (n = 10)	P Value
Age (years)			
Median	69	74.5	
Range	56 - 78	56 - 81	0.35
≥75 (%)	4 (31)	5 (50)	0.35
Gender, n (%)			
Male	8 (62)	9 (90)	
Female	5 (38)	1 (10)	0.12
PS at recurrence, n (%)			
0	0 (0)	3 (30)	
1	12 (92)	6 (60)	
2	1 (8)	1 (10)	0.10
Histological type, n (%)			
Adenocarcinoma	8 (62)	8 (80)	
Squamous	3 (23)	1 (10)	
Other	2 (15)	1 (10)	0.62
Stage at treatment, n (%)			
stage IV	10 (77)	9 (90)	
Postoperative or post-chemoradiotherapy recurrence	3 (23)	1 (10)	0.41
PD-L1 expression, n (%)			
50−74%	4 (31)	1 (10)	
75−100%	9 (69)	9 (90)	0.23
Smoking Status, n (%)			
Current or Former	12 (92)	9 (90)	
Never	1 (8)	1 (10)	0.85
Number of BM, n			
median	2	3.5	
range	1 - ≥10	1 - ≥10	0.43
Maximum diameter of BM			
median	17.5mm	6.0 mm	
range	6.8 - 60.6 mm	2.6 - 16.4 mm	>0.01
Symptomatic BM, n (%)	6 (46)	0 (0)	0.01
Treatment against BM, n (%)			
SRS / SRT	10 (77)		
WBRT	1 (8)		
SRS + surgery	2 (15)		
ds-GPS at the start of pembrolizumab, n (%)			
0 - 1.0	5 (38)	4 (40)	
1.5 - 2.0	5 (38)	4 (40)	
2.5 - 3.0	2 (15)	2 (20)	
3.5 - 4.0	1 (8)	0 (0)	0.84

Abbreviations: PS: performance status, PD-L1: programmed cell death ligand 1, BM: brain metastasis, SRS: stereotactic radiosurgery, SRT: stereotactic radiotherapy, WBRT: whole-brain radiotherapy, ds-GPA: diagnosis-specific Graded Prognostic Assessment.

Table 3
Best overall response and BM response to first-line pembrolizumab in the BM and non-BM groups.

	Best overall response		BM response
	BM group (N = 23)	Non-BM group (N = 64)	BM group (N = 23)
Best response, n (%)			
CR	0 (0)	0 (0)	12 (52)
PR	13 (57)	27 (42)	4 (18)
SD	3 (13)	9 (14)	1 (4)
PD	6 (26)	22 (34)	1 (4)
non CR / non PD	0 (0)	3 (5)	0 (0)
NE	1 (4)	3 (5)	5 (22)
Response rate (%)	57	42	70
P value	0.24		

Abbreviations: BM: brain metastasis, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable.

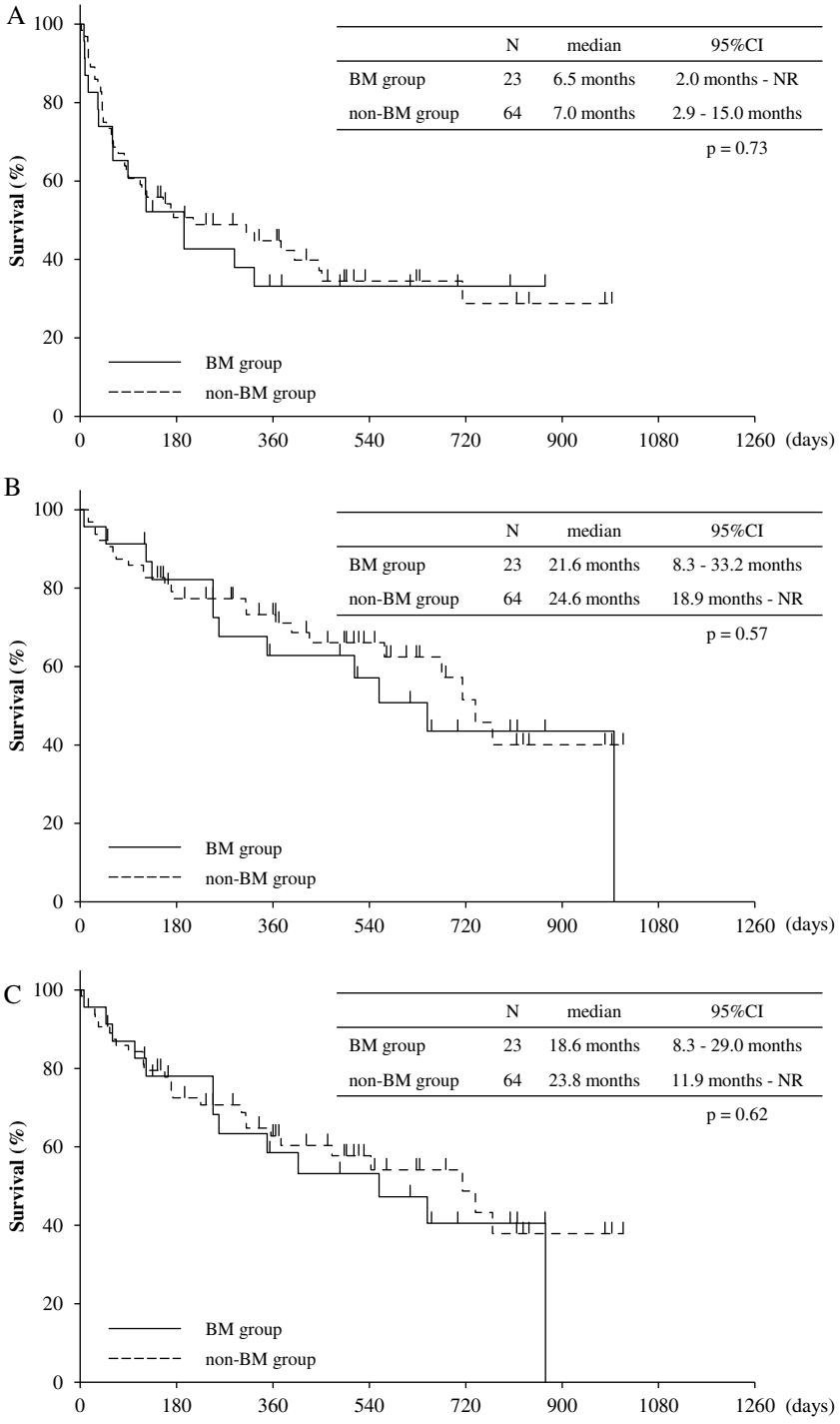

Fig. 1. (A) Progression-free survival, (B) overall survival, and (C) progression-free survival of brain metastasis in the BM and non-BM groups.

CI = 8.6 to not reached) in the BM-T group, compared with 18.6 months (95 % CI = 4.1–33.2 months) in the BM-not T group (P = 0.63, Fig. 2B). The median PFS of BM was 13.6 months (95 % CI = 3.4 months to not reached) in the BM-T group, versus 18.6 months (95 % CI = 2.0–29.0 months) in the BM-not T group (P = 0.90, Fig. 2C). Only one patient was received WBRT during the course of treatment in the BM-not T group.

3.3. Safety

Adverse events (AEs) are listed in Table 5. The most frequent AE was rash (five patients in the BM-T group and four patients in the BM-not T group). Diarrhea was observed in three patients in the BM-T group and two patients in the BM-not T group. Endocrine disorders, such as hypothyroidism and adrenal insufficiency, were observed in four patients in the BM-T group and one patient in the BM-not T group, but these AEs were controllable with replacement therapy. Grade 3 pneumonitis was observed in two patients in each group and was treated with systemic steroids. The proportion of patients with treatment-related adverse events leading to discontinuation of pembrolizumab was 2 patients (15.4 %) in the BM-T group and 3 patients (30.0 %) in the BM-not T group. There were no-treatment related deaths. Two patients in the BM-T group developed radiation necrosis of BM after RT. One patient developed radiation necrosis 132 days after the start of pembrolizumab therapy, and he was treated with systemic steroids because he had

Table 4
Best overall response and BM response to first-line pembrolizumab in the BM-T and BM-not T groups.

	Best overall response		BM response	
	BM-T group (N = 13)	BM-not T group (N = 10)	BM-T group (N = 13)	BM-not T group (N = 10)
Best response, n (%)				
CR	0 (0)	0 (0)	6 (46)	6 (60)
PR	7 (54)	6 (60)	4 (31)	0 (0)
SD	2 (15)	1 (10)	1 (8)	0 (0)
PD	3 (23)	3 (30)	0 (0)	1 (10)
non CR / non PD	0 (0)	0 (0)	0 (0)	0 (0)
NE	1 (8)	0 (0)	2 (15)	3 (30)
Response rate (%)	54	60	77	60
P value	0.77		0.21	

Abbreviations: BM: brain metastasis, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable.

symptoms of incomplete hemiplegia. The other patient developed radiation necrosis 402 days after the start of pembrolizumab. He was not treated because he had only imaging findings.

4. Discussion

This study demonstrated the efficacy of pembrolizumab for BM in patients with previously untreated NSCLC with high tumor PD-L1 expression. The BMRR was 70 % among all patients with BM. In addition, ORR, PFS, and OS did not significantly differ between the non-BM group and BM groups. Although the maximum diameter of BM and rate of symptomatic BM were significantly smaller in the BM-not T group, the response of BM was complete response for all patients in the BM-not T group. Meanwhile, only one patient was received WBRT during the course of treatment in the BM-not T group.

The central nervous system (CNS) includes the blood–brain barrier (BBB), which regulates homeostasis of the CNS by forming a tightly regulated neurovascular unit [19]. Although the BBB plays an important role in protecting the brain, it limits drug penetration into the brain parenchyma. The ability of drugs to cross the BBB is affected by several factors, such as molecular size, liposolubility, and charge [20]. It was reported that monoclonal antibodies, such as rituximab and trastuzumab, have low BBB penetrability due to their high molecular weights. In the case of ICI therapy, one study assessed the concentrations of nivolumab and pembrolizumab in serum and cerebrospinal fluid (CSF) [21]. The serum/CSF ratios of nivolumab ranged from 52 to 299, and the CSF penetration rate of nivolumab was similarly as low as those of rituximab and trastuzumab. In a recent review of the use of ICIs in the treatment of NSCLC BM, the potentially relevant mechanisms of action of ICIs in the CNS were mentioned [15]. First, some of the injected dose reaches the microenvironment of the BM. The local T-lymphocytes are reinvigorated, and they produce IFNγ, which is one of the mediators of innate immunity. IFNγ binds to brain microvascular endothelial cells and weakens the BBB. Finally, antigen-specific lymphocytes infiltrate the CNS. In addition, circulating tumor-specific lymphocyte counts are increased, and the antigen repertoire is expanded. This mechanism is partly attributable to extracranial lymphocyte reinvigoration. The mechanism of action of ICIs is related not to the direct action against BM but to modified immune cell activity. Although we included patients with high PD-L1 expression in our study, we could not assess PD-L1 expression in BM. Several studies assessed the concordance of PD-L1 levels between BM and primary lesions in patients with NSCLC [22–24]. However, the results of these studies were inconsistent, and it was unclear whether PD-L1 expression is comparable between BM and primary lesions. Further large studies assessing the biomarkers of efficacy of pembrolizumab against BM are expected.

A phase II trial that assessed the efficacy of pembrolizumab for BM of melanoma or. NSCLC was reported in 2016 [25]. This study included 18 patients with melanoma and 34 patients with NSCLC. The BMRR was 22 % in the melanoma cohort and 33 % in the NSCLC cohort. In 2020, the updated analysis of this study was reported, and 42 patients were included [26]. Patients were divided into two cohorts according to PD-L1 expression using a cutoff of 1 %. The BMRR of the cohort a PD-L1 tumor proportion score of less than 1 % or not evaluable was 0 %, compared with approximately 30 % for the cohort with higher PD-L1–positive rates. Although only 36 % of patients had previously untreated NSCLC and almost half of the patients harbored gene alteration in their report, PD-L1 might be a predictive factor for the efficacy of pembrolizumab against BM. The BMRR in our study, which included only patients with untreated NSCLC with high PD-L1 tumor expression, was higher than reported in their research. In 2020, a multicenter retrospective study assessed the efficacy of pembrolizumab in patients with or without BM caused by advanced NSCLC with a PD-L1 expression $\geq$ 50 % was reported [27]. A total of 282 patients were included and 56 patients had BM. The MST of patients with BM was 10.8 months and the BMRR was 67.5 % in this report. Because the proportion of patients with poor PS and symptomatic BM were greater compared with our study, the MST might have been shorter than our result. In fact, multivariate analysis of this report showed that PS $\geq$ 2 was an independent predictive factor for a poorer OS. There were several reports about the efficacy of ICI for patients with poor PS, and careful consideration of treatment with ICI might be necessary in case of patients with poor PS [28–30].

In 2019, Kim et al. reported a network meta-analysis comparing pembrolizumab monotherapy with pembrolizumab plus chemotherapy [31]. Pembrolizumab plus chemotherapy was linked to better PFS than pembrolizumab monotherapy for patients with NSCLC and PD-L1 TPS $\geq$ 50 %. Since the results of our study described the efficacy of pembrolizumab monotherapy against BM with high PD-L1 tumor expression, pembrolizumab combined with chemotherapy might have enhanced efficacy in these patients. A phase III trial comparing pembrolizumab monotherapy with pembrolizumab plus chemotherapy for previously untreated patients with NSCLC and PD-L1 TPS $\geq$ 50 % are ongoing (NCT04547504, PERSEE study). The results of the PERSEE study may reveal better strategies for patients with BM caused by previously untreated NSCLC and PD-L1 TPS $\geq$ 50 %. It has been suggested that angiogenesis inhibitors such as bevacizumab might be effective against BM caused by NSCLC [32,33]. In 2020, an exploratory analysis of the IMpower 150 study, which compared atezolizumab plus chemotherapy or atezolizumab plus bevacizumab and chemotherapy with bevacizumab plus chemotherapy, was reported [34]. This study found that a trend toward delayed development of new BM was observed for bevacizumab-containing regimens. Currently, several clinical trials including angiogenesis inhibitors are ongoing, and the results of these trials are anticipated (Table 6).

In our study, pneumonitis was observed in four patients (17 %) in the BM group. Although the reason was unclear, the small sample size may have affected the rate of occurrence. Because one patient who presented with pneumonitis received palliative thoracic RT following pembrolizumab, the cause of pneumonitis in this patient may have been thoracic RT. However, patients with BM may need to be treated with caution. In the BM-T group, two patients (15 %) displayed radiation necrosis of BM. It has been reported that radiation necrosis occurs in approximately 5 %–10 % of patients treated with SRS, and immunotherapy significantly increased the rate of radiation necrosis in patients treated with SRS compared with the findings in patients who received cytotoxic chemotherapy or targeted therapy [35–37]. In our study, both patients who developed radiation necrosis of BM received SRS before pembrolizumab. One of two patients had symptoms of incomplete hemiplegia, and he was treated with systemic steroids starting 132 days after the initiation of pembrolizumab therapy. It was reported that

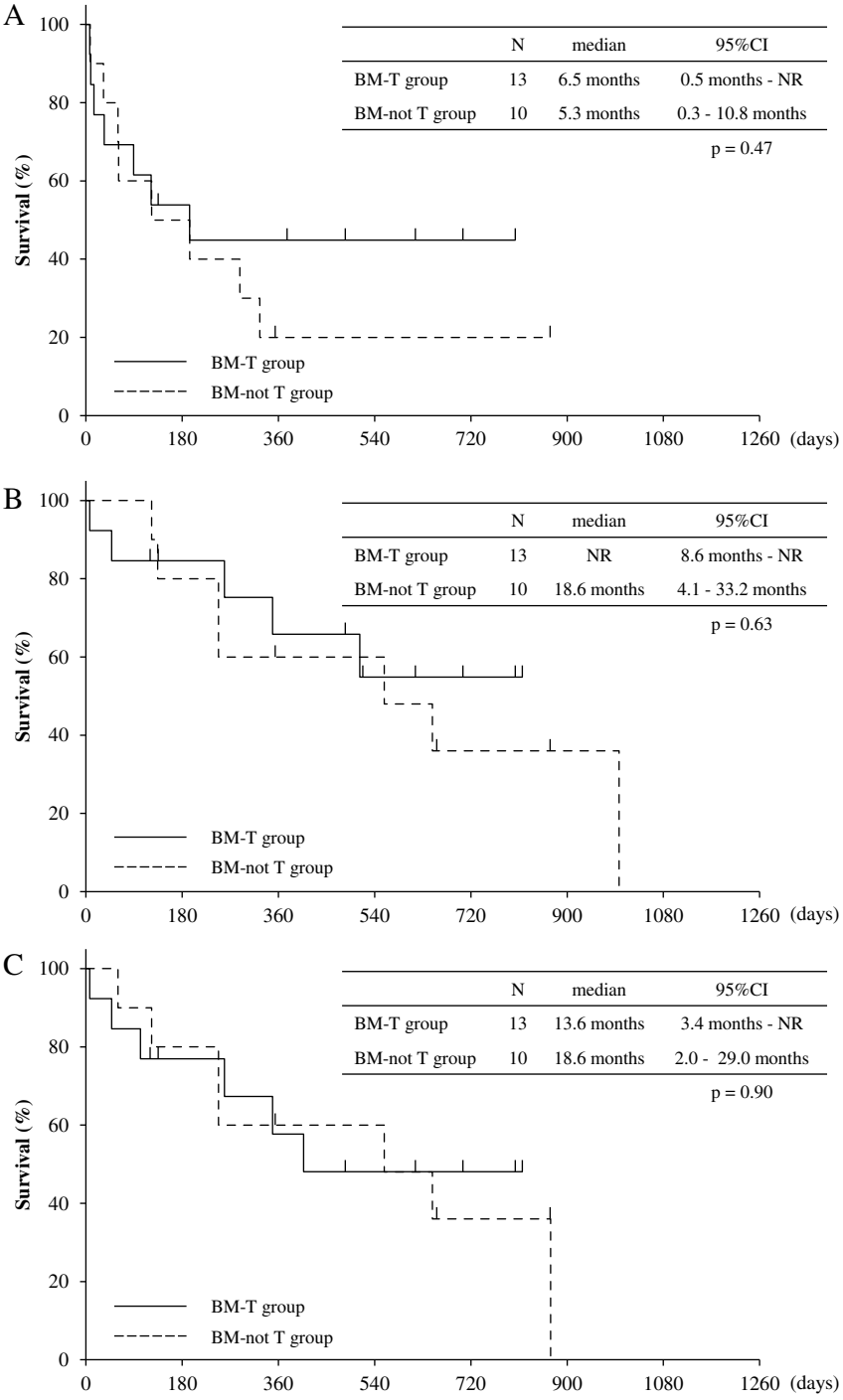

Fig. 2. (A) Progression-free survival, (B) overall survival, and (C) progression-free survival of brain metastasis in the BM-T and BM-not T groups.

baseline steroid use was associated with poorer outcomes in patients with NSCLC treated with ICIs [38]. In 2019, Hendriks et al. reported the outcomes of patients with NSCLC and BM who received ICIs [39]. They reproducibly reported that corticosteroid use was associated with poorer OS in the BM subgroup in multivariate analysis. Although our patients with radiation necrosis did not receive systemic steroids at the start of pembrolizumab, steroid use might have affected the prognosis of these patients. Meanwhile, there was no difference in treatment efficacy between the BM-T and BM-not T groups. It is unclear whether RT or pembrolizumab should be administered first. Considering the risk of radiation necrosis, patients with asymptomatic and small BM caused by previously untreated NSCLC with high PD-L1 expression may be effectively treated with pembrolizumab before RT.

Our study had several limitations. First, the sample size was small, and this was a single-center study. However, the KEYNOTE-024 study did not include patients with untreated BM. In addition, only 18 patients who received pembrolizumab had BM. Because a prospective study assessing the efficacy of pembrolizumab for BM caused by previously untreated NSCLC with high tumor PD-L1 expression is difficult, we believe that our study is important as real-world evidence for clinical practice. Second, the timing of the response assessment was decided by each physician, which might bias the results for PFS. Although five patients (22 %) in the BM group were not assessed for the response of BM, OS, which was the hard endpoint, was not significantly different

Table 5
AEs in the BM-T and BM-not T groups.

	BM-T group (N = 13)			BM-not T group (N = 10)		
	Grade 1	Grade 2	>Grade 3	Grade 1	Grade 2	>Grade 3
AE, n (%)						
Rash	3 (23 %)	1 (8%)	1 (8%)	3 (30 %)	1 (10 %)	0 (0%)
Pruritus	2 (15 %)	2 (15 %)	0 (0%)	3 (30 %)	1 (10 %)	0 (0%)
Dry skin	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Appetite loss	3 (23 %)	0 (0%)	0 (0%)	1 (10 %)	0 (0%)	0 (0%)
Fatigue	1 (8%)	0 (0%)	0 (0%)	1 (10 %)	0 (0%)	0 (0%)
Mucositis	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	3 (23 %)	0 (0%)	0 (0%)	1 (10 %)	1 (10 %)	0 (0%)
Hyperthyroidism	3 (23 %)	0 (0%)	0 (0%)	2 (20 %)	0 (0%)	0 (0%)
Hypothyroidism	1 (8%)	2 (15 %)	0 (0%)	0 (0%)	1 (10 %)	0 (0%)
Adrenal insufficiency	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AST increased	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (10 %)	0 (0%)
ALT increased	1 (8%)	1 (8%)	0 (0%)	1 (10 %)	0 (0%)	1 (10 %)
Blood bilirubin increased	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10 %)	0 (0%)
Creatinine increased	2 (15 %)	0 (0%)	0 (0%)	1 (10 %)	0 (0%)	0 (0%)
Proteinuria	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pneumonitis	0 (0%)	0 (0%)	2 (15 %)	0 (0%)	0 (0%)	2 (20 %)
Central nervous system necrosis	1 (8%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Systemic steroid against AE, n (%)	4 (31 %)			4 (40 %)		

Abbreviations: AE: Adverse event, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

Table 6
Clinical trials of ICI treatment in previously untreated patients with non-small cell lung cancer.

Trial number	phase	PD-L1	treatment	1 st EP
NCT04547504 (PERSEE)	III	≥50 %	Pembrolizumab Pembrolizumab + chemotherapy	Progression-free survival
NCT04294810 (SKYSCRAPER-01)	III	≥50 %	Tiragolumab + atezolizumab Atezolizumab	Progression-free survival Overall survival
NCT03829332 (LEAP-007)	III	≥1%	Pembrolizumab + lenvatinib Pembrolizumab + placebo	Progression-free survival Overall survival
NCT03631706	III	≥50 %	M7824 Pembrolizumab	Progression-free survival Overall survival
NCT03976362 (KEYLYNK-008)	III	All	Pembrolizumab + chemotherapy →Pembrolizumab + olaparib Pembrolizumab + chemotherapy →Pembrolizumab + placebo	Progression-free survival Overall survival
NCT03976323 (KEYLYNK-006)	III	All	Pembrolizumab + chemotherapy →Pembrolizumab + olaparib Pembrolizumab + chemotherapy →Pembrolizumab + pemetrexed	Progression-free survival Overall survival
NCT03867175	III	All	ICI + chemotherapy →SBRT + pembrolizumab ICI + chemotherapy →Pembrolizumab	Progression-free survival
NCT04475939 (ZEAL-1 L)	III	All	Pembrolizumab + chemotherapy →Pembrolizumab + niraparib Pembrolizumab + chemotherapy →Pembrolizumab + placebo	Progression-free survival Overall survival
NCT04139317	II	≥50 %	Pembrolizumab + capmatinib Pembrolizumab	Progression-free survival
NCT04262856 (ARC-7)	II	Positive	Zimberelimab Zimberelimab + AB154 Zimberelimab + AB154 + AB928	Objective response rate Progression-free survival
NCT04515979	II	≥1%	Pembrolizumab + vactosertib	Objective response rate
NCT03896074 (BEAT)	II	≥1%	Atezolizumab Atezolizumab + bevacizumab	Overall survival
NCT04164745	II	≥1%	Pembrolizumab + anlotinib	Progression-free survival
NCT03322540 (KEYNOTE-654)	II	≥50 %	Pembrolizumab + epacadostat Pembrolizumab + placebo	Objective response rate
NCT04524689 (CARMEN-LC05)	II	≥1%	Pembrolizumab Pembrolizumab + SAR408701	Dose-limiting toxicity Objective response rate
NCT03563716 (CITYSCAPE)	II	≥1%	Atezolizumab + placebo Atezolizumab + MTIG7192A	Objective response rate Progression-free survival
NCT03417882	II	≥50 %	Pembrolizumab + GRN-1201	Response rate
NCT03353675	I / II	<50 %	Nivolumab + chemotherapy + TG4010	Objective response rate
NCT03786692	II	NA	Atezolizumab + chemotherapy + bevacizumab → Atezolizumab + pemetrexed + bevacizumab Chemotherapy + bevacizumab →Pemetrexed + bevacizumab	Progression-free survival

Abbreviations: PD-L1: programmed cell death ligand 1, 1 st EP: Primary endpoint, ICI: immune checkpoint inhibitor, SBRT: stereotactic body radiotherapy.

between the BM and non-BM groups. Finally, we included only patients with high PD-L1 expression. Since only two BM samples were resected, we did not assess PD-L1 levels in BM. Therefore, PD-L1 levels in BM were unclear. However, the assessment of PD-L1 expression in BM is difficult, and patients with NSCLC and high tumor PD-L1 expression are treated with pembrolizumab in clinical practice. We believe the results of our study are relevant to clinical practice.

5. Conclusions

In conclusion, pembrolizumab may have efficacy for BM in patients with previously untreated NSCLC and high PD-L1 expression. Patients

with asymptomatic and small BM are suitable for pembrolizumab therapy prior to RT, and this strategy may prevent AEs caused by RT, such as radiation necrosis and cognitive disorder. Larger real-world studies are warranted in the future.

CRediT authorship contribution statement

Kazushige Wakuda: Conceptualization, Methodology, Resources, Writing - original draft. **Michitoshi Yabe:** Writing - review & editing. **Hiroaki Kodama:** Writing - review & editing. **Naoya Nishioka:** Writing - review & editing. **Taichi Miyawaki:** Writing - review & editing. **Eriko Miyawaki:** Writing - review & editing. **Nobuaki Mamesaya:** Resources, Writing - review & editing. **Takahisa Kawamura:** Resources, Writing - review & editing. **Haruki Kobayashi:** Resources, Writing - review & editing. **Shota Omori:** Resources, Writing - review & editing. **Akira Ono:** Resources, Writing - review & editing. **Hirotsugu Kenmotsu:** Resources, Writing - review & editing. **Tateaki Naito:** Resources, Writing - review & editing. **Haruyasu Murakami:** Resources, Writing - review & editing. **Hideyuki Harada:** Writing - review & editing. **Masahiro Endo:** Writing - review & editing. **Yasuhiro Gon:** Investigation, Writing - review & editing. **Toshiaki Takahashi:** Investigation, Resources, Writing - review & editing.

Declaration of Competing Interest

All authors have no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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和文要約

題名

PD-L1 高発現、未治療非小細胞肺癌の脳転移に対する Pembrolizumab の有効性の検討

氏名

和久田一茂

概要

PD-L1 高発現例を対象とした KEYNOTE-024 試験の結果、PD-L1 高発現例に対するペムブロリズマブ単剤療法の有効性が示され、現在、治療選択肢の 1 つとなっている。しかし、多くの臨床試験で未治療脳転移症例は除外されており、未治療脳転移を有する症例に対するペムブロリズマブ単剤療法の有効性は明らかではない。そこで、脳転移を有する PD-L1 高発現、非小細胞肺癌に対するペムブロリズマブの有効性を後方視的に解析した。

2017 年 3 月から 2019 年 9 月にペムブロリズマブ単剤療法が実施された PD-L1 高発現、非小細胞肺癌患者を対象とし、脳転移を有する群 (BM 群)、脳転移を有さない群 (non-BM 群) の 2 群に分け有効性を後方視的に解析した。また、BM 群を対象に、ペムブロリズマブ投与前に脳転移に対する治療が行われた群 (BM-T 群)、治療が行われていない群 (BM-not T 群) の 2 群に分け有効性を後方視的に解析した。

87 例が対象となり BM 群: 23 例、non-BM 群: 64 例であった。BM 群で診断時病期が IV 期である症例を有意に多く認めたが、年齢や性別、PS などの患者背景は両群で有意差は認めなかった。奏効割合、無増悪生存期間、生存期間は両群で有意差を認めず、BM 群の脳転移奏効割合は 70%であった。次いで、BM 群を、BM-T 群、BM-not T 群の 2 群に分け解析を行った。BM-T 群: 13 例、BM-not T 群: 10 例であり、BM-T 群では、有意に脳転移巣最大径が大きく、症候性脳転移例が多かった。無増悪生存期間、生存期間は両群で有意差を認めず、脳転移無増悪生存期間は BM-T 群: 13.6 ヵ月、BM-not T 群: 18.6 ヵ月であった。

これらの結果から、PD-L1 高発現、未治療非小細胞肺癌の脳転移に対するペムブロリズマブの有効性が示唆された。

本文

Introduction

肺癌は癌死亡の原因として最も多く、非小細胞肺癌は肺癌患者の約 85%を占めると報告されている。非小細胞肺癌の約 60%は診断時に遠隔転移を認めており、10〜20%は診断時に脳転移を有している。脳転移に対して、全脳照射や定位照射が行われるが、臨床試験における生存期間中央値は 4〜8 ヵ月であり、治療効果は限定的である。また、晩期障害として認知機能障害などのリスクもあり、脳転移に対する適切な治療開発が必要である。

2022 年の肺癌診療ガイドラインでは、未治療非小細胞肺癌の化学療法を行う際に、ドライバー遺伝子変異と 22C3 抗体や SP142 抗体による PD-L1 を評価して薬剤を選択することが推奨されている。ドライバー遺伝子変異陽性例に対しては各遺伝子変異に応じた標的治療薬、PD-L1 が 0〜49%の症例に対しては殺細胞性抗癌剤と免疫チェックポイント阻害剤の併用、PD-L1 が 50%以上の症例に対しては免疫チェックポイント阻害剤単剤療法がそれぞれ推奨されている。PD-L1 が 50%以上の症例に対する免疫チェックポイント阻害剤の有効性については、KEYNOTE-024 試験で示されている。KEYNOTE-024 試験は、全身化学療法未治療の PD-L1 高発現、進行非小細胞肺がんを対象にペムブロリズマブ単剤療法とプラチナ製剤を含む殺細胞性抗癌剤の併用療法を比較した第 III 相試験であり、主要評価項目である無増悪生存期間中央値はそれぞれ 10.3 ヵ月、6.0 ヵ月、ハザード比は 0.50 (95%信頼区間：0.37 - 0.68) という成績が報告されている。しかしながら、本試験では無治療の脳転移を有する患者は除外されており、脳転移を有する患者では治療後 4 週間増悪を認めていないことが求められていた。そのため、PD-L1 高発現の脳転移を有する非小細胞肺癌に対するペムブロリズマブ単剤療法の有効性は明らかではない。

Material and Methods

2017 年 3 月から 2019 年 9 月に静岡県立静岡がんセンターで初回治療が行われた患者のうち、1) 非小細胞肺癌の診断となっている、2) 22C3 による評価で PD-L1 発現が 50%以上である、3) 初回治療としてペムブロリズマブ単剤療法がおこなわれている、4) ドライバー遺伝子変異を有していない、5) 診断時に脳 MRI が行われている、6) 間質性肺炎の既往がない、の条件を満たす患者を対象に後方視的に解析を行った。術後、もしくは化学放射線療法後の患者は最終治療日から 6 か月を経て増悪を認めている場合に本研究の対象とした。

次いで上記対象を、ペムブロリズマブ単剤療法前に脳転移がある群 (BM 群)、脳転移がない群 (non-BM 群) の 2 群に分け、ペムブロリズマブ単剤療法の有効性を比較した。また、BM 群を対象に、ペムブロリズマブ単剤療法前に脳転移に対する治療が行われた群 (BM-T 群)、治療が行われていない群 (BM-not T 群) の 2 群に分け同様の解析を行った。

ペムブロリズマブ単剤療法の有効性は RECIST ver1.1 により評価した。脳転移の奏効は MRI を用いて行い、脳転移のみを RECIST ver1.1 と同様の定義で解析し、測定可能病変は

長径で 10mm 以上の病変とした。RECIST では放射線治療後の病変は測定可能病変としないが、本研究では放射線治療の有無による脳転移縮小効果を検討するために、放射線治療後の病変も測定可能病変とした。無増悪生存期間、生存期間、脳転移無増悪生存期間はそれぞれ、ペムブロリズマブ単剤療法開始日から増悪または死亡まで、死亡まで、脳転移巣増悪または死亡までと定義した。上記のイベントが生じていない症例は打ち切りとして解析を行い、無増悪生存期間のイベントである「増悪・死亡」の前に次治療が行われた症例は、次治療開始日を打ち切り日として無増悪生存期間の解析を行った。また、本解析では、ds-GPA スコアという予後評価スコアを収集し、解析を行った。全ての p 値は 0.05 未満で有意とし、カテゴリカルデータは $\chi 2$ 検定、Fisher 正確度検定で解析した。また、本解析は JMP ver9.0 で行った。本研究は静岡県立静岡がんセンターの倫理委員会で承認されている。

Results

BM 群と non-BM 群

87 例が対象となり、23 例が BM 群、64 例が non-BM 群であった。年齢、性別、PS、組織型、増悪後の後治療の有無は両群で有意差を認めなかったが、診断時病期は BM 群で有意に IV 期を多く認めた (表 1)。また、BM 群の脳転移個数中央値は 3 個、長径の中央値は 13.6mm であった。

奏効割合、脳転移奏効割合、無増悪生存期間、生存期間、脳転移無増悪生存期間は BM 群、non-BM 群で有意差を認めなかった (表 2、図 1)。

BM-T 群と BM-not T 群

13 例が BM-T 群、10 例が BM-not BM 群であった。年齢、性別、PS、組織型、増悪後の後治療の有無は両群で有意差を認めなかったが、BM-T 群で脳転移最大径が有意に大きく、症候性脳転移例を有意に多く認めた (表 3)。

奏効割合、脳転移奏効割合、無増悪生存期間、生存期間、脳転移無増悪生存期間は BM-T 群、BM-not T 群で有意差を認めなかった (表 4、図 2)。

安全性

最も多く認めた有害事象は Rash であった。また、掻痒、食欲不振、甲状腺機能障害、GOT・GPT 増加などの有害事象を認めたが、いずれも軽度であり、管理可能であった (表 5)。肺臓炎については、BM 群で 4 例 (17%)、non-BM 群で 7 例 (12%) に認め、non-BM 群の 1 例は Grade 5 の肺臓炎であったが、その他の肺臓炎はいずれも改善を認めていた。BM 群では脳転移に対する抗浮腫療法を含め、8 例 (35%) でステロイド投与が行われていたが、治療関連死亡は認めなかった。また、BM-T 群と BM-not T 群の両群の解析でも最も多く認めた有害事象は Rash であった。BM-T 群の 2 例で脳転移巣の放射線壊死を認め、発現までの期間は 132 日、402 日であり、2 例いずれも抗浮腫療法としてステロイドが投与されていた (表 6)。

Discussion

本研究の結果、PD-L1 高発現の脳転移を有する未治療非小細胞肺癌に対するペムブロリズマブ単剤療法の有効性が示され、ペムブロリズマブ単剤療法の脳転移奏効割合は 70%であった。また、ペムブロリズマブ単剤療法の奏効割合、無増悪生存期間、生存期間、脳転移無増悪生存期間は脳転移の有無による有意差を認めなかった。

中枢神経系には血液脳関門があるため、殺細胞性抗癌剤などの薬剤の透過性が低いことが知られている。また、リツキシマブやトラスツズマブのようなモノクローナル抗体も血液脳関門の透過性が低いことが報告されている。免疫チェックポイント阻害剤については、血清と髄液におけるニボルマブの濃度を解析した報告があり、ニボルマブの血清/髄液比は 52 から 299 であり、リツキシマブやトラスツズマブと同様に髄液移行率が低いことが報告されている。しかしながら、投与された免疫チェックポイント阻害剤の一部が血液脳関門を通過し、局所の T リンパ球を活性化することで抗腫瘍効果を示す可能性が言及されている。

脳転移に対するペムブロリズマブの有効性については、2016 年に非小細胞肺癌とメラノーマを対象とした第 II 相試験の結果が報告されているが、PD-L1 高発現例以外も含んでおり、ペムブロリズマブ単剤療法の有効性は我々の研究と比較して限定的なものであった。2020 年には PD-L1 高発現例に対するペムブロリズマブ単剤療法の有効性を検討した多施設後方視的解析の結果が報告されている。本検討は、282 例の PD-L1 高発現例を対象としており、56 例が脳転移を有していた。脳転移例の生存期間中央値は 10.8 ヵ月、脳転移奏効割合は 67.5%と報告されているが、PS 不良例、症候性脳転移例が我々の研究と比較して多く含まれていることが、生存期間が短くなっている原因と考えられた。実際に、PS 不良は生存期間の独立した予後不良因子であることが報告されており、ペムブロリズマブ単剤療法の有効性を過小評価している可能性がある。また、本解析では脳転移に対する治療歴の有無別のペムブロリズマブ単剤療法の有効性は検討されていない。

2019 年にペムブロリズマブ単剤療法とペムブロリズマブ、化学療法併用療法を比較したネットワーク解析の結果が報告され、PD-L1 高発現例に対しても化学療法を併用することで治療効果が高い可能性が示されている。しかしながら、実診療において、PD-L1 高発現例に対してペムブロリズマブ、化学療法併用療法を行うことは少なく、本研究ではペムブロリズマブ単剤療法のみの解析を行っているが、化学療法を併用することでより有効性が高まる可能性が示唆される。PD-L1 高発現例を対象としたペムブロリズマブ単剤療法とペムブロリズマブ、化学療法併用療法の比較試験が行われており、その結果が期待される。

本研究では、BM-T 群の 2 例で放射線壊死を認めた。放射線壊死は SRS が行われた症例の 5〜10%で認めることが報告されており、免疫チェックポイント阻害剤による治療例では、殺細胞性抗癌剤や標的治療薬が行われた症例と比較して有意に多く発症することが報告されている。今回の検討では、BM-T 群、BM-not T 群で有効性に有意差はなく、放射線壊死とその治療としてのステロイドによる免疫チェックポイント阻害剤の治療効果減弱の

リスクを鑑みると少なくとも、無症候性脳転移例や小さな脳転移例では、RT の前にペムブロリズマブ単剤療法を先行してもよいと考えられる。

本研究の limitation として、サンプルサイズが少なく単施設の検討であること、後方視的解析であり腫瘍評価のタイミングが一律でないこと、PD-L1 高発現例に限った検討であることが挙げられるが、同様の報告は限られており、実臨床において重要な検討であったと思われる。

Conclusions

ペムブロリズマブ単剤療法は、脳転移を有する未治療 PD-L1 高発現非小細胞肺癌に対して有効であることが示唆された。無症候性脳転移症例や小さな脳転移症例では、放射線治療による放射線壊死や認知機能障害などの有害事象を鑑みて、ペムブロリズマブ単剤療法を先行することも検討する必要があると思われる。脳転移に対するペムブロリズマブ単剤療法を先行することが可能な脳転移の大きさなどの解析については、今後、より大規模な real-world 研究が望まれる。

表 1) BM 群と non-BM 群の患者背景

		BM 群 (N = 23)	non-BM 群 (N = 64)	P 値
年齢	中央値	70 歳	70.5 歳	
	範囲	56 - 81 歳	45 - 87 歳	0.77
性別	男性	17 例 (74%)	47 例 (73%)	
	女性	6 例 (26%)	17 例 (27%)	0.96
PS	0	3 例 (13%)	8 例 (13%)	
	1	18 例 (78%)	49 例 (77%)	
	2	2 例 (9%)	7 例 (10%)	0.95
組織型	腺癌	16 例 (70%)	44 例 (69%)	
	扁平上皮癌	4 例 (17%)	12 例 (10%)	
	その他	3 例 (13%)	8 例 (12%)	0.99
診断時病期	IV	19 例 (83%)	35 例 (55%)	
	その他	4 例 (17%)	29 例 (45%)	0.02
二次治療	あり	8 例 (35%)	23 例 (36%)	
	プラチナ併用療法	8 例 (35%)	16 例 (25%)	
	なし	15 例 (65%)	41 例 (64%)	1.00
三次治療	あり	5 例 (22%)	12 例 (19%)	
	ドセタキセル	3 例 (13%)	3 例 (5%)	
	S-1	1 例 (5%)	7 例 (11%)	
	なし	18 例 (78%)	52 例 (81%)	0.77
脳転移個数	中央値	3 個		
	範囲	1 - ≥10 個		
最大脳転移長径	中央値	13.6mm		
	範囲	2.6 - 60.6mm		
ds-GPS	0 - 1.0	9 例 (39%)		
	1.5 - 2.0	9 例 (39%)		
	2.5 - 3.0	4 例 (17%)		
	3.5 - 4.0	1 例 (5%)		

表 2) BM 群と non-BM 群の解析

	BM 群 (N = 23)	non-BM 群 (N = 64)	P 値
最良効果			
完全奏効	0 例 (0%)	0 例 (0%)	
部分奏効	13 例 (57%)	27 例 (42%)	
安定	3 例 (13%)	9 例 (14%)	
増悪	6 例 (26%)	22 例 (34%)	
非完全奏効 / 非増悪	0 例 (0%)	3 例 (5%)	
評価不能	1 例 (4%)	3 例 (5%)	
奏効割合	57%	42%	0.24
脳転移最良効果			
完全奏効	12 例 (52%)		
部分奏効	4 例 (18%)		
安定	1 例 (4%)		
増悪	1 例 (4%)		
非完全奏効 / 非増悪	0 例 (0%)		
評価不能	5 例 (22%)		
脳転移奏効割合	70%	-	-
無増悪生存期間			
中央値	6.5 ヵ月	7.0 ヵ月	
95%信頼区間	2.0 ヵ月 – 未到達	2.9 – 15.0 ヵ月	0.73
増悪例における後治療	8 例 / 15 例 (53%)	14 例 / 39 例 (36%)	
全生存期間			
中央値	21.6 ヵ月	24.6 ヵ月	
95%信頼区間	8.3 – 33.2 ヵ月	18.9 ヵ月 – 未到達	0.57
脳転移無増悪生存期間			
中央値	18.6 ヵ月	23.8 ヵ月	
95%信頼区間	8.3 – 29.0 ヵ月	11.9 ヵ月 – 未到達	0.62

表 3) BM-T 群と BM-not BM 群の患者背景

		BM-T 群 (N = 13)	BM-not T 群 (N = 10)	P 値
年齢	中央値	69 歳	74.5 歳	
	範囲	56 - 78 歳	56 - 81 歳	0.35
性別	男性	8 例 (62%)	9 例 (90%)	
	女性	5 例 (38%)	1 例 (10%)	0.12
PS	0	0 例 (0%)	3 例 (30%)	
	1	12 例 (92%)	6 例 (60%)	
	2	1 例 (8%)	1 例 (10%)	0.10
組織型	腺癌	8 例 (62%)	8 例 (80%)	
	扁平上皮癌	3 例 (23%)	1 例 (10%)	
	その他	2 例 (15%)	1 例 (10%)	0.62
診断時病期	IV	10 例 (77%)	9 例 (90%)	
	その他	3 例 (23%)	1 例 (10%)	0.41
二次治療	あり	4 例 (31%)	4 例 (40%)	
	プラチナ併用療法	4 例 (31%)	4 例 (31%)	
	なし	9 例 (69%)	6 例 (60%)	0.69
三次治療	あり	2 例 (15%)	3 例 (30%)	
	ドセタキセル	2 例 (15%)	1 例 (10%)	
	S1	0 例 (0%)	1 例 (10%)	
	なし	11 例 (85%)	7 例 (70%)	0.62
脳転移個数	中央値	2 個	3.5 個	
	範囲	1 - ≥10 個	1 - ≥10 個	0.43
最大脳転移長径	中央値	17.5mm	6.0mm	
	範囲	6.8 - 60.6mm	2.6 - 16.4mm	<0.01
症候性脳転移		6 例 (46%)	0 (0%)	0.01
治療歴	SRS / SRT	10 例 (77%)		
	WBRT	1 例 (8%)		
	SRS + 手術	2 例 (15%)		
ds-GPS	0 - 1.0	5 例 (38%)	4 例 (40%)	
	1.5 - 2.0	5 例 (38%)	4 例 (40%)	
	2.5 - 3.0	2 例 (15%)	2 例 (20%)	
	3.5 - 4.0	1 例 (8%)	0 例 (0%)	0.84

表 4) BM-T 群と BM-not T 群の解析

	BM-T 群 (N = 13)	BM-not T 群 (N = 10)	P 値
最良効果			
完全奏効	0 例 (0%)	0 例 (0%)	
部分奏効	7 例 (54%)	6 例 (60%)	
安定	2 例 (15%)	1 例 (10%)	
増悪	3 例 (23%)	3 例 (30%)	
非完全奏効 / 非増悪	0 例 (0%)	0 例 (0%)	
評価不能	1 例 (8%)	0 例 (0%)	
奏効割合	54%	60%	0.77
脳転移最良効果			
完全奏効	6 例 (46%)	6 例 (60%)	
部分奏効	4 例 (31%)	0 例 (0%)	
安定	1 例 (8%)	0 例 (0%)	
増悪	0 例 (0%)	1 例 (10%)	
非完全奏効 / 非増悪	0 例 (0%)	0 例 (0%)	
評価不能	2 例 (15%)	3 例 (30%)	
脳転移奏効割合	77%	60%	0.21
無増悪生存期間			
中央値	6.5 ヵ月	5.3 ヵ月	
95%信頼区間	0.5 ヵ月 – 未到達	0.4 – 10.8	0.47
増悪例における後治療	5 例 / 8 例 (63%)	3 例 / 7 例 (43%)	
全生存期間			
中央値	未到達	18.6 ヵ月	
95%信頼区間	8.6 – 未到達	4.1 – 33.2 ヵ月	0.63
脳転移無増悪生存期間			
中央値	13.6 ヵ月	18.6 ヵ月	
95%信頼区間	3.4 ヵ月 – 未到達	2.0 – 29.0 ヵ月	0.90

表 5) BM 群、non-BM 群の有害事象

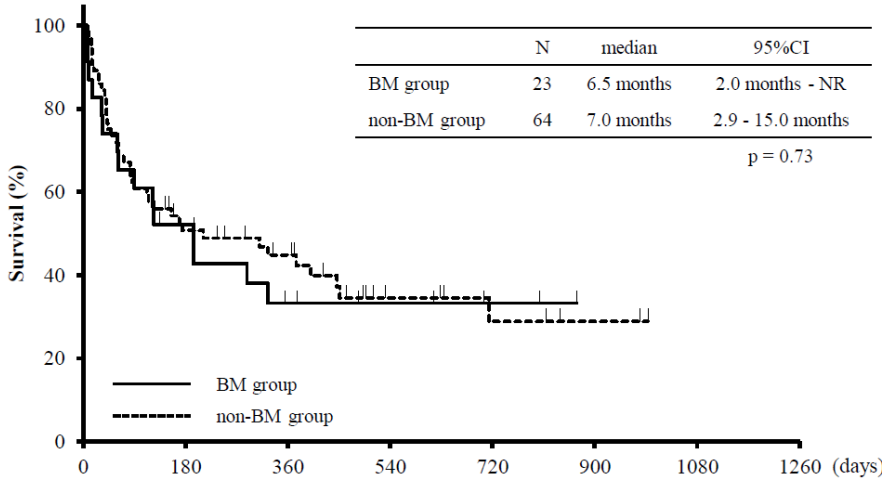
	BM 群 (N = 23)			non-BM 群 (N = 64)		
	Gr 1	Gr 2	> Gr 3	Gr 1	Gr 2	> Gr 3
Rash	6 (26%)	2 (9%)	1 (4%)	14 (22%)	3 (5%)	0 (0%)
掻痒	5 (22%)	3 (13%)	0 (0%)	12 (19%)	0 (0%)	0 (0%)
乾燥症	0 (0%)	1 (4%)	0 (0%)	3 (5%)	0 (0%)	0 (0%)
食欲不振	4 (17%)	0 (0%)	0 (0%)	6 (9%)	3 (5%)	0 (0%)
疲労	2 (9%)	0 (0%)	0 (0%)	8 (13%)	3 (5%)	0 (0%)
粘膜炎	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
下痢	4 (17%)	1 (4%)	0 (0%)	6 (9%)	0 (0%)	0 (0%)
甲状腺機能亢進症	5 (22%)	0 (0%)	0 (0%)	3 (5%)	0 (0%)	0 (0%)
甲状腺機能低下症	1 (4%)	3 (13%)	0 (0%)	7 (11%)	3 (5%)	0 (0%)
副腎不全	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
AST 増加	1 (4%)	1 (4%)	0 (0%)	10 (16%)	2 (4%)	1 (2%)
ALT 増加	2 (9%)	1 (4%)	1 (4%)	9 (14%)	5 (8%)	1 (2%)
クレアチニン増加	3 (13%)	0 (0%)	0 (0%)	7 (11%)	0 (0%)	0 (0%)
肺臓炎	0 (0%)	0 (0%)	4 (17%)	2 (4%)	4 (6%)	1 (2%)
CNS 壊死	1 (4%)	1 (4%)	0 (0%)	-	-	-
ステロイド投与		8 例 (35%)			5 例 (8%)	

表 6) BM 群、BM-T 群と BM-not T 群の有害事象

	BM 群 (N = 23)			BM-T 群 (N = 13)			BM-not T 群 (N = 10)		
	Gr 1	Gr 2	>Gr 3	Gr 1	Gr 2	>Gr 3	Gr 1	Gr 2	>Gr 3
Rash	6 (26%)	2 (9%)	1 (4%)	3 (23%)	1 (8%)	1 (8%)	3 (30%)	1 (10%)	0 (0%)
掻痒	5 (22%)	3 (13%)	0 (0%)	2 (15%)	2 (15%)	0 (0%)	3 (30%)	1 (10%)	0 (0%)
乾燥症	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
食欲不振	4 (17%)	0 (0%)	0 (0%)	3 (23%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
疲労	2 (9%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
粘膜炎	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
下痢	4 (17%)	1 (4%)	0 (0%)	3 (23%)	0 (0%)	0 (0%)	1 (10%)	1 (10%)	0 (0%)
甲状腺機能亢進症	5 (22%)	0 (0%)	0 (0%)	3 (23%)	0 (0%)	0 (0%)	2 (20%)	0 (0%)	0 (0%)
甲状腺機能低下症	1 (4%)	3 (13%)	0 (0%)	1 (8%)	2 (15%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)
副腎不全	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AST 増加	1 (4%)	1 (4%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)
ALT 増加	2 (9%)	1 (4%)	1 (4%)	1 (8%)	1 (8%)	0 (0%)	1 (10%)	0 (0%)	1 (10%)
クレアチニン増加	3 (13%)	0 (0%)	0 (0%)	2 (15%)	0 (0%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
肺臓炎	0 (0%)	0 (0%)	4 (17%)	0 (0%)	0 (0%)	2 (15%)	0 (0%)	0 (0%)	2 (20%)
CNS 壊死	1 (4%)	1 (4%)	0 (0%)	1 (8%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ステロイド投与		8 例 (35%)			4 例 (31%)			4 例 (40%)	

図 1) BM 群と non-BM 群の無増悪生存期間 (Figure 1A)、生存期間 (Figure 1B)、脳転移無増悪生存期間 (Figure 1C)

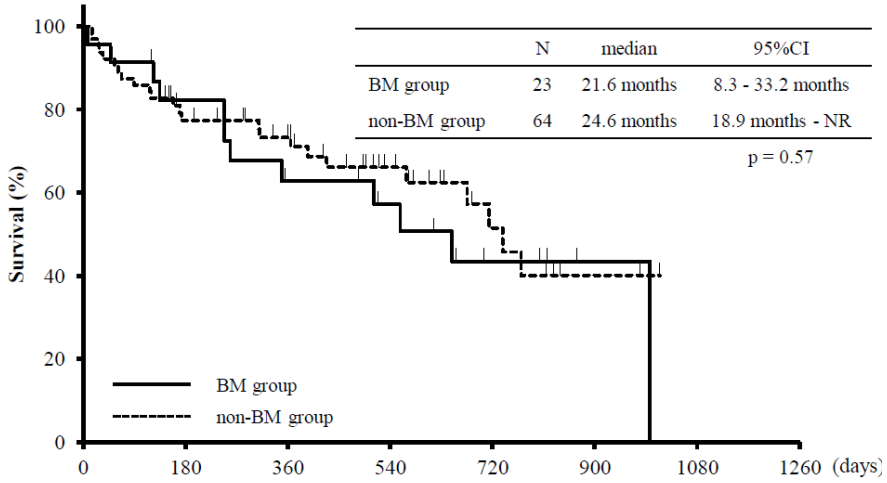
Figure 1A



	N	median	95%CI
BM group	23	6.5 months	2.0 months - NR
non-BM group	64	7.0 months	2.9 - 15.0 months

p = 0.73

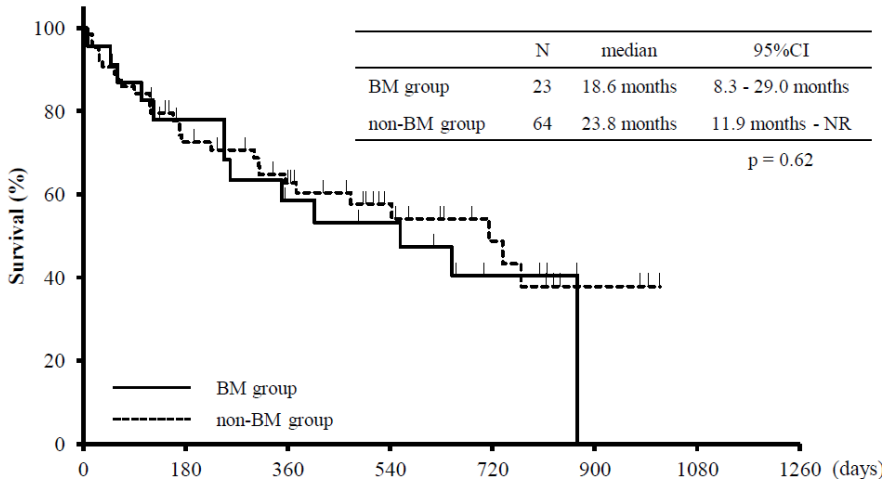
Figure 1B



	N	median	95%CI
BM group	23	21.6 months	8.3 - 33.2 months
non-BM group	64	24.6 months	18.9 months - NR

p = 0.57

Figure 1C



	N	median	95%CI
BM group	23	18.6 months	8.3 - 29.0 months
non-BM group	64	23.8 months	11.9 months - NR

p = 0.62

脳転移無増悪生存期間は「ペムブロリズマブ開始日から脳転移の増悪もしくは死亡のいずれか早いイベントまで」と定義

図 2) BM-T 群と BM-not T 群の無増悪生存期間 (Figure 2A)、生存期間 (Figure 2B)、脳転移無増悪生存期間 (Figure 2C)

Figure 2A

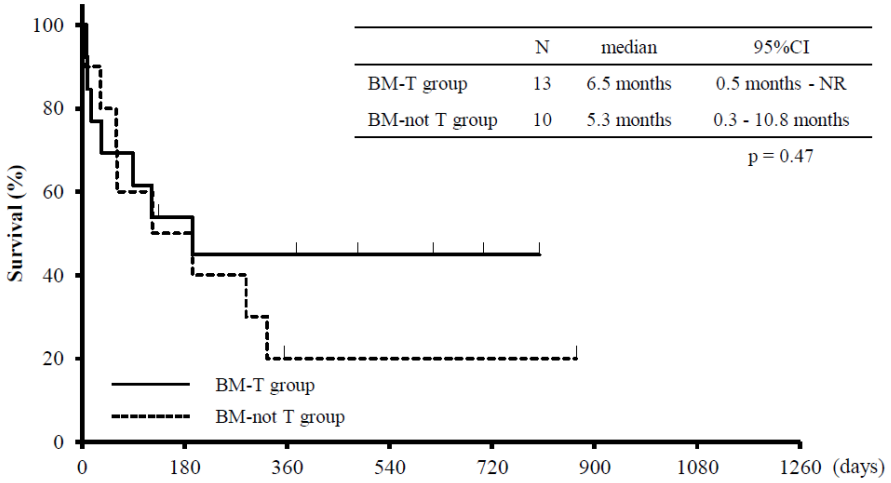


Figure 2B

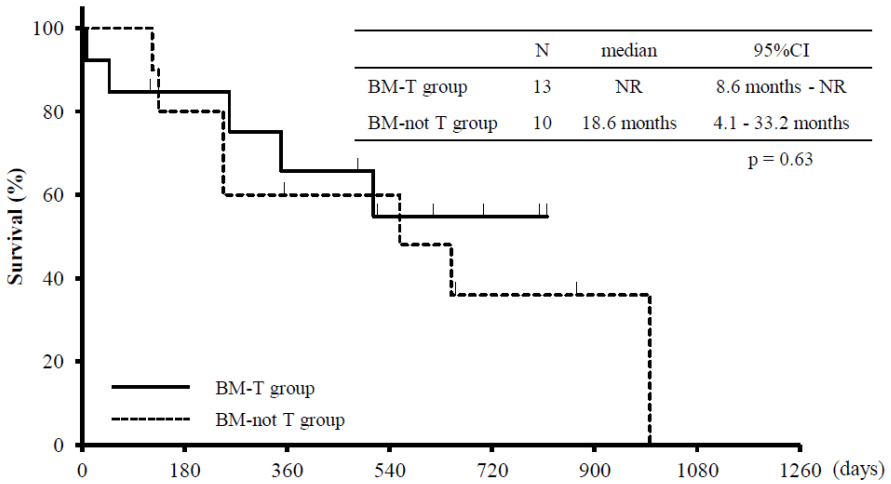
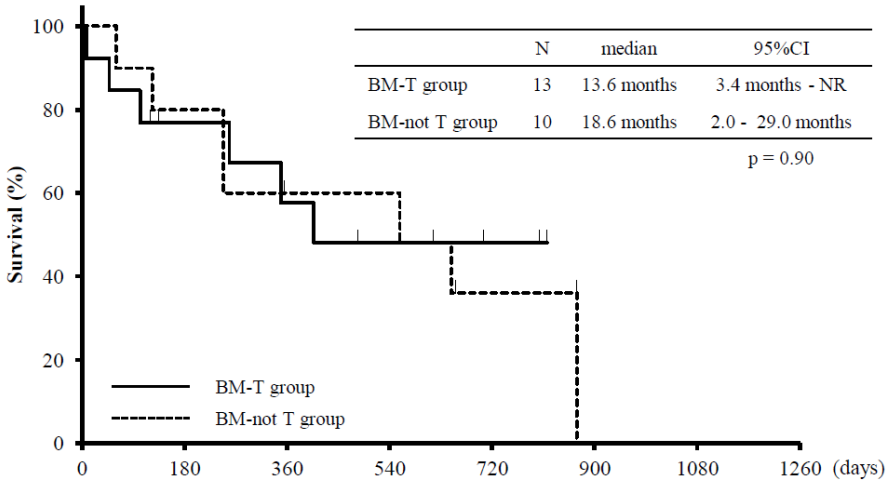


Figure 2C



脳転移無増悪生存期間は「ペムブロリズマブ開始日から脳転移の増悪もしくは死亡のいずれか早いイベントまで」と定義