Outcome of Patients with Non-Small Cell Lung Cancer and Brain Metastases Treated with Checkpoint Inhibitors

ORIGINAL ARTICLE

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ABSTRACT

Introduction: Although frequent in NSCLC, patients with brain metastases (BMs) are often excluded from immune checkpoint inhibitor (ICI) trials. We evaluated BM outcome in a less-selected NSCLC cohort.

Methods: Data from consecutive patients with advanced ICI-treated NSCLC were collected. Active BMs were defined as new and/or growing lesions without any subsequent local treatment before the start of ICI treatment. Objective response rate (ORR), progression-free survival, and overall survival (OS) were evaluated. Multivariate analyses were performed by using a Cox proportional hazards model and logistic regression.

Results: A total of 1025 patients were included; the median follow-up time from start of ICI treatment was 15.8 months. Of these patients, 255 (24.9%) had BMs (39.2% active, 14.3% symptomatic, and 27.4% being treated with steroids). Disease-specific Graded Prognostic Assessment (ds-GPA) score was known for 94.5% of patients (35.7% with a score of 0–1, 58.5% with a score of 1.5–2.5, and 5.8% with a score of 3). The ORRs with BM versus without BM were similar: 20.6% (with BM) versus 22.7% (without BM) ($p = 0.484$). The intracranial ORR (active BM with follow-up brain imaging [n = 73]) was 27.3%. The median progression-free survival times were 1.7 (95% confidence interval [CI]: 1.5–2.1) and 2.1 (95% CI: 1.9–2.5) months, respectively ($p = 0.009$). Of the patients with BMs, 12.7% had a dissociated cranial-extracranial response and two (0.8%) had brain pseudoprogression. Brain progression occurred more in active BM than in stable BM (54.2% versus 30% [$p < 0.001$]). The median OS times were 8.6 months (95% CI: 6.8–12.0) with BM and 11.4 months (95% CI: 8.6–13.8) months with no BM ($p = 0.035$). In the BM subgroup multivariate analysis, corticosteroid use (hazard ratio [HR] = 2.37) was associated with poorer OS, whereas stable BMs (HR = 0.62) and higher ds-GPA classification (HR = 0.48–0.52) were associated with improved OS.

Conclusion: In multivariate analysis BMs are not associated with a poorer survival in patients with ICI-treated NSCLC. Stable patients with BM without baseline corticosteroids and a good ds-GPA classification have the best prognosis.

Keywords: NSCLC; Checkpoint inhibition; Brain metastases; survival; Disease specific Graded Prognostic Assessment

Introduction

In up to 40% of molecularly unselected patients with NSCLC, brain metastases (BMs) are diagnosed during the course of their disease.[1] Despite this high incidence, patients with untreated and/or unstable BMs, or even all BMs, were excluded from most pivotal immune checkpoint inhibitor (ICI) trials.[2–13] Use of corticosteroids (which might abrogate an immune response), the probable inability to cross the blood-tumor barrier (although the peripherally activated T cell can cross the blood-tumor barrier), and the risk of brain pseudoprogression were possible reasons to exclude these patients.[14,15] As a result, patients with BMs were underrepresented in trials, comprising from 6.2% to 17.5% of enrolled patients.[2–9,13] Moreover, patients were not stratified according to the presence of BMs, and only a few trials had a preplanned BM subgroup analysis.[2,3,5,9] In the first line KEYNOTE-024 trial (pembrolizumab versus platinum-doublet chemotherapy)[5] and in the second line CheckMate 017 and 057 trials (nivolumab versus docetaxel),[2,3,16] the survival of patients with BMs was not significantly superior with ICI treatment versus with chemotherapy. Conversely, in the first-line KEYNOTE-189 trial (pembrolizumab platinum-doublet chemotherapy versus platinum-doublet chemotherapy)[9] and the second-line OAK trial (atezolizumab versus docetaxel),[17] patients with ICI-treated BMs had a longer overall survival (OS) than did patients with chemotherapy-treated BMs. So far, only one prospective phase II trial with pembrolizumab has specifically addressed the question of ICI efficacy for patients with BMs: a 29.4% intracranial objective response rate (ORR) was observed in the programmed death ligand 1 (PD-L1)-positive cohort (n = 34), which was similar to the extracranial ORR.[18] Therefore, ICI treatment might also result in favorable outcomes for patients with NSCLC and BMs, but data on larger, less-selected cohorts are needed.

Available series on patients with BMs treated with an ICI in daily practice mainly come from expanded access programs (EAPs) or from small retrospective series.[19–27] The EAP cohorts have the same biases as the randomized trials, as they generally required BMs to be treated, stable, and asymptomatic.[23,24] As a result, many questions, such as the prognostic value of the disease-specific Graded Prognostic Assessment (ds-GPA) classification

(Supplementary Table 1)[28] or the optimal timing of cranial irradiation, remain unsolved.

In this study, we aimed to compare outcome of less-selected patients with ICI-treated NSCLC and BMs with outcome of patients without BMs and to identify prognostic factors.

Patients and Methods

Prospectively collected lists of patients with advanced NSCLC that started between November 2012 and May 2018 with ICI treatment in six European centers (five French and one Dutch) were merged. All consecutive patients with advanced NSCLC were included when they were treated with programmed cell death 1 (PD-1)/PD-L1 inhibitors with or without anti–cytotoxic T-lymphocyte antigen 4 within routine clinical care, EAPs, compassionate use programs, and clinical trials. Patients were excluded when they were treated with a concurrent combination of anti–PD-1/PD-L1 therapy and chemotherapy. Patients with leptomeningeal metastases (LMs) were excluded, as the prognosis of patients with LMs is usually poorer than that of patients with BMs.[29] These patients will be reported separately.

Data on demographics and clinical, pathological, and molecular data were retrospectively extracted from the medical records between November 2017 and April 2018. For patients with a diagnosis of central nervous system metastases, ds-GPA score at the start of ICI treatment was also collected. The ds-GPA scores were grouped according to Sperduto et al. as follows: 0 to 1 (worst prognostic group), 1.5 to 2.5, 3, and 3.5 to 4 (best group).[28]

Active BMs were defined as newly diagnosed and nonirradiated lesions and/or growing lesions (investigator/local radiologist–assessed) on brain imaging (including treated lesions that secondarily progressed) *without* any subsequent local treatment before the start of ICI treatment (compare with Goldberg et al.[30]). Stable BMs were defined as those that had been treated (with radiotherapy or surgery) before ICI treatment and showed no progression on brain imaging no more than 6 weeks before the start of ICI treatment. Treated patients with BMs who were symptomatic but had stable or decreasing symptoms at the start of ICI treatment were classified as stable.

Data for local assessment of PD-L1 expression were analyzed on tumor cells by immunohistochemistry. Expression of at least 1% was considered positive. Radiological assessments of brain and extracranial disease were performed (usually every 6–9 weeks), and response was determined locally at each institution by the investigator.

This study was approved by the institutional review board of Gustave Roussy (Institutional Review Board) and the ethical committee of Maastricht University Medical Center+ (No. 2018-0530). Informed consent was not necessary, as clinical and imaging data were retrospectively added.

Statistical Analysis

Comparisons between patient characteristics were performed by using the chi-square or Fisher exact test for discrete variables and the unpaired *t* test, Wilcoxon signed rank test, or analysis of variance for continuous variables when applicable. Disease control rate (DCR) was defined as complete plus partial response plus stable disease, and ORR as complete response plus partial response. OS was calculated from the date of first administration of immunotherapy until death due to any cause. Progression-free survival (PFS) was calculated from the date of first administration of immunotherapy until progressive disease (PD) or death due to any cause. A Cox proportional hazards regression model was used to evaluate factors independently associated with OS and PFS. Variables included in the final multivariate model were selected according to their clinical relevance and statistical significance in a univariate analysis (cutoff $p = .10$).

The proportional hazard hypothesis was verified by using the Schoenfeld residual method. Correlation between variables was verified before construction of the multivariate models to deal with potential colinearity. Statistical analyses were performed with RStudio software.

Results

Population with BMs

Data on 1052 patients were collected. Of these patients, 11 were excluded because of combination anti–PD-1/PD-L1 with chemotherapy and 16 were excluded because of LMs (with or without BMs) at the start of ICI treatment, resulting in 1025 included patients (CONSORT diagram [Fig. 1]). The median follow-up time was 15.8 (95% confidence interval [95% CI]: 14.6–17.0) months. A total of 534 patients (52.1%) had brain imaging no more than 6 weeks before the start of ICI treatment; 172 (32.2%) underwent magnetic resonance imaging, whereas the others underwent computed tomography. Reasons for brain imaging were screening, follow-up of known BMs, and neurological symptoms.

In all, 255 patients (24.9%) had BMs at the start of ICI treatment. Baseline characteristics for those with and without BM are presented in Table 1. Compared with patients without BMs, those with BMs were significantly younger, had the adenocarcinoma histologic type more often, had a WHO performance status (PS) of 2 or higher,

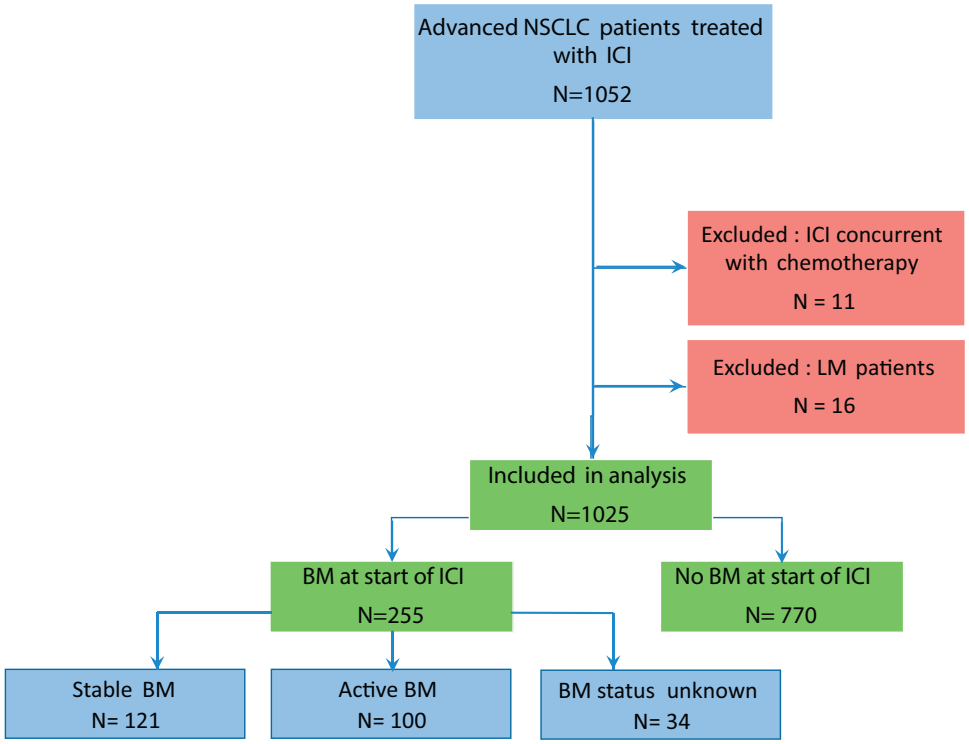

Figure 1. CONSORT diagram: patient inclusion. ICI: immune checkpoint inhibitor; LM: leptomeningeal metastasis; BM: brain metastasis.

had used corticosteroids at the start of ICI treatment more frequently, and had a higher median number of organs with metastases.

Details on patients with BMs are shown in Table 2. In all, 37 patients (14.3%) had symptomatic BMs at the start of ICI treatment and 69 (27.4%) received corticosteroids.

ds-GPA classification was available for 241 of 255 patients (94.5%); and was 0 to 1 in 86 patients (35.7%), 1.5 to 2.5 in 141 (58.5%), and 3 in 14 (5.8%). None of the patients had a score of 3.5 or 4. Patients with a lower ds-GPA classification used corticosteroids at the start of ICI treatment significantly more often (38.8% with a ds-GPA classification of 0 to 1, 23.4% with a ds-GPA classification of 1.5–2.5, and 0% with a ds-GPA classification of 3 [$p = 0.003$]). Of the 255 patients, 100 (39.2%) had active BMs at the start of ICI treatment, 121 (47.5%) had stable BMs, and BM status (i.e., active or not) was unknown for 34 (13.3%).

Outcome with ICI Treatment

Responses. Overall ORR was not significantly different for patients with (n = 255) and without (n = 770) BMs: 20.6% versus 22.7% ($p = 0.484$), but DCR was significantly lower in patients with BMs: 43.9% versus 52.0% ($p = 0.024$). Of 100 patients with active BMs, 73 (73.0%) underwent brain imaging during ICI treatment. The intracranial ORR was 27.3%, and intracranial DCR was 60.3%. For 23 patients with active BMs with baseline brain imaging and comparable brain imaging available during ICI treatment (31.5% [i.e., only magnetic resonance imaging or only computed tomography]), PD-L1 status was available; 14 patients (60.9%) had a PD-L1 expression level of 1% or higher, with an ORR of 35.7% versus 11.1% in PD-L1–negative patients. Of the 27 patients with active BMs, three (11.1%) without brain imaging during ICI treatment died with neurological deterioration during ICI treatment.

Only two patients with BMs (0.8%) experienced pseudoprogression in the brain (growing and/or new BMs on imaging, with subsequent shrinkage on imaging). Nine patients with BMs had resection of a BM during ICI treatment because of symptomatic growth. For one patient, radiological growth was comparable with radiation necrosis, and this was histologically confirmed. For five patients, only vital tumor tissue was found; for the others, a mixture of vital tumor tissue and necrosis was found (example in Supplementary Fig. 1).

PFS. Of the 255 patients with BMs, 204 (80%) progressed, whereas 589 of 770 patients without BMs (76.5%) progressed ($p = 0.246$). The median PFS times for patients with and without BMs were

Table 1. Baseline Characteristics Overall and Brain Metastases Subgroups

Characteristic	Total Population (N = 1025)	Patients without Baseline Brain Metastases (n = 770)	Patients with Baseline Brain Metastases (n = 255)	*p* Value[a]
Sex, n (%)				
Male	646 (63.0)	488 (63.4)	158 (62.0)	0.685
Median age at start of ICI treatment, y (range)	64.3 (30.2-92.8)	65.4 (30.7-92.8)	61.5 (30.2-80.8)	<0.001
Smoking status at start of ICI treatment, n (%)				
Current	402 (41.6)	299 (41.2)	103 (42.7)	0.666
Former	488 (50.5)	366 (50.4)	122 (50.7)	
Never	77 (8.0)	61 (8.4)	16 (6.6)	
Unknown	58	44	14	
Histologic type, n (%)				
Adenocarcinoma	681 (66.4)	482 (62.6)	199 (78.0)	<0.001
Squamous carcinoma	268 (26.2)	230 (29.9)	38 (14.9)	
NSCLC, other	76 (7.4)	58 (7.5)	18 (7.1)	
Molecular alteration,[b] n (%)				
EGFR mutation (737 tested)	39 (5.3)	29 (5.3)	10 (5.2)	0.921
ALK rearrangement (713 tested)	6 (0.8)	5 (1.0)	1 (0.5)	1.00
KRAS mutation (708 tested)	241 (34.0)	174 (33.6)	67 (35.3)	0.677
BRAF mutation (613 tested)	23 (3.8)	19 (4.3)	4 (2.4)	0.346
ROS1 rearrangement (439 tested)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
PD-L1 status, n (%)				
Positive	230 (64.1)	179 (64.9)	51 (61.5)	0.57
Negative	129 (35.9)	97 (35.1)	32 (38.5)	
Unknown	666	494	172	
Performance status (WHO)				
0-1	823 (82.2)	630 (84.0)	197 (77.2)	0.011
≥2	178 (17.8)	120 (16.0)	58 (25.8)	
Unknown	24	20	0	
Corticosteroid use at start of ICI treatment, n (%)				
Yes	141 (13.9)	72 (9.4)	69 (27.4)	<0.001
No	875 (86.1)	692 (90.6)	183 (72.6)	
Unknown	9	6	3	
Brain imaging ≤6 weeks of start of ICI treatment, n (%)	534 (52.1)	328 (42.6%)	206 (80.8)	<0.001
MRI	172 (32.2)	68 (20.7%)	104 (50.5)	<0.001
CT	362 (67.8)	260 (79.35)	102 (49.5)	
Median No. of organs with metastases at start of ICI treatment (range)	2 (1-10)	2 (1-9)	3 (1-10)	<0.001
Median line of ICI treatment (range)	2 (1-12)	2 (1-12)	2 (1-8)	0.555
PD-1/PD-L1 inhibitor as monotherapy, n (%)	963 (94.0)	721 (93.6)	242 (94.9)	0.541
PD-1 inhibitor	927 (96.3)	687 (95.3)	240 (99.2)	0.003
PD-L1 inhibitor	36 (3.7)	34 (4.7)	2 (0.8)	

[a]Patients with and without brain metastases are compared.
[b]Percentage computed for patients with known results, numbers tested (positive or negative) after each molecular alteration.
ICI, immune checkpoint inhibitor; *ALK*, ALK receptor tyrosine kinase gene; PD-L1, programmed death ligand 1; MRI, magnetic resonance imaging; CT, computed tomography; PD-1, programmed cell death 1.

1.7 months (95% CI: 1.5–2.1) and 2.1 months (95% CI: 1.9–2.5), respectively ($p = 0.009$) (Fig. 2*A*). The patients with BMs had brain PD significantly more often than did those without (46.3% versus 11.4% [$p < 0.001$]). The patients with active BMs had brain PD (with or without extracranial PD) significantly more often than did those with stable BMs (54.2% versus 30% [$p < 0.001$]).

Patterns of progression are depicted in Supplementary Figure 2. In the subgroup of patients with BMs, 26 of 204 progressing patients (12.7%) had a dissociated central nervous system and extracranial response (i.e., six of 24 patients [25.0%] had brain-only PD with an extracranial response at that time, and 20 of 97 patients had only extracranial PD but had a cranial response at that time [seven (35.0%) of these had undergone cranial radiotherapy less than 3 months before starting ICI treatment]).

In multivariate analysis for PFS, smoking was associated with an improved PFS, whereas more than two

Table 2. Baseline Characteristics of Patients with Stable versus Active Brain Metastases

Characteristic	Patients with Baseline Brain Metastases (n = 255)	Patients with Active Baseline Brain Metastases (n = 100)	Patients with Stable Baseline Brain Metastases (n = 121)	*p* Value[a]
Median time between first diagnosis of brain metastases and start of ICI treatment, mo (range)	5.8 (0-68.8)	4.7 (0-41.1)	6.0 (0.1-68.8)	0.248
Brain surgery before start of ICI treatment, n (%)	36 (14.1)	9 (9.0)	23 (19.0)	0.035
Brain radiotherapy before start of ICI treatment, n (%)	173 (68.1)	43 (43.0)	110 (90.9)	< 0.001
WBRT	72 (41.6)	18 (41.9)	44 (40.0)	0.664
SRT	99 (57.2)	24 (55.8)	65 (59.1)	
WBRT + boost SRT	2 (1.2)	1 (2.3)	1 (0.9)	
Median time between end of last brain radiotherapy and start of ICI treatment, mo (range)	3.6 (0-66.3)	5.2 (1.7-38.9)	1.4 (0-66.3)	<0.001
Brain imaging before start of ICI treatment, n (%)	206 (80.8)	96 (87.3)	121 (100.0)	< 0.001
MRI	104 (50.5)	53 (53.0)	59 (48.8)	0.316
CT	102 (49.5)	47 (47.0)	59 (48.8)	
Unknown CT or MRI	0	0	3 (2.5)	
Brain metastases at start of ICI treatment, n (%)				
≤2	120 (47.1)	52 (52.0)	57 (47.1)	0.769
3-5	49 (19.2)	18 (18.0)	24 (19.8)	
≥6	86 (33.7)	30 (30.0)	40 (33.1)	
Brain metastases symptomatic at start of ICI treatment, n (%)				
Yes	37 (14.7)	12 (12.0)	22 (18.5)	0.187
No	214 (85.3)	88 (88.0)	97 (81.5)	
Unknown	4	0	2	
Corticosteroid use at start of ICI treatment, n (%)	69 (27.4)	22 (22.0)	39 (32.2)	0.100
≤10 mg of prednisolone equivalent/d	20 (33.3)	6 (31.6)	10 (29.4)	0.869
>10 mg of prednisolone equivalent/d	40 (66.7)	13 (68.4)	24 (70.6)	
Unknown dose	9	3	5	
WHO PS at start of ICI treatment, n (%)				
0-1	197 (77.3)	73 (73.0)	98 (81.0)	0.158
≥2	58 (22.7)	27 (27.0)	23 (19.0)	
ds-GPA at start of ICI treatment, n (%)				
0-1	86 (35.7)	33 (33.3)	43 (36.8)	0.869
1.5-2.5	141 (58.5)	60 (60.6)	67 (57.2)	
3	14 (5.8)	6 (6.1)	7 (6.0)	
3.5-4	0 (0)	(0)	(0)	
Unknown	14	1	4	

[a]Patients with stable and active brain metastases are compared.
ICI, immune checkpoint inhibitor; WBRT, whole brain radiotherapy; SRT, stereotactic radiotherapy; MRI, magnetic resonance imaging; CT, computed tomography; PS, performance status; ds-GPA, disease-specific Graded Prognostic Assessment.

organs with metastases, a WHO PS of 2 or higher, and use of corticosteroids at the start of ICI treatment were associated with a decreased PFS (Table 3). The results regarding presence of BM (not associated with PFS) did not change significantly when we analyzed the subgroup with baseline brain imaging only (Supplementary Table 2)

For ds-GPA classifications of 0 to 1, 1.5 to 2.5, and 3, the median PFS times were 1.4 months (95% CI: 1.2–1.6), 2.4 months (95% CI: 1.5–3.3), and 5.5 months (95% CI: 0.1–11.8), respectively. The median PFS was significantly longer for ds-GPA classifications of 1.5 to 2.5 ($p < 0.001$) and 3 ($p = 0.023$) than for classification of 0 to 1. In multivariate analysis for the BM subgroup, more than two organs with metastases, and use of corticosteroids at the start of ICI treatment were associated with poorer PFS, whereas stable BM and a higher ds-GPA score were associated with improved PFS (Table 4). Previous cranial radiotherapy (yes versus no) was not associated with PFS in univariate analysis (HR = 0.80, 95% CI: 0.60–1.08, $p = 0.144$) and as such was not carried forward to multivariate analysis.

OS. The median OS times were 8.6 months (95% CI: 6.8–12.0) for patients with BMs and 11.4 months (95% CI: 8.6–13.8) for patients without BMs, respectively ($p = 0.035$) (Fig. 2*B*). Except for smoking, the same factors associated with PFS in multivariate analysis were

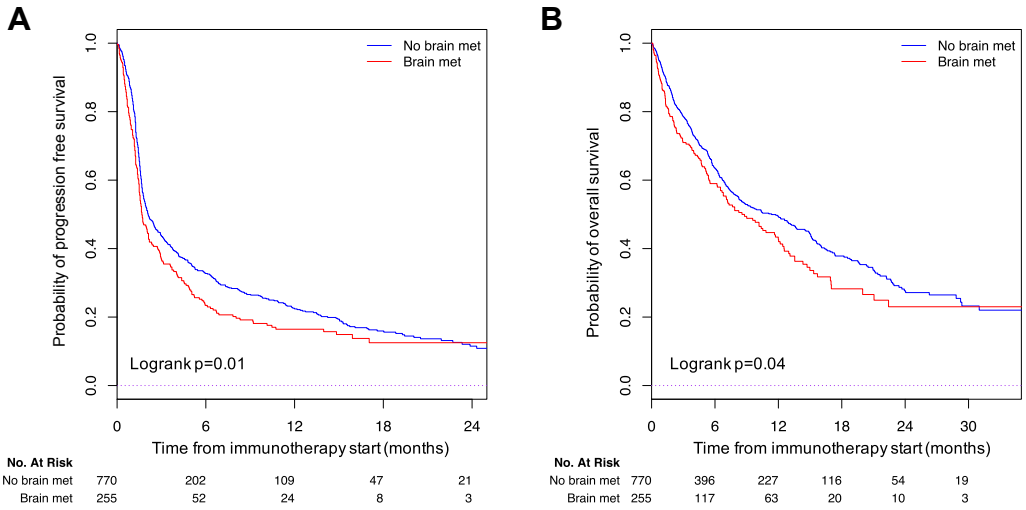

Figure 2. Kaplan-Meier curves for progression-free survival (*A*) and overall survival (*B*) according to presence of brain metastases. met, metastasis.

identified for OS. Presence of BMs was not associated with OS in multivariate analysis (see Table 3). The results did not change significantly regarding presence of BMs when we analyzed the subgroup with baseline brain imaging only (see Supplementary Table 2). Because of the large number of patients with unknown PD-L1 status (65.0%), PD-L1 status was not evaluated in the multivariate analysis.

The median OS times were 4.4 months (95% CI: 2.0–6.7), 13.7 months (95% CI: 10.2–17.2), and 13.7 months (95% CI: 1.5–26.1) for ds-GPA classifications of 0 to 1, 1.5 to 2.5, and 3, respectively. The median OS was significantly longer with ds-GPA classifications of 1.5 to 2.5 ($p < 0.001$) and 3 ($p = 0.010$) than with classifications of 0 to 1. In multivariate analysis for the BM subgroup, use of corticosteroids at the start of ICI treatment was associated with poorer PFS, whereas stable BMs and a higher ds-GPA score were associated with improved PFS (see Table 4). Previous cranial radiotherapy (yes versus no) was not associated with survival in univariate analysis (HR = 0.80, 95% CI: 0.57–1.13, $p = 0.204$) and as such was not carried forward to multivariate analysis.

Discussion

BMs are frequent in NSCLC, but patients with BMs are often fully excluded from clinical trials, or only selected patients are included, resulting in underrepresentation of these patients in clinical trials (6.2%–17.5% of included patients had BMs).[2–13] EAPs also allowed only selected patients with BMs.[23,24] As data on ICI efficacy in less-selected patients with BMs are lacking, we performed the current study to evaluate response and survival of patients with BMs treated with ICIs.

In this large, multicenter cohort of patients with advanced ICI-treated NSCLC, 255 (24.9%) had BMs at the start of ICI treatment. This percentage is higher than that reported in clinical trials (6.2%–17.5%) but comparable with the rates reported in other, mostly smaller retrospective ICI series (10.2%–31%)[2,3,5,7–9,13,22,23,25,26] and in line with what is expected in this patient population (25%–40% with BMs).[31,32] To the best of our knowledge, only two large EAP series on patients with NSCLC and BMs treated with ICIs have previously been reported,[23,25] with 26% (409 of 1588) and 22% (197 of 902) of patients with BMs included, respectively. Important factors for patients with BMs such as ds-GPA score, use of steroids and classification of BM (active or not) were not mentioned. In our study, 39.2% of patients with BMs had active BMs, 14.7% had symptomatic BMs, 22.7% had a WHO PS of 2 or higher, and 15.7% had corticosteroid doses higher than 10 mg of prednisolone equivalent/day (all exclusion criteria in EAP or clinical trial).

The overall ORR of 20.6% (with BMs) to 22.7% (no BMs) in our series is comparable with that in the existing literature.[2,3,8] The 27.3% intracranial ORR of the patients with active BMs is similar to that of the PD-L1–positive patients included in the phase II trial of Goldberg et al. (none of the PD-L1–negative patients responded in this trial),[18] and is slightly higher than that reported in retrospective series.[20,23,26] Furthermore, patients with BMs progressed more often in the brain than did patients without preexisting BMs. As severe neurological symptoms can develop in these patients because of their brain progression, careful monitoring, especially of active BM, during the first months of ICI treatment seems needed. In general, a growing BM indicates real PD, as pseudoprogression was rare (0.8%) in our BM cohort.

Table 3. Multivariate Analysis of PFS and OS of the Overall Population

Factor	PFS HR (95% CI)	*p* Value	OS HR (95% CI)	*p* Value
Age, >65 y vs. ≤65 y	1.03 (0.89-1.20)	0.667	1.11 (0.93-1.33)	0.26
Smoking, yes vs. no	0.52 (0.41-0.67)	<0.0001	0.79 (0.59-1.06)	0.112
Histologic type				
Squamous vs. adeno	1.04 (0.87-1.24)	0.86	1.18 (0.95-1.45)	0.28
NSCLC, other vs. adeno	1.06 (0.80-1.42)		1.14 (0.81-1.60)	
No. of organs with metastases, >2 vs. ≤2	1.29 (1.10-1.50)	0.001	1.42 (1.18-1.71)	<0.0001
ICI line, >2 vs. ≤2	1.01 (0.87-1.18)	0.881	1.07 (0.90-1.29)	0.44
WHO PS, ≥2 vs. 0-1	2.29 (1.89-2.77)	<0.0001	3.37 (2.72-4.16)	<0.0001
Use of corticosteroids, yes vs. no	1.31 (1.07-1.62)	0.01	1.46 (1.16-1.84)	0.001
Brain metastases, yes vs. no	1.10 (0.92-1.31)	0.28	0.99 (0.81-1.23)	0.96

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; adeno, adenocarcinoma; ICI, immune checkpoint inhibitor; PS, performance status.

The median PFS and OS times of patients with BM in our study are comparable with those in other, mostly smaller ICI series.[18,20–25] The median PFS and OS times were shorter for patients with BMs than for those without BMs, but in multivariate analysis presence of BMs (when compared with absence of BMs) was not significantly associated with a poorer survival with ICI treatment. This finding is in contrast to the findings of the French EAP series, but in the French series there was no adjustment for corticosteroid use or number of organs with metastases in multivariate analysis,[25] which were both associated with poorer PFS and OS in our and in other series.[15,33]

Patients with stable BMs had PFS and OS times superior to those of patients with active BMs; use of corticosteroids at the start of ICI treatment was associated with worse PFS and OS. Furthermore, symptomatic BMs were associated with worse PFS and OS in univariate analysis (for PFS, HR = 1.90, 95% CI: 1.30–2.77, $p = 0.001$; and for OS, HR = 2.03, 95% CI: 1.33–3.11, $p = 0.001$). Corticosteroid use at the start of ICI treatment was already described as deleterious.[15,34] However, as there was colinearity with symptomatic BMs and use of corticosteroids and use of corticosteroids was more significant, only the latter was carried forward to the multivariate analysis. Interestingly, ds-GPA score is prognostic not only patients with in newly diagnosed BMs[28] but also in patients with previously diagnosed BMs who start ICI treatment. ds-GPA score combined with use of corticosteroids, symptoms, BM status (active versus stable), and PD-L1 status could be used in the decision regarding whether to administer ICI to a patient with BM.

In our study, cranial radiotherapy before start of ICI treatment (yes versus no) was not associated with OS in the BM subgroup in univariate analysis (HR = 0.80, 95% CI: 0.57–1.13, $p = 0.204$); however, this analysis did not take into account time from cranial radiotherapy to start of ICI treatment, or brain PD after cranial irradiation before the start of ICI treatment. Indeed, patients with stable BMs (i.e., locally treated [mostly with radiotherapy] and no radiological progression or new BMs at the start of ICI treatment) had a better OS than did those with active BM. In a retrospective, single-center (N = 98) analysis of the KEYNOTE-001 trial, patients who were treated with any radiotherapy (n = 42) or extracranial

Table 4. Multivariate Analysis of PFS and OS in the BM Subgroup

Factor	PFS HR (95% CI)	*p* Value	OS HR (95% CI)	*p* Value
Sex, male vs. female	0.95 (0.68-1.33)	0.765	1.42 (0.94-2.16)	0.100
Smoking, yes vs. no	0.81 (0.40-1.64)	0.561	0.74 (0.34-1.64)	0.464
Histologic type				
Squamous vs. adeno	0.97 (0.60-1.57)	0.99	1.09 (0.63-1.90)	0.750
NSCLC, other vs. adeno	0.98 (0.53-1.83)		0.79 (0.38-1.65)	
No. of organs with metastases, >2 vs. ≤2	1.72 (1.15-2.57)	0.009	1.39 (0.87-2.22)	0.174
ICI treatment line, >2 vs. ≤2	0.98 (0.70-1.39)	0.922	1.09 (0.73-1.65)	0.671
Use of corticosteroids at start of ICI treatment, yes vs. no	2.78 (1.90-4.08)	<0.0001	2.37 (1.54-3.63)	<0.0001
BMs stable at start ICI, yes vs. no	0.62 (0.44-0.88)	0.007	0.62 (0.41-0.93)	0.019
ds-GPA, 1.5-2.5 vs. 0-1	0.55 (0.38-0.78)	0.004	0.48 (0.31-0.72)	0.002
ds-GPA, 3 vs. 0-1	0.65 (0.31-1.35)		0.54 (0.22-1.32)	

BM, brain metastasis; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival; ICI, immune checkpoint inhibitor; ds-GPA, disease-specific Graded Prognostic Assessment.

radiotherapy (n = 38) before the start of ICI treatment had a survival superior to that of patients who were not treated with radiotherapy.[35] However, an updated analysis including all patients included in the KEYNOTE-001 trial did not demonstrate this benefit anymore.[36] As it is possible that recent cranial irradiation before the start of ICI treatment improves the survival of patients with BMs treated with ICIs owing to improved local control, we divided (in an exploratory analysis) the stable BM group (i.e., those with local brain therapy before the start of ICI treatment, regardless of timing of local treatment before ICI treatment, but without brain progression on brain imaging before ICI) into (1) stable patients without cranial irradiation within 3 months of ICI treatment and (2) stable patients who received cranial irradiation within 3 months of ICI treatment. When compared to active BMs, cranial irradiation within 3 months of the start of ICI treatment was associated with a superior survival (HR = 0.52, 95% CI: 0.30–0.72, $p = 0.04$), whereas no cranial irradiation within 3 months of the start of ICI treatment was not (Supplementary Table 3).

The drawbacks of the current study are inherent to the retrospective data collection, although the overview of patients who received an ICI was prospectively collected. Not all patients underwent baseline brain imaging, and the reasons for brain imaging varied. However, when we analyzed the subgroup with baseline brain imaging only, the results did not change significantly. Furthermore, follow-up was not standardized, and imaging was not reviewed according to the Response Criteria in Solid Tumors 1.1/Response Assessment in Neuro-oncology BM criteria (the differences between response assessment methods are summarized in El Rassy et al.[37]). The definition of active BM was according to Goldberg et al.,[30] but the decision to administer local treatment for BM before ICI treatment was according to the treating physician, making the stable BM group more heterogeneous. The number of patients with active BMs who had cranial response evaluation during ICI treatment was small, and for most of these patients PD-L1 status was unknown, making further subgroup analysis of the active BM group difficult. Moreover, additional data such as steroid dosage or type and severity of neurological symptoms would have enabled further subgroup analyses. As whether neurological adverse events were to be attributed to immunotherapy, previous cranial radiotherapy, or brain progression was not always clear, we choose not to report these events. Cause of death (cranial versus extracranial progression) was not documented for most patients. We could not evaluate the possible different efficacy of PD-1/PD-L1 inhibitors in relation to BMs, as only two patients with BMs were treated with PD-L1 inhibition monotherapy. Lastly, we did not use the update of the ds-GPA for lung cancer (the molecular GPA,[38] also incorporating the presence of *EGFR* and ALK receptor tyrosine kinase gene [*ALK*] drivers in the nonsquamous subgroup). However, this molecular GPA was validated in patients with newly diagnosed BMs. Patients with driver mutations included in the molecular GPA analysis would have had the option of receiving effective targeted therapy, improving their OS (patients with driver mutations had the best survival in the molecular GPA).[38] In contrast, patients with driver mutations often have a poor survival when treated with an ICI.[39–41] Therefore, we choose to use the ds-GPA instead of the molecular GPA.

In conclusion, in multivariate analysis, the presence of BM was not associated with response and survival when treated with an ICI. Patients with (untreated) BM, a good ds-GPA classification, and no requirement for corticosteroids should not be excluded from clinical trials, although especially those patients with active BM should undergo regular brain imaging, as brain progression occurs more frequently in this subgroup of patients. Future studies should also focus on the timing of cranial irradiation, as cranial irradiation within 3 months of the start of ICI treatment was associated with improved OS compared with cranial irradiation more than 3 months before the start of ICI treatment.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.02.009.

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