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Predictive Factors of Intracranial Response of Immune Checkpoint Inhibitors in Patients with Brain Metastasis from Non-Small Cell Lung Cancer

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Abstract

Background: Immune checkpoint inhibitors (ICI)s were recently approved for the treatment of advanced non-small cell lung cancer (NSCLC). Whereas brain metastases (BM) are frequent in NSCLC patients, data are missing regarding ICIs intracranial efficacy and tolerance in patients with BM from NSCLC. **Methods:** This retrospective study was performed in the Multidisciplinary Oncology and Therapeutic Innovation department, Marseille, France between April 2013 and February 2016. Data from patients with NSCLC with at least one BM, and treated with ICIs (anti-PD1, anti-PDL1 or anti-CTL4) were analyzed. Clinical, biological data and outcomes were retrieved from electronic patients' records. We assessed ICIs intracranial efficacy and tolerance. **Results:** Data from 55 patients were analyzed. Objective Response Rate (ORR) and Disease Control Rate (DCR) were respectively of 1.8 and 36.4%. Median overall survival was 17.2 months and median progression free survival was 2.9 months. Intracranial ORR (icORR) and intracranial DCR (icDCR) were respectively 16.4% and 45.5%. Both were independent of smoking status, intracranial treatment, performance status, pathology, molecular profile and the presence or number of BM at diagnosis. However, there was a trend towards an association between icORR and ECOG PS ($p = 0.05$), tobacco status ($p = 0.057$) and intracranial treatment. Adverse events were seen in 38.2% patients without identified predictive factor. Neurological symptoms appeared in 5.5% patients during immunotherapy and improved in 3.63% pa-

tients. **Conclusions:** ICIs can be used safely on patients with BM from NSCLC. However, intracranial response is heterogeneous in such patients and we showed ECOG PS, tobacco smoking and intracranial treatment to be associated with an improved icORR. This is the first study looking for predictive factors of intracranial response of ICIs in patients with BM from NSCLC.

Keywords

Lung Cancer, Brain Metastasis, Immunotherapy, Efficacy, Tolerance

1. Introduction

Lung cancer is the leading cause of brain metastases (BM): 40% to 50% of BMs come from lung cancers [1] and in autopsy series, up to 50% of patients with lung cancer were found with BM [2]. BMs are discovered at the time of diagnosis in 10% of patients with non-small cell lung cancer (NSCLC) [3]. They are known to be associated with a poor prognosis and are the immediate cause of death in 50% of patients with solid tumors [4]. Local treatments to the brain such as surgery, whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) improve the outcomes of patients with BM from NSCLC [5]. However, overall survival is still short (14 months) [5]. The blood brain barrier (BBB), a network of endothelial cells, basal membrane, astrocytes, and pericytes, contributes to this poor prognosis [6]. Most systemic therapies do not cross the BBB and are not effective for the treatment of BM. However, intracranial responses can be seen with some targeted therapies such as erlotinib [7], and CSF (cerebro-spinal fluid) concentration was shown to be higher for targeted therapies than for chemotherapy [8]. The addition of bevacizumab to standard first- or second-line chemotherapy increased overall survival (OS) of patients with NSCLC BM up to 16 months in a phase II study [9]. Nevertheless, there is still a need for new systemic treatments to improve intracranial responses and patients' outcomes.

Recently, immunotherapy has become part of advanced NSCLC treatment strategy. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies targeting anti-tumor immunity. Programmed cell death 1 (PD-1) is expressed by T cells while its ligand, programmed death-ligand 1 (PD-L1), is expressed by tumor cells. They both participate in anti-tumor immunity inhibition signal [10]. Nivolumab and pembrolizumab are anti-PD-1 antibodies and have been shown to have a better efficacy and tolerance profile than chemotherapy with docetaxel for second- or third-line treatment of metastatic NSCLC [11] [12] [13]. They are both approved in this indication. Additionally, pembrolizumab showed a better efficacy than standard chemotherapy for first-line treatment of advanced PD-L1 positive NSCLC with PD-L1 expression ≥ 50% [14]. Recently, pembrolizumab in combination with chemotherapy also showed longer OS and progression-free survival (PFS) than platinum-based standard chemotherapy, in patients with pre-

viously untreated advanced NSCLC [15] [16]. Anti-PD-L1 treatments have also been shown to be effective for second-line treatment of advanced NSCLC [17]. However, these trials did not include patients with active BM and intracranial efficacy and tolerance of ICIs were not part of the objectives. For these reasons, clinical data supporting the hypothesis of ICIs intracranial efficacy are limited.

Until recently, BBB was thought to be responsible for brain poor immunogenicity [18]. However, this hypothesis is controversial. It was previously shown that PD-L1 expression was higher and tumor-infiltrating lymphocytes (TILs) density lower in brain metastases in comparison with matched primary tumors [19]. Later, a phase II monocentric clinical trial of pembrolizumab 10 mg/kg every 2 weeks enrolled 18 patients with melanoma and 18 patients with NSCLC having at least 1% PD-L1 staining. All patients had untreated or progressing BM. Among patients with NSCLC, 6 (33%) had a response, including 4 complete response [20]. However, 6 (33%) other NSCLC patients had intracranial progressive disease and median overall survival (OS) was 7.7 months [20]. In the same way, in the phase II CheckMate 063 study, 2 patients with squamous NSCLC treated with Nivolumab were evaluated for intracranial efficacy and they both had intracranial response [21]. These studies reported only grade 1 and 2 neurological toxicities [22]. Although ICIs are well tolerated in patients with BM from NSCLC, reported ICIs intracranial efficacy seems to be heterogeneous and there is a lack of factors identified to predict ICIs intracranial efficacy.

As the use of ICIs for the treatment of advanced NSCLC is growing and because of the high prevalence of BM in this disease, there is a real need for data regarding predictive factors of ICIs intracranial efficacy, neurotoxicity and interaction with brain local treatment.

In this study, we tried to identify predictive factors of intracranial efficacy and tolerance of immunotherapy in patients with brain metastasis from NSCLC.

2. Material and Methods

2.1. Patients

This retrospective single-center study was performed in the Multidisciplinary Oncology and Therapeutic Innovation department, Marseille, France. Patients were selected as follows: advanced NSCLC, at least one brain metastasis diagnosed before immunotherapy, at least one cycle of immunotherapy with ICIs between April 2013 and February 2016. The study protocol was approved by a national ethical committee, the Institutional Review Board of the French learned society for respiratory medicine -Société de Pneumologie de Langue Française- on June 27, 2016, with reference number CEPRO 2016-024. All patients signed a consent form allowing the use of clinical, biological and radiological data collected during routine care for research purposes.

2.2. Data Collection

Data were retrieved from the electronic patient records. The following data were

collected: patients background characteristics (age, sex, smoking history), disease characteristics (pathology, stage at diagnosis, molecular profile, number of brain metastases at diagnosis), treatment data (ECOG performance status PS at the beginning of immunotherapy, brain local treatment, adverse events, neurological symptoms) and outcome data (disease control rate DCR, intracranial disease control rate icDCR, objective response rate ORR, intracranial objective response rate icORR, progression-free survival PFS and overall survival OS).

ORR and DCR were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. CT-scan was used instead of magnetic resonance imaging (MRI) to evaluate brain response because CT-scan was performed routinely to assess disease response to ICIs and because MRI was only available for patients treated with brain local treatment. The first assessment was performed 6 to 8 weeks after the beginning of immunotherapy.

icORR was defined by complete response or partial response of brain metastases and icDCR was defined by complete response, partial response or stable disease in the brain.

Toxicity was evaluated according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

The primary objective of the study was to identify predictive factors for ICIs intracranial efficacy in terms of icDCR and icORR. Secondary objectives were the identification of predictive factors for ICIs intracranial efficacy in terms of OS, intracranial progression-free survival (icPFS) and tolerance.

2.3. Statistical Analyses

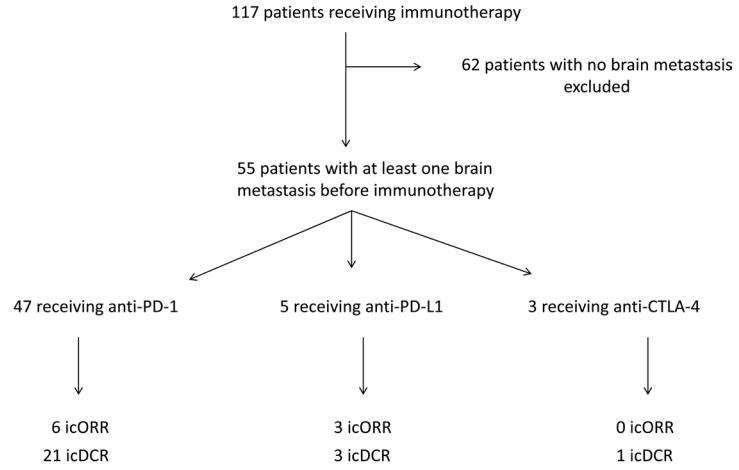
Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM SPSS Inc., Chicago, IL, United States of America (USA)). Comparisons of mean values between two groups were performed using student t-test or Mann-Whitney U test. Comparisons of percentages were performed using Chi-Square test or Fisher's exact test, as appropriate. Time-to-event endpoints were estimated by the Kaplan-Meier method and compared using the log-rank test. OS was defined as the time from the beginning of immunotherapy to death from any cause, censored at the date of the last follow-up. PFS was defined as the time from the beginning of immunotherapy to documented disease progression or death, censored at the date of the last follow-up. Medians were reported with 95% confidence interval.

3. Results

3.1. Patients' Characteristics

A total of 117 patients who received at least one cycle of immunotherapy for advanced NSCLC between April 2013 and February 2016 were retrieved from the database. Among them, 55 patients had BM (**Figure 1**).

Patients' main characteristics were summarized in **Table 1**. Forty-nine (89.1%) patients were smokers or former smokers. Pathology report found squamous cell



icORR: intracranial objective response rate; icDCR: intracranial disease control rate.

Figure 1. Flow chart of the study.

Table 1. Patients' characteristics.

Characteristics	N	%
Sex		
Male	38	69.1
Female	17	30.9
Tobacco smoking		
Never smoker	6	10.9
Smoker	21	38.2
Former smoker	28	50.9
Pathology		
Non-squamous	46	83.6
Squamous	9	16.4
Mutation status		
No molecular alteration	25	45.5
Molecular alteration	17	30.9
Disease stage		
I, II, IIIA	7	12.7
IIIB, IV	48	87.3
Brain metastases		
Synchronous	26	47.3
Metachronous	29	52.7
Number of brain metastases at diagnosis		
0	29	52.7
1 to 5	19	34.5
>5	7	12.7
Brain metastases treatment		
Surgery or radiosurgery	42	76.4
Whole brain radiation therapy	7	12.7
None	6	10.9
Immunotherapy type		
Anti-PD-1	47	85.5
Anti-PD-L1	5	9.0
Anti-CTLA-4	3	5.5
ECOG PS		
0 - 1	45	81.8
≥2	10	18.2

carcinoma in 9 patients (16.4%) and non-squamous NSCLC in 46 patients (83.6%). A genomic alteration was found in 17 (30.9%) patients: 1 patient had an *ALK*-rearranged tumor, 2 patients had *EGFR*-mutant tumors, 13 patients had KRAS-mutant tumors and 1 patient had a *MET*-amplified tumor.

BMs were present at the diagnosis of NSCLC in 26 (47.3%) patients. Thirty-two (58.2%) patients had active BM at the beginning of immunotherapy. The other 23 patients (41.8%) had previously treated BMs at the beginning of immunotherapy.

Forty-seven (76.4%) patients received anti-PD-1 treatment, five (9%) patients received anti-PD-L1 and 3 (5.5%) received anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4) treatments.

Brain local treatment was performed for 49 patients (89.1%); among them, 42 had surgery or SRS and 7 had WBRT. Forty-seven patients (85.5%) were treated with PD-1 inhibitors while 8 (14.5%) patients received anti-PD-L1 or anti-CTAL-4 inhibitors.

3.2. Efficacy

Regarding systemic response to immunotherapy, only one patient (1.8%) had a partial response (PR) while 19 patients (34.6%) had a stable disease (SD) and 29 patients (52.7%) had a progressive disease (PD) as the best response. Response assessment was missing for six patients mainly because of clinical progression or death before the first radiological assessment.

Median PFS calculated from the beginning of immunotherapy was 86 days (2.9 months) and median OS calculated from the beginning of immunotherapy was 515 days (17.2 months) (Figure 2).

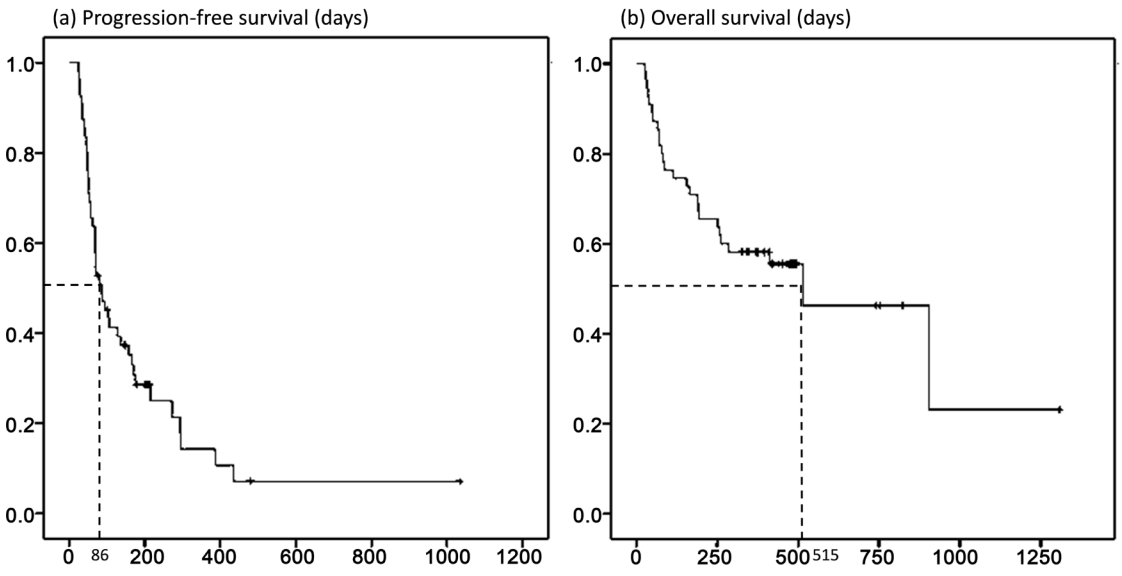


Figure 2. Progression-free survival (a) and overall survival (b) from the beginning of immunotherapy. (a) median progression-free survival was 86 days (2.9 months); (b) median overall survival was 515 days (17.2 months).

Regarding intracranial efficacy, 5 patients (9.1%) had complete intracranial response icCR, 4 (7.3%) had intracranial partial response icPR, 16 (29.1%) had intracranial stable disease icSD and 29 (41.8%) had intracranial progressive disease icPD. Intracranial response data were missing for seven patients. Intracranial Overall Response Rate was 16.4% (n = 9) and intracranial Disease Control Rate was 45.5% (n = 25). Intracranial response is shown in Figure 3. During the treatment, sixteen patients developed brain metastasis.

3.3. Predictive Factors of Intracranial Efficacy

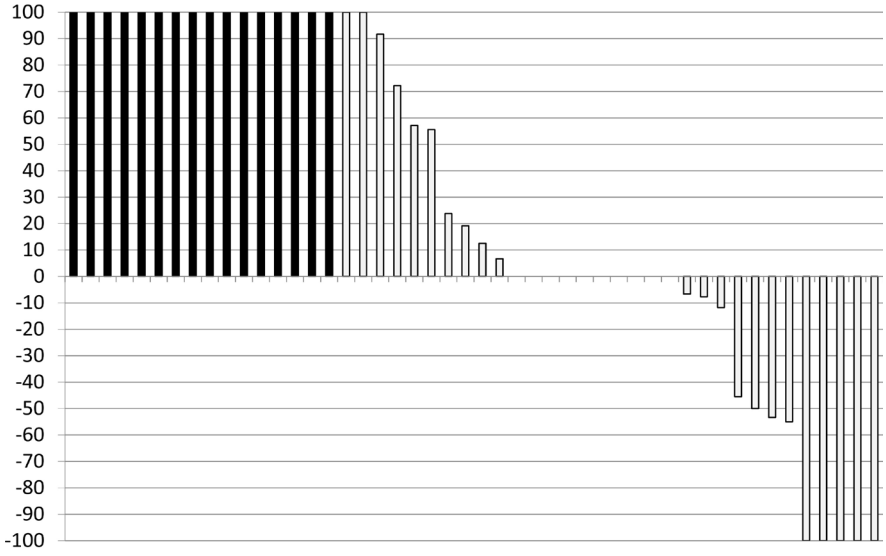
Fifty percent of patients with poor ECOG PS (≥ 2) at the beginning of immunotherapy (N = 10) had an intracranial response (p = 0.05). On the contrary, patients with PS < 2 (N = 45) had lower icORR. No difference was found regarding icDCR according to ECOG PS (p = 0.242).

A significant difference in icORR, but not in icDCR, was found depending on the type of immunotherapy: patients treated with anti-PD-L1 had better icORR than patients treated with anti-PD-1 (p = 0.035) or anti-CTLA-4.

Tobacco status was not significantly associated with icDCR (p = 0.560), however, there was a trend towards better icORR for current smokers in comparison with non-smokers (p = 0.057).

Previous brain local treatment was not significantly associated with intracranial efficacy. However, 20% of patients who received surgery or radiosurgery had intracranial objective response whereas 0% of patients who received whole brain radiation therapy (WBRT) or no local treatment had intracranial objective response.

There was no significant association between icORR/icDCR and pathology (p = 0.990/p = 0.466), mutation status (p = 0.990/0.549) and number of brain metastasis at diagnosis (p = 0.477/p = 0.089) (Table 2).



In black: patients with new brain metastases developed during immunotherapy; In white: patients with no new brain metastases during immunotherapy.

Figure 3. Waterfall plot of intracranial response to immunotherapy.

Table 2. Intracranial response to immunotherapy depending on patients' characteristics.

Characteristics	Objective Response Rate		Disease Control Rate	
	%	p Value	%	p Value
Tobacco smoking				
Never smoker	0.0	0.060	50.0	0.560
Smoker	37.5		62.5	
Former smoker	11.5		46.2	
Brain local treatment				
Surgery or radiosurgery	25.0	0.246	58.3	0.224
Whole brain radiation therapy	0.0		50.0	
None	0.0		16.7	
Immunotherapy type				
Anti-CTLA-4	0.0	0.056	33.3	0.866
Anti-PD-1	15.0		52.5	
Anti-PD-L1	60.0		60.0	
ECOG PS				
0 - 1	14.3	0.071	50.0	0.668
≥2	50.0		66.7	
Pathology				
Non-squamous	17.9	0.990	48.7	0.466
Squamous	22.2		66.7	
Mutation status				
Mutation	17.4	0.990	43.5	0.549
No mutation	15.4		53.8	
Brain metastases				
Synchronous	23.8	0.477	66.7	0.089
Metachronous	14.8		40.7	
Number of brain metastases at diagnosis				
0	14.8	0.660	40.7	0.170
1 to 5	25.0		62.5	
>5	20.0		80.0	

3.4. Tolerance

In our population, twenty-one patients developed immunotherapy-induced adverse events. Endocrine toxicity was the most common and 10 patients (18.2%) had hypo or hyperthyroidism. Six patients had diarrhea (10.9%), lung and skin effects were seen in 2 patients (3.6%), and only 1 (1.8%) patient reported arthritis.

Regarding neurological toxicity, 3 patients had increased or new neurological symptoms during immunotherapy: 1 had vertigo, 1 had sensitive deficiency and 1 had motor deficiency. Among them one patient had intracranial progressive disease.

On the contrary, 2 patients described an improvement of neurological symptoms during immunotherapy, one of them with intracranial partial response and the other with intracranial stable disease.

No patient had any grade 3 or 4 neurological side effect during immunotherapy.

3.5. Predictive Factors of Tolerance

No significant association was found between immune-related adverse events and tobacco status (p = 0.164 for smokers and p = 0.054 for former smokers in comparison with never-smokers), brain local treatment (p = 0.694 for WBRT and p = 0.186 for SRS in comparison with surgery), the type of immunotherapy (p = 0.900 for PD-1 and p = 0.472 for PD-L1), ECOG PS (p = 0.428 for ECOG PS ≥ 2 in comparison with ECOG PS 0 - 1) at the beginning of immunotherapy, pathology (p = 0.273 for squamous versus non-squamous NSCLC), mutation status (p = 0.530), the presence of BM at diagnosis (p = 0.620 for synchronous BM versus metachronous BM) or the number of brain metastasis at diagnosis (p = 0.252 for 1 - 5 BM and p = 0.295 for >5 BM in comparison with no BM) (Table 3).

Table 3. Tolerance depending on patients' characteristics and treatments.

Characteristics	Adverse Events (%)	OR	95% Confidence Interval	p Value
Tobacco smoking				
Never smoker	80.0	Ref		
Smoker	42.9	0.188	0.018 - 1.977	0.164
Former smoker	28.6	0.100	0.010 - 1.038	0.054
Brain local treatment				
Surgery or radiosurgery	50.0	Ref		
Whole brain radiation therapy	41.5	0.708	0.127 - 3.943	0.694
None	14.3	0.167	0.012 - 2.368	0.186
Immunotherapy type				
Anti-CTLA-4	33.3	Ref		
Anti-PD-1	37.0	1.172	0.099 - 13.916	0.900
Anti-PD-L1	60.0	3.000	0.150 - 59.890	0.472
ECOG PS				
0 - 1	36.4	Ref		
≥2	50.0	1.750	0.439 - 6.980	0.428
Pathology				
Non-squamous	42.2	Ref		
Squamous	22.2	0.391	0.073 - 2.096	0.273
Mutation status				
No molecular alteration	40.0	Ref		
Molecular alteration	50.0	1.500	0.423 - 5.315	0.530
Brain metastases				
Synchronous	42.3	1.320		
Metachronous	35.7	Ref	0.441 - 3.953	0.620
Number of brain metastases at diagnosis				
0	35.7	Ref		
1 to 5	52.6	2.000	0.610 - 6.553	0.252
>5	14.3	0.300	0.032 - 2.857	0.295

4. Discussion

ICIs have revolutionized treatment strategies of advanced NSCLC, but data are missing regarding their efficacy and tolerance in patients with brain metastasis, and no predictive factors are available to better select patients before immunotherapy. Our study is the first and largest series reporting factors associated with favorable outcomes in patients with BM from NSCLC treated with ICIs.

In a population of 55 patients, we have shown that intracranial disease control was achieved in nearly half patients, regardless of local brain treatments received previously. However, intracranial efficacy was heterogeneous, with new BM appearing during immunotherapy treatment in 16 patients, highlighting the need for predictive markers of intracranial efficacy. Furthermore, ICIs were well tolerated with a weak proportion of patients with neurological symptoms and no serious (grade 3 or 4) neurological adverse event.

Our data were collected from a daily-practice population of patients with BM from NSCLC receiving immunotherapy whereas patients enrolled in immunotherapy trials are over-selected regarding ECOG performance status, comorbidities or brain metastases control before enrollment.

We tried to identify predictive factors associated with intracranial response. A significant difference was found regarding ECOG PS, patients with poor PS having a better icORR than patients with ECOG PS 0 or 1. These results show that ICIs can be used in patients with brain metastasis even if they have poor ECOG PS (≥2). In addition, tobacco status seemed to be associated with intracranial efficacy in our study. Current smokers had a trend towards better icORR than former or never smokers. This result can be explained by the association between tobacco smoking and higher tumor mutational burden potentially responsible for better response to ICIs. Moreover, whereas no significant difference was shown in icORR or icDCR regarding brain local treatment, only patients who received surgery or radio surgery (22%) had an intracranial objective response. Patients who did not receive brain local treatment had a trend towards worst icDCR than patients who received surgery, radiosurgery or WBRT, highlighting a potential association between brain local treatment and a better intracranial response to ICIs. It is still unclear whether this difference was explained by immunotherapy efficacy on brain metastasis independently from brain local treatment or by surgery or radiosurgery efficacy on brain metastasis independently from immunotherapy, or by an interaction between immunotherapy and brain local treatment. Some studies reported a potential benefit on safety and efficacy of concurrent cranial radiation therapy and immunotherapy [23] [24] but further studies investigating the interaction between immunotherapy and intracranial treatments are needed to clarify these results.

Our survival results are consistent with randomized phase III trials of anti-PD-1 treatments for second or third-line treatment of advanced NSCLC regardless PD-L1 expression: PFS was 2.9 months in our study versus 2.3 months in the CheckMate 057 trial and 3.5 months in the CheckMate 017 trial [12] [11].

However, the objective response rate in our study was lower than in CheckMate studies (1.82% versus 19% and 20%) [11] [12]. This can be explained by patients' selection criteria. Some patients received immunotherapy after more than three lines of treatment and 18.2% of patients were ECOG PS 2 or 3 at the beginning of immunotherapy. Therefore, the outcomes in our population were poorer than in phase II or III clinical trials with over-selected patients.

Disease response or control rate was not dependent on any clinical criteria, but we found a trend towards an association between tobacco status and response ($p = 0.06$), with better responses in smokers than in non-smokers. These results are consistent with the CheckMate 057 study [11], where hazard ratio for OS favored nivolumab in smokers but not in non-smokers (OR = 0.70 (0.56 - 0.86) for smokers and OR = 1.02 (0.64 - 1.61) in never smokers). On the contrary, in the OAK study [15], median overall survival with atezolizumab was better in never-smokers than in current or former smokers (16.3 vs 13.2 months). These results suggest a relationship between immunotherapy response and tobacco status, but more studies are needed to assess this relationship.

In addition, whereas intracranial response to ICIs in our study was not significantly associated with prior intracranial treatment, patients previously treated with surgery or radiosurgery seemed to have better intracranial response than patients who did not receive any intracranial treatment. However, data are missing regarding potential interaction between ICIs and brain local treatments such as surgery, SRS or WBRT. In a retrospective study, Choong ES *et al.* [25] included seventy-nine patients with BM from melanoma treated by SRS, who received immunotherapy, and found favorable brain control and overall survival. Silk AW *et al.* [26] also revealed that ipilimumab may be associated with a significantly reduced risk of death in patients with melanoma BMs who underwent WBRT. One of their hypotheses is the enhancement of tumor cells (injured by radiation therapy) immunogenicity by immunotherapy. On the other hand, immunotherapy combined with WBRT may induce specific injuries such as radiation necrosis needing specific management [27]. This hypothesis is consistent with case reports of pseudo-progressions and radiation necrosis, but larger studies are required to understand the interaction between ICIs and local treatments.

Other studies have already tried to assess intracranial efficacy of ICIs, mainly assessing melanoma patients. Goldberg *et al.* provided in a phase 2-trial, an evidence of intra-cranial activity of pembrolizumab on thirty-six patients with untreated or progressive brain metastasis from melanoma and NSCLC. Only NSCLC with PDL-1 expression ≥ 1% were included. Patients had no neurological symptoms, steroids treatment or local brain treatment. Response was achieved on four patients with melanoma and six with NSCLC. These results showed an effect of immunotherapy on brain metastasis in NSCLC but only for patients with PDL-1 positive tumors. However, there were no data available regarding potential predictive factors for intracranial response [20]. In a retrospective study on 185 patients, Stokes *et al.* tried to assess the impact of immunothe-

rapy on brain metastases from patients with melanoma receiving brain radiotherapy [28]. Immunotherapy in combination with brain radiotherapy was associated with an improved survival. Furthermore, this study looked for predictive factors for intracranial response and evidenced that younger age, academic facility, lower extracranial disease burden and stereotactic radiotherapy were associated with an improved survival. In CheckMate-204, safety and intracranial efficacy of ipilimumab plus nivolumab were evaluated in patients with untreated brain metastasis from melanoma. Intracranial efficacy was concordant with extracranial response rate and safety was similar to patients without brain metastasis [29].

All these studies assessed ICIs efficacy on brain metastasis. However, our study is the largest one to report predictive factors of ICIs efficacy and tolerance in patients with NSCLC metastatic to the brain treated in a daily routine practice. In all these publications, ICIs were well tolerated, with no severe (grade 3 or more) neurologic adverse events. Cohen *et al.* however reported the case of a patient with brain pseudo-progression after pembrolizumab treatment for metastatic melanoma [30]. In our series, we also observed a case of brain pseudo-progression in a patient treated with pembrolizumab who previously received gamma-knife radiosurgery for BM. Surgery was performed on the progressive BM and the pathology report could not identify any tumor cell but only radiation-induced necrosis.

Furthermore, several studies tried to find better criteria to assess BM response for patients treated with ICIs. Qian JM *et al.* [31] from the Response Assessment in Neuro-Oncology (RANO) working group compared four BM response criteria on thirty-six patients treated by pembrolizumab, brain response was initially performed with RECIST 1.1 (2 BM > 10 mm in one diameter). During the trial, new criteria for brain metastasis response were evaluated, RANO-BM (5 BM > 10 mm in one diameter), mRECIST (5 BM > 5 mm in one diameter), and RANO high-grade glioma RANO-HGG (5 BM > 10 mm in two diameters). Concordance among the four criteria studied was high, but response rate changed from 12% with RANO-HGG to 28% with mRECIST. In our study, we chose to evaluate ORR and DCR with RECIST version 1.1 since these criteria were used in randomized phase III trials leading to ICIs approval in NSCLC [11] [12] [13] [17].

The main limitation of the study is its retrospective design with fifty-five patients analyzed. However, this is the largest series studying brain response to ICIs in patients with NSCLC.

Despite these encouraging results, BMs from NSCLC are still correlated with a poor prognosis and a better knowledge of BM microenvironment and immunogenicity would help physicians to improve the outcomes and treatments of patients with BM. In a review by Hamilton A *et al.* [32], different interactions between BM and immune cells were explored. Metastasis-associated inflammation activated by macrophages or mast cells in the CNS could be responsible for me-

tastatic growth. These results are interesting to understand brain response mechanisms, and further studies are needed to improve patients' selection for immunotherapy. Furthermore, recent work found a correlation between brain metastasis and NSCLC molecular profile [33]. *EGFR* mutations could be predictive for a higher incidence of BM while *KRAS* mutations could be predictive for a lower rate of BM recurrence after local treatment and shorter survival. Mutation status may also be predictive for ICIs intracranial efficacy and further studies are required in this field.

In our study, PD-1, PD-L1 or CTLA-4 expression was absent for most patient because when data were collected, we did not search these expressions systematically, and we can think that it can maybe change intracranial response.

In conclusion, we have shown that ICIs can be used safely for patients with BM from NSCLC, including patients with poor ECOG PS, and that intracranial response may be associated with current tobacco smoking and previous brain local treatment but it is still necessary to discuss each case in a multidisciplinary tumor boards (MTB) dedicated to the treatment of BMs [34]. These discussions are helpful to assess different systemic treatment options for BMs and potential interactions between systemic and local treatments to the brain.

Importance of the Study

Lung cancer is one of the leading causes of brain metastasis and they are associated with a poor prognosis. Immune checkpoint inhibitors (ICIs) use is rising in this disease and their consequence on brain metastases is still unclear. This is the largest case series of non-small cell lung cancer patients with brain metastases providing data about potential predictive factors of efficacy and tolerance of ICIs on brain metastases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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