



First-line single-agent pembrolizumab for PD-L1-positive (tumor proportion score $\geq 50\%$) advanced non-small cell lung cancer in the real world: impact in brain metastasis: a national French multicentric cohort (ESCKEYP GFPC study)

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Received: 18 January 2022 / Accepted: 25 May 2022

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Abstract

Background Few real-world data are available in patients with advanced metastatic non-small cell lung cancer (NSCLC) treated with first-line immunotherapy, particularly in those with brain metastases at treatment initiation.

Methods This was a national, retrospective, multicenter study that consecutively included all patients with PD-L1-positive (tumor proportion score $\geq 50\%$) advanced NSCLC who initiated first-line treatment with pembrolizumab as a single agent between May 2017 (date of availability of pembrolizumab in this indication in France) to November 22, 2019 (approval of the pembrolizumab-chemotherapy combination). Data were collected from medical records with local response assessment.

Results The cohort included 845 patients and 176 (20.8%) had brain metastases at diagnosis. There were no significant differences in outcomes for patients with and without brain metastases: 9.2 (95% CI 5.6–15) and 8 (95% CI 6.7–9.2, $p=0.3$) months for median progression-free survival (PFS) and, 29.5 (95% CI 17.2–NA) and 22 (95% CI 17.8–27.1, $p=0.3$) months for median overall survival (OS), respectively. Overall response rates were 47% and 45% in patients with and without cerebral metastases. In multivariate analysis, performance status 2–4 vs. 0–1 and neutrophil-to-lymphocyte ratio ≥ 4 vs. < 4 were the main independent negative factors for OS; brain metastasis was not an independent factor for OS.

Conclusion In this large multicenter cohort, nearly 20% of patients initiating pembrolizumab therapy for advanced NSCLC had cerebral metastases. There was no significant difference in response rates, PFS and OS between patients with and without brain metastases.

Keywords Pembrolizumab · Non-small cell lung cancer · Advanced stage · Brain metastases · Real-world study

Introduction

Most patients (86.5%) with advanced non-small cell lung cancer (NSCLC) do not harbor oncogenic drivers, such as *EGFR* mutations or *ALK* translocation [1]. Until the recent advances in immunotherapy, treatment options in these patients at advanced stages were limited to cytotoxic chemotherapy. Among NSCLC patients, 23% to 28% have a high level of programmed death ligand 1 (PD-L1) expression

defined by a tumor proportion score (TPS) $\geq 50\%$ [2, 3]. Blocking the interaction between PD-1 expressed on effector T-cells and PD-L1 on neoplastic cells prevents tumor cells from evading anti-tumor immunity [4]. Pembrolizumab is a humanized anti-PD1 monoclonal antibody that has been evaluated in various malignancies. In the phase 1 KEYNOTE-001 and phase 3 KEYNOTE-010 studies, patients with advanced NSCLC and a TPS $\geq 50\%$ responded more frequently to pembrolizumab than patients with lower TPS [3, 5, 6]. The results of the KEYNOTE-024 trial demonstrated the superiority of single-agent pembrolizumab over chemotherapy for the first-line treatment of advanced

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NSCLC characterized by a PD-L1 TPS $\geq 50\%$ and the absence of *EGFR* mutation or *ALK* rearrangement [2].

Single-agent pembrolizumab is now a validated first-line option for the subgroup of patients with PD-L1 expression levels $\geq 50\%$. However, the results of the KEYNOTE-024 trial were obtained in highly selected patients. Patients were excluded if they had ECOG performance status ≥ 2 , untreated brain metastases, corticosteroid treatment or a history of autoimmune disease [2]. Real-world data are important to assess the efficacy of pembrolizumab in routine care, including patients not eligible or under-represented in clinical trials [7]. The main objective of the ESCKEYP trial was to determine real-world outcomes with first-line single-agent pembrolizumab for advanced PD-L1-positive (TPS $\geq 50\%$) NSCLC with a focus on patients with brain metastasis at baseline, to assess the efficacy of pembrolizumab in these patients.

Materials and methods

Type of study and patients

The ESCKEYP study (GFPC 05-2018) was a national, retrospective and multicentric trial that consecutively included patients with advanced PD-L1 $\geq 50\%$ NSCLC initiating first-line single-agent pembrolizumab.

Treatment-naïve adult patients were included if they had histologically or cytologically confirmed advanced NSCLC expressing PD-L1 on more than 50% of tumor cells and if they were negative for *EGFR* and *ALK* mutations. Brain metastases at inclusion, asymptomatic, pre-treated or not, or if symptomatic, pretreated with stereotactic or pan-cerebral radiation therapy, were allowed (brain MRI was recommended). At least one measurable lesion, cerebral or extra-cerebral, must be present. Patients with autoimmune disease contraindicating immunotherapy or active infection (hepatitis B, C, HIV) and patients with organ or bone marrow transplant were excluded.

PD-L1 expression on tumor cells was determined using immunohistochemistry (IHC) by the local pathology laboratory, based on its own routine IHC platform with 22C3 (Dako), SP263 (Ventana), 28-8 (Dako), or E1L3N (Cell Signaling Technology) antibody, all approved in France for this purpose. Considering the study design, no centralized testing was performed.

Pembrolizumab was administered intravenously at a dose of 200 mg every 3 weeks, according to its first French registration in 2015. The drug was discontinued in the event of progressive disease or unacceptable toxicity, as assessed by the investigator.

The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. It

was approved by a national independent Ethics Committee (2019-A02073-54, on December, 11, 2019). Patients received written and oral information on the study and gave their consent to participate in the study and for the use of their medical data for research purposes.

Data collected

Data were collected from patient medical records using electronic case report forms: sociodemographic data (performance status, smoking status, occupational exposure, disease history); NSCLC characteristics (histology, stage, metastatic sites at diagnosis); PD-L1 expression, *ALK* and *EGFR* status (and other mutations or rearrangements); brain metastases at diagnosis (number, size, symptoms, treatments); other metastatic sites at diagnosis (number, locations); radiation therapy; progression (new sites or existing sites), a previous treatment in the month before pembrolizumab administration of corticosteroids (more than 10 mg/day, for more than 10 days) and a previous course of antibiotics (more than 10 days), leucocytes and lymphocytes counts.

Tumor response was assessed locally according to RECIST 1.1.

Statistical analysis

Comparisons between patient characteristics were performed using the chi-square test or Fisher's exact test for discrete variables. The Kaplan–Meier method was used to estimate PFS and OS. OS was defined as the time from index date to the date of death from any cause or censoring, measured at the last contact date or the cut-off date. The index date was defined as the start date of the first pembrolizumab administration after diagnosis of advanced NSCLC. The cut-off date was January 18, 2021 (i.e., database extraction date). PFS was defined as the time from index date to the date of first disease progression or death from any cause. Patients without disease progression at last contact were censored at the date of last contact, or the cut-off date, if earlier. The log-rank test was used to compare survival distributions between groups.

Univariate Cox models were applied to select the most promising prognostic variables (threshold $p = 0.20$). A multivariate Cox model was then applied to adjust for potential confounders. The multivariable analysis was conducted using backward stepwise Cox regression modeling, with OS or PFS as the dependent variable and prognostic factors as the explanatory variables. Hazard ratios (HR) with their respective 95% CI and p -values were calculated. p -value < 0.05 was considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

Patient disposition and characteristics

A total of 845 patients with PD-L1 $\geq 50\%$ advanced NSCLC treated in first line with pembrolizumab were included in 33 centers in France from May 2017 (date of availability of pembrolizumab in this indication in France) to November 22, 2019 (approval of the pembrolizumab-chemotherapy combination).

Patients had a median (range) age of 65 (59–72) years and 176 (20.8%) had brain metastases; 74 (42%) of them had radiotherapy just before or concurrently with immunotherapy. Compared to patients without brain metastasis, patients with brain metastases at diagnosis were significantly more often female (40.9% vs. 29.9%, $p = 0.005$), under 70 y of age (73.9% vs. 63.4%, $p < 0.01$), treated with corticosteroids (23.3% vs. 7.7%, $p < 0.0001$) and with adenocarcinomas (85.1% vs. 66.3%, $p < 0.0001$) (Table 1).

Tumor response rates

For the overall cohort ($n = 791$ evaluable patients), the best response was complete response for 37 (4.7%) patients, partial response for 334 (42.2%), stable disease for 189 (23.9%) and progressive disease for 231 (29.2%). The overall response rate was 45% (95% CI 42–49). The mean duration of response was 11.7 (95% CI 10.8–12.6) months.

The best systemic response according to the presence or absence of cerebral metastases is described in Table 2; there was no significant difference between the groups for the response rate. Regarding brain response in the 74 patients with brain metastases who had brain radiotherapy at diagnosis or at initiation of pembrolizumab, 48.6% (36/74), 24.3% (18/74) and 27% (20/74) had objective response, stable disease and progression of central nervous system (CNS) disease, respectively; in the 76 patients with brain metastases who did not have cerebral radiotherapy ($n = 76$), these rates were 35.5% (27/76), 15.8% (12/76) and 48.7% (37/76), respectively.

Survival

The median duration of follow-up was 25.8 (95% CI 24.8–26.7) months for the entire cohort.

Median PFS was 8.2 (95% CI 6.9–9.5) months (Fig. 1); the median time to pembrolizumab discontinuation was 8 (95% CI 7–9) months. Median PFS was 8 (95% CI 6.7–9.2) months in patients without brain metastases and 9.2 (95% CI 5.6–15) months in patients with brain metastases ($p = 0.33$).

Median OS was 22.6 (95% CI 18.5–27.4) months (Fig. 2). Survival rates at 6, 12 and 18-month were 76.8%, 64.8% and 54.3%, respectively. Median OS was 22 (95% CI 17.8–27.1) in patients without brain metastases and 29.5 (95% CI 17.2–not reached) months in patients with brain metastases ($p = 0.37$).

Patients with white blood cell count $\leq 10,000/\text{mL}$ at pembrolizumab initiation had higher OS (29.8 vs. 15.8 months; $p < 0.0001$) and PFS (10.3 vs. 5.9 months; $p = 0.0027$) than those with $> 10,000/\text{mL}$ white blood cell count. A neutrophil-to-lymphocyte ratio < 4 was significantly associated to a higher OS (32.7 vs. 14.3 months; $p < 0.0001$) and PFS (15.7 vs. 5 months; $p < 0.0001$) in comparison with a neutrophil-to-lymphocyte ratio ≥ 4 .

In the multivariate analysis, neutrophil-to-lymphocyte ratio ≥ 4 vs. < 4 was an independent predictive factor for shorter PFS (HR 1.64, 95% CI 1.30–2.07; $p < 0.0001$) (Table 3). Performance status 2–4 vs. 0–1 (1.68, 95% CI 1.26–2.22) and neutrophil-to-lymphocyte ratio ≥ 4 vs. < 4 (1.67, 95% CI 1.25–2.22) were independent predictive factors for shorter OS. The presence of brain metastases at diagnosis was not an independent factor for OS.

Discussion

In this large real-world cohort of patients with PD-L1 $\geq 50\%$ advanced NSCLC, including 20.8% of patients with brain metastases at diagnosis and 20.2% of PS ≥ 2 , treated as first-line therapy with single-agent pembrolizumab, median PFS (primary endpoint) was 8.2 (95% CI 6.9–9.5) months and median OS was 22.6 (95% CI 18.5–27.4) months. These outcomes were less favorable compared to the results of the pivotal studies, but patients were less selected in our study. In the KEYNOTE-024 trial, median PFS was 10.3 months (95% CI 6.7–not reached) in the single-agent pembrolizumab arm [2]; median OS was 26.3 (95% CI,

18.3 to 40.4) months in an updated analysis [8]. In this trial, only patient with PS 0 or 1 can be included and patients with not-treated brain metastasis or with > 10 mg of corticosteroids were excluded. As a consequence, patients with brain metastases (20.8% treated or untreated vs. 11.7% treated), corticosteroid treatment (10.9% vs 0%) and performance status ≥ 2 (20.2% vs. $< 1\%$) were more frequent in our study than in the KEYNOTE-024 trial, respectively.

An Italian analysis including advanced NSCLC, PD-L1 $\geq 50\%$, also in real-world management, reported comparable rates of treated PS ≥ 2 patients (15.2%) and patients with brain metastasis (18.3%). The outcomes associated to the pembrolizumab treatment in the Italian cohort were close to our results with PFS and OS of 7.9 (95% CI 6.9–9.5) months and 17.2 (95% CI 15.3–22.3) months, respectively [9]. The ORR, 46.9% in our cohort,

Table 1 Characteristics of patients with and without brain metastases at initiation of first-line pembrolizumab

	All population (<i>n</i> = 845)	With brain metas- tases (<i>n</i> = 176)	Without brain metastases (<i>n</i> = 669)	<i>p</i> -value
Female gender, <i>n</i> (%)	272 (32.2)	72 (40.9)	200 (29.9)	0.005
Age ≥ 70 y, <i>n</i> (%)	290 (34.3)	46 (26.1)	244 (36.5)	0.01
Smoking status, <i>n</i> (%)	<i>n</i> = 818	<i>n</i> = 170	<i>n</i> = 648	
Current/former smoker	764 (93.4)	160 (94.1)	604 (93.2)	0.67
No smoker	54 (6.6)	10 (5.9)	44 (6.8)	
Weight loss, <i>n</i> (%)	<i>n</i> = 722	<i>n</i> = 150	<i>n</i> = 572	
< 5%	461 (63.9)	102 (68.0)	359 (62.8)	0.23
≥ 5%	261 (36.1)	48 (32.0)	213 (37.2)	
BMI kg/m, <i>n</i> (%)	<i>n</i> = 805	<i>n</i> = 169	<i>n</i> = 636	
< 18	51 (6.3)	15 (8.9)	36 (5.7)	0.26
18–30	692 (85.9)	143 (84.6)	549 (86.3)	
≥ 30	62 (7.7)	11 (6.5)	51 (8.0)	
ECOG performance status, <i>n</i> (%)	<i>n</i> = 781	<i>n</i> = 169	<i>n</i> = 612	
0–1	610 (78.1)	133 (78.7)	477 (77.9)	0.83
2–3	171 (20.2)	36 (21.3)	135 (22.1)	
Corticosteroid treatment, <i>n</i> (%)	<i>n</i> = 845	<i>n</i> = 176	<i>n</i> = 669	
Yes	92 (10.9)	41 (23.3)	51 (7.7)	< 0.0001
Antibiotic treatment ^a <i>n</i> (%)	<i>n</i> = 826	<i>n</i> = 173	<i>n</i> = 653	
Yes	142 (17.2)	17 (9.8)	125 (19.1)	0.004
Histology, <i>n</i> (%)	<i>n</i> = 838	<i>n</i> = 174	<i>n</i> = 664	
Adenocarcinoma	588 (70.2)	148 (85.1)	440 (66.3)	< 0.0001
Other	250 (29.8)	26 (14.9)	224 (33.7)	
Metastases, <i>n</i> (%)	<i>n</i> = 845	<i>n</i> = 176	<i>n</i> = 669	
Bone	549 (65.0)	122 (69.3)	427 (63.8)	0.17
Liver	296 (35.0)	54 (30.7)	242 (36.2)	0.37
PD-L1-positive tumor, <i>n</i> (%)	<i>n</i> = 774	<i>n</i> = 161	<i>n</i> = 613	
TPS > 75%	413 (53.4)	86 (53.4)	327 (53.3)	0.98
Genetics, <i>n</i> (%)	<i>n</i> = 845	<i>n</i> = 176	<i>n</i> = 669	
KRAS	234 (27.7)	58 (33.0)	176 (26.3)	0.07
BRAF	29 (3.4)	5 (2.8)	24 (3.6)	0.62
Biological parameters, <i>n</i> (%)				
Albumin	<i>n</i> = 460	<i>n</i> = 100	<i>n</i> = 360	
≤ 30 g/L	107 (23.3)	20 (20)	87 (24.2)	0.38
C-reactive protein	<i>n</i> = 352	<i>n</i> = 77	<i>n</i> = 275	
> 5 mg/L	304 (86.4)	60 (77.9)	244 (88.7)	0.01
White blood cells	<i>n</i> = 678	<i>n</i> = 145	<i>n</i> = 533	
> 10,000/mm ³	288 (42.5)	63 (43.4)	225 (42.2)	0.78
Neutrophil-to-lymphocyte ratio	<i>n</i> = 642	<i>n</i> = 139	<i>n</i> = 503	
≥ 4	388 (60.4)	76 (54.7)	312 (62.0)	0.11

TPS tumor proportion score

^aWithin 3 months before pembrolizumab

44.5% in the Italian cohort and 44.8% in KEYNOTE-024 study, suggested a comparable efficacy of single-agent pembrolizumab in real-world management compared to the phase III pivotal study. Differences in OS were most likely related to more unfavorable prognostic conditions in real-world setting. In multivariate analysis, PS ≥ 2 was an

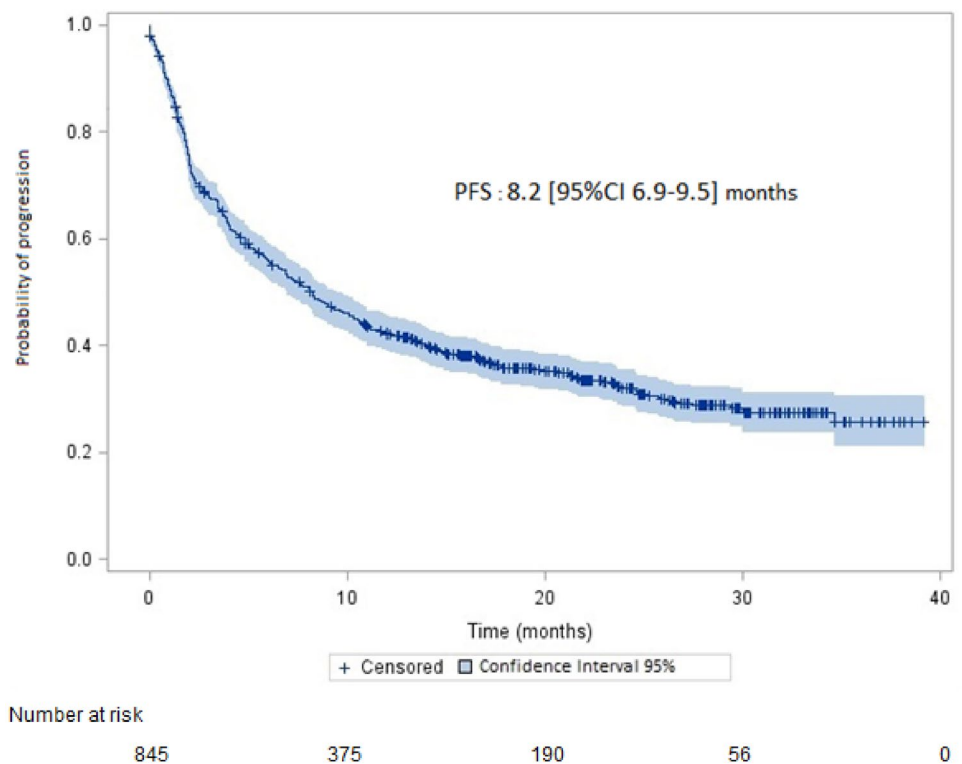
independent factor for poorer OS in our cohort. This was also reported in other analyses [9–11].

Despite the high frequency of brain metastases in NSCLC patients [12], few studies evaluated first-line immunotherapy in patients with untreated brain metastases at baseline. Indeed, in the phase III studies that evaluated immune

Table 2 Response rates of patients with and without brain metastases to first-line single-agent pembrolizumab

	With brain metastases		Without brain metastases	
	N=176	% (95% CI) ^a	N=669	% (95% CI) ^a
<i>Best response</i>				
Objective response rate (ORR) ^b	N=80	47 (39–55)	N=291	45 (41–49)
Stable disease	N=36	20 (14–26)	N=153	23 (20–26)
Progressive disease	N=55	31 (24–38)	N=206	31 (27–34)
Not evaluable	N=5	–	N=19	–

NA not applicable

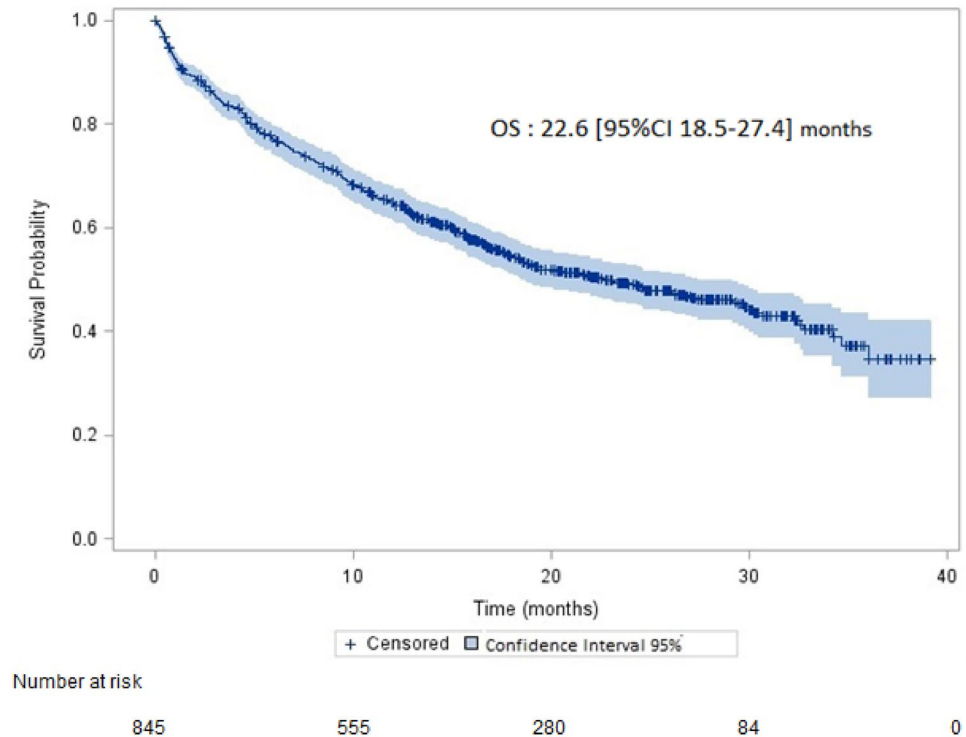
^aExact method for binomial confidence interval^bComplete response plus partial response rates**Fig. 1** Progression-free survival (PFS) (95% confidence interval in light blue on the survival curve)

checkpoint inhibitors (ICI), patients must have been irradiated and brain metastases must be stable; patients with untreated brain metastases were excluded [2, 6, 13–18]. In a retrospective study, Gauvain et al. included 43 NSCLC patients with brain metastases at diagnosis (treated in 34 patients and active in 16 patients) who received nivolumab [19]. Intracerebral and extracerebral ORR were equal to 9% (95% CI 3–23) and 11% (95% CI 4–26), respectively. A recent meta-analysis of 12 studies (566 patients), mostly retrospective, has evaluated the potential benefit of ICI in NSCLC patients with brain metastases [20]. ICI treatment was associated to an intracerebral ORR of 16.4% (95% CI 9.8–24) and intracerebral disease control rate (DCR) equal to 45%. There was no significant difference among patients with brain metastases previously treated or not treated with

radiation therapy before ICI administration. In the 9 studies that evaluated extracranial response, ORR was 16.4% (95% CI 10.0–23.9). However, almost all of these studies assessed the efficacy of ICIs in second line and above in a patient population not selected on PD-L1 status, making it difficult to compare with first-line results in patients with PD-L1 \geq 50%.

In a phase 2 prospective study, Goldberg et al. evaluated the intracerebral efficacy of pembrolizumab in patients with asymptomatic brain who did not require corticosteroids [21]. Brain MRI was performed at 4 weeks and brain response was evaluated by modified RECIST in which the sum of diameters of up to 5 brain metastases were allowed and lesions were considered measurable if they were at least twice the MRI section thickness. Patients should have a PS < 2 and no

Fig. 2 Overall survival (OS)
(95% confidence interval in
light blue on the survival curve)



neurological symptoms. Of the 37 PD-L1 positive patients, 11 (29.7%, 95% CI 15.9–47.0%) had a confirmed brain metastasis response (7 partial responses and 4 complete responses). An additional 4 patients had stable disease in the brain (2 unconfirmed), 16 had progressive disease and 6 were unevaluable due to rapid systemic progression precluding adequate imaging of the CNS. Eleven of the 37 patients (29.7%, 95% CI 15.9–47.0%) had a systemic response. Among the 27 patients evaluable for both CNS and systemic response, 6 had discordant outcomes. Of these cases, the brain was the site of progression in 3 patients (11.1%) with response in the body, whereas the other 3 (11.1%) had the reverse scenario. Median duration of systemic response was 6.9 (IQR 3.7–22.4) months. More recently, a pooled retrospective data for advanced or metastatic PD-L1 \geq 1% NSCLC patients with previously treated or untreated brain metastasis included in clinical trials evaluated outcomes to determine whether baseline brain metastases were associated with the efficacy of pembrolizumab versus chemotherapy [22]. All studies included patients with previously treated stable brain metastases. A total of 3170 patients were included, 293 (9.2%) with and 2877 (90.8%) without brain metastases at baseline. In patients with PD-L1 \geq 50%,

pembrolizumab improved OS versus chemotherapy with an HR of 0.67 (95% CI 0.44–1.02).

This study allowed to include a large number of patients managed consecutively at a time when only pembrolizumab as monotherapy was available. Therefore, selection bias was reduced. Nevertheless, this study has some limitations. Thus, response rates were assessed locally and there was no centralized evaluation. Even though MRI was recommended at inclusion, not all patients had the same type of imaging. Moreover, when cerebral radiotherapy was performed, the modalities and the delays from the start of pembrolizumab treatment were not homogeneous. Similarly, it was recommended that an assessment be performed every 6 to 8 weeks, but some assessments may have been delayed, which may have resulted in some bias in the calculation of PFS. Finally, there were no adjustments for multiple comparisons and there might be heterogeneity in the group with brain metastases (treated or untreated).

In conclusion, in this large multicenter cohort, nearly 20% of patients initiating pembrolizumab therapy for advanced NSCLC had brain metastases. There were no significant differences in response rates, PFS and OS between patients with and without brain metastases.

Table 3 Independent predictive factors of progression-free survival and overall survival in multivariate analysis (Cox proportional hazards model)

Factors	Test vs. reference	HR ^a	95% CI	<i>p</i> -value
<i>Progression-free survival^b</i>				
Neutrophil-to-lymphocyte ratio	≥ 4 vs. < 4	1.64	1.30–2.07	< 0.0001
Smoker	No vs. current/former	1.35	0.90–2.00	0.15
Performance status	2–4 vs. 0–1	1.24	0.96–1.60	0.10
Liver metastases	Yes vs. no	1.24	0.94–1.64	0.13
Bone metastases	Yes vs. no	1.16	0.93–1.44	0.20
Histology	No vs. adenocarcinoma	1.13	0.89–1.45	0.32
Brain metastases	Yes vs. no	1.08	0.83–1.40	0.58
Age, years	≥ 70 vs. < 70	1.05	0.84–1.32	0.66
Leukocytes	> 10,000 vs. ≤ 10,000	0.97	0.78–1.22	0.80
Gender	Female vs. male	0.90	0.71–1.14	0.38
PD-L1 > 75%	Yes vs. no	0.89	0.72–1.10	0.27
Corticosteroid treatment	No vs. yes	0.83	0.59–1.16	0.27
Antibiotic treatment	No vs. yes	0.80	0.62–1.03	0.08
<i>Overall survival^c</i>				
Performance status	2–4 vs. 0–1	1.68	1.26–2.22	0.0004
Neutrophil-to-lymphocyte ratio	≥ 4 vs. < 4	1.67	1.25–2.22	0.0005
Smoker	No vs. current/former	1.65	1.06–2.57	0.02
Histology	No vs. adenocarcinoma	1.4	1.05–1.86	0.02
Bone metastases	Yes vs. no	1.32	1.03–1.71	0.03
Age, years	≥ 70 vs. < 70	1.31	1.02–1.70	0.04
Brain metastases	Yes vs. no	1.17	0.87–1.59	0.29
Leukocytes	> 10,000 vs. ≤ 10,000	1.13	0.86–1.48	0.38
Liver metastases	Yes vs. no	1.11	0.81–1.53	0.51
Corticosteroid treatment	No vs. yes	0.91	0.6–1.3	0.65
PD-L1 > 75%	Yes vs. no	0.85	0.67–1.09	0.20
Gender	Female vs. male	0.81	0.62–1.09	0.15
Antibiotic treatment	No vs. yes	0.75	0.56–0.99	0.04

^aHazard ratio (HR) above 1 indicates poorer survival

^bFactors (*p*-values) of progression-free survival in univariate analysis: gender (*p*=0.3), age ≥ 75 y (*p*=0.03), smoker (*p*=0.14), weight loss ≥ 5% (*p*=0.12), performance status (*p*=0.004), body mass index (*p*=0.8), corticosteroid treatment (*p*=0.09), antibiotic treatment (*p*=0.0004), histology (*p*=0.5), brain metastases (*p*=0.3), bone metastases (*p*=0.002), liver metastases (*p*=0.0007), PD-L1 > 75% (*p*=0.46), white blood cells > 10,000 (*p*<0.003), neutrophil-to-lymphocyte ratio ≥ 4 (*p*<0.0001)

^cFactors (*p*-values) of overall survival in univariate analysis: gender (*p*=0.12), age ≥ 75 y (*p*=0.0002), smoker (*p*=0.056), weight loss ≥ 5% (*p*=0.014), performance status (*p*<0.0001), body mass index (*p*=0.7), corticosteroid treatment (*p*=0.051), antibiotic treatment (*p*=0.002), histology (*p*=0.004), brain metastases (*p*=0.3), bone metastases (*p*<0.0001), liver metastases (*p*=0.008), PD-L1 > 75% (*p*=0.51), white blood cells > 10,000 (*p*<0.0001), neutrophil-to-lymphocyte ratio ≥ 4 (*p*<0.0001)

Declarations

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by RD, LG, CC and CD. The first draft of the manuscript was written by RD, CC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding No funding was received for conducting this study.

Availability of data and material Datasets analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest L. Greillier reports grants, personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, Roche, Sanofi Aventis, Bristol-Myers Squibb, Merck Sharp & Dohme, Lilly, Novartis, Pfizer, Takeda, Bayer and Amgen, outside the submitted work. C. Chouaid reports grants, personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, Bristol-Myers Squibb, Merck Sharp & Dohme, Lilly, Novartis, Pfizer, Takeda, Bayer and Amgen, outside the submitted work. C. Decroisette reports personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim, Roche, Sanofi Aventis, Bristol-Myers Squibb, Merck Sharp & Dohme, Lilly, Novartis, Pfizer, Takeda, and Amgen, outside the submitted work. M. Pérol reports

personal fees and non-financial support from Roche, Eli Lilly, Pfizer, Boehringer Ingelheim, Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis, AstraZeneca, Takeda, Gritstone, Sanofi, GlaxoSmithKline, Amgen, Chugai, Illumina, Daiichi-Sankyo and Abbvie outside the submitted work. R. Descourt reports personal fees and non-financial support from AstraZeneca, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer, Takeda, and Chugai, outside the submitted work. C. Ricordel, J.B. Auliac, L. Falchero, R. Gervais, R. Veillon, S. Vieillot, F. Guisier, M. Marçq, G. Justeau, L. Bigay-Game, M. Bernardi, P. Fournel, H. Doubre, J. Pinsolle and K. Amrane report no conflict of interest.

Ethical approval The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. It was approved by a national independent Ethics Committee (2019-A02073-54, on December, 11, 2019).


Consent to participate Patients received written and oral information on the study and gave their consent to participate in the study and for the use of their medical data for research purposes.

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Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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