Three-Year Overall Survival of Patients with Advanced Non-Small-Cell Lung Cancers with ≥50% PD-L1 Expression Treated with First-Line Pembrolizumab Monotherapy in a Real-World Setting (ESCKEYP GFPC study)

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Summary: Outside clinical trials, few data are available on the impact of long-term first-line pembrolizumab in patients with advanced non-small-cell lung cancers (aNSCLCs) with ≥50% of tumor cells expressing programmed cell death protein-1 ligand (PD-L1). This French, multicenter study included consecutive aNSCLCs patients given first-line pembrolizumab alone between May 2017 (authorization date for this indication) and November 2019 (authorization date for pembrolizumab–chemotherapy combination). Information was collected from patients' medical files, with local evaluation of the response and progression-free survival (PFS). Overall survival (OS) was calculated from pembrolizumab onset using the Kaplan–Meier method. The analysis concerned 845 patients, managed in 33 centers: median age: 65 (range 59–72) years; 67.8% men; 78.1% Eastern Cooperative Oncology Group performance status (ECOG PS) 0/1; 38.9%/51.5%/6.6% active, ex- or never-smokers, respectively; 10.9%/16.8% taking or recently took corticosteroids/antibiotics; 69.6% non-squamous histology; 48.9% ≥75% PD-L1-positive; 20.8% had brain metastases at diagnosis. After median [95% CI] follow-up of 45 [44.1–45.9] months, respective median [95% CI] PFS and OS lasted 8.2 [6.9–9.2] and 22 [8.5–25.9] months; 3-year PFS and OS rates were 25.4% and 39.4%, respectively. Multivariate analysis retained never-smoker status, adenocarcinoma histology, ECOG PS ≥2 and neutrophil/lymphocyte ratio >4 as being significantly associated with shorter survival, but not brain metastases at diagnosis or <75% PD-L1 tumor-cell expression. These long-term results of pembrolizumab efficacy based on a nationwide "real-world" cohort reproduced those obtained in clinical trials.

Key Words: pembrolizumab, non-small-cell lung cancer, advanced stage, long-term survivor, real-world study

Introduction

Anti-programmed cell-death protein-1 or its ligand (PD1/PD-L1) immunotherapy has completely modified the management of patients with advanced non-small-cell lung cancer (aNSCLCs), especially for those with ≥50% of tumor cells expressing PD-L1. The phase 3 KEYNOTE 024 trial compared pembrolizumab monotherapy to doublet platin-based chemotherapy in such a population;[1,2] respective median progression-free survival (PFS) lasted 7.7, 95% confidence interval (CI) 6.1-10.2 and 5.5 (4.2-6.2) months, hazard ratio (HR) [95% CI]: 0.50 [0.37–0.68]; p<0.001. Respective median [95% CI] overall survival (OS) lasted 26.3 [18.3–40.4] and 13.4 (95% CI, 9.4–18) months (HR: 0.62 [0.48–0.81]. Kaplan–Meier estimated OS [95% CI] rates were 31.9% [24.5%–39.5%] and 16.3% [10.6%–23.0%], with estimated 3- and 5-year PFS rates, respectively, of 22.8% [16.3%–29.9%] and 12.8% [7.4–19.8] for pembrolizumab recipients, and 4.1% [1.3%–9.4%] and not assessable for the chemotherapy group[1,2]. Those results were obtained in a highly selected population that excluded patients with Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, with active or treated brain metastases or life expectancy <3 months. In addition, participating patients could not be taking >10 mg of corticosteroids/day at inclusion. For that trial, 1934 patients were screened, 500 (30.2%) had ≥50% PD-L1 expression but only 305/500 (61%) satisfied the criteria necessary for randomization. Among the 154 patients randomized to receive pembrolizumab, only 3.3% were never-smokers and 81.2% had non-squamous histology; their median age was 64.5 years.

Several analyses of real-world data obtained from less-selected aNSCLCs[3–7] confirmed the findings of the Keynote 024 trial. A French nationwide study evaluated the efficacy of pembrolizumab monotherapy given to 845 patients, 20% with brain metastases at diagnosis and >20% with ECOG PS = 2.[3] After median [95% CI] follow-up of 25.8 [24.8–26.7] months, PFS and OS lasted 8.2 [6.9–9.5] and 22.6 [18.5–27.4] months, respectively. Durations for patients with brain metastases and without, respectively, did not differ significantly: median PFS lasted 9.2 [5.6–15] and 8 [6.7–9.2] (P = 0.3) months, and median OS 29.5 [17.2–NR] and 22 [17.8–27.1] (p = 0.3) months. An Italian assessment of patients' with aNSCLCs expressing ≥50% PD-L1, also receiving real-world management, including 15.2% with ECOG PS ≥2 and 18.3% with brain metastases at diagnosis found PFS lasted 7.9 [6.9–9.5] months and

OS 17.2 [15.3–22.3] months.[4] According to the findings of those 2 studies, ECOG PS ≥2 was an independent factor associated with poorer OS.[3,4] That observation was echoed in other reports.[5–12] The results of a prospective, observational study on 40 patients with ECOG PS = 2 or ≥75 years old, with ≥1% PD-L1 expression on their aNSCLC cells showed that median [95% CI] OS on first-line pembrolizumab lasted 11.6 [1.4–NR] months for patients with ECOG PS = 2 and 11.6 [7.4–18.1] months for the elderly.[9] However, long-term, real-world efficacy data for pembrolizumab in this indication are scarcer.[12]

The objective of this study was to evaluate, at long term, the efficacy of pembrolizumab monotherapy in a real-world setting in patients with aNSCLC expressing ≥50% PD-L1.

Methods

ESCKEYP-trial methodology was published previously.[3] The main eligibility criteria were the following: treatment-naïve adults with histologically or cytologically confirmed aNSCLCs, ≥50% PD-L1 tumor-cell expression, negative for epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) mutations and with ≥1 measurable lesion(s). Patients with brain metastases could be included. Patients with an autoimmune disease contraindicating immunotherapy, active hepatitis B or C, or human immunodeficiency virus infection, or organ or bone-marrow transplant were excluded. In accordance with the first European authorization, 200 mg of pembrolizumab were administered intravenously every 3 weeks. Pembrolizumab was discontinued because of investigator-judged progressive disease or unacceptable toxicity. The study was conducted in accordance with the Declaration of Helsinki; it was approved by a national independent Ethics Committee (2019-A02073-54; December 11, 2019). Patients received written and oral information about the study, and gave their consent to participate in it and for the use of their medical data for research purposes.

The main information collected for the present analysis was: sociodemographic characteristics, disease history, smoking status, ECOG PS, NSCLC characteristics (histology, stage, metastatic sites at diagnosis, PD-L1 expression, mutations or rearrangements), taking corticosteroids (>10 mg/day for >10 days), recent antibiotic intake (for >10 days during the preceding weeks), tumor progression (new sites or existing sites) and leukocyte and lymphocyte counts. Tumor responses according to

RECIST 1.1 criteria were assessed locally.

OS was defined as the time—from the date of pembrolizumab onset to the date of any-cause death—determined at the date of last contact or cutoff date (January 18, 2021). PFS was defined as the time—from the date of pembrolizumab start to the date of first disease progression or any-cause death.

Univariate Cox models selected the most promising prognostic variables for OS and PFS (threshold $P = 0.20$). A multivariate Cox model was used to adjust for potential confounders. The multivariable analysis used 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 are reported, with $P < 0.05$ considered significant.

Statistical analyses were computed using SAS version 9.4 (SAS Institute. Inc., Cary, North Carolina, USA).

Results

Between May 2, 2017 (when pembrolizumab became available for this indication in France) and November 22, 2019 (when the pembrolizumab–chemotherapy combination was approved), 33 centers in France included 845 patients with aNSCLCs, whose tumor cells expressed ≥50% PD-L1 and who had received first-line pembrolizumab. Their median (range) age was 65 (59–72) years, a third were >70 years, two-thirds were men and three-quarters had ECOG PS = 0/1 (**Table 1**). Among them, almost 40% were active smokers, half were former-smokers and but only 6.6%never-smokers. aNSCLC histology was predominantly non-squamous (73.2%), with almost half expressing ≥75% PD-L1. At diagnosis, brain, bone and liver metastases were found, respectively, in 20.8%, 35.0% and 13.5% of the patients. In addition, about a tenth were taking corticosteroids at pembrolizumab onset or had recently taken antibiotics.

After median [95% CI] follow-up of 45 [44.1–45.9] months, median [95% CI] PFS and OS lasted 8.2 [6.9–9.2] and 22 [8.5–25.9] months; 3-year PFS and OS rates, respectively, were 25.4% and 39.4%.

Multivariate analyses retained never-smokers, taking corticosteroids and a neutrophil/lymphocyte (NLR) >4 as being independently associated with shorter PFS (**Table 2**), and never-smokers, NLR >4 and ECOG PS ≥2 as being significantly associated with shorter OS (**Table 3**). Surprisingly, neither brain metastases at diagnosis or a PD-L1–expression rate ≥75% impacted OS.

Discussion

This analysis of non-selected pembrolizumab-treated aNSCLC patients, 21.9% with ECOG PS 2, 30.4% squamous-cell histology and 20.8% brain metastases at diagnosis, showed respective 3-year PFS and OS rates of 25.4% and 39.4% after a median follow-up of 45 months.

Our long-term outcomes are similar to those of the Keynote 024 trial conducted on a highly selected population.[2] They also agree with recently published real-life findings.[10–12] According to a retrospective analysis of 2 American cohorts[10]—deidentified electronic health records (EHR cohort) and an enhanced manual chart review (spotlight cohort)—of adult patients, with ECOG PS = 0–1, stage-IV NSCLCs, ≥50% PD-L1–expression, no documented *EGFR*/*ALK*/proto-oncogene tyrosine-protein kinase-1 (*ROS1*) genomic anomaly, and who had received first-line pembrolizumab monotherapy, their respective median [95% CI] OS lasted 19.6 months [16.6–24.3] and 21.1 months [16.2–28.9]; 3-year OS rates were 36.2% and 38.2%. Another real-world examination of first-line pembrolizumab alone vs. pembrolizumab–chemotherapy combination enrolled 351 aNSCLC patients; that analysis found that, after median [95% CI] follow-up of 23.5 months, median OS and real-world PFS for pembrolizumab recipients (37% 75-years old, 52% women, 90% former or active smokers, 26% with brain metastases) lasted, respectively, 22.1 [18.3–30.3] and 11.5 [8.1–15.0] months.[6]

Authors of a Japanese study[11] on 300 patients (76.0% men, 26.6% ≥ 75 years and 7.0% with ECOG PS 2) observed that, for the 164 who received first-line pembrolizumab, median [95% CI] OS lasted 23.2 [18.4–27.9]) months. Their multivariate analysis retained ECOG PS = 2, squamous histology and corticosteroid use as significantly associated with shorter OS. The negative impact of ECOG PS = 2 was also found in an American study based on deidentified electronic medical record data.[12] After median follow-up of 34 months, median real-world time on first-line pembrolizumab monotherapy was 7.4 [6.3–8.1] months for the entire cohort but only 2.1 [1.4–2.8] months for the 237 patients with ECOG PS = 2.[12] The same impact was also observed in a multicenter Japanese study on 40 elderly patients (median age 78.5 years) and/or ECOG PS = 2 (40%);[9] the objective response rate (ORR) was 40.5% and the disease-control rate was 62%. After median [95% CI] follow-up of 9.5 [0.3–27.1] months, median PFS and OS for patients ≥75 years old were, respectively, 5.3 [2.9–9.4] and 11.6 [7.4–18.1] months, with respective durations for those with

ECOG PS = 2 of 4.4 [0.9–14.4] and 11.6 [1.4–NR] months.

According to our multivariate analysis, never-smoker status was associated with shorter survival. That finding is in agreement with some published studies. A retrospective study of 315 patients with aNSCLCs and PD-L1 tumor proportion score ≥50% conducted at 5 American academic medical centers compared ORRs, PFS and durations of response (DORs) between never-smokers (36, 11%), light smokers (<10-pack years, 42, 13%) and heavy smokers (237, 75%).[13] Although median PFS and DORs were shorter for never- and light smokers than heavy smokers (respectively, PFS 3.0 vs. 4.0 vs. 5.4 months; median DOR 6.9 vs. 10.8 vs. 17.8 months), they did not differ significantly according to smoking status.

Based on systematic review and meta-analysis of the data from 6497 aNSCLCs (5569 (85.7%) active/former smokers and 928 (14.3%) never-smokers) included in 12 randomized clinical trials, active/former smokers had pooled HRs [95% CI] for immune checkpoint inhibitors (ICIs) vs. chemotherapy for OS and PFS of 0.74 [0.67–0.81] and 0.72 [0.59–0.88], respectively; for never-smokers, the pooled values for the same analysis were not significant, respectively, 0.81 [0.60–1.08] and 0.92 [0.55–1.54].[14] We did not highlight any difference in efficacy linked to sex, whereas the data in the literature are discordant on this subject [15,16], and nor on the level of expression of PDL1. This last point had been suggested by various retrospective works.[17,18]

The neutrophil/lymphocyte ratio greater than or equal to 4 is a factor associated with poorer OS at 3 years in our study. This had been found by other authors, and summarized in a meta-analysis of 1225 patients from 14 retrospective studies[19],

In our cohort, the presence of a thromboembolic event was also linked to poorer survival. Nichetti et al. had also pointed this point, particularly in high (>50%) PD-L1 patients, raising the question of preventive treatment.[20]

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. 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.

To conclude, the long-term efficacy of pembrolizumab in our real-world nationwide cohort reproduced the results obtained in clinical trials.

Authors' contributions: All authors contributed to the study conception and design. R Descourt, L Greillier, C Chouaïd and C Decroisette: data collection and analysis. R Descourt and C Chouaïd wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and material: Datasets analyzed for this study are available from the corresponding author on reasonable request.

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Table 1. Demographics and Tumor Characteristics of 845 aNSCLC Patients

Characteristic	n (%)
Sex, M/F	573 (67.8)/272 (32.5)
Age, years	
<70	554 (65.6)
≥70	290 (36.4)
Smoker status	
Active	329 (38.9)
Former	435 (51.5)
Never	54 (6.6)
<5% body-weight loss (n = 722)	461 (63.9)
ECOG PS (n = 781)	
0–1	610 (78.1)
2–4	171 (21.9)
Taking corticosteroids	92 (10.9)
Recent antibiotic intake	142 (16.8)
No squamous histology	588 (69.6)
Metastases at diagnosis	
Brain	176 (20.8)
Bone	296 (35.0)
Liver	117 (13.5/13.8)
>75% PD-L1 tumor-cell expression	413 (48.9)
Gene mutation	
KRAS	234 (27.7)
BRAF	29 (3.4)

ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, Kirsten rat-sarcoma viral oncogene; *BRAF*, homolog-B v-*RAF* murine sarcoma viral oncogene; PD-L1, programmed cell-death protein-1 ligand; NLR, neutrophil/lymphocyte ratio

Table 2. Multivariate Analysis: Factors Associated with Progression-Free Survival Based on 565 aNSCLC Patients with Available Data

Factor	Test	Reference	HR [95% CI]	*P* value
Sex	F	M	0.93 [0.75–1.16]	0.52
Age, years	≥70	<70	1.16 [0.94–1.42]	0.18
Smoker	Never	Active/Former	1.48 [1.02–2.14]	0.04
Histology	Not ADC	ADC	1.06 [0.84–1.34]	0.61
ECOG PS	2–4	0–1	1.25 [0.99–1.59]	0.07
Taking corticosteroids	No	Yes	0.72 [0.53–0.98]	0.04
Recent antibiotic intake	No	Yes	0.82 [0.64–1.05]	0.12
Metastases at diagnosis				
Brain	Yes	No	1.13 [0.89–1.45]	0.32
Bone	Yes	No	1.13 [0.92–1.40]	0.25
Liver	Yes	No	1.26 [0.96–1.64]	0.09
>75% PD–L1 TC expression	Yes	No	0.86 [0.71–1.05]	0.13
KRAS	Yes	No	1.09 [0.81–1.36]	0.55
BRAF	Yes	No	0.86 [0.48–1.55]	0.62
Thrombosis	Yes	No	1.31 [1.00–1.70]	0.05
Neutrophil/lymphocyte ratio	≥4	<4	1.46 [1.17–1.81]	0.001
Leukocyte (/mm^3)	>10	≤10	0.97 [0.78–1.20]	0.75

ADC, adenocarcinoma ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, Kirsten rat-sarcoma viral oncogene; *BRAF*, homolog-B v-*RAF* murine sarcoma viral oncogene; PD-L1, programmed cell-death protein-1 ligand; TC, tumor cell.

Table 3. Multivariate Analysis: Factors Associated with Overall Survival Based on 565 aNSCLC Patients with Available Data

Factor	Test	Reference	HR [95% CI]	*P* value
Sex	F	M	0.87 [0.68–1.11]	0.27
Age, years	≥70	<70	1.29 [0.97–1.55]	0.08
Smoker status				
Smoker	No	Active/former	1.55 [1.04–2.31]	0.03
Histology	Not ADC	ADC	1.34 [1.04–1.72]	0.02
ECOG PS	2–4	0–1	1.51 [1.17–1.94]	0.001
Taking corticosteroids	No	Yes	0.91 [0.64–1.29]	0.59
Recent antibiotic intake	No	Yes	0.79 [0.61–1.03]	0.08
Metastases at diagnosis				
Brain	Yes	No	1.24 0.95–1.62]	0.12
Bone	Yes	No	1.23 [0.98–1.54]	0.08
Liver	Yes	No	1.12 [0.84–1.49]	0.44
>75% PD–L1 TC expression	Yes	No	0.82 [0.66–1.01]	0.07
Gene mutation				
KRAS	Yes	No	1.15 [0.89–1.50]	0.29
BRAF	Yes	No	0.99 [0.54–1.83]	0.98
Thrombosis	Yes	No	1.35 [1.02–1.80]	0.04
Neutrophil/lymphocyte ratio	≥4	<4	1.70 [1.32–2.19]	<0.0001
Leukocyte, ((/mm^3)	>10	≤10	1.10 [0.87–1.40]	0.42

ADC, adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; *KRAS*, Kirsten rat-sarcoma viral oncogene; *BRAF*, homolog-B v-*RAF* murine sarcoma viral oncogene; PD-L1, programmed cell-death protein-1 ligand; TC, tumor cell.