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ORIGINAL ARTICLE

Clinicopathologic correlates of first-line pembrolizumab effectiveness in patients with advanced NSCLC and a PD-L1 expression of ≥ 50%

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Abstract

Background Single-agent pembrolizumab represents the standard first-line option for metastatic non-small-cell lung cancer (NSCLC) patients with a PD-L1 (programmed death-ligand 1) expression of ≥ 50%.

Methods We conducted a multicenter retrospective study aimed at evaluating the clinicopathologic correlates of pembrolizumab effectiveness in patients with treatment-naïve NSCLC and a PD-L1 expression of ≥ 50%.

Results One thousand and twenty-six consecutive patients were included. The objective response rate (ORR) was 44.5% (95% CI 40.2–49.1), while the median progression free survival (PFS) and overall survival (OS) were 7.9 months (95% CI 6.9–9.5; 599 events) and 17.2 months (95% CI 15.3–22.3; 598 censored patients), respectively. ECOG-PS ≥ 2 ($p < 0.0001$) and bone metastases ($p = 0.0003$) were confirmed to be independent predictors of a worse ORR. Former smokers ($p = 0.0002$), but not current smokers ($p = 0.0532$) were confirmed to have a significantly prolonged PFS compared to never smokers at multivariate analysis. ECOG-PS ($p < 0.0001$), bone metastases ($p < 0.0001$) and liver metastases ($p < 0.0001$) were also confirmed to be independent predictors of a worse PFS. Previous palliative RT was significantly related to a shortened OS ($p = 0.0104$), while previous non-palliative RT was significantly related to a prolonged OS ($p = 0.0033$). Former smokers ($p = 0.0131$), but not current smokers ($p = 0.3433$) were confirmed to have a significantly prolonged OS compared to never smokers. ECOG-PS ($p < 0.0001$), bone metastases ($p < 0.0001$) and liver metastases ($p < 0.0001$) were also confirmed to be independent predictors of a shortened OS. A PD-L1 expression of ≥ 90%, as assessed by recursive partitioning, was associated with significantly higher ORR ($p = 0.0204$), and longer and OS ($p = 0.0346$) at multivariable analysis.

Conclusion Pembrolizumab was effective in a large cohort of NSCLC patients treated outside of clinical trials. Questions regarding the effectiveness in clinical subgroups, such as patients with poorer PS and with liver/bone metastases, still remain to be addressed. We confirmed that the absence of tobacco exposure, and the presence of bone and liver metastasis are associated with worse clinical outcomes to pembrolizumab. Increasing levels of PD-L1 expression may help identifying a subset of patients who derive a greater benefit from pembrolizumab monotherapy.

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Extended author information available on the last page of the article

Keywords Smoking status · PD-L1 · Radiotherapy · Bone metastases · Liver metastases · Performance status

Introduction

Based on the results of the Keynote-024 trial, single-agent pembrolizumab has become the standard of care for the first-line treatment of metastatic non-small-cell lung-cancer (NSCLC) patients with a tumor proportion score (TPS) of PD-L1 (programmed death-ligand 1) ≥ 50%, lacking *EGFR* mutation and *ALK* rearrangement [1–3]. However, clinical trials data often do not apply to real life populations. Recent real-world experiences with pembrolizumab monotherapy showed inferior progression free survival (PFS) and overall survival (OS), compared to the Keynote-024 experimental arm [4–6], as patients with poor performance status are usually excluded form clinical trials. For instance, a retrospective multicenter study of pembrolizumab monotherapy in NSCLC patients, with PD-L1 TPS ≥ 50% and Eastern Cooperative Performance Status (ECOG-PS) of 2, has revealed poor clinical outcomes to treatment, particularly in those patients whose poor PS was related to a high disease burden [7].

More recently, the Keynote-189 and Keynote-407 trials have shown that the addition of pembrolizumab to a platinum-based chemotherapy, improved clinical outcomes to placebo, in both the adenocarcinoma and squamous NSCLC, regardless of PD-L1 expression [8, 9]. However, the subgroups analyses according to PD-L1 expression levels, confirmed that the efficacy was higher among patients with PD-L1 TPS ≥ 50% [8, 9].

The effectiveness of pembrolizumab monotherapy in patients treated outside of clinical trials is still in need of further investigation. To address this need, we conducted this multicenter study, aimed at evaluating clinicopathologic correlates of pembrolizumab monotherapy effectiveness in NSCLC patients with a PD-L1 expression of ≥ 50%, in a large real-life cohort.

Materials and methods

Study design

This multicenter retrospective study evaluated metastatic NSCLC patients with PD-L1 TPS of ≥ 50%, consecutively treated with first-line pembrolizumab monotherapy, from January 2017 to October 2019, at 34 institutions (Supplementary file 3). Considering that in clinical practice baseline *EGFR* and *ALK* status might sometimes not be available (due to insufficiency of the tissue specimen for instance), their assessment was not mandatory for the inclusion in this study. The sample size was estimated according to the expected enrollment of the participating centers.

The primary aim of this analysis was to describe clinical outcome of metastatic NSCLC patients receiving pembrolizumab monotherapy in clinical practice. The measured clinical outcomes were objective response rate (ORR), median PFS and median OS. Secondly, to evaluate whether some baseline clinical factors affected clinical outcomes, univariate and multivariate analyses of ORR, PFS and OS were performed (using a stepwise selection of covariates, with an entry significance level of 0.05).

Each patient underwent a baseline full-body computed tomography scan; baseline brain magnetic resonance imaging was performed according to the participating centers local clinical practice and to the respective national guidelines. The patients were assessed with radiological imaging in clinical practice, with a frequency ranging from 12 to 16 weeks, according to the monitoring requirements for high-cost drugs of the respective national drug regulatory agencies (e.g., the online monitoring dashboard of the "Agenzia Italiana del Farmaco" requires a disease assessment at least every 16 weeks; available at: https://servizionline.aifa.gov.it/). RECIST (v. 1.1) criteria were used [10], and a subsequent confirming imaging was recommended. However, treatment beyond disease progression was allowed when clinically indicated. ORR was defined as the portion of patients experiencing an objective response (complete or partial response) as best response to immunotherapy. PFS was defined as the time from treatment's start to disease progression or death whichever occurred first; OS as the time from the beginning of treatment to death.

The analyzed clinical factors in the univariate/multivariate analyses were:

- PD-L1 expression (< vs. ≥ the computed optimal cutoff for);
- Smoking status (never smokers vs. former smokers [≥ 1 year]/current smokers) [11];
- Age (< 70 vs. ≥ 70 years old) [12];
- Sex (male vs. female);
- ECOG-PS (0–1 vs. ≥ 2);
- Histology (squamous vs. non-squamous [including mixed hisologies]);
- Central nervous system (CNS) metastases (yes vs. no);
- Bone metastases (yes vs. no);
- Liver metastases (yes vs. no);
- Corticosteroids administration (dose equivalent or higher to 10 mg prednisone per day) within the 30 days before treatment commencement (named baseline steroids) (yes vs. no);

- Radiation therapy (RT) within the previous 6 months the immunotherapy commencement (no RT vs. non-palliative RT [e.g., single-fraction stereotactic radiosurgery, stereotactic RT to a metastatic site]/palliative RT [e.g., whole brain radiation therapy, and any other treatment administered for symptoms palliation and/or without a curative intent]) [13];

In order to properly weighing the role of baseline clinical factors, and to find appropriate covariates to be used in the multivariate analyses, the correlations between baseline steroids, previous RT and ECOG-PS/disease burden (CNS metastases, bone metastases and liver metastases) were evaluated with the χ^2 test and χ^2 test for trend [14]. In case of significant associations, baseline steroids and previous RT were not used in the multivariate analyses, in order to avoid collinearity problems [15–17]. The χ^2 test and χ^2 test for trend were also used to compare ORR among subgroups [14]; logistic regression was used for the multivariate analysis of ORR, and adjusted odds ratios (ORs) with 95% confidence intervals (95% CI) were computed [18]. Median PFS and median OS were evaluated using the Kaplan–Meier method [19]. Median period of follow-up was computed according to the reverse Kaplan–Meier method [20]. Cox proportional hazards regression was used to evaluate predictor variables and estimate the hazard ratios (HRs) for PFS and OS [21]. Data cutoff period was February 2020. All statistical analyses were performed using MedCalc Statistical Software version 18.11.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019). Recursive partitioning was performed using the R package rpart (R version 3.6.2).

PD-L1 expression evaluation and *EGFR/ALK* ancillary analysis

PD-L1 expression was reported as a percentage of tumor cells with positive membranous staining, using a variety of immunohistochemical antibodies and platforms according to local institutional clinical practice (including the 22C3, SP263, E1L3N and 28-8 antibodies). Being the TPS evaluation validated only with the 22C3 [22], we referred to "PD-L1 expression" in our study. To determine whether among patients with a PD-L1 expression ranging from 50 to 100%, increasing levels of PD-L1 were predictive of pembrolizumab effectiveness, a ROC curve analyses of ORR was performed [23]. As complementary analysis, to identify an optimal grouping according to PD-L1 expression, with respect to ORR, PFS and OS, a recursive partitioning algorithm was used, using the Rpart function in R, as previously done [4, 24]. As in clinical practice, the PD-L1 expression of some patients was reported as "$\geq$50%", and not as discrete value, we included in this analysis only the patients with data availability regarding the absolute estimated value of PD-L1.

Considering that, for PD-L1 estimation, the concordance between metachronous and synchronous formalin-fixed paraffin-embedded (FFPE) tissue and the reliability of non-FFPE samples such as liquid-based cytology are still matter of debate [25–27], a one-way analysis of variance of PD-L1 expression according to the tissue specimen type was performed [28]. Tissue specimens were categorized in surgical samples (both metachronous and synchronous), tissue biopsies and cytological specimens. A one-way analysis of variance of PD-L1 expression according to the smoking status was also performed.

An ancillary analysis of clinical outcomes according to the *EGFR* and *ALK* molecular status was also performed, classifying patients as mutant, unknown and wild type (wt) accordingly. χ^2 test was used for the ORR analysis, while the log-rank test was used for the PFS and OS analyses [14, 29].

Results

Patients characteristics

One thousand and twenty-six consecutive metastatic NSCLC patients, with PD-L1 expression $\geq$ 50%, were included. Patient characteristics, *EGFR* and *ALK* molecular status and RT details are summarized in Table 1 in Supplementary file 1. As reported in Table 2 in Supplementary file 2, baseline steroids and previous RT were significantly related with CNS metastases ($p < 0.0001$ and $p < 0.0001$, respectively) and bone metastases ($p < 0.0001$ and $p = 0.0389$, respectively). Baseline steroids were also significantly related to liver metastases ($p = 0.0225$). No significant associations were found between previous RT and liver metastases. Significant associations were also found between previous RT ($p = 0.0187$), baseline steroids ($p < 0.0001$) and ECOG-PS. Among the 628 patients (61.2%) who discontinued first-line pembrolizumab at the data cutoff, only 200 patients (31.8%) underwent a second-line disease-oriented treatment, while among the 599 patients (58.4%) who experienced disease progression, 428 patients (71.5%) were deceased. Among the 428 deceased patients, 332 (77.6%) did not received a second-line disease-oriented treatment.

PD-L1 analysis

The ROC curve analysis for PD-L1 expression of ORR revealed a weak predictive performance within the range 50–100% (AUC = 0.55 [95% CI 0.51–0.59], $p = 0.0303$) (Fig. 1a). The absolute value of PD-L1 expression was available for 731 patients (71.2%) and the median value was 70%. The mean PD-L1 expression for cytological specimens, surgical samples and tissue biopsies were 69% (standard deviation [sd]: 14), 68% (sd: 13) and 73% (sd: 13), respectively;

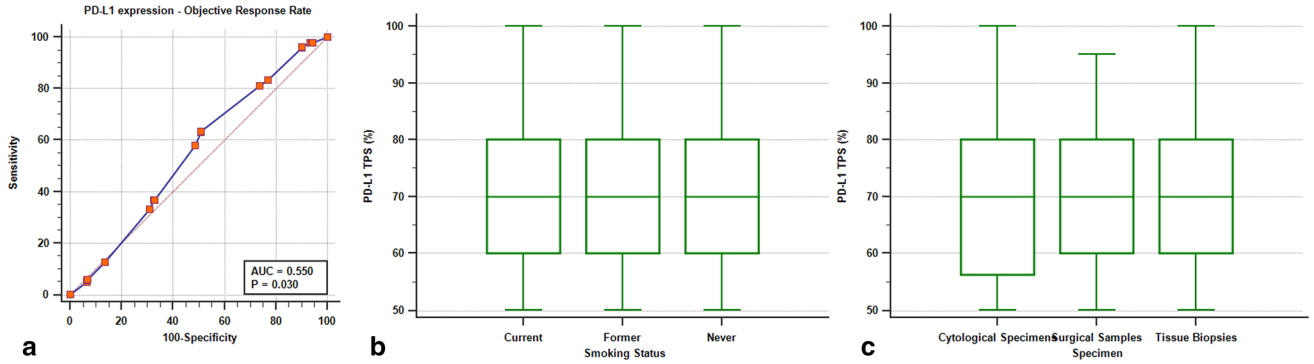

Fig. 1 ROC curve analysis according to PD-L1 expression of ORR (**a**). Multiple comparison graphs of PD-L1 TPS according to the smoking status (**b**) and to the tissue specimen (**c**)

the analysis of variance showed that the tissue specimen type significantly affected the PD-L1 expression evaluation [$F(2668) = 3.19$, $p = 0.042$]. The mean PD-L1 expression of current smokers, former smokers and never smokers were 73% (sd: 14), 72% (sd: 14) and 70% (sd: 11), respectively; smoking status significantly affected the PD-L1 expression estimation [$F(2728) = 0.92$, $p = 0.008$]. Figure 1b, c reported the respective multiple comparison graph. The recursive partitioning algorithm, however, identified a primary split at a PD-L1 expression level of 91.9% ($p = 0.019$) and 92% ($p = 0.022$) for ORR and OS, respectively. No significant splits were found regarding PFS. We therefore used the optimal grouping cutoff of 90% for clinical outcome analysis.

Clinical outcomes analysis

In the entire study population, the ORR was 44.5% (95% CI 40.2–49.1% [899 evaluable patients for ORR]). Table 1 summarizes the univariate and multivariate analysis of ORR. The use of baseline steroids was significantly related to inferior ORR at the univariate analysis (29.9% vs. 48.7%, $p < 0.0001$). A PD-L1 expression of < 90%, ECOG-PS ≥ 2 and baseline bone metastases were confirmed to be independent predictors of a worse ORR.

At the data cutoff, the median follow-up was 14.6 months (95% CI 13.5–15.6). The median PFS and median OS of the study population were 7.9 months (95% CI 6.9–9.5; 599 events) and 17.2 months (95% CI 15.3–22.3; 598 censored patients), respectively (Fig. 2a, b).

The median PFS of patients with PD-L1 expression < 90% was 6.9 months (95% CI 5.8–8.4), which was significantly shorter compared the PFS of 12.0 (95% CI 6.3–19.4) months of patients with a PD-L1 expression of ≥ 90% (unadjusted HR = 1.29 [95% CI 1.01–1.66], $p = 0.0487$) (Fig. 3a). PD-L1 expression was not confirmed an independent predictor for PFS at the multivariate analysis (Table 2). At the univariate analysis, baseline steroids and previous palliative RT were significantly related to a shortened PFS (Table 2). Only former smokers were confirmed to have a significantly prolonged PFS compared to never smoker patients at the multivariate analysis (Table 2). ECOG-PS, bone metastases and liver metastases were also confirmed to be independent predictors of shortened PFS (Table 2). The median PFS of current smokers, former smokers and never smokers was 7.2 months (95% CI 5.7–10.2; 205 events), 9.5 months (95% CI 8.01–11.6; 316 events) and 4.1 months (95% CI 3.3–5.7; 78 events), respectively (Fig. 3c). Median PFS of patients who received previous palliative RT, non-palliative RT and patients who did not received previous RT was 4.8 months (95% CI 3.3–6.9; 115 events), 17.4 months (95% CI 6.2–20.1; 19 events) and 8.4 months (95% CI 7.3–10.2; 465 events), respectively (Fig. 3e).

The median OS was also significantly shorter among patients with PD-L1 expression of < 90% as compared to those with a PD-L1 expression of ≥ 90% (14.7 months [95% CI 11.1–17.3] months versus not reached, HR = 1.51 [95% CI 1.10–2.07], $p = 0.0093$) (Fig. 3b). A PD-L1 expression of < 90% was confirmed an independent predictor for shorter OS at the multivariate analysis (Table 3). At the univariate analysis, baseline steroids and previous palliative RT were significantly related to a shortened OS. On the other hand, previous non-palliative RT was significantly related to a prolonged OS. At the multivariate analysis, former smokers were confirmed to have a significantly prolonged OS compared to never smoker patients, in contrast to what reported for current smokers. Even in this case, ECOG-PS, bone metastases and liver metastases were confirmed to be independent predictors of a shortened OS (Table 3). Median OS of current smokers, former smokers and never smokers was 16.9 months (95% CI 13.1–21.2; 199 censored patients), 19.9 months (95% CI 16.8–27.5; 350 censored patients) and 9.4 months (95% CI 6.9–15.0; 49 censored patients), respectively (Fig. 3d). Median OS of patients who received previous palliative RT, non-palliative RT and patients who did not

Table 1 Univariate and multivariate analysis of ORR

Variable (comparator)	Univariate analysis			Multivariate			
	Response/ratio	ORR (95% CI)	*p* value	Coeff.	St. Err.	*p* value	Adjusted OR (95% CI)
Overall	400/899	44.5 (40.2–49.1)	–	–	–	–	–
PD-L1 expression[a]			0.0347	−0.0137	0.0059	0.0204	0.98 (0.97–0.99)
< 90%	224/524	42.7 (37.3–48.7)					
≥ 90%	67/126	53.2 (41.2–67.5)					
Smoking status							
(Never smoker)	32/92	34.8 (23.8–49.1)					
Former smoker	239/508	47.0 (42.2–53.4)	0.0791	–	–	–	–
Current smoker	129/299	43.1 (36.0–51.2)	0.5948[b]				
Sex			0.9545	–	–	–	–
Male	263/592	44.4 (39.2–50.1)					
Female	137/307	44.6 (37.4–52.7)					
Age			0.6023	–	–	–	–
Elderly	209/461	45.3 (39.4–51.9)					
Non-elderly	191/438	43.6 (37.6–50.2)					
Histology			0.5997	–	–	–	–
Non-squamous	301/684	44.0 (39.1–49.2)					
Squamous	99/215	46.0 (37.4–56.1)					
ECOG PS			< 0.0001	0.9580	0.2080	< 0.0001	2.60 (1.73–3.91)
≥ 2	36/143	25.2 (17.6–34.8)					
0–1	364/756	48.1 (43.3–53.3)					
CNS metastases			0.6060	–	–	–	–
Yes	70/164	42.7 (33.2–53.9)					
No	330/735	44.9 (40.1–50.1)					
Bone metastases			< 0.0001	0.5626	0.1544	0.0003	1.75 (1.29–2.37)
Yes	92/272	33.8 (27.2–41.4)					
No	308/627	49.1 (43.8–54.9)					
Liver metastases			0.0195	0.3110	0.2033	0.1260	1.36 (0.91–2.03)
Yes	46/131	35.1 (25.7–46.8)					
No	354/768	46.1 (41.4–51.1)					
Baseline steroids			< 0.0001	–	–	–	–
Yes	61/204	29.9 (22.8–38.4)					
No	339/695	48.7 (43.7–54.2)					
Previous RT							
(No)	321/710	45.2 (40.4–50.4)					
Non-palliative intent	23/42	54.8 (34.7–82.1)	0.1120	–	–	–	–
Palliative intent	56/147	38.1 (28.8–49.4)	0.1939[b]				

[a]Available for 650 patients, not used in the multivariate analysis of the overall study population; ECOG-PS (≥ 2 vs. 0–1), bone metastases (yes vs. no) and liver metastases (yes vs. no) were used as adjusting factors for PD-L1 analysis

[b]χ^2 test for trend

received previous RT was 13.4 months (95% CI 8.6–21.2; 82 censored patients), not reached (38 censored patients) and 17.2 months (95% CI 15.2–19.9; 478 censored patients), respectively (Fig. 3f). Figure 4 reported the Kaplan–Meier survival curves of PFS and OS according to baseline CNS, bone and liver metastases.

The median OS of *EGFR* wt, unknown and mutant patients was 18.4 months (95% CI 15.7–22.8, 552 censored patients), 15.2 months (95% CI 8.7–17.3, 42 censored patients) and 4.6 months (95% CI 0.5–11.3, 4 censored patients), respectively ($p = 0.3706$). The median PFS of *EGFR* wt, unknown and mutant patients was 8.0 months (95% CI 6.9–9.7, 552 events), 9.8 months (95% CI 4.6–26.2, 38 events) and 1.8 months (95% CI 0.4–4.1, 9 events), respectively ($p = 0.0150$). The ORR of *EGFR* wt, unknown and mutant patients was 41.1% (95% CI 36.3–46.3), 39.1%

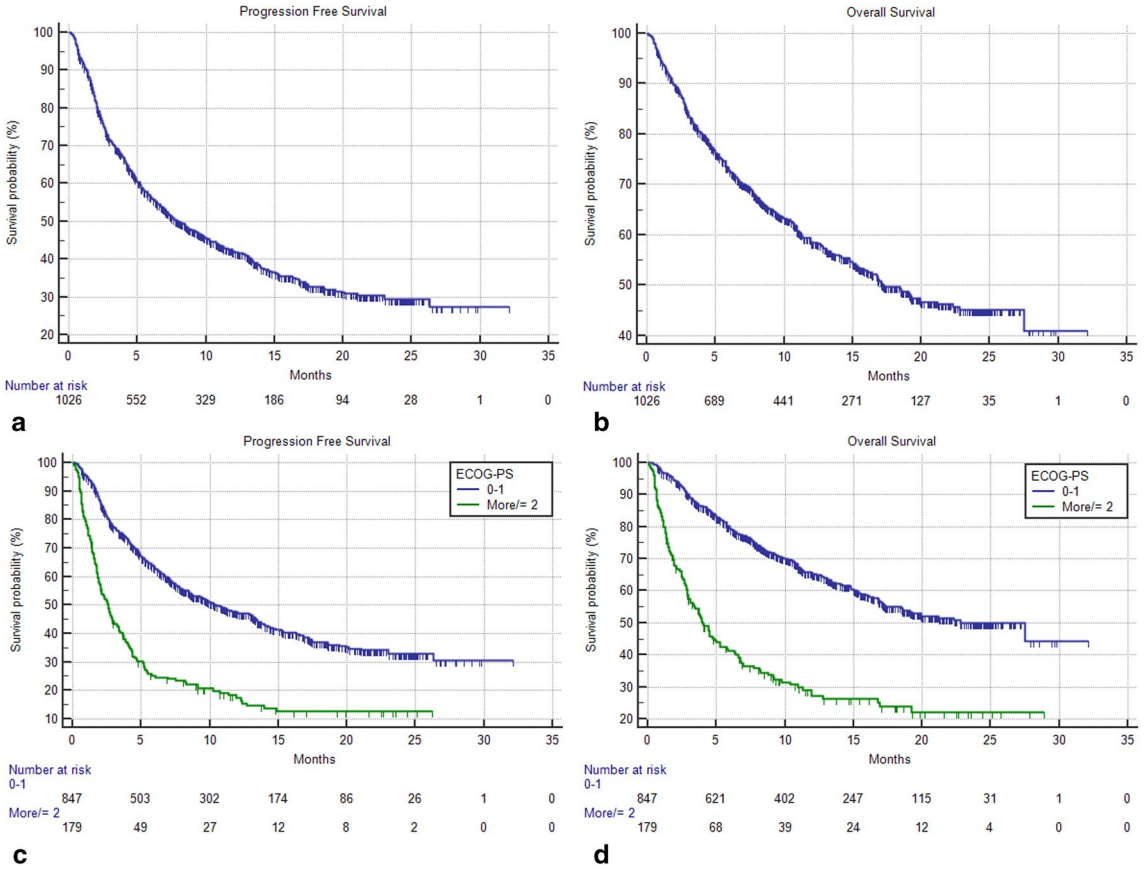

Fig. 2 Kaplan–Meier survival curves. **a** Median PFS in the overall study population was 9 months (95% CI 6.9–9.5; 599 events); **b** median OS in the overall study population was 17.2 months (95% CI 15.3–22.3; 598 censored patients); **c** median PFS of patient with ECOG-PS 0–1 and ECOG-PS ≥ 2 was 10.4 months (95% CI 8.7–13.0; 453 events) and 2.6 months (95% CI 1.9–3.30; 146 events), respectively; **d** median OS of patient with ECOG-PS 0–1 and ECOG-PS ≥ 2 was 22.8 months (95% CI 18.6–27.5; 543 censored patients) and 3.9 months (95% CI 2.9–5.3; 55 censored patients)

(95% CI 25.2–57.6) and 50% (95% CI 13.6–128.0), respectively ($p = 0.8308$). The median OS of *ALK* wt and unknown patients was 18.4 months (95% CI 15.7–22.8, 550 censored patients) and 14.8 months (95% CI 8.5–17.3, 48 censored patients), respectively ($p = 0.5033$). The median PFS of *ALK* wt and unknown patients was 7.9 months (95% CI 6.8–9.5, 552 events) and 8.7 months (95% CI 4.6–26.2, 47 events), respectively ($p = 0.9232$). The ORR of *ALK* wt and unknow patients was 41.3% (95% CI 36.5–46.4) and 38.9% (95% CI 25.8–56.2), respectively ($p = 0.6962$).

Discussion

In this multicenter real-life study, we reported an ORR of 44.5%, a median PFS of 7.9 months and a median OS of 17.2 months (median follow-up of 14.6 months) to first-line pembrolizumab among patients with newly diagnosed advanced NSCLC and a PD-L1 expression of ≥ 50%. While the ORR in our study is similar to the ORR of 44.8% reported in the Keynote 024 study, the median PFS and OS observed in our population are shorter, which is compatible with the fair representation of patients with a PS of ≥ 2 and untreated brain metastasis, which is common in real-life clinical practice [1–3]. The subgroup analysis of patients with PD-L1 TPS ≥ 50% receiving pembrolizumab (compared to standard platinum-based chemotherapy) within the Keynote-042 trial, otherwise reported an ORR of 39%, a PFS of 7.1 months and a median OS of 20.0 months (median follow-up of 12.8 months), which were slightly worse compared to our study population in terms of ORR [30]. Our effectiveness results are also comparable to recent real-life studies [4–6]; however, to properly evaluate the comparability with clinical trials, we must consider some several key differences in the study population, beside the significant differences regarding the reported follow-up. Consistently with other recent retrospective analysis [4–6], also in our study patients with an ECOG-PS ≥ 2 (15.4%) were included, differently from the Keynote-024 trial [1].

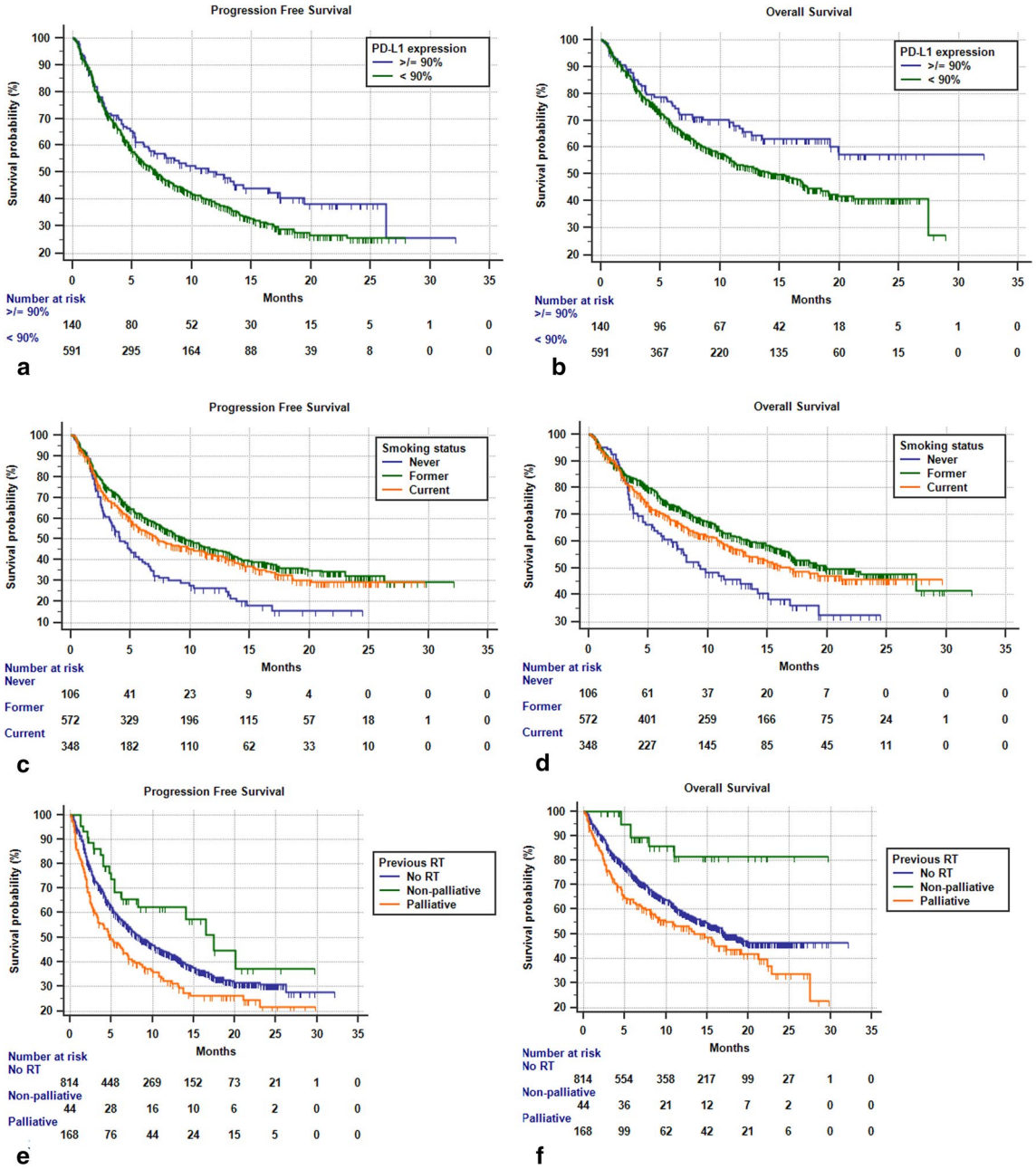

Fig. 3 Kaplan–Meier survival curves of PFS (**a**) and OS (**b**) according to the computed PD-L1 TPS optimal cutoffs. Kaplan–Meier survival curves according to the smoking status of PFS (**c**) and OS (**d**), and according to previous RT of PFS (**e**) and OS (**f**)

Other differences in the study populations regard the exclusion from the Keynote-024 of oncogene-addicted patients, patients with untreated baseline CNS metastases and patients requiring high-dose steroids overall (both for cancer-related and unrelated indications). Data regarding baseline bone and liver metastases, which were already known to negatively affect immunotherapy clinical outcomes in NSCLC patients [31, 32], were not provided within the Keynote-024 trial population. However, our results confirmed that both these metastatic sites were independently related to worse ORR (only bone metastases), PFS and OS, also in the first-line setting of patients with PD-L1 expression $\geq 50\%$ treated with pembrolizumab monotherapy. The proportion of the deceased patients who did not received 2nd-line treatments (77.6%), and of the patients who discontinued pembrolizumab receiving a second-line treatment (31.8%), reflects that the study population has been treated outside of clinical trials. Differently, 49.1% of the patients who discontinued pembrolizumab in

Table 2 Univariate and multivariate analyses of PFS

Variable (comparator)	Progression-free survival	
	Univariate analysis	Multivariate analysis
	HR (95% CI); *p* value	HR (95% CI); *p* value
PD-L1 expression[a]		
< 90% versus ≥ 90%	1.29 (1.01–1.66); $p = 0.0487$	1.17 (0.91–1.510; $p = 0.2155$
Smoking status		
(Never smoker)		
Former smoker	0.57 (0.44–0.73); $p < 0.0001$	0.62 (0.48–0.79); $p = 0.0002$
Current smoker	0.65 (0.50–0.85); $p = 0.0016$	0.77 (0.59–1.01); $p = 0.0532$
Sex		
Male versus female	0.97 (0.82–1.15); $p = 0.7326$	–
Age		
Elderly versus non-elderly	1.01 (0.85–1.17); $p = 0.9983$	–
Histology		
Non-sq. versus squamous	1.01 (0.83–1.20); $p = 0.9805$	–
ECOG PS		
≥ 2 versus 0–1	2.65 (2.20–3.21); $p < 0.0001$	2.48 (2.05–3.01); $p < 0.0001$
CNS metastases		
Yes versus no	1.32 (1.07–1.61); $p = 0.0076$	1.22 (0.99–1.49); $p = 0.0529$
Bone metastases		
Yes versus no	1.75 (1.48–2.06); $p < 0.0001$	1.46 (1.23–1.74); $p < 0.0001$
Liver metastases		
Yes versus No	1.97 (1.62–2.41); $p < 0.0001$	1.69 (1.38–2.08); $p < 0.0001$
Baseline steroids		
Yes versus no	2.05 (1.72–2.45); $p < 0.0001$	–
Previous RT		
(No)		
Non-palliative intent	0.66 (0.42–1.05); $p = 0.0827$	–
Palliative intent	1.39 (1.14–1.71); $p = 0.0013$	

[a]Available for 731 patients, not used in the multivariate analysis of the overall study population; ECOG-PS (≥ 2 vs. 0–1), CNS metastases (yes vs. no), bone metastases (yes vs. no) and liver metastases (yes vs. no) were used as adjusting factors for PD-L1 analysis

the experimental arm of the Keynote-024 trial received a further disease-oriented treatment [2].

Overall, our results reflect an effectiveness profile lower than expected. Poorer clinical conditions of patients outside clinical trials might explain these findings. ECOG-PS was indeed confirmed to be an independent predictor of worsened clinical outcome at each multivariate analysis. Of note, patients with an ECOG-PS of 2 are known not to be the best candidates for single-agent immunotherapy [7]. Interestingly, Facchinetti et al. reported that patients with a PS 2 due to comorbidities had significantly better outcomes compared to patients with a disease burden-induced PS 2 [7]. From this perspective, in clinical practice, there could be a not negligible amount of patients with high PD-L1 expression and disease burden-related poor clinical conditions, who might benefit from a front-line chemo-immunotherapy combination, rather than a single-agent PD-1 inhibitor. Recent network meta-analyses revealed that in NSCLC patients with a PD-L1 TPS of ≥ 50%, the addition of pembrolizumab to first-line chemotherapy might have beneficial results in terms of ORR and PFS, compared to single-agent pembrolizumab, apparently without any OS advantage [33, 34]. However, these data were derived from clinical trials, and their reproducibility in clinical practice have yet to be evaluated.

The ROC analysis for PD-L1 TPS of ORR of the Keynote-001 trial population reported a good diagnostic ability within the range 1–100%, in identifying NSCLC patients to be treated with single-agent pembrolizumab, establishing 50% as PD-L1 TPS cutoff (Youden's J statistics between 45 and 50%) [35]. On the other hand, the ROC curve analysis for ORR did not identify a strong cutoff of PD-L1 expression within the range 50–100%, to discriminate responders versus non-responders. Importantly, when used the recursive partition algorithm, we were able to identify the same cutoff of 90% recently reported by Aguilar et al. [4], that significantly discriminated patients who were more likely to have

Table 3 Univariate and multivariate analyses of OS

Variable (comparator)	Overall survival	
	Univariate analysis	Multivariate analysis
	HR (95% CI); *p* value	HR (95% CI); *p* value
PD-L1 expression[a]		
< 90% versus ≥ 90%	1.51 (1.10–2.07); $p = 0.0093$	1.41 (1.02–1.92); $p = 0.0346$
Smoking status		
(Never smoker)		
Former smoker	0.61 (0.46–0.82); $p = 0.0013$	0.69 (0.51–0.92); $p = 0.0131$
Current smoker	0.72 (0.53–0.98); $p = 0.0355$	0.86 (0.63–1.17); $p = 0.3433$
Sex		
Male versus female	1.08 (0.88–1.32); $p = 0.4408$	–
Age		
Elderly versus non-elderly	1.04 (0.86–1.26); $p = 0.6923$	–
Histology		
Non-sq. versus squamous	1.03 (0.82–1.29); $p = 0.8051$	–
ECOG PS		
≥ 2 versus 0–1	3.18 (2.58–3.92); $p < 0.0001$	3.01 (2.43–3.72); $p < 0.0001$
CNS metastases		
Yes versus no	1.28 (1.01–1.63); $p = 0.0472$	1.16 (0.91–1.47); $p = 0.2316$
Bone metastases		
Yes versus no	1.82 (1.50–2.21); $p < 0.0001$	1.53 (1.25–1.88); $p < 0.0001$
Liver metastases		
Yes versus no	1.96 (1.55–2.45); $p < 0.0001$	1.66 (1.31–2.10); $p < 0.0001$
Baseline steroids		
Yes versus no	2.43 (1.99–2.96); $p < 0.0001$	–
Previous RT		
(No)		
Non-palliative intent	0.29 (0.13–0.67); $p = 0.0033$	–
Palliative intent	1.37 (1.07–1.72); $p = 0.0104$	

[a]Available for 731 patients, not used in the multivariate analysis of the overall study population; ECOG-PS (≥ 2 vs. 0–1), CNS metastases (yes vs. no), bone metastases (yes vs. no) and liver metastases (yes vs. no) were used as adjusting factors for PD-L1 analysis

improved ORR, PFS and OS to pembrolizumab monotherapy, at univariate analysis. Of note, the multivariate analysis confirmed the 90% PD-L1 expression an independent predictor for improved ORR and OS.

The smoking status was already found to be related to clinical outcome of NSCLC patients receiving immunotherapy [36]. A recent study of patients with PD-L1 TPS ≥ 50%, treated with several immune checkpoint inhibitors across multiple lines, revealed a significantly improved ORR and a non-statistically significant trend toward an improved PFS/duration of response for heavy/light smokers compared to never smokers [11]. The authors identified a higher median tumor mutational burden (TMB) among heavy smokers as the potential mechanisms driving the difference in the clinical outcomes. Consistently, we confirmed the significant association between improved PFS and OS and smoking in the first-line setting of PD-L1 high NSCLC patients. Interestingly, only former smokers were confirmed to have significantly longer PFS and OS at the multivariate analysis. Moreover, the net values of ORR, PFS and OS of former smokers were numerically higher compared to current smokers, and the respective adjusted OR/HRs (for the comparison with never smokers) were concordantly lower. This might be related to the global/functional benefit of smoking cessation, which might has positively affected the clinical outcomes, without impairing the TMB gain-related to the smoking habit.

Our efficactiveness results according to previous RT raise some questions which still need to be addressed. Palliative-RT was significantly related to shortened PFS and OS, while non-palliative RT was significantly related to a prolonged OS. We also noticed that the HRs for palliative and non-palliative RT were opposite in both the PFS and OS analyses. Recent evidences suggested the positive role of adding stereotactic RT preceding pembrolizumab in NSCLC patients [37], and a recent study have shown a

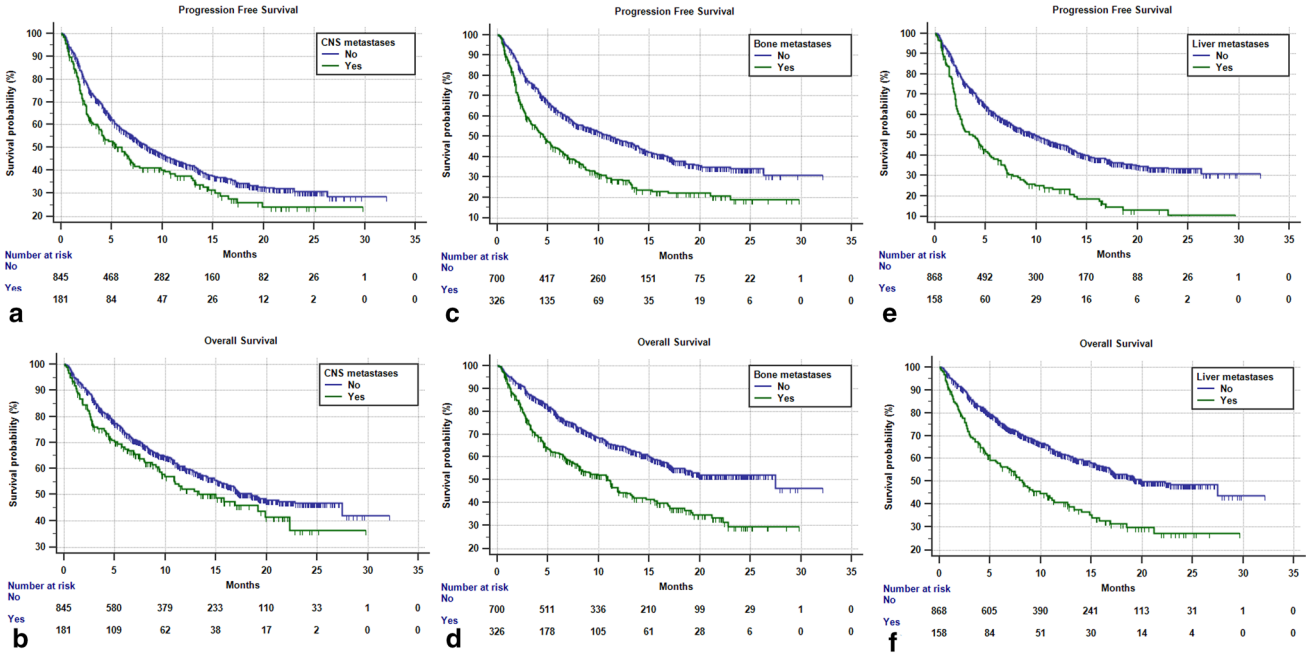

Fig. 4 Kaplan–Meier survival curves according to baseline CNS, bone and liver metastases. Median PFS of patients with and without baseline CNS metastases was 5.9 months (95% CI 3.9–7.1; 115 events) and 8.6 months (95% CI 7.5–10.2; 484 events), respectively (S1A). Median OS of patients with and without baseline CNS metastases was 15.0 months (95% CI 9.6–22.3; 99 censored patients) and 18.5 months (95% CI 16.1–27.5; 499 censored patients), respectively (S1B). Median PFS of patients with and without baseline bone metastases was 4.5 months (95% CI 3.4–5.7; 224 events) and 11.1 months (95% CI 9.2–13.4; 375 events), respectively (S1C). Median OS of patients with and without baseline bone metastases was 10.9 months (95% CI 8.1–12.8; 155 censored patients) and 27.5 months (95% CI 18.5–27.5; 443 censored patients), respectively (S1D). Median PFS of patients with and without baseline liver metastases was 3.7 months (95% CI 2.5–4.9; 125 events) and 9.8 months (95% CI 8.0–11.3; 474 events), respectively (S1E). Median OS of patients with and without baseline liver metastases was 8.2 months (95% CI 5.7–11.1; 62 censored patients) and 19.9 months (17.1–27.5; 536 censored patients), respectively (S1F)

negative shift of the balance between favorable and unfavorable immune-modulating effects of RT according to its intent (palliative vs. non-palliative) [13]. However, while interpreting these results, we must take into account the significant correlation between previous RT and both CNS and bone metastases. In particular, bone metastases resulted to be a key negative prognostic factor and patients receiving palliative RT had the highest incidence of bone metastases (68.5%), while patients who received non-palliative RT the lowest (6.8%). On the other hand, the association with non-palliative RT might explain the absence of a significant prognostic role of CNS metastases. The significant association with the disease burden and worse ECOG-PS is also likely to explain the association between corticosteroid administration and impaired immunotherapy effectiveness. Accordingly, a recent study has reported that baseline steroids administered for non-cancer-related indication were not related to worse outcomes in NSCLC patients receiving PD-1 checkpoint inhibitors [38]. Despite the data lack availability regarding the steroids indication in our data set, we can assume that in most cases, they were administered for symptoms palliation.

Being a real-world study, *EGFR* and *ALK* molecular status might not have been available at the time of pembrolizumab commencement. This might partially explain the small amount of *EGFR* mutant patients included in the study population. The samples size according to the *EGFR*/*ALK* status do not allow any conclusive considerations, nevertheless, the better clinical outcomes reported for wt patients are aligned to what is already known regarding clinical efficacy of single-agent checkpoint inhibitors in oncogene addicted patients [39]. Among the limitations of the present study, we must cite the retrospective design, which exposes to selection biases, and the lack of centralized review (histological and imaging). Moreover, the radiological assessment performed according to the respective clinical practice of the participating centers, might had affected the analysis.

Conclusion

In this study, we confirmed the effectiveness of first-line single-agent pembrolizumab in metastatic NSCLC patients with a PD-L1 expression of ≥ 50% in a large real-life cohort, and confirmed the significant association of the smoking status and non-palliative RT, with improved clinical outcomes, establishing them as key features to be investigated in prospective clinical trials. Questions regarding the effectiveness in clinical subgroups, such as patients with poorer PS and with liver/bone metastases, still remain to be addressed. In particular, whether adding chemotherapy to pembrolizumab in these categories or not, in case of a PD-L1 expression of ≥ 50%, remains to be determined.

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Availability of data and materials The datasets used during the present study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest Dr. Alessio Cortellini received speaker fees and grant consultancies by Astrazeneca, MSD, BMS, Roche, Novartis, Istituto Gentili, Astellas and Ipsen. Dr. Emilio Bria received speaker and travel fees from MSD, Astra-Zeneca, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis and Roche. Dr. Emilio Bria received grant consultancies by Roche and Pfizer. Dr. Marcello Tiseo received speaker fees and grant consultancies by Astrazeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Takeda and Pierre Fabre. Dr. Alessandro Morabito received speaker fees by Astra, Roche, BMS, MSD, Boehringer, Pfizer, Takeda. Dr. Francesca Mazzoni received grant consultancies by MSD and Takeda. Dr. Raffaele Gisti received speaker fees and grant consultancies by Astrazeneca and Roche. Dr. Francesco Passiglia received grant consultancies by MSD and Astrazeneca. Dr. Paolo Bironzo received grant consultancies by Astrazeneca and Boehringer-Ingelheim. Dr. Alex Friedlaender received grant consultancies by Roche, Pfizer, Astellas and BMS. Dr. Alfredo Addeo received grant consultancies by Takeda, MSD, BMJ, Astrazeneca, Roche and Pfizer. Dr. Rita Chiari received speaker fees by BMS, MSD, Takeda, Pfizer, Roche and Astrazeneca. Dr. Carlo Genova received speaker fees/grant consultancies by Astrazeneca, BMS, Boehringer-Ingelheim, Roche and MSD.

Consent for publication Not applicable.

Ethical approval All patients provided written, informed consent to treatment with immunotherapy. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was approved by the respective local ethical committees on human experimentation of each institution, after previous approval by the coordinating center (Comitato Etico per le provice di L'Aquila e Teramo, verbale N.15 del 28 Novembre 2019).

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