ACTA ONCOLOGICA
2020, VOL. 59, NO. 9, 1058–1063
https://doi.org/10.1080/0284186X.2020.1781249

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ORIGINAL ARTICLE

Impact of performance status on non-small-cell lung cancer patients with a PD-L1 tumour proportion score ≥50% treated with front-line pembrolizumab

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ABSTRACT

Objectives: We retrospectively analysed patients with advanced non-small-cell lung cancer (NSCLC) harbouring high PD-L1 expression (>50%) and treated with front-line pembrolizumab, comparing outcomes of patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 to those with PS 0-1.

Methods: Data were collected by 16 participating centres. All patients with NSCLC and high PD-L1, treated with first-line pembrolizumab were included. We collected medical data from patient files, pathology and laboratory reports. Patient characteristics, comorbidities, PS, and tumour characteristics were reported. Overall survival (OS), progression-free survival (PFS) and response rate (RR) were calculated.

Results: 302 patients were included, 246 with PS 0-1, 56 with PS 2. RR was 72% among patients with PS 0-1 compared to 45% with PS2 (odds ratio (OR) 0.31 (95% CI: 0.17–0.57), $p < .001$). Median PFS was 2.6 months (95% CI: 1.9–5.1) among patients with PS2 and 11.3 months (95% CI: 8.5–14.4) among those with PS 0-1. Median OS was 7.8 months (95% CI: 2.5–10.7) in the PS2 group, not reached in the PS 0-1 group. PS 2 remained predictive of poor outcomes in multivariate analysis.

Conclusion: PS 2 is a strong independent predictor of poor response and survival in NSCLC patients with high PD-L1, treated with front-line pembrolizumab. Prospective randomised trials comparing immunotherapy to chemotherapy in this population would be welcome.

ARTICLE HISTORY
Received 28 March 2020
Accepted 4 June 2020

Introduction

Representing 80–85% of all cases of lung cancer, non-small-cell lung cancer (NSCLC) is one of the leading causes of cancer-related deaths worldwide [1]. Over the course of the last decade, the prognosis improved drastically, in large part thanks to the advent of immune checkpoint inhibitors (ICIs) [2,3].

Approximately 35% of NSCLC patients [4,5] have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2. While it is a known negative prognostic factor for survival, its predictive significance with ICIs is less clear. Instinctively, as chemotherapy improves outcomes in patients with PS2, one would want to extend the benefit to less toxic ICIs, and not undertreat these patients [6]. Unfortunately, data on the efficacy of ICIs in patients with PS2 are scant, stemming mainly from small trials, subgroup analyses or expanded access registries [7–9]. The recent PePS2 trial [10], Checkmate 171[9] and Checkmate 817 [11] also provide insight into this topic, without giving definitive answers.

The front-line efficacy of the anti-programmed death 1 (PD-1) antibody, pembrolizumab, was proven first in NSCLC patients harbouring tumours with programmed death ligand-1 (PD-L1) expression over 50% [12], then in all PD-L1 expressing NSCLC patients, though the survival benefit is driven by high PD-L1 expressors [13]. The three year follow-up in the Keynote 024 trial shows a significant overall survival (OS) benefit, with a median OS of 26.3 months in the pembrolizumab group compared to 14.2 months in the chemotherapy group [14]. These results were recently mirrored with atezolizumab, an anti-PD-L1

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antibody [15]. Unfortunately, none of the trials include patients with a PS of 2.

To date, despite the lack of data showing benefit in patients with PS 2, international guidelines [16,17] recommend pembrolizumab in first-line for patients with PD-L1 $\geq$ 50%. On the other hand, due to the limited data, pembrolizumab is not approved for this indication in some countries [18].

In our real world multi-centric study, we described the clinical outcomes of patients with metastatic NSCLC harbouring high PD-L1 expression (>50%) who received with first-line pembrolizumab with a focus on the potential different impact of having an ECOG PS2 compared to PS 0-1.

Patients and methods

In this observational retrospective study, data were collected by 16 participating centres throughout Europe. The trial was approved by local ethics committees and living patients included signed a general consent form or trial specific consent form, depending on the centre.

All patients with advanced NSCLC, unamenable to curative treatment, with PD-L1 expression $\geq$50%, and treated with at least one cycle of first-line pembrolizumab (200 mg flat dose every 3 weeks), were eligible. Data were collected from the introduction of first-line pembrolizumab, starting in December 2016, to January 2020. PD-L1 testing was performed by immunohistochemistry with either the 22C3, SP263, 28-8, as these have been shown to be equivalent, and central reanalysis was not performed [19].

We collected medical data from patient files, pathology reports and laboratory reports for all patients.

Patient and treatment characteristics collected included date of birth, comorbidities graded using the simplified comorbidity score (SCS) [20], PS evaluated according to the ECOG criteria, smoking status, start date of immunotherapy, duration of treatment, reason for discontinuation and immune-related adverse events. The use of local therapy for central nervous system lesions at diagnosis, as well as the use of subsequent treatments after pembrolizumab were also reported.

Tumour characteristics included the histology, PD-L1 evaluation by tumour proportion score (TPS), evaluated by immunohistochemistry, staging according to the AJCC TNM 8 criteria, the presence of brain metastases, as well as of concurrent oncogenic driver mutations excluding *KRAS* [21,22] (Table 1).

Endpoints

The primary objective was to assess overall survival (OS) of patients with ECOG PS 2 compared to patients with ECOG PS 0-1 treated with first line pembrolizumab in the same centres. OS was calculated from the date of the first cycle of pembrolizumab to death from any cause.

Secondary endpoints were:

1. Response Rate (RR) according to the response Evaluation Criteria for Solid Tumours (RECIST) 1.1 or clinically, when indicated. 2) Progression free survival (PFS) that was calculated from the date of the first cycle of pembrolizumab to progression or death from any cause.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 criteria.

Statistical analysis

Patient characteristics were described overall and by performance status (PS 0-1 and PS 2). Qualitative data were

Table 1. Patient characteristics.

	All ($n = 302$)	PS 0-1 ($n = 246$)	PS 2 ($n = 56$)	p Value
Gender				
Female	106 (35%)	86 (35%)	20 (36%)	1
Male	196 (65%)	160 (65%)	36 (64%)	
Age (years)				
Mean	67.4	67.0	69.3	.118[a]
Baseline autoimmune disease				
No	286 (95%)	232 (94%)	54 (96%)	.745[b]
Yes	16 (5%)	14 (6%)	2 (4%)	
Histology				
Non-squamous	227 (75%)	185 (75%)	42 (75%)	1
Squamous	75 (25%)	61 (25%)	14 (25%)	
Smoking history				
No	31 (10%)	24 (10%)	7 (12%)	.714
Yes	271 (90%)	222 (90%)	49 (88%)	
Simplified comorbidity score				
0–9	252 (83%)	212 (86%)	40 (71%)	.013
>9	50 (17%)	34 (14%)	16 (29%)	
Brain metastases at baseline				
No	243 (80%)	203 (83%)	40 (71%)	.089
Yes	59 (20%)	43 (17%)	16 (29%)	
Brain radiotherapy/surgery				
No	258 (85%)	216 (88%)	42 (75%)	.025
Yes	44 (15%)	30 (12%)	14 (25%)	
PD-L1 level				
50–89%	244 (81%)	196 (80%)	48 (86%)	.397
>90%	58 (19%)	50 (20%)	8 (14%)	

Data are n (%) unless otherwise specified; p values are from chi-squared test except: [a]Welch Student test and [b]Fisher exact test.

described as frequencies and percentages, quantitative data as median. Overall survival and progression free survival were estimated according to the Kaplan–Meier method and were compared between groups (PS 0-1 versus PS 2) using the log-rank test. Adjusted effect of a PS 2 on OS and PFS was estimated using Cox regression models including gender, brain metastases and SCS (0–9 vs. >9). Separate baselines were used for age (<70 versus >70) and smoking status (never versus current/former) to address non-proportional hazards. RR was compared between PS groups using a logistical regression model. The adjusted PS effect on RR was estimated using a multivariable logistic regression model including gender, age, smoking status, brain metastases and SCS.

All analyses were performed at a two-sided alpha level of 0.05 for statistical significance. All analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria. www.R-project.org/).

Results

Overall, 305 patients were identified, of whom 302 were eligible. 246 patients had a PS of 0-1, and 56 a PS of 2. Three patients with PS3 were excluded. None had targetable EGFR or ALK alterations, 1 had a ROS1 translocation. The median age was 69 with a range from 19 to 87 years old. There were 196 males and 106 females. Ninety percent were active or former smokers, 20% had brain lesions at diagnosis and 15% received brain radiotherapy or surgery. The majority of patients had non-squamous histology, only 25% had squamous cell carcinoma. All PD-L1 tests were performed before treatment, and 81% of patients had a TPS of 50–89%, while 19% were above 90%. Seventeen percent of patients had more important comorbidities, representing a score >9 on the SCS.

Outcomes

At the time of data-analysis, the median follow-up was 8.6 months. RR was 72% among patients with PS0-1 compared to 45% in the PS2 group, resulting in an OR of 0.31 (95% CI: 0.17–0.57). Median PFS was 2.6 months (95% CI: 1.9–5.1) among patients with PS2 and 11.3 months (95% CI: 8.5–14.4) among those with PS0-1. Median OS was 7.8 months (95% CI: 2.5–10.7) in the PS2 group and not reached in the PS0-1 group (Figure 1). While the median OS could not be estimated in the group of patients with PS0-1, the 24 months survival is estimated to be superior to 50%.

There was no difference in second-line treatment use among groups, with 25% of patients receiving subsequent treatments ($p = .345$).

Multivariate analysis

In multivariable analyses adjusting for gender, age, smoking status, presence of brain metastases, and comorbidities, PS remained a strong risk factor for survival and response, with a hazard ratio (HR) of 3.8 (95% CI 2.5–5.8) for OS, 3.0 (95% CI 2.0–4.3) for PFS and an odds ratio of 0.30 (95% CI 0.16–0.56) for response (Table 2).

Toxicity

In terms of immune-related adverse events, there were 9% of grade 1–2 events among patients with PS0-1 and 9% in the PS2 group. For more severe adverse events, the incidence of grade 3–4 toxicity was 7% in the PS0-1 group and 9% in the PS2 group, but the difference was not statistically significant ($p = .164$). There was no difference in treatment discontinuation between groups, with 11% among patients with PS0-1 and 12% with PS2 ($p = .857$).

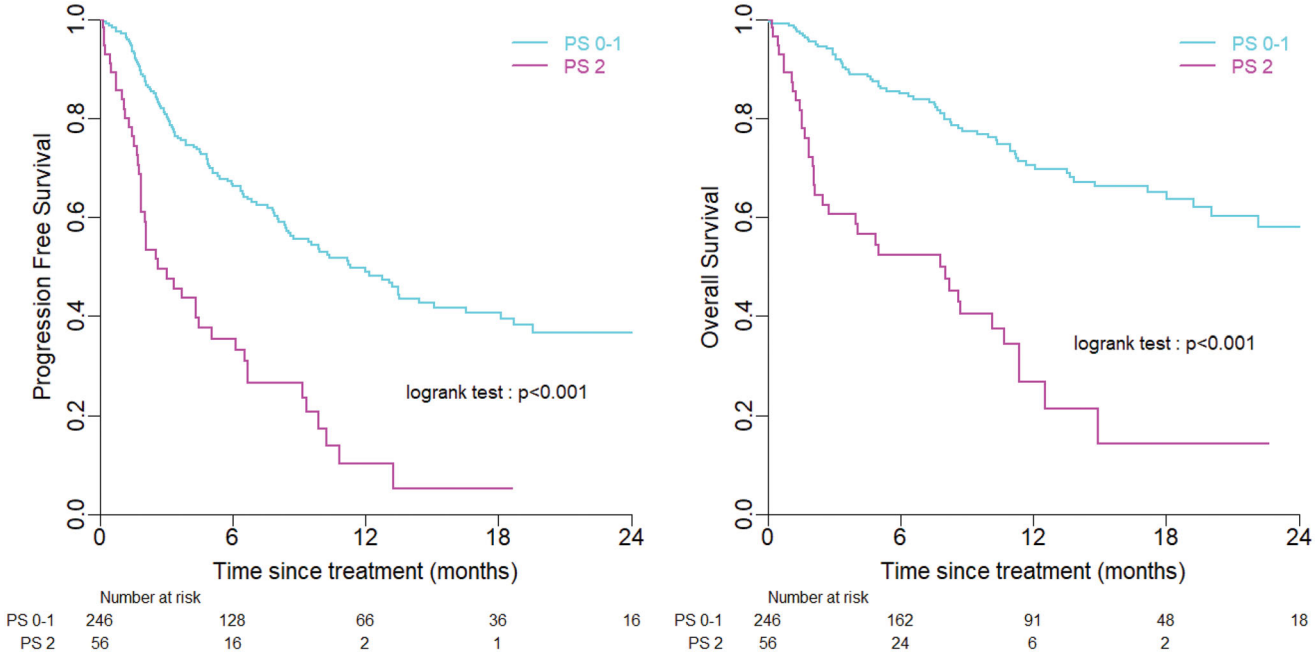

Figure 1. Progression-free and overall survival by performance status.

Table 2. Multivariable analyses.

Variable	*n*	Progression Free Survival[a] Hazard ratio (95% CI)	Overall Survival[a] Hazard ratio (95% CI)	Overall response Odds ratio (95% CI)
Performance status				
0-1	246	1	1	1
2	56	3.0 (2.0 to 4.3)	3.8 (2.5 to 5.8)	0.30 (0.16 to 0.56)
Gender				
Female	106	1	1	1
Male	196	1.0 (0.74 to 1.4)	1.3 (0.84 to 2.0)	0.93 (0.54 to 1.6)
Brain metastases				
No	243	1	1	1
Yes	59	1.4 (0.91 to 2.0)	1.7 (1.1 to 2.7)	0.64 (0.35 to 1.2)
Comorbidity (SCS)				
0–9	252	1	1	1
>9	50	0.97 (0.62 to 1.5)	1.3 (0.76 to 2.2)	0.80 (0.40 to 1.6)
Smoking status				
Never	31	–	–	1
Current/former	271	–	–	1.4 (0.61 to 3.2)
Age				
<70	168	–	–	1
≥70	134	–	–	2.1 (1.2 to 3.6)

[a]Separate baseline were used for age (<70 vs. ≥70) and smoking status to address non-proportional hazards.

Discussion

Patients in daily practice and clinical trials often represent divergent populations. Guidelines do not capture this nuance and in order to allow for a greater therapeutic arsenal, results are often extrapolated and generalised to real-world situations. While the vast majority of ICI trials in first line have shown benefit in patients with PS0-1, patients with ECOG PS2 have been dramatically underrepresented making it quite difficult to ascertain the real benefit of ICIs in this patient population. As roughly 35% of advanced NSCLC patients have an ECOG PS of 2, this represents a major therapeutic challenge. These patients are known to have a worse prognosis than fitter patients. Having said that, it remains imperative to properly manage these cases. Chemotherapy has been shown to have a potential OS benefit and improve quality of life in this setting [23,24].

Some real world data about the role of ICIs in patients with a PS of 2 come from the Expanded Access Programme (EAP) for nivolumab, another anti-PD-1 antibody. The French EAP enrolled 92 patients with PS2 receiving second-line therapy. In this setting, the median OS was only 3.6 months [8]. In the Italian EAP[7], of 1959 patients, 7% had a PS of 2. Again, PS2 was identified as an independent risk factor for lower OS. Similarly, in the phase III/IV single arm TAIL trial evaluating atezolizumab after one or more prior lines of treatment, the cohort of patients with a PS of 2 had dismal survival outcomes, with a median OS of 3.5 months [25].

As in the recent PePS2 trial, Checkmate 171 and Checkmate 817, we see that some patients with PS2 do appear to benefit from checkpoint inhibitors [9,26]. The PePS2 trial prospectively collected safety and efficacy outcomes on 60 NSCLC patients with PS2 treated with single agent pembrolizumab [10]. The study population was heterogeneous, including front-line and pre-treated patients. Nonetheless, it showed an acceptable toxicity profile and 33% durable clinical benefit, defined as stability or better at 18 weeks. The major limitation is the absence of a control arm and lack of overall survival data.

The Checkmate 817 trial evaluated the role of combined nivolumab and ipilimumab, an anti-CTLA4, in special populations of NSCLC patients, including those with PS2 [26]. While the treatment-related adverse events were not increased compared to patients with a PS of 0-1, the efficacy was lower among patients with PS2, with a 19% overall response rate (ORR) and 3.6 months median progression-free survival (PFS), compared to a 36% and 5.8 months, respectively, among fitter patients.

Similarly, the phase II Checkmate 171 trial evaluated the role of nivolumab in previously treated squamous cell carcinoma [9]. With its broad eligibility criteria, it included a cohort of 103 patients with PS2. The toxicity profile and response were comparable regardless of PS, but the OS among patients with PS2 was 5.2 months, while it was 10.0 months in the overall study population.

The question remains whether these patients fare better than those treated with the hitherto standard, chemotherapy. As no study has evaluated this and none is ongoing comparing these treatment arms, we descriptively compared our results to those found in historical chemotherapy trials in NSCLC patients with a PS of 2. For example, in the phase III trial comparing single-agent pemetrexed to carboplatin and pemetrexed in patients with advanced NSCLC and a PS of 2, the median PFS was 2.8 and 5.8 months and median OS 5.3 and 9.3 months for single-agent and doublet chemotherapy, respectively [24].

In our study there was a 45% RR among patients with PS2, lower than the 72% found in the PS0-1 group. In spite of the RR, patients with PS2 had a median PFS of 2.9 months and OS of 7.8 months, reinforcing the importance of the PS and suggesting a lower benefit within the PS2 group compared to historical data with doublet platinum-based chemotherapy [27].

To put things in perspective, the results are a far cry from the results seen in Keynote 024[12]. In this registration trial for advanced NSCLC with high PD-L1 expression, including only patients with PS of 0-1, the median OS was 30 months and PFS 10.3 [14]. These results appear to mirror ours in the fit patient cohort.

One could surmise that the poor outcomes in our PS2 cohort were due to the comorbidities of these patients, who had a higher SCS than patients in the PS0-1 group. However, this variable did not appear to be associated with poor survival, and upon multivariate analysis, PS2 remained an independent predictor of poor survival and response. Our results mirror those found in the literature [28].

Our study has some limitations. The first one is its retrospective observational nature, with inherent flaws that come with that design. There is a possible selection bias, and there was no independent verification of the PS of each patient. As all treatments were performed on an outpatient basis though, it decreases the risk of underestimating poor performance, as patients with a PS of 3–4 are likely hospitalised. Furthermore, it was not a randomised trial including a standard chemotherapy control arm, so we cannot say whether having a PS of 2 is only predictive or prognostic or even both. However, the similarity between our data and published data on front-line pembrolizumab in patients with a PS of 0-1 supports the validity of our results.

Conclusion

In conclusion, our data suggest that PS2 is an independent predictor of poor survival compared to PS0-1 in patients with advanced NSCLC and PD-L1 $\geq$ 50% treated with first-line pembrolizumab, even after adjusting for comorbidities.

While PS assessment is subjective, it remains a quick, easy and clinically relevant tool. In daily practice, our results could serve as a reminder to evaluate therapeutic choices cautiously for each patient, especially those with a PS of 2.

In our study, PS2 is predictive of poorer response and shorter survival compared to PS 0-1. As this was not a chemotherapy comparator arm, we are unable to comment about the prognostic value of PS2. Prospective randomised trials comparing immunotherapy to doublet platinum-based chemotherapy in this population are warranted.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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