Article

The Efficacy of First-Line Pembrolizumab Monotherapy in Patients with Metastatic NSCLC Aged ≥70 Years with High PD-L1 (TPS ≥ 50%) Expression: A Multicenter Real-World Study

Filip Marković [1,*] , Maximilian Hochmair [2,3] , Nino Müser [4], Hannah Fabikan [3], Vania Mikaela Rodriguez [3], Urska Janzic [5,6] , Mihailo Stjepanović [1,7] and Milica Kontić [1,7,*]

1   Clinic for Pulmonology, University Clinical Center of Serbia, 11000 Belgrade, Serbia;
    mihailo.stjepanovic@kcs.ac.rs
2   Department of Respiratory and Critical Care Medicine, Clinic Floridsdorf, Vienna Healthcare Group,
    1130 Vienna, Austria; maximilian.hochmair@gesundheitsverbund.at
3   Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, Clinic Floridsdorf,
    1210 Vienna, Austria; hannah.fabikan@extern.gesundheitsverbund.at (H.F.);
    vaniamikaela.rodriguez@extern.gesundheitsverbund.at (V.M.R.)
4   Karl Landsteiner Institute of Lung Research and Pulmonary Oncology, 2nd Department of Internal Medicine
    with Pulmonology, Klinik Ottakring, Vienna Healthcare Group, 1210 Vienna, Austria;
    nino.mueser@gesundheitsverbund.at
5   Medical Oncology Unit, University Clinic Golnik, 4204 Golnik, Slovenia; urska.janzic@klinika-golnik.si
6   Medical Faculty, University of Ljubljana, 1000 Ljubljana, Slovenia
7   School of Medicine, University of Belgrade, 11000 Belgrade, Serbia
*   Correspondence: flp.mark@gmail.com (F.M.); milicakontic@yahoo.com (M.K.)

Simple Summary

This real-world study assessed the effectiveness of first-line pembrolizumab monotherapy in patients with metastatic non-oncogene-addicted NSCLC and PD-L1 TPS ≥ 50%, comparing those aged ≥70 years to younger patients. Results showed no significant differences in outcomes—objective response rate, time on treatment (ToT), and overall survival (OS)—between the two age groups. In older patients, a history of smoking and good performance status (ECOG PS 0–1) were associated with better outcomes. Poor ECOG PS (≥2) was linked to shorter ToT and OS, regardless of age. Older patients were less likely to receive second-line therapy due to comorbidities and functional decline. These findings highlight the importance of performance status over chronological age in predicting benefit from immunotherapy and support pembrolizumab monotherapy as an effective first-line option for older patients with good functional status.

Abstract

Introduction: Elderly patients with metastatic non-small-cell lung cancer (NSCLC) are underrepresented in clinical trials evaluating immune checkpoint inhibitors (ICIs). This study assesses the efficacy of first-line pembrolizumab monotherapy in patients with metastatic NSCLC aged ≥70 years with a programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) ≥ 50%. **Materials and Methods:** We retrospectively analyzed 381 patients with metastatic NSCLC without oncogenic driver mutations treated with pembrolizumab monotherapy between 2017 and 2023 at three academic centers in Central and Southeastern Europe. Clinical outcomes, including median time on treatment (mToT) and overall survival (mOS), were compared between patients aged ≥70 and <70 years. **Results:** Of 381 patients, 149 (39.1%) were aged ≥70. No significant differences in mToT (12.7 vs. 14.3 months; $p = 0.125$) or mOS (18.2 vs. 27.4 months; $p = 0.124$) were observed between older and younger groups. Good ECOG PS (0–1) was independently associated

with longer mToT and mOS in older patients. Additionally, a history of smoking was linked to improved outcomes compared to never-smokers, suggesting potential immunogenic effects. Older patients were significantly less likely to receive second-line therapy after progression ($p = 0.04$). **Conclusions:** First-line pembrolizumab monotherapy is effective across all age groups and provides similar treatment efficacy in patients with metastatic NSCLC and a PD-L1 TPS $\geq$ 50%. Patients older than 70 with a smoking history and ECOG PS 0–1 derive the most benefit from this treatment modality. The adaptation of this treatment strategy for elderly patients is especially important, since only a minority of them are capable of receiving second-line therapy.

Keywords: non-small-cell lung cancer; pembrolizumab; elderly; PD-L1; smoking; real-world data

1. Introduction

Lung cancer remains a significant global health challenge, as it is the most frequently diagnosed cancer and the leading cause of cancer-related mortality worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancer cases [2].

Data from the Surveillance, Epidemiology, and End Results (SEER) program (2017–2021) reveal that the highest incidence occurs in individuals aged 65 to 74 years, with 35.6% of new cases [3]. Additionally, 36.6% of cases occur in patients aged 75 or older according to data from the United States [3]. Moreover, the median age of death for patients with lung cancer is 73 years, underscoring the disproportionate burden of this disease on the elderly population.

Despite the high prevalence of NSCLC in patients aged 70 years or older, elderly individuals remain underrepresented in clinical trials, including those evaluating immunotherapy [4]. This discrepancy exists despite the promising advancements offered by immune checkpoint inhibitors (ICIs), which have revolutionized the treatment landscape for metastatic non-oncogene-addicted NSCLC. Pembrolizumab monotherapy, in particular, has demonstrated superior efficacy and tolerability compared to standard chemotherapy for the treatment of metastatic non-oncogene-addicted NSCLC patients with a programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) $\geq$ 50% [5]. These findings established pembrolizumab as a cornerstone treatment in this setting [6].

The effectiveness of ICIs in the elderly is not uniform and may decline with advancing age, largely due to immunosenescence. This age-related decline and remodeling of immune functions have been hypothesized to limit the benefits of ICIs in patients aged 75 years and older, posing a challenge to optimizing treatment outcomes [7].

Although the age of 65 is commonly used as a cutoff in clinical trials to define "elderly," geriatric assessments and cancer care guidelines frequently use 70 years as a threshold to identify and address the needs of older patients [4].

Given the aging global population and the high prevalence of NSCLC among older adults, there is a need to refine treatment strategies for this demographic.

This paper aims to evaluate the efficacy of pembrolizumab monotherapy in metastatic non-oncogene-addicted NSCLC patients with a PD-L1 TPS $\geq$ 50% aged 70 and older and compare it to patients younger than 70 based on real-world data collected from academic institutions in Central and Southeastern Europe. Furthermore, we aim to determine the clinicopathological characteristics that may be associated with favorable outcomes in this population.

2. Materials and Methods

2.1. Patients

This study included patients with histologically confirmed metastatic NSCLC with PD-L1 TPS ≥ 50% that started treatment with pembrolizumab monotherapy between December 2017 and October 2023. The cutoff date was 22 May 2024. The study was conducted at three academic European centers. There were 294 patients included from the Clinic for Pulmonology, University Clinical Centre of Serbia, 41 patients from the University Clinic Golnik, Slovenia, and 46 patients from several municipal hospitals in Vienna, Austria. Data was retrieved from hospital-based lung cancer registries.

All patients underwent routine PD-L1 testing performed on formalin-fixed, paraffin-embedded histology or cytology samples using PD-L1 monoclonal antibodies (22C3 clone by DAKO, Glostrup, Denmark, or SP263 clone by Ventana/Roche, Oro Valley, AZ) prior to initiating the first line of treatment. Patients in the Serbian cohort were tested for EGFR mutations by the Cobas® EGFR Mutation Test v2 (Basel, Switzerland) and ALK rearrangements by immunohistochemistry prior to first-line treatment initiation. Patients in the Slovenian cohort were reflex-tested for EGFR mutations and ALK and ROS1 rearrangements in the same manner up until January 2022; after that, all the molecular tests were performed with the NGS Oncomine Precision Assay by ThermoFisher Scientific (Waltham, MA, USA). Patients in the Austrian cohort were also reflex-tested using NGS (Ion GeneStudio S5 ((Thermo Fisher Scientific) (Waltham, MA, USA))/Ion Torrent Oncomine Focus Assay) and simultaneous immunohistochemistry for ALK rearrangements.

Patients with detected driver oncogenes were excluded, so none of the included patients had a known driver oncogene. All patients were followed up with and assessed for the best response to therapy according to RECIST criteria according to local practice.

2.2. Ethics Approval

Data on patients with newly diagnosed lung cancer are prospectively collected within a clinical lung cancer registry that collects demographics and pathological and molecular characteristics, as well as treatment and survival data, of all patients with lung cancer diagnosed and treated at the center. All data were collected anonymously. The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Board Reviews and Ethics Committees of the institutions involved in the study (EK 20-061-VK; 602/3; 12 March 2024).

2.3. Statistical Analysis

Descriptive methods were used on the demographic characteristics of patients. Baseline information is presented as the number of patients and percentages. Median time on treatment (ToT) and overall survival (OS) were calculated as the time from the start of therapy to therapy discontinuation or the date of death. Patients still alive on the last day of follow-up were censored. Median ToT and OS were estimated by the Kaplan–Meier method and compared by the log-rank test. Univariable and multivariable Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and confidence intervals (CIs). In the univariate analysis, covariates included age (<70 years vs. ≥70 years), sex, histology (non-squamous- vs. squamous-cell lung cancer), smoking status (current or former smoker vs. never-smoker), PD-L1 expression (TPS 50–79% vs. ≥80%), ECOG PS (0–1 vs. ≥2), and the presence of brain metastasis at baseline (yes vs. no). Multivariate analysis included variables with a significance level of $p < 0.10$ in the univariate analysis. The Chi-square test was used to determine the association between response to treatment and a patient's age. Calculated p-values were two-sided. We used SPSS v26 for statistical analysis.

3. Results

There were 381 patients with metastatic NSCLC and a PD-L1 TPS ≥ 50% without detectable oncogene addiction that started treatment with pembrolizumab monotherapy up to 2023. Among them, the mean age was 66.2 (35–90) years, and 63.8% were male. There were 149 (39.1%) patients that were 70 years or older at the time of the treatment starting. Most of them were smokers or former smokers, 58.5% and 32.3%, respectively. Adenocarcinomas were detected in 66.4% and squamous-cell carcinomas in 23.1% of cases. There were 303 (79.5%) patients with good performance status, defined as Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 (Table 1).

Table 1. Patient characteristics.

N = 381		N (%)
Mean age at treatment start (range) [years]		66.21 (35–90)
Aged ≥70 years Yes No		149 (39.1) 232 (60.8)
Patients ≥ 70 (N = 149)	Patients < 70 (N = 232)	*p* value
Sex		0.54
Male 84 (56.4%)	138 (59.5%)	
Female 65 (43.6%)	94 (40.5%)	
Smoking status		0.01
Current or former 123 (84.5%)	220 (94.8%)	
Never 26 (15.5%)	12 (5.2%)	
ECOG PS		0.35
0–1 123 (82.5%)	180 (77.6%)	
≥2 26 (17.5%)	52 (22.4%)	
Histology		0.88
Non-squamous 114 (76.5%)	179 (77.3%)	
Squamous 35 (23.5%)	53 (22.8%)	
PD-L1 status		0.37
50–79% 72 (48.3%)	123 (53%)	
80–100% 77 (51.7%)	109 (47%)	
CNS metastasis at baseline		0.07
Yes 23 (15.4%)	53 (22.8%)	
No 126 (84.6%)	179 (77.2)	
Radiotherapy		0.52
Yes 38 (25.5%)	66 (28.5%)	
No 111 (74.5)	166 (71.5%)	
PD as per RECIST Yes Received systemic treatment in 2nd line of therapy Did not receive systemic treatment in 2nd line of therapy No		215 (56.4) 36 (16.7) 179 (83.3) 166 (43.6)
Best response to pembrolizumab (RECIST) PD SD PR CR		101 (26.6) 141 (37.0) 127 (33.3) 12 (3.1)
Real-world DCR		279 (73.4)
Real-world ORR		138 (36.4)
Median ToT (95% confidence interval) [months]		14.0 (10.5–17.5)
Median overall survival (95% confidence interval) [months]		22.63 (16.7–28.6)

Median time on treatment (mToT) and overall survival (mOS) for the whole cohort were 14.0 months (95% CI 10.5–17.5) and 22.63 (95% CI 16.7–28.6), respectively, at a median follow-up of 23.43 months. The best overall response to pembrolizumab was complete response, partial response, and stable disease in 3.1%, 33.3%, and 37%, respectively, adding up to an overall response rate (ORR) of 36.4% and disease control rate (DCR) of 73.4% (Table 1). Pembrolizumab was discontinued due to radiologically confirmed disease progression (215 patients; 56.4%), the development of high-grade immune-related adverse events (irAEs) (31 patients; 8.1%), or a decline in ECOG performance status, either from advanced NSCLC itself or from new or worsening comorbid conditions that precluded further immunotherapy (23 patients; 8%). An additional 24 patients (6.2%) completed the planned 2-year treatment duration, with their drug being discontinued at that time, but such instances were not included as an event in ToT analysis. There were no statistically significant differences in pembrolizumab discontinuation rates between patients aged <70 and those ≥70 years ($p = 0.66$), regardless of the reason for treatment cessation (Table 2).

Table 2. Response rates of older and younger patients.

Discontinuation Reason	<70 Years (*n* = 167)	≥70 Years (*n* = 102)
Disease progression	129 (77.2%)	86 (84.3%)
High-grade irAEs	22 (13.2%)	9 (8.8%)
Decline in ECOG PS/comorbidities	16 (9.6%)	7 (6.9%)

The comparison between patients younger than 70 years and those aged ≥70 years revealed no significant differences in clinical outcomes. The median time on treatment (mToT) was 14.3 months versus 12.7 months ($p = 0.218$; HR 1.195; 95% CI 0.900–1.588), and the median overall survival (mOS) was 27.4 months versus 18.2 months ($p = 0.124$; HR 1.264; 95% CI 0.940–1.701) (Figure 1). Similarly, no significant differences were observed in treatment response rates between the two groups ($p = 0.55$). (Table 3)
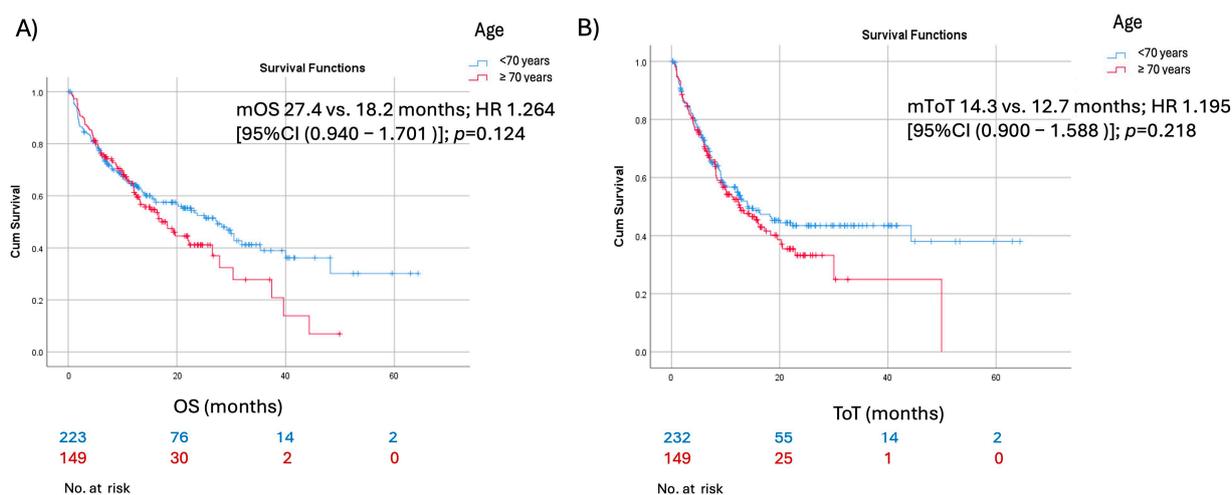

Figure 1. Kaplan–Meier survival curves of elderly patients and their younger counterparts for (**A**) overall survival and (**B**) time on treatment.

Table 3. Response rates of older and younger patients.

	Age $\geq$70 Years (N = 149)-N (%)	Age <70 Years (N = 232)-N (%)
CR	6 (4.0%)	6 (2.6%)
PR	53 (35.6%)	74 (31.9%)
SD	51 (34.2%)	91 (39.2%)
PD	39 (26.2%)	61 (26.3%)

In the elderly patient group (aged $\geq$70 years), univariate analysis identified current or former smoking status and good performance status (ECOG PS 0–1) as factors associated with favorable time on treatment (ToT) and overall survival (OS). (Figures 2 and 3) However, in multivariate analysis, only good performance status remained significantly associated with improved ToT and OS. Factors such as sex, histology, PD-L1 expression, and the presence of CNS metastases were not predictive of better ToT or OS (Tables 4 and 5). Additionally, among 215 patients that experienced radiological PD, only 36 (16.7%) received systemic therapy in the second line. Patients were significantly more likely to receive treatment if they were younger than 70 years (26 patients vs. 10 patients; *p* = 0.04) (Table 6).
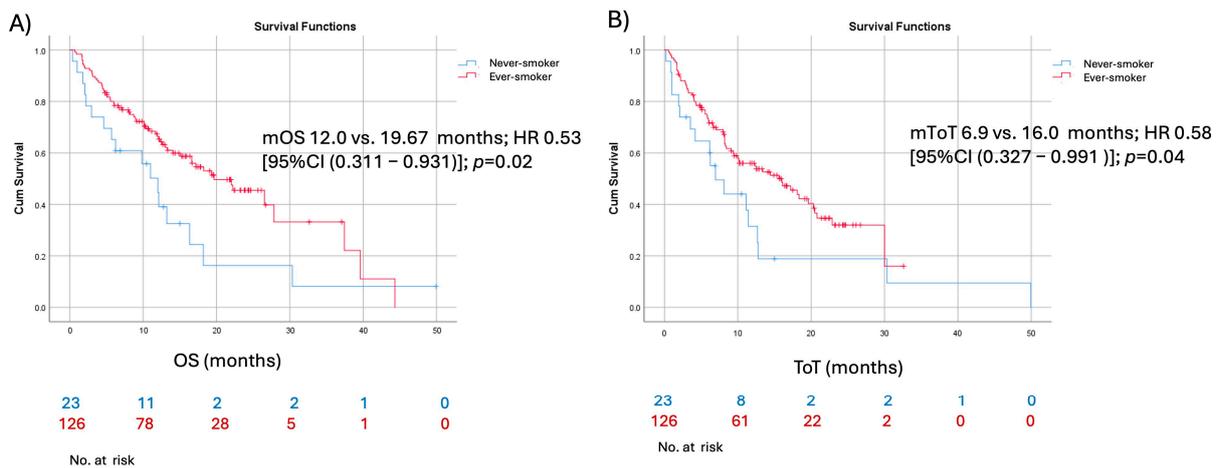

Figure 2. Kaplan–Meier survival curves comparing (**A**) overall survival and (**B**) time on treatment for elderly patients stratified by smoking status.
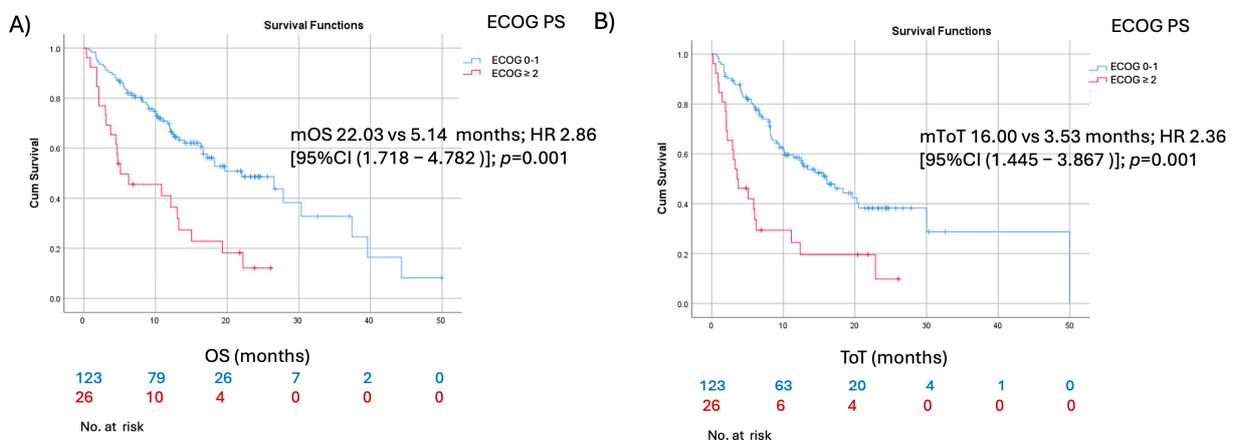

Figure 3. Kaplan–Meier survival curves comparing (**A**) overall survival and (**B**) time on treatment for elderly patients stratified by ECOG PS.

Table 4. Univariate regression analysis of elderly patients for ToT.

	Univariate Regression Analysis			Multivariate Regression Analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Radiotherapy (yes vs. no)	0.677	0.423–1.143	0.134			
Sex (male vs. female)	1.393	0.926–2.094	0.111			
Histology (non-squamous vs. squamous)	1.085	0.707–1.665	0.708			
Smoking status (current or former smoker vs. never-smoker)	0.581	0.327–0.991	0.048	0.645	0.379–1.098	0.108
PD-L1 (50–79 vs. 80%+)	0.979	0.648–1.480	0.920			
ECOG PS (0–1 vs. ≥2)	2.364	1.445–3.867	0.001	2.266	1.380–3.720	0.001
CNS mets (yes vs. no)	1.024	0.568–1.847	0.937			

Table 5. Univariate regression analysis of elderly patients for OS.

	Univariate Regression Analysis			Multivariate Regression Analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Radiotherapy (yes vs. no)	0.685	0.416–1.214	0.134			
Sex (male vs. female)	1.308	0.834–2.051	0.242			
Histology (non-squamous vs. squamous)	1.050	0.610–1.805	0.861			
Smoking status (current or former smoker vs. never-smoker)	0.538	0.311–0.931	0.027	1.104	0.8–1.524	0.546
PD-L1 (50–79 vs. 80%+)	0.992	0.644–1.530	0.973			
ECOG PS (0–1 vs. ≥2)	2.867	1.718–4.782	0.001	2.789	1.659–4.690	0.001
CNS mets (yes vs. no)	1.189	0.638–2.216	0.585			

Table 6. Patients receiving second-line systemic therapy following PD.

	Patients Receiving Second-Line Systemic Therapy Following PD as per RECIST (N = 215; 100%)	
	Yes (N = 36; 16.7%)	No (N = 179; 83.3%)
Age < 70 years	26 (12%)	83 (38.6%)
Age ≥ 70 years	10 (4.6%)	96 (44.4%)

4. Discussion

Our results have shown that there was no significant difference in the efficacy of first-line pembrolizumab monotherapy in patients with metastatic NSCLC and a PD-L1 TPS ≥ 50% aged 70 and older when compared to their younger counterparts. Among the patients aged ≥70 years, a smoking history and ECOG PS 0–1 were associated with favorable outcomes in terms of ToT and OS. Multivariable analysis showed that ECOG PS 0–1 was both prognostic and predictive in this patient group.

Patients older and younger than 70 years had an equivalent ORR, ToT, and mOS. This is in line with the findings of other real-world-based data studies [8–11]. While some of these studies involved large cohorts, they lacked therapeutic consistency due to the inclusion of multiple immunotherapeutic agents and varying lines of treatment. To address

this, we aimed to evaluate the impact of age on patients receiving pembrolizumab as a first-line therapy, similarly to the studies by Alessi et al. and Grosjean et al., but with a larger sample size [8,10].

In the older patient group (aged ≥70 years), univariate analysis identified current or former smoking status and good performance status (ECOG PS 0–1) as factors associated with favorable ToT and OS. The relationship between smoking status and treatment outcomes with ICIs remains a subject of debate. Ever-smokers have been found to exhibit higher tumor mutational burden (TMB), leading to increased neoantigen presentation and greater tumor immunogenicity, which can enhance ICI efficacy [12]. Additionally, smoking-related mutations may create a more inflamed tumor microenvironment with increased T-cell infiltration, further promoting the response to immunotherapy [13]. While some studies suggest that smoking may enhance the response to immunotherapy in patients with NSCLC, others present contradictory findings.

In a study by Popat et al., ever-smokers with advanced NSCLC and PD-L1 TPS ≥ 50% who initiated first-line pembrolizumab exhibited significantly prolonged OS compared to never-smokers [14]. Similarly, Cortellini et al. demonstrated that ever-smokers derived greater benefit in terms of OS and PFS compared to never-smokers [15]. Conversely, a recent meta-analysis of ICI-based registrational trials in advanced NSCLC found no association between smoking status and the efficacy of immunotherapy [16]. However, it is important to note that this meta-analysis included trials that enrolled patients with varying PD-L1 TPSs and evaluated different ICI-based regimens, including combination therapies. The discrepancies in findings mentioned above may be attributed to variations in study designs, patient populations, and treatment regimens. Factors such as differences in PD-L1 expression levels, tumor mutational burden, and the specific ICIs used could contribute to the inconsistent findings.

In our cohort, 20.5% of patients had ECOG PS ≥ 2. Previous reports suggest that patients with an ECOG of ≥2 comprise 30–48% of those with advanced NSCLC [17,18]. However, most pivotal trials of ICIs completely excluded this patient population [19]. A recent publication by Meyers et al. investigating the impact of ECOG PS on the treatment outcomes of patients with NSCLC undergoing ICI therapy reported that 29.2% of patients had ECOG PS ≥2 [20]. This study included patients that also received ICI therapy in the second line and further lines of treatment. The authors found that patients with ECOG PS > 2 were statistically more prevalent in the group of patients receiving ICI therapy in the second line and further lines of treatment, rather than as a first-line treatment. The relatively low proportion of patients with ECOG performance status (PS) ≥ 2 in our cohort (20.5%) is likely due to national prescribing and reimbursement policies. In Central and Southeastern Europe, first-line pembrolizumab monotherapy is generally approved only for patients with ECOG PS 0–1, consistent with regulatory indications and international guidelines. As a result, patients with poorer performance status were included only in exceptional circumstances. These access restrictions, common in many healthcare systems, contribute to the selection of patients with a better functional status who are more likely to tolerate and benefit from immunotherapy. Another more recent multicentric study that only included patients with advanced NSCLC and PD-L1 ≥ 50% that received pembrolizumab monotherapy in a first-line setting, as was the case with our cohort, reported a near-identical prevalence of ECOG PS ≥ 2 patients of 20.2% [21]. Similarly to our findings, Meyers et al. also reported no association between poor ECOG PS and older age [20].

A fairly limited number of studies have focused on patients with poor ECOG PS. Notably, registration trials for nivolumab [22,23], atezolizumab [24], and pembrolizumab [25–27] excluded individuals with an ECOG PS 2.

Data stemming from real-world studies has consistently shown that ECOG PS ≥ 2 has been found to be associated with worse treatment outcomes among patients with NSCLC undergoing ICI therapy [10,11,17,20,21,28–33]. This is in line with our findings where ECOG PS ≥ 2 was a negative prognostic factor and associated with shorter mToT and OS.

The PePS2 study demonstrated that checkpoint inhibitors could benefit patients with ECOG PS 2, showing outcomes comparable to registrational studies. The study included only patients with PS 2 (median age: 72 years, IQR 65–75) who received pembrolizumab monotherapy in either the first line or subsequent therapy lines. An important limitation was the absence of a control group with ECOG PS 0–1 [34].

Similarly, the IPSOS phase 3 trial provided important insights into treatment options for patients deemed ineligible for platinum-based chemotherapy due to poor ECOG PS ≥ 2, advanced age, or significant comorbidities [19]. In this trial, patients were randomized to receive either single-agent chemotherapy or atezolizumab as a first-line treatment regardless of the PD-L1 TPS. The results showed that atezolizumab improved median OS (10.3 vs. 9.2 months; $p = 0.028$). These findings reinforce the notion that while ECOG PS ≥ 2 remains a poor prognostic factor, mono-ICI therapy may still be a viable option for select patient populations with advanced NSCLC who cannot tolerate platinum-based regimens.

We found that older patients were less likely to receive second-line treatment following disease progression. After progression on first-line ICIs, second-line treatment with chemotherapy poses significant challenges. Advanced age is often accompanied by increased comorbidities, polypharmacy, diminished physiological reserve, and poor performance status at the time of disease progression, all of which can limit tolerance to further systemic treatment [35,36]. Due to the challenges posed by second-line therapy, clinicians sometimes opt to continue pembrolizumab beyond radiological progression if there is evidence of clinical benefit. This approach is both reasonable and proven to be efficacious, since radiological improvement is often preceded by a clinical enhancement of patient status. Additionally, immune-related or cumulative toxicities from first-line immunotherapy may preclude continuation with subsequent regimens. Cognitive or functional decline, social support limitations, and patient or caregiver preferences may also influence decisions to forego further therapy. To address this unmet need, individualized geriatric assessments, closer monitoring, and the early integration of supportive care are critical to preserving treatment eligibility. Furthermore, treatment sequencing strategies that maximize the benefit from first-line therapy—such as selecting patients with good ECOG PS and predictive biomarkers—are especially important in elderly populations, where opportunities for later-line interventions are often limited.

5. Conclusions

First-line pembrolizumab monotherapy is effective across all age groups and provides similar treatment efficacy in patients with metastatic NSCLC and PD-L1 TPS $\geq 50\%$. Patients older than 70 with a smoking history and good ECOG PS derive the most benefit from this treatment modality. The adaptation of this treatment strategy for elderly patients is especially important, since only a minority of them are capable of receiving second-line therapy.

6. Limitations

As a retrospective observational study, certain clinical information was either unavailable or inconsistently recorded in physician charting. Additionally, due to the retrospective nature of this study, we did not collect data on geriatric assessments and safety, which are particularly relevant when evaluating elderly populations. The absence of structured tools such as the G8 screening tool or comprehensive geriatric assessments limits our ability

to assess frailty, functional status, and their influence on treatment decision-making and outcomes. Similarly, the lack of comprehensive toxicity data prevents us from evaluating not only treatment tolerability and potential trade-offs between efficacy and safety in this vulnerable group but also their capacity as potential prognostic and predictive markers of treatment response. Furthermore, for the purpose of analysis, age was treated as a dichotomous variable, whereas in reality, age is a continuous parameter, and this simplification might limit the nuance of our findings. Moreover, there are local differences in treatment approaches across the countries and centers included, making it more difficult to precisely determine some variables, such as the exact time of disease progression, etc.

The high proportion of censored cases may reflect several factors, including patients still on treatment at the time of data cutoff, limited follow-up duration, loss to follow-up, or incomplete documentation in medical records. In particular, a notable number of patients initiated treatment toward the end of the enrollment period, further contributing to shorter follow-up. These factors may have affected the accuracy of long-term estimates, including survival and time on treatment. While all patients were tested for the presence of EGFR and ALK driver mutations, only a subset underwent more comprehensive genomic testing. The Serbian and Slovenian cohorts initially relied on single-gene testing, whereas broader NGS panels were introduced later in the Slovenian cohort and were standard in the Austrian cohort throughout the study period. Heterogeneity in molecular profiling, along with incomplete data capture from NGS results, limited our ability to assess the prognostic or predictive relevance of other genomic alterations (e.g., STK11, KEAP1, KRAS). Consequently, molecular data beyond EGFR and ALK could not be systematically analyzed, which limited our ability to assess the prognostic and predictive capabilities of these findings.

References

1. Bray, F.; Laversanne, M.; Sung, H.; Ferlay, J.; Siegel, R.L.; Soerjomataram, I.; Jemal, A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2024**, *74*, 229–263. [CrossRef] [PubMed]
2. Lung Cancer Statistics. How Common Is Lung Cancer? American Cancer Society. Available online: https://www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html (accessed on 11 December 2024).
3. Lung and Bronchus Cancer—Cancer Stat Facts. Available online: https://seer.cancer.gov/statfacts/html/lungb.html (accessed on 11 December 2024).
4. Montrone, M.; Rosati, G.; Longo, V.; Catino, A.; Massafra, R.; Nardone, A.; Pesola, F.; Montagna, E.S.; Marech, I.; Pizzutilo, P.; et al. Immunotherapy in Elderly Patients Affected by Non-Small Cell Lung Cancer: A Narrative Review. *J. Clin. Med.* **2023**, *12*, 1833. [CrossRef] [PubMed]
5. Reck, M.; Rodríguez-Abreu, D.; Robinson, A.G.; Hui, R.; Csőszi, T.; Fülöp, A.; Gottfried, M.; Peled, N.; Tafreshi, A.; Cuffe, S.; et al. Five-Year Outcomes with Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer with PD-L1 Tumor Proportion Score ≥ 50%. *J. Clin. Oncol.* **2021**, *39*, 2339–2349. [CrossRef]
6. Hendriks, L.; Kerr, K.; Menis, J.; Mok, T.; Nestle, U.; Passaro, A.; Peters, S.; Planchard, D.; Smit, E.; Solomon, B.; et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann. Oncol.* **2023**, *34*, 358–376. [CrossRef]
7. Hou, C.; Wang, Z.; Lu, X. Impact of immunosenescence and inflammaging on the effects of immune checkpoint inhibitors. *Cancer Pathog. Ther.* **2024**, *2*, 24–30. [CrossRef]
8. Grosjean, H.A.I.; Dolter, S.; Meyers, D.E.; Ding, P.Q.; Stukalin, I.; Goutam, S.; Kong, S.; Chu, Q.; Heng, D.Y.C.; Bebb, D.G.; et al. Effectiveness and Safety of First-Line Pembrolizumab in Older Adults with PD-L1 Positive Non-Small Cell Lung Cancer: A Retrospective Cohort Study of the Alberta Immunotherapy Database. *Curr. Oncol.* **2021**, *28*, 4213–4222. [CrossRef] [PubMed]
9. Galli, G.; De Toma, A.; Pagani, F.; Randon, G.; Trevisan, B.; Prelaj, A.; Ferrara, R.; Proto, C.; Signorelli, D.; Ganzinelli, M.; et al. Efficacy and safety of immunotherapy in elderly patients with non-small cell lung cancer. *Lung Cancer* **2019**, *137*, 38–42. [CrossRef]
10. Alessi, J.V.; Ricciuti, B.; Jiménez-Aguilar, E.; Hong, F.; Wei, Z.; Nishino, M.; Plodkowski, A.J.; Sawan, P.; Luo, J.; Rizvi, H.; et al. Outcomes to first-line pembrolizumab in patients with PD-L1-high (≥50%) non–small cell lung cancer and a poor performance status. *J. Immunother. Cancer* **2020**, *8*, e001007. [CrossRef]
11. Kontić, M.; Marković, F.; Nikolić, N.; Samardžić, N.; Stojanović, G.; Simurdić, P.; Petkov, S.; Bursać, D.; Zarić, B.; Stjepanović, M. Efficacy of Atezolizumab in Subsequent Lines of Therapy for NSCLC Patients: Insights from Real-World Data. *Cancers* **2024**, *16*, 3696. [CrossRef]
12. Sun, L.; Cen, W.; Tang, W.; Long, Y.; Yang, X.; Ji, X.; Yang, J.; Zhang, R.; Wang, F.; Shao, J.; et al. Smoking status combined with tumor mutational burden as a prognosis predictor for combination immune checkpoint inhibitor therapy in non-small cell lung cancer. *Cancer Med.* **2021**, *10*, 6610–6617. [CrossRef]
13. Sun, Y.; Yang, Q.; Shen, J.; Wei, T.; Shen, W.; Zhang, N.; Luo, P.; Zhang, J. The Effect of Smoking on the Immune Microenvironment and Immunogenicity and Its Relationship with the Prognosis of Immune Checkpoint Inhibitors in Non-small Cell Lung Cancer. *Front. Cell Dev. Biol.* **2021**, *9*, 745859. [CrossRef] [PubMed]
14. Popat, S.; Liu, S.V.; Scheuer, N.; Gupta, A.; Hsu, G.G.; Ramagopalan, S.V.; Griesinger, F.; Subbiah, V. Association Between Smoking History and Overall Survival in Patients Receiving Pembrolizumab for First-Line Treatment of Advanced Non–Small Cell Lung Cancer. *JAMA Netw. Open* **2022**, *5*, e2214046. [CrossRef]
15. Cortellini, A.; De Giglio, A.; Cannita, K.; Cortinovis, D.L.; Cornelissen, R.; Baldessari, C.; Giusti, R.; D'Argento, E.; Grossi, F.; Santoni, M.; et al. Smoking status during first-line immunotherapy and chemotherapy in NSCLC patients: A case–control matched analysis from a large multicenter study. *Thorac. Cancer* **2021**, *12*, 880–889. [CrossRef]
16. Luo, D.; Yang, D.; Cao, D.; Gong, Z.; He, F.; Hou, Y.; Lin, S. Effect of smoking status on immunotherapy for lung cancer: A systematic review and meta-analysis. *Front. Oncol.* **2024**, *14*, 1422160. [CrossRef]
17. Sehgal, K.; Gill, R.R.; Widick, P.; Bindal, P.; McDonald, D.C.; Shea, M.; Rangachari, D.; Costa, D.B. Association of Performance Status with Survival in Patients with Advanced Non–Small Cell Lung Cancer Treated with Pembrolizumab Monotherapy. *JAMA Netw. Open* **2021**, *4*, e2037120. [CrossRef]
18. Passaro, A.; Spitaleri, G.; Gyawali, B.; de Marinis, F. Immunotherapy in Non–Small-Cell Lung Cancer Patients with Performance Status 2: Clinical Decision Making with Scant Evidence. *J. Clin. Oncol.* **2019**, *37*, 1863–1867. [CrossRef]
19. Lee, S.M.; Schulz, C.; Prabhash, K.; Kowalski, D.; Szczesna, A.; Han, B.; Rittmeyer, A.; Talbot, T.; Vicente, D.; Califano, R.; et al. First-line atezolizumab monotherapy versus single-agent chemotherapy in patients with non-small-cell lung cancer ineligible for treatment with a platinum-containing regimen (IPSOS): A phase 3, global, multicentre, open-label, randomised controlled study. *Lancet* **2023**, *402*, 451–463. [CrossRef] [PubMed]

20. Meyers, D.E.; Pasternak, M.; Dolter, S.; Grosjean, H.A.; Lim, C.A.; Stukalin, I.; Goutam, S.; Navani, V.; Heng, D.Y.; Cheung, W.Y.; et al. Impact of Performance Status on Survival Outcomes and Health Care Utilization in Patients with Advanced NSCLC Treated with Immune Checkpoint Inhibitors. *JTO Clin. Res. Rep.* **2023**, *4*, 100482. [CrossRef] [PubMed]

21. Descourt, R.; Greillier, L.; Perol, M.; Ricordel, C.; Auliac, J.-B.; Falchero, L.; Gervais, R.; Veillon, R.; Vieillot, S.; Guisier, F.; et al. First-line single-agent pembrolizumab for PD-L1-positive (tumor proportion score ≥ 50%) advanced non-small cell lung cancer in the real world: Impact in brain metastasis: A national French multicentric cohort (ESCKEYP GFPC study). *Cancer Immunol. Immunother.* **2023**, *72*, 91–99. [CrossRef]

22. Borghaei, H.; Paz-Ares, L.; Horn, L.; Spigel, D.R.; Steins, M.; Ready, N.E.; Chow, L.Q.; Vokes, E.E.; Felip, E.; Holgado, E.; et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N. Engl. J. Med.* **2015**, *373*, 1627–1639. [CrossRef]

23. Brahmer, J.; Reckamp, K.L.; Baas, P.; Crinò, L.; Eberhardt, W.E.E.; Poddubskaya, E.; Antonia, S.; Pluzanski, A.; Vokes, E.E.; Holgado, E.; et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2015**, *373*, 123–135. [CrossRef] [PubMed]

24. Herbst, R.S.; Giaccone, G.; de Marinis, F.; Reinmuth, N.; Vergnenegre, A.; Barrios, C.H.; Morise, M.; Felip, E.; Andric, Z.; Geater, S.; et al. Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC. *N. Engl. J. Med.* **2020**, *383*, 1328–1339. [CrossRef] [PubMed]

25. Reck, M.; Rodríguez-Abreu, D.; Robinson, A.G.; Hui, R.; Csőszi, T.; Fülöp, A.; Gottfried, M.; Peled, N.; Tafreshi, A.; Cuffe, S.; et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2016**, *375*, 1823–1833. [CrossRef] [PubMed]

26. Gandhi, L.; Rodríguez-Abreu, D.; Gadgeel, S.; Esteban, E.; Felip, E.; De Angelis, F.; Domine, M.; Clingan, P.; Hochmair, M.J.; Powell, S.F.; et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *378*, 2078–2092. [CrossRef]

27. Paz-Ares, L.; Luft, A.; Vicente, D.; Tafreshi, A.; Gümüş, M.; Mazières, J.; Hermes, B.; Çay Şenler, F.; Csőszi, T.; Fülöp, A.; et al. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. *N. Engl. J. Med.* **2018**, *379*, 2040–2051. [CrossRef]

28. Tomasik, B.; Bieńkowski, M.; Braun, M.; Popat, S.; Dziadziuszko, R. Effectiveness and safety of immunotherapy in NSCLC patients with ECOG PS score ≥2—Systematic review and meta-analysis. *Lung Cancer* **2021**, *158*, 97–106. [CrossRef]

29. Ahmed, T.; Lycan, T.; Dothard, A.; Ehrlichman, P.; Ruiz, J.; Farris, M.; Topaloglu, U.; Levine, B.; Grant, S.; Klepin, H.D.; et al. Performance Status and Age as Predictors of Immunotherapy Outcomes in Advanced Non–Small-Cell Lung Cancer. *Clin. Lung Cancer* **2020**, *21*, e286–e293. [CrossRef]

30. Marković, F.; Stjepanović, M.; Samardžić, N.; Kontić, M. The Association of Immune-Related Adverse Events with the Efficacy of Atezolizumab in Previously Treated Advanced Non-Small-Cell Lung Cancer Patients: A Single-Center Experience. *Cancers* **2024**, *16*, 2995. [CrossRef]

31. Marković, F.; Stjepanović, M.; Rančić, M.; Cekić, M.; Kontić, M. Real-World Outcomes of First-Line Pembrolizumab Monotherapy in Metastatic NSCLC with High PD-L1 Expression (TPS ≥ 50%): A Multicenter Study from Serbia. *Biomedicines* **2025**, *13*, 1175. [CrossRef]

32. Yao, J.; Li, S.; Bai, L.; Chen, J.; Ren, C.; Liu, T.; Qiu, J.; Dang, J. Efficacy and safety of immune checkpoint inhibitors in elderly patients with advanced non-small cell lung cancer: A systematic review and meta-analysis. *eClinicalMedicine* **2025**, *81*, 103081. [CrossRef]

33. Tateishi, K.; Mizugaki, H.; Ikezawa, Y.; Morita, R.; Yokoo, K.; Sumi, T.; Aso, M.; Kikuchi, H.; Nakamura, A.; Sekikawa, M.; et al. Real-world data of first-line treatment with pembrolizumab for NSCLC with high PD-L1 expression in elderly patients: A subgroup analysis of HOT/NJLCG2001. *Ultrasound Med. Biol.* **2025**, *55*, 253–260. [CrossRef] [PubMed]

34. Middleton, G.; Brock, K.; Savage, J.; Mant, R.; Summers, Y.; Connibear, J.; Shah, R.; Ottensmeier, C.; Shaw, P.; Lee, S.-M.; et al. Pembrolizumab in patients with non-small-cell lung cancer of performance status 2 (PePS2): A single arm, phase 2 trial. *Lancet Respir. Med.* **2020**, *8*, 895–904. [CrossRef] [PubMed]

35. Seegobin, K.; Majeed, U.; Zhou, K.; Shi, H.; Lou, Y.; Zhao, Y.; Manochakian, R. P40.18 Second Line Immunotherapy After Progression on a Different First Line Immunotherapy in Advanced Non-Small Cell Lung Cancer with Focus on Elderly. *J. Thorac. Oncol.* **2021**, *16*, S1077–S1078. [CrossRef]

36. Liguori, L.; Giorgio, G.; Polcaro, G.; Pagliara, V.; Malandrino, D.; Perri, F.; Cascella, M.; Ottaiano, A.; Conti, V.; Servetto, A.; et al. Checkpoint based immunotherapy in non-small cell lung cancer: A real-world retrospective study. *Front. Immunol.* **2024**, *15*, 1419544. [CrossRef]