Original Study

First-Line Pembrolizumab Efficacy in Octogenarians With NSCLCs Expressing ≥ 50% PD-L1 (ESCKEYP GFPC 05-2018)

Romain Corre,[1] Chantal Decroisette,[2] Jean-Bernard Auliac,[3] Lionel Falchero,[4] Hubert Curcio,[5] Karim Amrane,[6] Maurice Perol,[2] Stéphane Hominal,[7] Sabine Vieillot,[8] Eric Huchot,[9] Anne Laure Desage,[10] Marie Bernardi,[11] Remi Veillon,[12] Hélène Doubre,[13] Suzanna Bota,[14] Gwenaelle Legarff,[15] Grégoire Justeau,[16] Oliver Bylicki,[17] Magali Roa,[18] Renaud Descourt,[19] Christos Chouaïd,[3] Laurent Greillier[20]

Abstract

In this retrospective, multicenter study including all consecutive patients with metastatic NSCLC PD-L1 ≥ 50%, first-line pembrolizumab efficacy in octogenarians seems inferior to that obtained in younger with a respective median OS for of 12.0 (95% CI: 7.7-16.2) vs. 23.9 (95% CI: 19.5-27.4) months ($P = .0002$), and median PFS for 5.0 (95% CI: 2.8-9.2) versus 8.3 (95% CI: 7.2-9.8) months ($P = .039$). The higher percentage of nonsmokers and fewer adenocarcinomas could partially explain that finding.

Background: Pembrolizumab alone is a first-line therapeutic option for patients with metastatic non-small cell lung cancer (NSCLC) with ≥ 50% PD-L1 expression, but few data are available for elderly patients, specifically octogenarians. **Methods:** This retrospective, multicenter study included all consecutive patients with metastatic NSCLC PD-L1 ≥ 50% treated with first-line pembrolizumab monotherapy between May 2017 and November 2019. Information was collected from medical files with local evaluation of therapeutic response and progression-free survival (PFS). **Results:** Among the 844 patients included, 73 (8.4%) were ≥ 80 (median: 82) years old, 74% men, 23.3% with ECOG-PS ≥ 2, 26% had ≥ 5% weight loss, PD-L1 50%-75%/≥ 75%: 45.2%/46.6%, respectively, with significantly more nonsmokers and (17.4% vs. 5.6%, $P = .0002$) and fewer adenocarcinomas (57.5% vs. 70.8%, $P = .0217$) than those < 80 years. After median follow-up of 45.7 (95% CI: 43.0-49.1) months, respective median overall survival (OS) for octogenarians versus younger patients lasted 12.0 (95% CI: 7.7-16.2) versus 23.9 (95% CI: 19.5-27.4) months ($P = .0002$), and median PFS for 5.0 (95% CI: 2.8-9.2) versus 8.3 (95% CI: 7.2-9.8) months ($P = .039$). Their respective objective response rates did not differ significantly: 42% (95% CI: 24-60) vs. 49% (95% CI: 43-54). **Conclusions:** Based on the results of this large multicenter population, first-line pembrolizumab efficacy against NSCLCs expressing ≥ 50% PD-L1 in octogenarians seems inferior to that obtained in younger patients. The higher percentage of nonsmokers and fewer adenocarcinomas could partially explain that finding.

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[1]Centre Hospitalier de Cornouaille, Quimper, France
[2]Centre Léon-Bérard, Lyon, France
[3]Centre Hospitalier Intercommunal, Créteil, France
[4]Hôpital Nord-Ouest, Villefranche-sur-Saône, France
[5]Centre François-Baclesse, Caen, France
[6]Centre Hospitalier des Pays de Morlaix, Morlaix, France
[7]Centre Hospitalier Annecy Genevois, Pringy, France
[8]Centre Catalan d'Oncologie, Perpignan, France
[9]CHU de la Réunion, Saint-Pierre, France
[10]CHU Hôpital Nord, Saint-Priest-en-Jarez, France
[11]Centre Hospitalier du Pays d'Aix, Aix-en-Provence, France
[12]Hôpital Haut Lévêque, Pessac, France
[13]Hôpital Foch, Paris, France
[14]Hôpital Charles-Nicolle, Rouen, France
[15]Centre Hospitalier de Saint-Brieuc, Saint-Brieuc, France
[16]Pneumologie, CHU Angers, Angers, France
[17]Hôpital d'Instruction des Armées Sainte-Anne, Toulon, France
[18]CHI Fréjus-Saint-Raphaël, Fréjus, France
[19]CHRU Morvan Institut de Cancérologie et d'Hématologie Oncologie Thoracique, Brest, France
[20]Hopital Nord, APHM, Multidisciplinaire et Innovations Thérapeutiques, Marseille, France

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Address for correspondence: Christos Chouaïd, MD, PhD Service de Pneumologie, Centre Hospitalier Intercommunal de Créteil, 40 avenue de Verdun, Créteil 94010, France.
E-mail contact: christos.chouaid@chicreteil.fr

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Introduction

Anti-programmed cell-death protein-1 or its ligand (PD-1/PD-L1) immune-checkpoint immunotherapies (ICIs) have completely revolutionized the management of patients with metastatic non-small-cell lung cancer (NSCLC), especially for those with ≥ 50% of tumor cells expressing PD-L1. The phase-3 Keynote-024 trial compared pembrolizumab alone versus doublet platin-based chemotherapy efficacies in such a population[1,2]; respective median progression-free survival (PFS) lasted 7.7 versus 5.5 months, and respective median overall survival (OS) lasted 26.3 and 13.4 months (hazard ratio (HR): 0.62: 0.48-0.81). However, those results were obtained from a highly selected population, excluding patients with Eastern Cooperative Oncology Group-performance status (ECOG-PS) ≥ 2, active or treated brain metastases (BMs), or life expectancy < 3 months. In addition, participants could not be taking > 10 mg of corticosteroids/day at inclusion. For that trial, 1934 patients were screened, 500 (30.2%) had ≥ 50%-PD-L1 expression but only 305/500 (61%) satisfactorily met the randomization criteria. Among the 154 patients randomized to receive pembrolizumab, only 3.3% were never-smokers.[1,2]

Given improved treatment outcomes and quality of life achieved with ICIs, they have emerged as a preferred therapeutic option for elderly patients.[3-12] Nevertheless, ICI efficacy in the elderly has raised concerns of immunosenescence ie, the process of immune-system aging of adaptive and innate immunities that leads to diminished responsiveness towards cancer cells and other stimuli.[13-17] The aging characteristics include lower proliferative activities of T cells and other immune cells, with decline of their corresponding functionalities.[15,16] Aging is also associated with the upregulation of immune inhibitory signals.[17] All aging-related innate- and adaptive-immunity modifications can potentially dampen the responses to ICIs in older populations and impact the safety profile. However, very limited data are available about this population, especially very old patients. In a prospective cohort analysis[18] of 140 patients, comparing older (≥ 70 years) versus younger (< 70 years) patients, even though the older group had significantly higher comorbidity and polypharmacy rates, no significant difference was found in the grade 3-5 immune-related adverse event (irAE) rates between older and younger groups (18.6% vs. 12.9%, respectively).

This study was undertaken to evaluate the efficacy and safety profile of first-line pembrolizumab in octogenarians with metastatic NSCLC with ≥ 50%-PD-L1 expression (henceforth ≥ 50%-PD-L1 NSCLC).

Methods

ESCKEYP-trial methodology was published previously.[3] The main eligibility criteria were: treatment-naïve adults with histologically or cytologically confirmed metastatic NSCLCs, ≥ 50% PD-L1 tumor-cell expression, epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) mutation-negative and with at least 1 measurable lesion. Patients with BMs were eligible. Patients with an autoimmune disease contraindicating immunotherapy, active hepatitis B or C, or human immunodeficiency virus infection, or organ or bone-marrow transplantees were excluded. In accordance with the first European authorization, 200 mg of pembrolizumab were administered intravenously every 3 weeks. When the investigator considered disease to be progressive or toxicity unacceptable, pembrolizumab was discontinued.

The study was conducted in accordance with the Declaration of Helsinki; it was approved by a national independent Ethics Committee (2019-A02073-54; December 11, 2019). Patients received oral and written information about the study, and gave their consent to participate in it and for the use of their medical data for research purposes.

The main information collected for the present analysis was: sociodemographic characteristics, disease history, smoking status, ECOG-PS, NSCLC characteristics (histology, stage, metastatic sites at diagnosis, PD-L1 expression, mutations or rearrangements), corticosteroid intake (> 10 mg/day for > 10 days), recent antibiotic use (for > 10 days during the preceding weeks), tumor progression (new sites or existing sites), and leukocyte and lymphocyte counts. Tumor responses according to RECIST 1.1 criteria were assessed locally.

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

Univariate Cox models selected the most promising prognostic variables for OS and PFS (threshold $P = .20$). A multivariate Cox model was used to adjust for potential confounders. The multivariable analysis used backward, stepwise, logistic-regression Cox modeling, with OS or PFS as the dependent variable and prognostic factors as the explanatory variables. HR (95% confidence interval [CI]) and *P*-values are reported, with $P < .05$ considered significant.

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

Results

Between May 2, 2017 (when pembrolizumab became available for this indication in France) and November 22, 2019 (when the pembrolizumab–chemotherapy combination was approved), 33 centers in France included 845 patients with metastatic ≥ 50%-PD-L1-expressing NSCLCs, who had received first-line pembrolizumab. Among the 844 patients analyzed, 73 (8.4%) were ≥ 80 (median: 82) years, 74% were men, 23.3% were ECOG-PS ≥ 2, 26% had ≥ 5% weight loss, respective 50%-75%/≥ 75% PD-L1–expression rates were 45.2%/46.6%. Comparing octogenarians to younger patients, respectively, the percentage of octogenarian nonsmokers was higher (17.4% vs. 5.6%; $P = .0002$) and adenocarcinomas were less frequent (57.5% vs. 70.8%, $P = .0217$) (Table 1).

After median follow-up of 45.7 (95% CI: 43.0-49.1) months, median OS and PFS (Figures 1A and B, respectively) were significantly shorter for octogenarians than younger patients, respectively: 12 (95% CI: 7.7-16.5) versus 23.9 (95% CI: 19.5-27.4) months ($P < .0002$) and 5.0 (95% CI: 2.8-9.2) versus 8.3 (95% CI: 7.2-9.8) months ($P < .04$). In contrast, their respective objective response rates did not differ 42% (95% CI: 24-60) versus 49% (95% CI: 43-54).

Subgroup analyses showed pembrolizumab efficacy to differ highly significantly according to ECOG-PS, with median OS at

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Figure 1 Overall survival curves, with shading of the 95% confidence intervals, for the entire ≥ 50%-PD-L1–NSCLC population according to: (A) age category: < 80 or ≥ 80 years, and (B) Eastern Cooperative Oncology Group performance status of those ≥ 80 years: 0-1 or ≥ 2.

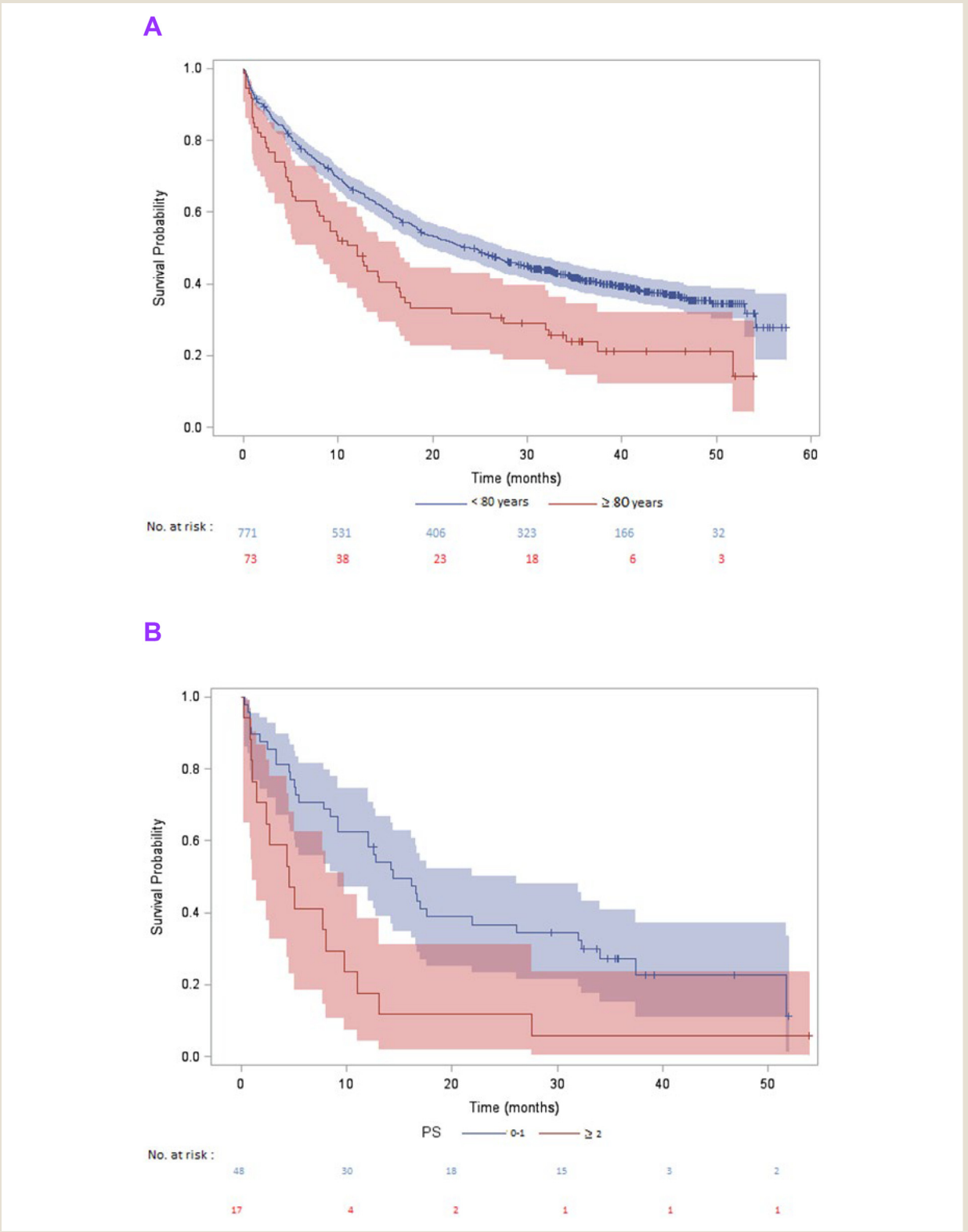

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Table 1 Characteristics of Elderly ≥ 50%-PD-L1-Expressing NSCLC Patients According to age < 80 or ≥ 80 Years

Characteristics	≥80 Y *n* = 73 (%)	<80 Y *n* = 771 (%)	*P*-Value
Sex			
Male	54 (74)	518 (67.2)	.23
Smoking history			
Active or former/ex-smoker	57 (78.1)	706 (91.6)	**.0002**
Non/Never-smoker	12 (16.4)	42 (5.4)	
Weight loss < 5%	41 (56.2)	419 (54.3)	.45
ECOG PS 0-1	48 (65.8)	561 (72.8)	.39
Not taking corticosteroids	62 (84.9)	686 (89)	.40
Not taking antibiotics	60 (82.2)	623 (80.8)	.50
Adenocarcinoma histology	42 (57.5)	546 (70.8)	**.022**
No brain metastases	61 (83.6)	607 (78.7)	.50
With bone metastases	20 (27.4)	276 (35.8)	.15
With liver metastases	6 (8.2)	111 (14.4)	.14
Immunohistochemistry PD-L1 > 75%	34 (46.6)	379 (49.2)	.29
KRAS mutated	25 (34.2)	209 (27.1)	.3
BRAF mutated	5 (6.8)	24 (3.1)	.18

Results are expressed as number (%).
Abbreviations: ECOG-PS = Eastern Cooperative Oncology Group performance status; PD-L1 = programmed cell death ligand-1.

Table 2 Univariate and Multivariate Analysis of Parameters Associated With Overall Survival

Parameter		Univariate Model		Multivariate Model	
	N	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value
ECOG PS					
0-1	48	1.00	.005	1	
2-4	17	2.38 (1.30-4.36)		2.5 (1.25-5.02)	.01
Bone metastases					
No	53	1.00	.016	1	
Yes	20	1.99 (1.13-3.50)		3.31 (1.54-7.09)	.002
Leukocyte counts					
≤ 10,000/mm^3	37	1.00	.002	1	
> 10,000/mm^3	23	3.42 (1.59-7.36)		2.28 (1.15-4.5)	.02
PD-L1 expression					
< 75%	39	1.00	.094		
≥ 75%	34	1.57 (0.93-2.66)			
Weight loss					
< 5%	41	1.00	.12		
≥ 5%	19	1.61 (8.88-2.92)			
Neutrophil/lymphocyte ratio					
< 4	17	1.00	.002		
≥ 4	43	3.42 (1.59-7.36)			

14.4 (95% CI: 9.1-26.1) months for 0-1 versus 4.5 (95% CI: 1-9.8) months for ≥ 2 ($P = .0037$) (Figure 2).

Univariate and multivariate analyses (Table 2) selected and retained ECOG-PS ≥ 2, bone metastases and leukocytosis >10 000/mm^3 as factors significantly associated with shorter OS.

Grade-1/2 toxicity rates did not differ significantly but higher percentages of octogenarians had grade-3/4 gastrointestinal or respiratory toxicities (Table 3). Compare to youngers, there is numerically more patients ever 80 y who discontinued pembrolizumab for AE and/or others reasons outsides progression (13.4% versus 23.2%) but this difference was not significant.

Discussion

The results of this retrospective analysis of nonselected patients with metastatic ≥ 50%-PD-L1 NSCLCs highlighted significantly lower first-line pembrolizumab efficacy in octogenarians. Data on

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Figure 2 Progression-free survival curve, with shading of the 95% confidence interval, for the entire ≥ 50%-PD-L1–NSCLC population to age: < 80 or ≥ 80 years.

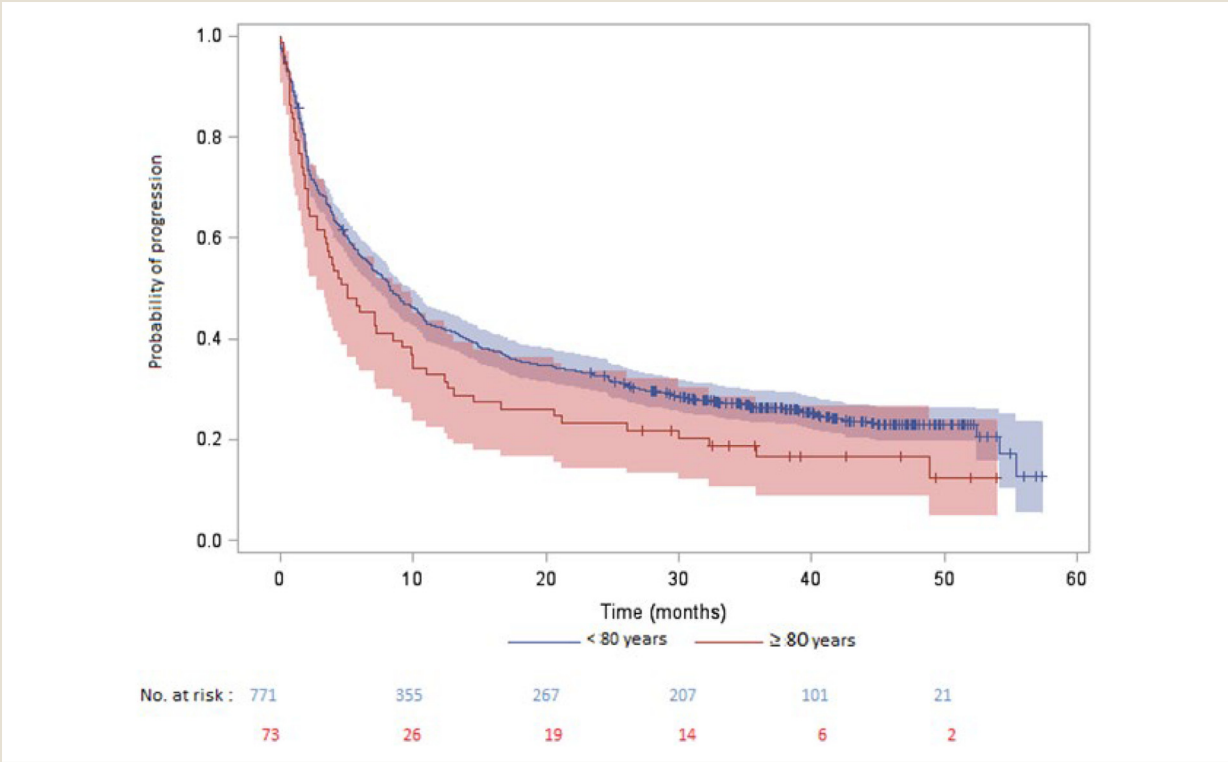

Table 3 Adverse Events in ≥ 50%-PD-L1-NSCLC Patients According to Age < 80 or ≥ 80 Years

Type	Grade 1/2		Grade 3/4	
	<80 Y (*n* = 771)	≥80 Y (*n* = 73)	<80 Y (*n* = 771)	≥80 Y (*n* = 73)
Gastrointestinal	114 (14.8)	9 (12.3)	6 (0.8)	6 (8.2)
Hepatobiliary	17 (2.2)	1 (1.4)	16 (2.1)	1 (1.4)
Respiratory	53 (9)	3 (4.1)	26 (3.4)	5 (6.8)
Cutaneous	148 (19.2)	16 (21.9)	16 (2.1)	0
Renal	17 (2.2)	11 (15.1)	7 (0.9)	1 (1.4)
Thyroid	73 (9.5)	6 (8.2)	3 (0.4)	0
Asthenia	155 (20.1)	10 (13.7)	18 (2.3)	1 (1.4)
Articular	40 (5.2)	9 (12.3)	3 (0.4)	
Others	20 (2.6)	9 (12.3)	0	0

Results are expressed as number (%).

ICI effectiveness in very old patients have been contradictory. Compared to chemotherapy in phase 3 trials, the elderly seemed to have the same amplitude of ICI benefit[19] but the age cut-off threshold most frequently retained was 65 years and most studies had limited information for patients > 75 years old and even less for octogenarians.

The IMpower 110 study[20] that compared atezolizumab to platin-based chemotherapy enrolled 54 patients (among 554 randomized) ≥ 74 years old, and the older subgroup did not differ significantly from the younger participants but the small sample size precluded drawing definitive conclusions.

A pooled analysis of efficacy based on 264 patients > 75 years with PD-L1–positive NSCLCs who received first-line pembrolizumab versus chemotherapy during Keynote-010, Keynote-024 and Keynote-042 trials[21] found that pembrolizumab prolonged median OS among the elderly patients with PD-L1 Tumor Proportion Scores (TPS) ≤ 1% (15.7 vs. 11.7 months; HR: 0.76 [95% CI: 0.56-1.02]) and ≥50% (23.1 vs. 8.3 months; HR:

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0.40 [95% CI: 0.25-0.64]) but those were post hoc analyses that should be considered exploratory.

Prospective studies including very old persons are rare. In a single-arm, open-label, phase II clinical trial, the Spanish Lung Cancer Group included, at 10 sites, 83 pembrolizumab-treated patients ≥ 70 years old with stage-IIIB or -IV metastatic ≥ 50%-PD-L1 NSCLCs, between February 2018 and November 2019.[22] Most (86.5%) were male and former smokers (68.9%). With median follow-up at 18.0 (range: 0.1-47.7) months, the estimated 1-year OS was 61.7% (95% CI: 49.6%-71.8%) and median OS lasted 19.2 months (95% CI: 11.3-25.5), better than the median 12-month OS reached by our octogenarians.

Pembrolizumab efficacy has also been evaluated in metastatic NSCLC patients in real-world studies but they were often conducted in single centers on small sample sizes. Endo et al.[23] retrospectively analyzed their center's data and found no PFS or disease-control rate differences between 41 patients > 75 years old and 70 younger participants. The median ages of the older and younger groups, respectively, were 78 (range: 75-88) and 68 (range: 46-74) years, with other characteristics (eg, sex, smoking history, stage, histology, ECOG-PS, PD-L1 expression, *EGFR*/*ALK* gene mutations, ICI treatment details, and the numbers of ICI cycles) being comparable.

Data specific to octogenarians are even more scarce. In an American study that enrolled 1,898,210 patients with NSCLCs between 2015 and 2018,[24] 42 356 (2.2%) were > 80 years old. In that subgroup, median age was 83 years, with 68.4% 80-85 years old; 51.8% males, 62.1% adenocarcinomas and 70.1% with stage-IV disease. The majority (59.5%) received no systemic therapy. Median OS for no therapy, ICI alone, chemotherapy alone and chemotherapy plus ICI, respectively, lasted 2.6, 10.7, 12.3, and 14.03 months. Indeed, defining the study cohorts exclusively based on a chronological age cut-off is debatable. Chronological age has limited value to predict safety outcomes or prognosis, and standard-fitness assessments, such as PS, are less reliable at assessing the functional level of older patients. Those limitations highlight the importance of implementing geriatric assessments to better select older patients according to treatment tolerance and care outcomes. Before the era of immunotherapy, our group showed, in a large phase 3 randomized study, that in elderly patients with advanced NSCLC, treatment allocation based on a standardized geriatric assessment, failed to improve PFS or OS but slightly reduced treatment toxicity.[25] In a multivariate analysis, mobility (Test Get up and Go), instrumental activity of daily living dependence and weight loss were associated with a reduced 3 months PFS and 3-month mortality.[26]

Safety data have also been contradictory in elderly population.[20-25] In a prospective study, with tolerance being the primary objective, the authors[20] reported significantly higher polypharmacy rates and comorbidity burdens in the elderly than younger patients but the impact on the frequencies of grade 3-5 irAEs was not evaluated. The irAE profile was the same for both groups but the duration of exposure to systemic corticosteroids prescribed for any-grade irAEs, was longer for the older patients. Finally, hospital-admission rates were similar and most often for non-irAEs. Similarly, a study[27] focusing on a large cohort of 135 patients given a single-ICI and included in a pharmacovigilance registry found no evidence of a higher risk of grade 3-5 toxicity in older patients. However, their grade-2 toxicities were more frequent and more often multiple.

We acknowledge that our study has certain limitations, especially its retrospective design and nonstandardized evaluations of therapeutic responses, no centralized rereading of those responses and a likely underestimation of AEs, especially grade 1/2. Furthermore, all patients don't have a complete NGS, which does not allow to exclude an imbalance between the molecular profile of the 2 groups, even if the patients with EGFR mutation and ALK translocation were not included and there were no differences between the 2 groups for the KRAS and BRAF mutations.

Conclusion

In this large, multicenter population, first-line pembrolizumab seemed less effective against ≥ 50%-PD-L1-expressing NSCLCs in octogenarians than younger patients. That result underscores the need for further investigation to comprehensively understand immune response mechanisms in elderly patients and to identify predictive biomarkers for elderly patients with cancer.

Data availability

Datasets analyzed for this study are available from the corresponding author on reasonable request.

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Group Français de Pneumo-Oncologie.

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CRediT authorship contribution statement

Romain Corre: Writing – review & editing, Validation, Formal analysis, Data curation, Conceptualization. **Chantal Decroisette:** Writing – review & editing, Writing – original draft, Validation,

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