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ORIGINAL ARTICLE

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Immune checkpoint inhibitors in patients aged 80 or older with advanced non-small cell lung cancer or melanoma: a real-life multicentre study

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ABSTRACT

Background: Data regarding characteristics, safety and survival outcomes of patients aged 80 or older treated with immune checkpoint inhibitors (ICI) in routine oncology practice are limited.

Materials and methods: We retrospectively collected data of patients aged 80 and older with advanced non-small cell lung cancer (NSCLC) or melanoma treated with anti-PD1, anti-PD-L1 or anti-CTLA-4 regardless of the treatment line, in 14 institutions, between January 2014 and June 2017. Progression-free survival (PFS) and overall survival (OS) were estimated with the Kaplan Meier method. Toxicity was assessed according to CTCAE 5.0. Multivariate analyses were performed with the Cox model.

Results: Eighty-two patients were included (36 with NSCLC, 45 with melanoma). Their median age was 82 years (range 80–93). Nivolumab and pembrolizumab were mainly used. In the NSCLC group, median PFS and OS were 2.3 months (95%CI 1.8–6.1) and 8.8 months (95%CI 5.5–18.1), respectively. In the melanoma group, median PFS and OS were 10.2 months (95%CI 4.5–20.0) and 24.5 months (95%CI 14.1–NR), respectively. The albumin level was found to be independently associated with a better OS in both groups. Grade 3–4 toxicities occurred in 15 patients (18.5%). One patient died from ICI-induced pulmonary toxicity.

Conclusion: Our study findings suggest that treatment with ICI in elderly patients with NSCLC and melanoma has a risk-benefit ratio that supports its use. However, we report in this cohort that one in five patients has a grade 3–4 IRAEs leading to treatment discontinuation. Geriatric assessment prior to initiation of therapy and during therapy should be routine in patients aged 80 years and older.

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Immune checkpoint inhibitors; elderly; efficacy; safety; melanoma; non-small cell lung cancer

Introduction

Over the last few years, numerous trials have proven the efficacy and usually favorable safety profile of immune checkpoint inhibitors (ICI) in first and more advanced lines of treatment in melanoma and NSCLC [1–12]. Even if these ICI are now largely used in clinical practice, even in older patients, dedicated trials are lacking in this specific population.

Both in melanoma and NSCLC, patients aged 80 or older are greatly underrepresented in phase III, pivotal clinical trials [1–12]. The large heterogeneity of patients aged 80 or older in terms of comorbidities, nutritional status, functional activities, dependence, polypharmacy and cognitive impairment makes the decision of treatment difficult for clinicians. There is a real unmet need for data regarding patients aged 80 or older treated with ICI.

The aim of the present study was to evaluate the efficacy and safety of ICI among patients aged 80 or older patients treated for advanced/metastatic melanoma or NSCLC regardless of the treatment line.

Material and methods

Study population and procedures

We conducted a multicenter, non-interventional, retrospective cohort study in fourteen centers throughout the Brittany region, in France.

The objective of this study was to describe the efficacy and safety of ICI in octogenarians treated for advanced NSCLC or melanoma. Inclusion criteria were the following: patients aged 80 or older at the initiation of the ICI, advanced NSCLC or melanoma (at least one intravenous ICI injection), regardless of the number of prior treatment lines. The ICI could be an anti-PD-1 (nivolumab, pembrolizumab),

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an anti-PD-L1 (avelumab, durvalumab) and/or an anti-CTLA-4 (ipilimumab). The first injection of the ICI was performed between January 2014 and June 2017. The exclusion criterion was a refusal from the patients to participate.

The primary endpoint was to assess the efficacy of ICI in NSCLC and melanoma using the progression-free survival (PFS) defined as the time from ICI initiation to the first sign of progression or death from any cause.

The secondary objectives for each type of tumors were as follows: overall survival (OS) defined as the time interval between the first administration of ICI and death from any cause, best overall response defined as the best response across all time-point responses according to RECIST 1.1 criteria [13] evaluated by radiologists from each center, analysis of the safety profile according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 including Immune-Related Adverse Events (IRAEs). Finally, we aimed to determine factors associated with survival and toxicity.

Biological monitoring during the treatment was as follows: Blood electrolytes, kidney function (creatinine level, uremia, estimated glomerular filtration rate) and liver function (total serum bilirubin, aspartate transaminase, alanine transaminase, γ-glutamyl transferase, alkaline phosphatase levels) were assessed before each injection. Thyroid-stimulating hormone and free T4 were assessed every month. Other biological tests were performed according to clinical examination and suspicion of treatment toxicity.

There was no standardized protocol for CT evaluation. CT evaluation was scheduled according to the choice of the investigator at each center.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the French Advisory Committee on Information Processing in Health Research (CCTIRS). If patients were alive, they received written information on the study. For deceased patients, an exemption of information was obtained from CCTIRS.

Patient data were obtained retrospectively from medical files and included demographics, performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) score [14], nutritional status (albumin, body mass index, weight loss), number of medications, geriatric parameters (G8 score [15], Charlson comorbidity index, Instrumental Activities of Daily Living score, Activities of Daily Living score), characteristics of NSCLC or melanoma, number and localization of metastatic sites, use of antibiotics or baseline corticosteroids (taken during the previous three months of treatment or during treatment) or treatment with corticosteroids for toxicity management, previous anticancer treatments, and anticancer treatments after progression. Former smokers were patients who had quit smoking for more than 6 months.

Statistical analysis

Descriptive analyses were used to summarize study sample characteristics, toxicity, and efficacy data. PFS and OS were estimated using the Kaplan Meier method. Baseline clinical and laboratory parameters were evaluated in a univariable model. For the multivariate analysis, the choice of variables to include in the final model was made taking into account current clinical and literature data or 10% statistical significance in univariate analysis were entered into a Cox proportional hazards model. Hazard ratios (HR) and 95% confidence intervals (95% CI) were computed from the estimated parameters of the final regression model. Groups were compared using the Chi-square or Fisher Exact test, as appropriate, for categorical variables, or by the Student *t*-test or Wilcoxon-Mann Whitney test, as appropriate, for continuous variables. The first-degree error alpha was fixed to 0.05 bilaterally. Statistical analysis was performed using 'R' statistical software, version 3.6.3.

Results

Patient characteristics

A total of eighty-two patients were enrolled in fourteen centers, one patient was excluded because he had two types of cancer. Forty-five patients had melanoma, 36 patients had NSCLC. The baseline characteristics of the patients are summarized in Table 1 and are detailed by type of cancer. The median age of patients at the beginning of ICI was 82 (range 80–93). Their comorbidities are summarized in Supplementary table S1. Thirty-two (88.9%) patients with NSCLC and 39 (86.7%) patients with melanoma had at least one comorbidity. The patients treated for NSCLC had more comorbidities than those treated for melanoma, especially regarding the cardiovascular diseases. The median number of comorbidities was 3 (range 0–9), 2 (0–6) in the melanoma group and 4 (0–9) in the NSCLC group. The median Charlson comorbidity index was 11 (range 6–14), 10 (6–13) in the melanoma group and 11 (6–14) in the NSCLC group. The median LDH level in the melanoma group was 352.5 IU/L (IQR 289.2–422.2). A large majority of the patients (84%) lived at home at the beginning of the treatment by ICI, with no disparity between NSCLC and melanoma. 22% of them lived alone, five patients lived in an institution. The median number of medications by patient was 5 (range 0–14), there was no difference between the two groups. The screening geriatric tool G8 was notified in only 27.2% of the patients, with no difference between NSCLC and melanoma. 19/22 (86.4%) patients had a G8 score $\leq$ 14. Finally, 25.9% of the patients underwent a geriatric evaluation before treatment by ICI (14.4% in NSCLC and 31.1% in melanoma).

In the NSCLC group, EGFR was mutated in 4.8% of cases. In the melanoma group, BRAF was mutated in 4.4% of cases, NRAS in 28.9% and cKIT in 2.2%.

A very large majority of patients ($n = 76$, 93.8%) had a metastatic disease at the beginning of the treatment by ICI. Ten (12.4%) patients had brain metastases, one (2.8%) in the NSCLC group and nine (20.0%) in the melanoma group. Prior to the ICI, a surgery was performed in 19.4% and 75.6% in the NSCLC and melanoma groups, respectively. Only 11.1% of the total population received a previous radiotherapy. For patients with brain metastases, three patients were treated with radiotherapy and one patient was treated with surgery followed by radiotherapy, shortly before initiation of ICI,

Table 1. Patient characteristics by disease.

Characteristics	Overall population ($n = 81$)	NSCLC ($n = 36$)	Melanoma ($n = 45$)
Sex, *n* (%)			
Female	40 (49.4)	10 (27.8)	30 (66.7)
Male	41 (50.6)	26 (72.2)	15 (33.3)
Median age at treatment initiation, years (range)	82 (80–93)	82 (80–87)	83 (80–93)
Smoking status, *n* (%)			
Nerve smoker	45 (55.6)	9 (25.0)	36 (80.0)
Smoker	4 (4.9)	3 (8.3)	1 (2.2)
Former smoker	28 (34.6)	21 (58.3)	7 (15.6)
Passive smoker	2 (2.5)	2 (5.6)	0
Unknown	2 (2.5)	1 (2.8)	1 (2.2)
ECOG performance status, *n* (%)			
0	18 (22.2)	4 (11.1)	14 (31.1)
1	45 (55.6)	22 (61.1)	23 (51.1)
2	10 (12.4)	7 (19.4)	3 (6.7)
3	1 (1.2)	3 (8.3)	1 (2.2)
Unknown	7 (8.6)	0	4 (8.9)
Metastatic disease, *n* (%)			
Yes	76 (93.8)	33 (91.7)	43 (95.6)
No	5 (6.2)	3 (8.3)	2 (4.4)
Number of sites of metastasis, *n* (%)			
1	32 (39.5)	15 (41.7)	17 (37.8)
2	23 (28.4)	10 (27.8)	13 (28.9)
3	12 (14.8)	7 (19.4)	5 (11.1)
$\geq$4	14 (17.2)	2 (5.6)	8 (17.8)
Site of metastasis, *n* (%)			
Lymph node	43 (53.1)	16 (44.4)	27 (60.0)
Lung	34 (42.0)	15 (41.7)	19 (42.2)
Cutaneous/subcutaneous	18 (22.2)	0	18 (40.0)
Bone	14 (17.3)	8 (22.2)	6 (13.3)
Liver	13 (16.1)	7 (19.4)	6 (13.3)
Pleural	11 (13.6)	11 (30.6)	0
Central nervous system	10 (12.4)	1 (2.8)	9 (20.0)
Number of prior systematic therapies, *n* (%)			
0	43 (53.1)	3 (8.3)	40 (88.9)
1	22 (27.2)	18 (50.0)	4 (8.9)
2	15 (18.5)	14 (38.9)	1 (2.2)
3	1 (1.2)	1 (2.8)	0
Baseline corticosteroid therapy, *n* (%)	14 (17.3)	7 (19.4)	7 (15.6)

ECOG: Eastern Cooperative Oncology Group.

in the melanoma group. The patient with brain metastases in the NSCLC group was not specifically treated.

Fifty-five patients (67.9%) received nivolumab, twenty-three (28,4%) received pembrolizumab, two (2.5%) ipilimumab, and one (1.2%) avelumab. In the NSCLC group, the ICI was administered in first line in 8.3% of the patients, 50.0% in second line, 41.7% in third line or more. In the melanoma group, ICI was administered in first line in 88.9% of the patients, 8.9% in second line, 2.2% in third line or more. The median number of doses of ICI received by patients was five doses (range 1–38) in the NSCLC group and nine doses (range 1–61) in the melanoma group.

Survival rates

After a median follow-up of 12.6 months (range 0.4–43.3), median PFS was 2.3 months (95%CI 1.8–6.1) in the NSCLC group. Median OS was 8.8 months (95%CI 5.5–18.1). OS rate at 12 months was 42% (Figure 1). The best overall response was partial response in 4 (11.1%) patients, stable disease in 9 (25.0%), dissociated response in 1 (2.8%) and progressive disease in 22 (61.1%). There was no complete response in the NSCLC group.

The univariate and multivariate analyses revealed no factor associated with PFS in the NSCLC group, including age (Supplementary table S2). A Cox regression model was used to explore the association of the BMI, the albumin level and the treatment discontinuation for toxicity with OS. At multivariate analysis, a higher BMI (HR = 0.85, 95%IC 0.74–0.98, *p* value 0.02) and albumin level (HR = 0.87, 95%IC 0.78–0.96, *p* value 0.008) were found to be independently associated with a better OS (Table 2).

In the melanoma group, median PFS was 10.2 months (95%CI 4.5–20.0). Median OS was 24.5 months (95%CI 14.1-NR). OS rate at 12 months was 69% (Figure 2). The best overall response was complete response in 4 (8.9%) patients, partial response in 17 (37.8%), stable disease in 3 (6.7%), dissociated response in 3 (6.7%) and progressive disease in 18 (40%).

The univariate and multivariate analyses revealed no factor of interest associated with PFS in the melanoma group, including age (Supplementary table S3). A Cox regression model was used to explore the association of the albumin level and a baseline corticosteroid therapy (during the previous three months or during the treatment by ICI, not for treatment of toxicity) with OS. At multivariate analysis, the albumin level (HR = 0.87, 95%IC 0.77–0.99, *p* value 0.03) was found to be independently associated with a better OS (Table 3).

A large majority of patients ($n = 78$, 96.2%) died due to disease progression. One patient died from treatment toxicity. Two patients died due to other causes.

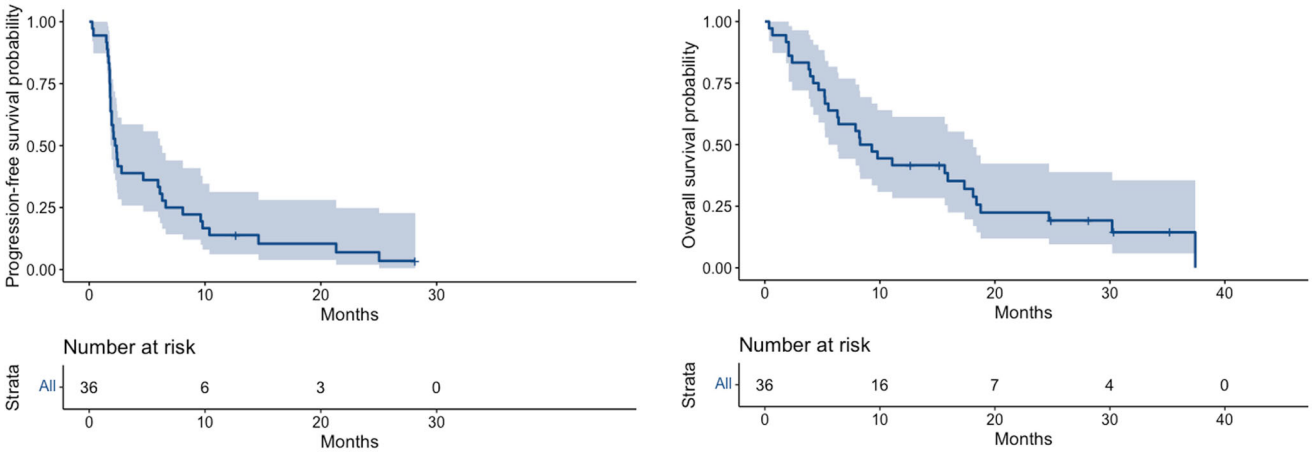

Figure 1. Progression-free survival and overall survival curves for the non-small cell lung cancer group.

Table 2. Univariate and multivariate survival analyses (overall survival) in the NSCLC group.

	Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (continuous)	1.04 (0.88–1.23)	0.66	–	–
Body mass index (continuous)	**0.91 (0.82–0.99)**	**0.04**	**0.85 (0.74–0.98)**	**0.02**
Weight loss (continuous)	0.65 (0.14–3.01)	0.58	–	–
Albumin level (continuous)	**0.90 (0.83–0.98)**	**0.01**	**0.87 (0.78–0.96)**	**0.008**
Performance status (from 0 to 3)	1.03 (0.54–1.97)	0.93	–	–
Metastatic disease (yes vs no)	0.42 (0.12–1.48)	0.18	–	–
Brain metastases (yes vs no)	1.27 (0.17–9.54)	0.81	–	–
Number of treatment lines (from 0 to 2)	0.99 (0.53–1.86)	0.96	–	–
Charlson comorbidity index (continuous)	0.92 (0.67–1.25)	0.59	–	–
Number of medications (continuous)	1.03 (0.91–1.17)	0.64	–	–
Baseline corticosteroid therapy (yes vs no)	0.40 (0.08–2.04)	0.27	–	–
Antibiotherapy (yes vs no)	0.86 (0.25–2.97)	0.81	–	–
Treatment after ICI (yes vs no)	0.60 (0.28–1.36)	0.23	–	–
Treatment discontinuation for toxicity (yes or no)	**0.27 (0.08–0.91)**	**0.04**	1.38 (0.24–7.83)	0.71

HR: hazard ratio; 95% CI: 95% confidence interval; *p*: *p*-value.
Values in bold are the statistically significant results of the analysis.

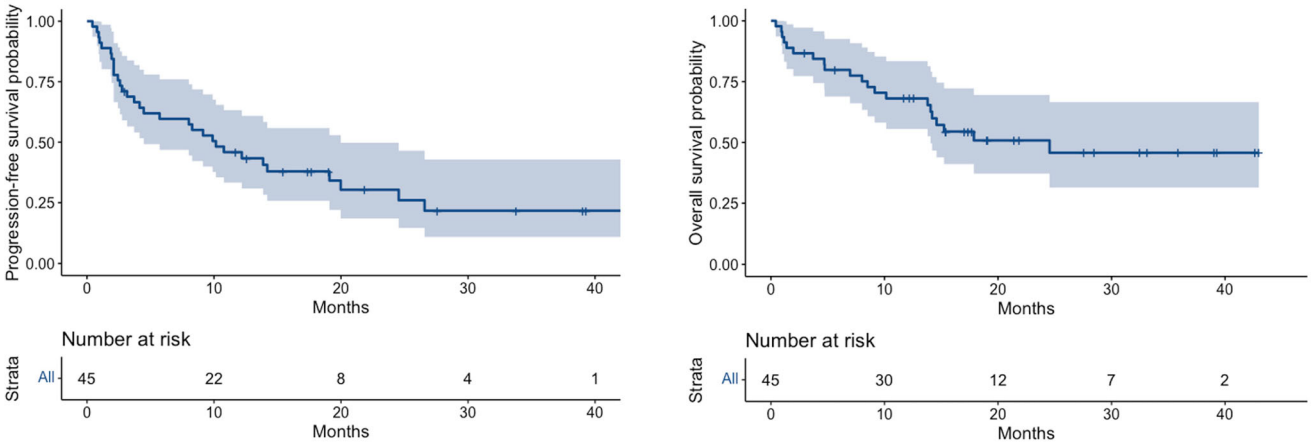

Figure 2. Progression-free survival and overall survival curves for the melanoma group.

Safety

Thirty-four patients (42%) experienced IRAEs of any grade, 44% in the NSCLC group and 40% in the melanoma group. Grade 1–2 toxicities occurred in eighty patients (22.2%), 25% in the NSCLC group and 20% in the melanoma group. Grade 3–4 toxicities occurred in fifteen patients (18.5%), 16.7% in the NSCLC group and 20% in the melanoma group. One patient died from ICI-induced pulmonary toxicity in the melanoma group. The most frequently reported IRAEs of any grade were cutaneous toxicity (11.1%), diarrhea (9.9%), fatigue (9.9%), pneumonitis (6.2%), thyroid dysfunction (4.9%). Two patients had increased blood creatinine level and two had autoimmune hepatitis. The ICI was discontinued for toxicity in 17.3% of the patients, 19.4% in the NSCLC group and 15.6% in the melanoma group. In each group, systemic corticosteroids were used for 5 patients. In the melanoma group, one patient received anti TNFα. Hospitalization was required for 9 patients (11.1%) due to treatment toxicity, three (8.3%) and six (13.3%) in the NSCLC and melanoma groups, respectively.

Table 3. Univariate and multivariate survival analyses (overall survival) in the melanoma group.

	Univariate analysis		Multivariate analysis	
Characteristics	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (continuous)	1.01 (0.90–1.13)	0.92	–	–
Body mass index (continuous)	1.05 (0.95–1.17)	0.32	–	–
Weight loss (continuous)	1.46 (0.44–4.80)	0.24	–	–
Albumin level (continuous)	**0.88 (0.78–0.99)**	**0.04**	**0.87 (0.77–0.99)**	**0.03**
Performance status (from 0 to 3)	1.83 (0.96–3.49)	0.07	–	–
Metastatic disease (yes vs no)	1.46 (0.20–10.97)	0.71	–	–
Brain metastases (yes vs no)	2.13 (0.77–5.86)	0.14	–	–
Number of treatment lines (from 0 to 2)	1.20 (0.50–2.92)	0.68	–	–
Charlson comorbidity index (continuous)	1.09 (0.76–1.57)	0.63	–	–
Number of medications (continuous)	1.02 (0.92–1.15)	0.65	–	–
Baseline corticosteroid therapy (yes vs no)	**3.10 (1.13–8.54)**	**0.03**	1.68 (0.18–15.93)	0.65
Antibiotherapy (yes vs no)	2.40 (0.25–23.36)	0.45	–	–
Treatment after ICI (yes vs no)	0.48 (0.06–3.58)	0.47	–	–
Treatment discontinuation for toxicity (yes or no)	0.96 (0.32–2.87)	0.95	–	–

HR: Hazard ratio; 95% CI: 95% confidence interval; *p*: *p*-value.
Values in bold are the statistically significant results of the analysis.

The univariate analysis revealed no factor of interest associated with toxicity, including age. Grade 3–4 IRAEs were not associated with OS (HR = 0.65, 95%CI 0.31–1.40, *p* value 0.27), PFS (HR = 0.66, 95%CI 0.34–1.26, *p* value 0.21) or response rate ($p = 0.14$).

Discussion

Our study was exclusively dedicated to patients aged 80 or older to evaluate efficacy and safety of ICI.

In the melanoma group, median PFS was 10.2 months (95%CI 4.5–20.0), median OS was 24.5 months (95%CI 14.1–NR) and OS rate at 12 months was 69%. Our results are close to those reported in randomized controlled trials on younger populations (Table 4). We showed a lower OS, however the median follow-up of the study was short (12.6 months) and the upper bound of the confidence interval was not reached [16]. Our results are in line with the literature comparing patients aged 80 or older and younger patients with melanoma receiving ICI, showing similar efficacy [17]. Jain et al. even showed a greater benefit for older patients, comparing patients 60 years or older to younger patients [18].

Surprisingly, BRAF mutation rate was lower in our study compared to the literature: 4.4% versus 40–60% in patients with cutaneous melanoma regardless of age. In contrast, NRAS mutation rate was higher: 28.9% versus 10–20%, respectively [19]. The low BRAF mutation rate may be explained by selection bias. Patients with melanoma without BRAF mutation are treated with ICI. Patients with BRAF-mutated melanoma are treated in first line with either ICI or targeted therapy depending on the disease progression. In the melanoma group, ICI was administered in first line in 88.9% of the patients. It is therefore likely that in our real-life cohort we have more patients without BRAF mutation due to a selection bias. Moreover, Egberts et al. showed that BRAF V600E mutations were significantly more prevalent in younger patients ($p = 0.002$) and NRAS in older patients ($p = 0.026$) [20]. An active role for UV irradiation in induction of the NRAS mutation has been suggested [21].

In the lung cancer group, median PFS, median OS and OS rates at 12 months were 2.3 months (95%CI 1.8–6.1), 8.8 months (95%CI 5.5–18.1) and 42%, respectively. These results were lower to those reported in the literature (Table 4). The lower median OS in the NSCLC group may be due to the higher proportion of patients treated in third line. The high proportion of comorbidities (88.9% of the patients, median of 4 (range 0–9) comorbidities, median Charlson comorbidity index of 11 (range 6–14)) in the NSCLC group may be another plausible explanation. The presence of comorbidities in patients with lung cancer has been shown to be independently associated with short-term mortality [22]. This result appears to be consistent with patients with advanced NSCLC treated with ICI [23].

At multivariate analysis, a higher BMI was independently associated with a better OS in the NSCLC group. The albumin level was independently associated with a better OS in both groups. Albumin level has been shown to be a prognostic marker of survival in patients with cancer [24]. However, the pathophysiology of this association remains unclear. Albumin reflects the patient's nutritional status and state of inflammation. Low albumin level may reflect a cachexia-sarcopenia syndrome that impacts mortality [25]. Albumin also has an impact on the pharmacokinetics of ICI. Low albumin has been shown to increase the clearance of ICI, which might have an impact on the efficacy of ICI [26]. However, BMI or albumin was not a factor associated with PFS in any group. Albumin level does not appear to be associated with response to treatment in our study, but only with survival. Baseline corticosteroid therapy was associated with poorer OS in univariate analysis but not in multivariate analysis in the melanoma group. This effect might be driven by a poor prognosis of patients who receive corticosteroids for palliative indications [27].

The most frequently reported IRAEs in our study were cutaneous toxicity (11.1%), diarrhea (9.9%), fatigue (9.9%), pneumonitis (6.2%), thyroid dysfunction (4.9%), which is in line with what has been previously described [28,29].

Grade 3–4 toxicities occurred in 16.7% of the NSCLC group and 20% of the melanoma group, which was higher than in other cohorts of patients aged 75 and older (7% reported by Grossi et al. [28]; 6% reported by Ridolfi et al. [29]). Therefore, IRAEs leading to discontinuation occurred

Table 4. Comparative table of randomized controlled studies, real-life studies, and the present study.

Cancer type	NSCLC				Melanoma			
Trial	Brahmer et al. [6]	Borghaei et al. [5]	Grossi et al. [28]	The present study	Robert et al. [1]	Robert et al. [16]	Ridolfi et al. [29]	The present study
Design	Phase III RCT	Phase III RCT	Retrospective analysis of a prospective cohort	Retrospective cohort study	Phase III RCT	Phase III RCT (post-hoc 5-year results)	Retrospective cohort study	Retrospective cohort study
Number of patients treated by the ICI	135	292	232 $\geq$ 75 years	36	210	556	174	45
Treatment line	Second (all but one)	Second or third	Second and more	Second and more mostly	First	First or second	First and more	First mostly
Median age (range)	62 (39–85)	61 (37–84)	77 (75–89)	82 (80–87)	64 (18–86)	62 (18–89)	79 (75–93)	83 (80–93)
Follow up	Minimum of 11 months	Minimum of 13.2 months	Median of 8.3 months (range 0.1–20)	Median of 12.6 months (range 0.4–43.3)	Median of 8.9 months	Median of 57.7 months (IQR 56.7–59.2)	Median of 8.97 months (range 0.43–45.53)	Median of 12.6 months (range 0.4–43.3)
ICI type	Nivolumab	Nivolumab	Nivolumab	Nivolumab	Nivolumab	Pembrolizumab	Nivolumab and pembrolizumab	Nivolumab and pembrolizumab mostly
Median number of dose (range)	8 (1–48)	6 (1–52)	11 (range 1–39)	5 (1–38)	Not available	Not available, but median drug exposure duration of 6.0 months (IQR 2.8–20.3)	Not available	9 (1–61)
Median OS with ICI	9.2 months (95%CI 7.3–13.3)	12.2 months (95%CI 9.7–15.0)	12.0 months (95% CI 9.2–14.8)	8.8 months (95%CI 5.5–18.1)	Not reached	32.7 months (95%CI 24.5–41.6)	17.2 months (95%CI 8.87-not reached)	24.5 months (95%CI 14.1-not reached)
Median PFS with ICI	3.5 months (95%CI 2.1–4.9)	2.3 months (95%CI 2.2–3.3)	4.2 months (95% CI 3.0–5.4)	2.3 months (95%CI 1.8–6.1)	5.1 months (95% CI 3.5–10.8)	8.4 months (95%CI 6.6–11.3)	8.11 months (95% CI 6.6–13.37)	10.2 months (95%CI 4.5–20.0)
All grades toxicity, %	58	69	34	44	74.3	80	Not available	40
Grade 3–4 toxicity with ICI, %	7	10	7	16.7	5.8	17	6.3	20
Treatment discontinuation because of toxicity, %	3	5	Not available	19.4	6.8	10	Not available	15.6
Treatment-related death, *n*	0	1 (Encephalitis)	0	0	0	1 (Sepsis)	0	1 (Pneumonitis)

NSCLC: non-small cell lung cancer; RCT: randomized controlled trials; IQR: interquartile range; 95% CI: 95% confidence interval.

more frequently in our study: 19.4% in NSCLC group and 15.6% in melanoma group. In a large cohort of patients aged 80 and older, Nebhan et al. found close results [30]. In checkmate 171 [31], the percentages of treatment-related adverse events (TRAEs) and grade 3–4 toxicities slightly increased with age between patients $\geq$70 years and $\geq$75 years. Table 4 provides a comparison of two randomized controlled pivotal studies, a retrospective study focused on the population of interest, and the present study in each group. Ten (12.3%) patients were receiving corticosteroid therapy for IRAEs. The recommended starting dose of corticosteroids is 0.5–2 mg/kg/day depending on the grade of toxicity [32]. Corticosteroids, especially at high doses, can induce decompensation of comorbidities (diabetes, congestive heart failure, underlying mood disorder), but also lead to drug interactions in these patients with polypharmacy.

In our study, less than one-third of the patients had a G8 score assessment before the initiation of the treatment. A large majority of the patients evaluated had a G8 score $\leq$ 14. Therefore, it was not possible to distinguish fit from unfit patients. Gomes et al. showed in patients with advanced NSCLC or melanoma aged 70 years or older treated with ICI that 50% of them had a G8 score $\leq$ 14. Moreover, a G8 score $\leq$ 14 was associated with a greater risk of hospitalization and death. These patients completed a global geriatric assessment, which revealed that comorbidity, polypharmacy and capacity to perform activities of daily living were the most commonly affected components [33]. Geriatric assessment should be routine in this population prior to initiation of ICI and during treatment, especially if toxicity occurs, to identify frail patients [34].

The main strength of this study is its real-life design concerning unselected patients aged 80 years or older, which can help the clinician for therapeutic choices. The study was conducted in 14 centers, improving the generalizability of the results. However, the retrospective nature of this study implies some limitations, including missing data, heterogeneity of population and follow-up. The small sample size also limited our ability to conclude and identify predictive factors of efficacy and toxicity in subgroup analysis. Nonsystematic G8 score and geriatric assessments could have deemed our ability to discriminate fit from unfit octogenarians.

Conclusion

Our study findings suggest that treatment with ICI in elderly patients with NSCLC and melanoma has a risk-benefit ratio that supports its use. However, we report in this cohort that one in five patients has a grade 3–4 IRAEs leading to treatment discontinuation. Geriatric assessment prior to initiation of therapy and during therapy should be routine in patients aged 80 years and older. Nutritional assessment and intervention, if necessary, should be systematically considered. More data about unfit patients aged 80 or older are needed, especially in NSCLC.

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Disclosure statement

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Data availability statement

Data could be provided if needed.

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