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ORIGINAL ARTICLE

Older melanoma patients aged 75 and above retain responsiveness to anti-PD1 therapy: results of a retrospective single-institution cohort study

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Abstract

Introduction The utility of immunotherapy in elderly melanoma patients is debated. We aimed in this study to evaluate the efficacy and tolerability of immunotherapy among elderly patients.

Method This is a retrospective single-institution cohort study. Patients aged 75 years and above who had been treated with nivolumab, pembrolizumab or ipilimumab for advanced or metastatic melanoma, were included. Patients and disease characteristics were collected using electronic medical records. Objective response was determined according to the immune-related response criteria. Drug-related toxicities (DRT) were graded according to the CTCAE v4.03.

Results 99 patients were included with a mean age of 80 years (SD = 4). One patient received nivolumab and ipilimumab combination, but died because of drug-related diverticulitis. Median PFS on pembrolizumab, nivolumab or ipilimumab were equal to 11.9 (95% CI 5.4–18.4), 1.4 (95% CI 0.01–2.8), and 2.8 months (95% CI 2.6-3), respectively, while objective response rates were equal to 51.6, 12.5, and 17.3%, respectively. Median OS was not reached in patients who received only pembrolizumab, 8.7 months in the ipilimumab only group, and 23 months in patients receiving several immune therapies sequentially. Pembrolizumab, nivolumab, and ipilimumab grade 3–4 DRT rates were equal to 24.2, 62.5, and 32.7% respectively, while discontinuation rates were equal to 43.5, 62.5, and 28.8%, respectively.

Conclusions Our study suggests that immunotherapy is effective and well tolerated in the elderly. The PFS on pembrolizumab was greater than expected, a finding that needs to be investigated further.

Keywords Melanoma · Immunotherapy · Elderly · Anti-PD1 · Anti-CTLA4

Abbreviations

ADL	Activities of daily living
AJCC	American Joint Committee on Cancer
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DRT	Drug-related toxicity
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
irRC	Immune-related response criteria
mAb	Monoclonal antibodies
ORR	Overall response rate
PASW	Predictive Analytics Software
PR	Partial response
PS	Performance status
RCT	Randomized controlled trial
StD	Stable disease

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Introduction

The incidence of melanoma is increasing, especially among the elderly [1]. Immunotherapy is a major breakthrough in modern cancer therapy which has led to the approval of anti-CTLA-4 and anti-PD-(L)1 monoclonal antibodies (mAb) for

the treatment of patients with advanced or metastatic melanoma [2]. Although there was no age limit among the criteria for inclusion of clinical trials that led to the approval of these drugs, the proportion of elderly people was small [3]. This is partly due to physicians and patients worries about adverse events in a more vulnerable population. Furthermore, some physicians believe that immunotherapy is less effective in the elderly because of immune senescence. This is supported by in vitro and animal studies which showed that immune function is weakened by age [4, 5]. A meta-analysis was published by Nishijima et al. and concluded that immunotherapy could be of less or no benefit in patients aged more than 75 years [6]. However, this meta-analysis included different types of cancer and different age cut-offs. A few studies suggested the opposite, but included a limited number of patients [7–9]. Furthermore, tolerability of anti-PD-(L)1 and anti-CTLA-4 mAb has not been specifically evaluated in the elderly [10, 11], except in the study reported by Betof et al. [9] which found no significant difference in immune-related toxicity across age groups.

The aim of the present study was to evaluate the efficacy and tolerability of immunotherapy among elderly patients diagnosed with advanced or metastatic melanoma.

Method

This retrospective cohort study included all patients aged 75 years and above and who were treated with nivolumab, pembrolizumab or ipilimumab for advanced or metastatic melanoma between January 2013 and December 2016 in the dermatology department of the Gustave Roussy Institut (Villejuif–France). Patients who lacked essential information about the efficacy and tolerability of treatment were excluded. Data were collected using electronic medical records. The following characteristics were registered prior to immunotherapy: age, sex, known or unknown primary, histologic sub-type of melanoma [12], presence or absence of ulceration, BRAF and NRAS mutational status, cancer stage according to the American Joint Committee on Cancer (AJCC) seventh version [13], performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) score [14], previous cancer therapy, presence or absence of lymph node invasion, and the presence or absence of visceral or central nervous system (CNS) metastasis. Progression-free survival (PFS) was defined as the time from initiation of immunotherapy to objective clinical or radiological tumor progression. Overall survival (OS) was defined as the time from initiation of immunotherapy till death from any reason. Overall response rate (ORR) was defined as the sum of complete response (CR) and partial response (PR) according to the immune-related response criteria (irRC) [15], while disease control rate (DCR) was defined as the sum of ORR and stable disease (StD). Drug-related toxicities (DRT) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [16]. July 2017 was the last date of follow up. Statistical analysis was performed using the Predictive Analytics SoftWare (PASW) version 22. Kaplan–Meier estimates were used to calculate the probability of survival and multivariate Cox regression model to explore the association between survival and patients/disease characteristics. The first-degree error alpha was fixed to 0.05 bilaterally.

Results

One hundred eighteen patients were included among whom 19 patients had to be excluded (Fig. 1). Among the excluded patients, 7 received only one cycle of treatment in our

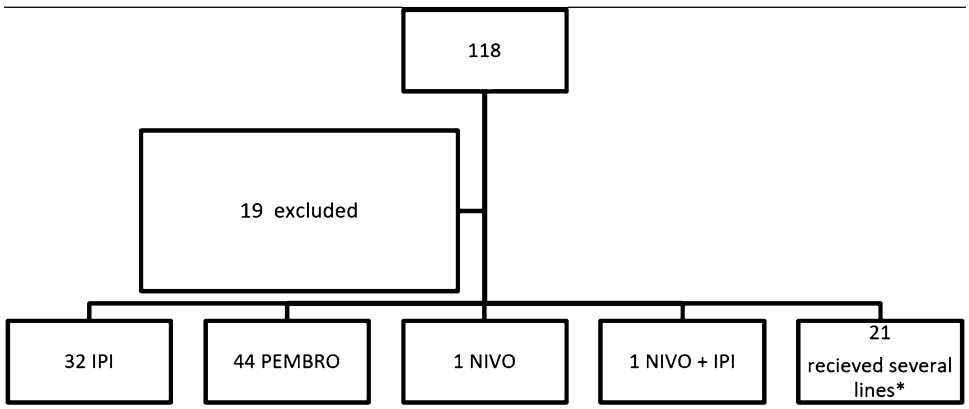

Fig. 1 Consort diagram. *Eighteen patients received 2 lines of immunotherapy as follows: 8 received ipilimumab then pembrolizumab, 6 pembrolizumab then ipilimumab, 3 ipilimumab then nivolumab, and 1 pembrolizumab then nivolumab. Three patients received 3 lines of immunotherapy as follows: 2 received ipilimumab then pembrolizumab then nivolumab and 1 pembrolizumab then ipilimumab then nivolumab. *ipi* ipilimumab, *nivo* nivolumab, *pembro* pembrolizumab

institution but were lost to follow up, 7 other patients took part in randomized double-blind trials evaluating immunotherapy versus placebo, and 5 patients received immunotherapy combined with other drugs. Of the remaining 99 eligible patients, 53 were males and 46 females. BRAF was mutated in 18.9% of cases, NRAS in 37%, and cKIT in 6.2%. Mean age at first immunotherapy was 80 years [standard deviation (SD) = 4 and a range between 75 and 92 years]. Most patients had metastatic melanoma before first immunotherapy (77.8%). As for the PS, 68.7, 27.3, and 4% had ECOG PS 0, 1, and 2, respectively. Tumor characteristics at diagnosis as well as previous therapies received before immunotherapy are summarized in Table 1.

Only one patient received the combination of nivolumab and ipilimumab for one cycle but died because of severe drug-related diverticulitis. Sixty-two patients (62.2%) received pembrolizumab, 8 (8.1%) nivolumab, and 52 (52.5%) ipilimumab. Response rates are summarized in Table 2, while PFS and OS survival curves are illustrated in Figs. 2 and 3, respectively. After a median follow-up of 24 months, 41 patients were still alive (among whom 5 patients were still receiving immunotherapy), 51 were reported to be dead and 7 lost to follow up (4 patients in the pembrolizumab group after a median follow up of 8 months, and 3 patients in the ipilimumab group after a median follow up of 10 months). Median follow up of the whole sample was equal to 18.3 months [95% confidence interval (CI) 8.6–28]. Median OS in the group of 44 patients who received only pembrolizumab as immunotherapy was not reached, while it was equal to 8.7 months for the 32 patients who received only ipilimumab, and 23 months for the 21 patients who received several types of immunotherapy sequentially (Fig. 3).

Table 1 Tumor characteristics at diagnosis

	%
Histologic subtype $n = 73$	
Superficial spreading melanoma of the skin	39.8
Nodular melanoma	19.2
Acral lentiginous melanoma	17.8
Mucosal melanoma	13.7
Lentigo maligna melanoma	5.5
Not otherwise specified	3.8
Uveal melanoma	1.4
Ulceration $n = 49$	
No	40.8
Yes	59.2
Primary tumor location $n = 99$	
Known	91.8
Unknown	8.1
Stage at diagnosis $n = 99$	
Stage I–II	58.6
Stage III	28.3
Stage IV	13.1
Type of systemic therapies prior to first immunotherapy $n = 99$	
Interferon	3
Chemotherapy	22.2
BRAF inhibitors	8.1
BRAF + MEK inhibitors	5.1
No prior therapy	61.6
The site of metastatic involvement prior to immunotherapy $n = 99$	
Lymph nodes	80.8
Visceral metastasis	62.6
Central nervous system metastasis	20.2

Table 2 Best response according to each immunotherapy

	ORR (%)	DCR (%)
Pembrolizumab	51.6	67.7
Nivolumab	12.5	37.5
Ipilimumab	17.3	23.1

DCR disease control rate, *ORR* overall response rate

Among the 62 patients who received pembrolizumab, the median number of cycles was equal to 9 (SD 8, range 1–31). After a median follow up of 26.5 months, median PFS was equal to 11.9 months (95% CI 5.4–18.4) (Fig. 2a), and 1 and 2-year PFS rates were equal to 46 and 23%, respectively. A Cox regression model was used to explore the association between PFS and the following factors: age, sex, BRAF and NRAS status, ulceration, ECOG PS, and cancer stage (metastatic or locally advanced). Age was found to be independently associated with a better survival (regression coefficient $B = 0.2$, p value 0.045).

Among the 8 patients who received nivolumab, the median number of cycles was equal to 5 (SD 7, range 2–24). After a median follow up of 5.7 months, median PFS was equal to 1.4 months (95% CI 0.01–2.8) (Fig. 2b). Among the 4 patients who received nivolumab as a re-challenge after pembrolizumab (Fig. 1), 2 patients had StD (PFS 14.1 and 34.8 months) but discontinued treatment because of DRT, while 2 other patients progressed at 7.1 and 13.7 months.

Among the 52 patients who received ipilimumab, the full course (4 cycles) was administered to 30 patients (57.7%) among whom one patient received 2 additional cycles as a re-challenge. As for the others, 3 (5.8%), 12 (23%), and 7 patients (13.5%) received 1, 2 and 3 cycles, respectively. After a median follow up of 50 months, median PFS was equal to 2.8 months (95% CI 2.6–3), while 1 and 2-year PFS rates were both equal to 13% (Fig. 2c). No factor was independently associated with survival on the Cox regression model (data not shown).

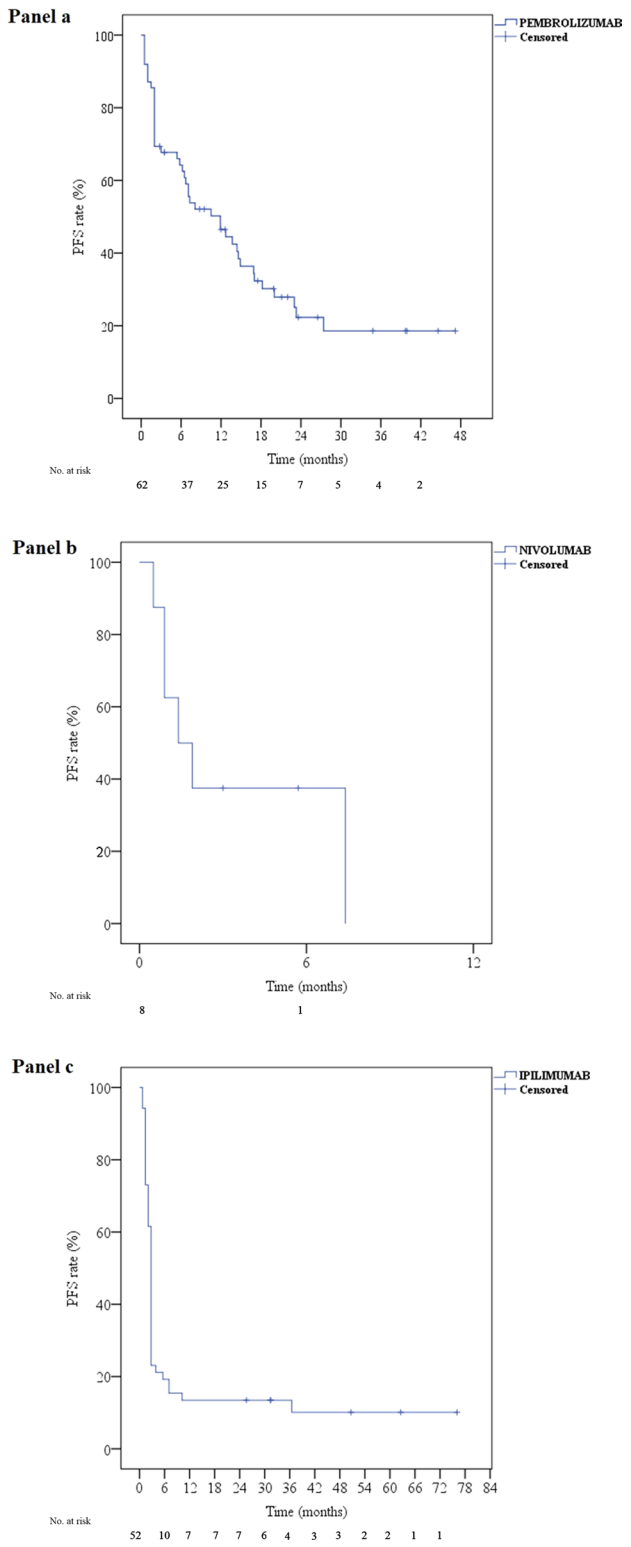

Fig. 2 progression free survival curves for pembrolizumab (**a**), nivolumab (**b**) and ipilimumab (**c**). *PFS* progression free survival

Tolerability

In total, 80.6, 100, and 86.5% of patients had at least grade 1 DRT during the treatment with pembrolizumab, nivolumab, and ipilimumab respectively. Because of drug toxicity, 43.5, 62.5, and 28.8% discontinued pembrolizumab, nivolumab, and ipilimumab, respectively. Serious DRT occurred in 15 patients (24.2%) receiving pembrolizumab, in 5 patients (62.5%) receiving nivolumab, and in 17 patients (32.7%) receiving ipilimumab. During treatment with pembrolizumab, 4 patients suffered from acute kidney injury (interstitial nephritis), 3 developed hypersensitivity pneumonitis, 3 severe colitis, 3 severe fatigue limiting self-care activities of daily living (ADL), 1 liver failure, 1 severe deep vein thrombosis (DVT), and 1 peripheral auditory neuropathy. During nivolumab treatment, 1 patient developed acute hepatitis, 1 fatigue limiting ADL, 1 severe colitis, 1 peripheral motor neuropathy, and 1 pneumonitis. During ipilimumab treatment, 9 patients developed colitis, 1 confusion, 3 fatigue limiting ADL, 2 severe maculopapular rash, 1 acute kidney injury, and 1 acute hepatitis. All immune-related toxicities were successfully treated with steroids, except 2 patients who suffered severe colitis refractory to steroids and who had required infliximab therapy (one patient receiving pembrolizumab and another patient receiving ipilimumab).

Grade 1–2 DRT were mainly cutaneous rash and diarrhea. Vitiligo occurred in 11 patients (17.7%) during pembrolizumab treatment. Endocrine disorders occurred in 5 patients among whom 4 had hypothyroidism and 1 adrenal insufficiency treated with hormone replacement therapies. Immune-related grade 2 adverse events occurred in 3 patients: 1 bullous pemphigoid, 1 anterior uveitis, and 1 Sjogren's syndrome, and were all successfully treated with steroids.

Discussion

This study showed that nearly half of elderly patients treated with pembrolizumab did not experience melanoma progression after 1 year of follow up, and one-fourth after 2 years. Median PFS was equal to nearly 1 year, and the survival curve reached a plateau of 18% after 28 months of follow up. If we compare these results with those reported in randomized controlled trials (RCT) we may assume that pembrolizumab could perform better in elderly patients than in younger ones. For instance, median PFS was equal to 4.1 months in naïve melanoma patients [17], and 2.9 months in ipilimumab refractory patients [18]. The higher the age of the patient the better the efficacy

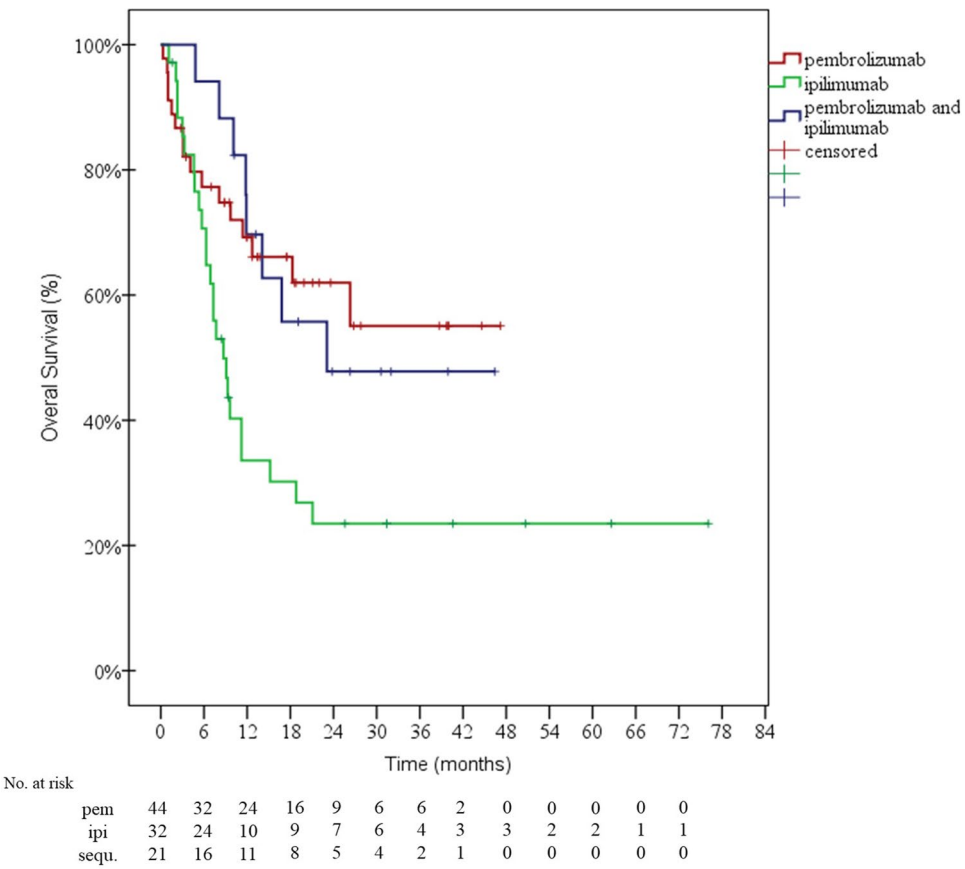

Fig. 3 overall survival curves of the three groups of patients: group A who received only pembrolizumab, group B who received only ipilimumab and group C who received several lines of immunotherapy sequentially. *ipi* ipilimumab, *pem* pembrolizumab, *sequ* sequential therapy

of pembrolizumab was, as shown by the Cox regression model. As for nivolumab, the results reported in this study may not adequately assess its efficacy neither its tolerability. In fact, 7 out of 8 patients had received nivolumab as a re-challenge after pembrolizumab (Fig. 1). In a recent systematic review, Daste et al. showed that the hazard ratio for death among the 67 patients included in the checkmate 006 and who were aged more than 75 years, was equal to 0.25 (95% CI 0.10–0.61) [2, 19]. Regarding the treatment with ipilimumab, 57.7% of patients received 4 cycles of induction while 11.2% progressed during treatment. The results shown in this study are similar to those reported by clinical trials, with a median PFS of nearly 3 months, an ORR between 10 and 15%, and a 1-year PFS rate between 10 and 15% [20–23]. Chiarion Sileni et al. reported the efficacy and safety of ipilimumab in 188 pretreated patients aged 70 years and above who were enrolled in an expanded access program in Italian centers [24]. The results were similar to those reported in this study, with a DCR of 38%, a median PFS of 4 months, and a 1-year PFS rate of 21%.

The combination of nivolumab and ipilimumab could not be evaluated in our study because only one patient had received the combination, but died because of digestive toxicity. In the clinical trials which evaluated nivolumab and ipilimumab combination in patients with advanced or metastatic melanoma, there was no age limit among the inclusion criteria [15, 25, 26], but the proportion of elderly patients was small. For example, only 11.1% of the patients who received the nivolumab and ipilimumab in the checkmate 067 were aged 75 years and above [27]. The results regarding the efficacy and tolerability of the combination in this age group were not available.

Even though the results of this descriptive real-life study could not be directly compared with registration trials, the fact that the response to anti-CTLA-4 mAb was similar to those reported in clinical trials while the response to pembrolizumab was higher than expected, is intriguing. This could be related to the particular molecular profile of melanoma in this age group. The BRAF gene was less frequently mutated in this study compared to the literature (18 versus 40–60% in patients with cutaneous melanoma regardless of age). In contrast, NRAS mutation rate was higher in this study (37 versus 10–20% in large studies) [28, 29]. These findings are consistent with previous studies which have shown that melanoma in the elderly has a different molecular profile than that in young people [30]. It has been suggested that UV-radiations have an active role in inducing RAS mutations [31]. In addition, advanced age was associated with a higher incidence of TP53 mutations in cutaneous

melanoma [30]. Additionally, studies have shown that the mutational load of cancer cells increased with age [32], which might explain why the efficacy of anti-PD(L)-1 is more pronounced in the elderly. Another potential explanation could be related to the cytotoxic T cells. The percentage of highly differentiated CD 28− and CD 27− T cells within the CD8+ T cell pool increases significantly with age [33, 34]. This subgroup is less efficient and contributes to immunosenescence. Henson et al. showed that this subgroup of T cells expresses significantly higher levels of PD1 compared to the undifferentiated more efficient type. Anti-PD-(L)1 mAb were able to enhance the proliferation and activation of differentiated T cells taken from older individuals [34]. More studies highlighted the importance of PD-(L)1 in the age-dependent decline of T cells function, which could be at least partially restored by antibodies targeting PD-(L)1 [35]. Little is known concerning the role of CTLA-4 in the immunosenescence. One study showed that anti-CTLA-4 mAb alone were able to deplete regulatory T cells and induce tumor rejection in young but not in old BL6 mice (melanoma model) [36]. However, this hypothesis is not conclusive, and the difference in efficacy between anti-PD-(1) and anti-CTLA-4 in elderly melanoma patients warrants further investigation.

Except for the only patient who had received the combination of nivolumab and ipilimumab, there was no treatment-related death. The rate of grade 1–2 toxicity related to pembrolizumab was similar to those reported in the literature (between 65 and 85%), with a predominance of skin rash, fatigue, and diarrhea [17, 18, 37]. However, it seemed that vitiligo appears more frequently in the elderly during the treatment with pembrolizumab. The frequency of vitiligo in this study was equal to 17.7% compared to 8.3% (95% CI 4.4–15.2%) in the meta-analysis conducted by Bellum et al. [38].

The frequency of patients who discontinued pembrolizumab due to adverse events was higher than what have been reported in clinical trials (43.5% in our study versus 4–8% in RCTs). In the same way, the frequency of grade 3–4 DRT was also higher in this study (24.2% compared to 10–15% in clinical trials) [17, 18, 39]. It should be noted, however, that the median follow-up and the median number of cycles (or the duration of exposure to treatment) were higher in our study. The types of toxicity were similar to those reported in RCTs apart from immune nephropathy which was described more frequently in our study. Even if we have found higher toxicity rate in patients who received nivolumab, no conclusion could be withdrawn from this study for the same reasons mentioned above. As for ipilimumab, the frequency of DRT as well as treatment discontinuation rate were also higher than what have been reported in clinical trials [20–23], but did not differ from the results published in real-life studies [40–42]. This could be related to patients selection.

Limitation:

This study was mainly limited by its retrospective design. We tried to limit this bias by collecting all the information from electronic medical records. On the other hand, not all patients had geriatric evaluation before treatment initiation, and as it has been already shown in different studies ECOG PS or Karnofsky performance status scale are not good estimators of fitness in the elderly. The use of validated tools like the G8 is highly recommended before starting immunotherapy.

Conclusions

This study suggested that checkpoint inhibitor monotherapy is effective and well tolerated in elderly melanoma patients. The PFS of patients treated with pembrolizumab in this study was greater than expected which could be due to a higher mutational load. However, this finding should be interpreted with caution taking into account the retrospective design of this study and needs to be investigated further.

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Compliance with ethical standards

Conflict of interest the authors declare that they have no conflict of interest.

Ethical approval This study was approved by the Ethical Committee of the Gustave Roussy Institut.

Informed consent all patients signed a written informed consent allowing authors to exploit data anonymously.

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