European Journal of Cancer 108 (2019) 61–68

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Immunotherapy comes of age in octagenarian and nonagenarian metastatic melanoma patients

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Received 8 September 2018; received in revised form 18 November 2018; accepted 10 December 2018
Available online 14 January 2019

KEYWORDS
Immunotherapy;
Metastatic melanoma;
Elderly patients anti −PD-1;
Elderly metastatic melanoma patients;
Anti−PD-1 therapy

Abstract Immunotherapy with anti−programmed cell death-1 (PD-1) agents is an effective treatment for metastatic melanoma. Recent data hint at better response to therapy for patients over age 65 years. Patients with metastatic melanoma in their 80's and 90's pose a clinical challenge. We describe a cohort of 144 patients ≥65 years and analyse the efficacy and toxicity of anti−PD-1 therapy in ages 80−100 years compared with ages 65−79 years. Records of metastatic melanoma patients aged 65−100 years treated with anti−PD-1 were collected retrospectively. Baseline parameters, response rate (overall response rate [ORR]), best response, progression-free survival (PFS) and overall survival (OS) and immune-related adverse events were analysed. Cox regression, t test, and chi-square test were used for statistical analysis. Five hundred patients were treated with anti−PD-1 agents between 2013 and 2018.Eighty-two patients were aged 65−79 years (group A, median 71.5 years), and 62 patients were aged 80−100 years (group B, median 84 years, range 80−97 years). Baseline parameters were comparable except for worse PS in group B ($p = 0.001$). One hundred twenty-four patients were evaluable for analysis of response (76 group A, 48 group B). A trend was noted for higher ORR in the older group with 62.3% for group A and 73.9% for group B ($p = 0.09$). Complete response was significantly higher in group B versus group A (47.9% versus 20%, $p = 0.001$). No significant difference was found in PFS or OS between

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https://doi.org/10.1016/j.ejca.2018.12.012

the groups. Toxicity for all patients was similar at 22.8%–25.6% G2-4 adverse events. Elderly patients show enhanced response to anti–PD-1 therapy. Increasing age within the elderly patients group may predict an even better response to therapy and comparable survival in patients of very old age.

1. Introduction

Immunotherapy with anti–programmed cell death-1 (PD-1) agents has been proven efficacious for treating metastatic melanoma in all age groups across multiple clinical trials with response rates (RRs) in the range of 35%–45% [1,2] and tolerable toxicity profiles with grade 3-4 adverse events (AEs) in the range of 10%–15% [2,1]. Recent data suggest these responses remain durable with impressive survival rates of over 50% at 2 years [3].

Although a significant proportion of patients in clinical trials are of old age, it is still not ascertained whether tolerability and efficacy of anti–PD-1 agents are similar across age groups. Various studies [4–6] showed that melanoma is more aggressive in the elderly patients. It is usually diagnosed at a later stage with deeper Breslow scores [7], ulcerated [8] and with positive sentinel nodes [4]. Older age has been shown in multiple in vitro and mouse models to be associated with a waning immune response. This is characterised by a reduction in effector-to-memory T cell ratio [9,10], increase in T-regulatory cell population [11,12] and an increase in PD-1 expression [13].

In contrast to the diminished immune response, retrospective data in a recently published report showed similar efficacy of anti–PD-1 agents when comparing young to elderly metastatic melanoma patients [14]. In this study, toxicity to anti–PD-1 agents was shown to be comparable across age groups [14]. Notably, another recent report [15] showed an increased RR to anti–PD-1 agents in metastatic melanoma patients aged >60 years and an interesting correlation between response and CD8:Treg ratio. Large-scale prospective data from phase III clinical trials of anti–PD-1 agents in melanoma have shown similar results. Analysis of data from two pembrolizumab studies [16,2] showed comparable hazard ratio (HR) for progression-free survival (PFS) and overall survival (OS) in age >65 years versus. age <65 years. Recent analysis of data from another large phase III study [17] showed patients over age 65 years were more likely to achieve a complete response (CR) to therapy, a correlation that remained statistically significant in multivariate analysis. Data for nivolumab showed a numerical benefit in HR for death with increasing age, especially for patients older than 75 years [1].

The clinical efficacy and the favourable toxicity profile of PD-1 blocking antibodies render the very old patient subpopulation of over 80 years old viable for therapy. However, efficacy and toxicity measures in this subpopulation are lacking. Here, we evaluate the clinical efficacy and tolerability of anti–PD-1 agents in retrospective cohorts of real-world metastatic melanoma patients aged 80–100 years and compared them to ages 65–79 years.

2. Methods

2.1. Patients and data

Retrospective cohort study of metastatic melanoma patients treated with anti–PD-1 monotherapy between the years 2013 and 2018 at the Ella Lemelbaum Institute for Immuno-Oncology and Melanoma at Sheba Medical Center. Inclusion criteria included confirmed diagnosis of inoperable or metastatic melanoma, treatment with anti PD-1 as monotherapy and age ≥65 years.

Patient records were reviewed, and the following baseline parameters were recorded at the time of initiation of anti–PD-1 therapy: age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), M stage (American Joint Committee on Cancer [AJCC] 7th edition), line of therapy for anti–PD-1 agent, lactate dehydrogenase (LDH) level, and BRAF mutation status. Efficacy included best response according to Response Evaluation Criteria in Solid Tumours 1.1, duration of therapy, PFS and OS. Non-evaluable patients were excluded from response analysis but were included in survival analyses. Toxicity was analysed as per the Common Terminology Criteria for Adverse Events v5.01. Patients were retrospectively divided into two age groups: 65-79 years (group A) and 80–100 years (group B).

2.2. Ethics

This retrospective study and a waiver from obtaining informed consent were approved by the Institutional Review Board of Sheba Medical Center (4387-17-SMC).

2.3. Statistics

Categorical variables were examined using chi-square analysis, means were compared using t test and Cox regression analysis was conducted to assess survival

data. All statistical analyses were performed using Stata v.13. All tests were two tailed, and statistical significance was determined by p value < 0.05.

3. Results

Five hundred metastatic melanoma patients were treated between the years 2013 and 2018 with anti–PD-1 agents as monotherapy. One hundred forty-four (28.8%) patients were at least 65 years old and met the inclusion criteria for this study. Of those patients, 82 (57%) patients were aged 65–79 years (group A, median age 71.5) and 62 (43%) patients were aged 80–100 years (group B, median age 84). Seventy-five percent of the patients were treated with pembrolizumab, and 25% of the patients were treated with nivolumab. Patients were followed up for a median of 15 months (range 1–55 months). Baseline parameters were comparable for BRAF status, LDH level and M stage (Table 1). A trend was noted for the use of anti–PD-1 as a more advanced line of therapy in group A. Thirty-two (39%) patients in group A were given second-line to third-line treatment in comparison to 14 (21%) patients in group B ($p = 0.076$, chi-square test). Patients in group B had a statistically significant worse ECOG PS ($p = 0.001$, chi-square test). Table 2 details previous lines of therapy and the medical background. A fully detailed medical history was not available for all the patients; however, a higher rate of patients with a history of ischaemic heart disease and arrhythmias was noted in group B (Table 2).

Twenty (13.8%) patients were non-evaluable for response to therapy; of them, six and 14 were from group A and group B, respectively. Fourteen patients died before radiological evaluation, and six patients were lost to follow-up. The non-evaluable patients were older ($p = 0.009$, chi-square test), were more likely to be BRAF mutant ($p = 0.009$, chi-square test) and had a worse ECOG PS ($p = 0.001$, chi-square test). A trend was noted for more patients being treated for an M1c disease ($p = 0.054$, chi-square test).

Patients were treated for a median of 6 months (range 1–55 months) with a significant difference noted between the age groups (group B median of 5 months versus 10 months in group A, $p = 0.001$, t test). Therapy was discontinued by 68.5% of the patients in group A due to either PD or toxicity versus 55% in group B. Patients in group B discontinued therapy more frequently due to death (17.6%) or at treating physicians' discretion (27.4%), compared with 9.6% and 21.9%, respectively, in group A (Table 3). The main reasons for physician's discretion to stop therapy included completion of predefined therapy protocol, patient's election to stop therapy and lost to follow-up.

Response to therapy in the evaluable patient cohort (124 patients; 76 in group A and 48 in group B) revealed a trend toward a higher RR in the older population.

Table 1
Baseline clinical and disease-related characteristics.

Age group	Evaluable (n)	Age	Gender % (n)		BRAF mut % (n)			Elev. LDH % (n)			Stage % (n)				Line of therapy % (n)				ECOG PS % (n)			Drug % (n)	
			M	F	Y	N	Unk	Y	N	Unk	IIIc/M1a	M1b	M1c	Unk	1	2	3+	Unk	0–1	2+	Unk	Pmb	Nivo
65–79	All (n = 82)	71.5	61 (50)	39 (32)	19.5 (16)	71 (59)	9.5 (8)	13.4 (11)	57.3 (47)	29.3 (24)	21.9 (18)	31.7 (26)	37.8 (31)	8.5 (7)	58.5 (48)	31.7 (26)	7.4 (6)	2.4 (2)	89 (73)	6.1 (5)	4.9 (4)	69.5(57)	30.5 (25)
	Yes (n = 76)	71.5	60.5 (46)	39.5 (31)	14.4 (11)	76.3 (58)	9.3 (7)	13.2 (10)	56.6 (43)	30.3 (23)	21 (16)	34.2 (26)	35.5 (27)	9.2 (7)	59.2 (45)	30.3 (23)	7.9 (6)	2.6 (2)	86.8 (66)	6.6 (5)*	6.6 (5)	76.3 (58)	31.7 (24)
	No (n = 6)	70	16.6 (1)	83.3 (5)	66.6 (4)	16.6 (1)	16.6 (1)	16.6 (1)	83.3 (5)	0 (0)	16.6 (1)	0 (0)	83.3 (5)	0 (0)	50 (3)	50 (3)	0 (0)	0 (0)	100 (6)	0 (0)	0 (0)	83.3(5)	16.6 (1)
80–100	All (n = 62)	84	61.2 (38)	38.8 (23)	16.2 (10)	72.5 (45)	11.3 (7)	20.9 (13)	51.6 (32)	27.5 (17)	25.8 (16)	24.2 (15)	50 (31)	0 (0)	77.4 (48)	19.4 (12)	1.6 (1)	1.6 (1)	*62.9 (39)*	25.8 (16)*	11.2 (7)	82.3(51)	17.7 (11)
	Yes (n = 48)	84	68.7 (33)	31.3 (15)	14.6 (7)	72.9 (35)	12.5 (6)	14.5 (7)	58.3 (28)	27.2 (13)	29.2 (14)	25 (12)	45.8 (22)	0 (0)	81.2 (39)	18.8 (9)	0 (0)	0 (0)	70.8 (34)	18.8 (9)	10.4 (5)	83.3(40)	16.6 (8)
	No (n = 14)	85.5	35.7 (5)	64.3 (9)	21.4 (3)	71.4 (10)	7.2 (1)	42.8 (6)	28.6 (4)	28.6 (4)	14.3 (2)	21.4 (3)	64.3 (9)	0 (0)	64.3 (9)	21.4 (3)	7.1 (1)	7.1 (1)	35.7 (5)	57.1 (8)	7.2 (1)	78.6 (11)	21.4 (3)

F = female; ECOG PS = Eastern Cooperative Oncology Group performance status; Elev LDH = elevated lactate dehydrogenase; M = male; N = mo; n = number; Nivo = nivolumab; Pmb = pembrolizumab; Unk = unknown; Y = yes.
*Denotes $p = 0.001$ for interaction, chi-square test.

Table 2
Previous lines of therapy and medical comorbidities.

Age	Previous treatment lines, % (n)							Medical background, % (n)						
	Second line			Third line		All lines								
	ICI	TT	Chem	ICI + TT	ICI + Chem	Total ICI exposure	Total TT exposure	IHD	HTN	DM-II	CVD	Endocrine	COPD	Arrhythmia
65-79 (n = 32)	56.2 (18)	25 (8)	3.1 (1)	6.2 (2)	9.4 (3)	78.1 (25)	31.2 (10)	15.8 (13)	52.4 (43)	32.9 (27)	2.4 (2)	18.3 (15)	6.1 (5)	4.9 (4)
80-100 (n = 14)	57.1 (8)	35.7 (5)	0 (0)	0 (0)	7.1 (1)	64.3 (9)	35.7 (5)	25.8 (16)	59.7 (37)	32.3 (20)	6.4 (4)	11.3 (7)	4.8 (3)	22.6 (14) **

Chem = chemotherapy (temozolomide); COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; DM-II = type II diabetes mellitus; HTN = hypertension; ICI = immune checkpoint inhibitor; IHD = ischaemic heart disease; TT = targeted therapy.
Arrhythmias include sick sinus syndrome, atrial fibrillation or flutter and supraventricular tachycardias.
**Denotes $p < 0.001$ chi-square test.

Table 3
Reasons for treatment discontinuation in each age subgroup, according to major categories.

	Reason for treatment discontinuation, % (n)			
Age	PD	Toxicity	Death	Other*
65-79 (n = 73)	56.2 (41)	12.3 (9)	9.6 (7)	21.9 (16)
80-100 (n = 51)	39.2 (20)	15.8 (8)	17.6 (9)	27.4 (14)

PD = progression of disease; AE = adverse events
*Other includes the physician's choice, termination of predefined clinical trial or lost to follow-up.

Patients in group A had an overall response rate (ORR) of 62.3% versus 73.9% for patients in group B ($p = 0.09$, chi-square test). A significantly higher rate of CR was noted in the older population, as CR rate increased from 22% in group A to 47.9% in group B ($p = 0.001$, chi-square test) (Fig. 1). Analysis of time until development of CR showed a median of 5 months with comparable medians between both groups (6 months in group A, 4 months in group B, p = non-significant [NS]).

Survival analyses for all patients revealed a numerical difference for PFS between the groups (group A median PFS 13 months, group B median PFS 11 months, $p = 0.88$, Fig. 2A) and a trend for longer OS in the younger patients (median OS [mOS] = 13 months for group A versus 10 months for group B, $p = 0.11$, Fig. 2B). In an attempt to correct for age-related comorbidities that could affect survival, the data were reanalysed with adjustment for ECOG PS = 0–1. In this analysis, both PFS and OS were comparable (median PFS 13 months versus 12 months, mOS 13 months versus 10 months, p = NS, Fig. 2C and D). Notably, patients in group B were more likely to die with no evidence of prior disease progression, probably due to other reasons (20.9% versus. 8.5% in group B and group A, respectively, $p = 0.033$, chi-square test). Indeed, 52.5% of patients in group A died of melanoma-related cause as per the investigator's discretion in comparison to 31% of patients in group B ($p = 0.1$). A higher proportion of unknown cause of death was noted in group B (51.8%) versus group A (40%). Analysis of the response-evaluable patients showed similar results to the total study population. Median PFS of patients aged 80–100 years was 13 months versus 11 months for the younger population and a mOS of 14 months versus 11 months (p = NS for both comparisons, Fig. 2E and F).

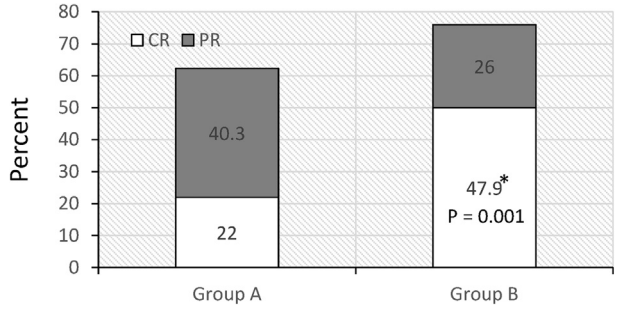

Fig. 1. Response rate to immunotherapy according to age groups. Figure shows the overall response rate, complete response (CR) rate, and partial response (PR) rate, clustered according to the age groups: group A (age 65–79 years) and group B (age 80–100 years). *Denotes P value of 0.001.

Analyses of survival of patients who achieved a complete response showed prolonged PFS for both age groups (median PFS not reached both groups). In these patients, overall survival was significantly longer (Fig. 3; mOS = 29 months for group A and 18 months for group B).

Anti–PD-1 agents showed no difference in ORR, PFS or OS when compared to either nivolumab or pembrolizumab.

Toxicity analysis revealed a similar profile of immune-related AEs (irAEs); 22.8% and 25.6% of patients in group A and group B, respectively, developed a grade 2 or higher irAE with comparable rates of grade 2 and grade 3–4 (Table 4). Notably, patients in group B developed irAE earlier than those in group A (4.5 months versus 6.5 months, respectively; $p = 0.03$, chi-square test). No difference was found in probability of developing an irAE and treatment with either anti–PD-1 agent.

Ninety percent of patients in group B with a grade 2–4 irAE received corticosteroids treatment compared

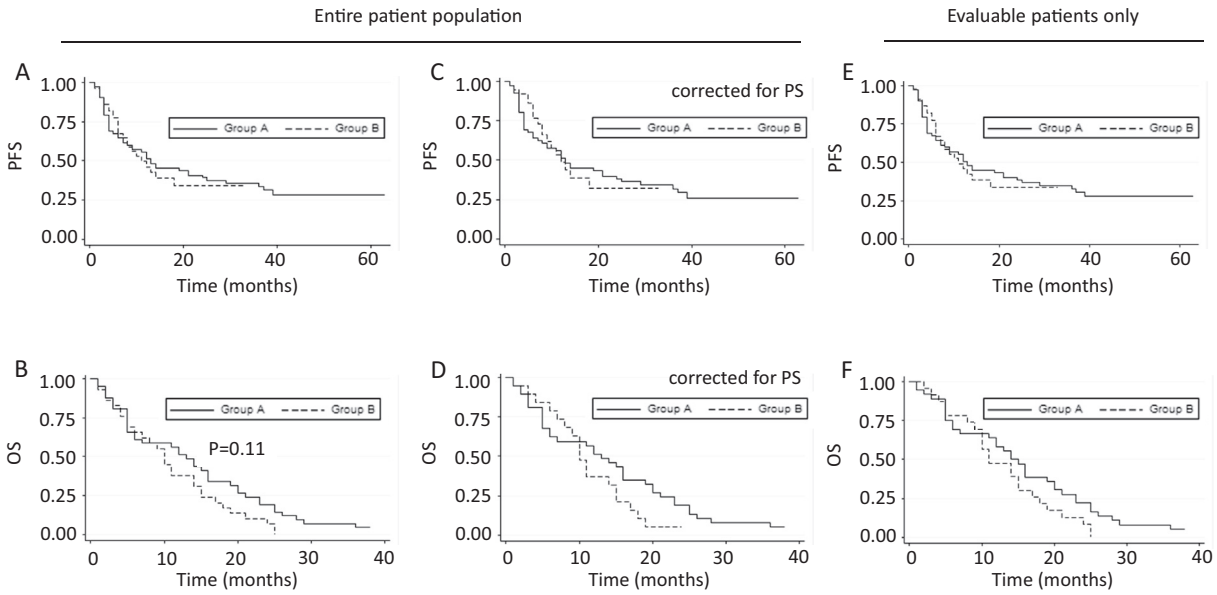

Fig. 2. Survival analyses according to age groups. Figure shows the progression-free survival (PFS) and overall survival (OS) Kaplan–Meier analysis to immunotherapy according to the age groups: group A (age 65–79 years) and group B (age 80–100 years). (A-B) PFS and OS analyses for the entire patient population; (C-D) PFS and OS analyses for the entire patient population corrected for performance status (PS); (E-F) PFS and OS analysis for the evaluable patients only.

with 62.5% of patients in group A. Other immunomodulatory agents (anti-TNF alpha, methotrexate) were used with a similar proportion of ~18% in both groups. Time to resolution of corticosteroids treatment was similar between the groups at 4.5 months for group A versus 5 months for group B (Table 4). Toxicity strongly correlated with prognosis in the total patient population >65 years as the OS of patients that developed grade 2–4 irAE was significantly longer (20 months versus 11 months, p = 0.04, Fig. 4A). This correlation was statistically significant only for patients in group A (p = 0.03, Fig. 4B) and not for those in group B (p = 0.3, Fig. 4C). No correlation was found between PFS and toxicity. Twelve patients had developed early irAE within 3 months of treatment initiation. These patients achieved similar ORR (58.3% for early AE, 72.8% for late AE, p = NS), a significantly shorter PFS (11 months versus not reached, p = 0.037) but with a similar OS (13 months versus 11 months, p = NS).

4. Discussion

Immunotherapy with anti–PD-1 agents is a very effective treatment modality in patients with metastatic melanoma. Patients with metastatic melanoma who respond to anti–PD-1 therapy show extremely promising durable responses, with more than 90% of patients remaining progression free at 24 months after achieving CR and completing 2 years of therapy [17]. Unfortunately, the RRs for first-line therapy have not risen above 45% in most trials [1,3,2]. Finding predictive markers for response has been challenging. The most

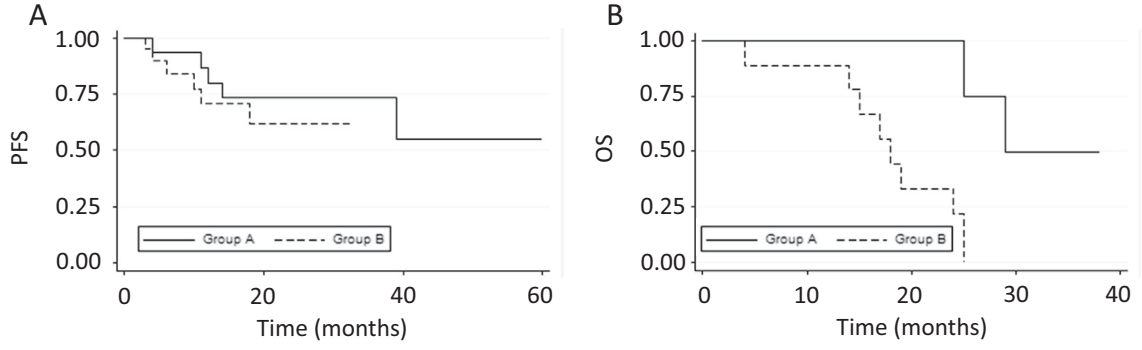

Fig. 3. Survival analysis among complete responders according to age groups. Figure shows the progression-free survival (PFS) and overall survival (OS) Kaplan–Meier analysis among complete responders to immunotherapy, according to the age groups: group A (age 65–79 years) and group B (age 80–100 years).

Table 4
Toxicity in relation to age group, per organ system.

irAE category	Age group 65-79			Age group 80-100		
	G2	G3-4	Total	G2	G3-4	Total
All	13.2%	9.6%	22.8%	17.6%	8%	25.6%
Skin	2.4%	4.8%	7.2%	1.6%	1.6%	3.2%
Colitis	1.2%	1.2%	2.4%	3.2%	3.2%	6.4%
Pneumonitis	2.4%	1.2%	3.6%	3.2%	–	3.2%
Hepatitis	1.2%	–	1.2%	1.6%	1.6%	3.2%
Arthritis	3.6%	1.2%	4.8%	4.8%	1.6%	6.4%
Endocrine	2.4%	–	2.4%	3.2%	–	3.2%
Other	–	1.2%	1.2%	–	–	–
Steroid treatment	42.9%	77.8%	62.5%	87.5%	100%	90.9%
Other immunomodulatory treatments	14.3%	22.2%	18.7%	0%	66.7%	18.1%
Median time to resolution (months)	3	5	4.5	3.5	5	5

G = grade; irAE = immune-related adverse events.

significant efforts have been with the programmed cell death ligand-1 (PD-L1), which was linked to higher ORR and more durable responses [18,19]. Nevertheless, as some patients with PD-L1–negative melanoma still respond and develop durable responses, the utility of PD-L1 is experimental.

Old age is emerging as an important clinical factor associated with response [15]. Our cohort confirms that response rate in the elderly population of ≥65 years is high, exceeding 62%. We hypothesised that the waning immune system may be even more significant in very elderly patients older than 80 years, which could be translated to improved efficacy of PD-1 blockade. Supporting this hypothesis, we observed a trend towards an even higher RR in patients aged ≥80 years, reaching 73.9% (Fig. 1). Importantly, two thirds of the responders achieved a CR, compared to only a third of the responders among the age group of 65–79 years (Fig. 1). The two age groups were reasonably balanced; however, it should be noted that more patients in the older age group received anti–PD-1 agent as first-line treatment, albeit this difference was not statistically significant. On the other hand, the PS of the older patients was significantly worse (Table 1), and they had more major comorbidities (Table 2). We, therefore, doubt that this would have significantly impacted the differences in the response rate and the probability of achieving CR. In addition, it is worth mentioning that the CR rate in patients younger than 65 years was shown in randomised trials to be in about one fifth of responders [2], implying a potential continuum of CR rate as age progresses. The exact mechanism is still unclear but may reside in increasing dominance of PD-1–mediated immune senescence mechanisms with age [13], which could be amenable to PD-1 blockade. These observations are corroborated by data from a prospective clinical trial with nivolumab monotherapy that suggested a trend towards increased CR rates in patients >75 years [1]. Interestingly, our data show that old patients achieve a CR within 5 months only, as compared with previously published data of 13 months [17]. No significant difference was noted in this regard between the two age groups. This finding further emphasises the relative efficacy of anti–PD-1 agents in this age group and possibly hints at quicker response dynamics in older patients.

Despite the higher ORR and especially CR rates, PFS and OS were similar among the two groups in analyses of the evaluable-only patients and of the total population (Fig. 2). However, as stated earlier, over a median follow-up period of 15 months, 20.9% of the very elderly patients died without disease progression as compared with 8.5% of the younger patients (p = 0.033), probably from other comorbidities and non-melanoma–related deaths or treatment-induced death. A trend for a higher probability of melanoma-related deaths was noted in group A, in which more patients died of non-melanoma causes or from unknown causes. Patients in group B had a significantly higher rate of major comorbidities such as ischaemic heart disease and arrhythmias (Table 2). We did not correct survival for these differences in comorbidities as it is unclear how to judge which conditions or combination of conditions would affect the possible survival of the patients. These data support the notion that these deaths are more likely to represent natural differences in life expectancy. For example, in the

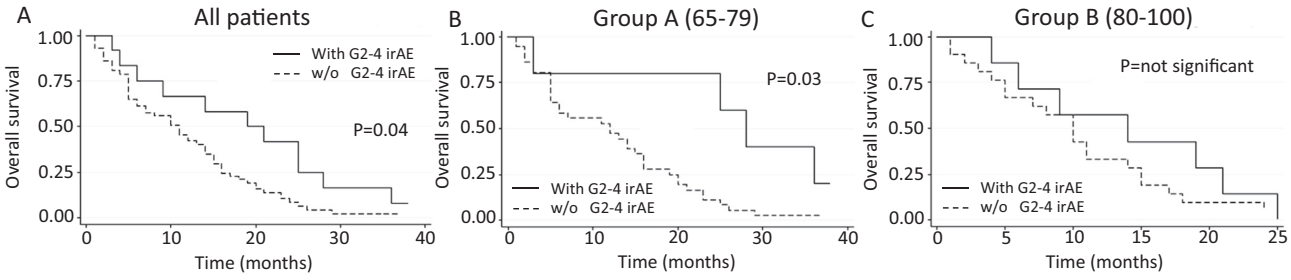

Fig. 4. Association of immune-related adverse events (irAEs) with overall survival. (A-C) The association of irAEs with overall survival among all patients, patients in group A and patients in group B, as indicated in the figure. Patients were categorised based on whether they developed grade 2–4 irAE. G2-4 = grade 2–4; NS = non-significant; w/o = without. P values for Kaplan–Meier test are indicated in each panel.

United States, the probability of death within one year at age 71.5 years is around 2.6% and 1.8% for males and females, respectively, while at the age of 84 years it is 8.9% and 6.7% [20]. Furthermore, 13.8% of the patients were non-evaluable for response (Table 1) but were still included in the survival analyses. Survival analysis of the evaluable patients still demonstrated only similar overall survival of the two age groups (Fig. 2), which lowers the probability of a bias inferred by the higher number of non-evaluable patients in group B versus group A (Table 1). Finally, it should be emphasised that exposure to therapy was 50% shorter for the older population at a median duration of therapy of 5 months versus 10 months for the ages 65–79 years. Altogether, it seems that the statistically similar survival curves may hint at some survival benefit for patients older than 80 years, masked by the inherently higher chances for death conferred by their age. As presented before, we repeated survival analyses limited to patients with ECOG PS = 0–1 only. In these analyses, no apparent difference was noted in either PFS or OS, and the trend noted in the primary survival analyses for longer OS in the younger group disappeared.

In accordance with recently published data [17], patients who achieved CR showed very prolonged PFS and OS. mOS was 29 months for patients in group A compared with 18 months for patients in group B ($p = 0.03$). mOS was not far from median PFS in group B, and this finding may further emphasise our hypothesis that deaths in this age group occur in a high proportion for non-melanoma–related events.

Keeping with previously published data [3,21], toxicity profile among the two cohorts was comparable at a rate of 22.8%–25.6% grade 2–4 (Table 2). However, group B developed irAE significantly earlier. This may be again linked to quicker dynamics of immune activation, leading to earlier toxicity. Finally, a strong association between appearance of irAE and longer survival was demonstrated. OS almost doubled (20 months) in patients who had developed irAE, in agreement with previous retrospective analyses [22–24]. Interestingly, on breakdown according to age groups, this association remained statistically significant in group A only. This finding may be explained by older age group with shorter OS as presented before. To account for bias with patients developing late AEs potentially due to longer drug exposure, response and survival data were analysed in patients who developed early irAE, defined as within 3 months of treatment initiation. These patients exhibited similar RR with a shorter PFS, but this did not translate into OS differences. Owing to the small number of patients in this analysis, conclusions cannot be safely drawn, and further breakdown according to age did not lead to a meaningful analysis.

This study has several limitations. As a retrospective analysis, it is susceptible to inherent biases which are embedded in this kind of analysis. In addition, 13.8% of patients in the total cohort were not evaluable for response, and this may have increased the RR noticed. We did not have the exact cause of death and comorbidities of all patients, and this may have impacted our results. Despite these limitations, this is, to our knowledge, the first study to analyse the difference in response and survival of patients aged 80 years and older and the first to compare efficacy and toxicity parameters within the elderly population aged 65 years and older. Treatment of very old patients aged 85–90 years and older is becoming more common as populations across the Western world live longer. The findings of very high response rates and close to 50% complete response rates in the very old age group coupled with a mild toxicity profile may help guide decision-making when facing the elderly metastatic melanoma patient in the clinic.

Conflict of interest statement

G.M. received honoraria from MSD, Roche, BMS and Novartis; served on advisory boards of MSD, BMS and Biond Biologics; received a research grant from Novartis and holds IP and shares of FameWave and 4C BioMed; J.S. received honoraria from MSD, Roche, BMS and Novartis; serves on advisory boards of MSD, BMS and Novartis and hold IP and shares of 4C BioMed; R.S.-F. received honoraria from MSD, Roche, BMS, Novartis and AstraZeneca; Y.S.-S. received honoraria from MSD, BMS and Novartis; G.B.-B. received honoraria from MSD, Roche, BMS and Novartis; N.A. received honoraria from MSD, Roche, BMS and Novartis.

Acknowledgements

The authors would like to thank Haya and Nehemya Lemelbaum for their continuous generous support, as well as patients and their families.

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