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Original Research

Age favoured overall survival in a large population-based Danish patient cohort treated with anti-PD1 immune checkpoint inhibitor for metastatic melanoma

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Abstract ***Background and patients:*** Age-related immune dysfunction (ARID) describes age-associated changes in immunity that may affect the efficacy of immunotherapy with checkpoint inhibitors. We evaluated the efficacy of treatment with ipilimumab (530 patients) or pembrolizumab (562 patients) in a Danish national cohort of metastatic melanoma patients.
Results: We confirmed known prognostic biomarkers related to treatment with ipilimumab and found no impact of age on survival or progression-free survival. In patients treated with pembrolizumab, we also confirmed known prognostic biomarkers. Overall survival (OS) and progression-free survival was significantly higher in patients aged between 70 and 80 years compared with younger patients. In multivariate analysis with OS as end-point, age was shown to be an independent good prognostic biomarker in these patients. Survival in patients aged above 80 years was not better than in younger patients, probably because of increase in significant comorbidity.
Conclusions: Our analyses have revealed a higher survival rate when using drugs targeting PD1 in metastatic melanoma patients between the age of 70 and 80 years. ARID does not seem to negatively impact the efficacy of treatment with checkpoint inhibitors in metastatic melanoma patients. Despite these encouraging data for elderly patients, clinicians still need

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to carefully consider the higher risk of more serious outcomes of the immune-related adverse events in the elderly patient population, before deciding to treat old patients with checkpoint inhibitors.

1. Introduction

Ageing represents a process accumulating physical, psychological and social changes. Repeated cell replications lead to increased risk of developing somatic mutations, which again may lead to uncontrolled cell growth and cancer [1,2].

Age-related immune dysfunction (ARID) [3] is a term describing the observed age-associated changes in immunity [3,4]. The changes observed affect both the innate and the adaptive immune system, with the most significant changes in the latter.

ARID may lead to an altered antitumour immune response in elderly patients and, in theory, hamper the response to immunotherapy with checkpoint inhibitors because of a less efficiently working immune system. In contrast, Kugel *et al.* [5] actually have shown that old mice respond better to anti-PD1 immunotherapy, perhaps because of differences in number of regulatory T-cells (Tregs) and CD28+ effector cells between old and young mice in the tumour microenvironment.

To investigate the potential influence of age-related immune changes on the efficacy of modern immunotherapy, we compared the efficacy of the CTLA-4 inhibitor ipilimumab and the PD-1 inhibitor pembrolizumab in elderly patients versus younger patients with metastatic melanoma. We evaluated the efficacy in a real-world setting based on nationwide data from the Danish Metastatic Melanoma Database (DAMMED).

2. Material and methods

DAMMED is a population-based database, established in 2011. The database retrospectively collects data on efficacy and treatment-related biomarkers in relation to metastatic melanoma patients.

Patients with metastatic melanoma, cutaneous or unknown primary, treated with either single drug ipilimumab or pembrolizumab after national approval as standard of care, were included.

Regarding age cut-point, 70 years of age was chosen, based on a definition from International Society of Geriatric Oncology [6,7]. This definition has been adapted at Odense University Hospital, Academy of Geriatric Cancer Research (AgeCare), establishing the chronological definition of being old at 70 years of age.

2.1. Statistics

Descriptive statistics were used to report baseline characteristics of the two study populations. The two populations (ipilimumab and pembrolizumab) were analyzed separately. Baseline characteristics (gender, Eastern Cooperative Oncology Group [ECOG] performance status [PS], M-stage, leucocyte count, granulocyte count, lymphocyte count, lactate dehydrogenase (LDH), line of therapy, presence of central nervous system (CNS) metastases and BRAF status) were analysed for differences using cross table analyses.

Kaplan-Meier estimates were used to calculate the probability of survival. Progression-free survival (PFS) was defined as the time from initiation of immunotherapy to objective clinical or radiological tumour progression or death. Overall survival (OS) was defined as the time from initiation of immunotherapy to death from any reason. Overall response rate (ORR) was defined according to Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1. Disease control rate (DCR) was defined as the sum of ORR and stable disease rate.

The database includes clinical and biomarker data, enabling us to perform multivariate analyses to evaluate a potential age-effect. Logistical regression analyses were used to investigate age related to PFS, OS and response to treatment. Cox multivariate analyses were performed using known independent prognostic markers at baseline (M-stage, brain metastases, line of therapy, LDH, ECOG PS, BRAF status and absolute neutrophil count) to explore the association between time end-points and patient/disease characteristics. We used Lowess (Locally Weighted Scatterplot Smoothing) [8] as a tool in regression analysis to visually test the relationship between age and OS rate at 12 months. Data analyses were performed using Stata Statistical Software, release 15 (StataCorp LLC; College Station, Texas).

3. Results

3.1. Patient characteristics

In Denmark, 530 patients received treatment with ipilimumab between July 2010 and January 2018, and 562 patients received pembrolizumab between February 2014 and January 2018. Among patients treated with ipilimumab, 235 patients received the treatment as first line, while 334 patients received pembrolizumab as first-line treatment.

Median follow-up time for patients treated with ipilimumab was 3.4 years, and for patients who received pembrolizumab, it was 1.7 years.

Median age of patients treated with ipilimumab was 64.7 years (range 16.9–87.9), and median age of pembrolizumab-treated patients was 68.9 years (range 24.6–91.2). In both treatment groups, median age increased over time. For ipilimumab treated patients, it increased from 55.2 years in 2010 to 68.8 in 2017 (Fig. 1A). Among the patients treated with ipilimumab, 171 patients (32%) were aged 70 years or above. Median age of patients treated with pembrolizumab increased over time, from 59.9 years in 2014 to 71.3 in 2017 (Fig. 1B). 256 patients (46%) treated with pembrolizumab were aged 70 or above.

Patient characteristics are depicted in Table 1. We found a larger fraction of males as well as a larger fraction receiving their treatment as 1st line therapy in the elderly patients. The fraction of patients with M1c

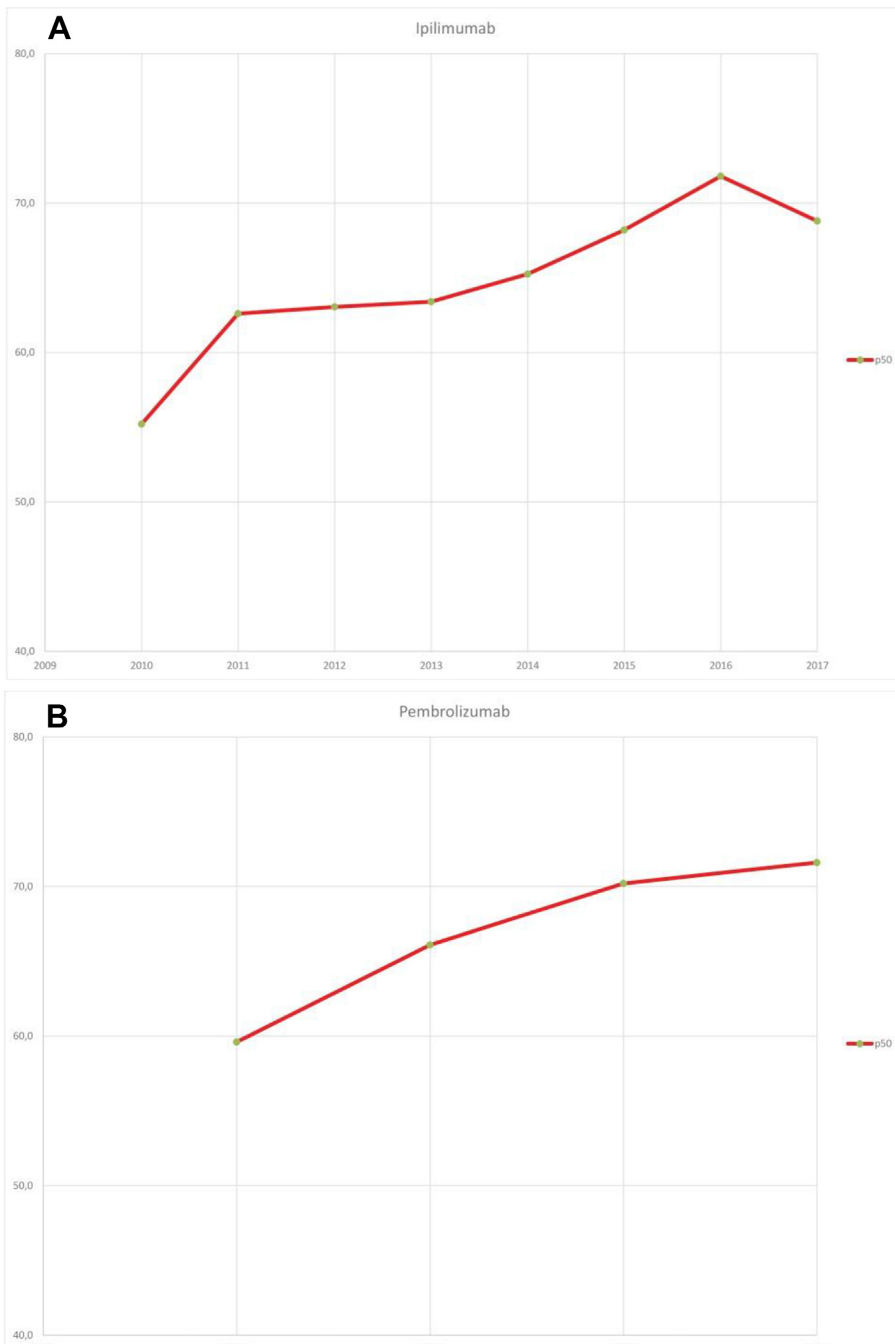

Fig. 1. Increasing median age over time for ipilimumab (A) and pembrolizumab (B) treated patients.

Table 1
Baseline patient characteristics of metastatic melanoma patients treated with pembrolizumab or ipilimumab.

Characteristic	Ipilimumab n = 530		Pembrolizumab n = 562	
	Age <70 years (n = 359) n (%)	Age ≥ 70 years (n = 171) n (%)	Age <70 years (n = 306) n (%)	Age ≥ 70 years (n = 256) n (%)
Gender				
Male	198 (55.2)	107 (62.6)	180 (58.8)	164 (64.1)
Female	161 (44.8)	64 (37.4)	126 (41.2)	92 (35.9)
Line of therapy				
1st	146 (40.7)	89 (52.0)	152 (49.7)	182 (71.1)
≥2nd	213 (59.3)	82 (48.0)	154 (50.3)	74 (28.9)
Primary melanoma				
Cutaneous	308 (85.8)	151 (88.3)	268 (87.6)	224 (87.5)
Unknown primary	51 (14.2)	20 (11.7)	38 (12.4)	32 (12.5)
M-stage				
M1a	60 (16.7)	34 (19.9)	50 (16.3)	61 (23.8)
M1b	48 (13.3)	33 (19.3)	40 (13.1)	46 (18.0)
M1c	251 (70.0)	104 (60.8)	216 (70.6)	149 (58.2)
ECOG PS				
0-1	326 (92.4)	158 (94.6)	266 (90.5)	219 (88.3)
≥2	27 (7.6)	9 (5.4)	28 (9.5)	29 (11.7)
Missing	6	4	12	8
BRAF status				
Wild-type	141 (43.8)	108 (68.4)	134 (44.4)	170 (68.3)
Mutated	181 (56.2)	50 (31.6)	168 (55.6)	79 (31.7)
Unknown	37	13	4	7
LDH				
< ULN	191 (54.7)	86 (52.4)	156 (52.5)	127 (51.6)
1-2 x ULN	117 (33.5)	68 (41.5)	114 (38.4)	103 (41.9)
> 2 × ULN	41 (11.8)	10 (6.1)	27 (9.1)	16 (6.5)
Missing	10	7	9	10
WBC				
< ULN	287 (80.6)	148 (88.6)	239 (79.9)	219 (88.3)
≥ ULN	69 (19.4)	19 (11.4)	60 (20.1)	29 (11.7)
Missing	3	4	7	8
ANC				
< ULN	311 (87.6)	150 (90.4)	242 (80.7)	228 (91.2)
≥ ULN	44 (19.4)	16 (9.6)	58 (19.3)	22 (8.8)
Missing	4	5	6	6
Brain metastases				
Yes	62 (17.3)	19 (11.1)	78 (25.5)	29 (11.3)
No	297 (82.7)	152 (88.9)	228 (74.5)	227 (88.7)

ANC, absolute neutrophil count; ULN, upper limit of normal; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; WBC, white blood cells.

disease was lower in the elderly patients, as was the fraction of patients with no *BRAF* mutation. No major differences were found between the two treatment categories in regard to primary melanoma site, ECOG PS, LDH level or presence of brain metastases. The fraction of patients with white blood cell count and absolute neutrophil count (ANC) above the upper limit of normal (ULN) was higher in the younger patients.

Prior and subsequent treatments for pembrolizumab and ipilimumab treated patients in the two age groups are summarised in Supplementary Tables S1 (ipilimumab) and S2 (pembrolizumab).

3.2. Treatment efficacy

3.2.1. Response to treatment

For patients treated with ipilimumab, we observed an ORR of 18% in patients <70 years of age and 21% in patients ≥70 years. This difference was not statistically significant (Table 2). For pembrolizumab, we found that ORR was 35% for patients aged <70 years and 40% for patients aged ≥70 years. The difference in ORR was not statistically significant. The rate of patients with progressive disease as best response (failure rate) for ipilimumab was 56% in patients aged <70 years and 54% in the elderly patients. For pembrolizumab-treated patients, the rates 45% and 37% in the two age groups (Table 2). The difference in failure rate for pembrolizumab-treated patients was statistically significant ($p = 0.05$).

3.2.2. Lowess regression analysis

Using the Lowess regression analysis (Fig. S1), cut points for age were determined with a subclassification of the older patient group based on analysis of this graph for age and 12 months survival rate in the pembrolizumab-treated patients. In this patient cohort, the

Table 2
Response to treatment according to age in metastatic melanoma patients treated with pembrolizumab or ipilimumab.

Response to treatment	Ipilimumab, % (n)			Pembrolizumab, % (n)		
Age (years)	<70	≥70	p-value	<70	≥70	p-value
CR	7.8% (28)	7.0% (12)	0.76	13.9% (39)	10.0% (25)	0.26
PR	10.0% (36)	14.0% (24)	0.17	22.1% (66)	30.0% (75)	0.04
ORR	17.8%	21.1%	0.37	35.2%	39.8%	0.27
SD	26.5% (95)	24.6% (42)		19.5% (58)	23.1% (58)	
DCR	44.2%	45.6%		53.3%	61.7%	
PD	55.6% (199)	53.8% (92)	0.75	45.3% (135)	37.1% (93)	0.05
NE	1	1		8	5	
N	359	171		306	256	

CR, complete response; PR, partial response; ORR, overall response rate; DCR, disease control rate; SD, stable disease; PD, progressive disease; NE, not evaluable.

Lowess regression analysis showed a near-linear increase in 12-month survival with increasing age, until the age of 80 years. Hereafter, a decline in 12-month survival thereafter was observed. Based on this observation, we decided to base our efficacy analyses on three age groups: <70 years, 70–80 years and 80+ years.

3.2.3. Progression-free survival

Ipilimumab: Median PFS for ipilimumab-treated patients was 3.4, 3.6 and 6.2 months in the three defined age groups (Fig. 2A). No significant difference in PFS between age group <70 years and 70–80 years ($p = 0.69$) and between <70 years and >80 (0.08) years (Table 3).

Pembrolizumab: For pembrolizumab-treated patients median PFS was 5.7, 10.3 and 7.1 months in the three age-groups, respectively (Fig. 2B). The difference of 4.6 months between age group <70 years and 70–80 years was significant in univariate analysis ($p = 0.011$), as well as in the multivariate analysis ($p = 0.032$). The difference between <70 and >80 was not significant ($p = 0.52$) in the univariate analysis. The difference between the age group <70 years and 70–80 years remained significant in multivariate analysis with PFS as end-point (Table 5).

3.2.4. Survival (OS)

Ipilimumab: Median OS in the cohort of ipilimumab-treated patients was 14.2, 11.9 and 20.5 months in the

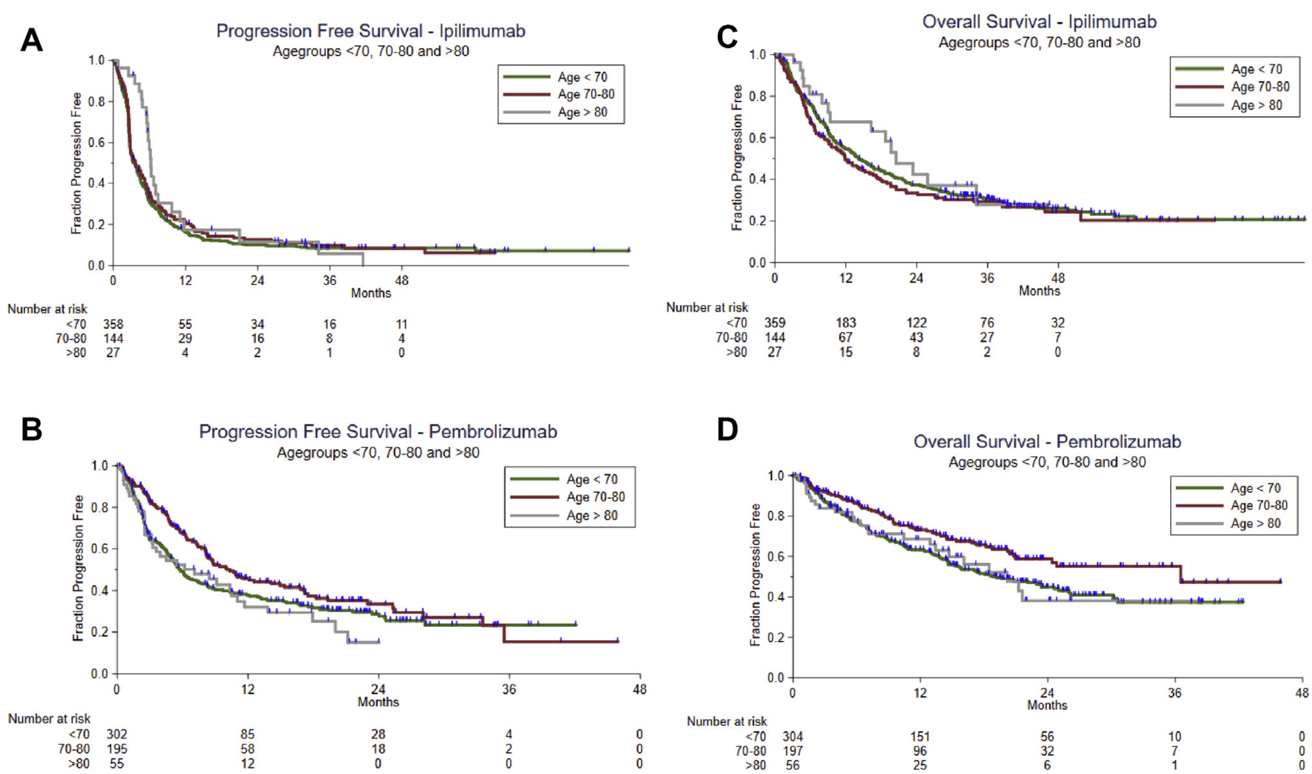

Fig. 2. Progression-free survival (PFS) and overall survival (OS) in three age groups (<70, 70–80, >80), for patients treated with either ipilimumab (A and B) or pembrolizumab (C and D) for metastatic melanoma.

Table 3
Landmark efficacy data after treatment of metastatic melanoma patients with ipilimumab or pembrolizumab.

PFS	Ipilimumab			Pembrolizumab		
Age	<70	70–80	>80	<70	70–80	>80
Median (months)	3.4	3.6	6.2	5.7	10.3	7.1
95% CI	(2.9–4.1)	(2.8–5.2)	(5.6–7.4)	(4.9–7.5)	(8.2–15.4)	(3.2–11.0)
12 months	16.4%	21.0%	17.4%	37.8%	45.8%	32.1
24 months	10.1%	12.7%	11.6%	28.7%	33.5%	–
36 months	8.5%	9.8%	5.8%	23.5%	15.5%	–
OS	Ipilimumab			Pembrolizumab		
Age	<70	70–80	>80	<70	70–80	>80
Median (months)	14.2	11.9	20.5	18.8	36.5	20.2
95% CI	(11.7–17.6)	(8.9–16.6)	(9.4-)	(14.6–25.0)	(21.0-)	(13.4-)
12 months	54.5%	49.5%	67.6%	63.3%	73.2%	68.5%
24 months	37.4%	33.4%	42.4%	44.9%	58.8%	38.2%
36 months	30.9%	29.2%	27.8%	37.4%	55.1%	38.2%

CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Table 4
Univariate analyses of clinical and biochemical parameters with OS/PFS as end-point.

Characteristic	Ipilimumab (n = 530)		Pembrolizumab (n = 562)			
	OS		OS		PFS	
	HR	P	HR	p	HR	p
Age (years)						
< 70	Ref		Ref		Ref	
70-80	1.12 (0.89–1.42)	0.32	0.65 (0.48–0.88)	0.005	0.73 (0.58–0.93)	0.011
≥80	0.80 (0.47–1.33)	0.39	1.02 (0.66–1.57)	0.92	1.12 (0.79–1.60)	0.52
Gender						
Male	1.12 (0.91–1.38)	0.28	1.15 (0.88–1.51)	0.30	0.98 (0.79–1.21)	0.83
Female	ref		Ref		ref	
Line of therapy						
1st	0.61 (0.50–0.76)	<0.0001	0.64 (0.50–0.84)	0.001	0.81 (0.65–1.00)	0.05
≥2nd	Ref		Ref		Ref	
Primary melanoma						
Cutaneous	1.02 (0.75–1.39)	0.88	1.19 (0.79–1.82)	0.39	1.10 (0.80–1.54)	0.54
Unknown primary	Ref		Ref		Ref	
M-stage						
M1a	0.49 (0.37–0.66)	<0.0001	0.43 (0.30–0.64)	<0.0001	0.54 (0.54–0.93)	0.013
M1b	0.46 (0.33–0.63)	<0.0001	0.40 (0.26–0.63)	<0.0001	0.53 (0.38–0.75)	<0.0001
M1c	Ref		Ref		Ref	
ECOG PS						
0-1	4.01 (2.79–5.75)	<0.0001	2.76 (1.91–3.97)	<0.0001	1.84 (1.31–2.59)	<0.0001
≥2	Ref		Ref		Ref	
BRAF status						
Wildtype	0.98 (0.78–1.22)	0.85	1.13 (0.87–1.47)	0.35	1.47 (1.19–1.82)	<0.0001
Mutated	Ref		Ref		Ref	
LDH						
< ULN	Log-rank test, f trend	<0.0001	Log-rank test, f trend	<0.0001	Log-rank test, f trend	<0.0001
1-2 x ULN						
> 2 × ULN						
WBC						
≥ULN	1.64 (1.28–2.12)	<0.0001	1.84 (1.36–2.49)	<0.0001	1.55 (1.19–2.01)	0.001
<ULN	Ref		Ref		Ref	
ANC						
≥ULN	1.86 (1.40–2.48)	<0.0001	2.05 (1.61–2.79)	<0.0001	1.54 (1.17–2.03)	0.002
< ULN	Ref		Ref		Ref	
ALC						
≥LLN	0.68 (0.53–0.88)	0.004	0.69 (0.51–0.95)	0.022	0.87 (0.67–1.14)	0.31
< LLN	Ref		Ref		Ref	
Brain metastases						
Yes	1.89 (1.45–2.46)	<0.0001	2.27 (1.70–3.03)	<0.0001	1.69 (1.31–2.18)	<0.0001
No	Ref		Ref		Ref	

ANC, absolute neutrophil count; ULN, upper limit of normal; OS, overall survival; PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; WBC, white blood cells; ALC, absolute lymphocyte count; LLN, lower limit of normal.

Table 5
Cox multivariate analysis of clinical and biochemical parameters with OS/PFS as end-point.

Characteristic	Ipilimumab n = 530		Pembrolizumab n = 537			
			OS		PFS	
	HR	p	HR	p	HR	p
Age (years)						
<70 versus 70–80	1.18 (0.92–1.52)	0.18	0.73 (0.53–0.99)	0.049	0.76 (0.59–0.98)	0.032
<70 versus ≥ 80	0.66 (0.39–1.14)	0.14	1.16 (0.73–1.83)	0.54	1.16 (0.80–1.68)	0.45
M-stage						
M1a versus M1b	0.80 (0.53–1.22)	0.31	0.73 (0.42–1.28)	0.27	0.61 (0.41–0.93)	0.02
M1a versus M1c	1.68 (1.23–2.30)	0.001	1.29 (0.85–1.97)	0.24	0.98 (0.72–1.34)	0.92
Brain metastases						
No BM versus BM	1.41 (1.06–1.88)	0.018	1.94 (1.40–2.69)	<0.0001	1.53 (1.15–2.04)	0.004
Line of therapy						
1st line versus > 1st line	0.62 (0.50–0.78)	<0.001	0.77 (0.58–1.01)	0.059	0.85 (0.68–1.07)	0.059
Gender						
Female versus male	0.96 (0.78–1.19)	0.73	1.20 (0.91–1.59)	0.19	1.20 (0.91–1.59)	0.16
ECOG PS						
0 versus 1	1.59 (1.26–2.02)	<0.0001	1.68 (1.24–2.27)	0.001	1.41 (1.11–1.81)	0.006
0 versus ≥ 2	4.01 (2.72–5.93)	<0.0001	2.41 (1.60–3.64)	<0.0001	1.95 (1.27–2.66)	0.001
LDH						
<ULN versus 1-2 × ULN	1.74 (1.38–2.20)	<0.0001	1.52 (1.12–2.07)	0.007	1.31 (1.03–1.68)	0.030
<ULN versus > 2 × ULN	2.44 (1.78–3.35)	<0.0001	3.41 (2.24–5.19)	<0.0001	1.95 (1.34–2.85)	0.001
ANC						
< ULN versus ≥ ULN	1.65 (1.22–2.27)	0.001	1.35 (0.97–1.90)	0.079	1.16 (0.79–1.24)	0.94

ANC, absolute neutrophil count; ULN, upper limit of normal; OS, overall survival; PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

three defined age groups (Fig. 1C, Table 3), with non-significant differences in 12, 24 and 36-month OS-rates.

Pembrolizumab: For pembrolizumab-treated patients (Fig. 1D, Tables 3 and 4), a statistically significant difference was found, with a median OS of 18.8 months in the younger patients below 70 years, compared with 36.5 months in the group of patients 70–80 years of age (HR 0.73, p = 0.011). Patients aged above 80 years had a median OS of 20.2 months, and the HR compared to patients aged <70 years was 1.12 (p = 0.52). 12, 24 and 36-month OS rates in the pembrolizumab-treated patients were 63%, 45% and 37% in the group below 70 and 73%, 59% and 55% in the group between 70 and 80 years of age.

3.2.5. Univariate analyses of OS

Ipilimumab: In the univariate analyses of patients treated with ipilimumab (Table 4), no difference in OS was found between male and female patients, primary tumour site or BRAF mutation status.

Pembrolizumab: For patients treated with pembrolizumab, no difference in OS or PFS was found between male and female patients, primary tumour site or BRAF status.

Univariate analyses in patients treated with either ipilimumab or pembrolizumab confirmed the impact on survival for other clinical and biochemical biomarkers. Thus, patients treated in later lines, patients with M1c disease compared to M1a/M1b and patients with high values of LDH and ANC and the presence of brain metastases all had a poorer survival. We chose to include variables being of significant importance in univariate analyses as well as gender because gender has previously been reported to be of significance. Based on this, M-stage, line of therapy, gender, brain metastases, PS, LDH and ANC was included in the multivariate analysis.

3.2.6. Cox multivariate analyses of OS

Results from Cox multivariate analyses are depicted in Table 5.

Ipilimumab: In the ipilimumab-treated patients, the overall multivariate analysis confirmed M-stage M1c, presence of brain metastases, PS >1, LDH > ULN and ANC > ULN to be independent poor prognostic factors. Age above 70 years did not independently impact survival in this cohort.

Pembrolizumab: In the pembrolizumab-treated cohort, the presence of brain metastases, PS >1 and LDH > ULN had a significant negative impact on survival, together with age comparing patients aged below 70 years with the group between 70 and 80 years of age. M-stage, line of therapy, gender and ANC did not have significant independent influence on survival in the pembrolizumab-treated patients.

4. Discussion

We report real-life data obtained from a Danish national database on immunotherapy offered to younger and older patients with metastatic melanoma. It is well-known that elderly cancer patients are underrepresented in clinical trials [9,10], and therefore real-life data are needed to perform a solid evaluation of the age-effect.

ARID is a well-documented change in the human immune system that increases with age. This may, in theory, because of a less efficiently working immune system, hamper the response to modern immunotherapy with immune checkpoint inhibitors (ICIs).

The availability of effective ICIs for treating metastatic melanoma paved the way for a new era of medical treatment in metastatic melanoma. The new mechanism of action and milder toxicity meant that age-related organ dysfunctions were of less concern when considering melanoma patients for treatment. On the other hand, even though there is no obvious influence from the presence of comorbidities, the addition of toxicity on top of existing comorbidities may be more problematic for elderly patients. The reduced frequency of serious toxicities for ICI treatment have led to a gradual increase in the median age of treated patients.

Among the surrogate parameters for the efficacy of ICI, objective response according to RECIST [11] can be a difficult parameter to use. In the ipilimumab-treated cohort, we found an ORR of 18% in patients aged below 70 years and 21% in the elderly group. The corresponding figures for DCR were 44% and 46%, respectively. These figures correspond with data from Chiarion Sileni *et al.* [12]. In their national Italian data set on melanoma patients treated with ipilimumab in the expanded access program, they found an ORR of 13% in 645 patients below the age of 70 years and 15% in 188 patients above 70 years of age. The corresponding figures for DCR were 33% and 38%. For pembrolizumab-treated patients ORR was 35% and 40% in the two age groups, a difference which was not statistically significant. The ORR and DCR we found for pembrolizumab-treated patients are comparable to data from the Keynote 006 study by Robert *et al.* [13].

The failure rate in ipilimumab-treated patients were 55.6% and 53.8% in the two age groups, while failure rate of younger patients treated with pembrolizumab was 45.3%, compared to 37.1% in the older patients. This difference was statistically significant ($p = 0.05$). This is in agreement with data from Kugel *et al.* [5], reporting 48% failure rate in patients below the age of 62 years compared with 37% in patients above 62 years of age, despite the difference in cut-point for age.

The original plan was to analyze two age groups (<70 and ≥70). However, applying the Lowess regression analysis on our data, indicated that the age effect we discovered for pembrolizumab-treated patients was limited to patients below the age of 80 years (Fig. S1). The positive correlation between age and survival appears to have a natural upper limit, probably reflecting the fact that with increasing age an increase in known significant as well as unknown comorbidities also becomes important in terms of survival. Our databases does not include data on comorbidities, which might have enabled us to analyse this in more detail.

PFS for ipilimumab-treated patients was not significantly different when comparing patients in the three age groups. For pembrolizumab-treated patients, a significant difference in PFS was found comparing patients aged below 70 years with patients between 70 and 80 years of age, in univariate analysis. This indicates that the relation between age and efficacy is not the same for ipilimumab and pembrolizumab.

We found no difference in OS comparing young and elderly patients treated with ipilimumab. This confirms data from pivotal anti-CTLA4 trials [14–16] and the Italian EAP for ipilimumab reporting no difference in HR comparing young and old patients [12].

However, for pembrolizumab, we did find a significant difference in OS. In univariate analysis, OS was significantly longer in the pembrolizumab-treated patients between 70 and 80 years of age compared with younger patients. Several subgroup analyses of trials forming the basis for approval of anti-PD1 therapy in metastatic melanoma [13,17–19] have unanimously concluded that no deterioration of efficacy was noted in the elderly patients. Most of these trials have used 65 years of age as the point of intersection, and if any trend was noted, it was a HR indicating a better OS in the elderly patients. The same holds true in a retrospective analysis of 254 melanoma patients treated with either anti-PD1 or anti PD-L1 drugs presented by Betof *et al.* [20]. In the study of Betof *et al.,* it was concluded that efficacy did not decline with increasing age. Kugel *et al.* [5] presented retrospective clinical data on 538 patients treated at seven centres in the USA, Germany and Australia with anti-PD1 drugs, showing that metastatic melanoma patients above the age of 62 years responded more efficiently to anti-PD1 immunotherapy. They were, however, unable to perform a multivariate analysis as their data set was incomplete regarding known key prognostic markers.

Our multivariate analysis of OS included M-stage, line of therapy, gender, brain metastases, PS, LDH, absolute neutrophil count and age. Body mass index (BMI) recently have been shown to be an independent prognostic factor in metastatic melanoma [21]. Unfortunately, we were not able to include BMI as a factor in our analysis as data on height and weight at baseline were not available. For ipilimumab, the analysis confirmed known prognostic biomarkers correlated to a poorer survival (ECOG PS, M-stage, brain metastases, LDH and ANC) [22]. Importantly, for pembrolizumab, the multivariate analysis confirmed the known negative prognostic factors (presence of brain metastases, poor ECOG PS and increased LDH), but also that survival in patients between 70 and 80 was significantly better compared with younger patients, while this age effect disappeared above 80 years of age.

There was a trend that baseline characteristics in both the ipilimumab or pembrolizumab group, favoured older patients, probably because of careful patient selection. However, this finding is comparable in the two treatment cohorts, and the difference in OS was found only in the pembrolizumab cohort. Therefore, other explanations for the observed improved efficacy of pembrolizumab in elderly patients, not found in the ipilimumab treated group, should be looked for.

The evaluation of immune system functioning reveals that thymic production of naïve T-cells decreases with age, and also the number of CD4+ T-cells will decline with increasing age, leading to a decrease in response to antigens. Furthermore, the number of CD8+ T-cells increases with age, but the cells are dysfunctional, with reduced T-cell receptor capacity and functional defects, i.e. with reduced expression of CD28 on T-cells, a costimulatory signal that is essential for activation of T-cells [3,23,24].

However, little is known about the impact of age on the immune system changes in the intratumoural microenvironment and, with that, the changes in response to immunotherapy with increasing age. Kugel *et al.* [5] have shown that the levels of FOXP3-positive Tregs are significantly higher in both younger mice and in younger humans and that younger patients also have a lower level of CD8+ effector T-cells. In a murine model, they were able to revert this partial resistance in younger mice by treatment with anti-CD25, targeting Tregs [25]. As these changes take place only in the tumour microenvironment, this may also explain why we find age to be an independent prognostic parameter only for pembrolizumab-treated patients, with the immune effector phase being their primary site of action, in contrast to ipilimumab exerting most of its effects in the immune induction phase.

Our data underline the importance of not refusing patients a treatment option with ICIs based on evaluation of age alone. This, combined with data from several studies implying no significant increase in toxicity with increasing age, must, however, not lead to a treatment scenario where we think that the older the patient the better the efficacy. Friedman *et al.* [26] reported that despite the higher efficacy seen in elderly patients, it is important to focus on the functional status of the patient, including comorbidities with special emphasis on those that are autoimmune in nature. The cognitive and social support status must be evaluated to ensure that patients report symptoms between treatments and comply with their medication. Furthermore, as treatment of toxicities often involves steroids, we must focus on the fact that elderly patients are more prone to develop delirium and altered mental status during steroid therapy.

Future focus on the relationship between age and efficacy of immunotherapy with drugs targeting anti-PD1 should be to clarify the reason for this difference. The goal must be to search for a way to increase the survival of both younger and older patients in whom immunotherapy with ICIs is indicated. An obvious focus in the younger patients could be on creating a tumour microenvironment that makes the treatment with ICIs more effective.

Conflict of interest statement

Dr. L.B. reports personal fees from Novartis, personal fees from Merck MSD, personal fees from Incyte, personal fees from Roche and personal fees from BMS, outside the submitted work;

Dr. I.M.S. reports personal fees from Pierre Fabre, personal fees from Novartis, personal fees from MSD, personal fees from Incyte, personal fees from Celgene, personal fees from Roche and grants from BMS, outside the submitted work.

Dr. J.K.B. has nothing to disclose.

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Appendix A. Supplementary data

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