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Outcomes for systemic therapy in older patients with metastatic melanoma: Results from the Dutch Melanoma Treatment Registry

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ABSTRACT

Background: The incidence of metastatic melanoma is increasing in all ages. Multiple trials with targeted drugs and immune checkpoint inhibitors showed improved survival in metastatic melanoma. However, patients aged ≥75 years are often under-represented in clinical trials, therefore raising questions on safety and efficacy of treatment.
Patients and methods: We analyzed a real-world cohort of 3054 patients with metastatic melanoma stratified for age (≤65 years, 66–74 years and ≥ 75 years), and BRAF status, providing data on treatment strategies, toxicity, and survival. Kaplan Meier curves and Cox Proportional Hazard Models were used to present overall survival (OS) and Melanoma Specific Survival (MSS).
Results: Overall, 52.2% of patients were ≤ 65 years and 18.4% of patients ≥75 years. BRAF mutated tumors were found less often in patients ≥75 years: 34.5% versus 65% in patients ≤65 years. Patients ≥75 years received systemic therapy less frequently compared to their younger counterparts independent of the BRAF status. When receiving treatment, no statistical significant difference in grade 3 or 4 toxicity was observed. Three year Overall Survival rate was 13.7% (9.1–19.3) in patients ≥75 years versus 26.7% (23.1–30.4) in patients ≤65 years, with a Hazard Ratio (HR) of 1.71 (95%CI 1.50–1.95), $p < 0.001$. Three year Melanoma Specific Survival was 30.4% (22.0–39.2) versus 34.0% (29.7–38.2), HR 1.26 (95% CI 1.07–1.49), $p = 0.005$ with an adjusted HR of 1.21 (1.00–1.47), $p = 0.049$.
Conclusion: Patients with metastatic melanoma ≥75 years are less frequently treated, but when treated there is no statistical significant increase in toxicity and only a borderline statistical significant difference in Melanoma Specific Survival was seen, compared to younger patients.

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1. Introduction

Malignant melanoma is an aggressive cancer and the global incidence of melanoma is increasing. In The Netherlands, between 1990 and 2018, an increase in all stages of melanoma was seen, with the number of newly diagnosed patients aged 60 years or older increasing from 34.3% to 55.2% (all stages) [1]. In 2018, even 34.3% of all melanoma patients was aged 75 years or older [1]. Most cases of melanoma are diagnosed at an early stage when surgical excision is curative. However, patients can present with metastatic disease or develop metastases after their initial treatment. For decades, metastatic melanoma was associated with poor prognosis. Prior to the era of targeted therapies and immune checkpoint inhibitors, the median overall survival for metastatic melanoma treated with chemotherapy was less than 1 year [2]. Since 2010, several drugs targeting the BRAF pathway [3–6] and the immune checkpoint inhibitors, consisting of anti-CTLA-4 and anti-PD1 antibodies, [7–11] have shown efficacy in treating metastatic melanoma. Also, for patients at risk of developing metastatic disease (stage III), these therapies are currently given as adjuvant treatment [12–15]. Older patients with cancer generally have more comorbidities and impaired functional status and might differ in socio-demographic factors (for instance less social support) than younger patient with cancer [16]. Due to these comorbidities, older patients are at increased risk of developing toxicity and research is done to identify those at increased risk of chemotherapy related toxicity [17]. Also, a recent study showed a higher rate of immune related adverse events in older patients receiving anti-PD(L)1 treatment, although this was not a significant difference [18]. Besides increasing toxicity rates, the risk of dying from other causes than cancer increases with age [19]. These factors are important to weigh the risks and benefits of anti-cancer treatment in older patients. As mentioned, checkpoint inhibitors and targeted therapies improve the survival of patients with metastatic melanoma, but clinical trial populations are highly-selected and not always generalizable to the real-world population of cancer patients. Patients aged 75 years or older are often under-represented in clinical trials raising questions on safety and efficacy of these drugs in this specific group of patients. It has been postulated that immune checkpoint inhibitors may be less efficient in older patients because of the aging immune system leading to a wide range of alterations in immunity [21,22]. However, retrospective, observational studies and meta-analyses from clinical trials with older patients with metastatic melanoma, have shown that targeted therapies and immune checkpoint inhibitors show comparable safety and outcome as observed in the selected younger and healthier patients included in clinical trials [23–29]. In this study, we compare data on toxicity and outcomes (overall and melanoma specific survival) of patients with metastatic melanoma who received treatment in a population-based cohort of Dutch patients, stratified by age and BRAF status.

2. Patients and Methods

2.1. Data Collection: The Dutch Melanoma Treatment Registry (DMTR)

Data was retrieved from the Dutch Melanoma Treatment Registry (DMTR), a prospective population-based registry of patients with unresectable stage IIIc or IV melanoma, facilitated by the Dutch Institute for Clinical Auditing [30]. The DMTR contains information on baseline patient and tumor characteristics, local and systemic treatment, adverse events (only ≥ grade 3 according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0), and clinical outcome [31]. In compliance with Dutch regulations, the DMTR was approved by a medical ethical committee (METC Leiden University Medical Center, 2013) and is not considered subject to the Medical Research Involving Human Subjects Act. Patients were offered an opt-out option on the registration in the DMTR.

Between July 2013 and June 2017, 3054 patients with metastatic cutaneous melanoma were included for analysis. The data cut-off date for follow up was June 2019. Patients were assigned to one of three age cohorts, 1: age ≤ 65 years (younger patients), 2: age 66–74 years, 3: age ≥ 75 years (older patients). Historically, age was used as a selection criterium for the inclusion of patients in clinical randomized trials, where the age was usually fixed at "age between 18-65 years". Although age has been abandoned as a specific criterion for inclusion, patients ≥75 years are still under-represented in clinical trials. Because of the focus on safety and outcome in treatment of older patients, we will report the study results of all three age cohorts in the tables because of different definitions used to define older patients. Frequently, older patients are defined as ≥75 years and in text we will focus on the results of this cohort compared to their youngest counterparts.

Until 2015, treatment of metastatic melanoma in The Netherlands consisted of monotherapy with a BRAF inhibitor (in BRAF mutated tumors) or the anti-CTLA-4 checkpoint inhibitor ipilimumab. After 2015, combination treatment with BRAF and MEK inhibitors, ipilimumab as a first line treatment, anti-PD1 checkpoint inhibitors and the combination of anti-CTLA-4 and anti-PD-1 checkpoint inhibitors were registered as standard of care in treating metastatic melanoma patients.

2.2. Statistical Analysis

Descriptive statistics were employed to summarize baseline characteristics, chi-2 or Fishers exact test were used to test differences in distribution. Overall survival (OS) was defined as time from diagnosis to death due to any cause or end of follow-up. Kaplan Meier curves were used to present the survival curves. Cox proportional hazard models were used to calculate Hazard Ratios (HR) and corresponding two-sided 95% confidence intervals (CI). To calculate the adjusted HR, adjustment was made for sex, localization of the primary tumor, histology, comorbidity, number of metastases, and level of Lactate Dehydrogenase (LDH). Analyses were stratified for BRAF status and age. For Melanoma Specific Survival (MSS), time from diagnosis to death due to melanoma, as event, was used. To estimate progression, cumulative incidence curves with death as competing risk were used. To estimate subdistribution HR (sHR) and corresponding 95%CI, Fine and Gray competing risk models were used with progression as event and death as competing risk.

All statistical analyses were conducted using STATA/SE (version 12.0, StataCorp LP, Texas, USA).

3. Results

A total of 3054 patients were identified for analysis, 52.2% of patients aged ≤65 years, 29.3% of patients aged 66–74 years and 18.4% of patients aged ≥75 years. Baseline characteristics of all patients are presented in Table 1. Patients aged ≥75 years had more comorbidities and more often, a WHO performance score of ≥1. The number of patients with a BRAF mutated tumor decreased with increasing age, only 34.5% of patients aged ≥75 years had a BRAF mutated tumor versus 65% of patients aged ≤65 years ($p < 0.001$). Brain metastases were less often reported at the moment of registration in the DMTR in patients aged ≥75 years than in patients aged ≤65 years, 19.9% versus 31.2% respectively ($p < 0.001$). In 79 patients aged ≥75 (14%) the information on the presence of brain metastases was unknown, compared to 116 patients ≤65 years (7.3%). Diagnostic imaging was less frequently performed in the cohort of older patients ($p < 0.001$).

Table 1
Patient characteristics according to age.

		≤65 years	66–74 years	≥75 years	*p*-value
Sex (%)	Male	900 (56.4)	568 (63.4)	340 (60.4)	0.003
	Female	695 (43.6)	328 (36.6)	223 (39.6)	
Localisation (%)	Unknown primary melanoma	272 (17.0)	125 (13.9)	67 (11.9)	<0.001
	Head – neck	190 (11.9)	120 (13.4)	122 (21.7)	
	Trunk	643 (40.3)	352 (39.3)	179 (31.8)	
	Extremities	475 (29.7)	295 (32.9)	192 (34.1)	
	Unknown	15 (0.9)	4 (0.5)	3 (0.5)	
Histology (%)	Superficial	726 (45.5)	350 (39.1)	211 (37.5)	<0.001
	Nodular	307 (19.2)	239 (26.7)	144 (25.6)	
	Acrolentiginous	11 (0.7)	7 (0.8)	6 (1.1)	
	Lentigo maligna	19 (1.2)	19 (2.1)	16 (2.8)	
	Desmoplastic	8 (0.5)	9 (1.0)	11 (1.9)	
	Other	55 (3.5)	37 (4.1)	23 (4.1)	
	Unknown	469 (29.4)	235 (26.2)	152 (27.0)	
Breslow Thickness (%)	≤1 mm	214 (13.4)	83 (9.3)	48 (8.5)	<0.001
	1.01–2.0 mm	434 (27.2)	160 (17.9)	97 (17.2)	
	2.01–4.0 mm	378 (23.7)	250 (27.9)	185 (32.9)	
	≥4.01 mm	289 (18.1)	190 (21.2)	146 (25.9)	
	Unknown	280 (17.6)	213 (23.8)	87 (15.5%)	
BRAF mutation (%)	Negative	490 (30.7)	394 (44.0)	290 (51.5)	<0.001
	Positive	1036 (65.0)	446 (49.8)	194 (34.5)	
	Unknown	69 (4.3)	56 (6.2)	79 (14.0)	
Number of comorbidities (%)	None	792 (49.7)	197 (22.0)	57 (10.1)	<0.001
	1–2	626 (39.2)	473 (52.8)	275 (48.9)	
	3 or more	125 (7.8)	181 (20.2)	206 (36.6)	
	Unknown	52 (3.3)	45 (5.0)	25 (4.4)	
WHO performance score (%)	WHO 0	833 (52.2)	399 (44.5)	170 (30.2)	<0.001
	WHO 1	410 (25.7)	242 (27.0)	191 (33.9)	
	WHO 2	106 (6.6)	79 (8.8)	76 (13.5)	
	WHO 3	43 (2.7)	36 (4.0)	27 (4.8)	
	WHO 4	9 (0.6)	6 (0.7)	3 (0.5)	
	Unknown	194 (12.2)	134 (15.0)	96 (17.1)	
M stage[a] (%)	M1a	152 (9.5)	79 (8.8)	48 (8.5)	<0.001
	M1b	216 (13.5)	164 (18.3)	103 (18.3)	
	M1c	538 (33.7)	295 (32.9)	191 (33.9)	
	M1d	498 (31.2)	238 (26.6)	112 (19.9)	
	Undefined	74 (4.6)	44 (4.9)	24 (4.3)	
	Missing	117 (7.3)	76 (8.5)	85 (15.1)	
Number of metastatic sites (%)	≤ 3	963 (60.4)	567 (63.3)	326 (57.9)	<0.001
	≥ 4	434 (27.2)	218 (24.3)	122 (21.7)	
	Unknown	198 (12.4)	111 (12.4)	115 (20.4)	
Brain metastases (%)	Yes	498 (31.2)	238 (26.6)	112 (19.9)	< 0.001
	No	981 (61.5)	584 (65.2)	372 (66.1)	
	Unknown	116 (7.3)	74 (8.3)	79 (14.0)	
LDH[b] (%)	Not determined	84 (5.3)	64 (7.1)	62 (11.0)	<0.001
	Normal (until 250 U/L)	954 (59.8)	493 (55.0)	293 (52.0)	
	Elevated (> 250 U/L)	537 (33.7)	323 (36.1)	181 (32.2)	
	Unknown	20 (1.2)	16 (1.8)	27 (4.8)	
Imaging (%)	**CT scan**				<0.001
	Yes	1114 (69.8)	614 (68.5)	322 (57.2)	
	No	451 (28.3)	257 (28.7)	211 (37.5)	
	Unknown	30 (1.9)	25 (2.8)	30 (5.3)	
	PET-CT scan				<0.001
	Yes	1075 (67.4)	593 (66.2)	368 (65.4)	
	No	498 (31.2)	285 (31.8)	164 (29.1)	
	Unknown	22 (1.4)	18 (2.0)	31 (5.5)	
	Brain MRI scan / CT scan				<0.001
	Yes	1065 (66.8)	557 (62.2)	280 (49.7)	
	No	503 (31.5)	308 (34.4)	246 (43.7)	
	Unknown	27 (1.7)	31 (3.5)	35 (6.2)	
	Missing			2 (0.4)	

WHO performance score: World Health Organisation performance score.
[a] M stage: according to AJCC 8th edition.
[b] LDH: lactate dehydrogenase. LDH normal until 250 U/L, LDH level elevated >250 U/L.

3.1. Treatment Strategies

By identifying the treatment strategies used for patients diagnosed with metastatic melanoma, we stratified patients having a tumor with a BRAF mutation (BRAF positive) versus those without a BRAF mutation (BRAF negative). These results showed differences in receiving a first line systemic treatment between the age cohorts, with 53.2% of patients with a BRAF negative tumor aged ≥75 years receiving first line systemic

Table 2
Treatment strategies (first line) in BRAF negative and BRAF positive patients.

	≤65 years	66–74 years	≥75 years	*p*-value
BRAF negative				
Supportive care (%)[a]	31 (6.4)	47 (12.1)	68 (23.9)	p < 0.001
Local (%)[b]	101 (20.8)	78 (20.2)	65 (22.9)	
Systemic (%)	354 (72.8)	262 (67.7)	151 (53.2)	
BRAF positive				
Supportive care (%)[a]	43 (4.2)	19 (4.3)	31 (16.2)	p < 0.001
Local (%)[b]	130 (12.6)	55 (12.4)	23 (12.0)	
Systemic (%)	858 (83.2)	369 (83.3)	137 (71.7)	

[a] Supportive care without systemic treatment.
[b] Local treatment: metastasectomy or radiotherapy.

treatment, compared to 72.8% of patients aged ≤65 years ($p < 0.001$). This difference was also seen in patients with a BRAF positive tumor, although to a lesser extent: 71.7% of patients aged ≥75 years versus 83.2% of patients aged ≤65 years ($p < 0.001$). (Table 2). The older patients also received second or third line systemic therapy less frequently, 79.3% of patients with a BRAF negative tumor and 69.1% of BRAF positive tumor patients aged ≥75 years received no treatment after first line failure, compared to 63.1% of patients with a BRAF negative tumor and 45.5% of patients with a BRAF positive tumor in patients aged ≤65 years (Supplemental Table 1).

3.2. Changes Over Time

In the years analyzed (2013–2017), the introduction of targeted therapies and immune checkpoint inhibitors established a role in treating patients with metastatic melanoma in The Netherlands. This was seen in the proportion of patients receiving treatment in all age cohorts and irrespective on the subdivision on BRAF status. (Fig. 1).

3.3. Toxicity

There was no statistical significant difference in the occurrence of grade 3 or 4 adverse events, reported for all kind of therapies, between the three age cohorts. In the cohort of patients aged ≥75 years, more adverse events during treatment with the combination of BRAF/MEK inhibitors were reported ($p = 0.098$), but this was not a significant difference (Table 3). The most commonly reported toxicity was of dermatologic origin, i.e. rash, photo-sensitivity and hyperkeratosis.

3.4. Survival

Median follow up time in this analysis was 211 days (IQR 110–454 days). Survival differences were seen between the three cohorts, with patients ≥75 years having a worse prognosis with a hazard ratio (HR) for death of 1.71 (95%CI 1.50–1.95), $p < 0.001$, compared to patients aged ≤65 years. The three year overall survival (OS) rate in all patients ≥75 years was 13.7% (9.1–19.3) versus 26.7% (23.1–30.4) in all patients ≤65 years, adjusted HR for death 1.53 (95% CI 1.30–1.80), $p < 0.001$. During follow up, patients with a BRAF mutated tumor had a better OS than patients with BRAF negative tumors (adjusted HR 0.81, (0.72–0.92), $p = 0.001$). These differences in OS rates were seen in all age cohorts, but only during the 1 year OS. Death due to melanoma (Melanoma Specific Survival, MSS) showed smaller differences between the age cohorts, three year MSS rate in patients ≥75 years was 30.4% (22.0–39.2) versus 34.0% (29.7–38.2) in patients ≤65 years (HR

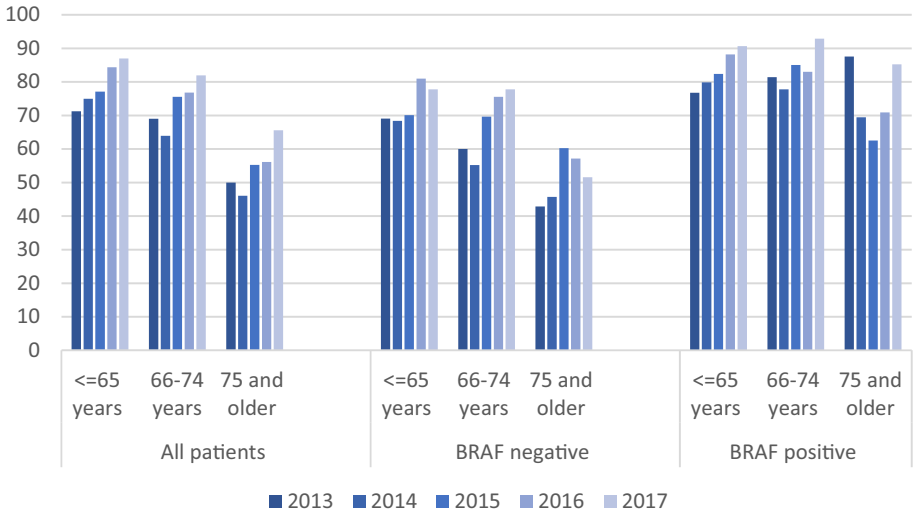

Fig. 1. Proportion of patients who received systemic treatment over time, and according to BRAF status.

Table 3
Grade 3–4 adverse events according to age and treatment.

Adverse events (grade 3 or 4)	≤65 years	66–74 years	≥75 years	*p*-value
Treatment 1st or 2nd line	n (toxicity) / N (patients receiving specific treatment) (%)			
Chemotherapy	2/82 (2.4)	0/32 (0.0)	2/22 (9.1)	0.14
BRAF & MEK inhibitor	159/642 (24.8)	67/276 (24.3)	36/105 (34.3)	0.098
Ipilimumab	102/372 (27.4)	67/225 (29.8)	25/77 (32.5)	0.62
Anti-PD1 antibody	52/400 (13.0)	28/243 (11.5)	24/132 (18.2)	0.18
Ipilimumab & nivolumab	55/89 (61.8)	12/22 (54.5)	1/1 (100)	0.59
Trial drugs[a]	55/178 (30.9)	14/55 (25.4)	5/16 (31.2)	0.73

[a] Trial drugs: Basket group which cannot be further determined.

Table 4
Overall and Melanoma specific survival according to age (all patients).

All patients	≤65 years $N = 1548$	66–74 years $N = 864$	≥75 years $N = 547$
1-year OS rate	62.2 (59.2–64.9)	52.9 (48.9–56.7)	44.5 (39.6–49.3)
3-years OS rate	26.7 (23.1–30.4)	24.4 (19.6–29.4)	13.7 (9.1–19.3)
HR (95%CI)	References	1.22 (1.08–1.37); p = 0.001	1.71 (1.50–1.95); p < 0.001
Adjusted HR (95%CI)	References	1.16 (1.01–1.32); $p = 0.029$	1.53 (1.30–1.80); p < 0.001
1-year MSS rate	68.0 (65.1–70.7)	61.8 (57.7–65.6)	61.7 (56.4–66.6)
3-years MSS rate	34.0 (29.7–38.2)	34.0 (28.2–39.9)	30.4 (22.0–39.2)
HR (95%CI)	References	1.16 (1.01–1.32); $p = 0.03$	1.26 (1.07–1.49); p = 0.005
Adjusted HR (95%CI)	References	1.11 (0.95–1.29); $p = 0.175$	1.21 (1.00–1.47); p = 0.049

Adjusted for sex, localisation of the primary tumor, histology, comorbidity, number of metastases and LDH level.

1.26 (95%CI 1.07–1.49); $p = 0.005$, adjusted HR 1.21 (95%CI 1.21 (1.00–1.47), $p = 0.049$). (Table 4 and Fig. 2 with Kaplan Meier Estimates stratified for age and BRAF status).

4. Discussion

To our knowledge, this study presents the largest cohort of patients aged ≥75 years with metastatic melanoma published so far. The DMTR is a nation-wide, real-world cohort of patients with metastatic melanoma, providing extensive results in addition to the knowledge from selected patients included in the randomized controlled trials (RCT) on safety and outcome. In this large cohort, we focused on the safety and outcome of 563 patients aged ≥75 years, 18.4% of all patients with metastatic cutaneous melanoma included in the DMTR between 2013 and 2017. Toxicity was not significantly different between the age cohorts. A worse overall survival (OS) was observed in these older patients compared to the younger patients aged ≤65 years, but melanoma specific survival (MSS) showed more comparable results, reflecting the competing risk of death from other causes than metastatic melanoma in older patients.

In general, cancer in older patients appears in the context of physical and/or cognitive impairment and increased risk of treatment toxicity [16,17]. In our cohort, patients aged ≥75 years showed more comorbidities and less favourable WHO performance score compared to patients aged ≤65 years. Consistent with literature, BRAF mutated tumors were found less frequently in the cohort of patients aged ≥75 years [20]. As a consequence, less treatment options were available for these patients. In the cohort of patients aged ≥75 years more patients were diagnosed with higher Breslow thickness melanomas than their younger counterparts. Higher Breslow thickness is associated with poorer prognosis. Thicker melanoma in older patients was also seen in recent research [33], where in time, a decrease in Breslow thickness melanomas in older patients was observed, suggesting increased awareness of the signs and symptoms of melanoma. We also observed a lower percentage of brain metastases reported in the group of older patients, but this is probably more a matter of underreporting due to less imaging performed in patients aged ≥75 years. Therefore, this is more likely to be a confounder, than a real difference between the age cohorts. In a sensitivity analysis to investigate the possible impact of this unknown status of brain metastases on melanoma specific survival we did not find a statistical difference between the age cohorts (data not shown).

Several studies have shown the effectiveness of targeted therapies and immune checkpoint inhibitors for metastatic melanoma [3–15]. In the years analyzed, the availability of these drugs outside clinical trials increased, and combinations of these drugs became the standard of care in The Netherlands. During the first years of the availability of these drugs, patients ≥75 years less frequently received treatment for metastatic melanoma compared to patients ≤65 years. This was seen in first line setting, but mostly in subsequent treatment lines. This inequitable distribution between older and younger patients changed over time and the proportion of patients receiving systemic therapy increased in all age cohorts. These significant differences in treatment between the cohorts might be of importance in weighing the impact of treatment on toxicity and survival. In recent years, retrospective, observational studies on safety and efficacy of treating patients with metastatic melanoma outside clinical trials [24–29,32] became increasingly available. In The Netherlands, treatment of patients with metastatic melanoma became centralized to fourteen expert hospitals who all register their data into the DMTR [31]. The shift in treatment availabilities and central management of metastatic melanoma has led to older patients receiving standard of care more frequently in The Netherlands.

In our study, no significant difference in grade 3–4 toxicity in all types of treatment was observed between the age cohorts. A trend towards more adverse events whilst treating with BRAF/MEK inhibitors was seen in patients ≥75 years, with the most reported toxicity of dermatologic origin (i.e. rash, photo-sensitivity and hyperkeratosis), but this was not statistically different. The combination of BRAF/MEK inhibitors has less skin toxicity and this combination is the standard of care when treating with targeted drugs [5,6]. Our observation on toxicity is consistent with other studies on treating older patients with targeted therapies and immune checkpoint inhibitors [23–29]. Some of these articles, also show a trend towards increased toxicity occurring in the age ≥ 75 years group, but this was not statically significant [18,27]. An Italian study on the results of the open access programme with ipilimumab confirms the generally well tolerability of anti-CTLA-4 treatment in older patients [24]. Although, there was no statistical significant difference in toxicity in treated patients, it has to be mentioned that in our study patients ≥75 years less frequently received systemic treatment than their younger counterparts. Perhaps, the experiences and knowledge on the endurance of general anti-cancer treatment with chemotherapy in older patients with comorbidities has influenced the choice of both patient and physician on starting treatment. None of the observational studies, nor our DMTR data, provided data on geriatric assessment. Future follow up data from the DMTR combined with the information obtained during geriatric assessments may provide tools in selecting patients who will benefit from systemic treatment for metastatic melanoma.

Immunosenescence is defined as age related immune dysfunction and chronic inflammation, which can theoretically reduce the effect of immune checkpoint inhibitors in cancer treatment [21,22]. In our cohort, 3-year OS in patients aged ≥75 years was significantly lower compared to patients ≤65 years, both in patients with a BRAF mutated tumor as well as in patients with BRAF negative tumors. The MSS was more comparable between the age cohorts, reflecting the competing risk of dying from other causes than metastatic melanoma in older patients [19]. Our positive outcome on MSS for treatment of older patients compared to younger patients is consistent with data available from other studies [24,25,28,29], which contributes to the statement that efficacy of treatment with immune checkpoint inhibitors in older metastatic melanoma patients is not strongly influenced by the decline of immune function with increasing age. Positive results, both on safety and outcome during treatment with immune checkpoint inhibitors in older patients are seen in other tumor types (i.e. lung cancer, urogenital cancer)

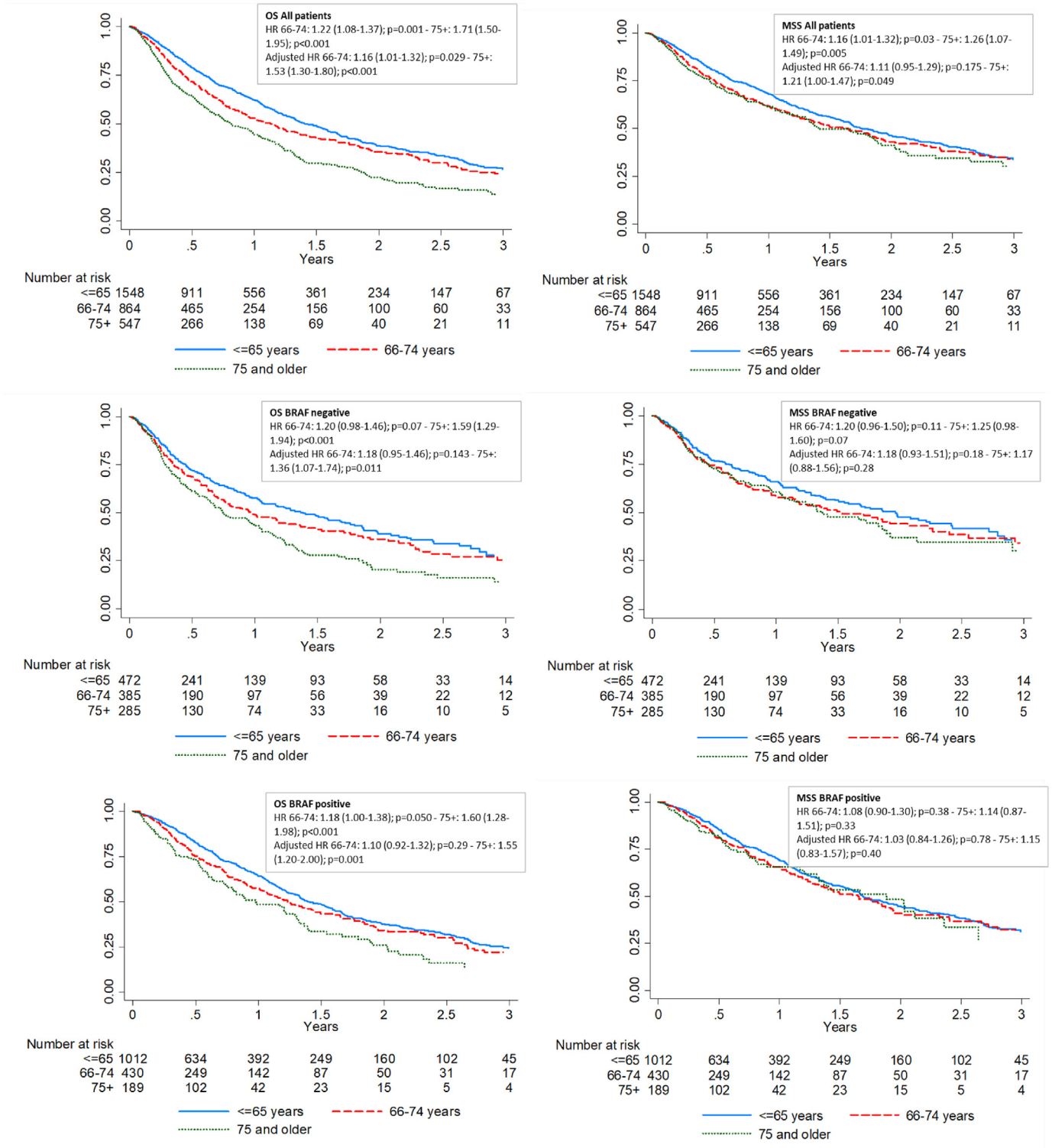

Fig. 2. Kaplan Meier estimates for overall survival (OS) and Melanoma Specific Survival (MSS) according to age and BRAF status.

as well [28,29]. The significant difference between the age cohorts with patients ≥75 years less frequently receiving systemic treatment than their younger counterparts probably affects MSS in the cohort of older patients.

A limitation to our study might be the lack of information on grade 1–2 adverse events, the quality of life during treatment, and the effect on whether this had consequences for continuing treatment for metastatic melanoma. Although no significant difference between grade 3–4 toxicities were reported, an increase in (ongoing) grade 1–2 adverse events might be present and probably has greater impact in older patients with a less favourable WHO performance score and more comorbidities than in younger patients. Another limitation in interpreting the results from our study, is the absence of using a geriatric assessment to identify frail older patients, but also to prevent under-

treatment of fit older patients. The DMTR does not contain information on the use of these screening tools.

As there is no consensus definition for "older patients ", we analyzed three age cohorts and decided to discuss in the text patients aged ≥75 years compared to younger patients aged ≤65 years. DMTR research results on toxicity and outcome of patients aged ≥65 years will be discussed in more detail in another manuscript.

A strength of our study is the nation-wide coverage of all patients with metastatic melanoma in the DMTR. Due to the centralisation of care for patients with metastatic melanoma and the mandatory registration in the DMTR, this observational study provides data on all patients diagnosed with metastatic melanoma, not only on those patients receiving treatment. To ensure high-quality data, data managers were extensively trained and supervised by oncologists [31]. Nevertheless, given the observational design of the study, we cannot fully rule out confounding by indication or selection bias. However, its multicentered design attenuates the potential selection bias.

5. Conclusions

During the years analyzed, a shift in treatment paradigm was seen to older patients receiving standard of care more frequently, although older patients still received systemic treatment less frequently than younger patients. In our daily practice, treatment with BRAF/MEK inhibitors and immune checkpoint inhibitors was generally well tolerated with no significant increase in serious adverse events. Although overall survival in older patients aged ≥75 years was worse compared to patients ≤65 years, the melanoma specific survival between the age cohorts was only borderline significantly different, reflecting death from other causes than melanoma in the older patient. This difference in survival is most likely associated with the increased comorbidity and higher Breslow thickness. Together with known literature, our study emphasizes that age should not be used as a specific criterion to withhold treatment to patients with metastatic melanoma. The role for geriatric assessment needs to be strongly considered for better risk stratification of patients and avoid unnecessary treatment for frail patients, as well as holding treatment for fitter patients.

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Disclosures

MBS has consultancy relationships with Pierre-Fabre, MSD and Novartis. AvdE has advisory relationships with Amgen, Bristol-Myers Squibb, Roche, Novartis, MSD, Pierre-Fabre, Sanofi, Pfizer, Ipsen, Merck and has received research study grants not related to this paper from Sanofi, Roche, Bristol- Myers Squibb, Idera and TEVA and has received travel expenses from MSD Oncology, Roche, Pfizer and Sanofi and has received speaker honoraria from Bristol-Myers Squibb and Novartis. JdG has advisory relationships with Bristol-Myers Squibb, Pierre- Fabre, Servier, MSD, Novartis. JH has advisory relationships with Aimm, Achilles Therapeutics, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Celsius Therapeutics, GSK, Immunoscore, Ipsen, MSD, Merck Serano, Novartis, Neogene Therapeutics, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics, Third Rock Ventures, Vaximm and has received research grants not related to this work from Bristol-Myers Squibb, MSD, Neon Therapeutics and Novartis. GH has consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Roche, MSD, Pfizer, Novartis, Pierre-Fabre and has received research grants not related to this work from Bristol-Myers Squibb, Seerave. KS has consultancy/advisory relationships with Bristol-Myers Squibb, Novartis, MSD, Pierre-Fabre and received research honoraria not related to this work from Novartis, MSD and Roche. AvdV has consultancy/advisory relationships with Bristol-Myers Squibb, MSD, Roche, Novartis, Pierre-Fabre, Pfizer, Sanofi, Ipsen, Eisai, Merck. EK has consultancy/advisory relationships with Bristol-Myers Squibb, Novartis, Merck, Pierre-Fabre and received research grants not related to this work from Bristol-Myers Squibb.
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Authorship Contributions

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2021.04.006.

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