European Journal of Cancer 212 (2024) 115056

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Original research

Adjuvant immunotherapy in older patients with stage III and resected stage IV melanoma: Toxicity and recurrence-free survival outcomes from the Dutch melanoma treatment registry

A. Özkan [a], E. Kapiteijn [a], F. van den Bos [b], M.J.B. Aarts [c], F.W.P.J. van den Berkmortel [d], C.U. Blank [a,e], M. Bloem [f,g,h], W.A.M. Blokx [i], M.J. Boers-Sonderen [j], J.J. Bonenkamp [k], A.J.M. van den Eertwegh [l], J.W.B. de Groot [m], J.B. Haanen [n], C.E. Holtslag [a], G.A.P. Hospers [°o], D. Piersma [p], R.S. van Rijn [q], A.M. Stevense-den Boer [r], K.P.M. Suijkerbuijk [s], A.A.M. van der Veldt [t], G. Vreugdenhil [u], M.W.J.M. Wouters [f,g,h], J.E.A. Portielje [a], N.A. de Glas [a,v,*]

[a] Department of Medical Oncology, Leiden University Medical Center, Albinusdreef 2, Leiden 2333ZA, the Netherlands
[b] Department of Gerontology and Geriatrics, Leiden University Medical Center, Albinusdreef 2, Leiden 2333ZA, the Netherlands
[c] Department of Medical Oncology, GROW School for Oncology and Reproduction, Maastricht University Medical Center, P. Debyelaan 25, Maastricht 6229 HX, the Netherlands
[d] Department of Medical Oncology, Zuyderland Medical Center Sittard, Dr. H. van der Hoffplein 1, Sittard-Geleen 6162BG, the Netherlands
[e] Department of Molecular Oncology & Immunology, Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066CX, the Netherlands
[f] Department of Biomedical Data Sciences, Leiden University Medical Center, Einthovenweg 20, Leiden 2333ZC, the Netherlands
[g] Department of Surgical Oncology, Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066CX, the Netherlands
[h] Dutch Institute for Clinical Auditing, Rijnsburgerweg 10, Leiden 2333AA, the Netherlands
[i] Department of Pathology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584CX, the Netherlands
[j] Department of Medical Oncology, Radboud University Medical Center, Geert Grooteplein Zuid 10, Nijmegen 6525GA, the Netherlands
[k] Department of Surgery, Radboud University Medical Center, Geert Grooteplein Zuid 10, Nijmegen 6525GA, the Netherlands
[l] Department of Medical Oncology, Amsterdam UMC, VU University Medical Center, Cancer Center Amsterdam, De Boelelaan 1118, Amsterdam 1081HZ, the Netherlands
[m] Isala Oncology Center, Isala, Dokter van Heesweg 2, Zwolle 8025AB, the Netherlands
[n] Department of Medical Oncology & Immunology, Netherlands Cancer Institute, Plesmanlaan 121, Amsterdam 1066CX, the Netherlands
[°o] Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, Groningen 9713GZ, the Netherlands
[p] Department of Internal Medicine, Medisch Spectrum Twente, Koningsplein 1, Enschede 7512KZ, the Netherlands
[q] Department of Internal Medicine, Medical Center Leeuwarden, Henri Dunantweg 2, Leeuwarden 8934AD, the Netherlands
[r] Department of Internal Medicine, Amphia Hospital, Molengracht 21, Breda 4818CK, the Netherlands
[s] Department of Medical Oncology, University Medical Center Utrecht, Utrecht University, Heidelberglaan 100, Utrecht 3584CX, the Netherlands
[t] Department of Medical Oncology and Radiology & Nuclear Medicine, Erasmus Medical Center, 's-Gravendijkwal 230, Rotterdam 3015CE, the Netherlands
[u] Department of Internal Medicine, Maxima Medical Center, De Run 4600, Eindhoven 5504DB, the Netherlands
[v] Department of Medical Oncology, Helse Førde, Svanehaugvegen 2, 6812 Førde, Norway

ARTICLE INFO

Keywords:
Oncology
Melanoma
Immune checkpoint inhibitors
Immune-related adverse events
Recurrence-free survival

ABSTRACT

Background: Adjuvant anti-PD-1 therapy improves relapse free survival in stage III melanoma, but also leads to immune-related adverse events (irAEs). Older patients are of particular interest due to comorbidities and frailty, which may impact their ability to tolerate irAEs and benefit from anti-PD-1 therapy. This study aimed to explore associations between clinical parameters and the occurrence of grade ≥ 3 irAEs and recurrence-free survival (RFS) in older patients with radically resected stage III/IV cutaneous melanoma treated with adjuvant anti-PD-1 therapy.

Methods: Patients aged ≥ 65 with resected stage III/IV cutaneous melanoma treated with adjuvant anti-PD-1 therapy between 2018 and 2022 were selected using real-world data from the nationwide Dutch Melanoma Treatment Registry (DMTR). A univariate and multivariable logistic regression was used to compare

* Corresponding author at: Albinusdreef 2, 2300 RC Postzone C7-R, Leiden, the Netherlands.
E-mail address: N.A.de_Glas@lumc.nl (N.A. de Glas).

https://doi.org/10.1016/j.ejca.2024.115056
Received 2 July 2024; Received in revised form 28 August 2024; Accepted 12 September 2024
Available online 30 September 2024

determinants of grade ≥ 3 irAEs, and univariate and multivariable Cox-proportional hazard models were fitted to identify factors influencing RFS.
Results: The study included 885 patients, with 280 aged 75 and older. The incidence of grade ≥ 3 irAEs was 15.5 % in the 65–74 age group and 13.9 % in the ≥ 75 age group. No significant correlation was found between age and grade ≥ 3 irAEs. However, an increasing number of comorbidities was associated with a higher risk of grade ≥ 3 irAEs (multivariable analyses: OR 1.83, 95 % C.I. 0.99–3.40). The 1-year RFS rate of 80.0 % of this study was comparable to those reported in previous registration trials and real-world data. Having ≥ 3 comorbidities was significantly associated with a decrease in RFS (HR: 1.68, 95 % C.I. 1.15–2.44).
Conclusion: Older patients had similar benefit of adjuvant immunotherapy compared to older subgroups in previous trials. However, patients with multiple comorbidities were at increased risk of grade ≥ 3 irAEs and had a lower RFS. This should be considered when deciding upon adjuvant treatment.

1. Introduction

Immune checkpoint inhibitors, in particular anti-CTLA-4 and anti-PD-1 antibodies have revolutionized melanoma treatment. Whereas historically tumor regression and long-term cancer control was possible in less than 10 % of the patients with metastatic melanoma, with immune checkpoint inhibitors this is now attainable in nearly 50 % of the patients [1]. Anti-PD-1 antibodies have also been introduced in the adjuvant setting and more recently in the neo-adjuvant setting [2].

Studies have demonstrated that adjuvant immunotherapy provides a substantial improvement in recurrence-free survival (RFS) compared to placebo in high risk melanoma patients, as shown in trials including Checkmate-238 and EORTC1325/Keynote-054 (70.5–75.4 % 1-year RFS rate compared to placebo (61.0 %)) [3]. However, despite these advancements, only 40 % of these patients remain disease-free after four years [4]. Additionally, treatment-related grade 3–4 toxicity was 14.4 % with nivolumab and 14 % with pembrolizumab (anti-PD-1 antibodies) [2,5]. Currently, there are no data available that show an overall survival benefit of adjuvant anti-PD1 therapy [6]. As of 2019 and following consensus of the Dutch immunotherapy working group (WIN-O), all Dutch patients with a completely resected melanoma stage IIIA (with at least one microscopic metastasis >1 mm), stage IIIB-D and IV can be treated with anti-PD-1 antibodies in the adjuvant setting for one year [3,7–9]. Alternatively, patients with a V600E/K mutated melanoma can also be treated with BRAF/MEK inhibitors.

As with other adjuvant treatment strategies, most patients who receive adjuvant anti-PD1 will not benefit from therapy as they would never have developed recurrence or metastases, or experience recurrence despite receiving adjuvant immunotherapy. Unfortunately, patients who do not experience benefit are still at risk of immune-related adverse events (irAEs) [10]. Therefore, there is a need for predictive factors to more accurately identify which patients will benefit from adjuvant treatment and who are at increased risk for adverse events.

The aging population in the Netherlands has led to a rising number of older patients with melanoma, with 45 % of melanoma patients now being aged 65 or older [11]. Within the context of melanoma treatment, older patients present with unique challenges. They experience higher melanoma-specific mortality rates, thicker tumors, and increased rates of ulceration, which contribute to a higher risk of disease recurrence [12]. Additionally, it is important to note that in older patients, the effectiveness of adjuvant therapies may be diminished by other-cause mortality. Older patients often experience a reduced life expectancy and commonly face comorbid illnesses, polypharmacy, and frailty, which impacts their capacity to endure cancer treatments and side effects. Therefore, treatment benefits may not outweigh potential side effects [13,14]. In both randomized clinical trials and observational research on immunotherapy in advanced melanoma, younger and older patients did not exhibit significantly different (severe) toxicity or recurrence outcomes [15,16]. However, patients over 75 discontinued treatment more frequently due to toxicity [15]. Importantly, previous randomized clinical trials included relatively few older patients, and all patients were generally fit with a good performance status and few comorbidity [17]. Population-based studies can provide a more realistic overview of "real-world" patients. To our knowledge, adjuvant immunotherapy has not yet been studied specifically in older adults in population-based studies. Hence, the aim of this study was to explore associations between clinical parameters and the occurrence of grade ≥ 3 irAEs, and RFS in older patients with completely resected stage III/IV cutaneous melanoma who were treated with adjuvant immunotherapy in real-world, using data from the nationwide Dutch Melanoma Treatment Registry (DMTR).

2. Materials and methods

2.1. Patient inclusion

Advanced melanoma care in the Netherlands is concentrated in 14 hospitals. The DMTR is a nationwide prospective population-based registry initiated in 2013, is supported by the Dutch Institute for Clinical Auditing (DICA) to ensure the quality of care and safety in these hospitals [18]. This registry includes information of all consecutive patients who are diagnosed with a stage III or IV cutaneous melanoma and receive systemic therapy in the Netherlands. Data are registered by trained data managers and include baseline patient characteristics, tumor characteristics, local and systemic therapy, adverse events (only grade ≥3 according to Common Terminology Criteria for Adverse Events (CTCAE) version 5), and clinical outcomes including staging according to the AJCC-8 classification and mortality. Detailed information on data registry and included information has been previously published [18]. For the current study, all patients aged ≥ 65 with stage III and resected IV cutaneous melanoma who were treated with monotherapy anti-PD-1 antibodies (nivolumab or pembrolizumab) in the adjuvant setting between June 2018 and September 2022 were included from the DMTR, and data cut-off was December 31, 2023. To maintain an appropriate follow-up timeframe, only patients who had initiated ICI therapy at least 1 year before the data cut-off were included in the analysis. During the year of diagnosis, there were two registration points where all interim episodes and follow-up events were documented. After the completion of therapy, follow-up continued with annual registration points for up to five years, where all interim episodes and follow-up moments were recorded. The study design was approved by the scientific board of the DMTR and is not considered subject to the Medical Research Involving Human Subjects Act as all data are anonymized.

2.2. Variables

As the primary objective of this study was safety outcome in treatment of older patients, the treatment-related toxicity results were reported in two age cohorts; 1: age 65–74 years, 2: ≥ 75 years, to evaluate whether there was an upward trend between toxicity and age within an elderly population. The cut-off of 75 years aligns with common age classifications in medical literature: youngest-old (65–74 years), middle-old (75–84 years), and oldest-old (≥85 years). The middle-old and oldest-old age groups were combined to ensure sufficient sample sizes for analysis. Baseline patient characteristics included the two age groups, sex, comorbid diseases, and ECOG (Eastern Cooperative

Oncology Group) performance status [19]. Total number of specific comorbidities per patient was categorized into 0 comorbidities, 1–2 comorbidities, 3 or more comorbidities or unknown. The DMTR utilizes a predefined list of relevant comorbidities that can be checked for each patient, as detailed in a previous publication [18]. Although no formal comorbidity score (such as the Charlson or CIRG-score) is included in the DMTR, prior research has demonstrated that a simple comorbidity count is equally effective in predicting outcomes in older adults [20]. It is important to note that the DMTR excludes less clinically significant comorbidities, to ensure a more meaningful assessment of patient health [21]. To provide a more comprehensive analysis, we not only assessed overall comorbidity status but also conducted a detailed examination of specific comorbidities, including autoimmune, cardiovascular, pulmonary, and endocrine diseases. These conditions were selected due to their high prevalence and their potential to significantly impact overall health, particularly in relation to the patient's capacity to tolerate the side effects of cancer treatments. We have included a supplementary table (Table S1) that outlines the subcategories of these conditions for further clarity.

Baseline tumor characteristics included location of the primary tumor (melanoma of unknown primary, head-neck, trunk, extremities, acral), disease stage, Breslow thickness, BRAF mutation, ulceration, PET-CT and LDH (with a cut-off of 250 mmol/L). The specific anti-PD-1 therapy administered to patients (nivolumab or pembrolizumab) was also reported. Furthermore, we described the type of $\geq$ 3 irAEs that occurred in more detail. These included: endocrine toxicity, colitis, neuropathy, nephritis, pneumonitis, hepatitis, arthralgia, and cutaneous toxicity. Patients could have had more than one type of irAE. For all variables, to account for missing data within a variable, an additional category denoted as "unknown" was included in the analysis alongside the available data.

2.3. Statistical analyses

For all analyses, SPSS version 25 was used, and significance level was chosen at $\alpha = 0.05$. Descriptive statistics were used to describe patient and tumor characteristics. We used the chi-squared test to compare categorical outcomes in the two age groups. A univariate logistic regression was used to compare the following possible determinants of grade $\geq$ 3 irAEs; age, sex, number of comorbidities, auto-immune, cardiovascular, pulmonary, and endocrine diseases, ECOG performance status. Additionally, a multivariable analysis was conducted, including determinants that were statistically significant or clinically relevant and could potentially act as confounders. Furthermore, specific associations were examined between different types of comorbidities and grade $\geq$ 3 irAEs. Recurrence-free survival (RFS) was defined as the time from surgery until recurrence or death, censored at the last follow-up. Patients who did not meet the endpoint (recurrence or death) were censored at the date of last follow-up. We generated a Kaplan-Meier plot to assess the RFS in older melanoma patients treated with adjuvant anti-PD-1 therapy. The RFS at 12 and 24 months was estimated by construction of life tables in SPSS. Additionally, we generated several plots to compare the exposures of interest, including the number of comorbidities, ECOG performance status, and tumor stage respectively. Plots were created with GraphPad PRISM 9.3.1.

Univariate and multivariable Cox-proportional hazard models were fitted to identify factors influencing RFS. All factors that were either statistically significant or clinically relevant in the univariate analysis were included in the multivariable analysis.

3. Results

3.1. Patient characteristics

A total of 885 patients ages 65 years or older, with completely resected stage III/IV cutaneous melanoma received adjuvant treatment and were identified for analysis, with 68 % of patients falling within the age range of 65–74 years and the remaining 32 % comprising patients aged 75 years or older. Table 1 presents baseline characteristics categorized by age. Within the entire cohort, the majority of patients was male, accounting for 61.1 % compared to 38.9 % who were female. Patients aged $\geq$ 75 years exhibited a significant higher prevalence of $\geq$ 3 comorbidities (55.4 % versus 45.3 % in the 65–74 age group, $p < 0.001$), whereas the occurrence of 1 or 2 comorbidities was comparable between the groups (36.1 % versus 36.7 % in the 65–74 age group). The incidence of cardiovascular disease was also significantly higher in the patients aged 75 years or older ($p < 0.001$). There were no evident differences observed between the age groups in the occurrence of auto-immune diseases, pulmonary diseases or endocrine diseases.

Most patients (83.5 %) were diagnosed with either stage IIIB or IIIC melanoma. Among patients aged 75 years or older, there was a higher incidence of stage IIIC melanoma (53.6 % compared to 42.3 %, $p = 0.028$), while those in the 65–74 age group showed a higher prevalence of resected stage IV melanoma (6.5 % compared to 3.9 %, $p = 0.005$). The primary tumor was predominantly localized on the trunk (42.5 %) and extremities (33.0 %). Only 1.5 % of the patients displayed a ECOG performance status score of $\geq$ 2, while most patients (94.3 %) exhibited a ECOG performance status of 0 or 1. In total, 36.6 % of the patients had a known BRAF-mutation. Only a minority (11.3 %) of patients in this adjuvant group exhibited elevated levels of LDH (lactate dehydrogenase).

3.2. Immune-related adverse events

Overall, 15.0 % of patients experienced grade $\geq$ 3 irAEs, comprising 15.5 % in the 65–74 age group and 13.9 % in the age group $\geq$ 75 (Odds Ratio (OR) 0.88, 95 % confidence interval (C.I.) 0.59–1.32). Table 2 presents specific grade $\geq$ 3 irAEs. Among the reported grade $\geq$ 3 irAEs, colitis was the most frequently observed, occurring in 4.2 % of all patients. Endocrine toxicity followed with a prevalence of 2.4 % among all patients, while hepatitis was observed in 2.0 % of the total patient population.

The determinants of grade $\geq$ 3 irAEs are presented in Table 3. Univariate analyses revealed a significant association between an increasing number of comorbidities and grade $\geq$ 3 irAEs ($\geq$3 comorbidities: OR 1.92, 95 % C.I. 1.05–3.51). Covariate analyses showed a trend toward an increased risk of grade $\geq$ 3 irAEs in patients with multiple comorbidities ($\geq$3 comorbidities: OR 1.83, 95 % C.I. 0.99–3.40). Fig. S1, available in the supplementary materials, depicts the incidence of grade $\geq$ 3 irAEs per comorbidity category in older melanoma patients treated with adjuvant anti-PD-1 therapy.

Specifically, 10.7 % of patients without comorbidities experienced grade $\geq$ 3 irAEs, while those with 1 or 2 comorbidities and 3 or more comorbidities exhibited grade $\geq$ 3 irAEs in 12.1 % and 18.6 % of cases, respectively. Of all specific comorbidities, including autoimmune, cardiovascular, pulmonary, and endocrine diseases, only autoimmune diseases exhibited a significant association with grade $\geq$ 3 irAEs in the univariate analyses (OR 2.80, 95 % C.I. 1.69–4.64, $P < 0.001$). The autoimmune diseases analyzed are detailed in Supplementary Table S1.

A higher ECOG performance status demonstrated a trend toward increased odds of grade $\geq$ 3 irAEs in the univariate analyses (ECOG performance status 1: OR 1.52, 95 % C.I. 0.92–2.50, and 2: OR 2.03, 95 % C.I. 0.42–9.84). This trend persisted in the covariate analyses (ECOG performance status 1: OR 1.37, 95 % C.I. 0.91–2.06, and 2: OR 1.84, 95 % C.I. 0.48–7.04). Furthermore, no statistically significant associations were found between grade $\geq$ 3 irAEs and age or sex in both the univariate and multivariable analyses.

To evaluate the impact of irAEs on the discontinuation of anti-PD-1 therapy, we analyzed the frequency of therapy discontinuation due to grade $\geq$ 3 irAEs. Specifically, we examined how often therapy was discontinued across various time intervals (in months), this is illustrated in Fig. S6.

Table 1
Patient characteristics according to age.

	All Patients (n = 885)	Patients Aged 65-74 (n = 605)	Patients Aged ≥ 75 (n = 280)	p-value
	N(%)	*N(%)*	*N(%)*	
Patient characteristics				
Median age (range)	72 (65–90)	69 (65–74)	78 (75–90)	
Sex				*0.569*
Male	541 (61.1 %)	366 (60.5 %)	175 (62.5 %)	
Female	344 (38.9 %)	239 (39.5 %)	105 (37.5 %)	
Number of comorbidities				*<0.001*
0	131 (14.8 %)	108 (17.9 %)	23 (8.2 %)	
1–2	323 (36.5 %)	222 (36.7 %)	101 (36.1 %)	
≥ 3	429 (48.5 %)	274 (45.3 %)	155 (55.4 %)	
Unknown	2 (0.2 %)	1 (0.2 %)	1 (0.4 %)	
Auto-immune diseases				*0.662*
No	799 (90.3 %)	548 (90.6 %)	251 (89.6 %)	
Yes	86 (9.7 %)	57 (9.4 %)	29 (10.4 %)	
Cardiovascular diseases				*<0.001*
No	408 (46.1 %)	309 (51.1 %)	99 (35.4 %)	
Yes	477 (53.9 %)	296 (48.9 %)	181 (64.6 %)	
Pulmonary diseases				*0.128*
No	783 (88.5 %)	542 (89.6 %)	241 (86.1 %)	
Yes	102 (11.5 %)	63 (10.4 %)	39 (13.9 %)	
Endocrine diseases				*0.390*
No	673 (76.0 %)	455 (75.2 %)	218 (77.9 %)	
Yes	212 (24.0 %)	150 (24.8 %)	62 (22.1 %)	
ECOG performance status				*0.069*
0	582 (65.8 %)	415 (68.6 %)	167 (59.6 %)	
1	252 (28.5 %)	161 (26.6 %)	91 (32.5 %)	
2	12 (1.4 %)	7 (1.2 %)	5 (1.8 %)	
3–4	1 (0.1 %)	1 (0.2 %)	0 (0.0 %)	
Unknown	38 (4.3 %)	21 (3.5 %)	17 (6.1 %)	
Tumor characteristics				
Tumor stage				*0.028*
IIIA	88 (9.9 %)	66 (10.9 %)	22 (7.9 %)	
IIIB	333 (37.6 %)	241 (39.8 %)	92 (32.9 %)	
IIIC	406 (45.9 %)	256 (42.3 %)	150 (53.6 %)	
IIID	8 (0.9 %)	3 (0.3 %)	5 (1.8 %)	
IVM1a	30 (3.4 %)	23 (3.8 %)	7 (2.5 %)	
IVM1b	9 (1.0 %)	7 (1.2 %)	2 (0.7 %)	
IVM1c	9 (1.0 %)	7 (1.2 %)	2 (0.7 %)	
IVM1d	2 (0.2 %)	2 (0.3 %)	0 (0.0 %)	
Location of primary tumour				*0.021*
Melanoma of unknown primary	64(7.2 %)	46(7.6 %)	18(6.4 %)	
Head – neck	121(13.7 %)	68(11.2 %)	53(18.9 %)	
Trunk	376(42.5 %)	264(43.6 %)	112(40.0 %)	
Extremities	292(33.0 %)	200(33.1 %)	92(32.9 %)	
Acral	30(3.4 %)	25(4.1 %)	5(1.8 %)	
Unknown	2 (0.2 %)	2(0.3 %)	0(0.0 %)	
Breslow thickness (mm); median [range]	2.90 [0.10–32.00]	2.80 [0.30–32.00]	3.30 [0.10–30.00]	*0.545*
Ulceration				*0.148*
No	429(48.5 %)	301(50.0 %)	128(45.7 %)	
Yes	289(32.7 %)	185(30.6 %)	104(37.1 %)	
Unknown	167(18.9 %)	119(19.7 %)	48(17.0 %)	
PET-CT				*0.391*
No	58(6.6 %)	40(6.6 %)	18(6.4 %)	
Yes	822(92.9 %)	563(93.1 %)	259(92.5 %)	
Unknown	5(0.6 %)	2(0.3 %)	3(1.1 %)	
BRAF mutation				*0.349*
Negative	398(45.0 %)	264(43.6 %)	134(47.9 %)	
Positive	324(36.6 %)	231(38.2 %)	93(33.2 %)	
Unknown	163(18.4 %)	110(18.2 %)	53(18.9 %)	
LDH				*0.515*
Not determined	8(0.9 %)	5(0.8 %)	3(1.1 %)	
Normal	774(87.5 %)	536(88.6 %)	238(85.0 %)	
Elevated (≥ 250 U/L)	100(11.3 %)	62(10.2 %)	38(13.6 %)	
Unknown	3(0.3 %)	2(0.3 %)	1(0.4 %)	
Type of anti-PD 1 treatment				*0.452*
Pembrolizumab	223(25.2 %)	146(24.1 %)	77(27.5 %)	
Nivolumab	661(74.7 %)	458(75.7 %)	203(72.5 %)	
Unknown	1(0.1 %)	1(0.2 %)	0(0.0 %)	

Table 2
Specific grade ≥ 3 Immune-related Adverse Events of anti-PD-1 therapy.

	All patients (n = 885)	Patients Aged 65-74 (n = 605)	Patients Aged ≥ 75 (n = 280)	p-value
irAEs grade ≥3	133(15.0 %)	94(15.5 %)	39(13.9 %)	*0.533*
Specific irAEs grade ≥				
Neuropathy	7(0.8 %)	5(0.8 %)	2(0.7 %)	*0.861*
Colitis	37(4.2 %)	27(4.5 %)	10(3.6 %)	*0.538*
Nephritis	9(1.0 %)	6(1.0 %)	3(1.1 %)	*0.912*
Pneumonitis	12(1.4 %)	11(1.8 %)	1(0.4 %)	*0.080*
Endocrine	21(2.4 %)	17(2.8 %)	4(1.4 %)	*0.209*
Hepatitis	18(2.0 %)	8(1.3 %)	10(3.6 %)	*0.027*
Cutaneous	9(1.0 %)	5(0.8 %)	4(1.4 %)	*0.406*
Arthralgia/ arthritis	5(0.6 %)	3(0.5 %)	2(0.7 %)	*0.687*
Other	46(5.2 %)	27(4.5 %)	19(6.8 %)	*0.148*

Additionally, we included a detailed table in the supplementary materials (Table S2) summarizing the reasons for premature termination of anti-PD-1 therapy. Notably, the overall discontinuation rate due to all grades of irAEs was higher (21.2 %) compared to the incidence of grade ≥ 3 irAEs (15.0 %).

3.3. Recurrence-free survival outcomes

The results of the univariate and multivariable Cox regression model for factors associated with RFS are presented in Table 4. Median follow-up was 26.5 months (IQR:16.8–38.4 months) for the whole cohort and at the time of this report, median RFS rate had not been reached. The 1-year RFS rate was 80 % (95 % C.I. 78–83 %) and the 2-year RFS rate was 67 % (95 % C.I. 63–70 %). Additionally, we conducted a Kaplan-Meier analysis of all patients (N = 188) who discontinued treatment due to irAEs of any grade; the 1-year RFS rate for these patients was 87 %, and the 2-year RFS rate was 70 %.

The Cox regression analysis indicated that in patients aged 65 years or older there was no association between age and risk of recurrence in either the univariate (Hazard Ratio (HR): 1.10, 95 % C.I. 0.88–1.39, p = 0.406) or multivariable analyses (HR: 0.92, 95 % C.I. 0.72–1.16, p = 0.473). The number of comorbidities was predictive for an increased risk of melanoma recurrence in the univariate (≥3 comorbidities HR: 1.98, 95 % C.I. 1.36–2.81, p < 0.001) and the multivariable analyses (≥3 comorbidities HR1.68, 95 % C.I. 1.15–2.44, p = 0.007). Patients with a ECOG score ≥ 2 had a significantly higher risk of recurrence in the univariate analyses, compared to patients with a score of 0–1 (HR: 2.50, 95 % C.I. 1.30–4.91, p = 0.007 for patients with a ECOG score ≥2). The risk of melanoma recurrence remained elevated, although not statistically significant, in the multivariable analyses (HR: 1.88, 95 % C.I. 0.95–3.72, p = 0.072 for patients with a ECOG score ≥2).

Female sex was significantly associated with a decreased risk of

Table 3
Determinants of grade ≥ 3 Immune-related Adverse Events.

	Anti-PD1	Univariate			Covariate		
	% of irAEs within subgroup	OR	95% C.I.	p-value	OR	95% C.I.	p-value
Age							
65-74	15.5	Ref.			Ref.		
75+	13.9	0.88	(0.59-1.32)	*0.534*	0.80	(0.53-1.21)	*0.289*
Sex							
Male	15.5	Ref.					
Female	14.2	0.90	(0.62-1.32)	*0.603*			
Number of comorbidities							
0	10.7	Ref.			Ref.		
1-2	12.1	1.15	(0.60-2.19)	*0.677*	1.14	(0.59-2.19)	*0.692*
≥3	18.6	1.92	(1.05-3.51)	*0.035*	1.83	(0.99-3.40)	*0.055*
Unknown	0.0	0.00	(-)	*0.999*	0.00	(-)	*0.999*
Autoimmune diseases							
No	13.4	Ref.					
Yes	30.2	2.80	(1.69-4.64)	*<0.001*			
Cardiovascular diseases							
No	13.2	Ref.					
Yes	16.6	1.30	(0.90-1.89)	*0.168*			
Pulmonary diseases							
No	14.6	Ref.					
Yes	18.6	1.34	(0.79-2.30)	*0.281*			
Endocrine diseases							
No	14.1	Ref.					
Yes	17.9	1.33	(0.88-2.01)	*0.177*			
ECOG performance status 0	13.2	Ref.			Ref.		
1	18.3	1.47	(0.98-2.18)	*0.061*	1.37	(0.91-2.06)	*0.130*
2	25.0	2.19	(0.58-8.25)	*0.249*	1.84	(0.48-7.04)	*0.371*
3 or 4	0.0	0.00	(-)	*1.000*	0.00	(-)	*1.000*
Unknown	18.4	1.48	(0.63-3.48)	*0.368*	1.39	(0.59-3.30)	*0.454*

recurrence in the multivariable analyses (HR: 0.79, 95 % C.I. 0.63–0.99, p = 0.041). The presence of in-transit metastases, ulceration and elevated LDH levels (>250 U/L) were significantly associated with risk of melanoma recurrence in both the univariate and multivariable analyses. Patients diagnosed with stage IIIC exhibited a significantly higher risk of recurrence in the univariate analyses in comparison to those with stage IIIA (HR: 1.66, 95 % C.I. 1.11–2.48, p = 0.014). Furthermore, the Cox regression analysis showed no significant association, in both the univariate and multivariable analyses, between increasing Breslow thickness, BRAF mutation, and RFS. A Kaplan-Meier plot to assess the RFS in older melanoma patients treated with adjuvant anti-PD-1 therapy and additional plots to compare the exposures of interest, including the number of comorbidities, ECOG performance status, tumor stage, respectively, can be found in the supplementary materials (Fig. S2-S5). In total, 175 patients have deceased. Most patients (87.4 %) experienced mortality specifically due to melanoma, while 5.2 % succumbed to comorbidity-related causes. It is possible that among the 7.4 % of unknown causes of death, comorbidity could also be a contributing factor.

4. Discussion

The current study demonstrated that in contrast to previous research, having multiple comorbidities at baseline was associated with grade ≥ 3 irAEs in patients ≥ 65 treated with adjuvant anti-PD-1 therapy. In addition, we report similar 1-year rate of RFS in older patients compared to the RFS rate in patients of all ages at 1-year in registration trials, but older patients with ≥ 3 comorbidities had poorer RFS. Consistent with previous studies, age alone was not a predictor of grade ≥ 3 irAEs or RFS [15].

In our population, grade ≥ 3 irAEs were observed in 15.0 % of the patients, which is consistent with findings from earlier adjuvant trials, such as the 14.4 % reported in the Checkmate-238 trial and the 14.7 % in the EORTC 1325/Keynote-054 trial [5,22]. Furthermore, the observed rate of grade ≥ 3 irAEs in older patients appears to be lower than the previously reported 18 % among the adjuvant population across all age groups in the same registry between 2018 and 2021 [23]. Our findings on the association between comorbidity and grade ≥ 3 irAEs align with a recent study conducted in patients who received monotherapy checkpoint inhibitor treatment, and demonstrated that impairments in aging-related domains including comorbidity, were predictive for hospital admission and was also associated with higher risk of death [24]. The overall discontinuation rate of anti-PD-1 therapy due to all grades of irAEs was higher than the incidence of grade ≥ 3 irAEs. This finding aligns with previous research, which suggests that frail older patients may have a lower tolerance for grade 1–2 irAEs [25].

To investigate whether specific health conditions contributed to the association between comorbidity and grade ≥ 3 irAEs, we also examined cardiovascular, pulmonary, endocrine and autoimmune diseases, and their association with grade ≥ 3 irAEs. Among these diseases, only baseline autoimmune diseases were associated with grade 3 or higher irAEs. In our cohort, 86 (9.7 %) of the patients had an autoimmune disease, with incidences of grade ≥ 3 irAEs occurring in 30.2 % of this subgroup. Interestingly, this particular association was not found in a previous DMTR study, that showed that the incidence of grade ≥ 3 irAEs in patients with autoimmune disease at 17 % with anti-PD-1 [26]. This may be explained by the fact that their patients, unlike our cohort, were of all ages and had advanced melanoma. The adjuvant administration of ICI is believed to enhance systemic T cells to eradicate micro-metastases. The incidence of irAEs appears to be higher in patients treated in both the neoadjuvant and adjuvant settings [27]. The immune system can also display excessive reactivity, as seen in autoimmune diseases, where the presence of minimal tumor antigens can lead to an increased incidence of immune-related adverse events (irAEs) [28]. For instance, IL-17, a cytokine upregulated in inflammatory bowel disease, has been linked to the development of grade 3 diarrhea or colitis in patients with melanoma treated with neoadjuvant ipilimumab [29,30]. Therefore, the potential association between baseline autoimmune diseases and irAEs might be attributed to the influence of further triggering autoimmunity in autoimmune diseases.

The observed RFS of 80.0 % at 1 year is a slightly higher RFS

Table 4
Univariate and multivariable Cox regression model for factors associated with recurrence-free survival in older melanoma patients treated with adjuvant anti-PD-1 therapy.

		Univariate			Multivariable		
Characteristics	**2-year Recurrence %**	**HR**	**(95 % C.I.)**	**p-value**	**HR**	**(95 % C.I.)**	**p-value**
Age, years							
65–74	32 %	Ref.	(0.88–1.39)	*0.406*	Ref.	(0.72–1.16)	*0.458*
≥75	34 %	1.10			0.91		
Sex							
Male	36 %	Ref.	(0.64–1.00)	*0.052*	Ref.	(0.62–0.98)	*0.034*
Female	29 %	0.80			0.78		
Number of comorbidities							
0	24 %	Ref.	(0.70–1.54)	*0.836*	Ref.	(0.65–1.44)	*0.875*
1–2	28 %	1.04	(1.36–2.81)	*<0.001*	0.97	(1.16–2.46)	*0.006*
≥3	39 %	1.98	*NA*[a]		1.69	*NA*[a]	*NA*[a]
Unknown	0 %	0.00		*NA*[a]	0.00		
ECOG performance status							
0–1	32 %	Ref.	(1.30–4.91)	*0.007*	Ref.	(0.94–3.69)	*0.076*
≥2	66 %	2.50	(0.78–2.03)	*0.362*	1.86	(0.77–2.02)	*0.362*
Unknown	38 %	1.25			1.25		
Tumor stage							
IIIA	25 %	Ref.	(0.71–1.65)	*0.705*	Ref.	(0.62–1.48)	*0.836*
IIIB	28 %	1.09	(1.11–2.48)	*0.014*	0.96	(0.75–1.83)	*0.488*
IIIC	39 %	1.66	(0.20–3.49)	*0.798*	1.17	(0.12–2.22)	*0.367*
IIID	25 %	0.83	(0.48–1.73)	*0.769*	0.51	(0.43–1.62)	*0.583*
IV (resectable)	28 %	0.91			0.83		
Breslow thickness (mm)							
0–2.000		Ref.	(0.95–1.67)	*0.103*	Ref.	(0.86–1.55)	*0.349*
2.001–4.000	30 %	1.26	(1.00–1.78)	*0.050*	1.15	(0.78–1.52)	*0.614*
≥4.000	35 %	1.34	(0.47–1.10)	*0.132*	1.09	(0.48–1.42)	*0.490*
Unknown	39 %	0.72			0.83		
	21 %						
Ulceration							
No	29 %	Ref.	(1.20–1.90)	*<0.001*	Ref.	(1.10–1.85)	*0.007*
Yes	43 %	1.51	(0.63–1.19)	*0.384*	1.43	(0.63–1.43)	*0.795*
unknown	26 %	0.87			0.95		
In-transit metastases							
No	30 %	Ref.	(1.14–1.81)	*0.002*	Ref.	(1.11–1.80)	*0.005*
Yes	41 %	1.44	*NA*[a]	*NA*[a]	1.41	NA[a]	*NA*[a]
Unknown	0 %	0.00			0.00		
BRAF mutation							
Negative	39 %	Ref.	(0.65–1.02)	*0.071*	Ref.	(0.69–1.10)	*0.248*
Positive	34 %	0.81	(0.25–0.52)	*<0.001*	0.87	(0.26–0.56)	*<0.001*
Missing	16 %	0.36			0.38		
LDH							
Normal	29 %	Ref.	(2.20–3.71)	*<0.001*	Ref.	(2.09–3.62)	*<0.001*
Elevated (>250 U/L)	60 %	2.86	(0.04–1.91)		2.75	(0.05–2.38)	*0.272*
Unknown	10 %	0.27		*0.190*	0.33		

[a] No analysis was performed as there were no events recorded in the specific subgroup.

compared to the EORTC 1325/Keynote-054 trial (75.4 %) and the Checkmate-238 trial (70.5 %). However, it aligns with the observed RFS of 78 % of a recently published nationwide Danish study sourced from the Danish Metastatic Melanoma Database [31]. This retrospective population-based study also had a comparable median follow-up duration of 25.6 months [31]. Older patients with ≥ 3 comorbidities had worse RFS. This could be partly attributed to a more advanced tumor stage, as 50 % of patients ≥ 3 comorbidities in our cohort had stage IIIC melanoma. However, even after adjusting for multiple variables including tumor stage, this association remained significant. This may be explained by the presence of indication bias, since older patients with multiple comorbidities are usually only treated adjuvant therapy if they have a melanoma with a high risk of recurrence. Interestingly, patients who discontinued treatment due to irAEs of any grade did not have a higher risk of recurrence compared to the overall patient population in our cohort.

There is a significant paucity of scientific evidence addressing the use of immunotherapy in patients over the age of 75 and specifically frail older patients. This patient group is particularly at risk for experiencing long-term impairments, functional decline, and a deterioration of their quality of life as a result of treatment-related toxicity of cancer therapy [32]. A significant complication of ICI is its potential for lifelong toxicity, such as thyroid and adrenal dysfunction [33]. Previous studies that have been conducted on frailty or impairments in aging-related domains and irAEs, suggest a potential association [24,34]. Older patients, who often have a reduced life expectancy and a higher prevalence of comorbidities, polypharmacy, and frailty, frequently face challenges in tolerating cancer treatments and managing the potential adverse events that accompany them. Consequently, the potential benefits of treatment may not outweigh the risks of experiencing significant side effects, highlighting the need to identify predictors for toxicity in this population. Interestingly, The Danish Metastatic Melanoma Database, showed a significant association between health-related quality of life (HRQoL) and comorbidity among real-world patients with resected stage III/IV melanoma who received adjuvant immunotherapy. Specifically, patients with a Charlson Comorbidity Index of ≥ 3 exhibited a substantial decrease in HRQoL [35]. Whether the decrease in HRQoL is related to the increased occurrence of irAEs in the patient group with more comorbidity is not known. It is noteworthy that this real-world data, similar to previous research, demonstrates a minimal difference in irAEs among the majority of older patients treated with immunotherapy. This is an encouraging result, especially in comparison to the frequently elevated toxicity associated with conventional chemotherapy. These findings indicate that immunotherapy treatments may be

better tolerated by older patients than chemotherapy.

4.1. Strengths and limitations

To our knowledge, this is the first nationwide registry database investigation that specifically examined irAEs and RFS in older patients with melanoma treated with adjuvant anti-PD-1 therapy. One of the major strengths of this study is the utilization of a national registration database, which has facilitated the inclusion of a large sample size of older patients, specifically those aged 75 years and older. This provides detailed and reliable data of all patients in the Netherlands who received this treatment.

However, certain limitations exist in relation to the available data. Firstly, there is a lack of information on grade 1–2 adverse events, quality of life during treatment, geriatric screening and/or assessment, and polypharmacy. The absence of these data prevents the examination of their association with irAEs and survival outcomes. Since our study relies on registry data, we are dependent on the accuracy and completeness of the data entered. As a result, we encountered some missing data that we were unable to explain fully. Moreover, 94.3 % of the included patients had ECOG performance status of 0–1, suggesting a selection bias towards fitter patients. It is crucial to note that some patients, who did not receive adjuvant treatment due to medical reasons such as poor performance status or contraindications, were not included in the nationwide database.

Taking competing disease risk into account is important in older patients because they can significantly impact survival and may confound the association between the treatment and the outcome of interest. However, we chose not to account for competing disease risk in our study, due to the high proportion of patients who experienced mortality specifically due to melanoma, which made that competing risk was not a relevant issue in this study.

In conclusion, age did not impact grade $\geq$ 3 irAEs and RFS in older patients receiving adjuvant ICI therapy. However, having three or more comorbidities, as well as autoimmune disease, was found to be associated with the occurrence of grade $\geq$ 3 irAEs. The overall discontinuation rate of anti-PD-1 therapy due to irAEs of any grade was higher than the incidence of grade $\geq$ 3 irAEs, potentially reflecting the lower tolerance of frail older patients to grade 1–2 irAEs. Having three or more comorbidities was also associated with a decrease in RFS. To gain further insights, future studies should conduct a comprehensive evaluation of comorbidities and grade 1–5 irAEs in older patients undergoing checkpoint inhibitor treatment. Given these findings, it is crucial for oncologists to carefully consider whether to provide adjuvant treatment to patients with a high burden of comorbidities, also because adjuvant treatment has not been proven to have an overall survival benefit up till now.

CRediT authorship contribution statement

A. A. M. van der Veldt: Writing – review & editing, Data curation. **M. J. Boers-Sonderen:** Writing – review & editing, Data curation. **K. P. M. Suijkerbuijk:** Writing – review & editing, Data curation. **W. A. M. Blokx:** Writing – review & editing, Data curation. **M. W. J. M. Wouters:** Data curation. **A. J. M. van den Eertwegh:** Writing – review & editing, Data curation. **G. Vreugdenhil:** Data curation. **J. J. Bonenkamp:** Data curation. **N.A. de Glas:** Writing – review & editing, Supervision, Methodology, Funding acquisition. **J. B. Haanen:** Writing – review & editing, Data curation. **E. Kapiteijn:** Writing – review & editing, Data curation, Conceptualization. **J.E.A. Portielje:** Writing – review & editing, Supervision. **J. W. B. de Groot:** Data curation. **Aslı Özkan:** Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **M. J. B. Aarts:** Writing – review & editing, Data curation. **C.E. Holtslag:** Data curation. **F. van den Bos:** Writing – review & editing. **D. Piersma:** Data curation. **F. W. P. J. van den Berkmortel:** Writing – review & editing, Data curation. **G. A. P. Hospers:** Data curation. **A. M. Stevense-den Boer:** Data curation. **M. Bloem:** Writing – review & editing. **R. S. van Rijn:** Data curation. **C. U. Blank:** Data curation.

Funding

This study was supported by a personal grant of the last author of the Leiden University Medical Center and the ZonMW / Veni program (09150161810003). This work was supported by Stichting Fonds Oncologie Holland (project number 22-01) and Leiden University Fund project (W20361-2-38). For the Dutch Melanoma Treatment Registry (DMTR), the Dutch Institute for Clinical Auditing foundation received a start-up grant from governmental organization The Netherlands Organization for Health Research and Development (ZonMW, project number 836002002). The DMTR is structurally funded by Bristol Myers Squibb, Merck Sharpe & Dohme, Novartis, and Pierre Fabre. Roche Pharma stopped funding in 2019, Novartis in 2024 and Pierre Fabre started funding the DMTR in 2019.

Declaration of Competing Interest

All remaining authors have declared no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115056.

References

[1] Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. Lancet 2021;398(10304):1002–14.
[2] Patel SP, Othus M, Chen Y, Wright GP, Yost KJ, Hyngstrom JR, et al. Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma. N Engl J Med 2023;388(9):813–23.
[3] Eggermont AMM, Blank CU, Mandalà M, Long GV, Atkinson VG, Dalle S, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2021;22(5):643–54.
[4] Eggermont AM, Suciu S, Rutkowski P, Kruit WH, Punt CJ, Dummer R, et al. Long term follow up of the EORTC 18952 trial of adjuvant therapy in resected stage IIB-III cutaneous melanoma patients comparing intermediate doses of interferon-alpha-2b (IFN) with observation: Ulceration of primary is key determinant for IFN-sensitivity. Eur J Cancer 2016;55:111–21.
[5] Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. N Engl J Med 2017;377(19):1824–35.
[6] Ascierto PA, Del Vecchio M, Mandalá M, Gogas H, Arance AM, Dalle S, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2020;21(11):1465–77.
[7] Thomas D, Bello DM. Adjuvant immunotherapy for melanoma. J Surg Oncol 2021;123(3):789–97.
[8] Eskens FALM WA, Beerepoot LV, et al. Adjuvant nivolumab bij stadium IIIb, IIIc of IV melanoom na volledige chirurgische resectie. NVMO-commissie BOM. Med Oncol 2018;21(9):53–6. 2018.
[9] B.O.M. N-c, op LinkedIn D. Adjuvant nivolumab bij stadium IIIb, IIIc of IV melanoom na volledige chirurgische resectie Inleiding.
[10] Kobeissi I, Tarhini AA. Systemic adjuvant therapy for high-risk cutaneous melanoma. Ther Adv Med Oncol 2022;14. 17588359221134087.
[11] van Holstein Y, Kapiteijn E, Bastiaannet E, van den Bos F, Portielje J, de Glas NA. Efficacy and adverse events of immunotherapy with checkpoint inhibitors in older patients with cancer. Drugs Aging 2019;36(10):927–38.
[12] Sasson DC, Smetona JT, Parsaei Y, Papageorge M, Ariyan S, Olino K, et al. Malignant melanoma in older adults: different patient or different disease? Cureus 2023;15(2):e34742.
[13] Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International society of geriatric oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32(24):2595–603.
[14] Hurria A, Togawa K, Mohile SG, Owusu C, Klepin HD, Gross CP, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29(25):3457–65.
[15] de Glas NA, Bastiaannet E, van den Bos F, Mooijaart SP, van der Veldt AAM, Suijkerbuijk KPM, et al. Toxicity, response and survival in older patients with metastatic melanoma treated with checkpoint inhibitors. Cancers (Basel) 2021;13(11).

[16] Elias R, Giobbie-Hurder A, McCleary NJ, Ott P, Hodi FS, Rahma O. Efficacy of PD-1 & PD-L1 inhibitors in older adults: a meta-analysis. J Immunother Cancer 2018;6(1):26.
[17] Bastiaannet E, Battisti N, Loh KP, de Glas N, Soto-Perez-de-Celis E, Baldini C, et al. Immunotherapy and targeted therapies in older patients with advanced melanoma; Young International Society of Geriatric Oncology review paper. J Geriatr Oncol 2019;10(3):389–97.
[18] Jochems A, Schouwenburg MG, Leeneman B, Franken MG, van den Eertwegh AJ, Haanen JB, et al. Dutch Melanoma Treatment Registry: quality assurance in the care of patients with metastatic melanoma in the Netherlands. Eur J Cancer 2017;72:156–65.
[19] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649–55.
[20] de Boer AZ, Bastiaannet E, Putter H, Marang-van de Mheen PJ, Siesling S, de Munck L, et al. Prediction of other-cause mortality in older patients with breast cancer using comorbidity. Cancers (Basel) 2021;13(7).
[21] DMTR Manual, Version 3.8 [Internet]. [Accessed on August 19, 2024]. Available from: ⟨https://support.mrdm.com/nl/downloads/documenten/?org=dica&set=dmtr⟩.
[22] Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med 2018;378(19):1789–801.
[23] de Meza MM, Ismail RK, Rauwerdink D, van Not OJ, van Breeschoten J, Blokx WAM, et al. Adjuvant treatment for melanoma in clinical practice – Trial versus reality. Eur J Cancer 2021;158:234–45.
[24] Gomes F, Lorigan P, Woolley S, Foden P, Burns K, Yorke J, et al. A prospective cohort study on the safety of checkpoint inhibitors in older cancer patients – the ELDERS study. ESMO Open 2021;6(1):100042.
[25] Tran Van Hoi E, Trompet S, Van Holstein Y, Van Den Bos F, Van Heemst D, Codrington H, et al. Toxicity in older patients with cancer receiving immunotherapy: an observational study. Drugs Aging 2024;41(5):431–41.
[26] van der Kooij MK, Suijkerbuijk KPM, Dekkers OM, Kapiteijn E. Safety and efficacy of checkpoint inhibition in patients with melanoma and preexisting autoimmune disease. Ann Intern Med 2021;174(9):1345–6.
[27] Feng Y, Guo K, Jin H, Jiang J, Wang M, Lin S. Adverse events of neoadjuvant combination immunotherapy for resectable cancer patients: a systematic review and meta-analysis. Front Immunol 2023;14:1269067.
[28] Kennedy LB, Salama AKS. A review of cancer immunotherapy toxicity. CA: A Cancer J Clin 2020;70(2):86–104.
[29] Feng T, Qin H, Wang L, Benveniste EN, Elson CO, Cong Y. Th17 cells induce colitis and promote Th1 cell responses through IL-17 induction of innate IL-12 and IL-23 production. J Immunol 2011;186(11):6313–8.
[30] Tarhini AA, Zahoor H, Lin Y, Malhotra U, Sander C, Butterfield LH, et al. Baseline circulating IL-17 predicts toxicity while TGF-β1 and IL-10 are prognostic of relapse in ipilimumab neoadjuvant therapy of melanoma. J Immunother Cancer 2015;3:39.
[31] Holmstroem RB, Pedersen S, Jurlander R, Madsen K, Donia M, Ruhlmann CH, et al. Outcome of adjuvant immunotherapy in a real-world nation-wide cohort of patients with melanoma. Eur J Cancer 2024;202:114023.
[32] Kirkhus L, Šaltytė Benth J, Grønberg BH, Hjermstad MJ, Rostoft S, Harneshaug M, et al. Frailty identified by geriatric assessment is associated with poor functioning, high symptom burden and increased risk of physical decline in older cancer patients: prospective observational study. Palliat Med 2019;33(3):312–22.
[33] Chang L-S, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr Rev 2018;40(1):17–65.
[34] Bruijnen CP, Koldenhof JJ, Verheijden RJ, van den Bos F, Emmelot-Vonk MH, Witteveen PO, et al. Frailty and checkpoint inhibitor toxicity in older patients with melanoma. Cancer 2022;128(14):2746–52.
[35] Pedersen S, Holmstroem RB, von Heymann A, Tolstrup LK, Madsen K, Petersen MA, et al. Quality of life and mental health in real-world patients with resected stage III/IV melanoma receiving adjuvant immunotherapy. Acta Oncol 2023;62(1):62–9.