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Original Research

Adjuvant treatment for melanoma in clinical practice – Trial versus reality

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Quality of health care

Abstract ***Background:*** Little is known about outcomes of adjuvant-treated melanoma patients beyond the clinical trial setting. Since 2019, adjuvant-treated melanoma patients have been registered in the DMTR, a population-based registry to monitor the quality and safety of melanoma care in the Netherlands. This study aims to describe treatment patterns, relapse, and toxicity rates of adjuvant-treated melanoma patients beyond the clinical trial setting.
Methods: Analyses were performed on adjuvant-treated melanoma patients included in the DMTR. Descriptive statistics were used to analyse patient-, and treatment characteristics. A baseline registration completeness analysis was performed, and an analysis on trial eligibility in clinical practice patients. Recurrence-free survival (RFS) at 12-months was estimated with the Kaplan–Meier method.
Results: A total of 641 patients were treated with adjuvant anti-PD-1 therapy. RFS at 12-months was 70.6% (95% CI, 66.9–74.6) with a median follow-up of 12.8 months. Sex, stage of disease and Breslow thickness were associated with a higher hazard for RFS. Eighteen per cent of the anti-PD-1-treated patients developed grade ≥3 toxicity. Sixty-one per cent of patients prematurely discontinued anti-PD-1 therapy.
Conclusion: Adjuvant anti-PD-1 treatment of resected stage III/IV melanoma in daily practice showed slightly higher toxicity rates and more frequent premature discontinuation but similar RFS rates compared to trials.

1. Introduction

Since 2011, the treatment landscape of metastatic melanoma has changed dramatically [1]. With the introduction of immunotherapy and targeted therapy, the survival of these patients has improved [2,3]. In July 2013, the Dutch Melanoma Treatment Registry (DMTR) was initiated, and advanced melanoma care in the Netherlands was centralized in 14 melanoma centres to assure the safety and quality of care for these patients [4].

The DMTR is one of the 22 national quality registries facilitated by the Dutch Institute for Clinical Auditing (DICA) [5]. The DMTR is a population-based nationwide registry, including all irresectable stage IIIC and stage IV melanoma patients in the Netherlands [4]. After the approval and reimbursement of adjuvant systemic therapy with checkpoint inhibitors in December 2018, the inclusion criteria of the DMTR were extended in 2019 also to include patients with resectable stage III and IV melanoma, who were referred to one of the melanoma centres for adjuvant systemic treatment [6,7]. All patients with a completely resected melanoma stage IIIA (≥1 mm metastasis) or higher are eligible for adjuvant systemic treatment in the Netherlands [8].

The Checkmate-238 trial and EORTC 1325/Keynote-054 trial were the clinical trials that led to the registration and approval of immune checkpoint inhibitors as

adjuvant systemic treatment in resected stage III and IV melanoma. In the Checkmate-238, nivolumab demonstrated longer recurrence-free survival at 12-months compared to ipilimumab in patients with resected stage IIIB-C and stage IV melanoma. In the nivolumab group recurrence-free survival at 12-months was 70.5% (95% IC, 66.1–74.5) compared to 60.8% (95% CI, 56.0–65.2) in the ipilimumab group [9]. Nivolumab also demonstrated lower toxicity compared to ipilimumab 14.4% versus 45.9% treatment-related grade 3–4 toxicity in the nivolumab and ipilimumab group, respectively [9]. In the EORTC 1325/Keynote-054 trial, pembrolizumab was compared to placebo in high-risk resected stage III melanoma patients. At 12 months, the recurrence-free survival rate was 75.4% (95% CI, 71.3–78.9) in the pembrolizumab group, compared to 61.0% (95% CI, 56.5–65.1) in the placebo group. Treatment-related grade 3–5 toxicity was reported in 14.7% of patients in the pembrolizumab group, compared to 3.4% in the placebo group.

Little is known about the outcomes of adjuvant systemic therapy beyond the clinical trial setting. Previous studies on real-world results of adjuvant treatment of stage III melanoma patients showed that anti-CTLA-4 therapy in stage III melanoma patients improved overall survival [10]. In another study in daily practice patients, Owen *et al.* demonstrated the poor outcomes of patients who recur on adjuvant anti-PD-1 therapy [9]. Here, we aim to give an overview of patients receiving adjuvant systemic treatment for resected stage III/IV melanoma in daily clinical practice and describe the first adjuvant treatment results with checkpoint inhibitors in the Netherlands.

2. Methods

2.1. Study population and database

Data for this study were derived from the nationwide prospective DMTR [4]. Data are registered into the DMTR through an online survey by trained data managers. The coordinating oncologist then approves these data derived from the patients' electronic medical records. The DMTR database is updated annually to reflect new developments in melanoma care and changes in clinical practice. These include new treatment modalities or drugs, novel treatment regimens, or insight into new biomarkers or mutations. Fourteen data entry items were added to the DMTR to include (neo-)adjuvant treated patients. These items are listed in Supplement 1 and consist of, for example, the additional registration of stage III substage, the presence and extent of in-transit metastases, lymph node dissection procedures and their radicality, and the context of the combination of systemic therapy and surgery (adjuvant or neo-adjuvant). In Supplement 2, the structure of the dataset is shown.

This study' patient population consisted of all resectable stage III and IV cutaneous melanoma patients diagnosed between 01 and 07-2018 and 31-12-2019 and treated with adjuvant systemic treatment as the first line of systemic therapy. The data cut off date was 1st March, 2021. Adjuvant systemic therapy was defined as 'systemic therapy after complete resection of melanoma'. Per the Dutch consensus on stage III/IV resected melanoma treatment, adjuvant systemic treatment is given for 12 months and should be initiated within 12 weeks of complete surgical resection [8]. Patients who received adjuvant treatment underwent FDG-PET-CT or CT scanning within three months before the start of systemic therapy. In the inclusion period, adjuvant anti-PD-1 (nivolumab or pembrolizumab) for 12 months was the only adjuvant systemic therapy reimbursed in the Netherlands. For this reason, only a limited number of patients were treated with BRAF/MEK inhibitors. These patients were excluded from further analysis.

2.2. Statistical analysis

2.2.1. Study population

Descriptive statistics were used to describe patient- and tumour characteristics. A baseline patient record was considered complete if the following items were registered: age, gender, Eastern Cooperative Oncology Group performance score (ECOG PS), primary tumour location, Breslow thickness (BT), and presence of ulceration, date of surgery, starting date of systemic therapy, type of systemic therapy. Items registered as 'unknown' were considered incomplete. In melanoma with an unknown primary location, the patient record was considered complete if age, gender, ECOG PS, date of surgery, starting date of systemic therapy, and type of systemic therapy were registered. Data completeness was analysed to give insight into the data quality of patients treated with adjuvant systemic treatment.

We performed an analysis on the eligibility for trial participation in our study population, based on the patient- and tumour characteristics used as in- and exclusion criteria for the EORTC 1325/Keynote-054 and the Checkmate-238 trial [9–11]. Patients were considered ineligible if they met one or more of the following criteria: age $\leq$15 years, ECOG PS $\geq$ 2, uveal melanoma, presence of auto-immune disease, and presence of HIV infection.

We provide a description of the treatment characteristics of our study population, and give an overview of toxicity rates and estimate the recurrence-free survival (RFS) at 12-months. The RFS at 12-months was estimated with the Kaplan–Meier method. Patients who did not meet the endpoint (recurrence or death) were censored at the date of last followup. The median follow-up duration was calculated with the reversed Kaplan–Meier method. Comparison between different stages of the disease was performed using a log-rank test at a two-sided alpha level. The stage of the disease was

classified using the American Joint Committee on Cancer (AJCC) 7th and AJCC 8th edition [12,13]. A univariate and multivariate Cox-proportional hazard model analysis was performed to identify factors (age, gender, performance score, stage of disease, Breslow thickness, ulceration, BRAF-V600-status, in-transit metastases) influencing RFS. Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria. Only CTCAE grade $\geq$3 treatment-related toxicity and any grade toxicity necessitating treatment discontinuation are registered in the DMTR.

2.2.2. One-year follow-up group

Analyses of toxicity and early discontinuation rates were performed in patients with a minimum follow-up time of 12 months since starting adjuvant anti-PD-1 treatment or death within 12 months. We will refer to this group as the one-year follow-up group.

The treatment patterns and responses of the one-year follow-up group were described and visualized in a Swimmer plot. Early treatment discontinuation was defined as discontinuation of therapy within 12 months of starting systemic treatment. Since anti-PD-1 is administered in up to 6-weekly intervals, 46 weeks between the dates of the first and last infusion was considered as one full year of treatment. Treatment discontinuation because of COVID-19 was registered as 'other'.

Data handling and statistical analyses were performed using the R software system for statistical computing (version 4.0.2.; packages lubridate, ggthemes, plyr, stringr, readxl, survminer, EnvStats, survival, forestmodel, RColorBrewer, dplyr, car, tidyverse, magrittr, tidyr tableone, ggplot2) [14–30].

3. Results

3.1. Patient- and tumour characteristics

In total, 2199 patients were registered in the DMTR database between 01 and 07-2018 and 31-12-2019. Of these patients, 641 received adjuvant anti-PD-1 therapy (Fig. 1).

The patient- and tumour characteristics of these patients are shown in Table 1. Of this group, 362 patients (56.5%) were males, and the median age was 62 years (range 19–90). Eleven per cent of the patients had AJCC-7 stage IIIA disease, 39.5% stage IIIB, 40.1% stage IIIC, and 6.9% stage IV. The majority of the patients (93.4%) had an ECOG PS $\leq$ 1. The primary

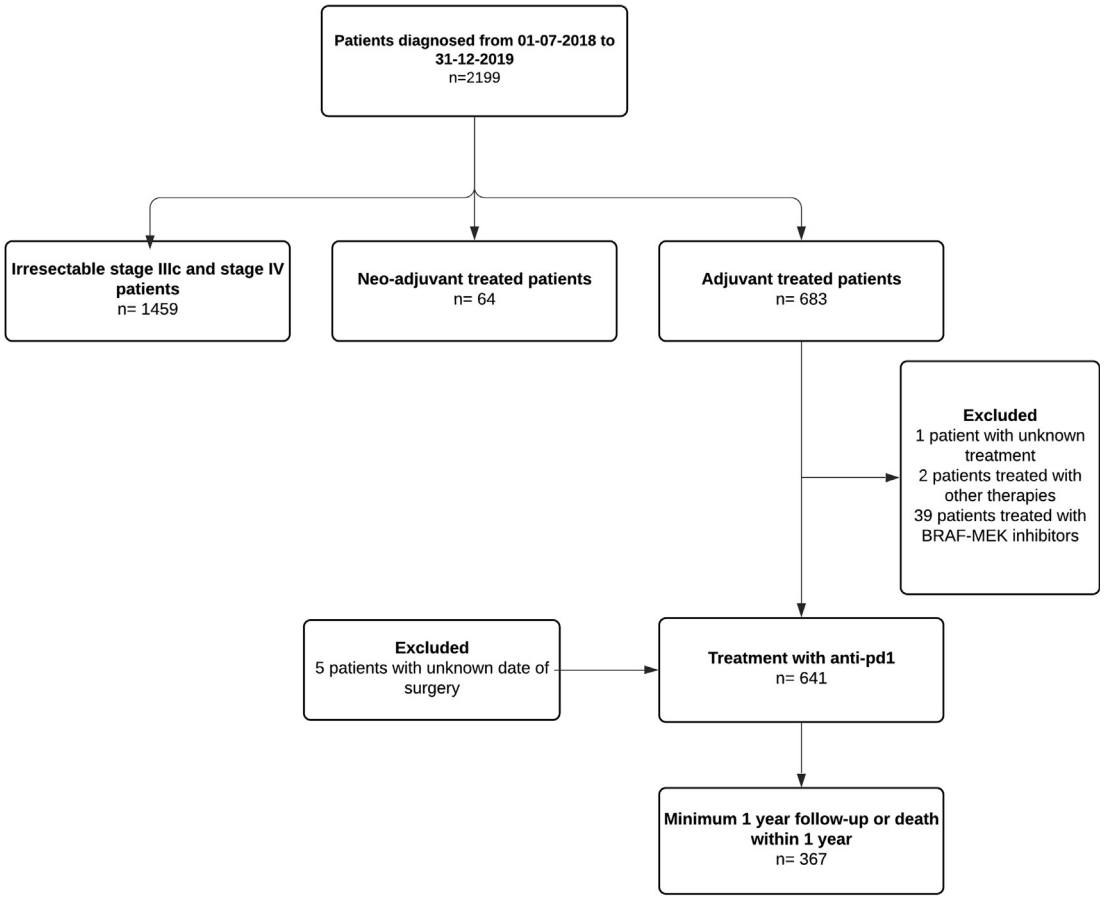


Fig. 1. Flowchart of the study population.

Table 1
Patient- and tumour characteristics of adjuvant treated patients (study population and patient with minimum 1-year follow-up).

		Study population	One-year follow-up group
N		641	367
Sex; n (%)	Male	362 (56.5)	206 (56.1)
	Female	279 (43.5)	161 (43.9)
Age in years; median (range)		62 (19–90)	62 (22–90)
Stage; n (%) AJCC v7	IIIA	71 (11.1)	34 (9.3)
	IIIB	253 (39.5)	137 (37.3)
	IIIC	257 (40.1)	153 (41.7)
	IV (resectable)	44 (6.9)	30 (8.2)
	Unknown	16 (2.5)	13 (3.5)
Stage; n (%) AJCC v8	IIIA	36 (5.6)	20 (5.4)
	IIIB	231 (36.0)	111 (30.2)
	IIIC	255 (39.8)	156 (42.5)
	IIID	7 (1.1)	6 (1.6)
	IV	46 (7.2)	31 (8.4)
	Unknown	66 (10.3)	43 (11.7)
ECOG PS; n (%)	0	466 (72.7)	253 (68.9)
	1	133 (20.7)	83 (22.6)
	≥2	10 (1.6)	7 (1.9)
	Unknown	32 (5.0)	24 (6.5)
Location; n (%)	Unknown primary	38 (5.9)	26 (7.1)
	Cutaneous[b]	598 (93.3)	336 (91.6)
	Mucosal	2 (0.3)	2 (0.5)
	Location unknown	3 (0.5)	3 (0.8)
Type melanoma; n (%)	Superficial spreading	326 (50.9)	181 (49.3)
	Nodular	161 (25.2)	92 (25.1)
	Acrolentiginous	16 (2.5)	11 (3.0)
	Lentigo maligna	7 (1.1)	2 (0.5)
	Desmoplastic	3 (0.5)	1 (0.3)
	Other	4 (0.6)	2 (0.5)
	Unknown	123 (19.2)	78 (21.3)
Breslow thickness (mm); median [range][a]		2.7 [0.1–21.8]	2.8 [0.4–18.5]
	Unknown	74 (11.5)	55 (15.0)
Ulceration; n (%)[a]	No	322 (54.2)	165 (49.3)
	Yes	201 (33.8)	122 (36.4)
	Unknown	71 (12.0)	51 (15.0)
In transit metastases; n (%)[a]	No	442 (69.0)	261 (77.0)
	Yes	160 (25.0)	78 (23.0)
	Unknown	39 (6.0)	0 (0.0)
BRAF-V600 Mutation	Wild-type	224 (34.9)	146 (39.8)
	Mutant	271 (42.3)	143 (39.0)
	Unknown	146 (22.8)	78 (21.3)
LDH U/L; n (%)	<250	603 (94.1)	337 (91.8)
	250-500	22 (3.4)	18 (4.9)
	Not determined	10 (1.6)	7 (1.9)
	Unknown	6 (0.9)	5 (1.4)
Type of systemic therapy; n (%)	Nivolumab	534 (83.3)	317 (86.4)
	Pembrolizumab	107 (16.7)	50 (13.6)

[a] Patients with an unknown primary tumour (n = 38 and n = 26) were excluded from the analyses on Breslow thickness, ulceration, and in-transit metastases.

[b] Including patients with acral melanoma (n = 20 and n = 17). AJCC = American Joint Committee on Cancer, ECOG PS = Eastern Cooperative Oncology Group performance score, LDH = lactate dehydrogenase.

melanoma was cutaneous in 93.3% of the cases, and 5.9% had an unknown primary. Twenty-five per cent of the patients had in-transit metastases. The baseline registration completeness of these patients was 92.7%. (See Supplement 3 for an overview of the incomplete data items.) Of these patients, 85.6% began treatment within 12 weeks of definitive surgical resection. The median duration between resected stage III/IV diagnosis and the start of anti-PD-1 therapy was 66 days (IQR 47–89). The median time between the last surgery and anti-PD-1 therapy in this group was 58 days (IQR 42–77). Fifteen patients (2.3%) were not included in these analyses due to missing data. The one-year follow-up group included 367 patients (Table 1).

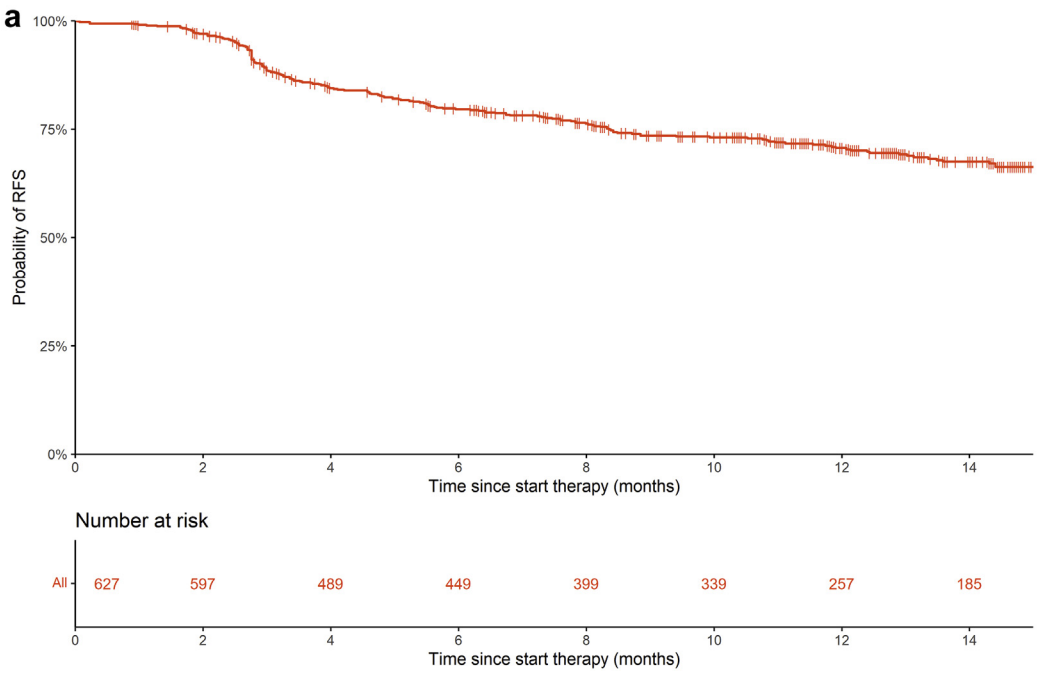
3.2. Ineligibility for trial participation

Forty-five of the 641 patients (7.0%) treated with adjuvant anti-PD-1 therapy had one or multiple patient- or tumour characteristics registered in the DMTR, which would have made them ineligible for trial participation (Supplement 4). Ten patients had ECOG PS ≥ 2, 32 patients had a history of auto-immune disease (other than thyroid disease), two patients had HIV, and one patient had both an auto-immune disease, as well as HIV.

3.3. Recurrence-free survival

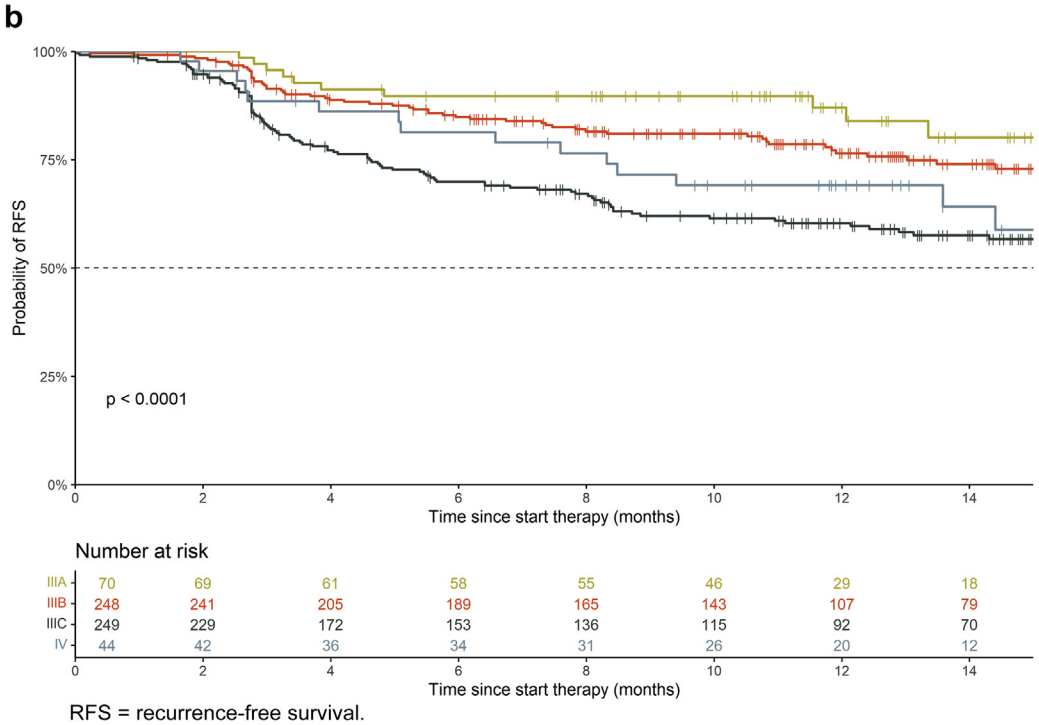
The recurrence-free survival rate at 12-months was 70.6% (95% CI, 66.9–74.6) for the entire study population (Fig. 2a). Fourteen patients were excluded from this analysis due to missing follow-up data. The median follow-up time in this population was 12.8 months. At the time of this report, the median recurrence-free survival rate had not been reached. A total of 188 (30.0%) patients had recurred or died at the data cut-off. The recurrence-free survival rate at 12-months differed significantly ($p < 0.001$) between disease stages according to the AJCC-7 and AJCC-8 classification (Fig. 2b and Supplement 5).

Among patients with AJCC-7 stage IIIA disease, the recurrence-free survival rate at 12-months was 87.0% (95% CI, 78.7–96.2). In stage IIIB and IIIC, the recurrence-free survival rate at 12-months was 76.5% (95% CI, 70.9–82.5) and 60.3% (95% CI, 54.2–67.2), respectively. Among those with stage IV disease, the 12-month recurrence-free survival rate was 69.1% (95% CI, 56.4–84.6). Male sex, higher disease stage, ulceration present in primary melanoma, Breslow thickness and BRAF-V600 mutation were significantly associated with a higher hazard for RFS (Table 2). Male sex, disease stage and Breslow thickness were significantly associated with a higher hazard for RFS rates after adjustments for covariates (Supplement 6).



RFS = recurrence-free survival.

Fourteen patients were not included in this analysis due to missing data necessary for calculating RFS.



RFS = recurrence-free survival.

Thirty patients were not included in this analysis due to missing data (e.g. stage of disease) necessary for calculating RFS.

Fig. 2. a: Kaplan–Meier estimate of recurrence-free survival in melanoma patients treated with adjuvant anti-PD-1 therapy. RFS = recurrence-free survival. Fourteen patients were not included in this analysis due to missing data necessary for calculating RFS. b: Kaplan–Meier estimate of recurrence-free survival (RFS) in melanoma patients treated with adjuvant anti-PD-1 therapy, according to the AJCC 7th edition stage of disease classification. RFS = recurrence-free survival. Thirty patients were not included in this analysis due to missing data (e.g. stage of disease) necessary for calculating RFS.

Table 2
Univariate Cox regression model for factors associated with recurrence-free survival in melanoma patients treated with adjuvant anti-PD-1 therapy.

Characteristic	N	Events	Hazard Ratio (95% CI)	P-value
Age in years	627	188	1.00 (0.99, 1.02)	0.441
Sex				
Male	355	123	Reference	
Female	272	65	0.64 (0.48, 0.87)	0.004
ECOG PS				
0	455	129	Reference	
1	131	43	1.05 (0.74, 1.48)	0.787
2	9	2	0.65 (0.16, 2.63)	0.545
Stage AJCC 7th				
Stage IIIA	70	10	Reference	
Stage IIIB	248	57	1.66 (0.85, 3.25)	0.141
Stage IIIC	249	99	3.30 (1.72, 6.33)	<0.001
Stage IV	44	17	2.77 (1.27, 6.06)	0.010
Breslow Thickness (mm)	557	175	1.08 (1.04, 1.13)	<0.001
Ulceration				
No	315	81	Reference	
Yes	198	75	1.51 (1.10, 2.07)	0.010
ITM				
No ITM	433	125	Reference	
ITM	155	48	1.15 (0.83, 1.61)	0.397
BRAF-V600 Mutation				
Wild Type	218	75	Reference	
Mutant	263	78	0.91 (0.66, 1.25)	0.571
Missing	146	35	0.67 (0.45, 1.00)	0.051

3.4. One-year follow-up group

This group consisted of 367 patients with a minimum follow-up period of 12 months or death within 12 months (n = 31) (Fig. 3). The median follow-up period in these patients was 15.6 months. A CT- or FDG-PET-scan was performed in 98.9%, and an MRI scan of the brain was performed in 64.6% of patients before starting adjuvant systemic treatment. A total of 67 (18.3%) of patients developed grade ≥3 toxicity. The most common grade ≥3 toxicities were colitis/diarrhoea (4.6%), hepatitis (1.1%), rash/pruritus (0.5%), dyspnoea/pneumonitis (1.1%), and 'other' in 6.8%. The relative proportion of grade ≥3 toxicities is displayed in Fig. 4. There were no treatment-related deaths during the study period.

Two hundred and twenty-four patients (61.0%) discontinued anti-PD-1 therapy within 12 months. Reasons for premature discontinuation were any grade toxicity (18.0%), progression (17.4%), agreed on by physician and patient (13.1%), patients' choice (0.5%), poor clinical condition (1.1%), unknown (0.5%), or, other reasons (10.4%). Fig. 5 shows the treatment duration of the patients who prematurely discontinued anti-PD-1 treatment and the reason and timing of discontinuation. Fifty-eight (15.8%) of the one-year follow-up patients discontinued treatment within three months, 14.7% between three and six months, 13.9% between six and nine months, and 16.6% between nine and twelve months. Since the start of the COVID-19 pandemic (starting in March 2020), more patients prematurely discontinued treatment because of 'other' reasons compared to before the pandemic (38.7% versus 7.4%). We also note an increased discontinuation rate registered as 'agreed on with treating physician' in the last three months of a treatment since the COVID-19 pandemic (79% versus 64%, respectively).

The 12-months RFS rate for patients in the one-year follow-up group was 69.5% (95% CI, 64.9–74.4) (Supplement 7). The median RFS had not been reached for this group at the time of this report. A total of 134 (36.5%) patients had recurred or died at dataset cut-off.

4. Discussion

The current study is, to our knowledge, the first nationwide cohort study comparing daily clinical practice outcomes in adjuvant-treated melanoma patients to the registration trials. We report a similar recurrence-free survival rate at 12-months in our study population compared to those treated in the registration trials. However, we report higher rates of treatment-related adverse events (grade ≥3) and, strikingly, higher rates of premature treatment discontinuation in patients treated with adjuvant anti-PD-1 compared to the registration trials.

4.1. Adjuvant systemic treatment in the Netherlands

Data of the first year of adjuvant patients in the DMTR demonstrates that most patients treated in the Netherlands received anti-PD-1 checkpoint inhibitors, specifically nivolumab. Until November 2020, adjuvant BRAF-MEK inhibition was only available in an expanded access program for patients with contraindications to immunotherapy. Therefore, the number of patients treated with adjuvant BRAF/MEK inhibitors in our study is limited. The majority of patients treated with adjuvant anti-PD-1 started systemic therapy within 12 weeks after definitive surgical resection, which is in accordance with the trial designs of the EORTC 1325/Keynote-054 trial and the Checkmate-238 trial [9,10].

4.2. Real-world versus trial

We report similar recurrence-free survival rates at 12-months compared to the trials. In our study recurrence-free survival rate at 12-months was 87.0% (95% CI, 78.7–96.2) for AJCC-7 stage IIIA, compared to 93.4% (95% CI, 84.9–97.2) in the EORTC 1325/Keynote-054 trial [31]. For stage IIIB and IIIC, we report a recurrence-free survival rate at 12-months of 76.5% (95% CI, 70.9–82.5) and 60.3% (95% CI, 54.2–67.2) compared to 75.8% (95% CI, 69.7–80.9) and 67.7% (95% CI, 60.6–73.8) in the EORTC 1325/Keynote-054 trial. Similarly, RFS rates per stage of disease according to the AJCC 8th edition were roughly comparable to

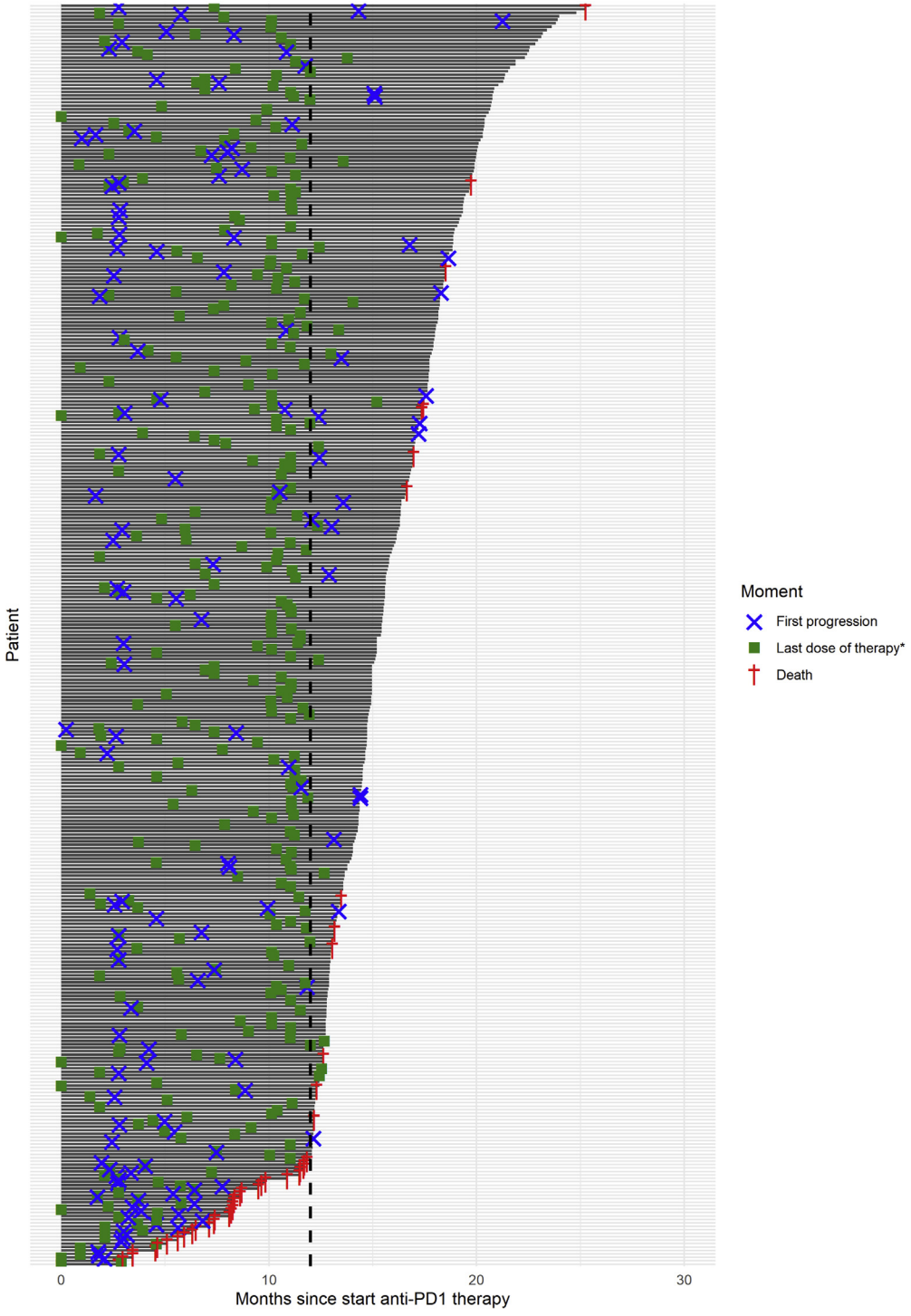


Fig. 3. Swimmer plot of anti-PD-1 adjuvant treated melanoma patients in the one-year follow-up group. ∗This represents the date of the first dose of the last cycle (adjuvant anti-PD-1 given in 2-weekly up to 6-weekly doses).

those of the EORTC 1325/Keynote-054 trial [31] (Supplement 5).

In the Checkmate-238 trial, 12 month RFS for stage IIIB/C was not reported separately but was 72.3% (95% CI, 67.4–76.7) for stages IIIB and IIIC combined [9]. For stage IV patients, we report a recurrence-free survival rate at 12-months of 69.1% (95% CI, 56.4–84.6) compared to 63.0% (95% CI, 51.6–72.5) in the Checkmate-238 trial.

Our eligibility analysis also shows similarities between daily clinical practice patients and trial patients, with only 7.0% of daily clinical practice patients not

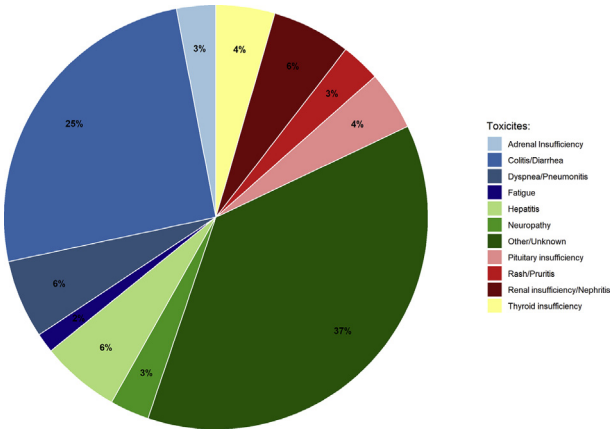


Fig. 4. Type of grade ≥3 toxicity during or after treatment with anti-PD-1 therapy.

meeting eligibility criteria [9,10]. This is in contrast to our previous research in which we showed that up to 44% of the metastatic melanoma patients in daily practice did not meet the eligibility criteria for trial participation [32]. This difference can be explained by the fact that patients treated with adjuvant therapy do not have brain metastases, which was the main factor for ineligibility in advanced melanoma patients. The eligibility analysis was based on available information in the DMTR. Since the DMTR lacks information on items such as organ function, actual numbers of ineligible patients might thus be higher than reported.

Factors associated with a higher hazard for RFS in our patient population were sex, stage IIIC disease and Breslow thickness (Supplement 6). Women represented 43.5% of our study population compared to 43.0% and 37.0% in the registration trials. In our study population, 34.4% of patients had ulcerated primary melanoma compared to 40.5% and 41.5% in the trials. Breslow thickness of the primary melanoma was not specified in the trial population. Interestingly, the presence of ITM, which is generally considered prognostically unfavourable [33], was not associated with a higher hazard for RFS.

Toxicity rates in our study appear slightly higher than reported in previous adjuvant trials (18.2% grade ≥3 treatment-related adverse events, compared to 14.4% in Checkmate-238 and 14.7% in EORTC 1325/Keynote-054 trial). Additionally, 17.9% of premature treatment discontinuation in our population was caused by any grade treatment-related adverse events, which was higher than the 7.7% and 13.0% reported in the Checkmate-238 and EORTC 1325/Keynote-054 trial, respectively. Furthermore, the 18% of patients experiencing severe toxicity in our adjuvant populations appears higher than the 11% we previously reported for advanced anti-PD-1 treated melanoma patients in the same registry [34]. Altogether we show that although adjuvant treated patients in daily clinical practice based on eligibility criteria seem to adequately reflect the trial population, they experience more severe adverse effects and discontinue treatment more frequently than patients in the registration trials.

Furthermore, the all-cause rate of premature discontinuation of therapy was 61.0% in our follow-up population. These rates are remarkable higher than reported in the registration trials, in which 39.2% and 44.6% of patients discontinued treatment within one year [9,10].

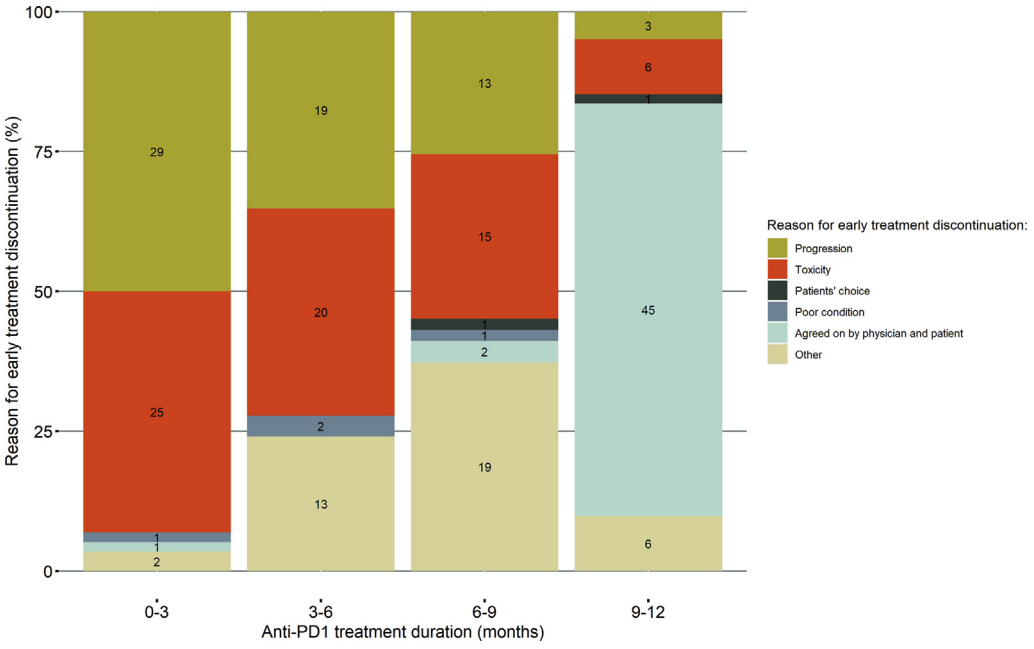


Fig. 5. Reasons for early discontinuation of anti-PD-1 adjuvant treated patients.

The higher discontinuation rates in our population do not seem to be caused by more frequent progressive diseases. We report lower rates of treatment discontinuation due to progressive disease compared to trials, respectively, 17.4% compared to 21.4% [9] and 26.7% [10]. Early discontinuation of treatment in our population might, however, in part, have been due to factors related to the COVID-19 pandemic, where patients who started systemic therapy after March 2019 potentially discontinued treatment before reaching the one-year mark. This is supported by our findings that during the COVID-19 pandemic, more patients discontinued treatment due to 'other reasons'. We are currently conducting further research into the effects of the COVID-19 pandemic on adjuvant therapy for melanoma. Additionally, trial patients could be more motivated to continue treatment in spite of toxicity.

4.3. Benchmarking and comparison with other nationwide registries

The goal of the DMTR is to monitor patient safety and quality of care. The scientific committee of the DMTR consists of medical oncologists representing the 14 melanoma centres in the Netherlands, melanoma surgeons, pathologists, and delegates from a Health Technology Assessment Institute. Quarterly meetings in which quality indicators are discussed lead to the identification of potential differences in clinical practice that can be associated with variation in outcomes between melanoma centres. By discovering discrepancies and potential blind spots, melanoma centres can use this information to improve their care.

To our knowledge, the Danish Metastatic Melanoma Database (DAMMED) is the only other nationwide registry of adjuvant treated melanoma [35]. To facilitate the comparison of treatment patterns and outcomes from registries across Europe, the authors believe that there should be a consensus on data collection in European countries. Initiatives such as EuMelaReg will, in the future, possibly enable such comparisons [36].

4.4. Strengths and limitations

The high level of baseline data completeness in the DMTR illustrated the quality of data registration. Nevertheless, we are continuously improving the methods of data collection to minimize registration delays. The future addition of automatic linkage of pathology data from the pathology database in the Netherlands (PALGA) will facilitate patient inclusion, reduce registration burden, and further increase case completeness and quality of DMTR data. Additionally, this will facilitate the early detection of relapses, resulting in a more real-time follow-up of our study population.

For daily clinical practice, it is essential to indicate the effectiveness of all available adjuvant treatment options. With the recent approval and reimbursement of BRAF/MEK inhibitors for adjuvant treatment of resected stage III melanoma in the Netherlands, research into the use of these drugs in daily practice will be carried out as soon as data are available. Furthermore, analyses on overall survival will be presented once data are more mature.

5. Conclusion

Despite similar patient characteristics, premature discontinuation of adjuvant anti-PD-1 in daily clinical practice occurs more often than reported in clinical trials, while toxicity rates also appear slightly higher. Nevertheless, recurrence-free survival at 12-months is similar between daily clinical practice and trial patients. Future analyses into factors contributing to premature treatment cessation and its effect on overall survival are needed once follow-up data in daily clinical practice patients are more mature.

Authors' contributions

Melissa M. de Meza: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review and editing, **Rawa K. Ismail:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review and editing, **Daan Rauwerdink:** Writing – review and editing, **Olivier J. van Not:** Writing – review and editing, **Jesper van Breeschoten:** Writing – review and editing, **Willeke A.M. Blokx:** Conceptualization, Writing – review and editing, Supervision, **Anthonius de Boer:** Writing – review and editing, **Maaike van Dartel:** Writing – review and editing, **Doranne L. Hilarius:** Writing – review and editing, **Eva Ellebaek:** Writing – review and editing, **Han J. Bonenkamp:** Writing – review and editing, **Christian U. Blank:** Writing – review and editing, **Maureen J.B. Aarts:** Writing – review and editing, **Alexander C.J. van Akkooi:** Writing – review and editing, **Franchette W.P.J. van den Berkmortel:** Writing – review and editing, **Marye J. Boers-Sonderen:** Writing – review and editing, **Jan Willem B. de Groot:** Writing – review and editing, **John B. Haanen:** Writing – review and editing, **Geke A.P. Hospers:** Writing – review and editing, **Ellen W. Kapiteijn:** Writing – review and editing, **Djura Piersma:** Writing – review and editing, **Roos S. van Rijn:** Writing – review and editing, Astrid A.M. van Writing – review and editing, **Art Vreugdenhil:** Writing – review and editing, **Hans M. Westgeest:** Writing – review and editing, **Alfons J.M. van den Eertwegh:** Writing – review and editing, **Karijn P.M. Suijkerbuijk:** Conceptualization, Writing – review and editing, Supervision, **Michel**

W.J.M. Wouters: Conceptualization, Writing – review and editing, Supervision.

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Conflict of interest statement

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 BMS and Novartis. MBS has consultancy/advisory relationships with Pierre Fabre, MSD and Novartis. JdG has consultancy/advisory relationships with Bristol Myers Squibb, Pierre Fabre, Servier, MSD, Novartis. GH consultancy/advisory relationships with Amgen, Bristol Myers Squibb, Roche, MSD, Pfizer, Novartis, Pierre Fabre and has received research grants not related to this paper from Bristol Myers Squibb, Seerave. EK has consultancy/advisory relationships with BristolMyers Squibb, Novartis, Merck, Pierre Fabre, and received research grants not related to this paper from Bristol Myers Squibb. KS has advisory relationships with Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, Abbvie and received honoraria from Novartis, MSD and Roche. AvdV has consultancy relationships with Bristol Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, Eisai, Merck. JH has advisory relationships with Achilles Therapeutics, Bristol Myers Squibb, BioNTech, Immunocore, Ipsen, MSD, Merck Serono, Molecular Partners, Novartis, Neogene Therapeutics, PokeAcel, Pfizer, Roche/Genentech, Sanofi, T-Knife, Third Rock Ventures, and has received research grants not related to this paper from Amgen, Bristol Myers Squibb, MSD, BioNTech, Neogene Therapeutics and Novartis. All grants were paid to the institutions. The funders had no role in the writing of this article or decision to submit it for publication. AvA has advisory board/consultancy honoraria from Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Sirius Medical, 4SC. Research grants from Amgen, Merck-Pfizer. All outside of current work and all paid to institute. MA has advisory board/consultancy honoraria from Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas, Bayer. Research grants Merck-Pfizer. Not related to current work and paid to institute. HMW has received travel expenses from Ipsen and Astellas and has received honoraria from Roche and Astellas. RvR has received expert meeting fees from Roche and advisory board fees from Pfizer. EE has received speaker honoraria from BMS, Pierre Fabre, Kyowa Kirin, and travel/conference expenses from MSD. All remaining authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.08.044.

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