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Real-world Outcomes of First-line Anti-PD-1 Therapy for Advanced Melanoma: A Nationwide Population-based Study

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Summary: The efficacy of anti-programmed death-1 (PD-1) monotherapy for advanced melanoma has been established, but it is unknown to what extent patients benefit in the real world. In this observational study with nationwide population-based data from the Dutch Melanoma Treatment Registry, we analyzed real-world outcomes of first-line anti-PD-1 monotherapy in advanced melanoma patients diagnosed in 2015 to 2016. Overall survival (OS) was estimated with the Kaplan-Meier method. Competing risks analysis was used to estimate probabilities for second-line treatment, with death as competing risk. With a Cox model, the association of factors with OS was estimated. Patients who received anti-PD-1 monotherapy (n = 550) had a median age of 65 years and 502 (95%) patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1, 383 (70%) had normal lactate dehydrogenase (LDH), 370 (67%) had stage IV-M1c disease, and in 441 (81%), brain metastases were absent. The median OS was 24 months [95% confidence interval (CI): 20-30 mo]. The median OS of patients normally eligible for phase III trial participation was 31 months (95% CI: 23-not estimable). The BRAF mutation was associated with superior OS. ECOG PS of ≥ 1, symptomatic brain metastases, and liver metastases were associated with inferior OS and, together with elevated LDH, with death before second-line treatment. Patients with a complete response had a 2-year OS probability from first reported complete response of 92% (95% CI: 86%-99%). Real-world advanced melanoma patients in the Netherlands have benefitted from anti-PD-1 monotherapy. ECOG PS ≥ 1, symptomatic brain metastasis, liver metastasis, and elevated LDH are important prognostic factors for survival. The additional information that this study provides could help to improve more effective use in the real world.

Key Words: nivolumab, pembrolizumab, anti-PD-1 antibody, anti-PD-1 therapy, real-world, population-based, competing risks, immunotherapy

(*J Immunother* 2020;43:256–264)

From the discovery of the programmed death-1 (PD-1) protein by Ishida et al, it took > 20 years to reveal its role in cancer immunology and develop anti-PD-1 antibodies for advanced melanoma.[1] PD-1 receptors are expressed on the surface of T-cells and when PD-1 binds to its ligand programmed death-ligand 1 (PD-L1) on peripheral tissue, their negative regulatory effect on the immune response ensures self-tolerance.[2] Expression of PD-L1 by tumor cells or immune-infiltrating cells in melanoma metastases can induce immune-tolerance and may result in immune-escape of the tumor. Anti-PD-1 antibodies can block the inhibitory interaction between PD-1 on T-cells and its ligand PD-L1 expressed in the tumor microenvironment, thereby enhancing antitumor immunity.

In 2015, the anti-PD-1 antibodies nivolumab and pembrolizumab were approved for the treatment of advanced melanoma based on the phase III trials, CHECKMATE-066 and KEYNOTE-006. The anti-PD-1 antibodies nivolumab and pembrolizumab showed superiority over chemotherapy and ipilimumab, respectively.[3,4] Anti-PD-1 antibodies achieved

Received for publication March 8, 2020; accepted July 7, 2020.

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Ethics approval and consent to participate: In compliance with Dutch regulations, the Dutch Melanoma Treatment Registry was approved by the medical ethical committee and was not subject to the Medical Research Involving Human Subjects Act.

M.C.T.v.Z., L.C.d.W., M.W.J.M.W., A.J.M.v.d.E., and J.B.A.G.H. designed the study, analyzed and interpreted the data, and prepared the first version of the manuscript. M.C.T.v.Z. and L.C.d.W. performed quality control of the data and statistical analysis. A.J.M.v.d.E., J.B.A.G.H., M.J.B.A., F.W.P.J.v.d.B., J.W.B.d.G., G.A.P.H., H.W.K., D.P., R.S.v.R., K.P.M.S., A.J.t.T., A.A.M.v.d.V., G.V., and J.J.M.v.d.H. carried out data acquisition and were responsible for data approval. All authors have reviewed and edited the manuscript. All authors have read and approved the final manuscript.

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Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.immunotherapy-journal.com.

objective response rates of 33% to 40%, with a 1-year overall survival (OS) probability of 73% to 75%, and only 10% to 12% of patients had treatment-related grade 3-4 adverse events (AEs). Median OS ranging from 20.3 to 37.5 months have been reported in the extended follow-up studies of these trials.[5–8]

The efficacy of anti-PD-1 antibodies has been well established on the basis of phase III trials, but by creating a homogenous study population, a large proportion of the general patient population was excluded from these trials.[9] Outcomes of the real-world population (and setting) are needed to investigate which patients treated in daily practice benefit from anti-PD-1 therapy.

Melanoma care for advanced (unresectable stage III/IV) melanomas was centralized in 2013 in the Netherlands. Since then, patients with advanced melanoma can only receive new systemic therapies in 14 designated melanoma centers. All these patients are registered in the Dutch Melanoma Treatment Registry (DMTR). Using this nationwide population-based registry, we report in-depth outcomes of first-line anti-PD-1 therapy in the real world.

MATERIALS AND METHODS

Study Design and Patient Population

For this longitudinal cohort study, data from the DMTR were used. In this comprehensive nationwide registry, all patients with advanced melanoma of any kind who are seen in a melanoma center were followed from the diagnosis of advanced melanoma until death. A detailed description of the DMTR setup has been previously published by Jochems et al.[10]

We selected patients 18 years of age and older diagnosed with unresectable stage IIIC and IV melanoma treated with systemic therapy in 2015 and 2016 (the dataset cut-off date was June 1, 2019). Patients with uveal melanoma were excluded. First-line anti-PD-1 therapy was defined as single-agent therapy with nivolumab or pembrolizumab.

Statistical Analysis

Baseline characteristics of patients treated with first-line anti-PD-1 antibodies were compared to patients treated with another first-line systemic therapy. Categorical variables were analyzed using the χ^2 test and numerical variables using the unpaired t test. Distribution of categories was based on non-missing data and a missing category was not reported for variables with <2.5% missing data. The median follow-up time was estimated with the reverse Kaplan-Meier method.[11] OS was defined as time from the start of first-line anti-PD-1 therapy to death from any cause. Patients alive or lost to follow-up were right-censored at the time of last registered contact. Progression-free survival (PFS) was defined as time from the start of first-line anti-PD-1 therapy to first registered progressive disease (PD) or death, whichever occurred first. Both OS and PFS were estimated using the Kaplan-Meier method. Probabilities for second-line treatment were estimated with cumulative incidence curves, in which second-line treatment and death before second-line treatment were considered competing risks. Time of second-line treatment was defined as the start date of second-line systemic therapy of any kind.[12]

A Cox proportional hazards model was used to assess the association of prognostic factors with OS. Prognostic factors assessed were age at diagnosis (≤ 50, 50-59, 60-69, and ≥ 70), baseline Eastern Cooperative Oncology Group performance status (ECOG PS 0, 1, and ≥ 2), baseline lactate dehydrogenase value (LDH; normal and >1x upper limit of normal), stage at diagnosis (unresectable IIIC and IV-M1a-b and IV-M1c according to the 7th edition of the American Joint Committee on Cancer Melanoma Staging System),[13] distant metastases (<3 organ sites and ≥ 3 organ sites involved), and BRAF mutational status. Brain metastasis (absent, asymptomatic, and symptomatic) and liver metastasis were analyzed in a separate Cox model in which stage at diagnosis was not included because of its correlation with brain and liver metastasis. Cox proportional hazards models were also used to estimate the association between prognostic factors and the cause-specific hazards of second-line treatment.[12] Survival outcomes of patients who fulfilled the inclusion criteria of KEYNOTE-006 and CHECKMATE-066 trials (eligible) were compared with patients who did not fulfill these inclusion criteria (ineligible; inclusion criteria can be found in the Supplemental Material Fig. S3, Supplemental Digital Content 1, http://links.lww.com/JIT/A563).[3,4]

In all 14 melanoma centres, response status was based on a combination of RECIST v1.1 criteria and on (clinical) judgment by the medical team. We evaluated best overall response (BOR) and response status at 3, 6, 12, 18, and 24 months, using Sankey diagrams, to gain insight into the change of response status over time. BOR was defined as best response to first-line anti-PD-1 therapy in the time period preceding a follow-up moment as assessed and reported by the medical team. Response status was defined as actual response status of first-line anti-PD-1 therapy around the prescheduled evaluation moment. If the prescheduled evaluation moment exceeded the follow-up duration, the last response status was carried forward. Death was always reported, even if it occurred in a subsequent treatment line. With 2 landmark models, OS stratified by response status was estimated from 3 and 6 months.

Data handling and statistical analyses were carried out using R (version 3.6.1.; packages car, lubridate, tidyverse, survival, and cmprsk).

RESULTS

From 2015 to 2016, a total of 1442 patients with advanced melanoma were registered in the DMTR. After exclusion of uveal melanoma, 1394 patients remained. A total of 550 patients received first-line anti-PD-1 therapy and 844 patients received another first-line systemic therapy. Baseline patient characteristics, apart from sex, were different across patients receiving first-line anti-PD-1 therapy and another first-line systemic therapy (Table 1). Patients who received first-line anti-PD-1 antibody were older, with a median age of 65 years, but had favorable ECOG PS and lower tumor burden. LDH was elevated in 161 (30%) patients, of whom 25 (5% of all patients) had LDH >2x upper limit of normal, 370 (67%) patients had stage IV-M1c disease, 105 (19%) patients had brain metastasis, and 121 (22%) patients had liver metastasis. Of the patients who received first-line anti-PD-1 therapy, 40% (217/550) had a BRAF-mutated melanoma compared with 73% (615/844) of patients who received another first-line systemic therapy.

At dataset cut-off date, the median follow-up was 32 months and in 533 of 550 (97%) patients, anti-PD-1 therapy had been discontinued. The most common reasons for discontinuation were PD, planned discontinuation, AEs, and poor condition of the patient (50%, 24%, 12%, and 4.9%, respectively). A total of 202 of 533 (38%) patients had received second-line systemic therapy after first-line anti-PD-1 antibody. The most common second-line systemic

TABLE 1. Baseline Characteristics of All Patients Treated With First-line Anti-PD-1 Therapy

	Anti-PD-1 (n = 550)	Other* (n = 844)	Total (n = 1394)	*P*†
Age [median (range)] (y)	65 (21, 94)	61 (19, 96)	63 (19, 96)	< 0.001
Age categories				< 0.001
< 50jr	75 (13.6)	177 (21.0)	252 (18.1)	
50-59jr	111 (20.2)	208 (24.6)	319 (22.9)	
60-69jr	164 (29.8)	233 (27.6)	397 (28.5)	
≥ 70jr	200 (36.4)	226 (26.8)	426 (30.6)	
Female	212 (38.5)	342 (40.5)	554 (39.7)	0.496
ECOG PS				< 0.001
0	335 (63.7)	427 (52.8)	762 (57.1)	
1	167 (31.7)	265 (32.8)	432 (32.4)	
2	23 (4.4)	77 (9.5)	100 (7.5)	
≥ 3	1 (0.2)	40 (4.9)	41 (3.1)	
Unknown	24	35	59	
LDH value				< 0.001
Normal	383 (70.4)	470 (56.2)	853 (61.8)	
1x ULN	136 (25.0)	225 (26.9)	361 (26.2)	
> 2x ULN	25 (4.6)	141 (16.9)	166 (12.0)	
Stage				< 0.001
IIIc	42 (7.7)	57 (6.8)	99 (7.1)	
IV-M1a	61 (11.1)	60 (7.1)	121 (8.7)	
IV-M1b	76 (13.8)	68 (8.1)	144 (10.4)	
IV-M1c	370 (67.4)	657 (78.0)	1027 (73.8)	
Metastases in ≥ 3 organ sites	198 (36.0)	409 (48.5)	607 (43.6)	< 0.001
Brain metastasis				< 0.001
Absent	441 (80.8)	586 (70.5)	1027 (74.6)	
Asymptomatic	42 (7.7)	80 (9.6)	122 (8.9)	
Symptomatic	63 (11.5)	165 (19.9)	228 (16.6)	
Liver metastasis	121 (22.1)	263 (31.7)	384 (27.9)	< 0.001
BRAF-mutant	217 (39.5)	615 (72.9)	832 (59.7)	< 0.001

Values are n (%) unless otherwise indicated.

Baseline characteristics were compared with patients receiving treatment with another first-line systemic therapy. Missing data of <2.5% are not shown.

*Patients treated with another first-line systemic therapy.

†*P*-value of statistical tests comparing the characteristics of patients diagnosed in 2013, 2014, 2015, and 2016 (excluding missing values).

ECOG PS indicates Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PD-1, programmed death 1; ULN, upper limit of normal.

TABLE 2. Treatment-related Grade 3-4 Adverse Events of Patients Treated With First-line Anti-PD-1 Therapy

Grade 3 or 4 Adverse Events	n (%)
Patients with grade 3-4 AEs	82 (14.9)
Anti-PD-1 discontinued due to AEs	62 (11.3)
Patients with ≥ 1 grade 3 or 4 AEs	24 (4.4)
Leukopenia	2 (0.4)
Neuropathy	5 (0.9)
Colitis	16 (2.9)
Kidney function disorder	8 (1.4)
Dyspnea	4 (0.7)
Pneumonitis	5 (0.9)
Adrenal insufficiency	3 (0.5)
Hypophysitis	2 (0.4)
Thyroid insufficiency	5 (0.9)
Fatigue	8 (1.5)
Skin toxicity	17 (3.1)
Hepatitis/liver toxicity	14 (2.5)
Diabetes mellitus type 1	5 (0.9)
Myocarditis	3 (0.5)
Other*	19 (3.5)
Consequences of adverse events	
Short-term medication use	35 (6.4)
Long-term medication use	44 (8.0)
Day-care without hospital admission	2 (0.4)
Hospital admission	39 (7.1)
ICU admission	5 (0.9)
Surgery	1 (0.2)
Permanent damage	4 (0.7)
Death	4 (0.7)
Myocarditis	2 (0.4)
Neurotoxicity	2 (0.4)

A total number of 116 treatment-related grade 3-4 AEs occurred in 82 patients.

*Other grade 3-4 toxicities are listed in the supplement (Supplemental Digital Content 1, http://links.lww.com/JIT/A563).

AEs indicates adverse events; ICU, intensive care unit.

therapies included BRAF and/or MEK inhibitors [103/202 (51%)] and ipilimumab [60/202 (30%)].

A total of 116 treatment-related grade 3-4 AEs occurred in 82 (15%) patients treated with a first-line anti-PD-1 antibody. The most common grade 3-4 AEs of anti-PD-1 therapy were colitis (2.9%), endocrinal AEs (2.8%), hepatitis (2.5%), and kidney function disorder (1.4%) (Table 2). Hospital admission was necessary in 39 (7.1%) patients and in 44 (8.0%) patients, grade 3-4 AE led to long-term medication use. Two patients died of neurotoxicity and 2 died of myocarditis (Table 2). Nineteen (3.5%) patients had grade 3-4 AEs specified as "other," which are summarized in the Supplemental Material Table S1 (Supplemental Digital Content 1, http://links.lww.com/JIT/A563).

At the dataset cut-off date, a total of 301 (55%) deaths were observed. The median OS was 24 months [95% confidence interval (CI): 21-30 mo], with 12-month and 24-month survival probabilities of, respectively, 67% (95% CI: 64%-71%) and 49% (95% CI: 45%-54%; Fig. 1A). The median PFS was 9.3 months (95% CI: 7.5-13.8 mo; Fig. 1B) and the treatment duration of anti-PD-1 therapy was 181 days (interquartile range: 68 to 377 d).

ECOG PS of 1 and ≥ 2, stage IV-M1c, liver metastases, and symptomatic brain metastases were negatively associated with survival. Hazard ratios (HRs) for death of ECOG PS of 1 and ≥ 2, with ECOG PS 0 as the reference category, were, respectively, 1.37 (95% CI: 1.06-1.77) and 2.20 (95% CI: 1.33-3.63; Table 3). Symptomatic brain metastases and liver metastases had HRs of, respectively, 1.77 (95% CI: 1.17-2.68) and 1.47 (95% CI: 1.05-2.06) compared to reference category no brain and no liver metastases. BRAF-mutated melanoma was associated with a superior survival compared with BRAF wild-type melanoma (HR: 0.60; 95% CI: 0.44-0.81; Table 3). In the univariable Cox model, elevated LDH was associated with inferior survival, and age of 70 years or older showed a trend toward inferior survival, but these differences disappeared in the multivariable Cox regression analysis.

The probability of still being in first-line anti-PD-1 therapy at 12 and 24 months was 50% (95% CI: 43%-58%) and 36% (95% CI: 28%-44%), respectively (Fig. 1C). The cumulative incidence of second-line treatment at 12 and 24 months was 28% (95% CI: 24%-32%) and 37% (95% CI: 33%-41%) and the cumulative incidence of death before second-line treatment was 22% (95% CI: 18%-25%) and 27% (95% CI: 23%-31%), respectively (Fig. 1C). The Cox model for the cause-specific hazard of death showed that elevated LDH, liver, and symptomatic brain metastasis and ECOG

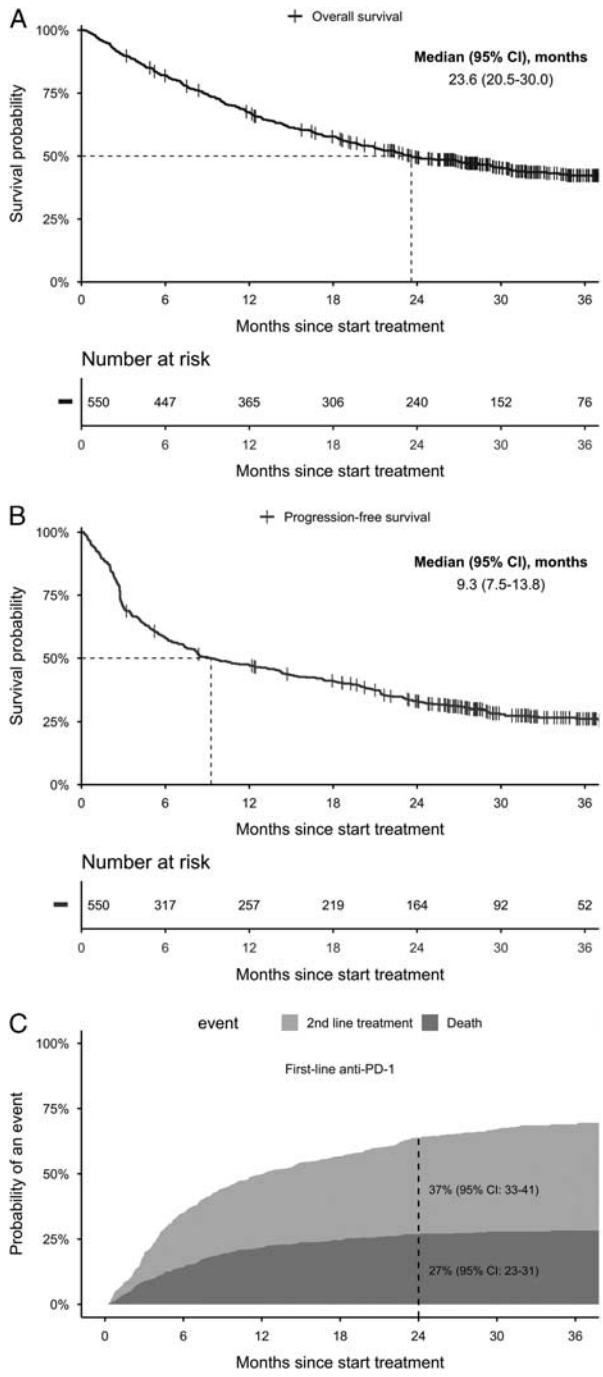

FIGURE 1. Outcomes of patients treated with first-line anti-PD-1 therapy. A, Overall survival and progression-free survival from first-line anti-PD-1 therapy, estimated using the Kaplan-Meier method (B). C, Cumulative incidences of second-line treatment and death before second-line treatment, both estimated with competing risks analysis (probabilities are stacked). CI indicates confidence interval; PD-1, programmed death 1.

PS of ≥ 1 were all significantly associated with death within first-line anti-PD-1 therapy. Patients with BRAF-mutated melanoma were less at risk of dying during the first-line anti-PD-1 therapy and more likely to reach second-line treatment (Supplemental Material Table S2, Supplemental Digital Content 1, http://links.lww.com/JIT/A563).

Two years after the start of first-line anti-PD-1 therapy, 105 (19%) patients had achieved a complete response (CR), 166 (30%) had achieved a partial response (PR), and 103 (19%) patients had stable disease (SD) as the BOR (Fig. 2A). In 172 (31%) patients, the BOR was PD or death. However, as an "actual" response status at the evaluation moment of 24 months, 87 (16%) patients had a CR, 80 (16%) had a PR, and 16 (2.9%) had SD. A total of 366 (67%) patients had progression or were dead after 2 years (Fig. 2B). In the supplement, various Sankey diagrams show how the stage of patients with PR, SD, and PD at 3 and 6 months develops over time (Supplemental Material Fig. S1, Supplemental Digital Content 1, http://links.lww.com/JIT/A563). For example, of the 154 patients who had a SD at 3 months, 22 (14%) achieved a CR, 22 (14%) achieved a PR, and 97 (63%) patients had PD or had died at the 2-year evaluation timepoint (Supplemental Material Fig. S1a, Supplemental Digital Content 1, http://links.lww.com/JIT/A563). Moreover, of the 170 patients with a PR at 3 months, 55 (32%) achieved a CR, 52 (31%) achieved a PR, and 63 (37%) patients had PD or had died at the 2-year evaluation timepoint (Supplemental Material Fig. S1b, Supplemental Digital Content 1, http://links.lww.com/JIT/A563).

The proportion of patients with a CR gradually increased over time (Fig. 2). Patients with a CR at 24 months mostly had ECOG PS of 0 (72%) and a lower disease burden at baseline reflected in the normal LDH value in 83%, distant metastases in <3 organ sites in 79%, and absence of brain and liver metastases in 90% and 92%, respectively (Supplemental Material Table S2, Supplemental Digital Content 1, http://links.lww.com/JIT/A563). At the dataset cut-off, a total of 113 (21%) patients had reached a CR as the BOR. Estimated from the first reported CR, the 2-year survival probability for this subgroup was 92% (95% CI: 86%-99%) and the median OS was not reached (Supplemental Material Fig. S2, Supplemental Digital Content 1, http://links.lww.com/JIT/A563).

The 3-month landmark survival analysis showed that patients with PD had a 24-month survival probability from landmark of 15% (95% CI: 10%-22%) and a median survival of 9.1 months (95% CI: 7.1-10.9 mo; Fig. 3A). The 24-month survival probability from landmark for patients who had SD or PR was, respectively, 57% (95% CI: 49%-65%) and 80% (95% CI: 74%-86%). All 5 patients with CR at 3 months were alive at the dataset cut-off timepoint. From the start of anti-PD-1 therapy, the 3-month survival probability of the whole cohort was 90% (95% CI: 88%-93%).

In the 6-month landmark survival analysis, 138 (25%) patients had PD, 74 (13%) had SD, 199 (36%) had PR, and 23 (4.1%) patients had CR. From the start of anti-PD-1 therapy, the 6-month survival probability was 82% (95% CI: 79%-85%). Patients with PD had a 24-month survival probability from landmark of 16% (95% CI: 11%-24%) and a median survival of 8.3 months (95% CI: 6.9-10.5 mo; Fig. 3B). The 24-month survival probability from the 6-month landmark of patients with SD or PR was 60% (95% CI: 49%-73%) and 79% (95% CI: 73%-85%), respectively. For CR, the 24-month survival probability was 96% (95% CI: 89%-100%).

In total, 158 (29%) patients did not fulfill 1 or more of the inclusion criteria of the immunotherapy phase III trials. The median OS of these "ineligible" patients was

TABLE 3. Univariable and Multivariable Cox Regression Models for Overall Survival of Patients Treated With First-line Anti-PD-1 Therapy

	Univariable				Multivariable			
	n	**HR**	**95% CI**	***P***	**n**	**HR**	**95% CI**	***P***
Univariable and multivariable cox regression models for overall survival of patients treated with first-line anti-programmed death 1 therapy (brain and liver metastases were excluded from this model)								
Age (y)								
≤ 50	75	0.88	0.60-1.29	0.505	72	0.86	0.58-1.28	0.45
50-59	111	0.81	0.57-1.15	0.237	106	0.90	0.63-1.30	0.59
60-69	164	1			152	1		
≥ 70	200	1.31	0.99-1.72	0.056	190	1.19	0.89-1.59	0.23
Sex								
Male	338	1			318	1		
Female	212	1.09	0.87-1.38	0.45	202	1.16	0.91-1.48	0.22
ECOG PS								
0	335	1			331	1		
1	167	1.55	1.21-1.99	< 0.001	166	1.37	1.06-1.77	0.015
≥ 2	24	2.32	1.42-3.77	0.001	23	2.20	1.33-3.63	0.002
LDH								
Normal	383	1			370	1		
> 1x ULN	161	1.54	1.21-1.96	< 0.001	150	1.23	0.94-1.61	0.14
Stage								
IIIc, IV-M1a-b	179	1			167	1		
IV-M1c	370	1.48	1.15-1.91	0.002	353	1.38	1.01-1.90	0.045
Distant metastases								
< 3 organ sites	352	1			333	1		
≥ 3 organ sites	198	1.23	0.97-1.55	0.081	187	1.03	0.79-1.35	0.82
BRAF-mutant								
No	333	1			309	1		
Yes	217	0.58	0.46-0.74	< 0.001	211	0.61	0.47-0.79	< 0.001
Separate multivariable Cox model for brain and liver metastases adjusted for age, sex, ECOG performance score, lactate dehydrogenase, distant metastases, and BRAF mutation (stage was excluded)								
Brain metastasis								
Absent	441	1			418	1		
Asymptomatic	42	1.07	0.7-1.63	0.749	38	1.15	0.73-1.81	0.539
Symptomatic	63	1.70	1.22-2.35	0.001	58	1.91	1.34-2.72	< 0.001
Liver metastasis								
No	426	1			397	1		
Yes	121	1.70	1.32-2.18	< 0.001	117	1.61	1.19-2.17	0.002

CI indicates confidence interval; ECOG PS, ECOG performance score; HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal.

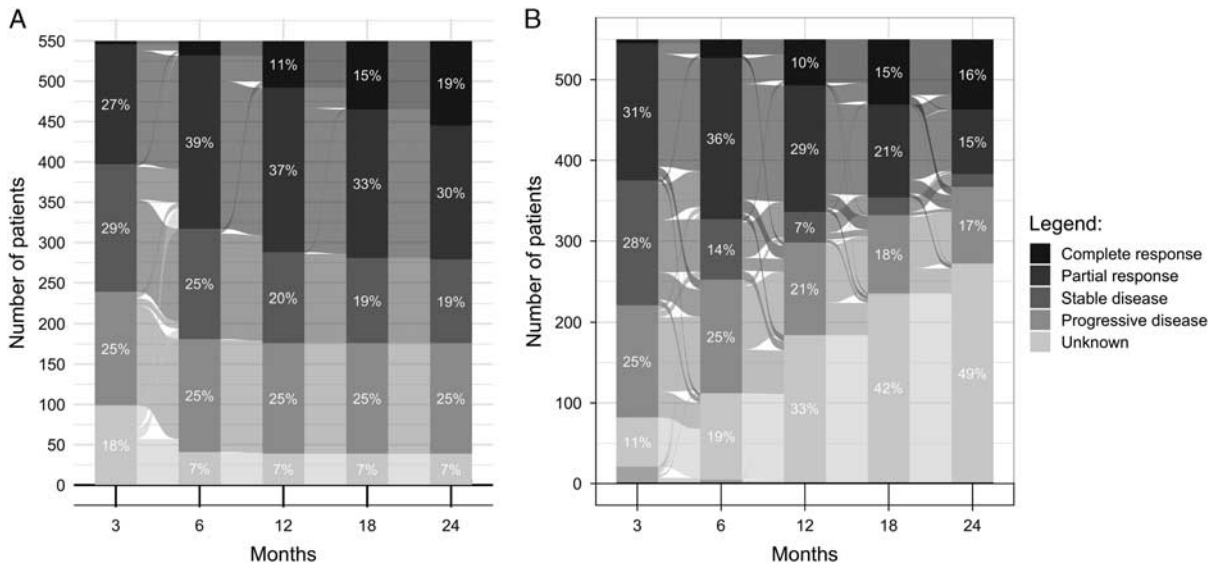

FIGURE 2. Sankey diagram of changes in response status of patients treated with first-line anti-programmed death 1 therapy between 0 and 24 months. A, Best overall response and response status (B).

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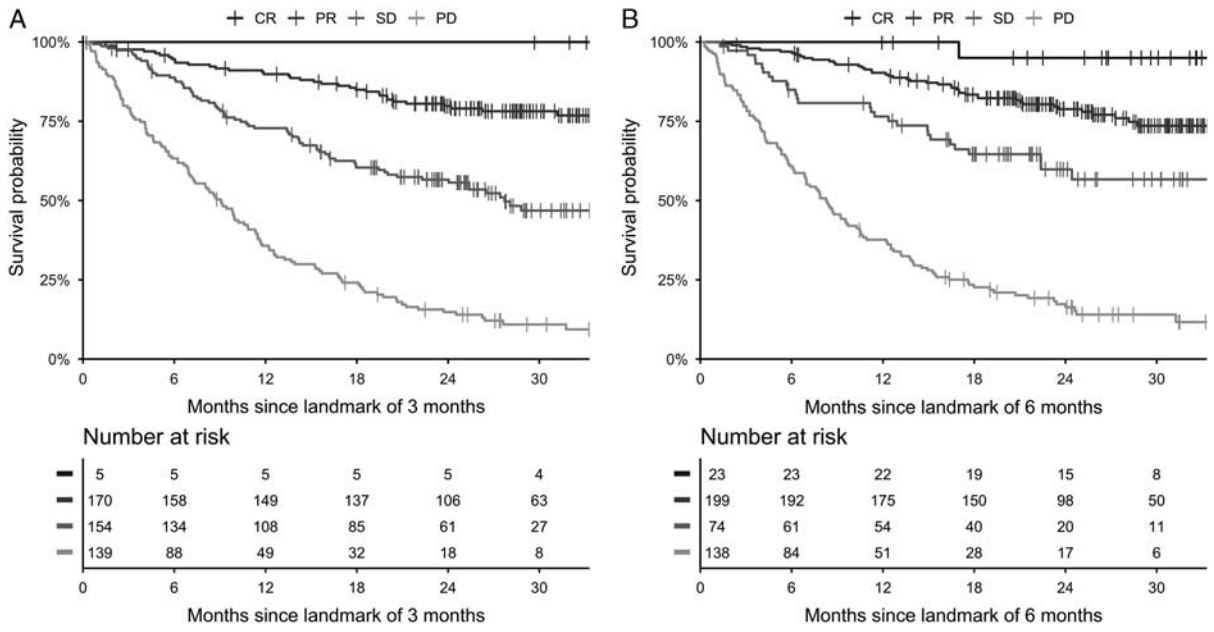

FIGURE 3. Landmark analysis of survival stratified by response status at 2 timepoints after the start of first-line anti-PD-1 therapy. A, Landmark analysis from 3 months. From the start of anti-PD-1 therapy, the 3-month OS probability was 90% (95% CI: 88%-93%). B, Landmark analysis from 6 months. From the start of anti-PD-1 therapy, the 6-month OS probability was 82% (95% CI: 79%-85%). CI indicates confidence interval; CR, complete response; OS, overall survival; PD-1, programmed death 1; PD, progressive disease; PR, partial response; SD, stable disease.

17.1 months (95% CI: 13.6-23.7 mo) and their 24-month survival probability was 41% (95% CI: 34%-50%). Patients who fulfilled these inclusion criteria, and who would normally have been "eligible" for trial participation, showed a median OS of 31.1 months (95% CI: 23.4-not estimable) and their 24-month survival probability was 54% (95% CI: 49%-60%; Supplemental Material Fig. S3, Supplemental Digital Content 1, http://links.lww.com/JIT/A563).

Patients with BRAF wild-type melanoma treated with anti-PD-1 therapy were younger and a higher proportion had normal LDH values (Table S4, Supplemental Digital Content 1, http://links.lww.com/JIT/A563). The median OS of patients with BRAF wild-type melanoma who were treated with anti-PD-1 therapy was 18.2 months (95% CI: 13.9-22.8) versus 42.2 months (95% CI: 27.5-NE) for patients with BRAF-mutated melanoma (Supplemental Material Fig. S4, Supplemental Digital Content 1, http://links.lww.com/JIT/A563). For BRAF wild-type melanoma, the 24-month probability for death before second-line treatment was higher compared with BRAF-mutated melanoma [40% (95% CI: 35%-45%) vs. 6.5% (95% CI: 3.2%-9.9%); Supplemental Material Fig. S5, Supplemental Digital Content 1, http://links.lww.com/JIT/A563)], whereas the 24-month probability for second-line treatment was lower [26% (95% CI: 21%-31%) vs. 54% (95% CI: 48%-61%)]. Of the 217 patients with BRAF-mutated melanoma, 123 (57%) received second-line treatment. The predominant second-line treatments for patients with BRAF-mutated melanoma were combination therapy with BRAF pus MEK inhibitor (69%) and monotherapy with a BRAF inhibitor (15%). Of the 333 patients with BRAF wild-type melanoma, 77 (24%) received second-line treatment that mainly consisted of ipilimumab monotherapy (64%). The characteristics and survival outcomes of anti-PD-1 therapy in BRAF wild-type and BRAF-mutant patients can be found in the supplement (Table S4 and Figs. S4–S6, Supplemental Digital Content 1, http://links.lww.com/JIT/A563).

DISCUSSION

To our knowledge, this is the first report of outcomes of an unselected real-world population of patients with advanced melanoma treated with first-line anti-PD-1 antibodies. We observed a median OS of 24 months and a median PFS of 9 months, both in line with findings in phase III trials on anti-PD-1 antibodies.[7,8] Elevated LDH, ECOG PS of ≥ 1, liver metastases, and symptomatic brain metastases were negatively associated with OS and these factors, plus elevated LDH values, were also associated with death before reaching second-line treatment. BRAF-mutated melanoma was associated with superior OS. The percentage of patients achieving a CR increased gradually over time and 2 years after start of anti-PD-1 therapy; 33% of patients had a CR or PR. Treatment-related grade 3-4 AEs occurred in 15% of first-line anti-PD-1 antibody-treated patients, which is in line with phase III trials.[7,8] Four treatment-related deaths were observed, but no new safety signals were found. We argue that the introduction of anti-PD-1 therapy in the real-world setting in the Netherlands can be considered effective and safe.

The median OS of 31 months for patients who fulfilled the inclusion criteria of the anti-PD-1 antibody phase III trials is comparable to the median OS observed in these trials.[7,8] Although it is reassuring that the results from phase III trials apply to patients in the real world (setting) who resemble these trial patients, patients who did not fulfill these inclusion criteria had a worse prognosis. This underscores that results from phase III trials do not automatically apply to all patients in the real world. We found that

symptomatic brain metastases, liver metastases, and ECOG PS of ≥1 were associated with inferior OS. Nevertheless, the prognosis of "ineligible" patients appears to have improved when comparing the median OS of 17 months with the median OS of 6.2 months estimated in a study with historical data of trial patients with advanced melanoma in the pre immune and targeted therapy era (from 1977 through 2005).[14]

One of our findings was that BRAF-mutated melanoma was statistically significantly associated with superior OS, but we argue that this is not evidence that anti-PD-1 therapy is more effective in BRAF-mutated melanoma. The consequence of analyzing OS is that the impact of the entire treatment strategy that started with first-line anti-PD-1 therapy is investigated. In the CHECKMATE-067 trial, patients with BRAF-mutated melanoma treated with ipilimumab plus nivolumab or nivolumab monotherapy had a small OS advantage compared with BRAF wild-type melanoma, but a considerable proportion of these patients subsequently received targeted therapy.[15] Also, in the KEYNOTE-006 trial, BRAF mutational status did not affect the benefit of pembrolizumab.[4] If anti-PD-1 therapy is as effective in BRAF-mutated as in BRAF wild-type melanoma, our results suggest that for BRAF-mutated melanoma, sequential treatment with targeted therapy is an effective treatment strategy. There is some evidence that previous immunotherapy does not reduce the effectiveness of targeted therapy.[16–18] In the KEYNOTE-006 trial, 119 of 195 (61%) patients with BRAF-mutated melanoma were able to receive targeted therapy after pembrolizumab, but unfortunately, analysis of this subgroup could not be carried out.[7] In our cohort, 57% of the patients with BRAF-mutated melanoma were able to receive second-line therapy, of whom 69% were treated with BRAF plus MEK inhibitors and 15% with monotherapy with a BRAF inhibitor. However, only 25% of the patients with a BRAF wild-type melanoma received second-line therapy (Supplemental Material Fig. S4–S6, Supplemental Digital Content 1, http://links.lww.com/JIT/A563).

To specifically investigate the effectiveness of first-line anti-PD-1 therapy only, we estimated time to the subsequent systemic treatment. Examining second-line treatment poses the problem that some patients die before being able to reach second-line treatment. If the event of death is then censored, the underlying assumption is made that patients who have died may still be able to reach the event of interest. This impossible assumption would overestimate failure probability.[12] With the competing risks method, both the event of interest, second-line treatment, and its competing risk, death, could be investigated, allowing for a more specific analysis of the outcomes of first-line anti-PD-1 therapy.

Elevated LDH, ECOG PS of ≥1, symptomatic brain metastases, and liver metastases were associated with death before reaching second-line treatment and, thus, failure to successfully treat patients with anti-PD-1 therapy. All of these prognostic factors are well established for advanced melanoma in general and for OS of patients treated with immunotherapy.[19–23] Our results suggest that patients with ≥1 of these factors, especially with elevated LDH and symptomatic brain metastasis, gain less benefit from anti-PD-1 therapy. BRAF plus MEK-inhibitors dabrafenib plus trametinib could be a treatment strategy for these patients who have BRAF-mutated melanoma, as it showed antitumor activity in patients with brain metastasis, but durability of response was short.[24] Trials of ipilimumab plus nivolumab combination therapy showed promising results in a patient population with brain metastasis and elevated LDH.[25,26] However, the patient's disease status and condition must be able to tolerate the delayed response that is typical of immunotherapy and the burden of ipilimumab plus nivolumab combination therapy.

BRAF-mutated melanoma was statistically significantly associated with second-line treatment and not with death before second-line treatment, but the relevance of this finding is questionable. After failure to reach a response with an anti-PD-1 antibody, a switch to targeted therapy can easily be made. This causes a selection of patients with a BRAF-mutated melanoma remaining in anti-PD-1 therapy who have favorable patient and/or disease characteristics and/or who respond to anti-PD-1 therapy. Because treatment is equally effective for BRAF-mutant and wild-type melanoma, there is no clinical consequence to this finding.[3,4,7,8,27] The higher proportion of patients with BRAF-mutated melanoma who received second-line treatment and the superior OS compared with BRAF wild-type melanoma are evidence that these patients benefit from sequential treatment with targeted therapy.

The landmark analysis and the Sankey diagrams in the supplement showed that reaching CR or PR at 3 or 6 months was associated with favorable OS (2-y OS probabilities of 100% and 79%, respectively), but for SD this was less evident (57%). Having SD still entails a high risk of not achieving disease control with anti-PD-1 therapy. Treatment should perhaps be directed at developing PR or CR in patients with a SD. A switch to other or combination immunotherapy or targeted therapy in patients who have SD after anti-PD-1 therapy could perhaps be considered sooner, but it is uncertain what the best treatment strategy is.

The proportion of patients who had a CR at 2 years was similar to CR rates of 13% to 19% reported in phase III trials (16% vs. 13% to 19%).[7,8] Patient and disease characteristics of these trials were favorable compared with our study population, except that in the CHECKMATE-066 trial, more patients had elevated LDH. Our study indicates that anti-PD-1 therapy is more effective in achieving a CR in patients with favorable baseline patient and disease characteristics and that patients who achieved a CR have superior OS from the first reported CR (Supplemental Material Table S3 and Fig. S2, Supplemental Digital Content 1, http://links.lww.com/JIT/A563). This is consistent with the findings in previous studies.[28,29]

There are limitations to our study, however. The effectiveness of anti-PD-1 therapy could not be compared head to head with other systemic therapies because of the observational nature of our study and the fact that there are no guidelines for new systemic therapies. Confounding by indication does not allow fair comparison as allocation of a treatment depends on a patient's suitability to receive a treatment as judged by the medical oncologist. That our cohort is highly selected is reflected in the favorable baseline characteristics of patients who received anti-PD-1 therapy compared with patients receiving another first-line systemic treatment (Table 1).

Data quality can be a limitation of observational studies and must always be considered. Since the start of the DMTR in 2013, data managers have been intensively trained and an online registration platform warns data managers for missing data and inconsistencies. All registered data are checked and approved by medical oncologists. Therefore, we argue that the data in the DMTR are of high quality.

One important limitation is that the response status in all melanoma centers was not strictly based on the anatomic tumor burden and its change using the RECIST v1.1 criteria but also on the clinical/symptomatic judgment by the medical team. Especially in patients with pseudo-progression or a sustained PR (on or off treatment) with minimal lesions that persisted on imaging, the response status evaluated with RECIST v1.1 criteria could have been overruled by the judgment of the medical team. We believe that this only had a limited influence on the reported response status and the clinical response reflects the effectiveness of anti-PD-1 therapy in daily practice.

We were unable to analyze whether all patients with advanced melanoma in the Netherlands were included in the DMTR. Since 2013, however, care for patients with advanced melanoma is centralized in 14 melanoma centers across the country. Structural regional (multidisciplinary) consultation between oncology specialists is well integrated in the Dutch hospital care. Furthermore, a quality standard in the Netherlands stipulates that all patients with an advanced melanoma, if the patient agrees and the patient's condition permits, must be referred to a melanoma center for evaluation and treatment. We estimate that only a small proportion of patients with an advanced melanoma had an infaust prognosis and were not referred to a melanoma center and therefore not registered in the DMTR.

The proliferation of effective therapies for advanced melanoma has greatly improved the outcomes of patients with advanced melanoma. Allocating the most suitable systemic therapy and being able to explain what a patient's situation means for his or her prognosis are important and can be challenging for a medical oncologist. Detailed information on the effect size of risk factors on prognosis is a first step to better inform and treat (or not treat) patients. This study provides additional information to phase III trials to improve the use of anti-PD-1 therapy for patients with advanced (nonuveal) melanoma. The use of a nationwide population-based registry ensures external validity making outcomes generalizable to the real-world patient population.

CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

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 Roche Pharma. Roche Pharma stopped funding in 2019 and Pierre Fabre started funding of the DMTR in 2019.

A.J.M.v.d.E. has advisory relationships with Amgen, Bristol-Myers Squibb, Roche, Novartis, MSD, and Pierre Fabre. J.W.B.d.G. has received personal fees outside the submitted work from Bristol-Myers Squibb, Roche, Pierre Fabre, Servier, MSD, and Novartis. G.A.P.H. has consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Roche, MSD, Pfizer, and Novartis, and has received research grants not related to this paper from Bristol-Myers Squibb, and Seerave. E.W.K. has consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Novartis, Roche, Merck, Pierre Fabre, EISAI, Bayer, and Genzyme-Sanofi and received research grants not related to this paper from Novartis and Bristol-Myers Squibb. K.P.M.S. has advisory relationships with Bristol-Myers Squibb, Roche, Novartis, MSD, and Pierre Fabre. A.A.M.v.d.V. has consultancy relationships with Bristol-Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, and Eisai. J.B.A.G.H. has advisory relationships with Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Celsius Therapeutics, GSK, Immunocore, Ipsen, MSD, Merck Serono, Novartis, Neon Therapeutics, Pfizer, Roche/Genentech, Sanofi, and Seattle Genetics, and has received research grants not related to this paper from Novartis, Bristol-Myers Squibb, MSD, and Neon Therapeutics. All grants were paid to the institutions. The remaining authors declare no conflicts of interest.

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