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Real-world Outcomes of Ipilimumab Plus Nivolumab Combination Therapy in a Nation-wide Cohort of Advanced Melanoma Patients in the Netherlands

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Summary: In phase III trials, ipilimumab plus nivolumab combination therapy is highly efficacious for advanced melanoma, despite many treatment-related grades 3–4 adverse events. Here, we report real-world safety and survival outcomes of ipilimumab plus nivolumab for advanced melanoma. Patients with advanced melanoma who received first-line ipilimumab plus nivolumab between January 1, 2015 and June 30, 2021 were selected from the Dutch Melanoma Treatment Registry. We evaluated response status at 3, 6, 12, 18, and 24 months. OS and PFS were estimated with the Kaplan-Meier method. Separate analyses were performed for patients with or without brain metastases and for patients who met the inclusion criteria of the Checkmate-067 trial. In total, 709 patients received first-line ipilimumab plus nivolumab. Three hundred sixty (50.7%) patients experienced grade 3–4 adverse events, with 211 of the (58.6%) patients requiring hospital admission. The median treatment duration was 42 days (IQR = 31–139). At 24 months, disease control was achieved in 37% of patients. Median PFS since the start of treatment was 6.6 months (95% CI: 5.3–8.7), and median OS was 28.7 months (95% CI: 20.7–42.2). CheckMate-067 trial-like patients had a 4-year OS of 50% (95% CI: 43–59). Among patients with no asymptomatic or symptomatic brain metastases, the 4-year OS probabilities were 48% (95% CI: 41–55), 45% (95% CI: 35–57), and 32% (95% CI: 23–46). Ipilimumab plus nivolumab can achieve long-term survival in advanced melanoma patients in a real-world setting, including patients not represented in the CheckMate-067 trial. However, the proportion of patients with disease control in the real world is lower compared with clinical trials.

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Monotherapy with immune checkpoint-blocking antibodies ipilimumab or nivolumab for advanced melanoma is associated with response rates of 10% to 15% and 40%, respectively.[1,2] The hypothesis that double CTLA-4 and PD-1 inhibition could lead to a higher anti-tumor response for advanced melanoma was first confirmed in a phase I study in 2013.[3] Tumor reduction of more than 80% was observed in patients who achieved an objective response with ipilimumab plus nivolumab combination therapy.[3] Most patients in this cohort had stage IV-M1c [American Joint Committee on Cancer (AJCC) seventh edition] disease and other known predictors of poor outcome in melanoma, such as elevated lactate dehydrogenase (LDH) and visceral organ involvement, including hepatic metastases. In the Checkmate-067 phase III trial, 4 doses of ipilimumab plus nivolumab every 3 weeks followed by maintenance nivolumab every 3 weeks was compared with ipilimumab monotherapy in patients with advanced melanoma.[4] Long-term analysis showed a 5-year overall survival (OS) and progression-free survival (PFS) probabilities of 52% and 36% for ipilimumab plus nivolumab versus 26% and 8% for ipilimumab monotherapy, respectively.[5] A complete response or partial response was observed in 22%, and 36% of ipilimumab plus nivolumab treated patients.[5]

These positive results come at the expense of high percentages of patients experiencing grade 3–4 adverse events (AEs). Severe treatment-related AEs were reported in more than 50% of patients, with 36% of patients discontinuing treatment due to AEs.[4] However, analysis of phase II and III trials on ipilimumab plus nivolumab showed that this did not seem to affect survival outcomes.[6]

The Checkmate-067 trial review as previously shown was a randomized controlled trial with stringent inclusion and exclusion criteria. We provide real-world evidence from a nationwide population-based registry on the safety and effectiveness of ipilimumab and nivolumab in patients with advanced melanoma. Effectiveness is investigated by analyzing the effect of prognostic factors (BRAF-mutational status, brain metastases, LDH levels) on PFS and OS, outcomes of trial-(in)eligible patients, and patients (not) experiencing grade 3–4 AEs.

MATERIALS AND METHODS

Study Design and Patients

For this observational research, data from the Dutch Melanoma Treatment Registry (DMTR) were used. In the DMTR, all advanced melanoma patients who are evaluated for treatment in one of the 14 designated melanoma treatment centers in the Netherlands are followed from diagnosis of unresectable stage IIIC or stage IV (advanced) melanoma until death or 10 years of follow-up.[7] We selected patients aged $\geq$18 years diagnosed with advanced melanoma from January 1, 2015 to June 30, 2021, who were treated with first-line ipilimumab plus nivolumab combination therapy. In general, the majority of the patients were treated with the following dosages: nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) every 3 weeks for 4 doses, followed by nivolumab (3 mg/kg) or flat dose 240 mg every 2 weeks, or flat dose 480 mg every 4 weeks. The dosage of ipilimumab (1 mg/kg) and nivolumab (3 mg/kg) was rarely administered. Uveal and mucosal melanoma were excluded. The data set cutoff date was April 12, 2022.

Statistical Analysis

Baseline characteristics were analyzed using descriptive statistics. Adverse events were graded according to Common Terminology Criteria for Adverse Events (CTCAE). Overall survival (OS) was defined as the time from the start of first-line ipilimumab plus nivolumab therapy to death from any cause. Patients alive at the end of follow-up or lost to follow-up were right-censored at the time of last registered contact. Progression-free survival (PFS) was defined as the time from the start of first-line ipilimumab plus nivolumab therapy to the first registered progressive disease or death. Both OS and PFS were estimated with the Kaplan-Meier method. Median follow-up time was estimated with the reverse Kaplan-Meier method.[8] The time of second-line treatment was defined as the start time of second-line systemic therapy of any kind.

A Cox proportional hazards model was used to assess the association of prognostic factors with OS. Covariates were chosen based on clinical experience/relevance and previous research identifying these prognostic risk factors.[9,10] In a subgroup analysis, OS of patients who met the inclusion criteria of the CHECKMATE-067 trial (eligible patients) were compared with patients who did not meet these inclusion criteria (ineligible patients). Inclusion criteria can be found in the supplement.[11]

The effect that AEs may have on survival was (due to limitations of the data set) assessed with a landmark survival analysis to reduce immortal time bias as it takes time to develop an AE.[12] A landmark point of 9 weeks was chosen because most of the AEs of ipilimumab plus nivolumab occur within this timeframe.[5] To further investigate the effect of AEs, we also assessed the OS of patients with a partial response (PR) or complete response (CR) at 3 months who stopped treatment due to AEs after 1 to 4 courses of ipilimumab plus nivolumab.

We evaluated response status at 3, 6, 12, 18, and 24 months, which was visualized with Sankey diagrams to give insight into the change of response status over time. Response status was defined as the actual response status of first-line ipilimumab plus nivolumab therapy around the prescheduled evaluation moment. Response status was based on the RECIST v1.1 criteria and (clinical) judgment by the treating medical team. In patients with radiologic 'progression' but stable or improving clinical condition, pseudoprogression was often considered and treatment was continued. In general, treatment was discontinued if a follow-up scan would show progressive disease. 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 current response status was estimated from 3 and 6 months.

Data handling and statistical analyses were performed with R-studio (version 4.2.1.; packages, tidyverse,[13] survival,[14] and survminer[15]).

RESULTS

Patients

From January 1, 2015 to June 30, 2021, 5856 patients were diagnosed with unresectable stage IIIC or stage IV

TABLE 1. Patient Characteristics at Diagnosis of all Patients Who Received Ipilimumab Plus Nivolumab Combination Therapy in First-line

	Ipilimumab plus nivolumab (n = 709)	All patients* (n = 4664)
Median age, y (range)	61 (21–85)	65 (19–97)
Age categories		
< 50jr	125 (17.6)	689 (14.8)
50–69jr	374 (52.8)	2191 (47.0)
≥ 70jr	210 (29.6)	1784 (38.3)
Female	269 (37.9)	1826 (39.2)
ECOG performance status		
0	359 (52.8)	2235 (51.4)
1	269 (39.6)	1561 (35.9)
≥ 2	52 (7.7)	554 (12.7)
Unknown	29	314
LDH level		
Normal	360 (51.2)	2872 (63.1)
1×ULN	225 (32.0)	1107 (24.3)
> 2 ULN	118 (16.8)	572 (12.6)
Stage		
IIIc	35 (5.0)	493 (10.6)
IV-M1a	24 (3.4)	308 (6.6)
IV-M1b	30 (4.2)	471 (10.1)
IV-M1c	618 (87.4)	3374 (72.6)
Metastases in ≥ 3 organ sites	390 (55.2)	2065 (44.3)
Brain metastases		
Absent	359 (56.7)	2877 (69.4)
Asymptomatic	163 (25.8)	559 (13.5)
Symptomatic	111 (17.5)	712 (17.2)
Unknown	76	516
Liver metastasis	257 (36.6)	1252 (27.1)
BRAF-mutant	294 (41.5)	2758 (59.1)
Prior (neo)-adjuvant treatment	63 (8.9)	339 (7.3)

Values are n (%) unless otherwise indicated.
*All patients diagnosed with advanced melanoma from 2015 to June 30, 2021 were treated with systemic therapy.
ECOG indicates Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

melanoma in the Netherlands, of whom 4893 (83.6%) received treatment with systemic therapy. After exclusion, a total of 709 patients were treated with first-line ipilimumab plus nivolumab (Figure S1, Supplemental Digital Content 1, http://links.lww.com/JIT/A717).

The median age of patients who received first-line ipilimumab plus nivolumab was 61 years (range: 21–89) (Table 1). The majority had an ECOG performance score (ECOG PS) of 0 or 1 [359 (52.8%) and 269 (39.6%) patients, respectively] and stage IV-M1c disease [618 (87.4%) patients]. Lactate dehydrogenase (LDH) level was elevated in 343 (48.8%) patients, and brain metastases were present in 274 (43.3%) patients. Three hundred ninety (55.2%) patients had distant metastases in ≥ 3 organ sites; liver metastases were observed in 257 (36.6%) patients, and 294 (41.5%) patients had a BRAF mutation (Table 1).

Treatment Characteristics

Five hundred and twenty-nine (74.6%) patients only received the combination phase of ipilimumab plus nivolumab (Table 2). Median treatment duration from the start of combination therapy to the stop of either combination therapy or maintenance therapy was 44 days [interquartile Range (IQR = 31–139)]. The main reasons for discontinuation were adverse events [327 (50.3%) patients] and progressive disease [138 (21.2%) patients] and by mutual decision between patient and oncologist (ie, planned discontinuation; [67 (10.3%)] patients.

TABLE 2. Treatment Characteristics of First-line Ipilimumab Plus Nivolumab Combination Therapy

Treatment characteristics	N = 709, n (%)
Received combination phase only	529 (74.6)
Received combination and maintenance phase	180 (25.4)
Combination phase	n = 529
No. courses ipilimumab received	
1	125 (23.6)
2	187 (35.3)
3	144 (27.2)
4	228 (43.1)
Unknown	5 (0.9)
No. courses nivolumab received	
1	124 (23.4)
2	184 (34.8)
3	144 (27.2)
4	228 (43.1)
Unknown	9 (1.7)
Maintenance phase	n = 180
No. courses nivolumab, median (IQR)	7 (3–15)
Stopped treatment	650 (91.7)
Reason for stopping	n = 650
Planned*	67 (10.3)
Progression	138 (21.2)
Adverse events	327 (50.3)
Patient's choice	10 (1.5)
Patient's condition	36 (5.5)
Death	35 (5.4)
Other	16 (2.5)
Unknown	11 (1.7)

Values are n (%) unless otherwise indicated.
*Voluntary treatment discontinuation after a mutual decision by the patient and oncologist.

Grade 3–4 Adverse Events

In total, 360 (50.8%) patients had grade 3–4 AEs, of whom 15.1% (107 patients) had 2 or more grade 3–4 AEs (Table S1, Supplemental Digital Content 2, http://links.lww.com/JIT/A718). The most common grade 3–4 AE were hepatitis and colitis, affecting 125 (17.6%) and 133 (18.8%) patients, respectively. Endocrine AEs that clinically presented as grade 3–4 were present in 44 (16.0%) patients; 12 (1.7%) adrenal insufficiency, 18 (2.5%) hypophysitis, and 14 (2.0%) thyroid insufficiency. Hospital admission due to AEs was necessary for 211 (29.8%) patients, admission to ICU was necessary for 12 (3.3%) patients, and 3 deaths due to AEs of ipilimumab plus nivolumab was reported.

Survival Outcomes

The median follow-up of patients treated with first-line ipilimumab plus nivolumab was 26.3 months (95% CI: 24.8–28.8), and the estimated median OS from the start of the treatment was 28.7 months (95% CI: 20.7–42.2). The 2- and 4-year OS probabilities were 51% (95% CI: 47–56) and 43% (95% CI: 38–49, respectively; Fig. 1B). Median PFS was 6.6 months (95% CI: 5.3–8.7), and the 2- and 4-year PFS probabilities were 35% (95% CI: 31–39) and 28% (95% CI: 23–33), respectively (Fig. 1A).

OS and PFS were also estimated for patient subgroups. Survival outcomes stratified for LDH- levels, brain metastases,

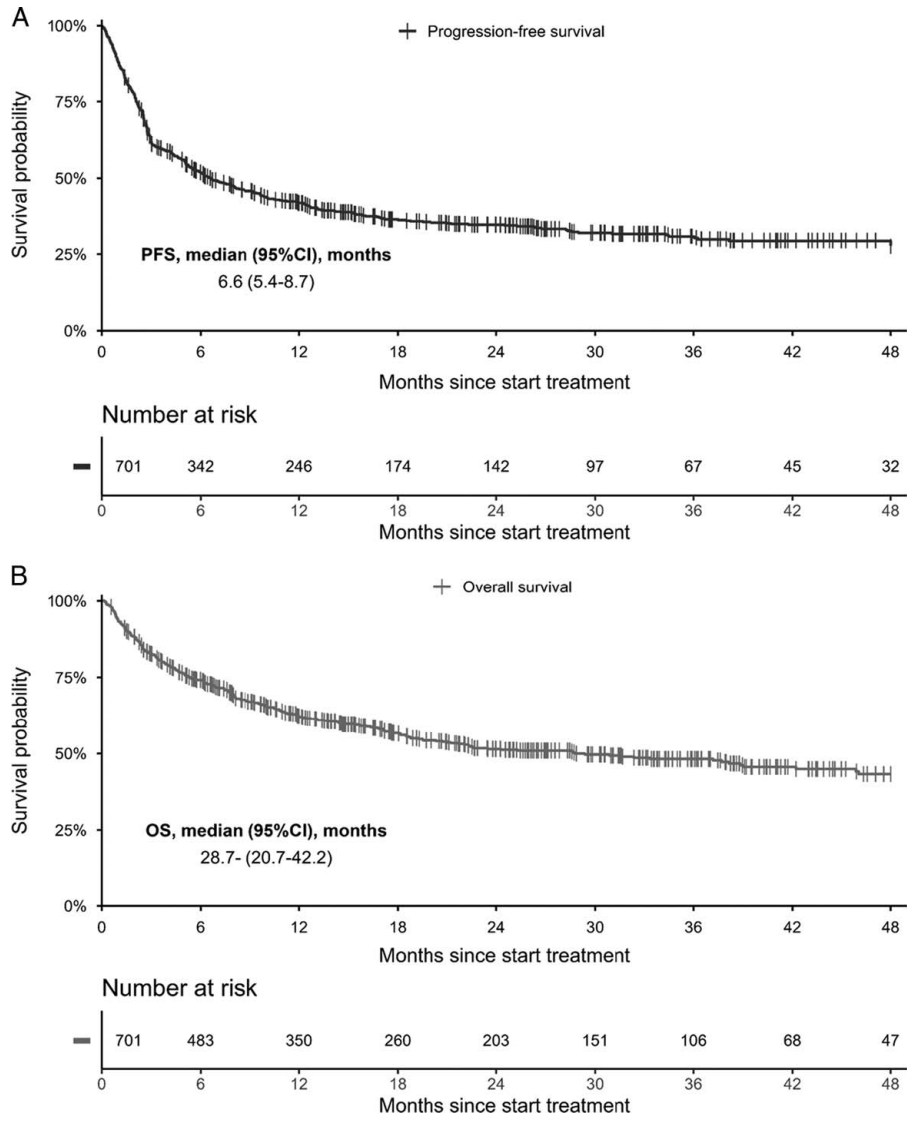

FIGURE 1. Kaplan-Meier curves of (A) progression-free survival and (B) overall survival of ipilimumab plus nivolumab in stage III or IV melanoma patients.

and BRAF mutation are shown in Figure S3-5, Supplemental Digital Content 3, http://links.lww.com/JIT/A719, Supplemental Digital Content 4, http://links.lww.com/JIT/A720, Supplemental Digital Content 5, http://links.lww.com/JIT/A721. Among patients with a normal LDH level, LDH level of 1–2× ULN or > 2 ULN, the 4-year OS probabilities were 46% (95% CI: 39–55), 45% (95% CI: 38–54), and 31% (95% CI: 23–41), respectively. The 4-year PFS probabilities of normal LDH level and LDH level of 1–2× ULN were 36% (95% CI: 31–42) and 29% (95% CI: 22–37). For LDH levels of > 2× ULN, the number of patients at risk at 4 years was too low to give a valid estimate of OS probabilities. Among patients with no, asymptomatic or symptomatic brain metastases, the 4-year OS probabilities were 48% (95% CI: 41–55), 45% (95% CI: 35–57), and 32% (95% CI: 23–46), respectively, and the 4-year PFS probabilities were 34% (95% CI: 29–41), 31% (95% CI: 22–43), and 20% (95% CI: 13–31), respectively. Of the patients with symptomatic brain metastases, 41 patients (36.9%) also received radiotherapy compared with 44 (27.0%) patients with asymptomatic brain metastases (Table 3). The majority of patients with symptomatic brain metastases received palliative radiation (52.3%), meant for pain management of metastases. Of the patients with surgery and symptomatic brain metastases, 10 patients (90.9%) received brain surgery.

The OS of patients with a BRAF-mutated melanoma was superior to that of patients with a BRAF wild-type melanoma. (Figure S5, Supplemental Digital Content 5, http://links.lww.com/JIT/A721) Second-line treatment of BRAF-mutant and BRAF wild-type patients are shown in Table S2, Supplemental Digital Content 6, http://links.lww.com/JIT/A722. In total, 300 patients (42.3%) were deemed trial-ineligible for second-line treatment mostly because of active brain metastases and a poor Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥ 2. The 4-year OS probability for trial-eligible patients was higher compared with trial-ineligible patients [50% (95% CI: 43–59) and 39% (95% CI: 32–48)], and the 4-year PFS probabilities were 34% (95% CI: 28–41) and

TABLE 3. Uni- and Multivariable Cox Regression Models for Overall Survival

	Univariable			Multivariable		
	n	**HR 95% CI**	***P***	***n***	**HR 95% CI**	***P***
Age	701	1.02 (1.00–1.03)	<0.001	595	1.01 (1.00–1.02)	0.059
Sex	—	—	—	—	—	—
Male	436	1	—	357	1	—
Female	265	0.99 (0.79–1.24)	0.961	238	1.01 (0.77–1.27)	0.903
ECOG PS	—	—	—	—	—	—
0–1	621	1	—	547	1	—
≥2	51	3.26 (2.32–4.59)	<0.001	48	2.45 (1.69–3.54)	<0.001
LDH level	—	—	—	—	—	—
Normal	356	1	—	302	1	—
1–2× ULN	222	1.42 (1.10–1.83)	0.007	190	1.46 (1.10–1.98)	0.010
>2× ULN	118	2.60 (1.97–3.44)	<0.001	103	2.38 (1.68–3.31)	<0.001
Distant metastases	—	—	—	—	—	—
<3 organ sites	313	1	—	256	1	—
≥3 organ sites	387	1.30 (1.04–1.63)	0.020	339	0.93 (0.67–1.19)	0.452
Brain metastases	—	—	—	—	—	—
Absent	356	1	—	339	1	—
Yes, asymptomatic	161	1.18 (0.89–1.56)	0.241	151	1.40 (1.03–1.89)	0.031
Yes, symptomatic	110	1.61 (1.20–2.15)	0.001	105	1.47 (1.02–2.14)	0.040
Liver metastasis	—	—	—	—	—	—
No	441	1	—	382	1	—
Yes	255	1.51 (1.21–1.88)	<0.001	213	1.32 (1.01–1.74)	0.045
BRAF-mutational status	—	—	—	—	—	—
Mutant	293	1	—	248	1	—
Wild-type	377	2.18 (1.72–2.77)	<0.001	347	1.82 (1.39–2.37)	<0.001
Corticosteroid use	—	—	—	—	—	—
No	359	1	—	305	1	—
Yes	96	1.71 (1.27–2.32)	<0.001	79	1.69 (1.11–2.56)	0.005
Missing	246	0.75 (0.58–0.96)	0.025	211	0.93 (0.70–1.23)	0.605

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

27% (95% CI: 22-32; [Figure S6, Supplemental Digital Content 7, http://links.lww.com/JIT/A723)].

In a landmark survival analysis from 9 weeks, the PFS was not significantly different for patients who stopped treatment due to grade 3–4 AEs compared with patients who did not stop treatment due to grade 3–4 AEs (the 3-year PFS probability was 38% (95% CI: 32–45) and 46% (95% CI: 39–55), respectively; Figure S7, Supplemental Digital Content 8, http://links.lww.com/JIT/A724). The OS was comparable between patients who stopped treatment due to and who did not stop treatment due to grade 3–4 AEs; the 4-year OS probabilities were 49% (95% CI: 42–57) and 50% (95% CI: 43–59), respectively (Figure S7, Supplemental Digital Content 8, http://links.lww.com/JIT/A724). We also assessed the OS of patients with a PR or CR at 3 months, who stopped due to AEs after 1–4 courses of ipilimumab plus nivolumab (Figure S8, Supplemental Digital Content 9, http://links.lww.com/JIT/A725).

Multivariable Cox Model

In the multivariable Cox regression model for OS, an ECOG PS ≥2 [Hazard ratio (HR): 2.45, (95% CI: 1.69–3.54], LDH level 1–2× ULN (HR: 1.46, 95% CI: 1.10–1.98), LDH level >2× ULN (HR: 2.38, 95% CI: 1.68–3.31), asymptomatic brain metastases (HR: 1.40, 95% CI: 1.03–1.89), symptomatic brain metastases (HR: 1.47, 95% CI: 1.02–2.14), BRAF-wild-type melanoma (HR: 1.82, 95% CI: 1.39–2.37), and corticosteroid use were associated with a higher hazard of death (Table 4).

Response Status

At the 24-month evaluation moment, 66 (12.5%) patients had achieved a CR, 123 (23.3%) a PR, and 5 (0.1%) a stable disease (SD) and 423 (62.6%) had progressive disease and/or died (Figure S2, Supplemental Digital Content 10, http://links.lww.com/JIT/A726). In the landmark survival analysis from 3 months since starting therapy (Fig. 2A), patients with a CR (n = 18) or PR (*n* = 275) at

TABLE 4. Local Treatments for Asymptomatic and Symptomatic Brain Metastases Within the First Line of Treatment

	Asymptomatic brain metastases (N = 163)	**Symptomatic brain metastases (N = 111)**
Surgery		
No	159 (97.5)	100 (90.1)
Yes	4 (2.5)	11 (9.9)
Brain surgery	1 (25.0)	10 (90.9)
Radiotherapy		
No	119 (73.0)	70 (63.1)
Yes	44 (27.0)	41 (36.9)
Type of radiotherapy		
Adjuvant (after resection)	0 (0.0)	3 (7.3)
Stereotactic	20 (45.5)	24 (58.5)
Palliative	23 (52.3)	11 (26.8)
Other	0	2 (4.9)
Missing	1 (2.3)	1 (2.4)

Palliative radiation consists of pain management of metastases. The percentage of brain surgery is calculated from the total number of patients with surgery.

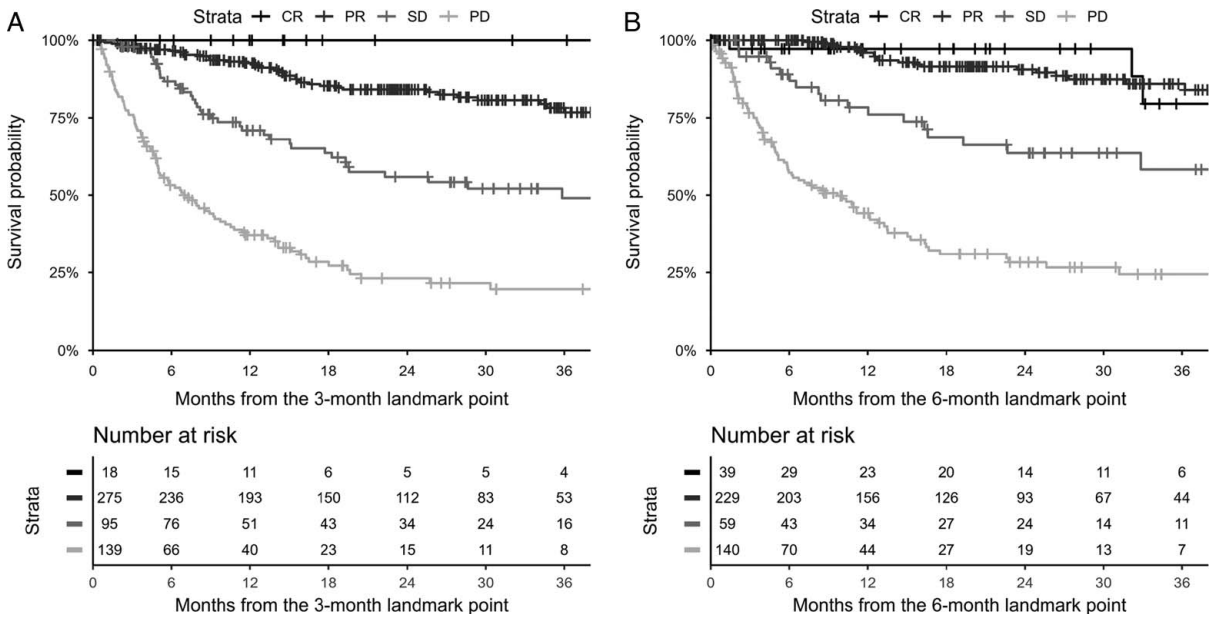

FIGURE 2. Landmark analysis of survival stratified by response status at landmark time after the start of first-line ipilimumab plus nivolumab. (A) Landmark analysis from 3 months. From the start of treatment, the 3-month OS probability was 83% (95% CI: 80–86). (B) Landmark analysis from 6 months. From the start of treatment, the 6-month survival probability was 74% (95% CI: 71–78). A total of 182 and 242 patients had died before the landmark moment, and these patients are excluded from these figures.

3 months had a 3-year OS probability since the LM of respectively 100% (95% CI: 100–100) and 77% (95% CI: 70–84). Patients with an SD (n = 95) or PD ($n = 139$) at 3 months had a 3-year OS probability of respectively 49% (95% CI: 38–63) and 20% (95% CI: 13–30). In the landmark survival analysis from 6 months (Fig. 2B), patients with a CR ($n = 39$) or PR ($n = 229$) at 6 months had a 3-year OS probability of 80% (95% CI: 60–100) and 86% (95% CI: 80–92), respectively. Patients with an SD (n = 59) or PD (n = 140) at 6 months had a 3-year OS probability of 58% (95% CI: 44–77) and 24% (95% CI: 17–36), respectively.

DISCUSSION

We report the largest observational study of ipilimumab plus nivolumab combination therapy in a nationwide population-based cohort of patients with advanced melanoma, up to now. Compared with the CheckMate-067 trial, Dutch patients in daily clinical practice were younger but more often had worse ECOG PS, stage IV-M1c disease, elevated LDH levels, and brain metastases.[5] The 4-year OS probability of first-line ipilimumab plus nivolumab in advanced melanoma was 43%. The majority of patients treated met the inclusion criteria for the CheckMate-067 trial (57%) regarding their patient and tumor characteristics.[5] The OS of these trial-eligible patients was similar to the OS in the CheckMate-067 trial (4-year OS probability of 50% vs. 53%, respectively).[5,11] Furthermore, long-term survival was also achieved in trial-ineligible patients: a 4-year OS probability of 39%.

In the real world, the use of ipilimumab plus nivolumab was safe as no new safety signals were observed, and only 3 patients died due to treatment. Nonetheless, the effect of adverse events is high, considering that almost one-third required hospital admission. Nearly all patients with grade 3-4 AEs in this real-world setting discontinued treatment, which is higher compared with the CheckMate-067 trial.[4] A clinically relevant question is whether this 'involuntary' discontinuation, and thus not receiving ipilimumab plus nivolumab as per protocol, has a negative effect on survival. Previous research suggests that survival was similar between patients who discontinued ipilimumab plus nivolumab due to AE(s) compared with patients who did not discontinue due to AE(s).[5,6] Because of the limitations of our data, we were unable to replicate this analysis, but we observed similar survival of patients who experienced grade 3–4 AE(s) and patients who did not experience AE(s) in our landmark analysis. In line with the previous study of Schadendorf et al,[6] it seems that experiencing grade 3–4 AE(s), even though this may lead to discontinuation, does not negatively affect survival outcomes.

This study presents real-world evidence that first-line ipilimumab plus nivolumab is an effective treatment option for advanced melanoma patients with brain metastases. In trials, ipilimumab plus nivolumab was found to have meaningful intracranial anti-tumor activity and even comparable intracranial and extracranial responses.[16–18] In our real-world cohort, the 4-year OS between patients with no and asymptomatic brain metastases was comparable (48% vs. 45%), but in the multivariable Cox model for survival, asymptomatic brain metastases were associated with poorer OS. Patients with symptomatic brain metastases used to have a poor prognosis. It is interesting to note that we observed a 4-year OS probability of 32%, which is similar to the 3-year OS probability found by Tawbi et al [36.6% (95% CI: 14.0–59.8)].[19] Historically, the median OS for patients with brain metastases was 3.5 months, and these results illustrate the progress that has been made that translates to the real-world setting.[20]

Patients with BRAF-mutated melanoma treated with first-line ipilimumab plus nivolumab have a superior OS compared with patients with BRAF wild-type melanoma,

despite similar PFS. Seventy-five percent of patients with BRAF-mutant melanoma received BRAF plus MEK inhibitors as a second-line treatment. In other words, part of the OS benefit of first-line ipilimumab plus nivolumab we observed was due to the sequential treatment with BRAF plus MEK inhibitors. That ipilimumab plus nivolumab followed by dabrafenib plus trametinib was superior compared with dabrafenib plus trametinib followed by ipilimumab plus nivolumab in BRAF-mutant melanoma was already shown in the DREAMseq trial.[21] Our results provide real-world evidence for the effectiveness of sequential treatment with BRAF plus MEK inhibitors upon progression after first-line ipilimumab plus nivolumab.

That the response status was evaluated using the RECIST v1.1 criteria in combination with the clinical judgment by the medical team could be seen as a limitation. Especially pseudoprogression or a continued partial response (on or off treatment) with minimal lesions that persisted on imaging, the medical team could have overruled the response status according to the RECIST v1.1 criteria. We believe that this had a limited influence, and the response status in our study reflects the effect of ipilimumab plus nivolumab in daily practice.

Factors associated with death were an ECOG PS ≥ 2, LDH level $> 1\times$ ULN, brain metastases, and/or BRAF wild-type melanoma. Patients with one or more prognostically unfavorable factors should be carefully selected for treatment. The effectiveness of ipilimumab plus nivolumab on a population level could be increased if patients with a combination of prognostically the most unfavorable factors (eg, $\geq 2\times$ LDH plus ECOG PS of ≥ 2) are excluded from treatment. The dilemma in daily clinical practice for these patients is that on an individual level, ipilimumab plus nivolumab is the most effective treatment that still can provide a survival benefit and long-term survival. Using the evidence from real-world data, these patients can be better informed about their prognosis to make a well-informed decision weighing the risks and benefits of ipilimumab plus nivolumab combination therapy.

In the real world, ipilimumab plus nivolumab is safe and achieves long-term survival in patients with advanced melanoma. First-line ipilimumab plus nivolumab is effective in asymptomatic and (to a lesser extent) symptomatic brain metastases. Patients with BRAF-mutant melanoma have superior survival that cannot be explained by differences in the efficacy of first-line ipilimumab plus nivolumab. In addition to the efficacy proven by the CheckMate-067 trial, this study demonstrates the effectiveness of ipilimumab plus nivolumab in the real world as well.

CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

A.J.M.vd.E. has advisory relationships with Amgen, Bristol-Myers Squibb, Roche, Novartis, MSD, and Pierre Fabre. J.W.B.dG. has received personal fees outside the submitted work from Bristol-Myers Squibb, Roche, Pierre Fabre, Servier, MSD, and Novartis. G.A.P.H. 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, Seerave. E.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, Pierre Fabre, and Bristol-Myers Squibb. K.P.M.S. has advisory relationships with Bristol-Myers Squibb, Roche, Novartis, MSD, and Pierre Fabre. A.vd.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, Neon Therapeutics. The remaining authors have no conflicts to disclose.

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