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Ipilimumab in a real-world population: A prospective Phase IV trial with long-term follow-up

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Abstract

Ipilimumab was the first treatment that improved survival in advanced melanoma. Efficacy and toxicity in a real-world setting may differ from clinical trials, due to more liberal eligibility criteria and less intensive monitoring. Moreover, high costs and lack of biomarkers have raised cost-benefit concerns about ipilimumab in national healthcare systems and limited its use. Here, we report the prospective, interventional study, Ipi4 (NCT02068196), which aimed to investigate the toxicity and efficacy of ipilimumab in a real-world population with advanced melanoma. This national, multicentre, phase IV trial included 151 patients. Patients received ipilimumab 3 mg/kg intravenously and were followed for at least 5 years or until death. Treatment interruption or cessation occurred in 38%, most frequently due to disease progression (19%). Treatment-associated grade 3 to 4 toxicity was observed in 28% of patients, and immune-related toxicity in 56%. The overall response rate was 9%. Median overall survival was 12.1 months (95% CI: 8.3-15.9); and progression-free survival 2.7 months (95% CI: 2.6-2.8). After 5 years, 20% of patients were alive. In a landmark analysis from 6 months, improved survival was associated with objective response (HR 0.16, $P = .001$) and stable disease (HR 0.49, $P = .005$) compared to progressive disease. Poor performance status, elevated lactate dehydrogenase and C-reactive protein were identified as biomarkers. This prospective trial represents the longest reported follow-up of a real-world melanoma population treated with ipilimumab. Results indicate safety and efficacy comparable to phase III

Abbreviations: AE, adverse event; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CI, confidence intervals; CR, complete response; CRP, C-reactive protein; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte antigen-4; EAP, expanded access programme; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; LDH, lactate dehydrogenase; NLR, neutrophil lymphocyte ratio; OS, overall survival; PD, progressive disease; PD-1, antiprogrammed cell death protein-1; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SAE, serious adverse event; SD, stable disease; WBC, white blood cells.

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trials and suggest that the use of ipilimumab can be based on current cost-benefit estimates.

KEYWORDS
ipilimumab, phase IV trial, real-world, safety, stage IV melanoma

What's new?

A common concern with expensive, targeted therapies is: will patients in real-world practice benefit to the same extent as patients enrolled in carefully designed clinical trials? In this prospective, long-term study, the authors asked that question regarding ipilimumab in the treatment of metastatic melanoma. They found that toxicity and efficacy were comparable to clinical trials. These results suggest that the use of ipilimumab can therefore be based on current cost-benefit estimates. The study also found that CRP, LDH, and performance status predicted survival, which may help to identify patients benefitting from ipilimumab.

1 | INTRODUCTION

Ipilimumab is a monoclonal antibody blocking cytotoxic T-lymphocyte antigen-4 (CTLA-4) from binding to its ligands on antigen-presenting cells[1] and was the first immune checkpoint inhibitor (ICI) to improve survival in cancer patients in a randomised trial.[2] Median overall survival (OS) in clinical trials ranges 10.1 to 19.9 months,[2-5] with 20% to 30% of patients obtaining long-term survival,[3,6,7] a rare encounter before the introduction of ICIs. Currently, first line treatment with ICIs or combined BRAF and MEK inhibitors are the standard of care in metastatic melanoma.[8]

With the introduction of ICIs, new clinical challenges emerged. First, a new spectrum of toxicity, known as immune-related adverse events (irAEs), was observed, requiring careful monitoring and prompt intervention such as immunosuppression.[9] Second, clinical and radiological responses could be slow-onset and even mimic progression, followed by a decrease in tumour size, a much debated phenomenon known as pseudoprogression.[10] Third, as illustrated by a median progression-free survival (PFS) of approximately 3 months,[2,11,12] most patients do not respond to treatment, but are still at risk of potentially harmful side effects. No biomarker has yet been discovered to reliably predict treatment benefit,[13] but baseline clinical features such as poor performance status and extensive organ involvement as well as elevated lactate dehydrogenase (LDH) are associated with poor survival in patients receiving ipilimumab.[14-20] Moreover, a prognostic index involving these characteristics was found to significantly predict OS.[21] Elevated C-reactive protein (CRP) has previously been related to worse clinical outcome in patients treated with ipilimumab.[22,23] Other biomarkers available from routine blood analyses suggested to be associated with an improved prognosis in patients receiving ICIs include a low total white blood cell count (WBC), low absolute neutrophil count (ANC), high absolute lymphocyte count (ALC) and low neutrophil lymphocyte ratio (NLR).[19,24]

Additionally, the cost of ipilimumab, when opening the markets postapproval, was perceived a substantial economic burden to the health care system, with an estimated cost-effectiveness of €100 112 per life-year gained.[25] Using drugs in daily clinical practice, there is a concern that efficacy may be decreased and toxicity increased compared to clinical trials due to less stringent eligibility criteria and less intensive monitoring. A number of reports on real-world data from expanded access, named patient and compassionate-use programmes exist,[15-18,22,26-31] but are restrained by factors such as retrospective study design, patient selection, single centre experiences and/or limited follow-up.

Thus, this national prospective phase IV trial addresses the use of ipilimumab in a real-world population with metastatic melanoma, investigating toxicity and long-term efficacy assessed by clinical oncologists in out-patient departments throughout Norway.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a prospective, national, multicentre, open label, single-armed, phase IV interventional clinical trial (NCT02068196). The primary objective was to estimate the incidence and severity of adverse events (AEs) in patients with metastatic melanoma treated with ipilimumab in a real-world setting, and to describe the management and outcome of AEs. Secondary objectives were to assess OS, PFS, overall response rate and duration of response.

The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki (1964) and the International Conference on Harmonization of Good Clinical Practice and approved by an independent ethics committee and the appropriate national and institutional review boards.

2.2 | Patients

Patients ≥18 years of age with a histologically confirmed diagnosis of unresectable Stage III/IV metastatic melanoma, Eastern Cooperative

Oncology Group performance status (ECOG PS) 0-1 and an adequate renal, hepatic and haematological function were recruited from eight sites throughout Norway. Patients were classified according to the American Joint Committee on Cancer version 8. Any previous treatment was allowed. Patients with active brain metastases that required other treatment were not permitted, but patients with known brain metastases that were previously treated, or considered not in need of radiotherapy or surgery, were allowed. No screening for brain metastases was conducted to identify the presence of asymptomatic brain involvement. Patients with a history of autoimmune disease, immunodeficiency, splenic surgery or irradiation, allogeneic stem cell transplantation, known hypersensitivity to recombinant protein products, uncontrolled infectious disease, pregnant or breastfeeding were excluded. All patients provided written informed consent. The intention-to-treat population equalled the safety population and was defined as all patients that received a dose of ipilimumab.

2.3 | Treatment

Ipilimumab 3 mg/kg intravenously was administered every 3 weeks for a total of four doses. Patients that had obtained objective response or stable disease for ≥3 months beginning week 12 and with subsequently documented progression according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1,[32] who had not previously discontinued ipilimumab for any reason, were eligible for retreatment given an adequate performance status, renal, hepatic and haematological function.

2.4 | Study assessments

Safety was assessed by physical examination and blood analyses at each treatment visit. AEs were recorded in coherence with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Serious adverse events (SAEs) were defined according to Good Clinical Practice Guidelines. Subjects were followed for AEs for a minimum of 90 days after the last dose of ipilimumab. After 90 days, only ipilimumab-related AEs were recorded. An irAE was defined as an adverse event that was associated with the study drug and was consistent with an immune phenomenon.Computed tomography (CT) was conducted at baseline, week 12, 16 and 24 after the first dose of ipilimumab, and then every 3 months until disease progression. Tumour response was evaluated using RECIST 1.1.[32]

2.5 | Statistics

Survival analyses were conducted using Kaplan-Meier estimates and univariate and multivariate Cox proportional hazard modelling, and were reported as hazard ratios (HR) with 95% confidence

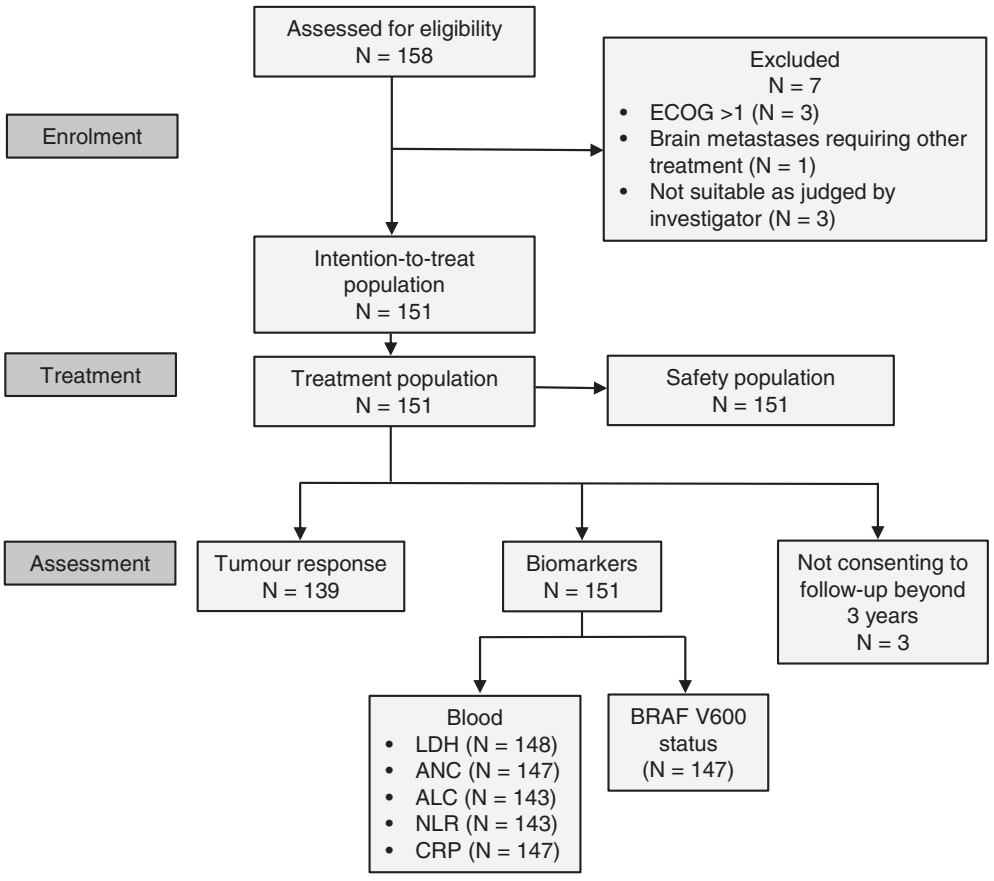


FIGURE 1 Consort diagram. Overview of trial population eligible for treatment and assessments. The intention-to-treat population included all patients enrolled in the trial. All enrolled patients received at least one dose of ipilimumab

intervals (CI). OS was defined as time from treatment initiation to death, and PFS as time from treatment initiation to objective tumour progression or death. Patients were followed for at least 5 years or until death. Three patients did not consent to follow-up for more than 3 years and were then treated as censored. Patients without an event were treated as censored June 1, 2020.

The assumption of proportionality was checked by visual inspection of log-log plots. The association between irAEs and baseline characteristics was assessed by chi-square test, using Pearson's chi-square test or the chi-square test for trend as appropriate. Statistical analyses were performed in IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

3 | RESULTS

3.1 | Patient characteristics

A total of 151 patients were included from January 2014 to March 2015 (Figure 1). Baseline characteristics are presented in Table 1. The majority of patients were ECOG PS 0 and had visceral metastases. Known brain involvement, not requiring other treatment at the time of inclusion, was present in 9% of patients. LDH was elevated in 42% of patients. *BRAF*^{V600} mutation was identified in 48% of patients. Approximately two thirds of patients (66%) were treatment-naïve. Prior therapy comprised chemotherapy (17%), BRAF and MEK inhibitors (21%), ipilimumab (4%) and other medical treatments including interferon, bevacizumab, isolated limb perfusion and isolated liver perfusion (3%).

TABLE 1 Patient baseline characteristics (N = 151)

Age, years		
Median (range)	63	(27-84)
Sex, N (%)		
Female	55	(36)
Male	96	(64)
ECOG PS,[a] N (%)		
0	110	(73)
1	37	(25)
≥2	3	(2)
M-stage, N (%)		
M1a[b]	15	(10)
M1b	26	(17)
M1c	97	(64)
M1d	13	(9)
BRAF status,[c,d] N (%)		
Mutated	72	(48)
Wild type	75	(50)
LDH,[e] N (%)		
≤ULN	85	(56)
>ULN	63	(42)
Prior therapy,[f] N (%)		
Chemotherapy	25	(17)
BRAF+/− MEK inhibitors	32	(21)
Ipilimumab	6	(4)
Other[g]	5	(3)
Prior lines of therapy, N (%)		
0	100	(66)
1	36	(24)
≥2	15	(10)

Abbreviations: ECOG PS, Eastern Co-operation Oncology Group performance status; LDH, lactate dehydrogenase; M-stage, metastatic stage according to TNM vs 8; ULN, upper limit normal at cut-off 205 U/L.
[a]One patient not available.
[b]Including 1 M0 in M1a.
[c]*BRAF*^{V600} genotype.
[d]Four patients not available.
[e]Three patients not available.
[f]Systemic treatments.
[g]Interferon, bevacizumab, isolated limb perfusion, isolated liver perfusion.

3.2 | Treatment and toxicity

The safety population included all patients that had received at least one dose of ipilimumab (N = 151). Treatment is summarised in Figure 2A. Treatment cessation was observed in 32% of patients and was caused by disease progression in 19% of patients and drug-related toxicity in 13%. In 3% of patients, treatment was interrupted due to treatment-related toxicity and later resumed. All but one patient developed immune-related toxicity after resuming ipilimumab.

Treatment-associated AEs were reported in 73% of patients, and are summarised in Table 2. Grade 3 to 5 AEs were reported in 28% of patients, while 44% reported low-grade toxicity only. Pruritus, rash, diarrhoea, fatigue, infection, nausea and abdominal pain were the most commonly reported grade 1 to 2 AEs. Hypophysitis, diarrhoea, colitis, infection and rash were the most frequently reported grade 3 to 4 AEs. Treatment-associated SAEs were recorded in 34% of patients. No excess toxicity was found in patients after retreatment. Three deaths (2%) were reported by investigators. One death was due to perforated colitis and was considered definitely related. Two deaths were reported as unlikely related to ipilimumab and were not associated with irAEs. One patient with a history of cardiovascular disease died of an intracranial haemorrhage following a cerebrovascular event after the third dose of ipilimumab, and a patient with known cardiovascular disease died of heart failure following the surgical removal of a peripheral arterial embolus 1 month after the first dose of ipilimumab.

The median time from treatment initiation to the first treatment-associated AE was 25 days (range, 0-173) with a median duration of 10.5 days. Figure 2B depicts time to onset of irAEs. Seventeen patients experienced irAEs more than 100 days after treatment initiation, including diarrhoea, colitis, rash, myositis, hypophysitis and

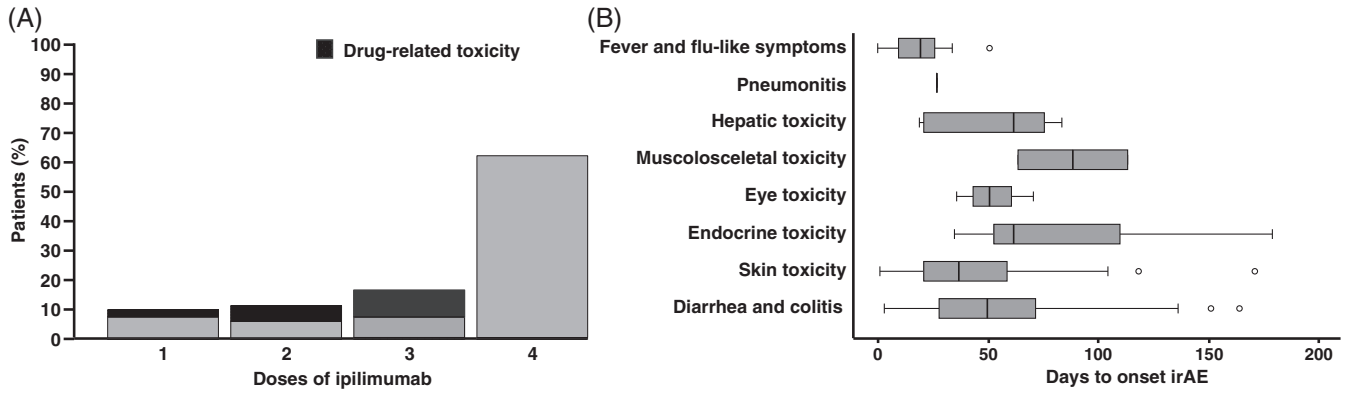


FIGURE 2 Drug-related toxicity and onset of immune-related adverse events (irAEs). (A) Overview of treatment and of toxicity-related treatment interruption and cessation (N = 151). 62% of patients (N = 94) received all four doses of ipilimumab, 17% (N = 25) received three doses, 11% (N = 17) received two doses and 10% (N = 15) received one dose. Drug-related toxicity was the cause of treatment cessation in 20% of patients (N = 3) receiving one dose, 44% (N = 7) of patients receiving two doses and 56% (N = 10) of patients receiving three doses. In 3% of patients (N = 5), ipilimumab was interrupted due to drug-related toxicity and later resumed; four patients received three doses in total and one patient received two doses. Four out of five patients developed irAEs after resuming ipilimumab. In 2% of patients (N = 3), treatment was interrupted due to hospital admissions that were not considered treatment-related, and ipilimumab was later resumed. (B) Box plot showing time to onset irAEs in days from treatment initiation. Boxes depict 25%-75% with whiskers indicating minimum and maximum excluding outliers. 56% of patients (N = 84) experienced irAEs. Median time to onset hepatic toxicity was 62 days (range, 19-84). Median time to onset fever and flu-like symptoms was 19.5 days (range, 0-51). One pneumonitis was reported starting at 27 days after treatment initiation. Median time to onset musculoskeletal toxicity was 89 days (range, 64-114). Median time to onset eye toxicity was 51 days (range, 36-71). Median time to onset endocrine toxicity was 62 days (range, 35-180). Median time to onset skin toxicity was 37 days (range, 1-172). Median time to onset diarrhoea and colitis was 50 days (range, 3-165). An irAE was defined as an adverse event that was associated with exposure to the study drug, and that was consistent with an immune phenomenon. Some patients reported multiple irAEs

hypothyroidism. Hypophysitis was the only grade 3 to 4 AE reported as lasting more than 100 days.

Medical treatment of AEs was prescribed to 67% of patients, including 28% of patients that received systemic corticosteroids. The most common indications for prescribing systemic corticosteroids were diarrhoea and colitis, followed by hypophysitis and skin-related toxicity. Additionally, corticosteroids were administered systemically to 13% of patients. Four patients were prescribed corticosteroids due to symptomatic worsening of known brain metastases, and seven patients with previously undetected brain involvement developed symptomatic brain metastases requiring corticosteroids. Other indications for corticosteroids were liver metastases, dyspnoea, nausea and anorexia. Three patients received other immunosuppressive drugs due to insufficient effects of corticosteroids; two patients with colitis received infliximab, and one patient with hepatitis received sirolimus and mycophenolate mofetil.

Brain involvement was associated with a lower incidence of irAEs within the first 3 months (M1d 15% vs M1a 67%, M1b 54% and M1c 53%, $P = .041$). We did not identify baseline characteristics that significantly predisposed to treatment toxicity.

3.3 | Clinical response

In the intention-to-treat population, three patients (2%) achieved a complete response (CR), 11 (7%) partial response (PR), 39 (26%) stable disease (SD) and 86 (57%) progressive disease (PD) as best overall response. All, but one response were confirmed by at least one additional CT scan at a later point in time. This patient had a PR at week 12, but due to contrast allergy later CTs were conducted without IV contrast. Twelve patients (8%) who were considered nonevaluable according to RECIST 1.1 either progressed clinically or died before evaluation and must therefore be considered early progressors. Thus, the overall response rate was 9% and the disease control rate 35%. No cases of pseudoprogression were identified. Median time to response was 3.2 months (range, 2.5-14.3), and median duration of response 20.8 months (range, 0.9-not reached).

Three patients received retreatment with ipilimumab per protocol. Following retreatment, one patient who had previously achieved PR regained PR, one patient who initially had obtained SD regained SD, and the third patient who had experienced SD progressed.

3.4 | Survival

The median follow-up was 68.1 months in patients alive at censoring (range, 0.6-75.8 months). The median PFS was 2.7 months (95% CI: 2.6-2.8), and the median OS was 12.1 months (95% CI: 8.3-15.9) (Figure 3). Five-years OS was 20%.

Subgroup analyses of OS according to clinical baseline characteristics are shown in Supplementary Figure 1. In univariate analysis, the patient characteristics most strongly associated with inferior OS were male sex (HR 1.53, 95% CI: 1.04-2.26, $P = .032$), ECOG PS ≥1 (HR 1.76, 95% CI: 1.18-2.62, $P = .006$) and ≥3 organs involved (HR 1.76,

TABLE 2 Adverse events in the safety population (N = 151)

	Total		Grade 3-4	
Adverse events[a]	**N**	**(%)**	**N**	**(%)**
Any associated event	110	(73)	43	(28)
Any immune-related event[b]	84	(56)	31	(21)
Gastrointestinal disorders				
Diarrhoea	34	(23)	8	(5)
Colitis	7	(5)	7	(5)
Intestinal perforation[c]	3	(2)	3	(2)
Abdominal pain	11	(7)	1	(1)
Constipation	6	(4)	0	(0)
Nausea	12	(8)	0	(0)
Vomiting	6	(4)	1	(1)
Skin and subcutaneous tissues disorders				
Pruritus	17	(11)	0	(0)
Rash	38	(25)	4	(3)
Alopecia	1	(1)	0	(0)
Endocrine disorders				
Hypothyroidism	3	(2)	1	(1)
Increase in serum TSH level	1	(1)	0	(0)
Hypophysitis	9	(6)	8	(5)
Hepatobiliary disorders				
Hepatitis	4	(3)	2	(1)
Increased transaminases	3	(2)	0	(0)
Respiratory disorders				
Pneumonitis	1	(1)	0	(0)
Cough	3	(2)	0	(0)
Eye disorders				
Uveitis	1	(1)	0	(0)
Conjunctivitis and dry eyes	4	(3)	0	(0)
Musculoskeletal disorders				
Myositis	1	(1)	1	(1)
Muscle weakness	1	(1)	0	(0)
Nervous system disorders				
Headache	5	(3)	0	(0)
Dizziness	6	(4)	2	(1)
Other				
Fatigue	18	(12)	2	(1)
Anorexia	8	(5)	2	(1)
Pyrexia	6	(4)	0	(0)
Flulike symptoms	3	(2)	0	(0)
Infection	17	(11)	6	(4)
Infusion reaction	1	(1)	0	(0)
Hypokalaemia	6	(4)	0	(0)

[a]Adverse events by patient. The most common adverse events reported by investigators as related are listed. Some patients reported multiple adverse events.
[b]An immune-related adverse event was defined as an adverse event that was associated with exposure to the study drug, and that was consistent with an immune phenomenon.
[c]One patient died due to perforated colitis.

95% CI: 1.23-2.52, $P = .002$) (Table 3). For metastatic stage, and $BRAF^{V600}$ status, no statistically significant association with OS was observed. No significant difference in OS was observed between pretreated patients vs treatment-naïve patients (HR 0.77, 95% CI: 0.52-1.14, $P = .193$). In $BRAF^{V600}$ mutated patients, OS was independent of prior BRAF inhibitors vs none (HR 0.92, 95% CI: 0.54-1.57, $P = .769$). Nonetheless, patients who previously received chemotherapy had a significantly lower risk of death than those who did not receive prior chemotherapy (HR 0.58, 95% CI: 0.34-0.98, $P = .040$), with patients receiving prior chemotherapy living for a median of 20.5 months (95% CI: 0.0-54.0), vs patients not receiving prior chemotherapy living for 10.3 months (95% CI: 6.6-13.9). In subset analyses, no significant difference in PFS was identified apart from prior chemotherapy predicting longer PFS compared to no prior chemotherapy (HR 0.59, 95% CI: 0.37-0.93, $P = .022$). In patients receiving chemotherapy, median PFS was 4.0 months (95% CI: 0.2-7.8) vs 2.7 months (95% CI: 2.5-2.8) in patients that received no prior chemotherapy.

Baseline biomarkers identified as significantly related to a worse OS in univariate analyses were LDH > ULN (205 U/L) (HR 2.29, 95% CI: 1.58-3.30, $P < .001$), CRP ≥ 10 mg/L (HR 2.06, 95% CI: 1.42-2.99, $P < .001$) and white blood cells $>10 \times 10^9$/L (HR 1.89, 95% CI: 1.17-3.07, $P = .010$). In multivariate analysis, ECOG PS ≥ 1 (HR 1.98, 95% CI: 1.29-3.03, $P = .002$), LDH > ULN (HR 2.06, 95% CI: 1.38-3.07, $P < .001$) and CRP ≥10 mg/L (HR 1.58, 95% CI: 1.06-2.35, $P = .025$) were statistically significantly associated with a worse OS (Table 3).

Clinical efficacy is outlined in Figure 4A. Landmark OS from 6 months after treatment initiation, when patients were expected to have obtained their best overall response, confirmed an improved OS in responders (median not reached) as compared to patients obtaining SD (30.6 months, 95% CI: 8.6-52.7) and PD (7.5 months, 95% CI: 4.7-10.2) as best overall response (Figure 4B). The risk of death was significantly reduced in patients having achieved an objective response (HR 0.16, 95% CI: 0.06-0.45, $P = .001$), at a higher level than patients obtaining SD (HR 0.49, 95% CI: 0.30-0.81, $P = .005$), when compared to patients that progressed. The three patients that achieved CR had not progressed and were all alive at censoring.

In a landmark analysis, grade 3 to 4 irAEs within 3 months after treatment initiation was associated with a worse OS (HR 0.50, 95% CI: 0.30-0.83, $P = .007$) (Supplementary Figure 2). However, irAEs of all grades appeared not to be associated with OS (HR 0.71, 95% CI: 0.47-1.08, $P = .113$).

We applied the prognostic index published by Diem et al,[21] based on ECOG PS, organ involvement and LDH (Supplementary Figure 3). In our data set, ≥2 risk factors were significantly associated with a worse OS compared to no risk factors (HR 3.47, 95% CI: 2.11-5.69, $P < .001$), but no significant difference was observed between one risk factor and none (HR 1.37, 95% CI: 0.84-2.23, $P = .209$). When applying the prognostic index to PFS, there was a statistically significantly increased risk of disease progression with one risk factor (HR 1.81, 95% CI: 1.18-2.78, $P = .007$) and ≥2 risk factors (HR 2.22, 95% CI: 1.42-3.46, $P < .001$) vs none.

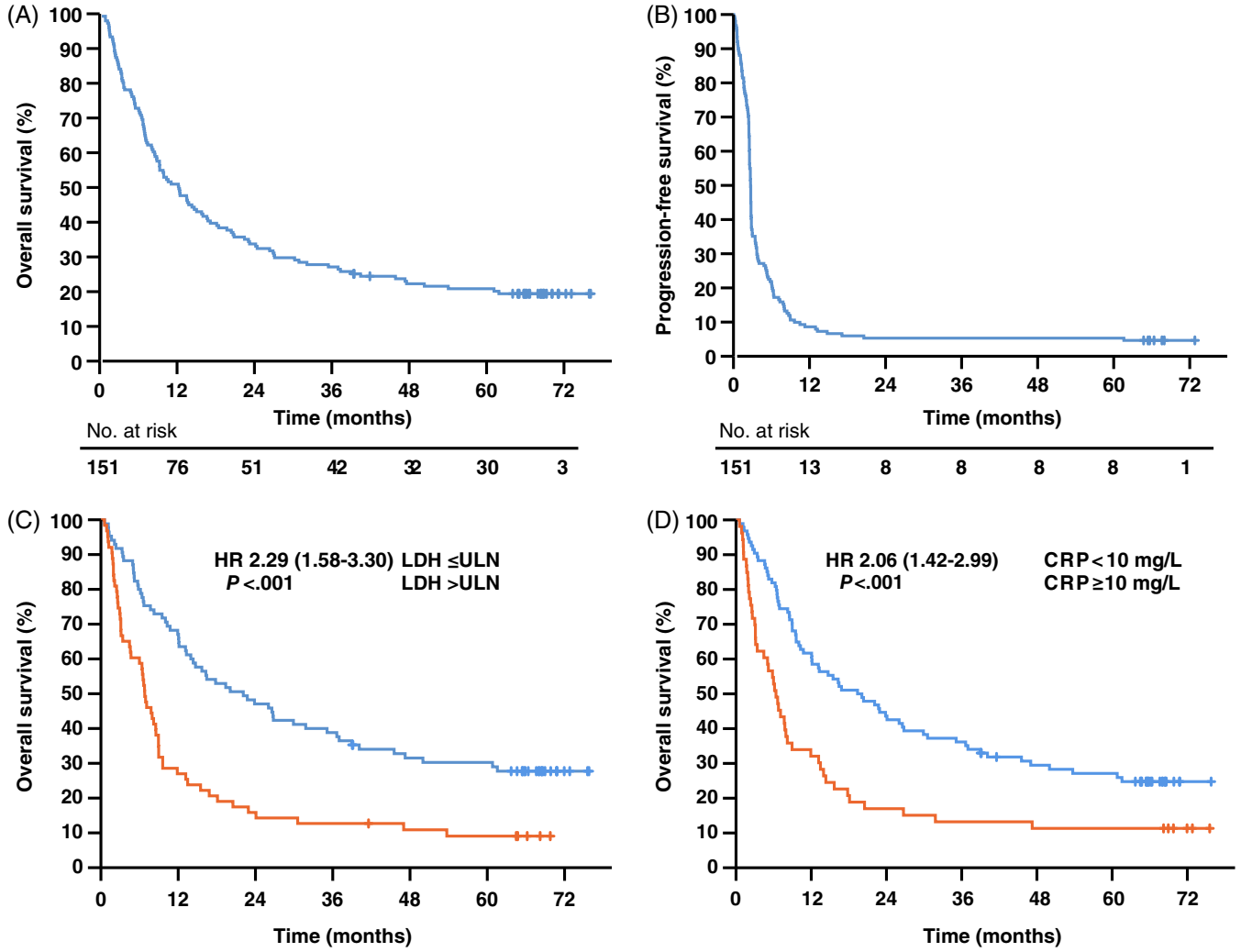


FIGURE 3 Kaplan-Meier curves for survival. (A) Progression-free survival (PFS). Median PFS was 2.7 months (95% CI: 2.6-2.8). Seven patients had not progressed at data censoring. (B) Overall survival (OS). Median OS was 12.1 months (95% CI: 8.3-15.9). 50% of patients were alive at 1 year, 34% at 2 years, 28% at 3 years and 20% at 5 years. (C) OS by baseline LDH. In patients with LDH > ULN (205 U/L) (N = 63), median OS was 6.8 months (95% CI: 5.3-8.3), and in patients with LDH ≤ ULN (N = 85) median OS was 22.1 months (95% CI: 11.8-32.4). (D) OS by CRP at baseline. Median OS was 6.4 months (95% CI: 4.4-8.3) in patients with CRP ≥ 10 mg/L (N = 53) and 19.4 months (95% CI: 11.6-27.2) in patients with CRP < 10 mg/L (N = 94)

4 | DISCUSSION

The prospective data reported herein represents the longest published follow-up of a real-world population with metastatic melanoma treated with ipilimumab. Overall baseline characteristics reflect a trial population representative of patients with Stage IV melanoma[15,16,18,27,29,30]; suggesting our results may be of use in patients treated with ipilimumab in everyday clinical practice.

The UK ipilimumab expanded access programme illustrated the fact that real-world patients may differ from study populations as only 111 of 193 patients matched the registrational trial inclusion criteria.[16] Patients who met these criteria lived longer than those who did not. Thus, phase IV trials are important tools in postregistrational analyses, evaluating drug efficacy and safety in real-world treatment populations. Participating in a clinical trial involves more close monitoring, and therefore increases the likelihood of detecting toxicity at an earlier point in time. Hence, there is a concern that patients in daily clinical practice may develop more severe toxicity. This would also increase the costs. A study on the real-world use of ipilimumab in second line reported increased rates of hospitalisation compared to historical controls receiving other second line treatments.[33] In this trial, however, the overall toxicity is in line with phase III trials reporting on ipilimumab in metastatic melanoma, with diarrhoea, rash, pruritus, fatigue and nausea being the most commonly reported AEs.[2,11,12] Safety reports from published real-world data do not contradict our findings,[15,16,18,28-30] but the majority of these reports are challenged by retrospective data collection, and hence, associated with a reporting bias.

Colitis is one of the most serious side effects of ipilimumab, and was observed at rate comparable to phase III trials.[2,11,12] Treatment-

TABLE 3 Estimated associations between patient characteristics and overall survival

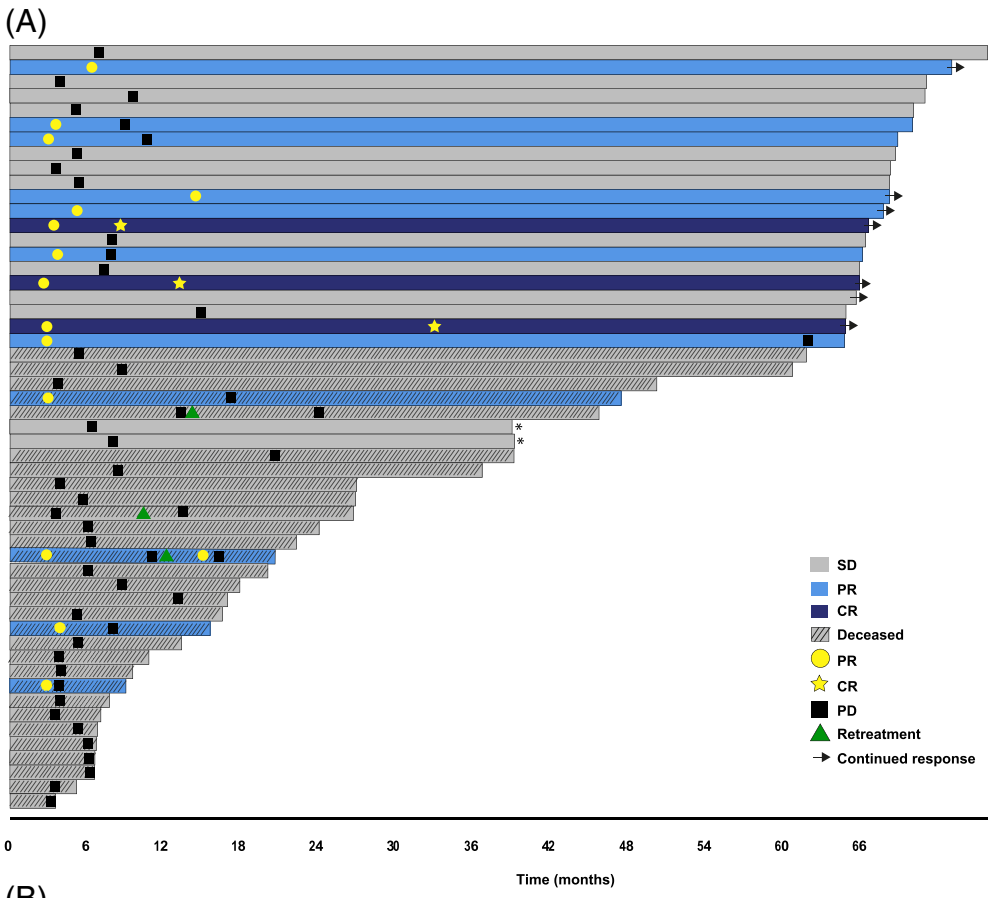
	Univariate (N = 151)			Multivariate (N = 136)		
	HR	(95% CI)	P	HR	(95% CI)	P
Male vs female	1.53	(1.04-2.26)	.032	1.33	(0.88-2.00)	.172
ECOG PS ≥ 1 vs 0[a]	1.76	(1.18-2.62)	.006	1.98	(1.29-3.03)	.002
M1a[b] vs M1c	0.52	(0.26-1.03)	.060	0.91	(0.43-1.92)	.797
M1b vs M1c	0.62	(0.37-1.03)	.066	0.85	(0.49-1.46)	.545
M1d vs M1c	1.02	(0.53-1.98)	.943	0.87	(0.43-1.77)	.698
NOI ≥ 3 vs <3	1.76	(1.23-2.52)	.002	1.31	(0.85-2.00)	.221
BRAF mutation vs WT[c,d]	0.88	(0.61-1.27)	.488			
Prior therapy vs none	0.77	(0.52-1.14)	.193			
LDH > ULN vs ≤ULN[e]	2.29	(1.58-3.30)	<.001	2.06	(1.38-3.07)	<.001
CRP ≥ 10 vs <10[d]	2.06	(1.42-2.99)	<.001	1.58	(1.06-2.35)	.025
WBC > ULN vs ≤ULN	1.89	(1.17-3.07)	.010			
ANC > ULN vs ≤ULN[d]	1.34	(0.78-2.30)	.293			
ALC < ULN vs ≥ULN[f]	1.10	(0.72-1.70)	.661			
NLR ≥ 5 vs <5[f]	1.34	(0.87-2.07)	.181			

Note: Patients with missing data were excluded from analysis.
Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperation Oncology Group performance status; NOI, number of organs involved; WT, wild type; ULN, upper limit normal; LDH, lactate dehydrogenase cut-off 205 U/L; CRP, C-reactive protein cut-off 10 mg/L; WBC, white blood cells cut-off 10×10^9/L; ANC, absolute neutrophil count cut-off 7.3×10^9/L; ALC, absolute lymphocyte count cut-off 1.1×10^9/L; NLR, neutrophil lymphocyte ratio.
[a]One patient not available.
[b]One patient with M0 included in M1a.
[c]$BRAF^{V600}$ genotype.
[d]Four patients not available.
[e]Three patients not available.
[f]Eight patients not available.

associated deaths are at the same rate as previously reported,[2,11,12,16] and management largely adhering to applicable guidelines at the time, supporting the use of ipilimumab in a real-life setting.

Infection is not a recognised consequence of ICIs, but was reported as treatment-associated in 17 patients (11%) in this trial. Six patients experienced lower respiratory tract infections, four upper respiratory tract infections, two enteritis, one urinary tract infection and four unspecific infections. The majority were reported as unlikely related. Infections are common in advanced cancer, and may rather reflect that this trial represented the first experience with immunotherapy for many clinicians, thus, constituting a reporting bias. Notably, a retrospective report on 740 melanoma patients receiving ICIs, of which the majority received ipilimumab, found that 7.3% of patients developed serious infections.[34] Immunosuppression with corticosteroids or infliximab to treat ICI-induced irAEs was identified as the main risk factor for developing serious infection,[34] supported by a study on melanoma patients developing diarrhoea and colitis from ICIs.[35] In the Ipi4 trial, 10 out of 17 patients with reported associated infections received corticosteroids on study, and were, thus, more susceptible to opportunistic infections. Hence, infections observed in this trial may at least partly be a consequence of immunosuppression of irAEs rather than directly linked to ipilimumab. Additionally, other comorbidity predisposing to infections, such as diabetes mellitus, has been identified as increasing the risk of developing infections secondary to ICIs.[36]

It has been hypothesised that irAEs may be associated with the efficacy of ipilimumab, based on the assumption that increased immune activity may affect both tumour and normal tissues,[37] but it has not been clarified whether such an association exists. In this population, no significant association was observed between an irAE of any grade and OS. High-grade irAEs were, however, significantly associated with a shorter OS despite only one death being attributed to immune-related toxicity. To our knowledge, high-grade irAEs have not previously been related to poor OS. Some previous reports have suggested that irAEs predict a favourable clinical outcome,[15,28,37,38] but the literature is diverging as an analysis of the pivotal phase III trial found no significant association between irAEs and treatment benefit.[39] A meta-analysis studying the association between irAEs and outcomes of ICIs highlighted the use of inappropriate methodology, as the majority of studies failed to recognise irAEs as a time-dependent variable.[40] Thus, it has not been taken into account that patients that are followed for a longer time have an increased risk of experiencing irAEs. Further, these patients may have had greater treatment exposure and are therefore both more likely to obtain a clinical benefit and develop irAEs. Patients that die or exit the study due to progressive disease, on the other hand, may not have had time to develop irAEs.



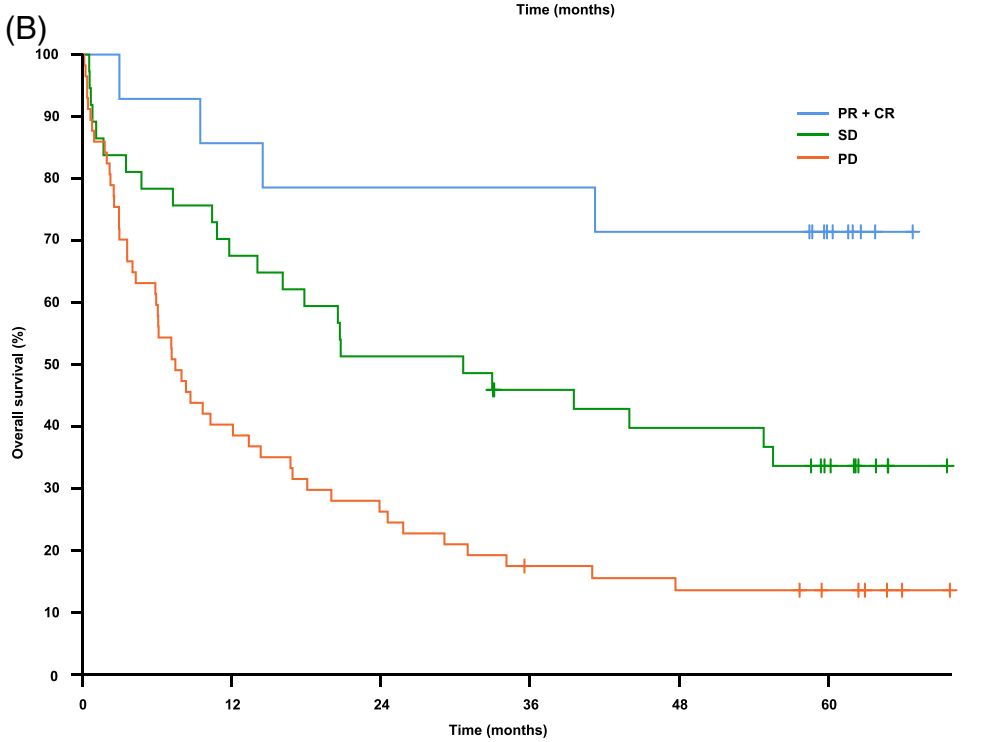


FIGURE 4 Clinical efficacy in patients. (A) Swimmer plot illustrating efficacy assessment in selected patients obtaining complete response (dark blue; N = 3), partial response (light blue; N = 11) and disease stabilisation (grey; N = 39) as best overall response according to RECIST 1.1. Patients are depicted as individual bars, illustrating duration of overall survival (OS) in months. Shaded bar implies patient is deceased. Responses and new systemic treatments are indicated by designated symbols. Most patients had obtained best overall response within 6 months, excluding one patient that developed a partial response at 14.3 months after treatment initiation, and the three patients achieving complete responses at 8.0 to 33.7 months, preceded by partial responses. At data censoring, seven patients had continued responses. *Patients were censored due to loss of follow-up. (B) Kaplan-Meier curves for landmark analysis of OS from 6 months after treatment initiation by response to treatment according to RECIST 1.1. (N = 108). Median OS in patients responding to treatment (partial or complete, N = 14) was not reached at data censoring. In patients obtaining stable disease (N = 37), median OS was 30.6 months (95% CI: 8.6-52.7). In patients experiencing progressive disease as best overall response (N = 57), median OS was 7.5 months (95% CI: 4.7-10.2). Patients that were not alive at 6 months after treatment initiation (N = 43) were excluded from analyses, of which two patients obtained stable disease and 30 patients progressive disease as best overall response. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

This is known as immortal time bias, and may cause overestimation of the association between irAE and outcome.[40] Landmark analyses have been pointed to as a method of avoiding this bias.[40] A recently published pooled analysis of patients with metastatic melanoma receiving pembrolizumab in three clinical trials concluded with no association between irAEs and OS when applying the landmark approach.[41] We conducted a landmark analysis with a cut-off at 3 months by which the majority of irAEs were encountered. However, this approach

excluded patients who died before 3 months (N = 25) and did not address patients that developed irAEs after 3 months. Importantly, treatment exposure may have influenced OS, as patients with grade 3 to 4 irAEs were less likely to receive all doses of ipilimumab than those without grade 3 to 4 irAEs (17% vs 71%), as well as subsequent antiprogrammed cell death protein-1 (PD-1) blockade (25% vs 46%). Thus, OS in patients with grade 3 to 4 irAEs is likely to have been influenced by the lack of further therapy. Arguably, the immunosuppressive effects of corticosteroids may have had negative impact on survival in patients experiencing high-grade irAEs. Evidence on the effect of lower dose corticosteroids on ICI efficacy and toxicity is contradicting.[42,43] Moreover, the effect of high dose corticosteroids on survival is hard to assess as it is heavily confounded by the presence of irAEs.

An overall response rate of 9% is slightly lower than reported in phase III trials,[2,11,12] although, disease control was reached for 35%, comparable to the registrational trial and other reported real-world data.[2,15,16,27,30] Nevertheless, differing populations, as reflected by patient eligibility criteria, and response assessment methods challenge a direct comparison of overall response rate. Best overall response obtained within 6 months was in fact prognostic for OS, with PR conferring a better prognosis than SD. Moreover, our results confirmed that durable SD might be associated with survival benefits, as previously reported.[10] Despite other reports of pseudoprogression,[9,10] our data did not support this. A median PFS of 2.7 months is in line with phase III trials,[2,11,12] indicating that half of patients were progressing by the first evaluation. Notably, seven patients had at censoring still not progressed from treatment.

Median OS in this trial is comparable to other real-world reports, ranging 6.1 to 14.3 months,[15,18,26,27,29,30] and in fact improved compared to the registrational trial with an OS of 10.2 months.[2] In two, more recent phase III trials randomising ipilimumab against ipilimumab combined with PD-1 inhibitor and/or PD-1 inhibitor monotherapy, median OS in the ipilimumab arms were 16.0 months[7] and 19.9 months,[6] respectively. Following these trials, 30% and 46% of patients received PD-1 inhibitors, and 29% and 23% BRAF inhibitor and/or MEK inhibitors upon progression.[4,6] These are treatments shown to significantly improve OS.[44-46] In the current trial, 44% received PD-1 inhibitors and 26% BRAF inhibitors or combined BRAF and MEK inhibitors postprogression (Supplementary Table 1). In comparison, in a trial investigating sequential ICIs with a planned switch, patients receiving ipilimumab followed by nivolumab had a median OS of 16.9 months.[47] Hence, access to novel drugs postprogression is likely to have affected OS, emphasising the challenges of historical controls in this context.

Most prior reports on ipilimumab address the use in pretreated patients. In the current trial, two thirds of patients were treatment naïve. A statistically significant association between OS and prior therapy was not identified in our study. This is in contrast with findings in the Dutch EAP where treatment-naïve patients had an improved OS to pretreated patients (14.3 vs 8.7 months).[18] Interestingly, patients receiving prior chemotherapy had a significantly longer OS and was the only subgroup in this trial identified to have a somewhat improved PFS. The observed differences in median PFS were, nevertheless, modest, whereas median OS differed substantially. Only 17% of patients in this trial had received prior chemotherapy. Our hypothesis is that compared to treatment-naïve patients, these patients represented a more selected subgroup that survived beyond first line chemotherapy and were deemed fit for inclusion in the trial, thereby indicating a slower tumour progression and better prognosis, encouraging the use of ipilimumab in the second line setting. Conversely, PFS and OS in *BRAF*-mutated patients were independent of prior BRAF and/or MEK inhibitors.

Several predictive markers available from routine blood tests and clinical assessment have been suggested for ipilimumab.[19] Due to single-armed design, this trial is only qualified to explore possible prognostic biomarkers. Nevertheless, our data supports baseline ECOG PS ≥ 1, elevated LDH and CRP as markers of poor prognosis in a Cox proportional hazards model adjusting for other factors. While the ipilimumab registrational trial found survival benefit to be independent of LDH,[2] other reports have recognised an association between normal LDH and treatment efficacy.[14,16,17,20,22,30]

In our data, baseline CRP ≥ 10 mg/L is associated with an increased risk of death. A recent report elucidates the immunosuppressive mechanisms of CRP, suggesting that CRP restricts activated CD4+ and CD8+ T cells by inhibiting proliferation, activation-associated phenotypes and effector functions.[48] Moreover, CRP-treated T cells expressed high levels of interleukin-1β, known to enhance CRP production from the liver, inhibited early events in T cell receptor engagement and downregulated the expression of costimulatory molecules on mature dendritic cells. This included CD80 and CD86, the costimulatory ligands enabled to engage CD28 as ipilimumab blocks CTLA-4. A correlation between improved OS and a normal baseline CRP or decrease in CRP during ipilimumab treatment has previously been identified.[17,22,23,49]

No patients received prior PD-1 inhibitors before inclusion in this trial, and our report does therefore not address the use of ipilimumab in this setting. Importantly, less than a year after trial enrolment completed, PD-1 inhibitors were granted reimbursement by national health authorities and replaced ipilimumab as the standard of care in first line treatment of metastatic melanoma. Thus, the current role of ipilimumab is in combination with nivolumab in first line treatment or following progression on PD-1 inhibitors, and BRAF/MEK blockade in *BRAF*-mutated patients.[8]

In conclusion, this prospective phase IV trial indicates that the efficacy and toxicity of ipilimumab are in line with the registrational study, despite concerns that outcomes in a real-world population would be inferior to clinical trials. Long-term survival was similar to a pooled analysis of patients receiving ipilimumab in phase II and III trials.[3] We find that ECOG PS, LDH and CRP are independent predictors of OS in patients with metastatic melanoma, and may be useful in identifying patients benefitting and not benefitting from treatment in everyday clinical practice. Although, ipilimumab monotherapy is no longer a preferred first line treatment in metastatic melanoma, our data supports the use of ipilimumab in a real-world setting. As the current role of ipilimumab monotherapy is second line following

progression on PD-1 inhibitors, there is a need for prospective studies investigating the real-world use of ipilimumab in this setting.

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CONFLICT OF INTEREST

Elin Aamdal, Kari D. Jacobsen, Kirsten T. Hagene, Kjersti Holmsen, Stein Kaasa, Steinar Aamdal and Tormod K. Guren have received clinical research support from the Norwegian Ministry of Health and Care Services. Marta Nyakas has received personal fees/honoraria for lectures and expert meetings from Bristol-Meyers Squibb, Novartis, Merck Sharpe and Dohme and Pierre-Fabre. Cornelia Schuster has received honoraria for lectures from Bristol-Meyers Squibb. Jon A. Kyte has received honoraria for lectures and clinical research support from the Norwegian Ministry of Health and Care Services, Bristol-Meyers Squibb and Roche. Oluf Herlofsen reports honoraria for lectures from Bristol-Meyers Squibb, Merck Sharpe and Dohme and has received research funding from Novartis. Christian Kersten reports former employment with Roche. The remaining authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The datasets generated during and analyzed during the current trial are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The Ipi4 trial (https://clinicaltrials.gov/ct2/show/NCT02068196) was approved by the Regional Committee for Medical and Health Research Ethics South East (REC ID 2013/1518) and conducted in accordance with the ethical principles of the Declaration of Helsinki (1964). All patients provided written informed consent to participate in the trial.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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