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Original Research

Real-world outcomes with ipilimumab and nivolumab in advanced melanoma: a multicentre retrospective study☆

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Abstract ***Purpose:*** To assess efficacy and toxicity of combination immunotherapy with ipilimumab plus nivolumab in routine practice in a retrospective multicentre cohort of patients with advanced melanoma.
Patients and methods: This retrospective analysis included patients with advanced melanoma treated with ipilimumab and nivolumab between October 2015 and January 2020 at six centres

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Immunotherapy

in Australia, Europe and the United States of America. We describe efficacy outcomes (overall survival [OS], progression-free survival [PFS] and objective response rate [ORR]) in treatment-naïve and pre-treated patients, with and without brain metastases, plus treatment-related adverse events (trAEs) in all patients treated.

Results: A total of 697 patients were identified; 472 were treatment-naïve of which 138 (29.2%) had brain metastases, and 225 were previously treated of which 102 (45.3%) had brain metastases. At baseline, 32.3% had stage M1c and 34.4% stage M1d disease. Lactate dehydrogenase was high in 280 patients (40.2%). With a median follow-up of 25.9 months, median OS in the 334 treatment-naïve patients without brain metastases was 53.7 months (95% confidence interval [CI] 40.8-NR) and 38.7 months (95% CI 18.6-NR) for the 138 treatment-naïve patients with brain metastases. For the entire cohort the ORR was 48%, for treatment-naïve patients without brain metastases ORR was 56.6% with a median PFS of was 13.7 months (95% CI 9.6–26.5). Median PFS was 7.9 months (95% CI 5.8–10.4) and OS 38 months (95% CI 31-NR) for the entire cohort. Grade 3–4 trAE were reported in 44% of patients, and 4 (0.7%) treatment-related deaths (1 pneumonitis, 2 myocarditis and 1 colitis) were recorded.

Conclusion: The outcome and toxicity of combination immunotherapy with ipilimumab and nivolumab in a real-world patient population are similar to those reported in pivotal trials.

1. Introduction

The introduction of checkpoint inhibitors (anti-CTLA-4 and anti-PD-1 monoclonal antibodies) has dramatically improved outcomes for patients with advanced melanoma [1,2]. The pivotal Checkmate-067 trial for patients with untreated melanoma without brain metastases, showed a response rate of 58% for combined ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1), compared to 44% and 19% for nivolumab and ipilimumab monotherapy, respectively. At 5 years, the progression-free survival (PFS) rate was 36% and overall survival (OS) rate 52% for ipilimumab and nivolumab combined [3]. The rate of grade 3–4 treatment-related adverse events (trAEs) was 59% for combination therapy [1]. This benefit was maintained over time with a 6.5 year-PFS rate of 34% and median OS of 72.1 months. Subgroup analysis identified a number of prognostic factors, including baseline lactate dehydrogenase (LDH) level and BRAF mutation status [1]. Based on this trial, combination immunotherapy with ipilimumab and nivolumab is considered a standard of care for advanced melanoma patients.

Brain metastases (BM) are common in patients with metastatic melanoma and usually associated with a poor prognosis. Two small prospective trials have evaluated ipilimumab plus nivolumab in patients with asymptomatic untreated BM not requiring corticosteroids [4,5]. The Checkmate-204 trial reported an intracranial (IC) response rate of 50% and extracranial (EC) response rate of 56% for 94 patients treated with ipilimumab and nivolumab [4]. The ABC trial reported a 63% EC and 59% IC response rates in a similar group of 27 patients [5,6]. The rate of trAEs was similar in both trials, with grade 3–4 events reported in 54–55% of patients. As a result of these trials, upfront combination immunotherapy with ipilimumab and nivolumab is considered a standard of care in patients with asymptomatic BM and a good Eastern Cooperative Oncology Group Perfomance Status (ECOG PS) 0-1.

Despite the outcomes for ipilimumab plus nivolumab being the best reported for any treatment strategy in this indication, the use of this combination varies greatly across clinicians and centres, driven in part by both concerns about toxicity and uncertainty about how applicable this approach is to a real-world patient population. In a recent communication of use of immunotherapy in England with data taken from National Cancer Registration Dataset, approximately one third of patients receiving immunotherapy in the metastatic setting were treated with combination ipilimumab and nivolumab [7]. In this study, we aimed to analyse treatment-related outcomes with ipilimumab plus nivolumab in routine practice in patients with advanced melanoma.

2. Methods

2.1. Patients and study design

We conducted a retrospective analysis of patients with stage 3 unresectable and stage 4 melanoma treated with combination immunotherapy. Patients received up to four cycles of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg every 3 weeks followed by maintenance nivolumab at 3 mg/kg every 2 weeks, 240 mg every 2 weeks or 480 mg every 4 weeks, usually up to 2 years of treatment, until progressive disease (PD) or indefinitely depending on the centre's practice. Data were collected for patients treated between October 2015 and January 2020 at six

centres across Australia, Europe and the United States of America (USA). Patients must have received at least one cycle of ipilimumab plus nivolumab to be eligible for inclusion in this study.

Baseline characteristics collected included demographic data, melanoma subtype, the presence of brain or liver metastases, prior systemic therapies, TNM staging according to the eight edition of American Joint Committee on Cancer melanoma staging system [8], BRAF mutation status and LDH levels. Outcome data, including treatment response, OS, PFS and trAEs were collected. Date of last follow-up was defined as the date of last survival follow-up or date of death, whichever occurred later.

Tumour response to ipilimumab plus nivolumab was determined with routine radiologic assessment based on clinical assessment, and when available based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [9]. PFS was defined as the time between the first dose of ipilimumab plus nivolumab and the date of clinical or radiological progression determined by RECIST 1.1 or date of death. OS was defined as the time between first dose and date of death or last follow-up. TrAEs were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

For our analyses, we divided the patients in two groups - systemic drug treatment-naive (treatment-naïve) and previously systemically treated (previously treated) patients. Our focus was to describe the outcomes in treatment-naïve patients without BM and in treatment-naïve patients with BM: OS, investigator-assessed PFS and objective response rate (ORR). We also describe the outcomes in previously treated population, and safety outcomes (trAEs) in the whole cohort. Additionally, a subgroup analysis on patients who were treated with maintenance nivolumab was performed. Patients with PD as best overall response were excluded, as in our retrospective dataset it could not be determined whether the nivolumab was used as rescue rather than maintenance therapy in case of progression.

2.2. Ethical considerations

The Christie NHS Foundation Trust as coordinating study centre, obtained approval of the local institutional review board for conducting this study (reference 2766). In all other participating centres, local institutional review board approval for data collection was obtained according to local guidelines.

2.3. Statistical analyses

Descriptive statistics were used to summarise patient and treatment characteristics. The associations between categorical variables were assessed using chi-squared tests or Fisher's exact tests, whichever was appropriate. The associations between continuous variables and categorical variables were assessed using independent variable t-tests. A Cox proportional hazard model was used to assess the association between clinical variables and treatment outcomes (PFS/OS). This analysis started from a univariable analysis that included each clinical factor as a sole covariate in the model, with the significance of association evaluated using a Wald test and assumption of proportionality was verified based on Schoenfeld residuals [10]. A plot of the Martingale residuals from each marker specific analysis was examined for evidence of non-linearity in the biomarker–hazard relationship [11]. Significant clinical factors were selected for subsequent multivariable analysis, for which a backward stepwise method was applied to identify the subset of clinical factors that were significantly associated with PFS/OS in the multivariable model. Interactions between clinical factors were explored for variables demonstrating significant association between each other. In these Cox proportional hazard analyses, patients with PFS or OS smaller than 14 days were excluded to avoid competing risk of survival, i.e. progression/death are too short and may not be treatment-related. Kaplan–Meier curves were used to illustrate patient survival.

The analysis present in this study follows the REMARK guideline [12]. P-values smaller than 0.05 were considered statistically significant. All analyses were implemented using R, version 4.0. Multiple comparisons were not adjusted due to the exploratory nature of the study.

3. Results

3.1. Patients

A total of 697 patients were included across six sites between October 2015 and January 2020, 472 treatment-naïve and 225 previously treated patients. Brain metastases were present in 138 (29.2%) of the treatment-naïve patients and 102 (45.3%) of the previously treated patients (Supplementary Fig. 1).

The demographic and clinical characteristics of patients are summarised in Table 1. Treatment-naïve patients with BM had a significantly higher age compared with the other patients ($p = 0.006$). Patients from the USA comprised a higher proportion of treatment-naïve patients without BM ($p < 0.001$). While the majority (69.9%) had a cutaneous primary melanoma, in 19.1% of patients the primary was unknown and 11% were either of acral, mucosal or uveal origin. Patients with cutaneous melanoma were more likely to have received previous lines of treatment ($p < 0.001$). The majority of patients had more advanced stage disease with 32.3% of patients having stage M1c and 34.4% stage M1d disease. Liver metastases were present in 31.9% of patients, and 30.6% of patients had $\geq$4 different metastatic sites.

Table 1
Baseline characteristics of all included patients and reported for both patients with and without brain metastases in the treatment-naïve patient and the previously treated patient groups.

	All patients		Treatment-naïve patients (n = 472)				Previously treated patients (n = 225)				p value
	(n = 697)		No brain metastases (n = 334)		Brain metastases (n = 138)		No brain metastases (n = 123)		Brain metastases (n = 102)		
Age (median, IQR)	58	(48–68)	59	(48–68)	61	(51–70)	56	(45–65)	54	(45–63)	0.006
Sex											0.309
Male	401	(57.5)	187	(56.0)	87	(63.0)	65	(52.8)	62	(60.8)	
Female	296	(42.5)	147	(44.0)	51	(37.0)	58	(47.2)	40	(39.2)	
Geographic region											<0.001
Australia	59	(8.5)	27	(8.1)	16	(11.6)	10	(8.1)	6	(5.9)	
Europe	549	(78.8)	241	(72.2)	108	(73.3)	105	(85.4)	95	(93.1)	
United States of America	89	(12.8)	66	(19.8)	14	(10.1)	8	(6.5)	1	(1.0)	
Tumour type											<0.001
Cutaneous	487	(69.9)	216	(64.7)	88	(63.8)	104	(84.6)	79	(77.5)	
Unknown primary	133	(19.1)	63	(18.9)	39	(28.3)	12	(9.8)	19	(18.6)	
Mucosal	39	(5.6)	33	(9.9)	3	(2.2)	2	(1.6)	1	(1.0)	
Acral	21	(3.0)	9	(2.7)	7	(5.1)	3	(2.4)	2	(2.0)	
Uveal	17	(2.4)	13	(3.9)	1	(0.7)	2	(1.6)	1	(1.0)	
Stage at start treatment											NA
IIIC/D	48	(6.9)	38	(11.4)	0		10	(8.1)	0		
M1a	88	(12.6)	65	(19.5)	0		23	(18.7)	0		
M1b	96	(13.8)	76	(22.8)	0		20	(16.3)	0		
M1c	225	(32.3)	155	(46.4)	0		70	(56.9)	0		
M1d	240	(34.4)	0		138	(100.0)	0		102	(100.0)	
Number of metastatic sites											<0.001
0	5	(0.7)	4	(1.2)	0		1	(0.8)	0		
1	162	(23.2	100	(29.9)	17	(12.3)	33	(26.8)	12	(11.8)	
2	190	(27.3)	103	(30.8)	19	(13.8)	49	(39.8)	19	(18.6)	
3	127	(18.2)	59	(17.7)	34	(24.6)	15	(12.2)	19	(18.6)	
4 or more	213	(30.6)	68	(20.4)	68	(49.3)	25	(20.3)	52	(51.0)	
Liver metastases	222	(31.9)	106	(31.7)	43	(31.2)	38	(30.9)	35	(34.3)	0.947
ECOG performance status											0.228
0-1	678	(97.3)	326	(97.6)	136	(98.6)	120	(97.6)	96	(94.1)	
2-3	19	(2.7)	8	(2.4)	2	(1.4)	3	(2.4)	6	(5.9)	
Baseline LDH level											0.255
<ULN	397	(57.0)	205	(61.4)	71	(51.4)	70	(56.9)	51	(50.0)	
>ULN	280	(40.2)	124	(37.1)	62	(44.9)	47	(38.2)	47	(46.1)	
Missing	20	(2.9)	5	(1.5)	5	(3.6)	6	(4.9)	4	(3.9)	
BRAF status											<0.001
Mutant	352	(50.5)	127	(38.0)	51	(37.0)	86	(69.9)	88	(86.3)	
Wild-type	345	(49.5)	207	(62.0)	87	(63.0)	37	(30.1)	14	(13.7)	
First-line treatment	472	(67.7)	334	(100.0)	138	(100.0)	0		0		NA
Prior treatment											NA
Targeted therapy	138	(61.3)	0		0		66	(53.7)	72	(70.6)	
Checkpoint inhibitors	56	(24.9)	0		0		42	(34.1)	14	(13.7)	
Both	22	(9.8)	0		0		8	(6.5)	14	(13.7)	
Other	9	(4.0)	0		0		7	(5.7)	2	(2.0)	
Prior treatment setting											NA
Neoadjuvant	5	(2.2)	0		0		5	(4.1)	0		
Adjuvant	26	(11.6)	0		0		22	(17.9)	4	(3.9)	
Metastatic	181	(80.4)	0		0		90	(73.2)	91	(89.2)	
Unknown	13	(5.8)	0		0		6	(4.9)	7	(6.9)	

IQR: interquartile range, ULN: upper limit of normal.
P values are reported for comparison between the 4 different cohorts: treatment-naïve no brain metastasis, treatment-naïve with brain metastasis, previously treated no brain metastasis and previously treated with brain metastasis.

LDH was above the upper limit of normal in 280 patients (40.2%) and tumours from 352 patients (50.5%) harboured a BRAF mutation, of which a significantly higher proportion had received previous treatment ($p < 0.001$). Of the 225 previously treated patients, the vast majority (80.4%) received their previous treatment for metastatic disease. Most previously treated patients had received targeted therapy (138 patients, 61.3%), 56

Table 2
Response rates of all included patients and reported for both patients with and without brain metastases in the treatment-naïve patient and the previously treated patient groups.

	All patients		Treatment-naïve patients (n = 472)				Previously treated patients (n = 225)				p value
	(n = 697)		No brain metastases (n = 334)		Brain metastases (n = 138)		No brain metastases (n = 123)		Brain metastases (n = 102)		
Best overall response											<0.001
Complete response	112	(16.1)	73	(21.9)	19	(13.8)	18	(14.6)	2	(2.0)	
Partial response	226	(32.4)	116	(34.7)	58	(42.0)	33	(26.8)	19	(18.6)	
Stable disease	66	(9.5)	30	(8.0)	11	(8.0)	14	(11.4)	11	(10.8)	
Progressive disease	293	(42.0)	115	(36.2)	50	(36.2)	58	(47.2)	70	(68.6)	
Overall response rate	338	(48.5)	189	(56.6)	77	(55.8)	51	(41.5)	21	(20.6)	<0.001
Disease control rate	404	(58.0)	219	(65.6)	88	(63.8)	65	(52.8)	32	(31.4)	<0.001

P values are reported for comparison between the 4 different cohorts: treatment-naïve no brain metastasis, treatment-naïve with brain metastasis, previously treated no brain metastasis and previously treated with brain metastasis.

patients (24.9%) received another form of checkpoint inhibition and 9.8% (22 patients) had received both (Table 1).

The median number of cycles of combination therapy administered was 3 (interquartile range [IQR] 2–4), with only 32.7% of patients completing four cycles. A total of 253 (36.3%) of patients went on to receive maintenance nivolumab, receiving a median of eight cycles (IQR 3–19) of treatment (Supplementary Table 1). In total, 93 patients (13.3%) with fewer than four cycles of combination therapy, continued with nivolumab maintenance. Data on reason for discontinuation of treatment were not collected.

At baseline, 240 (34.4%) patients had brain metastases of which treatment details were known for 239 patients. Among these, 135 patients (56.5%) had three or more brain metastases and 135 (56.5%) had not received any local therapy for their brain metastases (Supplementary Table 2). Of the total cohort, 33.9% were receiving steroids, similar in both the treatment-naïve and the previously treated patients (33.3% and 34.7%, respectively).

3.2. Efficacy

In the whole patient population (n = 697), the ORR was 48.5% (Table 2). The response rates were lower in the patients with acral (42.9%), mucosal (28.2%) and uveal melanoma (5.9%) (Supplementary Table 3). For the survival analyses, 25 patients were not included in PFS analyses (PFS not available for 2 and PFS <14 days for 23) and 7 were not included in OS analyses (OS < 14 days), because of the risk that these progression and death events are not treatment-related. With a median follow-up of 25.9 months, the median PFS for the whole patient population was 7.9 months (95% CI 5.8–10.4) and median OS 38.7 months (95% CI 31.6-NR) (Supplementary Fig. 2).

The ORR was 56.6% in the treatment-naïve non-BM population (n = 334), with 21.9% patients achieving a complete response (Table 2). The response rate in the treatment-naïve brain metastases patients was very similar (55.8%) but the complete response rate was lower (13.8%). Median PFS was 13.7 months (95% CI 9.1–26.5) and median OS was 53.7 months (95% CI 40.8-NR) in the treatment-naïve non-BM group compared to a median PFS of 10.0 months (95% CI 5.6–24.6) and a median OS of 38.7 months (95% CI 18.6-NR) (Fig. 1A–B) in the treatment-naïve BM patients. The 3-year PFS rate was estimated at 35.3% and 3-year OS rate in this population was 54.5%.

For previously treated patients, the ORR was 41.5% for patients without BM and 20.6% for patients with brain metastases (Table 2). Disease progression occurred in 63.4% of patient with previously treated brain metastases (Supplementary Table 2). Outcomes for the previously treated patients were worse than for treatment-naïve patients, with a median PFS of 5.5 months (95% CI 3.6–8.2) for the non-BM group and 2.3 months (95% CI 1.7–3.3) for the BM patients, median OS was 37.6 months (95% CI 17.1-NR) and 7.6 months (95% CI 5.1–10.6) respectively (Fig. 1C–D).

3.3. Safety

Treatment-related AEs of any grade were observed in 76.3% and grade 3–4 trAEs occurred in 44.9% of patients (Table 3), but were significantly less frequent in previously-treated patients with BM (27.5%, p < 0.001 for both). The most common overall (all grade and grade 3–4) trAEs were diarrhoea/colitis, skin rash and hepatitis. Treatment of these trAEs included systemic steroids in 445 patients (83.6%) and in 146 patients (27.4%) non-steroid treatment (details can be found in Table 3). At least one hospital admission was required

Table 3
Treatment-related adverse events and its treatment of all included patients and reported for both patients with and without brain metastases in the treatment-naïve patient and the previously treated patient groups.

	All patients		Treatment-naïve patients (n = 472)				Previously treated patients (n = 225)				p value
	(n = 697)		No brain metastases (n = 334)		Brain metastases (n = 138)		No brain metastases (n = 123)		Brain metastases (n = 102)		
All grade adverse events	532	(76.3)	276	(82.6)	118	(85.5)	91	(74.0)	47	(46.1)	<0.001
Grade 3-4 adverse events	313	(44.9)	154	(46.1)	73	(52.9)	56	(45.5)	28	(27.5)	<0.001
Colitis and diarrhoea											
All grade adverse events	211	(30.3)	111	(33.2)	50	(36.2)	37	(30.1)	13	(12.7)	
Grade 3-4 adverse events	146	(20.9)	75	(22.5)	36	(26.1)	24	(19.5)	11	(10.8)	
Skin											
All grade adverse events	197	(28.3)	119	(35.6)	37	(26.8)	27	(22.0)	14	(13.7)	
Grade 3-4 adverse events	27	(3.9)	11	(3.3)	7	(5.1)	4	(3.3)	5	(4.9)	
Hepatitis											
All grade adverse events	188	(27.0)	93	(27.8)	39	(28.3)	33	(26.8)	23	(22.5)	
Grade 3-4 adverse events	112	(16.1)	55	(16.5)	23	(16.7)	21	(17.1)	13	(12.7)	
Hypothyroidism											
All grade adverse events	93	(13.3)	50	(15.0)	19	(13.8)	20	(16.3)	4	(3.9)	
Grade 3-4 adverse events	2	(0.3)	0		2	(1.4)	0		0		
Hypophysitis											
All grade adverse events	61	(8.8)	32	(9.6)	19	(13.0)	8	(6.5)	3	(2.9)	
Grade 3-4 adverse events	10	(1.4)	5	(1.5)	3	(2.2)	1	(0.8)	1	(1.0)	
Pneumonitis											
All grade adverse events	49	(7.0)	27	(8.1)	13	(9.4)	7	(5.7)	2	(2.0)	
Grade 3-4 adverse events	19	(0.6)	9	(2.7)	7	(5.1)	2	(1.6)	1	(1.0)	
Arthralgia											
All grade adverse events	44	(6.3)	29	(8.7)	5	(3.6)	6	(4.9)	4	(3.9)	
Grade 3-4 adverse events	4	(0.6)	3	(0.9)	1	(0.7)	0		0		
Adrenal insufficiency											
All grade adverse events	30	(4.3)	17	(5.1)	7	(5.1)	2	(1.6)	4	(3.9)	
Grade 3-4 adverse events	0		0		0		0		0		
Nephritis											
All grade adverse events	27	(3.9)	17	(5.1)	5	(3.6)	3	(2.4)	2	(2.0)	
Grade 3-4 adverse events	10	(1.4)	7	(2.1)	1	(0.7)	1	(0.8)	1	(1.0)	
Other gastrointestinal adverse events[a]											
All grade adverse events	14	(2.0)	9	(2.7)	2	(1.4)	2	(1.6)	1	(1.0)	
Grade 3-4 adverse events	6	(0.9)	3	(0.9)	1	(0.7)	1	(0.8)	1	(1.0)	
Neurological adverse events[b]											
All grade adverse events	12	(1.7)	4	(1.2)	3	(2.2)	5	(4.1)	0		
Grade 3-4 adverse events	6	(0.9)	4	(1.2)	1	(0.7)	1	(0.8)	0		
Myocarditis											
All grade adverse events	9	(1.3)	6	(1.8)	1	(0.7)	2	(1.6)	0		
Grade 3-4 adverse events	6	(0.9)	3	(0.9)	1	(0.7)	2	(1.6)	0		
Diabetes mellitus											
All grade adverse events	7	(1.0)	2	(0.6)	3	(2.2)	2	(1.6)	0		
Grade 3-4 adverse events	6	(0.9)	2	(0.6)	3	(2.2)	1	(0.8)	0		
Uveitis											
All grade adverse events	6	(0.9)	4	(1.2)	1	(0.7)	1	(0.8)	0		
Grade 3-4 adverse events	0		0		0		0		0		
Myositis											
All grade adverse events	5	(0.7)	2	(0.6)	1	(0.7)	1	(0.8)	1	(1.0)	
Grade 3-4 adverse events	3	(0.4)	1	(0.3)	1	(0.7)	1	(0.8)	0		
Other adverse events[c]											
All grade adverse events	35	(5.0)	20	(6.0)	5	(3.6)	8	(6.5)	2	(2.0)	
Grade 3-4 adverse events	12	(1.7)	7	(2.1)	3	(2.2)	1	(0.8)	1	(1.0)	
Treatment of adverse events[d]											
Steroids	445	(83.6)	227	(68.0)	100	(72.5)	79	(64.2)	39	(38.2)	
Infliximab	105	(19.7)	56	(16.8)	26	(18.8)	16	(13.0)	7	(6.9)	
Mycophenolate mofetil	56	(10.5)	29	(8.7)	10	(7.2)	11	(8.9)	6	(5.9)	
Tacrolimus	9	(1.7)	4	(1.2)	1	(0.7)	2	(1.6)	2	(2.0)	
Other[e]	5	(0.9)	2	(0.6)	1	(0.7)	2	(1.6)	2	(2.0)	
Admission due to adverse events[d]	252	(47.4)	120	(35.9)	58	(42.0)	53	(17.1)	21	(20.6)	
Length admission in days (median, IQR)	7	(4–15)	9	(5–17)	6	(4–16)	8	(4–11)	7	(3–14)	

Table 3 (*continued*)

	All patients		Treatment-naïve patients (n = 472)				Previously treated patients (n = 225)				p value
	(n = 697)		No brain metastases (n = 334)		Brain metastases (n = 138)		No brain metastases (n = 123)		Brain metastases (n = 102)		
Resolution adverse events[d]	427	(80.3)	219	(65.6)	95	(68.8)	75	(61.0)	38	(37.3)	
Death due to adverse events[d,f]	4	(0.8)	3	(0.9)	1	(0.7)	0		0		

IQR: interquartile range.

P values are reported for comparison between the 4 different cohorts: treatment-naïve no brain metastasis, treatment-naïve with brain metastasis, previously treated no brain metastasis and previously treated with brain metastasis.

[a] other gastrointestinal adverse events include gastritis (n=6), mucositis (n=4), duodenitis (n=2), enteritis (n=1) and oesophagitis (n=1).

[b] neurological adverse events include (poly)neuropathy (n=5), meningitis (n=4), encephalitis (n=3).

[c] other adverse events: vitiligo (n=6), pancreatitis/increased lipase (n=5), arthritis (n=4), anaemia (n=2), SIRS (n=2), Sjögren's syndrome (n=2), thrombocytopenia (n=2), acute demyelination (n=1), fatigue (n=1), flare-up of polymyalgia rheumatic (n=1), gout (n=1), hilar adenopathy (n=1), hyperthyroidism (n=1), infusion reaction (n=1), myalgia (n=1), ophthalmoplegia (n=1), panniculitis mesenterica (n=1), polymyalgia rheumatic (n=1), pruritus (n=1), sinus pain (n=1).

[d] reported as percentage of patients with adverse events (n=532).

[e] other treatment: IVIG (n=1), adalimumab (n=1), plasmapheresis (n=1), hydroxychloroquine (n=1), rituximab (n=1).

[f] death due to myocarditis (n=2), colitis (n=1) and pneumonitis (n=1).

for management of AEs in 252 patients (47.4%), with a median length in hospital of 7 days (IQR 4–15). Four (0.8%) treatment-related deaths occurred: two patients died due to myocarditis, one due to colitis and one due to pneumonitis.

3.4. Prognostic factors for treatment outcomes

Univariable analysis indicated that worse ECOG performance status, elevated LDH levels and presence of liver or brain metastasis were associated with significantly reduced PFS and OS (Supplementary Table 4).

In the multivariable model for PFS, mucosal and uveal subtypes, ECOG-1 or higher, BRAF mutation, presence of liver metastasis, elevated LDH levels and previous line of therapy were significantly associated with worse outcomes (Fig. 2A). Patients with brain metastases had a trend towards reduced PFS, but this was not significant (p = 0.068, HR 1.223, 95% CI 0.986–1.519). With the exception of BRAF mutation status and the presence of liver metastases, the clinical factors prognostic for PFS remained significant for OS (Fig. 2B). In a subset of patients with brain metastases (both treatment-naïve and previously treated), the impact of steroid treatment on treatment outcomes were assessed (Supplementary Fig. 3). Patients that had received steroids other than management of trAE had significantly reduced PFS (p = 0.005, HR 1.64, 95%CI 1.16–2.33), but not significantly reduced OS (p = 0.116, HR 1.36, 95%CI 0.93–1.99), after adjusting for prognostic clinical factors, compared to those who received no steroids.

An exploratory analysis was carried out to interrogate the impact of the presence of BRAF mutation and the use of BRAF-targeted therapy on survival by categorising patients into two categories: treatment-naïve with BRAF mutation, and previously treated with BRAF-targeted therapy. Patients previously treated with prior BRAF-targeted therapy had significantly shorter PFS and OS in univariable analysis ($p < 0.001$, Supplementary Fig. 4 and Table 5).

A subgroup analysis on the number of cycles of combination in patients who received nivolumab maintenance therapy, revealed that patients who received four cycles of combination therapy and then continued on maintenance nivolumab, have a better OS than patients who received less than four cycles (Supplementary Fig. 5). Baseline characteristics between these patient groups were comparable, except that European patients more often received four cycles and USA patients more often less than four cycles before going on nivolumab maintenance, and more patients who received less then four cycles were on first-line treatment (Supplementary Table 6). Patients who received less than four cycles had more adverse events and a higher rate of resolution of adverse events (Supplementary Table 6).

4. Discussion

The combination of ipilimumab and nivolumab is a standard of care in the treatment of metastatic melanoma, based on the pivotal trial showing good long-term outcomes in treatment-naïve patients. This is however at the cost of significant toxicity with 59% of patients experiencing grade 3–4 trAEs [1]. The combination also showed significant activity in patients with asymptomatic brain metastases not requiring steroids [4,5], resulting in this treatment becoming a standard of care. Whilst uptake of this combination has been high, there are limited data on its use outside the context of a clinical trial.

Although several retrospective studies of real-world, unselected metastatic melanoma patients treated with ipilimumab plus nivolumab have been reported [13–15], this study represents the largest series to date, and

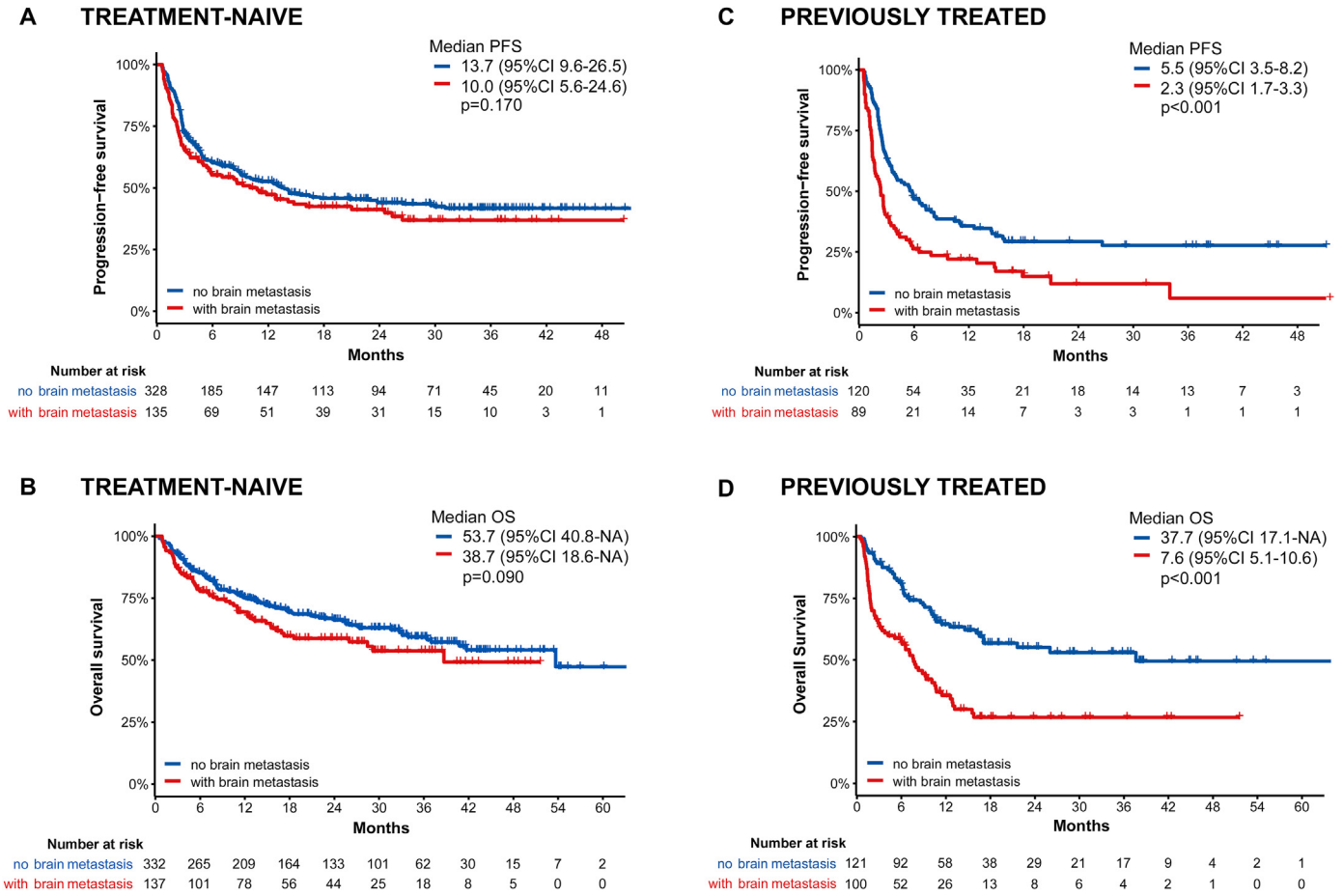


Fig. 1. Survival curves. A. Progression-free survival of treatment-naïve patients, compared for patients with and without brain metastases. B. Overall survival of treatment-naïve patients, compared for patients with and without brain metastases. C. Progression-free survival of previously treated patients, compared for patients with and without brain metastases. D. Overall survival of previously treated patients, compared for patients with and without brain metastases.

includes patients treated in the first and subsequent line setting, with and without brain metastases.

The outcomes seen for our real-world data series are similar to those published for randomised studies of ipilimumab plus nivolumab in the first-line setting. Among the treatment-naïve patients, response rates of non-BM (n = 321, 58.8%) and BM patients (n = 137, 56.2%), are comparable with the Checkmate-067 (n = 314, 58%), Checkmate-204 (n = 94, 51%) and ABC trials (n = 27, 56% intracranial and 63% extracranial response rates) [1,4,5]. For treatment-naïve patients with brain metastases, the intracranial response in our cohort was lower (49.2%) than reported in the latter trials (56% in the Checkmate-204 trial, 56% in the ABC trial), probably in part due to a higher burden of intracranial disease (49% versus 40% patients with three or more brain metastases), including leptomeningeal melanomatosis (eight patients versus zero) and use of steroids for symptoms in 34% of patients in our cohort.

With a longer median follow-up for survival analysis than previous retrospective cohorts, the rates of PFS and OS of this population are comparable to the data of published trials. In the treatment-naïve without brain metastases group, the Checkmate-067 trial reported at 3 years, a PFS rate of 39% and OS rate of 58% [16]. In our series, the estimated 3-years PFS and OS rates in this population was 45.5% and 64.7%.

For the treatment-naïve patients with brain metastases, our cohort had estimated 2-year PFS and OS rates of 42.0% and 59.4% respectively. In the ABC trial, intracranial PFS rate at 2 years was higher at 56%, while the OS rate was comparable at 63% [17]. In a recent update of outcomes of ABC trial, the 5-year intracranial PFS and OS rates were 52% and 55% [6].

As expected, the outcomes for patients treated in the second or subsequent line setting were poorer than for treatment-naïve patients. Of key importance is the outcome after targeted therapy, as this will inform how best to sequence targeted and immunotherapy in patients with a BRAF mutation. For the 157 BRAF-mutation positive patients who progressed after BRAF targeted therapy, the ORR was 29.9% and median PFS 3.0 months, both comparable to other reports showing a ORR of 21% and median PFS of 2 months [15]. A recent randomised study comparing first line combination immunotherapy followed by targeted therapy or the inverse sequence, showed an ORR of 30% for combination in the second line setting [18]. It was observed that these patients in our cohort had the shortest PFS and OS and highest risk of progression and death after adjustment for prognostic clinical factors. On the contrary, the longest OS and least risk of death was observed in treatment-naïve patients with BRAF mutation, further supporting the use of combination immunotherapy upfront in patients with BRAF mutation.

The number of grade 3–4 trAE is lower than that reported for the prospective randomised trials, which is likely to reflect less rigorous recording of toxicity in a non-trial setting. However, our data confirm the significant toxicity grade 3–4 toxicity rates, the number of admissions to hospital because of toxicity, and the duration of admission. The number of patients completing four cycles of treatment (32.7%) was lower than reported for the Checkmate-067 trial (median of four cycles) [1].

We observe that the grade 3–4 trAE of 27.2% is remarkably lower in the previously treated BM cohort (n = 102). The poorer outcomes in this population in terms of ORR, PFS and OS correlate with the fact that they received fewer cycles of combination immunotherapy and of maintenance nivolumab on average (Supplementary Table 1). The lower grade 3–4 trAE rate may be explained by the fact that these patients did not receive as many cycles as the other populations due to rapid disease progression indicated by short PFS (2.3 months) and deteriorating ECOG PS, before they can develop more serious toxicity.

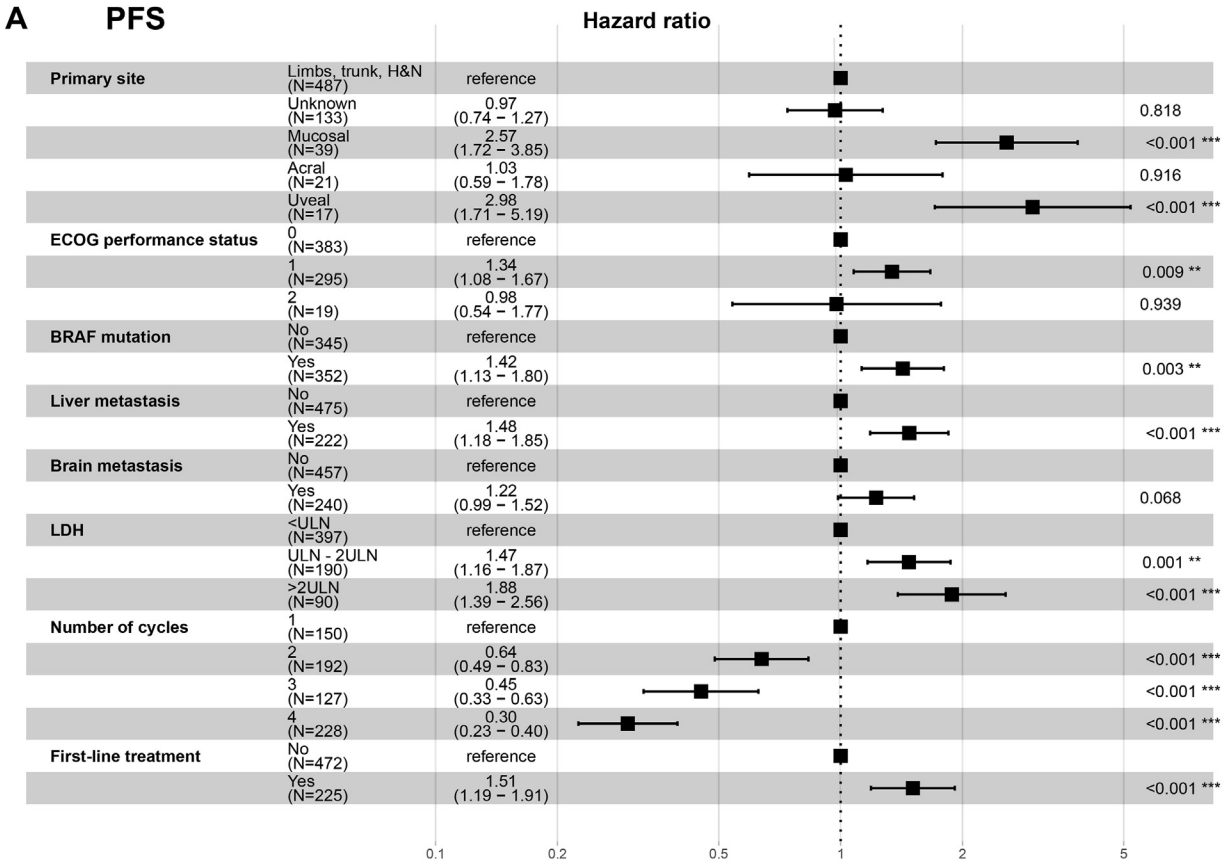
Our study included 77 patients with rare subtypes of melanoma, including acral (n = 21), mucosal (n = 39) and uveal (n = 17). These subtypes are known to respond less well to immunotherapy. In our cohort, the response rate for acral melanoma was 43%, whereas for mucosal and uveal melanoma response rates were 28% and 6% respectively, lower than previously reported [19,20].

Our multivariable analysis identified prognostic factors as previously established in literature: elevated LDH, presence of liver and brain metastases are associated with reduced PFS and OS rates [21,22]. Patients with brain metastases in our cohort receiving steroids for symptomatic brain metastases, did worse than patients with asymptomatic brain metastases. This is also in line with prior studies [23,24].

The subgroup analysis on patients on maintenance nivolumab according to cycles of combination therapy, revealed a difference in OS for patients receiving four cycles of combination which could partly be explained due to a higher rate of patients treated with their first-line therapy, and as a result have more treatment options when progression occurs.

Centres were selected via an international mailing list and based on the numbers and experience of the center in dealing with combination immunotherapy. There is a possible selection bias as centres included were keen to participate and had treated patients with ipilimumab and nivolumab in sufficient numbers to make a meaningful contribution to the study. However, centres included all patients treated in their institutions with combination immunotherapy in that time period. We do not think therefore that this will have had a major impact on the findings of the study.

Data collection was retrospectively based on paper and electronic records from patients. Patients were not



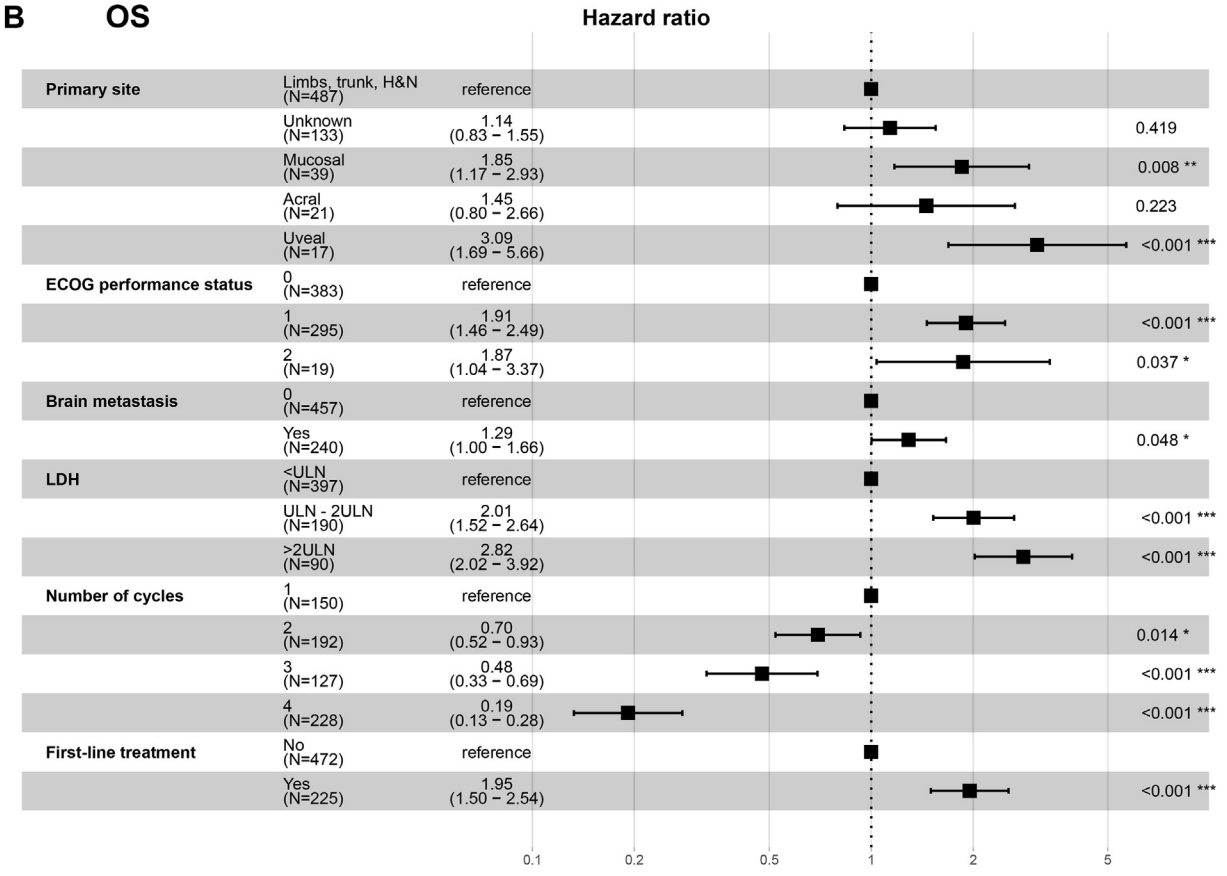


Fig. 2. Multivariable Cox regression. A. Multivariable Cox regression model for progression-free survival in all patients included. B. Multivariable Cox regression model for overall survival in all patients included.

managed according to a trial protocol, therefore data on response rates, PFS and toxicity rates are less reliable. However, the fact that this study includes many different centres with a large number of patients makes the study finding more robust and applicable to a real-world population. Outcomes data were similar across different centres.

We have shown that combination immunotherapy with ipilimumab and nivolumab in a real-world setting has similar clinical outcomes and toxicity rates to those reported in the pivotal randomised trial. Our data further supports the use of this treatment in the real-world setting and adds insights as to which populations are more likely to benefit.

Author contributions

Conception and design: Patricio Serra-Bellver, Paul Lorigan. **Provision of study material or patients:** Patricio Serra-Bellver, Judith M. Versluis, Honey K. Oberoi, Timothy D. Slattery, Yasir Khan, James R. Patrinely, Inês Pires da Silva. **Collection and assembly of data:** Patricio Serra-Bellver, Judith M. Versluis, Honey K. Oberoi, Timothy D. Slattery TDS, Yasir Khan K, James R. Patrinely, Inês Pires da Silva. **Data analysis and interpretation:** Cong Zhou, Patricio Serra-Bellver, Judith M. Versluis, Honey K. Oberoi, Natalie Cook, Paul Lorigan. **Manuscript writing:** Patricio Serra-Bellver, Judith M. Versluis JMV, Honey K. Oberoi, Cong Zhou, Paul Lorigan. **Final approval of manuscript:** all authors. **Accountable for all aspects of the work:** all authors.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

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