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Ipilimumab in the real world: the UK expanded access programme experience in previously treated advanced melanoma patients

Saif S. Ahmad[a,*], Wendi Qian[b,*], Sarah Ellis[c], Elaine Mason[d], Muhammad A. Khattak[e], Avinash Gupta[f], Heather Shaw[g], Amy Quinton[h], Jarmila Kovarikova[i], Kiruthikah Thillai[j], Ankit Rao[k], Ruth Board[l], Jenny Nobes[m], Angus Dalgleish[n], Simon Grumett[k], Anthony Maraveyas[o], Sarah Danson[p], Toby Talbot[q], Mark Harries[j], Maria Marples[r], Ruth Plummer[i], Satish Kumar[h], Paul Nathan[g], Mark R. Middleton[f], James Larkin[e], Paul Lorigan[d], Matthew Wheater[c], Christian H. Ottensmeier[c] and Pippa G. Corrie[a]

Before licensing, ipilimumab was first made available to previously treated advanced melanoma patients through an expanded access programme (EAP) across Europe. We interrogated data from UK EAP patients to inform future clinical practice. Clinicians registered in the UK EAP provided anonymized patient data using a prespecified variable fields datasheet. Data collected were baseline patient characteristics, treatment delivered, toxicity, response, progression-free survival and overall survival (OS). Data were received for 193 previously treated metastatic melanoma patients, whose primary sites were cutaneous (82%), uveal (8%), mucosal (2%), acral (3%) or unknown (5%). At baseline, 88% of patients had a performance status (PS) of 0–1 and 20% had brain metastases. Of the patients, 53% received all four planned cycles of ipilimumab; the most common reason for stopping early was disease progression, including death from melanoma. Toxicity was recorded for 171 patients, 30% of whom experienced an adverse event of grade 3 or higher, the most common being diarrhoea (13%) and fatigue (9%). At a median follow-up of 23 months, the median progression-free survival and OS were 2.8 and 6.1 months, respectively; the 1-year and 2-year OS rates were 31 and 14.8%, respectively. The 2-year OS was significantly lower for patients with poorer PS ($P < 0.0001$), low albumin concentrations ($P < 0.0001$), the presence of brain metastases ($P = 0.007$) and lactate dehydrogenase levels more than two times the upper limit of normal ($P < 0.0001$) at baseline. These baseline characteristics are negative predictors of benefit from ipilimumab and should be taken into consideration before prescription. *Melanoma Res* **25:432–442** **Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.**

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[a]Department of Oncology, [b]Cambridge Cancer Trials Centre, Cambridge Clinical Trials Unit – Cancer Theme, Cambridge University Hospitals NHS Foundation Trust, Cambridge, [c]Southampton Experimental Cancer Medicine Center, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, [d]Department of Medical Oncology, The Christie, Manchester, [e]Department of Medicine, Royal Marsden NHS Foundation Trust, London, [f]Oxford NIHR Biomedical Research Centre, Oxford, [g]Department of Medical Oncology, Mount Vernon Hospital, Northwood, [h]Department of Medical Oncology, Velindre Cancer Centre, Cardiff, [i]Northern Centre for Cancer Care, Newcastle upon Tyne, [j]Directorate of Haematology and Oncology, Guy's and St. Thomas' NHS Foundation Trust, London, [k]Department of Medical Oncology, Royal Wolverhampton Hospitals, [l]Department of Medical Oncology, Royal Preston Hospital, [m]Clinical Oncology, Norfolk and Norwich University Hospital, [n]Division of Clinical Sciences, St George's Hospital Medical School, London, [o]Department of Oncology, Castle Hill Hospital, Hull, [p]Sheffield Experimental Cancer Medicine Centre, University of Sheffield, Weston Park Hospital, Sheffield, [q]Clinical Oncology Department, Royal Cornwall Hospitals and [r]St. James's Institute of Oncology, St. James's University Hospital, Leeds, UK

Correspondence to Pippa G. Corrie, Oncology Centre (Box 193), Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ, UK
Tel: +44 1223 274401; fax: +44 1223 217094;
e-mail: pippa.corrie@addenbrookes.nhs.uk

*Saif Ahmad and Wendi Qian contributed equally to the writing of this article.

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Introduction

Melanoma is the cause for more than 12 000 patient deaths across Europe each year (*http://eco.iarc.fr/eucan/Cancer.aspx?Cancer=20-block-table-m*). The incidence is increasing rapidly worldwide, particularly because of environmental and behavioural factors associated with ultraviolet light exposure. Until recently, patients with advanced, unresectable melanoma had a median life expectancy of around 8 months, with limited treatment options, which did not impact survival. Ipilimumab is a fully human monoclonal antibody that blocks CTLA-4 from binding to its ligands, B7-1 and B7-2, on antigen-presenting cells, potentiating a cytotoxic T-cell response. In 2010, ipilimumab became the first systemic therapy to show a survival benefit in previously treated advanced melanoma patients in an international multicentre

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Table 1 Patient baseline characteristics

Variable	*n* (%) (*N* = 193)
Age (years)	
n	193
Median	60
Range	25–81
Sex	
Male	114 (59)
Female	79 (41)
Primary site	
Cutaneous	158 (82)
Uveal	15 (8)
Acral	6 (3)
Mucosal	4 (2)
Unknown	10 (5)
ECOG PS	
0	66 (35)
1	100 (53)
2	22 (12)
3	2 (1)
Unknown	3
AJCC disease stage	
M1a	22 (11)
M1b	25 (13)
M1c	144 (75)
III/IV	2 (1)
Presence of brain metastases	
No	140 (80)
Yes	35 (20)
Unknown	18
LDH > 2 × ULN	
No	130 (73)
Yes	49 (27)
Unknown	14
LDH > 1 × ULN	
No	48 (27)
Yes	131 (73)
Unknown	14
Albumin ≥ 35	
No	35 (27)
Yes	97 (73)
Unknown	64
BRAF status	
Mutant	20 (28)
Wild type	51 (72)
Unknown	122
Prior lines of treatment	
0	2 (1)
1	123 (77)
2	25 (16)
3	9 (6)
4	1 (1)
Unknown	33
Prescribed steroids	
No	108 (83)
Yes	22 (17)
Unknown	63

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; ULN, upper limit of normal.

Table 2 Frequency of CTCAE grade ≥ 3 adverse events reported

AEs	*n* (%) (*N* = 171)
Diarrhoea	22 (13)
Fatigue	15 (9)
Pain	5 (3)
Rash	5 (3)
Deranged AST/ALT	4 (2)
Nausea	3 (2)
Hypophysitis	3 (2)
Anaemia	2 (1)
Pruritus	2 (1)
SIADH	2 (1)
Cough	1 (1)
Thrombocytopenia	1 (1)
Uveitis	1 (1)
Thyroiditis	1 (1)
Other	3 (2)

AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

randomized phase III trial [1], achieving a median overall survival (OS) benefit of 10 months, compared with 6.4 months (hazard ratio 0.68, $P < 0.01$) in the control (gp100 vaccine) arm. A first-line trial [2] demonstrated that ipilimumab combined with dacarbazine improved the median OS to 11.2 months versus 9.1 months with dacarbazine alone (HR 0.72, $P < 0.001$). The results led to licensing of ipilimumab in both settings.

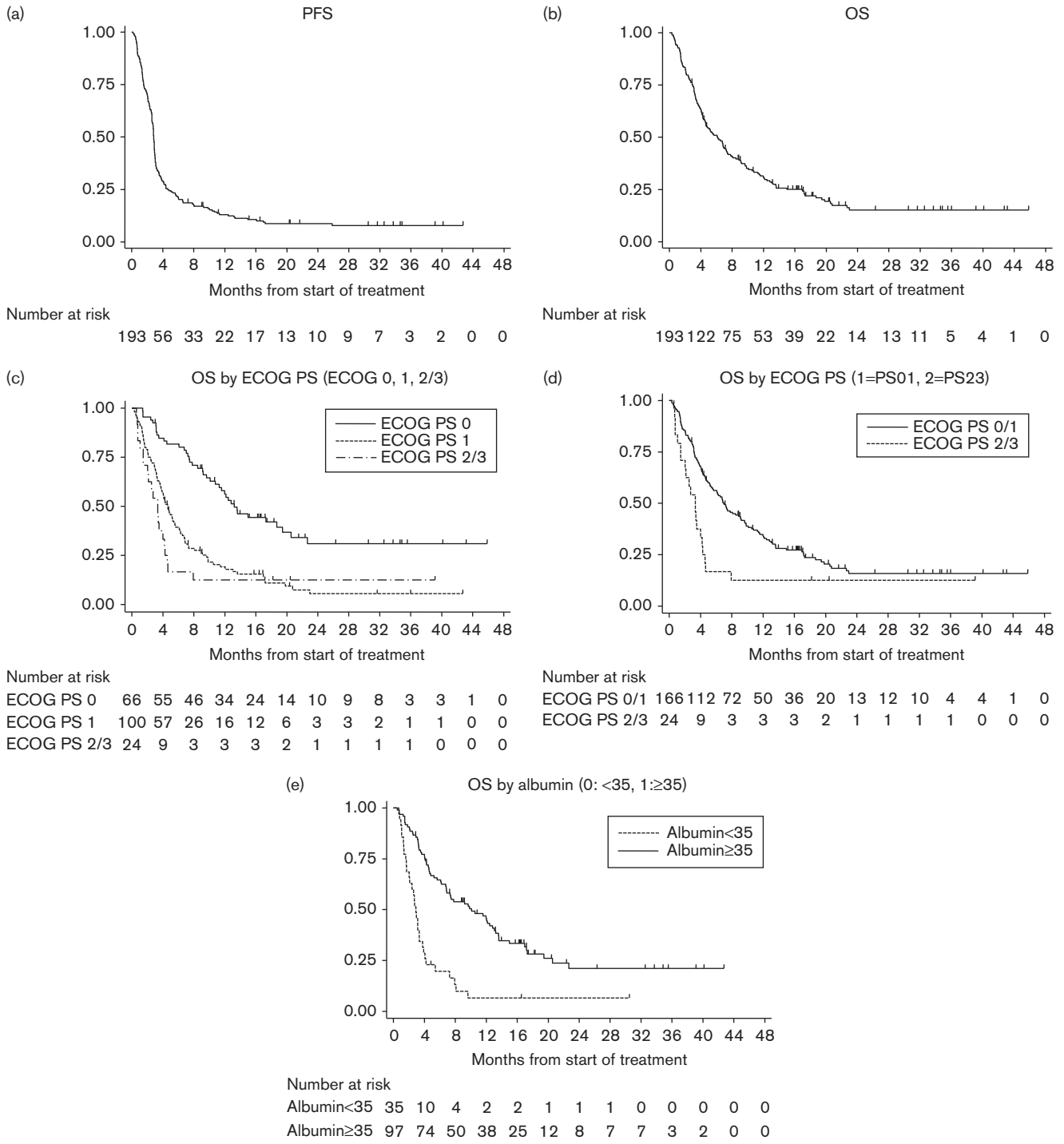
Longer follow-up of increasing numbers of advanced melanoma patients recruited to ipilimumab trials, as well as expanded access programmes (EAPs) worldwide, has confirmed that, in those patients who benefit from treatment, survival gain is sustained over several years, with a 3-year OS rate in the order of 20% [3]. Even so, most patients receiving ipilimumab do not benefit from treatment, and biomarkers predictive of response remain elusive. Ipilimumab is now routinely available in most western countries, and the licensed indication is less stringent than the registration clinical trial eligibility criteria; hence, patient access has extended to a wider melanoma population than that originally rigorously studied. The health economic burden of this high-cost drug, alongside significant drug-related toxicity, which is life-threatening in some instances [1,2], is considerable: the sales of ipilimumab in 2013 totalled $960M.

Before licensing, international EAPs afforded doctors and patients alike early access to and experience with ipilimumab. Clinicians treating patients in the EAP were required to register and complete a training programme set by the manufacturer to assure patient safety. The drug was supplied free of charge. These registered patient cohorts provide a useful window to interrogate patient outcomes in a routine clinical setting. We undertook a retrospective review of previously treated advanced melanoma patients in the UK who accessed ipilimumab in the European EAP and compared their outcomes with relevant clinical trial and EAP patient data reported in the literature to date.

Methods

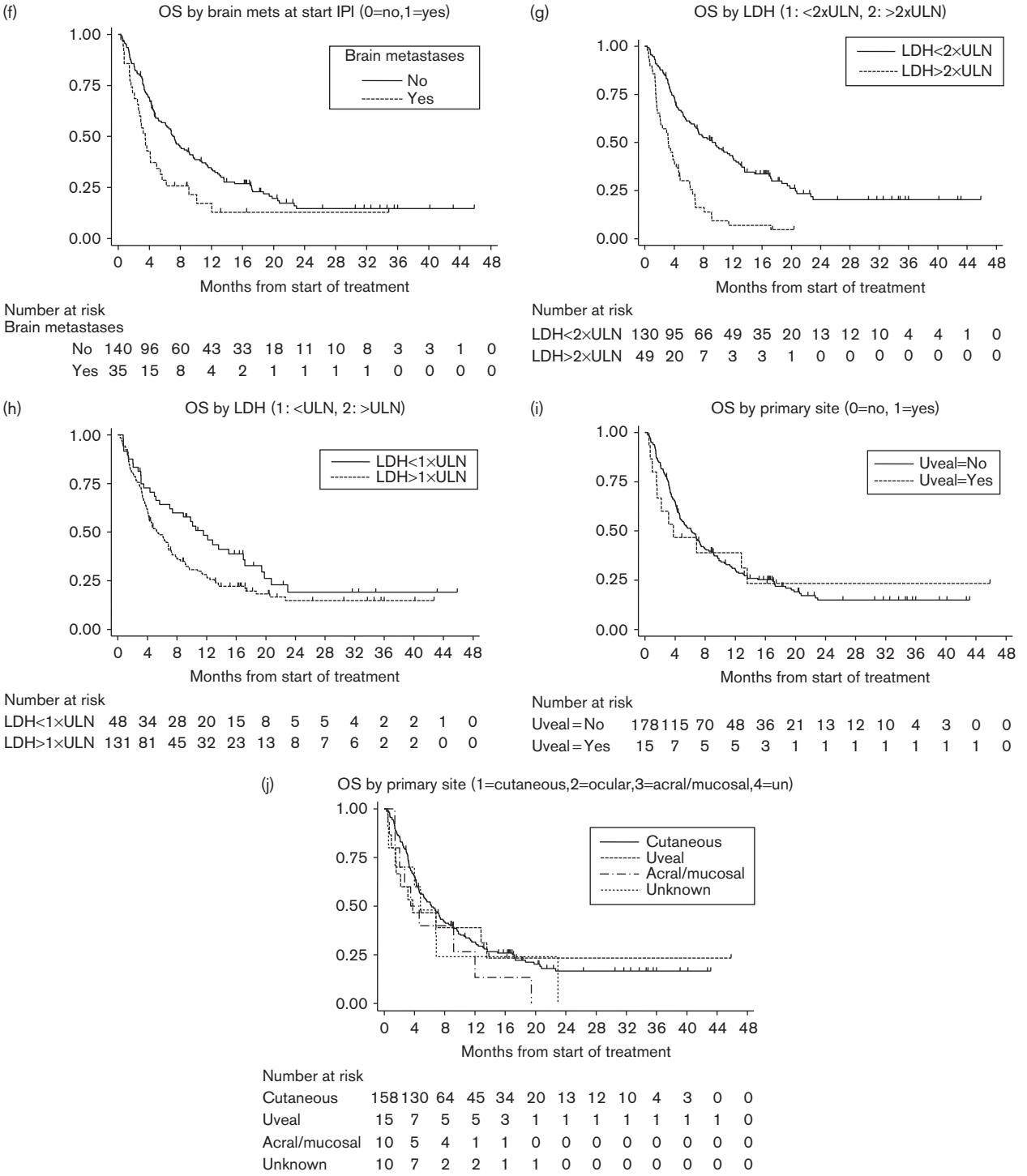
This was an ethics committee-approved, retrospective cohort study of UK advanced melanoma patients who met the criteria to access ipilimumab through an EAP provided by Bristol Myers Squibb in Europe between 2010 and 2011. Patients were required to have had previously treated, unresectable American Joint Committee on Cancer (AJCC) stage III or IV metastatic melanoma. Patients with brain metastases were not excluded as long

Fig. 1



Kaplan–Meier curves of (a) progression-free survival (PFS) and (b) overall survival (OS) for all patients, and of OS by patient characteristics such as (c, d) Eastern Cooperative Oncology Group (ECOG) performance status (PS), (e) serum albumin level, (f) presence of brain metastases, (g, h) lactate dehydrogenase (LDH) level and (i, j) primary melanoma site. ULN, upper limit of normal; IPI, Ipilimumab.

Fig. 1 (*Continued*)



as they were asymptomatic, stable and used systemic steroids at the lowest clinically effective dose. All patients were to be administered 3 mg/kg ipilimumab, three times a week, intravenously, for up to four cycles.

Design of study and data collection

Information was retrospectively collated by reviewing case notes of patients registered in the EAP. A standard anonymous data collection form was designed to collect data on patient characteristics before treatment: age, sex,

Table 3 Overall survival rates for all patients and subgroups defined by ECOG PS, serum albumin level, LDH level and the presence or absence of brain metastases

	1-year OS rate (%)		2-year OS rate (%)		Median OS (months)		*P*-value	
Subgroup	Rate	95% CI	Rate	95% CI	Median	95% CI	Univariate	Multivariate
ECOG 0	56	44–68	31	18–44	13.2	10.1–19.4	< 0.0001	0.0002
ECOG 1	19	11–27	5.6	0–11	4.6	3.7–5.6	0.23	0.83
ECOG 2/3	13	0–26	13	0–26	3.3	1.4–4.2		
Albumin ≤ 35	6.5	0–15	7	0–15	2.9	2.0–3.3	< 0.0001	0.001
Albumin > 35	46	35–56	21	11–31	10.1	6.8–13.0		
LDH ≤ 2 × ULN	42	34–51	20	12–29	9.6	6.7–12.1	< 0.0001	0.14
LDH > 2 × ULN	7	0–14	0		3.2	2.0–4.3		
LDH ≤ 1 × ULN	48	34–63	19	6–32	11.6	5.7–17.0	0.048	
LDH > 1 × ULN	27	19–35	15	7–22	5.4	4.1–6.9		
Brain metastases absent	34	26–42	15	7.8–21	7.2	5.2–9.1	0.0069	0.073
Brain metastases present	17	3.4–31	13	0.27–25	3.5	2.5–4.9		
Uveal = no	30	23–37	15	8.7–21	6.2	4.6–7.4	0.76	0.50
Uveal = yes	39	13–64	23	0.79–46	3.8	0.95–13.6		
LDH ≤ 1.5 × ULN[a]	45	35–55	20	11–30	10.1	6.7–13.2	0.0003	0.53
LDH > 1.5 × ULN[a]	18	9.0–26	9.5	1.5–17	4.3	3.2–6.1		

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OS, overall survival; PS, performance status; ULN, upper limit of normal.
[a]Post-hoc analysis.

primary site of melanoma, disease stage, presence or absence of brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status (PS), serum lactate dehydrogenase (LDH) level and albumin level. Data on the treatment delivered, including start date, dates of each cycle delivered, total number of cycles, drug doses, treatment modifications and reasons for modification, were recorded. Toxicity was assessed on the basis of internationally defined criteria (NCI CTCAE 4.03). Response was assessed by the investigators, with categories assigned retrospectively according to RECIST 1.1, clinical, or other. Progression-free survival (PFS) and OS were measured from the date of starting treatment.

Statistical analysis

PFS was defined from the date of starting ipilimumab treatment until the date of progression or the date of death from all causes, whichever occurred first; patients with unknown progression status at the time of data collection were censored at the date they were last known not to have progressed. OS was defined from the date of starting ipilimumab until the date of death from all causes; surviving patients at the time of data collection were censored at the date they were last known to be alive. PFS and OS were estimated using Kaplan–Meier analysis. Initially the subgroup analyses were to be carried out using the log-rank test on OS by age (≤ 60 vs. > 60 years), sex, ECOG PS (0 vs. 1 vs. 2/3) and ECOG PS (0/1 vs. 2/3), disease stage (cutaneous vs. uveal vs. acral vs. mucosal vs. unknown) and disease stage (uveal vs. other), brain involvement (yes vs. no), albumin level (≤ 35 vs. > 35 g/l) and LDH level greater than one time and two times the upper limit of normal (ULN; yes vs. no). Multivariate analyses were carried out after the initial analyses. Univariate and multivariate analyses using Cox regression models were reported. In addition, the correlation between the number of cycles and the ECOG PS was estimated after the initial analysis.

The OS of the UK EAP cohorts were compared with the results of the published cohorts, with their data read from the OS curves. A review of the literature and a literature search were performed as described by Chasset *et al.* [4]. Briefly, we searched EMBASE (1974–January 2014), MEDLINE (1966–February 2015) and the Cochrane Database of Systematic Reviews (The Cochrane Library, 2015, issue 1) for original articles without language restrictions. The search strategy combined free text search, exploded MESH/EMTREE terms and all synonyms of the following Medical Subject Headings terms: ipilimumab, immunotherapy, compassionate use, expanded access programme, melanoma. We also searched for additional articles from the reference lists of relevant papers obtained within the electronic search. The grey literature was also explored through a manual search of conference abstracts from the European Cancer Congress and the American Society of Clinical Oncology.

Results

Data collection forms were sent to 30 UK sites registered in the EAP and were returned from 17 of those sites. Data were collected on 195 patients, representing 70% of all UK patients registered in the ipilimumab EAP. Two patients did not go on to receive treatment because of deterioration in health. Therefore, data on 193 patients treated between 29 June 2010 and 20 September 2011 were included in the analyses. The dataset was locked for final analysis on 10 July 2014.

Key patient characteristics are summarized in Table 1. The median age of the patients treated was 60 years (range 25–81 years). Of the patients, 166 had PS 0 or 1 at the time of starting ipilimumab, 22 patients had PS 2 and

Table 4 Patient characteristics of those patients surviving for more than 24 months after starting ipilimumab

Variables (*n*)	*n* (%) (*N* = 14)
Age (years)	
n	14
Median	56
Range	25–70
Sex	
Male	5 (36)
Female	9 (64)
Primary site	
Cutaneous	13 (93)
Uveal	1 (7)
ECOG PS	
0	10 (71)
1	3 (21)
2	1 (7)
AJCC disease stage	
M1a	4 (29)
M1b	2 (14)
M1c	7 (50)
III/IV	1 (7)
Presence of brain metastases	
No	11 (92)
Yes	1 (8)
Unknown	2
LDH > 1 × ULN	
No	5 (38)
Yes	8 (62)
Unknown	1
Albumin ≥ 35	
No	1 (11)
Yes	8 (89)
Unknown	5
BRAF status	
Mutant	3 (50)
Wild type	3 (50)
Unknown	8
Response by RECIST criteria 1.1	
Progressive disease	1 (7)
Stable disease	5 (36)
Partial response	7 (50)
Complete response	1 (7)
Further lines of treatment after ipilimumab	
Yes	3 (30)
No	7 (70)
Unknown	4

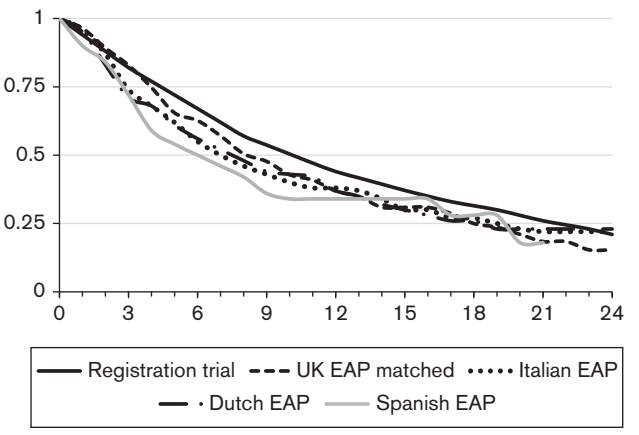
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; OS, overall survival; PS, performance status; ULN, upper limit of normal.

two patients had PS 3. The majority of patients had received one prior therapy; 35 patients had received two or more lines of prior therapy. Although the vast majority of patients had confirmed metastatic cutaneous melanoma, 15 patients had uveal primary sites and four had mucosal primary sites. Of the patients, 144 were disease stage IV M1c patients, and 35 patients had confirmed brain metastases. Twenty-two patients were receiving steroids at the time of starting ipilimumab, among whom 10 were known to have brain metastases. At the time of the EAP, *BRAF* mutation testing was not routinely available in the UK. Of the tumours tested, 51 were wild type and 20 had a *BRAF* V600 mutation.

Treatment and toxicity

All treated patients received ipilimumab at the approved dose of 3 mg/kg. Of the patients, 103 (53%) received the planned four cycles of ipilimumab. Poorer PS patients were less likely to receive the full planned treatments: the median number of cycles delivered to patients with PS 0–1 versus PS 2–3 was four versus two (correlation coefficient = −0.39, $P < 0.0001$). Among those patients who failed to complete four cycles ($n = 90$), the main reason for discontinuation was disease progression or death from melanoma for 67 (74%) patients.

Fig. 2



Overall survival of national multisite EAP cohorts compared with the ipilimumab registration trial, obtained by directly reading survival rate from the published Kaplan–Meier curves within the respective articles. EAP, expanded access programme.

Toxicity data were available for 171 patients. Of the patients, 70% were reported to have had at least one significant toxicity, defined as any grade 3 or greater adverse event, or any grade 1 or 2 adverse event deemed clinically significant by the treating clinician. Fifty-two (30%) of the 171 patients experienced CTC adverse events of grade 3 or higher (Table 2). The most common adverse event of grade 3 or higher was diarrhoea in 22 (13%) patients and fatigue in 15 (9%) patients. Significant immune-related adverse events (irAEs) were reported in 69 (40%) patients and 31 (19%) patients suffered irAEs of grade 3 or higher. Nine (10%) patients discontinued treatment because of unacceptable toxicity: five diarrhoea, one fatigue, one thrombocytopenia, one aseptic meningitis, one cardiac failure.

Three patient deaths were reported to be drug-related. Two patients developed severe diarrhoea after a second cycle of ipilimumab, and despite hospitalization and high-dose steroids, they died because of bowel perforation. A third patient with a history of previous heart valve surgery died suddenly of heart failure after her third ipilimumab treatment. As the death occurred 2 days after drug administration, the possibility of a drug effect could not be excluded. No *post mortem* was conducted.

Table 5 Comparison of patient demographics and outcomes from selected European EAP cohorts and the ipilimumab registration trial

Study	*N*	Median follow-up (months)	ECOG PS [*n* (%)]				Active brain metastases	Primary site of melanoma			Median OS (months)	Median PFS (months)	1-year OS (%)	2-year OS (%)
			0	1	2	3		Cutaneous	Mucosal	Uveal				
Registration trial [1]	137	27.8	72 (53)	64 (47)	1 (<1)	0	0	137 (100)		0	10.1	2.76	46	24
Italian EAP cohort [5]	855	6.7	563 (66)	267 (31)	25 (3)	0	146 (17)	631 (74)	71 (8)	83 (10)	7.2	3.7	35	20
Italian EAP cohort – uveal melanoma [8]	82	5.6	57 (69)	25 (30)	1 (1)	0	1 (1)	0	0	82 (100)	6.0	3.6	31	–
Dutch EAP cohort [6]	166	17.9	98 (59)	60 (36)	8 (5)	0	NR	NR	NR	NR	7.5	2.9	37.8	22.9
Spanish study [7]	153	NR	124 (81)	29 (19)	0	29 (18)	NR	NR	NR	6.5	NR	32.9%	NR	
UK EAP cohort	193	22.7	66 (35)	100 (53)	22 (12)	2 (1)	35 (20)	158 (82)	4 (2)	15 (8)	6.1	2.8	31	15

EAP, expanded access programme; ECOG, Eastern Cooperative Oncology Group; NR, not reported; OS, overall survival; PFS, progression-free survival.

Outcomes

Response assessment was conducted for 188 patients: 127 (67%) using RECIST 1.1 criteria, a further 52 (28%) by clinical assessment and nine (5%) by whole body computed tomography-PET or MRI brain imaging not reported according to RECIST. Among the 127 patients with RECIST response measurements available, one complete response (CR) and 23 partial responses (PR) were documented, giving a 19% overall objective response rate. All 52 patients with response assessed clinically were reported as having progressive disease except three patients (one PR, two stable disease). The treatment responses recorded in nine patients who underwent imaging but for whom RECIST measurements were not submitted were as follows: one CR, one PR, one stable disease, one mixed response, and five progressive disease. Therefore, the overall response rate for 188 evaluable patients was 14%.

At a median follow-up of 23 months, 42 patients were alive, of whom 18 were alive without evidence of disease progression. The median PFS was 2.8 months (95% confidence interval = 2.6–2.9 months) and PFS at 1 and 2 years were 13 and 9%, respectively (Fig. 1a). The median OS was 6.1 months (95% confidence interval = 4.6–7.3 months) and OS at 1 and 2 years were 31 and 15%, respectively (Fig. 1b).

The 1-year and 2-year OS rates and the median OS of patient subgroups of clinical interest are summarized in Table 3. Patient characteristics most likely to predict worse OS on univariate analyses were ECOG PS greater than 0 ($P < 0.0001$), low serum albumin level ($P < 0.0001$), serum LDH level greater than two times the ULN ($P < 0.0001$) and the presence of brain metastases ($P = 0.0069$). On multivariate analysis, statistical significance (at $P = 0.05$) was reached for ECOG PS greater than 0 and low serum albumin level, with a nonsignificant trend for the presence versus the absence of brain metastases ($P = 0.073$). The 2-year OS was 31% for ECOG PS 0 patients, but only 7% for patients with an ECOG PS of 1 or higher. Normal versus low serum albumin levels were associated with a 2-year OS of 21 versus 7%. Although the median survival of patients with brain metastases was short (3.5 months), some patients were long-term survivors: 1-year OS was 17% compared with 34% for those without brain involvement, whereas at 2 years, the OS rates were similar at 13 versus 15%. The primary site of melanoma did not appear to influence OS.

The review of the 14 patients who lived for more than 2 years (Table 4) for markers of good outcome is limited by the small cohort size. However, univariate analysis identified baseline PS and objective response to treatment as the most important factors ($P = 0.01$ and < 0.0001, respectively). Three of the long-term survivors received subsequent lines of treatment after ipilimumab: one underwent surgical resection of peritoneal disease,

Table 6 Update of literature review by Chasset *et al.* [4] of ipilimumab experience in expanded access programmes (EAPs)

References	Single (S)/multicenter (M)	Location	No. of patients	Melanoma subtype [*n* (%)]				No. of patients with brain metastases	Dose (mg/kg)	Median OS (months)	Factors positively associated with OS	Factors not associated with OS
				Cutaneous	Uveal	Mucosal	Unknown/ other					
Ku *et al.* [13]	S	MSKCC, New York, USA	53	42 (79)	5 (9)	3 (6)	3 (6)	NR	10	7.2	W3 + W6 ↑ALC	Baseline ALC
Wiater *et al.* [14]	M	Poland	50	41 (82)	9 (18)	0	0	9 (18)	3	8	PS ≤ 1	NR
Delyon *et al.* [15]	S	Gustave Roussy Institute, Paris, France	73	53 (73)	1 (1)	11 (15)	8 (11)	26 (36)	3	9.1	Four infusions. Baseline low LDH. W3↑ALC AEC	No. of prior therapies. Baseline corticosteroid use, ALC, AEC
Wilgenhof *et al.* [16]	S	UZ Brussel, Belgium	50	44 (88)	0 (0)	2 (4)	4 (8)	15 (30)	3	7	Baseline PS < 2, low LDH, CRP. W6 ↑ALC	NR
Di Giacomo *et al.* [17]	S[a]	University Hospital of Siena, Italy	27	23 (85)	3 (11)	1 (4)	0 (0)	NR	10	9.6	W7↑ICOS+ T cells, N/L < 2.81	Baseline ICOS+ T cells, N/L
Altomonte *et al.* [18]	M[a]	Italy	74	57 (77)	9 (12)	2 (2.7)	6 (8.1)	11 (15)	10	7	Baseline low LDH	NR
Konstantinou *et al.* [12]	M	France	38	NR	NR	NR	NR	38 (100)	3	3.3	NR	NR
Shapira-Frommer *et al.* [19]	M	Israel	183	NR	NR	NR	NR	63 (34)	3	9.2	IIIc, M1a, b. Baseline low LDH. ↑W6 ALC	NR
Simeone *et al.* [20]	S[a]	National Cancer Institute, Naples, Italy	95	76 (80)	7 (7)	7 (7)	5 (5)	30 (32)	3	9.6	W12↑ ALC↓ CRP, LDH, Foxp3 T cells	BRAF/NRAS status
Kelderman *et al.* [6]	M	The Netherlands	166	166 (100)	0 (0)	0 (0)	0 (0)	NR	3	7.5	PS0, M1a, b. Baseline high ALC, low LDH. W6 ↑ALC	irAEs, sex, ↑Breslow, prior therapy, site of melanoma
Chiaron-Sileni *et al.* [21]	M[a]	Italy	193	NR	NR	NR	NR	17 (9)	3	8.9	NR	Age > 70 vs. < 70
Queirolo *et al.* [22]	M[a]	Italy	146	NR	1 (1)	5 (3)	NR	146 (100)	3	4.3	Age > 60, PS0, no liver metastases, baseline LDH < 480 UI/l, no previous BRAF inhibitor nor corticosteroid use	NR
Ascierto *et al.* [5]	M[a]	Italy	855	631 (74)	83 (10)	71 (8)	70 (8)	146 (17)	3	7.2	NR	BRAF/NRAS + irAE
Alexander *et al.* [23]	S	Peter MacCallum Cancer Centre, Melbourne, Australia	104	79 (76)	11 (11)	8 (8)	6 (6)	44 (42)	3	11.7	NR	BRAF +, sex, age, brain metastases, irAEs, baseline LDH
Berrocal *et al.* [7]	M	Spain	153	NR	NR	NR	NR	29 (18)	3	6.5	Baseline LDH < 1.5 × ULN, high ALC	Age > 70 years
Chasset *et al.* [4]	S	Saint Louis Hospital, Paris, France	45	40 (89)	NR	0 (0)	5 (11)	23 (51)	3	8	Baseline low LDH, ↑W3 ALC and AEC, no baseline corticosteroid use	PS0-1, BRAF +, brain metastases, baseline AEC and ALC CRP
Maio *et al.* [8]	M[a]	Italy[a]	82	0 (0)	82 (100)	0 (0)	0 (0)	1 (1)	3	6	LDH < 480 U/l	NR
Present study	M	UK	193	158 (82)	15 (8)	4 (2)	14 (7)	35 (20)	3	6.1	Baseline PS <2, low LDH, albumin. Brain metastases	NR

AEC, absolute eosinophil count; ALC, absolute lymphocyte count; CRP, C-reactive protein; FoxP3, forkhead box P3; ICOS, inducible T cells COStimulator; irAEs, immune-related adverse events; LDH, lactate dehydrogenase; N/L, neutrophil to lymphocyte ratio; NR, not reported; OS, overall survival; PS, performance status; W3, W6: week3/6; IIIc, M1a, b, c, TMN melanoma staging; ↑, increased.
[a]Studies using a proportion of the same patients for their cohort.

another received selective internal radiation spheres for liver metastases and the third patient underwent metastasectomy, followed by targeted therapy with a combination of dabrafenib and trametinib within a clinical trial.

In the UK cohort, 111 patients matched the eligibility criteria of the original ipilimumab registration trial – that is ECOG PS 0–1, nonocular primary site and no active brain metastases. On plotting their OS against that of patients in the registration trial, as well as other published large nontrial datasets, the outcomes were similar (Fig. 2).

Discussion

We have reported outcomes of 193 previously treated advanced melanoma patients who accessed ipilimumab through the European EAP. There are clearly limitations to this retrospective cohort study, including the potential for patient selection bias, the wide range of patient populations and the lack of systematic methods as well as timing of assessments. However, this UK cohort represents the European EAP cohort with the longest follow-up to date and provides valuable outcome data for patients treated outside of a clinical trial. OS is an unbiased outcome measure. These survival outcomes – that is, a median OS of 6.1 months and a 1-year and 2-year OS of 31 and 15% – are inferior to those of the ipilimumab registration trial [1] – that is, a median OS of 10.1 months and a 1-year and 2-year OS of 46 and 24%, respectively – most probably reflecting wider eligibility criteria in the EAP compared with the randomized controlled trial. Outcomes of those EAP patients who met the more restrictive trial entry criteria were more comparable to those of the registration trial patients (Fig. 2). We also compared the UK EAP outcomes with outcomes from the three largest published EAP datasets from other European countries: Italy [5], the Netherlands [6] and Spain [7] (Table 5, Fig. 2). The lowest median and 1-year and 2-year OS rates were seen within the UK EAP. Of note, the UK cohort had the highest proportion of patients with ECOG PS greater than 0 and the highest percentage of patients with brain metastases. These findings argue for careful patient selection when considering this therapeutic intervention.

Most melanomas arise from the skin, but rarer sites of origin include the uveal tract and mucosal membranes. Uveal melanoma patients are frequently excluded from melanoma trials because of different biology and behaviour compared with melanomas of cutaneous and mucosal origin. Both UK and Italian European EAP cohorts provide useful insights into the role of ipilimumab in the treatment of advanced uveal melanoma patients, who were excluded from the registration trial. Both European EAP series suggest that outcomes of these patients did not differ greatly from those of other melanoma patients: the Italian group reported a 1-year OS of 31% for 82 advanced uveal melanoma patients compared with 35% for all 855 EAP patients [5,8]. In the UK cohort, 1-year and 2-year OS were 39 and 23%, respectively, for 15 advanced uveal melanoma patients, compared with 30 and 15% for 178 patients with nonuveal melanoma. Accepting the retrospective nature of these findings, the data suggest that a uveal site of origin should not exclude access to ipilimumab.

The UK EAP cohort provides important insight into treating melanoma patients with brain metastases. The registration ipilimumab trial excluded patients with active, untreated brain metastases. In clinical practice at the time, most brain metastases were diagnosed in patients presenting with neurological symptoms, and 20% of patients in the UK EAP had confirmed brain metastases. Specific information on their symptomatology and use of other treatments, including neurosurgery or radiotherapy, was not collected, but the main reason cited for 11% of patients being on steroids at the start of ipilimumab treatment was the presence of brain metastases. Only 29% (10 out of 35) of patients with brain metastases in the UK EAP were taking steroids before commencing ipilimumab, which might indicate a more favourable prognosis. Despite this, the OS of patients with and those without brain metastases was significantly different at 1 year (34 vs. 17%), but it was almost identical at 2 years (15 vs. 13%; Table 3, Fig. 1), suggesting that long-term outcome of patients with brain involvement is not uniform. One potential explanation for these results might be BRAF inhibitors, as a new treatment option for controlling *BRAF* mutant melanoma metastasizing to the brain [9], becoming widely available for use outside of trials [10]. However, data on subsequent treatments received after ipilimumab, which were available for 27 out of 35 patients with brain metastases, confirmed that none of them received a BRAF inhibitor. Alternatively, survival 1 year from ipilimumab treatment may be indicative of long-term disease control among those patients with brain involvement.

The median OS of patients with brain metastases in our cohort was 3.5 months, and this is consistent with the only published prospective, single-arm study of ipilimumab in patients with brain metastases, which reported a variable median OS depending on the presence (3.7 months) or absence (7 months) of symptoms [11]. Further retrospective series from Italy and France report median OS of 4.5 and 3.3 months, respectively, in patients with brain metastases [12]. Combining systemic therapies for melanoma with conventional treatments for brain metastases, including whole-brain radiotherapy, radiosurgery or indeed surgery, is an evidence-poor region, and formal studies are needed to guide future clinical management of this poor prognostic group.

As demonstrated by the pooled analysis of 1861 patients recruited to phase II and III ipilimumab trials, as well as US EAPs, long-term survival from ipilimumab is gained by around one in five treated patients, with a 22% 3-year

survival now demonstrated [3]. The challenge remains to identify predictive markers of response, given that the majority of treated patients will not benefit. Table 6 summarizes published experience with ipilimumab in EAPs, highlighting factors reported to be predictive of treatment outcome. The heterogeneity of factors illustrate well the absence of and need for a reliable predictive biomarker. Moreover, the majority of factors reported significance on univariate analysis. Our UK experience identified ECOG PS and serum albumin to be the strongest predictors of survival in a multivariate analysis. LDH level was reported to be the strongest predictor of poor outcome in 166 previously treated melanoma patients receiving ipilimumab in the EAP conducted in the Netherlands [6]. Retrospective multivariate analysis of the Netherlands cohort and an independent cohort of 64 UK patients (some of whom received ipilimumab in the EAP and are therefore represented in the current review) identified that long-term survival benefit was unlikely for patients with a baseline serum LDH level greater than two times the ULN. In the UK patient cohort, an elevated LDH level and the presence of brain metastases were strong predictors of poor outcome in a univariate analysis. Consistent with the Dutch findings, an LDH level greater than two times the ULN was a stronger predictor than an LDH level greater than one time the ULN. However, in our multivariate analysis, in which a total of 109 patients (82 OS events) had complete data for all factors included, both an LDH level greater than two times the ULN and brain metastases were of borderline significance. We also carried out a post-hoc analysis based on the results from the Spanish EAP, which identified baseline lymphocyte counts over 1000/ml and an LDH level greater than 1.5 times the ULN as factors predictive of survival, on univariate analysis alone [7]. In the UK cohort, an LDH level greater than 1.5 times the ULN was statistically significant on univariate analysis; however, on multivariate analysis this was no longer the case.

These inconsistencies may reflect differences between the national patient cohorts. For example, the UK validation cohort used by the Dutch group was confined only to cutaneous melanoma, and 95% of its patients had PS 0–1. Alternatively, they may be illustrative of the weakness of post-hoc analyses and may signify the need to evaluate putative biomarkers in prospective studies. Even so, there is a set of biochemical and clinical parameters – serum LDH and albumin levels, PS and brain metastases – that are established poor prognostic indicators in advanced melanoma, and until there is better evidence, they should be taken into account when selecting patients for ipilimumab treatment.

In terms of safety, a consistent theme with ipilimumab across multiple clinical trials is risk for irAEs, and, rarely, death due to colitis. The registration trial reported that around 45% of patients experienced a grade 3 or 4 event, of which 17–24% were considered to be drug-related. In addition, 10–15% of patients were reported to experience grade 3 or 4 immune-related toxicities, and there were five (1%) patient deaths due to colitis or bowel perforation [1]. Routine clinical practice is often associated with less close patient monitoring and hence with the risk of higher rates of drug-induced deaths. In the UK, EAP, reassuringly, 30% grade 3 or 4 toxicities were reported, of which two-thirds were considered to be immune-related. Treatment-related deaths resembled those reported in the registration trial in both frequency and cause: two of the three deaths were associated with colitis and bowel perforation despite active intervention; the risk of death from ipilimumab was 1.6% in the UK EAP versus 2.1% in the registration trial.

In summary, the 193 UK melanoma patients reviewed in this study, who were treated with ipilimumab in the European EAP, represented a population with characteristics considerably wider than those of the population in the controlled registration trial. A consequence of widening access to poorer prognostic group patients was overall poorer survival outcomes, although the outcomes of those patients matching the entry criteria of the registration trial were similar. Our data suggest that careful patient selection is important. In particular, ipilimumab should probably be avoided in patients with poor PS and with other evidence of high tumour burden, including low serum albumin and high LDH levels. However, interrogation of the data suggests a similar safety profile compared with controlled trials, whereas our findings lend weight to the use of ipilimumab in advanced uveal melanoma patients and selected patients with brain metastases.

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Conflicts of interest

P.G.C. has received payment for attending BMS advisory boards. C.H.O. has received payment for attending BMS advisory boards, and his institution has received money for travel to a BMS meeting. R.P. has received payment from BMS for consultancy and travel expenses. For the remaining authors there are no conflicts of interest.

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