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Health Care Resource Utilization and Associated Costs Among Metastatic Cutaneous Melanoma Patients Treated with Ipilimumab (INTUITION Study)

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Disclosures of potential conflicts of interest may be found at the end of this article.

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Abstract

Background. There are limited real-world data on health care resource utilization (HCRU) among advanced melanoma patients. The objective of this study was to describe HCRU and health care costs associated with the management of advanced melanoma patients receiving ipilimumab.

Methods. This retrospective multinational, observational study included advanced melanoma patients from Australia, Germany, Italy, and Spain who had received at least 1 dose of ipilimumab. Data extracted from medical charts included inpatient admissions, outpatient visits, surgical procedures, laboratory investigations, radiation therapy, imaging studies, and concomitant medications. Cost estimates were based on unit costs from country-specific standard reimbursement sources. Subgroup analyses were performed for BRAF mutation status and ipilimumab refractory patients, who had disease progression within 24 weeks of their last dose of ipilimumab.

Results. Mean age of 362 enrolled patients was 60.6 years (standard deviation [SD] 14.4). During a median follow-up period of 30.2 weeks, 57% of patients were admitted to hospital and 16% underwent surgery. Health care resource utilization rates varied substantially across countries and were highest in Germany. Concomitant medications to treat adverse events were commonly used. Subgroup analyses showed higher utilization rates among ipilimumab refractory and BRAF mutant patients. Mean weekly total costs associated with HCRU were lower in the pre-progression period (€107; 95% confidence interval (CI): 79–145) than in the post-progression period (€216; 95% CI: 180–259).

Conclusion. Health care resource utilization pattern and associated costs among patients treated with ipilimumab varied greatly among countries and between pre- and post-progression periods. There is a high economic burden associated with ipilimumab refractory melanoma. *The Oncologist* 2017;22:951–962

Implications for Practice: Metastatic melanoma patients treated with the anti-CTLA-4 inhibitor ipilimumab have a high utilization of various types of health care services, such as inpatient hospital stays or doctor visits. There are differences across countries regarding patterns of health care utilization and economic burden of the disease. Health care services are used more frequently after patients experience progression of their disease. The study highlights that better therapies leading to durable response in patients with metastatic melanoma have the potential to decrease health care costs and patient burden in terms of hospitalizations and other health care services.

Introduction

The worldwide incidence of melanoma is increasing by 4.5% per year with approximately 232,000 new cases diagnosed every year [1, 2]. Early stage cutaneous melanoma has an excellent prognosis following local resection, yet the prognosis is poor with unresectable stage III and IV disease [3]. Until 2011, the median length of survival with stage IV melanoma was 6.2 months, the 1-year overall survival (OS) rate was 25.5% [4], and dacarbazine was the standard of care in most countries, while participation in a clinical trial was also recommended [5].

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The treatment algorithm for advanced melanoma changed in 2011 with the approval of the anti-CTLA-4 inhibitor ipilimumab dosed at 3 mg/kg in Australia and the European Union (EU) for previously treated unresectable or metastatic melanoma. By 2013, several targeted agents (vemurafenib, dabrafenib, and trametinib) were also granted regulatory approval for the approximately 50% of melanoma patients whose tumors express a BRAF mutation [9]. The EU approval of ipilimumab was extended to first-line treatment in October 2013, supported by data from two retrospective observational studies conducted in treatment-naïve patients [6, 7]. Ipilimumab demonstrated a significant benefit in OS [8], yet 10%–15% of patients experienced an immune-related adverse reaction of grade 3 or higher severity [8].

The timing of patients' access to ipilimumab varied by country, while local reimbursement terms were negotiated. In Germany, ipilimumab was reimbursed through the statutory health insurance as of EU approval and was further supported by a positive vote from German Federal Joint Committee (Gemeinsamer Bundesausschuss [G-BA]). In November 2012, the Australian Pharmaceutical Benefits Advisory Committee recommended reimbursement of ipilimumab for first- or second-line therapy, beyond the second-line indication specified in the regulatory approval; however, funding did not commence until August 2013. In Spain and Italy, ipilimumab was reimbursed as of October 2012, following positive decisions made by regional reimbursement bodies in Spain and the Italian Medicines Agency in February 2013.

Historically, hospitalizations have been more frequent during supportive care than during systemic therapy [11]. Toy et al. analyzed administrative claims data from the U.S. to compare total health care resource utilization (HCRU) and associated costs between patients treated with ipilimumab and those treated with vemurafenib as the initial treatment [12]. The study showed twofold higher total health care costs, but a lower rate of outpatient visits for the ipilimumab cohort compared with the vemurafenib cohort. However, the study had a very short follow-up period of only 6 months and may not fully reflect health care utilization after the initial treatment.

Tarhini et al. conducted a retrospective chart review of stage IV patients receiving first-line ipilimumab in the U.S. and observed high hospitalization rates for short-term survivors and a considerable increase in health care costs associated with grade 3 or 4 adverse events [13]. Costs of imaging or concomitant medications used to manage immune-related adverse events, such as colitis or hypophysitis, were not considered [13, 14]. There is heterogeneity across studies with regard to study settings, populations, and approaches to describe HCRU and associated costs related to these treatments. Considering the unique safety profile of ipilimumab, the aim of this study was to assess real-world HCRU and costs associated with managing advanced melanoma treated with ipilimumab, excluding the costs of anti-melanoma therapy.

MATERIALS AND METHODS

Study Design

INTUITION (INternational STUdy on Ipilimumab Treatment utilizatION in real world clinical practice) was a retrospective chart review study including adult patients with confirmed unresectable stage III or IV cutaneous melanoma as defined by the American Joint Committee on Cancer [15] who were treated with ipilimumab. Subjects from 19 sites in Germany, Australia, Italy, and Spain were enrolled from sites which had treated a minimum of 30 patients with ipilimumab and a minimum of six after local regulatory approval. To avoid potential bias introduced by including predominantly heavily pretreated subjects treated just after regulatory approval, a consecutive sampling strategy was employed. Working in reverse order from the latest to the earliest index date, sites enrolled all eligible subjects until the target minimum number of 50 patients per country was achieved. Recruitment was then competitive at all sites until the total enrollment target was achieved.

Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and radiographic evidence of disease at treatment initiation. Patients with primary ocular or mucosal melanoma or who were enrolled in a clinical trial or early access program were excluded.

Ethics committee approvals and informed consents were obtained in accordance with local practice and regulations prior to any data abstraction. This was a hypothesis-generating, descriptive study; no sample size calculation was undertaken.

Data Collection

Individual patient data, including demographic characteristics, clinical treatment history, HCRU, and clinical outcomes, were abstracted by the treating physician and site personnel. Data on HCRU included inpatient admissions, surgeries, health care visits (outpatient, office-based, emergent care) laboratory investigations, radiation therapy, imaging studies, and concomitant medications, excluding visits for administration of anti-melanoma therapy. Attribution of HCRU and use of concomitant medications for management of adverse events was reported per investigator judgment.

Costs

Cost estimates were calculated as the products of HCRU items multiplied by the corresponding unit cost. Country-specific unit costs were identified from standard costing sources as well as publications, if official data were not available (Table 1). The reference year for the unit costs was 2014, the year the study was commenced. In cases where unit costs from 2014 were not available, the latest reference was used and was inflated to 2014-year cost using the health care price index. Costs were reported in local currency for country-specific summaries. For overall cost summaries, Australian dollars were converted to Euros using the 2014 currency exchange rate (1 AUD = 0.677 EUR). Cost analyses were conducted from the health care payer perspective based on reimbursement for non-privately insured patients.

Costs for concomitant medications were calculated by multiplying the cost of a defined daily dose (DDD) by the number of days the drug was taken [16]. The price for the lowest priced product in each particular drug group was used and costs per DDD were calculated based on the largest disposable package. To reflect the payer perspective, co-payments of the insured as well as potential pharmacy or manufacturer's discounts were subtracted from gross pharmacy retail prices [17, 18]. Concomitant medication included all drugs used for management of adverse events.

Table 1. Items and sources used for costing (unit costs)

Cost category	Items used for costing	Australia	Germany	Italy	Spain
				Sources used for costing	
Inpatient cost	Cost per day in hospital Cost per day in ICU	• AR-DRG v6.0 and IPD data [21] • Cost of Care Standards 2009/10 NSW Health [22]	Bock et al. 2015 [23]	Maio et al. 2012 [24]	Averages across the following sources: • Órgano consejeria de sanidad y asuntos sociales 2014, Castilla-la-Mancha [25] • Precios públicos pruebas realizadas en el Servicio Murciano de Salud 2014, Murica [26] • Disposiciones generales 2014, Extremadura [27] • Diario Oficial de Galicia 2014 [28] • Consejería de Sanidad 2013, Madrid [29]
Outpatient care cost	Cost per outpatient hospital visit Cost per office-based visit	• Cost of Care Standards 2009/10 NSW Health [22] • MBS item 105 [30]	Bock et al. 2015 [23]	Region Emilia Romagna Tariffario. Nomenclatore tariffario regionale (updated 2014) [31].	
Imaging cost	Cost per imaging procedure	MBS online [30]	Catalogue of the Physician Association: KBV – EBM 01/2015 [32]	Region Emilia Romagna Tariffario. Nomenclatore tariffario regionale (updated 2014) [31]	
Surgery cost	Cost per type of surgery	AR-DRG v6.0 [21]	DRG Research Group; Web grouper, Universität Münster [33]	• Gazetta ufficiale [34]; • Cassa autonoma di assistenza integrativa dei giornalisti italiani (CASAGIT) – Il Tariffario [16]; • Conferenza Delle Regioni E Delle Province Autonome. Tariffa Unica Convenzionale per le Prestazioni Di Assistenza Ospedaliera [36]; • Maio et al. 2012 [24]; • Colombo et al. 2008 [37]	Almazan-Fernandez et al. 2009 [38]
Radiation cost	Cost per treatment session	Cost of Care Standards 2009/10 NSW Health [22]	Koerber et al. 2014 [39]	• Gazetta ufficiale [34]; • Maio et al. 2012 [24]	Diario Oficial de Galicia 2014 [28]
Laboratory investigations cost	Cost per laboratory test	MBS online [30]	Catalogue of the Physician Association: KBV - EBM 01/2015 [32]	Cassa autonoma di assistenza integrativa dei giornalisti italiani (CASAGIT) – Il Tariffario [35]	Almazan-Fernandez et al. 2009 [38]
Concomitant medication cost	Cost per day of treatment (based on defined daily dose)	Pharmaceutical Benefits Scheme (effective 1 August 2014–31 August 2014) [40]	Rote Liste Service GmbH: Rote Liste [41]	• BBFarma srl. Italian Medicines Database (2009–2015) [42]; • Network Pagine Sanitarie. Farmaci ricerca analitica [43]	Colegio de Farmacéuticos de Pontevedra [44]

Abbreviations: AR-DRG, Australian Refined Diagnosis Related Group; ICU, intensive care unit; IPD, inpatient day; KBV, Kassenärztliche Bundesvereinigung; MBS, Medicare Benefits Schedule; NSW, New South Wales.

Statistical Analysis

The analyses included all subjects who received at least one dose of ipilimumab. Results on HCRU and costs are reported for the entire period from initiation of ipilimumab to end of study (EOS) and stratified by pre-and post-progression health states. The pre-progression health state includes utilization data up to 3 weeks prior to date of confirmed progression or the date an investigator suspected disease progression which was later confirmed. The post-progression health state includes data from disease progression to EOS/death, whichever occurred earlier. Summaries of HCRU and health care costs were reported for the entire patient sample as well as stratified by country.

Subgroup analyses were conducted for BRAF mutant patients and for ipilimumab refractory patients who had received at least 2 doses of ipilimumab and confirmed progression of disease as reported by the investigator within 24 weeks of their last dose of ipilimumab.

Utilization of each type of health care service is described by the number and percentage of subjects utilizing the service, and the total and weekly number of events, calculated as the total number of events divided by the time in weeks the subject was followed up in that health state. For inpatient visits, the duration of hospitalization was further summarized.

To summarize the use of concomitant medications, the most common concomitant medications (in ≥5% of all patients) were reported. Costs were summarized by type of health care service and were described in terms of total costs and weekly costs. In addition, bootstrapped 95% CIs were calculated for the total weekly cost per health state.

RESULTS

Demographics and Disease History

The study included 362 eligible patients who received at least 1 dose of ipilimumab. The mean follow-up time from ipilimumab initiation to the last contact/death was 41.3 weeks (median: 30.2; minimum [min]: 1.3; maximum [max]: 185.6). In Australia, the earliest treatment initiation date was September 2010, followed by Spain and Germany (both July 2011), and Italy (April 2013). The latest date of data abstraction was between August 2014 (Australia) and April 2015 (Italy and Spain). At the end of data abstraction, 252 (69.6%) patients had died (Table 2).

The mean age of all patients was 60.6 (SD 14.4) years. The majority of patients were male (61.9%). Most patients had either an ECOG performance status of 0 (54.7%) or 1 (40.1%). Among all included patients, 82.3% had non-metastatic melanoma at the initial diagnosis and most (86.9%) had undergone complete surgical resection after their initial melanoma diagnosis. At ipilimumab initiation, 96.4% of patients had stage IV melanoma, and the greatest percentage of patients had lung metastases. Of 346 patients tested, 121 (35.0%) had BRAF mutant disease. A majority of patients received chemotherapy prior to ipilimumab, most commonly dacarbazine (38.1%), vemurafenib (16.6%), or "other specific inhibitors" (16.9%). The mean time from diagnosis of stage IV cancer to first dose of ipilimumab was 12.0 months (median: 6.8; interquartile range: 6.8–13.7), and the majority (66.9%) of patients initiated ipilimumab as a second line of therapy.

The highest percentage of patients (56.4%) received 4 doses of ipilimumab, with a mean number ipilimumab doses per patient of 3.4 (min: 1; max: 8). The median duration of ipilimumab therapy was 12.0 weeks with a median dosing interval between consecutive doses of ipilimumab of 21 days. Retreatment with ipilimumab was uncommon and predominantly seen in Australia. A total of 226 patients were ipilimumab refractory.

Health Care Resource Utilization

Overall, 205 (56.6%) patients were admitted to the hospital between initiation of ipilimumab and EOS, with a total of 471 hospital admissions (Table 3). The mean length of stay was 9.5 days (median: 3.0; min: 0; max: 113). Overall, 67.7% (281 of 415) of hospitalizations were related to the management of melanoma and 8.4% were due to complications of melanoma treatment, of which 10.1% (42 of 415) of hospitalizations were attributed to ipilimumab regardless of whether they were due to treatment complications. During the post-progression period, the mean weekly totals for hospital admissions (0.031) and length of hospital stay (0.249 days) were higher than during treatment with ipilimumab (0.013 admissions and 0.093 days, respectively). The same was true for the number of patients affected, with 145 (52.9%) of patients being admitted to hospital after disease progression and 74 (22.4%) of patients being admitted pre-progression. Hospitalization rates varied significantly between countries, being highest in Germany, where 115 (78.2%) patients had at least one hospitalization, and lowest in Italy (15 patients [20.0%]).

Among patients who received outpatient care, 55 (15.2%) had outpatient hospital visits, 52 (14.4%) had office-based visits, and 24 (6.6%) had visits for emergent care. The weekly totals of outpatient hospital and emergent care visits were each higher during post-progression, whereas the weekly total of office-based visits was higher during treatment with ipilimumab. The average number of office-based visits per week (0.052) was about 5 times higher in Spain than in Germany or Australia (0.009).

Of all 362 patients, 58 (16.0%) underwent surgery, comprising 4 (1.1%) patients with bowel resections and 54 (14.9%) patients with other surgeries. All bowel resections ($n = 7$) and most other surgeries, 69 (92%), were attributed to melanoma disease or treatment. No surgery was attributed to ipilimumab. There were no differences in mean weekly surgeries between pre- and post-progression. The percentage of patients having surgeries was more than 4 times higher in Germany (30.6%, $n = 45$) than in the other countries (ranging from 2.7% to 7.9%). Overall, 102 (28.2%) patients received radiation therapy, totaling 126 radiation treatment periods. Disease progression was associated with an increased rate of radiotherapy: There were 29 (10.6%) patients who underwent radiation therapy prior to disease progression, compared to 68 (24.8%) patients in the post-progression period. The overall mean number of radiotherapy sessions per patient was 2.1 (min: 0; max: 31; SD: 4.6).

Overall, most patients underwent hematology ($n = 235$; 64.9%) and chemistry ($n = 225$; 62.2%) investigations; just over half ($n = 187$; 51.7%) were tested for thyroid function and 14.4% ($n = 52$) were tested for pituitary function using the adrenocorticotropic hormone (ACTH) stimulation test (supplemental online Table 1). With the exception of ACTH

Table 2. Disposition of patients and baseline characteristics

Characteristics	Australia n = 102	Germany n = 147	Italy n = 75	Spain n = 38	Total n = 362
Disposition at end of data abstraction					
Deceased, n (%)	54 (52.9)	115 (78.2)	54 (72.0)	29 (76.3)	252 (69.6)
Cause of death, n (%)[a]					
Melanoma disease related	40 (74.1)	105 (91.3)	45 (83.3)	27 (93.1)	217 (86.1)
Melanoma treatment related complication	0	1 (0.9)	0	0	1 (0.4)
Other	2 (3.7)	1 (0.9)	1 (1.9)	2 (6.9)	6 (2.4)
Unknown	12 (22.2)	8 (7.0)	8 (14.8)	0	28 (11.1)
Alive, n (%)[a]	48 (47.1)	32 (21.8)	21 (28.0)	9 (23.7)	110 (30.4)
Follow-up time in wk, mean (SD)	44.8 (44.5)	42.2 (36.0)	37.4 (23.7)	35.5 (30.8)	41.3 (36.1)
Demographics					
Age, yr					
Mean (SD)	58.2 (15.7)	62.6 (13.4)	62.3 (13.9)	55.8 (14.3)	60.6 (14.4)
Median (min, max)	59.5 (22.0, 88.0)	65.0 (25.0, 88.0)	65.0 (23.0, 88.0)	54.0 (26.0, 81.0)	63.0 (22.0, 88.0)
Gender, n (%)					
Female	34 (33.3)	53 (36.1)	33 (44.0)	18 (47.4)	138 (38.1)
Male	68 (66.7)	94 (63.9)	42 (56.0)	20 (52.6)	224 (61.9)
ECOG performance status, n (%)					
0	43 (42.2)	86 (58.5)	51 (68.0)	18 (47.4)	198 (54.7)
1	47 (46.1)	58 (39.5)	23 (30.7)	17 (44.7)	145 (40.1)
2	12 (11.8)	3 (2.0)	1 (1.3)	3 (7.9)	19 (5.2)
Disease history					
Time from melanoma diagnosis to first dose of ipilimumab in yr, mean (SD)	4.4 (3.8)	5.0 (5.8)	4.0 (4.2)	3.6 (5.6)	4.5 (4.9)
BRAF status, n (%)					
No test performed	0	12 (8.2)	3 (4.0)	1 (2.6)	16 (4.4)
Positive	29 (28.4)	53 (36.1)	29 (38.7)	10 (26.3)	121 (33.4)
BRAF V600D[b]	0	0	0	1 (10.0)	1 (0.8)
BRAF V600E[b]	20 (69.0)	27 (50.9)	25 (86.2)	6 (60.0)	78 (64.5)
BRAF V600K[b]	4 (13.8)	6 (11.3)	2 (6.9)	0	12 (9.9)
BRAF V600R[b]	1 (3.4)	0 (0.0)	0 (0.0)	0	1 (0.8)
Other[b]	0	2 (3.8)	1 (3.4)	0	3 (2.5)
Unknown if BRAF V600D,-E,-K, or -R[b]	4 (13.8)	18 (34.0)	1 (3.4)	3 (30.0)	26 (21.5)
Uncertain	2 (2.0)	0	0	1 (2.6)	3 (0.8)
Wild-type	71 (69.6)	82 (55.8)	43 (57.3)	26 (68.4)	222 (61.3)
Advanced melanoma diagnosis type, n (%)					
Metastatic disease	100 (98.0)	138 (93.9)	74 (98.7)	35 (92.1)	347 (95.9)
Unresectable Stage III	2 (2.0)	9 (6.1)	1 (1.3)	3 (7.9)	15 (4.1)
Location of metastasis, n (%)					
Cutaneous	45 (44.1)	50 (34.0)	19 (25.3)	12 (31.6)	126 (34.8)
Lung	65 (63.7)	89 (60.5)	53 (70.7)	21 (55.3)	228 (63.0)
Brain	29 (28.4)	50 (34.0)	14 (18.7)	4 (10.5)	97 (26.8)
Other	66 (64.7)	112 (76.2)	60 (80)	24 (63.2)	262 (72.4)

(continued)

Table 2. (continued)

Characteristics	Australia n = 102	Germany n = 147	Italy n = 75	Spain n = 38	Total n = 362
Utilization of ipilimumab					
Line of initial administration of ipilimumab, n (%)					
1	10 (9.8)	20 (13.6)	2 (2.7)	4 (10.5)	36 (9.9)
2	74 (72.5)	91 (61.9)	57 (76.0)	20 (52.6)	242 (66.9)
3	16 (15.7)	27 (18.4)	12 (16.0)	12 (31.6)	67 (18.5)
4	2 (2.0)	9 (6.1)	4 (5.3)	2 (5.3)	17 (4.7)
Doses per patient, mean (SD)	3.5 (1.8)	3.2 (1.2)	3.5 (0.9)	3.2 (1.3)	3.4 (1.4)
Regimen duration in wk, median	12.0	12.0	12.0	11.9	12.0

Table includes all eligible patients who received at least 1 dose of ipilimumab.
Follow-up time was calculated as the date of first dose of ipilimumab to last contact date.
Regimen duration is defined as the number of weeks from first to last dose of ipilimumab plus 21 days.
[a]Percentages based on cumulative total.
[b]Percentages are based on the number of patients that are BRAF positive.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum.

stimulation tests, the weekly number of laboratory investigations was higher during the post-progression health state. Positron emission tomography (PET) or computer tomography (CT) imaging was received by 216 (59.7%) of patients, followed by 104 (28.7%) receiving magnetic resonance imaging (MRI), 51 (14.1%) receiving ultrasonography, and 43 (11.9%) receiving conventional radiography. The proportion of patients receiving MRIs was higher in Germany (53.1%; n = 78 out of 147) than in the other countries (4.0% to 28.7%). Imaging was more frequent after progression than during treatment with ipilimumab.

Health care resource utilization in the subgroups of ipilimumab refractory patients and patients with BRAF mutated tumors are shown in Table 4 and supplemental online Table 2. Results indicate that patients in the refractory analysis set had higher weekly utilization rates than patients in the full analysis set for almost all resource categories, including laboratory investigations and imaging. Higher weekly utilization rates were also observed among BRAF mutant melanoma patients, with the exception of weekly totals for thyroid function tests and ACTH stimulation tests, which were slightly lower than in the full analysis set.

Concomitant medications most commonly used to treat adverse events included dexamethasone (19.1% of patients; n = 69), oxycodone hydrochloride (HCl) (9.1%; n = 33) and paracetamol (5.0%; n = 18), methimazole sodium (7.7%), and metoclopramide (5.8%; n = 21) (Supplemental Table 3). Infliximab was used only for 2 out of the 362 patients. Similar patterns were observed for ipilimumab refractory and BRAF mutant patients.

Health Care Resource Costs

Excluding drug costs for systemic anti melanoma therapy, total weekly costs from start of treatment with ipilimumab until EOS were highest in Germany (€233), followed by Australia (215 AUSD, corresponding to €146), Spain (€129), and Italy (€91). In each country and for almost all cost categories, weekly total costs were higher in the post-progression health state than in the pre-progression health state (Table 5). The only exceptions are costs for laboratory testing (each country), surgery costs in Australia, and concomitant drug costs in Germany, where pre-

progression costs were higher than post-progression costs. Overall, inpatient stays accounted for the highest portion of overall weekly total costs (€107), followed by costs for radiotherapy (€18), and costs for surgeries (€16). However, this rank order was not consistent across countries.

DISCUSSION

This was a multi-site retrospective study conducted in four different countries utilizing real-world data to describe HCRU and associated costs among advanced melanoma patients treated with ipilimumab. The focus was to estimate the economic impact associated with monitoring patients for and managing immune-related toxicities associated with use of ipilimumab.

Overall, patients had high rates of HCRU, both while on ipilimumab treatment and after disease progression. More than half of the patients were admitted to a hospital and one in six patients underwent surgery. Rates of HCRU varied substantially across countries and were highest in Germany, especially with respect to the frequency of hospitalization and surgery. In contrast, the number of weekly office-based visits was highest in Spain and imaging costs were highest in Australia. Health care resource utilization was higher in the post-progression period than in the pre-progression period, except for office-based visits, surgeries, and some laboratory investigations. Subgroup analyses showed that weekly utilization was mostly higher for ipilimumab refractory and BRAF mutant patients as compared to the full analysis set. Concomitant medication to treat adverse events was common but consisted mostly of dexamethasone. Only two patients received Infliximab. Total weekly costs over the study period were highest in Germany, but in every country and for almost all cost categories, weekly total costs were higher in the post-progression health state than in the pre-progression health state. Overall, inpatient stays accounted for the highest proportion of weekly total costs, followed by costs for radiotherapy and surgeries.

Our findings that HCRU and associated costs varied across countries is consistent with results from the MELODY study [CA184068; Bristol-Myers Squibb], a retrospective chart review conducted in three European countries prior to the availability of ipilimumab and vemurafenib [11]. The MELODY study also

Table 3. Inpatient visits, outpatient visits, surgeries, and radiation therapies

	Total			Australia			Germany			Italy			Spain		
	Pre-progression n = 331	From PD to EOS n = 274	Total n = 362	Pre-progression n = 94	From PD to EOS n = 76	Total n = 102	Pre-progression n = 130	From PD to EOS n = 115	Total n = 147	Pre-progression n = 71	From PD to EOS n = 57	Total n = 75	Pre-progression n = 36	From PD to EOS n = 26	Total n = 38
Inpatient visits															
Admitted to hospital, n (%)[a]	74 (22.4)	145 (52.9)	205 (56.6)	22 (23.4)	32 (42.1)	52 (51.0)	42 (32.3)	86 (74.8)	115 (78.2)	3 (4.2)	12 (21.1)	15 (20.0)	7 (19.4)	15 (57.7)	23 (60.5)
Total hospital admissions, n	110	277	471	23	35	70	76	210	353	3	15	19	8	17	29
Weekly total[b]	0.013	0.031	0.024	0.007	0.011	0.010	0.029	0.052	0.048	0.002	0.013	0.006	0.007	0.029	0.015
Time in hospital in days, mean (SD)[c]	2.4 (6.8)	8.2 (12.5)	9.5 (13.8)	1.9 (4.9)	5.0 (8.9)	6.6 (10.6)	3.8 (8.8)	12.8 (14.8)	15.1 (16.4)	0.4 (2.0)	3.0 (6.9)	2.7 (6.6)	2.4 (7.7)	8.6 (13.1)	9.0 (12.8)
Weekly total[b]	0.093	0.249	0.178	0.057	0.117	0.098	0.189	0.366	0.300	0.019	0.151	0.066	0.074	0.376	0.172
Outpatient visits															
Patients with any hospital visit, n (%)[a]	32 (9.7)	37 (13.5)	55 (15.2)	7 (7.4)	5 (6.6)	10 (9.8)	24 (18.5)	29 (25.2)	42 (28.6)	1 (1.4)	3 (5.3)	3 (4.0)	0	0	0
Hospital visits, mean (SD)	0.4 (1.6)	0.8 (2.7)	1.1 (3.4)	0.1 (0.5)	0.2 (0.8)	0.3 (1.1)	0.8 (2.5)	1.8 (4.0)	2.4 (4.9)	0.0 (0.2)	0.1 (0.2)	0.1 (0.4)	0	0	0
Weekly total[b]	0.014	0.024	0.020	0.004	0.004	0.004	0.040	0.051	0.047	0.001	0.003	0.002	0	0	0
Patients with any office-based visit, n (%)[a]	34 (10.3)	28 (10.2)	52 (14.4)	10 (10.6)	6 (7.9)	12 (11.8)	14 (10.8)	12 (10.4)	24 (16.3)	0	0	0	10 (27.8)	10 (38.5)	16 (42.1)
Office-based visits, mean (SD)	0.3 (1.0)	0.3 (1.0)	0.7 (2.1)	0.3 (1.0)	0.3 (1.2)	0.6 (2.0)	0.3 (1.1)	0.2 (0.6)	0.5 (1.4)	0	0	0	0.8 (1.4)	1.1 (1.9)	2.7 (4.3)
Weekly total[b]	0.011	0.008	0.012	0.009	0.008	0.009	0.013	0.005	0.009	0	0	0	0.023	0.047	0.052
Patients with any emergent care visit, n (%)[a]	3 (0.9)	17 (6.2)	24 (6.6)	1 (1.1)	7 (9.2)	8 (7.8)	0	3 (2.6)	4 (2.7)	1 (1.4)	2 (3.5)	4 (5.3)	1 (2.8)	5 (19.2)	8 (21.1)
Emergent care visits, mean (SD)	< 0.1 (0.1)	0.1 (1.1)	0.1 (1.0)	< 0.1 (0.1)	0.1 (0.3)	0.1 (0.3)	0	< 0.1 (0.2)	< 0.1 (0.3)	< 0.1 (0.1)	< 0.1 (0.2)	0.1 (0.2)	0.1 (0.3)	1.0 (3.6)	0.8 (3.0)
Weekly total[b]	< 0.001	0.004	0.002	< 0.001	0.002	0.001	0	0.001	0.001	0.001	0.002	0.001	0.002	0.042	0.015
Surgeries															
Any surgery, n (%)[a]	22 (6.6)	34 (12.4)	58 (16.0)	5 (5.3)	2 (2.6)	8 (7.8)	16 (12.3)	27 (23.5)	45 (30.6)	0	2 (3.5)	2 (2.7)	1 (2.8)	2 (7.7)	3 (7.9)
Bowel resection surgery, n (%)[a]	1 (0.3)	3 (1.1)	4 (1.1)	1 (1.1)	0	1 (1.0)	0	3 (2.6)	3 (2.0)	0	0	0	0	0	0
Total no. of bowel resections, n	1	5	7	1	0	1	0	5	6	0	0	0	0	0	0
Weekly total[b]	< 0.001	0.001	< 0.001	< 0.001	0	< 0.001	0	0.001	0.001	0	0	0	0	0	0
Other surgery, n (%)[a]	21 (6.3)	31 (11.3)	54 (14.9)	4 (4.3)	2 (2.6)	7 (6.9)	16 (12.3)	25 (21.7)	42 (28.6)	0	2 (3.5)	2 (2.7)	1 (2.8)	2 (7.7)	3 (7.9)
Total no. of others, n	31	36	75	4	2	7	26	30	63	0	2	2	1	2	3
Weekly total[b]	0.004	0.004	0.004	0.001	0.001	0.001	0.010	0.007	0.009	0	0.002	0.001	0.001	0.003	0.002
Radiation															
Patients with any radiation, n (%)[a]	18 (5.4)	68 (24.8)	102 (28.2)	8 (8.5)	18 (23.7)	35 (34.3)	8 (6.2)	34 (29.6)	48 (32.7)	2 (2.8)	11 (19.3)	14 (18.7)	0	5 (19.2)	5 (13.2)
Total no. of radiation treatment periods[d]	19	76	126	9	21	46	8	37	58	2	13	17	0	5	5
Radiotherapy days, mean (SD)	0.9 (4.6)	3.8 (22.8)	4.6 (21.8)	1.4 (5.8)	1.9 (4.5)	4.1 (10.8)	0.8 (3.7)	6.5 (34.4)	6.9 (32.2)	0.8 (5.2)	1.7 (8.3)	2.5 (9.1)	0	1.8 (4.0)	1.2 (3.4)
Weekly total[b]	0.036	0.116	0.086	0.043	0.045	0.062	0.042	0.187	0.136	0.038	0.088	0.060	0	0.079	0.024
Radiotherapy sessions, mean (SD)	0.4 (2.2)	1.5 (3.9)	2.1 (4.6)	0.6 (2.2)	1.1 (2.9)	2.3 (4.0)	0.5 (2.2)	2.3 (5.1)	3.0 (5.7)	0.4 (2.4)	0.6 (2.0)	0.9 (3.0)	0	1.3 (2.9)	0.9 (2.5)
Weekly total[b]	0.017	0.046	0.040	0.018	0.026	0.034	0.024	0.065	0.059	0.016	0.031	0.022	0	0.057	0.017

Pre-progression included data up to 3 weeks prior to the confirmed progression suspected date as reported by the investigator; *Progression* included 3 weeks prior to and 3 weeks after suspected date of confirmed progression as reported by the investigator.
Percentages are provided when the denominator >10.
[a]Percentages are based on the number of patients reporting within a specific time period.
[b]Weekly totals are the reported number admissions/visits/surgeries/radiation sessions divided by weeks of follow-up.
[c]Means are based on the reported number admissions divided by weeks of follow-up for all patients in the column.
[d]Radiation treatment periods indicated the number of radiation periods reported, from start to end date for each radiation treatment and assigned to health state using the start date of the treatment period.
Abbreviations: EOS, end of study; IPI, ipilimumab; PD, progressive disease; SD, standard deviation.

Table 4. Inpatient visits, outpatient visits, surgeries, and radiation therapies in ipilimumab refractory and BRAF positive patients

	Ipilimumab refractory patients					BRAF positive patients				
	Total n = 226	Australia n = 59	Germany n = 96	Italy n = 49	Spain n = 22	Total (N = 121)	Australia (N = 29)	Germany (N = 53)	Italy (N = 29)	Spain (N = 10)
Inpatient visits										
Admitted to hospital, n (%)[a]	136 (60.2)	32 (54.2)	78 (81.3)	12 (24.5)	14 (63.6)	72 (59.5)	14 (48.3)	43 (81.1)	8 (27.6)	7 (70.0)
Total hospital admissions, n	326	42	250	16	18	168	18	130	11	9
Weekly total[b]	0.029	0.011	0.052	0.009	0.023	0.031	0.012	0.055	0.011	0.023
Time in hospital in days, mean (SD)[c]	10.8 (14.8)	7.3 (11.2)	16.9 (17.3)	3.6 (7.7)	10.0 (13.7)	10.6 (13.7)	5.1 (8.7)	16.7 (15.6)	4.9 (9.3)	10.9 (13.3)
Weekly total[b]	0.222	0.116	0.340	0.099	0.281	0.241	0.095	0.372	0.139	0.281
Outpatient visits										
Patients with any hospital visit, n (%)[a]	34 (15.0)	6 (10.2)	25 (26.0)	3 (6.1)	0	23 (19.0)	3 (10.3)	19 (35.8)	1 (3.4)	0
Hospital visits, mean (SD)	1.0 (3.2)	0.4 (1.4)	1.9 (4.5)	0.1 (0.5)	0.0 (0.0)	1.6 (4.3)	0.1 (0.4)	3.6 (6.0)	0.0 (0.2)	0.0 (0.0)
Weekly total[b]	0.020	0.006	0.039	0.003	0.000	0.037	0.003	0.081	0.001	0.000
Patients with any office-based visit, n (%)[a]	37 (16.4)	10 (16.9)	15 (15.6)	0	12 (54.5)	17 (14.0)	2 (6.9)	11 (20.8)	0	4 (40.0)
Office-based visits, mean (SD)	0.8 (2.4)	0.9 (2.5)	0.4 (1.1)	0.0 (0.0)	3.9 (5.0)	0.8 (2.5)	0.5 (1.9)	0.6 (1.4)	0.0 (0.0)	4.6 (6.6)
Weekly total[b]	0.016	0.015	0.008	0.000	0.108	0.017	0.010	0.013	0.000	0.119
Patients with any emergent care visit, n (%)[a]	20 (8.8)	6 (10.2)	4 (4.2)	4 (8.2)	6 (27.3)	7 (5.8)	2 (6.9)	1 (1.9)	1 (3.4)	3 (30.0)
Emergent care visits, mean (SD)	0.2 (1.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	1.2 (3.9)	0.1 (0.5)	0.1 (0.3)	0.0 (0.1)	0.0 (0.2)	0.7 (1.6)
Weekly total[b]	0.004	0.002	0.001	0.002	0.034	0.002	0.001	0.000	0.001	0.018
Surgeries										
Any surgery, n (%)[a]	40 (17.7)	4 (6.8)	32 (33.3)	2 (4.1)	2 (9.1)	25 (20.7)	2 (6.9)	20 (37.7)	2 (6.9)	1 (10.0)
Bowel resection surgery, n (%)[a]	3 (1.3)	0	3 (3.1)	0	0	2 (1.7)	0	2 (3.8)	0	0
Total no.of bowel resections, n	6	0	6	0	0	3	0	3	0	0
Weekly total[b]	0.001	0.000	0.001	0.000	0.000	0.001	0.000	0.001	0.000	0.000
Other surgery, n (%)[a]	37 (16.4)	4 (6.8)	29 (30.2)	2 (4.1)	2 (9.1)	23 (19.0)	2 (6.9)	18 (34.0)	2 (6.9)	1 (10.0)
Total no. of others, n	45	4	37	2	2	36	2	31	2	1
Weekly total[b]	0.004	0.001	0.008	0.001	0.003	0.007	0.001	0.013	0.002	0.003
Radiation										
Patients with any radiation, n (%)[a]	81 (35.8)	25 (42.4)	39 (40.6)	13 (26.5)	4 (18.2)	41 (33.9)	10 (34.5)	21 (39.6)	6 (20.7)	4 (40.0)
Total no. of radiation treatment periods[d]	102	34	48	16	4	48	13	24	7	4
Radiotherapy days, mean (SD)	6.5 (27.2)	5.6 (13.4)	9.7 (39.5)	3.4 (10.8)	1.7 (4.0)	3.9 (7.2)	4.2 (7.0)	5.4 (8.8)	0.8 (2.4)	3.7 (5.3)
Weekly total[b]	0.132	0.089	0.194	0.093	0.047	0.088	0.079	0.121	0.022	0.096
Radiotherapy sessions, mean (SD)	2.7 (5.1)	2.7 (4.3)	3.8 (6.4)	1.0 (2.4)	1.3 (3.0)	2.6 (5.1)	2.5 (4.6)	3.9 (6.3)	0.3 (0.7)	2.9 (4.0)
Weekly total[b]	0.054	0.043	0.076	0.027	0.037	0.060	0.047	0.088	0.009	0.075

Pre-progression included data up to 3 weeks prior to the confirmed progression suspected date as reported by the investigator; *Progression* included 3 weeks prior to and 3 weeks after suspected date of confirmed progression as reported by the investigator.

The ipilimumab refractory analysis set includes all eligible patients who received at least 2 doses of ipilimumab and who had a confirmed progression with a suspected date within the period from first dose to 24 weeks after last dose of ipilimumab.

Percentages are provided when the denominator >10.

[a]Percentages are based on the number of patients reporting within a specific time period.

[b]Weekly totals are the reported number admissions/visits/surgeries/radiation sessions divided by weeks of follow-up.

[c]Means are based on the reported number admissions divided by weeks of follow-up for all patients in the column.

[d]Radiation treatment periods indicated the number of radiation periods reported, from start to end date for each radiation treatment and assigned to health state using the start date of the treatment period.

Abbreviations: EOS, end of study; IPI, ipilimumab; PD, progressive disease; SD, standard deviation.

Table 5. Costs associated with health care resource utilization

HCRU cost,	Total (EUR)			Australia (AUD)			Germany (EUR)			Italy (EUR)			Spain (EUR)		
	Pre-progression n = 331	From PD to EOS n = 274	Total n = 362	Pre-progression n = 94	From PD to EOS n = 76	Total n = 102	Pre-progression n = 130	From PD to EOS n = 115	Total n = 147	Pre-progression n = 71	From PD to EOS n = 57	Total n = 75	Pre-progression n = 17	From PD to EOS n = 26	Total n = 38
Inpatient cost, mean (SD)	1607 (6184)	4724 (7028)	5709 (9268)	3565 (14847)	6156 (10882)	9228 (19044)	1789 (4143)	6222 (7092)	7254 (7792)	331 (1626)	2420 (5633)	2207 (5352)	1353 (4238)	4768 (7246)	5184 (7171)
Weekly total cost	63.0	143.4	107.1	109.2	143.1	137.4	89.0	177.5	144.4	15.0	122.2	53.8	40.9	208.2	99.1
Surgery cost, mean (SD)	354 (1930)	587 (2668)	865 (3157)	877 (4127)	438 (3172)	1203 (4800)	468 (1932)	1115 (3636)	1492 (4029)	0	134 (743)	102 (649)	19 (114)	87 (333)	78 (294)
Weekly total cost	13.9	17.8	16.2	26.9	10.2	17.9	23.3	31.8	29.7	0	6.8	2.5	0.6	3.8	1.5
Outpatient care cost, mean (SD)	36 (137)	81 (319)	114 (378)	70 (244)	127 (391)	184 (541)	24 (60)	46 (89)	66 (110)	27 (195)	53 (208)	69 (340)	64 (119)	287 (846)	363 (818)
Weekly total cost	1.4	2.5	2.1	2.1	3.0	2.7	1.2	1.3	1.3	1.2	2.7	1.7	1.9	12.5	6.9
Radiation cost, mean (SD)	194 (1050)	775 (2277)	963 (2448)	206 (793)	400 (1016)	732 (1310)	314 (1427)	1456 (3286)	1769 (3500)	145 (1003)	251 (832)	371 (1233)	0	383 (853)	262 (724)
Weekly total cost	7.6	23.5	18.1	6.3	9.3	10.9	15.6	41.5	35.2	6.6	12.7	9.1	0	16.7	5.0
Laboratory investigations cost, mean (SD)	87 (130)	132 (233)	220 (288)	81 (133)	77 (127)	156 (197)	156 (161)	270 (302)	430 (333)	37 (58)	18 (38)	65 (102)	20 (69)	0	22 (70)
Weekly total cost	3.4	4.0	4.1	2.5	1.8	2.3	7.8	7.7	8.5	1.7	0.9	1.6	0.6	0	0.4
Imaging cost, mean (SD)	247 (741)	471 (871)	598 (1087)	906 (1753)	1375 (2116)	1886 (2523)	162 (489)	422 (468)	490 (613)	35 (87)	109 (113)	119 (134)	14 (57)	140 (155)	137 (161)
Weekly total cost	9.7	14.3	11.2	27.8	32.0	28.1	8.1	12.0	9.7	1.6	5.5	2.9	0.4	6.1	2.6
Concomitant medication cost, mean (SD)	208 (935)	344 (1172)	522 (1735)	383 (1681)	762 (1807)	1049 (2392)	144 (664)	68 (177)	196 (677)	302 (1237)	529 (1588)	813 (2639)	119 (247)	652 (2022)	703 (2392)
Weekly total cost	8.2	10.4	9.8	11.7	17.7	15.6	7.2	1.9	3.9	13.7	26.7	19.8	3.6	28.5	13.4
Total cost per time period, mean (SD)	2733 (7662)	7114 (9098)	8990 (11696)	6087 (17251)	9335 (12004)	14439 (21694)	3057 (6351)	9600 (10217)	11696 (10971)	877 (2231)	3513 (6825)	3746 (7324)	1589 (4315)	6317 (8039)	6748 (8427)
Weekly total cost	107	216	169	187	217	215	152	274	233	40	177	91	48	276	129
95% bootstrapped CI	79.5, 144.9	179.9, 258.9	145.1, 195.6	101.7, 333.7	147.8, 307.7	153.1, 293.1	107.5, 203.1	217.7, 342.3	195.7, 274.8	18.0, 68.6	94.4, 288.8	53.8, 140.9	12.1, 110.3	123.6, 579.2	72.9, 212.4

Pre-progression included data up to 3 weeks prior to the confirmed progression suspected date as reported by the investigator; *Progression* included 3 weeks prior to and 3 weeks after suspected date of confirmed progression as reported by the investigator.

Concomitant medication cost exclude drug costs for systemic anti melanoma therapy.

Abbreviations: CI, confidence interval; EOS, end of study; EUR, European Euro; AUD, Australian Dollar; HCRU, health care resource utilization; IPI, ipilimumab; PD, progressive disease; SD, standard deviation.
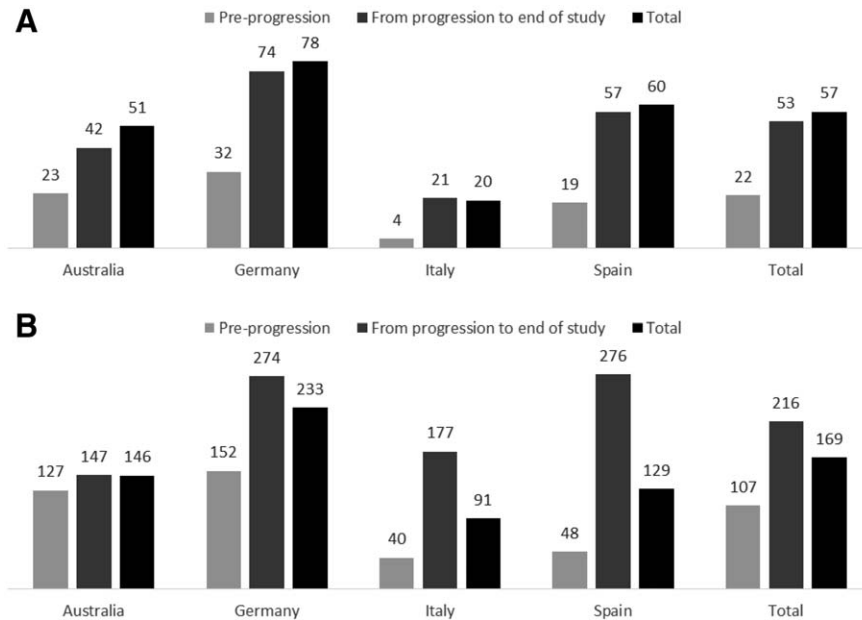
Figure 1. Percentage of patients admitted to hospital (**A**) and weekly total costs associated with health care resource utilization (€) (**B**).

found that inpatient stays accounted for the highest portion of overall total costs, and reported similar estimates of total inpatient cost per patient. The variation in inpatient costs observed in this study can partly be explained by different rates of hospitalizations, which were highest in Germany and lowest in Italy. The low number of hospitalizations in Italy is consistent with results from the MELODY study and data reported from an Italian extended access program, and may be explained by the likely preference of Italian health care providers to treat patients on an outpatient basis [11, 19]. However, as the number of outpatient visits for Italy was low as well, this may also be indicative of some general underreporting for hospitalizations and outpatient visits in Italy. Further differences in HCRU may be caused by different treatment preferences, national guidelines and reimbursement for treatment of melanoma, or to the different time periods covered by the country-specific data. For example, follow-up time for Italy was shorter than other countries, with the earliest first dose of ipilimumab being administered in April 2013.

Two other studies examined HCRU and associated costs in patients treated with ipilimumab. Toy et al., an administrative U.S. claims database analysis, included patients who received ipilimumab as the initial treatment for metastatic melanoma [12]. The overall monthly total of hospitalizations reported by Toy et al. (0.14) was slightly higher, but of the same order of magnitude as the corresponding estimate in this study (0.10 per month, or 0.024 per week). Tarhini et al. conducted a retrospective chart review of 273 stage IV patients receiving first-line ipilimumab in the U.S. [13]. Excluding costs of systemic therapy, this study reported monthly total healthcare costs of $690 during and $1,071 following treatment with ipilimumab, which are comparable with the mean total costs in our study, which were €463 per month (€107 per week) in the pre-progression health state, and €935 per month (€216 per week) in the post-progression health state. Similar to our study, Tarhini et al. found that mean monthly costs in almost all categories were higher in the post-regimen period than during the treatment period [13].

Our study showed that a large number of patients received concomitant medications to manage adverse events, both during treatment and after progression. Most commonly used medications were corticosteroids and various types of pain medication. Costs for concomitant medications were similarly high before and after progression on ipilimumab. This may indicate that there is a potential to decrease costs for therapies associated with a better adverse events profile. The economic impact of adverse events is also highlighted in the study of Tarhini et al., which observed a substantial increase in temporal healthcare costs for dosing intervals with at least one grade 3 or 4 adverse event [13].

Our study showed high rates of hospitalizations and other health care resources for patients after progressing on ipilimumab, and HCRU was generally higher in ipilimumab refractory patients. This demonstrates that, despite the availability of modern therapies for metastatic melanoma, there is still a high unmet medical need, especially in ipilimumab refractory patients. Research in this space has recently resulted in, for example, the regulatory approval of PD-1 inhibitors (pembrolizumab, nivolumab) in patients with metastatic melanoma in the U.S., Australia, and the EU, as well as new combination treatments for BRAF-V600-mutation positive patients. Recently, data was presented comparing ipilimumab at 10 mg per kg to the on-label dose of 3 mg per kg. The higher dose demonstrated superior OS (HR 0.84 95% CI 0.74–0.99) but was associated with greater toxicity: 30% versus 14% of patients experiencing a grade 3–4 immune-mediated adverse event [48]. Given melanoma patients tend to be relatively young and are members of the working-age population, treatment options with durable responses and better toxicity profiles have the potential to reduce the indirect cost of melanoma to society.

Data from clinical trials are unlikely to represent the spectrum of patients treated in clinical practice. A strength of this study is its use of data obtained from medical charts to analyze the real-world use of ipilimumab in four different countries. There may be a variation in reporting and documentation

across sites and countries [20]. Use of medical chart data may underestimate HCRU given its completeness depends on exchange of information among health care service providers. As costing approaches were based on unit costs and national average costs per resource used, and/or reimbursement tariffs, rather than the actual patient specific costs, there is some uncertainty in the estimation of health care costs related to the availability and quality of published unit cost estimates. Finally, in some cases, the follow-up period after the end of ipilimumab therapy was relatively short; this may have limited the validity of HCRU estimates for the post-treatment period.

The cost of new drug therapies now composes a greater proportion of the total cost of managing patients compared to the situation 5 years ago. Cross-country comparisons on drug costs are complex since each health system utilizes unique criteria to determine value and to negotiate reimbursement terms for their populations. Several health technology bodies have considered drug costs in their evaluations. In 2012 and 2014, the German G-BA issued two resolutions referencing an ipilimumab cost per patient per year of €91,022.76 [45] and €82,461.56 [46], respectively. In 2012, the public summary document from the Australian PBAC does not reference a price but recommends the listing of ipilimumab for metastatic melanoma subject to a risk-share arrangement involving aspects of appropriate use, maintenance of cost-effectiveness, and managing financial risk to the government [47].

CONCLUSION

This study found that rates of resource utilization and associated health care costs for managing metastatic melanoma patients treated with ipilimumab were high during treatment and after disease progression, but they remained substantially higher after progression than pre-progression. The results highlight the high unmet need for therapies that are more effective and have better toxicity profiles. Given the unique toxicity profile of immune checkpoint inhibitors, additional research is warranted using real-world observational data to assess the incremental cost of managing advanced melanoma patients

who may be treated with alternative regimens or newer immune-oncologic agents.

AUTHOR CONTRIBUTIONS

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DISCLOSURES

Grant McArthur: Pfizer, Roche, Ventana (RF); **Peter Mohr**: Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Roche (C/A, H, RF, ET); **Paolo A. Ascierto**: Amgen, Array, Bristol-Meyers Squibb, Merck-Serono, Merck Sharp & Dohme, Novartis, Roche-Genentech (CA); Array, Bristol-Meyers Squibb, Roche-Genentech (RF); **Ana Arance**: Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis (CA, H); **Peter Kaskel**: Merck Sharp & Dohme Gmbh (E), Merck & Co. Inc. (OI); **Michael Weichenthal**: Merck Sharp & Dohme (CA, RF); **Reshma R. Shinde**: Merck & Co. Inc. (E); **Kendall Stevinson**: Merck & Co. Inc. (E, OI). The other author indicated no financial relationships.

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