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Direct costs associated with adverse events of systemic therapies for advanced melanoma

Systematic literature review

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Abstract

Background: Treatments for advanced melanoma are associated with different adverse events (AEs), which may be costly to manage. This study aimed to evaluate direct costs associated with managing treatment-related AEs for advanced melanoma through a systematic literature review.

Methods: Systematic searches were conducted of the PubMed, Embase, Cochrane, BIOSIS, and EconLit medical literature databases to identify studies providing estimates of direct costs and health care resource utilization for the management of AEs of melanoma treatments, published between January 1, 2007, and February 23, 2017. Gray literature searches also were conducted. Studies reporting direct costs for patients with advanced melanoma that were published in English between 2007 and 2017 were eligible. Studies were systematically screened in 2 phases by 2 independent reviewers. Study design details and data on direct costs by country were extracted.

Results: Seven studies evaluating the cost of AEs in patients with advanced melanoma were included; most estimated the costs for grade 3 or 4 events. In a United States study, monthly AE costs constituted 36.9% of overall health care costs for dacarbazine, 30.3% for paclitaxel, 9.2% for temozolomide, 6.4% for vemurafenib, and 4.0% for ipilimumab. A multicountry study found the greatest cost per event to be for grade 3 or 4 AEs associated with ipilimumab, including colitis (A$1471 [Australia]–€3313 [France]) and diarrhea (£2836 [United Kingdom]), and chemotherapy (neutropenia/leukopenia in Germany [€1744] and Italy [€804]). Across studies, cost drivers for the most expensive AEs to manage were requiring hospitalization or use of expensive outpatient medications and/or procedures (eg, erythropoietin and blood transfusions for anemia). Some currently available therapies were not available during the research period, and their associated AEs are not reflected. Results may not be comparable across countries. For some studies, resource-use estimates reflect practice patterns from a limited number of centers, limiting generalizability.

Conclusion: Costs for managing each type of AE associated with the treatment of advanced melanoma are substantial. Effective treatments with improved safety profiles may help reduce total AE management costs.

Abbreviations: AE = adverse event, CI = confidence interval, CNS = central nervous system, CSCC = cutaneous squamous cell carcinoma, FDA = Food and Drug Administration, IL-2 = interleukin-2, NCCN = National Comprehensive Cancer Network, NHS = National Health Service, NR = not reported, SCC = squamous cell carcinoma, SD = standard deviation, UK = United Kingdom, US = United States.

Keywords: advanced melanoma, adverse event, direct costs

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1. Introduction

Advanced melanoma is generally treated with systemic therapy. Systemic therapies in use before 2011 included cytotoxic chemotherapy (eg, dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, or carboplatin/paclitaxel, alone or in combination), high-dose interleukin-2 (IL-2), interferon, and biochemotherapy (combination of chemotherapy with IL-2). Since 2011, 8 agents have been approved, alone or in combination, for advanced melanoma, some of which have significantly improved survival.[1–6] These agents include the targeted therapies vemurafenib and dabrafenib (both proto-oncogene B-Raf [BRAF] inhibitors) and trametinib and cobimetinib (both mitogen-activated extracellular signal-regulated kinase [MEK] inhibitors); and the immunotherapies ipilimumab (a cytotoxic T-lymphocyte antigen 4 [CTLA-4]–blocking antibody), talimogene laherparepvec (a genetically modified oncolytic viral therapy), pembrolizumab, and nivolumab (both programmed death 1 protein [PD-1]–blocking antibodies).[7–11] Treatment patterns for advanced melanoma vary by region, in part owing to access restrictions in some countries; for instance, in Australia, use of BRAF and MEK inhibitors is restricted to the first line.[12–14]

Classes of melanoma agents have different adverse event (AE) profiles.[15] Chemotherapy and IL-2 treatments are most likely to lead to hematologic (eg, neutropenia or anemia) and gastrointestinal (eg, nausea and vomiting) AEs.[16] More recently, the approval of immuno-oncologic agents has introduced immune-related AEs into the array of AEs. Specifically, ipilimumab is associated with an increased risk of immune-related AEs, involving the gastrointestinal, liver, skin, nervous, endocrine, ocular, or other organ systems.[17] Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, adverse skin reactions, and encephalitis may occur during treatment with PD-1-blocking antibodies.[10,11] Targeted therapies including BRAF inhibitors are associated with an increased risk of new cutaneous AEs (squamous cell carcinoma [SCC] and/or keratoacanthoma),[18,19] and MEK inhibitors are associated with grade 3 or 4 AEs including hypertension and rash.[8,20] With talimogene laherparepvec, the most common AEs are cellulitis, local reactions, and flu-like symptoms.[9]

Management of AEs may be costly from a health care system perspective. As new therapies are studied and approved for advanced melanoma, it is important to characterize the economic burden associated with managing treatment-related AEs. A more complete understanding of the costs of AE management will improve estimates of the incremental costs associated with adoption of new therapies and can inform economic models. The objective of this study was to evaluate the economic burden and incremental cost of managing AEs associated with advanced melanoma treatments through a systematic review of the literature.

2. Methods

A systematic literature search was conducted in PubMed, Embase, Cochrane, BIOSIS, and EconLit, according to a literature review protocol. Prespecified search criteria were used to identify economic studies in patients with advanced melanoma evaluating direct costs and health care resource utilization (eg, medications, physician consultations, hospitalizations) published from 2007 to 2017. Studies of interest presented robust primary data on AE costs in advanced melanoma. Table S-1 (Supplemental Digital Content, http://links.lww.com/MD/C368) presents the PubMed search strategy, which was adapted for the other databases. Published abstracts from 12 relevant conferences were identified via the Embase searches (2015–2016 proceedings for the International Society for Pharmacoeconomics and Outcomes Research, American Society of Clinical Oncology, and European Society for Medical Oncology). The National Institute for Health and Care Excellence website was searched to identify company submissions estimating health care resource utilization and costs. Electronic searches were not limited to English-language publications.

The identified studies were screened systematically in 2 phases. During level 1 screening, titles and abstracts of identified studies were screened independently by 2 researchers according to the inclusion and exclusion criteria (Table S-2, Supplemental Digital Content, http://links.lww.com/MD/C368). At level 2, full texts of studies selected at level 1 were screened independently by 2 researchers according to the same criteria. If there was disagreement about study relevance, consensus was reached with a third researcher. Study design details and data on direct costs by country were extracted.

Because this study did not directly involve any human participants, review by an institutional review board was not required.

3. Results

3.1. Literature search results

Figure 1 presents the results of the literature search and screening. The searches identified 446 sources for level 1 screening, after duplicates were excluded. Of these sources, 66 progressed to level 2 screening, after which 7 relevant studies evaluating the cost of AEs in patients with advanced melanoma were included. All included studies were full-text publications identified in the database searches.

The included studies considered AEs associated with dabrafenib, dacarbazine, fotemustine, IL-2, interferon-alfa, IL-2, ipilimumab, paclitaxel, talimogene laherparepvec, temozolomide, trametinib, and vemurafenib. One study was a Canadian cost-effectiveness modeling analysis[21]; 3 were economic burden analyses using published literature and physician interviews or a Delphi panel (1 conducted in the United States [US][16] and 2 with a multicountry perspective[7,22]); 2 were cost analyses using US claims data[15,23]; and 1 was a United Kingdom (UK) medical records review.[24]

3.2. Included studies

3.2.1. Design features of included studies. Three publications identified AEs through a literature review[7,16,22]; of these, 2 studies considered study quality in their inclusion criteria (ie, phase 3 study, large sample size, and use of recommended dosing),[7,16] and 1 did not.[22] Other included studies identified AEs through clinical trial publications and other relevant clinical publications,[21] package inserts[15] (also in consultation with a clinical expert[23]), or medical records.[24]Table 1 summarizes the design of each included study, including the treatments considered and criteria applied for selection of AEs.

The studies collected medical resource use related to AEs primarily from physician input from an online survey with Canadian physicians[21]; blinded Delphi panels in Australia, France, Germany, Italy, and the UK[22]; physician interviews[7,16]; a medical record review[24]; and a US claims database.[15,23] Unit costs for resource use were obtained from

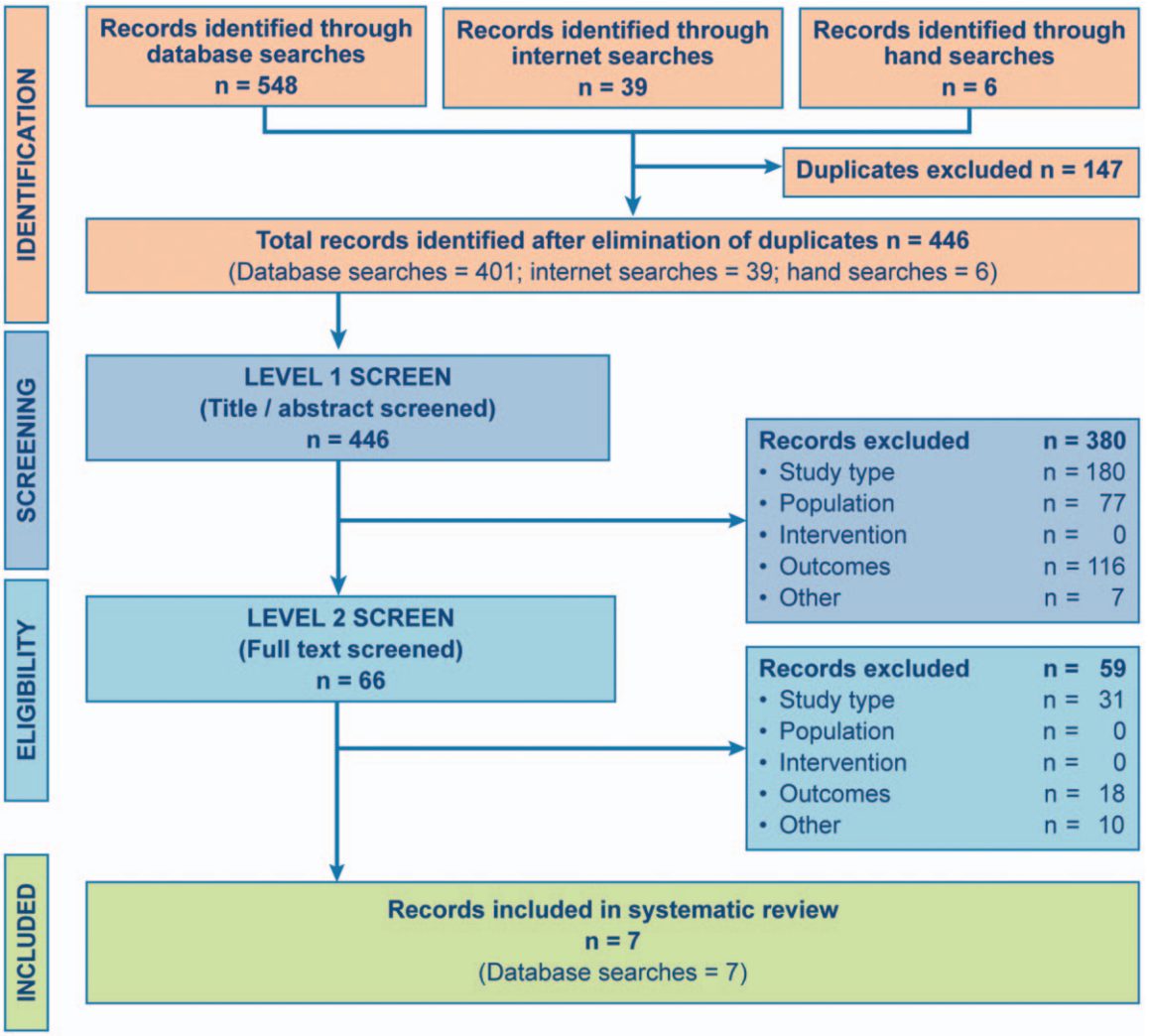

Figure 1. PRISMA diagram: literature search results (N = 7).

country-specific published costs[7,16,21,22,24] or a US claims database.[15,23] Cost-years were all fairly recent and consistent; most ranged from 2012 to 2014,[7,21,22,24] with longer timeframes for the US claims database studies (2005–2012,[15] 2004–2012,[16] and 2009–2012[23]).

3.2.2. Cost of adverse events. Most studies estimated the cost for grade 3 or 4 events. The rank order of costs assigned to grade 3 or 4 AEs varied by study, treatment setting (inpatient vs outpatient), and country. As expected, the costliest AEs were those leading to hospitalization or expensive outpatient medications and/or procedures. Tables 2–5 summarize the costs of AEs presented in the identified studies.

3.2.2.1. United States. The 3 US studies found a different rank order of AEs by cost.[15,16,23] Bilir et al[16], the most recent, aimed to explore the US economic burden of toxicities associated with dacarbazine, temozolomide, IL-2, ipilimumab, vemurafenib, dabrafenib, trametinib, and talimogene laherparepvec. The study design included conduct of interviews with clinicians (2013) to estimate health care resource use and applied Medicare reimbursement rates (2013) for the treatment of specified AEs in an outpatient setting to estimate costs and conduct of a national claims database analysis (using claims for July 2004–November 2012) to identify hospitalization costs and length of stay for the specified AEs. Inpatient (Table 2) and outpatient (Table 3) costs per event for grade 3 or 4 AEs were estimated. Among the toxicities evaluated, neutropenia had the highest cost per event in the outpatient setting, followed by headache, peripheral neuropathy, cutaneous SCC (CSCC), and dyspnea. Hospitalizations resulting from acute myocardial infarction and sepsis (both associated with IL-2) incurred the longest median length of stay. The highest inpatient cost per event was observed for events associated with IL-2, including acute myocardial infarction, sepsis, coma, and acute kidney failure (also associated with trametinib, dabrafenib, and vemurafenib); hospitalizations for neuropathy (associated with ipilimumab) and pneumonitis (associated with trametinib) were also costly. By contrast, the lowest mean inpatient costs per event were for cellulitis, fever, rash, and nausea.

Arondekar et al[15] conducted a US retrospective claims database analysis to evaluate the incremental 30-day health care costs associated with specific categories of AEs associated with advanced melanoma treatments. The study evaluated claims for inpatient services, outpatient services, and noncancer-directed drugs (July 2004–April 2012) among patients with a diagnosis of metastatic melanoma who were treated with paclitaxel,

Table 1

Cost of adverse events: study design.

Author (date)	Country and cost year	Data source	Population	Description of costs reported
Canada				
Delea et al[21]	Canada 2012	Cost-effectiveness model: ■ AEs were identified from the BREAK-3 or BRIM-3 trials (≥5% incidence for dabrafenib, dacarbazine, or vemurafenib) and/or those considered important from a clinical or economic perspective based on clinical opinion. ■ Medical resource utilization of AEs was obtained from a nationwide online survey (conducted between November 30, 2012 and January 10, 2013) with 59 Canadian physicians of treatment and health care utilization patterns in patients with metastatic melanoma. ■ Costs were obtained from Canadian-specific unit cost estimates for treating that AE	Patients treated with dabrafenib vs dacarbazine and vemurafenib as first-line therapy for metastatic melanoma or *BRAF* V600 mutation-positive unresectable melanoma	AE costs for events with an incidence of 5% or more in either the BREAK-3 or BRIM-3 trials and/or those considered important from a clinical or economic perspective based on clinical opinion
Australia, Canada, and Europe				
Vouk et al[22]	Australia France Germany Italy UK 2013	■ AEs were identified through systematic literature review of phase 1–3 studies with ≥1 treatment arm using dacarbazine, paclitaxel, fotemustine, ipilimumab, or vemurafenib as monotherapy; retrospective chart review studies and case reports describing any of the 5 agents as monotherapy; and original studies. Studies of combination therapy were excluded. ■ Medical resource-use data associated with managing AEs were collected through 2 blinded Delphi panels in each of the 5 countries; published costs of resources were used to estimate per-event costs	Patients with metastatic melanoma treated with chemotherapy (dacarbazine, paclitaxel, and fotemustine), ipilimumab, and vemurafenib	Mean cost per patient per event for grade 3 or 4 AEs; SD and range
Wehler et al[7]	Australia Canada France Germany Italy The Netherlands Spain UK 2014	■ A literature search was conducted to identify grade 3 or 4 AEs associated with dabrafenib, dacarbazine, fotemustine, ipilimumab, interleukin-2, temozolomide, trametinib, or vemurafenib. ■ Resource use for the management of AEs was determined from interviews with 5 melanoma clinicians in each country. ■ Outpatient and inpatient costs were estimated using country-specific tariffs or government/published sources	Patients receiving monotherapy agents, including ipilimumab, approved for use for first- or second-line treatment of metastatic melanoma in the 8 countries	Outpatient total costs and inpatient total costs to manage the AE
Yousaf et al[24]	UK 2013/2014	■ All nontrial patients with ipilimumab were identified using an electronic pharmacy database. ■ AEs associated with ipilimumab were identified from patient records (chart review). ■ Resource use was obtained from patient records (chart review). ■ Costs per resource were based on standard NHS tariff.	110 patients treated with ipilimumab at a single center; 29 patients had ≥1 grade 3 or higher AEs; 81 patients served as the control	■ Cost per event for each patient ■ Median cost of managing events for the cohort
US				
Arondekar et al[15]	US 2012	MarketScan commercial and Medicare supplemental databases: ■ AEs were identified from a review of the package inserts for paclitaxel, vemurafenib, ipilimumab, dacarbazine, temozolomide, IL-2, or interferon-alfa and in consultation with one of the coauthors (clinical expert). An AE was selected if it occurred in ≥20% of patients for any grade event or in ≥5% of patients for grades 3 and 4. AEs associated with dabrafenib and trametinib (ie, fever and hypertension) were also considered. ■ Resource use and cost were identified from the claims database.	Patients with melanoma with ≥1 diagnosis of metastases and ≥1 claim for the 7 treatments N = 2621 ■ Vemurafenib, n = 119 ■ Ipilimumab, n = 152 ■ Dacarbazine, n = 254 ■ Temozolomide, n = 847 ■ High-dose interleukin-2, n = 227 ■ Paclitaxel, n = 153 ■ Interferon, n = 869	30-day incremental costs: ■ Incremental cost per AE was determined by comparing the 30-day expenditures in patients with the event to patients without the event based on a shadow event date ■ Multivariate generalized linear models were used to control for baseline differences between groups
Bilir et al[16]	US 2014	■ A literature review was conducted to identify AEs related to treatment of metastatic melanoma. AEs associated with dacarbazine, temozolomide, IL-2, ipilimumab, vemurafenib, dabrafenib, trametinib, and talimogene laherparepvec were considered. ■ Resource use was obtained via interviews with 5 melanoma specialists conducted in 2013. ■ Unit costs were assigned using Medicare reimbursement rates for outpatient costs, and inpatient costs were obtained from the Optum Clinformatics DataMart claims. Database (using claims for July 1, 2004 to Nov 30, 2012)	Patients who received monotherapy agents, including ipilimumab, approved by the FDA or referenced in NCCN guidelines for first- or second-line treatment of metastatic melanoma or talimogene laherparepvec	Outpatient and inpatient costs per event per patient
Chang et al[23]	US NR	■ IMS PharMetrics Plus ■ Grade 3/4 AEs occurring in ≥5% of patients from the package inserts for vemurafenib, ipilimumab, dacarbazine, temozolomide, and paclitaxel were considered. ■ Resource use and cost of AEs were obtained from the claims database.	Patients with metastatic melanoma initiating vemurafenib, ipilimumab, dacarbazine, paclitaxel, or temozolomide N = 541	Mean (SD) and median costs by study drug: ■ Any AE ■ Cardiovascular ■ Gastrointestinal ■ Hemic and lymphatic disorders and effects ■ Metabolic and nutritional disorders ■ Pain ■ Skin and subcutaneous tissue

AE = adverse event, FDA = Food and Drug Administration, IL-2 = interleukin-2, NCCN = National Comprehensive Cancer Network, NHS = National Health Service, NR = not reported, SD = standard deviation, UK = United Kingdom, US = United States.

Table 2

Inpatient costs of grade 3 or 4 adverse events in 9 countries: Wehler et al[7] and Bilir et al[16].

	Wehler et al[7]: inpatient cost per incident for grade 3 or 4 AEs*								Bilir et al[16]: mean inpatient cost per incident for grade 3 or 4 AEs†
AE category; AE	Italy (€)	Spain (€)	Germany (€)	France (€)	Netherlands (€)	UK (£)	Australia (A$)	Canada (Can$)	US (US$)
Cardiovascular									
Acute myocardial infarction	NR	NR	NR	NR	NR	NR	NR	NR	$47,069
Hypertension	€1573	€2405	€2246	€1619	€1702	£3852	$4711	$7028	$20,349
Hypotension	NR	NR	NR	NR	NR	NR	NR	NR	$25,889
CNS/psychiatric									
Coma	NR	NR	NR	NR	NR	NR	NR	NR	$31,682
Psychosis	NR	NR	NR	NR	NR	NR	NR	NR	$13,078
Gastrointestinal									
Diarrhea	€1456	€4113	€1348	€1585	€1456	£4284	$4572	$420	$26,861
Diarrhea (immune related)	€1456	€4113	€1348	€1585	€1456	£4284	$4572	$4320	NR
Vomiting	€1456	€1755	€1348	€1585	€2045	£1702	$4572	$3543	$14,043
Hemic/lymphatic									
Acidosis	NR	NR	NR	NR	NR	NR	NR	NR	$26,648
Anemia	€2667	€1801	€2367	€2000	€2839	£2246	$4380	$5181	$19,122
Febrile neutropenia	€2357	€5480	€2388	€2000	€2152	£4444	$5224	$7843	NR
Hypophysitis	€1589	€10,265	€1979	€5316	€1683	£2417	$7231	$9735	NR
Neutropenia	€2357	€1529	€2388	€2000	€877	£2194	$5224	$7843	NR
Sepsis	NR	NR	NR	NR	NR	NR	NR	NR	$35,172
Thrombocytopenia	NR	NR	NR	NR	NR	NR	NR	NR	$22,856
Metabolic/nutritional									
Acute kidney failure	NR	NR	NR	NR	NR	NR	NR	NR	$31,213
Elevated liver enzymes	€2159	€3356	€1\809	€6913	€1305	£1−19	$6594	$8030	$19,122
Hyperglycemia	NR	NR	NR	NR	NR	NR	NR	NR	$15,827
Hyponatremia	NR	NR	NR	NR	NR	NR	NR	NR	$22,124
Other									
Fever	€3433	€2822	€1686	€1658	€1411	£1598	$4375	$5008	$15,438
Infection	€3433	€4477	€2099	€3018	€1806	£1918	$7199	$6563	NR
Oliguria/anuria	NR	NR	NR	NR	NR	NR	NR	NR	$20,874
Pain									
Headache	€2366	€2489	€1644	€1002	€1718	£1372	$1935	$3479	NR
Neuropathy	NR	NR	NR	NR	NR	NR	R	NR	$29,669
Peripheral neuropathy	€1972	€4144	€2004	€2625	€6977	£2617	$4923	$9472	NR
Respiratory									
Dyspnea	€1689	€1755	€9077	€1466	€1431	£1209	$3671	$5506	$13,588
Pneumonitis	NR	NR	NR	NR	NR	NR	NR	NR	$28,330
Skin/subcutaneous									
Cellulitis	NR	NR	NR	NR	NR	NR	NR	NR	$17,230
CSCC	€1589	€1221	€1544	€1416	€2122	£1692	$2379	$8934	$25,091
Palmar-plantar hyperkeratosis	€1308	€5121	€1544	NR	€1606	£1692	$2654	$4177	NR
Rash	€1308	€2087	€1544	NR	€1764	£1692	$2654	$3223	$14,674

AE = adverse event, CNS = central nervous system, CSCC = cutaneous squamous cell carcinoma, FDA = Food and Drug Administration, NCCN = National Comprehensive Cancer Network, NR = not reported, UK = United Kingdom, US = United States.

* Costs of AEs associated with monotherapy agents, including ipilimumab, approved for first- or second-line treatment of metastatic melanoma in the 8 study countries were evaluated. AEs were identified through a literature search, and resource use for management of the AEs was determined through interviews with clinicians in in each country. Inpatient costs were estimated using country-specific tariffs or government/published sources.

† Costs of AEs associated with monotherapy agents, including ipilimumab, approved by the FDA or referenced in NCCN guidelines for first- or second-line treatment of metastatic melanoma or talimogene laherparepvec were evaluated. AEs were identified through a literature search, and resource use for management of the AEs was determined through interviews with clinicians. Inpatient costs were obtained from claims data.

vemurafenib, ipilimumab, dacarbazine, temozolomide, IL-2, or interferon-alfa. The AEs considered were those associated with the study drugs and fever and hypertension (associated with the newer treatments dabrafenib and trametinib). Incremental cost per AE was determined by comparing 30-day expenditures in patients with the event to patients without the event. The 30-day period began with the date of the first AE claim for patients with an event and on a corresponding "shadow" event date for patients without an AE. The 30-day costs for patients who experienced specific categories of AEs then were compared with costs for matched patients without those AEs to determine the incremental costs for the AE category. For the following AE categories, adjusted incremental costs were greater for patients with the AE than for patients without the AE (in descending order): metabolic and nutritional disorders, hematologic and lymphatic disorders, cardiovascular disorders, gastrointestinal disorders, central nervous system disorders, psychiatric disorders, and pain (Table 5). Incremental costs for skin and subcutaneous tissue AEs were not significantly different between patients with and without AEs.[15]

Chang et al[23] investigated costs of AEs associated with specific melanoma therapies. This retrospective claims study

Table 3

Outpatient Costs of Grade 3 or 4 Adverse Events in 9 Countries: Wehler et al[7] and Bilir et al[16].

		Wehler et al[7]: outpatient cost per incident for grade 3 or 4 AEs*								Bilir et al[16]: total outpatient cost needed to manage AEs per Event†
AE category; AE	Grade	Italy (€)	Spain (€)	Germany (€)	France (€)	Netherlands (€)	UK (£)	Australia (A$)	Canada (Can$)	US (US$)
Cardiovascular										
Hypertension	3	€46	€104	€61	€30	€79	£251	$97	$164	$110
Gastrointestinal										
Diarrhea	3	€46	€134	€46	€33	€86	£251	$91	$162	$131
	4	€46	€134	€46	€33	€86	£126	$91	$162	$109
Diarrhea (immune related)	3	€30	€134	€46	€29	€86	£251	$1121	$162	$110
Vomiting	3	€64	€132	€76	€31	€80	£251	$147	$239	$184
	4	€64	€132	NR	€31	€80	£251	NA‡	$239	NA‡
Hemic/lymphatic										
Anemia	3	€1329	€1443	€46	€1285	€ 936	£730	$890	$370	$145
	4	€1281§	€1443	€46	€1285	€936	£730	$890	$370	$145
Febrile neutropenia	3	€436	€598	€46	€29	€81	NA‡	NA‡	$258	NA‡
	4	€436	€598	€46	€29	€81	NA‡	NA‡	$258	NA‡
Hypophysitis (immune related)	3	€326	€460	€46	€107	€465	£251	$283	$168	$132
Neutropenia	3	€89	€598	€46	€28	€79	£251	$141	$160	$2088
	4	€497	€755	€46	€28	€79	NA‡	$210	$160	$2088
Metabolic/nutritional										
Elevated liver enzymes	3	€47	€97	€46	€28	€79	£251	$304	$160	$109
	4	€47	€97	€46	€28	€79	£251	$304	$160	$109
Other										
Fever	3	€21	€104	€46	€28	€82	£251	$94	$161	$110
Infection	3	€34	€99	NR	€67	€81	£251	NA‡	$161	$113
	4	€34	€99‖	NR	€67	NA‡	£251	NA‡	$161	$109
Pain										
Headache	3	€255	€98	€46	€314	€82	£251	$99	$227	$609
Peripheral neuropathy	3	€173	€1289	€46	€28	€83	£126	$152	$183	$539
	4	€173	€1289	€46	€28	€83	£251	$218	$210	$109
Respiratory										
Dyspnea	3	€23	€99	€46	€156	€188	£251	$129	$194	$227
	4	€25	€99	NR	€156	NR	NR	$393	$194	NA‡
Skin/subcutaneous										
CSCC	3	€297	€297	€406	€71	€1063	£720	$424	$205	$378
Palmar-plantar hyperkeratosis	3	€43	€173	€46	€28	€158	£126	$203	$160	$109
Rash	3	€47	€184	€46	€32	€86	£251	$380	$171	$139
	4	€47	€184‖	NR	€32	€82¶	£251	$373§	$162#	$139

AE = adverse event, CSCC = cutaneous squamous cell carcinoma, FDA = Food and Drug Administration, NCCN = National Comprehensive Cancer Network, NR = not reported, UK = United Kingdom, US = United States.

* Costs of AEs associated with monotherapy agents, including ipilimumab, approved for first- or second-line treatment of metastatic melanoma in the 8 study countries were evaluated. AEs were identified through a literature search, and resource use for management of the AEs was determined through interviews with clinicians in in each country. Outpatient costs were estimated using country-specific tariffs or government/published sources.

† Costs of AEs associated with monotherapy agents, including ipilimumab, approved by the FDA or referenced in NCCN guidelines for first- or second-line treatment of metastatic melanoma or talimogene laherparepvec were evaluated. AEs were identified through a literature search, and resource use for management of the AEs was determined through interviews with clinicians. Unit costs were assigned using Medicare reimbursement rates for outpatient costs.

‡ 100% inpatient admission.

§ Grade 4 outpatient treatment is less expensive than grade 3 because more physicians recommended hospitalization for a grade 4 event.

‖ Clinicians provided outpatient resource use but indicated that patients would always be hospitalized.

¶ Physicians suggested more prescription products for a grade 3 event than for a grade 4 event.

Topical treatment (steroids) for grade 3 was more expensive than oral treatment for grade 4 because topical treatment can be purchased only in a tube.

(January 2009–September 2012) estimated costs for grade 3 or 4 AEs by drug among patients with metastatic melanoma initiating vemurafenib, ipilimumab, dacarbazine, paclitaxel, or temozolomide. Treatment episodes with dacarbazine and paclitaxel were associated with a greater percentage of hematologic and gastrointestinal AEs, with higher related monthly costs, than vemurafenib ($P < .001$ for both comparisons) (Table 5). Treatment episodes with vemurafenib had a higher percentage of skin and subcutaneous AEs, with higher related AE costs, compared with other drugs ($P < .0001$ for all comparisons). After controlling for age, sex, sequencing of treatment episodes, number of metastatic sites, pre-existence of AEs, and health care costs in the preceding 6 months, treatment episodes of vemurafenib had lower total adjusted monthly AE costs than other drugs ($P < .05$ for all comparisons except temozolomide). Adjusted monthly AE costs constituted 36.9% of overall monthly health care costs for dacarbazine, 30.3% for paclitaxel, 9.2% for temozolomide, 6.4% for vemurafenib, and 4.0% for ipilimumab.

3.2.2.2. Multicountry[7,22]. Vouk et al[22] and Wehler et al[7] compared the cost of AEs across multiple countries. Wehler et al[7] evaluated the costs of managing AEs associated with

Table 4

Inpatient and Outpatient Cost of Grade 3 or 4 Adverse Events in 5 Countries: Vouk et al[22].

	Mean cost of grade 3 or 4 AEs per event per patient*; Percentage of patients hospitalized per event†									
Adverse event	Australia (A$)	% inpatient stay	France (€)	% inpatient stay	Germany (€)	% inpatient stay	Italy (€)	% inpatient stay	UK (£)	% inpatient stay
Gastrointestinal										
Colitis	$1471	73.3%	€3404	96.7%	€1444	73.3%	€184	14.7%	£2836	100%
Diarrhea	$1333	66.7%	€1247	66.7%	€1274	73.3%	€332	33.3%	£2836	100%
Hemic/lymphatic										
Hypophysitis (immune-related)	$503	1.7%	€1823	55.0%	€1011	40.0%	€405	6.7%	£2717	100%
Neutropenia/leukopenia	$1005	66.7%	€1123	18.3%	€1744	26.7%	€804	10.7%	£272	11.5%
Thrombocytopenia	$129	8.3%	€891	33.3%	€1095	30.0%	€515	16.7%	£277	7.5%
Other										
Anaphylaxis	$381	26.0%	€3313	100%	€924	76.7%	€712	65.0%	£198	30.0%
Pain										
Peripheral neuropathy	$11	0%	€214	35.0%	€501	13.3%	€370	0%	£432	0%
Skin/subcutaneous										
CSCC	$228	0%	€372	27.5%	€323	12.5%	€92	0%	£1281	0%
Rash	$223	5.0%	€759	28.8%	€392	17.5%	€103	3.8%	£356	10.0%

AE = adverse event, CSCC = cutaneous squamous cell carcinoma, UK = United Kingdom.

* Costs of AEs associated with chemotherapy (dacarbazine, paclitaxel, and fotemustine), ipilimumab, and vemurafenib were identified. AEs were identified through a systematic literature review, and resource use for management of the AEs was determined through two blinded Delphi panels in each of the 5 study countries. Costs were estimated using published costs of resources.

† Mean estimates of the percentage of patients who would be hospitalized or undergo a prolonged stay for each AE, as reported by experts during the second Delphi panel cycle.

dacarbazine, temozolomide, fotemustine, IL-2, ipilimumab, vemurafenib, dabrafenib, and trametinib in 8 countries; Tables 2 and 3 present inpatient and outpatient costs for the AEs evaluated. Results varied by country, reflecting variation in unit costing across countries, but trends indicated that hospitalization, outpatient procedures, and certain high-cost medications led to expensive AE management. The costliest events to manage in the inpatient setting included hypophysitis (in Spain [€10,265 per incident], Canada [Can$9735], and Australia [A$7231]), dyspnea (in Germany [€9077]), febrile neutropenia (in UK [£4444]), peripheral neuropathy (in the Netherlands [€6977]), elevated liver enzymes (in France [€6913]), and fever (in Italy [€3433]). Management of grade 3 or 4 anemia occurred primarily in the outpatient setting, where use of erythropoietin and/or blood transfusions required high-cost outpatient care across all countries except for Germany; outpatient costs per incident for grade 3 or 4 anemia ranged from Can$370 in Canada to €1443 in Spain. Other events that were costly to manage in the outpatient setting were CSCC (in the Netherlands [€1063], UK [£720], and Germany [€406]), immune-related diarrhea (in Australia [A$1121]), and grade 4 neutropenia or febrile neutropenia (in Italy [€436–€497] and Spain [€598–€755]). Some of the AEs most commonly associated with ipilimumab (hypophysitis, dyspnea, and diarrhea) and vemurafenib/dabrafenib (CSCC and elevated liver enzymes) were among the most expensive AEs.

Vouk et al[22] evaluated AEs and the corresponding costs associated with chemotherapy (dacarbazine, paclitaxel, and fotemustine), immunotherapy (ipilimumab), and targeted therapy (vemurafenib) in Australia, France, Germany, Italy, and the UK (August 2012–May 2013). AEs of interest were identified through a systematic literature review. Resource use was estimated through conduct of 2 Delphi panel cycles in each study country; published costs of resources using local references were used to estimate per-event costs. Taking a societal health care perspective, the 10 costliest AEs per patient per event were ranked. Most of the cost-intensive AEs (ranked 1–3) across the three treatment categories were grade 3 or 4 in severity; the primary drivers of costs to manage these AEs were hospitalization and medication. The costliest AE types were grade 3 and 4 events

Table 5

Total cost of adverse event categories in the US: Arondekar et al[15] and Chang et al[23].

	Arondekar et al,[15] Mean (95% CI), US$*	Chang et al[23] mean (SD), US$†				
Adverse event	incremental 30-day adjusted costs	Vemurafenib	Ipilimumab	Dacarbazine	Temozolomide	Paclitaxel
Any adverse event	NR	1093 (2397)	2480 (7924)	7873 (20,165)	1499 (4305)	5185 (7411)
Cardiovascular	6476 (4667–8541)	203 (904)	713 (4401)	431 (2381)	234 (1876)	238 (950)
CNS and psychiatric disorders	5903 (3842–8313)	–	–	–	–	–
Gastrointestinal disorders	6338 (4740–8122)	176 (1022)	958 (4912)	3006 (9735)	405 (2250)	1383 (4065)
Hemic and lymphatic disorders and effects	8450 (6528–10,633)	535 (1744)	1409 (7048)	5213 (17,872)	829 (3052)	2952 (4741)
Metabolic and nutritional disorders	9135 (6404–12,392)	2 (19)	12 (142)	0 (0)	38 (489)	92 (937)
Pain	5078 (3392–7012)	90 (426)	301 (2473)	23 (157)	21 (111)	10 (50)
Skin and subcutaneous tissue disorders	−900 (−1899 to 237)	124 (437)	10 (42)	11 (72)	21 (198)	38 (340)

AE = adverse event, CI = confidence interval, CNS = central nervous system, NR = not reported, SD = standard deviation, US = United States.

* Incremental 30-day cost per AE was determined by comparing the 30-day expenditures (excluding costs for study drugs and other cancer therapies) for patients with the event to patients without the event. Resource use and cost were identified from a claims database.

† Mean costs, by study drug, for AE categories of interest were estimated. Resource use and cost of AEs were obtained from the claims database.

associated with immunotherapy (colitis in Australia [A$ 1471] and France [€3313]; diarrhea in the UK [£2836]) and chemotherapy (neutropenia/leukopenia in Germany [€1744] and Italy [€804]) (Table 4). Chemotherapy-associated AEs were associated with the highest population-level burden in Australia, Germany, Italy, and France (mainly due to neutropenia and leukopenia), whereas in the UK, the AE with the highest population-level cost was CSCC associated with vemurafenib.

3.2.2.3. Other supporting studies. In a small, single-center UK analysis of the cost of toxicities associated with ipilimumab, Yousaf et al[24] found that colitis was the most common and costly AE for ipilimumab (£1033–£26786 per patient; 83% of colitis cases were managed with an inpatient stay).

In a cost-effectiveness analysis of first-line dabrafenib versus dacarbazine and vemurafenib as a first-line treatment for advanced melanoma in Canada, Delea et al[21] estimated the cost of AEs by multiplying the incidence of palmar-plantar erythrodysesthesia (PPE) (2.1% with dabrafenib), pyrexia (3.2%, dabrafenib), SCC (3.2%, dabrafenib; 11.9%, vemurafenib), neutropenia (13.6%, dacarbazine), and rash (7.7%, vemurafenib) by utilization of services reported in a survey of 14 Canadian clinicians by the Canadian-specific unit costs for treating that AE. The direct costs of treating AEs were estimated to be Can$58.65 for PPE, Can$106.31 for pyrexia, Can$452.51 for SCC, Can $772.35 for neutropenia, and Can$68.82 for rash.

4. Discussion

This review aimed to explore costs of managing AEs associated with advanced melanoma treatments across the globe and identified 7 relevant studies conducted in North America, Europe, and/or Australia. Among the identified studies, estimated costs of treating a grade 3 or 4 AE varied considerably by country. Grade 3 or 4 AEs resulted in high population-level costs in Australia, France, Germany, and Italy, with hospitalization being the primary cost driver.[22] Overall, the costliest AEs to manage were those requiring hospitalization or the use of expensive outpatient medications and/or procedures.[16] Chemotherapy had the highest cost burden in Australia, Germany, Italy, and France, mainly because of incidence of neutropenia/leukopenia; the highest cost burden in the UK was associated with use of targeted therapy with a selective BRAF inhibitor because of the cost of treating CSCC.[22]

The AE costs also varied within a given treatment setting. In the European and Australian outpatient settings, anemia was one of the costliest AEs, driven primarily by use of erythropoietin and blood transfusions.[7] CSCC and immune-related diarrhea were also costly.[7] In the European and Australian inpatient settings, hypophysitis, elevated liver enzymes, peripheral neuropathy, dyspnea, diarrhea, CSCC, and febrile neutropenia incurred higher costs relative to other AEs related to melanoma treatments.[7] Some common AEs associated with ipilimumab (hypophysitis, dyspnea, and diarrhea) and vemurafenib/dabrafenib (CSCC and elevated liver enzymes) were among the most expensive AEs evaluated in Europe and Australia.[7]

Differences between countries in the costs reported for the same AE are likely driven by differing care strategies and resource-use patterns. Previous research found that hospitalization rates are high in France and low in Italy,[25] reflecting the preferential attitude of Italian centers to treat patients on an outpatient basis, both for therapy administration and supportive care. Italy also has a high proportion of nonacademic hospital sites, which tend to treat patients with less-severe disease; however, for patients hospitalized, total hospitalization costs are high due to higher per-diem costs and longer hospital stays relative to other countries. In the UK, both outpatient and hospice care are more common than in Italy and France.[25] There are shortcomings in making comparisons across countries[22] due to potential differences in drug reimbursement status, physicians' choice of treatment, and patients' disease characteristics. Further, a goal for future research should be to examine whether the costs of managing treatment-related AEs decrease as clinical practice standards within and across countries evolve toward earlier detection and more optimal management of side effects.

Additional research will be needed to evaluate the cost burden of AEs in advanced melanoma as the treatment landscape evolves. None of the studies identified in this review included the PD-1-blocking antibodies pembrolizumab and nivolumab, thus highlighting a gap in the evidence. AEs associated with these therapies are similar to those associated with ipilimumab but with immune-related AEs occurring less frequently.[26] Table S-3 (Supplemental Digital Content, http://links.lww.com/MD/C368) presents the incidence rates for AEs associated with these treatments, as well as selected treatments included in the reviewed studies, based on US package inserts. It is anticipated that the AE-associated total cost burden associated with use of PD-1-blocking antibodies would be less costly than those for other drugs as presented in the reviewed studies, namely because of a decreased overall frequency of side effects associated with PD-1-blocking antibodies and reduced frequencies of grade 3 or 4 fatigue, elevated gamma-glutamyltransferase, cutaneous AEs (eg, CSCC), and (relative to ipilimumab) diarrhea and enterocolitis.

Some limitations of this study must be considered. Limited data are available to quantify AE management costs, and the AEs evaluated in the reviewed studies were driven by the therapies included. Because some currently available therapies were not available during the research period, their associated AEs were not reflected in these articles. Comparisons of results between countries should be undertaken with caution. Due to the challenges hindering cross-country comparisons, cost data are presented as reported by the studies, without inflation to current prices or conversion to a single currency. Some studies used Delphi panels[22] or physician interviews[7,16] from a limited number of centers to estimate resource use and treatment setting, which may not be generalizable or representative of all treatment practices within the studied countries. Nevertheless, the study involving Delphi panels used a robust approach with multiple clinician interviews and attempts to achieve consensus, lending credibility to their results. The incidence rates of specific AEs were derived from studies of different durations of follow-up[22] or from clinical trials,[7] which may not capture the full set of real-world AEs. In addition, some AEs were assumed to have occurred only once per patient.[22] Finally, differing experience or familiarity with managing AEs associated with newer therapies may lead to management differences across countries and, hence, different costs.

In conclusion, the costs of managing each AE associated with the treatment of advanced melanoma are substantial but may be reduced by effective treatments with improved safety profiles.

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