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
1. Introduction
Advanced melanoma is generally treated with systemic therapy. Systemic therapies in use before 2011 included cytotoxic chemotherapy (eg, dacarbazine, temozolomide, paclitaxel, albu- min-bound paclitaxel, or carboplatin/paclitaxel, alone or in combination), high-dose interleukin-2 (IL-2), interferon, and biotherapy (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.[10–16] 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 onco- lytic 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.[15] 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.[18,20] 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 Pharmacoconomics 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,[25] 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
country-specific published costs\cite{7,16,21,22,24} or a US claims database\cite{15,23}. Cost-years were all fairly recent and consistent; most ranged from 2012 to 2014,\cite{7,21,22,24} with longer timeframes for the US claims database studies (2005–2012,\cite{15} 2004–2012,\cite{16} and 2009–2012\cite{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:\cite{15,16,23} Bilir et al\cite{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\cite{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,
| Author (date) | Country and cost year | Data source | Population | Description of costs reported |
|--------------|-----------------------|-------------|------------|-------------------------------|
| Copley-Merriman et al. Medicine (2018) 97:31 | Australia, Canada, and Europe | | | |
| Delea et al.[17] 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 | | | |
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| Australia, Canada, and Europe | | | | |
| Vauk et al.[12] 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 | | | |
| Weihl 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, interferon-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 for medical resource-use data associated with managing AEs. | | | |
| | ▪ 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. | | | |
| Yousaf et al.[24] UK 2013/2014 | ▪ All patients treated 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. | | | |
| US | | | | |
| Arondekar et al.[11] 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. | | | |
| | ▪ 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 Clininformatics Datamart claims database (using claims for July 1, 2004 to Nov 30, 2012). | | | |
| Bilir et al.[14] 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 Clininformatics Datamart claims database (using claims for July 1, 2004 to Nov 30, 2012). | | | |
| 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 pazopanib were considered. | | | |
| | ▪ Resource use and cost of AEs were obtained from the claims database. | | | |
| | ▪ Costs per resource were based on standard NHS tariff. | | | |
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Inpatient costs of grade 3 or 4 adverse events in 9 countries: Wehler et al[7] and Bilir et al[16].

| AE category; AE                        | 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† |
|----------------------------------------|---------------------------------------------------------------------|------------------------------------------------------------------------|
|                                        | 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    |
| Hypoglycemia                           | 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    |
| Hematologic/lymphatic                  |        |       |          |         |              |     |                |              |            |
| Acidosis                               | NR     | NR    | NR       | NR      | NR           | NR | NR             | NR           | $26,648    |
| Anemia                                 | €2667  | €1801 | €2367    | €2000   | €2839        | £2246 | £4380  | £5181        | $19,122    |
| Ferritin neuropenia                    | €2357  | €5480 | €2388    | €2000   | €2152        | £4444 | £5224  | £7843        | NR         |
| Hypophysitis                           | €1589  | €10265| €1979    | €5316   | €1683        | £2417 | £7231  | £9735        | NR         |
| Neuropenia                             | €2357  | €1529 | €2388    | €2000   | €877         | £2194 | £5224  | £7843        | NR         |
| Sepsis                                 | NR     | NR    | NR       | NR      | NR           | NR | NR             | NR           | $35,172    |
| Metabolic/nutritional                  |        |       |          |         |              |     |                |              |            |
| Acute kidney failure                   | NR     | NR    | NR       | NR      | NR           | NR | NR             | NR           | $31,213    |
| Elevated liver enzymes                 | €2159  | €3356 | €1890    | €6913   | €1305        | £119 | £6594  | £8030        | $19,122    |
| Hypertypericemia                       | NR     | NR    | NR       | NR      | NR           | NR | NR             | NR           | $15,827    |
| Hypertension                           | 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         |
| Nephroticopathy                        | 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    | €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 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-alpha. 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. Chang et al[23] investigated costs of AEs associated with specific melanoma therapies. This retrospective claims study
| AE category, AE                                      | 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 |
|-----------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
|                                                     | 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                                    | 3         | €46       | €134        | €46         | €33            | £86    | £251           | £91          | £162      | €131 |
| Diarrhea (immunotherapy-related)                   | 4         | €46       | €134        | €46         | €33            | £86    | £126           | £91          | £162      | €109 |
| Vomiting                                            | 3         | €64       | €132        | €76         | €31            | £80    | £251           | £147         | £239      | €184 |
| Hemic/lymphatic                                     | 4         | €64       | €132        | NR          | €31            | £80    | £251           | NA²          | NA³       |      |
| Anemia                                              | 3         | €132     | €144        | €46         | £1285          | £936   | £730           | £890         | £370      | €145 |
| Fever                                               | 4         | €128¹    | €144        | €46         | £1285          | £936   | £730           | £890         | £370      | €145 |
| Neutropenia                                         | 3         | €436     | €598        | €46         | £29            | £81    | NA¹            | NA¹          | £258      | NA³ |
| Hypophysitis (immune-related)                       | 4         | €436     | €598        | €46         | £29            | £81    | NA¹            | NA¹          | £258      | NA³ |
| Neutropenia                                         | 3         | €326     | €460        | €46         | £107           | £465   | £251           | £283         | £168      | €132 |
| Neutropenia                                         | 4         | €497     | €755        | €46         | £28            | £79    | £251           | £141         | £160      | €2088 |
| Metabolic/nutritional                               |           |           |             |             |                |        |                |                |          |
| Elevated liver enzymes                              | 3         | €47      | €97         | €46         | £28            | £79    | £251           | £304         | £160      | €109 |
| Other                                               | 4         | €47      | €97         | €46         | £28            | £79    | £251           | £304         | £160      | €109 |
| Pain                                                |           |           |             |             |                |        |                |                |          |
| Headache                                            | 3         | €21      | €104        | €46         | £28            | £82    | £251           | £94          | £161      | €110 |
| Peripheral neuropathy                               | 3         | €34      | €99         | NR          | €67            | £81    | £251           | NA³          | £161      | €113 |
| Respiratory                                         | 4         | €34      | €99¹        | NR          | €67            | NA³   | £251           | NA³          | £161      | €109 |
| Dyspnea                                             |           |           |             |             |                |        |                |                |          |
| 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      | €184¹       | NR          | £32            | £82²  | £251           | £380         | £171      | €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.

¹Costs 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 each country. Outpatient costs were estimated using country-specific tariffs or government/published sources.

²Costs 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.

³100% inpatient admission.

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

²Clinicians provided outpatient resource use but indicated that patients would always be hospitalized.

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

⁴Topical 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 dacarbazone 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 dacarbazone, 30.3% for paclitaxel, 9.2% for temozolomide, 6.4% for vemurafenib, and 4.0% for ipilimumab.
Inpatient and outpatient cost of grade 3 or 4 adverse events in 5 countries: Vouk et al[22].

| Adverse event                          | Mean cost of grade 3 or 4 AEs per event per patient | Percentage of patients hospitalized per 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/lymphic                          |                                      |                                      |                |                                      |                |                                      |                |                                      |                |
| Hypophysis (immune-related)            | $503 1.7%    | €823 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%   | €313 100%               | €924 76.7%         | €712 65.0%              | €198 30.0%  |                                      |                |                                      |                |
| Pain                                   | $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.

Mean cost of grade 3 or 4 AEs per event per patient 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.
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$38.65 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.[^21] Overall, the costliest AEs to manage were those requiring hospitalization or the use of expensive outpatient medications and/or procedures.[^4] 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.[^21]

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.[[^21][^25]]

There are shortcomings in making comparisons across countries 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.

Acknowledgments
The authors gratefully acknowledge James A. Kaye of RTI Health Solutions for reviewing the manuscript and Daniel Siepert of RTI Health Solutions for editing the manuscript.
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