Economic Evaluation of Systemic Treatments for Advanced Melanoma: A Systematic Review
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A B S T R A C T

Background: Many high cost treatments for advanced melanoma have become available in recent years. National health technology assessment agencies have raised concerns regarding uncertainty in their clinical and cost-effectiveness.

Objective: The aim of this systematic review is to identify economic evaluations of treatments for advanced melanoma and review model assumptions, outcomes, and quality as preparation for a health technology assessment.

Methods: A search of Embase, MEDLINE, EconLit, and the Cochrane Database was conducted. Only studies using decision-analytic models were included. Two authors independently completed full-text review and data extraction.

Results: Fifteen studies were identified. There were major differences in the structural assumptions underpinning the models. There was general agreement in study conclusions, although the predicted costs and quality-adjusted life years for each treatment varied. BRAF monotherapy (vemurafenib, dabrafenib) or BRAF/MEK combination therapy (BRAF monotherapy with cobimetinib or trametinib) has not been shown to be cost-effective in any jurisdiction. PD-1 inhibitors (pembrolizumab, nivolumab) are consistently found to be cost-effective compared with ipilimumab, although their cost-effectiveness compared with chemotherapy is not established. Combination therapy with nivolumab and ipilimumab is unlikely to be cost-effective in any setting. One study including all agents found that none of the new treatments were cost-effective relative to chemotherapy. Publication of the study in a health economics journal is associated with better reporting of and higher-quality assessment than those published in clinical journals.

Conclusion: Despite differences in model structures and assumptions, the conclusions of most included studies were consistent. Health technology assessment has a key role in maximizing value from high-cost innovative treatments. Consideration should be given to divestment from BRAF/MEK inhibitors and ipilimumab in favor of reimbursement of PD-1 inhibitors.

Keywords: cost-effectiveness, economic evaluation, health technology assessment, melanoma, systematic review.
Trametinib were subsequently authorized for concomitant administration with BRAF inhibitors, overcoming acquired resistance,\textsuperscript{12,13} and prolonging PFS and OS with durable responses seen in some patients.\textsuperscript{14-16} Patients with a BRAF mutation are also eligible for treatment with immunotherapy agents.

These new treatments have transformed the treatment landscape in melanoma, delivering meaningful improvements in survival with reduced toxicity compared to CC. Owing to the high costs of these treatments, there is large disparity in access across Europe.\textsuperscript{17} Many of these treatments received rapid regulatory approval, in some instances based on surrogate endpoints. National health technology assessment (HTA) agencies have raised concerns regarding uncertainty in clinical effectiveness and cost-effectiveness.\textsuperscript{18-22}

The objective of this review is to identify published economic evaluations of treatments for melanoma. The purpose is to review the structural and methodological assumptions considered appropriate, the model outcomes, and the quality of published evaluations using a published appraisal checklist for economic evaluations.

Methods

A systematic review protocol was developed in line with the objectives of the review, with reference to published literature on systematic review of economic evaluations and the Guidelines for the Retrieval and Interpretation of Economic Evaluations of Health Technologies in Ireland.\textsuperscript{23} The search strategy was derived based on published search filters for economic evaluations (see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.07.003). We searched EconLit via EBSCOhost, Cochrane Library (restricted to NHS Economic Evaluation Database and HTA database), Embase, and MEDLINE via Ovid from inception. Searches were conducted on August 9, 2017 and updated on September 17, 2018.

Decision analytic models examining the cost-effectiveness of pharmacologic treatments for patients with advanced (unresectable or metastatic) melanoma, irrespective of line of treatment, were included. All studies with an outcome of cost per quality-adjusted life year (QALY), cost per life year gained (LYG), or alternative measure of health outcome, and cost-minimization studies were included. Cost-of-illness and non-English-language studies were excluded. Conference abstracts were excluded owing to a lack of information to assess quality.

Titles and abstracts were screened by 1 author (C.G.). The full texts of the remaining articles were reviewed by 2 reviewers independently (C.G, L.Mc.C.) in accordance with the eligibility criteria. Disagreements were resolved by discussion and arbitration (M.B.) where necessary.

Study data were extracted using a data extraction form, which included the study title, author, country, perspective, model type, time horizon, discount rate, treatment(s), resource use, modeling of adverse events (AEs), survival extrapolation, utility, funding sources, and cost and effectiveness outcomes. Data extraction was conducted independently by 2 authors (C.G., L.Mc.C.). Extracted total costs and incremental cost-effectiveness ratios (ICERs) were inflated to 2017 costs using the country-specific Consumer Price Index (CPI) for health (or overall CPI if CPI health not available), then converted to US dollars using the Organisation for Economic Cooperation and Development Purchasing Price Parity index.\textsuperscript{24} For studies where the cost year was not specified, it was assumed to be the year of publication.

Completeness of reporting was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, which provides 25 recommendations to optimize reporting of health economic evaluations.\textsuperscript{25} Quality of the evaluation was assessed using the Philips Quality Checklist, which is designed to inform critical appraisal of the methodological quality of economic modeling.\textsuperscript{26} Both are qualitative instruments with no overall score produced. The number of compliances with the CHEERS checklist and positive assessments of quality for each field of the Philips checklist are reported. Checklists were completed independently by 2 authors (C.G. and L.Mc.C.), and disagreements were resolved by discussion. Pearson’s correlation coefficient was used to examine the relationship between completeness of reporting and study quality. Logistic regression models were used to investigate associations among journal type (health economics vs clinical), reporting, and study quality. Chi-square tests were performed to determine if there were relationships between study conclusions (cost-effective or not) and journal type or study sponsor (industry vs other). Statistical analysis was conducted in RStudio using R version 3.5.0.

Results

A total of 660 records were identified, and 636 were screened after duplicates were removed. Following title and abstract screening, 505 publications were excluded, and 131 underwent full text review. Most did not meet the eligibility criteria: 15 studies were included in the final review. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram is presented in Figure 1. Summary details of the included studies are provided in Table 1. Excluded studies and reasons for exclusion are provided (see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.07.003).

Study Design and Structural Assumptions

The identified studies were published between 2000 and 2018. Nine studies were sponsored by the pharmaceutical industry, 5 were funded independently, and 1 did not include declarations of funding.

Most studies (n = 8) used a Markov modeling approach. One study used a decision tree model,\textsuperscript{27} 4 used a partitioned survival model,\textsuperscript{28-31} and the modeling approach was not described in 2 studies.\textsuperscript{32,33} Most studies used the conventional 3-health state model of PFS, progressive disease, and death (n = 10). Health state descriptions were not specified in 2 studies.\textsuperscript{32,33} One study examining the effects of treatment sequencing modeled 7 health states incorporating various progression states, and a response state with or without AEs.\textsuperscript{14} One model had 2 substates in the PFS state, defined according to PD-L1 status.\textsuperscript{25}

Time horizons varied from 1 year to 40 years, were not always clearly specified or justified, and were specifically mentioned as drivers of uncertainty in 3 studies.\textsuperscript{28,36,37} Cycle length varied from 1 week to 9 weeks, and was not reported in 5 studies.\textsuperscript{37,32,33,37,38} The most common cycle length was 1 month (n = 4); half cycle correction was the exception rather than the rule (n = 1). Most studies were set in the United States (n = 8), with 5 from European countries, and 1 each from Canada and Australia. The payer perspective was most common (n = 13). Two studies provided the societal perspective,\textsuperscript{32,33} whereas 2 stated a societal perspective was taken but did not document the inclusion of indirect costs and were classified as payer perspective.\textsuperscript{37,35} Three studies did not apply or specify a discount rate.\textsuperscript{32,33,37} One study applied a different discount rate to costs (3%) and outcomes (6%);\textsuperscript{40} the remaining studies applied the same rate to both costs and outcomes. Discount rates applied varied from 3% to 6%. Nine studies estimated model costs in USD, with the cost year ranging from 1999 to 2016. Cost year was not stated in 3 studies.\textsuperscript{37,39,40}
One study obtained evidence for clinical inputs through a de novo systematic review and evidence synthesis process; 1 identified clinical evidence inputs through published systematic reviews. For all remaining studies, no evidence of a systematic approach to the identification of clinical inputs was presented. Only one study performed a quality assessment of the included studies. Six studies included only 1 comparator, using evidence from a single phase III clinical trial. For the remaining studies, approaches to evidence synthesis were varied and sometimes unclear, and included naïve comparison, Bucher indirect comparison, mixed covariate adjusted indirect comparisons using individual patient data, and network meta-analysis.

Most commonly, PFS and OS outcomes from clinical trials were the source of treatment effects in the studies. Two studies incorporated response rates into the modeling of treatment effects, using mean and median times to response from the pivotal trials. In most cases, it was necessary to extrapolate the data to the time horizon of the model; parametric extrapolation methods were the most common. One study carried forward the last observed transition probability, assumed constant hazard, and another used the declining exponential approximation of life expectancy (approximation of survival by a simple exponential function) method. No data extrapolation was required in 1 study because the data were relatively mature at the model time horizon. Extrapolation of OS curves used external data sources (eg, cancer registries, long-term follow-up of ipilimumab trials) in a number of the studies to capture the natural history of the disease. Only 1 study reported adjusting the OS data for treatment crossover. With 1 exception, studies did not consider the suitability of parametric modeling or explore alternative options.

Thirteen cost-utility analyses were identified. Utility values were sourced from the literature derived using standard gamble methods, or from pivotal clinical trials using the EuroQol-5D-3L. Three studies adopted a time to death approach to modeling utility in the base case; 2 used a response-based approach, and the remainder modeled utility based on progression status. Five studies applied a utility decrement for AEs. The value set used to generate the utility values was stated in only 2 studies. Estimated total QALYs with each treatment are shown in Table 2.

The estimation of costs varied in the studies. Treatment acquisition costs were commonly based on the publicly available price, with 3 exceptions where confidential discount prices were used. Administration and monitoring costs were excluded.
<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Perspective, time horizon</th>
<th>Discount rate</th>
<th>Model type</th>
<th>Sponsor</th>
<th>ICER (cost/QALY), 2017 US$</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohn, 2017, United States</td>
<td>Treatment sequences of immunotherapy</td>
<td>Treatment sequences of immunotherapy</td>
<td>Third-party payer, lifetime</td>
<td>3%</td>
<td>MM</td>
<td>National Cancer Institute, Wellcome</td>
<td>1L Pembrolizumab: dominant 1L Ipilimumab: $72 117 1L Nivolumab: $93 154 1L NIVO + IPI: $203 862</td>
<td>PD-1 monotherapy followed by ipilimumab is the most cost-effective sequence in the United States. NIVO + IPI followed by chemo is not cost-effective.</td>
</tr>
<tr>
<td>Oh, 2017, United States</td>
<td>NIVO + IPI</td>
<td>(a) Nivolumab, (b) ipilimumab</td>
<td>Societal, 15 years</td>
<td>3%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MM</td>
<td>No funding</td>
<td>NS (cost/progression-free QALY)</td>
<td>NIVO + IPI is not cost-effective compared to nivolumab; nivolumab is dominant over ipilimumab in the United States.</td>
</tr>
<tr>
<td>Matter-Walstra, 2015, Switzerland</td>
<td>Dabrafenib and trametinib</td>
<td>Vemurafenib</td>
<td>Payer, lifetime</td>
<td>3%,&lt;sup&gt;b&lt;/sup&gt; 6%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>MM</td>
<td>State secretariat for Education, Research, and Innovation</td>
<td>$275 472</td>
<td>Dabrafenib and trametinib are unlikely to be cost-effective in the Swiss setting.</td>
</tr>
<tr>
<td>Barzey, 2013, United States</td>
<td>Ipilimumab</td>
<td>BSC</td>
<td>Third-party payer, lifetime</td>
<td>3%</td>
<td>MM</td>
<td>Bristol-Myers Squibb</td>
<td>$157 434</td>
<td>Ipilimumab is associated with an increase in costs and QALYs, likely to be cost-effective in the United States at a threshold of $200 000/QALY.</td>
</tr>
<tr>
<td>Bohensky, 2016, Australia</td>
<td>Nivolumab</td>
<td>Ipilimumab</td>
<td>Payer, 10 years</td>
<td>5%</td>
<td>MM</td>
<td>Bristol-Myers Squibb</td>
<td>$32 424</td>
<td>Nivolumab is cost-effective in the Australian setting.</td>
</tr>
<tr>
<td>Curl, 2014, United States</td>
<td>Vemurafenib</td>
<td>(a) Dacarbazine, (b) vemurafenib followed by ipilimumab</td>
<td>Societal, lifetime</td>
<td>3%</td>
<td>Decision tree</td>
<td>No funding</td>
<td>$395 782 vs dacarbazine</td>
<td>Vemurafenib and subsequent ipilimumab are associated with an increase in QALYs, but likely in excess of accepted WTP thresholds.</td>
</tr>
<tr>
<td>Delea, 2015, Dabrafenib Canada</td>
<td>(a) Dacarbazine, (b) vemurafenib</td>
<td>Payer, 5 years</td>
<td>5%</td>
<td>PSM</td>
<td>Glaxo SmithKline</td>
<td>$311 028 vs dacarbazine. Dabrafenib dominant over vemurafenib.</td>
<td>Dabrafenib is not cost-effective at common WTP thresholds. Likely to be cost saving vs vemurafenib, with similar QALYs.</td>
<td></td>
</tr>
<tr>
<td>De Francesco, 2016, Italy</td>
<td>Ipilimumab</td>
<td>(a) Dacarbazine, (b) vemurafenib</td>
<td>Payer, 15 years</td>
<td>3%</td>
<td>PSM</td>
<td>Bristol Myers Squibb</td>
<td>$66 691&lt;sup&gt;f&lt;/sup&gt; vs dacarbazine. Ipilimumab dominant over vemurafenib.</td>
<td>Ipilimumab is associated with increase in costs and QALYs; ICER similar to other countries; likely to be dominant over vemurafenib at discounted price in Italy.</td>
</tr>
<tr>
<td>Miguel, 2017, Portugal</td>
<td>Pembrolizumab</td>
<td>Ipilimumab</td>
<td>Payer, 40 years</td>
<td>5%</td>
<td>PSM</td>
<td>Merck, Sharpe &amp; Dohme</td>
<td>$63 286</td>
<td>Pembrolizumab cost-effective at a WTP threshold of €50 000/QALY ($84 459/QALY) in Portugal.</td>
</tr>
<tr>
<td>Shih, 2015, United States</td>
<td>Dabrafenib, vemurafenib</td>
<td>Dacarbazine</td>
<td>Societal, lifetime</td>
<td>NA</td>
<td>MM</td>
<td>NS</td>
<td>Dabrafenib vs Dacarbazine: $1 66 636 Vemurafenib: Dominated Vemurafenib vs Dacarbazine: $357 745</td>
<td>Dabrafenib is associated with an increase in QALYs but not cost-effective at a threshold of $100 000/QALY in United States. Dabrafenib is dominant over vemurafenib.</td>
</tr>
<tr>
<td>Wang, 2017, Pembrolizumab United States</td>
<td>Ipilimumab</td>
<td>Payer, 20 years</td>
<td>3%</td>
<td>PSM</td>
<td>Merck, Sharpe and Dohme</td>
<td>$86 277</td>
<td>Pembrolizumab is cost-effective at a WTP threshold of $100 000-$150 000/QALY in United States.</td>
<td></td>
</tr>
<tr>
<td>Jensen, 2016, United States</td>
<td>NIVO + IPI</td>
<td>Dabrafenib in combination with trametinib</td>
<td>Payer and societal, NS</td>
<td>NS</td>
<td>NS</td>
<td>Novartis</td>
<td>NS</td>
<td>Dabrafenib and trametinib are associated with lower total costs, lower total costs, cost/month PFS, cost/responder in United States.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Discounting not applied to progression free QALYs. <sup>b</sup> Only 10% of costs related to refractory melanoma included. <sup>c</sup> Only 10% of costs related to relapsed melanoma included. <sup>f</sup> Year of cost analysis is 2015. <sup>g</sup> Year of cost analysis is 2013. <sup>h</sup> Year of cost analysis is 2016. <sup>i</sup> Year of cost analysis is 2017. <sup>j</sup> Year of cost analysis is 2015. <sup>k</sup> Year of cost analysis is 2016. <sup>l</sup> Year of cost analysis is 2017. <sup>m</sup> Year of cost analysis is 2015. <sup>n</sup> Year of cost analysis is 2016. <sup>o</sup> Year of cost analysis is 2017.
from 2 studies, \(^{39,40}\) whereas the approach was not clearly described in 3 studies.\(^{27,30,31}\) Most studies included costs for AEs (n = 13), while the application of costs for subsequent treatments was variable.

### Model Outcomes

**Immunotherapies**

Ipilimumab was compared with CC in 2 studies, in first-line and second-line treatment populations, respectively.\(^{29,37}\) Ipilimumab was associated with an increase in costs and QALYs compared to CC in both studies. The predicted QALYs associated with ipilimumab varied from 1.76 (second line)\(^{37}\) to 1.9 (first line).\(^{29}\) The predicted total costs ranged from $107,124 (first line) to $206,315 (second line)\(^{37}\); drug acquisition cost in first line included a confidential discount available to the Italian health service.\(^{29}\) Incremental treatment cost was the driver of the increased cost in both models. It was concluded that ipilimumab was likely to be cost-effective as a second-line treatment at a willingness-to-pay (WTP) threshold of $200,000/QALY in the United States. No clear conclusion on cost-effectiveness was presented for the first-line indication, but the ICER was in line with that in other countries such as the UK and Sweden. In a comparison with vemurafenib as first-line treatment for BRAF-positive patients, ipilimumab was dominant, with some uncertainty noted in the probabilistic sensitivity analysis where 24% of the iterations were in the southwest quadrant.\(^{29}\)

Nivolumab and pembrolizumab were compared with ipilimumab in 4 studies. All models predicted that the PD-1 inhibitors were associated with an increase in costs and QALYs and were likely to be cost-effective at the national WTP thresholds. They were associated with costs ranging from $110,340\(^{41}\) to $322,914\(^{28}\) and QALYs ranging from 0.38\(^{28}\) to 4.31.\(^{28}\) Discounted prices were used in 1 study and so generalizability is questionable.\(^{38}\) All studies were from a payer perspective, and spanned a range of continents including the United States, Australia, and Europe.

One study compared NIVO-IPI to monotherapy with nivolumab or ipilimumab, based on PFS results from CheckMate 067.\(^{25}\) This study found that NIVO-IPI was associated with the highest costs and QALYs of the 3 interventions; nivolumab was dominant of ipilimumab and NIVO-IPI was associated with an ICER of $483,131 versus nivolumab monotherapy (incremental costs $62,807, incremental progression-free QALYs 0.13). It concluded that at a threshold of $100,000/QALY, nivolumab was cost-effective, and NIVO-IPI was not cost-effective even in PD-1-negative patients where relative efficacy is greatest.\(^{10}\) These conclusions were robust to sensitivity analysis, including higher WTP thresholds.

Two studies compared all 4 immunotherapy regimens with conflicting findings.\(^{34,41}\) One study examining sequences of immunotherapy and chemotherapy treatments found first-line pembrolizumab to be associated with the lowest costs, and it was dominant of CC and ipilimumab; the ICER for nivolumab versus pembrolizumab was $304,755/QALY ($45,713 incremental costs, 0.16 incremental QALYs).\(^{34}\) The NIVO-IPI regimen was associated with an incremental QALY gain of 0.02 versus nivolumab and an ICER of $1,753,774. By contrast, pembrolizumab was dominated by nivolumab (higher costs and lower QALYs) in a separate study that found that none of the new treatments were cost-effective in the Norwegian setting relative to CC, with an ICER of $92,113 for nivolumab versus CC.\(^{41}\)

### BRAF targeted treatment

Three models examined the cost-effectiveness of BRAF inhibitor monotherapy compared with CC for the treatment of BRAF

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**Table 1. Continued**

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Perspective, time horizon</th>
<th>Discount rate</th>
<th>Model type</th>
<th>Sponsor</th>
<th>ICER (cost/ QALY), 2017 US$</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pike, 2015, Norway(^{11})</td>
<td>All licensed treatments</td>
<td>Dacarbazine</td>
<td>Payer, 10 years</td>
<td>4%</td>
<td>MM</td>
<td>NOKC</td>
<td>Vs Dacarbazine: NIVO-IPI: $172,031 Nivo: $113,925 Pembro: $119,381 Ipi: $172,444 Dab + Tram: $292,176 Vem + Cobi: $268,800 Vem: $264,057 Dab: $229,126</td>
<td>None of the treatments are cost-effective compared to dacarbazine in Norway.</td>
</tr>
<tr>
<td>Hillner, 2000, United States(^{32})</td>
<td>Dacarbazine</td>
<td>Societal, 1 year</td>
<td>NA</td>
<td>NS</td>
<td>Schering Plough</td>
<td>NS</td>
<td>Nivolumab vs Ipilimumab (BRAF negative): $34,338(^{38}) Ipilimumab (BRAF positive): $24,351(^{38}) Vemurafenib: Dominant(^{1}) Dabrafenib: Dominant(^{1})</td>
<td>There is a trend toward greater survival with temozolomide at an acceptable cost/LYG.</td>
</tr>
<tr>
<td>Meng, 2018, Nivolumab England(^{13})</td>
<td>(a) Ipilimumab, (b) dacarbazine, (c) vemurafenib, (d) dabrafenib</td>
<td>Payer, 40 years</td>
<td>3.5%</td>
<td>MM</td>
<td>Bristol-Myers Squibb</td>
<td>NIVO-IPI: $172,031</td>
<td>Nivolumab is cost-effective at discounted price compared to ipilimumab and BRAF monotherapy, in both BRAF positive and negative patients, in UK.</td>
<td></td>
</tr>
</tbody>
</table>

BSC indicates best supportive care; NS, not specified; NA, not applicable; MM, Markov model; PSM, partitioned survival model; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; LYG, life year gained; WTP, willingness to pay.

*Applied to costs only.
\(^{1}\)Applied to outcomes only.
\(^{2}\)Based on discount prices.
V600 mutant melanoma.27,28,39 All concluded that BRAF inhibitor monotherapy was associated with an increase in QALYs (ranging from 0.29 to 1.66) and costs, and was unlikely to be cost-effective at national WTP thresholds.27,28,39 Two models compared dabrafenib to vemurafenib, and both concluded that dabrafenib was dominant.28,39 One study compared the cost-effectiveness of combination BRAF/MEK therapy to BRAF inhibitor monotherapy.40 It found that combination therapy was associated with an increase in QALYs and a significant increase in costs, producing an ICER far in excess of the national WTP. In a study comparing all the melanoma treatments, BRAF inhibitor monotherapy and dabrafenib and trametinib combination therapy were excluded due to dominance, and vemurafenib with cobimetinib was associated with an ICER in excess of $2 million versus nivolumab.41 Finally, a study (with outcomes in cost/month PFS)33 compared dabrafenib and trametinib combination therapy versus NIVO-IPI. Dabrafenib and trametinib combination therapy was associated with a lower per-patient treatment cost ($207 338 vs $275 875), a lower cost per month PFS ($18 849 vs $23 578), and a lower cost per responder ($300 490 vs $413 605).

### Cytotoxic chemotherapy

One study compared the cost-effectiveness of temozolomide, an oral form of the CC dacarbazine, to intravenous dacarbazine using results from the Schering I95-018 clinical trial.32 The outcome was cost/LYG. The ICER for temozolomide versus dacarbazine was $70 165/LYG; there was a 60% chance of cost-effectiveness at a threshold of $50 000/LYG.

### Reporting and Quality Assessment

The CHEERS checklist was used to review completeness of reporting of the evaluation. Compliance with the CHEERS checklist was variable. No studies were found to have perfect compliance with the CHEERS reporting requirements; 3 studies were assessed as having only 1 noncompliance.28,29,41 One study was judged to have 13 of a possible 25 noncompliances,27 1 had 12,33 and 2 were judged to have 11.32,39 Almost all studies did not provide reasons for the type of decision model used (n = 11), even when a detailed description of the model was provided. Most (n = 11) did not report differences in costs and outcomes in subgroups and failed to report on all relevant aspects of the setting and location (n = 8). The descriptions of structural assumptions underlying the model were poorly reported in many studies (n = 8), with some providing inadequate discussion of uncertainty on inputs, structure, and assumptions (n = 5). Many studies did not report the dates of estimated resource use and unit costs (n = 7), although they did provide some description of the method for converting costs. The Philips checklist was used to perform an assessment of the quality of the economic evaluation. No study was considered to have a positive quality assessment for each field of the Philips checklist. No study considered competing theories about model structure or provided evidence of testing the mathematical logic of the model. No study considered all feasible options (talimogene laherparepvec was not included in any study), but 3 did provide justification.20,32,34 Only 1 study provided adequate assessment of the 4 principal types of uncertainty;2 2 other studies did address methodological.

### Table 2. Extracted total costs and QALYs from each study, 2017 US$. Figures given are the total predicted costs and QALYs, rather than incremental values.

<table>
<thead>
<tr>
<th>Drug Treatment</th>
<th>USA</th>
<th>UK‡</th>
<th>Norway§</th>
<th>Portugal¶</th>
<th>Australia≠</th>
<th>Canada≠</th>
<th>Switzerland≠</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytotoxic chemotherapy</strong></td>
<td></td>
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</tr>
<tr>
<td>Dacarbazine</td>
<td>$275 875, 2.5 QALYs</td>
<td>$312 838, 3.4 QALYs</td>
<td>$322 914, 3.45 QALYs</td>
<td>$164 395, 2.61 QALYs</td>
<td>$175 545, 0.54 QALYs</td>
<td>$180 823, 0.54 QALYs</td>
<td>$97 894, 0.29 QALYs</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>$156 231, 0.34 QALYs</td>
<td>$150 462, 0.26 QALYs</td>
<td>$211 620, 1.7 QALYs</td>
<td>$66 607, 1.23 QALYs</td>
<td>$187 345, 1.76 QALYs</td>
<td>$255 163, 2.67 QALYs</td>
<td>$93 82, 0.3 QALYs</td>
</tr>
<tr>
<td>Temozolomide with cobimetinib</td>
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<tr>
<td>Dabrafenib</td>
<td>$175 345, 0.72 QALYs</td>
<td>$103 788, 1.7 QALYs</td>
<td>$97 894, 1.19 QALYs</td>
<td>$151 612, 1.66 QALYs</td>
<td>$128 823, 1.48 QALYs</td>
<td>$110 340, 1.7 QALYs</td>
<td>$200 869, 1.45 QALYs</td>
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<td>Vemurafenib</td>
<td>$43 097, 0.34 QALYs</td>
<td>$100 296, 1.69 QALYs</td>
<td>$97 834, 1.23 QALYs</td>
<td>$128 823, 1.48 QALYs</td>
<td>$128 823, 1.48 QALYs</td>
<td>$128 823, 1.48 QALYs</td>
<td>$74 040, 0.99 QALYs</td>
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<td>Vemurafenib with cobimetinib</td>
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<tr>
<td>Dabrafenib</td>
<td>$207 338, 1.32 QALYs</td>
<td>$257 892, 1.71 QALYs</td>
<td>$176 351, 1.76 QALYs</td>
<td>$207 338, 1.32 QALYs</td>
<td>$207 338, 1.32 QALYs</td>
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BSC indicates best supportive care; Dab, dabrafenib; Dab + Tram, dabrafenib and trametinib; DTIC, dacarbazine; PFQALYs, progression-free quality-adjusted life years; Tem, temozolomide; Vem, vemurafenib; Vem + Cobi, vemurafenib and cobimetinib.

*Undiscounted QALYs

‡No QALYs reported.

§Based on discount prices.
uncertainty. All studies provided clear statements of the decision problem. Only 1 study described and justified the choices made between data sources. This study was also the only study performing a quality assessment of the included studies. Three studies were deemed to have performed appropriate synthesis of evidence, for 1 study the outcome was unclear, whereas the remainder were considered not to meet best-practice standards.

The relationships between reporting and study quality, and among study conclusion, sponsor, and journal type, were examined. A data table was constructed with the numbers of compliances with CHEERS and positive Philips assessments (higher numbers indicating better reporting or quality) for each study. The relationship between reporting compliance and a positive assessment of study quality was examined using Pearson’s correlation coefficient. There was a strong positive correlation between CHEERS reporting compliances and positive assessments on the Philips quality checklist (P = .72), showing a strong relationship between reporting and quality assessment.

Logistic regression models were used to investigate the relationship between the CHEERS and Philips assessments and journal type. Publication in an economics journal was associated with better compliance with the CHEERS checklist (P = .002) and a greater number of positive assessments on the Philips checklist (P = .01). Pharmaceutical industry sponsorship was not associated with better reporting (P = .385) or higher quality (P = .247).

Chi-square tests were used to investigate the relationship between journal type or study sponsor and studies producing positive conclusions regarding cost-effectiveness. Two studies were excluded from these analyses: no conclusions regarding cost-effectiveness were advanced in one of the studies, and no funding declaration was available in the other. For both comparisons, the P value was >.05, suggesting that the null hypothesis of independence could not be rejected (Table 3). Nevertheless, there is a clear trend that industry-sponsored studies are likely to produce conclusions regarding the cost-effectiveness of the interventions. Nevertheless, many national HTA bodies cast doubt on the cost-effectiveness of immunotherapies at the time of marketing authorization. Since immunotherapies may not have been cost-effective in the first incidence compared with CC, assessing new treatments such as PD-1 inhibitors versus immunotherapies may be inappropriate where it has been reimbursed at prices higher than the national WTP threshold. The consequences of this are illustrated by the Norwegian study, which found that all treatments are not cost-effective relative to CC, the original comparator in this new era of treatment.

All publications agree that PD-1 agents are associated with higher QALYs than ipilimumab, and in many instances are dominant, and that NIVO-IPI is unlikely to be cost-effective even in biomarker-enriched populations. Because ipilimumab is excluded from all cost-effective treatment options and is associated with a lower QALY gain than other immunotherapies, we suggest that divestment opportunities could be considered and pursued by healthcare systems.

All studies found that BRAF monotherapy is associated with an increase in QALYs compared with CC, but the increase in costs is such that the treatment is unlikely to be cost-effective. Similarly, BRAF/MEK therapy is associated with an increase in QALYs compared with BRAF monotherapy but is considered unlikely to be cost-effective at national WTP thresholds. Three studies include a comparison between immunotherapies and BRAF monotherapy; immunotherapy was likely dominant over BRAF monotherapy in 2 studies, and the estimated ICER for vemurafenib and cobimetinib versus nivolumab was $2,053,845/QALY in the third. Any form of BRAF targeted therapy is unlikely to be cost-effective regardless of comparator or the national WTP threshold, and divestment from these costly therapies could allow reimbursement of PD-1 inhibitors.

All identified models derived estimates of relative treatment effects from randomized controlled trials. Recently it has been highlighted that approximately 50% patients with metastatic melanoma do not meet the eligibility criteria for treatment within these randomized controlled trials, raising concerns regarding the generalizability of the results to the real-world population. Cost-effectiveness in the real-world population is not established.

<table>
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Discussion

Our systematic review identified 15 economic evaluations of the cost-effectiveness of treatments for advanced melanoma, published between 2000 and 2018. These new drug treatments are associated with significant clinical benefits in some patients and a high cost per patient, posing challenges to cost-effectiveness and affordability. Public health systems have struggled to make these drugs available to all eligible patients, and they are subject to prescribing restrictions even in Europe’s wealthiest countries.

Although most studies used a simplified 3-health-state model, there were major differences in the structural assumptions underpinning the models, including in the modeled time horizons, model type, application of discounting, estimation of utility, and extrapolation of survival. There were large variations in the predicted costs and QALYs associated with each treatment, for example, the predicted QALY gains with pembrolizumab and nivolumab varied from 0.38 to 4.31. Some of the variation in total costs is likely to be explained by different healthcare resource use and costs across jurisdictions. It may also be accounted for by differing approaches to capturing treatment options post-progression, where some studies assumed no post-progression drug costs were incurred while others included these costs. Variations in QALY gains are at least partially explained by the use of utility values derived by different methods, differing time horizons, and alternative approaches to survival extrapolation. Despite these variations, there was consistency in the conclusions across most of the studies.

Six industry-sponsored studies evaluated the cost-effectiveness of immunotherapies. Ipilimumab was associated with an increase in costs and QALYs compared with CC, and PD-1 inhibitors were associated with an increase in cost and QALYs compared with ipilimumab. All studies had positive conclusions regarding the cost-effectiveness of the interventions. Nevertheless, many national HTA bodies cast doubt on the cost-effectiveness of immunotherapies at the time of marketing authorization. Since immunotherapies may not have been cost-effective in the first incidence compared with CC, assessing new treatments such as PD-1 inhibitors versus immunotherapies may be inappropriate when it has been reimbursed at prices higher than the national WTP threshold. The consequences of this are illustrated by the Norwegian study, which found that all treatments are not cost-effective relative to CC, the original comparator in this new era of treatment.

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All identified models derived estimates of relative treatment effects from randomized controlled trials. Recently it has been highlighted that approximately 50% patients with metastatic melanoma do not meet the eligibility criteria for treatment within these randomized controlled trials, raising concerns regarding the generalizability of the results to the real-world population.
No paper was found to have perfect compliance with the CHEERS reporting requirements, but publication in an economics journal was associated with fewer noncompliances (P = .002). The CHEERS statement is an assessment of reporting, not methodology, quality, and failure to follow all the requirements in the CHEERS statement is not indicative of a poor-quality study. Poor reporting can make assessment of quality difficult.30 The strong correlation between CHEERS compliances and Philips quality assessment in our study supports the finding that their assessment is interdependent.

Quality assessment of the studies highlighted significant deficiencies, mainly in the areas of identifying the evidence and the synthesis of relative treatment effects, with only 1 study describing and justifying the choices made between data sources.31 The exploration of uncertainty in the models was also of a poor standard.

In our sample, publication in a health economics journal was associated with better reporting and higher-quality assessment. Studies with industry sponsors were more likely to conclude positively on cost-effectiveness relative to standard-of-care therapy, although this finding did not demonstrate statistical significance at the P < .05 level. Pharmaceutical industry sponsorship was not associated with higher quality of economic evaluation.

We developed and executed a comprehensive search strategy in line with best-practice recommendations; we recently updated the search to ensure completeness. Both quality of reporting and study quality were assessed, recognizing the distinction and dependence between both. The quality assessment conducted is subjective in that it is framed by the Irish national reference case and therefore may not be directly applicable to other jurisdictions.

Our study excluded 1 non-English publication and 3 studies where poor standard.

Conclusion

BRAF monotherapy or BRAF/MEK combination therapy have not been shown to be cost–effective in any jurisdiction. PD-1 inhibitors are consistently found to be cost-effective compared with ipilimumab, although their cost-effectiveness relative to CC is not widely assessed. The NIVO-IPI regimen is unlikely to be cost-effective in any setting where PD-1 inhibitors are standard of care. Consideration could be given to pursuing divergent strategies from older, less effective treatments in favor of more cost-effective treatment with PD-1 inhibitors.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.07.003.

REFERENCES


