Cost-Effectiveness of Drug Treatments for Advanced Melanoma: A Systematic Literature Review

Darío Rubio-Rodríguez, Silvia De Diego Blanco, Maite Pérez & Carlos Rubio-Terrés

PharmacoEconomics

ISSN 1170-7690

PharmacoEconomics
DOI 10.1007/s40273-017-0517-1

Springer

PharmacoEconomics
DOI 10.1007/s40273-017-0517-1

SYSTEMATIC REVIEW

Cost-Effectiveness of Drug Treatments for Advanced Melanoma: A Systematic Literature Review

Darío Rubio-Rodríguez[1] · Silvia De Diego Blanco[2] · Maite Pérez[3] · Carlos Rubio-Terrés[1]

Abstract

Background Until recently, advanced melanoma (unresectable and metastatic) has had a poor prognosis and has been treated with chemotherapy. The introduction of new treatments (BRAF and MEK inhibitors and immunotherapy) has improved overall survival and progression-free survival of some patients.

Objective The objective of this study was to review the published evidence on the cost-effectiveness of pharmacological treatments for advanced melanoma.

Methods A systematic literature search was conducted, without date or language restrictions, in PubMed, EMBASE, Scopus, the Cochrane Library, the UK National Institute for Health and Care Excellence databases and the *Health Technology Assessment* journal. Internet searches were also made to identify possible grey literature. Main study characteristics, methods and outcomes were extracted and critically assessed. The quality of health economic studies was assessed by the Quality Assessment of Economic Evaluation in Health Care checklist.

Results The search identified nine full-text pharmacoeconomic analyses of advanced melanoma treatments. According to the economic analyses published in the articles, the new treatments have been shown to be more effective (with more life-years and quality-adjusted life-years) than chemotherapy, although generally the cost per quality-adjusted life-year gained was above the commonly accepted threshold. Because of the variability of the available analyses comparing the new treatments, we cannot determine which treatment is the most cost-effective.

Conclusions From the available data, it cannot be concluded that the new drugs (BRAF and MEK inhibitors and immunotherapy) are cost effective compared with chemotherapy or which is the most cost-effective new treatment.

Key Points

New treatments have been shown to be more effective (with more life-years and quality-adjusted life-years) than chemotherapy in patients with advanced melanoma, but with higher acquisition costs.

In most of the studies, the incremental cost-effectiveness ratios were above the commonly accepted thresholds. For this reason, it cannot be concluded that the new treatments are cost effective compared with chemotherapy.

Moreover, because of the variability of the available analyses comparing the new treatments, no conclusions can be made on which treatment is the most cost effective.

✉ Carlos Rubio-Terrés
drubiorodriguez@healthvalue.org

[1] Health Value, C/Virgen de Aránzazu, 21, 5° B, 28034 Madrid, Spain

[2] Market Access Department, Astellas Pharma, SA, Madrid, Spain

[3] Medical Department, AstraZeneca Farmacéutica Spain, Barcelona, Spain

Published online: 27 May 2017

1 Introduction

Cutaneous melanoma is a malignant tumour originating from epidermal melanocytes. Unlike other types of skin cancer, melanoma is a tumour with a marked tendency to produce lymphatic or haematic metastases, sometimes prematurely [1]. The advanced disease includes unresectable stage III or stage IV disease [2].

The incidence in Europe of malignant cutaneous melanoma varies from three to five per 100,000 patients per year in Southern European countries to 12–25 per 100,000 patients per year in Northern European countries [2]. In USA, 22 out of 100,000 men and 14 out of 100,000 women are affected [3]. Melanoma detected in the initial stages is considered curable. However, advanced melanoma has a worse prognosis. Until recently, median survival in patients with advanced melanoma was 6.2 months, with only 25% surviving 1 year and 10% surviving 2 years [4].

New and promising pharmacological treatments of advanced melanoma have been introduced in recent years. Dabrafenib and vemurafenib are indicated in the treatment of patients with inoperable metastatic melanoma with BRAF (B-Raf proto-oncogene, serine/threonine kinase) V600 mutation (approximately 45% of patients with melanoma have this mutation). The median progression-free survival (PFS) observed with dabrafenib and vemurafenib was 5.3 and 5.1 months, respectively, compared with 1.6 and 2.7 months, respectively, obtained with dacarbazine [5]. Ipilimumab is also indicated for the treatment of advanced melanoma, obtaining an overall survival at 3 years of 22% [5].

In the UK, the annual direct medical costs associated with melanoma have been estimated to be £22.5 million, and projected to substantially increase in coming years [6]. The objective of this study was to review the published evidence on the cost-effectiveness of treatments for advanced melanoma.

2 Methods

2.1 Search Strategy

A systematic review of the literature was made by an Internet search conducted in PubMed, EMBASE, SCOPUS, the Cochrane Library, MEDES (Medicine in Spanish), the UK National Institute for Health and Care Excellence and the *Health Technology Assessment* journal. Internet searches were also made to identify possible grey literature in Google Scholar, the Agency for Healthcare Research and Quality website, Grey Literature Report and Grey Literature International databases.

The search strategy used the following keywords: 'melanoma', 'metastatic', 'cost-effectiveness', 'cost utility', 'cost benefit', 'cost minimization' and 'cost minimisation'. Although the review was carried out only for analysis of cost-effectiveness and cost-utility, cost minimisation and cost-benefit studies were also searched, as in some cases they could contain cost-effectiveness/cost-utility results. The search in PubMed, EMBASE, Scopus and the other sources was conducted in April 2017 (full electronic search strategies are available in the "Appendix"). The search had no date or language restrictions.

The titles and abstracts obtained in the databases and other sources were reviewed by DRR and CRT, who evaluated if the studies met the following inclusion criteria: (1) full text available (article); (2) referred to patients with advanced melanoma (in inoperable stage III or in stage IV); (3) only original investigations, not review articles; (4) cost-effectiveness analysis; and (5) referred exclusively to pharmacological treatments.

Articles that met these inclusion criteria were analysed in greater detail by two reviewers independently (DRR and CRT). Discrepancies were resolved by consensus. The lists of references of these articles were also reviewed manually to identify other potential studies not identified with the Internet search. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7].

2.2 Data Extraction

The data extracted from the articles included the following characteristics of the studies: (1) first author, year of publication, country; (2) type of study (model, alongside randomised clinical trial) and patient population characteristics (advanced melanoma, previously treated or untreated); (3) study perspective ('healthcare payer' including only healthcare or 'societal' costs including all relevant costs inside and outside the healthcare sector), time horizon; (4) funding; (5) drug therapy described; (6) difference in total costs; (7) difference in outcomes [life-years gained, quality-adjusted life years (QALYs) gained, progression free survival (PFS), overall response rate (ORR)]; (8) incremental cost-effectiveness ratio (ICER); and (9) authors' conclusion. Data extraction was performed by one author (DRR) and checked by another author (CRT).

2.3 Quality Assessment

We used the Quality Assessment of Economic Evaluation in Health Care checklist published by Abellán et al. [8] for systematic assessment of the quality of the papers because it provides a quantitative score. The quality assessment was

performed by two independent reviewers (DRR and CRT). If the results differed between reviewers, consensus was reached through discussion. The maximum score is 100 points. Three Quality Assessment of Economic Evaluation in Health Care-based quality levels are as follows: category 1 (<40 points); category 2 (40–59 points); and category 3 (≥60–100 points) [8].

2.4 Critical Assessment of Methods and Outcomes

In addition to the short narrative description of the studies and the evaluation of their quality with the checklist indicated, the following additional issues regarding methods and outcomes were further explored and discussed in detail: (1) study design (including cycle length and model states), (2) time horizon, (3) analytical approach, (4) efficacy vs. effectiveness and (5) transferability issues, in a similar manner to a recently published study [9].

3 Results

3.1 Search Results

The literature search resulted in 135 hits. After reviewing titles and abstracts, 58 references were excluded because they did not meet the inclusion criteria and 77 papers were included for full-text review. Subsequently, nine papers met the inclusion criteria [10–18]. Of the 68 articles excluded, 30 were because they did not have full-text [19–48] 18 because they were not original investigations but rather review articles [49–66], nine because they were not cost-effectiveness or cost-utility analyses [67–75], four because they did not assess pharmacological interventions [76–79] and, finally, seven because they did not refer to advanced melanoma [80–86]. Figure 1 is a flow diagram showing the inclusion and exclusion of papers at various stages of the process.

3.2 Main Study Findings

Table 1 summarises the main features of the nine studies included in the review [10–18]. The publication date ranges from 2000 to 2017. The drugs included in the nine articles analysed are shown in Table 1. Seven of the nine economic analyses modelled patients with previously untreated advanced melanoma [10, 13–18].

3.2.1 Chemotherapy

In the past 30 years, the standard treatment for advanced melanoma has been chemotherapy with drugs such as temozolomide or dacarbazine and immunotherapy with interleukin-2 (IL-2) [2]. A modelled cost-effectiveness analysis conducted in USA [10] was published in 2000. The mean increase in survival of temozolomide over dacarbazine was 1.1 months, which would not be clinically relevant. The ICER ranges from −$US65,180 (dacarbazine is more effective) to $US18,670 per life-year gained. Chemotherapy with temozolomide, dacarbazine or paclitaxel plus carboplatin (which currently are no longer treatments of choice) was considered the best supportive care (BSC) in some economic models made in the period 2013–15 [11–15] (Table 1).

3.2.2 BRAF and MEK Inhibitors

New therapeutic strategies such as immunotherapy or the therapy based on the genetic mutations of the melanoma have demonstrated considerable efficacy in the treatment of advanced melanoma [2, 87]. Approximately 40–60% of patients with metastatic melanoma have a mutation in the *BRAF* gene [88], which gives rise to uncontrolled cell growth [87]. People who have this mutation may benefit from treatment with a drug inhibitor of BRAF (blocker of the abnormal BRAF protein kinase) such as vemurafenib or dabrafenib, which slows down the growth of melanoma cells [87]. MEK1 and MEK2 are enzymes downstream of BRAF in the mitogen-activated protein kinase pathway. Adding a MEK inhibitor (such as trametinib) to a BRAF inhibitor reduced some resistance to BRAF inhibition [87].

Four analyses have been published that compare the efficiency of inhibitors of BRAF among themselves or compared with BSC [12–15] (Table 1). According to these studies, treatment with vemurafenib would not be cost effective vs. dacarbazine in USA [12] and dabrafenib would not be cost effective vs. dacarbazine in Canada [13]. When the efficiency of dabrafenib (alone or in combination with trametinib) and vemurafenib were compared, it was concluded that the former would not be cost effective compared with the latter in USA for a willingness to pay of $US100,000/QALY [15] or in Switzerland [14]. However, in the Canadian study, dabrafenib would be the dominant treatment (with lower costs and greater effectiveness than vemurafenib) [13].

3.2.3 Immunotherapy

Given that only about half of the patients with advanced melanoma express the BRAF mutation, other treatment options are necessary. Immunotherapy, which uses antibodies that bind to the inhibitors of the activation of T cells [such as ipilimumab, which inhibits the cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4] and nivolumab, which inhibits programmed cell death 1 (PD-1)], has shown significant efficacy in patients with advanced melanoma [2].

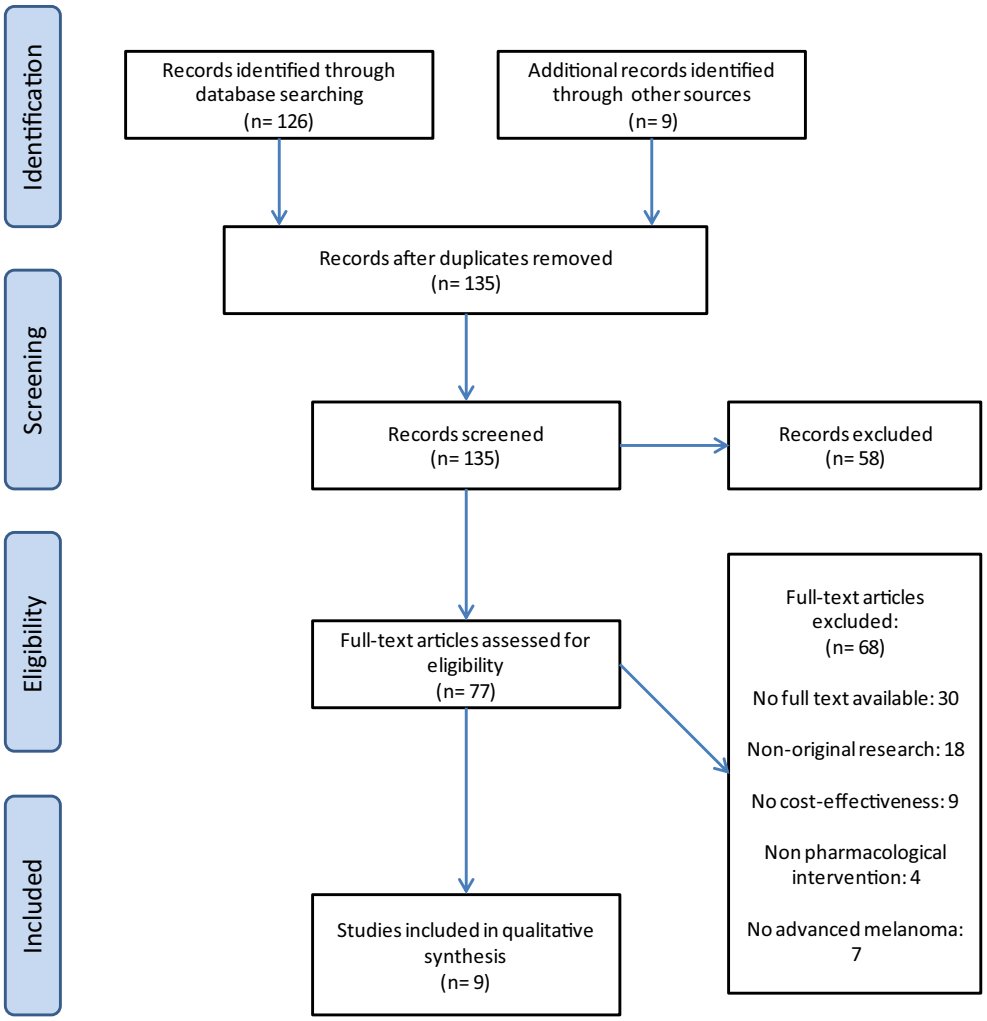

Fig. 1 Flow diagram of the search performed

Four articles have been published analysing the efficiency of immunotherapy. According to the model of Barzey et al. [11] the treatment of advanced melanoma with ipilimumab would be cost effective with a probability of 95% vs. the BSC, for a willingness to pay of $US146,000 (it should be noted that the usual willingness-to-pay threshold in USA is $US50,000 or $US100,000.). In the study of Bohensky et al. [16], it is concluded that novolimumab would be cost effective compared with ipilimumab and, in the study of Jensen et al. [17], the authors indicate that dabrafenib plus trametinib is associated with less patient time and lower costs relative to nivolumab plus ipilimumab. Finally, in the recently published study of Kohn et al. [18], it was concluded that, compared with the first-line dacarbazine treatment strategy, first-line nivolumab followed by ipilimumab produced an ICER of $US90,871 per QALY gained, and first-line nivolumab plus ipilimumab followed by carboplatin plus paclitaxel chemotherapy produced an ICER of $US198,867 per QALY gained (Table 1).

3.2.4 Life-Years Gained and Quality-Adjusted Life-Years Gained

In comparison with the BSC, 1.88 life-years and between 0.15 and 1.14 QALYs would be gained with the new treatments, according to the studies (Table 1). These gains in quantity and quality of life would be clinically relevant, according to several studies that have proposed that the minimally clinically important difference in utility would be 0.03 or 0.04 [89, 90].

3.3 Critical Assessment of Methods and Outcomes

3.3.1 Study Design

Most of the studies combined efficacy data from one or several clinical trials, which extrapolated to the long term using a Markov model. In one case a semi-Markov survival model was conducted [13]. These survival partition models are, like the Markov models, a commonly used approach in

Table 1 Main study characteristics of the cost-effectiveness assessment of advanced melanoma pharmacological treatment

First author, year (country)	Type of study, patient population	Perspective, time horizon	Funding	Drug therapy described (dose)	Total costs (year of valuation)[d]	Total outcomes[d]	ICER	Authors' conclusion	QHES category[e]
Hillner et al. 2000 (USA) [10]	Post-hoc economic analysis within a clinical trial (CEA) Advanced melanoma[a]/PUT	Societal, 1 year	American Cancer Society and Schering–Plough	1. Temozolomide (200 mg/m^2/day for 5 days every 28 days) 2. Dacarbazine (250 mg/m^2/day for 5 days every 21 days)	1. $US6902 2. $US3697 (1999)	1 vs. 2: 1.04 months gained (NS)[c]	$US36,990/LYG	Efficacy difference of temozolomide vs. dacarbazine was NS	2
Barzey 2013 (USA) [11]	Markov model Probabilistic (CEA/CUA) Advanced melanoma[a]/PT	Health payer, lifetime	Bristol–Myers Squibb	1. Ipilimumab (3 mg/kg) 2. BSC (dacarbazine, temozolomide, paclitaxel + carboplatin)	1. $US168,602 2. $US21,886 (2012)	1. 2.88 LY, 1.76 QALY 2. 1.00 LY, 0.62 QALY	$US78,218/LYG $US128,656/QALY	Ipilimumab was 95% likely to be cost effective at a WTP of $US146,000/QALY	3
Curl et al. 2014 (USA) [12]	Decision tree model Deterministic (CUA) BRAF-mutated metastatic melanoma/PT	Societal, lifetime	No	1. Vemurafenib 2. Vemurafenib followed by ipilimumab 3. Dacarbazine (N/A)	1. $US156,831 2. $US254,695 3. $US8391 (2013)	1. 0.72 QALY 2. 1.34 QALY 3. 0.30 QALY	1 vs. 3: $US353,993/QALY 2 vs. 1: $US158,139/QALY	Strategies 1 and 2 may become cost effective with lower drug prices or a durable response without continued treatment	3
Delea et al. 2015 (Canada) [13]	Semi-Markov survival model Probabilistic (CUA) BRAF-mutated advanced melanoma[a]/PUT	Canadian healthcare system, 5 years	GlaxoSmithKline	1. Dabrafenib 2. Dacarbazine 3. Vemurafenib (N/A)	1. $CAN111,199 2. $CAN36,576 3. $CAN150,405 (2012)	1. 1.52 QALY 2. 1.32 QALY 3. 1.47 QALY	1 vs. 2: $CAN363,136/QALY 1 vs. 3: Dabrafenib is dominant[b]	At a threshold of CAN$200,000/QALY, dabrafenib is unlikely to be cost effective compared with dacarbazine	3

Table 1 continued

First author, year (country)	Type of study, patient population	Perspective, time horizon	Funding	Drug therapy described (dose)	Total costs (year of valuation)[d]	Total outcomes[d]	ICER	Authors' conclusion	QHES category[e]
Matter-Walstra et al. 2015 (Switzerland) [14]	Markov model Probabilistic (CUA) BRAF-mutated metastatic melanoma/ PUT	Swiss healthcare system, lifetime	State Secretariat for Education, Research and Innovation (SERI)	1. Trametinib + drabrafenib 2. Vemurafenib (N/A)	1. CHF311,421 2. CHF111,773 (2015)	1. 1.54 QALY 2. 1.02 QALY	CHF385,603/ QALY	A reduction in the total price of the combination therapy is required to achieve an acceptable cost-effectiveness ratio	3
Shih et al. 2015 (USA) [15]	Markov model (CUA) Probabilistic BRAF-mutated advanced melanoma[a]/ PUT	Societal, lifetime	No	1. Dabrafenib 2. Dacarbazine 3. Vemurafenib (N/A)	1. $US38,547 2. $US15,221 3. $US49,938 (2013)	1. 0.34 QALY 2. 0.18 QALY 3. 0.29 QALY	1 vs. 2: $US149,042/ QALY 1 vs. 3: Dabrafenib is dominant[b]	Compared with dacarbazine, dabrafenib was not cost effective at a WTP threshold of $US100,000/QALY. Dabrafenib is dominant vs. vemurafenib[b]	3
Bohensky et al. 2016 (Australia) [16]	Markov model Probabilistic (CEA/ CUA) BRAF-negative advanced melanoma[a]/ PUT	Australian health system, 10 years	Bristol–Myers Squibb	1. Nivolumab 2. Ipilimumab (3 mg/kg both)	1. $US178,612 2. $US138,987 (2015)	1. 3.1 LY, 2.5 QALY 2. 1.5 LY, 1.2 QALY	1 vs. 2: $US25,201/ LYG $US30,475/ QALY	Nivolimumab is costeffective vs. ipilimumab	3
Jensen et al. 2016 (USA) [17]	Decision analytical model Probabilistic (CEA) BRAF-mutated advanced melanoma[a]/ PUT	Health payer/societal, progression or dead	Novartis	1. Nivolumab + ipilimumab 2. Dabrafenib + trametinib (N/ A)	1. $US259,293 2. $US194,876 (health payer) (2015)	1 vs. 2: ORR: − 0.2% PFS: 0.7 months[c]	1 vs. 2: Cost per OR: − $US106,316 Cost per month of PFS: − $US4446	Dabrafenib + trametinib is associated with less patient time and lower costs relative to nivolumab + ipilimumab	2

Table 1 continued

First author, year (country)	Type of study, patient population	Perspective, time horizon	Funding	Drug therapy described (dose)	Total costs (year of valuation)[d]	Total outcomes[d]	ICER	Authors' conclusion	QHES category[e]
Kohn et al. 2017 (USA) [18]	Markov model (CUA) BRAF wild-type advanced melanoma	Health payer	National Cancer Institute and Burroughs Wellcome Fund	1. NIV/IPI 2. NIV + IPI/ CAR + PAC 3. PEM e2w/IPI 4. PEM e3w/IPI 5. IPI/NIVO 6. DAC/IPI/ NIVO (first/ second/third line)	1. $US172,219 2. $US206,435 3. $US164,871 4. $US127,626 5. $US152,403 6. $US146,775 (2016)	1. 0.54 QALYs 2. 0.56 QALYs 3. 0.43 QALYs 4. 0.38 QALYs 5. 0.34 QALYs 6. 0.26 QALYs	Best ICER vs .6: 4: Dominant 5: $US70.350 1: $US90.871 3: $US106,447 2: $US198,867	First-line PEM e2w/IPI or NIV/IPI are the most cost-effective, immune-based treatment strategies for metastatic melanoma	3

BSC best supportive care, *e2w/e3w* every 2 or 3 weeks, *CAN* Canadian Dollar, *CAR* carboplatin, *CEA* cost-effectiveness analysis, *CHF* Swiss francs, *CUA* cost-utility analysis, *DAC* dacarbazine, *ICER* incremental cost-effectiveness ratio, *IPI* ipilimumab, *LY* life-year, *LYG* life-year gained, *N/A* not available, *NIV* nivolumab, *NS* not statistically significant, *OR* overall response, *ORR* overall response rate, *PAC* paclitaxel, *PEM* pembrolizumab, *PT* pretreated, *PUT* previously untreated, *QALYs* quality adjusted life-years, *QHES* Quality of Health Economic Studies, *WTP* willingness-to-pay

[a] Unresectable or metastatic melanoma

[b] Dominant: lower costs, higher effectiveness vs. comparator

[c] Individual data not available

[d] Per patient

[e] The Quality Assessment of Economic Evaluation in Health Care-based quality levels are as follows: category 1 (<40 points); category 2 (40–59 points); category 3 (≥60–100 points). The higher the score, the higher the quality [8]

advanced oncology indications and use area under the survival curves (for PFS and overall survival) to calculate the proportion of patients at given timepoint in each health state. The advantage of this method is that it does not require explicit transitions between the health states because it directly models overall survival from clinical trial results [91]. However, it must be borne in mind that this type of model can suffer from inherent bias in favour of treatments that impact on disease progression [92].

The cycle lengths (from 1 week up to 1–3 months) and the model states (progression-free; progression; death) were consistent with the usual design of the economic models in oncology [58]. Almost all studies gave the result of efficiency as cost per LY gained or as cost per QALY gained, except for the study of Jensen et al. [17] that calculated the cost per overall response and the cost per month of PFS. In this respect, we believe this type of result should be accompanied by an ICER per life-year gained or per QALY gained because it allows the comparison of ICERs of different treatments.

The utilities used in the cost-utility analysis were obtained in different ways. In the studies of Barzey et al. [11], Delea et al. [13] and Bohensky et al. [16] they were obtained directly from patients with melanoma, using the EuroQol 5-dimension (EQ-5D) tool in the latter two studies. In other studies, they were obtained from previously published data, using the standard gamble method [12, 14, 15, 18].

The perspective of economic analysis must be that of the intended recipient of its results. The perspective of most of the analyses was that of the health payer (the national health system in European countries). However, in two cases, the perspective was that of society, including direct non-medical costs in one study [10] and indirect costs in another [17]. In two of the studies analysed, both from USA, it is noted that the perspective was that of society [12, 15]. However, both studies included only direct health costs.

3.3.2 Time Horizon

According to a recent systematic review, currently, 5-year survival in patients with advanced melanoma is estimated to be 41–71% in stage III and 9–28% in stage IV [93]. The time horizon used in the economic models was generally for life [11, 12, 14, 15] or until the progression of the disease or death of the patient [17]. These approaches are correct because they meet the life expectancy observed in the clinical studies and the simulation of the model ends when the entire hypothetical cohort of patients dies. In some studies, however, shorter time horizons were adopted that ranged between 1 year for evaluation of chemotherapy [10], 5 years for evaluation of the BRAF inhibitors [13] and 10 years for immunotherapy[16] (Table 1). In these cases, the horizon considered may be too short to obtain all the outcomes owing to the drugs evaluated.

3.3.3 Analytical Approach

Conducting a probabilistic analysis is very important for two reasons: (1) it allows us to calculate the ICER confidence interval; and (2) it allows us to calculate the probability of a treatment being cost effective vs. a comparison treatment [94]. However, in two of the nine economic analyses, this type of analysis was not conducted [10, 12].

3.3.4 Efficacy vs. Effectiveness

The efficacy data used in the economic models were obtained from explanatory clinical trials, not pragmatic clinical trials [95], and therefore, effectiveness data were not used.

3.3.5 Transferability Issues

Most of the studies published as articles were conducted in USA (n = 5), followed by Canada, Switzerland and Australia each with one study. In this respect, it must be stressed that the results of the economic analyses are not transferable between different countries, owing to both differences in the unit costs and in the use of the health resources inherent of different health systems.

3.4 Quality Assessment Results

Of the nine studies analysed, seven studies were classified as high quality (category 3) [11–16, 18] and the rest (two studies) as medium quality [10, 17] (category 2) (Tables 1, 2). The medium quality studies were classified as such mainly for one of the following reasons: (1) the time horizon was very short to adjust to that of the clinical trial [10]; (2) a probabilistic analysis was not performed [10]; (3) the structure of the model was not detailed sufficiently; and (4) no annual discount rates were applied [17].

4 Discussion

According to the analyses published in articles, new treatments (BRAF and MEK inhibitors and immunotherapy) have been shown to be more effective than chemotherapy in the extension of survival, but with higher acquisition costs. In this respect, it can be concluded that in most of the studies, the ICERs were above the commonly accepted thresholds (e.g. $US50,000–100,000 per QALY gained, in USA). For this reason, with the available data, it cannot be concluded that the new treatments are cost

Table 2 Quality assessment of selected pharmacoeconomics analyses using the Quality Assessment of Economic Evaluation in Health Care[a] (adapted from Abellán et al. [8])

Criteria/references	Points	Hillner 2000 [10]	Barzey 2013 [11]	Curl 2014 [12]	Delea 2015 [13]	Matter-Walstra 2015 [14]	Shih 2015 [15]	Bohensky 2016 [16]	Jensen 2016 [17]	Kohn 2017 [18]
1. Perspective	Max. 8	4	4	4	4	4	4	4	8	4
1.1a. The study was performed from the social perspective (parallel to the healthcare payer perspective) (if only social perspective: 4 points)	4/8	4	0	4	0	0	0	0	8	0
1.1b. The study was only performed from the healthcare payer perspective	4	0	4	0	4	4	4	4	0	4
2. Costs and outcomes source	Max. 8	6	6	6	6	6	6	6	4	4
2.1a. Randomized pragmatic clinical trials	4	0	0	0	0	0	0	0	0	0
2.1b. Randomized controlled clinical trials	2	2	2	2	2	2	2	2	2	2
2.1c. Observational studies	2	0	0	0	0	0	0	0	0	0
2.2a. Direct comparison of technologies	4	4	4	4	4	4	4	4	0	0
2.2b. Indirect comparison of technologies using a common comparator	2	0	0	0	0	0	0	0	2	2
3. Target population	Max. 8	4	4	4	4	4	4	4	4	0
3.1. The target population is described in detail	4	4	4	4	4	4	4	4	4	0
3.2. A subgroup analysis for the disparate characteristics of patients is performed	4	0	0	0	0	0	0	0	0	0
4. What does it compare with?	Max. 8	4	4	4	4	4	4	4	4	4
4.1a. It is compared to the dominant practice (if it exists)	4	4	4	4	4	4	4	4	4	0
4.1b. If there is no dominant practice, multiple comparisons are performed	4	0	0	0	0	0	0	0	0	4
4.2. It has been compared to the "do nothing" option or the "minimal intervention"	4	0	0	0	0	0	0	0	0	0
5. Results measurement	Max. 12	4	12	8	8	4	4	6	4	4
5.1a. A cost-effectiveness analysis has been carried out with measures of final results (e.g. LYG)	4	4	4	0	0	0	0	0	4	0
5.1b. The willingness to pay is used as a measure of results (cost-benefit analysis)	8	0	0	0	0	0	0	0	0	0
5.1c. QALYs are used as a measure of results (cost-utility analysis)	4	0	4	4	4	4	4	4	0	4
5.2. If QALYs are used, utilities were obtained using standard gamble or time trade-off methods	4	0	0	0	4	0	0	0	0	0
5.3a. If QALYs are used, utilities were obtained from preferences of general population	4	0	4	4	0	0	0	0	0	0
5.3b. If QALYs are used, utilities were obtained directly from patients	2	0	0	0	0	0	0	2	0	0

Table 2 continued

Criteria/references	Points	Hillner 2000 [10]	Barzey 2013 [11]	Curl 2014 [12]	Delea 2015 [13]	Matter-Walstra 2015 [14]	Shih 2015 [15]	Bohensky 2016 [16]	Jensen 2016 [17]	Kohn 2017 [18]
6. Costs included	Max. 8	4	8	4	8	8	8	8	8	8
6.1. All relevant costs to the study perspective are included	4	4	4	4	4	4	4	4	4	4
6.2. A detailed and precise measure of the resources consumed is shown	4	0	4	0	4	4	4	4	4	4
7. Time horizon	Max. 8	0	4	8	4	8	8	4	4	8
7.1. A sufficiently broad time horizon, equal to costs and benefits	4	0	4	4	4	4	4	4	4	4
7.2a. The study has primary data covering the entire time horizon	4	0	0	0	0	0	0	0	0	0
7.2b. If only primary data are available for the short term, a decision model is used to extrapolate the data over the long term	4	0	0	4	0	4	4	0	0	4
8. Discount rate	Max. 8	4	4	4	8	8	8	8	0	4
8.1. A discount rate of between 3% and 5% applies to costs and benefits	4	0	4	4	4	4	4	4	0	4
8.2. Results are presented for alternative discount rates	4	4	0	0	4	4	4	4	0	0
9. Uncertainty management	Max. 8	2	8	6	8	8	8	8	8	8
9.1a. A probabilistic sensitivity analysis (e.g. bootstrapping, Monte Carlo, …) is performed	4	0	4	0	4	4	4	4	4	4
9.1b. A deterministic sensitivity analysis is performed	2	2	0	2	0	0	0	0	0	2
9.2. The sensitivity analysis results are presented in detail (tables and figures)	4	0	4	4	4	4	4	4	4	4
10. Decision models used	Max. 8	0	4	4	4	4	4	4	0	4
10.1. The structural assumptions of the model are detailed (e.g. duration of a cycle in a Markov model)	4	0	4	4	4	0	0	4	0	4
10.2. The model results are validated in some way (e.g. by comparison with the other published models for the same disease and intervention)	4	0	0	0	0	4	4	0	0	0
11. Transferability of results	Max. 8	0	4	4	4	4	4	4	4	4
11.1a. The area of origin of the data coincides exactly with the application of the technology	8	0	0	0	0	0	0	0	0	0
11.1b. The scope of application of the technology does not match with the source of the data, but the results of the study have somehow adapted to the application context	4	0	0	4	4	4	4	4	4	4
11.2. The data have been obtained from multinational or multi-centre studies, among which is a centre belonging to the area of application of technology	4	0	4	0	0	0	0	0	0	0

Table 2 continued

Criteria/references	Points	Hillner 2000 [10]	Barzey 2013 [11]	Curl 2014 [12]	Delea 2015 [13]	Matter-Walstra 2015 [14]	Shih 2015 [15]	Bohensky 2016 [16]	Jensen 2016 [17]	Kohn 2017 [18]
12. Results presentation	Max. 8	8	8	8	8	8	8	8	8	8
12.1. Costs and effects are presented in an aggregated and disaggregated manner	4	4	4	4	4	4	4	4	4	4
12.2. The appropriate decision indices are calculated and presented (incremental ratios for cost-effectiveness and cost-utility analyses, benefit/cost ratios and return rates for cost-benefit analyses)	4	4	4	4	4	4	4	4	4	4
Total score sections 1–12 (maximum 100 points)		40	70	64	70	70	70	68	56	60
Quality assessment category		2	3	3	3	3	3	3	2	3

LYG life-years gained, *Max.* maximum score per section, *QALYs* quality-adjusted life-years

[a] The Quality Assessment of Economic Evaluation in Health Care-based quality levels are as follows: category 1 (<40 points); category 2 (40–59 points); category 3 (≥60–100 points). The higher the score, the higher the quality (maximum score: 100 points). The items identified with a letter (e.g. 4.1a, 4.1b, 7.2a, 7.2b) are mutually excluding

effective compared with chemotherapy. Second, the comparative analyses of the new treatments do not allow general conclusions to be made given the diversity of the designs of the models, of the assumptions made and of the health systems they apply to. Furthermore, there are no head-to-head clinical trials directly comparing the new treatments. This conclusion is equivalent to that reached by Johnston et al. [58]. Considering Johnston et al. [58] was already available, the rationale behind our systematic review was two fold. First, the Johnston et al. review included resectable and unresectable melanoma, while ours was limited to advanced melanoma, and second, our review (to be more recent) includes new studies not included in the previous review.

According to all models analysed, treatment with new drugs would generate LY gained and QALY gained compared with chemotherapy. However, virtual differences in survival and QALY obtained in models comparing new treatments among themselves are based on the differences in effectiveness observed in the meta-analysis of indirect comparisons. In this sense, a recently published Bayesian network meta-analysis [96] analysed 15 randomised clinical trials involving 6662 patients and concluded that: (1) there was no significant difference in overall survival between BRAF/MEK inhibitors and PD-1 (hazard ratio 1.02; 95% credible interval 0.72–1.45); (2) the network meta-analysis showed a significant advantage of BRAF/MEK compared with all other treatment strategies (chemotherapy, PD-1 inhibitors, cytotoxic T-lymphocyte-associated antigen 4) for PFS; (3) BRAF/MEK inhibitors were associated with higher overall response rates (odds ratio 2.00; 95% credible interval 1.64–2.45) compared with BRAF alone, with both being superior in achieving overall response rates compared with other treatments; (4) chemotherapy and PD-1 were associated with the lowest risk of serious adverse events; and (5) there was no significant difference in the risk of serious adverse events between chemotherapy and PD-1 (odds ratio 1.00; 95% credible interval 0.74–1.34) [96].

In light of these results, it would be interesting to perform a new cost-utility analysis to compare all the treatments of advanced melanoma currently available. The problems that would arise in the face of this challenge would include: (1) there is no standardised or agreed economic model on the treatment of advanced melanoma, and therefore, the results would be considered model driven and would not be universally accepted (although this is an inherent problem to the economic models, it is expected that in the future it will be possible to have consensual minimum recommendations for the realisation of economic models by indications or therapeutic groups); and (2) even with a standard model, it would be necessary to adapt it to each health system to be able to estimate the cost-effectiveness at the national level.

This systematic review has several strengths and limitations. Among the strengths would be its implementation following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [7], searching three major databases (PubMed, EMBASE, Scopus) and other databases, and the consistency with a previous review that included all previous melanoma treatment cost-effectiveness analyses [58]. Another strength is the fact that the systematic review had no date or language limitations, and therefore, a possible source of bias was avoided [97–100].

The aforementioned variability of the models is a limitation of this systematic review, which prevents the making of reliable comparisons between them and valid conclusions on the cost-effectiveness of the new treatments of advanced melanoma. Another limitation, and not less important, is that the review only included complete studies (articles) and numerous posters available in congresses were excluded. The grounds for excluding the posters of communications to congresses were the following: (1) they do not include all the relevant information of the study; (2) they often include preliminary results, not final results, of the studies; and (3) as they are incomplete publications, a reliable assessment of the quality of the studies cannot be made. For these reasons, posters of studies were excluded with the following conclusions in advanced melanoma: (1) the cost of gaining a QALY with ipilimumab vs. BSC would be £65,303 vs. BSC in the previously treated patient, in the UK [25] and €41,459 and £38,405 vs. dacarbazine in the previously treated patient in Spain [31] and Scotland [37], respectively; (2) the cost of gaining a QALY with trametinib vs. BSC would be $CAN142,177 in Canada [32]; (3) dabrafenib dominates vemurafenib in Slovenia [35]; (4) the cost per overall response rate with vemurafenib and ipilimumab as a first-line treatment in patients with BRAF mutations was €111,928 (95% confidence interval €108,403–115,969) and €447,462 (95% confidence interval €370,285–538,214), respectively, in Spain [43]; and (5) pembrolizumab would not be cost effective compared with ipilimumab in USA according to one study [46] and would be in another different model [48].

5 Conclusions

According to the systematic review of economic analyses published as articles, new treatments (BRAF and MEK inhibitors and immunotherapy) have been shown to be more effective (with more life-years and QALYs) than chemotherapy in patients with advanced melanoma, but with higher acquisition costs. As a consequence, in most of the studies, the ICERs were above the commonly accepted thresholds (e.g. $US50,000–100,000 per QALY gained, in USA). For this reason, with the available data, it cannot be concluded that the new treatments are cost effective compared with chemotherapy. Moreover, because of the variability of the available analyses comparing the new treatments, we cannot determine which of the new treatments is the most cost effective.

Data Availability Statement The datasets generated during and/or analysed in the current study are available from the corresponding author on reasonable request.

Author contributions DRR, SDDB, MP and CRT designed the study. DRR and CRT assessed inclusion and performed the article quality assessments. DRR and CRT performed the analyses. DRR and CRT wrote the first draft. All authors interpreted the data and commented on the first draft. All authors revised the first draft. All authors agreed with the final version.

Compliance with Ethical Standards

Funding No funding was received for the preparation of this study.

Conflict of interest None of the authors has expressed any conflicts of interest. DRR and CRT are employed by Health Value, Madrid, Spain. MP is employed by AstraZeneca Farmacéutica Spain, Barcelona, Spain. SDDB is employed by Astellas Pharma, SA, Madrid, Spain.

Appendix

Search Strategy

PubMed

((“secondary”[Subheading] OR “secondary”[All Fields] OR “metastatic”[All Fields]) AND (“melanoma”[MeSH Terms] OR “melanoma”[All Fields])) AND ((“cost-benefit analysis”[MeSH Terms] OR (“cost-benefit”[All Fields] AND “analysis”[All Fields]) OR “cost-benefit analysis”[All Fields] OR “cost benefit analysis”[All Fields] OR (“cost”[All Fields] AND “effectiveness”[All Fields]) OR “cost-effectiveness”[All Fields] OR “cost-effectiveness”[All Fields] OR (“cost”[All Fields] AND “utility”[All Fields]) OR “cost-utility”[All Fields] OR “cost utility”[All Fields] OR “cost-minimization”[All Fields] OR “cost minimization”[All Fields] OR “cost-minimisation”[All Fields] OR “cost minimisation”[All Fields]))

EMBASE

((cost:ti and (((((((secondary:ti or ‘metastasis’/exp/mj) or (secondary:ti or metast*:ti)) and ‘melanoma’/exp/mj) and melanoma:ti) and ‘cost benefit analysis’/exp) and cost:ti) or (((((secondary:ti or ‘metastasis’/exp/mj) or (secondary:ti or metast*:ti)) and ‘melanoma’/exp/mj) and melanoma:ti) and ‘cost benefit analysis’/exp))) or (((((secondary:ti or ‘metastasis’/exp/mj) or (secondary:ti or metast*:ti)) and ‘melanoma’/exp/mj) and melanoma:ti) and ‘cost-effectiveness analysis’/exp/mj)) or (((((secondary:ti or ‘metastasis’/exp/mj) or (secondary:ti or metast*:ti)) and ‘melanoma’/exp/mj) and melanoma:ti) and ‘cost utility analysis’/exp)

Scopus

(KEY (secondary) OR TITLE (secondary) OR KEY (metastatic) OR TITLE (metastatic)) AND (KEY

(melanoma) OR TITLE (melanoma)) AND ((KEY ("cost-benefit analysis") OR (TITLE-ABS ("cost-benefit") AND TITLE-ABS (analysis)) OR TITLE-ABS ("cost benefit analysis") OR (TITLE-ABS (cost) AND TITLE-ABS (effectiveness)) OR TITLE-ABS ("cost-effectiveness") OR TITLE-ABS ("cost-effectiveness") OR (TITLE-ABS (cost) AND TITLE-ABS (utility)) OR TITLEABS ("cost-utility") OR TITLE-ABS ("cost utility") OR TITLE-ABS ("cost minimization") OR TITLE-ABS ("cost minimization") OR TITLE-ABS ("cost minimisation") OR TITLE-ABS ("cost minimisation")))

References

1. Guía de prevención y tratamiento del melanoma. Valencia: Generalitat Valenciana; 2006.
2. Dummer R, Hauschild A, Lindenblatt N, et al. ESMO Guidelines Committee. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl. 5):v126–32.
3. Surveillance Research Program. Cancer Statistics Branch, Surveillance, Epidemiology and End Results (SEER) Program. Washington, DC: National Cancer Institute; 2005.
4. Korn EL, Liu PY, Lee SJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol. 2008;26:527–34.
5. Camacho LH. CTLA-4 blockade with ipilimumab: biology, safety, efficacy, and future considerations. Cancer Med. 2015;4:661–72.
6. Vallejo-Torres J, Morris S, Kinge J, et al. Measuring current and future cost of skin cancer in England. J Public Health (Bangkok). 2014;36:140–8.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–9.
8. Abellán Perpiñán JM, Sánchez Martínez FI, Martínez Pérez JE. Quality assessment of economic evaluations in health care: a checklist and user guide (Spanish). Rev Esp Salud Pública. 2009;83:71–84.
9. van der Schans S, Goossens LM, Boland MR, et al. Systematic review and quality appraisal of cost-effectiveness analyses of pharmacologic maintenance treatment for chronic obstructive pulmonary disease: methodological considerations and recommendations. Pharmacoeconomics. 2017;35(1):43–63.
10. Hillner BE, Agarwala S, Middleton MR. Post hoc economic analysis of temozolomide versus dacarbazine in the treatment of advanced metastatic melanoma. J Clin Oncol. 2000;18:1474–80.
11. Barzey V, Atkins MB, Garrison LP, et al. Ipilimumab in 2nd line treatment of patients with advanced melanoma: a cost-effectiveness analysis. J Med Econ. 2013;16:202–12.
12. Curl P, Vujic I, van't Veer LJ, et al. Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma. PLoS One. 2014;9:e107255.
13. Delea TE, Amdahl J, Wang A, et al. Cost effectiveness of dabrafenib as a first-line treatment in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma in Canada. Pharmacoeconomics. 2015;33:367–80.
14. Matter-Walstra K, Braun R, Kolb C, et al. A cost-effectiveness analysis of trametinib plus dabrafenib as first-line therapy for metastatic BRAF V600-mutated melanoma in the Swiss setting. Br J Dermatol. 2015;173:1462–70.
15. Shih V, Ten Ham RM, Bui CT, et al. Targeted therapies compared to dacarbazine for treatment of BRAF(V600E) metastatic melanoma: a cost-effectiveness analysis. J Skin Cancer. 2015;2015:505302.
16. Bohensky MS, Pasupathi K, Gorelik A, et al. A cost-effectiveness analysis of nivolumab compared with ipilimumab for the treatment of BRAF wild-type advanced melanoma in Australia. Value Health. 2016;19(8):1009–1015. doi:10.1016/j.jval.2016.05.013.
17. Jensen IS, Zacherle E, Blanchette CM, et al. Evaluating cost benefits of combination therapies for advanced melanoma. Drugs Context. 2016;5:212297. doi:10.7573/dic.212297.
18. Kohn CG, Zeichner SB, Chen Q, et al. Cost-effectiveness of immune checkpoint inhibition in BRAF wild-type advanced melanoma. J Clin Oncol. 2017;35(11):1194–202. doi:10.1200/JCO.2016.69.6336.
19. Ding M, Xing Y, Shih T, et al. Cost-effectiveness (CE) analysis of interferon-alpha in high-risk melanoma patients. Value Health. 2004;7:221.
20. Machado M, Cashin R, Lui P, et al. Advanced cutaneous malignant melanoma systematic review of pharmacoeconomic and quality of life studies. Value Health. 2006;9:A295.
21. Kasteng F, Stadler R, Wagenius G, Lundkvist J. Cost-effectiveness of human interferon-alpha as adjuvant treatment for patients with resected cutaneous malignant melanoma in stage IIB & III. Value Health. 2007;10:A330.
22. Oster G, Taneja C, Penrod JR, et al. Economic burden of advanced melanoma: findings from a large US health insurance database. Value Health. 2011;A507.
23. Alva M, Gay J, Sanchez Kobashi R. Cost effectiveness evaluation of vemurafenib, an orphan drug for BRAF mutant metastatic melanoma. Value Health. 2012;15:A423.
24. Ignateva V, Derkach EV, Omelyanovsky V, Avxentyera M. Economic burden of melanoma in Russia. Value Health. 2012;15:A417.
25. Lee D, Winn B, Lebmeier M, Batty A. Modelling the cost-effectiveness of ipilimumab for previously treated, metastatic melanoma. Value Health. 2012;15:A423.
26. Peniche-Otero G, Herrera-Rojas J, Ramírez-Ramírez MA, et al. Budget impact analysis of melanoma treatment in Mexico. Value Health. 2012;15:A212.
27. Teimouri F, Nikfar S, Abdollahi M. Evaluation of the efficacy and side effects of dacarbazine in comparison to temozolomide therapies in treatment of malignant melanoma: a meta-analysis. Value Health. 2012;5:A411.
28. Teimouri F, Nikfar S, Abdollahi M. Comparative efficacy and economic evaluation of dacarbazine and temozolomide in treatment of malignant melanoma in Iran. Value Health. 2012;15:A656.
29. Adami S, Aiello A, Palozzo AC, et al. Budget impact analysis of ipilimumab for the treatment of advanced melanoma in the Veneto region, Italy. Value Health. 2013;16:A399.
30. Radford M, Cortes P, Carrasco J. Cost-effectiveness of ipilimumab in previously treated patients for advanced melanoma in Portugal. Value Health. 2013;16:A139.
31. Aceituno S, Canal C, Paz S, et al. Cost-effectiveness of ipilimumab for previously untreated patients with advanced metastatic melanoma in Spain. Value Health. 2014;17:A631.
32. Amdahl J, Wang A, Thabane M, et al. Cost effectiveness of trametinib as first-line (1L) treatment for BRAF V600 positive advanced or metastatic melanoma: a Canadian societal perspective. Value Health. 2014;17:A83.
33. Barzey V, Asukai Y, Gueron B, et al. Cost-effectiveness of ipilimumab in previously untreated patients for advanced melanoma in Sweden. Health Value. 2014;17:A642.

34. Delea TE, Amdahl J, Wang A, et al. Cost-utility analysis of dabafenib/trametinib combination (D + T) for BRAFV600 mutation-positive metastatic melanoma (MM) from the United Kingdom (UK) National Health Service (NHS) perspective. Value Health. 2014;17:A88.
35. Hren H. Cost-effectiveness and budget impact analysis of BRAF inhibitors in patients with metastatic malignant melanoma (MMM) in Slovenia. Value Health. 2014;17:A623.
36. Kontoudis I, Harries M, Mohr P, et al. Economic burden of melanoma in three European countries: a retrospective observational study. Value Health. 2014;17:A626.
37. Lee D, Porter J, Hastwell AJ, et al. Cost-effectiveness analysis of ipilimumab in previously untreated patients with unresectable malignant melanoma in Scotland. Value Health. 2014;17:A549.
38. Marriot ER, Praet C, Aguilar-Ibañez R, et al. Cost effectiveness of pembrolizumab for unresectable metastatic melanoma after progression with ipilimumab in England. http://www.ispor.org/research_pdfs/51/pdffiles/PCN134.pdf. Accessed 9 Nov 2016.
39. Ohna A, Ullenhag GJ, Linder CM, Delea TE. Cost-effectiveness of dabrafenib versus dacarbazine (DTIC) in patients with BRAF V600 mutation-positive advanced or metastatic melanoma (BRAF+MM) in Sweden. Pigment Cell Melanoma Res. 2014;27:1216.
40. Rétel VP, Steuten LMG, Mewes JC, van Harten WH. Early cost-effectiveness modelling for tumor infiltrating lymphocytes (TIL): treatment versus ipilimumab in metastatic melanoma patients. Value Health. 2014;17:A640.
41. Tarhini A, Rao AS, Corman S, et al. Health care costs in patients treated with ipilimumab for advanced melanoma results of a retrospective chart review. Value Health. 2014;17:A615.
42. Roselli D, Castañeda-Cardona C, Bayona JG, et al. Cost-effectiveness of vemurafenib vs ipilimumab plus dacarbacine in the treatment of non-resectable metastatic melanoma with BRAF600E mutation in Colombia. http://www.ispor.org/RESEARCH_STUDY_DIGEST/details.asp. Accessed 9 Nov 2016.
43. Rubio-Terrés C, Orofino J, Armas J, Parra J, et al. Cost-effectiveness of vemurafenib as a first-line treatment in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma in Spain. Value Health. 2015;18:A453.
44. Jansen JP, Stevinson K, Wang J. Indirect comparison of pembrolizumab to vemurafenib and dabrafenib monotherapy for first-line treatment of advanced melanoma in BRAF mutation positive ipilimumab naïve patients. Value Health. 2016;19:A138.
45. Li Z, Whisman T, Tang J, et al. Evaluating expected medication costs and budget impact of systemic therapies for unresectable/metastatic melanoma. Value Health. 2016;19:A143.
46. Lu T, Hay JW. Cost effectiveness of pembrolizumab and ipilimumab in advanced melanoma. Value Health. 2016;19:A149.
47. Tran DM, McDowell LC, Oh A, et al. Cost effectiveness of nivolumab–ipilimumab combination therapy compared to monotherapy for metastatic melanoma from a US societal perspective. http://www.ispor.org/RESEARCH_STUDY_DIGEST/details.asp. Accessed 9 Nov 2016.
48. Wang J, Pellissier J, Xu R, et al. Cost effectiveness of pembrolizumab (Keytruda) versus ipilimumab in patients with advanced melanoma in the United States. Value Health. 2016;19:A154.
49. Cashin RP, Lui P, Machado M, et al. Advanced cutaneous malignant melanoma: a systematic review of economic and quality-of-life studies. Value Health. 2008;11:259–71.
50. NICE. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma: technology appraisal guidance. London: National Institute for Health and Care Excellence; 12 Dec 2012. https://www.nice.org.uk/guidance/ta268. Accessed 9 Nov 2016.
51. NICE. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma: technology appraisal guidance. London: National Institute for Health and Care Excellence, 12 Dec 2012. https://www.nice.org.uk/guidance/ta269. Accessed 9 Nov 2016.
52. Beale S, Dickson R, Bagust A, et al. Vemurafenib for the treatment of locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma: a NICE single technology appraisal. Pharmacoeconomics. 2013;31:1121–9.
53. NICE. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma. Technology appraisal guidance. London: National Institute for Health and Care Excellence; 22 Oct 2014. https://www.nice.org.uk/guidance/ta321. Accessed 9 Nov 2016.
54. NICE. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma: technology appraisal guidance. London: National Institute for Health and Care Excellence; 23 Jul 2014. https://www.nice.org.uk/guidance/ta319. Accessed 9 Nov 2016.
55. Curl PK. Navigating uncertainty: a valuable cost-effectiveness analysis in the rapidly changing field of metastatic melanoma treatment. Br J Dermatol. 2015;173:1365–6.
56. Fleeman N, Bagust A, Beale S, et al. Dabrafenib for treating unresectable, advanced or metastatic BRAF V600 mutation-positive melanoma: an evidence review group perspective. Pharmacoeconomics. 2015;33:893–904.
57. Giannopoulou C, Sideris E, Wade R, et al. Ipilimumab for previously untreated unresectable malignant melanoma: a critique of the evidence. Pharmacoeconomics. 2015;33:1269–79.
58. Johnston KM, McPherson E, Osenenko K, et al. Cost-effectiveness of therapies for melanoma. Expert Rev Pharmacoecon Outcomes Res. 2015;15:229–42.
59. NICE. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab: technology appraisal guidance. London: National Institute for Health and Care Excellence; 7 Oct 2015. https://www.nice.org.uk/guidance/ta357. Accessed 9 Nov 2016.
60. NICE. Pembrolizumab for advanced melanoma not previously treated with ipilimumab: technology appraisal guidance. London: National Institute for Health and Care Excellence; 25 Nov 2015. https://www.nice.org.uk/guidance/ta366. Accessed 9 Nov 2016.
61. NICE. Nivolumab in combination with ipilimumab for treating advanced melanoma: technology appraisal guidance. London: National Institute for Health and Care Excellence; 27 Jul 2016. https://www.nice.org.uk/guidance/ta400. Accessed 9 Nov 2016.
62. NICE. Nivolumab for treating advanced (unresectable or metastatic) melanoma: technology appraisal guidance. London: National Institute for Health and Care Excellence; 18 Feb 2016. https://www.nice.org.uk/guidance/ta384. Accessed 9 Nov 2016.
63. NICE. Talimogene laherparepvec for treating unresectable metastatic melanoma: technology appraisal guidance. London: National Institute for Health and Care Excellence; 28 Sep 2016. https://www.nice.org.uk/guidance/ta410. Accessed 9 Nov 2016.
64. NICE. Trametinib in combination with dabrafenib for treating unresectable or metastatic melanoma: technology appraisal guidance. London: National Institute for Health and Care Excellence; 22 Jun 2016. https://www.nice.org.uk/guidance/ta396. Accessed 9 Nov 2016.
65. Matter-Walstra K, Braun R, Kolb C, et al. Treatment specific utility-weightings are needed for cost-utility analysis in metastatic melanoma: reply from the authors. Br J Dermatol. 2016;174:463.

66. Sebaratnam DF, Anforth R, Fernández-Peñas P. Treatment-specific utility weightings are needed for cost-utility analysis in metastatic melanoma. Br J Dermatol. 2016;174:462–3.
67. Kirkwood JM, Tarhini AA, Moschos SJ, Panelli MC. Adjuvant therapy with high-dose interferon α2b in patients with high-risk stage IIB/III melanoma. Nat Clin Pract Oncol. 2008;5:2–3.
68. Quaglino P, Mortera C, Osella-Abate S, et al. Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases. Ann Surg Oncol. 2008;15:2215–22.
69. Alexandrescu DT. Melanoma costs: a dynamic model comparing estimated overall costs of various clinical stages. Dermatol Online J. 2009;15:1.
70. Livingstone E, Krajewski C, Eigentler TK, et al. Prospective evaluation of follow-up in melanoma patients in Germany: results of a multicentre and longitudinal study. Eur J Cancer. 2015;51:653–67.
71. McCarron CE, Ernst S, Cao JQ, Zaric GS. Population-based estimates of survival and cost for metastatic melanoma. Curr Oncol. 2015;22:326–32.
72. Tarhini A, Corman SL, Rao S, et al. Healthcare resource utilization and associated costs in patients with advanced melanoma receiving first-line ipilimumab. J Cancer Therapy. 2015;6:833–40.
73. Guglieri-López B, Pérez-Pitarch A, Porta Oltra B, et al. Effectiveness, toxicity, and economic evaluation of ipilimumab for the treatment of patients with metastatic melanoma in the Spanish outpatient setting. Anticancer Drugs. 2016;27:679–84.
74. Potluri R, Okoro T, BhandarL H, et al. Healthcare cost comparison analysis of nivolumab plus ipilimumab regimen (NIVO + IPI) and nivolumab (NIVO) monotherapy versus established advanced melanoma therapies utilizing clinical trial and real world data. http://www.ispor.org/research_pdfs/52/pdffiles/PCN58.pdf. Accessed 9 Nov 2016.
75. van der Meijde E, van den Eertwegh AJ, Linn SC, et al. The melanoma MAICare framework: a microsimulation model for the assessment of individualized cancer care. Cancer Inform. 2016;15:115–27.
76. Hofmann U, Szedlak M, Rittgen W, et al. Primary staging and follow-up in melanoma patients: monocenter evaluation of methods, costs and patient survival. Br J Cancer. 2002;87:151–7.
77. Bastiaannet E, Uyl-de Groot CA, Brouwers AH, et al. Cost-effectiveness of adding FDG-PET or CT to the diagnostic work-up of patients with stage III melanoma. Ann Surg. 2012;255:771–6.
78. Stoffels I, Müller M, Geisel MH, et al. Cost-effectiveness of preoperative SPECT/CT combined with lymphoscintigraphy vs. lymphoscintigraphy for sentinel lymph node excision in patients with cutaneous malignant melanoma. Eur J Nucl Med Mol Imaging. 2014;41:1723–31.
79. Look Hong NJ, Petrella T, Chan K. Cost-effectiveness analysis of staging strategies in patients with regionally metastatic melanoma. J Surg Oncol. 2015;111:423–30.
80. Messori A, Becagli P, Trippoli S, Tendi E. A retrospective cost-effectiveness analysis of interferon as adjuvant therapy in high-risk resected cutaneous melanoma. Eur J Cancer. 1997;33:1373–9.
81. Hillner BE. Cost-effectiveness assessment of interferon alfa-2b as adjuvant therapy of high-risk resected cutaneous melanoma. Eur J Cancer. 1998;34(Suppl. 3):S18–21.
82. Crott R. Cost effectiveness and cost utility of adjuvant interferon alpha in cutaneous melanoma: a review. Pharmacoeconomics. 2004;22:569–80.
83. Cormier JN, Xing Y, Ding M, et al. Cost effectiveness of adjuvant interferon in node-positive melanoma. J Clin Oncol. 2007;25:2442–8.
84. González-Larriba JL, Serrano S, Alvarez-Mon M, et al. Cost-effectiveness analysis of interferon as adjuvant therapy in high-risk melanoma patients in Spain. Eur J Cancer. 2000;36:2344–52.
85. Wilson LS, Reyes CM, Lu C, et al. Modelling the cost-effectiveness of sentinel lymph node mapping and adjuvant interferon treatment for stage II melanoma. Melanoma Res. 2002;12:607–17.
86. Dixon S, Walters SJ, Turner L, Hancock BW. Quality of life and cost-effectiveness of interferon-alpha in malignant melanoma: results from randomised trial. Br J Cancer. 2006;94:492–8.
87. Atkinson V. Medical management of malignant melanoma. Aust Prescr. 2015;38:74–8.
88. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010;363:809–19.
89. Kaplan RM. The minimally clinically important difference in generic utility-based measures. COPD. 2005;2:91–7.
90. Wee HL, Machin D, Loke WC, et al. Assessing differences in utility scores: a comparison of four widely used preference-based instruments. Value Health. 2007;10:256–65.
91. Minacori R, Bonastre J, Lueza B, et al. How to model survival in cost-effectiveness analysis? Differences between Markov and partitioned survival analysis models. In: ISPOR 18th Annual European Congress; 11 Nov 2015; Milan (PRM 123). http://www.ispor.org/research_pdfs/51/pdffiles/PRM123.pdf. Accessed 10 Nov 2016.
92. Coyle D, Coyle K. The inherent bias from using partitioned survival models in economic evaluation. Value Health. 2014;17:A194.
93. Svedman FC, Pillas D, Taylor A, et al. Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe: a systematic review of the literature. Clin Epidemiol. 2016;8:109–22.
94. Rubio-Terrés C, Rubio-Rodríguez D. Probabilistic analysis: sensitivity analysis or main result? Pharmacoeconomics. 2016;1:2.
95. Schwartz D, Flamant R, Lellouch J. Clinical trials. London: Academic Press; 1980.
96. Devji T, Levine O, Neupane B, et al. Systemic therapy for previously untreated advanced BRAF-mutated melanoma: a systematic review and network meta-analysis of randomized clinical trials. JAMA Oncol. 2017;3(3):366–73.
97. Gregoire G, Derderian F, Le Lorier J. Selecting the language of the publications included in a meta-analysis: is there a Tower of Babel bias? J Clin Epidemiol. 1995;48:159–63.
98. Egger M, Zellweger-Zahner T, Schneider M, et al. Language bias in randomised controlled trials published in English and German. Lancet. 1997;350:326–9.
99. Jüni P, Holenstein F, Sterne J, et al. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol. 2002;31:115–23.
100. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28:138–44.