PharmacoEconomics
DOI 10.1007/s40273-017-0517-1
The final publication is available at link.springer.com

The 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]

[1]Health Value, Madrid, Spain. [2]Market Access Department, Astellas Pharma, SA, Madrid, Spain. [3]Medical Department. AstraZeneca Farmacéutica Spain. Barcelona. Spain.

Correspondence: Carlos Rubio-Terrés, Health Value, C/Virgen de Aránzazu, 21. 5º B, 28034 Madrid, Spain. Email: drubiorodriguez@healthvalue.org; Phone: +34 917293503; Fax: +34 917293503.

Running title: Cost-effectiveness of Drug Treatments for Advanced Melanoma.

Word count: 7,449 (Word count up to 10,000)

Abstract

Background:

Until recently, advanced melanoma (unresectable and metastatic) has had 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:

Review the published evidence in relation to the cost-effectiveness of pharmacological treatments of 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 (NICE) databases and the Health Technology Assessment journal. Internet searches were also made in order to identify possible grey literature. Main study characteristics, methods and outcomes were extracted and critically assessed. The quality of health economic studies was assessed through the Quality Assessment of Economic Evaluation in Health Care (QAEEHC) checklist.

Results:

The search identified 9 full-text pharmacoeconomic analyses of advanced melanoma treatments. According to the economic analyses published in articles, the new treatments have been shown to be more effective (with more life-years and QALY) than

chemotherapy, although generally the cost per QALY gained is above the commonly accepted thresholds. The variability of the available analyzes that compare the new treatments with each other does not allow to conclude which of the new treatments is the most cost-effective.

Conclusions:

The available data do not allow to state that the new drugs (BRAF and MEK inhibitors and immunotherapy) are cost-effective compared to chemotherapy nor conclude which is the most cost-effective new treatment.

Number of words: 245 (Word count up to 250)

Key points for decision makers

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

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

- Moreover, the variability of the available analyzes that compare the new treatments with each other does not allow to conclude which of the new treatments is the most cost-effective.

1. Introduction

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

Incidence in Europe of malignant cutaneous melanoma varies from 3 to 5 per 100000 patients per year in Southern European countries to 12-25 per 100000 patients per year in Northern European countries[2]. In the 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% 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 metastatic melanoma not operable 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 in comparison 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 increase substantially in coming years [6].

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

2. Methods

2.1. Search Strategy

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

The search strategy used to review the literature concerning the cost-effectiveness analyses of the treatments of advanced melanoma used the following keywords: "melanoma", "metastatic", "cost effectiveness", "cost utility", "cost benefit", "cost minimization", "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 were 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 or in the other sources were reviewed by DRR and CRT, evaluating if the studies met the following inclusion criteria: (i) Full text available (article); (ii) Referred to patients with advanced melanoma (in inoperable stage III or in stage IV); (iii) Only original investigation, not review articles; (iv) Cost-effectiveness analysis; and (v) 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 was made following 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: (i) First author, year of publication, country; (ii) Type of study (model, alongside randomised clinical trial [RCT]) and patient population characteristics (advanced melanoma, previously treated or untreated); (iii) Study perspective ("healthcare payer" including only healthcare or “societal” costs including all relevant costs inside and outside the healthcare sector), time horizon; (iv) Funding; (v) Drug therapy described; (vi) Difference in total costs; (vii) Difference in outcomes (life-years [LYs] gained, quality-adjusted life years [QALYs] gained, progression free survival [PFS], overall response rate [ORR]); (viii) Incremental cost-effectiveness ratio (ICER); and (ix) 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 (QAEEHC) 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 QAEEHC-based quality levels have been established: category 1 (<40 points); category 2 (40-59 points); 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 way to as was done in 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, 9 papers met the inclusion criteria[10-18]. Of the 68 articles excluded, 30 were due to not having full-text[19-48], 18 because they were not original but rather review articles[49-66], 9 because they were not cost-

effectiveness or cost-utility analyses[67-75], 4 because they did not assess pharmacological interventions[76-79] and, finally, 7 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 9 studies included in the review[10-18]. The publication date ranges from 2000 to 2017. The drugs included in the 9 articles analyzed 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, 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 the 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 incremental cost-effectiveness ratio range from -$US 65,180 (dacarbazine is more effective) to $US 18,670 per year of life gained. Chemotherapy with temozolomide, dacarbazine or paclitaxel + carboplatin (which today are no longer treatments of choice) was considered the best supportive care (BSC) in some economic models made in the period 2013 to 2015[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]. 40% to 60% of patients with metastatic melanoma have a mutation in the BRAF gene[88] which gives rise to uncontrolled cell growth[87]. People who suffer from 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 slow 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 the 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 the USA for a willingness to pay of $US 100,000/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 (like 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].

Four articles have been published that analyse 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 $US 146,000 (it should be noted that the usual WTP threshold in the 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 + trametinib is associated with less patient time and lower costs relative to nivolumab + 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 incremental cost-effectiveness ratio of $US90,871 per QALY gained, and first-line nivolumab + ipilimumab followed by carboplatin + paclitaxel chemotherapy produced an incremental cost-effectiveness ratio of $US198,867 per QALY gained (Table 1).

3.2.4. Life-years gained and QALY gained

In comparison with the BSC, 1.88 life-years and between 0.15 and 1.14 QALY 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 advanced oncology indications and use area under the survival curves (for progression-free survival [PFS] and overall survival [OS]) to calculate the proportion of patients at given time point in each health state. The advantage of this method is that it does not require explicit transitions between the health states, since it directly models OS from clinical trial results[91]. However, it must be borne in mind that this type of models can suffer from inherent bias in favour of treatments which 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 LYG or as cost per QALY gained, except for the study of Jensen et al.[17] that calculated the cost per overall response (OR) and the cost per month of PFS. In this respect, we think that this type of result should be accompanied by an incremental cost-effectiveness ratio (ICER) per LYG or per QALY gained, because it allows comparing the ICER 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 last 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 analyzed, both from USA, it is said 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 from 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 due to the drugs evaluated.

3.3.3 Analytical Approach

Conducting probabilistic analysis is very important for two reasons: (i) allows us to calculate the ICER confidence interval; and (ii) allows us to calculate the probability of a treatment being cost-effective versus a comparison treatment[94]. However, in 2 of the 9 economic analyses, this kind of analysis was not conducted[10,12].

3.3.4 Efficacy vs. Effectiveness

As usually happens, 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 the United States of America (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, due 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 9 studies analysed, 7 studies were classified as high quality (category 3)[11-16,18] and the rest (2 studies) as medium quality[10,17] (category 2) (Tables 1 and 2). The medium quality studies were classified like that, mainly for one of the following reasons: (i) The time horizon was very short to adjust to that of the clinical trial[10]; (ii) A probabilistic analysis was not performed[10]; and (iii) The structure of the model was not detailed sufficiently and (iv) 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 extension of survival, but with a higher acquisition cost. In this respect, it can be concluded that: (i) In most of studies the ICERs were above the

commonly accepted thresholds (eg. 50,000 to 100,000 $US per QALY gained, in the USA); for this reason, with the available data, it cannot be concluded that the new treatments are cost-effective compared to chemotherapy; and (ii) The comparative analyses of the new treatments do not allow reaching general conclusions given the diversity of the designs of the models, of the assumptions made, of the health systems they apply to and, above all, as 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] is already available, the rationale behind our systematic review is twofold. First, the Johnston et al. review included resectable and unresectable melanoma, while ours was limited to advanced melanoma; 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 LYG and gain of QALY compared with chemotherapy. However, virtual differences in survival and QALY obtained in models that compare new treatments among themselves are based on the differences in effectiveness observed in meta-analysis of indirect comparisons. In this sense, a recently published Bayesian network meta-analysis[96] that analysed 15 randomised clinical trials involving 6,662 patients, concludes that: (i) There was no significant difference in OS between BRAF/MEK inhibitors and PD-1 (HR, 1.02; 95% credible interval [CrI], 0.72-1.45); (ii) The network meta-analysis showed a significant advantage of BRAF/MEK compared with all other treatment strategies (chemotherapy, programmed death receptor [PD-1] inhibitors, cytotoxic T-lymphocyte–associated antigen 4 [CTLA-4]) for PFS; (iii) BRAF/MEK inhibitors was associated with higher ORR (OR, 2.00; 95% CrI, 1.64-2.45) compared with BRAF alone, with both being superior in achieving ORR compared with other treatments; (iv)

Chemotherapy and PD-1 were associated with lowest risk of serious adverse events; and (v) There was no significant difference in the risk of serious adverse events between chemotherapy and PD-1 (OR, 1.00; 95% CrI, 0.74-1.34)[96]. In the 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 be, among others, the following: (i) 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, which is currently insoluble, it is expected that in the future it will be possible to have consensual minimum recommendations for the realization of economic models by indications or therapeutic groups); and (ii) 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 PRISMA guidelines[7], searching 3 major databases (PubMed, Embase, Scopus), 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 that possible source of bias was avoided[97-100]. The aforementioned variability of the models is a limitation of this systematic review, which prevents making a reliable comparison between them and reaching valid conclusions on the cost-effectiveness of the new treatments of advanced melanoma. Another limitation, and not less important, is because the review only included complete studies (articles) and numerous posters available in congresses were excluded. The grounds for excluding

353 the posters of communications to congresses were the following: (i) They do not include
354 all the relevant information of the study; (ii) They often include preliminary results, not
355 final results, of the studies; and (iii) As they are incomplete publications, a reliable
356 assessment of the quality of the studies cannot be made. For these reasons, posters of
357 studies were excluded with the following conclusions in advanced melanoma: (i) The
358 cost of gaining a QALY with ipilimumab vs. BSC would be £65,303 vs. BSC in the
359 previously-treated patient, in the United Kingdom[25] and €41,459 and £38,405 vs.
360 dacarbazine in the previously-treated patient in Spain[31] and Scotland[37], respectively; (ii)
361 The cost of gaining a QALY with trametinib vs. BSC would be $CAN 142,177 in
362 Canada[32]; (iii) dabrafenib dominates vemurafenib in Slovenia[35]; (iv) The cost per ORR
363 with vemurafenib and ipilimumab as a first-line treatment in patients with BRAF-
364 mutation was €111,928 (95% CI €108,403; €115,969) and €447,462 (95% CI €370,285;
365 €538,214) respectively, in Spain[43]; (v) Pembrolizumab would not be cost-effective
366 compared to ipilimumab in the USA according to one study[46] and would be in another
367 different model[48].

368 ## 5. Conclusions

369 According to the systematic review of economic analyses published as articles, new
370 treatments (BRAF and MEK inhibitors and immunotherapy) have been shown to be
371 more effective (with more life-years and QALY) than chemotherapy in patients with
372 advanced melanoma, but with higher acquisition cost. As a consequence, in most of
373 studies the ICERs were above the commonly accepted thresholds (eg. 50,000 to 100,000
374 $US per QALY gained, in the USA). For this reason, with the available data, it cannot
375 be concluded that the new treatments are cost-effective compared to chemotherapy.
376 Moreover, the variability of the available analyzes that compare the new treatments with

each other does not allow to conclude which of the new treatments is the most cost-effective.

Data Availability Statement

The datasets generated during and/or analysed during 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:

Competing interests: None of the authors have expressed any conflict of interest. DRR and CRT are employed of Health Value, Madrid, Spain. MP is employed by AstraZeneca Farmacéutica Spain. Barcelona. Spain. SDDB is employed by Astellas Pharma, SA, Madrid, Spain.

Funding: No funding was received for this study.

References

1. Guía de prevención y tratamiento del melanoma. Valencia: Generalitat Valenciana, 2006.
2. Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U; 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, Chapman JA, Niedzwiecki D, Suman VJ, 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, Kocks JW, Postma MJ, van Boven JF, 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. 2016 Sep 3. [Epub ahead of print].
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, Asukai Y, Kotapati S, Penrod JR. 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, Ortiz-Urda S, Kahn JG. Cost-effectiveness of treatment strategies for BRAF-mutated metastatic melanoma. PLoS One. 2014; 9: e107255.
13. Delea TE, Amdahl J, Wang A, Amonkar MM, Thabane M. 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, Ademi Z, Dummer R, Pestalozzi BC, Schwenkglenks M. 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, Tran DN, Ting J, Wilson L. 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, Hons B, Gorelik A, Kim H, Harrison JP, 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; In Press.
17. Jensen IS, Zacherle E, Blanchette CM, Zhang J, Yin W. Evaluating cost benefits of combination therapies for advanced melanoma. Drugs Context. 2016; 5: 212297.
18. Kohn CG, Zeichner SB, Chen Q, Montero AJ, Goldstein DA, Flowers CR. Cost-Effectiveness of Immune Checkpoint Inhibition in BRAF Wild-Type Advanced Melanoma. J Clin Oncol. 2017; 35: 1194-1202.
19. Ding M, Xing Y, Shih T, Cox D, Cantor S, Cormier J. Cost-effectiveness (CE) analysis of interferon-alpha in high-risk melanoma patients. Value Health. 2004; 7: 221.
20. Machado M, Cashin R, Lui P, Hemels M, Corey-Lisle P, Einarson TR. 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, Yang AS, Edelsberg J. 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.

473 24. Ignateva V, Derkach EV, Omelyanovsky V, Avxentyera M. Economic burden of
474 melanoma in Russia. Value Health. 2012; 15: A417.
475 25. Lee D, Winn B, Lebmeier M, Batty A. Modelling the cost-effectiveness of
476 Ipilimumab for previously treated, metastatic melanoma. Value Health. 2012; 15:
477 A423.
478 26. Peniche-Otero G, Herrera-Rojas J, Ramírez-Ramírez MA, Nuño-Langre C, Baeza-
479 Cruz G, Bolaños-Cornejo D. Budget impact analysis of melanoma treatment in
480 Mexico. Value Health. 2012; 15: A212.
481 27. Teimouri F, Nikfar S, Abdollahi M. Evaluation of the efficacy and side effects of
482 Dacarbazine in comparison to Temozolomide therapies in treatment of malignant
483 melanoma. A meta-analysis. Value Health. 2012; 15: A411.
484 28. Teimouri F, Nikfar S, Abdollahi M. Comparative efficacy and economic evaluation
485 of Dacarbazine and Temozolomide in treatment of malignant melanoma in Iran.
486 Value Health. 2012; 15: A656.
487 29. Adami S, Aiello A, Palozzo AC, Magrí MR, Visentin E, Chiarion V, et al. Budget
488 impact analysis of Ipilimumab for the treatment of advanced melanoma in the
489 Veneto region, Italy. Value Health. 2013; 16: A399.
490 30. Radford M, Cortes P, Carrasco J. Cost-effectiveness of ipilimumab in previously
491 treated patients for advanced melanoma in Portugal. Value Health. 2013; 16: A139.
492 31. Aceituno S, Canal C, Paz S, González P, Marquez-Rodas I. Cost-effectiveness of
493 Ipilimumab for previously untreated patients with advanced metastatic melanoma in
494 Spain. Value Health. 2014; 17: A631.
495 32. Amdahl J, Wang A, Thabane M, Amonkar M, Delea TE. Cost effectiveness of
496 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, Holmberg C, Kotapati S. 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, Amonkar M, Smith HW, Balaratnam S, 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, Grange F, Ehness R, Benjamin L, 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, Hertel N, Walker A. 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, Pellissier J, Xu R, Wang J. Cost effectiveness of pembrolizumab for unresectable metastatic melanoma after progression with ipilimumab in England. Available from: http://www.ispor.org/research_pdfs/51/pdffiles/PCN134.pdf. Accessed on 09/11/2016.
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, Botteman M, Ji X, Mehta 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, Díaz YR, Saenz SA. Cost-effectiveness of Vemurafenib vs Ipilimumab plus Dacarbacine in the treatment of non-resectable metastatic melanoma with BRAF600E mutation in Colombia. Available from: http://www.ispor.org/RESEARCH_STUDY_DIGEST/details.asp. Accessed on 09/11/2016.
43. Rubio-Terrés C, Orofino J, Armas J, Parra J, Rubio-Rodríguez D, Grau S. 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, Grzegorzewski K, Quadri S, Mahmood S, et al. Evaluating expected medication costs and budget impact of systemic therapies for unresectable/metastatic melanoma. Value Health. 2016; 19: A143.

546 46. Lu T, Hay JW. Cost effectiveness of Pembrolizumab and Ipilimumab in advanced
547 melanoma. Value Health. 2016; 19: A149.
548 47. Tran DM, McDowell LC, Oh A, Barcelon JA, Keyvani D, Merino O, et al. Cost
549 effectiveness of Nivolumab-Ipilimumab combination therapy compared to
550 monotherapy for metastatic melanoma from a US societal perspective. Available
551 from: http://www.ispor.org/RESEARCH_STUDY_DIGEST/details.asp. Accessed
552 on 09/11/2016.
553 48. Wang J, Pellissier J, Xu R, Liu FX, Stevinson K, Chmielowski B. Cost effectiveness
554 of Pembrolizumab (Keytruda) versus Ipilimumab in patients with advanced
555 melanoma in the United States. Value Health. 2016; 19: A154.
556 49. Cashin RP, Lui P, Machado M, Hemels ME, Corey-Lisle PK, Einarson TR.
557 Advanced cutaneous malignant melanoma: a systematic review of economic and
558 quality-of-life studies. Value Health. 2008; 11: 259-71.
559 50. NICE. Ipilimumab for previously treated advanced (unresectable or metastatic)
560 melanoma. Technology appraisal guidance. London: National Institute for Health
561 and Care Excellence, 12 December 2012. Available from:
562 https://www.nice.org.uk/guidance/ta268. Accessed on 09/11/2016.
563 51. NICE. Vemurafenib for treating locally advanced or metastatic BRAF V600
564 mutation-positive malignant melanoma. Technology appraisal guidance. London:
565 National Institute for Health and Care Excellence, 12 December 2012. Available
566 from: https://www.nice.org.uk/guidance/ta269. Accessed on 09/11/2016.
567 52. Beale S, Dickson R, Bagust A, Blundell M, Dundar Y, Boland A, Marshall E,
568 Plummer R, Proudlove C. Vemurafenib for the treatment of locally advanced or
569 metastatic BRAF V600 mutation-positive malignant melanoma: a NICE single
570 technology appraisal. Pharmacoeconomics. 2013; 31: 1121-9.

571 53. NICE. Dabrafenib for treating unresectable or metastatic BRAF V600 mutation-
572 positive melanoma. Technology appraisal guidance. London: National Institute for
573 Health and Care Excellence, 22 October 2014. Available from:
574 https://www.nice.org.uk/guidance/ta321. Accessed on 09/11/2016.
575 54. NICE. Ipilimumab for previously untreated advanced (unresectable or metastatic)
576 melanoma. Technology appraisal guidance. London: National Institute for Health
577 and Care Excellence, 23 July 2014. Available from:
578 https://www.nice.org.uk/guidance/ta319. Accessed on 09/11/2016.
579 55. Curl PK. Navigating uncertainty: a valuable cost-effectiveness analysis in the
580 rapidly changing field of metastatic melanoma treatment. Br J Dermatol. 2015; 173:
581 1365-6.
582 56. Fleeman N, Bagust A, Beale S, Boland A, Dickson R, Dwan K, Richardson M,
583 Dundar Y, Davis H, Banks L. Dabrafenib for Treating Unresectable, Advanced or
584 Metastatic BRAF V600 Mutation-Positive Melanoma: An Evidence Review Group
585 Perspective. Pharmacoeconomics. 2015; 33: 893-904.
586 57. Giannopoulou C, Sideris E, Wade R, Moe-Byrne T, Eastwood A, McKenna C.
587 Ipilimumab for Previously Untreated Unresectable Malignant Melanoma: A
588 Critique of the Evidence. Pharmacoeconomics. 2015; 33: 1269-79.
589 58. Johnston KM, McPherson E, Osenenko K, Vergidis J, Levy AR, Peacock S. Cost-
590 effectiveness of therapies for melanoma. Expert Rev Pharmacoecon Outcomes Res.
591 2015; 15: 229-42.
592 59. NICE. Pembrolizumab for treating advanced melanoma after disease progression
593 with ipilimumab. Technology appraisal guidance. London: National Institute for
594 Health and Care Excellence, 7 October 2015. Available from:
595 https://www.nice.org.uk/guidance/ta357. Accessed on 09/11/2016.

596 60. NICE. Pembrolizumab for advanced melanoma not previously treated with
597 ipilimumab. Technology appraisal guidance. London: National Institute for Health
598 and Care Excellence, 25 November 2015. Available from:
599 https://www.nice.org.uk/guidance/ta366. Accessed on 09/11/2016.
600 61. NICE. Nivolumab in combination with ipilimumab for treating advanced melanoma.
601 Technology appraisal guidance. London: National Institute for Health and Care
602 Excellence, 27 July 2016. Available from: https://www.nice.org.uk/guidance/ta400.
603 Accessed on 09/11/2016.
604 62. NICE. Nivolumab for treating advanced (unresectable or metastatic) melanoma.
605 Technology appraisal guidance. London: National Institute for Health and Care
606 Excellence, 18 February 2016. Available from:
607 https://www.nice.org.uk/guidance/ta384. Accessed on 09/11/2016.
608 63. NICE. Talimogene laherparepvec for treating unresectable metastatic melanoma.
609 Technology appraisal guidance. London: National Institute for Health and Care
610 Excellence, 28 September 2016. Available from:
611 https://www.nice.org.uk/guidance/ta410. Accessed on 09/11/2016.
612 64. NICE. Trametinib in combination with dabrafenib for treating unresectable or
613 metastatic melanoma. Technology appraisal guidance. London: National Institute
614 for Health and Care Excellence, 22 June 2016. Available from:
615 https://www.nice.org.uk/guidance/ta396. Accessed on 09/11/2016.
616 65. Matter-Walstra K, Braun R, Kolb C, Ademi Z, Dummer R, Pestalozzi BC,
617 Schwenkglenks M. Treatment specific utility-weightings are needed for cost-utility
618 analysis in metastatic melanoma: reply from the authors. Br J Dermatol. 2016; 174:
619 463.

620 66. Sebaratnam DF, Anforth R, Fernández-Peñas P. Treatment-specific utility
621 weightings are needed for cost-utility analysis in metastatic melanoma. Br J
622 Dermatol. 2016; 174: 462-3.
623 67. Kirkwood JM, Tarhini AA, Moschos SJ, Panelli MC. Adjuvant therapy with high-
624 dose interferon α2b in patients with high-risk stage IIB/III melanoma. Nature Clin
625 Practice. 2008; 5: 1-3.
626 68. Quaglino P, Mortera C, Osella-Abate S, Barberis M, Illengo M, Rissone M, et al.
627 Electrochemotherapy with intravenous bleomycin in the local treatment of skin
628 melanoma metastases. Ann Surg Oncol. 2008; 15: 2215-22.
629 69. Alexandrescu DT. Melanoma costs: a dynamic model comparing estimated overall
630 costs of various clinical stages. Dermatol Online J. 2009; 15: 1.
631 70. Livingstone E, Krajewski C, Eigentler TK, Windemuth-Kieselbach C, Benson S,
632 Elsenbruch S, et al. Prospective evaluation of follow-up in melanoma patients in
633 Germany - results of a multicentre and longitudinal study. Eur J Cancer. 2015; 51:
634 653-67.
635 71. McCarron CE, Ernst S, Cao JQ, Zaric GS. Population-based estimates of survival
636 and cost for metastatic melanoma. Curr Oncol. 2015; 22: 326-32.
637 72. Tarhini A, Corman SL, Rao S, Margolin K, Mehta S, Botteman MF. Healthcare
638 Resource Utilization and Associated Costs in Patients with Advanced Melanoma
639 Receiving First-Line Ipilimumab. J Cancer Therapy. 2015; 6: 833-40.
640 73. Guglieri-López B, Pérez-Pitarch A, Porta Oltra B, Ferriols-Lisart F, Royo-Peiró Á,
641 Climente-Martí M. Effectiveness, toxicity, and economic evaluation of ipilimumab
642 for the treatment of patients with metastatic melanoma in the Spanish outpatient
643 setting. Anticancer Drugs. 2016; 27: 679-84.

644 74. Potluri R, Okoro T, BhandarL H, Sabater J, Ranjan S, Kotapati S. Healthcare Cost
645 Comparison Analysis of Nivolumab + Ipilimumab Regimen (NIVO+IPI) and
646 Nivolumab (NIVO) Monotherapy Versus Established Advanced Melanoma
647 Therapies Utilizing Clinical Trial and Real World Data. Available from:
648 http://www.ispor.org/research_pdfs/52/pdffiles/PCN58.pdf. Accessed on
649 09/11/2016.
650 75. van der Meijde E, van den Eertwegh AJ, Linn SC, Meijer GA, Fijneman RJ, Coupé
651 VM. The Melanoma MAICare Framework: A Microsimulation Model for the
652 Assessment of Individualized Cancer Care. Cancer Inform. 2016; 15: 115-27.
653 76. Hofmann U, Szedlak M, Rittgen W, Jung EG, Schadendorf D. Primary staging and
654 follow-up in melanoma patients--monocenter evaluation of methods, costs and
655 patient survival. Br J Cancer. 2002; 87: 151-7.
656 77. Bastiaannet E, Uyl-de Groot CA, Brouwers AH, van der Jagt EJ, Hoekstra OS,
657 Oyen W, et al. Cost-effectiveness of adding FDG-PET or CT to the diagnostic
658 work-up of patients with stage III melanoma. Ann Surg. 2012; 255: 771-6.
659 78. Stoffels I, Müller M, Geisel MH, Leyh J, Pöppel T, Schadendorf D, et al. Cost-
660 effectiveness of preoperative SPECT/CT combined with lymphoscintigraphy vs.
661 lymphoscintigraphy for sentinel lymph node excision in patients with cutaneous
662 malignant melanoma. Eur J Nucl Med Mol Imaging. 2014; 41: 1723-31.
663 79. Look Hong NJ, Petrella T, Chan K. Cost-effectiveness analysis of staging strategies
664 in patients with regionally metastatic melanoma. J Surg Oncol. 2015; 111: 423-30.
665 80. Messori A, Becagli P, Trippoli S, Tendi E. A retrospective cost-effectiveness
666 analysis of interferon as adjuvant therapy in high-risk resected cutaneous melanoma.
667 Eur J Cancer. 1997; 33: 1373-9.

668 81. Hillner BE. Cost-effectiveness assessment of interferon alfa-2b as adjuvant therapy
669 of high-risk resected cutaneous melanoma. Eur J Cancer. 1998; 34: S18-21.
670 82. Crott R. Cost effectiveness and cost utility of adjuvant interferon alpha in cutaneous
671 melanoma: a review. Pharmacoeconomics. 2004; 22: 569-80.
672 83. Cormier JN, Xing Y, Ding M, Cantor SB, Salter KJ, Lee JE, Mansfield PF,
673 Gershenwald JE, Ross MI. Cost effectiveness of adjuvant interferon in node-
674 positive melanoma. J Clin Oncol. 2007; 25: 2442-8.
675 84. González-Larriba JL, Serrano S, Alvarez-Mon M, Camacho F, Casado MA, Díaz-
676 Pérez JL, et al. Cost-effectiveness analysis of interferon as adjuvant therapy in high-
677 risk melanoma patients in Spain. Eur J Cancer. 2000; 36: 2344-52.
678 85. Wilson LS, Reyes CM, Lu C, Lu M, Yen C. Modelling the cost-effectiveness of
679 sentinel lymph node mapping and adjuvant interferon treatment for stage II
680 melanoma. Melanoma Res. 2002; 12: 607-17.
681 86. Dixon S, Walters SJ, Turner L, Hancock BW. Quality of life and cost-effectiveness
682 of interferon-alpha in malignant melanoma: results from randomised trial. Br J
683 Cancer. 2006; 94: 492-8.
684 87. Atkinson V. Medical management of malignant melanoma. Aust Prescr. 2015; 38:
685 74-8.
686 88. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al.
687 Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med.
688 2010; 363: 809-19.
689 89. Kaplan RM. The minimally clinically important difference in generic utility-based
690 measures. COPD. 2005; 2: 91-7.

691 90. Wee HL, Machin D, Loke WC, Li SC, Cheung YB, Luo N, Feeny D, Fong KY,
692 Thumboo J. Assessing differences in utility scores: a comparison of four widely
693 used preference-based instruments. Value Health. 2007; 10: 256-65.
694 91. Minacori R, Bonastre J, Lueza B, Marguet S, Levy P. How to model survival in
695 cost-effectiveness analysis? Differences between Markov and Partitioned survival
696 analysis models. ISPOR 18th Annual European Congress, 11 November 2015,
697 Milan, Italy (PRM 123). Available from:
698 http://www.ispor.org/research_pdfs/51/pdffiles/PRM123.pdf. Accessed on
699 10/11/2016.
700 92. Coyle D, Coyle K. The inherent bias from using partitioned survival models in
701 economic evaluation. Value Health. 2014; 17: A194.
702 93. Svedman FC, Pillas D, Taylor A, Kaur M, Linder R, Hansson J. Stage-specific
703 survival and recurrence in patients with cutaneous malignant melanoma in Europe -
704 a systematic review of the literature. Clin Epidemiol. 2016; 8: 109-22.
705 94. Rubio-Terrés C, Rubio-Rodríguez D. Probabilistic Analysis: Sensitivity Analysis or
706 Main Result? Pharmacoeconomics: open access. 2016; 1: 2.
707 95. Schwartz D, Flamant R, Lellouch J. Clinical trials. London: Academic Press, 1980.
708 96. Devji T, Levine O, Neupane B, Beyene J, Xie F. Systemic Therapy for Previously
709 Untreated Advanced BRAF-Mutated Melanoma: A Systematic Review and
710 Network Meta-Analysis of Randomized Clinical Trials. JAMA Oncol. 2016 Oct 27.
711 doi: 10.1001/jamaoncol .2016.4877. [Epub ahead of print]
712 97. Gregoire G, Derderian F, Le Lorier J: Selecting the language of the publications
713 included in a meta-analysis: Is there a Tower of Babel bias? J Clin Epidemiol. 1995;
714 48: 159-63.

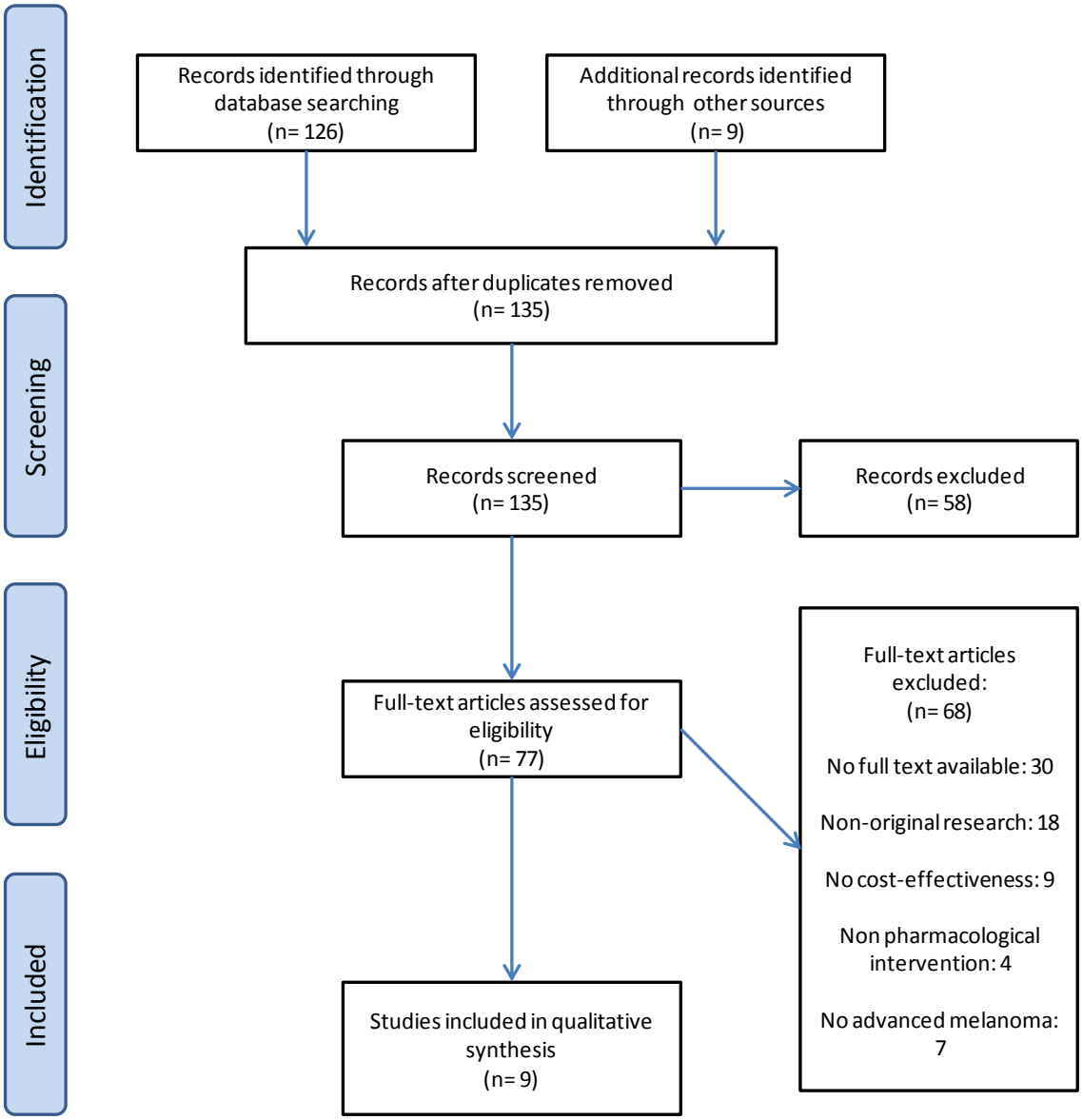
98. Egger M, Zellweger-Zahner T, Schneider M, Junker C, Lengeler C, Antes G: Language bias in randomised controlled trials published in English and German. Lancet. 1997; 350: 326-9.

99. Jüni P, Holenstein F, Sterne J, Bartlett C, Egger M. 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, Moulton K, Clark M, Fiander M, Mierzwinski-Urban M, Clifford T, Hutton B, Rabb D. 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.

740 **Figure 1.** Flow diagram of the search performed.

741



742

743

744 **Table 1.** Main study characteristics of advanced melanoma pharmacological treatment cost-effectiveness assessment.

First author Year (country)	Type of study Patient population	Perspective Time horizon	Funding	Drug therapy described (dose)	Total costs (year of valuation)¶	Total outcomes¶	ICER	Authors´ conclusion	QHES Category+
Hillner et al. 2000 (USA) [10]	Post hoc economic analysis within a clinical trial (CEA) Advanced melanoma*/PUT	Societal 1 year	American Cancer Society & 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. $US 6,902 2. $US 3,697 (1999)	1 vs. 2: 1.04 months gained (NS)***	$US 36,990/LYG	Efficacy difference of temozolomide vs. dacarbazine was NS	2
Barzey 2013 (USA) [11]	Markov model Probabilistic (CEA/CUA) Advanced melanoma*/PT	Health payer Lifetime	Bristol-Myers Squibb	1. Ipilimumab (3 mg/kg) 2. BSC (dacarbazine, temozolomide, paclitaxel+carboplatin)	1. $US 168,602 2. $US 21,886 (2012)	1) 2.88 LY 1.76 QALY 2) 1.00 LY 0.62 QALY	$US 78,218/LYG $US 128,656/QALY	Ipilimumab was 95% likely to be cost-effective at a WTP of $US 146000/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. $US 156,831 2. $US 254,695 3. $US 8,391 (2013)	1) 0.72 QALY 2) 1.34 QALY 3) 0.30 QALY	1 vs. 3: $US 353,993/QALY 2 vs. 1: $US 158,139/QALY	Strategies 1 & 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*/PUT	Canadian healthcare system 5 years	GlaxoSmithKline	1. Dabrafenib 2. Dacarbazine 3. Vemurafenib (N/A)	1. $CAN 111,199 2. $CAN 36,576 3. $CAN 150,405 (2012)	1) 1.52 QALY 2) 1.32 QALY 3) 1.47 QALY	1 vs. 2: $CAN 363,136/QALY 1 vs. 3: Dabrafenib is dominant**	At a threshold of CAN$200,000/QALY, Dabrafenib is unlikely to be cost effective compared with dacarbazine	3
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. CHF 311,421 2. CHF 111,773 (2015)	1) 1.54 QALY 2) 1.02 QALY	CHF 385,603/QALY	A reduction in the total price of the combination therapy is required to achieve an acceptable cost-effectiveness ratio	3

745

746 **Table 1.** Main study characteristics of advanced melanoma pharmacological treatment cost-effectiveness assessment (cont. 1).

First author Year (country)	Type of study Patient population	Perspective Time horizon	Funding	Drug therapy described (dose)	Total costs (year of valuation)¶	Total outcomes¶	ICER	Authors´ conclusion	QHES Category+
Shih et al. 2015 (USA) [15]	Markov model (CUA) Probabilistic BRAF-mutated advanced melanoma*/PUT	Societal Lifetime	No	1. Dabrafenib 2. Dacarbazine 3. Vemurafenib (N/A)	1. $US 38,547 2. $US 15,221 3. $US 49,938 (2013)	1) 0.34 QALY 2) 0.18 QALY 3) 0.29 QALY	1 vs. 2: $US 149,042/QALY 1 vs. 3: Dabrafenib is dominant**	Compared with dacarbazine, dabrafenib was not cost-effective at a WTP threshold of $US 100,000/QALY. Dabrafenib is dominant versus vemurafenib**	3
Bohensky et al. 2016 (Australia) [16]	Markov model Probabilistic (CEA/CUA) BRAF-negative advanced melanoma*/PUT	Australian Health System 10 years	Bristol-Myers Squibb	1. Nivolumab 2. Ipilimumab (3 mg/kg both)	1. $US 178,612 2. $US 138,987 (2015)	1) 3.1 LY 2.5 QALY 2) 1.5 LY 1.2 QALY	1 vs. 2: $US 25,201/LYG $US 30,475/QALY	Nivolimumab is cost-effective vs. ipilimumab.	3
Jensen et al. 2016 (USA) [17]	Decision analytical model Probabilistic (CEA) BRAF-mutated advanced melanoma*/PUT	Health payer/ Societal Progression or dead	Novartis	1. Nivolumab+ipilimumab 2. Dabrafenib+trametinib (N/A)	1. $US 259,293 2. $US 194,876 (Health Payer) (2015)	1 vs. 2: ORR: -0,2% PFS: 0.7 months ***	1 vs. 2: Cost per OR: -$US 106,316 Cost per month of PFS: -$US 4,446	Dabrafenib+Trametinib is associated with less patient time and lower costs relative to nivolumab+ipilimumab	2
Kohn et al. 2017 (USA) [18]	Markov model (CUA) BRAF Wild-type advanced melanoma	Health payer	National Cancer Institute & 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. $US 172,219 2. $US 206,435 3. $US 164,871 4. $US 127,626 5. $US 152,403 6. $US 146,775 (2016)	1) 0.54 QALY 2) 0.56 QALY 3) 0.43 QALY 4) 0.38 QALY 5) 0.34 QALY 6) 0.26 QALY	Best ICER vs 6: 4: Dominant 5: $US 70,350 1: $US 90,871 3: $US 106,447 2: $US 198,867	First-line PEM e2w/IPI or NIV/IPI are the most cost-effective, immune -based treatment strategies for metastatic melanoma.	3

747 *Unresectable or metastatic melanoma. **Dominant: Lower costs, higher effectiveness vs. comparator. ***Individual data not available. ¶ Per patient. + Three QAEEHC-based quality levels
748 have been established: category 1 (<40 points); category 2 (40-59 points); category 3 (≥60-100 points). The higher score, the higher quality[8].
749 BSC: Best supportive care; c2w/c3w: every 2 or 3 weeks; CAN: Canadian dollar; CAR: carboplatin; CEA: Cost-effectiveness analysis; CHF: Swiss francs; CUA: Cost-utility analysis; DAC:
750 dacarbazine; ICER: Incremental cost-effectiveness ratio; IPI: ipilimumab; LY: Life-year; LYG: Life-years gained; N/A: Not available; NIV: nivolumab; NS: Not statistically significant; OR:
751 Overall response; ORR: Overall response rate; PAC: paclitaxel; PEM: pembrolizumab; PT: Pretreated; PUT: Previously untreated; QHES: Quality of Health Economic Studies; USA: United
752 States of America; WTP: Willingness-to-pay.

753 **Table 2.** Quality assessment of selected pharmacoeconomics analyses. Quality Assessment of Economic Evaluation in Health Care* (QAEEHC).
754 Adapted from Abellán *et al.* [8].
755

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 (eg. 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
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

756
757

758 **Table 2.** Quality assessment of selected pharmacoeconomics analyses. Quality Assessment of Economic Evaluation in Health Care* (QAEEHC).
759 Adapted from Abellán *et al.* [8]. (cont. 1)
760

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]
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 (eg. 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 (eg 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 (eg 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-center studies, among which is a center belonging to the area of application of technology	4	0	4	0	0	0	0	0	0	0
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 to 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**

761 * Three QAEEHC-based quality levels have been established: category 1 (<40 points); category 2 (40-59 points); category 3 (≥60-100 points). The higher score, the higher quality (maximum score: 100 points). The
762 items identified with a letter (eg 4.1a, 4.1b, 7.2a, 7.2b) are mutually excluding. LYG: Life-years gained; Max: Maximum score per section; QALY: Quality-adjusted Life-years.