GRHTA
ISSN 2284-2403

Global & Regional Health Technology Assessment 2016; 3(2): 67-79
DOI: 10.5301/GRHTA.5000230
ORIGINAL ARTICLE

Open Access

Economic evaluation of ipilimumab in first line treatment of advanced melanoma in Italy

Maria De Francesco[1], Mark Lamotte[1], Paolo Antonio Ascierto[2], Paolo Di Rienzo[3], Yumi Asukai[4*]

[1] IMS Health, Zaventem - Belgium
[2] Istituto Nazionale Tumori Fondazione "G. Pascale", Naples - Italy
[3] Bristol-Myers Squibb, Rome - Italy
[4] IMS Health, London, UK

*Current affiliation: Glaxo Smith Kline, London - UK

ABSTRACT

Background: Ipilimumab, a fully human monoclonal antibody that blocks CTLA-4 to promote anti-tumour immunity, was the first treatment in metastatic melanoma to show a significant survival benefit.
Methods: A three-health-state partitioned survival model was developed to assess ipilimumab 3 mg/kg compared to dacarbazine and vemurafenib in first line therapy of advanced melanoma treatment-naive patients in Italy. The outcomes considered were costs, life years (LYs) and quality-adjusted life years (QALYs). Given the lack of trials assessing ipilimumab 3 mg/kg in this subgroup of patients, the efficacy was derived from a dataset of chemo-naive patients. Patient's management costs were estimated based on a micro-costing approach and the cost of adverse events based on both outpatient and inpatient care. Utilities considered were elicited from ipilimumab's clinical trials.
Results: Basecase results showed that ipilimumab was both more costly and more effective than dacarbazine, with ratios of €38,345/LYs and €49,466/QALYs. By contrast, results vs. vemurafenib showed a marginal increase in health outcomes accompanied by a saving of €32,999, thus making ipilimumab the dominant strategy over vemurafenib in the base-case analysis. Sensitivity analysis showed overall robustness of the model.
Conclusions: Treatment with ipilimumab showed better results in terms of LYs and QALYs against both comparators. Moreover, ipilimumab was the dominant strategy compared to vemurafenib, thus highly likely to bring both health benefits and cost savings in the Italian setting.

Keywords: Advanced melanoma, First line treatment, Ipilimumab, Micro-costing

Introduction

Across the world, malignant melanoma is the sixteenth and seventeenth most frequent cancer among women and men, respectively, and the incidence has been increasing over the years (1). Although less prevalent than others, malignant melanoma is the major cause of death from skin cancer due to its aggressive progression (2). Identified risk factors for melanoma are family history, presence of epidermal nevi and previous history of melanoma (3). Moreover, excess exposure to ultraviolet light is considered to be an important etiological factor. The incidence of melanoma varies across Europe and approximately 11,000 new cases of melanoma have been diagnosed in Italy throughout 2014 (4). Despite the growing incidence and underlying aggression of melanoma, survival has improved over the past decade mostly thanks to early diagnosis of the disease (5).

Up to a few years ago, treatment options for malignant melanoma were limited. For patients in the advanced stages of the disease (IIIC and IV) surgery is considered an option in selected cases (6). For over 30 years, chemotherapy with dacarbazine was considered the standard of care in advanced melanoma and as such this treatment was used as the control arm in all randomized comparative trials. Aside from dacarbazine, fotemustine and temozolomide were considered alternative chemotherapy regimens in the first line treatment of advanced melanoma (4). However, none of these treatments showed considerable improvements in survival (7). Recent developments in targeted therapy and immunotherapy have brought some improvements in overall survival for patients with advanced melanoma – i.e. ipilimumab and vemurafenib, followed by dabrafenib, alone and in combination with the MEK inhibitor trametinib. Recent studies showed that the MEK inhibitor cobimetinib in combination with vemurafenib and the anti PD-1 agents, nivolumab and pembrolizumab, have positive efficacy results in the treatment of metastatic

Accepted: April 28, 2016
Published online: June 14, 2016

Corresponding author:
Maria De Francesco
IMS Health – Real World Evidence Solutions
Da Vincilaan 7, 1935 Zaventem, Belgium
mdefrancesco@be.imshealth.com

melanoma. At the time of this analysis only ipilimumab and vemurafenib were approved in Italy, thus the novel above-mentioned treatments were not included in our analysis.

Vemurafenib, a BRAF kinase inhibitor, has been approved in Italy for the treatment of patients with a BRAF V600 mutation, estimated to occur in 40-50% of patients with melanoma. Results from the BRAF Inhibitor in Melanoma-3 (BRIM-3) study, a randomized, double blind, phase III trial comparing vemurafenib to dacarbazine in patients with previously untreated, metastatic melanoma with the BRAF V600E mutation, showed a median overall survival (OS) and progression free survival (PFS) of 13 and 6.9 months, respectively, in patients treated with vemurafenib (8-10).

Ipilimumab is a fully human monoclonal antibody (IgG1) that blocks CTLA-4 to promote anti-tumour immunity. It is currently licensed in the US and Europe at a dose of 3 mg/kg in first and second line treatment of melanoma. Ipilimumab was the first treatment in metastatic melanoma to show a significant survival benefit (11). Ipilimumab reduced the risk of death by 34% when compared to the experimental vaccine GP100 in second line therapy. In the first line setting, a multinational, randomized, double-blind, phase III trial (CA184-024) compared ipilimumab 10 mg/kg in combination with dacarbazine to dacarbazine alone as a potential treatment regimen and showed a 94% increase in OS at 3 years and more than doubled OS at 5 years (12). A more recent study on the long term benefit of ipilimumab showed that 20% of patients were still alive after 10 years from treatment start (13).

A cost-effectiveness (CE) analysis was conducted comparing ipilimumab to best supportive care (BSC) in second line treatment of advanced melanoma in the US and results showed that ipilimumab could be considered cost-effective (14). However, so far, no economic evaluations have been conducted to compare ipilimumab to dacarbazine and vemurafenib in first line treatment of advanced melanoma in Italy. The current CE analysis was the first attempt to assess ipilimumab 3 mg/kg compared to dacarbazine and vemurafenib in first line therapy of treatment-naive patients with advanced melanoma from the Italian National Health Service (NHS) perspective. The objective was to compare costs and outcomes, in terms of life years (LYs) and quality-adjusted life years (QALYs), associated with ipilimumab and the alternatives, based on efficacy and safety data presented in the regulatory submission dossier.

Method

Model structure

A semi-Markov partitioned survival model was developed using Microsoft Excel™ to assess costs and effects, LYs and QALYs, of the different comparators in a cohort of advanced melanoma treatment-naive patients. Treatment naive patient is defined as a patient who had not previously received chemotherapy for melanoma. The cohort transitioned across three health states: stable disease (SD), progressive disease (PD) and death (Fig. 1). At the start of the simulation the entire cohort was located in the SD state and at each subsequent cycle patients moved across states based on the extrapolated OS and PFS curves. This structure

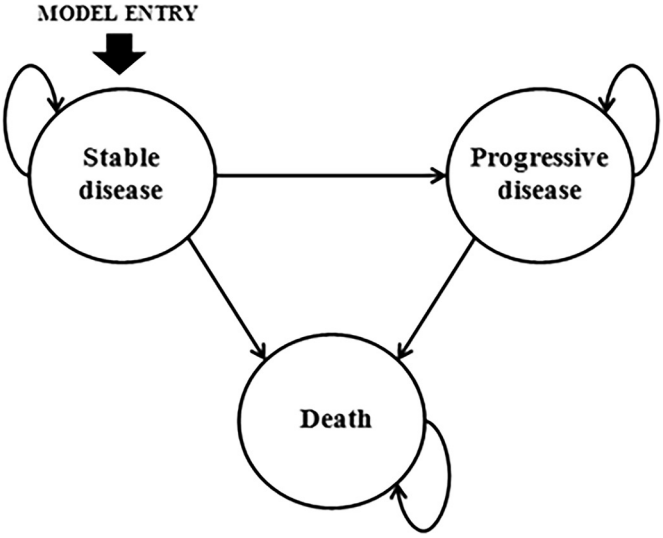

Fig. 1 - Schematic overview of the model structure.

has been commonly used in economic evaluations of cancer treatment as it allows the explicit incorporation of OS and PFS, which are the two most widely assessed endpoints in randomized clinical trials (RCTs) and observational studies of solid tumour cancer treatment (15).

Model cycles were set to 3 weeks, which correspond to the interval between the four infusions of ipilimumab, as well as to the standard chemotherapy treatment cycle. The time horizon was 15 years, which represented a sufficiently long period of time to account for all costs and health outcomes associated with treatment and can be considered life-long. The model adopted the perspective of the Italian NHS and both costs and outcomes were discounted at an annual rate of 3.0% (16). The two comparators considered in the analysis were dacarbazine, which has been the standard of care until the introduction of ipilimumab, and vemurafenib. The choice of comparators has been validated by experts from different European countries and is relevant to Italy.

Clinical data

Clinical data for ipilimumab in first line treatment are available from a phase III randomized clinical trial (study CA184-024) comparing ipilimumab at a dose of 10 mg/kg in combination with dacarbazine to dacarbazine + placebo; however the dosing for the regulatory filing was later amended to 3 mg/kg as per the second line marketing authorization. For this reason the efficacy data for ipilimumab 3 mg/kg were obtained from a pooled dataset of phase II and III trials of ipilimumab: CA184-004, CA184-022, MDX-010-08 and MDX-010-20 (Tab. I), which was validated by clinical and health economic experts. Survival data were extrapolated from the chemotherapy naive subpopulations (total of 78 patients) in each trial. Alternative pooled datasets included survival data from two observational studies, CA184-338 and CA184-332. However they were not selected as the basecase given PFS data were not collected and the follow-up period was shorter compared to studies included in the chemo-naive dataset.

TABLE I - Phase II and III clinical trials included in ipilimumab efficacy pooled dataset (total patients = 78)

Study reference	Description	Patients, n
CA184-004	A Randomized Phase II Study To Determine Potential Predictive Markers of Response to Mdx-010 (Bms-734016) in Patients with Unresectable Stage III or IV Malignant Melanoma	17
CA184-022	A Randomized, Double-Blind, Multi-Center, Phase II Fixed Dose Study of Multiple Doses of Ipilimumab (Mdx-010) Monotherapy in Hla-A2-Negative Patients with Previously Treated Unresectable Stage III or IV Melanoma	8
MDX010-08	A Randomized Study Comparing MDX-010 Alone or in Combination with DTIC in the Treatment of Patients with Chemotherapy Naïve Metastatic Melanoma	40
MDX010-20	MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/MDX-1379 Combination Treatment for Patients with Unresectable or Metastatic Melanoma	13

Data from chemo-naive patients, rather than treatment-naive, were extrapolated from the ipilimumab pooled dataset based on the following reasons: firstly, the sample of treatment - naive patients from the phase II and III studies included in the dataset was too small (n = 35) to allow robust extrapolation of survival data; secondly, the survival outcomes between the treatment - naive and the chemo-naive groups did not differ significantly; and thirdly, the definition of treatment naive is debatable as an argument can be made that adjuvant therapies were not an exclusion criteria in ipilimumab -024 trial (17) and therefore patients defined as treatment - naive may have received adjuvant treatment with interferon post surgery. The trial exclusion criteria can only guarantee that previous chemotherapy was never part of the treatment provided in the adjuvant setting.

Currently, there are no head-to-head comparisons between ipilimumab 3 mg/kg and dacarbazine or vemurafenib. The model employs a single-arm approach to compare ipilimumab OS and PFS from the chemo-naive dataset to dacarbazine or vemurafenib OS and PFS from the -024 and BRIM-3 trials, respectively. In order to increase the robustness of the comparison, a regression model based on the -024 trial was built to derive the OS and PFS of dacarbazine in a population of patients with the same characteristics as patients in ipilimumab chemo-naive dataset (18). This approach was used as the basecase setting. In a scenario analysis, we explored a further option for extrapolation of dacarbazine OS based on the Korn algorithm. The Korn algorithm was developed based on a meta-analysis of 42 Phase II melanoma trials involving 2,100 patients in order to benchmark single arm trials to historical OS by adjusting for key prognostic factors, including gender, ECOG performance status, presence of visceral disease, and brain metastases (19). Vemurafenib OS and PFS results from the BRIM-3 study have been published in the literature (8-10). Due to the lack of patient-level data, it was not possible to build a regression model to match the BRIM-3 population to the characteristics of the population in the chemo-naive dataset; however, different prognostic factors may be expected to have limited effect on the results.

Kaplan-Meier (K-M) estimates of OS and PFS were available over the study's follow-up period and parametric models were used to extrapolate survival beyond the observation period. Different parametric models were tested for the best-fit using visual inspection and Akaike's Information Criterion methods. The log-normal and log-logistic distributions had the best fit for the extrapolation of ipilimumab OS and PFS, respectively. The Gompertz and log-logistic were the best fit parametric distribution for both OS and PFS of dacarbazine and vemurafenib, respectively (Tab. II). Although the extrapolation of efficacy beyond the follow-up period is a well accepted approach to estimate long-term treatment outcomes, we recognize that, even while adhering to all the good practices of the method, it may be inherently uncertain in the absence of empirical data against which to validate. The 'Area Under the Curve' (AUC) method was used to estimate the period of time spent in the SD and PD states.

The incidence of grade III and IV adverse events associated with ipilimumab was obtained from a multisite retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab 3 mg/kg as first-line therapy (CA184-338) (Tab. II). This study was preferred to the chemo-naive dataset by the advisory board involved in the validation of the global model as it reported 'real-life' data. The incidence of grade III and IV adverse events associated with dacarbazine and vemurafenib was obtained from the respective clinical trials, -024 and BRIM-3 (20) (Tab. II).

Resource use and costs

The costs included in the model can be grouped into active drugs, management of patients and management of adverse events. The estimation of costs followed a micro-costing approach and it was largely based on the Italian outcomes of a clinician survey, which had the objective to estimate resource use and costs of first and second line treatment of advanced melanoma, associated grade III/IV adverse events and palliative/terminal care in five European countries (21). The cost of systemic therapy post progression was not considered in the analysis.

The active drug acquisition costs of ipilimumab and vemurafenib as reported in Table III were derived from the official ex-factory prices published in the Italian Official Journal, inclusive of official discounts (law of 3 July 2006 and 27 September 2006 (22, 23)). Note that also a confidential discount and a Payment by Results agreement was closed between the manufacturing company and the Italian Medicine Agency. On the basis of this Payment by Results agreement the manufacturer has to reimburse the Italian NHS the

TABLE II - Clinical and quality of life data

	Data	Source
Mean extrapolated OS (months)		
Ipilimumab	32	Log-Normal from chemo-naive dataset (Tab. I)
	33.2	Log-Normal from chemo-naive (Tab. I) + CA184-338 dataset
Dacarbazine	9.6	Gompertz from adjusted DTIC arm in -024 trial (17)
	7.7	Korn algorithm (19)
Vemurafenib	27.2	Log-Logistic from BRIM 3 trial (8-10)
Mean extrapolated PFS (months)		
Ipilimumab	9.7	Log-Logistic from chemo-naive dataset (Tab. I)
Dacarbazine	2.8	Gompertz from adjusted DTIC arm in -024 trial (17)
Vemurafenib	8.6	Log-Logistic from BRIM 3 trial (8-10)
Average treatment length		
Ipilimumab (21 days cycles)	3.32	Chemo-naive dataset (Tab. I)
Dacarbazine (21 days cycles)	4.56	DTIC arm in CA184-024 trial (17)
Vemurafenib (months)	Until progression	PFS curve extrapolated from BRIM 3 (8-10)
	6.9	Median PFS from BRIM 3 (8-10)
Adverse event (grade III/IV) incidence, ipilimumab		
Adrenal insufficiency	0.025	CA184-338 observational study
Colitis	0.042	CA184-338 observational study
Diarrhea	0.017	CA184-338 observational study
Fatigue	0.033	CA184-338 observational study
Hypophysitis	0.017	CA184-338 observational study
Hypothyroidism	0.008	CA184-338 observational study
Thrombocytopenia	0.008	CA184-338 observational study
Enterocolitis	0.025	CA184-338 observational study
Dermatitis	0.025	CA184-338 observational study
Hepatitis	0.008	CA184-338 observational study
Adverse event (grade III/IV) incidence, dacarbazine		
Weight loss	0.004	CA184-024 trial (17)
Incr. alanine aminotransferase	0.008	CA184-024 trial (17)
Incr. aspartate aminotransferase	0.012	CA184-024 trial (17)
Enterocolitis	0.004	CA184-024 trial (17)
Adverse event (grade III/IV) incidence, vemurafenib		
Diarrhea	0.01	BRIM 3 trial (8-10)
Fatigue	0.02	BRIM 3 trial (8-10)
Headache	0.01	BRIM 3 trial (8-10)
Nausea	0.01	BRIM 3 trial (8-10)
Neutropenia	0.01	BRIM 3 trial (8-10)
Rash	0.09	BRIM 3 trial (8-10)
Vomiting	0.01	BRIM 3 trial (8-10)
Utilities		
Stable disease	0.80	EORTC method based on MDX010-020 (Tab. I)
	0.84	EORTC method based on CA184-024 (17)
Progressive disease	0.76	EORTC method based on MDX010-020 (Tab. I)
	0.83	EORTC method based on CA184-024 (17)
Death	0	

OS = overall survival; PFS = progression free survival.

TABLE III - Active drug acquisition cost per treatment cycle

	Unit data	Source
Dosage		
Ipilimumab	3 mg/kg every 21 days (max 4 infusions)	Registered dose
Dacarbazine	850 mg/m^2 every 21 days	CA184-024 trial
Vemurafenib	2 × 960 mg tablets per day	BRIM 3 trial
List drug cost per cycle (including official discounts) - including wastage		
Ipilimumab*	€21,250	Re-elaboration from Italian O.J. (23)
Dacarbazine**	€0	Re-elaboration from Italian O.J. (25)
Vemurafenib	€6,227	Re-elaboration from Italian O.J. (22)
List drug cost per cycle (including official discounts) - excluding wastage		
Ipilimumab*	€19,124	Re-elaboration from Italian O.J. (23)
Dacarbazine**	€0	Re-elaboration from Italian O.J. (25)
Vemurafenib	€6,227	Re-elaboration from Italian O.J. (22)

*Body weight = 75 kg
**Body surface area = 1.79 m^2
O.J. = Official Journal (Gazzetta Ufficiale)

drug cost for all patients who do not benefit from treatment (23, 24). Following the official statement "Determina Deticene" published in the Italian Official Journal (25), dacarbazine is provided free of charge to all hospitals. In addition to the acquisition cost, an additional cost of €414 per infusion was considered for ipilimumab and dacarbazine, which require health assistance for intravenous administration (25).

The healthcare resources employed for the management of patients can be grouped into health assistance, diagnostic tests and hospitalizations and were used in the model to calculate the cost attributed to each health state. Although the model had three health states, resource consumption was expected to vary across four different subgroups: patients with stable disease, patients at terminal disease, patients at disease progression and patients post-disease progression, where the latter two were both accounted for in the PD state. The type and quantity of resources used per cycle was obtained from the Oxford Outcomes survey (21), whereas the associated unitary costs were obtained from relevant studies published in the literature and official national documents. Table IV shows resource use and associated unit costs, as well as the estimated total cycle cost per patient across the four subgroups, whereas sources for each specific unit cost are presented in Table V.

For each adverse events of grade III/IV included in the model, the proportions of patients treated in outpatient and inpatient care reported from the Oxford Outcomes survey (21) were used to estimate the total event cost (Tab. VI). The costs associated with outpatient care were also obtained from the survey Oxford Outcomes (21) and included health visits, diagnostic tests and pharmacological treatment. All costs of inpatient care were drawn from the Italian Diagnosis Related Groups (DRGs) tariffs (26) (Tab. VI).

All costs were actualized to 2014 using the Inflation Index reported by the Italian Institute of National Statistics (ISTAT) (34).

Quality of life

Utilities associated with SD and PD health states were elicited from the population included in two trials investigating efficacy and safety of ipilimumab, namely study CA184-024 and a phase III study of ipilimumab 3 mg/kg in combination with gp 100 peptide vaccine (MDX010-020) (Tab. II). Utility values from both studies were estimated using the quality of life (QoL) questionnaires by the European Organization for Research and Treatment of Cancer (EORTC), which develops multi-attribution classification systems that are specific to measure the quality of life of patients with cancer. Utility values were generated using the EORTC-8D preference-based measure by Rowen et al (35) and subsequently mapped to EQ-5D. The utilities elicited from the -020 trial were used in the basecase analysis because they reflect the quality of life of patients treated with the correct posology for ipilimumab, i.e. 3 mg/kg. This choice was validated by the experts and results using the -024 trial EORTC were explored in the scenario analysis. Moreover, QoL estimates from the RCT were preferred over those reported from studies in the literature as they provide utility values better reflecting the QoL of patients with same characteristics as the cohort included in the model.

The elicited utility values from both -020 and -024 trials also incorporated the negative impact of adverse events on QoL. Hence, no further utility decrements were accounted for grade III and IV adverse events.

Sensitivity analysis

Both one-way sensitivity analysis (OWSA) and a scenario analysis were performed to assess how variation in model parameters and model assumptions impact basecase results. In OWSA, the model parameters were varied within a predefined range of ±20%, whereas in the scenario analysis

TABLE IV - Cost of management of patients across disease stages

	Unit cost* (€ 2014)	Resource use	Proportion of patients	Cost applied in the model (€)
Management of patients with stable disease				
Oncology visit	€46.48	1.7	0.7	€55.31
Hospitalization (day)	€806.70	3.8	0.13	€398.51
ICU (day)	€1,315.35	8	0	€0.00
Full blood count	€3.17	1.2	0.9	€3.42
Complete metabolic profile	€27.62	1.2	0.82	€27.18
Abdomen CT	€158.84	0.7	0.8	€88.95
Chest CT	€124.11	0.7	0.8	€69.50
Brain MRI	€247.50	0.7	0.28	€48.51
Brain CT	€120.42	0.7	0.65	€54.79
PET	€1,071.65	0.6	0.35	€225.05
Total				**€971.22**
Management of patients at disease progression				
Oncology visit	€ 46.48	2.5	0.62	€72.04
Hospitalization (day)	€806.70	3.4	0.14	€383.99
ICU (day)	€1,315.35	5.5	0.04	€289.38
Full blood count	€3.17	1.3	0.87	€3.59
Complete metabolic profile	€27.62	1.3	0.78	€28.01
Abdomen CT	€158.84	1.3	0.87	€179.65
Chest CT	€124.11	1.3	0.87	€140.37
Brain MRI	€247.50	1.5	0.27	€100.24
Brain CT	€120.42	1.3	0.77	€120.54
PET	€1,071.65	1.5	0.3	€482.24
Total				**€1,800.04**
Management of patients post-progression				
Home care (day)	€100	9	0.16	€144.00
Oncology visit	€46.48	1.2	0.1	€5.58
Radiological visit	€20.66	0	0	€0.00
General practitioner visit	€18.20	2.3	0.1335	€5.59
Psychologist visit	€42.50	1.7	0.835	€60.33
Physiotherapist visit	€20.66	2.3	0.492	€23.38
Occupational therapy	€20.66	0	0	€0.00
Hospitalization (day)	€806.70	1.6	0.3416	€440.91
ICU (day)	€1,315.35	7	0.0025	€23.02
Morphine (oral)	€29.1	1	0.246	€7.16
Morphine (IV)	€33.6	1	0.115	€3.86
Morphine (patches)	€32	1	0.2653	€8.49
Ibuprofen	€5.208	1	0.2333	€1.22
Prednisone	€9.8	1	0.1166	€1.14
Total				**€724.67**
Management of patients in terminal care				
Hospitalization (day)	€806.70	8	0.2	€1,290.72
Hospice (day)	€283.50	16.6	0.3333	€1,568.54
Home care (day)	€100	21	0.48	€1,008.00
Total				**€3,867.26**

CT = computed tomography; ICU = intensive care unit; MRI = magnetic resonance imaging; PET = positron emission tomography.
*The specific sources of unit costs are presented in Table V.

TABLE V - Sources of unit costs considered in the model

Health care resource	Source
Oncology visit	Consulto, definito complessivo. National tariffs (26)
GP visit	Cost-opportunity evaluation, studio DYSCO (27)
Radiological visit	Visita generale. National tariffs (26)
Psychologist visit	Visita generale. National tariffs (26)
Occupational therapy	Visita generale. National tariffs (26)
Home care	1 day tariff. Hospice in Italia: Seconda rilevazione Ufficiale (28)
Physiotherapist visit	Visita generale. Tariffe ambulatoriali. National tariffs (26)
Full blood count	Emocromo: Hb, GR, GB, HCT, PLT, IND. DERIV., F. L. 3,17. National tariffs (26)
Complete metabolic profile	Exams included* National tariffs (26)
Chest CT	TC del torace senza e con contrasto. National tariffs (26)
Brain CT	TC del capo, senza e con contrasto. National tariffs (26)
Abdomen CT	TC addome completo. National tariffs (26)
Brain MRI	RM del cervello e del tronco encefalico, senza e con contrasto. National tariffs (26)
PET	Tomoscintigrafia globale corporea (PET). National tariffs (26)
Hospitalization (day)	Average cost per day (29)
Hospitalization in ICU (day)	Cost per day in ICU (30)
Hospice (day)	Cost per day. Hospice in Italia: Seconda rilevazione Ufficiale (28)
Morphine (oral)	Medicinali di classe H in commercio (31)
Morphine (IV)	Medicinali di classe H in commercio (31)
Morphine (patches)	Medicinali di classe H in commercio (31)
Ibuprofen	Liste di trasparenza farmaci equivalenti (32)
Prednisone	Medicinali di classe A in commercio (33)

CT = computed tomography; GP = general practitioner; ICU = intensive care unit; MRI = magnetic resonance imaging; PET = positron emission tomography. *creatinina [s/u/du/la], acido lattico, acido piruvico, ceruloplasmina, corpi chetonici, crioglobuline ricerca, fenilalanina, ferro [du], glucosio [s/p/u/du/la], colesterolo totale, trigliceridi.

TABLE VI - Cost of adverse event (grade III/IV) management

Adverse event	Outpatient care proportion	Outpatient unit cost* (€)	Inpatient care proportion	Inpatient unit cost** (€)	Cost applied in the model (€)
Treatment with ipilimumab					
Adrenal insufficiency	0.667	€74.27	0.333	€901.00	€349.57
Colitis	0.85	€575.67	0.15	€959.00	€633.17
Diarrhea	0.93	€192.68	0.07	€959.00	€246.32
Fatigue	0.93	€65.52	0.07	€1,748.00	€183.29
Hypophysitis	0.88	€0.00	0.13	€901.00	€117.13
Hypothyroidism	0.92	€125.92	0.08	€901.00	€187.93
Thrombocytopenia	0.90	€525.27	0.10	€2,748.00	€747.54
Enterocolitis	0.85	€575.67	0.15	€959.00	€633.17
Dermatitis	1.00	€61.90	0.00	€728.00	€61.90
Hepatitis	0.97	€207.64	0.03	€1,407.00	€243.62
Treatment with dacarbazine					
Decreased appetite	1.00	€0.00	0.00	€0.00	€0.00
Increased alanine aminotransferase	1.00	€0.00	0.00	€0.00	€0.00
Increased aspartate aminotransferase	1.00	€0.00	0.00	€0.00	€0.00
Enterocolitis	0.99	€576.43	0.01	€959.00	€580.26
Treatment with vemurafenib					
Diarrhea	0.96	€133.53	0.04	€959.00	€166.55
Fatigue	0.93	€138.39	0.07	€1,748.00	€251.06
Headache	0.98	€62.25	0.02	€2,049.00	€101.99
Nausea	0.99	€68.09	0.01	€959.00	€77.00
Neutropenia	1.00	€426.45	0.00	€1,704.00	€426.45
Rash	0.99	€61.03	0.01	€728.00	€67.70
Vomiting	0.94	€79.98	0.06	€959.00	€132.72

* Inpatient costs were obtained from the costing study by Oxford Outcomes (21) and they vary across active therapies.
** Outpatient costs were derived from Italian National DRG tariffs, last updated in January 2013 (26).

TABLE VII - Assumptions explored in the scenario analysis

	Basecase assumption	Alternative assumption
Ipilimumab efficacy dataset	Chemo-naive	Chemo-naive + observationl study -338
Dacarbazine comparative efficacy	Adjusted dacarbazine (trial -024)	Korn algorithm
Active treatment costs	Cost with wastage	Cost without wastage
Adverse event costs	Different across comparators	Equal across comparators
Utility source	EORTC (trial -020)	EORTC (trial -024)
Vemurafenib treatment length	Until progression	Median PFS cut-off
Outcome discount rate	3%	2%-4%
Cost discount rate	3%	2%-4%

EORTC = European Organisation for Research and Treatment of Cancer; PFS = progression free survival.

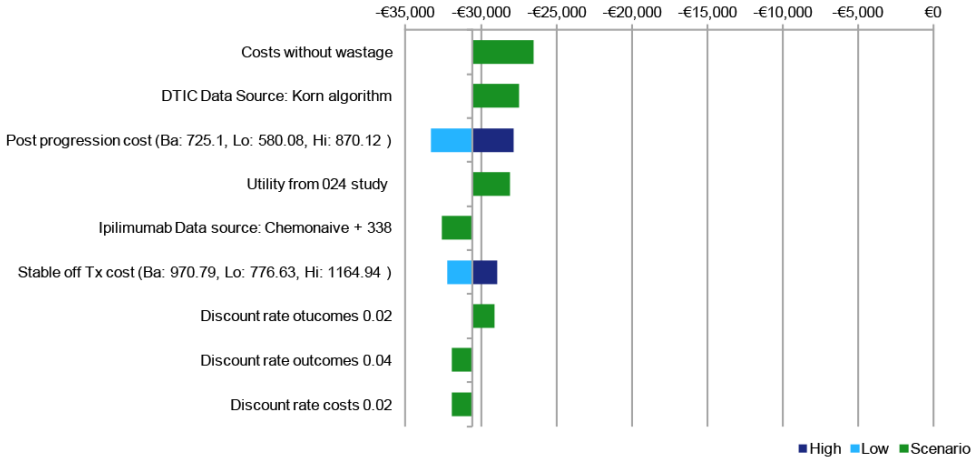

Fig. 2 - Tornado diagram around basecase NMB (QALYs) of -€30,573 for ipilimumab vs. dacarbazine.

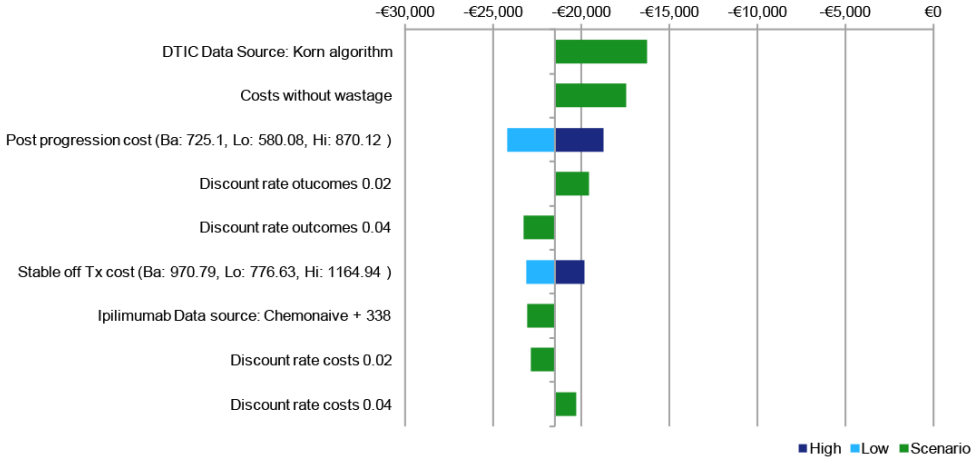

Fig. 3 - Tornado diagram around basecase NMB (LYs) of -€21,513 for ipilimumab vs. dacarbazine.

basecase assumptions were modified on the basis of alternative valid options (Tab. VII). Results were presented through a Tornado diagram around basecase net monetary benefit (NMB), which allows less ambiguity in result interpretation compared to incremental cost-effectiveness ratio (ICER). The Tornado diagram allowed visualizing simultaneously the impact of variations in the ten most influent parameters/assumptions on basecase NMB results (Figs. 2-5).

Probabilistic sensitivity analysis (PSA) allows controlling for the impact of uncertainty in parameters on the model results. A distribution was assigned to each parameter based on specific characteristics. In the current analysis, a Gamma

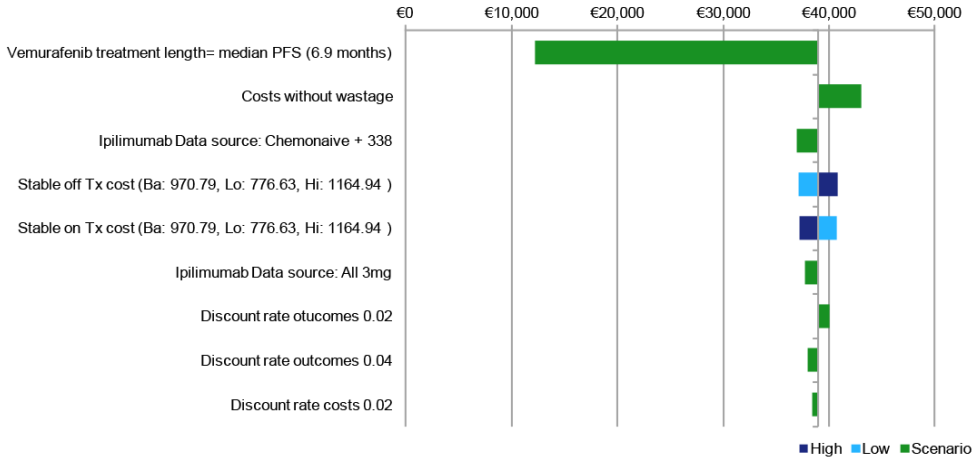

Fig. 4 - Tornado diagram around basecase NMB (QALYs) of €38,975 for ipilimumab vs. vemurafenib.

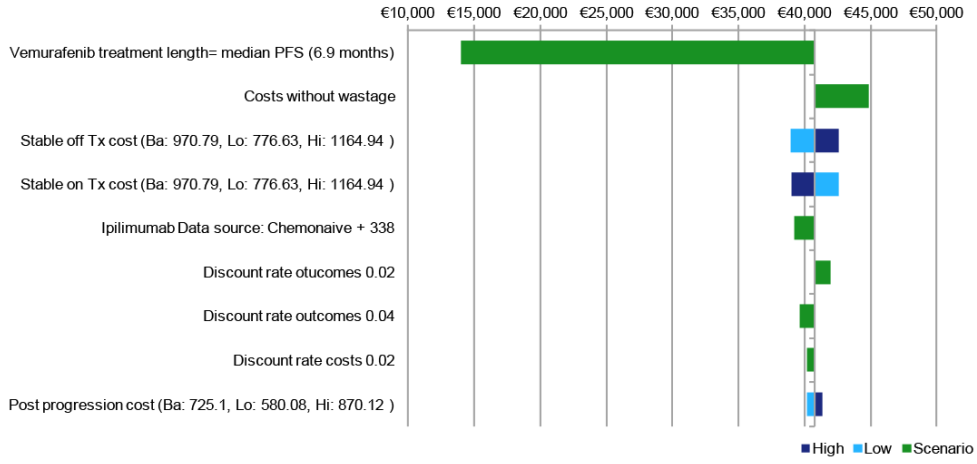

Fig. 5 - Tornado diagram around basecase NMB (LYs) of €40,776 for ipilimumab vs. vemurafenib.

distribution was assigned to costs and resource use and a Beta distribution was assigned to patient proportions, incidence of adverse events and utilities (Supplementary Table I, available online at www.grhta.com). The PSA was performed with 1,000 Monte Carlo simulations and the results were presented in a CE plane and through a cost-effectiveness acceptability curve (CEAC), which together quantified the level of confidence that can be placed in the model results (36).

Results

Basecase analysis

Deterministic results of the basecase analysis conducted in adult treatment-naive patients with advanced melanoma showed first line treatment with ipilimumab to increase LYs and QALYs compared to both treatment with dacarbazine and treatment with vemurafenib (Tab. VIII). Ipilimumab higher treatment cost compared to dacarbazine drove the total cost increment. Hence, the higher net health benefit associated with ipilimumab treatment versus dacarbazine treatment was partially outweighed by the large additional total cost, resulting in an ICER and incremental cost-utility ratio (ICUR) of €38,345/LY and €49,466/QALY respectively (Tab. VIII). By contrast, the treatment with ipilimumab was associated with a lower active drug acquisition cost compared to treatment with vemurafenib, which mostly contributed to the resulting overall savings. Deterministic results therefore showed that treatment with ipilimumab is dominant related to treatment with vemurafenib given the positive increment in health outcomes and the associated total cost saving, i.e. the joint incremental cost and effect was located in the South-East quadrant of the CE plane.

Sensitivity analysis

Deterministic sensitivity analysis showed overall robustness of basecase results, which were only marginally impacted by variations around parameters and model assumptions. Results around NMB calculated on QALYs and around LYs are presented in Figures 2 and 4, and Figures 3 and 5, respectively. The exclusion of wastage from the active drug cost calculation, the use of the Korn algorithm to estimate dacarbazine efficacy and the use of utilities from the -024 study all improved the results to some extent. The inclusion of the US observational study (-338) to estimate ipilimumab efficacy

TABLE VIII - Deterministic results of ipilimumab vs. dacarbazine and vemurafenib in treatment-naive patients

	Ipilimumab	Dacarbazine	Incremental	Vemurafenib	Incremental
LYs	2.45	0.84	1.61	2.14	0.31
QALYs	1.90	0.65	1.25	1.66	0.24
Active treatment cost	€41,715	€1,666	€40,050	€77,869	-€36,154
Total cost	€79,456	€17,642	€61,814	€112,454	-€32,999
Incremental cost/LY	-	-	€38,345	-	Ipi dominant
Incremental cost/QALY	-	-	€49,466	-	Ipi dominant

Ipi = ipilimumab; LY = life year; QALY = quality-adjusted life year.

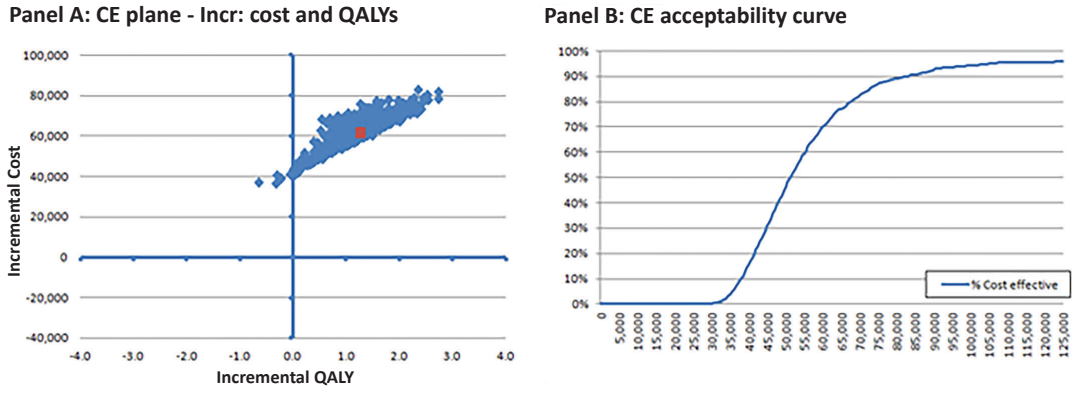

Fig. 6 - PSA results on ipilimumab vs. dacarbazine comparison.

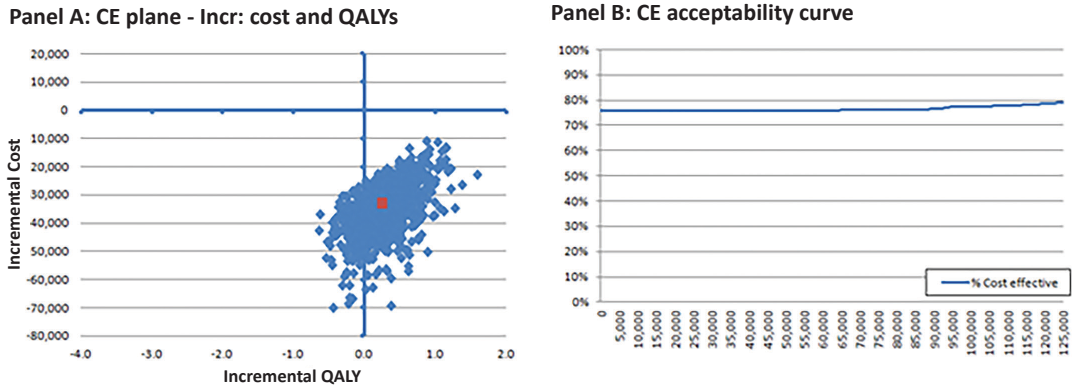

Fig. 7 - PSA results on ipilimumab vs. vemurafenib comparison.

worsened the NMB results and a large negative impact on results was observed assuming vemurafenib treatment length equal to median PFS, due to the resulting reduction in the associated active treatment cost compared to the basecase assumption to treat the entire cohort until progression, as recommended in the respective Summary of Product Characteristics published by the European Medicine Agency.

PSA results in both comparisons showed little uncertainty. Based on the 1,000 simulations performed, the treatment with ipilimumab was highly likely to be more effective and more costly than dacarbazine because most of the points (99%), representing the joint incremental cost and QALYs, lay in the North-East quadrant around basecase results (Fig. 6A). The projected CEAC showed an 80% probability of ipilimumab to be considered cost-effective at a threshold of €65,000/QALY (Fig. 6B). For the comparison versus vemurafenib, all of the joint incremental costs and QALY points were located below the €25,000/QALY threshold with 76% being dominant (Figs. 7A and 7B).

Discussion

The aim of the study was to evaluate ipilimumab in the first line treatment of treatment-naive patients with advanced melanoma compared to dacarbazine and vemurafenib, the standard of care before the introduction of ipilimumab and a novel treatment, respectively. Based on the results of the current CE analysis in the Italian setting, ipilimumab was the dominant strategy against vemurafenib, given the incremental health benefits in terms of both LYs and QALYs

and with associated savings of €32,999. Such results were obtained using the ex-factory price of ipilimumab discounted based on confidential discount and Payment by Result agreements, as previously explained in the methods. Ipilimumab showed a clear improvement in health outcomes compared to dacarbazine, however ipilimumab was also associated with a higher overall cost, mainly because dacarbazine is currently granted free of charge to Italian hospitals. This resulted in an ICER of €38,975/LY and an ICUR of €49,466/QALY, in line with ICURs obtained in other EU countries (UK and Sweden). Deterministic and probabilistic sensitivity analyses showed little variability and impact of second order uncertainty on basecase results, however in the analysis vs. vemurafenib approximately 24% of iterations were located in the South-West quadrant showing some uncertainty in clinical outcomes.

The important role played by the acquisition cost of the compared active treatments in driving the results of the cost-effectiveness analysis was confirmed by the results of a pharmaceutical budget impact (BI) model developed from the Italian NHS perspective. The purpose of the model was to estimate the impact on the Italian NHS budget of the introduction of ipilimumab in the first line therapy of treatment-naive patients with advanced melanoma (stage IIIC and IV) over a five-year time horizon, taking into account the pharmaceutical costs of all lines of therapy. In the world without ipilimumab, it was assumed that 5% of all patients in first line therapy were treated within a clinical trial. Based on data obtained from Italian market research (37), it was considered that 58% of all BRAF mutation positive patients in first line treatment, estimated at approximately 40% (4), were treated with vemurafenib and that the remaining 37% of the market share was distributed among dacarbazine (16%), temozolomide (7%) and fotemustine (14%), which together represented the standard-of-care chemotherapy for advanced melanoma treatment-naive patients in Italy. Among the 60% wild BRAF patients, of the 95% not involved in clinical trials, 40% were treated with dacarbazine, 18% with temozolomide, and 37% with fotemustine (37). The world without ipilimumab was compared to a future world where ipilimumab were to be administered also in first line advanced melanoma treatment based on an assumed initial uptake of 11.2% among wild BRAF patients, set to increase to 56% after 5 years. In the world with ipilimumab, it was assumed that the majority of patients currently receiving ipilimumab as second-line therapy would be likely to receive it as first-line if it were available, and a 0% uptake was assumed among BRAF mutation positive patients. The progression to the second line systemic therapy was simulated based on PFS data obtained from each treatment clinical trial (9, 16, 38, 39). In 2014, the number of naive patients with melanoma stage IIIC and IV, eligible for treatment in Italy was estimated as 1,551 for first line and as 1,396 for second line (4, 40). The number of patients starting first line treatment increased over the years based on an annual melanoma incidence growth of 3.55% (4).

The budget impact of the introduction of ipilimumab as first line treatment of advanced melanoma was estimated to be €638,815 in 2014 and it increased to €3,685,186 in 2018, directly proportionate to ipilimumab uptake. The estimated budget corresponded to approximately 5.1% of the total expenditure to treat advanced melanoma in Italy, based on available market shares. The results of the BI model clearly showed that the considerable incremental health benefits associated with ipilimumab treatment come at the expense of a greater financial burden on the Italian NHS budget. It is important to clarify that the pharmaceutical cost saving associated with ipilimumab treatment compared to vemurafenib treatment was not observed in the results of BI analysis because it was assumed that 0% of BRAF mutation positive patients would start first line treatment with ipilimumab. If a positive uptake of ipilimumab were to be assumed among this group of patients, the BI results would improve markedly, e.g. at a 58% ipilimumab uptake a negative impact was observed indicating savings for the NHS.

To our knowledge, this was the first economic evaluation of ipilimumab in first line therapy of advanced melanoma in treatment-naive patients in Italy. As previously mentioned, the current study involved the adaptation of a global CE and BI model to the Italian healthcare setting. Such global models were developed to allow a homogeneous economic evaluation of treatment with ipilimumab across different countries and it could therefore be expected that the results from this study could be generalized to countries with similar active drug acquisition costs, as well as similar use of resources for the management of patients and treatment toxicities.

The current economic evaluation presents some limitations. The most important one relates to the lack of efficacy and safety data of ipilimumab 3 mg/kg from a single study and the lack of direct comparative evidence for ipilimumab 3 mg/kg versus dacarbazine and vemurafenib. To overcome the lack of comparative efficacy estimates, different statistical methods were developed based on the availability of data for each comparator. The statistical methods used in the basecase analysis were validated and selected by an advisory board. The alternative statistical methods were tested in a scenario analysis and results were in line with the basecase, thus showing overall robustness of methods despite the lack of head-to-head data. Nevertheless, some uncertainty can be observed around the results versus vemurafenib, where basecase dominance of ipilimumab is confirmed in 76% of iterations and the remaining 24% were located in the South-West quadrant. Note also that in other countries, due to different country-specific prices and resource use in the disease management, dominance was not shown. For example, the Evidence Review Group in England reviewed the UK analysis of ipilimumab vs. vemurafenib and obtained a positive ICER (£28,600/QALY), still below the willingness-to-pay (WTP) threshold however (41). Future research should focus on trying to address the comparative data gap by conducting either a head to head trial or, feasible in a shorter time, an indirect comparison between ipilimumab and vemurafenib, based on the most updated BRIM 3 results. To date, conducting an indirect comparison was not possible due to data issues; i.e. ipilimumab data did not have BRAF status, while vemurafenib data were affected by the allowance of crossover. Finally, a further limitation refers to the source of utility values, given that the study -024 assessed ipilimumab with a dosage of 10 mg/kg rather than 3 mg/kg and the study -020 involved a population which was not treatment-naive.

Recognising methodological limitations, the economic evaluation presented here represents the first attempt to as-

sess ipilimumab 3 mg/kg against dacarbazine and vemurafenib, in terms of costs and outcomes, in the first line therapy of advanced melanoma treatment-naive patients in Italy. The results of the cost-effectiveness analysis showed improved outcomes associated with ipilimumab compared to both comparators in terms of LYs and QALYs. Given that active drug acquisition cost was a main driver of results, the marginal incremental health benefit vs. vemurafenib was accompanied by an overall cost saving, which therefore suggests treatment with ipilimumab as the dominant strategy. By contrast, ipilimumab had positive ICER and ICUR results compared to dacarbazine, due to the higher acquisition cost. However, given the clear improvements in health benefits, AIFA, the Italian Medicine Agency, decided to grant a full reimbursement of ipilimumab by the National Health Service (23).

Acknowledgement

The authors of this paper acknowledge the work of Victor Barzey (IMS Health) et al. who developed the global version of the described cost-effectiveness model.

Diclosures

Financial support: This study was funded by Bristol-Myers Squibb.
Conflict of interest: Bristol-Myers Squibb contracted IMS Health to develop the model and write the manuscript. MDF, ML, AY are employees of IMS Health, PA received a consulting fee from Bristol-Myers Squibb and PDR is an employee of Bristol-Myers Squibb.

References

1. Ferlay J, Shin HR, Bray F, et al. GLOBOCAN 2008: Cancer Incidence and Mortality Worldwide. In: IARC Cancer Base No. 10. Lyon, France: International Agency for Research on Cancer 2010. Available at: http://globocan.iarc.fr (accessed May 20, 2014).
2. WHO. Health effects of UV radiation. In: World Health Organization website 2014. Available at: http://www.who.int/uv/health/uv_health2/en/index1.html (accessed January 25, 2014).
3. Miller AJ, Mihm MC. Melanoma. N Engl J Med. 2006;355:51-65.
4. AIRTUM and AIOM. I numeri del cancro in Italia 2014. Associazione Italiana Registri Tumori e Associazione Italiana di Oncologia Medica: Roma, 2014. Available at: http://www.registri-tumori.it/PDF/AIOM2014/I_numeri_del_cancro_2014.pdf. (accessed June 20, 2015).
5. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. Lancet. 2005;365:687-701.
6. Mozzillo N, Ascierto PA. Melanoma: the role of surgery in the era of new therapies. J Transl Med. 2014;12:195.
7. Serrone L, Zeuli M, Sega FM, et al. Dacarbazine-based chemotherapy for metastatic melanoma: thirthy-year experience overview. J Exp Clin Cancer Res. 2000;19:21-34.
8. Chapman PB, Hauschild A, Robert C, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAF V600E-mutated melanoma. Presented at the ASCO Annual Meeting, June 1-5, 2012; Chicago, IL. J Clin Oncol. 2012;30(15 suppl):abs 8502.
9. Hauschild A, McArthur G, Robert C, et al. Vemurafenib improves overall survival compared with dacarbazine in advanced BRAFV600-Mutated melanoma: updated results from a phase 3 randomized, multicenter trial. Presented at the 10th International Meeting of the Society for Melanoma Research, November 17-20, 2013; Philadelphia PA.
10. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAFV600E and BRAFV600K mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomized, open-label study. Lancet Oncol. 2014;15(3):323-32.
11. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23.
12. Maio M, Grob JJ, Aamdal S, et al. Five-year survival rates for treatment-naïve patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol. 2015;33(10):1191-6.
13. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015;33(17):1889-94.
14. 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(2):202-12.
15. Davies S, Tappenden P, Cantrell A. A review of studies examining the relationship between progression-free survival and overall survival in advanced or metastatic cancer. Decision Support Unit, ScHARR, University of Sheffield, Sheffield, 2012. Available at: http://www.nicedsu.org.uk/PFSOS(2804601).htm (accessed January 14, 2014).
16. Capri S, Ceci A, Terranova L, et al. Guidelines for economic evaluations in Italy: Recommendations from the Italian Group of Pharmacoeconomic Studies. Drug Inf J. 2001;35:189-201.
17. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364(26):2517-26.
18. Mapi Values: data on file.
19. 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(4):527-34.
20. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;1056:1-10.
21. Oxford Outcomes. Advanced Melanoma Resource Use and Costs in Europe. Oxford Outcome 2011: data on file.
22. Agenzia Italiana del Farmaco (AIFA, Italian Medicine Agency). Regime di rimborsabilità e prezzo di vendita del medicinale per uso umano «Zelboraf (vemurafenib)», autorizzata con procedura centralizzata europea dalla Commissione europea (Determina n. 500/2013 del maggio 2013). Gazzetta Ufficiale della Repubblica Italiana n. 129 del 4/06/2013. Available at: http://www.gazzettaufficiale.biz/atti/2013/20130129/13A04712.htm (accessed 20 July 2014).
23. Gazzetta Ufficiale della Repubblica Italiana n. 214 del 15/09/2014.
24. Agenzia Italiana del Farmaco (AIFA, Italian Medicine Agency). Linea Guida per la gestione dei rimborsi condizionati applicabili a specialità medicinali soggette a monitoraggio tramite Registri su piattaforma AIFA, per gli anni 2012 e 2013. Roma, 15 aprile 2014.
25. Agenzia Italiana del Farmaco (AIFA, Italian Medicine Agency). Determina Deticene del 28 maggio 2007. Available at: http://www.agenziafarmaco.gov.it/sites/default/files/111.123319.1180955101510ed46.pdf (accessed 10 June 2014).
26. Ministero della Salute. Remunerazione delle prestazioni di assistenza ospedaliera per acuti, assistenza ospedaliera di

riabilitazione e di lungodegenza post acuzie e di assistenza specialistica ambulatoriale. Supplemento ordinario n. 8 alla Gazzetta Ufficiale n. 23 del 28/01/2013.
27. Garattini L, Castelnuovo E, Lanzeni D, et al. Durata e costo delle visite in medicina generale: il progetto DYSCO. Farmacoeconomia e Percorsi Terapeutici. 2003;4:109-14.
28. Zucco F. Hospice in Italia: Seconda Rilevazione Ufficiale. Bologna: Bononia University Press, 2010.
29. Ministero dell'Economia e delle Finanze. Commissione Tecnica per la Finanza Pubblica. Libro verde sulla spesa pubblica. Roma, 6 settembre 2007.
30. Ministero della salute. Progetto Mattoni SSN. Pronto Soccorso e Sistema 118: Proposta metodologica per la valutazione dei costi dell'emergenza. Roma, 2007.
31. Agenzia Italiana del Farmaco (AIFA, Italian Medicine Agency). Medicinali di classe H in commercio. Roma, 15 luglio 2014. Available at: http://www.agenziafarmaco.gov.it/it/content/tabelle-farmaci-di-classe-e-h-al-15072014 (accessed 30 July 2014).
32. Agenzia Italiana del Farmaco (AIFA, Italian Medicine Agency). Liste di trasparenza farmaci equivalenti. Roma, 15 luglio 2014. Available at: http://www.agenziafarmaco.gov.it/sites/default/files/elenco_farmaci_equivalenti_principio_attivo_15072014.pdf (accessed 30 July 2014).
33. Agenzia Italiana del Farmaco (AIFA, Italian Medicine Agency). Medicinali di classe A reperibili nel normale ciclo distributivo. Roma, 15 luglio 2014. Available at: http://www.agenziafarmaco.gov.it/it/content/tabelle-farmaci-di-classe-e-h-al-15072014 (accessed 30 July 2014).
34. ISTAT. FOI(nt) - Indici nazionali dei prezzi al consumo per le famiglie di operai e impiegati - Generale al netto dei tabacchi. Available at: http://www.istat.it/it/archivio/30440 (accessed 10 June 2014).
35. Rowen D, Young T, Brazier J, Gaugris S. Comparison of generic, condition-specific and mapped health state utility values. Discussion Paper. HEDS Discussion Paper (11/06). (Unpublished). HEDS 2011. Available at: http://eprints.whiterose.ac.uk/43216/ (accessed 15 December 2013).
36. Briggs A. Handling uncertainty in economic evaluations and presenting the results. In: Drummond M, McGuire A (eds). Economic Evaluation in Health Care: Merging Theory with Practice. New York: Oxford University Press, 2001:172-214.
37. IMS Health: data on file.
38. Avril MF, Aamdal S, Grob JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. J Clin Oncol. 2004;22:1118-25.
39. Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol. 2000;18(1):158-66.
40. Lebbe C, Lorigan P, Ascierto P, et al. Treatment patterns and outcomes among patients diagnosed with unresectable stage III or IV melanoma in Europe: A retrospective, longitudinal survey (MELODY study). Eur J Cancer. 2012;48:3205-14.
41. NICE. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance [TA319]. July 2014. Available at: https://www.nice.org.uk/guidance/ta319 (accessed March 2016].