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

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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
Ipilimumab in the first line treatment of advanced 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 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. 1), 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.
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

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**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 Naive 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 |
## 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 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)                        |
| Progressive disease                | 0.84 EORTC method based on CA184-024 (17)                             |
| Death                              | 0.76 EORTC method based on MDX010-020 (Tab. I)                        |
|                                   | 0.83 EORTC method based on CA184-024 (17)                             |

**OS** = overall survival; **PFS** = progression free survival.
drug cost for all patients who do not benefit from treatment (23, 24). Following the official statement “Determina Detice” 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), 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.

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-attribute 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

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**TABLE III - Active drug acquisition cost per treatment cycle**

| Dosage          | Unit data                                                                 | Source                      |
|-----------------|---------------------------------------------------------------------------|-----------------------------|
| 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 x 960 mg tablets per day                                                 | BRIM 3 trial                |

**List drug cost per cycle (including official discounts) - including wastage**

| Dosage          | Unit data  | Source                          |
|-----------------|------------|---------------------------------|
| 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**

| Dosage          | Unit data  | Source                          |
|-----------------|------------|---------------------------------|
| 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)
### TABLE IV - Cost of management of patients across disease stages

| Management of patients with stable disease | Unit cost* (€ 2014) | Resource use | Proportion of patients | Cost applied in the model (€) |
|-------------------------------------------|---------------------|--------------|------------------------|-----------------------------|
| 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                      | €60.00                      |
| 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 | Unit cost* (€ 2014) | Resource use | Proportion of patients | Cost applied in the model (€) |
|-----------------------------------------------|---------------------|--------------|------------------------|-----------------------------|
| 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       | Unit cost* (€ 2014) | Resource use | Proportion of patients | Cost applied in the model (€) |
|-----------------------------------------------|---------------------|--------------|------------------------|-----------------------------|
| 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       | Unit cost* (€ 2014) | Resource use | Proportion of patients | Cost applied in the model (€) |
|-----------------------------------------------|---------------------|--------------|------------------------|-----------------------------|
| 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) |
| Prednisonone         | 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                   | €187.99                     |
| 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                       | 0.98                        | €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).
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Table VII - Assumptions explored in the scenario analysis

| Assumption                                      | Basecase assumption | Alternative assumption |
|-------------------------------------------------|---------------------|------------------------|
| Ipilimumab efficacy dataset                     | Chemo-naive         | Chemo-naive + observation 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.

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 influential 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
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
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.

### 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.
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 pharmacoeconomic 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 -Q24 assessed ipilimumab with a dosage of 10 mg/kg rather than 3 mg/kg and the study -Q20 involved a population which was not treatment-naive.

Recognising methodological limitations, the economic evaluation presented here represents the first attempt to as-
Iressa ipilimumab 3 mg/kg against dacarbazine and vemurafenib, in terms of costs and outcomes, in the first line therapy of advanced melanoma treatment-naïve 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).

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