Medical and Clinical Research: Open Access

*Research Article*

# Disease Management and Resource Use for the Management of Melanoma stage IIIc or IV Positive for BRAF V600 Mutations in Greece

**Carayanni V[1*], Gogas H[2], Bafaloukos D[3], Boukovinas I[4], Latsou D[5], Stamuli E[5], Hatzikou M[5]**

[1]*Laboratory of Statistical modelling –Sepeh-lab, University of Western Attica, Athens, Greece.*
[2]*First Department of Medicine, National and Kapodistrian University of Athens, Greece.*
[3]*Metropolitan Hospital, Athens, Greece.*
[4]*Bioclinic Hospital, Thessaloniki, Greece.*
[5]*Pharmecons Easy Access, Athens, Greece.*

## ABSTRACT

**Objective:** Melanoma is one of the most aggressive cancers and is responsible for the majority of skin cancer deaths, with the presence of metastases prognostic for poor survival. At a time when most cancer incidences are falling, the annual incidence of melanoma has risen as rapidly as 4-6% in many European countries, with a substantial economic burden in advanced stages. The objective of this study is the investigation of treatment pathways and healthcare resource use related to advanced BRAF-mutated melanoma in Greece.

**Methods:** This study is based on the information collected by an expert panel comprising of 3 oncologists of major public and private melanoma clinics around Greece. A 3-round survey was undertaken, according to a modified Delphi method. The treatment phases studied were: pre-progression; disease progression and terminal care. Oncology drug costs, medical visits, laboratory tests, imaging examinations, hospitalization and concomitant medications were the resources considered in the context of the Greek National Services Organization (EOPYY).

**Results:** The most common management scenario (80% of cases) in Greece for patients of stage IV BRAF V600 mutated melanoma was: targeted therapies as first line treatment at 95%, followed by immunotherapies at 100% as second line as well as third line treatment at 65% of cases. The weighted annual cost of treatment was 89.215,78 €, (90%CI:62,451.05; 115,980.51) for first line treatment at list price and around 41.584,50 (90%CI:29,109.15; 54,059.85) based on the negotiated price. At second line, the cost of treatment has been estimated between 15,704.272 (90%CI:10,992.990; 20,415.553) and 19,800.92€, (90%CI: 16,489; 30,622) for the two most common management scenarios for immunotherapies. For third line treatment the cost was 37,778.93 (90%CI 26,445.25; 49,112.61€) for the mostly used management scenario (50% ipilimumab).

**Conclusions:** Metastatic BRAF mutant melanoma requires prolonged and costly treatment with new therapies shown to substantially increase life expectancy. Identifying the appropriate treatment options in order to optimize health outcomes should be an important priority in healthcare system.

## KEYWORDS

Skin cancer; Melanoma; Mutations; BRAF; Greece.

## Corresponding Author Information

Carayanni V
Laboratory of Statistical modelling –sepeh-lab, University of Western Attica, Athens, Greece, E-mail: vkaragian@uniwa.gr.

**Received:** December 30, 2020; **Accepted:** January 20, 2021; **Published:** January 28, 2021



**Citation:** Carayanni V, Gogas H, Bafaloukos D, Boukovinas I, Latsou D, et al. Disease Management and Resource Use for the Management of Melanoma stage IIIc or IV Positive for BRAF V600 Mutations in Greece. Med Clin Res Open Access. 2021; 2(1):1-8.

## Introduction

Cutaneous melanoma is a form of skin cancer, also known as melanoma or malignant melanoma. It is one of the most aggressive cancers and is responsible for the majority of skin cancer deaths [1-3]. Melanoma follows a slow but steady progression from benign melanocytic nevi to metastatic melanoma [4]. The majority of nevi are benign, melanocytic neoplasms seen on the skin of most people, which arise from a controlled proliferation of normal melanocytes. They usually appear by 4 to 5 years of age, increase in pigmentation during puberty, and involute in the elderly population (seventh to eighth decade of life). Also, 38% of melanoma patients are younger than 55 years, leading to a significant impact on productivity [5].

Melanoma develop from pre-existing nevi in about 20-40% of cases [6], while the remaining cases occur de novo. Patients with primary melanoma, are categorised into Stages I and II [7]. On the other hand, Stage III includes lesions with histopathologically documented involvement of regional lymph nodes or the presence of in-transit or satellite metastases. Stage IV melanoma is defined by the presence of distant metastases [8,9].

Cutaneous malignant melanoma represents a critical public health issue. A global incidence of melanoma in 2015 was estimated at 351,880 new cases with an age-standardised rate of five cases per 100,000 persons [9]. In 2012, in the European Union (EU-27), melanoma of the skin was the 7th most common cancer [10]. The incidence has been rising over the past decades, and more particularly in Northern Europe, with reported average annual percent increases of up to 4% in this region [11-13]. The vast majority of invasive melanoma cases are diagnosed at an early stage (>90%). Only 5–10% of patients are diagnosed with locally advanced tumours and 1–5% with unresectable or metastatic disease [14]. The frequency of BRAF V600 mutations in metastatic melanoma patients has been reported to range from 40 to 60% in Europe [15-17].

In the disease management of patients with BRAF V600 mutation-positive metastatic melanoma, an important knowledge gap has been identified on the appropriate sequence of immunotherapy and BRAF/MEK inhibition [18]. So far, there is no data from prospective randomized trials investigating the best sequence. In Europe, the ESMO guidelines, are the most important international treatment guidelines that are shaping the management of melanoma patients in clinical practice; Based on the current treatment algorithm published in September 2019 the recommendation for first-line treatment of metastatic or unresectable cutaneous melanoma, stage III/IV, in BRAF wild-type patients, are immunotherapy with either the anti-PD1 treatments pembrolizumab or nivolumab,PD-1 blockade (nivolumab) combined with CTLA-4 blockade (ipilimumab) and, in addition for BRAFV600-mutated melanoma, BRAF inhibition (vemurafenib, dabrafenib, encorafenib) combined with MEK inhibition (cobimetinib, trametinib, binimetinib) [19]. First-line decision between targeted therapies or immunotherapies is currently being studied to define the best sequencing combination treatment in terms of overall survival (OS), the primary efficacy variable. No direct randomised comparison exists between the two approaches, but meta-analyses suggest that, despite better outcome within the first 12 months for targeted therapies, immunotherapy patients may have a better survival after 1 year. In BRAF V600 mutation-positive tumours, immunotherapy can be given after BRAF inhibition and vice versa.

Melanoma is one of the most costly cancers to diagnose, treat, and monitor [20]. Costs increase with the stage of the disease, with metastatic melanoma being associated with the highest costs. The healthcare cost of metastatic melanoma in France was estimated to be €27 million (~€1.700 per stay), the main drivers being surgery (27%), chemotherapy (24%), and evaluations during follow up (12%) for the year 2004 [21]. In Sweden, between 2005 and 2012, the 1-year post diagnosis cost was estimated to be €8,390 per patient. Costs differed greatly between stages at diagnosis rising from €5,448 for stage I to €32,505 for stage IV [22]. According to a recent European study performed by Krensel et al. [23] on the metastatic melanoma cost of illness regarding data for 2012, the average annual cost per patient for Greece based on GDP, has been estimated at €2.854 and the total annual direct cost for all metastatic melanoma patients €1.589.000.

The aim of this study was to map the treatment pathway in melanoma stage IV positive for BRAF V600 mutations in Greece and to investigate the health care resource use associated with the management of the disease.

## Methods

The methodology followed was based on a two-step approach. First, the local treatment pathways and associated resource use were identified. Secondly, the total costs for each pathway were estimated, by assigning unit costs to resource use items.

### Local treatment pathway and resource use

An expert panel was convened, comprised of 3 melanoma experts from major Greek Centers treating patients with advanced melanoma. The patient pool that the physicians represented has been estimated at 620 patients suffering from metastatic melanoma stage IV per year. For the purposes of data collection, a questionnaire was developed, including questions on epidemiology, resource utilization, treatment algorithm for the management of melanoma stage IV positive for BRAF V600 mutations, as well as data on the management of adverse events in Greece.

Data collection was performed during an advisory board with the experts. The data elicitation method that was used was a modified Delphi technique, which is internationally recognized as a reliable, qualitative method for evidence generation [24]. This corresponds to the first phase of a SHELF elicitation for the most important quantities, using the tertile method assessment of individual judgments [24,25]. There is evidence that tertiles are elicited more accurately than quartiles. Therefore, tertiles do not suffer as much from overconfidence and anchoring [26]. Each expert should specify their upper and lower tertiles by considering the range from L (lower limit) to U (upper limit) and dividing it into three

equally likely intervals. In place of the second phase the experts' judgments and rationales are relayed anonymously back to the experts and they are asked to provide revised judgments [27,28]. In the second round, Delphi iteration process took place.

We have used behavioral aggregation approach which enables the experts' interaction to achieve consensus with the presence of a facilitator in order to ensure that individual as well as group biases do not detract from the benefits of pooling knowledge and sharing multiple perspectives [29]. We have elicited a single 'consensus' distribution from the experts. Experts were invited to revise their original judgements having seen what the other experts think. The group judgements were used as a basis for fitting a probability distribution, that is the outcome of the elicitation process, and so must be selected carefully and with full approval of the experts [28,29].

The micro-costing method was followed for the estimation of costs. The method has been demonstrated to be particularly useful for estimating the costs of new interventions, for interventions with large variability across providers, and for estimating the true costs to the health system and to society.

Only direct medical costs were considered, which consisted of pharmaceutical costs associated with visits to outpatient hospital settings and primary case visits, hospitalization costs for the management of adverse events, costs for laboratory and imaging tests. The cost analysis has been estimated on an annual basis.

## Unit costs

In order to estimate pharmaceutical costs, the average price per mg was calculated based on hospital prices per package including 5% price reduction (EOPYY reimbursement price), for all packages marketed in Greece (Drug Price Bulletin, Ministry of Health, December 2019).

For dosing schedules dependent on body weight or surface area, an average body weight of 80 kg and body surface area of 1.65m$^2$ were used. Costs associated with visits to private physicians were retrieved from publicly available sources (Ministry of Health, EOPYY). It is significant to mention that according to Ministry of Health (2014) 7,1% of patients visit afternoon outpatient department, but the cost for outpatients' department is zero in the context of the Greek National Services Organization (EOPYY). Hospitalization costs were estimated on the basis of the diagnosis related groups (DRG: Δ029) reimbursed by Social Insurance Funds for managing melanoma (Government Gazette B 946/27 March 2012). Also, cost for intensive care unit, high dependency unit and hospital clinic are published by the Ministry of Health (http://www.moh.gov.gr). Unit costs for laboratory and imaging tests were retrieved from publically available sources (Ministry of Health, EOPYY). The unit costs for pharmaceutical, hospital, medical treatment, lab and imaging tests and management of metastases are listed in Table 1.

| Pharmaceutical costs | | Hospital prices, Unit cost (€) |
|---|---|---|
| Dabrafenib [CAPS, 75MG/CAP (BTx28)] | | 1,042.72 |
| Trametinib [F.C.TAB, 2MG/TAB (BTx30)] | | 3,459.16 |
| Vemurafenib [F.C.TAB, 240MG/TAB (BTx56)] | | 1,099.07 |
| Cobimetinib [F.C.TAB, 20MG/TAB, (BTx63)] | | 4,318.41 |
| Ipilimumab [C/SSOLIN, 5MG/ML, (BTX1VIALX20)] | | 2,619.16 |
| Pembrolizumab [C/S.SOL.IN,50MG/VIAL (BTx1 VIAL)] | | 1,395.57 |
| Nivolumab [C/S.SOL.IN, 10MG/ML (BTx1 VIAL x 1)] | | 378,14 |
| Dacarbazine [PS.SOL.INF, 100MG/VIAL, (BTx1VIAL+10)] | | 2,23 |
| Temozolomide [CAPS, 100MG/CAP (BTx5)] | | 44,05 |
| Fotemustine [PS.SOL.INF, 208MG/VIA, (BTX1VIAL+1A)] | | 186,70 |
| Cisplatin [SOL.INF, 100MG/100ML (BT x 1 VIAL x 1)] | | 22,71 |
| Carboplatin [SOL.INF, 150MG/15ML (BT x 1 VIAL x 1)] | | 15,72 |
| Docetaxel [C/S.SOL.IN, 80MG/4ML (BTx1 VIAL x4)] | | 62,29 |
| Paclitaxel [C/S.SOL.IN, 6MG/1ML (BTx1 VIAL)] | | 64,89 |
| Costs for outpatient department and private practice | Private physicians visit* | 10 |
| Hospitalization costs | Intensive Care Unit | 200 |
| | High Dependency Unit | 93.91 |
| | Melanoma DRG mean price | 2,171 |
| | Daily hospitalization | 161 |
| Unit costs for laboratory tests | Complete blood count lab test | 2.88 |
| | Comprehensive metabolic panel lab test | 52.1 |
| | LDH | 4.75 |
| | Thyroid Function Panel | 53.46 |
| | ACTH (Cortrosyn) stimulation test (or morning cortisol and ACT) | 12.38 |
| | FSH, LH, or estradiol or morning testosterone | 12.61 |
| | Prolactin | 12.38 |
| | GH provocative testing | 12.38 |
| Unit costs for imaging tests | Upper / Lower abdomen CT | 128 |
| | Chest CT | 64 |
| | Brain MRI | 213.26 |
| | Brain CT | 64 |
| | PET / CT scan | 80 |
| | Skeletal scintigraphy (bone scan) | 34.42 |
| | Ultrasound | 8.28 |
| | Chest X-ray | 10 |
| | Thyroid ultrasound | 8.28 |

**Table 1:** Unit costs of resource use for the management of melanoma.

*private physician contracted with EOPYY (National Organization for Health Care Services Provision) only for prescription.
No cost for emergency department, palliative care unit and home care unit.

It is important to mention that as first line treatments, only the combination of Dabrafenib and Trametinib was administered due to the negotiation of the sick fund EOPYY which took place in March 2018 for BRAF inhibitors and Dabrafenib & Trametinib were positioned first line in the treatment algorithm in Greece for a 2-year duration.

Based on the negotiation, the two scenarios were used in order to estimate the treatment cost of the combination of Dabrafenib and Trametinib, which are the following: a) list price scenario which is only indicative and b) «negotiated price» scenario (which remains confidential), with a 45% price reduction which was based on the amount of rebates/clawback of a new active substance in Greece. The scenario with the lower price was important to perform in order for the analysis to be as realistic as possible.

### Statistical Analysis

Individual and consensus probability distributions were elicited. Probability distribution was assigned to each expert's judgement, and feedback was obtained. A single probability distribution was elicited from the group of experts for each resource use variable, using behavioral aggregation. Descriptive statistics to summarize the elicited median values, tables of fitted probabilities for each type of individual and consensus probability distribution and a variety of graphs were used. Cost values were attributed to elicited resource use values and cost distributions were fitted. R program (SHELF 4.0 package) was used. Results are presented as medians with 90% confidence intervals (5th and 95th percentiles).

## Results

### Individual and consensus fitted distributions

Different probability distributions such as normal, lognormal and beta were the best fitted distributions for each expert and we choose to use the beta instead, given it has the appropriate bounds for our qualitative/discrete data. Normal distributions presented the best fit for quantitative resource use data and Gamma and lognormal distributions presented the best fit for cost data. As an example, Figure 1a and b present the three individual distributions with linear pool and the consensus distribution of the proportion of patients undergoing brain CT scan. The results of all fitted distributions are presented in Appendix 1, Supplementary Material.

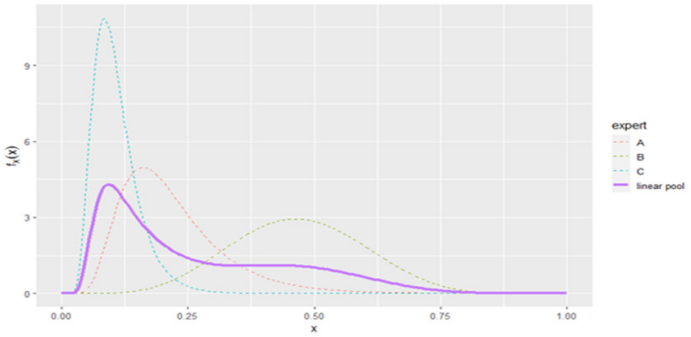


**Figure 1a:** The three fitted distributions (proportion of patients undergoing brain CT scan) and an equal-weighted linear pool.

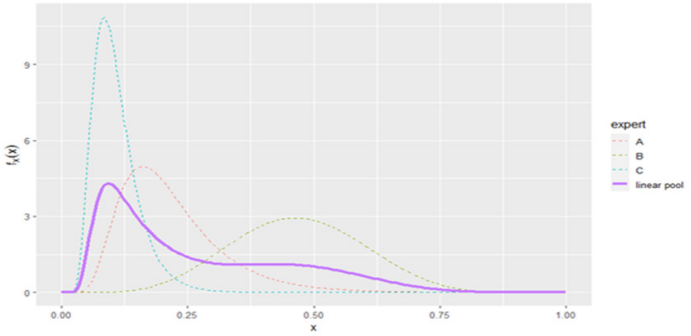


**Figure 1b:** The fitted consensus distributions (proportion of patients undergoing brain CT scan) and the fitted probabilities.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 0.6 | 0.33 | 0.332 | 0.332 | 0.329 | 0.328 | 0.328 | 0.336 |
| 0.7 | 0.5 | 0.497 | 0.497 | 0.502 | 0.504 | 0.504 | 0.489 |
| 0.8 | 0.66 | 0.662 | 0.662 | 0.659 | 0.658 | 0.658 | 0.665 |

### Treatment pathways

The treatment pathways that Greek physicians follow for patients Stage IV is presented at table 2. Based on current clinical practice, 100% of patients IV receive Dabrafenib & Trametinib as 1st line treatment. In stage IV Pembrolizumab or combination of Ipilimumab and Nivolumab were 2nd line treatment options. Finally, the 3rd line the treatment choices vary, but half of physicians administer Ipilimumab (Table 2).

| STAGE IV | | |
|---|---|---|
| **1st line** | Dabrafenib & Trametinib | 100% |
| **2nd line** | Nivolumab | 40% |
| | Pembrolizumab | 40% |
| | Ipilimumab & Nivolumab | 20% |
| **3rd line** | Dabrafenib & Trametinib | 5% |
| | Cobimetinib & Vemurafenib | 10% |
| | Ipilimumab | 50% |
| | Chemotherapy | 20% |
| | Ipilimumab & Nivolumab | 15% |

**Table 2:** Treatment pathway for melanoma in stage IV positive for BRAFV600 mutations.

### Health Care Resource Usage by Treatment Line in Stage IV

In stage IV 100% patients who receive 1st line therapies visit public outpatient department for regular monitoring approximately 12 times with 90% confidence intervals: (8;16) (the cost is zero for EOPYY). Also, and private clinic 8 (6;10) times per year. In 2nd line therapies over 90% (81%;99%) of patients visit public outpatient department approximately 15 times (11;20) and private clinic 8 times (6;10) per year. The 97% of patients (90%;100%). In 3rd line therapies visit public outpatient department14 times (10;18) and 75% (53%;97%) of patients visit private clinic7 (5;10) times per year. All patients who receive immunotherapies or chemotherapy, they are daily hospitalized for drug infusion or

routine examination.

Regarding the additional health care resources, which are used by patients in immunotherapies or chemotherapy, experts agree that 10% (7%;13%) of patients were admitted to the Intensive Care Unit and the same percentage to the High Dependency Unit once a year and with mean duration of hospitalization 4 days (3;5). 20% (14%;26%) of melanoma patients were hospitalized due to disease progression once a year and with mean duration of hospitalization 4 days. (3;5) Also,20% (14%;26%) visit the emergency department and palliative care unit approximately 2.5 (2;3) times per year.

The laboratory exams differ far as the types and frequency per year among targeted therapies, immunotherapies and chemotherapy. However, there are no differences across all over the treatment lines. Specifically, all patients who receive targeted therapies perform complete blood count 15. Times (11;20) per year, 13 times (9;17), comprehensive metabolic panel and 15 times (11;20) LDH per year. The most common laboratory exams which are mainly performed by patients who receive immunotherapies are complete blood count, 9 times (6;11) per year, comprehensive metabolic panel 13 times (9;17), LDH, 14 times (10;18), Thyroid Function Panel, 9 times (6;12) annually. Chemotherapy patients perform complete blood count and LDH 13 times, (9;17) comprehensive metabolic panel lab test 11 times (8;14) per year.

The imaging tests also vary among targeted therapies, immunotherapies and chemotherapy, regardless of treatment lines. The most common imaging tests which are mainly performed by patients who receive targeted therapies are Upper / Lower abdomen CT and Chest CT 6 times (4;8) and Ultrasound 5 times (4;7) per year. The majority of patients who are treated with immunotherapies or chemotherapy, perform Upper / Lower abdomen CT and Chest CT approx. 6 times (4;8) yearly and Brain MRI 3 times (2;4).

Furthermore, 45% (32%;59%) of patients at the end of life are hospitalized approximately 2.5 times (2;3) per year with average length of stay in hospitals 7 days (5;8) and 80% (65%; 95%) are daily hospitalized approximately 2.5 (2;3) times per year. All patients receive in their home supportive treatments, antibiotics, anti-inflammatory, antiemetics, analgesics, antidepressants, steroids, laxatives etc. The most common imaging tests are Chest X-ray with a median of 8 times (6;10), Ultrasound 8 times (6;10) and Brain MRI with a median of 4 times (3;5) annually. Approximately on a yearly basis half of the patients perform Complete blood count 9 times (7;11), Urine test 8 times, (6;10) Comprehensive metabolic panel lab test 10 times (7;13), LDH 10 times (7;13) annually.

## Direct Costs by Line in Stage IV

The median yearly cost of treatment for a patient of stage IV at first line with Dabrafenib and Trametinib has been estimated at €89.215.78, but according to the price scenario due to the negotiation process, the cost drops to €41.584.50. Results are presented on Table 3 with 90% confidence intervals.

| | 1st Line | |
|---|---|---|
| | Median (5th percentile; 95th percentile) | |
| | Dabrafenib & Trametinib | |
| | (list price) | price scenario |
| Annual Treatment Costs | 86,516.88 (60,561.82; 112,471.94) | 38,932.60 (35,039.70; 42,826.30) |
| Health Care Visits Costs to Hospital Outpatient departments | 0.00 | 0.00 |
| Health Care Visits Costs to Private physicians | 80.00 (68.48;91.52) | 80.00 (68.48;91.52) |
| Cost of Laboratory Exams | 767.43 (537.20 ;997.66) | 767.43 (537.20; 997.66) |
| Cost of Imaging Tests | 1,851.47 (1.296,03; 2,406.91) | 1,851.47 (1,296.03; 2,406.091) |
| TOTAL cost per patient | 89,215.78 (62,451.05; 115,980.51) | 41,584.50 (29,109.15; 54,059.85) |
| Patients shareper treatment* | | 100* |
| Weighted cost per patient share | 89,215.78 (62,451.05; 115,980.51) | 41,584.50 (54,059.85; 29,109.15) |

**Table 3:** Stage IV– Cost Per patient for 1st Line Treatment (in euro).

The yearly cost in 2nd line has been estimated at €19,800.92 for Pembrolizumab, €15,704.272 for Nivolumab and €16,675.356 for combination of Ipilumumab and Nivolumab (Table 4).

| | 2nd line | | |
|---|---|---|---|
| | Median (5th percentile; 95th percentile) | | |
| | Pembrolizumab | Nivolumab | Ipilimumab & Nivolumab |
| Annual Treatment Costs | 43,245.79 (30,272; 56,220) | 32,956.21 (23,069.34; 42,843.07) | 77,054.31 (53,938; 100,170) |
| Health Care Visits Costs to Hospital Outpatient departments | 0.00 | 0.00 | 0.00 |
| Health Care Visits Costs to Private physicians | 24.00 (16.800; 31.200) | 72.00 (50.400; 93.600) | 90.00 (49.84; 92.56) |
| Cost of Laboratory Exams | 1,441.95 (1,009; 1,875) | 1,441.95 (1,009; 1,875) | 1,441.95 (1,009; 1,875) |
| Cost of Imaging Tests | 2,858.52 (2,000.4; 3,716.0) | 2,858.52 (2,000.4; 3,716.0) | 2,858.52 (2,000.9; 3,716.) |
| Hospitalization | 1,932 (1,352.4-2,511.6) | 1,932 (1,352.400; 2511,6) | 1,932 (1,352.400; 2511,6) |
| TOTAL cost per patient | 49,502.31 (34,691; 64,427) | 39,260.68 (27,482.476; 51038.884) | 83,376.78 (58,297.96; 108,267.64) |
| Patients share per treatment* | 40% | 40% | 20% |
| Weighted cost per patient share | 19,800.92 (16,489; 30,622) | 15,704.272 (10,992.990; 20,415.553) | 16,675.356 (12,447.71; 23,117) |

**Table 4:** Stage IV– Cost Per patient for 2nd Line Treatment (in euro). *based on Table 2

| | 3rd line | | | | | |
|---|---|---|---|---|---|---|
| | Median (5th percentile; 95th percentile) | | | | | |
| | Dabrafenib & Trametinib | Dabrafenib & Trametinib (price scenario) | Cobimetinib & Vemurafenib | Ipilimumab | Chemotherapy | Ipilimumab & Nivolumab |
| Annual Treatment Costs | 86,516.88 (60,561 112,472) | 38,932.60 (27252.82;50612.78) | 95,658.96 (66,961.27; 124356.65) | 69,567.64 (48,697.35; 90,437.93) | 342 (239.40; 444.60) | 77,054.31 (53,938,02; 100,170.6) |
| Health Care Visits Costs to Hospital Outpatient departments | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| Health Care Visits Costs to Private physicians | 69.33 (48.53; 90.13) | 69.33 (48.53; 90.13) | 69.33 (48.53; 90.13) | 26.67 (18.67; 34,67) | 24.00 (16.80; 31.20) | 71.20 (49.84; 92.56) |
| Cost of Laboratory Exams | 767.43 (537.20; 997.66) | 767.43 (537.20; 997.66) | 767.43 (537.2; 997.66) | 1,441.95 (1,009.37; 1,874.54) | 657.47 (460.23; 854,71) | 1,441.95 (1,009.37; 1,874.54) |
| Cost of Imaging Tests | 1,841.71 (1,289.20; 2,394.22) | 1,841.71 (1,289.20; 2,394.22) | 1,841.71 (1,289.20; 2,394.22) | 1,696.23 (1.187.36; 2,205.10) | 1,847.57 (1,293. 30; 2401.84) | 1,847.57 (1,293.30; 2401.84) |
| Daily Hospitalization | 0.00 | 0.00 | 0.00 | 1,932 (1352,40; 2511,60) | 1,932 (1352,40; 2511,60) | 1,932 (1352,40; 2511,60) |
| Hospitalization | 896.57 (627.59; 1165.54) | 896.57 (627.59; 1165.54) | 896.57 (627.59; 1165.54) | 896.57 (627.59; 1165.54) | 896.57 (627.59; 1165.54) | 896.57 (627.59; 1165.54) |
| TOTAL cost per patient | 90,091.92 (63,064.344; 117,119) | 42,507.76 (29,755.36; 55,259.9) | 99,234.00 (69,463.8; 12004,20) | 75,561.86 (52,893,30; 98,230.42) | 5,699.61 (3,989.73; 7,409.49) | 82,436.687 (57,705.68; 107,167.6) |
| Patients share per treatment* | 5% | 5% | 10% | 50% | 20% | 15% |
| Weighted cost per patient share | 4,504.96 (3,153.217; 5,855.975) | 2,125.383 (1,487.77; 2,763.00) | 9,923.4 (6,946.38; 12,900.42) | 37,778.93 (26,445.25; 49,112.61) | 1,139.9288 (975.77; 1,304,07) | 12,365.503 (8,655.85; 16.075/15) |

**Table 5:** Stage IV – Cost Per patient at 3rd line (in euro) *. *based on Table 2

In the 3rd line of stage IV, the yearly cost has been estimated at €4,504.596 for Dabrafenib & Trametinib patients, €9,923.4 for Cobimetinib and Vemurafenib, €37,778.93 for Ipilumumab, €1,139.929 for Chemotherapy patients and €12,365.503for combination of Ipilumumab and Nivolumab (Table 5).

Regarding the end-of-life stage, has been estimated at €6,664.27 and the most important cost component is hospitalization (82%) (Table 6). The gamma fitted distribution and fitted probabilities of the total cost are presented in Figure 2.

| End of life care | Median (5th percentile; 95th percentile) |
|---|---|
| Supportive care | 67.95 (47.565;88.335) |
| Cost of Laboratory Exams | 344.61 (241.227;447.993) |
| Cost of Imaging Tests | 771.35 (539.945;1,002.755) |
| Hospitalization | 5,480.36 (3,836;7,124) |
| TOTAL COST | 6,664.27 (4,664.8;8,663.2) |

**Table 6:** Total cost of End of life: median and 90% confidence intervals.

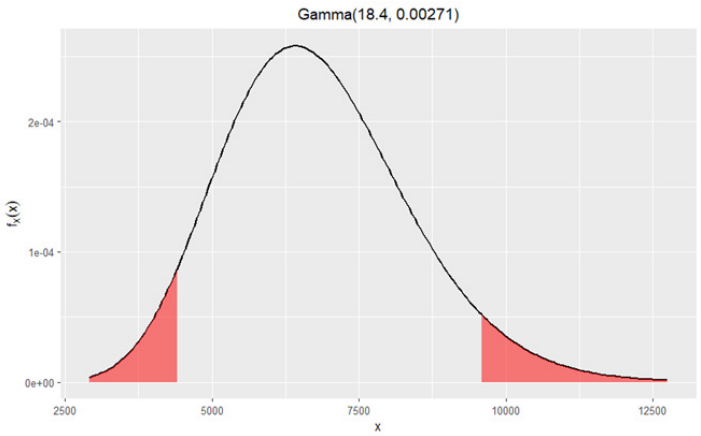


**Figure 2:** Probability distribution of total cost of End of life and fitted probabilities.

| - | elicited | normal | t | gamma | lognormal | logt | beta |
|---|---|---|---|---|---|---|---|
| 5997.6 | 0.33 | 0.332 | 0.332 | 0.33 | 0.329 | 0.329 | 0.342 |
| 6664.27 | 0.50 | 0.497 | 0.497 | 0.50 | 0.502 | 0.502 | 0.480 |
| 7330.4 | 0.66 | 0.662 | 0.662 | 0.66 | 0.659 | 0.659 | 0.669 |

## Discussion

The present study investigated and provided an overall view of the treatment pathway followed in the Greek health care system for a typical patient with melanoma IV positive for BRAF V600 mutations along with the resource use and associated costs of the overall patient journey. To the best of our knowledge, this is the first study to analytically map all costs associated with the management of the disease in the local health care setting.

At the time of the study all patients (100%) with melanoma at stage IV received combination of Dabrafenib & Trametinib as 1st line treatment due to the negotiation of the sick fund EOPPY. In 2nd 40% receive Nivolumab or Pembrolizumab and the rest combination of Ipilimumab & Nivolumab at stage IV. Finally, in 3rd line the majority of patients receive Ipilimumab.

Concerning health care resource usage stage IV, more than 90% of patients who receive targeted therapies or immunotherapies visit public outpatient departments or private physicians without significant difference in annually frequency of visits. Patients on targeted therapies and immunotherapies perform similar number of laboratory and imaging tests, apart from Ipilimumab which requires less number of imaging tests. However, chemotherapy patients require more imaging and laboratory tests.

Before 2011, when a series of innovative drugs in metastatic melanoma patients began reaching the market, medical costs were lower due to limited treatment options [19-21]. The cost associated with new therapies for melanoma both immunotherapies and targeted therapies, are the major driver of an increase in the total cost of managing melanoma compared to the situation before 2011 [30].

It is clear that the magnitude of the costs associated with advanced melanoma treatment is substantial. This finding is in agreement with the study of Serra-Arbeloa et al. (2017) [31] where the management cost of melanoma increases with the disease stage, ranging from a few thousand euros in stage I to almost €100,000 in stage IV. In Spain in 2015, the management cost 1-year post melanoma diagnosis was estimated to be €29,918 for stage III and €88,268 for stage IV, patients with distant metastases were assumed to be treated with four cycles of ipilimumab. Drug-related costs in metastatic patients was estimated to be €7,926, €33,766 and €82,173, according to whether patients were treated with dacarbazine (conventional chemotherapy), vemurafenib or ipilimumab (new-generation therapies), respectively. In Italy, the mean per-patient cost of the whole melanoma pathway ranged from€149 for stage 0 disease to €66,950 for stage IV disease32. The Intuition study reported the direct cost of advanced melanoma management while on treatment with ipilimumab; this management cost, excluding ipilimumab therapy, was reported to be €3,746 for Italy, €6,748 for Spain, €11,696 for Germany during a mean (median) follow-up of 41.3 (30.2) weeks [31].

There are some limitations that merit consideration. The first limitation is the number of clinicians filling out the survey. The second limitation is that the resource utilization considered in the analysis was based on physicians' reporting not from patients' files. However, the results of the current analysis should not be underestimated since they present similarities with results performed in other European studies and the analysis considered was based on micro-costing which is considered the most accurate cost analysis in the field of health economics and management. Also, physicians' uncertainty was taken into account and the elicitation method used does not suffer as much from overconfidence and anchoring [28].

## Conclusion

This study provided a detailed breakdown of resource utilization and direct costs of managing melanoma stage IV positive for BRAF V600 mutations patients in Greece. It is clear that the magnitude of the costs associated with melanoma treatment are considerable, among patients diagnosed with metastatic disease and in the terminal phase of care. Based on the analysis, the largest cost component was medicinal cost of the disease and hospitalization cost at the final stage of the disease. This analysis can serve as a basis for future economic evaluation studies in the management of melanoma in Greece, provide input for health care decision making and help understand the local management and associated costs of stage IV melanoma patients positive for BRAF mutations.


## Acknowledgment

The authors would like to thank Dr. E. Sideris for the continuous support during the study.

## Sponsorship

The current study was sponsored by Pierre Fabre Pharmaceuticals.


## References


1. Potrony, M. et al. Update in genetic susceptibility in melanoma. Ann Transl Med. 2015; 3.
2. Miller A.J., Mihm M.C.J. Melanoma. N Engl J Med. 2006; 355, 51–65.
3. Ryu S. et al. Therapeutic Inhibitors against Mutated BRAF and MEK for the Treatment of Metastatic Melanoma. Chonnam Med J. 2017; 53: 173–177.
4. Arrangoiz R. et al. Melanoma Review: Epidemiology, Risk Factors, Diagnosis and Staging. J. Cancer Treat. Res. 2016; 4: 1.
5. Jones C. et al. Unmet clinical needs in the management of advanced melanoma: findings from a survey of oncologists. Eur J Cancer Care (Engl.). 2015; 24: 867–872.
6. Duncan L.M. The classification of cutaneous melanoma. Hematol. Oncol. Clin. North Am. 2009; 23: 501–513.
7. Elaba Z, Murphy M.J, Kerr P, Grant-Kels J. M. Staging of Melanoma. in Diagnostic and Prognostic Biomarkers and Therapeutic Targets in Melanoma. Springer, New York, NY, 2012; 39–48.
8. Balch C. M. et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol Off J Am Soc Clin Oncol. 2009; 27: 6199–6206.

9. Karimkhani C. et al. The global burden of melanoma: results from the Global Burden of Disease Study 2015. Br J Dermatol. 2017; 177: 134–140.
10. EUCAN. Malignant melanoma of skin. (2012). Available at: http://eco.iarc.fr/eucan/Cancer.aspx?Cancer=20.
11. Arnold M. et al. Trends in incidence and confidences of cutaneous melanoma across Europe up to 2015. J Eur Acad Dermatol Venereol. JEADV. 2014; 28: 1170–1178.
12. Whiteman D.C., Green, A.C., Olsen C. M. The Growing Burden of Invasive Melanoma: Projections of Incidence Rates and Numbers of New Cases in Six Susceptible Populations through 2031. J Invest Dermatol. 2016; 136: 1161–1171.
13. van der Leest R. J. T. et al. Increasing time trends of thin melanomas in The Netherlands: What are the explanations of recent accelerations? Eur J Cancer Oxf Engl. 2015; 51: 2833–2841.
14. Shenenberger D.W. Cutaneous Malignant Melanoma: A Primary Care Perspective. Am Fam Physician. 2012; 85: 161–168.
15. Rutkowsi P. et al. Molecular alterations in clinical stage III cutaneous melanoma: Correlation with clinicopathological features and patient outcome. Oncol Lett. 2014; 8: 47–54.
16. Picard M. et al. Is BRAF a prognostic factor in stage III skin melanoma? A retrospective study of 72 patients after positive sentinel lymph node dissection. Br J Dermatol. 2014; 171: 108–114.
17. Arance Fernández A.M. et al. Epidemiological study to evaluate the prevalence of BRAF V600 mutation in patients (pts) diagnosed with advanced melanoma (AM) in routine clinical practice in Spain J Clin Oncol. 2015; 33: e20115–e20115.
18. Dummer R. et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol Off J Eur Soc Med Oncol. 2015; 26 Suppl 5: 126-132.
19. Michielin O, et al. Cutaneous melanoma: ESMO Clinical PracticeGuidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2019; 30: 1884–1901.
20. Hanly P, Soerjomataram I, Sharp L. Measuring the societal burden of cancer: the cost of lost productivity due to premature cancer-related mortality in Europe. Int J Cancer. 2015; 136, E136-145.
21. Chevalier J, Bonastre J, Avril M.F. The economic burden of melanoma in France: Assessing healthcare use in a hospital setting. Melanoma Res. 2008.
22. Lyth J, Carstensen J, Synnerstad I, Lindholm C. Stage-specific direct health care costs in patients with cutaneous malignant melanoma. J Eur Acad Dermatol Venereol. 2016.
23. Krensel M, Schäfer I, Augustin M. Cost-of-illness of melanoma in Europe–a modelling approach. Journal of the European Academy of Dermatology and Venereology. 2019; 33: 34-45.
24. Elicitation methods: applying elicitation methods to robust workforce planning. Centre for Workforce Intelligence. Technical Paper Series No. 0011. Online. 2015.
25. Guidance on expert knowledge elicitation in food and feed safety risk assessment. European Food Safety Authority Journal. 2014; 12(6): 3734.
26. Expert knowledge elicitation: Subjective but scientific. The American Statistician. 2019; 73: Sup 1, 69-81.
27. https://CRAN.R-project.org/package=SHELF
28. J. E., O'Hagan A. SHELF: the Sheffield Elicitation Framework (version 4). School of Mathematics and Statistics, University of Sheffield, UK. 2019. (http://tonyohagan.co.uk/shelf)
29. Uncertain judgements: eliciting experts' probabilities. John Wiley & Sons. 2006.
30. McArthur G.A. et al. Health Care Resource Utilization and Associated Costs Among Metastatic Cutaneous Melanoma Patients Treated with Ipilimumab (INTUITION Study). The oncologist. 2017.
31. Serra-Arbeloa P, Rabines-Juarez A.O, Alvarez-Ruiz M.S, Guillen-Grima F. Cost of Cutaneous Melanoma by Tumor Stage: A Descriptive Analysis. Actas Dermosifiliogr. 2017.
32. Buja A, Sartor G, Scioni M, Vecchiato A, Bolzan M, Rebba V, Baldo V. Estimation of direct melanoma-related costs by disease stage and by phase of diagnosis and treatment according to clinical guidelines. Acta dermato-venereologica. 2018; 98 (1-2): 218-224.