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Cost Estimate of Immune-Related Adverse Reactions Associated with Innovative Treatments of Metastatic Melanoma

Francesco S. Mennini[1,2] · Chiara Bini[1] · Andrea Marcellusi[1,2] · Michele Del Vecchio[3]

Abstract

Background and Objective Immuno-oncology therapies represent a new treatment opportunity for patients affected by metastatic melanoma. The purpose of this study was to estimate the costs of immune-related adverse events (irAEs) associated with the new anti-PD1 immuno-oncology therapies, with the anti-CTLA-4 immuno-oncology therapy and with the combined therapy (CTLA4 + anti-PD1) in patients affected by metastatic melanoma.

Materials and Methods A probabilistic cost-of-illness (COI) model was developed to estimate the management costs of grade ≥ 3 adverse events associated with the new anti-PD1 therapies (pembrolizumab and nivolumab), the anti-CTLA-4 therapy (ipilimumab) and the combined therapy CTLA4 + anti-PD1 (nivolumab + ipilimumab) for the treatment of patients with metastatic melanoma from the National Health Service (NHS) perspective in Italy. Identification of the epidemiological and cost parameters was carried out through a systematic literature review (SLR). Univariate and probabilistic sensitivity analyses were performed to account for uncertainty and variation in the model results.

Results The model estimated a cost associated with the management of grade ≥ 3 immune-related adverse events in patients with metastatic melanoma equal to €176.2 (95% CI 63.5–335.0) for anti-CTLA-4 therapy, €48.6 (95% CI 40.1–58.5) for the new anti-PDI therapies and €276.8 (95% CI 240.4–316.2) for the combined therapy. Among the innovative therapies for the considered metastatic melanoma, the combined therapy was the most expensive innovative treatment in terms of event management of immune-related grade ≥ 3 adverse events.

Conclusion This study may represent a useful tool to understand the economic burden associated with the management of irAEs associated with patients affected by metastatic melanoma.

Key Points

Evaluation of the economic dimension on the toxicity linked to the immuno-oncology therapies in patients affected by metastatic melanoma represents an essential element for economic evaluation of an innovative drug.

The greater burden was related to the immuno-oncology combined therapy associated with patients affected by metastatic melanoma.

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1 Introduction

With the advent of new immuno-oncology treatments, the approach to patients affected by advanced melanoma has changed considerably. The new therapies have had a major

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impact in terms of survival of patients with advanced/metastatic melanoma.

The anti-CTLA-4 and anti-PD-1 antibodies oppose the blockade of immune "checkpoints" and have been approved for the treatment of advanced melanoma. Ipilimumab, an anti-CTLA-4 drug approved in 2011, was the first immuno-oncology drug for the treatment of advanced melanoma [1]. Nivolumab and pembrolizumab are additional immuno-oncology monotherapy drugs that are available for the treatment of advanced melanoma. These are monoclonal antibodies that promote the anticancer activity mediated by T lymphocytes and oppose the PD-1 co-inhibitory molecule.

The most prominent evidence regarding the use of immune checkpoint inhibitors comes from studies on advanced melanoma [2]. The use of ipilimumab [3, 4], nivolumab [5, 6] and pembrolizumab [7, 8] has resulted in improved survival compared with cytotoxic chemotherapy, both for pre-treated and for naïve patients. Furthermore, combined immunotherapy with nivolumab and ipilimumab results in a higher response rate and a longer progression time compared with the action of ipilimumab alone [9]. Considering the success of immune checkpoint inhibitors, these agents may represent a basic component of a therapeutic strategy using checkpoint inhibitors in combination or with other anticancer agents [10, 11]. However, when therapeutic strategies use a combination of drugs, toxicity could be a limiting factor. Therefore, early recognition and a methodical design of baseline and adverse event management assessment are fundamental to the success of the treatment [10].

Many of the possible side effects of the new immunotherapy drugs are tightly linked with their specific mechanism of action [1]. Additionally, the immune system stimulation used to fight cancer may also trigger unwanted processes of autoimmune-like reactions [1]. So-called immune-related toxicity represents a secondary toxicity to an autoimmune-like reaction during treatment with immunotherapy drugs [1]. Such toxicity may take place anytime during the treatment and may involve many different organs [1], among which are the skin, the gastrointestinal tract, the liver and the endocrine system (thyroid, pituitary gland), in order of median time to onset [2]. These side effects are normally manageable, but in some cases they may be lethal [3, 7, 12, 13].

The objective of this study was to estimate the costs of grade ≥ 3 irAEs that are associated with new anti-PD1 therapies (pembrolizumab and nivolumab), with anti-CTLA-4 (ipilimumab) therapy and with the combined therapy CTLA4 + anti-PD1 (nivolumab + ipilimumab) in patients affected by metastatic melanoma.

2 Methods

2.1 Study Design

A probabilistic incidence-based cost-of-illness model was developed to estimate the aggregate measure of the economic impact of grade ≥ 3 irAEs (severe, life-threatening or disabling irAE) of immune-oncology therapies for the treatment of patients with metastatic melanoma.

The analysis was conducted from the National Health Service (NHS) perspective in Italy, and only direct health costs over a 1-year time horizon from the beginning of therapy were considered. The identification of the epidemiological and cost parameters to be included in the model was carried out through a systematic literature review (SLR) of available studies. For each treatment, the model calculated the cost associated with the irAE for each treatment by multiplying each incidence estimate by the respective adverse event cost.

Finally, deterministic and probabilistic sensitivity analyses were performed in order to consider the variability of the data used in the model.

A systematic literature review (SLR) of the available literature was aimed at identifying the epidemiological and cost data related to the irAEs associated with anti-PD1, anti-CTLA-4 and combined therapies for the treatment of metastatic melanoma. The search was carried out through the MEDLINE electronic database (PubMed) for English and Italian articles. Moreover, to identify further national literature, an analysis of Italian grey literature was performed by consulting non-indexed peer-reviewed scientific magazines on PubMed that examined the health economics aspects connected with the research being analysed in this work and in-line with the objectives of the study.

To identify the parameters required to build the model, this research was conducted by pursuing two different objectives. The first objective was to identify the epidemiological and incidence data of the adverse events associated with the anti-PD1, anti-CTLA-4 and combined therapies (CTLA4 + anti-PD1). The second objective was focused on the search of the cost data associated with the management of these adverse events following the treatments being analysed. In-line with the guidelines for the systematic analysis of the scientific literature, Fig. 1 shows the systematic process used to carry out the search. The systematic process comprised four stages: identification, screening, eligibility and inclusion. The search code used to identify the epidemiological parameters was as follows:

("Metastatic Melanoma"[Title/Abstract]) AND ("nivolumab"[Title/Abstract] OR "ipilimumab"[Title/Abstract] OR "pembrolizumab"[Title/Abstract] OR "combined immunotherapy"[Title/Abstract]) AND
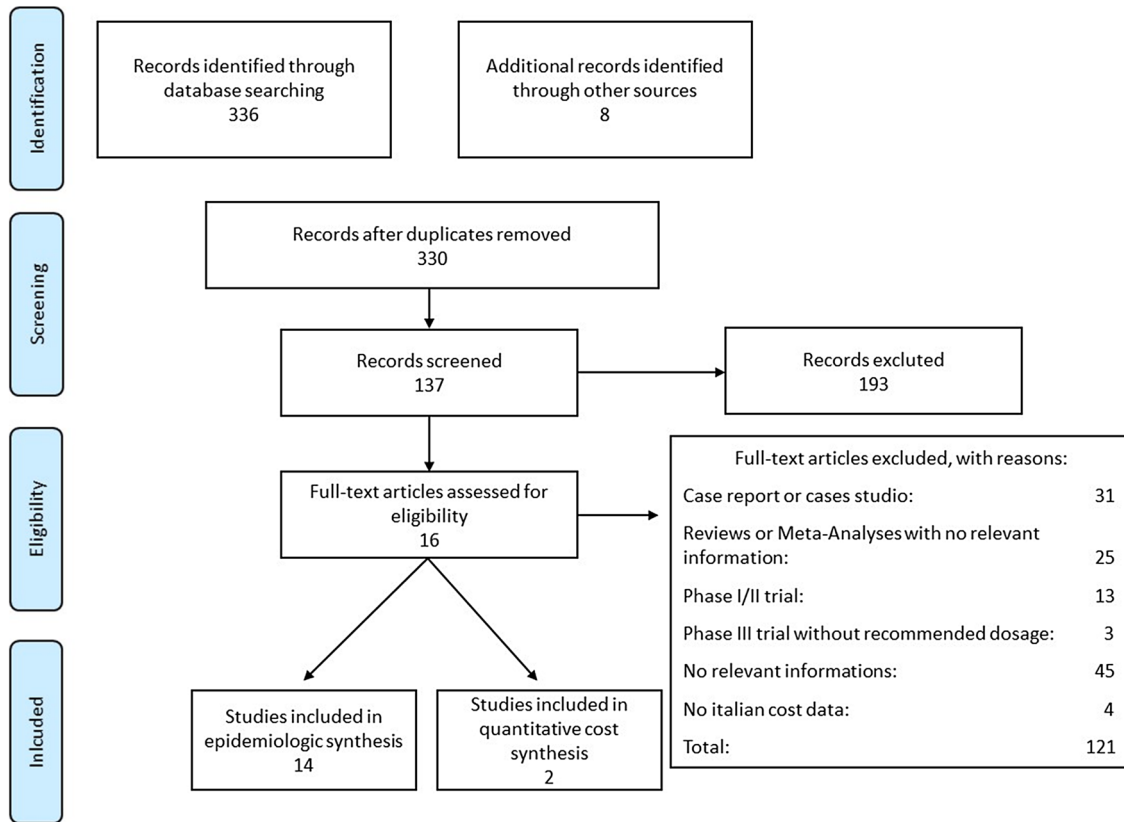
Fig. 1 PRISMA flow diagram

("safety"[Title/Abstract] OR "safety melanoma treatment"[Title/Abstract] OR "Adverse event"[Title/Abstract] OR "Adverse events"[Title/Abstract] OR "Adverse events"[Mesh] OR "Drug-Related Side Effects and Adverse Reactions"[Mesh]).

With reference to cost data, the search code was the same as that used to identify the epidemiological parameters but included the following search extensions: ("Economic burden"[Title/Abstract] OR "Cost of illness"[Title/Abstract] OR "costs"[Title/Abstract] OR "cost"[Title/Abstract]). Regarding the Italian scientific magazines, the articles were identified through the keyword "metastatic melanoma". Using the above-mentioned search codes, 366 articles in the MEDLINE electronic database were identified, while articles from other sources were identified after reading the articles found through the electronic database.

The eligibility criteria used to determine whether an article would be included in the cost-of-illness model were:

- Phase III clinical trial conducted on patients with metastatic melanoma to whom at least one of the innovative treatments considered in the search was administered, according to the dose indicated in the technical sheet (ipilimumab: 3 mg/kg every 3 weeks; nivolumab 3 mg/kg

every 2 weeks; pembrolizumab: 2 mg/kg every 3 weeks; nivolumab/ipilimumab: 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab every 3 weeks);
- Review/retrospective study conducted on patients with metastatic melanoma to whom at least one of the innovative treatments considered in the search was administered, according to the dose indicated in the technical sheet (ipilimumab: 3 mg/kg every 3 weeks; nivolumab 3 mg/kg every 2 weeks; pembrolizumab: 2 mg/kg every 3 weeks; nivolumab/ipilimumab: 1 mg/kg of nivolumab + 3 mg/kg of ipilimumab every 3 weeks);
- Article containing cost data, in the Italian National Health Service context.

The articles that did not meet these eligibility criteria were excluded. Two researchers independently reviewed the studies using the title, the abstract or the full text. The differences were discussed and solved through analyses and a confrontation with other experts. Following this procedure, a total of 16 articles were included in the model: 14 referred to epidemiological data and two referred to cost data. Five articles related to the epidemiological data were clinical trials conducted on patients with phase III or IV unresectable melanoma, who submitted to at least one of

the innovative treatments considered in the analysis [3, 5–7, 9]. The remaining eight articles were retrospective studies [14–21] and a review [22].

2.2 Epidemiological Parameters

The epidemiological parameters were referred to the incidence estimates of grade ≥ 3 adverse events associated with anti-PD1, anti-CTLA-4 and the combined therapies (according to the doses indicated in the technical sheet). The estimates obtained from the literature are shown in Tables 1, 2 and 3. Most of the studies included in the analysis involved anti-CTLA-4 therapy (ipilimumab) (Table 2). Only two articles covering a combination of nivolumab + ipilimumab combination [9] or anti-PD1 pembrolizumab therapy [7] were included.

In particular, with reference to pembrolizumab, the clinical trial included in the analysis used an administration regimen in patients affected by metastatic melanoma equal to 10 mg/kg every 2 or 3 weeks. Even if this regimen does not correspond to that indicated in the technical sheet, in the randomized phase I (KEYNOTE-001) and phase II (KEYNOTE-002) clinical trials, the administration of pembrolizumab corresponding to doses ranging from 2 mg/kg every 3 weeks to 10 mg/kg every 2 weeks did not influence the results [23–26].

Among all the grade ≥ 3 irAEs considered in the analysis, the highest incidence estimates were those corresponding to the combination therapy.

With reference to the grade ≥ 3 immune-related adverse events of the skin, rash was the most widespread immune-related adverse event among the patients with metastatic melanoma, with an average incidence of 1.9% in patients treated with anti-CTLA-4 therapy, 0.5% in those treated with anti-PD1 immuno-oncology therapy and 4.8% in patients treated with the nivolumab/ipilimumab combination. In this specific case, the term 'rash' includes both the rash adverse event and the maculopapular rash adverse event. Among the grade ≥ 3 gastrointestinal adverse events, diarrhoea was the most widespread immune-related adverse event in patients affected by metastatic melanoma treated with a nivolumab/ipilimumab combination (9.3% of the patients suffer from this adverse event) and anti-PD1 therapies (on average, 1.1% of the patients suffered from this adverse event). Of these, colitis also resulted in significant adverse events, especially in patients treated with the nivolumab/ipilimumab combination (7.7% of patients) and with anti-CTLA-4 therapy (incidence of 0.8%). The grade ≥ 3 immune-related hepatic adverse events are particularly widespread in patients with metastatic melanoma treated with the nivolumab/ipilimumab combination. Of these patients, 8.3% showed an increase in alanine aminotransferase, while 6.1% of the patients had an increase in aspartate aminotransferase.

Table 1 Grade ≥ 3 immune-related adverse events (irAEs) associated with anti-PD1 therapies (pembrolizumab, nivolumab) in patients affected by metastatic melanoma

Anti-PD1 therapies	Robert et al. [7]	Weber et al. [6]	Larkin et al. [9]	Robert et al. [5]	Eigentler et al. [22]
Sample size	834	390	915	410	474
Skin					
Pruritus (%)	0.0	0.0	0.0	0.5	0.2
Rash (%)	0.4	0.4	0.6	0.5	0.4
Vitiligo (%)	0.0	0.0	0.3	0.0	–
Gastrointestinal					
Diarrhoea (%)	1.1	0.4	2.2	1.0	0.6
Colitis (%)	1.8	0.7	0.6	0.5	0.6
Hepatic					
Increase in alanine aminotransferase (%)	0.4	0.7	1.3	1.0	1.1
Increase in aspartate aminotransferase (%)	0.4	0.4	1.0	0.5	0.6
Endocrine					
Hypothyroidism (%)	0.0	0.0	0.0	0.0	0.0
Hyperthyroidism (%)	0.0	0.0	0.0	0.0	0.2
Hypophysitis (%)	0.4	–	0.3	0.5	0.2
Pulmonary					
Pneumonia (%)	0.4	0.0	0.3	0.0	–

(–) indicates that the irAE has not been reported in the reference study

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Table 2 Grade ≥ 3 immune-related adverse events (irAEs) associated with anti-CTLA-4 therapy (ipilimumab) in patients affected by metastatic melanoma

Anti-CTLA-4 therapy	Hodi FS et al. 2010 [3]	Larkin et al. 2015 [9]	Wiater et al. 2013 [14]	Ahmad et al. 2015 [15]	Ascierto et al. 2014 [16]	Daly et al. 2017 [20]	Jung et al. 2017 [17]	Margolin et al. 2015 [21]	Robert et al. 2015 [7]	Del Vecchio et al. 2014 [18]	Sileni et al. 2014 [19]
Sample size	750	915	50	193	855	84	104	273	834	855	855
Skin											
Pruritus (%)	0.0	0.3	0.0	1.0	0.9	0.0	1.0	0.4	0.4	0.0	0.0
Rash (%)	0.8	1.9	0.0	3.0	0.9	8.3	1.0	0.7	1.2	1.0	<1
Vitiligo (%)	0.0	0.0	0.0	–	–	–	–	–	0.0	–	–
Gastrointestinal											
Diarrhoea (%)	4.6	6.1	4.0	13.0	2.0	4.8	0.0	1.5	3.1	4.0	1.0
Colitis (%)	5.3	8.7	–	–	–	6.0	–	4.1	6.3	–	–
Hepatic											
Increase in alanine aminotransferase (%)	0.0	1.6	–	–	–	–	–	–	0.8	–	–
Increase in aspartate aminotransferase (%)	0.0	0.6	–	–	–	–	–	–	0.8	–	–
Endocrine											
Hypothyroidism (%)	0.0	0.0	0.0	–	–	0.0	–	–	0.0	–	–
Hyperthyroidism (%)	–	0.0	2.0	–	–	–	–	–	0.4	–	–
Hypophysitis (%)	1.5	1.9	2.0	2.0	–	1.2	–	–	0.8	–	–
Pulmonary											
Pneumonia (%)	–	0.3	–	–	–	–	–	–	0.4	–	–

* (–) indicates that the irAE has not been reported in the reference study

Table 3 Grade ≥3 immune-related adverse events (irAEs) associated with the combined therapy (nivolumab + ipilimumab) in patients affected by metastatic melanoma

Combined therapy	Larkin et al. 2015 [9]
Sample size	915
Skin	
Pruritus (%)	1.9
Rash (%)	4.8
Vitiligo (%)	0.0
Gastrointestinal	
Diarrhoea (%)	9.3
Colitis (%)	7.7
Hepatic	
Increase in alanine aminotransferase (%)	8.3
Increase in aspartate aminotransferase (%)	6.1
Endocrine	
Hypothyroidism (%)	0.3
Hyperthyroidism (%)	1.0
Hypophysitis (%)	1.6
Pulmonary	
Pneumonia (%)	1.0

Among the grade ≥3 immune-related endocrine adverse events, the highest incidence estimate was detected for hypophysitis (on average, 1.6% of patients treated with anti-CTLA-4 therapy, 0.4% of patients treated with the new anti-PD1 immuno-oncology therapies and 1.6% of patients treated with the combination).

Finally, even grade ≥3 pneumonia was particularly widespread among the patients with metastatic melanoma being treated with the combination (1% of patients).

2.3 Cost Parameters

The cost parameters were associated with the management and treatment of adverse events in the patients affected by metastatic melanoma, following the administration of one of the above-mentioned innovative treatments. Table 4 reports the cost estimates obtained from two studies through a systematic review of the literature carried out internationally [27, 28]. For the adverse event 'pneumonia', the model takes into account the Italian national tariff associated with DRG 90 (simple pneumonia and pleurisy, age > 17 years, without complications) [29]. The cost associated with the hepatic adverse events (increase in alanine aminotransferase and increase in aspartate aminotransferase), vitiligo, hypothyroidism and hyperthyroidism was obtained through the reconstruction of the therapeutic path and the monitoring of patients affected by each adverse event. The evaluation of specialist services was made through the national tariff of specialist care services [30].

Specifically, the cost of vitiligo was calculated taking into account the cost of a general specialist visit (Code 89.7). The costs associated with the increase in alanine aminotransferase and aspartate aminotransferase were obtained considering the cost of a general specialist visit and the specific blood tests: an alanine aminotransferase test (ALT) (GPT) S/U (Code 90.04.5) for the increase in alanine aminotransferase and an aspartate aminotransferase test (AST) (GOT) S (Code 90.09.2) for the increase in aspartate aminotransferase.

Table 4 Costs associated with immune-related adverse events (irAEs)

Adverse event	Cost	Source
Pruritus (grade 1–2)	€ 11.26	[27]
Rash (grade 3–4)	€ 1,355.00	[28]
Vitiligo	€ 20.66	Specialist tariff (89.7: general visit) [30]
Diarrhoea (grade 3–4)	€ 1,486.00	[28]
Colitis (grade 3–4)	€ 183.98	[27]
Increase in alanine aminotransferase	€ 21.66	Specialist tariff (1 general visit [89.7] + 1 alanine aminotransferase test (ALT) (GPT) [S/U] [90.04.5]) [30]
Increase in aspartate aminotransferase	€ 21.70	Specialist tariff (1 general visit [89.7] + 1 aspartate aminotransferase test (AST) (GOT) [S] [90.09.2]) [30]
Hypothyroidism	€ 64.16	Specialist tariff (1 general visit [89.7] + 2 thyrotropine tests (TSH) [90.42.1] + 2 free thyroxine tests (FT4) [90.42.3]) [30], Farmadati (365 tablets of levothyroxine sodium)
Hyperthyroidism	€ 230.83	Specialist tariff (3 general visits [89.7] + 1 head and neck sonogram [88.71.4] + 6 thyrotropine tests (TSH) [90.42.1] + 6 free triiodothyronine tests (FT3) [90.43.3] + 6 free thyroxine tests (FT4) [90.42.3]) [30], Farmadati (653 thiamazole tablets)
Hypophysitis (grade 3–4)	€ 1,915.00	[28]
Pneumonia	€ 2,291.00	DRG (simple pneumonia and pleurisy, age > 17 years without complications) [29]

The cost associated with hyperthyroidism was assumed to be equal to that incurred for three general specialist visits, a head and neck sonogram (Code 88.71.4), six thyrotropine tests (TSH) (Code 90.42.1), six free thyroxine tests (FT4) (Code 90.42.23) and 653 tablets of thiamazole (4–6 tablets a day for 4 weeks + maintenance therapy of 1–2 tablets for 12–18 months). The cost associated with hyperthyroidism was calculated considering the cost incurred for a general specialist visit, two thyrotropine tests (TSH) (Code 90.42.1), two free thyroxine tests (FT4) (Code 90.42.3) and 365 tablets of levothyroxine sodium (one tablet per day).

2.4 Sensitivity Analysis

To consider the variability of the data obtained through a systematic literature review, the cost-of-illness model was developed following a probabilistic approach (probabilistic sensitivity analysis—PSA). This probabilistic analysis considers all the estimates obtained from the literature, indicating the minimum and maximum values of the probabilistic distribution of each parameter considered in the analysis. In particular, the choice of the probabilistic distribution to be associated with each parameter was made according to the scientific literature on the development of the probabilistic models in the economic evaluations, thus attributing a beta distribution to each epidemiological parameter and a gamma distribution to each cost parameter [31].

Based on these probabilistic distributions, 1,000 Monte Carlo simulations were performed to generate a 95% confidence interval, in which each result obtained through a cost-of-illness model could be included. The variability associated with the anti-CTLA-4 and nivolumab immuno-oncology therapies corresponds to the minimum and maximum values found in the literature. With reference to pembrolizumab and the combination, the model assumed 25% variability, as only two studies were eligible in the literature, one for each treatment.

Finally, a one-way deterministic sensitivity analysis was conducted to verify the sensitivity of the results compared to each parameter considered in the model. Such analysis consists of changing one parameter at a time, according to the minimum and maximum values found in the literature or assumed by the authors. In this specific case, the sensitivity analysis was conducted considering the minimum and maximum incidence estimates of the immune-related adverse events identified in the literature for the anti-CTLA-4 and anti-PD1 (Tables 1 and 2) therapies. For the combined therapy, the sensitivity analysis was conducted assuming ± 25% variability corresponding to each adverse immune-related event. With reference to the cost estimate, the minimum and maximum values were defined assuming ± 25% variability.

3 Results

To estimate the average costs associated with the management of grade ≥ 3 irAEs in patients affected by metastatic melanoma, the cost-of-illness model has specifically considered the articles of Larkin et al. [9] and Robert et al. [4, 5], the former for grade ≥ 3 adverse events referring to nivolumab, ipilimumab and the combination, the latter for grade ≥ 3 adverse events referring to pembrolizumab.

The incidence estimates of the irAEs associated with the new anti-PD1 therapies have been obtained as a simple average of the incidence estimates for pembrolizumab and nivolumab that have emerged from the literature. The 95% confidence intervals were estimated considering the minimum and maximum values from the literature in the case of anti-PD1 and anti-CTLA-4 therapies, while for the combined therapy, the model has assumed 25% variation compared with the incidence estimates from the article by Larkin et al. [9] (the only article that emerged from the literature). The model estimated a cost associated with the management of grade ≥ 3 immune-related adverse events in patients affected by metastatic melanoma equal to €176.2 (95% CI 63.5–335.0) for anti-CTLA-4 therapy, €48.6 (95% CI 40.1–58.5) for new anti-PDI immuno-oncology therapies, and €276.8 (95% CI 240.4–316.2) for immuno-oncology combined therapy. Among the innovative therapies for metastatic melanoma, immuno-oncology combined therapy was the most expensive treatment in terms of event management of grade ≥ 3 irAEs. Because of the greatest variability related to the incidence in the literature, the model estimated a large confidence interval for anti-CTLA-4 therapy.

Figures 2, 3 and 4 report the results of the one-way deterministic analysis conducted for each innovative treatment considered in this study. The costs shown in the figures represent the average associated with the management of grade ≥ 3 irAEs that would occur by applying the minimum and maximum incidence obtained from the literature for each irAE. In particular, the average cost associated with the management of grade ≥ 3 irAEs in a patient affected by metastatic melanoma was very sensitive to the variations in the event incidence towards diarrhoea for each therapeutic regimen. This is attributable to the greatest incidence of irAE for all therapeutic regimens, the high management cost and the greater variability from the literature.

4 Discussion

Immuno-oncology therapies represent a new treatment opportunity for patients affected by metastatic melanoma. However, in addition to the high effectiveness levels, the

Fig. 2 Sensitivity deterministic analysis for average cost associated with the management of grade ≥ 3 immune-related adverse events in a patient treated with anti-CTLA-4 therapy—tornado chart
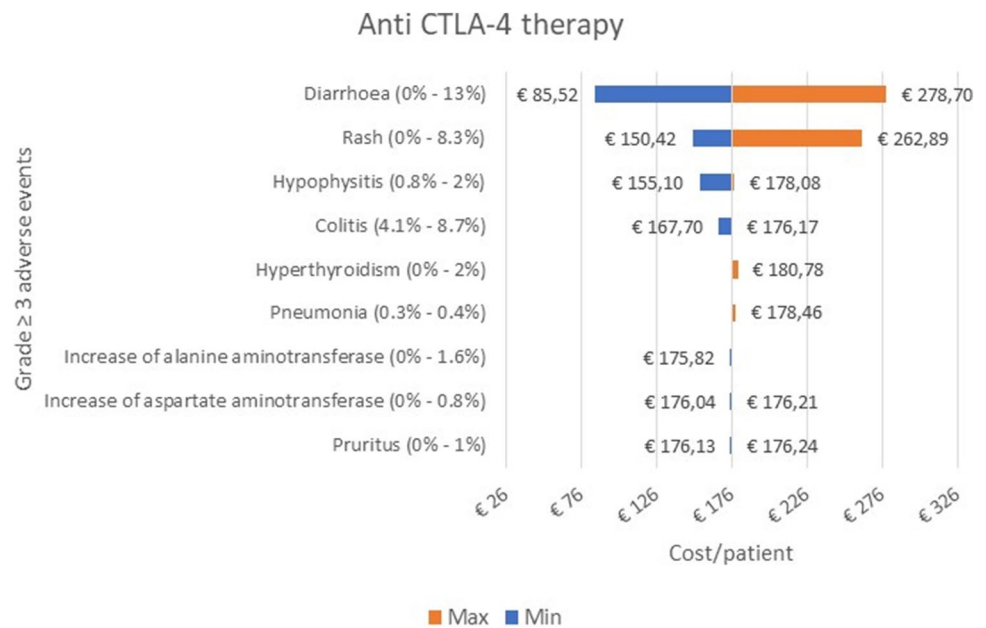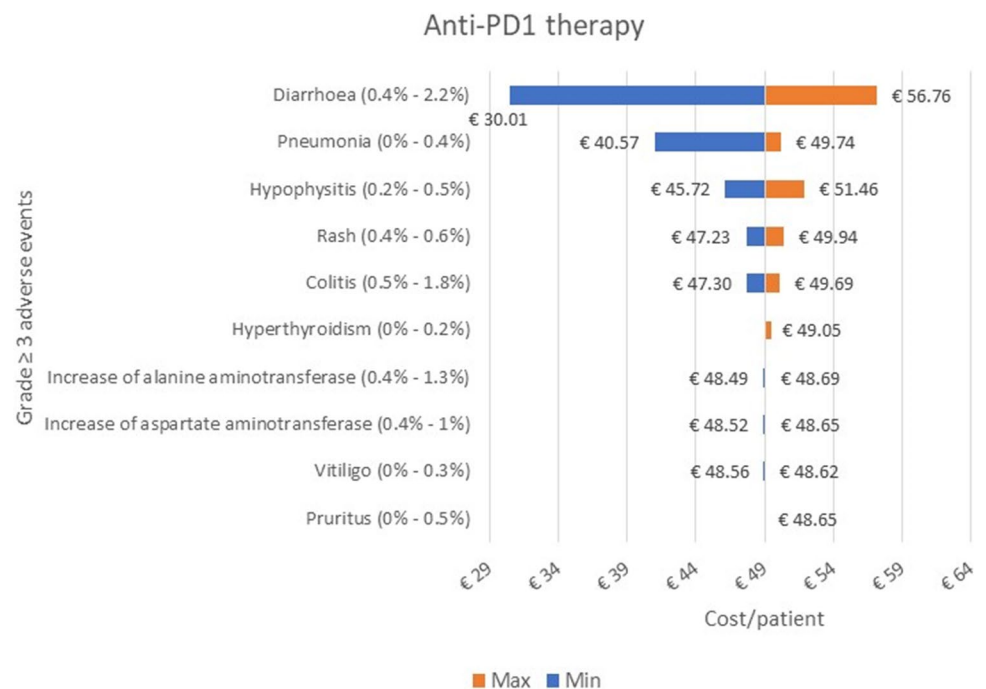
Anti CTLA-4 therapy

Grade ≥ 3 adverse events	Min	Max
Diarrhoea (0% - 13%)	€ 85,52	€ 278,70
Rash (0% - 8.3%)	€ 150,42	€ 262,89
Hypophysitis (0.8% - 2%)	€ 155,10	€ 178,08
Colitis (4.1% - 8.7%)	€ 167,70	€ 176,17
Hyperthyroidism (0% - 2%)		€ 180,78
Pneumonia (0.3% - 0.4%)		€ 178,46
Increase of alanine aminotransferase (0% - 1.6%)	€ 175,82	
Increase of aspartate aminotransferase (0% - 0.8%)	€ 176,04	€ 176,21
Pruritus (0% - 1%)	€ 176,13	€ 176,24

Cost/patient

■ Max ■ Min

Fig. 3 Sensitivity deterministic analysis for average cost associated with the management of grade ≥ 3 immune-related adverse events in a patient treated with anti-PD1 therapies—tornado chart

Anti-PD1 therapy

Grade ≥ 3 adverse events	Min	Max
Diarrhoea (0.4% - 2.2%)	€ 30.01	€ 56.76
Pneumonia (0% - 0.4%)	€ 40.57	€ 49.74
Hypophysitis (0.2% - 0.5%)	€ 45.72	€ 51.46
Rash (0.4% - 0.6%)	€ 47.23	€ 49.94
Colitis (0.5% - 1.8%)	€ 47.30	€ 49.69
Hyperthyroidism (0% - 0.2%)		€ 49.05
Increase of alanine aminotransferase (0.4% - 1.3%)	€ 48.49	€ 48.69
Increase of aspartate aminotransferase (0.4% - 1%)	€ 48.52	€ 48.65
Vitiligo (0% - 0.3%)	€ 48.56	€ 48.62
Pruritus (0% - 0.5%)		€ 48.65

Cost/patient

■ Max ■ Min

security and toxicity profiles that continue to improve with the development of new technologies should not be neglected. In addition to data that have been widely reported in the literature, this work tried to quantify the economic weight associated with the most severe immune-related adverse events (grade ≥ 3) in patients affected by metastatic melanoma who submitted to either anti-CTLA-4, new anti-PD1 or combined (CTLA4 + anti-PD1) therapies.

The study has limitations regarding the development of our estimation model. First, the eligibility criteria that were used in the systematic review resulted in the inclusion of different types of studies. Therefore, within these analyses, estimates coming from prospective, retrospective or descriptive studies were included. Despite that, these studies were included to collect the greatest amount of information concerning immune-related adverse events for which there is little evidence in the literature. Indeed, the second

Fig. 4 Sensitivity deterministic analysis for average cost associated with the management of grade ≥ 3 irAEs in a patient treated with combined therapy (CTLA4 + anti-PD1)—tornado chart
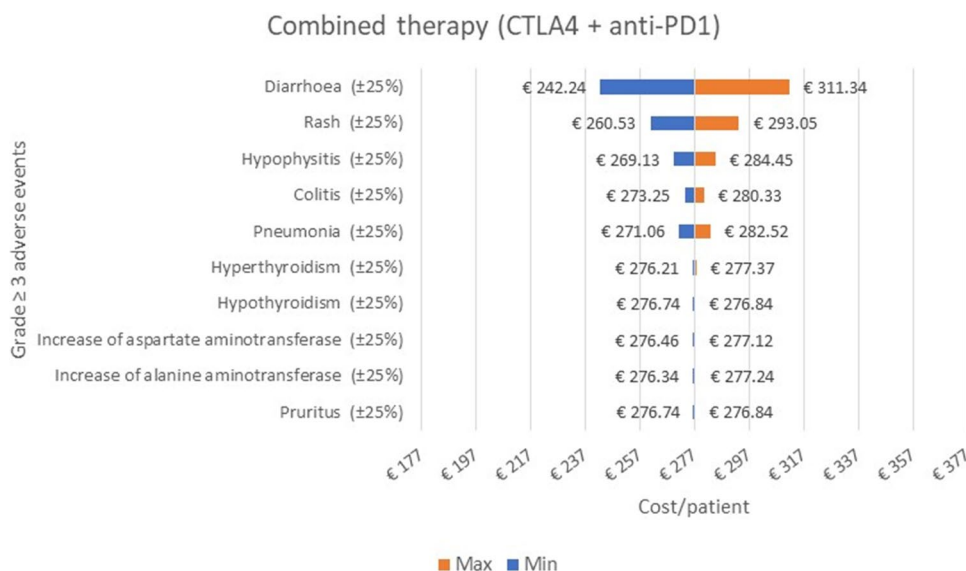
limitation of this work is the scarce availability of studies, specifically for pembrolizumab and for combination therapy, for which only two works are available, one for pembrolizumab and one for combination therapy. A third limitation concerns the cost estimates associated with each adverse event. These estimates have been obtained, when possible, from the literature. In particular, they have been obtained from two studies that estimated the costs associated with the management of adverse events in patients with metastatic melanoma when treated with drugs such as dacarbazine or DTIC, temozolomide, fotemustine, IL-2, ipilimumab, vemurafenib, dabrafenib and trametinib, in the study by Wheler et al., while the study by Vouk et al. considers only the costs associated with the management of immune-related adverse events that are related to ipilimumab. For both articles, the cost data are for 2013 (actualized at 2014 in the work of Wheler), and they were calculated using the national (Vouk) and regional (Wheler) DRG tariffs for hospitalizations, the tariffs supplied by AgneNaS (Wheler) and those associated with specialist services (Vouk) for outpatient costs. The cost estimates that have not been detected through the systematic review of the literature were obtained with the support of expert clinicians. Specifically, expert opinions were used to recreate the therapeutic and monitoring pathway experienced by patients experiencing a specific adverse event among those considered in the case study.

5 Conclusions

In our opinion this study represents a useful tool for understanding the economic burden of the management of irAEs associated with patients affected by metastatic melanoma.

The economic dimension of the toxicity linked to immuno-oncology therapies represents an essential element for economic evaluation of an innovative drug.

Certainly, the experience of the centre may lessen the economic burden of toxicity management by implementing an early identification and management system for adverse events, thereby enabling earlier and easier patient recovery, without hospitalization. In addition to this, the treatment would not be interrupted, and the desired clinical outcome would be obtained, with the additional benefit of cost-effective patient treatment.

Compliance with Ethical Standards

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