Brenda Leeneman

Evidence-based decision making on drug reimbursement in melanoma

Using real-world evidence to complement evidence from randomized controlled trials

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Evidence-Based Decision Making on Drug Reimbursement in Melanoma
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'Evidence-based' besluitvorming over de vergoeding van geneesmiddelen voor melanoom
Het gebruik van bewijs uit de dagelijkse praktijk ter aanvulling van bewijs uit gerandomiseerde, gecontroleerde trials

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1 General introduction

BACKGROUND

Cancer is a major public health problem. In 2020, the estimated incidence of cancer (excluding non-melanoma skin cancer) was 4.0 million in Europe.[1] Compared to 1995, in which the estimated incidence was 2.6 million, this represents an increase of more than 50%.[2] During the same period, the estimated number of deaths (i.e., mortality) due to cancer increased from 1.6 to 1.9 million, representing an increase of less than 20%.[1,2] The difference in the increase of incidence and mortality reflects improvements in survival. These improvements have been achieved by advances in cancer care. Besides advances in cancer screening and diagnostics, important advances have been made in the treatment of cancer. Novel cancer drugs, including immunotherapies and targeted therapies, have been developed by pharmaceutical companies.[3] Immunotherapies are drugs that engages the patient's immune system to recognize and eliminate cancer cells.[4] Targeted therapies are drugs that targets specific genes and proteins which are involved in the growth and spread of cancer cells.[5]

Although the novel drugs are of great value for cancer patients, they often come at a high price. In Europe, total health expenditure on cancer care amounted to €78 billion in 2005 and increased by 32% to €103 billion in 2018. At the same time, the proportion of cancer-specific health expenditure on cancer drugs almost tripled from 13% (€10 billion) to 31% (€32 billion).[6] To ensure the accessibility and affordability of health care in general and cancer care in particular, reimbursement authorities face the challenge of balancing timely access to novel cancer drugs and the need for valid evidence regarding their (long-term) effects and costs.

It is widely acknowledged that randomized controlled trials (RCTs) are the gold standard for assessing efficacy and safety because they ensure internal validity. RCTs are, however, often criticized for selecting patients who are not representative of patients in routine clinical practice, choosing irrelevant comparators, and using surrogate instead of final outcomes.[7] These factors may adversely affect the external validity of RCTs, which, in turn, may complicate decision making on drug reimbursement. Therefore, in recent years, reimbursement authorities have become increasingly interested in real-world evidence (i.e., evidence obtained from real-world data).[8-10]

DRUG DEVELOPMENT PROCESS: FROM DISCOVERY TO REIMBURSEMENT

The development of a drug is a long and complicated process. After its discovery, the drug is tested in the laboratory (i.e., preclinical testing) to determine whether the drug is sufficiently safe to test in humans (i.e., clinical testing). Clinical testing usually consists of three phases of trials. Phase I trials are conducted to test the drug in healthy volunteers, phase II (randomized controlled) trials to test the drug in a small group of patients, and phase III (randomized controlled) trials to test the drug in a large group of patients. If the trials demonstrate that the drug is of high-quality, efficacious, and safe, pharmaceutical companies can apply for marketing authorization.[11]

In the European Union (EU), the European Medicines Agency (EMA) is responsible for the assessment of marketing authorization applications. The main principles guiding the assessment are quality, efficacy, and safety. Based on EMA's assessment, the European Commission decides on the granting of a marketing authorization. Once a marketing authorization has been granted, national reimbursement authorities decide on reimbursement.[11,12]

In the Netherlands, all inhabitants are entitled to a comprehensive basic health insurance package. The National Health Care Institute (ZIN) advises the Minister of Health on the inclusion of drugs in the basic package. Their advice is based on four criteria: necessity (i.e., medical necessity and societal necessity to insure), effectiveness, cost-effectiveness, and feasibility (including organizational, ethical, and legal aspects). In order to control the economic impact of expensive novel drugs, the Minister can place a drug in the so-called 'lock for expensive drugs'. In that case, the drug will only be included in the basic package if ZIN has advised on its inclusion and/or if a financial arrangement has been established between the Minister and the pharmaceutical company.[12]

NOVEL DRUGS FOR MELANOMA

Cutaneous melanoma (hereafter: melanoma) is a type of skin cancer that originates from the melanocytes in the epidermis.[13] In 2020, it was the sixth most commonly diagnosed cancer in Europe, with an estimated age-standardized incidence rate of 11.4 per 100,000 person-years.[1] Most patients (approximately 90%) are diagnosed with stage I or II (i.e., localized melanoma). These patients have a good prognosis, with a five-year survival rate of approximately 95%.[14,15] Melanoma has, however, a strong tendency to metastasize, resulting in a relatively poor prognosis. Patients with stage III (i.e., regionally advanced melanoma) present with regional metastases, which can appear as satellite, in-transit, or regional lymph node metastases. In patients with stage IV, the disease has spread beyond the regional lymph nodes into distant parts of the body. Distant metastases most frequently occur in the lungs, liver, brain, bones, gastrointestinal tract, and soft tissues.[16] The five-year survival rates for patients with stage III or IV are approximately 65% and 20%, respectively.[14,15]

For many years, treatment options for patients with unresectable stage III and stage IV (hereafter: advanced or metastatic melanoma) were limited. Chemotherapy was the standard of care, but it never demonstrated to improve survival.[17] Advances in the understanding of melanoma biology has led to the introduction of novel immunotherapies and targeted therapies. Since 2011, four immunotherapies (ipilimumab, nivolumab, pembrolizumab, and nivolumab plus ipilimumab) and five targeted therapies (vemurafenib, dabrafenib, dabrafenib plus trametinib, vemurafenib plus cobimetinib, and encorafenib plus binimetinib) received a marketing authorization (see Figure 1).[18] Recently, nivolumab, pembrolizumab, and dabrafenib plus trametinib also became available as adjuvant therapy for patients with resectable stage III.[19]

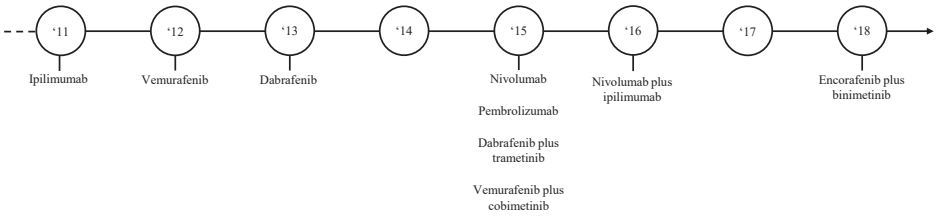

Figure 1. Immunotherapies and targeted therapies for advanced melanoma that received a marketing authorization (EU) since 2011

Dutch Melanoma Treatment Registry

In the Netherlands, the introduction of the first novel drugs for advanced melanoma (ipilimumab and vemurafenib) posed several important challenges: (1) the selection of patients who would benefit from the drugs, (2) the management of treatment-related adverse events, and (3) the cost-effectiveness of the drugs. Therefore, the Dutch Minister of Health made reimbursement of the drugs conditional on centralization of care and the set-up of the nationwide population-based registry. The Dutch Society for Medical Oncology (NVMO) selected 14 melanoma centers based on their expertise, infrastructure, and geographic distribution. The NVMO also initiated the Dutch Melanoma Treatment Registry (DMTR), which was implemented by the Dutch Institute for Clinical Auditing in July 2013. The DMTR is characterized by its unique collaboration between all relevant stakeholders involved in melanoma care: medical specialists, patient advocates, policymakers, pharmaceutical companies, health insurance companies, and scientific researchers.[20]

THESIS AIM

The aim of this thesis is to evaluate how and to what extent real-world evidence can complement evidence from RCTs in order to support evidence-based decision making on drug reimbursement in melanoma. To work towards this aim, the following research questions will be answered:

1. What are the limitations of RCTs for decision making on drug reimbursement?
2. What are the challenges in collecting and analyzing real-world data?
3. What is the added value of real-world data for decision making on drug reimbursement?

THESIS OUTLINE

Chapter 2 describes stage-specific trends in the incidence and survival of all patients diagnosed with invasive primary melanoma in the Netherlands between 2003 and 2018. In addition, this chapter reports the annual proportion of patients who received chemotherapy, immunotherapy, or targeted therapy for their primary diagnosis during that period. In *Chapter 3*, we present stage-specific survival from diagnosis, recurrence patterns, and post-recurrence survival of

patients initially diagnosed with localized and regionally advanced melanoma. *Chapter 4* reports the health care costs of these patients. In *Chapter 5*, we present a systemic literature review and network meta-analysis of phase III RCTs involving patients with advanced melanoma. *Chapter 6* reports health care costs of advanced melanoma in the era of immunotherapies and targeted therapies. Additionally, this chapter describes health care costs per line of therapy and (novel) drug. In *Chapter 7*, we present the time to first event, overall survival, and grade 3/4 immune-related adverse events of patients who received ipilimumab in routine clinical practice. *Chapter 8* reports the health care costs of these patients. Finally, *Chapter 9* provides a general discussion of the main findings, policy recommendations, and objectives for future research.

2 Stage-specific trends in incidence and survival of cutaneous melanoma in the Netherlands (2003-2018): A nationwide population-based study

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ABSTRACT

Objective

To examine stage-specific trends in the incidence and survival of cutaneous melanoma in the Netherlands between 2003 and 2018 as well as the uptake of the sentinel lymph node biopsy (SLNB) and novel drugs during that period.

Methods

Data were obtained from the nationwide population-based Netherlands Cancer Registry for all patients diagnosed with invasive primary cutaneous melanoma (*n*=60,267). We presented age-standardized incidence rates, the proportion of patients with an SLNB, the proportion of patients who received a novel drug (for their primary diagnosis), and one- and five-year relative survival rates.

Results

Between 2003 and 2018, the incidence rate increased from 10.9 to 23.9 for men and from 15.6 to 27.3 for women. This increase reflected the increasing incidence rate of patients with stage I and III. The proportion of patients with an SLNB increased from 23% to 64%. A reasonable increase was observed in the proportion of patients with a positive outcome (from 2% to 11%). For patients with stage IV, there was a shift from chemotherapy towards novel drugs as from 2013. The five-year relative survival rate increased from 81% to 92% for men and from 88% to 96% for women. This increase reflected the increasing five-year relative survival rate of patients with stage II, III, and IV.

Conclusion

We observed an increase in incidence for patients with stage I and III, and an improvement in survival for patients with stage II, III, and IV. These trends can be partly explained by the introduction of the SLNB and the novel drugs.

INTRODUCTION

Cutaneous melanoma (hereafter: melanoma) is a malignant tumor of the skin that originates from the melanocytes in the epidermis.[13] The incidence of melanoma has been steadily increasing over the last few decades. In 2020, melanoma was the sixth most commonly diagnosed cancer in Europe. A total of 150,627 patients were diagnosed with melanoma and 26,360 patients died from the disease. The Netherlands is one of the European countries with the highest incidence and mortality rate. In 2020, the Netherlands ranked second in terms of incidence (27.0 per 100,000 person-years) and seventh in terms of mortality (2.3 per 100,000 person-years).[1]

The treatment and survival of melanoma largely depends upon the stage of disease. Surgery is considered the gold standard for patients with localized disease (hereafter: stage I or II) and patients with regional lymph node metastases (hereafter: stage III). One of the most important developments in the surgical management of melanoma is the introduction of the sentinel lymph node biopsy (SLNB).[21] Information obtained from the SLNB has made it possible to stage patients more accurately, which has resulted in upstaging of patients whose regional lymph node metastases would otherwise have been missed.

Treatment options for patients with unresectable stage III and patients with distant metastases (hereafter: stage IV) have been limited for many years. Chemotherapy was the standard of care, but it never demonstrated to improve survival.[22] Advances in the understanding of melanoma biology has led to the introduction of novel immunotherapies and targeted therapies. The first two novel drugs, ipilimumab (an anti-CTLA-4 antibody) and vemurafenib (a BRAF inhibitor), were approved by the European Medicines Agency in 2011 and 2012, respectively. Since then, several other drugs became available for the treatment of patients with unresectable stage III and patients with stage IV.[18]

Although previous studies[23-26] examined trends in the incidence and survival of melanoma in the Netherlands, none of them reported recent or stage-specific trends. Therefore, we examined stage-specific trends in the incidence and survival of melanoma in the Netherlands between 2003 and 2018, i.e., the period in which the 6th, 7th, and 8th editions of the tumor-node-metastasis (TNM) classification were valid. In addition, we analyzed the uptake of the SLNB and the novel drugs during that period.

METHODS

Data source

Data were obtained from the nationwide population-based Netherlands Cancer Registry (NCR). The NCR is based on notification of all newly diagnosed cancer patients by the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA Foundation) and

the national registry of hospital discharge (for non-pathologically confirmed cancers). After notification, specially trained data managers routinely collect data on patient, tumor, and treatment characteristics from medical records. Data on vital status and date of death is annually retrieved from the database of deceased persons of the Central Bureau of Genealogy and the Personal Records Database.

Patient population

From the NCR, we selected all patients diagnosed with invasive primary cutaneous melanoma between 2003 and 2018. Patients with a prior malignancy (exception: basal cell carcinoma) and patients diagnosed at autopsy were excluded.

Data analysis

Data were extracted on year of diagnosis, age, gender, topography (i.e., site of the primary tumor), morphology (i.e., histology of the tumor), tumor thickness, tumor stage, number of metastatic lymph nodes, number of metastatic organs, surgery, systemic therapy, vital status, and date of death. Topography and morphology were coded according to the International Classification of Diseases for Oncology.[27] Tumor stage was coded according to the Union for International Cancer Control TNM classification valid at the time of diagnosis: 6th edition between 2003 and 2009, 7th edition between 2010 and 2016, and the 8th from 2017 onwards.[28-30] The pathological stage took precedence over the clinical stage. Patients who were diagnosed with melanoma of unknown primary (MUP) were staged accordingly.

Patients were stratified by year of diagnosis, stage at diagnosis, and/or gender. Baseline patient and tumor characteristics were summarized using descriptive statistics. Age was presented as mean and standard deviation as well as median and interquartile range. Topography, morphology, tumor thickness, tumor stage, number of metastatic lymph nodes, and number of metastatic organs were presented as counts and proportions. Incidence was presented as age-standardized incidence rates (European Standardized Rate [ESR] per 100,000 person-years). To examine trends in incidence, the annual percent change (APC) and 95% confidence intervals (CIs) were calculated using the Joinpoint Trend Analysis Software of the National Cancer Institute.[31] The uptake of the SLNB was analyzed by dividing the number of patients with an SLNB by the number of eligible patients (i.e., patients with pT1b or higher without clinically detected lymph node metastases). We additionally presented whether the outcome of the SLNB was positive, negative, or unknown. The uptake of the novel drugs was analyzed by calculating the proportion of patients who received chemotherapy, immunotherapy, or targeted therapy for their primary diagnosis. This was presented as from the introduction of the novel drugs in the Netherlands (in 2012) for patients with stage III and IV. Survival was presented as one- and five-year relative survival rates. Relative survival was calculated by dividing the survival of the melanoma population by the survival of the melanoma-free population. All analyses were conducted using STATA

statistical analysis software, version 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

RESULTS

Trends in baseline patient and tumor characteristics

A total of 60,267 patients were diagnosed with invasive primary cutaneous melanoma in the Netherlands between 2003 and 2018. Table 1 presents the trends in baseline patient and tumor characteristics. The median age at diagnosis increased from 50 years in 2003 to 59 years in 2018. During the same period, the proportion of men increased from 40% to 48%. Minor changes were observed in the categorical distribution of topography, morphology, and tumor thickness. Despite these changes, patients remained most frequently diagnosed with melanoma on the trunk, superficial spreading melanoma, and a tumor thickness of less than or equal to one millimeter.

Of all patients, 27,040 patients (45%) were men and 33,227 patients (55%) were women. Supplemental Table 1 presents the baseline patient and tumor characteristics by gender. In general, baseline characteristics were reasonably comparable between men and women, with the exception of age and morphology. Men were somewhat older and most frequently diagnosed with melanoma on the trunk. Women were most frequently diagnosed with melanoma on the lower extremities.

Trends in incidence

Figure 1 shows the trends in incidence. Between 2003 and 2018, the overall incidence rate (i.e., the incidence rate irrespective of stage at diagnosis) increased substantially for both genders: from 10.9 to 23.9 for men (APC 2003-2012: 6.5% [95% CI: 5.4%-7.6%]; APC 2012-2018: 3.2% [95% CI: 1.2%-5.2%]) and from 15.6 to 27.3 (APC 2003-2018: 4.0% [95% CI: 3.6%-4.5%]) for women. This increase reflected the increasing incidence rate of patients with stage I and III as the incidence rate of patients with other stages (II, IV, and MUP) remained reasonably stable.

Uptake of the sentinel lymph node biopsy

Figure 2 presents the uptake of the SLNB. The proportion of patients with an SLNB increased from 23% to 64% between 2003 and 2018. The steepest increase was observed as from 2013. Of the patients with an SLNB, the proportion of patients with a positive outcome increased from 2% to 11% during the same period. As the proportion of patients whose outcome was unknown decreased substantially (from 79% to 7%), there was also a substantial increase in the proportion of patients with a negative outcome (from 19% to 82%). Only minor differences were observed in the uptake of the SLNB between men and women (see Supplemental Figure 1).

Table 1. Trends in baseline patient and tumor characteristics (2003-2010)

	2003	2004	2005	2006	2007	2008	2009	2010
	n=2,327	*n*=2,492	*n*=2,720	*n*=2,740	*n*=2,909	*n*=3,185	*n*=3,364	*n*=3,626
Age, years								
Mean (SD)	51 (17)	52 (16)	52 (16)	53 (16)	53 (16)	54 (16)	54 (16)	55 (16)
Median (IQR)	50 (39-63)	51 (40-63)	51 (40-63)	52 (40-65)	52 (41-64)	53 (42-65)	53 (42-65)	55 (44-66)
Gender, *n* (%)								
Male	924 (40%)	1,065 (43%)	1,157 (43%)	1,163 (42%)	1,237 (43%)	1,389 (44%)	1,411 (42%)	1,644 (45%)
Female	1,403 (60%)	1,427 (57%)	1,563 (57%)	1,577 (58%)	1,672 (57%)	1,796 (56%)	1,953 (58%)	1,982 (55%)
Topography, *n* (%)								
Head and neck	284 (12%)	297 (12%)	327 (12%)	305 (11%)	318 (11%)	344 (11%)	388 (12%)	441 (12%)
Trunk	795 (34%)	885 (36%)	1,002 (37%)	1,001 (37%)	1,095 (38%)	1,193 (37%)	1,289 (38%)	1,388 (38%)
Upper extremity	425 (18%)	492 (20%)	509 (19%)	525 (19%)	539 (19%)	659 (21%)	692 (21%)	733 (20%)
Lower extremity	727 (31%)	728 (29%)	772 (28%)	805 (29%)	827 (28%)	869 (27%)	866 (26%)	917 (25%)
Unknown	96 (4%)	90 (4%)	110 (4%)	104 (4%)	130 (4%)	120 (4%)	129 (4%)	147 (4%)
Morphology, *n* (%)								
Superficial spreading	1,348 (58%)	1,470 (59%)	1,705 (63%)	1,740 (64%)	1,852 (64%)	2,050 (64%)	2,190 (65%)	2,473 (68%)
Nodular	344 (15%)	318 (13%)	349 (13%)	341 (12%)	314 (11%)	400 (13%)	433 (13%)	401 (11%)
Lentigo maligna	54 (2%)	71 (3%)	55 (2%)	78 (3%)	68 (2%)	91 (3%)	93 (3%)	126 (3%)
Acral lentiginous	17 (1%)	29 (1%)	22 (1%)	21 (1%)	19 (1%)	19 (1%)	19 (1%)	17 (0%)
Other	85 (4%)	97 (4%)	108 (4%)	95 (3%)	88 (3%)	78 (2%)	98 (3%)	96 (3%)
Unknown	479 (21%)	507 (20%)	481 (18%)	465 (17%)	568 (20%)	547 (17%)	531 (16%)	513 (14%)
Tumor thickness, mm, *n* (%)								
≤1.00	1,084 (47%)	1,215 (49%)	1,359 (50%)	1,327 (48%)	1,427 (49%)	1,696 (53%)	1,769 (53%)	1,990 (55%)
1.01-2.00	514 (22%)	520 (21%)	562 (21%)	610 (22%)	676 (23%)	657 (21%)	703 (21%)	729 (20%)
2.01-4.00	346 (15%)	360 (14%)	391 (14%)	370 (14%)	357 (12%)	360 (11%)	430 (13%)	420 (12%)

Table 1. Trends in baseline patient and tumor characteristics (2003-2010) (continued)

	2003	2004	2005	2006	2007	2008	2009	2010
	n=2,327	*n*=2,492	*n*=2,720	*n*=2,740	*n*=2,909	*n*=3,185	*n*=3,364	*n*=3,626
>4.00	208 (9%)	227 (9%)	215 (8%)	241 (9%)	239 (8%)	253 (8%)	237 (7%)	245 (7%)
Unknown	175 (8%)	170 (7%)	193 (7%)	192 (7%)	210 (7%)	219 (7%)	225 (7%)	242 (7%)
Tumor stage, *n* (%)								
I	1,490 (64%)	1,628 (65%)	1,819 (67%)	1,802 (66%)	1,969 (68%)	2,212 (69%)	2,308 (69%)	2,552 (70%)
II	475 (20%)	512 (21%)	504 (19%)	532 (19%)	504 (17%)	530 (17%)	579 (17%)	579 (16%)
III	206 (9%)	203 (8%)	225 (8%)	220 (8%)	258 (9%)	233 (7%)	275 (8%)	284 (8%)
IV	97 (4%)	84 (3%)	99 (4%)	105 (4%)	106 (4%)	116 (4%)	124 (4%)	133 (4%)
MUP	59 (3%)	63 (3%)	70 (3%)	79 (3%)	72 (2%)	94 (3%)	77 (2%)	77 (2%)
Unknown	0 (0%)	2 (0%)	3 (0%)	2 (0%)	0 (0%)	0 (0%)	1 (0%)	1 (0%)
Number of metastatic lymph nodes, *n* (%)								
No examination	1,781 (77%)	1,989 (80%)	2,227 (82%)	2,195 (80%)	2,294 (79%)	2,544 (80%)	2,594 (77%)	2,855 (79%)
0	369 (16%)	344 (14%)	326 (12%)	381 (14%)	429 (15%)	455 (14%)	548 (16%)	558 (15%)
1	103 (4%)	86 (3%)	96 (4%)	90 (3%)	112 (4%)	108 (3%)	127 (4%)	136 (4%)
2	38 (2%)	32 (1%)	30 (1%)	33 (1%)	31 (1%)	40 (1%)	49 (1%)	43 (1%)
3	11 (0%)	13 (1%)	9 (0%)	13 (0%)	20 (1%)	16 (1%)	17 (1%)	12 (0%)
≥4	14 (1%)	24 (1%)	24 (1%)	25 (1%)	17 (1%)	20 (1%)	26 (1%)	20 (1%)
Unknown	11 (0%)	4 (0%)	8 (0%)	3 (0%)	6 (0%)	2 (0%)	3 (0%)	2 (0%)
Number of metastatic organs, *n* (%)								
0	2,255 (97%)	2,408 (97%)	2,590 (95%)	2,611 (95%)	2,768 (95%)	3,044 (96%)	3,208 (95%)	3,457 (95%)
<3	58 (2%)	67 (3%)	107 (4%)	94 (3%)	92 (3%)	101 (3%)	102 (3%)	115 (3%)
≥3	14 (1%)	17 (1%)	23 (1%)	35 (1%)	49 (2%)	40 (1%)	54 (2%)	54 (1%)

Table 1. Trends in baseline patient and tumor characteristics (2011-2018)

	2011	2012	2013	2014	2015	2016	2017	2018
	n=3,985	*n*=4,081	*n*=4,344	*n*=4,482	*n*=4,666	*n*=5,216	*n*=4,938	*n*=5,192
Age, years								
Mean (SD)	55 (16)	56 (16)	56 (15)	57 (16)	57 (15)	58 (15)	59 (15)	59 (15)
Median (IQR)	54 (44-66)	56 (45-67)	56 (46-67)	57 (46-68)	57 (46-68)	58 (47-69)	59 (48-70)	59 (49-71)
Gender, *n* (%)								
Male	1,783 (45%)	1,891 (46%)	1,977 (46%)	2,061 (46%)	2,148 (46%)	2,403 (46%)	2,319 (47%)	2,468 (48%)
Female	2,202 (55%)	2,190 (54%)	2,367 (54%)	2,421 (54%)	2,518 (54%)	2,813 (54%)	2,619 (53%)	2,724 (52%)
Topography, *n* (%)								
Head and neck	461 (12%)	465 (11%)	482 (11%)	522 (12%)	538 (12%)	580 (11%)	601 (12%)	623 (12%)
Trunk	1,499 (38%)	1,622 (40%)	1,711 (39%)	1,769 (39%)	1,806 (39%)	1,986 (38%)	1,909 (39%)	2,035 (39%)
Upper extremity	794 (20%)	795 (19%)	932 (21%)	903 (20%)	977 (21%)	1,133 (22%)	1,056 (21%)	1,090 (21%)
Lower extremity	1,086 (27%)	1,063 (26%)	1,099 (25%)	1,144 (26%)	1,188 (25%)	1,345 (26%)	1,208 (24%)	1,299 (25%)
Unknown	145 (4%)	136 (3%)	120 (3%)	144 (3%)	157 (3%)	172 (3%)	164 (3%)	145 (3%)
Morphology, *n* (%)								
Superficial spreading	2,746 (69%)	2,801 (69%)	3,122 (72%)	3,247 (72%)	3,415 (73%)	3,982 (76%)	3,712 (75%)	3,947 (76%)
Nodular	445 (11%)	480 (12%)	483 (11%)	417 (9%)	453 (10%)	441 (8%)	441 (9%)	435 (8%)
Lentigo maligna	131 (3%)	176 (4%)	166 (4%)	196 (4%)	186 (4%)	180 (3%)	194 (4%)	218 (4%)
Acral lentiginous	30 (1%)	42 (1%)	49 (1%)	37 (1%)	42 (1%)	36 (1%)	40 (1%)	34 (1%)
Other	80 (2%)	71 (2%)	96 (2%)	97 (2%)	76 (2%)	64 (1%)	77 (2%)	73 (1%)
Unknown	553 (14%)	511 (13%)	428 (10%)	488 (11%)	494 (11%)	513 (10%)	474 (10%)	485 (9%)
Tumor thickness, mm, *n* (%)								
≤1.00	2,226 (56%)	2,295 (56%)	2,503 (58%)	2,555 (57%)	2,648 (57%)	3,095 (59%)	2,839 (57%)	2,991 (58%)
1.01-2.00	785 (20%)	821 (20%)	889 (20%)	929 (21%)	954 (20%)	1,040 (20%)	915 (19%)	990 (19%)
2.01-4.00	450 (11%)	471 (12%)	439 (10%)	542 (12%)	530 (11%)	530 (10%)	517 (10%)	533 (10%)

Table 1. Trends in baseline patient and tumor characteristics (2011-2018) (continued)

	2011	2012	2013	2014	2015	2016	2017	2018
	n=3,985	*n*=4,081	*n*=4,344	*n*=4,482	*n*=4,666	*n*=5,216	*n*=4,938	*n*=5,192
>4.00	280 (7%)	266 (7%)	310 (7%)	242 (5%)	310 (7%)	311 (6%)	357 (7%)	332 (6%)
Unknown	244 (6%)	228 (6%)	203 (5%)	214 (5%)	224 (5%)	240 (5%)	310 (6%)	346 (7%)
Tumor stage, *n* (%)								
I	2,816 (71%)	2,938 (72%)	3,179 (73%)	3,285 (73%)	3,378 (72%)	3,904 (75%)	3,532 (72%)	3,747 (72%)
II	627 (16%)	626 (15%)	644 (15%)	654 (15%)	705 (15%)	712 (14%)	694 (14%)	704 (14%)
III	327 (8%)	317 (8%)	338 (8%)	350 (8%)	376 (8%)	386 (7%)	427 (9%)	411 (8%)
IV	135 (3%)	122 (3%)	118 (3%)	142 (3%)	157 (3%)	169 (3%)	155 (3%)	151 (3%)
MUP	80 (2%)	76 (2%)	65 (1%)	51 (1%)	50 (1%)	42 (1%)	47 (1%)	63 (1%)
Unknown	0 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0%)	83 (2%)	116 (2%)
Number of metastatic lymph nodes, *n* (%)								
No examination	3,076 (77%)	3,129 (77%)	3,167 (73%)	3,162 (71%)	3,089 (66%)	3,466 (66%)	3,270 (66%)	3,415 (66%)
0	660 (17%)	692 (17%)	895 (21%)	1,027 (23%)	1,250 (27%)	1,431 (27%)	1,304 (26%)	1,405 (27%)
1	166 (4%)	161 (4%)	187 (4%)	183 (4%)	205 (4%)	208 (4%)	241 (5%)	249 (5%)
2	48 (1%)	44 (1%)	44 (1%)	61 (1%)	66 (1%)	68 (1%)	62 (1%)	66 (1%)
3	9 (0%)	31 (1%)	21 (0%)	20 (0%)	31 (1%)	21 (0%)	19 (0%)	26 (1%)
≥4	23 (1%)	20 (0%)	25 (1%)	27 (1%)	24 (1%)	19 (0%)	35 (1%)	27 (1%)
Unknown	3 (0%)	4 (0%)	5 (0%)	2 (0%)	1 (0%)	3 (0%)	7 (0%)	4 (0%)
Number of metastatic organs, *n* (%)								
0	3,810 (96%)	3,911 (96%)	4,190 (96%)	4,301 (96%)	4,466 (96%)	5,003 (96%)	4,750 (96%)	5,009 (96%)
<3	121 (3%)	120 (3%)	103 (2%)	118 (3%)	132 (3%)	135 (3%)	107 (2%)	107 (2%)
≥3	54 (1%)	50 (1%)	51 (1%)	63 (1%)	68 (1%)	78 (1%)	81 (2%)	76 (1%)

IQR, interquartile range; mm, millimeter; MUP, melanoma of unknown primary; *n*, number; SD, standard deviation.

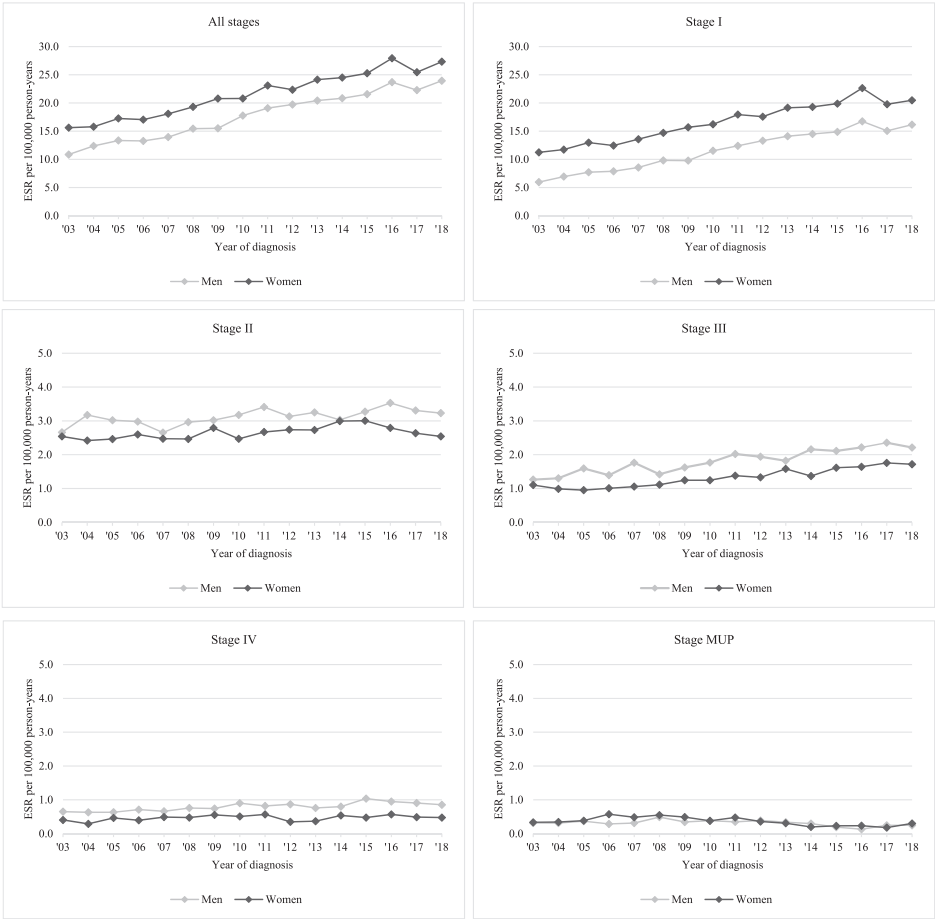


Figure 1. Trends in incidence stratified by stage at diagnosis and gender[a,b,c]
ESR, European Standardized Rate; MUP, melanoma of unknown primary.
[a]Please note the different scales on the y-axis.
[b]Incidence rates are presented in numbers in Supplemental Table 2.
[c]The annual percent change and 95% confidence intervals are presented in Supplemental Table 3.

Uptake of the novel drugs

Figure 3 shows the uptake of the novel drugs. As from 2012, only a minority of patients with stage III received a novel drug for their primary diagnosis. The annual proportion of patients who received targeted therapy was less than 4%. For patients who received immunotherapy, the annual proportion was less than 6%, except for 2018. Between 2017 and 2018, the proportion increased substantially: from 5% to 16%. For patients with stage IV, there was a shift from chemotherapy towards immunotherapy and targeted therapy as from 2013. Since then, the proportion of patients who received immunotherapy or targeted therapy for their primary diagnosis increased substantially: from 1% to 46% and from 1% to 27% between 2013 and 2018, respectively. The

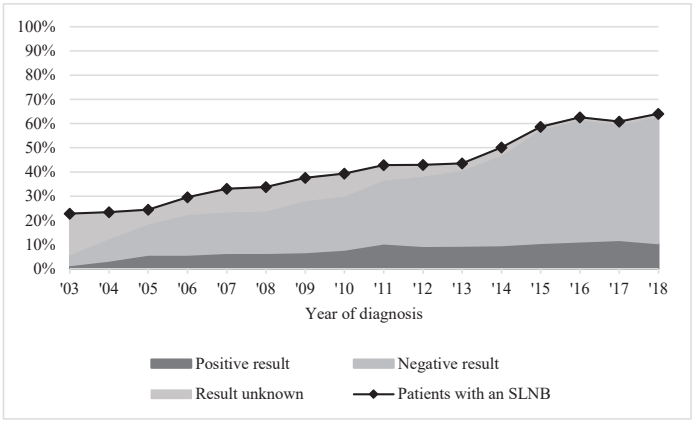


Figure 2. Uptake of the sentinel lymph node biopsy
SLNB, sentinel lymph node biopsy.

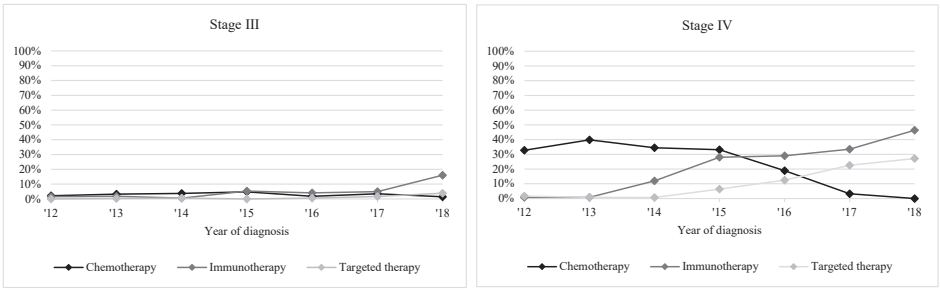


Figure 3. Uptake of the novel drugs stratified by stage at diagnosis

proportion of patients who received chemotherapy decreased from 40% to 0% during the same period. There were no remarkable differences in the uptake of the novel drugs between men and women (see Supplemental Figure 2).

Trends in survival

Figure 4 presents the trends in survival. Between 2003 and 2018, the overall one-year relative survival rate (i.e., the relative survival rate irrespective of stage at diagnosis) remained stable for both genders. The overall five-year relative survival rate increased, however, substantially: from 81% to 92% for men and from 88% to 96% for women. This increase predominantly reflected the increasing five-year relative survival rate of patients with stage II and III: from 66% to 81% (stage II) and from 62% to 69% (stage III) for men, and from 72% to 85% (stage II) and from 62% to 74% (stage III) for women, respectively. A steep increase in the five-year relative survival rate was also observed for patients with stage IV in recent years. Between 2013 and 2015, the five-year relative survival rate increased from 12% to 24% for men and from 21% to 31% for women. Although our observation period was not sufficient to evaluate the five-year relative

survival rate beyond 2015, it is worth noting that the one-year relative survival rate of patients with stage IV decreased as from 2016. Relative survival rates of patients with stage I and MUP remained reasonably stable.

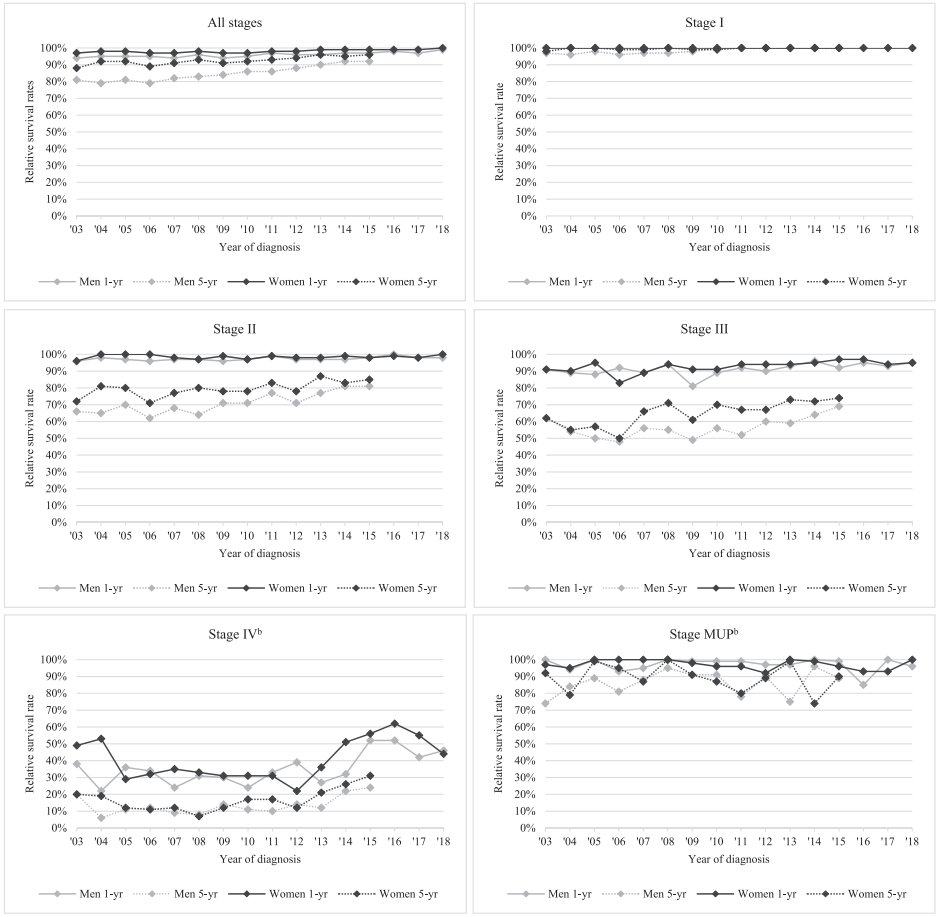


Figure 4. Trends in survival stratified by stage at diagnosis and gender[a]
MUP, melanoma of unknown primary; yr, year.
[a]Relative survival rates are presented in numbers in Supplemental Table 4.
[b]Please note the low patient numbers (see Supplemental Table 1).

DISCUSSION

In our study, we examined stage-specific trends in the incidence and survival of cutaneous melanoma in the Netherlands between 2003 and 2018 as well as the uptake of the SLNB and the novel drugs during that period. The incidence increased substantially for patients with stage I and III but remained reasonably stable for patients with other stages (II, IV, and MUP). For patients with stage I, this may have been driven by several factors, including increased exposure to ultraviolet

radiation and earlier diagnosis due to enhanced awareness. For example, it is commonly known that men are more reluctant to go to the doctor than women. Hence, greater attention has been given to men in awareness campaigns in recent years. The results of our study suggest that these efforts may have resulted in earlier diagnosis among men as the incidence of patients with stage I increased more steeply in men than in women.

Both factors also may have driven the increased incidence of patients with stage III. In addition, we believe that the increase is due to upstaging of patients. Because of the SLNB, patients who (without the SLNB) would have been diagnosed with stage II are now diagnosed with stage III. During our study period, the proportion of patients with an SLNB almost tripled: from 23% in 2003 to 64% in 2018. The increase was most pronounced as from 2013. This may be owing to changes in guideline recommendations. According to the fourth revision of the Dutch melanoma guideline (published in 2004)[32], the SLNB was only recommended for patients who wanted to be optimally informed about their prognosis. In the fifth revision of the guideline (published in 2012)[33], it became a standard diagnostic procedure for patients diagnosed with a tumor thickness of more than 1.0 millimeter and/or ulceration. Although we already observed a reasonable increase in the proportion of patients with a positive outcome (from 2% to 11%), there is room for improvement as one-third of the eligible patients still do not undergo an SLNB. Even if this would not result in a higher proportion of patients with a positive outcome, more patients will be accurately staged and can, therefore, receive the most appropriate care.

The upstaging of patients is probably also responsible for the increased survival of patients with stage II and III. As the survival of patients who are upstaged is worse than the survival of patients with stage II but better than the survival of patients who are clinically diagnosed with stage III, survival of both patient groups increases. This may suggest that we did not observe a real increase in survival, but rather a more accurate estimation of the survival. On the other hand, we should not underestimate the impact of the novel drugs. Even though only a small proportion of patients with stage III received a novel drug for their primary diagnosis, they may have received one or more novel drugs after developing disease progression. The same applies to patients with stage II. According to a previous Dutch study[34], approximately 30% of the patients with stage II and 50% of the patients with stage III will eventually develop disease progression. Two-thirds of these patients will develop distant metastases either as first or subsequent recurrence. Whether our patients received one or more novel drugs after developing disease progression could not be examined with our data.

Compared to patients with stage III, the proportion of patients who received a novel drug for their primary diagnosis was much higher for patients with stage IV. For these patients, there was a shift towards the novel drugs as from 2013. Patients more frequently received immunotherapy than targeted therapy. This is mainly because targeted therapy can only be applied to patients

whose melanoma harbors a mutation in the BRAF gene. Approximately 60% of the melanomas harbor this mutation.[5] The novel drugs have had a large impact on the survival of patients with stage IV. Between 2013 and 2015, there was an absolute change in the one- and five-year relative survival rate of 25% and 12% for men and 20% and 10% for women, respectively. It should, however, be noted that the one-year relative survival rate decreased as from 2016. This is, however, most likely due to low patient numbers as we only included patients who were primarily diagnosed with stage IV. A previous Dutch study[35] showed that the one-year survival rate of all patients with stage IV (irrespective of their stage at diagnosis) increased from 48% in 2013-2014 to 59% in 2015-2017.

Our study has some key strengths, including the national coverage and the extensiveness of the results. Furthermore, to our knowledge, we present the most recent insight into stage-specific trends in the incidence and survival of patients diagnosed with melanoma in a European country. Other studies[36-40] reported comparable trends but covered earlier time periods and/or did not report stage-specific trends.

Our study should, however, also be viewed in the light of some limitations. First, our analyses were limited to stage at diagnosis as only the primary diagnosis is recorded for all patients by the NCR. Therefore, we were not able to provide insight into the proportion of patients that received a novel drug after developing disease progression or to draw conclusions on the effect of disease progression and novel drugs on survival. Second, our data did not allow for differentiating between patients with resectable and unresectable stage III. This would have provided more adequate insight into the uptake of the novel drugs as they were only available for patients with unresectable stage III during our study period.

In conclusion, we observed an increase in incidence for patients with stage I and III, and an improvement in survival for patients with stage II, III, and IV. These trends can be partly explained by the introduction of the SLNB and the novel drugs. As the indication for these drugs recently expanded to resectable stage III, we expect that survival will continue to improve.

Supplemental Table 1. Trends in baseline patient and tumor characteristics stratified by gender (2003-2008)

	2003		2004		2005		2006		2007		2008	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	n=924	*n*=1,403	*n*=1,065	*n*=1,427	*n*=1,157	*n*=1,563	*n*=1,163	*n*=1,577	*n*=1,237	*n*=1,672	*n*=1,389	*n*=1,796
Age, years												
Mean (SD)	53 (15)	51 (17)	53 (15)	52 (17)	53 (16)	51 (17)	53 (15)	53 (17)	54 (15)	52 (17)	55 (15)	53 (17)
Median (IQR)	53 (41-63)	49 (38-62)	53 (41-64)	50 (39-63)	53 (42-64)	48 (38-62)	54 (41-63)	51 (40-66)	55 (43-65)	50 (40-63)	55 (44-65)	51 (40-64)
Topography, *n* (%)												
Head and neck	15%	10%	14%	11%	16%	9%	13%	10%	11%	11%	12%	10%
Trunk	45%	27%	48%	26%	46%	30%	47%	29%	51%	28%	50%	28%
Upper extremity	16%	19%	17%	22%	16%	21%	16%	21%	16%	20%	17%	23%
Lower extremity	19%	40%	16%	39%	16%	38%	18%	38%	15%	38%	15%	36%
Unknown	5%	3%	5%	2%	6%	3%	6%	2%	6%	3%	5%	3%
Morphology, *n* (%)												
Superficial spreading	53%	61%	54%	63%	59%	66%	61%	66%	62%	65%	61%	67%
Nodular	17%	13%	14%	12%	15%	11%	15%	11%	12%	10%	14%	11%
Lentigo maligna	2%	3%	2%	4%	1%	2%	2%	3%	2%	3%	3%	3%
Acral lentiginous	0%	1%	1%	1%	0%	1%	1%	1%	0%	1%	1%	1%
Other	4%	3%	5%	3%	5%	3%	4%	3%	4%	3%	3%	2%
Unknown	23%	19%	24%	18%	20%	16%	18%	16%	21%	19%	19%	16%
Tumor thickness, mm, *n* (%)												
≤1.00	38%	52%	41%	54%	41%	56%	41%	54%	42%	54%	48%	57%
1.01-2.00	22%	22%	20%	21%	21%	20%	23%	22%	25%	22%	20%	21%
2.01-4.00	19%	12%	17%	12%	17%	12%	17%	11%	14%	11%	14%	10%
>4.00	12%	7%	13%	6%	11%	6%	10%	8%	10%	7%	11%	6%
Unknown	10%	6%	9%	5%	9%	5%	8%	6%	9%	6%	8%	6%

Supplemental Table 1. Trends in baseline patient and tumor characteristics stratified by gender (2003-2008) (continued)

	2003		2004		2005		2006		2007		2008	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	n=924	*n*=1,403	*n*=1,065	*n*=1,427	*n*=1,157	*n*=1,563	*n*=1,163	*n*=1,577	*n*=1,237	*n*=1,672	*n*=1,389	*n*=1,796
Tumor stage, *n* (%)												
I	55%	70%	56%	72%	58%	74%	59%	71%	61%	73%	63%	74%
II	25%	18%	26%	17%	23%	15%	22%	17%	19%	16%	20%	14%
III	12%	7%	10%	6%	12%	6%	11%	6%	13%	6%	9%	6%
IV	6%	3%	5%	2%	5%	3%	6%	3%	5%	3%	5%	3%
MUP	3%	2%	3%	3%	3%	2%	2%	3%	2%	3%	3%	3%
Unknown	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Number of metastatic lymph nodes, *n* (%)												
No examination	73%	79%	76%	83%	78%	85%	76%	83%	75%	81%	77%	82%
0	16%	15%	15%	13%	14%	11%	17%	12%	15%	14%	15%	13%
1	6%	4%	5%	3%	4%	3%	4%	2%	6%	2%	4%	3%
2	2%	1%	2%	1%	2%	1%	1%	1%	2%	1%	2%	1%
3	1%	0%	1%	0%	1%	0%	0%	1%	1%	1%	1%	0%
≥4	1%	0%	1%	1%	1%	1%	1%	1%	1%	0%	1%	0%
Unknown	1%	0%	0%	0%	1%	0%	0%	0%	0%	0%	0%	0%
Number of metastatic organs, *n* (%)												
0	96%	98%	95%	98%	93%	97%	93%	97%	94%	96%	94%	97%
<3	3%	2%	4%	2%	6%	3%	5%	2%	4%	3%	4%	3%
≥3	1%	0%	1%	0%	1%	1%	2%	1%	2%	1%	2%	1%

Supplemental Table 1. Trends in baseline patient and tumor characteristics stratified by gender (2009-2014)

	2009		2010		2011		2012		2013		2014	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	n=1,411	*n*=1,953	*n*=1,644	*n*=1,982	*n*=1,783	*n*=2,202	*n*=1,891	*n*=2,190	*n*=1,977	*n*=2,367	*n*=2,061	*n*=2,421
Age, years												
Mean (SD)	55 (15)	53 (17)	56 (15)	54 (16)	57 (15)	54 (16)	58 (15)	55 (16)	58 (14)	55 (16)	58 (14)	55 (17)
Median (IQR)	56 (44-65)	52 (40-65)	57 (46-66)	53 (42-65)	57 (47-67)	52 (42-65)	59 (48-68)	54 (43-66)	58 (48-68)	54 (44-66)	59 (48-69)	54 (44-68)
Topography, *n* (%)												
Head and neck	14%	10%	15%	10%	14%	10%	13%	10%	13%	10%	15%	9%
Trunk	49%	31%	49%	30%	49%	29%	51%	30%	50%	31%	52%	29%
Upper extremity	18%	23%	17%	23%	17%	22%	17%	22%	19%	23%	16%	23%
Lower extremity	14%	34%	14%	34%	16%	36%	14%	36%	15%	34%	13%	36%
Unknown	5%	3%	5%	3%	4%	3%	5%	2%	4%	2%	4%	2%
Morphology, *n* (%)												
Superficial spreading	62%	67%	65%	71%	66%	71%	67%	70%	70%	73%	70%	74%
Nodular	14%	12%	12%	10%	13%	10%	13%	11%	12%	11%	11%	8%
Lentigo maligna	3%	3%	4%	3%	3%	3%	3%	5%	3%	4%	4%	5%
Acral lentiginous	0%	1%	1%	0%	1%	1%	1%	1%	1%	1%	1%	1%
Other	3%	3%	3%	2%	2%	2%	2%	2%	3%	2%	2%	2%
Unknown	17%	15%	16%	13%	15%	13%	14%	12%	11%	9%	12%	10%
Tumor thickness, mm, *n* (%)												
≤1.00	46%	57%	50%	59%	51%	60%	52%	60%	53%	62%	52%	62%
1.01-2.00	22%	20%	20%	20%	20%	20%	20%	20%	21%	20%	22%	19%
2.01-4.00	16%	11%	13%	11%	14%	9%	13%	10%	12%	9%	14%	11%
>4.00	9%	6%	9%	5%	9%	5%	7%	6%	9%	6%	6%	5%
Unknown	8%	6%	8%	5%	7%	5%	8%	4%	6%	3%	6%	4%

Supplemental Table 1. Trends in baseline patient and tumor characteristics stratified by gender (2009-2014) (continued)

	2009		2010		2011		2012		2013		2014	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	n=1,411	*n*=1,953	*n*=1,644	*n*=1,982	*n*=1,783	*n*=2,202	*n*=1,891	*n*=2,190	*n*=1,977	*n*=2,367	*n*=2,061	*n*=2,421
Tumor stage, *n* (%)												
I	63%	73%	64%	75%	65%	75%	67%	76%	68%	77%	69%	77%
II	20%	15%	18%	14%	19%	13%	16%	14%	17%	13%	15%	14%
III	11%	6%	10%	6%	10%	6%	10%	6%	9%	7%	10%	6%
IV	5%	3%	5%	2%	4%	3%	4%	2%	4%	2%	4%	2%
MUP	2%	2%	2%	2%	2%	2%	2%	2%	2%	1%	1%	1%
Unknown	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Number of metastatic lymph nodes, *n* (%)												
No examination	74%	80%	77%	80%	68%	75%	67%	74%	63%	70%	46%	53%
0	17%	16%	16%	15%	20%	17%	20%	19%	26%	23%	41%	40%
1	5%	3%	4%	3%	6%	3%	5%	3%	5%	3%	6%	3%
2	2%	1%	2%	1%	1%	1%	2%	1%	1%	1%	2%	1%
3	0%	1%	0%	0%	0%	0%	1%	1%	1%	0%	1%	0%
≥4	2%	0%	1%	0%	1%	0%	1%	0%	1%	0%	1%	0%
Unknown	0%	0%	0%	0%	4%	3%	5%	2%	3%	2%	3%	2%
Number of metastatic organs, *n* (%)												
0	94%	96%	94%	97%	95%	97%	94%	98%	95%	98%	95%	97%
<3	4%	2%	4%	2%	4%	2%	4%	2%	3%	2%	3%	2%
≥3	2%	1%	2%	1%	2%	1%	2%	1%	2%	1%	2%	1%

Supplemental Table 1. Trends in baseline patient and tumor characteristics stratified by gender (2015-2018)

	2015		2016		2017		2018	
	Men	Women	Men	Women	Men	Women	Men	Women
	n=2,148	*n*=2,518	*n*=2,403	*n*=2,813	*n*=2,319	*n*=2,619	*n*=2,468	*n*=2,724
Age, years								
Mean (SD)	58 (15)	56 (16)	59 (14)	56 (16)	60 (14)	57 (16)	61 (14)	57 (16)
Median (IQR)	59 (49-69)	55 (44-68)	60 (50-70)	56 (45-68)	60 (50-70)	57 (57)	61 (52-71)	56 (46-70)
Topography, *n* (%)								
Head and neck	13%	10%	15%	8%	14%	10%	15%	10%
Trunk	50%	29%	48%	29%	49%	30%	50%	29%
Upper extremity	17%	24%	19%	24%	19%	24%	18%	23%
Lower extremity	15%	35%	14%	36%	14%	33%	13%	36%
Unknown	5%	2%	4%	3%	4%	2%	3%	2%
Morphology, *n* (%)								
Superficial spreading	72%	75%	74%	78%	74%	77%	74%	78%
Nodular	10%	9%	10%	7%	10%	8%	9%	7%
Lentigo maligna	4%	4%	4%	3%	4%	4%	5%	4%
Acral lentiginous	1%	1%	0%	1%	1%	1%	1%	1%
Other	2%	2%	1%	1%	2%	1%	2%	1%
Unknown	12%	9%	10%	9%	10%	9%	10%	9%
Tumor thickness, mm, *n* (%)								
≤1.00	53%	60%	55%	63%	53%	61%	53%	62%
1.01-2.00	20%	21%	20%	20%	18%	19%	20%	18%
2.01-4.00	13%	10%	13%	8%	12%	9%	12%	8%
>4.00	8%	5%	7%	5%	9%	6%	7%	6%
Unknown	6%	4%	6%	4%	7%	5%	7%	6%

Supplemental Table 1. Trends in baseline patient and tumor characteristics stratified by gender (2015-2018) (continued)

	2015		2016		2017		2018	
	Men	Women	Men	Women	Men	Women	Men	Women
	n=2,148	*n*=2,518	*n*=2,403	*n*=2,813	*n*=2,319	*n*=2,619	*n*=2,468	*n*=2,724
Tumor stage, *n* (%)								
I	68%	76%	70%	79%	67%	76%	69%	75%
II	16%	14%	16%	12%	16%	12%	15%	12%
III	10%	7%	9%	6%	10%	7%	9%	7%
IV	5%	2%	4%	2%	4%	2%	4%	2%
MUP	1%	1%	1%	1%	1%	1%	1%	1%
Unknown	0%	0%	0%	0%	1%	2%	2%	2%
Number of metastatic lymph nodes, *n* (%)								
No examination	2%	1%	0%	1%	17%	17%	51%	55%
0	86%	91%	88%	92%	70%	74%	37%	36%
1	5%	4%	5%	3%	6%	4%	6%	4%
2	2%	1%	2%	1%	2%	1%	2%	1%
3	1%	0%	0%	0%	1%	0%	1%	0%
≥4	1%	0%	1%	0%	1%	1%	1%	0%
Unknown	3%	2%	4%	2%	4%	3%	3%	3%
Number of metastatic organs, *n* (%)								
0	94%	97%	95%	97%	95%	97%	95%	97%
<3	4%	2%	3%	2%	3%	2%	3%	2%
≥3	2%	1%	2%	1%	2%	1%	2%	1%

IQR, interquartile range; mm, millimeter; MUP, melanoma of unknown primary; *n*, number; SD, standard deviation.

Supplemental Table 2. Trends in incidence stratified by stage at diagnosis and gender

	All stages		Stage I		Stage II		Stage III		Stage IV		Stage MUP	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
2003	10.9	15.6	6.0	11.2	2.7	2.5	1.3	1.1	0.7	0.4	0.3	0.3
2004	12.4	15.8	6.9	11.7	3.2	2.4	1.3	1.0	0.6	0.3	0.3	0.3
2005	13.3	17.3	7.7	13.0	3.0	2.5	1.6	1.0	0.6	0.5	0.4	0.4
2006	13.3	17.0	7.9	12.4	3.0	2.6	1.4	1.0	0.7	0.4	0.3	0.6
2007	13.9	18.1	8.5	13.6	2.7	2.5	1.8	1.1	0.7	0.5	0.3	0.5
2008	15.4	19.3	9.8	14.7	3.0	2.5	1.4	1.1	0.8	0.5	0.5	0.6
2009	15.5	20.8	9.8	15.7	3.0	2.8	1.6	1.2	0.7	0.6	0.3	0.5
2010	17.8	20.8	11.5	16.2	3.2	2.5	1.8	1.2	0.9	0.5	0.4	0.4
2011	19.1	23.1	12.4	17.9	3.4	2.7	2.0	1.4	0.8	0.6	0.4	0.5
2012	19.7	22.3	13.3	17.6	3.1	2.7	1.9	1.3	0.9	0.4	0.4	0.4
2013	20.4	24.1	14.1	19.2	3.3	2.7	1.8	1.6	0.8	0.4	0.3	0.3
2014	20.8	24.5	14.5	19.3	3.0	3.0	2.2	1.4	0.8	0.5	0.3	0.2
2015	21.6	25.3	14.9	19.9	3.3	3.0	2.1	1.6	1.0	0.5	0.2	0.2
2016	23.7	27.9	16.7	22.6	3.5	2.8	2.2	1.6	1.0	0.6	0.1	0.2
2017	22.3	25.4	15.1	19.8	3.3	2.6	2.4	1.8	0.9	0.5	0.2	0.2
2018	23.9	27.3	16.1	20.5	3.2	2.5	2.2	1.7	0.9	0.5	0.2	0.3

MUP, melanoma of unknown primary.

Supplemental Table 3. Results of the Joinpoint Trend Analysis

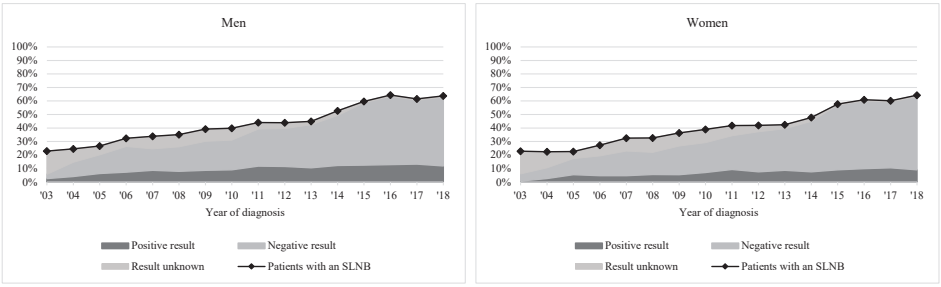
	Men					
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
All stages	2003-2012	6.5% (5.4%-7.6%)	2012-2018	3.2% (1.2%-5.2%)		
Stage I	2003-2013	8.8% (7.7%-9.8%)	2013-2018	2.3% (-0.5%-5.2%)		
Stage II	2003-2018	1.0% (0.3%-1.7%)				
Stage III	2003-2018	3.9% (2.9%-5.0%)				
Stage IV	2003-2018	2.9% (1.8%-4.0%)				
Stage MUP	2003-2012	3.8% (-1.7%-9.5%)	2012-2016	-25.2% (-44.4%-0.5%)	2016-2018	28.1% (-29.1%-131.6%)
	Women					
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
All stages	2003-2018	4.0% (3.6%-4.5%)				
Stage I	2003-2016	5.2% (4.6%-5.8%)	2016-2018	-4.4% (-13.9%-6.1%)		
Stage II	2003-2015	1.6% (0.8%-2.3%)	2015-2018	-4.9% (-10.6%-1.3%)		
Stage III	2003-2018	4.1% (3.3%-5.0%)				
Stage IV	2003-2018	1.8% (-0.2%-3.8%)				
Stage MUP	2003-2008	16.8% (2.8%-32.6%)	2008-2016	-14.6% (-20.0%--7.9%)	2016-2018	25.5% (-28.8%-121.4%)

APC, annual percent change; CI, confidence interval; MUP, melanoma of unknown primary.

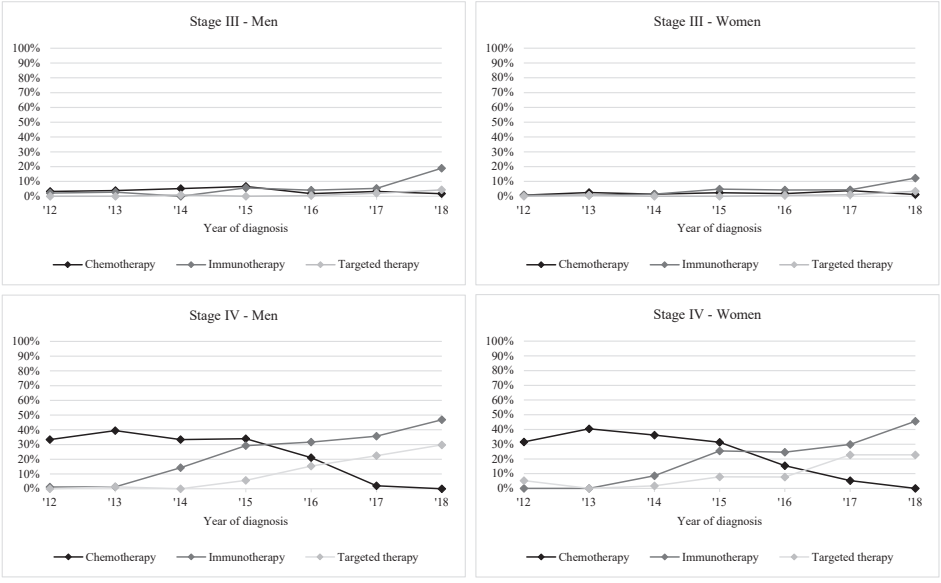
Supplemental Table 4. Trends in survival stratified by stage at diagnosis and gender

	All stages				Stage I				Stage II			
	Men		Women		Men		Women		Men		Women	
	1-yr	5-yr	1-yr	5-yr	1-yr	5-yr	1-yr	5-yr	1-yr	5-yr	1-yr	5-yr
2003	94%	81%	97%	88%	100%	97%	100%	98%	96%	66%	96%	72%
2004	95%	79%	98%	92%	100%	96%	100%	100%	98%	65%	100%	81%
2005	95%	81%	98%	92%	100%	98%	100%	100%	97%	70%	100%	80%
2006	95%	79%	97%	89%	100%	96%	100%	99%	96%	62%	100%	71%
2007	94%	82%	97%	91%	100%	97%	100%	99%	97%	68%	98%	77%
2008	96%	83%	98%	93%	100%	97%	100%	100%	97%	64%	97%	80%
2009	94%	84%	97%	91%	100%	98%	100%	99%	96%	71%	99%	78%
2010	95%	86%	97%	92%	100%	100%	100%	99%	97%	71%	97%	78%
2011	97%	86%	98%	93%	100%	100%	100%	100%	99%	77%	99%	83%
2012	96%	88%	98%	94%	100%	100%	100%	100%	97%	71%	98%	78%
2013	96%	90%	99%	96%	100%	100%	100%	100%	97%	77%	98%	87%
2014	97%	92%	99%	95%	100%	100%	100%	100%	97%	81%	99%	83%
2015	97%	92%	99%	96%	100%	100%	100%	100%	98%	81%	98%	85%
2016	98%		99%		100%		100%		100%		99%	
2017	97%		99%		100%		100%		98%		98%	
2018	99%		100%		100%		100%		98%		100%	
	Stage III				Stage IV				Stage MUP			
	Men		Women		Men		Women		Men		Women	
	1-yr	5-yr	1-yr	5-yr	1-yr	5-yr	1-yr	5-yr	1-yr	5-yr	1-yr	5-yr
2003	91%	62%	91%	62%	38%	20%	49%	20%	100%	74%	97%	92%
2004	89%	54%	90%	55%	22%	6%	53%	19%	94%	84%	95%	79%
2005	88%	50%	95%	57%	36%	11%	29%	12%	100%	89%	100%	99%
2006	92%	48%	83%	50%	34%	12%	32%	11%	93%	81%	100%	95%
2007	89%	56%	89%	66%	24%	9%	35%	12%	95%	88%	100%	87%
2008	94%	55%	94%	71%	31%	8%	33%	7%	100%	95%	100%	100%
2009	81%	49%	91%	61%	30%	14%	31%	12%	99%	91%	98%	91%
2010	89%	56%	91%	70%	24%	11%	31%	17%	99%	91%	96%	87%
2011	92%	52%	94%	67%	33%	10%	31%	17%	99%	78%	96%	80%
2012	90%	60%	94%	67%	39%	14%	22%	12%	97%	90%	92%	89%
2013	93%	59%	94%	73%	27%	12%	36%	21%	97%	75%	100%	99%
2014	96%	64%	95%	72%	32%	22%	51%	26%	100%	96%	99%	74%
2015	92%	69%	97%	74%	52%	24%	56%	31%	99%	89%	96%	90%
2016	95%		97%		52%		62%		85%		93%	
2017	93%		94%		42%		55%		100%		93%	
2018	95%		95%		46%		44%		96%		100%	

MUP, melanoma of unknown primary; yr, year.



Supplemental Figure 1. Uptake of the sentinel lymph node biopsy stratified by gender
SLNB, sentinel lymph node biopsy.



Supplemental Figure 2. Uptake of the novel drugs stratified by stage at diagnosis and gender

3 Stage-specific disease recurrence and survival in localized and regionally advanced cutaneous melanoma

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ABSTRACT

Objective

To investigate stage-specific survival from diagnosis, stage-specific disease recurrence, and post-recurrence survival in patients diagnosed with localized and regionally advanced cutaneous melanoma.

Methods

A retrospective observational cohort study was conducted in six Dutch hospitals. We included patients with a first diagnosis of stage I, II, or III melanoma between January 2003 and December 2011. Descriptive statistics were used to summarize time to first recurrence and type of first recurrence. Overall survival (OS) from diagnosis and post-recurrence OS were assessed using the Kaplan-Meier method.

Results

A total of 3,093 patients had a first diagnosis of stage I (*n*=2,299), II (*n*=565), or III (*n*=229) melanoma. Median OS was not yet reached for patients with stage I, 9.5 years for patients with stage II, and 6.8 years for patients with stage III. Fifty-seven patients (8%) with stage IB, 137 patients (29%) with stage II, and 81 patients (47%) with stage III developed disease recurrence. Median time to first recurrence was 2.8, 1.5, and 1.0 years for patients with stage IB, II, and III, respectively. Most patients (79%) developed regional lymph node or distant metastases as first recurrence. Median post-recurrence OS was 2.8, 3.9, and 0.5 years for patients with intralymphatic, regional lymph node, and distant metastases, respectively.

Conclusion

A substantial number of patients developed disease recurrence. Of these patients, a considerably high proportion developed distant metastases which had a great impact on survival. Identifying disease recurrence at its earliest stage is crucial because metastatic melanoma remains incurable for most patients.

INTRODUCTION

Cutaneous melanoma is one of the most common cancers in Europe, with more than 100,000 new cases each year.[41] The majority of patients (more than 80%) are diagnosed with localized melanoma (i.e., American Joint Committee on Cancer [AJCC] stage I and II) and have a rather favorable prognosis.[14,15] European five-year survival rates range from 95% to 100% for patients with stage I and from 65% to 93% for patients with stage II.[42]

In general, patients with localized melanoma can be cured by surgical excision of the primary tumor. More than ten percent of these patients will, however, develop disease recurrence. The rate of recurrence is even higher (more than 50%) in patients with regionally advanced melanoma (i.e., AJCC stage III).[43-53] As a consequence of disease recurrence, approximately 20% of patients will eventually develop metastatic disease (i.e., AJCC stage IV).[15] Despite recent development of novel immunotherapeutic and targeted drugs, metastatic melanoma remains incurable for most patients.[54] The European five-year survival rate ranges from 9% to 28%.[42]

Disease recurrence in localized and regionally advanced melanoma has been previously discussed in the literature.[43-53] Most studies were, however, limited to patients with disease recurrence[45,48,50-52] and/or did not report stage-specific disease recurrence.[43-46,49-52] Such knowledge is, however, essential for assessing the risk of disease recurrence at the moment of diagnosis. Furthermore, some studies[44,45,52,53] did not report post-recurrence survival, which is vital for providing insight into the impact of disease recurrence on survival. Therefore, the aim of this study was to investigate stage-specific survival from diagnosis, stage-specific disease recurrence, and post-recurrence survival in patients diagnosed with localized and regionally advanced cutaneous melanoma.

METHODS

Study population

We conducted an observational cohort study in six Dutch hospitals (four general and two academic). Patients were identified using data from the nationwide Netherlands Cancer Registry (NCR). We included all patients with a first diagnosis of AJCC stage I, II, or III cutaneous melanoma between January 2003 and December 2011.

Data collection

Data were retrospectively collected using a two-pronged approach. First, we retrieved two datasets from the NCR (data cut-off: April 2014): one for the entire Dutch melanoma population and one for the population in the study hospitals. Both datasets contained identical data (baseline patient and tumor characteristics, and survival) and were used to assess the representativeness of the population in the study hospitals for the Dutch melanoma population. Secondly, we col-

lected additional data on disease recurrence for all patients diagnosed with stage IB to III in the study hospitals using hospital medical records. No additional data were collected for patients diagnosed with stage IA because we assumed that disease recurrence would not be related to survival in these patients. Furthermore, no additional data were collected for patients who were diagnosed with a coexisting malignancy in the past five years (exceptions: basal cell carcinoma and squamous cell carcinoma of the skin), who were treated for melanoma outside the study hospitals, and/or who were diagnosed with multiple primary melanomas. Data collection was completed in December 2015. The medical research ethical committees exempted the study from informed consent because the study was not subject to the Medical Research Involving Human Subjects Act.

Statistical analysis

All patients were grouped according to their stage at diagnosis: I, II, or III. Baseline characteristics were summarized using descriptive statistics. Continuous variables were depicted as medians and interquartile ranges (IQR), and categorical variables as counts and proportions. Differences in proportions between the patient groups were analyzed using the two-tailed chi-squared test. The Kruskal-Wallis test was used to compare medians.

For all patients, follow-up, overall survival (OS), and survival rates were calculated from the date of diagnosis until the date of death or last follow-up using the Kaplan-Meier method. Survival curves were presented by stage and substage. For patients with stage IB to III, time to first event (i.e., disease recurrence or death) was also assessed using the Kaplan-Meier method. In this analysis, survival time was calculated from the date of diagnosis until the date of first recurrence, death, or last follow-up. The cumulative incidence of the first event was assessed according to the cumulative incidence competing risk method. For patients with disease recurrence, we evaluated the type of first recurrence, time to first recurrence, presence of distant metastases (either as first or subsequent recurrence), and post-recurrence survival. The type of first recurrence was classified as local recurrence, intralymphatic metastasis (either satellite or in-transit metastasis), regional lymph node metastasis, or distant metastasis and categorized by the most advanced recurrence (e.g., distant metastases outranked regional lymph node metastases). Time to first recurrence was calculated from the date of diagnosis until the date of first recurrence. Post-recurrence survival (OS and survival rates) was assessed according to the Kaplan-Meier method and calculated from the date of first recurrence until the date of death or last follow-up. Post-recurrence survival curves were presented by stage at initial diagnosis and type of first recurrence. All analyses were conducted using STATA statistical analysis software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

RESULTS

Study population

A total of 3,093 patients had a first diagnosis of stage I (*n*=2,299; 74%), II (*n*=565; 18%), or III (*n*=229; 7%) cutaneous melanoma in the six study hospitals (see Figure 1). Almost half of the patients (*n*=1,499; 48%) was diagnosed with stage IA. Of the patients with stage IB to III (*n*=1,594; 52%), we excluded 197 patients: 85 patients were diagnosed with a coexisting malignancy in the past five years, 108 patients were treated for melanoma outside the study hospitals, and four patients were diagnosed with multiple primary melanomas. The remaining 1,397 patients consisted of 755 patients (54%) with stage IB, 471 patients (34%) with stage II, and 171 patients (12%) with stage III.

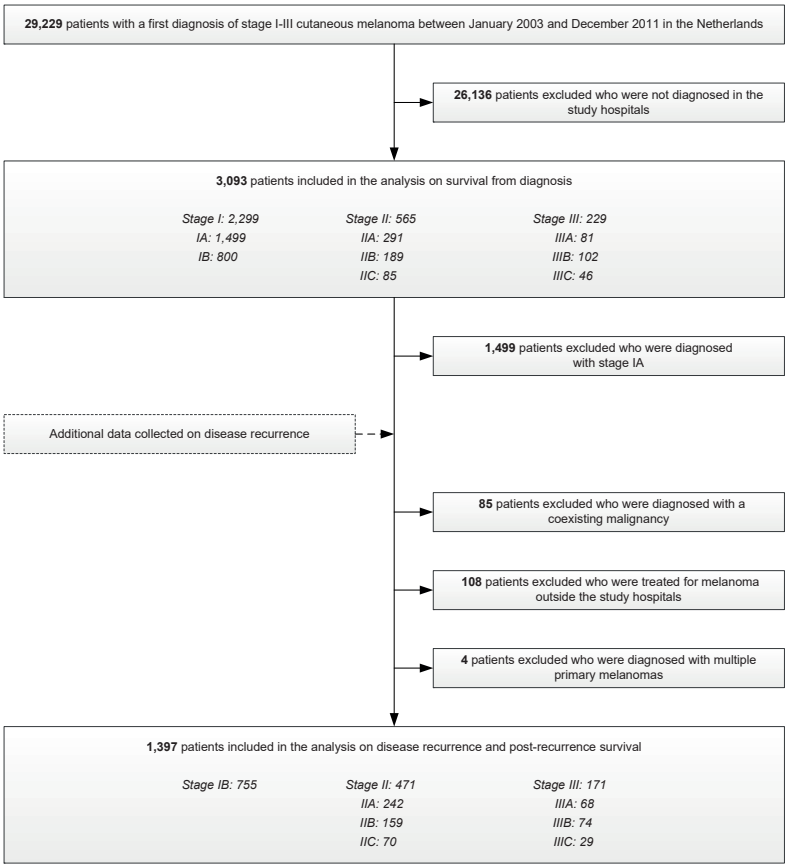


Figure 1. Patient flowchart

The baseline patient and tumor characteristics of the Dutch melanoma population and the population in the study hospitals were comparable (see Supplemental Table). Table 1 presents the baseline characteristics of the population in the study hospitals. Patients with stage I were younger and more often female than patients with stage II and III. In all stages, the majority of patients was diagnosed with melanoma on the trunk or lower extremities, and superficial spreading or nodular melanoma.

Table 1. Baseline characteristics

	Stage I	Stage II	Stage III
	n=2,299	*n*=565	*n*=229
Age, years			
Median (IQR)	54 (43-64)	63 (50-74)	58 (45-69)
Gender, *n* (%)			
Male	915 (40%)	286 (51%)	138 (60%)
Female	1,384 (60%)	279 (49%)	91 (40%)
Topography, *n* (%)			
Head and neck	267 (12%)	85 (15%)	27 (12%)
Trunk	925 (40%)	187 (33%)	99 (43%)
Upper extremity	484 (21%)	130 (23%)	27 (12%)
Lower extremity	619 (27%)	162 (29%)	74 (32%)
Unknown	4 (0%)	1 (0%)	2 (1%)
Morphology, *n* (%)			
Superficial spreading	1,846 (80%)	216 (38%)	106 (46%)
Nodular	83 (4%)	207 (37%)	74 (32%)
Lentigo maligna	96 (4%)	6 (1%)	0 (0%)
Acral lentiginous	10 (0%)	10 (2%)	2 (1%)
Other	38 (2%)	39 (7%)	9 (4%)
Unknown	226 (10%)	87 (15%)	38 (17%)
Tumor thickness, mm, *n* (%)			
≤ 1.00	1,662 (72%)	0 (0%)	14 (6%)
1.01 - 2.00	608 (26%)	73 (13%)	53 (23%)
2.01 - 4.00	0 (0%)	307 (54%)	85 (37%)
> 4.00	0 (0%)	180 (32%)	68 (30%)
Unknown	29 (1%)	5 (1%)	9 (4%)
Ulceration, *n* (%)			
No	2,098 (91%)	312 (55%)	131 (57%)
Yes	200 (9%)	252 (45%)	86 (38%)
Unknown	1 (0%)	1 (0%)	12 (5%)

IQR, interquartile range; mm, millimeter; *n*, number.

Stage-specific survival from diagnosis

Figure 2 shows the Kaplan-Meier curves for OS from diagnosis. At a median follow-up of 5.4 years, median OS was not yet reached for patients with stage I, 9.5 years (95% confidence interval [CI]: 7.9-not reached [NR]) for patients with stage II, and 6.8 years (95% CI: 5.3-NR) for patients with stage III. Five-year survival rates were 94%, 66%, and 59% for patients with stage I, II, and III, respectively. Within substages of stage I, the five-year survival rate was somewhat higher for patients with stage IA (95%) than for patients with stage IB (91%). Median OS within substages of stage II was longer for patients with stage IIA (10.5 years; 95% CI: 9.3-NR) than for patients with stage IIB (8.5 years; 95% CI: 5.8-NR) and IIC (4.5 years; 95% CI: 3.1-6.6). The five-year survival rate ranged from 74% for patients with stage IIA to 46% for patients with stage IIC. Within substages of stage III, median OS was not yet reached for patients with stage IIIA, 5.7 years (95% CI: 3.8-NR) for patients with stage IIIB, and 2.7 years (95% CI: 1.3-5.1) for patients with stage IIIC. The five-year survival rate was 77%, 52%, and 35% for patients with stage IIIA, IIIB, and IIIC, respectively.

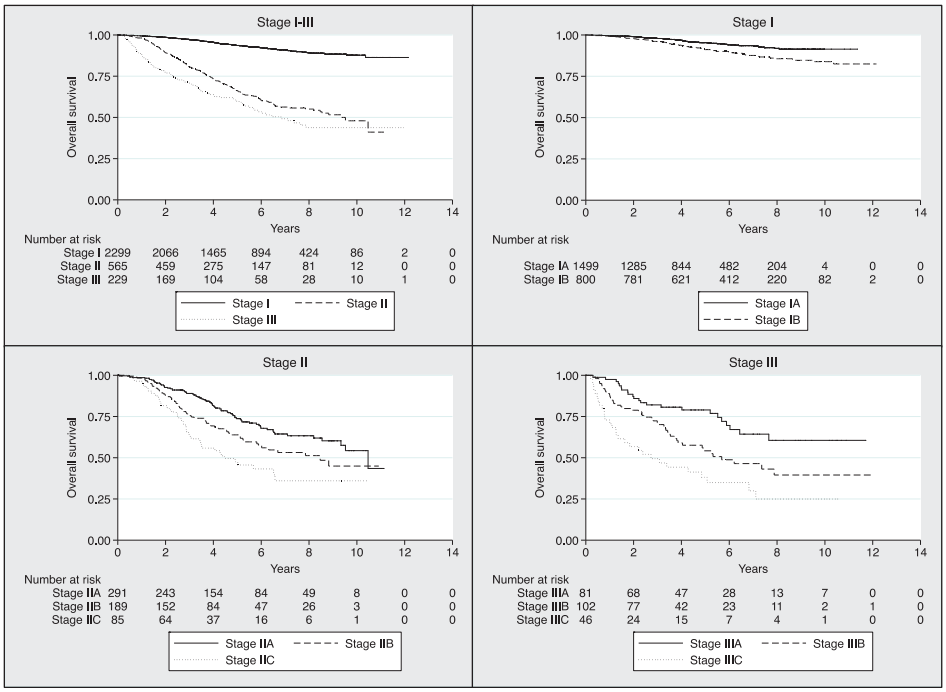


Figure 2. Kaplan-Meier curves for overall survival from diagnosis

Stage-specific disease recurrence

Figure 3 shows the Kaplan-Meier curves for the time to first event and the cumulative incidence curves of both events (i.e., disease recurrence and death). The median time to first event was not yet reached for patients with stage IB, 7.9 years (95% CI: 5.3-9.5) for patients with stage II,

and 3.7 years (95% CI: 1.8-5.1) for patients with stage III. In all stages, the five-year cumulative incidence of disease recurrence as first event was higher than the five-year cumulative incidence of death as first event: 7% versus 4% for patients with stage IB, 30% versus 13% for patients with stage II, and 47% versus 10% for patients with stage III, respectively.

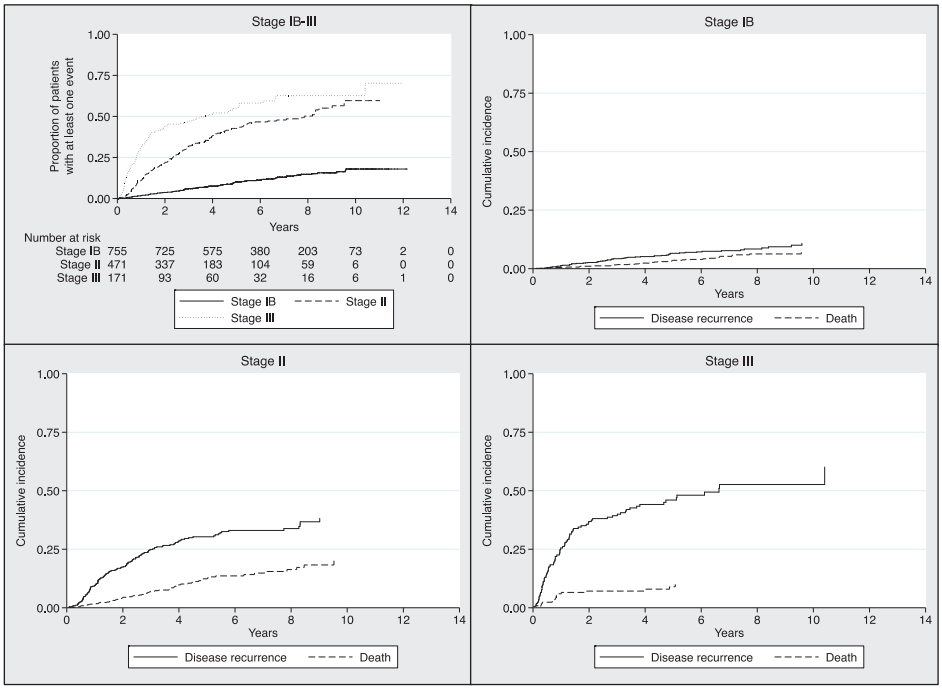


Figure 3. Kaplan-Meier curves for the time to first event and cumulative incidence curves of both events (disease recurrence and death)

Table 2 presents the type of first recurrence, time to first recurrence, and presence of distant metastases for patients with disease recurrence. In all stages, most patients developed regional lymph node (42%, 37%, and 31% of patients with stage IB, II, and III, respectively) or distant metastases (35%, 42%, and 48%, respectively) as first recurrence. The median time to first recurrence was longer for patients with stage IB (2.8 years; 95% CI: 0.5-8.4) than for patients with stage II (1.5 years; 95% CI: 0.4-5.5) and III (1.0 years; 95% CI: 0.2-5.1). By type of first recurrence, the median time to regional lymph node and distant metastases was 3.0 and 3.1 years for patients with stage IB, 0.8 and 2.2 years for patients with stage II, and 0.5 and 1.1 years for patients with stage III, respectively. In total, approximately two-thirds of the patients with disease recurrence developed distant metastases. Distant metastases occurred more often as first recurrence than as subsequent recurrence; this difference increased with advancing disease stages.

Table 2. Type of first recurrence, time to first recurrence, and presence of distant metastases

	Stage IB	Stage II	Stage III
	n=755	*n*=471	*n*=171
Recurrence status, *n* (%)			
Event-free	698 (92%)	334 (71%)	90 (53%)
Disease recurrence	57 (8%)	137 (29%)	81 (47%)
Type of first recurrence, *n* (%)			
Local recurrence	3 (5%)	4 (3%)	2 (2%)
Intralymphatic metastasis	10 (18%)	25 (18%)	15 (19%)
Regional lymph node metastasis	24 (42%)	51 (37%)	25 (31%)
Distant metastasis	20 (35%)	57 (42%)	39 (48%)
Time to first recurrence, years, median (95% CI)			
Any recurrence	2.8 (0.5-8.4)	1.5 (0.4-5.5)	1.0 (0.2-5.1)
Intralymphatic metastasis	2.1 (0.7-7.4)	2.1 (0.5-5.4)	1.3 (0.3-3.8)
Regional lymph node metastasis	3.0 (0.6-8.4)	0.8 (0.3-3.1)	0.5 (0.1-5.1)
Distant metastasis	3.1 (0.5-8.6)	2.2 (0.6-8.3)	1.1 (0.2-6.6)
Distant metastases, *n* (%)			
No	21 (37%)	46 (34%)	27 (33%)
Yes	36 (63%)	91 (66%)	54 (67%)
First recurrence	20 (56%)	57 (63%)	39 (72%)
Second recurrence or higher	16 (44%)	34 (37%)	15 (28%)

CI, confidence interval; *n*, number.

Post-recurrence survival

Figure 4 shows the Kaplan-Meier curves for post-recurrence OS. Median post-recurrence OS was 1.9 years (95% CI: 0.8-3.2) for patients initially diagnosed with stage IB, 1.5 years (95% CI: 1.1-2.1) for patients initially diagnosed with stage II, and 1.1 years (95% CI: 0.6-2.2) for patients initially diagnosed with stage III. Two-year post-recurrence survival rates were 41%, 42%, and 43% for patients initially diagnosed with stage IB, II, and III, respectively. By type of first recurrence, median post-recurrence OS was longer for patients with regional lymph node metastases (3.9 years; 95% CI: 2.5-NR) than for patients with intralymphatic (2.8 years; 95% CI: 1.9-4.6) and distant metastases (0.5 years; 95% CI: 0.3-0.6). The two-year post-recurrence survival rate was 57% for patients with intralymphatic metastases, 65% for patients with regional lymph node metastases, and 12% for patients with distant metastases.

DISCUSSION

We investigated stage-specific survival from diagnosis, stage-specific disease recurrence, and post-recurrence survival in patients with a first diagnosis of stage I, II, or III cutaneous melanoma in six Dutch hospitals. As expected, patients with stage I had a longer OS from diagnosis

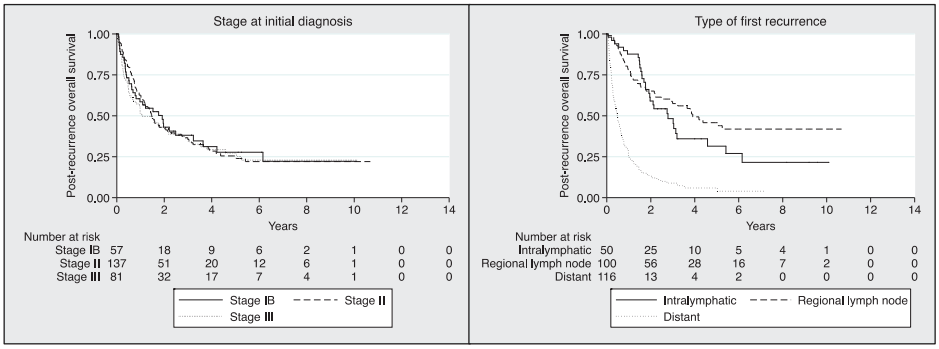


Figure 4. Kaplan-Meier curves for post-recurrence overall survival

(median not yet reached) than patients with stage II (9.5 years) and III (6.8 years). In line with this finding, disease recurrence occurred more often in patients with stage III (rate of recurrence: 47%) than in patients with stage I (8%) and II (29%). Most patients (79% of all patients with disease recurrence) developed regional lymph node or distant metastases as first recurrence. Post-recurrence OS stratified by stage at diagnosis was comparable. However, post-recurrence OS differed by type of first recurrence; patients with distant metastases had a shorter post-recurrence OS (median: 0.5 years) than patients with intralymphatic (2.8 years) and regional lymph node metastases (3.9 years).

To our knowledge, the rate of recurrence in patients with stage IB was only reported by one previous study.[55] Their rate was, however, higher than the rate in our study (18% versus 8%). The rate of recurrence in patients with stage II was more comparable to the rates reported by previous studies (33-40%).[43,47,55] One of these studies[43] also reported comparable results for patients with stage III. In contrast, three other studies[47,48,53] reported much higher rates in these patients, ranging from 66% to 82%. On the one hand, this may be due to differences between the patient populations. In two of the three studies, patients were treated in a melanoma referral center and, therefore, their patients may have been at a higher risk of disease recurrence. For example, compared to our study, the study by Romano et al.[48] had relatively more patients with stage IIIC (26% versus 17%). On the other hand, the difference in the rate of recurrence between the studies may be due to differences in initial staging (e.g., use of sentinel lymph node biopsy) and follow-up guidelines. Unfortunately, only one study, the study by Romano et al.[48], reported the follow-up schedule. Their patients had three monthly visits during the first two years and half-yearly thereafter. In contrast, our patients had three monthly visits during the first year, half-yearly visits during the second year and yearly visits up until the fifth year. Although all follow-up guidelines aim to identify disease recurrence at its earliest stage, there is still considerable variation in follow-up schedules and a lack of data to support them.[56,57]

The type of first recurrence is an important prognostic factor for post-recurrence survival. Previous studies[43,46,48,51] showed that patients with local recurrences or intralymphatic metastases had a longer post-recurrence survival than patients with regional lymph node or distant metastases. In accordance to these studies, the patients with distant metastases in our study had the shortest post-recurrence survival. In contrast, however, the observed post-recurrence survival was longer for patients with regional lymph node metastases than for patients with intralymphatic metastases. This may be due to the age of the patients at the moment of diagnosis of the first recurrence. The median age for patients with intralymphatic metastases was 71 years compared to 58 years for patients with regional lymph node metastases. It is most likely not related to the number of patients who developed distant metastases after first developing intralymphatic or regional lymph node metastases, because this was comparable between both patient groups (40% and 45% for patients with intralymphatic and regional lymph node metastases, respectively). Post-recurrence survival appeared to be independent from the stage at initial diagnosis. Although the median post-recurrence OS was somewhat longer for patients initially diagnosed with stage IB (1.9 years) than for patients initially diagnosed with stage II (1.5 years) and III (1.1 years), the Kaplan-Meier curves largely overlapped.

Our study has some limitations. First, the population in the six study hospitals covered only 11% of the total Dutch melanoma population. The population in the study hospitals was, however, considered to be a good representation of the Dutch melanoma population because the baseline (patient and tumor) characteristics and survival of both populations were comparable (see Supplemental Table and Supplemental Figure). Secondly, to ensure the feasibility of the study, we did not collect data on disease recurrence for patients with stage IA. Although Francken et al.[55] reported that 5% of these patients would have developed disease recurrence, we assumed that disease recurrence in patients with stage IA would not be related to survival. According to the NCR[15], the ten-year melanoma-specific survival rate of these patients is 100%.

Our study also has important strengths. First, in contrast to other studies[46,47], we evaluated the risk of disease recurrence while taking into account the risk of dying without disease recurrence. This resulted in a five-year cumulative incidence of disease recurrence of 7% for patients with stage IB, 30% for patients with stage II, and 47% for patients with stage III. In the presence of competing risks (e.g., dying without disease recurrence), the risk of an event of interest (e.g., disease recurrence) may be overestimated if the competing risk is not taken into account.[58] Therefore, our results provide a more precise estimate of the risk of disease recurrence at the moment of diagnosis compared to what is currently available in the literature. Secondly, we evaluated survival from diagnosis as well as post-recurrence survival, which provided insight into the impact of disease recurrence on survival. Our results showed that, depending on the type of first recurrence, survival decreases after developing disease recurrence.

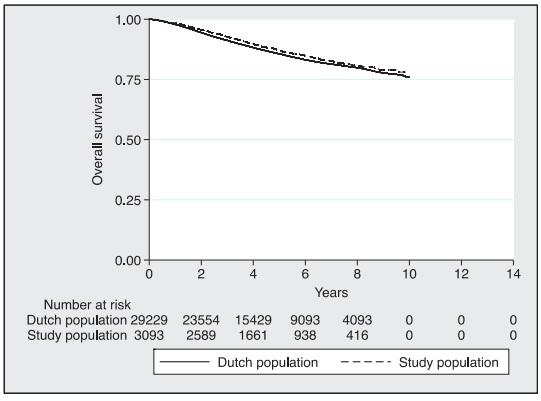
In conclusion, a substantial number of patients with localized and regionally advanced melanoma developed disease recurrence. Of these patients, a considerably high proportion developed distant metastases which had a great impact on survival. Identifying disease recurrence at its earliest stage is crucial because metastatic melanoma remains incurable for most patients. Further research on the most optimal follow-up schedule for melanoma patients is, therefore, of utmost importance.

SUPPLEMENTARY MATERIAL

Supplemental Table. Baseline characteristics of the Dutch and study population

	Dutch population	Study population
	n=29,229	*n*=3,093
Age, years		
Median (95% CI)	55 (29-81)	56 (30-81)
Gender, *n* (%)		
Male	12,657 (43%)	1,339 (43%)
Female	16,572 (57%)	1,754 (57%)
Topography, *n* (%)		
Head and neck	3,494 (12%)	379 (12%)
Trunk	11,245 (38%)	1,211 (39%)
Upper extremity	6,087 (21%)	640 (21%)
Lower extremity	8,336 (29%)	855 (28%)
Unknown	67 (0%)	8 (0%)
Morphology, *n* (%)		
Superficial spreading	19,910 (68%)	2,157 (70%)
Nodular	3,728 (13%)	349 (11%)
Lentigo maligna	223 (1%)	22 (1%)
Acral lentiginous	911 (3%)	102 (3%)
Other	657 (2%)	86 (3%)
Unknown	3,800 (13%)	377 (12%)
AJCC stage, *n* (%)		
I	21,438 (73%)	2,299 (74%)
II	5,684 (19%)	565 (18%)
III	2,107 (7%)	229 (7%)

CI, confidence interval; *n*, number.



Supplemental Figure. Kaplan-Meier curves for overall survival from diagnosis for the Dutch melanoma and study population

4 Real-world healthcare costs of localized and regionally advanced cutaneous melanoma in the Netherlands

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ABSTRACT

The aim of this study was to provide insight into real-world healthcare costs of patients initially diagnosed with localized or regionally advanced melanoma in three Dutch hospitals between 2003 and 2011. Patients were stratified according to their stage at diagnosis and recurrence status. Costs were calculated by applying unit costs to individual patient resource use and reported for the full disease course, the initial treatment episode, and treatment episodes for disease recurrence (stratified by type of recurrence). We included 198 patients with localized melanoma and 98 patients with regionally advanced melanoma. Total costs were much higher for patients with disease recurrence than for patients without disease recurrence: €20,007 versus €3,032 for patients with localized melanoma and €19,519 versus €5,951 for patients with regionally advanced melanoma. This was owing to the costs of disease recurrence because the costs of the initial treatment were comparable between patients with and without disease recurrence. Costs of disease recurrence were dependent on the type of recurrence: €4,414, €4,604, €8,129, and €10,393 for a local recurrence, intralymphatic metastases, regional lymph node metastases, and distant metastases, respectively. In conclusion, healthcare costs of patients with localized and regionally advanced melanoma were rather low for the initial treatment. Costs became, however, more substantial in case of disease recurrence. In the context of a rapidly changing treatment paradigm, it remains crucial to monitor treatment outcomes as well as healthcare expenditures.

INTRODUCTION

The incidence of cutaneous melanoma has been steadily increasing in Europe. In 2018, an estimated 144,209 European patients were diagnosed with the disease.[59] The vast majority of patients (approximately 85%) are diagnosed with localized melanoma (i.e., stage I and II). These patients generally have a good prognosis, with a five-year survival rate ranging from 65% to 100%. Patients who are diagnosed with regionally advanced melanoma (i.e., stage III) have a less favorable prognosis. Their five-year survival rate ranges from 41% to 71%.[60]

Surgery is considered the gold standard for patients with localized and regionally advanced melanoma. According to melanoma guidelines[61,62], the initial treatment consists of a diagnostic excision and therapeutic re-excision (with safety margins) of the primary tumor. To accurately stage patients without clinical or radiographic evidence of regional metastases (i.e., intralymphatic or regional lymph node metastases), it is recommended to perform a sentinel lymph node biopsy (SLNB) in patients with a tumor thickness of more than 0.8 millimeter or ulceration. The sentinel lymph node is the first draining lymph node in the regional lymphatic system. If regional metastases are detected, either clinically or via SLNB, a (complete) lymph node dissection (LND) should be performed. Adjuvant radiotherapy and adjuvant systemic therapy can be considered for patients with high-risk melanoma.

Previous studies reported healthcare costs associated with the treatment of localized and regionally advanced melanoma. However, in most of these studies[63-67], costs were based on recommendations in melanoma guidelines. Consequently, there is a lack of knowledge regarding actual healthcare costs in clinical practice. The aim of our study was, therefore, to provide insight into real-world healthcare costs of patients diagnosed with localized and regionally advanced cutaneous melanoma in the Netherlands.

METHODS

Study population

An observational cohort study was conducted in three hospitals (one academic and two general hospitals) located in the southwestern region of the Netherlands. Patients were identified using data from the nationwide Netherlands Cancer Registry (NCR). We selected all patients with a first diagnosis of localized or regionally advanced cutaneous melanoma between January 2003 and December 2011. Patients with a coexisting malignancy in the past five years (exceptions: basal cell carcinoma and squamous cell carcinoma of the skin) and patients who were treated for melanoma outside the study hospitals were excluded.

Data collection

Data were retrospectively collected using a three-pronged approach. First, we retrieved two datasets from the NCR: one for the Dutch melanoma population and one for the population in the study hospitals. Both datasets contained identical data on baseline characteristics and were used to assess the representativeness of the population in the study hospitals for the Dutch melanoma population. Second, data were collected on disease recurrence using hospital medical records. To ensure the feasibility of our study, we did not collect data on disease recurrence for patients with stage IA. Third, we collected additional data on type(s) of treatment and healthcare resource use. For patients with stage IA and patients with stage IB to II without disease recurrence, we only collected these data for a random selection of patients because we assumed that patients with and without disease recurrence were similarly treated for their initial diagnosis. Data collection was completed in December 2015. The medical research ethics committees exempted the study from informed consent because the study was not subject to the Medical Research Involving Human Subjects Act.

Cost analysis

The cost analysis was conducted from a hospital perspective using the methodology as described in the Dutch costing manual.[68] Costs were calculated by applying unit costs to individual patient resource use for the following cost components: medical imaging, pathology, hospital visits, hospital admissions, surgery, radiotherapy, and systemic therapy. Table 1 presents the unit costs. Unit costs of medical imaging, pathology, surgery, and radiotherapy were based on the tariffs issued by the Dutch Healthcare Authority.[69] The unit costs of hospital visits and hospital admissions were derived from the Dutch costing manual.[68] Drug costs were acquired from the Z-index (i.e., the Dutch drug database).[70] Costs of investigational drugs were set at zero. All costs were based on Euro 2018 cost data. Where necessary, costs were adjusted to 2018 prices using the consumer price index from Statistics Netherlands.[71]

Data analysis

Patients were stratified according to their stage at diagnosis (localized melanoma or regionally advanced melanoma) and recurrence status (with or without disease recurrence). Baseline patient and tumor characteristics were summarized using descriptive statistics. Age was presented as mean and standard deviation (SD) as well as median and interquartile range. Sex, topography, morphology, tumor thickness, and ulceration were presented as counts and proportions. Mean (SD) total costs per patient were reported for the full disease course, which was defined as the time from diagnosis until death or last follow-up (i.e., the observation period). To provide more insight into the disease course of each patient, we subsequently divided the disease course into episodes: the initial treatment episode and, in case of disease recurrence, all subsequent treatment episodes. For the initial treatment episode (determined from the diagnosis until disease recurrence, death, or last follow-up), we visualized all types of treatment and reported the mean (SD)

Table 1. Unit costs

Resource	Unit cost
Medical imaging	
X-ray	€46.59
Ultrasound	€90.76
CT scan	€153.35
MRI scan	€280.46
PET/CT scan	€1,069.76
Pathology	
Cytology/histology	€61.06
Hospital visits	
Consultation by telephone	€17.69
Emergency room visit	€269.50
Outpatient visit	€94.69
Daycare treatment	€287.19
Hospital admissions	
Inpatient hospital day	€495.30
Intensive care unit day	€1,234.08
Surgery	
Biopsy	€95.65
Excision	€95.65
Amputation	€2,175.27
Sentinel lymph node biopsy	€565.97
Lymph node dissection	€1,734.62
Isolated limb perfusion	€4,047.55
Metastasectomy[a]	€2,999.07-€6,239.07
Radiotherapy	
Short course (≤6 sessions)	€2,853.65
Standard course (>6 sessions)	€7,666.50
Hyperthermia	€14,205.16
Systemic therapy	
Dacarbazine	
Vial 200mg	€13.86
Vial 500mg	€46.33
Vial 1000mg	€87.15
Ipilimumab	
Vial 50mg	€4,250.00
Vial 200mg	€17,000.00
Vemurafenib	
Tablet 240mg	€30.70
Investigational drug	€0.00

CT, computed tomography; mg, milligram; MRI, magnetic resonance imaging; PET, positron emission tomography.
[a]Ranging from €2,999.07 for soft tissue metastases to €6,239.07 for pancreatic metastases.

episode costs. For patients who developed disease recurrence, a subsequent treatment episode was determined from disease recurrence until the next recurrence, death, or last follow-up. Mean (SD) episode costs per subsequent treatment episode were reported by type of recurrence: local recurrence, intralymphatic metastases (either satellite or in-transit metastases), regional lymph node metastases, and distant metastases. Details regarding stage-specific overall survival from diagnosis, disease recurrence, and post-recurrence survival have been previously published.[72] All analyses were conducted using STATA statistical analysis software, version 15.1 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

RESULTS

Baseline patient and tumor characteristics

The baseline patient and tumor characteristics of the population in the study hospitals and the Dutch melanoma population were comparable (see Supplemental Table). Table 2 presents the baseline patient and tumor characteristics of the patients included in the analysis. The group of patients with localized melanoma consisted of 144 patients with disease recurrence and 54 (randomly selected) patients without disease recurrence. At baseline, patients with disease recurrence were slightly younger (median age: 59 versus 63 years), and less often diagnosed with a tumor thickness of more than four millimeter (31% versus 44%) and ulceration (39% versus 56%). The group of patients with regionally advanced melanoma consisted of 47 patients with disease recurrence and 51 patients without disease recurrence. Patients with disease recurrence were slightly older (median age: 58 versus 55 years), and more often diagnosed with a tumor thickness of more than four millimeter (40% versus 25%) and ulceration (38% versus 27%) at baseline.

Healthcare costs of the full disease course

Table 3 presents the healthcare costs of the full disease course. For patients with localized melanoma, the mean (median) observation period was 4.4 years (3.9 years) for patients with disease recurrence and 3.8 years (3.3 years) for patients without disease recurrence. In total, 67% of the patients with disease recurrence and 19% of the patients without disease recurrence died during the observation period. Mean total costs were more than six times higher for patients with disease recurrence than for patients without disease recurrence (€20,007 versus €3,032).

For patients with regionally advanced melanoma, the mean (median) observation period was 3.5 years (3.3 years) for patients with disease recurrence and 4.3 years (4.7 years) for patients without disease recurrence. During the observation period, 70% of the patients with disease recurrence and 22% of the patients without disease recurrence died. Mean total costs were more than three times higher for patients with disease recurrence than for patients without disease recurrence (€19,519 versus €5,951).

Table 2. Baseline patient and tumor characteristics

	Localized melanoma		Regionally advanced melanoma	
	Patients without disease recurrence[a]	Patients with disease recurrence	Patients without disease recurrence	Patients with disease recurrence
	n=54	*n*=144	*n*=51	*n*=47
Age, years				
Mean (SD)	61 (17)	60 (16)	57 (19)	56 (17)
Median (IQR)	63 (48-78)	59 (48-71)	55 (46-72)	58 (44-70)
Gender, *n* (%)				
Male	17 (31%)	89 (62%)	26 (51%)	29 (62%)
Female	37 (69%)	55 (38%)	25 (49%)	18 (38%)
Topography, *n* (%)				
Head and neck	7 (13%)	29 (20%)	5 (10%)	6 (13%)
Trunk	17 (31%)	61 (42%)	22 (43%)	18 (38%)
Upper extremity	10 (19%)	23 (16%)	3 (6%)	6 (13%)
Lower extremity	20 (37%)	31 (22%)	19 (37%)	17 (36%)
Unknown	0 (0%)	0 (0%)	2 (4%)	0 (0%)
Morphology, *n* (%)				
Superficial spreading	24 (44%)	47 (33%)	23 (45%)	16 (34%)
Nodular	18 (33%)	55 (38%)	11 (22%)	17 (36%)
Lentigo maligna	1 (2%)	0 (0%)	0 (0%)	0 (0%)
Acral lentiginous	0 (0%)	2 (1%)	0 (0%)	0 (0%)
Other	7 (13%)	6 (4%)	3 (6%)	2 (4%)
Unknown	4 (7%)	34 (24%)	14 (27%)	12 (26%)
Tumor thickness, mm, *n* (%)				
≤1.00	10 (19%)	6 (4%)	3 (6%)	2 (4%)
1.01-2.00	9 (17%)	37 (26%)	15 (29%)	8 (17%)
2.01-4.00	11 (20%)	56 (39%)	18 (35%)	14 (30%)
>4.00	24 (44%)	45 (31%)	13 (25%)	19 (40%)
Unknown	0 (0%)	0 (0%)	2 (4%)	4 (9%)
Ulceration, *n* (%)				
No	24 (44%)	88 (61%)	35 (69%)	28 (60%)
Yes	30 (56%)	56 (39%)	14 (27%)	18 (38%)
Unknown	0 (0%)	0 (0%)	2 (4%)	1 (2%)

IQR, interquartile range; mm, millimeter; *n*, number; SD, standard deviation.
[a]Random selection of patients.

Healthcare costs of the initial treatment episode

Types of treatment

Figure 1 visualizes all types of treatment in the initial treatment episode. Of the 198 patients with localized melanoma, most patients (*n*=167; 84%) underwent a diagnostic excision followed by a therapeutic re-excision. The re-excision was combined with an SLNB in approximately a quarter

Table 3. Healthcare costs of the full disease course

	Localized melanoma		Regionally advanced melanoma	
	Patients without disease recurrence[a]	Patients with disease recurrence	Patients without disease recurrence	Patients with disease recurrence
	n=54	*n*=144	*n*=51	*n*=47
Observation period, years				
Mean (SD)	3.8 (2.9)	4.4 (2.5)	4.3 (2.7)	3.5 (2.5)
Median (IQR)	3.3 (1.4-5.5)	3.9 (2.7-5.7)	4.7 (1.2-6.4)	3.3 (1.4-5.0)
Deceased patients, %	19%	67%	22%	70%
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Medical imaging	€105 (€250)	€1,382 (€1,218)	€232 (€382)	€1,477 (€2,085)
Pathology	€191 (€108)	€385 (€221)	€204 (€131)	€404 (€283)
Hospital visits	€1,578 (€998)	€3,974 (€2,456)	€1,438 (€1,369)	€3,542 (€3,286)
Hospital admissions	€642 (€1,012)	€6,029 (€7,005)	€1,971 (€3,154)	€8,009 (€8,318)
Surgery	€374 (€266)	€2,175 (€2,169)	€1,956 (€837)	€3,191 (€2,706)
Radiotherapy	€142 (€1,043)	€3,283 (€5,791)	€150 (€1,074)	€2,489 (€4,532)
Systemic therapy	€0 (€0)	€2,778 (€13,608)	€0 (€0)	€407 (€2,423)
Total costs				
Mean (SD)	€3,032 (€2,338)	€20,007 (€20,284)	€5,951 (€4,575)	€19,519 (€12,947)
Median (IQR)	€2,579 (€251-€11,509)	€14,887 (€685-€130,901)	€4,484 (€1,270-€25,400)	€17,530 (€2,081-€52,709)

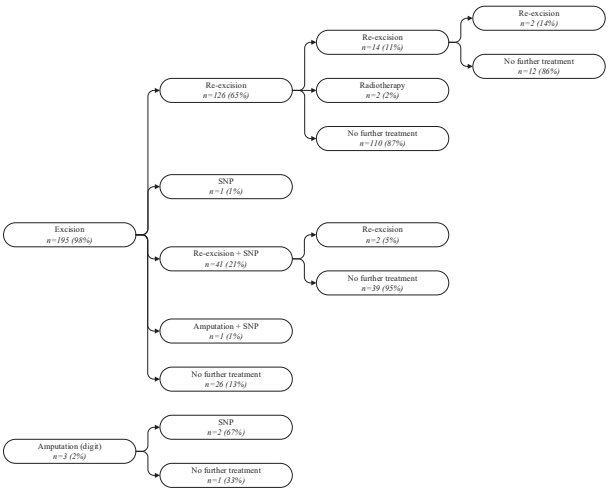
IQR, interquartile range; *n*, number; SD, standard deviation.
[a]Random selection of patients.

of the patients (*n*=41). After the re-excision, 149 patients (89%) did not receive further treatment, 16 patients (10%) underwent an additional re-excision, and two patients (1%) received adjuvant radiotherapy.

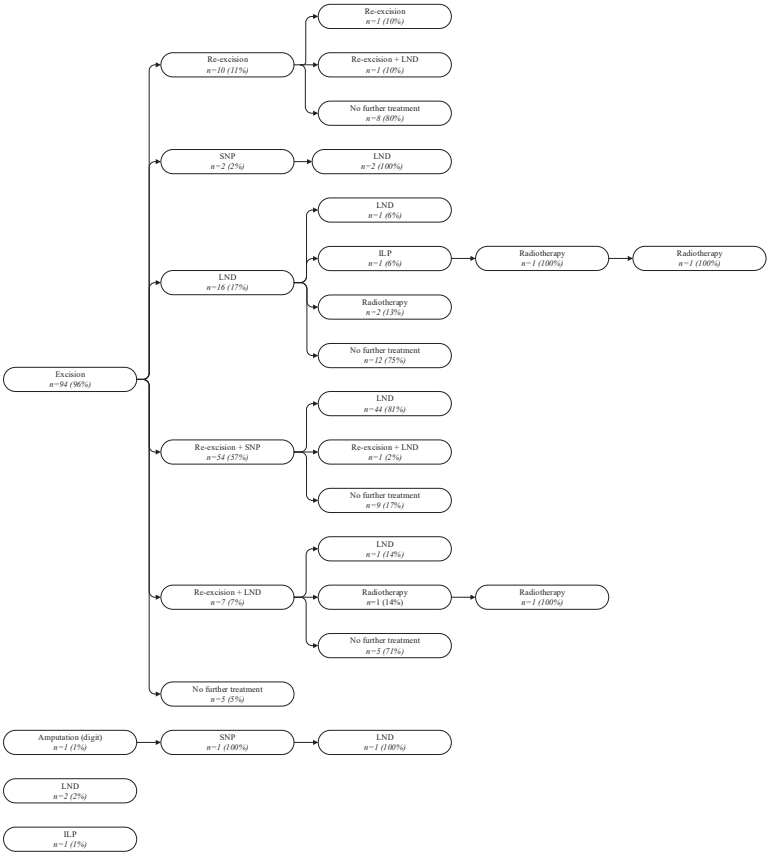
Of the 98 patients with regionally advanced melanoma, more than half of the patients (*n*=53; 54%) underwent a diagnostic excision followed by a therapeutic re-excision (with or without SLNB) and an LND. Eighteen patients (18%) underwent an LND without a therapeutic re-excision. After the LND, most patients (*n*=65; 92%) did not receive further treatment; three patients received (adjuvant) radiotherapy, two patients underwent an additional LND, and one patient received isolated limb perfusion.

Healthcare costs

Table 4 presents the healthcare costs of the initial treatment episode. For patients with localized melanoma, mean episode costs were comparable between patients with and without disease recurrence (€3,015 and €3,032, respectively). In both patient groups, hospital visits were the main cost driver (48% and 52% of the costs of patients with and without disease recurrence, respectively), followed by hospital admissions (24% and 21%, respectively) and surgery (15% and 12%, respectively).



a. Localized melanoma (*n*=198)



b. Regionally advanced melanoma (*n*=98)

Figure 1. Types of treatment in the initial treatment episode

ILP, isolated limb perfusion; LND, lymph node dissection; *n*, number; SLNB, sentinel lymph node biopsy.

Table 4. Healthcare costs of the initial treatment episode

	Localized melanoma				Regionally advanced melanoma			
	Patients without disease recurrence[a]		Patients with disease recurrence		Patients without disease recurrence		Patients with disease recurrence	
	n=54		*n*=144		*n*=51		*n*=47	
Episode duration, years								
Mean (SD)	3.8 (2.9)		2.5 (2.0)		4.3 (2.7)		1.7 (1.7)	
Median (IQR)	3.3 (1.4-5.5)		2.1 (1.0-3.3)		4.7 (1.2-6.4)		1.1 (0.5-2.1)	
	Mean resource use (SD)	Mean costs (SD)	Mean resource use (SD)	Mean costs (SD)	Mean resource use (SD)	Mean costs (SD)	Mean resource use (SD)	Mean costs (SD)
Medical imaging		€105 (€250)		€148 (€285)		€232 (€382)		€330 (€377)
X-ray	0.3 (0.7)	€15 (€32)	0.4 (1.0)	€20 (€47)	0.7 (2.0)	€34 (€95)	1.2 (2.2)	€55 (€105)
Ultrasound	0.5 (0.9)	€45 (€82)	0.7 (1.1)	€60 (€101)	0.7 (1.2)	€64 (€105)	1.0 (1.3)	€91 (€118)
CT scan	0.2 (1.0)	€34 (€154)	0.2 (0.5)	€29 (€81)	0.3 (0.5)	€39 (€80)	0.6 (1.0)	€98 (€158)
MRI scan	0.0 (0.3)	€10 (€76)	<0.1 (0.2)	€10 (€61)	<0.1 (0.2)	€11 (€55)	0.1 (0.4)	€42 (€117)
PET/CT scan	0.0 (NA)	€0 (€0)	<0.1 (0.2)	€30 (€176)	0.1 (0.3)	€84 (€290)	<0.1 (0.2)	€46 (€218)
Pathology		€191 (€108)		€182 (€90)		€204 (€131)		€200 (€102)
Cytology/histology	3.1 (1.8)	€191 (€108)	3.0 (1.5)	€182 (€90)	3.3 (2.2)	€204 (€131)	3.3 (1.7)	€200 (€102)
Hospital visits		€1,578 (€998)		€1,447 (€934)		€1,438 (€1,369)		€1,417 (€1,260)
Consultation by telephone	1.0 (1.6)	€18 (€28)	0.4 (0.9)	€7 (€16)	0.3 (0.9)	€6 (€16)	0.7 (1.6)	€12 (€28)
Emergency room visit	0.0 (0.2)	€10 (€51)	0.1 (0.4)	€26 (€112)	0.1 (0.6)	€32 (€158)	0.1 (0.4)	€29 (€116)
Outpatient visit	16.1 (10.4)	€1,524 (€987)	14.0 (8.9)	€1,328 (€846)	14.5 (14.1)	€1,372 (€1,333)	13.6 (12.1)	€1,291 (€1,147)
Daycare treatment	0.1 (0.4)	€27 (€101)	0.3 (0.7)	€86 (€192)	0.1 (0.4)	€28 (€104)	0.3 (0.6)	€86 (€179)
Hospital admissions		€642 (€1,012)		€709 (€1,261)		€1,971 (€3,154)		€2,988 (€5,555)
Inpatient hospital day	1.3 (2.0)	€642 (€1,012)	1.4 (2.5)	€709 (€1,261)	4.0 (6.4)	€1,971 (€3,154)	6.0 (11.2)	€2,961 (€5,538)
Intensive care unit day	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)	<0.1 (0.1)	€26 (€180)

Table 4. Healthcare costs of the initial treatment episode (continued)

	Localized melanoma				Regionally advanced melanoma			
	Patients without disease recurrence[a]		Patients with disease recurrence		Patients without disease recurrence		Patients with disease recurrence	
	n=54		*n*=144		*n*=51		*n*=47	
Surgery		€374 (€266)		€456 (€479)		€1,956 (€837)		€2,102 (€1,234)
Biopsy	0.2 (0.6)	€16 (€58)	0.1 (0.5)	€12 (€44)	0.4 (0.9)	€38 (€81)	0.3 (0.8)	€33 (€78)
Excision	2.8 (1.5)	€264 (€139)	2.5 (1.3)	€242 (€121)	2.5 (1.5)	€236 (€144)	1.9 (0.7)	€185 (€70)
Amputation	0.0 (NA)	€0 (€0)	<0.1 (0.2)	€60 (€359)	0.0 (NA)	€0 (€0)	<0.1 (0.1)	€46 (€317)
Sentinel lymph node biopsy	0.2 (0.4)	€94 (€213)	0.2 (0.4)	€141 (€246)	0.6 (0.5)	€322 (€283)	0.6 (0.5)	€337 (€281)
Lymph node dissection	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)	0.8 (0.4)	€1,360 (€721)	0.8 (0.5)	€1,329 (902)
Isolated limb perfusion	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)	<0.1 (0.2)	€172 (€826)
Radiotherapy		€142 (€1,043)		€73 (€680)		€150 (€1,074)		€611 (€2,704)
Short course (≤6 sessions)	0.0 (NA)	€0 (€0)	<0.1 (0.1)	€20 (€238)	0.0 (NA)	€0 (€0)	<0.1 (0.2)	€121 (€582)
Standard course (>6 sessions)	<0.1 (0.1)	€142 (€1,043)	<0.1 (0.1)	€53 (€639)	<0.1 (0.1)	€150 (€1,074)	0.1 (0.3)	€489 (€2,479)
Total episode costs								
Mean (SD)		€3,032 (€2,338)		€3,015 (€2,076)		€5,951 (€4,575)		€7,648 (€6,975)
Median (IQR)		€2,579 (€251-€11,509)		€2,392 (€342-€12,432)		€4,484 (€1,270-€25,400)		€6,175 (€924-€40,569)

CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; *n*, number; NA, not applicable; PET, positron emission tomography; SD, standard deviation.

[a]Random selection of patients.

Outpatient clinics were most frequently visited. On average, patients with disease recurrence had 14 visits and patients without disease recurrence 16 visits.

For patients with regionally advanced melanoma, mean episode costs were slightly higher for patients with disease recurrence than for patients without disease recurrence (€7,648 versus €5,951). Hospital admissions were the main cost driver in both patient groups (39% and 33% of the costs of patients with and without disease recurrence, respectively), followed by surgery (27% and 33%, respectively) and hospital visits (19% and 24%, respectively). Almost all hospital admissions were related to surgical procedures. On average, patients with disease recurrence stayed 6 days in the hospital and patients without disease recurrence 4 days.

Healthcare costs of subsequent treatment episodes

Table 5 presents the healthcare costs of subsequent treatment episodes for patients with disease recurrence. During our observation period, we observed 13 episodes with a local recurrence (among 13 patients), 67 episodes with intralymphatic metastases (among 40 patients), 83 episodes with regional lymph node metastases (among 73 patients), and 189 episodes with distant metastases (among 128 patients). The mean (median) episode duration ranged from 0.5 years (0.3 years) for distant metastases to 2.1 years (2.2 years) for a local recurrence. Mean episode costs were the highest for distant metastases (€10,393), followed by regional lymph node metastases (€8,129), intralymphatic metastases (€4,604), and a local recurrence (€4,414). Hospital admissions and hospital visits were the main cost drivers for a local recurrence, accounting for 40% and 37% of the costs, respectively. Half of the costs of intralymphatic metastases were related to radiotherapy (27% of the costs) and systemic therapy (22%). One patient received ipilimumab after experiencing multiple episodes with intralymphatic metastases. Costs of regional lymph node metastases were mainly driven by the costs of hospital admissions (32% of the costs), hospital visits (22%), and surgery (20%). Hospital admissions were the main cost driver for distant metastases (37% of the costs), followed by radiotherapy (19%) and systemic therapy (18%).

DISCUSSION

Our study provided insight into real-world healthcare costs of patients diagnosed with localized and regionally advanced cutaneous melanoma. Costs were separately reported for patients with and without disease recurrence. In both patient groups, total costs were much higher for patients with disease recurrence than for patients without disease recurrence (€20,007 versus €3,032 for patients with localized melanoma and €19,519 versus €5,951 for patients with regionally advanced melanoma). This was owing to the costs of disease recurrence because the costs of the initial treatment were reasonably comparable between patients with and without disease recurrence. Costs of disease recurrence were dependent on the type of recurrence, with the lowest

Table 5. Healthcare costs of subsequent treatment episodes

	Local recurrence		Intralymphatic metastases		Regional lymph node metastases		Distant metastases	
	$n_{episodes}$=13		$n_{episodes}$=67		$n_{episodes}$=83		$n_{episodes}$=189	
	$n_{patients}$=13		$n_{patients}$=40		$n_{patients}$=73		$n_{patients}$=128	
Episode duration, years								
Mean (SD)	2.1 (1.6)		1.3 (1.5)		1.8 (2.1)		0.5 (0.7)	
Median (IQR)	2.2 (0.5-2.9)		0.8 (0.3-2.0)		0.7 (0.4-3.0)		0.3 (0.1-0.6)	
	Mean resource use (SD)	Mean costs (SD)	Mean resource use (SD)	Mean costs (SD)	Mean resource use (SD)	Mean costs (SD)	Mean resource use (SD)	Mean costs (SD)
Medical imaging		€230 (€391)		€297 (€510)		€722 (€649)		€786 (€954)
X-ray	0.3 (0.5)	€14 (€22)	0.3 (0.7)	€15 (€34)	0.6 (1.1)	€29 (€52)	1.4 (2.2)	€64 (€105)
Ultrasound	0.8 (1.2)	€77 (€110)	0.6 (1.0)	€57 (€86)	1.8 (2.0)	€160 (€178)	0.7 (1.2)	€67 (€109)
CT scan	0.2 (0.4)	€35 (€67)	0.3 (0.7)	€53 (€105)	1.4 (2.2)	€209 (€333)	1.6 (2.0)	€251 (€307)
MRI scan	0.1 (0.3)	€22 (€78)	0.1 (0.4)	€29 (€99)	0.2 (0.6)	€54 (€155)	0.6 (1.1)	€162 (€298)
PET/CT scan	0.1 (0.3)	€82 (€297)	0.1 (0.4)	€144 (€452)	0.3 (0.4)	€271 (€468)	0.2 (0.6)	€243 (€694)
Pathology		€183 (€71)		€114 (€79)		€174 (€128)		€76 (€127)
Cytology/histology	3.0 (1.2)	€183 (€71)	1.9 (1.3)	€114 (€79)	2.9 (2.1)	€174 (€128)	1.2 (2.1)	€76 (€127)
Hospital visits		€1,653 (€887)		€946 (€729)		€1,781 (€1,424)		€1,223 (€1,278)
Consultation by telephone	1.5 (2.1)	€27 (€37)	1.0 (3.9)	€18 (€70)	1.4 (2.5)	€24 (€44)	1.3 (2.6)	€23 (€46)
Emergency room visit	0.1 (0.3)	€21 (€75)	<0.1 (0.1)	€4 (€33)	0.2 (0.6)	€65 (€155)	0.4 (0.8)	€113 (€222)
Outpatient visit	14.8 (7.4)	€1,406 (€705)	9.6 (7.2)	€907 (€679)	16.8 (12.8)	€1,595 (€1,215)	9.9 (11.9)	€934 (€1,122)
Daycare treatment	0.7 (1.4)	€199 (€396)	0.1 (0.2)	€17 (€69)	0.3 (1.3)	€97 (€371)	0.5 (1.3)	€153 (€372)
Hospital admissions		€1,771 (€2,961)		€625 (€1,164)		€2,599 (€3,881)		€3,818 (€5,258)
Inpatient hospital day	3.4 (5.7)	€1,676 (€2,842)	1.2 (2.2)	€606 (€1,090)	5.2 (7.8)	€2,584 (€3,872)	7.6 (10.6)	€3,766 (€5,241)
Intensive care unit day	0.1 (0.3)	€95 (€342)	<0.1 (0.1)	€18 (€151)	<0.1 (0.1)	€15 (€135)	<0.1 (0.3)	€52 (€419)

Table 5. Healthcare costs of subsequent treatment episodes (continued)

	Local recurrence		Intralymphatic metastases		Regional lymph node metastases		Distant metastases	
	$n_{episodes}$=13		$n_{episodes}$=67		$n_{episodes}$=83		$n_{episodes}$=189	
	$n_{patients}$=13		$n_{patients}$=40		$n_{patients}$=73		$n_{patients}$=128	
Surgery		€576 (€1,078)		€367 (€874)		€1,620 (€931)		€700 (€1,724)
Biopsy	0.2 (0.6)	€22 (€57)	0.2 (0.6)	€21 (€57)	0.2 (0.6)	€20 (€59)	<0.1 (0.3)	€4 (€31)
Excision	2.5 (1.4)	€243 (€133)	1.2 (1.2)	€113 (€113)	0.7 (1.2)	€68 (€110)	0.3 (0.8)	€25 (€78)
Lymph node dissection	0.0 (NA)	€0 (€0)	<0.1 (0.1)	€26 (€212)	0.8 (0.5)	€1,442 (€849)	0.1 (0.3)	€184 (€535)
Isolated limb perfusion	0.1 (0.3)	€311 (€1,123)	<0.1 (0.2)	€181 (€843)	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)
Metastasectomy	0.0 (NA)	€0 (€0)	0.3 (0.5)	€26 (€52)	0.1 (0.3)	€91 (€384)	0.2 (0.6)	€487 (€1,572)
Radiotherapy		€0 (€0)		€1,247 (€4,059)		€1,232 (€3,091)		€1,929 (€4,267)
Short course (≤6 sessions)	0.0 (NA)	€0 (€0)	0.1 (0.3)	€170 (€843)	<0.1 (0.2)	€138 (€615)	0.3 (0.7)	€951 (€1,862)
Standard course (>6 sessions)	0.0 (NA)	€0 (€0)	<0.1 (0.2)	€229 (€1,314)	0.1 (0.3)	€924 (€2,511)	0.1 (0.3)	€527 (€2,507)
Hyperthermia	0.0 (NA)	€0 (€0)	0.1 (0.2)	€848 (€3,391)	<0.1 (0.1)	€171 (€1,559)	<0.1 (0.2)	€451 (€2,497)
Systemic therapy		€0 (€0)		€1,007 (€8,244)		€0 (€0)		€1,861 (€10,953)
Dacarbazine	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)	0.1 (0.3)	€58 (€186)
Ipilimumab	0.0 (NA)	€0 (€0)	<0.1 (0.1)	€1,007 (€8,244)	0.0 (NA)	€0 (€0)	<0.1 (0.1)	€469 (€6,442)
Vemurafenib	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)	0.0 (NA)	€0 (€0)	<0.1 (0.2)	€1,335 (€8,940)
Total episode costs								
Mean (SD)		€4,414 (€3,868)		€4,604 (€11,181)		€8,129 (€5,926)		€10,393 (€14,345)
Median (IQR)		€3,241 (€747-€11,794)		€1,696 (€189-€86,785)		€7,027 (€95-€40,520)		€6,133 (€95-€105,483)

CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; *n*, number; NA, not applicable; PET, positron emission tomography; SD, standard deviation.

episode costs for a local recurrence (€4,414) and the highest episode costs for distant metastases (€10,393).

Costs of patients with localized melanoma differed between patients initially diagnosed with localized melanoma and patients with a local recurrence. Although guideline recommendations are comparable for both patient groups, costs were higher for patients with a local recurrence (€4,414 versus €3,019). This was mainly owing to the costs of hospital admissions (€1,771 versus €690). Patients with a local recurrence stayed on average 3.4 days in the hospital, whereas patients initially diagnosed with localized melanoma stayed on average 1.4 days. Costs of patients with regionally advanced melanoma were comparable between patients initially diagnosed with regionally advanced melanoma (€6,765) and patients with intralymphatic/regional lymph node metastases (€6,554).

We also provided insight into the types of treatment patients received in the initial treatment episode. In total, 84% of the patients with localized melanoma were treated in accordance with guideline recommendations. These patients underwent a diagnostic excision and therapeutic re-excision of the primary tumor. Approximately a quarter of the patients underwent an SLNB. Although this seems rather low, it is important to note that our patients were diagnosed between 2003 and 2011, while an SLNB was only recommended as a standard diagnostic procedure in the Dutch melanoma guideline since 2012.[73] Of the patients with regionally advanced melanoma, 54% were treated in accordance with guideline recommendations. They underwent an LND in addition to the diagnostic excision and therapeutic re-excision. Another 18% of the patients underwent an LND without a re-excision. None of the patients received adjuvant systemic therapy. This was owing to the time frame of our study in which novel effective drugs were not yet available for patients with (high-risk) regionally advanced melanoma. However, recent developments in adjuvant systemic therapy have changed the standard of care for these patients.[74]

Our results are rather difficult to compare to previously published results because previous studies[63-67] only reported healthcare costs based on recommendations in melanoma guidelines, whereas we reported actual healthcare costs in clinical practice. A Spanish study[66] estimated costs of diagnostic procedures, treatment(s), and follow-up (in Euro 2015). After three years of follow-up, total costs were €4,129 for stage IA, €12,643 for stage IB to IIA, €20,079 for stage IIB to IIC, and €36,925 for stage III. These costs did not include costs of disease recurrence. An Italian study[65] estimated costs of diagnostic procedures, treatment(s), follow-up, disease recurrence, and supportive care (in Euro 2016). The total costs ranged from €1,837 for stage IA to €10,210 for stage IIC and from €20,576 for stage III without in-transit metastases to €40,229 for stage III with in-transit metastases. Costs were not separately reported for patients with and without disease recurrence. As our study showed that not all patients were treated in accordance with guideline recommendations, we provided a more adequate insight into the healthcare costs of

patients with localized and regionally advanced melanoma. Moreover, our study showed that costs substantially differed between patients with and without disease recurrence, and between different types of recurrence.

It should be noted that our study has some limitations. First, we only included healthcare costs within the hospital setting. This may have led to an underestimation of the actual healthcare costs as, for example, suspicious moles may have been removed by a general practitioner.[75] Nevertheless, we believe that the impact will be rather limited because, in general, the treatment will be continued in the hospital once a patient has been diagnosed with melanoma. Second, costs were not yet complete for all patients because 49% were still alive at the end of the study. Although these patients can still accrue additional costs, we believe (based on our observation period) that the vast majority of the healthcare costs were incorporated in our study. Third, we used list prices for drugs, and reference prices and tariffs for other resources. Although these prices may not reflect actual costs, the use of these sources is recommended in the Dutch costing manual.[68] Finally, the reported costs of patients with (regionally) advanced melanoma are only representative for our study period (2003-2011). Due to the rapidly changing treatment paradigm[74,76], costs of patients with advanced melanoma (i.e., unresectable stage IIIC or stage IV) are higher in current clinical practice[77] and costs of patients with (high-risk) regionally advanced melanoma will increase the coming years.

In conclusion, most patients with localized and regionally advanced melanoma were treated in accordance with guideline recommendations for their initial diagnosis. The healthcare costs of the initial treatment were rather low. Costs became, however, more substantial in case of disease recurrence. As a considerable number of patients develop disease recurrence[72], it is not only important to identify disease recurrence at its earliest stage for improving survival but also for retaining low costs. In the context of a rapidly changing treatment paradigm, it remains crucial to monitor treatment outcomes as well as healthcare expenditures.

SUPPLEMENTARY MATERIAL

Supplemental Table. Representativeness of the population in the study hospitals for the Dutch melanoma population

	Localized melanoma		Regionally advanced melanoma	
	Dutch population	Population in the study hospitals	Dutch population	Population in the study hospitals
	n=27,122	*n*=1,271	*n*=2,107	*n*=98
Age, years				
Median (IQR)	55 (43-66)	55 (43-66)	56 (44-66)	57 (46-70)
Gender, %				
Male	42%	43%	56%	56%
Female	58%	57%	44%	44%
Morphology, %				
Superficial spreading	70%	63%	45%	40%
Nodular	11%	11%	30%	29%
Lentigo maligna	1%	1%	2%	0%
Acral lentiginous	3%	3%	0%	0%
Other	2%	2%	4%	5%
Unknown	13%	20%	19%	27%
Topography, %				
Head and neck	12%	14%	9%	11%
Trunk	38%	39%	46%	41%
Upper extremity	21%	20%	13%	9%
Lower extremity	28%	26%	32%	37%
Unknown	0%	0%	0%	2%

IQR, interquartile range; *n*, number.

5 A systematic literature review and network meta-analysis of effectiveness and safety outcomes in advanced melanoma

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ABSTRACT

Background

Although a myriad of novel treatments entered the treatment paradigm for advanced melanoma, there is lack of head-to-head evidence. We conducted a network meta-analysis (NMA) to estimate each treatment's relative effectiveness and safety.

Methods

A systematic literature review (SLR) was conducted in Embase, MEDLINE, and Cochrane to identify all phase III randomized controlled trials (RCTs) with a time frame from January 1, 2010 to March 11, 2019. We retrieved evidence on treatment-related grade III/IV adverse events, progression-free survival (PFS), and overall survival (OS). Evidence was synthesized using a Bayesian fixed-effect NMA. Reference treatment was dacarbazine. In accordance with RCTs, dacarbazine was pooled with temozolomide, paclitaxel, and paclitaxel plus carboplatin. To increase homogeneity of the study populations, RCTs were only included if patients were not previously treated with novel treatments.

Results

The SLR identified 28 phase III RCTs involving 14,376 patients. Nineteen and seventeen treatments were included in the effectiveness and safety NMA, respectively. For PFS, dabrafenib plus trametinib (hazard ratio [HR] PFS: 0.21) and vemurafenib plus cobimetinib (HR PFS: 0.22) were identified as most favorable treatments. Both had, however, less favorable safety profiles. Five other treatments closely followed (dabrafenib [HR PFS: 0.30], nivolumab plus ipilimumab [HR PFS: 0.34], vemurafenib [HR PFS: 0.38], nivolumab [HR PFS: 0.42], and pembrolizumab [HR PFS: 0.46]). In contrast, for OS, nivolumab plus ipilimumab (HR OS: 0.39), nivolumab (HR OS: 0.46), and pembrolizumab (HR OS: 0.50) were more favorable than dabrafenib plus trametinib (HR OS: 0.55) and vemurafenib plus cobimetinib (HR OS: 0.57).

Conclusions

Our NMA identified the most effective treatment options for advanced melanoma and provided valuable insights into each novel treatment's relative effectiveness and safety. This information may facilitate evidence-based decision making and may support the optimization of treatment and outcomes in everyday clinical practice.

INTRODUCTION

The incidence of cutaneous melanoma has been increasing in the past decades. The World Health Organisation (WHO) estimates around 132,000 new cases worldwide each year.[78] Although most patients are diagnosed at the local stage and have a rather favorable prognosis, advanced melanoma (i.e., unresectable stage III and stage IV) is associated with poor survival outcomes. Treatment options have been limited for many years. In March 2011, however, the Food and Drug Administration approved the Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) immune checkpoint inhibitor ipilimumab.[79] Ipilimumab was the first novel treatment that demonstrated improved survival (median overall survival [OS] of 10.1 months compared with 6.4 months for patients receiving glycoprotein 100 peptide vaccine [GP100]).[80] Since then, the treatment landscape rapidly changed as a myriad of novel treatments and combinations of treatments became available for patients with advanced melanoma. Although these novel regimens showed superior effectiveness in pivotal phase III randomized controlled trials (RCTs), direct head-to-head comparisons remain scarce. In specific, there is lack of comparative evidence between the different immune checkpoint inhibitors (anti-CTLA-4 and anti-programmed cell death protein 1 [anti-PD-1]) and mitogen-activated protein kinase pathway inhibitors (BRAFi and MEKi).

It is, therefore, not possible to evaluate the relative effectiveness and safety of each specific novel treatment using direct evidence from RCTs. A network meta-analysis (NMA) of available RCTs can provide such comparative evidence. NMAs will become increasingly important as there is a low incentive to initiate RCTs comparing treatment options with market approval.[81,82] Although performing NMAs is relatively new, the method has quickly gained popularity exemplified by the use of the method in clinical guidelines, Cochrane reviews, and a recent call for a more widespread use by the WHO.[81-84] NMAs combine direct and indirect evidence to rank-order competing treatments that were never directly compared head-to-head in an RCT. This also implies that indirect evidence can alter the effectiveness estimates from the RCT because NMAs use evidence from all RCTs included in the network that inform the treatment effect. Therefore, relative effectiveness estimates obtained by an NMA are more robust than outcomes of one single RCT.[85]

Although previous studies[86-88] reported NMA outcomes in advanced melanoma, most of them were conducted before the introduction of immunotherapies and targeted therapies. Two more recent studies[89,90] compared effectiveness across treatment classes (e.g., immunotherapies versus targeted therapies), but both studies were conducted earlier in time. More crucially, both studies did not investigate the relative effectiveness for treatments within the same class (e.g., nivolumab versus pembrolizumab within the immunotherapy class and vemurafenib versus dabrafenib within the BRAFi class).

We investigated the relative effectiveness and safety of each systemic treatment option. We performed a systematic literature review (SLR) to identify all phase III RCTs on patients with advanced

cutaneous melanoma and synthesized this evidence by means of an NMA to evaluate the relative effectiveness (progression-free survival [PFS] and OS) and safety (treatment-related adverse events [TRAEs]) of each systemic treatment. This provides relevant information to develop evidence-based clinical guidelines, to support medical decision making in everyday clinical practice, and to facilitate economic analyses evaluating the relative cost-effectiveness of all treatment options.

METHODS

Systematic literature review

An SLR was performed, in accordance with the PRISMA guidelines[91], in the databases Embase, MEDLINE, and Cochrane to identify relevant phase III RCTs (see Supplement 1). The time frame of the search was from January 1, 2010 to March 11, 2019. The title and abstract were first screened, followed by full text assessing for eligibility. Each step was independently conducted by two researchers, results were compared, and differences were resolved by consensus. Studies were included if they described a phase III RCT of a systemic treatment for unresectable stage III and/or stage IV cutaneous melanoma. The exclusion criteria were as follows: non-cutaneous melanoma, disease stage other than unresectable stage III and IV, study design other than phase III RCT (e.g., observational or review), subgroup analyses only, and non-English articles. Reference lists of published RCTs, reviews, and meta-analyses were manually screened to ensure the inclusion of all phase III RCTs on advanced melanoma.

Data extraction and risk of bias assessment

Data were extracted using a standardized data collection form in Excel. The following data were extracted: publication details (the year of publication and first author), trial details (the national clinical trial number, follow-up duration, intervention and comparator, and the number of patients), patient characteristics (age, disease status, treatment status [treatment-naive {TN} versus previously treated {PT}], and type of previous treatment), safety outcomes (counts/percentages of patients experiencing at least one grade III/IV TRAE), and effectiveness outcomes (median and hazard ratios [HRs] including 95% confidence intervals [CIs] for PFS and OS). Data of the most recent citation were reported in case extended follow-up was available. In case extended follow-up did not report on all outcomes (PFS, OS, and TRAE), the latest reported follow-up was retrieved for each outcome.

In case TRAE count data, HRs, and/or CIs for PFS and OS were not reported, the first author was approached by email. If these data remained unavailable, HRs and/or CIs for PFS and OS were estimated following the step-wise methodology as described by Tierney et al.[92]. If TRAE count data remained unavailable, studies were excluded from the safety NMA. The quality of the studies was assessed by means of the Cochrane collaboration's tool for assessing risk of bias in randomized trials.[93]

Network meta-analysis

A network was created from the identified treatment options which were head-to-head compared in the RCTs. To increase homogeneity between the studies, studies were only included in the main network if patients were either TN or only PT with 'older' treatments which never demonstrated efficacy[86,94,95] (i.e., dacarbazine, temozolomide, fotemustine, carboplatin, interleukin-2, sorafenib, interferon, and cytokine). Therefore, we assumed that all trials within the main network investigated first-line treatment and that previously receiving an 'older ineffective' treatment has no impact on current RCT outcomes. The impact of this assumption was explored by including all identified treatment options within a full extended network, irrespective of receiving previous treatment (extended network and results are presented in Supplemental Figure 1).

The NMA was conducted in WinBUGS in accordance with methods adopted by the National Institute for Health and Care Excellence[96-99] and recommended by the International Society for Pharmacoeconomics and Outcomes Research.[100,101] A random-effect model was deemed inappropriate as the number of studies was too low in comparison with the number of treatments (i.e., only one RCT provided direct evidence between most treatment nodes). Therefore, a Bayesian fixed-effect model was used to estimate the HR of a treatment's relative effectiveness for PFS and OS and the relative risk (RR) for experiencing a grade III/IV TRAE. For all comparisons, the following mathematical formula was used for estimating the HR for PFS and OS of treatment a versus b: $\widehat{HR}_{a,b} = e^{(\partial b - \partial a)}$. The mathematical formula for estimating the RR of TRAEs of treatment a versus b was $\widehat{RR}_{a,b} = e^{(\partial b - \partial a)}$. In all the estimations, uninformative priors were used implying that before seeing the data, all parameter values are deemed likely, but on average, the treatments are considered having no effect.

Dacarbazine was selected as reference treatment ($\partial_{REF} = 0$) as it has been the standard treatment for advanced melanoma until 2010.[86,87] In accordance with the included RCTs, dacarbazine was pooled in a reference group with temozolomide, paclitaxel, and paclitaxel in combination with carboplatin to establish the main network. Consequently, these treatments were assumed to have an identical safety profile and clinical benefit. This assumption was based on three RCTs[102-104] in which a novel treatment was compared with the investigator's choice of chemotherapy (dacarbazine[102-104], temozolomide[104], paclitaxel[102], or paclitaxel plus carboplatin[103]). This assumption was confirmed by clinical experts.

We corrected for the correlation between effect estimates in multi-arm trials using the methods as described by Franchini et al.[105]. The NMA was performed using a Markov Chain Monte Carlo (MCMC) simulation process by iteratively applying RRs for TRAEs and HRs for PFS and OS which were derived from the 95% CIs. The NMA outcomes are probability distributions for the parameters of interest from which summary statistics such as means and standard deviations can be derived (multiple testing is not required). This allows straightforward interpretation of

the outcomes (e.g., the probability that an HR has a certain value) which is in line with decision-making theory.[106] From the outcomes of the MCMC simulation process, we calculated the 95% credible interval (CrI) and the probability of being the best (PBB) treatment. For results for BRAF wild-type patients only, we excluded targeted therapies in the calculation of the PBB.

Convergence of the results was assessed using the Gelman and Rubin's diagnostic.[107] Model fit was assessed using overall residual deviance. Face validity was checked by comparing direct evidence from the RCTs with modelled outcomes. For further reading on NMA methodology, we refer to the studies by Caldwell et al.[83], Mills et al.[108], and Kanters et al.[84].

RESULTS

Systematic literature review

The search identified 2,023 citations. After removing duplicates, 1,684 citations were retrieved from the electronic databases. Title and abstract screening resulted in the exclusion of 1,552 citations. Assessing full text resulted in the exclusion of another 91 citations. In total, 41 citations describing 28 RCTs were included for data extraction for the qualitative analysis. Figure 1 shows the PRISMA flow diagram.

The 28 RCTs involved a total of 14,376 patients with advanced melanoma. The RCTs were conducted in TN patients (11 RCTs), in PT patients (four RCTs), and in TN and PT patients within one trial (13 RCTs). Of the trials including PT patients (17 RCTs), most included patients were previously treated with 'older' treatments. Five[109-113] of these 17 RCTs included a percentage of patients previously treated with a novel treatment (i.e., BRAFi, MEKi, anti-CLTLA-4, and anti-PD-1). One[109] of these RCTs, however, reported outcomes in the first publication irrespective of the line of treatment but reported outcomes differentiating between TN and PT patients in a follow-up publication.[114] The median/mean age of the patients was between 47 and 66 years. The follow-up time of the RCTs was often not reported (11 RCTs). In case it was reported, the method of computation greatly differed between the studies. Therefore, comparing reported follow-up times would be biased.[115] Nine RCTs published at least one extended follow-up publication. There was a large difference in the percentage of patients with a grade III/IV TRAE (ranging from 9% in patients receiving nivolumab[103] to 84% in patients receiving interleukin-2 plus GP100[116]). The median PFS ranged from 1.5 months for dacarbazine[102,111] and paclitaxel[102] to 14.9 months for encorafenib plus binimetinib[113]; the median OS ranged between 5.9 months for lenalidomide[117] and 37.6 months for nivolumab[118], and was not yet reached in five RCTs (i.e., dabrafenib[119], dabrafenib plus trametinib[120], nivolumab[121], pembrolizumab[109], and nivolumab plus ipilimumab[122]). None of the RCTs compared immunotherapy head-to-head with a BRAFi. Similarly, none of the RCTs compared head-to-head the two anti-PD-1 monotherapies, the three BRAFis, or the three BRAFi plus MEKi treatment combinations. Table 1 shows the summary characteristics extracted from the RCTs and Supplemental Table 1 provides additional details of the SLR.

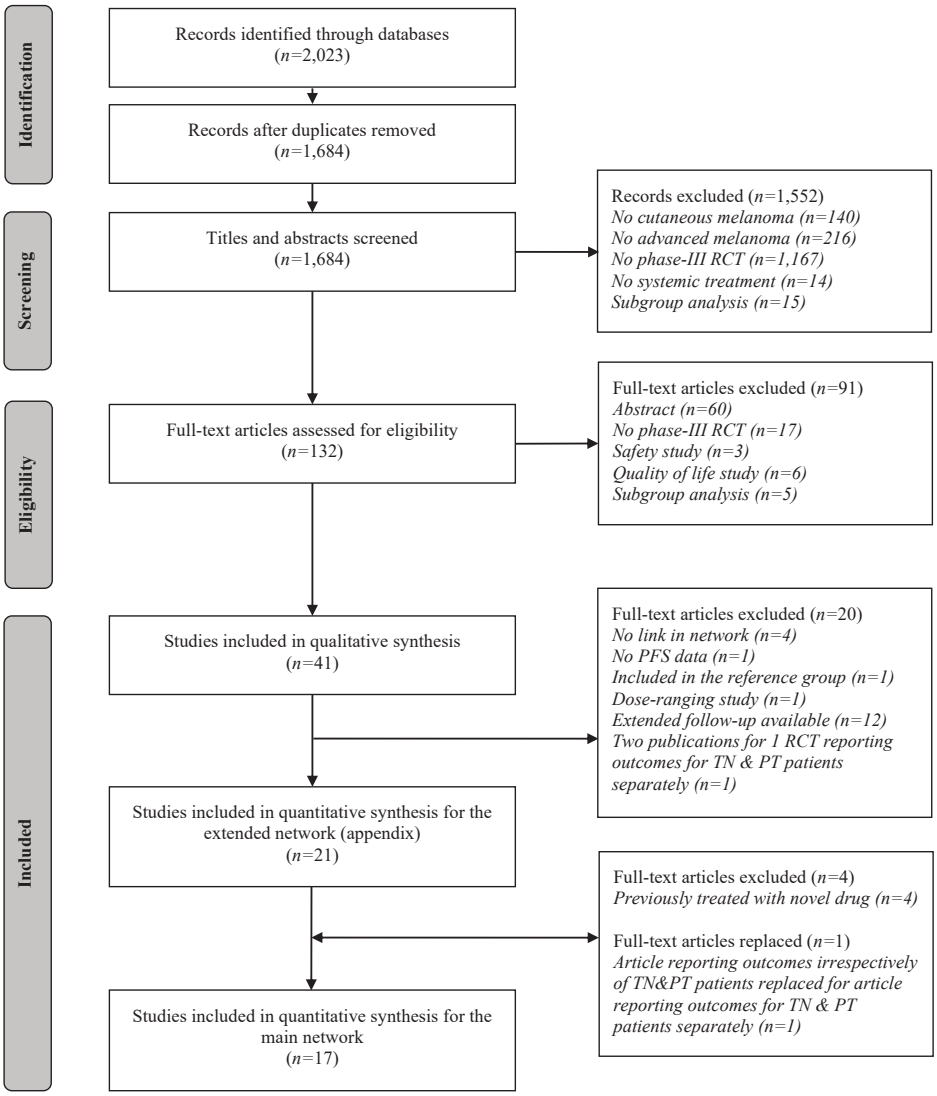


Figure 1. PRISMA flow diagram

n, number; PFS, progression-free survival; TN, treatment-naive; PT, previously-treated; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Supplemental Figure 2 shows the details of the results of the risk of bias assessment. The overall risk of bias was relatively low. In case there was a risk of bias, this was mainly related to reporting bias, violation of the proportional hazard assumption, permission of treatment crossover, and early stop of the study due to crossing predefined boundaries (e.g., futility, efficacy, or stopping boundary).

Table 1. Results of the systematic literature review (publication details, trial details, and patient characteristics)

NCT number	First author	Year	Intervention	Comparator	Treatment status	Number of patients in ITT population	
						Int versus Comp	
00057616	Eisen[a]	2010	Lenalidomide	Placebo	PT	152	154
00094653	Hodi	2010	A: Ipilimumab + GP100	C: GP100	PT	403	136
			B: Ipilimumab			137	
00087776	Bedikian[b]	2011	Docosahexaenoic acid-paclitaxel	Dacarbazine	TN	194	199
00005052	Patel[c]	2011	Temozolomide	Dacarbazine	TN & PT	429	430
00324155	Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	TN	250	252
00019682	Schwartzentruber[a]	2011	Interleukin-2 + GP100	Interleukin-2	TN & PT	91	94
01227889	Hauschild	2012	Dabrafenib	Dacarbazine	TN	187	63
01359956	Daponte[a]	2013	A: Fotemustine + dacarbazine	C: Dacarbazine	TN	64	70
			B: Fotemustine + dacarbazine + interferon alfa-2b	D: Dacarbazine + interferon alfa-2b		68	58
00110019	Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	TN & PT	410	413
00522834	O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	TN & PT	325	326
00257205	Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	TN	328	327
00518895	Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	TN & PT	157	157
01006252	Hamid	2014[1]	Tasisulam	Paclitaxel	PT	168	168
00769704	Andtbacka[a]	2015	Talimogene laherparepvec	Granulocyte-macrophage colony-stimulating factor	TN & PT	295	141
00864253	Hersh	2015	*nab*-Paclitaxel	Dacarbazine	TN & PT	264	265
01597908	Robert	2015	Dabrafenib + trametinib	Vemurafenib	TN	352	352
01689519	Ascierto	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	TN	247	248
01515189	Ascierto[d]	2017	Ipilimumab 10mg/kg	Ipilimumab 3mg/kg	TN & PT	365	362

Table 1. Results of the systematic literature review (publication details, trial details, and patient characteristics) (continued)

NCT number	First author	Year	Intervention	Comparator	Treatment status	Number of patients in ITT population	
						Int versus Comp	
01006980	Chapman	2017	Vemurafenib	Dacarbazine	TN	337	338
01763164	Dummer[f]	2017	Binimetinib	Dacarbazine	TN & PT	269	133
01721746	Larkin[f]	2017	Nivolumab	Paclitaxel + carboplatin or dacarbazine	PT	272	133
01584648	Long	2017	Dabrafenib + trametinib	Dabrafenib + placebo	TN	211	212
01866319	Schachter[f]	2017	A: Pembrolizumab: 2-weekly	C: Ipilimumab	TN & PT	279	278
			B: Pembrolizumab 3-weekly			277	
00779714	Ugurel[f]	2017	Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan + cytarabine	Dacarbazine	TN & PT	141	133
01866319	Carlino[g]	2018	Pembrolizumab	Ipilimumab	TN & PT	TN: 65	TN: 63
						PT: 59	PT: 58
01909453	Dummer[f]	2018	A: Encorafenib + binimetinib	B: Encorafenib	TN & PT	192	194
				C: Vemurafenib			191
01844505	Hodi	2018	A: Nivolumab + ipilimumab	B: Nivolumab	TN	314	316
				C: Ipilimumab			315
01721772	Ascierto	2019	Nivolumab	Dacarbazine	TN	210	208
01245062	Robert	2019	Trametinib	Dacarbazine or paclitaxel	TN & PT	214	108

Table 1. Results of the systematic literature review (publication details, trial details, and outcomes)

NCT number	First author	Year	Intervention	Comparator	RR grade 3/4 TRAEs (95% CI)	HR for PFS (95% CI)	HR for OS (95% CI)
00057616	Eisen[a]	2010	Lenalidomide	Placebo	NR	NR	1.16 (0.86-1.59)
00094653	Hodi	2010	A: Ipilimumab + GP100	C: GP100	A vs B: 0.76 (0.52-1.11)	A vs B: 1.25 (1.06-1.49)	A vs B: 1.04 (0.83-1.30)
			B: Ipilimumab		A vs C: 1.53 (0.90-2.58)	A vs C: 0.81 (0.66-0.99)	A vs C: 0.68 (0.55-0.85)
					B vs C: 2.02 (1.14-3.57)	B vs C: 0.64 (0.50-0.82)	B vs C: 0.66 (0.51-0.87)
00087776	Bedikian[b]	2011	Docosahexaenoic acid-paclitaxel	Dacarbazine	2.13 (1.72-2.64)	NR	NR
00005052	Patel[c]	2011	Temozolomide	Dacarbazine	1.21 (0.99-1.47)	0.92 (0.80-1.06)	1.00 (0.86-1.17)
00324155	Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	2.05 (1.63-2.57)	0.76 (0.63-0.93)	0.72 (0.59-0.87)
00019682	Schwartzentruber[a]	2011	Interleukin-2 + GP100	Interleukin-2	1.06 (0.92-1.23)	NR	NR
01227889	Hauschild	2012	Dabrafenib	Dacarbazine	NR	0.30 (0.18-0.51)	0.61 (0.25-1.48)
01359956	Daponte[a]	2013	A: Fotemustine + dacarbazine	C: Dacarbazine	A+B vs C+D: NR	A+B vs C+D: 0.93 (0.72-1.21)	A+B vs C+D: 0.93 (0.71-1.21)
			B: Fotemustine + dacarbazine + interferon alfa-2b	D: Dacarbazine + interferon alfa-2b	B+D vs A+C: NR	B+D vs A+C: 0.96 (0.73-1.25)	B+D vs A+C: 0.92 (0.70-1.20)
00110019	Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	1.08 (1.01-1.17)	0.90 (0.78-1.03)	1.01 (0.87-1.18)
00522834	O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	1.23 (1.00-1.50)	0.89 (0.73-1.08)	1.10 (0.92-1.32)
00257205	Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	1.40 (1.18-1.67)	0.94 (0.81-1.11)	0.88 (0.74-1.04)
00518895	Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	2.38 (1.68-3.36)	0.85 (0.67-1.09)	1.04 (0.81-1.34)
01006252	Hamid	2014[1]	Tasisulam	Paclitaxel	NR	1.30 (1.01-1.66)	1.23 (0.89-1.69)
00769704	Andtbacka[a]	2015	Talimogene laherparepvec	Granulocyte-macrophage colony-stimulating factor	2.32 (0.99-5.41)	NR	0.79 (0.62-1.00)
00864253	Hersh	2015	*nab*-Paclitaxel	Dacarbazine	NR	0.79 (0.63-0.99)	0.90 (0.71-1.13)
01597908	Robert	2015	Dabrafenib + trametinib	Vemurafenib	0.82 (0.73-0.94)	0.56 (0.49-0.69)	0.69 (0.53-0.89)
01689519	Ascierto	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	1.13 (0.96-1.33)	0.58 (0.46-0.72)	0.70 (0.55-0.90)
01515189	Ascierto[d]	2017	Ipilimumab 10mg/kg	Ipilimumab 3mg/kg	1.87 (1.44-2.43)	0.89 (0.76-1.40)	0.84 (0.70-0.99)

Table 1. Results of the systematic literature review (publication details, trial details, and outcomes) (continued)

NCT number	First author	Year	Intervention	Comparator	RR grade 3/4 TRAEs (95% CI)	HR for PFS (95% CI)	HR for OS (95% CI)
01006980	Chapman	2017	Vemurafenib	Dacarbazine	1.75 (1.51-2.03)	0.38 (0.32-0.46)[e]	0.81 (0.70-1.00)
01763164	Dummer[f]	2017	Binimetinib	Dacarbazine	NR	0.62 (0.47-0.80)	1.00 (0.75-1.33)
01721746	Larkin[f]	2017	Nivolumab	Paclitaxel + carboplatin or dacarbazine	0.41 (0.28-0.62)	1.00 (0.78-1.44)	0.95 (0.70-1.29)
01584648	Long	2017	Dabrafenib + trametinib	Dabrafenib + placebo	0.95 (0.78-1.16)	0.71 (0.57-0.88)	0.75 (0.58-0.96)
01866319	Schachter[f]	2017	A: Pembrolizumab: 2-weekly	C: Ipilimumab	A vs C: 0.87 (0.60-1.24)	A vs C: 0.61 (0.50-0.75)	A vs C: 0.68 (0.53-0.87)
			B: Pembrolizumab 3-weekly		B vs C: 0.85 (0.59-1.22)	B vs C: 0.61 (0.50-0.75)	B vs C: 0.68 (0.53-0.86)
00779714	Ugurel[f]	2017	Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan + cytarabine	Dacarbazine	3.27 (1.94-5.50)	0.91 (0.70-1.18)	1.08 (0.80-1.45)
01866319	Carlino[g]	2018	Pembrolizumab	Ipilimumab	TN: 0.95 (0.66-1.37)	TN: 0.57 (0.46-0.70)	TN: 0.69 (0.54-0.89)
					PT: 0.74 (0.42-1.31)	PT: 0.71 (0.53-0.94)	PT: 0.71 (0.51-0.99)
01909453	Dummer[f]	2018	A: Encorafenib + binimetinib	B: Encorafenib	A vs B: 0.87 (0.75-1.02)[h]	A vs B: 0.77 (0.59-1.00)	A vs B: 0.81 (0.61-1.06)
				C: Vemurafenib	A vs C: 0.91 (0.77-1.07)[h]	A vs C: 0.51 (0.39-0.67)	A vs C: 0.61 (0.47-0.79)
					B vs C: 1.04 (0.90-1.21)[h]	B vs C: 0.68 (0.52-0.88)	B vs C: 0.76 (0.58-0.98)
01844505	Hodi	2018	A: Nivolumab + ipilimumab	B: Nivolumab	A vs B: 2.64 (2.11-3.31)	A vs B: 0.79 (0.65-0.97)	A vs B: 0.84 (0.67-1.05)
				C: Ipilimumab	A vs C: 2.14 (1.75-2.62)	A vs C: 0.42 (0.35-0.51)	A vs C: 0.54 (0.44-0.67)
					B vs C: 0.81 (0.62-1.06)	B vs C: 0.53 (0.44-0.64)	B vs C: 0.65 (0.53-0.79)
01721772	Ascierto	2019	Nivolumab	Dacarbazine	0.86 (0.55-1.33)	0.42 (0.33-0.53)	0.46 (0.36-0.59)
01245062	Robert	2019	Trametinib	Dacarbazine or paclitaxel	1.37 (1.04-1.81)	0.54 (0.41-0.73)	0.84 (0.63-1.11)

CI, confidence interval; Comp, comparator; HR, hazard ratio; Int, intervention; ITT, intention-to-treat; kg, kilogram; mg, milligram; NR, not reported; OS, overall survival; PFS, progression-free survival; PT, previously treated; RR, relative risk; TN, treatment-naive; TRAEs, treatment-related adverse events.

[a]No link in main network.

[b]Not included in main network because data on progression-free survival was not presented.

[c]Temozolomide is pooled within the dacarbazine reference group.

[d]Dose-ranging study.

[e]Retrieved from McArthur et al. 2014.

[f]Only included in extended network (see Supplemental Figure 1).

[g]Treatment line specific outcomes of Schachter et al. 2017 (only included in main network).

[h]Retrieved from Dummer et al. 2018.

Network of treatment options

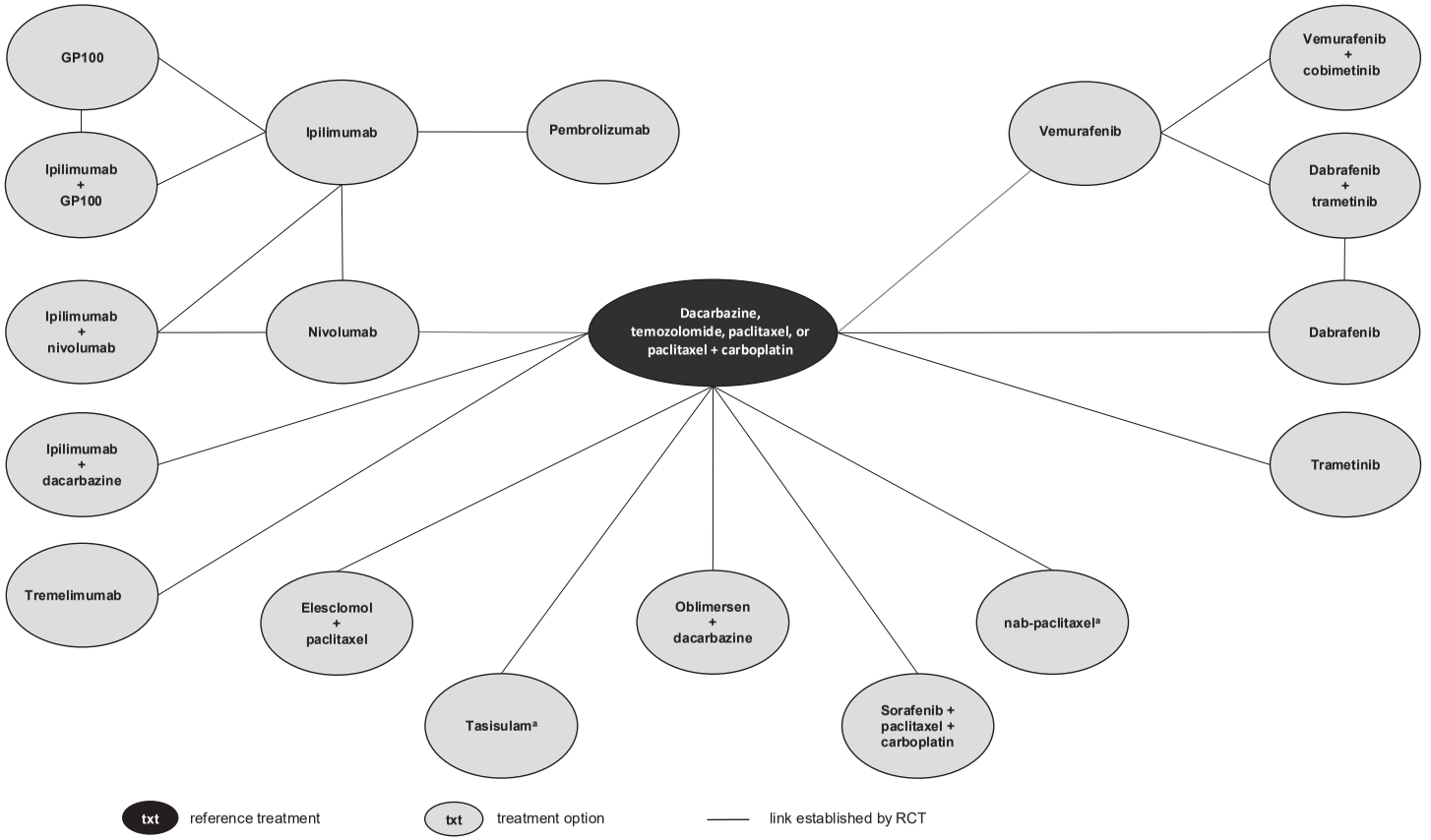
The treatment options of the RCTs were connected in a network (see Figure 2). Of the 28 identified RCTs, four[116,117,123,124] had no connection in the network. Another seven RCTs were excluded from the main network as one RCT[125] had no PFS data (only reported time to progression), one RCT[126] was included within the reference group (comparing temozolomide versus dacarbazine), one RCT[127] concerned a dose-ranging study, and four RCTs[110-113] included patients previously treated with a novel treatment (i.e., BRAFi, MEKi, anti-CLTLA-4, and anti-PD-1). One RCT[109] including TN and PT patients could be retained within the main network as the extended follow-up[114] published the outcomes for TN and PT patients separately. Consequently, a total of 17 RCTs could be connected within the main network including nineteen treatment options: (1) carboplatin, paclitaxel plus sorafenib, (2) dabrafenib, (3) dabrafenib plus trametinib, (4) dacarbazine reference group (including: paclitaxel, paclitaxel plus carboplatin, and temozolomide), (5) dacarbazine plus oblimersen, (6) elesclomol plus paclitaxel, (7) GP100, (8) ipilimumab, (9) ipilimumab plus dacarbazine, (10) ipilimumab plus GP100, (11) nanoparticle albumin-bound (nab-)paclitaxel, (12) nivolumab, (13) nivolumab plus ipilimumab, (14) pembrolizumab, (15) tasisulam, (16) trametinib, (17) tremelimumab, (18) vemurafenib, and (19) vemurafenib plus cobimetinib. Supplemental Table 2 shows RCT and NMA outcomes confirming face validity of our NMA results. Supplemental Figure 3 provides estimates of NMA outcomes for each head-to-head comparison.

Network meta-analysis for treatment-related grade III/IV adverse events

Two RCTs[128,129] within the network did not report TRAE count data; therefore, the NMA for TRAE included fifteen RCTs (excluding tasisulam and nab-paclitaxel from the main network). Figure 3 presents the estimated RR for grade III/IV TRAEs ranked according to RR compared with the dacarbazine reference group. The GP100 was most favorable both in terms of RR for grade III/IV TRAE (RR TRAE: 0.58 [95% CrI: 0.25-1.16]) and PBB (0.85). Although 95% CrIs were overlapping with 1, two other options ranked better than the reference group: ipilimumab plus GP100 (PBB: 0.04; RR TRAE: 0.85 [95% CrI: 0.42-1.54]) and nivolumab (PBB: 0.05; RR TRAE: 0.86 [95% CrI: 0.54-1.30]). Pembrolizumab (RR TRAE: 1.04) and ipilimumab (RR TRAE: 1.08) were slightly less favorable than the dacarbazine reference group, but the 95% CrIs were overlapping with 1. The remaining 11 treatments had a greater risk for grade III/IV TRAEs than the reference group (RR ranging from 1.08 to 2.38).

Network meta-analysis for progression-free survival

Figure 4 presents the estimated HRs for PFS ranked according to HR for PFS compared with the dacarbazine reference group. The two BRAFi plus MEKi combination treatments were identified as the most favorable ones. Although dabrafenib plus trametinib had a higher probability of being the best treatment (PBB: 0.59) and a slightly more favorable HR for PFS (0.21) than vemurafenib plus cobimetinib (PBB: 0.40; HR PFS: 0.22), the 95% CrIs were similar (0.17-0.27 versus 0.17-



[a]Only included in network-meta analyses for progression-free and overall survival (not in safety analyses).

Figure 2. Main network of treatments for advanced melanoma
GP100, glycoprotein 100 peptide vaccine; RCT, randomized controlled trial.

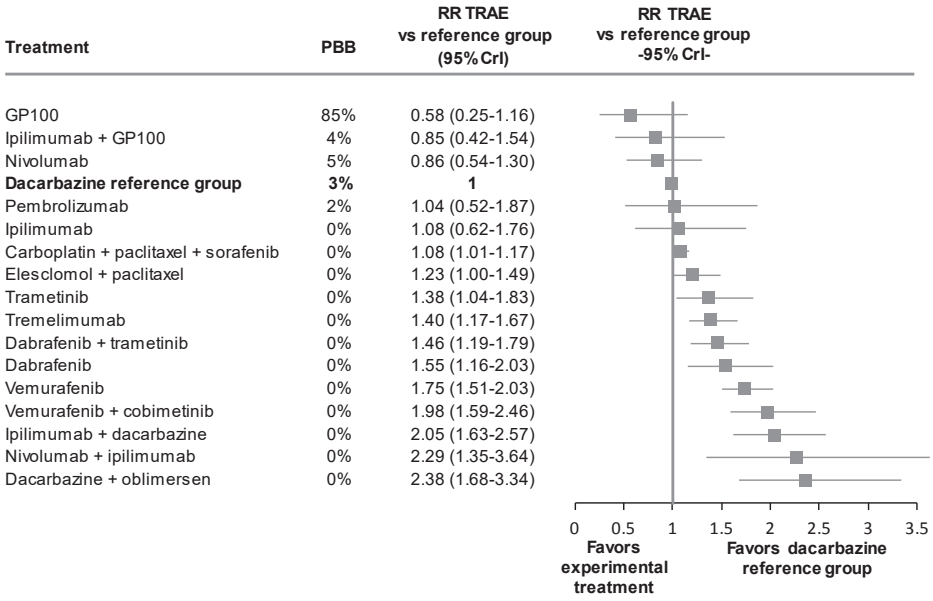


Figure 3. Results of the network meta-analysis for adverse events
CrI, credible interval; GP100, glycoprotein 100 peptide vaccine; PBB, probability of being the best; RR, relative risk; TRAE, treatment-related adverse event.

0.29). Fifteen treatments ranked better than the dacarbazine reference group; the HRs for PFS ranged between 0.21 and 0.94. Seven treatments reduced the risk of progression by more than 50% including dabrafenib plus trametinib, vemurafenib plus cobimetinib, dabrafenib, nivolumab plus ipilimumab, vemurafenib, nivolumab, and pembrolizumab. Trametinib, ipilimumab plus dacarbazine, and ipilimumab monotherapy reduced the risk of progression by 45%, 24%, and 20%, respectively. All chemotherapies were less likely reducing the risk of progression, most of whose HRs were overlapping with 1.

In BRAF wild-type patients, nivolumab plus ipilimumab ranked best (PBB: 0.97; HR PFS: 0.34 [95% CrI: 0.24-0.46]), followed by nivolumab monotherapy (PBB: 0.02; HR PFS: 0.42 [95% CrI: 0.33-0.53]) and pembrolizumab (PBB: 0.02; HR PFS: 0.46 [95% CrI: 0.31-0.65]).

Network meta-analysis for overall survival

Figure 5 presents the estimated HRs for OS ranked according to HR for OS compared with the dacarbazine reference group. Three treatments reduced the risk of death by 50% or more. Nivolumab plus ipilimumab had the highest probability of being the best treatment (PBB: 0.82) and the most favorable HR for OS (0.39 [95% CrI: 0.27-0.54]). Although nivolumab monotherapy (PBB: 0.04) and pembrolizumab (PBB: 0.06) had a somewhat less favorable HR for OS (0.46 and 0.50, respectively), the 95% CrI largely overlapped with nivolumab plus ipilimumab (nivolumab

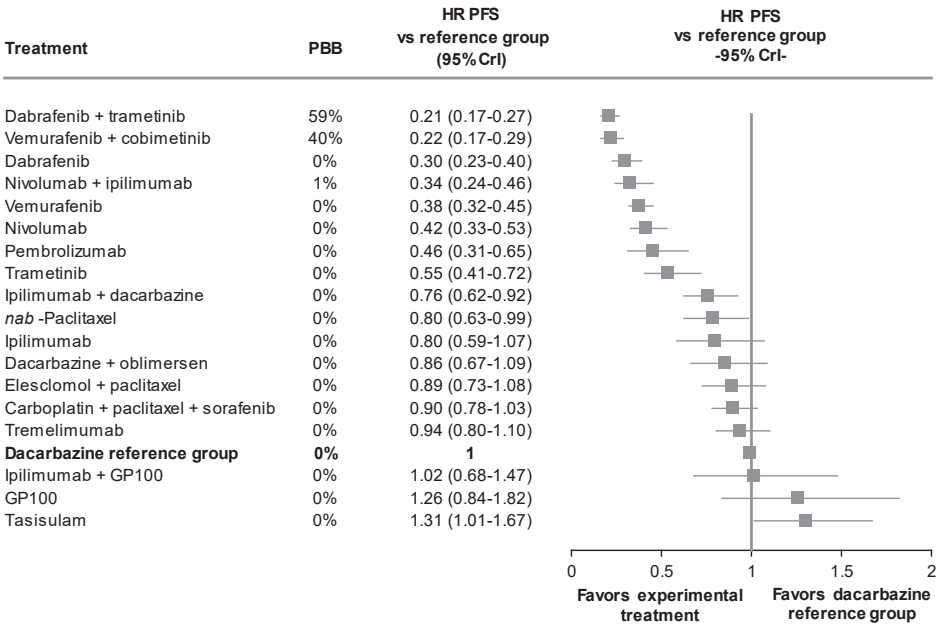


Figure 4. Results of the network meta-analysis for progression-free survival
CrI, credible interval; GP100, glycoprotein 100 peptide vaccine; PBB, probability of being the best; HR, hazard ratio; PFS, progression-free survival.

95% CrI: 0.36-0.59; pembrolizumab 95% CrI: 0.33-0.73). The two BRAFi plus MEKi combination treatment options closely followed (dabrafenib plus trametinib: PBB: 0.05; HR OS: 0.55 [95% CrI: 0.41-0.74] and vemurafenib plus cobimetinib: PBB: 0.03; HR OS: 0.57 [95% CrI: 0.42-0.76]). Another eight treatments ranked better than the dacarbazine reference group; these HRs for OS ranged between 0.72 and 0.91. Five treatments were less favorable than the dacarbazine reference group, but the 95% CrIs were overlapping with 1.

In BRAF wild-type patients, nivolumab plus ipilimumab ranked best (PBB: 0.88; HR OS: 0.39 [95% CrI: 0.27-0.54]), followed by both anti-PD-1 monotherapies (nivolumab: PBB: 0.05; HR OS: 0.46 [95% CrI: 0.36-0.59]; pembrolizumab: PBB: 0.06; HR OS: 0.50 [95% CrI: 0.33-0.73]).

DISCUSSION

A myriad of novel treatments entered the treatment paradigm for advanced melanoma in the last eight years. There is, however, a lack of head-to-head evidence. We conducted an SLR and synthesized all available phase III RCT evidence to assess the relative safety and relative effectiveness of each novel treatment. As there is a low incentive for comparing treatments with market approval head-to-head in an RCT, we believe that evidence from NMAs will become

Treatment	PBB	HR OS vs reference group (95% CrI)
Nivolumab + ipilimumab	82%	0.39 (0.27-0.54)
Nivolumab	4%	0.46 (0.36-0.59)
Pembrolizumab	6%	0.50 (0.33-0.73)
Dabrafenib + trametinib	5%	0.55 (0.41-0.74)
Vemurafenib + cobimetinib	3%	0.57 (0.42-0.76)
Ipilimumab	0%	0.72 (0.52-0.97)
Ipilimumab + dacarbazine	0%	0.72 (0.59-0.87)
Dabrafenib	0%	0.73 (0.50-1.04)
Ipilimumab + GP100	0%	0.74 (0.48-1.10)
Vemurafenib	0%	0.81 (0.68-0.96)
Trametinib	0%	0.85 (0.63-1.11)
Tremelimumab	0%	0.88 (0.74-1.04)
nab -Paclitaxel	0%	0.91 (0.71-1.13)
Dacarbazine reference group	**0%**	**1**
Carboplatin + paclitaxel + sorafenib	0%	1.01 (0.87-1.18)
Dacarbazine + oblimersen	0%	1.05 (0.81-1.34)
GP100	0%	1.10 (0.71-1.62)
Elesclomol + paclitaxel	0%	1.11 (0.92-1.32)
Tasisulam	0%	1.25 (0.89-1.70)

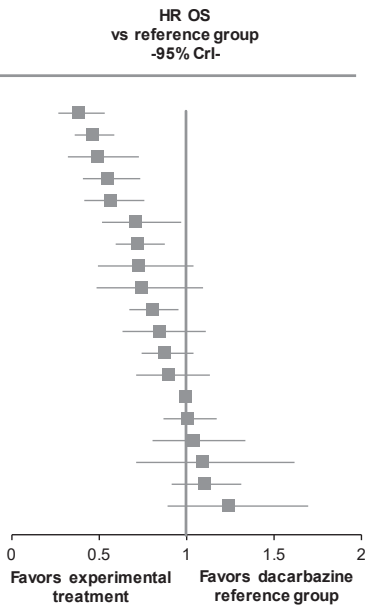


Figure 5. Results of the network meta-analysis for overall survival
CrI, credible interval; GP100, glycoprotein 100 peptide vaccine; PBB, probability of being the best; HR, hazard ratio; OS, overall survival.

increasingly important to inform evidence-based guideline development, to support medical decision-making in everyday practice, and to facilitate economic analysis.[81,82,84] There is, for example, no evidence from RCTs regarding the comparative effectiveness of immune checkpoint inhibitors versus mitogen-activated protein kinase pathway inhibitors. Our NMA results showed that for PFS, both dabrafenib plus trametinib and vemurafenib plus cobimetinib (both a BRAFi plus MEKi combination treatment) were the most favorable treatment options. Both had, however, less favorable safety profiles. A group of five other treatments closely followed (dabrafenib, nivolumab plus ipilimumab, vemurafenib, nivolumab, and pembrolizumab, respectively). As these five treatments had considerable overlap in 95% CrIs, all five can be considered as valuable treatment options for clinical practice guided by disease and patient characteristics.

In contrast to PFS results, however, our NMA results show that for OS nivolumab in combination with ipilimumab, nivolumab monotherapy, and pembrolizumab ranked better than both BRAFi plus MEKi combination treatments, albeit with a considerable overlap of the 95% CrIs. This trend is in line with the expectation of clinical experts who generally confirmed that targeted therapies reduce the risk for progression but that immunotherapies have better overall survival outcomes than targeted therapies. Nevertheless, the estimated OS outcomes should be interpreted with caution. Many RCTs had a relatively short follow-up and could be considered rather immature regarding OS (see Supplemental Table 1). Moreover, patients often receive further lines of treat-

ment which also have an impact on survival. It is, however, not feasible to make a distinction between the effect on OS from the first and subsequent treatments. In the SLR, we identified nine RCTs with at least one extended follow-up publication. These publications illustrate that the HRs for OS were lower for all six that published an HR for OS in the first publication. In one RCT (comparing vemurafenib with dacarbazine), the 95% CIs for the HRs for OS were not even overlapping (first published[130] HR OS: 0.37 [95% CI: 0.26-0.55] versus extended follow-up[131] HR OS: 0.81 [95% CI: 0.70-1.00]). This was not the case for PFS; although the HRs for PFS were most often somewhat lower in the extended follow-up publications, 95% CIs were largely overlapping. There is, however, no consensus to what extent PFS captures the effectiveness of a treatment in specific for immunotherapies. More importantly, there is no established evidence on the actual relationship between PFS and OS. Most studies (19 of 28 RCTs) did not (yet) report extended follow-up. It is a concern whether less favorable extended follow-up outcomes will get published.[81,132] For all types of evidence, a longer follow-up always provides more solid evidence.

As NMAs combine direct and indirect evidence of RCTs, the outcomes of an NMA can be considered more solid than outcomes of one single RCT.[85,132] It also implies that indirect evidence can alter the HRs from the RCT. For example (see Supplemental Figure 4), the link between the dacarbazine reference group and dabrafenib was computed not only using direct evidence from the RCT by Hauschild et al.[119] (HR OS: 0.61) but also from indirect evidence from three other studies.[120,133,134] Combining direct and indirect evidence resulted in a somewhat less favorable estimated HR for OS for dabrafenib versus the dacarbazine reference group (estimated HR OS: 0.73 in the NMA compared with the observed HR OS: 0.61 in the RCT).

To establish the network and conduct the NMA, we had to make assumptions which may have introduced some level of uncertainty. First, we pooled dacarbazine in a reference group with temozolomide, paclitaxel, and paclitaxel in combination with carboplatin. This assumption was based on three RCTs[102-104], in which a novel treatment was compared with the investigator's choice of chemotherapy consisting of drugs in our pooled reference group. Clinical experts confirmed the validity of this assumption. As a consequence, however, our network could not include the RCT published by Patel et al.[126] comparing the effectiveness of temozolomide with dacarbazine (HR PFS: 0.92). As the CI included an HR of 1, we believe, however, that this had a negligible impact on our results.

Second, a crucial assumption of an NMA is that the distribution of effect modifiers is comparable across the RCTs within the network. As long as prognostic factors have no influence on the treatment effect, this assumption is not violated irrespective of the (differences in) prognostic factors of the study populations in the RCTs. However, to increase homogeneity of the study populations of the included RCTs, we made a distinction between TN and PT patients. We also assumed that patients previously receiving an 'older' treatment had no impact on the results. We believe

that this assumption is valid as these 'older' treatments never demonstrated efficacy.[86,94,95] As a consequence, we excluded four RCTs[110-113] in our main network in which a percentage of patients were previously treated with a 'new' (effective) treatment (i.e., BRAFi, MEKi, anti-CLTLA-4, and anti-PD-1). This further increased, however, the homogeneity of the study populations of our included RCTs. Carlino et al.[114] reported, for example, outcomes of pembrolizumab for both TN (HR PFS: 0.57 [95% CI: 0.46-0.70] and HR OS: 0.69 [95% CI: 0.54-0.89]) and PT patients (HR PFS: 0.71 [95% CI: 0.53-0.94] and HR OS: 0.71 [95% CI: 0.51-0.99]). This suggests that TN and PT patients may have different outcomes, in specific for PFS, and it underpins our assumption to differentiate between TN and PT patients in our NMA.

Supplemental Figure 1 shows the impact of including all identified RCTs, irrespective of (type of) previous treatment. The extended network expands with several novel treatment options such as binimetinib, encorafenib, and encorafenib plus binimetinib. For PFS, encorafenib plus binimetinib was most favorable (PBB: 0.63), however, with largely overlapping 95% CrIs with both other BRAFi plus MEKi treatments. Similarly, for OS, encorafenib plus binimetinib was most favorable (PBB: 0.41) but with largely overlapping 95% CrIs with nivolumab plus ipilimumab, both other BRAFi plus MEKi treatments, and both anti-PD-1 monotherapies. The greatest impact of the inclusion of RCTs with patients previously treated with a novel drug is, however, related to the inclusion of the study by Larkin et al.[110]. This RCT investigated nivolumab versus paclitaxel plus carboplatin or dacarbazine. This is the crucial link in the network for any comparison between immunotherapies and targeted therapies. In the main network, this link was only based on Ascierto et al.[135]. The HR for PFS and OS were much more favorable in TN patients in the RCT by Ascierto et al.[135] (HR PFS: 0.42 and HR OS: 0.46) than in PT patients in the RCT by Larkin et al.[110] (HR PFS: 1.00 and HR OS: 0.95), even the 95% CIs were not overlapping. Therefore, the inclusion of the study by Larkin et al.[110] (in the extended network including RCTs with PT patients) resulted in less favorable outcomes for nivolumab compared with the dacarbazine reference group (HR PFS: 0.42 in the main network versus 0.58 in the extended network; HR OS: 0.46 in the main network versus 0.62 in the extended network). More crucially, however, all immunotherapies became less favorable in comparison with all targeted therapies owing to this link in the network (i.e., lower rank and less favorable estimated HR for PFS and OS).

To our knowledge, our study is the first study that investigated treatment-specific safety and effectiveness outcomes in advanced melanoma. Two recent NMAs[89,90] only compared outcomes across classes of immunotherapies and targeted therapies. Our study shows that the estimated HRs for PFS and OS are not identical for treatments within classes (e.g., within the BRAFi class: vemurafenib HR PFS: 0.38 and HR OS: 0.81 and dabrafenib HR PFS: 0.30 and HR OS: 0.73). The 95% CrIs were, however, largely overlapping for treatments within a class. Both previous NMAs were conducted earlier in time than our study. Therefore, we could include more recent phase III RCT evidence and information from extended follow-up publications. More importantly,

however, both Lima et al.[89] and Devji et al.[90] included phase III as well as phase II studies, and full publications as well as conference abstracts. This may have increased uncertainty and heterogeneity in their network. As the key underlying assumption of any NMA is exchangeability[83,97], we believe that inclusion of preliminary results of conference abstracts and phase II studies may introduce unnecessary bias which may lead to inconsistency.[99,136]

Nevertheless, both previous NMAs also found for PFS an advantage of the BRAFi plus MEKi class versus anti-PD-1 plus anti-CTLA-4 class, albeit to a varying degree. This was somewhat different for OS; both Lima et al.[89] and Devji et al.[90] found no difference in estimated effect of anti-PD-1 monotherapies versus the BRAFi plus MEKi class, whereas our estimates were in favor of nivolumab (HR OS: 0.86 versus dabrafenib plus trametinib and 0.80 versus vemurafenib plus cobimetinib). This difference was, however, not statistically significant as 95% CrIs were overlapping with 1. Both previous studies could not include the anti-PD-1 plus anti-CTLA-4 class for OS because of the time in which their study was conducted.

To conclude, our study identified the most effective treatment options for advanced melanoma and provided valuable insight into each treatment's relative safety and effectiveness. NMAs provide more solid evidence than single RCTs as they combine direct and indirect evidence, and NMAs provide evidence on treatment comparisons never compared head-to-head in an RCT. Such evidence is relevant for the development of evidence-based guidelines and may support medical decision making, and ultimately help optimize treatment and outcomes of patients with advanced melanoma in everyday clinical practice. Clinicians not only decide between treatment classes but also need to decide which treatment within the class is best for each individual patient. Moreover, our NMA results may facilitate economic analysis evaluating relative cost-effectiveness of all novel treatment options. Our study showed that, regarding PFS, both BRAFi plus MEKi combination treatments were identified as most effective treatment for patients with BRAF-mutant advanced melanoma. In contrast to PFS, however, anti-PD-1 plus anti-CTLA-4 and both anti-PD-1 monotherapies were identified as the most favorable regarding OS, irrespective of BRAF mutation. Given current clinical practice, it would be interesting to shed more light into the effectiveness of different sequences of novel treatments. Although currently lacking, such evidence may become available in the near future from new or ongoing RCTs[137] as well as from registry data.[138]

SUPPLEMENTARY MATERIAL

EMBASE

((melanoma/exp/mj AND ('advanced cancer'/de OR 'metastasis'/exp)) OR ((melano* OR naevocarcinom* OR nevocarcinom*) NEAR/3 (advanced* OR metasta*)):ti) AND (therapy/exp OR therapy:lnk OR 'antineoplastic agent'/exp OR 'treatment outcome'/exp OR 'B Raf kinase inhibitor'/exp OR 'mitogen activated protein kinase inhibitor'/exp OR (therap* OR treat* OR systemic* OR chemotherap* OR immunotherap* OR inhibitor* OR drug* OR agent* OR pharma* OR vemurafenib* OR dabrafenib* OR ipilimumab* OR nivolumab* OR pembrolizumab* OR dacarbazine* OR antibod* OR anti-pd-1 OR antictla-4 OR Temozolomid* OR trametinib* OR Cobimetinib* OR antineoplas* OR management* OR intervention* OR talimogene* OR virotherap* OR (oncolytic* NEAR/3 virus*)):ab,ti) AND ('clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR randomization/exp OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti) AND ('clinical effectiveness'/exp OR 'survival'/exp OR 'treatment response'/de OR adverse drug reaction/exp OR (effective* OR surviv* OR (treatment NEAR/3 response*) OR adverse*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

MEDLINE

((exp * melanoma/ AND ("Neoplasm Metastasis"/)) OR ((melano* OR naevocarcinom* OR nevocarcinom*) ADJ3 (advanced* OR metasta*)).ti.) AND (therapeutics/ OR therapy.xs. OR "Antineoplastic Agents"/ OR exp "treatment outcome"/ OR (therap* OR treat* OR systemic* OR chemotherap* OR immunotherap* OR inhibitor* OR drug* OR agent* OR pharma* OR vemurafenib* OR dabrafenib* OR ipilimumab* OR nivolumab* OR pembrolizumab* OR dacarbazine* OR antibod* OR anti-pd-1 OR anti-ctla-4 OR Temozolomid* OR trametinib* OR Cobimetinib* OR antineoplas* OR management* OR intervention* OR talimogene* OR virotherap* OR (oncolytic* ADJ3 virus*)).ab,ti.) AND (exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti.) AND (exp "survival"/ OR exp "Drug-Related Side Effects and Adverse Reactions"/ OR (effective* OR surviv* OR (treatment ADJ3 response*) OR adverse*).ab,ti.) NOT (exp animals/ NOT humans/) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

COCHRANE

(((melano* OR naevocarcinom* OR nevocarcinom*) NEAR/3 (advanced* OR metasta*)):ti) AND ((therap* OR treat* OR systemic* OR chemotherap* OR immunotherap* OR inhibitor* OR drug* OR agent* OR pharma* OR vemurafenib* OR dabrafenib* OR ipilimumab* OR nivolumab* OR pembrolizumab* OR dacarbazine* OR antibod* OR anti-pd-1 OR anti-ctla-4 OR Temozolomid* OR trametinib* OR Cobimetinib* OR antineoplas* OR management* OR intervention* OR talimogene* OR virotherap* OR (oncolytic* NEAR/3 virus*)):ab,ti) AND ((effective* OR surviv* OR (treatment NEAR/3 response*) OR adverse*):ab,ti)

Supplement 1. Search strategy systematic literature review

Supplemental Table 1. Details of the systematic literature review (publication details and trial details)

NCT number	First author	Year	Intervention	Comparator	Median FU in months (range)		Number of patients in ITT population	
					Int vs Comp		*Int vs Comp*	
NCT00057616	Eisen[a]	2010	Lenalidomide	Placebo	NR	NR	152	154
NCT00094653	Hodi	2010	A: Ipilimumab + GP100	C: GP100	21.0 (NR)	17.2 (NR)	403	136
			B: Ipilimumab		27.8 (NR)		137	
NCT00087776	Bedikian[b]	2011	Docosahexaenoic acid–paclitaxel	Dacarbazine	NR	NR	194	199
NCT01006980	Chapman[d]	2011	Vemurafenib	Dacarbazine	3.8 (NR)	2.3 (NR)	337	338
NCT00005052	Patel[f]	2011	Temozolomide	Dacarbazine	19 (NR)		429	430
NCT00324155	Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	NR	NR	250	252
NCT00019682	Schwartzentruber[a]	2011	Interleukin-2 + GP100	Interleukin-2	41.5 (NR)		91	94
NCT01245062	Flaherty[d]	2012	Trametinib	Dacarbazine or paclitaxel	NR	NR	214	108
NCT01227889	Hauschild	2012	Dabrafenib	Dacarbazine	4.9 (0-9.9)		187	63
NCT01359956	Daponte[a]	2013	A: Fotemustine + dacarbazine	C: Dacarbazine	NR	NR	64	70
			B: Fotemustine + dacarbazine + interferon alfa-2b	D: Dacarbazine + interferon alfa-2b	NR	NR	68	58
NCT00110019	Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	NR		410	413
NCT00522834	O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	NR		325	326
NCT00257205	Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	NR		328	327
NCT00518895	Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	NR		157	157
NCT01006252	Hamid	2014	Tasisulam	Paclitaxel	5.3 (NR)		168	168
NCT01689519	Larkin[d]	2014	Vemurafenib + cobimetinib	Vemurafenib + placebo	7.3 (0.5-16.5)		247	248
NCT01584648	Long[d]	2014	Dabrafenib + trametinib	Dabrafenib + placebo	9 (0-16)		211	212
NCT01006980	McArthur[d,h]	2014	Vemurafenib	Dacarbazine	12.5 (7.7-16.0)	9.5 (3.1-14.7)	337	338

Supplemental Table 1. Details of the systematic literature review (publication details and trial details) (continued)

NCT number	First author	Year	Intervention	Comparator	Median FU in months (range)		Number of patients in ITT population	
					Int vs Comp		*Int vs Comp*	
NCT00769704	Andtbacka[a]	2015	Talimogene laherparepvec	Granulocyte-macrophage colony-stimulating factor	44.4 (32.4-58.7)		295	141
NCT00864253	Hersh	2015	*nab*-Paclitaxel	Dacarbazine	NR	NR	264	265
NCT01844505	Larkin[d] [21]	2015	A: Nivolumab + ipilimumab	B: Nivolumab	12.2-12.5 (NR)		314	316
				C: Ipilimumab				315
NCT01584648	Long[d,h]	2015	Dabrafenib + trametinib	Dabrafenib + placebo	20 (0-30)	16 (0-32)	211	212
NCT01597908	Robert	2015a	Dabrafenib + trametinib	Vemurafenib	11 (NR)	10 (NR)	352	352
NCT01866319	Robert[d]	2015b	A: Pembrolizumab: 2-weekly	C: Ipilimumab	7.9 (6.1-11.5)		279	278
			B: Pembrolizumab 3-weekly				277	
NCT01721772	Robert[d]	2015c	Nivolumab	Dacarbazine	8.9 (NR)	6.8 (NR)	210	208
NCT01721746	Weber[d]	2015	Nivolumab	Paclitaxel + carboplatin or dacarbazine	8.4 (7.0-9.8)		272	133
NCT01689519	Ascierto[h]	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	PFS: 14.2 (8.5-17.3) OS: 18.5 (8.5-23.5)		247	248
NCT01515189	Ascierto[j]	2017	Ipilimumab 10mg/kg	Ipilimumab 3mg/kg	OS: 14.5 (4.6-42.3)	OS: 11.2 (4.9-29.4)	365	362
NCT01006980	Chapman[h]	2017	Vemurafenib	Dacarbazine	13.4 (0.4-59.6)	9.2 (0-56.2)	337	338
NCT01763164	Dummer[k]	2017	Binimetinib	Dacarbazine	PFS: 1.7 (1.4-4.1) OS: 9.2 (4.8-13.9)		269	133
NCT01721746	Larkin[h,k]	2017	Nivolumab	Paclitaxel + carboplatin or dacarbazine	NR	NR	272	133
NCT01584648	Long[h]	2017	Dabrafenib + trametinib	Dabrafenib + placebo	NR	NR	211	212
NCT01866319	Schachter[h,k]	2017	A: Pembrolizumab: 2-weekly	C: Ipilimumab	22.9 (NR)		279	278
			B: Pembrolizumab 3-weekly				277	

Supplemental Table 1. Details of the systematic literature review (publication details and trial details) (continued)

NCT number	First author	Year	Intervention	Comparator	Median FU in months (range)		Number of patients in ITT population	
					Int vs Comp		*Int vs Comp*	
NCT00779714	Ugurel[k]	2017	Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan + cytarabine	Dacarbazine	26.4 (NR)		141	133
NCT01844505	Wolchok[d,h]	2017	A: Nivolumab + ipilimumab	B: Nivolumab	38 (NR)	35.7 (NR)	314	316
				C: Ipilimumab		18.6 (NR)		315
NCT01866319	Carlino[l]	2018	Pembrolizumab	Ipilimumab	33.9 (NR)		TN: 368	TN: 181
							PT: 187	PT: 97
NCT01909453	Dummer[d,k]	2018a	A: Encorafenib + binimetinib	B: Encorafenib	PFS: 16.7 (16.3-18.4)	PFS: 16.6 (14.8-18.1)	192	194
				C: Vemurafenib		PFS: 14.4 (10.1-16.6)		191
NCT01909453	Dummer[h,k]	2018b	A: Encorafenib + binimetinib	B: Encorafenib	PFS: 32.3 (31.7-34.9) OS: 37.2 (36.1-38.5)	PFS: 32.0 (24.0-34.9) OS: 36.3 (34.8-37.3)	192	194
				C: Vemurafenib		PFS: 22.2 (11.0-32.3) OS: 35.9 (34.9-38.0)		191
NCT01844505	Hodi[h]	2018	A: Nivolumab + ipilimumab	B: Nivolumab	46.9 (10.9-51.8)	36.0 (10.5-51.4)	314	316
				C: Ipilimumab		18.6 (7.6-49.5)		315
NCT01721772	Ascierto[h]	2019	Nivolumab	Dacarbazine	38.4 (NR)	38.5 (NR)	210	208
NCT01245062	Robert[h]	2019	Trametinib	Dacarbazine or paclitaxel	14.7 (0-70)	8.7 (0-70)	214	108

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and patient characteristics)

NCT number	First author	Year	Intervention	Comparator	Treatment status	Previous treatments	Patient population	Median [mean] age	
								Int vs Comp	
NCT00057616	Eisen[a]	2010	Lenalidomide	Placebo	PT	Dacarbazine, interleukin-2, interferon-α, and/or interferon-β	Stage IV	62	56
NCT00094653	Hodi	2010	A: Ipilimumab + GP100	C: GP100	PT	Dacarbazine, temozolomide, fotemustine, carboplatin, and/or interleukin-2	Unresectable stage III or IV	[56]	[57]
			B: Ipilimumab					[57]	
NCT00087776	Bedikian[b]	2011	Docosahexaenoic acid–paclitaxel	Dacarbazine	TN	NA	Stage IV	61	62
NCT01006980	Chapman[d]	2011	Vemurafenib	Dacarbazine	TN	NA	Unresectable stage IIIC or IV BRAF mutated	56	52
NCT00005052	Patel[f]	2011	Temozolomide	Dacarbazine	TN & PT	Vaccine therapy (except for cytokine)	Stage IV	NR	NR
NCT00324155	Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	TN	NA	Unresectable stage III or IV	[58]	[56]
NCT00019682	Schwartzentruber[a]	2011	Interleukin-2 + GP100	Interleukin-2	TN & PT	Chemotherapy, interferon-α, and/or low-dose interleukin-2	Locally advanced stage III or IV	[47]	[50]
NCT01245062	Flaherty[d]	2012	Trametinib	Dacarbazine or paclitaxel	TN & PT	Chemotherapy, immunotherapy (other than ipilimumab), and/or sorafenib	Unresectable stage IIIC or IV BRAF mutated	55	54
NCT01227889	Hauschild	2012	Dabrafenib	Dacarbazine	TN	NA	Unresectable stage III or IV BRAF mutated	53	50

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and patient characteristics) (continued)

NCT number	First author	Year	Intervention	Comparator	Treatment status	Previous treatments	Patient population	Median [mean] age	
								Int vs Comp	
NCT01359956	Daponte[a]	2013	A: Fotemustine + dacarbazine	C: Dacarbazine	TN	NA	Stage IV	[54]	[59]
			B: Fotemustine + dacarbazine + interferon alfa-2b	D: Dacarbazine + interferon alfa-2b				[50]	[56]
NCT00110019	Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	TN & PT	Interferon, interleukin-2, granulocyte-macrophage colony-stimulating factor, and/or vaccine	Unresectable stage III or IV	61	59
NCT00522834	O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	TN & PT	Kinase inhibitor, immunotherapy, biologic therapy, and/or vaccine	Stage IV	60	60
NCT00257205	Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	TN	NA	Unresectable stage IIIC or IV	[57]	[56]
NCT00518895	Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	TN & PT	Immunotherapy, cytokine, biologic therapy, and/or vaccine	Unresectable stage III or IV	58	60
NCT01006252	Hamid	2014	Tasisulam	Paclitaxel	PT	Dacarbazine or temozolomide	Stage IV	60	60
NCT01689519	Larkin[d]	2014	Vemurafenib + cobimetinib	Vemurafenib + placebo	TN	NA	Unresectable stage IIIC or IV BRAF mutated	56	55
NCT01584648	Long[d]	2014	Dabrafenib + trametinib	Dabrafenib + placebo	TN	NA	Unresectable stage IIIC or IV BRAF mutated	55	57
NCT01006980	McArthur[d,h]	2014	Vemurafenib	Dacarbazine	TN	NA	Unresectable stage IIIC or IV BRAF mutated	56	53

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and patient characteristics) (continued)

NCT number	First author	Year	Intervention	Comparator	Treatment status	Previous treatments	Patient population	Median [mean] age	
								Int vs Comp	
NCT00769704	Andtbacka[a]	2015	Talimogene laherparepvec	Granulocyte-macrophage colony-stimulating factor	TN & PT	Unknown	Unresectable stage IIIB or IV	63	64
NCT00864253	Hersh	2015	*nab*-Paclitaxel	Dacarbazine	TN & PT	Kinase inhibitor and/or cytokine	Stage IV	62	64
NCT01844505	Larkin[d] [21]	2015	A: Nivolumab + ipilimumab	B: Nivolumab C: Ipilimumab	TN	NA	Unresectable stage III or IV	[59]	[59] [61]
NCT01584648	Long[d,h]	2015	Dabrafenib + trametinib	Dabrafenib + placebo	TN	NA	Unresectable stage IIIC or IV BRAF mutated	55	57
NCT01597908	Robert	2015a	Dabrafenib + trametinib	Vemurafenib	TN	NA	Unresectable stage IIIC or IV BRAF mutated	55	54
NCT01866319	Robert[d]	2015b	A: Pembrolizumab: 2-weekly B: Pembrolizumab 3-weekly	C: Ipilimumab	TN & PT	Chemotherapy, immunotherapy, and/or BRAF and MEK inhibitors	Unresectable stage III or IV	61 63	62
NCT01721772	Robert[d]	2015c	Nivolumab	Dacarbazine	TN	NA	Unresectable stage III or IV BRAF wildtype	64	66
NCT01721746	Weber[d]	2015	Nivolumab	Paclitaxel + carboplatin or dacarbazine	PT	Ipilimumab and/or BRAF inhibitor	Unresectable stage IIIC or IV	59	62
NCT01689519	Ascierto[h]	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	TN	NA	Unresectable stage IIIC or IV BRAF mutated	56	55

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and patient characteristics) (continued)

NCT number	First author	Year	Intervention	Comparator	Treatment status	Previous treatments	Patient population	Median [mean] age	
								Int vs Comp	
NCT01515189	Ascierto[j]	2017	Ipilimumab 10mg/kg	Ipilimumab 3mg/kg	TN & PT	Any treatment (except for BRAF inhibitors, CTLA-4 or PD-1 antagonists, and PD-L1 or CD137 agonists)	Unresectable stage III or IV	62	62
NCT01006980	Chapman[h]	2017	Vemurafenib	Dacarbazine	TN	NA	Unresectable stage IIIC or IV BRAF mutated	56	52
NCT01763164	Dummer[k]	2017	Binimetinib	Dacarbazine	TN & PT	Immunotherapy	Unresectable stage IIIC or IV NRAS mutated	65	62
NCT01721746	Larkin[h,k]	2017	Nivolumab	Paclitaxel + carboplatin or dacarbazine	PT	Ipilimumab and/or BRAF inhibitor	Unresectable stage IIIC or IV	59	62
NCT01584648	Long[h]	2017	Dabrafenib + trametinib	Dabrafenib + placebo	TN	NA	Unresectable stage IIIC or IV BRAF mutated	55	57
NCT01866319	Schachter[h,k]	2017	A: Pembrolizumab: 2-weekly B: Pembrolizumab 3-weekly	C: Ipilimumab	TN & PT	Chemotherapy, immunotherapy, and/or BRAF and MEK inhibitors	Unresectable stage III or IV	61 63	62
NCT00779714	Ugurel[k]	2017	Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan + cytarabine	Dacarbazine	TN & PT	Immunotherapy or targeted therapy	Stage IV	NR	NR
NCT01844505	Wolchok[d,h]	2017	A: Nivolumab + ipilimumab	B: Nivolumab C: Ipilimumab	TN	NA	Unresectable stage III or IV	[59]	[59] [61]

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and patient characteristics) (continued)

NCT number	First author	Year	Intervention	Comparator	Treatment status	Previous treatments	Patient population	Median [mean] age	
								Int vs Comp	
NCT01866319	Carlino[l]	2018	Pembrolizumab	Ipilimumab	TN & PT	Chemotherapy, immunotherapy, and/or BRAF and MEK inhibitors	Unresectable stage III or IV	TN: 65 PT: 59	TN: 63 PT: 58
NCT01909453	Dummer[d,k]	2018a	A: Encorafenib + binimetinib	B: Encorafenib	TN & PT	First-line immunotherapy	Unresectable stage IIIB/IIIC or IV BRAF mutated	57	54
				C: Vemurafenib					56
NCT01909453	Dummer[h,k]	2018b	A: Encorafenib + binimetinib	B: Encorafenib	TN & PT	First-line immunotherapy	Unresectable stage IIIB/IIIC or IV BRAF mutated	57	54
				C: Vemurafenib					56
NCT01844505	Hodi[h]	2018	A: Nivolumab + ipilimumab	B: Nivolumab	TN	NA	Unresectable stage III or IV	61	60
				C: Ipilimumab					62
NCT01721772	Ascierto[h]	2019	Nivolumab	Dacarbazine	TN	NA	Unresectable stage III or IV BRAF wildtype	64	66
NCT01245062	Robert[h]	2019	Trametinib	Dacarbazine or paclitaxel	TN & PT	Chemotherapy, immunotherapy (other than ipilimumab), and/or sorafenib	Unresectable stage IIIC or IV BRAF mutated	55	54

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and TRAEs)

NCT number	First author	Year	Intervention	Comparator	Percentage of patients with grade 3/4 TRAEs		RR grade 3/4 TRAEs (95% CI)
					Int vs Comp		
NCT00057616	Eisen[a]	2010	Lenalidomide	Placebo	NR	NR	NR
NCT00094653	Hodi	2010	A: Ipilimumab + GP100	C: GP100	17%	11%	A vs B: 0.76 (0.52-1.11)
			B: Ipilimumab		23%		A vs C: 1.53 (0.90-2.58)
							B vs C: 2.02 (1.14-3.57)
NCT00087776	Bedikian[b]	2011	Docosahexaenoic acid–paclitaxel	Dacarbazine	72%	34%	2.13 (1.72-2.64)
NCT01006980	Chapman[d]	2011	Vemurafenib	Dacarbazine	NR	NR	NR
NCT00005052	Patel[f]	2011	Temozolomide	Dacarbazine	35%[g]	29%[g]	1.21 (0.99-1.47)
NCT00324155	Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	56%[g]	27%[g]	2.05 (1.63-2.57)
NCT00019682	Schwartzentruber[a]	2011	Interleukin-2 + GP100	Interleukin-2	84%[g]	78%[g]	1.06 (0.92-1.23)
NCT01245062	Flaherty[d]	2012	Trametinib	Dacarbazine or paclitaxel	NR	NR	NR
NCT01227889	Hauschild	2012	Dabrafenib	Dacarbazine	NR	NR	NR
NCT01359956	Daponte[a]	2013	A: Fotemustine + dacarbazine	C: Dacarbazine	NR	NR	A+B vs C+D: NR
			B: Fotemustine + dacarbazine + interferon alfa-2b	D: Dacarbazine + interferon alfa-2b	NR	NR	B+D vs A+C: NR
NCT00110019	Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	82%[g]	76%[g]	1.08 (1.01-1.17)
NCT00522834	O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	41%	34%	1.23 (1.00-1.50)
NCT00257205	Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	52%	37%	1.40 (1.18-1.67)
NCT00518895	Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	49%	21%	2.38 (1.68-3.36)
NCT01006252	Hamid	2014	Tasisulam	Paclitaxel	NR	NR	NR
NCT01689519	Larkin[d]	2014	Vemurafenib + cobimetinib	Vemurafenib + placebo	63%[g]	58%[g]	1.08 (0.93-1.24)
NCT01584648	Long[d]	2014	Dabrafenib + trametinib	Dabrafenib + placebo	35%[g]	37%[g]	0.93 (0.72-1.20)
NCT01006980	McArthur[d,h]	2014	Vemurafenib	Dacarbazine	71%[i]	41%[i]	1.73 (1.49-2.02)

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and TRAEs) (continued)

NCT number	First author	Year	Intervention	Comparator	Percentage of patients with grade 3/4 TRAEs		RR grade 3/4 TRAEs (95% CI)
					Int vs Comp		
NCT00769704	Andtbacka[a]	2015	Talimogene laherparepvec	Granulocyte-macrophage colony-stimulating factor	11%	5%	2.32 (0.99-5.41)
NCT00864253	Hersh	2015	*nab*-Paclitaxel	Dacarbazine	NR	NR	NR
NCT01844505	Larkin[d] [21]	2015	A: Nivolumab + ipilimumab	B: Nivolumab	55%	16%	A vs B: 3.37 (2.57-4.42)
				C: Ipilimumab		27%	A vs C: 2.01 (1.63-2.47)
							B vs C: 0.60 (0.44-0.81)
NCT01584648	Long[d,h]	2015	Dabrafenib + trametinib	Dabrafenib + placebo	32%	31%	1.02 (0.77-1.36)
NCT01597908	Robert	2015a	Dabrafenib + trametinib	Vemurafenib	52%[g]	63%[g]	0.82 (0.73-0.94)
NCT01866319	Robert[d]	2015b	A: Pembrolizumab: 2-weekly	C: Ipilimumab	13%	20%	A vs C: 0.68 (0.46-1.01)
			B: Pembrolizumab 3-weekly		10%		B vs C: 0.52 (0.34-0.80)
NCT01721772	Robert[d]	2015c	Nivolumab	Dacarbazine	12%	18%	0.66 (0.41-1.07)
NCT01721746	Weber[d]	2015	Nivolumab	Paclitaxel + carboplatin or dacarbazine	9%	31%	0.29 (0.18-0.46)
NCT01689519	Ascierto[h]	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	57%	51%	1.13 (0.96-1.33)
NCT01515189	Ascierto[j]	2017	Ipilimumab 10mg/kg	Ipilimumab 3mg/kg	34%	18%	1.87 (1.44-2.43)
NCT01006980	Chapman[h]	2017	Vemurafenib	Dacarbazine	75%[i]	43%[i]	1.75 (1.51-2.03)
NCT01763164	Dummer[k]	2017	Binimetinib	Dacarbazine	NR	NR	NR
NCT01721746	Larkin[h,k]	2017	Nivolumab	Paclitaxel + carboplatin or dacarbazine	14%	34%	0.41 (0.28-0.62)
NCT01584648	Long[h]	2017	Dabrafenib + trametinib	Dabrafenib + placebo	48%[g]	50%[g]	0.95 (0.78-1.16)
NCT01866319	Schachter[h,k]	2017	A: Pembrolizumab: 2-weekly	C: Ipilimumab	17%	20%	A vs C: 0.87 (0.60-1.24)
			B: Pembrolizumab 3-weekly		17%		B vs C: 0.85 (0.59-1.22)
NCT00779714	Ugurel[k]	2017	Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan + cytarabine	Dacarbazine	40%	12%	3.27 (1.94-5.50)

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and TRAEs) (continued)

NCT number	First author	Year	Intervention	Comparator	Percentage of patients with grade 3/4 TRAEs		RR grade 3/4 TRAEs (95% CI)
					Int vs Comp		
NCT01844505	Wolchok[d,h]	2017	A: Nivolumab + ipilimumab	B: Nivolumab	59%	21%	A vs B: 2.75 (2.18-3.46)
				C: Ipilimumab		28%	A vs C: 2.13 (1.74-2.60)
							B vs C: 0.77 (0.59-1.02)
NCT01866319	Carlino[l]	2018	Pembrolizumab	Ipilimumab	TN: 19%	TN: 20%	TN: 0.95 (0.66-1.37)
					PT: 13%	PT: 18%	PT: 0.74 (0.42-1.31)
NCT01909453	Dummer[d,k]	2018a	A: Encorafenib + binimetinib	B: Encorafenib	58%[g]	66%[g]	A vs B: 0.87 (0.75-1.02)
				C: Vemurafenib		63%[g]	A vs C: 0.91 (0.77-1.07)
NCT01909453	Dummer[h,k]	2018b	A: Encorafenib + binimetinib	B: Encorafenib	NR	NR	NR
				C: Vemurafenib		NR	
NCT01844505	Hodi[h]	2018	A: Nivolumab + ipilimumab	B: Nivolumab	59%	22%	A vs B: 2.64 (2.11-3.31)
				C: Ipilimumab		28%	A vs C: 2.14 (1.75-2.62)
							B vs C: 0.81 (0.62-1.06)
NCT01721772	Ascierto[h]	2019	Nivolumab	Dacarbazine	15%	18%	0.86 (0.55-1.33)
NCT01245062	Robert[h]	2019	Trametinib	Dacarbazine or paclitaxel	53%[g]	38%[g]	1.37 (1.04-1.81)

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and PFS)

NCT number	First author	Year	Intervention	Comparator	Median PFS in months (95% CI)		HR for PFS (95% CI)
					Int vs Comp		
NCT00057616	Eisen[a]	2010	Lenalidomide	Placebo	NR	NR	NR
NCT00094653	Hodi	2010	A: Ipilimumab + GP100	C: GP100	2.8 (2.7-2.8)	2.8 (2.7-2.8)	A vs B: 1.25 (1.06-1.49)
			B: Ipilimumab		2.9 (2.8-3.0)		A vs C: 0.81 (0.66-0.99)
							B vs C: 0.64 (0.50-0.82)
NCT00087776	Bedikian[b]	2011	Docosahexaenoic acid–paclitaxel	Dacarbazine	1.6 (1.4-2.5)[c]	1.6 (1.4-2.0)[c]	NR
NCT01006980	Chapman[d]	2011	Vemurafenib	Dacarbazine	5.3 (NR)	1.6 (NR)	0.26 (0.20-0.33)
NCT00005052	Patel[f]	2011	Temozolomide	Dacarbazine	2.3 (NR)	2.2 (NR)	0.92 (0.80-1.06)
NCT00324155	Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	NR	NR	0.76 (0.63-0.93)
NCT00019682	Schwartzentruber[a]	2011	Interleukin-2 + GP100	Interleukin-2	2.2 (1.7-3.9)	1.6 (1.5-1.8)	NR
NCT01245062	Flaherty[d]	2012	Trametinib	Dacarbazine or paclitaxel	4.8 (NR)	1.5 (NR)	0.45 (0.33-0.63)
NCT01227889	Hauschild	2012	Dabrafenib	Dacarbazine	5.1 (NR)	2.7 (NR)	0.30 (0.18-0.51)
NCT01359956	Daponte[a]	2013	A: Fotemustine + dacarbazine	C: Dacarbazine	A+B: 2.7 (2.4-3.8)	C+D: 2.5 (2.3-3.7)	A+B vs C+D: 0.93 (0.72-1.21)
			B: Fotemustine + dacarbazine + interferon alfa-2b	D: Dacarbazine + interferon alfa-2b	B+D: 2.8 (2.4-3.9)	A+C: 2.5 (2.3-2.9)	B+D vs A+C: 0.96 (0.73-1.25)
NCT00110019	Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	4.9 (4.5-5.6)	4.2 (3.4-4.7)	0.90 (0.78-1.03)
NCT00522834	O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	3.4 (2.3-3.5)	1.9 (1.9-2.9)	0.89 (0.73-1.08)
NCT00257205	Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	NR	NR	0.94 (0.81-1.11)
NCT00518895	Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	2.8 (NR)	2.7 (NR)	0.85 (0.67-1.09)
NCT01006252	Hamid	2014	Tasisulam	Paclitaxel	1.9 (1.9-2.0)	2.1 (1.9-3.0)	1.30 (1.01-1.66)
NCT01689519	Larkin[d]	2014	Vemurafenib + cobimetinib	Vemurafenib + placebo	9.9 (9.0-not reached)	6.2 (5.6-7.4)	0.51 (0.39-0.68)
NCT01584648	Long[d]	2014	Dabrafenib + trametinib	Dabrafenib + placebo	9.3 (NR)	8.8 (NR)	0.75 (0.57-0.99)

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and PFS) (continued)

NCT number	First author	Year	Intervention	Comparator	Median PFS in months (95% CI)		HR for PFS (95% CI)
					Int vs Comp		
NCT01006980	McArthur[d,h]	2014	Vemurafenib	Dacarbazine	6.9 (6.1-7.0)	1.6 (1.6-2.1)	0.38 (0.32-0.46)
NCT00769704	Andtbacka[a]	2015	Talimogene laherparepvec	Granulocyte-macrophage colony-stimulating factor	NR	NR	NR
NCT00864253	Hersh	2015	*nab*-Paclitaxel	Dacarbazine	4.8 (3.7-5.5)	2.5 (2.0-3.6)	0.79 (0.63-0.99)
NCT01844505	Larkin[d] [21]	2015	A: Nivolumab + ipilimumab	B: Nivolumab	11.5 (8.9-16.7)	B: 6.9 (4.3-9.5)	A vs B: 0.74 (0.60-0.92)
				C: Ipilimumab		C: 2.9 (2.8-3.4)	A vs C: 0.42 (0.34-0.52)
							B vs C: 0.57 (0.49-0.67)
NCT01584648	Long[d,h]	2015	Dabrafenib + trametinib	Dabrafenib + placebo	11.0 (8.0-13.9)	8.8 (5.9-9.3)	0.67 (0.53-0.84)
NCT01597908	Robert	2015a	Dabrafenib + trametinib	Vemurafenib	11.4 (NR)	7.3 (NR)	0.56 (0.49-0.69)
NCT01866319	Robert[d]	2015b	A: Pembrolizumab: 2-weekly	C: Ipilimumab	5.5 (3.4-6.9)	2.8 (2.8-2.9)	A vs C: 0.58 (0.46-0.72)
			B: Pembrolizumab 3-weekly		4.1 (2.9-6.9)		B vs C: 0.58 (0.47-0.72)
NCT01721772	Robert[d]	2015c	Nivolumab	Dacarbazine	5.1 (3.5-10.8)	2.2 (2.1-2.4)	0.43 (0.34-0.56)
NCT01721746	Weber[d]	2015	Nivolumab	Paclitaxel + carboplatin or dacarbazine	4.7 (2.3-6.5)	4.2 (2.1-6.3)	0.82 (0.51-1.31)
NCT01689519	Ascierto[h]	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	12.3 (9.5-13.4)	7.2 (5.6-7.5)	0.58 (0.46-0.72)
NCT01515189	Ascierto[j]	2017	Ipilimumab 10mg/kg	Ipilimumab 3mg/kg	2.8 (2.8-3.0)	2.8 (2.8-2.8)	0.89 (0.76-1.40)
NCT01006980	Chapman[h]	2017	Vemurafenib	Dacarbazine	NR	NR	NR
NCT01763164	Dummer[k]	2017	Binimetinib	Dacarbazine	2.8 (2.8-3.6)	1.5 (1.5-1.7)	0.62 (0.47-0.80)
NCT01721746	Larkin[h,k]	2017	Nivolumab	Paclitaxel + carboplatin or dacarbazine	3.1 (2.3-3.5)	3.7 (2.3-5.3)	1.00 (0.78-1.44)
NCT01584648	Long[h]	2017	Dabrafenib + trametinib	Dabrafenib + placebo	NR	NR	0.71 (0.57-0.88)
NCT01866319	Schachter[h,k]	2017	A: Pembrolizumab: 2-weekly	C: Ipilimumab	5.6 (3.4-8.2)	2.8 (2.8-2.9)	A vs C: 0.61 (0.50-0.75)
			B: Pembrolizumab 3-weekly		4.1 (2.9-7.2)		B vs C: 0.61 (0.50-0.75)

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and PFS) (continued)

NCT number	First author	Year	Intervention	Comparator	Median PFS in months (95% CI)		HR for PFS (95% CI)
					Int vs Comp		
NCT00779714	Ugurel[k]	2017	Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan + cytarabine	Dacarbazine	2.5 (2.3-2.6)	2.3 (2.3-2.5)	0.91 (0.70-1.18)
NCT01844505	Wolchok[d,h]	2017	A: Nivolumab + ipilimumab	B: Nivolumab	11.5 (8.7-19.3)	6.9 (5.1-9.7)	A vs B: 0.78 (0.64-0.96)
				C: Ipilimumab		2.9 (2.8-3.2)	A vs C: 0.43 (0.35-0.52)
							B vs C: 0.55 (0.45-0.66)
NCT01866319	Carlino[l]	2018	Pembrolizumab	Ipilimumab	TN: 6.6 (4.4-9.8)	TN: 2.8 (2.8-3.0)	TN: 0.57 (0.46-0.70)
					PT: 2.9 (2.8-4.1)	PT: 2.8 (2.8-3.0)	PT: 0.71 (0.53-0.94)
NCT01909453	Dummer[d,k]	2018a	A: Encorafenib + binimetinib	B: Encorafenib	14.9 (11.0-18.5)	9.6 (7.5-14.8)	A vs B: 0.75 (0.56-1.00)
				C: Vemurafenib		7.3 (5.6-8.2)	A vs C: 0.54 (0.41-0.71)
NCT01909453	Dummer[h,k]	2018b	A: Encorafenib + binimetinib	B: Encorafenib	14.9 (11.0-20.2)	9.6 (7.4-14.8)	A vs B: 0.77 (0.59-1.00)
				C: Vemurafenib		7.3 (5.6-7.9)	A vs C: 0.51 (0.39-0.67)
							B vs C: 0.68 (0.52-0.88)
NCT01844505	Hodi[h]	2018	A: Nivolumab + ipilimumab	B: Nivolumab	11.5 (8.7-19.3)	6.9 (5.1-10.2)	A vs B: 0.79 (0.65-0.97)
				C: Ipilimumab		2.9 (2.8-3.2)	A vs C: 0.42 (0.35-0.51)
							B vs C: 0.53 (0.44-0.64)
NCT01721772	Ascierto[h]	2019	Nivolumab	Dacarbazine	5.1 (3.5-12.2)	2.2 (2.1-2.5)	0.42 (0.33-0.53)
NCT01245062	Robert[h]	2019	Trametinib	Dacarbazine or paclitaxel	4.9 (NR)	1.5 (NR)	0.54 (0.41-0.73)

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and OS)

NCT number	First author	Year	Intervention	Comparator	Median OS in months (95% CI)		HR for OS (95% CI)
					Int vs Comp		
NCT00057616	Eisen[a]	2010	Lenalidomide	Placebo	5.9 (range: 5.1-7.7)	7.4 (range: 5.5-8.2)	1.16 (0.86-1.59)
NCT00094653	Hodi	2010	A: Ipilimumab + GP100	C: GP100	10.0 (8.5-11.5)	6.4 (5.5-8.7)	A vs B: 1.04 (0.83-1.30)
			B: Ipilimumab		10.1 (8.0-13.8)		A vs C: 0.68 (0.55-0.85)
							B vs C: 0.66 (0.51-0.87)
NCT00087776	Bedikian[b]	2011	Docosahexaenoic acid–paclitaxel	Dacarbazine	8.8 (7.2-9.8)	7.4 (6.3-8.7)	NR
NCT01006980	Chapman[d]	2011	Vemurafenib	Dacarbazine	7.2 (NR)[e]	9.2 (NR)[e]	0.37 (0.26-0.55)
NCT00005052	Patel[f]	2011	Temozolomide	Dacarbazine	9.1 (NR)	9.4 (NR)	1.00 (0.86-1.17)
NCT00324155	Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	11.2 (9.4-13.6)	9.1 (7.8-10.5)	0.72 (0.59-0.87)
NCT00019682	Schwartzentruber[a]	2011	Interleukin-2 + GP100	Interleukin-2	17.8 (11.9-25.8)	11.1 (8.7-16.3)	NR
NCT01245062	Flaherty[d]	2012	Trametinib	Dacarbazine or paclitaxel	Not reached	Not reached	0.54 (0.32-0.92)
NCT01227889	Hauschild	2012	Dabrafenib	Dacarbazine	Not reached	Not reached	0.61 (0.25-1.48)
NCT01359956	Daponte[a]	2013	A: Fotemustine + dacarbazine	C: Dacarbazine	A+B: 7.9 (6.6-10.2)	C+D: 8.6 (6.3-10.4)	A+B vs C+D: 0.93 (0.71-1.21)
			B: Fotemustine + dacarbazine + interferon alfa-2b	D: Dacarbazine + interferon alfa-2b	B+D: 9.1 (6.3-11.1)	A+C: 7.7 (6.3-9.7)	B+D vs A+C: 0.92 (0.70-1.20)
NCT00110019	Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	11.1 (10.3-12.3)	11.3 (9.8-12.2)	1.01 (0.87-1.18)
NCT00522834	O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	10.6 (9.3-12.2)	11.4 (10.2-13.6)	1.10 (0.92-1.32)
NCT00257205	Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	12.6 (10.8-14.3)	10.7 (9.4-12.0)	0.88 (0.74-1.04)
NCT00518895	Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	13.5 (NR)	13.1 (NR)	1.04 (0.81-1.34)
NCT01006252	Hamid	2014	Tasisulam	Paclitaxel	6.8 (5.9-8.3)	9.4 (6.9-NR)	1.23 (0.89-1.69)
NCT01689519	Larkin[d]	2014	Vemurafenib + cobimetinib	Vemurafenib + placebo	Not reached	Not reached	0.65 (0.42-1.00)

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and OS) (continued)

NCT number	First author	Year	Intervention	Comparator	Median OS in months (95% CI)		HR for OS (95% CI)
					Int vs Comp		
NCT01584648	Long[d]	2014	Dabrafenib + trametinib	Dabrafenib + placebo	Not reached	Not reached	0.63 (0.42-0.94)
NCT01006980	McArthur[d,h]	2014	Vemurafenib	Dacarbazine	13.6 (12.0-15.2)	9.7 (7.9-12.8)	0.70 (0.57-0.87)
NCT00769704	Andtbacka[a]	2015	Talimogene laherparepvec	Granulocyte-macrophage colony-stimulating factor	23.3 (19.5-29.6)	18.9 (16.0-23.7)	0.79 (0.62-1.00)
NCT00864253	Hersh	2015	*nab*-Paclitaxel	Dacarbazine	12.6 (11.1-14.2)	10.5 (9.5-12.4)	0.90 (0.71-1.13)
NCT01844505	Larkin[d] [21]	2015	A: Nivolumab + ipilimumab	B: Nivolumab	NR	NR	NR
				C: Ipilimumab		NR	
NCT01584648	Long[d,h]	2015	Dabrafenib + trametinib	Dabrafenib + placebo	25.1 (19.2-not reached)	18.7 (15.2-23.7)	0.71 (0.55-0.92)
NCT01597908	Robert	2015a	Dabrafenib + trametinib	Vemurafenib	Not reached	17.2 (NR)	0.69 (0.53-0.89)
NCT01866319	Robert[d]	2015b	A: Pembrolizumab: 2-weekly	C: Ipilimumab	Not reached	Not reached	A vs C: 0.63 (0.47-0.83)
			B: Pembrolizumab 3-weekly			Not reached	B vs C: 0.69 (0.52-0.90)
NCT01721772	Robert[d]	2015c	Nivolumab	Dacarbazine	Not reached	10.8 (9.3-12.1)	0.42 (0.29-0.61)
NCT01721746	Weber[d]	2015	Nivolumab	Paclitaxel + carboplatin or dacarbazine	NR	NR	NR
NCT01689519	Ascierto[h]	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	22.3 (20.3-not estimable)	17.4 (15.0-19.8)	0.70 (0.55-0.90)
NCT01515189	Ascierto[j]	2017	Ipilimumab 10mg/kg	Ipilimumab 3mg/kg	15.7 (11.6-17.8)	11.5 (9.9-13.3)	0.84 (0.70-0.99)
NCT01006980	Chapman[h]	2017	Vemurafenib	Dacarbazine	13.6 (12.0-15.4)	9.7 (7.9-12.8)	0.81 (0.70-1.00)
NCT01763164	Dummer[k]	2017	Binimetinib	Dacarbazine	11.0 (8.9-13.6)	10.1 (7.0-16.5)	1.00 (0.75-1.33)
NCT01721746	Larkin[h,k]	2017	Nivolumab	Paclitaxel + carboplatin or dacarbazine	15.7 (12.9-19.9)	14.4 (11.7-18.2)	0.95 (0.70-1.29)
NCT01584648	Long[h]	2017	Dabrafenib + trametinib	Dabrafenib + placebo	NR	NR	0.75 (0.58-0.96)

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and OS) (continued)

NCT number	First author	Year	Intervention	Comparator	Median OS in months (95% CI)		HR for OS (95% CI)
					Int vs Comp		
NCT01866319	Schachter[h,k]	2017	A: Pembrolizumab: 2-weekly	C: Ipilimumab	Not reached (22.1-not reached)	16.0 (13.5-22.0)	A vs C: 0.68 (0.53-0.87)
			B: Pembrolizumab 3-weekly		Not reached (23.5-not reached)		B vs C: 0.68 (0.53-0.86)
NCT00779714	Ugurel[k]	2017	Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan + cytarabine	Dacarbazine	9.2 (8.0-12.1)	9.0 (7.3-11.6)	1.08 (0.80-1.45)
NCT01844505	Wolchok[d,h]	2017	A: Nivolumab + ipilimumab	B: Nivolumab	Not reached (38.2-not reached)	37.6 (29.1-not reached)	A vs B: 0.85 (0.68-1.07)
				C: Ipilimumab		19.9 (16.9-24.6)	A vs C: 0.55 (0.45-0.69)
							B vs C: 0.65 (0.53-0.80)
NCT01866319	Carlino[l]	2018	Pembrolizumab	Ipilimumab	TN: Not reached (27.3-not reached)	TN: 17.1 (13.8-26.2)	TN: 0.69 (0.54-0.89)
					PT: 23.5 (16.8-33.6)	PT: 13.6 (10.7-22.0)	PT: 0.71 (0.51-0.99)
NCT01909453	Dummer[d,k]	2018a	A: Encorafenib + binimetinib	B: Encorafenib	NR	NR	A vs B: NR
				C: Vemurafenib		NR	A vs C: NR
NCT01909453	Dummer[h,k]	2018b	A: Encorafenib + binimetinib	B: Encorafenib	33.6 (24.4-39.2)	23.5 (19.6-33.6)	A vs B: 0.81 (0.61-1.06)
				C: Vemurafenib		16.9 (14.0-24.5)	A vs C: 0.61 (0.47-0.79)
							B vs C: 0.76 (0.58-0.98)
NCT01844505	Hodi[h]	2018	A: Nivolumab + ipilimumab	B: Nivolumab	Not reached (38.2-not reached)	36.9 (28.3-not reached)	A vs B: 0.84 (0.67-1.05)
				C: Ipilimumab		19.9 (16.9-24.6)	A vs C: 0.54 (0.44-0.67)
							B vs C: 0.65 (0.53-0.79)

Supplemental Table 1. Details of the systematic literature review (publication details, trial details, and OS) (continued)

NCT number	First author	Year	Intervention	Comparator	Median OS in months (95% CI)		HR for OS (95% CI)
					Int vs Comp		
NCT01721772	Ascierto[h]	2019	Nivolumab	Dacarbazine	37.5 (25.5-not reached)	11.2 (9.6-13.0)	0.46 (0.36-0.59)
NCT01245062	Robert[h]	2019	Trametinib	Dacarbazine or paclitaxel	15.6 (NR)	11.3 (NR)	0.84 (0.63-1.11)

CI, confidence interval; Comp, comparator; FU, follow-up; HR, hazard ratio; Int, intervention; ITT, intention-to-treat; kg, kilogram; mg, milligram; NA, not applicable; NR, not reported; OS, overall survival; PFS, progression-free survival; PT, previously-treated; RR, relative risk; TN, treatment-naive; TRAEs, treatment-related adverse events.

[a]No link in main network.

[b]Not included in main network because data on progression-free survival was not presented.

[c]Time to progression instead of progression-free survival.

[d]Extended follow-up available.

[e]Derived from the Kaplan-Meier curves.

[f]Temozolomide is pooled within the dacarbazine reference group.

[g]Number of patients with grade 3 or 4 adverse events, irrespective of causality.

[h]Extended follow-up.

[i]Sum of patients with at least one grade 3 adverse event and patients with at least one grade 4 adverse event, irrespective of causality.

[j]Dose-ranging study.

[k]Only included in extended network (see Supplemental Figure 2).

[l]Treatment line specific outcomes of Schachter et al. 2017 (only included in main network).

Supplemental Table 2. Face validity of randomized controlled trial outcomes versus network meta-analysis outcomes

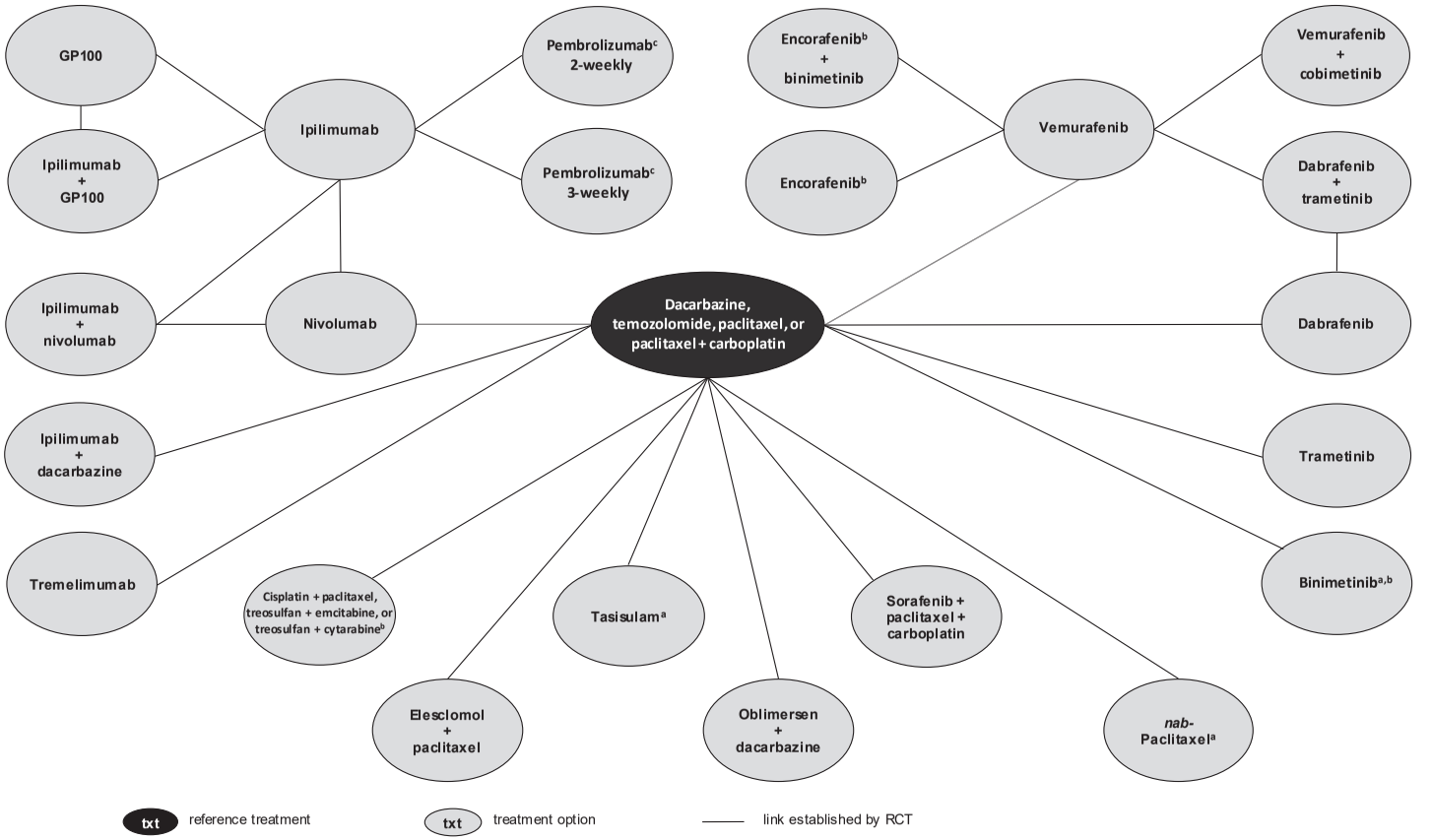
NCT number	First author	Year	Intervention	Comparator	RR grade 3/4 TRAEs (95% CI/CrI)	RR grade 3/4 TRAEs (95% CI/CrI)	HR for PFS (95% CI)		HR for OS (95% CI)	
					RCT	NMA	RCT	NMA	RCT	NMA
NCT00094653	Hodi	2010	A: Ipilimumab + GP100	C: GP100	A vs B: 0.76 (0.52-1.11)	A vs B: 0.78 (0.53-1.14)	A vs B: 1.25 (1.06-1.49)	A vs B: 1.28 (0.99-1.61)	A vs B: 1.04 (0.83-1.30)	A vs B: 1.04 (0.79-1.34)
			B: Ipilimumab		A vs C: 1.53 (0.90-2.58)	A vs C: 1.54 (0.91-2.56)	A vs C: 0.81 (0.66-0.99)	A vs C: 0.81 (0.66-0.99)	A vs C: 0.68 (0.55-0.85)	A vs C: 0.68 (0.55-0.84)
					B vs C: 2.02 (1.14-3.57)	B vs C: 1.86 (1.11-3.48)	B vs C: 0.64 (0.50-0.82)	B vs C: 0.64 (0.50-0.82)	B vs C: 0.66 (0.51-0.87)	B vs C: 0.65 (0.51-0.86)
NCT00324155	Robert	2011	Ipilimumab + dacarbazine	Dacarbazine + placebo	2.05 (1.63-2.57)	2.05 (1.63-2.57)	0.76 (0.63-0.93)	0.76 (0.62-0.92)	0.72 (0.59-0.87)	0.72 (0.59-0.87)
NCT01227889	Hauschild	2012	Dabrafenib	Dacarbazine	NR	NR	0.30 (0.18-0.51)	0.30 (0.23-0.40)	0.61 (0.25-1.48)	0.73 (0.50-1.04)
NCT00110019	Flaherty	2013	Carboplatin + paclitaxel + sorafenib	Carboplatin + paclitaxel + placebo	1.08 (1.01-1.17)	1.08 (1.01-1.17)	0.90 (0.78-1.03)	0.90 (0.78-1.03)	1.01 (0.87-1.18)	1.01 (0.87-1.18)
NCT00522834	O'Day	2013	Elesclomol + paclitaxel	Paclitaxel	1.23 (1.00-1.50)	1.23 (1.00-1.49)	0.89 (0.73-1.08)	0.89 (0.73-1.08)	1.10 (0.92-1.32)	1.11 (0.92-1.32)
NCT00257205	Ribas	2013	Tremelimumab	Temozolomide or dacarbazine	1.40 (1.18-1.67)	1.40 (1.17-1.67)	0.94 (0.81-1.11)	0.94 (0.80-1.10)	0.88 (0.74-1.04)	0.88 (0.74-1.04)
NCT00518895	Bedikian	2014	Dacarbazine + oblimersen	Dacarbazine + placebo	2.38 (1.68-3.36)	2.38 (1.68-3.34)	0.85 (0.67-1.09)	0.86 (0.67-1.09)	1.04 (0.81-1.34)	1.05 (0.81-1.34)
NCT01006252	Hamid	2014	Tasisulam	Paclitaxel	NR	NR	1.30 (1.01-1.66)	1.31 (1.01-1.67)	1.23 (0.89-1.69)	1.25 (0.89-1.70)
NCT00864253	Hersh	2015	*nab*-Paclitaxel	Dacarbazine	NR	NR	0.79 (0.63-0.99)	0.80 (0.63-0.99)	0.90 (0.71-1.13)	0.91 (0.71-1.13)

NCT01597908	Robert	2015	Dabrafenib + trametinib	Vemurafenib	0.82 (0.73-0.94)	0.84 (0.72-0.96)	0.56 (0.49-0.69)	0.56 (0.47-0.66)	0.69 (0.53-0.89)	0.69 (0.53-0.87)
NCT01689519	Ascierto	2016	Vemurafenib + cobimetinib	Vemurafenib + placebo	1.13 (0.96-1.33)	1.13 (0.96-1.33)	0.58 (0.46-0.72)	0.58 (0.46-0.73)	0.70 (0.55-0.90)	0.71 (0.55-0.89)
NCT01006980	Chapman	2017	Vemurafenib	Dacarbazine	1.75 (1.51-2.03)	1.75 (1.51-2.03)	0.38 (0.32-0.46)[a]	0.38 (0.32-0.45)	0.81 (0.70-1.00)	0.81 (0.68-0.96)
NCT01584648	Long	2017	Dabrafenib + trametinib	Dabrafenib + placebo	0.95 (0.78-1.16)	0.95 (0.78-1.15)	0.71 (0.57-0.88)	0.71 (0.58-0.87)	0.75 (0.58-0.96)	0.77 (0.60-0.97)
NCT01721772	Ascierto	2018	Nivolumab	Dacarbazine	0.86 (0.55-1.33)	0.86 (0.54-1.30)	0.42 (0.33-0.53)	0.42 (0.33-0.53)	0.46 (0.36-0.59)	0.46 (0.36-0.59)
NCT01866319	Carlino[b]	2018	Pembrolizumab	Ipilimumab	0.95 (0.66-1.37)	0.96 (0.66-1.37)	0.57 (0.46-0.70)	0.57 (0.46-0.70)	0.69 (0.54-0.89)	0.70 (0.54-0.89)
NCT01844505	Hodi	2018	A: Nivolumab + ipilimumab	B: Nivolumab	A vs B: 2.64 (2.11-3.31)	A vs B: 2.67 (2.13-3.35)	A vs B: 0.79 (0.65-0.97)	A vs B: 0.80 (0.64-0.98)	A vs B: 0.84 (0.67-1.05)	A vs B: 0.84 (0.66-1.05)
				C: Ipilimumab	A vs C: 2.14 (1.75-2.62)	A vs C: 2.14 (1.75-2.61)	A vs C: 0.42 (0.35-0.51)	A vs C: 0.42 (0.35-0.51)	A vs C: 0.54 (0.44-0.67)	A vs C: 0.54 (0.44-0.67)
					B vs C: 0.81 (0.62-1.06)	B vs C: 0.79 (0.61-1.05)	B vs C: 0.53 (0.44-0.64)	B vs C: 0.53 (0.44-0.64)	B vs C: 0.65 (0.53-0.79)	B vs C: 0.65 (0.53-0.79)
NCT01245062	Robert	2019	Trametinib	Dacarbazine or paclitaxel	1.37 (1.04-1.81)	1.38 (1.04-1.83)	0.54 (0.41-0.73)	0.55 (0.41-0.72)	0.84 (0.63-1.11)	0.85 (0.63-1.11)

CI, confidence interval; CrI, credible interval; HR, hazard ratio; NMA, network meta-analysis; NR, not reported; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RR, relative risk; TRAEs, treatment-related adverse events.

[a]Retrieved from McArthur et al. 2014.

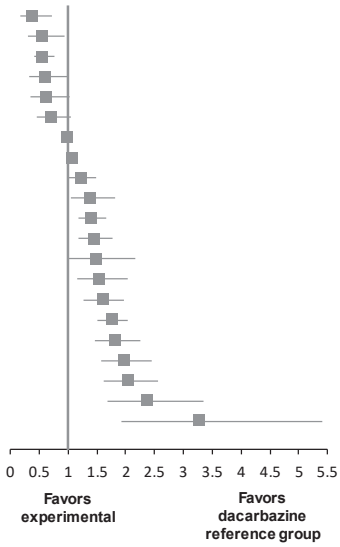
[b]Outcomes of treatment-naive patients.



[a]Only included in network-meta analyses for progression-free and overall survival (not in safety analyses);
[b]Only included in extended network;
[c]In extended network Schachter et al 2017 including treatment naïve and previously treated patients.

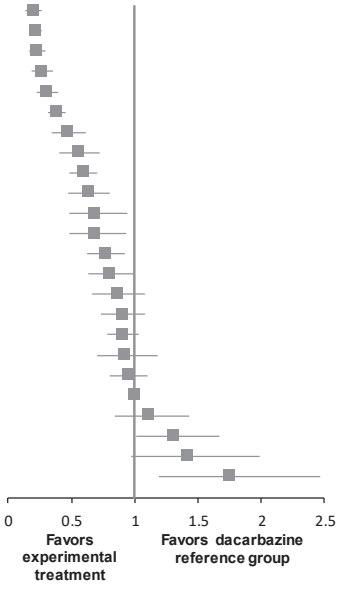
a. Network of treatment for advanced melanoma including phase III trials with previously treated patients

Treatment	PBB	RR TRAE vs reference group (95% CrI)
GP100	83%	0.38 (0.18-0.72)
Ipilimumab + GP100	4%	0.55 (0.30-0.93)
Nivolumab	5%	0.56 (0.41-0.75)
Pembrolizumab (every 3 wk)	5%	0.60 (0.33-1.00)
Pembrolizumab (every 2 wk)	4%	0.61 (0.34-1.02)
Ipilimumab	0%	0.71 (0.46-1.04)
Dacarbazine reference group	**0%**	**1**
Carboplatin + paclitaxel + sorafenib	0%	1.08 (1.01-1.17)
Elesclomol + paclitaxel	0%	1.23 (1.00-1.50)
Trametinib	0%	1.38 (1.05-1.82)
Tremelimumab	0%	1.40 (1.17-1.67)
Dabrafenib + trametinib	0%	1.46 (1.19-1.78)
Nivolumab + ipilimumab	0%	1.50 (1.01-2.16)
Dabrafenib	0%	1.55 (1.16-2.04)
Encorafenib + binimetinib	0%	1.60 (1.27-1.98)
Vemurafenib	0%	1.75 (1.51-2.03)
Encorafenib	0%	1.83 (1.47-2.24)
Vemurafenib + cobimetinib	0%	1.98 (1.58-2.46)
Ipilimumab + dacarbazine	0%	2.05 (1.63-2.57)
Dacarbazine + oblimersen	0%	2.38 (1.67-3.35)
Cisplatin + paclitaxel, treosulfan + gemcitabine, or treosulfan +	0%	3.27 (1.93-5.41)



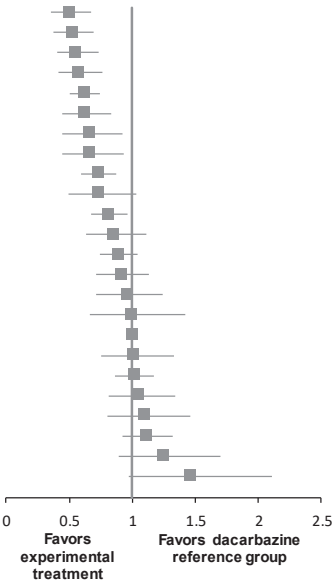
b. Results of the network meta-analysis for treatment-related adverse events

Treatment	PBB	HR PFS vs reference group (95% CrI)
Encorafenib + binimetinib	63%	0.20 (0.14-0.27)
Dabrafenib + trametinib	20%	0.21 (0.17-0.27)
Vemurafenib + cobimetinib	16%	0.22 (0.17-0.29)
Encorafenib	1%	0.26 (0.19-0.35)
Dabrafenib	0%	0.30 (0.23-0.40)
Vemurafenib	0%	0.38 (0.32-0.45)
Nivolumab + ipilimumab	0%	0.47 (0.35-0.61)
Trametinib	0%	0.55 (0.40-0.72)
Nivolumab	0%	0.58 (0.48-0.70)
Binimetinib	0%	0.63 (0.48-0.81)
Pembrolizumab (every 2 wk)	0%	0.68 (0.48-0.94)
Pembrolizumab (every 3 wk)	0%	0.68 (0.48-0.94)
Ipilimumab + dacarbazine	0%	0.76 (0.63-0.92)
nab -Paclitaxel	0%	0.80 (0.63-0.99)
Dacarbazine + oblimersen	0%	0.86 (0.67-1.09)
Elesclomol + paclitaxel	0%	0.89 (0.73-1.08)
Carboplatin + paclitaxel + sorafenib	0%	0.90 (0.78-1.03)
Cisplatin + paclitaxel, treosulfan + gen	0%	0.92 (0.70-1.18)
Tremelimumab	0%	0.94 (0.80-1.10)
Dacarbazine reference group	**0%**	**1**
Ipilimumab	0%	1.11 (0.84-1.43)
Tasisulam	0%	1.31 (1.01-1.67)
Ipilimumab + GP100	0%	1.41 (0.97-1.99)
GP100	0%	1.75 (1.19-2.47)



c. Results of the network meta-analysis for progression-free survival

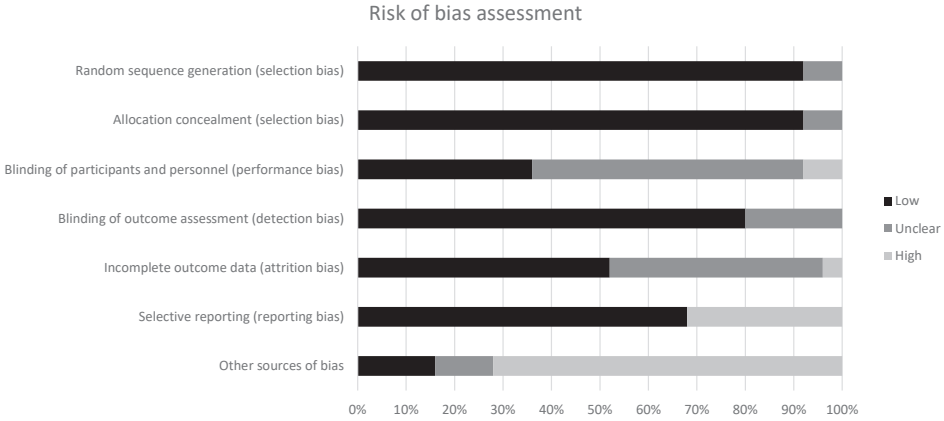
Treatment	PBB	HR OS vs reference group (95% CrI)
Encorafenib + binimetinib	41%	0.50 (0.36-0.67)
Nivolumab + ipilimumab	31%	0.52 (0.38-0.69)
Dabrafenib + trametinib	12%	0.55 (0.40-0.74)
Vemurafenib + cobimetinib	9%	0.57 (0.42-0.76)
Nivolumab	0%	0.62 (0.51-0.74)
Encorafenib	2%	0.62 (0.45-0.84)
Pembrolizumab (every 3 wk)	2%	0.65 (0.45-0.93)
Pembrolizumab (every 2 wk)	2%	0.65 (0.44-0.94)
Ipilimumab + dacarbazine	0%	0.72 (0.59-0.88)
Dabrafenib	0%	0.73 (0.50-1.04)
Vemurafenib	0%	0.81 (0.67-0.96)
Trametinib	0%	0.85 (0.63-1.11)
Tremelimumab	0%	0.88 (0.74-1.04)
nab -Paclitaxel	0%	0.91 (0.71-1.13)
Ipilimumab	0%	0.95 (0.72-1.25)
Ipilimumab + GP100	0%	0.99 (0.67-1.43)
Dacarbazine reference group	**0%**	**1**
Binimetinib	0%	1.01 (0.75-1.33)
Carboplatin + paclitaxel + sorafenib	0%	1.01 (0.87-1.18)
Dacarbazine + oblimersen	0%	1.05 (0.81-1.34)
Cisplatin + paclitaxel, treosulfan + gen	0%	1.09 (0.80-1.46)
Elesclomol + paclitaxel	0%	1.10 (0.92-1.32)
Tasisulam	0%	1.25 (0.89-1.69)
GP100	0%	1.46 (0.97-2.10)



d. Results of the network meta-analysis for overall survival

Supplemental Figure 1. Extended network and results of including phase-III trials with previously treated patients

AE, adverse event; CrI, credible Interval; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.



Supplemental Figure 2. Risk of bias assessment

Intervention / Comparator	Carboplatin + paclitaxel + sorafenib	Dabrafenib	Dabrafenib + trametinib	Dacarbazine + oblimersen	Dacarbazine reference group	Elesclomol + paclitaxel	GP100	Ipilimumab	Ipilimumab + dacarbazine	Ipilimumab + GP100	Nivolumab	Nivolumab + ipilimumab	Pembrolizumab	Trametinib	Tremelimumab	Vemurafenib	Vemurafenib + cobimetinib
Carboplatin + paclitaxel + sorafenib	1																
Dabrafenib	1.43 (1.06-1.89)	1															
Dabrafenib + trametinib	1.35 (1.08-1.67)	0.95 (0.78-1.15)	1														
Dacarbazine + oblimersen	2.20 (1.53-3.11)	1.49 (0.98-2.40)	1.58 (1.09-2.42)	1													
Dacarbazine reference group	0.92 (0.86-0.99)	0.65 (0.49-0.86)	0.68 (0.56-0.84)	0.42 (0.30-0.60)	1												
Elesclomol + paclitaxel	1.13 (0.91-1.40)	0.78 (0.56-1.12)	0.83 (0.63-1.12)	0.51 (0.35-0.77)	1.23 (1.00-1.49)	1											
GP100	0.54 (0.23-1.07)	0.38 (0.15-0.79)	0.40 (0.17-0.81)	0.25 (0.10-0.53)	0.58 (0.25-1.16)	0.48 (0.20-0.97)	1										
Ipilimumab	1.00 (0.57-1.63)	0.71 (0.38-1.23)	0.75 (0.41-1.25)	0.47 (0.24-0.83)	1.08 (0.62-1.76)	0.89 (0.49-1.49)	1.86 (1.11-3.48)	1									
Ipilimumab + dacarbazine	1.86 (1.48-2.40)	1.30 (0.92-1.90)	1.38 (1.03-1.90)	0.85 (0.57-1.30)	2.05 (1.63-2.57)	1.64 (1.23-2.26)	3.47 (1.70-8.47)	1.87 (1.10-3.44)	1								
Ipilimumab + GP100	0.78 (0.38-1.42)	0.56 (0.26-1.07)	0.58 (0.28-1.09)	0.37 (0.16-0.72)	0.85 (0.42-1.54)	0.70 (0.33-1.30)	1.54 (0.91-2.56)	0.78 (0.53-1.14)	0.42 (0.20-0.79)	1							
Nivolumab	0.79 (0.49-1.20)	0.56 (0.32-0.92)	0.59 (0.35-0.93)	0.37 (0.20-0.62)	0.86 (0.54-1.30)	0.71 (0.42-1.11)	1.47 (0.83-2.94)	0.79 (0.61-1.05)	0.42 (0.25-0.67)	1.01 (0.65-1.67)	1						
Nivolumab + ipilimumab	2.12 (1.24-3.38)	1.51 (0.81-2.55)	1.58 (0.89-2.61)	0.99 (0.51-1.73)	2.29 (1.35-3.64)	1.89 (1.07-3.11)	4.31 (2.29-7.63)	2.14 (1.75-2.61)	1.13 (0.63-1.88)	2.84 (1.78-4.26)	2.67 (2.13-3.35)	1					
Pembrolizumab	0.96 (0.48-1.73)	0.68 (0.32-1.29)	0.72 (0.35-1.33)	0.45 (0.20-0.87)	1.04 (0.52-1.87)	0.85 (0.41-1.57)	1.72 (0.94-3.65)	0.96 (0.66-1.37)	0.51 (0.25-0.95)	1.18 (0.72-2.08)	1.21 (0.75-1.87)	0.43 (0.29-0.68)	1				
Trametinib	1.27 (0.95-1.70)	0.91 (0.60-1.33)	0.95 (0.67-1.34)	0.60 (0.37-0.91)	1.38 (1.04-1.83)	1.13 (0.80-1.59)	2.32 (1.12-5.97)	1.37 (0.73-2.36)	0.68 (0.47-0.97)	1.60 (0.84-3.44)	1.69 (0.97-2.76)	0.59 (0.35-1.09)	1.48 (0.69-2.77)	1			
Tremelimumab	1.30 (1.07-1.56)	0.90 (0.65-1.27)	0.95 (0.73-1.26)	0.59 (0.40-0.87)	1.40 (1.17-1.67)	1.16 (0.88-1.50)	2.39 (1.19-5.76)	1.29 (0.77-2.32)	0.69 (0.52-0.91)	1.65 (0.89-3.42)	1.62 (1.04-2.70)	0.61 (0.37-1.07)	1.34 (0.73-2.74)	1.01 (0.73-1.42)	1		
Vemurafenib	1.62 (1.37-1.91)	1.13 (0.90-1.44)	1.20 (1.04-1.38)	0.76 (0.51-1.08)	1.75 (1.51-2.03)	1.44 (1.12-1.84)	2.99 (1.49-7.15)	1.61 (0.97-2.86)	0.87 (0.65-1.12)	2.06 (1.12-4.24)	2.03 (1.31-3.34)	0.76 (0.47-1.32)	1.68 (0.92-3.39)	1.26 (0.92-1.75)	1.26 (0.99-1.58)	1	
Vemurafenib + cobimetinib	1.83 (1.45-2.30)	1.30 (0.96-1.72)	1.36 (1.09-1.68)	0.86 (0.55-1.26)	1.98 (1.59-2.46)	1.63 (1.20-2.18)	3.36 (1.65-8.20)	1.81 (1.07-3.31)	0.98 (0.70-1.33)	2.31 (1.23-4.88)	2.43 (1.45-3.86)	0.85 (0.52-1.52)	1.89 (1.02-3.91)	1.42 (1.00-2.05)	1.42 (1.07-1.87)	1.13 (0.96-1.33)	1

a. Estimated mean relative risk for treatment-related adverse events (95% credible interval)

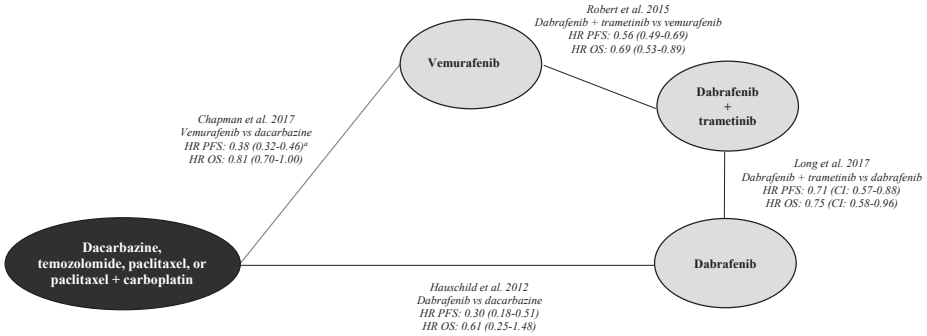
Intervention	Comparator	Carboplatin + pacli	Dabrafenib	Dabrafenib + trame	Dacarbazine + obli	Dacarbazine refere	Elesclomol + pacli	GP100	Ipilimumab	Ipilimumab + daca	Ipilimumab + GP1	*nab*-paclitaxel	Nivolumab	Nivolumab + ipilir	Pembrolizumab
Carboplatin + paclitaxel + sorafenib		1													
Dabrafenib		0.33 (0.24-0.45)	1												
Dabrafenib + trametinib		0.24 (0.18-0.31)	0.71 (0.58-0.87)	1											
Dacarbazine + oblimersen		0.95 (0.71-1.25	2.89 (1.96-4.11)	4.00 (2.86-5.56)	1										
Dacarbazine reference group		1.11 (0.97-1.28)	3.33 (2.50-4.35)	4.76 (3.70-5.88)	1.16 (0.92-1.49)	1									
Elesclomol + paclitaxel		1.00 (0.78-1.26)	3.02 (2.11-4.18)	4.17 (3.13-5.56)	1.03 (0.77-1.43)	0.89 (0.73-1.08)	1								
GP100		1.41 (0.91-2.08)	4.26 (2.56-6.68)	5.98 (3.72-9.14)	1.50 (0.92-2.31)	1.26 (0.84-1.82)	1.42 (0.90-2.14)	1							
Ipilimumab		0.89 (0.63-1.23)	2.71 (1.76-4.01)	3.80 (2.56-5.46)	0.95 (0.63-1.37)	0.80 (0.59-1.07)	0.90 (0.62-1.28)	0.64 (0.50-0.82)	1						
Ipilimumab + dacarbazine		0.84 (0.67-1.06)	2.50 (1.82-3.57)	3.57 (2.63-4.76)	0.88 (0.65-1.22)	0.76 (0.62-0.92)	0.85 (0.65-1.12)	0.60 (0.40-0.94)	0.94 (0.67-1.37)	1					
Ipilimumab + GP100		1.14 (0.74-1.68)	3.45 (2.08-5.40)	4.84 (3.01-7.41)	1.21 (0.75-1.87)	1.02 (0.68-1.47)	1.15 (0.73-1.74)	0.81 (0.66-0.99)	1.28 (0.99-1.61)	1.35 (0.86-2.04)	1				
nab-paclitaxel		0.89 (0.67-1.14)	2.68 (1.84-3.77)	3.70 (2.70-5.00)	0.94 (0.67-1.29)	0.80 (0.63-0.99)	0.90 (0.66-1.20)	0.62 (0.41-1.00)	0.98 (0.68-1.45)	1.05 (0.77-1.40)	0.77 (0.50-1.22)	1			
Nivolumab		0.47 (0.35-0.61)	1.43 (0.98-2.02)	2.00 (1.43-2.75)	0.50 (0.35-0.69)	0.42 (0.33-0.53)	0.48 (0.35-0.64)	0.34 (0.25-0.46)	0.53 (0.44-0.64)	0.56 (0.41-0.75)	0.41 (0.31-0.57)	0.54 (0.38-0.74)	1		
Nivolumab + ipilimumab		0.38 (0.26-0.52)	1.14 (0.73-1.70)	1.60 (1.06-2.32)	0.40 (0.26-0.58)	0.34 (0.24-0.46)	0.38 (0.26-0.54)	0.27 (0.20-0.37)	0.42 (0.35-0.51)	0.45 (0.30-0.64)	0.34 (0.24-0.45)	0.43 (0.29-0.62)	0.80 (0.64-0.98)	1	
Pembrolizumab		0.51 (0.34-0.74)	1.55 (0.95-2.40)	2.18 (1.38-3.28)	0.54 (0.34-0.83)	0.46 (0.31-0.65)	0.52 (0.33-0.77)	0.36 (0.26-0.51)	0.57 (0.46-0.70)	0.61 (0.39-0.90)	0.44 (0.33-0.62)	0.59 (0.37-0.88)	1.09 (0.81-1.42)	1.35 (1.02-1.79)	1
Tasisulam		1.46 (1.09-1.92)	4.42 (2.99-6.32)	5.88 (4.35-8.33)	1.55 (1.08-2.17)	1.31 (1.01-1.67)	1.48 (1.06-2.00)	1.02 (0.66-1.67)	1.61 (1.11-2.44)	1.73 (1.25-2.34)	1.27 (0.82-2.04)	1.61 (1.18-2.33)	3.03 (2.17-4.35)	3.85 (2.63-5.88)	2.7 (1.85-4
Tremelimumab		1.05 (0.85-1.29)	3.18 (2.28-4.32)	4.38 (3.36-5.83)	1.10 (0.83-1.47)	0.94 (0.80-1.10)	1.06 (0.82-1.36)	0.74 (0.50-1.15)	1.16 (0.85-1.67)	1.25 (0.96-1.59)	0.92 (0.62-1.42)	1.18 (0.90-1.57)	2.22 (1.69-2.94)	2.78 (1.96-4.00)	2.0 (1.39-3

b. Estimated mean hazard ratio for progression-free survival (95% credible interval)

Intervention	Comparator	Carboplatin + paclitaxel + sorafenib	Dabrafenib	Dabrafenib + trametinib	Dacarbazine + oblimersen	Dacarbazine reference group	Elesclomol + paclitaxel	GP100	Ipilimumab	Ipilimumab + dacarbazine	Ipilimumab + GP100	*nab* -paclitaxel	Nivolumab	Nivolumab + ipilimumab	Pembrolizumab	Tasisulam	Tremelimumab	Trametinib	Vemurafenib	Vemurafenib + cobimetinib
Carboplatin + paclitaxel + sorafenib		1																		
Dabrafenib		0.70 (0.48-1.06)	1																	
Dabrafenib + trametinib		0.55 (0.39-0.75)	0.77 (0.60-0.97)	1																
Dacarbazine + oblimersen		1.04 (0.77-1.38)	1.48 (0.93-2.26)	1.87 (1.29-2.80)	1															
Dacarbazine reference group		0.99 (0.85-1.15)	1.37 (0.96-2.01)	1.81 (1.36-2.46)	0.95 (0.75-1.24)	1														
Elesclomol + paclitaxel		1.10 (0.86-1.38)	1.57 (1.02-2.30)	1.98 (1.42-2.85)	1.05 (0.78-1.44)	1.11 (0.92-1.32)	1													
GP100		1.09 (0.68-1.65)	1.55 (0.86-2.60)	2.03 (1.18-3.27)	1.06 (0.63-1.68)	1.10 (0.71-1.62)	1.00 (0.62-1.53)	1												
Ipilimumab		0.71 (0.49-1.00)	1.02 (0.61-1.61)	1.33 (0.84-2.01)	0.70 (0.45-1.02)	0.72 (0.52-0.97)	0.65 (0.45-0.93)	0.65 (0.51-0.86)	1											
Ipilimumab + dacarbazine		0.71 (0.56-0.91)	0.98 (0.66-1.52)	1.30 (0.92-1.88)	0.68 (0.50-0.95)	0.72 (0.59-0.87)	0.65 (0.50-0.85)	0.65 (0.43-1.06)	1.00 (0.70-1.47)	1										
Ipilimumab + GP100		0.74 (0.47-1.12)	1.06 (0.59-1.76)	1.38 (0.80-2.22)	0.72 (0.43-1.14)	0.74 (0.48-1.10)	0.68 (0.42-1.04)	0.68 (0.55-0.84)	1.04 (0.79-1.34)	1.04 (0.64-1.60)	1									
nab -paclitaxel		0.90 (0.67-1.18)	1.28 (0.81-1.93)	1.62 (1.13-2.39)	0.88 (0.61-1.22)	0.91 (0.71-1.13)	0.83 (0.61-1.10)	0.82 (0.52-1.34)	1.25 (0.86-1.88)	1.27 (0.92-1.70)	1.20 (0.77-1.97)	1								
Nivolumab		0.46 (0.34-0.61)	0.66 (0.41-0.99)	0.86 (0.57-1.24)	0.45 (0.31-0.63)	0.46 (0.36-0.59)	0.42 (0.31-0.57)	0.42 (0.31-0.60)	0.65 (0.53-0.79)	0.65 (0.47-0.88)	0.62 (0.45-0.88)	0.52 (0.37-0.72)	1							
Nivolumab + ipilimumab		0.39 (0.26-0.55)	0.55 (0.32-0.88)	0.72 (0.44-1.10)	0.38 (0.24-0.56)	0.39 (0.27-0.54)	0.35 (0.24-0.51)	0.36 (0.25-0.50)	0.54 (0.44-0.67)	0.54 (0.36-0.79)	0.53 (0.38-0.73)	0.43 (0.28-0.64)	0.84 (0.66-1.05)	1						
Pembrolizumab		0.50 (0.31-0.74)	0.71 (0.39-1.18)	0.92 (0.54-1.48)	0.48 (0.29-0.76)	0.50 (0.33-0.73)	0.46 (0.28-0.69)	0.45 (0.32-0.66)	0.70 (0.54-0.89)	0.70 (0.43-1.06)	0.66 (0.47-0.96)	0.56 (0.34-0.86)	1.08 (0.77-1.46)	1.26 (0.92-1.77)	1					
Tasisulam		1.24 (0.85-1.74)	1.77 (1.06-2.79)	2.20 (1.45-3.49)	1.21 (0.79-1.78)	1.25 (0.89-1.70)	1.14 (0.77-1.62)	1.11 (0.68-1.94)	1.69 (1.10-2.73)	1.74 (1.17-2.49)	1.63 (1.00-2.85)	1.34 (0.92-2.04)	2.62 (1.78-4.02)	3.13 (2.01-5.15)	2.43 (1.50-4.22)	1				
Tremelimumab		0.88 (0.69-1.10)	1.25 (0.82-1.83)	1.59 (1.14-2.27)	0.84 (0.62-1.15)	0.88 (0.74-1.04)	0.81 (0.62-1.02)	0.80 (0.53-1.28)	1.22 (0.87-1.78)	1.23 (0.94-1.58)	1.18 (0.78-1.88)	0.97 (0.73-1.30)	1.89 (1.42-2.58)	2.26 (1.58-3.37)	1.76 (1.16-2.80)	0.70 (0.50-1.03)	1			
Trametinib		0.82 (0.60-1.15)	1.14 (0.74-1.86)	1.50 (1.02-2.32)	0.79 (0.55-1.18)	0.85 (0.63-1.11)	0.75 (0.55-1.07)	0.76 (0.48-1.29)	1.16 (0.77-1.81)	1.19 (0.83-1.65)	1.12 (0.70-1.90)	0.92 (0.65-1.35)	1.79 (1.26-2.66)	2.14 (1.41-3.43)	1.67 (1.05-2.82)	0.67 (0.45-1.05)	0.94 (0.69-1.33)	1		
Vemurafenib		0.80 (0.63-1.00)	1.14 (0.80-1.57)	1.46 (1.15-1.89)	0.78 (0.57-1.05)	0.81 (0.68-0.96)	0.74 (0.57-0.94)	0.73 (0.48-1.17)	1.12 (0.79-1.63)	1.13 (0.86-1.45)	1.08 (0.71-1.72)	0.88 (0.67-1.20)	1.73 (1.29-2.36)	2.06 (1.43-3.09)	1.61 (1.06-2.56)	0.67 (0.45-0.94)	0.92 (0.71-1.17)	0.97 (0.69-1.33)	1	
Vemurafenib + cobimetinib		0.57 (0.40-0.78)	0.80 (0.51-1.19)	1.05 (0.72-1.47)	0.55 (0.36-0.80)	0.57 (0.42-0.76)	0.52 (0.36-0.73)	0.51 (0.31-0.87)	0.78 (0.51-1.23)	0.80 (0.55-1.12)	0.75 (0.46-1.28)	0.64 (0.43-0.92)	1.25 (0.83-1.81)	1.43 (0.93-2.32)	1.12 (0.69-1.91)	0.47 (0.29-0.71)	0.65 (0.45-0.91)	0.69 (0.44-1.01)	0.71 (0.55-0.89)	1

c. Estimated mean hazard ratio for overall survival (95% credible interval)

Supplemental Figure 3. Details network meta-analysis estimates



CrI, credible interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; vs, versus.

[a]Retrieved from McArthur *et al.* 2017.

	RCT		NMA	
Progression-free survival	**HR**	**CI**	**HR**	**CrI**
Dabrafenib versus dacarbazine reference group	0.30	(0.18-0.51)	0.30	(0.23-0.40)
Dabrafenib + trametinib versus dacarbazine reference group	n/a		0.21	(0.17-0.27)
Vemurafenib versus dacarbazine reference group	0.38	(0.32-0.46)	0.38	(0.32-0.45)
Overall survival				
Dabrafenib versus dacarbazine reference group	0.61	(0.25-1.48)	0.73	(0.50-1.04)
Dabrafenib + trametinib versus dacarbazine reference group	n/a		0.55	(0.41-0.74)
Vemurafenib versus dacarbazine reference group	0.81	(0.70-1.00)	0.81	(0.68-0.96)

Supplemental Figure 4. Example of direct and indirect evidence within the network

6 Healthcare costs of metastatic cutaneous melanoma in the era of immunotherapeutic and targeted drugs

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ABSTRACT

Immunotherapeutic and targeted drugs improved survival of patients with metastatic melanoma. There is, however, a lack of evidence regarding their healthcare costs in clinical practice. The aim of our study was to provide insight into real-world healthcare costs of patients with advanced cutaneous melanoma. Data were obtained from the Dutch Melanoma Treatment Registry for patients who were registered between July 2012 and December 2018. Mean total/monthly costs per patient were reported for all patients, patients who did not receive systemic therapy, and patients who received systemic therapy. Furthermore, mean episode/monthly costs per line of therapy and drug were reported for patients who received systemic therapy. Mean total/monthly costs were €89,240/€6,809: €7,988/€2,483 for patients who did not receive systemic therapy (*n*=784) and €105,078/€7,652 for patients who received systemic therapy (*n*=4,022). Mean episode/monthly costs were the highest for nivolumab plus ipilimumab (€79,675/€16,976), ipilimumab monotherapy (€79,110/€17,252), and dabrafenib plus trametinib (€77,053/€12,015). Dacarbazine yielded the lowest mean episode/monthly costs (€6,564/€2,027). Our study showed that immunotherapeutic and targeted drugs had a large impact on real-world healthcare costs. As new drugs continue entering the treatment landscape for (metastatic) melanoma, it remains crucial to monitor whether the benefits of these drugs outweigh their costs.

INTRODUCTION

The global incidence of cutaneous melanoma has been increasing over the past decades.[139] In the Netherlands, the estimated incidence rate increased from 8.2 to 24.2 per 100,000 person-years between 1990 and 2018. Most patients (approximately 85%) are diagnosed with localized melanoma and have a relatively good prognosis. Melanoma has, however, a strong tendency to metastasize resulting in a poor prognosis. Historically, one- and five-year survival rates of patients with metastatic melanoma were only 39% and 12%, respectively.[140]

Until 2011, treatment options for metastatic melanoma were limited to chemotherapy (including dacarbazine and temozolomide) and interleukin-2. However, these drugs never demonstrated to improve survival.[141-143] Advances in the development of immunotherapeutic and targeted drugs dramatically changed the treatment landscape. In 2011, the first two new drugs were approved by the Food and Drug Administration: ipilimumab (an anti-CTLA-4 antibody) and vemurafenib (a BRAF inhibitor).[144] European approval by the European Medicines Agency followed in the same year for ipilimumab and in 2012 for vemurafenib.[145] Since then, several other drugs and combinations of drugs have been approved for the treatment of metastatic melanoma (see Supplemental Table 1).[144,145]

Although the new drugs demonstrated to improve survival[146], there is a lack of evidence regarding their healthcare costs in real-world clinical practice. Previous studies[147-149] only reported real-world healthcare costs of ipilimumab and vemurafenib. Therefore, the aim of our study was to provide insight into real-world healthcare costs of patients with metastatic cutaneous melanoma in the Netherlands since the approval of the new immunotherapeutic and targeted drugs.

MATERIALS AND METHODS

Data source and patient population

Data were obtained from the population-based Dutch Melanoma Treatment Registry (DMTR). The DMTR contains detailed data regarding baseline patient and tumor characteristics, treatment patterns, healthcare resource use, and survival of all Dutch patients with unresectable stage IIIC or stage IV melanoma (i.e., metastatic melanoma). In compliance with Dutch regulations, the DMTR was approved by the medical ethical committee and was not subject to the Medical Research Involving Human Subjects Act. A detailed description of the DMTR has been previously published.[150]

For this study, we selected all patients (≥18 years) with metastatic cutaneous melanoma who were registered in the DMTR between July 2012 and December 2018. Patients with incomplete data regarding the start or stop date of a systemic therapy and/or patients with insufficient follow-up (i.e., patients who were alive at the data cut-off date with an observation period of less than six months) were excluded. The data cut-off date was December 2019.

Cost analysis

The cost analysis was conducted from a hospital perspective using the methodology as described in the Dutch costing manual.[68] Costs were calculated by applying unit costs to individual patient resource use for the following cost components: medical imaging, genetic testing, hospital visits, hospital admissions, surgery, radiotherapy, hyperthermia, radiofrequency ablation (RFA), and systemic therapy. Missing data on resource use were imputed using conditional mean imputation. Table 1 presents the unit costs. Unit costs of medical imaging, genetic testing, surgery, radiotherapy, hyperthermia, and RFA were based on tariffs issued by the Dutch Healthcare Authority.[69] The unit costs of hospital visits and hospital admissions were derived from the Dutch costing manual.[68] Drug costs were acquired from the Z-index (i.e., the Dutch drug database) for two chemotherapeutic drugs (dacarbazine and temozolomide), three immunotherapeutic drugs (ipilimumab, nivolumab, and pembrolizumab), and six targeted drugs (vemurafenib, dabrafenib, trametinib, cobimetinib, encorafenib, and binimetinib).[70] Costs of investigational drugs were set at zero if the drug was given in a blinded trial or if the drug was not approved for metastatic melanoma in the Netherlands at the time of this study. All costs were based on Euro 2018 cost data. Where necessary, costs were adjusted to 2018 prices using the consumer price index from Statistics Netherlands.[71]

Table 1. Unit costs

Resource	Unit cost
Medical imaging	
CT scan	€154.21
MRI scan	€285.91
PET/CT scan	€1,069.76
Genetic testing	
Gene mutation testing[a]	€929.25
Hospital visits	
Outpatient visit	€94.69
Daycare treatment	€287.19
Hospital admissions	
Inpatient hospital day	€495.30
Intensive care unit day	€1,234.08
Surgery	
Excision	€95.65
Lymph node dissection	€1,734.62
Metastasectomy[b]	€2,999.07-€6,239.07
Radiotherapy	
Short course (≤6 sessions)	€2,034.13
Standard course (>6 sessions)	€4,840.38
Hyperthermia	
Hyperthermia	€10,877.17
RFA	
RFA	€1,490.84

Table 1. Unit costs (continued)

Resource	Unit cost
Systemic therapy	
Dacarbazine	
Vial 500mg	€46.33
Vial 1000mg	€87.15
Temozolomide	
Capsule 5mg	€2.60
Capsule 20mg	€4.80
Capsule 100mg	€17.40
Capsule 140mg	€24.00
Capsule 180mg	€30.40
Capsule 250mg	€40.20
Ipilimumab	
Vial 50mg	€4,250.00
Vial 200mg	€17,000.00
Nivolumab	
Vial 40mg	€405.03
Vial 100mg	€1,012.56
Vial 240mg	€2,430.15
Pembrolizumab	
Vial 50mg	€1,312.18
Vial 100mg	€2,624.37
Vemurafenib	
Tablet 240mg	€30.70
Dabrafenib	
Capsule 50mg	€35.53
Capsule 75mg	€52.16
Trametinib	
Tablet 0.5mg	€54.19
Tablet 2mg	€203.81
Cobimetinib	
Tablet 20mg	€86.89
Encorafenib	
Capsule 50mg	€24.41
Capsule 75mg	€36.05
Binimetinib	
Tablet 15mg	€34.09
Investigational drug[c]	€0.00

CT, computed tomography; mg, milligram; MRI, magnetic resonance imaging; PET, positron emission tomography; RFA, radiofrequency ablation.

[a]BRAF, NRAS, KIT, GNAQ, and GNA11.

[b]Ranging from €2,999.07 for soft tissue metastases to €6,239.07 for pancreatic metastases.

[c]Costs of investigational drugs were set at zero if the drug was given in a blinded trial or if the drug was not approved for metastatic melanoma in the Netherlands at the time of our study.

Data analysis

Baseline patient and tumor characteristics were summarized using descriptive statistics. Age was presented as mean and standard deviation (SD) as well as median and interquartile range. Gender, Eastern Cooperative Oncology Group (ECOG) performance status, lactate dehydrogenase (LDH) level, M category (i.e., site of distant metastases according to the seventh edition of the American Joint Committee on Cancer staging manual), and brain metastases were presented as counts and proportions.

Costs were reported for all patients irrespective of their treatment status. To provide further details, costs were also separately reported for patients who did not receive systemic therapy during the study period stratified by vital status (dead or alive) and patients who received at least one systemic therapy stratified by line of therapy and drug. Due to low numbers of patients, costs were only separately reported for the first, second, and third line. Similarly, costs were not separately reported for temozolomide and encorafenib plus binimetinib. Mean (SD) total costs per patient were calculated from the diagnosis of metastatic melanoma until death or last follow-up (i.e., the observation period). Mean (SD) episode costs per line of therapy and drug were calculated from the diagnosis of metastatic melanoma or the start of a systemic therapy until the start of a new systemic therapy, death, or last follow-up (i.e., the episode duration). To account for differences in observation periods or episode durations, costs were also reported as mean (SD) monthly costs. These costs were calculated by dividing the total costs by the observation period and the episode costs by the episode duration. All analyses were conducted using STATA statistical analysis software, version 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

RESULTS

Baseline patient and tumor characteristics

A total of 4,806 patients were included in our study. The median age was 64 years; 59% of the patients were male (see Table 2). Most patients had a good ECOG performance status (i.e., 0 or 1; 74%), a normal LDH level (58%), and were diagnosed with M1c disease (69%). More than one-third of the patients with M1c disease had brain metastases (39%).

Of all patients, 16% (*n*=784) did not receive systemic therapy during the study period and 84% (*n*=4,022) received at least one systemic therapy. Patients who received systemic therapy had more favorable baseline patient and tumor characteristics than patients who did not receive systemic therapy. They were younger (median age: 63 versus 72 years), had more often a good ECOG performance status (80% versus 44%) and a normal LDH level (60% versus 46%), and had less often brain metastases (36% versus 58% of the patients with M1c disease).

Table 2. Baseline patient and tumor characteristics

	All patients	Patients who did not receive systemic therapy	Patients who received systemic therapy
	n=4,806	*n*=784	*n*=4,022
Age, years			
Mean (SD)	63 (13)	70 (13)	62 (13)
Median (IQR)	64 (54-73)	72 (62-80)	63 (53-71)
Gender, *n* (%)			
Male	2,813 (59%)	447 (57%)	2,366 (59%)
Female	1,992 (41%)	336 (43%)	1,656 (41%)
Unknown	1 (0%)	1 (0%)	0 (0%)
ECOG performance status, *n* (%)			
0	2,168 (45%)	155 (20%)	2,013 (50%)
1	1,407 (29%)	193 (25%)	1,214 (30%)
≥2	623 (13%)	209 (27%)	414 (10%)
Unknown	608 (13%)	227 (29%)	381 (9%)
LDH level, *n* (%)			
≤1ULN	2,773 (58%)	361 (46%)	2,412 (60%)
>1ULN-≤2ULN	1,034 (22%)	136 (17%)	898 (22%)
>2ULN	619 (13%)	117 (15%)	502 (12%)
Unknown	380 (8%)	170 (22%)	210 (5%)
M category, *n* (%)			
M0	347 (7%)	53 (7%)	294 (7%)
M1a	303 (6%)	28 (4%)	275 (7%)
M1b	466 (10%)	60 (8%)	406 (10%)
M1c	3,338 (69%)	488 (62%)	2,850 (71%)
Unknown	352 (7%)	155 (20%)	197 (5%)
Brain metastases, *n* (%)			
No	3,357 (70%)	460 (59%)	2,897 (72%)
Yes	1,307 (27%)	285 (36%)	1,022 (25%)
Unknown	142 (3%)	39 (5%)	103 (3%)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactate dehydrogenase; *n*, number; SD, standard deviation; ULN, upper limit of normal.

Healthcare costs of all patients

Table 3 presents the healthcare resource use and costs of all patients (*n*=4,806). The mean (median) observation period was 18.0 (12.1) months; 66% of the patients died during this period. Mean total costs were €89,240 (SD: €86,489). Systemic therapy was by far the most important cost driver accounting for 83% of the costs (€73,998). On average, patients received 1.4 lines of therapy. The remaining 17% of the costs was related to hospital admissions (6%; €5,363), hospital visits (5%; €4,287), medical imaging (2%; €2,086), radiotherapy (1%; €1,318), surgery (1%; €1,224), genetic testing (1%; €891), hyperthermia (<1%; €70), and RFA (<1%; €2). Mean monthly costs were €6,809 (SD: €5,783).

Table 3. Healthcare resource use and costs of all patients

	All patients		Patients who did not receive systemic therapy		Patients who received systemic therapy	
	n=4,806		*n*=784		*n*=4,022	
Observation period, months						
Mean (SD)	18.0 (16.9)		11.7 (17.0)		19.3 (16.6)	
Median (IQR)	12.1 (5.4-25.4)		3.7 (1.4-13.2)		13.5 (6.8-26.9)	
Deceased patients, %	66%		81%		63%	
	Mean resource use (SD)	Mean costs (SD)	Mean resource use (SD)	Mean costs (SD)	Mean resource use (SD)	Mean costs (SD)
Medical imaging						
CT scan	4.4 (4.1)	€684 (€638)	1.7 (2.1)	€264 (€331)	5.0 (4.2)	€766 (€651)
MRI scan	2.1 (2.4)	€589 (€677)	0.9 (1.6)	€270 (€458)	2.3 (2.4)	€651 (€695)
PET/CT scan	0.8 (1.3)	€813 (€1,444)	0.5 (1.0)	€546 (€1,088)	0.8 (1.4)	€865 (€1,498)
Genetic testing						
Gene mutation testing	1.0 (0.2)	€891 (€185)	0.8 (0.4)	€753 (€365)	1.0 (0.1)	€918 (€102)
Hospital visits						
Outpatient visit	19.0 (15.6)	€1,798 (€1,480)	7.0 (6.6)	€665 (€624)	21.3 (15.8)	€2,019 (€1,497)
Daycare treatment	8.7 (10.5)	€2,489 (€3,020)	1.2 (2.0)	€345 (€588)	10.1 (10.9)	€2,907 (€3,124)
Hospital admissions						
Inpatient hospital day	10.4 (14.0)	€5,150 (€6,943)	5.4 (8.6)	€2,656 (€4,264)	11.4 (14.6)	€5,636 (€7,253)
Intensive care unit day	0.2 (1.2)	€213 (€1,531)	0.1 (0.9)	€175 (€1,098)	0.2 (1.3)	€221 (€1,602)
Treatment						
Surgery	0.4 (0.9)	€1,224 (€2,703)	0.4 (0.8)	€1,160 (€2,654)	0.4 (0.9)	€1,236 (€2,713)
Radiotherapy	0.5 (0.6)	€1,318 (€1,914)	0.4 (0.5)	€1,068 (€1,590)	0.5 (0.7)	€1,367 (€1,968)
Hyperthermia	<0.1 (0.1)	€70 (€871)	<0.1 (0.1)	€83 (€949)	<0.1 (0.1)	€68 (€855)
RFA	<0.1 (<0.1)	€2 (€61)	<0.1 (<0.1)	€2 (€53)	<0.1 (<0.1)	€3 (€62)

Table 3. Healthcare resource use and costs of all patients (continued)

	All patients		Patients who did not receive systemic therapy		Patients who received systemic therapy	
	n=4,806		*n*=784		*n*=4,022	
Systemic therapy	1.4 (1.2)	€73,998 (€80,716)	NA	NA	1.7 (1.1)	€88,422 (€80,682)
Total costs						
Mean (SD)		€89,240 (€86,489)		€7,988 (€7,490)		€105,078 (€85,963)
Median (IQR)		€67,882 (€22,004-€126,953)		€5,310 (€2,800-€11,131)		€83,092 (€43,715-€141,326)
Monthly costs						
Mean (SD)		€6,809 (€5,783)		€2,483 (€3,191)		€7,652 (€5,798)
Median (IQR)		€5,692 (€2,584-€9,443)		€1,304 (€393-€3,243)		€6,526 (€3,484-€10,348)

CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging; *n*, number; NA, not applicable; PET, positron emission tomography; RFA, radiofrequency ablation; SD, standard deviation.

Healthcare costs of patients who did not receive systemic therapy

The mean (median) observation period of patients who did not receive systemic therapy (*n*=784) was 11.7 (3.7) months (see Table 3). Mean total costs were €7,988 (SD: €7,490). These costs were mainly driven by the costs of hospital admissions, which accounted for 35% of the costs (€2,831). Almost half of all admissions (44%) was related to palliative care. The remaining 65% of the costs was attributable to surgery (15%; €1,160), medical imaging (14%; €1,080), radiotherapy (13%; €1,068), hospital visits (13%; €1,010), genetic testing (9%; €753), hyperthermia (1%; €83), and RFA (<1%; €2). Mean monthly costs were €2,483 (SD: €3,191).

Of the patients who did not receive systemic therapy, 81% (*n*=634) died during the observation period and 19% (*n*=150) was still alive at the data cut-off date. Their baseline patient and tumor characteristics are presented in Supplemental Table 2. Deceased patients had less favorable baseline characteristics than patients who were still alive. They were older (median age: 73 versus 65 years), had less often a good ECOG performance status (41% versus 58%) and a normal LDH level (43% versus 60%), and were more often diagnosed with M1c disease (71% versus 27%). Table 4 presents the healthcare costs of these patients. Mean total costs were lower for deceased patients than for patients who were still alive (€7,219 versus €11,237). Their mean monthly costs were, however, much higher (€2,981 versus €378). Costs of deceased patients were mainly driven by the costs of hospital admissions (41%; €2,961). Surgery (27%; €3,039) and medical imaging (21%; €2,350) were the main cost drivers for patients who were still alive.

Healthcare costs of patients who received systemic therapy

The mean (median) observation period of patients who received systemic therapy (*n*=4,022) was 19.3 (13.5) months; approximately two-thirds of the patients (63%) died during this period (see Table 3). Mean total costs were €105,078 (SD: €85,963). Systemic therapy was the main cost driver (84%; €88,422), followed by hospital admissions (6%; €5,857), hospital visits (5%; €4,926), medical imaging (2%; €2,282), radiotherapy (1%; €1,367), surgery (1%; €1,236), genetic testing (1%; €918), hyperthermia (<1%: €68), and RFA (<1%; €3). Mean monthly costs were €7,652 (SD: €5,798).

Table 5 presents the episode and monthly costs stratified by line of therapy. In total, 2,107 patients received one line of therapy, 1,077 patients received two lines of therapy, and 838 patients received three (or more) lines of therapy. Pembrolizumab was the most frequently prescribed drug in the first line (21%), ipilimumab in the second line (23%), and dabrafenib plus trametinib in the third line (28%). Mean episode costs were the highest for the second line (€59,701) and the lowest for the third line (€49,725). The mean monthly costs were also the highest for the second line (€11,939), but the lowest for the first line (€8,231).

Table 4. Healthcare costs of patients who did not receive systemic therapy stratified by vital status

	Deceased patients	Patients alive
	n=634	*n*=150
Observation period, months		
Mean (SD)	5.4 (7.9)	38.2 (19.6)
Median (IQR)	2.6 (1.1-6.3)	37.4 (19.6-58.8)
	Mean (SD)	Mean (SD)
Medical imaging	€780 (€772)	€2,350 (€2,467)
Genetic testing	€778 (€343)	€644 (€430)
Hospital visits	€797 (€881)	€1,911 (€1,076)
Hospital admissions	€2,961 (€4,671)	€2,279 (€3,827)
Treatment		
Surgery	€716 (€2,131)	€3,039 (€3,652)
Radiotherapy	€1,083 (€1,541)	€1,003 (€1,789)
Hyperthermia	€103 (€1,054)	€0 (€0)
RFA	€0 (€0)	€10 (€122)
Total costs		
Mean (SD)	€7,219 (€6,979)	€11,237 (€8,647)
Median (IQR)	€4,720 (€2,474-€9,497)	€9,262 (€4,425-€15,699)
Monthly costs		
Mean (SD)	€2,981 (€3,357)	€378 (€345)
Median (IQR)	€1,769 (€765-€4,130)	€293 (€139-€514)

IQR, interquartile range; *n*, number; RFA, radiofrequency ablation; SD, standard deviation.

Figure 1 presents the episode and monthly costs stratified by drug. Mean episode costs were the highest for nivolumab plus ipilimumab (€79,675; SD: €44,196), followed by ipilimumab monotherapy (€79,110; SD: €29,113), and dabrafenib plus trametinib (€77,053; SD: €63,451). Dacarbazine yielded the lowest mean episode costs (€6,564; SD: €5,090). The mean monthly costs were also the highest for nivolumab plus ipilimumab and ipilimumab monotherapy (€16,976 and €17,252, respectively), and the lowest for dacarbazine (€2,027). Mean monthly costs were similar between drugs within the same class: vemurafenib and dabrafenib (€6,710 and €6,460, respectively), dabrafenib plus trametinib and vemurafenib plus cobimetinib (€12,015 and €11,947, respectively), and nivolumab and pembrolizumab (€5,732 and €5,798, respectively). Detailed results regarding the episode costs stratified by drug are presented in Supplemental Table 3.

DISCUSSION

This study provides insight into real-world healthcare costs of patients with metastatic cutaneous melanoma in the Netherlands since the approval of the new immunotherapeutic and targeted

drugs. Mean total costs were €89,240 (SD: €86,489). Costs substantially differed between patients who did not receive systemic therapy (€7,988) and patients who received systemic therapy

Table 5. Episode and monthly costs stratified by line of therapy

	First line of therapy	Second line of therapy	Third line of therapy
	n=4,022	*n*=1,915	*n*=838
Episode duration, months			
Mean (SD)	11.3 (12.3)	8.9 (11.1)	7.6 (9.3)
Median (IQR)	6.6 (3.5-13.7)	4.9 (2.5-9.8)	4.2 (2.5-9.3)
Drug, *n* (%)			
Dacarbazine	154 (4%)	33 (2%)	29 (3%)
Ipilimumab	488 (12%)	440 (23%)	86 (10%)
Nivolumab	412 (10%)	205 (11%)	64 (8%)
Pembrolizumab	830 (21%)	370 (19%)	158 (19%)
Nivolumab plus ipilimumab	368 (9%)	249 (13%)	46 (5%)
Vemurafenib	540 (13%)	64 (3%)	53 (6%)
Dabrafenib	191 (5%)	85 (4%)	40 (5%)
Dabrafenib plus trametinib	588 (15%)	286 (15%)	233 (28%)
Vemurafenib plus cobimetinib	105 (3%)	66 (3%)	50 (6%)
Other	346 (9%)	117 (6%)	79 (9%)
Patients with a complete episode[a], %	80%	81%	80%
	Mean (SD)	Mean (SD)	Mean (SD)
Medical imaging	€1,349 (€1,145)	€941 (€1,109)	€806 (€937)
Genetic testing	€829 (€288)	€10 (€94)	€0 (€0)
Hospital visits	€2,789 (€2,764)	€2,554 (€2,859)	€2,179 (€2,314)
Hospital admissions	€2,993 (€5,525)	€3,206 (€5,209)	€2,805 (€4,456)
Treatment			
Surgery	€527 (€1,677)	€375 (€1,552)	€316 (€1,466)
Radiotherapy	€651 (€1,269)	€600 (€1,245)	€574 (€1,207)
Hyperthermia	€27 (€542)	€23 (€497)	€13 (€376)
RFA	<€1 (€24)	€1 (€34)	€4 (€73)
Systemic therapy	€49,336 (€49,118)	€51,993 (€47,431)	€43,028 (€43,465)
Episode costs			
Mean (SD)	€58,502 (€51,066)	€59,701 (€49,380)	€49,725 (€45,146)
Median (IQR)	€48,357 (€22,376-€80,885)	€50,392 (€22,907-€85,434)	€37,771 (€15,370-€69,036)
Monthly costs			
Mean (SD)	€8,231 (€7,374)	€11,939 (€11,463)	€10,366 (€10,415)
Median (IQR)	€6,587 (€3,416-€11,019)	€8,439 (€4,774-€14,877)	€7,716 (€3,974-€13,059)

IQR, interquartile range; *n*, number; RFA, radiofrequency ablation; SD, standard deviation.
[a]These patients either died during the line of therapy or received a new systemic therapy.

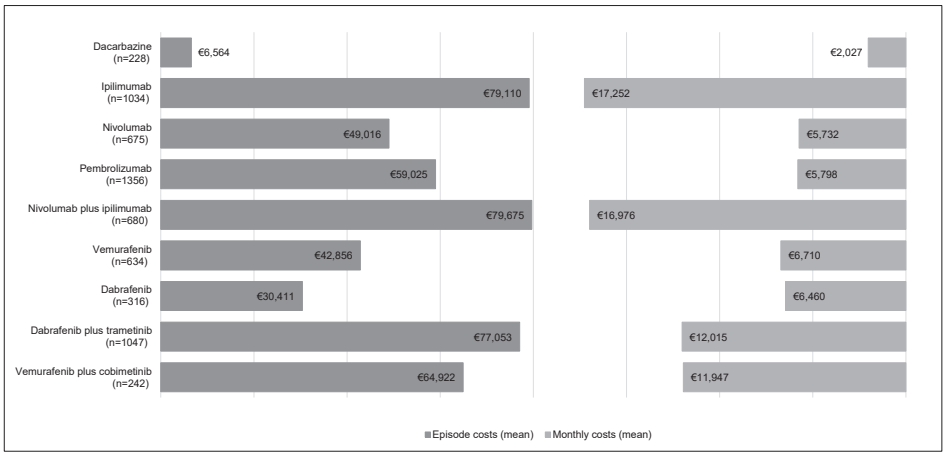

Figure 1. Episode and monthly costs stratified by drug
n, number.

(€105,078). This difference was largely owing to the costs of systemic therapy, which accounted for more than 80% of the costs.

Patients who did not receive systemic therapy were stratified by vital status because we assumed that these patients either had an infaust prognosis or a rather good prognosis (e.g., patients with oligometastatic disease). The results of our study confirm this assumption. First, deceased patients had less favorable baseline patient and tumor characteristics than patients who were still alive (see Supplemental Table 2). Second, the observation period was much shorter for deceased patients than for patients who were still alive (mean: 5.4 versus 38.2 months). Finally, hospital admissions were the main cost driver for deceased patients (41%), whereas costs of patients who were still alive were mainly driven by the costs of surgery (27%) and medical imaging (21%).

For patients who received systemic therapy, costs were stratified by drug. Although episode costs differed between drugs within the same class (vemurafenib and dabrafenib, dabrafenib plus trametinib and vemurafenib plus cobimetinib, and nivolumab and pembrolizumab), their monthly costs were similar. This underlines the importance of accounting for differences in episode durations (and observation periods). Moreover, a network meta-analysis[151] (NMA) showed that effectiveness and safety were also comparable between drugs within the same class. Therefore, it could be suggested that clinicians should not be restricted by differences in effectiveness, safety, and costs while choosing between these drugs.

Furthermore, our study also showed that episode costs were similar between ipilimumab monotherapy and nivolumab plus ipilimumab. This was mainly owing to the costs of ipilimumab, which were higher for ipilimumab monotherapy (€70,976) than for ipilimumab in combination

with nivolumab (€55,228). On average, patients received 3.2 cycles of ipilimumab monotherapy compared to 2.6 cycles of ipilimumab combination therapy. Due to a reasonably comparable episode duration (mean: 9.1 versus 9.6 months), monthly costs were also similar between ipilimumab monotherapy and nivolumab plus ipilimumab. The previously mentioned NMA[151] showed, however, that effectiveness was in favor of nivolumab plus ipilimumab, whereas safety was in favor of ipilimumab monotherapy. This underlines that evidence on effects, costs, and cost-effectiveness is crucial. It will provide insight into what extend the benefits of drugs will outweigh their costs, which may facilitate evidence-based decision making in clinical practice.

Three previous studies[147-149] reported real-world healthcare costs of ipilimumab and vemurafenib. One of these studies[149] was our own study in which we calculated healthcare costs of all Dutch patients who received ipilimumab. The two other studies calculated healthcare costs of United States (US) patients who received ipilimumab or vemurafenib. According to the study by Chang et al.[147], mean episode costs were US$153,062 (≈€113,480) for ipilimumab and US$77,687 (≈€57,597) for vemurafenib. In the study by Toy et al.[148], mean monthly costs were US$35,472 (≈€26,718) for ipilimumab and US$17,793 (≈€13,402) for vemurafenib. Both of these studies reported considerably higher costs than our study. It is, however, difficult to compare costs between countries as, for example, drug use and unit prices may differ. This information was not reported in both studies.

It should be noted that our study has some limitations. First, we used list prices for drugs, and reference prices and tariffs for other resources. Although these prices may not reflect actual costs (e.g., nivolumab and pembrolizumab are subjected to a confidential financial arrangement), the use of these sources is recommended in the Dutch costing manual.[68] Second, we did not include healthcare costs outside the hospital setting, such as costs of hospice care, which may have led to an underestimation of the actual healthcare costs. We believe, however, that the impact will be rather limited because costs were mainly driven by the costs of systemic therapy. Third, approximately 10% of the patients received at least one investigational drug. Costs of these drugs are paid by pharmaceutical companies. However, in our study, costs of investigational drugs were only set at zero if the drug was given in a blinded trial or if the drug was not approved for metastatic melanoma in the Netherlands at the time of this study. If costs of all investigational drugs were set at zero, mean total costs of patients who received systemic therapy would have been €102,450 instead of €105,078. Finally, costs were not yet complete for all patients because 34% of the patients were still alive at the date cut-off date. These patients will accrue additional costs during the remainder of their life.

CONCLUSIONS

Our study showed that immunotherapeutic and targeted drugs had a large impact on real-world healthcare costs of patients with metastatic melanoma. Compared to dacarbazine, episode costs were five times higher for dabrafenib, and 12 times higher for nivolumab plus ipilimumab, ipilimumab monotherapy, and dabrafenib plus trametinib. As new drugs continue entering the treatment landscape for (metastatic) melanoma, it remains crucial to monitor whether the benefits of these drugs outweigh their costs.

SUPPLEMENTARY MATERIAL

Supplemental Table 1. Immunotherapeutic and targeted drugs approved for the treatment of metastatic melanoma since 2011

Immunotherapeutic drugs	FDA approval	EMA approval
Ipilimumab	Mar 2011	Jul 2011
Nivolumab	PT: Dec 2014	Jun 2015
Pembrolizumab	PT: Sep 2014	Jul 2015
	TN: Dec 2015	
Nivolumab plus ipilimumab	BRAF wild-type: Oct 2015	May 2016
	Across BRAF status: Jan 2016	
Targeted drugs	**FDA approval**	**EMA approval**
Vemurafenib	Aug 2011	Feb 2012
Dabrafenib	May 2013	Aug 2013
Dabrafenib plus trametinib	Jan 2014	Sep 2015
Vemurafenib plus cobimetinib	Nov 2015	Nov 2015
Encorafenib plus binimetinib	Jun 2018	Sep 2018

EMA, European Medicines Agency; FDA, Food and Drug Administration; PT, previously-treated patients; TN, treatment-naive patients.

Supplemental Table 2. Baseline patient and tumor characteristics of patients who did not receive systemic therapy stratified by vital status

	Deceased patients	Patients alive
	n=634	*n*=150
Age, years		
Mean (SD)	71 (12)	64 (15)
Median (IQR)	73 (64-80)	65 (54-75)
Gender, *n* (%)		
Male	371 (59%)	76 (51%)
Female	262 (41%)	74 (49%)
Unknown	1 (0%)	0 (0%)
ECOG performance status, *n* (%)		
0	90 (14%)	65 (43%)
1	171 (27%)	22 (15%)
≥2	198 (31%)	11 (7%)
Unknown	175 (28%)	52 (35%)
LDH level, *n* (%)		
≤1ULN	271 (43%)	90 (60%)
>1ULN-≤2ULN	127 (20%)	9 (6%)
>2ULN	115 (18%)	2 (1%)
Unknown	121 (19%)	49 (33%)

Supplemental Table 2. Baseline patient and tumor characteristics of patients who did not receive systemic therapy stratified by vital status (continued)

	Deceased patients	Patients alive
	n=634	*n*=150
M category, *n* (%)		
M0	41 (6%)	12 (8%)
M1a	13 (2%)	15 (10%)
M1b	30 (5%)	30 (20%)
M1c	448 (71%)	40 (27%)
Unknown	102 (16%)	53 (35%)
Brain metastases, *n* (%)		
No	352 (56%)	108 (72%)
Yes	259 (41%)	26 (17%)
Unknown	23 (4%)	16 (11%)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactate dehydrogenase; *n*, number; SD, standard deviation; ULN, upper limit of normal.

Supplemental Table 3. Detailed results of episode costs stratified by drug[a]

	Dacarbazine	Ipilimumab	Nivolumab	Pembrolizumab	Nivolumab plus ipilimumab
	n=228	*n*=1,034	*n*=675	*n*=1,356	*n*=680
Episode duration, months					
Mean (SD)	5.6 (9.3)	9.1 (12.3)	12.5 (12.3)	14.0 (12.9)	9.6 (10.8)
Median (IQR)	3.4 (2.1-5.0)	4.8 (3.0-8.8)	8.5 (3.6-16.4)	9.2 (3.9-20.7)	5.4 (2.4-12.7)
Drug use, mean (SD)					
Number of cycles	3.7 (3.8)	3.2 (1.1)	13.4 (12.1)	10.4 (8.8)	N: 7.0 (9.4); I: 2.6 (1.1)
Number of days	NA	NA	NA	NA	NA
Patients with a complete episode[b], %	96%	89%	62%	67%	64%
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Medical imaging	€810 (€677)	€1,122 (€1,139)	€1,252 (€1,213)	€1,322 (€1,328)	€1,035 (€826)
Genetic testing	€583 (€450)	€374 (€455)	€477 (€457)	€489 (€459)	€436 (€461)
Hospital visits	€1,670 (€1,519)	€1,830 (€959)	€5,111 (€4,226)	€3,925 (€2,980)	€2,828 (€2,650)
Hospital admissions	€1,877 (€3,598)	€3,549 (€5,724)	€2,332 (€4,679)	€2,588 (€5,465)	€4,070 (€5,969)
Treatment					
Surgery	€219 (€922)	€444 (€1,708)	€550 (€1,667)	€515 (€1,776)	€512 (€1,580)
Radiotherapy	€753 (€1,277)	€772 (€1,336)	€607 (€1,247)	€692 (€1,346)	€629 (€1,251)
Hyperthermia	€0 (€0)	€42 (€676)	€48 (€724)	€8 (€295)	€16 (€417)
RFA	€0 (€0)	€1 (€46)	€1 (€29)	€1 (€40)	€0 (€0)
Systemic therapy	€652 (€749)	€70,976 (€28,149)	€38,637 (€33,968)	€49,485 (€43,072)	€70,149 (€42,074)
Episode costs					
Mean (SD)	€6,564 (€5,090)	€79,110 (€29,113)	€49,016 (€38,537)	€59,025 (€46,413)	€79,675 (€44,196)
Median (IQR)	€5,142 (€3,323-€8,465)	€82,536 (€59,172-€100,209)	€38,647 (€19,725-€71,366)	€47,315 (€24,658-€75,710)	€72,338 (€47,719-€103,312)
Monthly costs					
Mean (SD)	€2,027 (€1,871)	€17,252 (€11,146)	€5,732 (€5,279)	€5,798 (€3,846)	€16,976 (€13,279)
Median (IQR)	€1,478 (€970-€2,448)	€15,920 (€9,218-€23,314)	€4,963 (€3,148-€6,742)	€5,551 (€3,577-€7,464)	€14,077 (€7,036-€23,425)

Supplemental Table 3. Detailed results of episode costs stratified by drug[a] (continued)

	Vemurafenib	Dabrafenib	Dabrafenib plus trametinib	Vemurafenib plus cobimetinib
	n=634	*n*=316	*n*=1,047	*n*=242
Episode duration, months				
Mean (SD)	7.6 (10.4)	6.3 (8.9)	8.3 (8.7)	6.4 (6.8)
Median (IQR)	4.6 (2.6-8.0)	3.9 (2.6-6.5)	5.5 (3.3-9.8)	4.4 (1.9-7.9)
Drug use, mean (SD)				
Number of cycles	NA	NA	NA	NA
Number of days	153.8 (205.5)	120.9 (106.9)	D: 177.5 (157.2); T: 167.0 (151.5)	V: 125.7 (136.8); C: 115.2 (124.8)
Patients with a complete episode[b], %	97%	97%	82%	93%
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Medical imaging	€994 (€777)	€1,018 (€893)	€1,069 (€880)	€1,028 (€1,269)
Genetic testing	€731 (€367)	€492 (€456)	€434 (€435)	€365 (€441)
Hospital visits	€1,298 (€1,202)	€1,002 (€703)	€1,606 (€850)	€1,682 (€936)
Hospital admissions	€3,050 (€4,750)	€2,725 (€4,789)	€3,346 (€5,051)	€3,748 (€6,094)
Treatment				
Surgery	€262 (€1,118)	€387 (€1,257)	€468 (€1,551)	€377 (€1,594)
Radiotherapy	€719 (€1,205)	€611 (€1,155)	€509 (€1,112)	€376 (€976)
Hyperthermia	€51 (€747)	€0 (€0)	€21 (€475)	€0 (€0)
RFA	€0 (€0)	€0 (€0)	<€1 (€15)	€0 (€0)
Systemic therapy	€35,750 (€47,845)	€24,177 (€21,989)	€69,601 (€62,121)	€57,344 (€63,435)
Episode costs				
Mean (SD)	€42,856 (€49,334)	€30,411 (€23,569)	€77,053 (€63,451)	€64,922 (€65,120)
Median (IQR)	€31,210 (€16,399-€49,791)	€25,941 (€16,621-€37,153)	€64,645 (€39,948-€86,178)	€47,492 (€16,305-€83,183)
Monthly costs				
Mean (SD)	€6,710 (€2,843)	€6,460 (€2,869)	€12,015 (€7,732)	€11,947 (€6,538)
Median (IQR)	€6,936 (€5,113-€8,023)	€6,590 (€4,881-€7,525)	€12,146 (€9,238-€13,554)	€12,325 (€8,369-€15,078)

IQR, interquartile range; *n*, number; NA, not applicable; RFA, radiofrequency ablation; SD, standard deviation.

[a]Due to low numbers of patients, costs were not separately reported for temozolomide and encorafenib plus binimetinib.

[b]These patients either died during the line of therapy or received a new line of therapy.

7 Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in the Netherlands

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ABSTRACT

Phase III trials with ipilimumab showed an improved survival in patients with metastatic melanoma. We evaluated the use and safety of ipilimumab, and the survival of all patients with metastatic cutaneous melanoma (*n*=807) receiving ipilimumab in real-world clinical practice in the Netherlands using data from the Dutch Melanoma Treatment Registry. Patients who were registered between July 2012 and July 2015 were included and analyzed according to their treatment status: treatment-naive (*n*=344) versus previously treated (*n*=463). Overall, 70% of treatment-naive patients and 62% of previously-treated patients received all four planned doses of ipilimumab. Grade 3 and 4 immune-related adverse events occurred in 29% of treatment-naive patients and 21% of previously-treated patients. No treatment-related deaths occurred. Median time to first event was 5.4 months (95% confidence interval [CI]: 4.7-6.5 months) in treatment-naive patients and 4.4 months (95% CI: 4.0-4.7 months) in previously-treated patients. Median overall survival was 14.3 months (95% CI: 11.6-16.7 months) in treatment-naive patients and 8.7 months (95% CI: 7.6-9.6 months) in previously-treated patients. In both patient groups, an elevated lactate dehydrogenase level (hazard ratio: 2.25 and 1.70 in treatment-naive and previously-treated patients, respectively) and American Joint Committee on Cancer M1c-stage disease (hazard ratio: 1.81 and 1.83, respectively) were negatively associated with overall survival. These real-world outcomes of ipilimumab slightly differed from outcomes in phase III trials. Although phase III trials are crucial for establishing efficacy, real-world data are of great added value enhancing the generalizability of outcomes of ipilimumab in clinical practice.

INTRODUCTION

In 2012, 100,442 patients were diagnosed with cutaneous melanoma in Europe and 22,211 patients died from the disease.[41] Although less than five percent of all patients are initially diagnosed with metastatic melanoma (i.e., American Joint Committee on Cancer [AJCC] stage IV), approximately 20% will develop distant metastases as a consequence of disease recurrence. Five-year survival rates for metastatic melanoma are only 15% to 20%.[152-156]

Until 2011, dacarbazine was the most frequently applied drug for metastatic melanoma. Dacarbazine has, however, never been shown to improve survival in phase III trials.[94,95,157] Recently, regulatory pathways promoting antitumor immunity have become increasingly well characterized. Ipilimumab, a monoclonal antibody that blocks the cytotoxic T-lymphocyte associated antigen and thereby augmenting T-cell activation and proliferation, was the first drug demonstrating a survival benefit.[158,159] In 2010, a phase III trial[80] was conducted to compare ipilimumab (at a dose of 3 mg/kg) with or without a glycoprotein 100 (gp100) peptide vaccine with gp100 alone in patients with previously-treated metastatic melanoma. The median overall survival (OS) was 10.0 months in patients receiving ipilimumab plus gp100 compared with 6.4 months in patients receiving gp100 alone. The median OS in the group receiving ipilimumab alone was 10.1 months. A second phase III trial[160] with ipilimumab (at a dose of 10 mg/kg) plus dacarbazine versus dacarbazine alone in treatment-naive patients resulted in a median OS of 11.2 months in patients receiving ipilimumab plus dacarbazine, as compared with 9.1 months in patients receiving dacarbazine alone. Grade 3 and 4 immune-related adverse events (irAEs) were reported in 10-15% of previously-treated patients receiving ipilimumab with or without gp100 and in 42% of treatment-naive patients receiving ipilimumab plus dacarbazine. Treatment-related deaths only occurred in the trial conducted with previously-treated patients.[80,160]

On the basis of these results, ipilimumab became available as monotherapy for the treatment of metastatic melanoma. Outcomes of ipilimumab may, however, differ outside the setting of a phase III trial. Therefore, we evaluated the use and safety of ipilimumab, and survival of all treatment-naive and previously-treated patients with metastatic cutaneous melanoma receiving ipilimumab in real-world clinical practice in the Netherlands.

PATIENTS AND METHODS

Data source

A population-based registry, the Dutch Melanoma Treatment Registry (DMTR), was set up after the introduction of ipilimumab to assure safety and quality of care in the Netherlands. The DMTR registers data on baseline characteristics, drug use, grade 3 and 4 treatment-related adverse events (according to the Common Terminology Criteria for Adverse Events, version 4.0), and clinical outcomes of all Dutch patients with unresectable stage IIIC or IV melanoma (ac-

cording to the AJCC Cancer Staging Manual). In compliance with Dutch regulations, the DMTR was approved by the medical ethical committee and was not subject to the Medical Research Involving Human Subjects Act. Patients were offered an opt-out option. A detailed description of the DMTR has been published elsewhere.[138] For this study, the data cut-off date was March 20, 2016.

Patients

All patients with metastatic cutaneous melanoma receiving ipilimumab (at a dose of 3 mg/kg) in clinical practice who were registered in the DMTR between July 2012 and July 2015 were included. Patients were analyzed according to their treatment status: treatment-naive versus previously treated for metastatic melanoma. In the Netherlands, reimbursement of ipilimumab became available in 2012 for previously-treated patients and in 2014 for treatment-naive patients.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics (at the start of ipilimumab), use of ipilimumab, and grade 3 and 4 irAEs. Differences in proportions between both patient groups were analyzed using the two-tailed chi-squared test. The Mann-Whitney test was used to compare medians. Follow-up, time to first event (i.e., new treatment or death), and OS were determined according to the Kaplan-Meier method. The time to first event was calculated from the start of ipilimumab until the start of a new treatment, death, or last follow-up. The cumulative incidence of the first event was assessed according to the cumulative incidence competing risk method.[58] Survival time was calculated from the start of ipilimumab until death or last follow-up. Multivariate Cox proportional hazard models were estimated using backward selection by excluding nonsignificant covariates to evaluate the association of baseline characteristics with OS. Missing data were imputed using multiple imputation by chained equations.[161] In order to stabilize the results, ten imputed datasets were produced. All analyses were conducted using STATA statistical analysis software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Statistical significance was considered at a 5% significance level (two tailed).

RESULTS

Baseline characteristics

Of all 2,051 patients with metastatic cutaneous melanoma in the DMTR, 807 patients received ipilimumab in clinical practice: 344 (43%) treatment-naive patients and 463 (57%) previously-treated patients (see Table 1). Most patients in both groups had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (88% and 84% of treatment-naive and previously-treated patients, respectively), a normal lactate dehydrogenase (LDH) level (76% and 72%, respectively), and were diagnosed with AJCC M1c-stage disease (71% and 79%, respectively).

Table 1. Baseline characteristics

	Treatment-naive patients	Previously-treated patients	p-value[a]
	n=344	*n*=463	
Age, years			
Median (95% CI)	64 (41-79)	60 (38-76)	<0.001
Gender, *n* (%)			
Male	213 (62%)	264 (57%)	0.162
Female	131 (38%)	199 (43%)	
Performance status (ECOG), *n* (%)			
0	213 (62%)	258 (56%)	0.139
1	89 (26%)	129 (28%)	
≥2	12 (3%)	14 (3%)	
Unknown	30 (9%)	62 (13%)	
BRAF mutation, *n* (%)			
Not determined	10 (3%)	25 (5%)	0.057
Determined	331 (96%)	427 (92%)	
BRAF wildtype	199 (60%)	150 (35%)	<0.001
BRAF mutation	132 (40%)	277 (65%)	
Unknown	3 (1%)	11 (2%)	
Serum LDH (U/L), *n* (%)			
Normal (≤250)	261 (76%)	334 (72%)	0.213
Elevated (>250)	72 (21%)	119 (26%)	
Unknown	11 (3%)	10 (2%)	
AJCC M-stage, *n* (%)			
M0	13 (4%)	8 (2%)	0.076
M1a	36 (10%)	38 (8%)	
M1b	46 (13%)	45 (10%)	
M1c	243 (71%)	365 (79%)	
Unknown	6 (2%)	7 (2%)	
Brain metastases, *n* (%)			
No	264 (77%)	329 (71%)	0.170
Yes	75 (22%)	123 (27%)	
Asymptomatic	36 (48%)	61 (50%)	0.029
Symptomatic	39 (52%)	52 (42%)	
Unknown	0 (0%)	10 (8%)	
Unknown	5 (1%)	11 (2%)	
Time from the diagnosis of metastatic melanoma to the start of ipilimumab, months			
Median (95% CI)	0.8 (0.2-8.7)	4.2 (0.2-16.7)	<0.001

AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; *n*, number.

[a]Differences in proportions between both patient groups were analyzed using the two-tailed chi-squared test. The Mann-Whitney test was used to compare medians.

Approximately a quarter of the patients had brain metastases (22% and 27% of treatment-naive and previously-treated patients, respectively), of whom approximately 50% had symptomatic brain metastases. Baseline characteristics of both patient groups were reasonably similar, except for age (64 versus 60 years for treatment-naive and previously-treated patients, respectively), BRAF wild-type tumors (60% versus 35% of tested patients, respectively), and median time from the diagnosis of metastatic melanoma to the start of ipilimumab (0.8 versus 4.2 months, respectively). The imputed baseline characteristics were comparable with the observed baseline characteristics (see Supplemental Table).

Use and safety

Overall, 70% (*n*=240) of treatment-naive patients and 62% (*n*=286) of previously-treated patients received all four planned doses of ipilimumab (see Table 2). Main reasons for premature

Table 2. Use of ipilimumab

	Treatment-naive patients	Previously-treated patients
	n=344	*n*=463
Treatment line of ipilimumab, *n (%)*		
First line	344 (100%)	NA
Second line	NA	385 (83%)
≥Third line	NA	78 (17%)
Number of ipilimumab cycles, *n (%)*		
1	17 (5%)	56 (12%)
2	45 (13%)	66 (14%)
3	42 (12%)	55 (12%)
4	240 (70%)	286 (62%)
Reason for premature discontinuation, *n (%)*		
No premature discontinuation	240 (70%)	286 (62%)
Planned in advance	3 (1%)	5 (1%)
Progression	49 (14%)	117 (25%)
Toxicity	45 (13%)	41 (9%)
Patient choice	1 (0%)	1 (0%)
Death	4 (1%)	9 (2%)
Other	2 (1%)	2 (0%)
Unknown	0 (0%)	2 (0%)
Number of systemic treatments after ipilimumab, *n (%)*		
0	168 (49%)	258 (56%)
1	132 (38%)	132 (29%)
≥2	44 (13%)	73 (16%)

n, number; NA, not applicable.

discontinuation were disease progression (14% and 25% of treatment-naive and previously-treated patients, respectively) and toxicity (13% and 9%, respectively). Moreover, 51% (*n*=176) of treatment-naive patients and 44% (*n*=205) of previously-treated patients received systemic treatment(s) after ipilimumab. These treatments included chemotherapy, BRAF inhibitors (alone or in combination with a MEK inhibitor), anti-programmed cell death protein-1 antibodies, and adoptive T-cell therapy. At least one grade 3 or 4 irAE was reported in 29% (*n*=99) of treatment-naive patients and in 21% (*n*=97) of previously-treated patients (see Table 3). Gastrointestinal irAEs were most frequently reported (16% and 11% of treatment-naive and previously-treated patients, respectively). No treatment-related deaths occurred.

Table 3. Grade 3 and 4 immune-related adverse events

	Treatment-naive patients	Previously-treated patients
	n=344	*n*=463
Number of adverse events, *n (%)*		
0	245 (71%)	366 (79%)
1	82 (24%)	78 (17%)
≥2	17 (5%)	19 (4%)
Adverse events reported, *n (%[a])*		
Adrenal insufficiency	5 (1%)	10 (2%)
Bone marrow suppression	2 (1%)	3 (1%)
Colitis	55 (16%)	51 (11%)
Dermatologic	12 (3%)	4 (1%)
Gastrointestinal perforation	1 (0%)	1 (0%)
Hepatic	3 (1%)	9 (2%)
Hypophysitis	20 (6%)	18 (4%)
Neurologic	2 (1%)	3 (1%)
Thyroiditis	9 (3%)	6 (1%)
Uveitis	2 (1%)	1 (0%)
Other	9 (3%)	19 (4%)

n, number.
[a]Percentage of all patients.

Survival outcomes

Median follow-up was 11.5 months (95% confidence interval [CI]: 10.5-12.4 months) in treatment-naive patients and 20.9 months (95% CI: 17.4-22.7 months) in previously-treated patients (see Table 4). The median time to first event was 5.4 months (95% CI: 4.7-6.5 months) in treatment-naive patients and 4.4 months (95% CI: 4.0-4.7 months) in previously-treated patients (see Figure 1). The one-year cumulative incidence of a new treatment as first event was 58% in treatment-naive patients and 44% in previously-treated patients; the one-year cumulative inci-

Table 4. Survival outcomes

	Treatment-naive patients	Previously-treated patients
	n=344	*n*=463
Follow-up, months		
Median (95% CI)	11.5 (10.5-12.4)	20.9 (17.4-22.7)
Time to first event, months		
Median (95% CI)	5.4 (4.7-6.5)	4.4 (4.0-4.7)
One-year cumulative incidence of the first event, %		
New treatment	58%	44%
Death	23%	44%
Overall survival, months		
Median (95% CI)	14.3 (11.6-16.7)	8.7 (7.6-9.6)
Survival rates, %		
One-year	54%	38%
Two-year	39%	24%

CI, confidence interval; *n*, number.

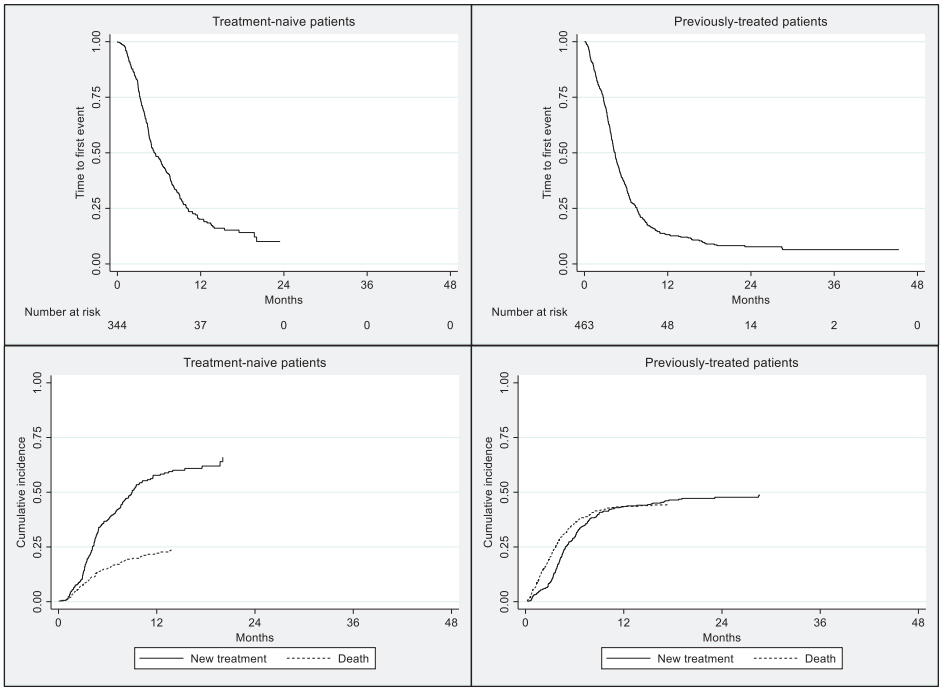


Figure 1. Time to first event and cumulative incidence of the first event

dence of death as first event was 23% in treatment-naive patients and 44% in previously-treated patients. Median OS was 14.3 months (95% CI: 11.6-16.7 months) in treatment-naive patients and 8.7 months (95% CI: 7.6-9.6 months) in previously-treated patients (see Figure 2). Corresponding one- and two-year survival rates were 54% and 39%, respectively, in treatment-naive patients, and 38% and 24%, respectively, in previously-treated patients. In both patient groups, patients with an elevated LDH level, a worse ECOG performance status, and AJCC M1c-stage disease had a significantly shorter median OS than patients with more favorable baseline characteristics (see Supplemental Figure).

Table 5. Association of baseline characteristics with overall survival

	Treatment-naive patients			Previously-treated patients		
	n=344			*n*=463		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	NS			1.01	1.00-1.02	0.011
Gender						
Male	1.00			NS		
Female	0.69	0.48-0.99	0.043			
Performance status (ECOG)						
0				1.00		
1	NS			1.52	1.19-1.95	0.001
≥2				4.63	2.33-9.21	<0.001
BRAF mutation						
BRAF wildtype	1.00			NS		
BRAF mutation	0.55	0.38-0.80	0.002			
Serum LDH (U/L)						
Normal (<250)	1.00			1.00		
Elevated (≥250)	2.25	1.51-3.33	<0.001	1.70	1.31-2.19	<0.001
AJCC M-stage						
M0-M1b	1.00			1.00		
M1c	1.81	1.09-3.01	0.021	1.83	1.31-2.56	<0.001

AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; *n*, number; NS, not significant (omitted).

The multivariate Cox proportional hazard model with treatment-naive patients showed that female sex (hazard ratio [HR]: 0.69) and a BRAF mutation (HR: 0.55) were positively associated with OS (see Table 5). In both patient groups, an elevated LDH level (HR: 2.25 and 1.70 in treatment-naive and previously-treated patients, respectively) and AJCC M1c-stage disease (HR: 1.81 and 1.83, respectively) were negatively associated with OS. Increasing age (HR: 1.01) and a worse ECOG performance status (HR: 1.52 and 4.63 for ECOG 1 and 2 or higher, respectively) were also negatively associated with OS in previously-treated patients.

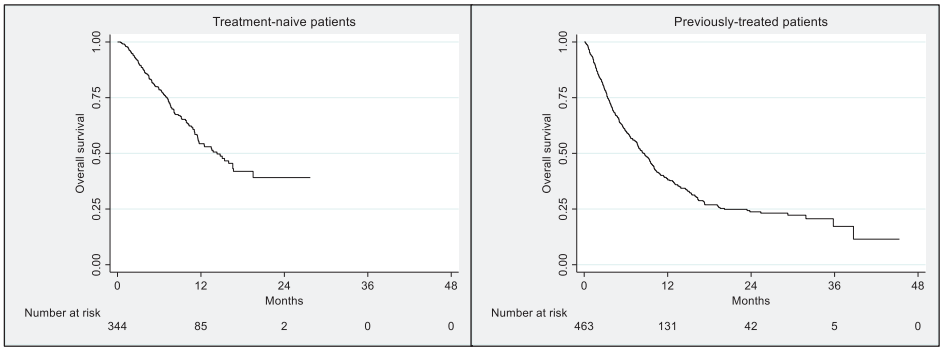


Figure 2. Overall survival

DISCUSSION

We evaluated the use and safety of ipilimumab, and survival of all treatment-naive and previously-treated metastatic cutaneous melanoma patients receiving ipilimumab in real-world clinical practice in the Netherlands. The majority of these patients (70% of treatment-naive patients and 62% of previously-treated patients) received all four planned doses of ipilimumab. The most frequent reason for premature discontinuation was disease progression, followed by toxicity.

Approximately a quarter of all patients experienced at least one grade 3 or 4 irAE. As in previous studies[80,160,162,163], these were primarily related to gastrointestinal, endocrine, and dermatologic irAEs. The most frequently reported irAE was colitis (16% of treatment-naive patients and 11% of previously-treated patients). The percentage of treatment-naive patients with grade 3 and 4 irAEs was lower in our study than in the phase III trial[160] (29% versus 42%). In contrast to our study (patients received ipilimumab monotherapy at a dose of 3 mg/kg), the trial patients received ipilimumab at a dose of 10 mg/kg plus dacarbazine. As shown in a phase III trial[127] comparing ipilimumab at a dose of 10 mg/kg with ipilimumab at a dose of 3 mg/kg, grade 3 and 4 irAEs were more common in patients receiving ipilimumab at a dose of 10 mg/kg (30% versus 14%). Although the phase III trial[80] with previously-treated patients, two expanded access programs (EAP)[164,165], and one retrospective study[162] reported treatment-related deaths, no treatment-related deaths occurred in our study. This may be owing to the effect of collaboration, knowledge transfer, and centralization of melanoma care in the Netherlands, which, in turn, may have resulted in good implementation and high adherence to guidelines for management of adverse events.[138]

The median OS and median time to first event were longer in treatment-naive patients than in previously-treated patients (14.3 versus 8.7 months and 5.4 versus 4.4 months, respectively). Similarly, the one- and two-year survival rates were higher in treatment-naive patients (54% versus 38% and 39% versus 24%, respectively). Although these survival outcomes are in favor of

treatment-naive patients, no conclusions can be made regarding the relative treatment effects of ipilimumab in these patient groups as we did not account for baseline characteristics. Furthermore, previously-treated patients received at least one systemic treatment before ipilimumab, whereas treatment-naive patients more often received systemic treatment(s) after ipilimumab (51% versus 44%). It is, however, impossible to distinguish between the benefits from prior or subsequent treatment(s) and the benefits from ipilimumab.

The median OS of our treatment-naive patients was noticeable longer than the median OS observed in the phase III trial[160] (14.3 versus 11.2 months). The reason for this difference is not fully understand, especially because our patients were older (mean age: 61.8 versus 57.5 years) and had brain metastases (22% versus 0%). However, our patients more frequently had a normal LDH level (76% versus 63%), which was positively associated with OS according to our multivariate Cox proportional hazard model. The higher percentage of patients with a normal LDH level may be due to a more stringent selection of patients eligible for treatment with ipilimumab, which may have been guided by a previous study[166] indicating that patients with a normal LDH level are more likely to benefit from ipilimumab. More importantly, our patients received ipilimumab in a later time frame in which novel drugs (e.g., BRAF inhibitors and anti-PD1 antibodies) and combinations of drugs were available. Although the percentage of patients who received subsequent treatment were comparable (51% in our study versus 55% in the phase III trial), our patients more often received novel drugs after ipilimumab (37% of all patients), whereas the trial patients more often received chemotherapy as subsequent treatment (38% of all patients).[160] Therefore, our patients may have had more benefit from subsequent treatment(s) than the patients in the phase III trial. The median OS of our previously-treated patients was shorter than the median OS observed in the phase III trial[80] (8.7 versus 10.1 months), which is probably owing to the greater patient heterogeneity in clinical practice. Compared with the trial patients, our patients were slightly older (mean age: 58.4 versus 56.8 years) and had more frequently brain metastases (27% versus 11%). Nevertheless, the two EAP reported an even shorter median OS in previously-treated patients: 6.1 months in the United Kingdom EAP[164] and 7.2 months in the Italian EAP.[165]

Our population-based study showed that real-world outcomes of ipilimumab in the Netherlands slightly differed from outcomes in phase III trials. In general, observational studies include larger sample sizes, more heterogeneous patients, and a longer follow-up. Although phase III trials are crucial for establishing efficacy, real-world data are of great added value enhancing the generalizability of outcomes of ipilimumab in clinical practice. Therefore, real-world data can complement trial data and may bridge the gap between clinical research and clinical practice.

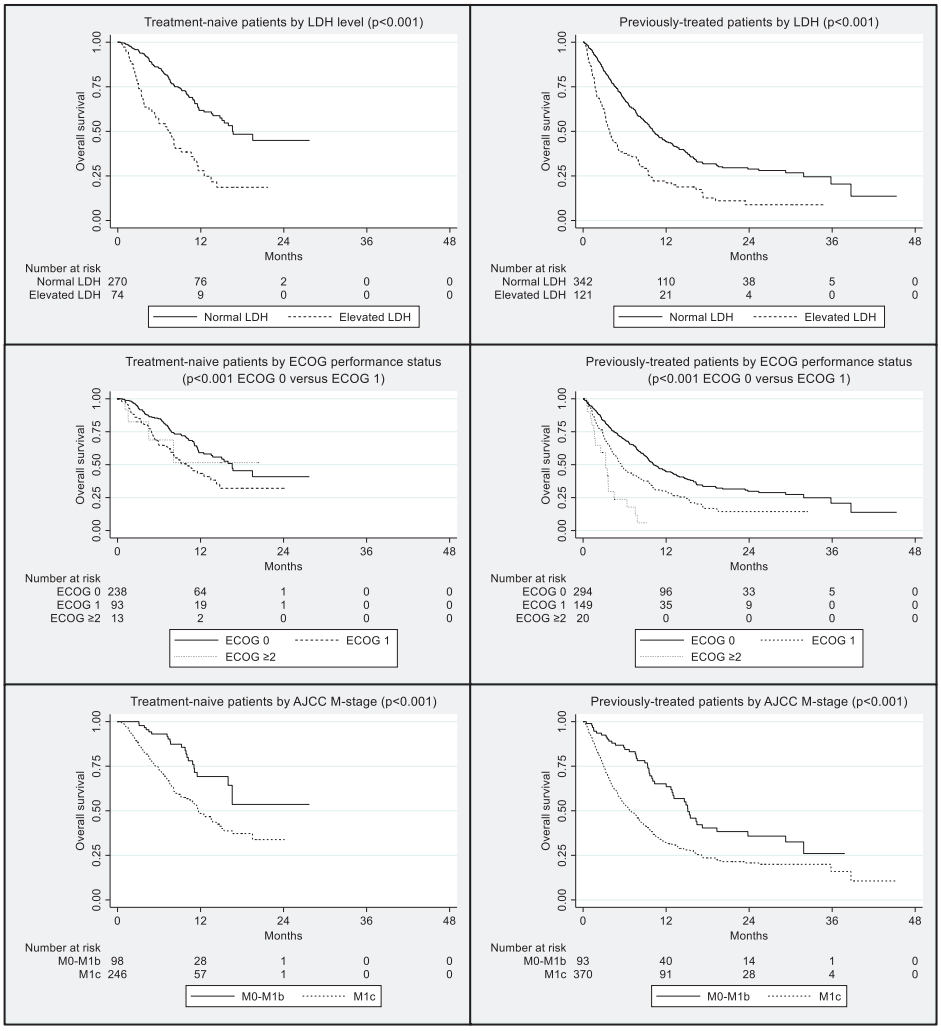
SUPPLEMENTARY MATERIAL

Supplemental Table. Imputed baseline characteristics

	Real-world data		Imputed data[a]	
	Treatment-naive patients	Previously-treated patients	Treatment-naive patients	Previously-treated patients
	n=344	*n*=463	*n*=344	*n*=463
Age, years				
Median (95% CI)	64 (41-79)	60 (38-76)	64 (41-79)	60 (38-76)
Gender, *n* (%)				
Male	213 (62%)	264 (57%)	213 (62%)	264 (57%)
Female	131 (38%)	199 (43%)	131 (38%)	199 (43%)
Performance status (ECOG), *n* (%)				
0	213 (68%)	258 (64%)	231 (67%)	298 (64%)
1	89 (28%)	129 (32%)	100 (29%)	149 (32%)
≥2	12 (4%)	14 (3%)	13 (4%)	16 (4%)
Unknown	9%	13%		
BRAF mutation, *n* (%)				
No BRAF mutation	199 (60%)	150 (35%)	206 (60%)	163 (35%)
BRAF mutation	132 (40%)	277 (65%)	138 (40%)	300 (65%)
Unknown	4%	8%		
Serum LDH (U/L), *n* (%)				
Normal (< 250)	261 (78%)	334 (74%)	269 (78%)	342 (74%)
Elevated (≥ 250)	72 (22%)	119 (26%)	75 (22%)	121 (26%)
Unknown	3%	2%		
AJCC M-stage, *n* (%)				
M0	13 (4%)	8 (2%)	14 (4%)	8 (2%)
M1a	36 (11%)	38 (8%)	38 (11%)	39 (8%)
M1b	46 (14%)	45 (10%)	47 (14%)	46 (10%)
M1c	243 (72%)	365 (80%)	245 (71%)	370 (80%)
Unknown	2%	2%		
Brain metastases, *n* (%)				
No	264 (78%)	329 (73%)	267 (78%)	337 (73%)
Yes	75 (22%)	123 (27%)	77 (22%)	126 (27%)
Unknown	1%	2%		
Time from the diagnosis of metastatic melanoma to the start of ipilimumab, months				
Median (95% CI)	0.8 (0.2-8.7)	4.2 (0.2-16.7)	0.8 (0.2-8.7)	4.2 (0.2-16.7)

AJCC, American Joint Committee on Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; *n*, number.

[a]Average results of all imputed datasets.



Supplemental Figure. Overall survival by LDH, ECOG, and M-stage
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

8 Real-world healthcare costs of ipilimumab in patients with advanced cutaneous melanoma in the Netherlands

Franken MG, Leeneman B, Jochems A, Schouwenburg MG, Aarts MJB, van Akkooi ACJ, van den Berkmortel FWPJ, van den Eertwegh AJM, de Groot JWB, van der Hoeven JJM, Hospers GAP, Kapiteijn E, Koornstra RH, Kruit WHJ, Louwman MWJ, Piersma D, van Rijn RS, Suijkerbuijk KPM, ten Tije AJ, Vreugdenhil G, Wouters MWJM, van Zeijl M, Haanen JBAG, Uyl-de Groot CA

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ABSTRACT

There is limited evidence on the costs associated with ipilimumab. We investigated healthcare costs of all Dutch patients with advanced cutaneous melanoma who were treated with ipilimumab. Data were retrieved from the nationwide Dutch Melanoma Treatment Registry. Costs were determined by applying unit costs to individual patient resource use. A total of 807 patients who were diagnosed between July 2012 and July 2015 received ipilimumab in Dutch practice. The mean (median) episode duration was 6.27 (4.61) months (computed from the start of ipilimumab until the start of a next treatment, death, or the last date of follow-up). The average total healthcare costs amounted to €81,484 but varied widely (range: €18,131-€160,002). Ipilimumab was by far the most important cost driver (€73,739). Other costs were related to hospital admissions (€3,323), hospital visits (€1,791), diagnostics and imaging (€1,505), radiotherapy (€828), and surgery (€297). Monthly costs for resource use other than ipilimumab were €1,997 (SD: €2,629). Treatment-naive patients (*n*=344) had higher total costs compared with previously-treated patients (*n*=463; €85,081 versus €78,811). Although patients with colitis (*n*=106) had higher costs for resource use other than ipilimumab (€11,426) compared with patients with other types of immune-related adverse events (*n*=90; €9,850) and patients with no immune-related adverse event (*n*=611; €6,796), they had lower total costs (€76,075 versus €87,882 and €81,480, respectively). In conclusion, this nationwide study provides valuable insights into the healthcare costs of advanced cutaneous melanoma patients who were treated with ipilimumab in clinical practice. Most of the costs were attributable to ipilimumab, but the costs and its distribution varied considerably across subgroups.

INTRODUCTION

The global incidence of cutaneous melanoma has been increasing over the last few decades. In 2012, a total of 232,130 new cases were diagnosed worldwide.[167] Most patients have a rather favorable prognosis because melanoma is most often (84%) diagnosed at the local stage.[168] Metastatic melanoma remains, however, incurable and, for many years, survival has been poor, with reported 1-year survival rates of 25%[169] to 35%[15], and 5-year survival rates of 6%[94] to 15%.[15]

Historically, treatment options have been limited. Before 2011, dacarbazine, temozolomide, high-dose interleukin-2, interferon α, and paclitaxel were common treatments for patients with metastatic melanoma.[95,170] However, these treatments have shown no or only modest response rates, and have never been shown to prolong survival.[86,94,95] In March 2011, the Food and Drug Administration approved the immune checkpoint inhibitor ipilimumab for patients with advanced (unresectable stage III or metastatic) melanoma.[79] European approval of the European Medicines Agency followed in May 2011.[171] Ipilimumab was the first novel agent that showed a prolonged survival compared with the glycoprotein 100 vaccine in the MDX010-20 phase III trial[80] in previously-treated patients (median overall survival [OS]: 10.1 versus 6.4 months). In 2011, the survival benefit of ipilimumab was also shown in treatment-naive patients (median OS of 11.2 months for patients receiving ipilimumab plus dacarbazine versus 9.1 months for patients receiving dacarbazine alone).[160] As it was the first novel treatment, it has been used widely in the USA and Europe after its Food and Drug Administration and European Medicines Agency approval.[172] Both the European Society for Medical Oncology and the National Comprehensive Cancer Network in the USA recommended the use of ipilimumab for advanced melanoma in their guidelines.[173-175]

Although most novel cancer treatments can be effective and can be of great value for cancer patients, they most often come, however, at high acquisition costs. In the context of increasing healthcare expenditures and limited resources, it is of utmost importance that all stakeholders are well informed on the actual healthcare costs of treating patients with these novel cancer treatments. There is, however, limited evidence on healthcare costs attributable to ipilimumab treatment. The literature only reports on studies describing healthcare costs before the introduction of ipilimumab[67,176-179], healthcare costs excluding the drug costs of ipilimumab[163], management costs of immune-related adverse events (irAEs)[180], management costs of irAEs on the basis of expert opinion[181], costs on the basis of low number of patients (n=11[182]; n=29[180]), and savings related to dose rounding of ipilimumab.[183]

Therefore, we investigated real-world healthcare costs of all patients with advanced cutaneous melanoma who received ipilimumab in clinical practice in the Netherlands and compared healthcare costs across subgroups of patients.

PATIENTS AND METHODS

Patients and data

All data were retrieved from the nationwide Dutch Melanoma Treatment Registry (DMTR). The DMTR contains data on all advanced melanoma patients in the Netherlands in terms of baseline characteristics, type of treatment and regime, dosages, irAEs, time to next treatment, survival, and healthcare resource use. The DMTR was approved by the medical ethical committee and was not subject to the Medical Research Involving Human Subjects Act. A detailed description of the DMTR has been published elsewhere.[138] All patients who received ipilimumab were included if they were diagnosed with advanced cutaneous melanoma between July 2012 and July 2015. The data cutoff was March 20, 2016.

Resource use and unit costs

Healthcare costs were determined by applying unit costs to individual patient resource use. The following cost components were included: hospital admissions, hospital visits, day-care treatments, molecular diagnostic tests, medical imaging, surgical procedures, radiotherapy, and ipilimumab. Table 1 presents the unit costs. All costs were based on Euro 2016 prices; where necessary, costs were adjusted to 2016 prices using the general price index from the Dutch Central Bureau of Statistics.[71] Unit costs for a hospital admission, hospital visit, and day-care treatment were based on the Dutch costing manual.[68] Costs of diagnostic tests, medical imaging, radiotherapy, and surgical procedures were valued using the tariffs issued by the Dutch Healthcare Authority.[184] Acquisition costs of ipilimumab were retrieved from the Dutch drug database.[70] Ipilimumab costs were based on actually applied dosages per individual patient (assuming no vial sharing, i.e., including wastage).

Statistical analyses

Total costs were determined from the start of ipilimumab until the start of a next line of systemic treatment, death, or the last date of follow-up (further called ipilimumab episode). Costs were reported as the average total costs and, for healthcare resource use other than ipilimumab, as average costs per month (to correct for differences in follow-up). To compare costs between specific subgroups, patients were stratified according to treatment status (treatment-naive versus previously treated) and irAE (no irAE versus any irAE, colitis, and irAE other than colitis). To assess the impact of follow-up status, costs were also compared for patients who were still within the ipilimumab episode at the end of follow-up (censored patients) and for patients who had finished the ipilimumab episode because they had started a new line of treatment, or because they died.

In addition to descriptive statistics, differences between patient groups for non-normally distributed continuous variables were assessed using the Kruskal-Wallis test for more than two related samples and the Mann-Whitney test for pairwise tests. Ordinal and categorical variables were

Table 1. Unit costs

	Euro 2016
Hospital admission	
Inpatient hospital day	€480.29
Intensive care unit day	€1,196.70
Visits	
Day-care	€278.49
Hospital visit	€91.82
Diagnostics and imaging	
Gene mutation	€754.72
PET-CT scan	€933.79
MRI scan	€263.34
CT scan	€165.55
Surgery	
Skin/subcutis	€1,764.47
Lymph node	€1,764.47
Soft tissues/bones	€2,908.23
Stomach/pancreas/milt	€6,050.08
Colon	€5,024.74
Brain	€4,371.12
Radiotherapy	
Radiotherapy only	€1,956.86
Radiotherapy and hyperthermia	€17,760.38
Ipilimumab (5 mg/ml)	
10ml	€4,250.00
40ml	€17,000.00

mg, milligram; mg/ml, milligrams per milliliter.

compared using the two-tailed chi-squared test. The mean absolute duration of the ipilimumab episode was computed from the start of ipilimumab until the start of a new systemic treatment, death, or the last date of follow-up. Differences were considered statistically significant when p-values were less than or equal to an α of 0.05. All analyses were carried out using the STATA statistical analyses software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

RESULTS

Baseline characteristics and immune-related adverse events

Table 2 shows the baseline patient characteristics at the start of ipilimumab for all patients and by subgroup. A total of 807 patients received ipilimumab in clinical practice. Most patients were men (59%), diagnosed with stage M1c disease (75%), had an Eastern Cooperative Oncology

Table 2. Baseline characteristics at the start of ipilimumab by subgroup

	All patients	Treatment-naive patients	Previously-treated patients	p-value[a]	No irAE	Colitis	Other type of irAE	p-value[a]
	n=807	*n*=344	*n*=463	TN versus PT	*n*=611	*n*=106	*n*=90	irAE groups
Age, years								
Median (95% CI)	61 (39-78)	64 (41-79)	60 (38-76)	<0.001	60 (37-78)	62 (42-78)	65 (42-81)	0.039[b]
Gender, *n* (%)								
Male	477 (59%)	213 (62%)	264 (57%)	0.162	360 (59%)	60 (57%)	57 (63%)	0.622
Female	330 (41%)	131 (38%)	199 (43%)		251 (41%)	46 (43%)	33 (37%)	
Performance status (ECOG), *n* (%)								
0	471 (58%)	213 (62%)	258 (56%)	0.139	346 (57%)	64 (60%)	61 (68%)	0.447
1	218 (27%)	89 (26%)	129 (28%)		170 (28%)	29 (27%)	19 (21%)	
≥2	26 (3%)	12 (3%)	14 (3%)		23 (4%)	2 (2%)	1 (1%)	
Unknown	92 (11%)	30 (9%)	62 (13%)		72 (12%)	11 (10%)	9 (10%)	
BRAF mutation, *n* (%)								
Not determined	35 (4%)	10 (3%)	25 (5%)	0.118	30 (5%)	3 (3%)	2 (2%)	0.669
Determined	771 (96%)	333 (97%)	438 (95%)		580 (95%)	103 (97%)	88 (98%)	
BRAF wildtype	349 (45%)	199 (60%)	150 (34%)	<0.001	253 (44%)	48 (47%)	48 (55%)	0.168
BRAF mutation	409 (53%)	132 (40%)	277 (63%)		319 (55%)	53 (51%)	37 (42%)	
Unknown	13 (2%)	2 (1%)	11 (3%)		8 (1%)	2 (2%)	3 (3%)	
Unknown	1 (0%)	1 (0%)	0 (0%)		1 (0%)	0 (0%)	0 (0%)	
Serum LDH (U/L), *n* (%)								
Normal (< 250)	595 (74%)	261 (76%)	334 (72%)	0.213	440 (72%)	81 (76%)	74 (82%)	0.287
Elevated (≥ 250)	191 (24%)	72 (21%)	119 (26%)		153 (25%)	23 (22%)	15 (17%)	
Unknown	21 (3%)	11 (3%)	10 (2%)		18 (3%)	2 (2%)	1 (1%)	
AJCC M-stage, *n* (%)								
M0	21 (3%)	13 (4%)	8 (2%)	0.076	15 (2%)	3 (3%)	3 (3%)	0.348
M1a	74 (9%)	36 (10%)	38 (8%)		56 (9%)	8 (8%)	10 (11%)	
M1b	91 (11%)	46 (13%)	45 (10%)		60 (10%)	14 (13%)	17 (19%)	

Table 2. Baseline characteristics at the start of ipilimumab by subgroup (continued)

	All patients	Treatment-naive patients	Previously-treated patients	p-value[a]	No irAE	Colitis	Other type of irAE	p-value[a]
	n=807	*n*=344	*n*=463	TN versus PT	*n*=611	*n*=106	*n*=90	irAE groups
M1c	608 (75%)	243 (71%)	365 (79%)		469 (77%)	80 (75%)	59 (66%)	
Unknown	13 (2%)	6 (2%)	7 (2%)		11 (2%)	1 (1%)	1 (1%)	
Brain metastases, *n* (%)								
No	593 (73%)	264 (77%)	329 (71%)	0.17	444 (73%)	81 (76%)	68 (76%)	0.248
Yes	198 (25%)	75 (22%)	123 (27%)		158 (26%)	21 (20%)	19 (21%)	
Asymptomatic	97 (49%)	36 (48%)	61 (50%)	0.029	70 (44%)	11 (52%)	16 (84%)	0.026[c]
Symptomatic	91 (46%)	39 (52%)	52 (42%)		79 (50%)	9 (43%)	3 (16%)	
Unknown	10 (5%)	0 (0%)	10 (8%)		9 (6%)	1 (5%)	0 (0%)	
Unknown	16 (2%)	5 (1%)	11 (2%)		9 (1%)	4 (4%)	3 (3%)	
Comorbidities, *n* (%)								
0	375 (46%)	152 (44%)	223 (48%)	0.669	286 (47%)	51 (48%)	38 (42%)	0.924
1	203 (25%)	92 (27%)	111 (24%)		150 (25%)	28 (26%)	25 (28%)	
≥2	211 (26%)	93 (27%)	118 (25%)		160 (26%)	26 (25%)	25 (28%)	
Unknown	18 (2%)	7 (2%)	11 (2%)		15 (2%)	1 (1%)	2 (2%)	
Other malignancy, *n* (%)								
No	343 (43%)	148 (43%)	195 (42%)	0.306	259 (42%)	42 (40%)	42 (47%)	0.197
Yes	116 (14%)	56 (16%)	60 (13%)		81 (13%)	23 (22%)	12 (13%)	
Unknown	348 (43%)	140 (41%)	208 (45%)		271 (44%)	41 (39%)	36 (40%)	
Time from diagnosis, months								
Median (95% CI)	1.9 (0.2-15.2)	0.8 (0.2-8.7)	4.2 (0.2-16.7)	<0.001	2.1 (0.2-14.9)	1.6 (0.2-16.4)	1.4 (0.2-13.5)	0.763

TN, treatment-naïve patients; PT, previously-treated patients; irAE, immune-related adverse event; AJCC, American Joint Committee on Cancer staging system; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; *n*, number.

[a]Differences between patient groups for non-normal distributed continuous variables were assessed using the Kruskal-Wallis test for more than two related samples and the Mann-Whitney test for pair-wise tests; ordinal and categorical variables were compared using the two-tailed chi-squared test.

[b]No irAE versus other irAE (p=0.016).

[c]No irAE versus other irAE (p=0.004).

Group (ECOG) performance status of 0-1 (85%), and had a normal LDH level (74%). Patients more often had been treated previously (57%) than treatment-naive (43%). Before ipilimumab, previously-treated patients received either chemotherapy (34%), targeted therapy with vemurafenib or dabrafenib (30%), treatment within a clinical trial (11%), or other types of (25%) treatments (e.g., combination of different treatments). Most patients did not experience an irAE (76%). Of the patients who experienced an irAE, 54% had colitis (*n*=106). The other irAEs (*n*=90) were hypophysitis (19%), skin-related (8%), adrenal insufficiency (8%), thyroiditis (8%), elevated liver enzymes (6%), neurological (3%), bone marrow suppression (3%), and other types of irAE (17%). Although some statistically significant differences were present, most of the baseline characteristics were similar across subgroups.

Costs

Table 3 presents a breakdown of the average total healthcare costs and the average monthly costs per patient. The total costs amounted to €81,484 (median: €88,032) but varied widely between patients (range: €18,131-€160,002). Patients less than 1 year within the ipilimumab episode (*n*=722; 89%) had lower total costs (€79,684) compared with patients between 1 and 2 years (*n*=71; 9%; €95,261) and patients more than 2 years (*n*=14; 2%; €104,451) in the ipilimumab episode.

Ipilimumab was by far the most important cost driver; 90.5% of the costs were attributable to ipilimumab (see Figure 1). Most patients (65%) received four cycles of ipilimumab; 12%, 14%, and 9% received three, two, or one cycles, respectively. Patients less than 1 year in the ipilimumab episode less often received all four cycles of ipilimumab (62%) compared with patients between 1 and 2 years (89%) and patients more than 2 years (100%) in the ipilimumab episode. The average dosage received was 240 mg (SD: 45.6 mg; range: 100-435 mg). This resulted in an average of €73,739 (median: €85,024) drug costs for ipilimumab (range: €12,756-€153,024; note that costs were computed per vial including wastage, i.e., assuming no vial sharing).

The other 9.5% of healthcare costs (€7,745) were related to hospital admissions, hospital visits, diagnostics and imaging, radiotherapy, and surgery (4.1%, 2.2%, 1.8%, 1.0%, and 0.4%, respectively). Although more than half of the patients (56%) were admitted to a hospital, only 3.5% were admitted to an ICU. Patients who were admitted to a hospital stayed on average 11.7 (median: 8) days in the hospital. Nine patients only had one day of admission, whereas four patients had 60 or more days of admission. One patient was admitted to a hospital for 125 days (in total, nine different admissions). Generally, total costs for resource use other than ipilimumab increased where patients were more than one year in the ipilimumab episode (<1 year: €7,461; ≥1 and <2 years: €9,999; ≥2 years: €10,927).

Table 3. Breakdown of the average total costs and monthly costs per patient (Euro 2016 prices)

	All patients					
	n=807					
	Number of patients	Frequency of HRU	Average total costs		Average costs per month	
			Average	SD	Average	SD
Hospital admissions, mean (SD) of all patients			€3,323	€5,420	€1,004	€2,246
Inpatient hospital day	455	6.57 (10.42)	€3,155	€5,005	€960	€2,175
Intensive care unit day	28	0.14 (1.37)	€168	€1,634	€44	€426
Hospital visits			€1,791	€733	€397	€205
Daycare treatment	807	3020	€1,042	€383	€244	€146
Hospital visit	766	6580	€749	€515	€153	€97
Diagnostic and imaging tests			€1,505	€956	€373	€458
Gene mutation	785	785	€734	€123	€223	€287
PET-CT	174	250	€289	€671	€60	€191
MRI	321	607	€198	€351	€38	€68
CT	476	1384	€284	€365	€52	€100
Surgery			€297	€1,153	€43	€179
Skin/subcutis	20	26	€57	€379	€8	€64
Lymph node	14	15	€33	€254	€5	€47
Soft tissues/bones	10	10	€36	€322	€7	€73
Stomach/pancreas/milt	1	1	€8	€213	€0	€7
Colon	12	12	€75	€609	€12	€116
Brain	11	13	€70	€631	€8	€84
Other	4	4	€19	€255	€2	€28
Radiotherapy			€828	€2,104	€180	€512
Radiotherapy only	221	269	€652	€1,212	€146	€316
Radiotherapy plus hyperthermia	8	8	€176	€1,761	€34	€412
Total resource use other than ipilimumab						
Mean, SD			€7,745	€6,507	€1,997	€2,629
Median			€5,672		€1,198	
Minimum-maximum			€1,114-€65,185		€66-€42,032	
Ipilimumab, number of cycles						
Mean, SD		3.33 (1.02)	€73,739	€26,655		
Median		4	€85,024			
Minimum-maximum		1-4	€12,756-€ 153,024			
Total health care costs including ipilimumab						
Mean, SD			€81,484	€27,100		
Median			€88,032			
Minimum-maximum			€18,131-€160,002			

HRU, healthcare resource use; *n*, number; SD, standard deviation.

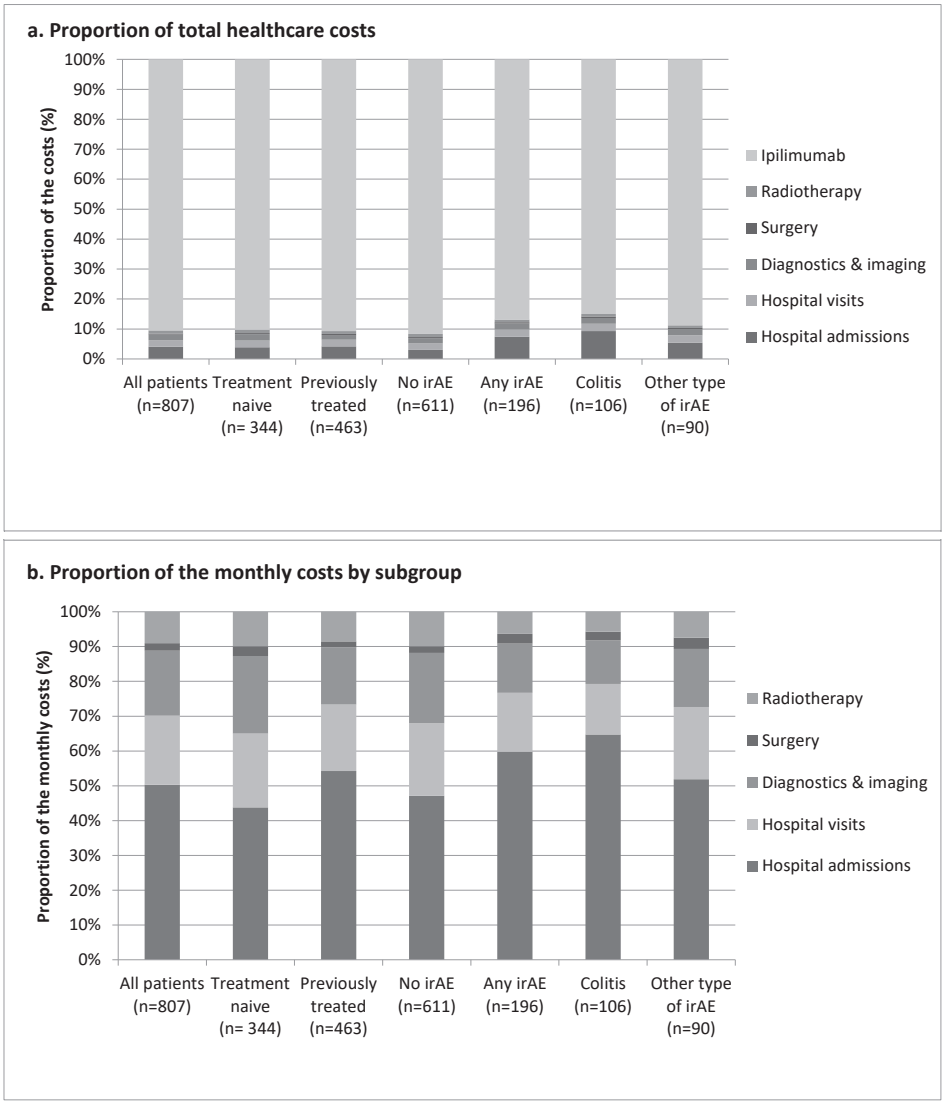


Figure 1. Proportion of the total healthcare costs (a) and proportion of monthly costs of resource use other than ipilimumab by subgroup (b)
irAE, immune-related adverse event; *n*, number.

The average monthly costs for healthcare resource use other than ipilimumab were €1,997 (median: €1,198; mean episode duration: 6.27 months [SD: 5.49]). Some patients (*n*=26) had an episode shorter than a month (seven patients ≤2 weeks and two patients ≤1 week); this pushed the monthly costs upwards and explains the rather high maximum (€42,032). Excluding these 26 patients yields average monthly costs of €1,792 (maximum: €15,121). Similar, excluding seven or two patients with a duration less than or equal to two weeks or less than or equal to one week

yields average monthly costs of €1,895 (maximum: €21,421) and €1,927 (maximum: €21,421), respectively. Generally, the average monthly costs for healthcare resource use other than ipilimumab decreased in case patients were more than one year in the ipilimumab episode (<1 year: €2,161; ≥1 and <2 years: €650; ≥2 years: €347).

Table 4 presents the average total healthcare costs and the monthly costs for different subgroups. Total costs were different for treatment-naive and previously-treated patients (€85,081 versus €78,811; p=0.003). Of the previously-treated patients, patients who received chemotherapy before ipilimumab had higher total costs (€84,838) compared with patients who received treatment within a trial (€79,653) and patients who received targeted treatment (€72,569) before ipilimumab (see Supplemental Table 1).

Table 4 and Figure 1 show that the total costs and the proportion of the costs are distributed differently across the subgroups. Although patients with colitis had the lowest total mean costs (€76,075) and the lowest mean costs for ipilimumab (€64,650), they had the highest costs for resource use other than ipilimumab (€11,426). Patients who did not experience an irAE had the lowest costs for resource use other than ipilimumab (€6,796).

Table 4 also shows the mean duration of the ipilimumab episode. Treatment-naive and previously-treated patients had comparable episode durations (6.62 and 6.02 months, respectively). Patients who experienced an irAE had a longer episode duration compared with patients with no irAE (7.39 versus 5.92 months; p<0.001). Patients with irAEs other than colitis had a longer episode duration (7.96 months) compared with patients with no irAE (5.92 months; p<0.001) and patients with colitis (6.91 months; p=0.035).

After correction for differences in the duration of the ipilimumab episode, patients with colitis had the highest monthly healthcare costs (€2,339) and patients with other types of irAE had the lowest (€1,734) monthly healthcare costs besides ipilimumab. Figure 1b shows the proportion of the monthly costs for resource use other than ipilimumab by subgroup.

Most of the patients finished the ipilimumab episode (i.e., 80% of the patients died or progressed to a next line of systemic treatment). Figure 2 presents the total healthcare costs and monthly costs excluding ipilimumab by status of the patient (see Supplemental Table 2). Total healthcare costs were lower for patients who died during the episode (*n*=267) compared with patients who progressed to a next line of systemic treatment (*n*=381; €71,030 versus €84,426). Because of the fact that ipilimumab was the most important cost driver, a similar difference was observed for drug costs of ipilimumab (€61,316 versus €77,960). However, patients who died had higher costs for resource use other than ipilimumab compared with patients who progressed to a next line of systemic treatment (€9,715 versus €6,466). This difference was more pronounced after correction

Table 4. Total healthcare costs and monthly costs for resources other than ipilimumab by subgroup (Euro 2016 prices)

	Hospital admissions	Hospital visits	Diagnostics and imaging	Surgery	Radiotherapy	Total HRU without ipilimumab	Ipilimumab	Total costs
All patients *n*=807; mean (median) episode duration=6.27 (4.61) months								
Average costs	€3,323	€1,791	€1,505	€297	€828	€7,745	€73,739	€81,484
SD	€5,420	€733	€956	€1,153	€2,104	€6,507	€26,655	€27,100
Average monthly costs	€1,004	€397	€373	€43	€180	€1,997		
SD	€2,246	€205	€458	€179	€512	€2,629		
Stratification according to treatment status								
Treatment-naive *n*=344; mean (median) episode duration=6.62 (5.05) months								
Average costs	€3,297	€1,908	€1,851	€320	€900	€8,276	€76,805	€85,081
SD	€6,148	€694	€971	€1,153	€2,133	€7,131	€24,845	€25,144
Average monthly costs	€779	€376	€397	€49	€176	€1,778		
SD	€1,586	€191	€553	€197	€388	€2,028		
Previously-treated *n*=463; mean (median) episode duration=6.02 (4.34) months								
Average costs	€3,342	€1,704	€1,248	€280	€775	€7,350	€71,462	€78,811
SD	€4,815	€750	€860	€1,154	€2,083	€5,979	€27,731	€28,197
Average monthly costs	€1,171	€413	€354	€38	€183	€2,159		
SD	€2,620	€215	€371	€164	€587	€2,990		
Stratification according to immune-related adverse events								
No irAE *n*=611; mean (median) episode duration=5.92 (4.28) months								
Average costs	€2,462	€1,727	€1,456	€285	€867	€6,796	€74,684	€81,480
SD	€4,054	€708	€934	€1,178	€2,298	€5,476	€27,247	€27,766
Average monthly costs	€931	€413	€399	€38	€196	€1,976		
SD	€2,339	€213	€513	€165	€571	€2,776		
Any irAE *n*=196; mean (median) episode duration=7.39 (5.77) months								
Average costs	€6,007	€1,990	€1,661	€335	€709	€10,702	€70,795	€81,497
SD	€7,774	€775	€1,009	€1,073	€1,324	€8,343	€24,551	€24,977
Average monthly costs	€1,232	€349	€291	€57	€131	€2,061		
SD	€1,915	€170	€181	€217	€247	€2,114		
Colitis *n*=106; mean (median) episode duration=6.91 (4.92) months								
Average costs	€7,067	€1,842	€1,517	€353	€646	€11,426	€64,650	€76,075
SD	€7,645	€676	€834	€1,055	€1,315	€8,113	€24,792	€24,894
Average monthly costs	€1,514	€340	€293	€58	€134	€2,339		
SD	€2,166	€149	€182	€206	€261	€2,345		

Table 4. Total healthcare costs and monthly costs for resources other than ipilimumab by subgroup (Euro 2016 prices) (continued)

	Hospital admissions	Hospital visits	Diagnostics and imaging	Surgery	Radiotherapy	Total HRU without ipilimumab	Ipilimumab	Total costs
Other types of irAE *n*=90; mean (median) episode duration=7.96 (6.38) months								
Average costs	€4,759	€2,165	€1,829	€314	€783	€9,850	€78,032	€87,882
SD	€7,781	€848	€1,164	€1,100	€1,338	€8,573	€22,305	€23,655
Average monthly costs	€900	€360	€289	€57	€128	€1,734		
SD	€1,514	€193	€180	€230	€230	€1,760		

HRU, healthcare resource use; irAE, immune-related adverse event; *n*, number; SD, standard deviation.

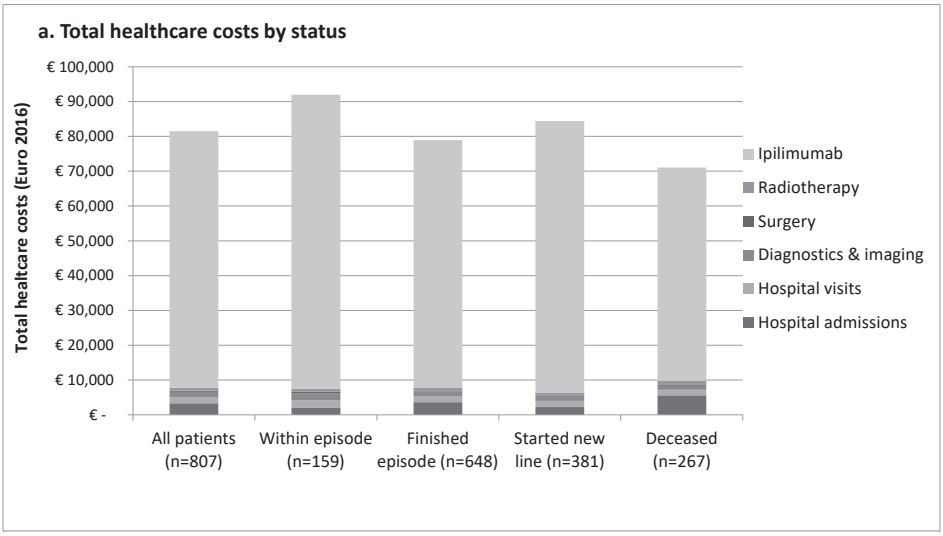
for duration (monthly costs: €3,159 versus €1,624). The difference was mainly because of higher costs for hospital admissions (€5,635 versus €2,203) and radiotherapy (€1,138 versus €597) for patients who died.

The 20% of censored patients (i.e., patients who were still within the ipilimumab episode because they were still alive and had not [yet] progressed to a next line of treatment) had, compared with patients who finished the episode, higher total healthcare costs (€91,989 versus €78,906), a longer ipilimumab duration (11.21 versus 5.06 months), and lower monthly costs for resource use other than ipilimumab (€939 versus €2,257).

DISCUSSION

We investigated the healthcare costs of all Dutch patients with advanced cutaneous melanoma who received ipilimumab in clinical practice. The average total healthcare costs were €81,484, but the costs varied markedly across subgroups of patients. Drug costs of ipilimumab were by far the most important cost driver, accounting for 85%-92% of the total healthcare costs across all subgroups. The average monthly costs for resources other than ipilimumab were €1,997 during the ipilimumab episode.

A noteworthy finding is that patients with colitis had the lowest total costs (€76,075). They had lower total costs compared patients with no irAE (€81,480) as well as compared with patients with irAEs other than colitis (€87,882). This difference was mainly because of the lower drug costs of ipilimumab for patients with colitis. More specifically, patients with colitis received fewer cycles of ipilimumab (mean 2.9 versus 3.4 and 3.5 for patients with colitis, patients with no



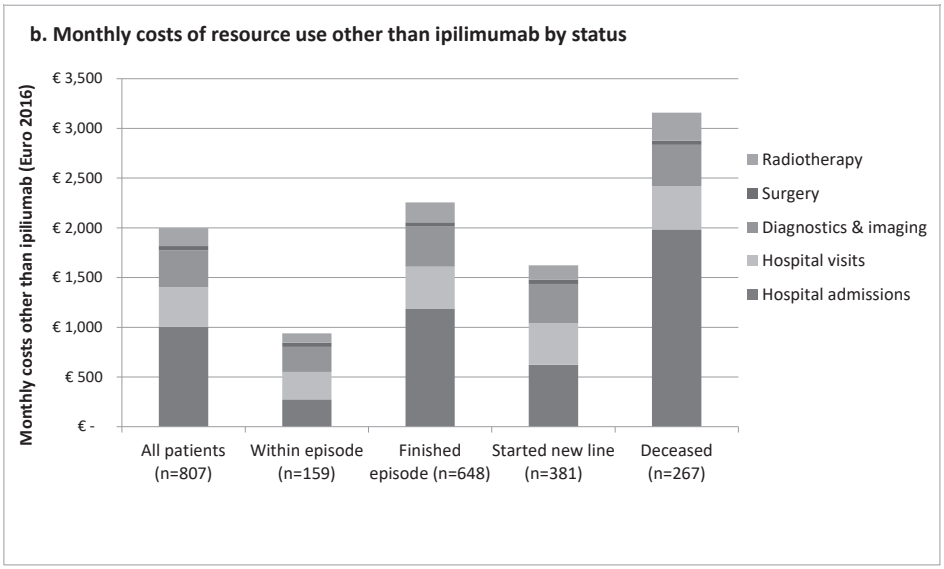


Figure 2. Total healthcare costs (a) and monthly costs of resource use other than ipilimumab by status (b)
n, number.

irAE, and patients with irAEs other than colitis, respectively). In contrast, healthcare costs for resources other than ipilimumab were higher for patients with colitis (€11,426) compared with patients with other types of irAEs (€9,850) and patients with no irAE (€6,796).

Interestingly, patients with an irAE other than colitis had a longer ipilimumab episode duration (mean [median]: 7.96 [6.38] months) compared with patients with no irAE (5.92 [4.28] months) and patients with colitis (6.91 [4.92] months). Other studies[180,185-187] previously observed that

patients who experienced autoimmune toxicity had improved response rates and/or survival. However, to our knowledge, no study has previously indicated that this benefit may be more favorable in patients with autoimmune toxicities other than colitis. Our observed differences in (absolute) episode duration across the irAE subgroups were consistent in case of using the outcome measures time to next treatment and OS by means of the Kaplan-Meier method.

Another finding is that treatment-naive patients had higher total costs compared with previously-treated patients (€85,081 versus €78,811). This difference was also mainly because of the drug costs of ipilimumab (€76,805 versus €71,262). Treatment-naive patients more often received all four cycles of ipilimumab (70% versus 62%) and less often discontinued treatment because of disease progression (14% versus 25%). To our knowledge, no previous study has compared healthcare costs between treatment-naive and previously-treated patients.

Previous studies[67,176-179] reported on healthcare costs before the introduction of ipilimumab. Because of study heterogeneity, it is, however, rather difficult to compare outcomes. Some studies[177,178] report the annual budget impact for a specific country or report lifetime costs. Nonetheless, healthcare costs were generally lower in the time before the introduction of ipilimumab. For example, Seidler et al.[179] reported annual costs of US$23,285 (≈€21,047) and Tsao et al.[67] reported annual costs of US$42,410 (≈€38,334) for patients with stage IV disease.

Although other studies reported on healthcare costs associated with ipilimumab, the available evidence is limited and rather difficult to compare with our study. One study in Spain[182] reported on only 11 patients. As costs are most often highly skewed, their outcomes are likely not sufficiently valid for comparison. Another study in the UK[180] reported costs related to the management of ipilimumab toxicities of 29 patients (including 12 patients with colitis). They reported mean costs of GBP4,851 (≈€5,937) for patients with an irAE and GBP6,355 (≈€7,778) for patients with colitis. This is lower than our results on resource use other than ipilimumab (€10,702 and €11,426, respectively). This may be related to their low number of patients and/or the inclusion of patients with zero cost but excluding these zero cost patients would still yield lower costs. We included, however, most of the healthcare costs other than ipilimumab (including costs for disease management) and not only costs related to toxicities. This increased our cost estimates. However, our cost estimates may still be an underestimation of real healthcare costs as we did not include costs for concomitant medication. For example, of all our patients with an irAE (*n*=196), 70% were treated with corticosteroids and 29% were treated with immunosuppressive agents.

Tarhini et al.[163] reported on monthly healthcare costs excluding drug costs of ipilimumab of 273 treatment-naive patients in the USA. They reported monthly costs in three (not mutually exclusive) periods: during ipilimumab (US$690 [≈€624]), postregimen (US$2,151 [≈€1,944]), and within 90 days before death (US$5,123 [≈€4,631]). In our data, we could not make such

a distinction. Even though Tarhini et al.[163] included costs for subsequent systemic treatment, our monthly costs (€1,997 all patients and €1,778 treatment-naive patients) were higher than the treatment period and reasonably comparable to the postregimen period costs. However, our monthly costs included costs of patients before death (33% of our patients) who had significantly higher monthly costs (€3,159) because of their relatively short episode duration. Similar to their findings, the total costs for resources other than ipilimumab were higher for patients with a worse performance status and patients with an irAE.

Barzey et al.[181] carried out a cost-effectiveness analysis and modeled lifetime costs of ipilimumab for previously-treated patients. The model inputs for costs of ipilimumab were based on the dosing regimen of ipilimumab in the MDX010-20 trial.[80] Their total drug costs for ipilimumab (US$114,735 [≈€103,709]) were higher than those in our study in which patients received ipilimumab in clinical practice (€73,739 all patients and €71,462 for previously-treated patients). This difference can be explained partly by the greater number of ipilimumab cycles that patients received in their economic model. In addition, their applied cycle costs of ipilimumab (US$30,000 [≈€27,117]) were fixed and almost 23% higher than our average cycle costs (€22,082). Our cycle costs were based on individual patient dosages (mean: 240 mg; range: 100-435 mg) and the Dutch unit price of ipilimumab. The lifetime costs for resources other than ipilimumab cannot be validly compared with our results. First, their cost input for disease management was based on melanoma patients not treated with ipilimumab and their cost input for toxicity management was based on expert opinion and published data. Second, Barzey et al.[181] modeled lifetime costs, whereas we computed costs from the start of ipilimumab until the start of a next systemic treatment, death, or the last date of follow-up.

Consequently, censoring of costs for resource use other than ipilimumab has occurred in our study, which can be considered a limitation. We believe, however, that the impact is rather limited. First, we had complete follow-up of most of our patients (i.e., 80% of the patients had finished the ipilimumab episode). Second, censoring of costs only occurred for costs related to resource use other than ipilimumab as ipilimumab is administered in the first 3 months. Third, we corrected for differences in follow-up by presenting monthly costs of resource use other than ipilimumab. Finally, we separately presented costs for patients who had finished the episode (i.e., complete follow-up data) as well as for patients who were censored (i.e., did not finish the episode). Our results showed that censored patients had higher total healthcare costs, a longer ipilimumab duration, and lower monthly costs for resources other than ipilimumab. Thus, the censored patients represent patients with relatively favorable survival outcomes. In case of a longer follow-up, the total costs most likely increase (patients are still monitored), whereas monthly costs for resources other than ipilimumab will decrease.

Another limitation to our study may be that it was based on observational data. This may have led to some degree of reporting bias. We believe, however, that the observational nature is a strength of our study. We used data from a nationwide registry (DMTR) and could thus include all patients who received ipilimumab in Dutch clinical practice. Furthermore, the DMTR was set up to ensure safety and quality of care in the Netherlands. To ensure high-quality data, data managers received multiple training sessions and were supervised by oncologists who validated all patient-level data.[138]

CONCLUSION

In the context of increasing healthcare expenditures, it is crucial to gain insights into healthcare costs associated with the ongoing introduction of novel cancer treatments, especially because of the rapidly changing treatment paradigm in cutaneous melanoma, where many novel cancer treatments are highly expensive, and quite often, used until progression and/or used in combination with other expensive novel treatments. To our knowledge, this is the first nationwide study of real-world healthcare costs of advanced cutaneous melanoma patients treated with ipilimumab in clinical practice. Most of the healthcare costs were attributable to the drug costs of ipilimumab, but the costs varied across subgroups of patients.

SUPPLEMENTARY MATERIAL

Supplemental Table 1. Total healthcare costs and monthly costs for resources other than ipilimumab by subgroup of previously-treated patients (Euro 2016 prices)

	Hospital admissions	Hospital visits	Diagnostics and imaging	Surgery	Radiotherapy	Total HRU without ipilimumab	Ipilimumab	Total costs
All previously-treated patients *n*=463; mean (median) episode duration=6.02 (4.34) months								
Average costs	€3,342	€1,704	€1,248	€280	€775	€7,350	€71,462	€78,811
SD	€4,815	€750	€860	€1,154	€2,083	€5,979	€27,731	€28,197
Average monthly costs	€1,171	€413	€354	€38	€183	€2,159		
SD	€2,620	€215	€371	€164	€587	€2,990		
Stratified by prior treatment								
Previously received chemotherapy *n*=156; mean (median) episode duration=7.46 (5.39) months								
Average costs	€2,938	€1,845	€1,287	€313	€679	€7,064	€77,774	€84,838
SD	€4,730	€736	€1,107	€1,042	€2,143	€5,907	€26,558	€27,408
Average monthly costs	€760	€367	€257	€45	€115	€1,545		
SD	€1,419	€204	€213	€188	€322	€1,691		
Previously received targeted therapy[a] *n*=139; mean (median) episode duration=5.43 (3.55) months								
Average costs	€2,965	€1,603	€1,144	€202	€747	€6,660	€65,909	€72,569
SD	€3,720	€799	€743	€1,390	€1,871	€5,106	€28,964	€29,205
Average monthly costs	€1,446	€447	€410	€10	€187	€2,499		
SD	€3,870	€230	€465	€55	€438	€4,277		
Previously received treatment within a trial *n*=53; mean (median) episode duration=5.46 (5.03) months								
Average costs	€3,934	€1,620	€1,264	€338	€628	€7,784	€71,868	€79,653
SD	€5,983	€695	€608	€1,119	€1,200	€7,388	€27,286	€28,078
Average monthly costs	€1,017	€378	€354	€63	€111	€1,923		
SD	€1,591	€171	€287	€226	€226	€1,853		
Previously received other treatments[b] *n*=115; mean (median) episode duration=5.01 (3.85) months								
Average costs	€4,075	€1,673	€1,315	€303	€1,007	€8,372	€69,423	€77,795
SD	€5,421	€710	€692	€1,002	€2,522	€6,256	€26,569	€26,646
Average monthly costs	€1,466	€450	€420	€52	€304	€2,692		
SD	€2,318	€215	€419	€181	€989	€2,769		

HRU, healthcare resource use; SD, standard deviation; *n*, number.

[a]Received either dabrafenib or vemurafenib.

[b]Received other treatment or combination of treatment or more lines of treatment.

Supplemental Table 2. Total healthcare costs and monthly costs of resource use other than ipilimumab by status (Euro 2016 prices)

	Hospital admissions	Hospital visits	Diagnostics and imaging	Surgery	Radiotherapy	Total HRU without ipilimumab	Ipilimumab	Total costs
All patients *n*=807; mean (median) episode duration=6.27 (4.61) months								
Average costs	€3,323	€1,791	€1,505	€297	€828	€7,745	€73,739	€81,484
SD	€5,420	€733	€956	€1,153	€2,104	€6,507	€26,655	€27,100
Average monthly costs	€1,004	€397	€373	€43	€180	€1,997		
SD	€2,246	€205	€458	€179	€512	€2,629		
Data observation complete								
All patients who finished the episode *n*=648; mean (median) episode duration=5.06 (4.14) months								
Average costs	€3,617	€1,725	€1,401	€242	€820	€7,804	€71,102	€78,906
SD	€5,693	€719	€845	€950	€1,944	€6,532	€27,417	€27,982
Average monthly costs	€1,183	€427	€402	€43	€201	€2,257		
SD	€2,456	€201	€496	€188	€551	€2,844		
Patients who progressed to the next line of treatment *n*=381; mean (median) episode duration=5.49 (4.57) months								
Average costs	€2,203	€1,833	€1,566	€267	€597	€6,466	€77,960	€84,426
SD	€4,249	€606	€936	€958	€1,591	€5,027	€24,652	€25,058
Average monthly costs	€622	€419	€394	€45	€143	€1,624		
SD	€1,661	€189	€539	€187	€358	€2,041		
Patients who deceased during the ipilimumab episode *n*=267; mean (median) episode duration=4.45 (3.68) months								
Average costs	€5,635	€1,570	€1,166	€206	€1,138	€9,715	€61,316	€71,030
SD	€6,789	€833	€625	€938	€2,324	€7,839	€28,226	€30,027
Average monthly costs	€1,983	€438	€413	€41	€284	€3,159		
SD	€3,104	€218	€427	€189	€737	€3,512		
Censored patients								
Patients still within the ipilimumab episode *n*=159, mean (median) episode duration=11.21 (8.85) months								
Average costs	€2,124	€2,061	€1,931	€521	€864	€7,501	€84,488	€91,989
SD	€3,916	€728	€1,231	€1,739	€2,665	€6,418	€20,033	€20,041
Average monthly costs	€274	€277	€252	€41	€95	€939		
SD	€602	€177	€212	€138	€290	€857		

HRU, healthcare resource use; SD, standard deviation; *n*, number.

9 General discussion

The aim of this thesis was to evaluate how and to what extent real-world evidence can complement evidence from randomized controlled trials (RCTs) in order to support evidence-based decision making on drug reimbursement in melanoma. This final chapter discusses the main findings, policy recommendations, and objectives for future research. The main findings will be discussed on the basis of (1) the limitations of RCTs for decision making on drug reimbursement, (2) the challenges in collecting and analyzing real-world data, and (3) the added value of real-world data for decision making on drug reimbursement.

LIMITATIONS OF RCTS FOR DECISION MAKING ON DRUG REIMBURSEMENT

Although the strength of RCTs is ensuring internal validity, they are often criticized for selecting patients who are not representative of patients in routine clinical practice, choosing irrelevant comparators, and using surrogate instead of final outcomes.[7] These limitations may adversely affect the external validity of RCTs, which, in turn, may complicate decision making on drug reimbursement.

Representativeness of patients who participate in RCTs

Only a small proportion of patients participate in RCTs. If these patients are not representative of patients in routine clinical practice, the external validity of the RCTs may be hampered.[7] In *Chapter 5*, we conducted a systemic literature review to identify all phase III RCTs involving patients with advanced melanoma (i.e., unresectable stage III and stage IV) that were published between January 2010 and March 2019. Of the 28 identified RCTs, there were seven immunotherapy and eight targeted therapy RCTs. The other RCTs mainly studied chemotherapy. A comparison of the baseline characteristics of patients participating in the immunotherapy/targeted therapy RCTs and the baseline characteristics of patients in routine clinical practice revealed important differences (see Table 1). First, patients who participated in the RCTs were generally younger than patients in routine clinical practice. Moreover, all RCTs excluded patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of two or higher (≥2) and patients with brain metastases. In routine clinical practice, however, approximately 40% of patients had one or both of these characteristics. It is well known that an advanced age, ECOG PS ≥2, and brain metastases are all associated with worse survival outcomes.[188] Hence, it can be concluded that patients who participated in the RCTs were not representative of patients in routine clinical practice.

Choice of comparator

The choice of comparator is a critical decision in designing an RCT. That choice affects the conclusions that can be drawn on the added (therapeutic) benefit of a novel drug for patients in routine clinical practice.[189] The European Network for Health Technology Assessment (EU-

Table 1. Baseline characteristics of patients participating in the immunotherapy/targeted therapy RCTs and patients in routine clinical practice

	Number of patients	Median age (years)	Male sex	ECOG PS ≥2	Elevated LDH level	Stage M1c	Brain metastases
Immunotherapy RCTs							
NCT00094653	676	56[b]	59%	Excluded	38%	71%	Excluded
NCT00324155	502	56-58[a,b]	60%	Excluded	40%	56%	Excluded
CheckMate 066	418	65	59%	Excluded	37%	61%	Excluded
CheckMate 037	405	59-62[a]	64%	Excluded	46%	75%	Excluded
Keynote-006	834	61-63[a]	60%	Excluded	32%	65%	Excluded
CheckMate 067	945	60[b]	65%	Excluded	36%	58%	Excluded
NCT01515189	727	NR	62%	Excluded	37%	62%	Excluded
Targeted therapy RCTs							
BRIM-3	675	52-56[a]	56%	Excluded	58%	65%	Excluded
BREAK-3	250	50-53[a]	60%	Excluded	34%	66%	Excluded
METRIC	322	54-55[a]	54%	Excluded	37%	64%	Excluded
CoBRIM	495	55-56[a]	58%	Excluded	44%	60%	Excluded
COMBI-d	423	56	53%	Excluded	35%	66%	Excluded
COMBI-v	704	55	55%	Excluded	33%	61%	Excluded
NEMO	402	62-65[a]	62%	Excluded	26%	68%	Excluded
COLUMBUS	577	54-57[a]	58%	Excluded	27%	64%	Excluded
Routine clinical practice							
DMTR[c]	4,806	64	59%	13%	34%	69%	27%

DMTR, Dutch Melanoma Treatment Registry; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NR, not reported; PS, performance status; RCTs, randomized controlled trials.
[a]Median age not reported for the total population.
[b]Mean instead of median.
[c]See also Table 1 of *Chapter 6*.

netHTA) recommends using the most relevant comparator, which is either the standard of care or the drug that is most likely to be replaced by the novel drug.[190] Of the 15 immunotherapy/targeted therapy RCTs, seven RCTs selected chemotherapy as comparator (see Table 2). While chemotherapy was the standard of care during the study period of five RCTs, two RCTs (CheckMate 066 and NEMO) were conducted in a time period in which immunotherapy and targeted therapy were the standard of care. At that time, chemotherapy was rarely used in routine clinical practice and, hence, not the most relevant comparator. A more relevant comparator for CheckMate 066, for example, would have been ipilimumab. This comparator was also used in two other RCTs (Keynote-006 and CheckMate 067), which were both conducted in the same period as the aforementioned CheckMate 066.

Table 2. Study characteristics of the immunotherapy/targeted therapy RCTs

	Intervention(s)	Comparator(s)	Primary outcome(s)	Secondary outcome(s)[a]
Immunotherapy RCTs				
NCT00094653	Ipilimumab plus gp100 or alone	gp100	OS	PFS; AEs; QoL
NCT00324155	Ipilimumab plus dacarbazine	Dacarbazine plus placebo	OS	PFS; AEs; QoL
CheckMate 066	Nivolumab	Dacarbazine	OS	PFS; AEs; QoL
CheckMate 037	Nivolumab	Dacarbazine or paclitaxel plus carboplatin	OS	PFS; AEs; QoL
Keynote-006	Pembrolizumab 2- or 3-weekly	Ipilimumab	PFS; OS	AEs; QoL
CheckMate 067	Nivolumab plus ipilimumab	Nivolumab or ipilimumab	PFS; OS	AEs; QoL
NCT01515189	Ipilimumab 10 mg/kg	Ipilimumab 3 mg/kg	OS	PFS; AEs; QoL
Targeted therapy RCTs				
BRIM-3	Vemurafenib	Dacarbazine	PFS; OS	AEs; QoL
BREAK-3	Dabrafenib	Dacarbazine	PFS	OS; AEs; QoL
METRIC	Trametinib	Dacarbazine or paclitaxel	PFS	OS; AEs; QoL
CoBRIM	Vemurafenib plus cobimetinib	Vemurafenib plus placebo	PFS	OS; AEs; QoL
COMBI-d	Dabrafenib plus trametinib	Dabrafenib plus placebo	PFS	OS; AEs; QoL
COMBI-v	Dabrafenib plus trametinib	Vemurafenib plus placebo	OS	PFS; AEs; QoL
NEMO	Binimetinib	Dacarbazine	OS	OS; AEs; QoL
COLUMBUS	Encorafenib plus binimetinib	Encorafenib or vemurafenib	PFS	OS; AEs; QoL

AEs, adverse events; mg/kg, milligrams per kilogram; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RCTs, randomized controlled trials.
[a]Or exploratory outcome.

Use of surrogate instead of final outcomes

RCTs often use surrogate outcomes as substitutes for final outcomes. In the field of oncology, a well-known example is using progression-free survival (PFS) as a surrogate for overall survival (OS). Whereas PFS is sufficient for drug regulatory agencies, OS is preferred by reimbursement authorities.[191] Assessing OS may, however, be challenging as patients may switch from the therapy of interest to another therapy. Therefore, RCTs frequently select PFS (instead of OS) as primary outcome.[192] Whether PFS is an appropriate surrogate for OS depends on the extent to which PFS can reliably predict OS. This is affected by the type and stage of disease and the type of therapy.[191,193] In *Chapter 5*, we showed that hazard ratios (HRs) for PFS were often better than HRs for OS, especially for targeted therapies. More importantly, the targeted therapies were more favorable than immunotherapies in terms of PFS, while it was the opposite for OS. This hampers the use of PFS as a surrogate for OS in RCTs involving patients with advanced melanoma. Nevertheless, five of the seven targeted therapy RCTs only selected PFS as primary outcome (see Table 2).

CHALLENGES IN COLLECTING AND ANALYZING REAL-WORLD DATA

Because of the limitations of RCTs for decision making on drug reimbursement, reimbursement authorities are increasingly interested in evidence obtained from real-world data. There are, however, a number of challenges that complicate the use of such data. The following challenges in relation to the collection and analysis of real-world data were (partly) addressed in this thesis: (1) missing data, (2) the need for sufficient patient numbers and follow-up, and (3) confounding.

Missing data

Missing data are common in both RCTs and real-world (or observational) studies. Real-world studies are, however, more vulnerable to missing data as exposure (e.g., the intervention), outcome, and confounding variables can all be missing.[194] As missing data may result in biased estimates, it may lead to invalid conclusions. To prevent missing data, data should be collected carefully.[195] In the Dutch Melanoma Treatment Registry (DMTR), the following efforts are made to prevent missing data: (1) data are prospectively collected by specially trained data managers, (2) oncologists supervise the registry and verify data at a patient level, and (3) missing or incorrect data are fed back to the data managers.[196] Despite these efforts, there were still some data missing. Of all methods for handling missing data, two were used in this thesis: mean imputation (in *Chapters 4, 6, and 8*, i.e., the costing studies) and multiple imputation (in *Chapter 7*). Mean imputation (or mean substitution) is a method in which missing values are replaced by the mean of observed values. Although mean imputation is commonly used, it may still result in biased estimates if patients with missing values differ from patients with observed values.[197] To reduce this risk, missing values were only replaced by the mean of observed values of patients with comparable characteristics. Multiple imputation is a method which uses the distribution of the observed values to estimate a set of plausible values for the missing values. It generates multiple complete datasets which can be analyzed (individually) using standard statistical techniques to obtain a set of estimates. These estimates can then be combined to obtain an overall estimate.[198] It is important to note that both methods assume missing (completely) at random. The extent to which this was true could, however, not be determined as this requires the values of the missing data.[199]

Sufficient patient numbers and follow-up

In order to support decision making on drug reimbursement, real-world data should be available in a timely manner. This may, however, be hampered by insufficient patient numbers and follow-up. Postponing analyses may then be necessary, which is particularly problematic in case of a rapidly changing treatment landscape. We faced this challenge in *Chapter 7*. Once patient numbers and follow-up were deemed sufficient to analyze the effectiveness and 'real-world' safety of ipilimumab, there was already a shift from ipilimumab to anti-PD-1 antibodies (nivolumab and pembrolizumab) and nivolumab plus ipilimumab.[200] This adversely affected the relevance of our study.

Confounding

Compared to RCTs, real-world studies offer advantages in terms of external validity. Questions are, however, raised on their internal validity. This is because real-world studies are much more vulnerable to confounding than RCTs (e.g., due to the lack of randomization).[201] Confounding occurs when the association between an exposure and outcome is distorted by another variable (i.e., the confounder).[202] There are several methods to control for confounding of which two were used in this thesis: stratification (in multiple chapters) and Cox proportional hazards regression (in *Chapter 7*). Stratification is the simplest method to control for confounding. It divides the data into subgroups on the basis of a potential confounder.[202,203] For example, in *Chapters 7 and 8*, we stratified patients by treatment status: treatment-naive versus previously treated. Treatment status was considered as a confounder because it may have distorted the association between ipilimumab and time to event. A Cox proportional hazards regression (or Cox regression) investigates the association between one or more predictor variables and the time to event (e.g., next treatment or death).[204] In *Chapter 7*, we performed a multivariate Cox regression to assess the association between baseline characteristics and OS (determined from start of ipilimumab until death or last follow-up). It should, however, be noted that, in spite of all methods to control for confounding, residual confounding may still occur.

ADDED VALUE OF REAL-WORLD DATA FOR DECISION MAKING ON DRUG REIMBURSEMENT

Despite the challenges in collecting and analyzing real-world data, such data can be of great value for decision making on drug reimbursement. In this thesis, we used data from the DMTR as well as data from other real-world data sources (such as the Netherlands Cancer Registry) to provide insight into the accessibility, uptake, effectiveness, safety, and health care costs of the novel drugs in routine clinical practice in the Netherlands.

Insight into the accessibility and uptake of drugs

Early access to novel drugs is of utmost importance for cancer patients. A study by Uyl-de Groot and colleagues[205], which assessed patient access to several novel cancer drugs in Europe, showed that the Netherlands ranks ninth in terms of 'time to market' (TTM). TTM was defined as the time between the date of marketing authorization and the date of first uptake. The average TTM was 128 days in the Netherlands, as compared to 403 days in Europe. For advanced melanoma, TTM was assessed for ipilimumab, nivolumab, pembrolizumab, vemurafenib, and dabrafenib. Of these drugs, ipilimumab and vemurafenib yielded the longest average TTM: 197 and 135 days, respectively. This may have been due to the fact that these drugs were the first novel drugs for advanced melanoma. As previously mentioned (in the general introduction), their introduction posed several important challenges.[196] Nevertheless, once the drugs entered the market (in 2012), there was a rapid shift from chemotherapy to ipilimumab and vemurafenib (see *Chapter 2*). A

few years later (in 2015), a second shift occurred from ipilimumab and vemurafenib to anti-PD-1 antibodies, nivolumab plus ipilimumab, and BRAF plus MEK inhibitors.[200]

In addition to the rapidly changing treatment landscape, we also observed notable trends in the incidence of melanoma (see *Chapter 2*). Between 2003 and 2018, the overall incidence rate (i.e., the incidence rate irrespective of stage at diagnosis) increased substantially: from 10.9 to 23.9 per 100,000 person-years for men and from 15.6 to 27.3 per 100,000 person-years for women. Insight into these trends as well as insight into recurrence patterns can be used to estimate changes in the number of patients eligible for the novel drugs. According to *Chapter 3*, approximately 10% of patients with stage IB, 30% of patients with stage II, and 50% of patients with stage III will develop disease progression. Two-thirds of these patients will eventually develop distant metastases. Hence, it can be expected that the number of patients eligible for the novel drugs will increase in the future.

Insight into a drug's effectiveness and safety

One of the shortcomings of the immunotherapy/targeted therapy RCTs was that patients who participated in the RCTs were not representative of patients in routine clinical practice. Therefore, it could be expected that the effectiveness of the novel drugs may differ from their efficacy. Real-world data can provide insight into this so-called 'efficacy-effectiveness gap'. In *Chapter 7*, we analyzed the effectiveness and 'real-world' safety of ipilimumab. We showed that the median time to event (which was used as proxy for PFS) of patients who received ipilimumab in routine clinical practice was longer than the median PFS of patients who received ipilimumab in the pivotal RCTs[80,160]: 5.4 months versus less than 3 months for treatment-naive patients and 4.4 months versus 2.9 months for previously-treated patients (non-overlapping confidence intervals). This may be due to a more stringent selection of patients in routine clinical practice. A study by Kelderman and colleagues[206], which analyzed patients who received ipilimumab through expanded access to identify markers for treatment benefit, showed that patients with an elevated LDH level were less likely to benefit from ipilimumab than patients with a normal LDH level. In routine clinical practice, 21% of treatment-naive patients and 26% of previously-treated patients had an elevated LDH level, as compared to 37% of treatment-naive patients and 39% of previously-treated patients in the pivotal RCTs.

With respect to safety, we showed that grade 3/4 immune-related adverse events (irAEs) were less common among treatment-naive patients who received ipilimumab in routine clinical practice than among treatment-naive patients who received ipilimumab in the pivotal RCT. This is most likely owing to the difference in dose of ipilimumab (3 mg/kg in clinical practice versus 10 mg/kg in the pivotal RCT). For previously-treated patients, irAEs were more common in routine clinical practice than in the pivotal RCT. However, while the pivotal RCT involving previously-treated patients reported treatment-related deaths, no treatment-related deaths occurred in routine

clinical practice. This may be the result of centralization of care which, in turn, may have led to good implementation and high adherence to guidelines for management of (ir)AEs.

Besides confirming (or disproving) RCT results, real-world data can also provide insight into results of patients who did not participate in RCTs. For example, as mentioned before, both pivotal RCTs excluded patients with brain metastases. Real-world studies[207-209] showed that patients with brain metastases who received ipilimumab had an improved survival compared to patients with brain metastases who did not receive ipilimumab.

Insight into health care costs

Costing studies can provide insight into the economic burden of a disease and can identify (the most important) cost drivers. These insights may facilitate decision making on resource allocation, which is relevant in the context of rising health care costs and scarce resources. In addition, cost data can be used for economic evaluations.

In this thesis, we performed three costing studies. In all studies, health care costs were based on real-world resource use. This was preferred over trial-based resource use because resource use in RCTs may not reflect resource use in routine clinical practice. On the one hand, resource use may be less as patients who participate in RCTs generally have a more favorable prognosis than patients in routine clinical practice. On the other hand, resource use may be more due to intensive monitoring in RCTs. The first costing study, in *Chapter 4*, presented the costs of patients with stage I, II, and III melanoma. This study showed that the mean costs of these patients were relatively low: €3,019 and €6,765 per patient for patients with stage I/II and III, respectively. The costing study in *Chapter 6* showed, however, that the mean costs of patients with advanced melanoma were substantial: €89,240 per patient. More than 80% of these costs were driven by drug costs. The tremendous difference in costs between patients with and without advanced melanoma emphasize the importance of identifying disease recurrence at its earliest stage for retaining low costs. The third costing study, in *Chapter 8*, presented the costs of patients who received ipilimumab in routine clinical practice. Focusing on only one drug facilitated a comparison of costs between specific subgroups. This study showed that the mean costs were higher for treatment-naive patients (compared to previously-treated patients) and patients with irAEs other than colitis (compared to patients without irAEs and patients with colitis), which indicates that costs are not only driven by drug costs but also by patient characteristics.

POLICY RECOMMENDATIONS AND OBJECTIVES FOR FUTURE RESEARCH

The findings of this thesis lead to several policy recommendations and objectives for future research. First, the findings contribute to the growing body of literature on the potential of real-

world evidence to complement evidence from RCTs. While this has been addressed for advanced melanoma by Makaday and colleagues[210], they did not actually use real-world data.

Further, although it is widely acknowledged that RCTs are the gold standard for assessing efficacy and safety, it is also well known that reimbursement authorities require additional evidence to decide on reimbursement.[8-10] As real-world data can only be collected after a novel drug enters the market, it is not possible to use such data for the initial assessment. Real-world data can, however, be used for re-assessments to answer questions that could not be answered at the moment of the initial assessment. This may become increasingly relevant as drug regulatory agencies are making increased use of expedited approval programs, which allow marketing authorization on the basis of less comprehensive data.[211] Even though these programs were not used for novel drugs for advanced melanoma, the challenges that were posed with the introduction of the novel drugs emphasize the importance of real-world data. In this thesis, we showed that real-world data provides insight into a drug's effectiveness, 'real-world' safety, and health care costs.

Besides these insights, reimbursement authorities often also require insight into cost-effectiveness.[12] Although we recognize the importance of evaluating to what extent the benefits of the drugs outweigh their costs, we did not conduct a cost-effectiveness analysis. Cost-effectiveness is, therefore, a key objective for future research. It is worth nothing that we are currently developing a disease model which can be used to perform cost-effectiveness analyses. In addition, our model can also be used to assess (cost-)effectiveness of treatment sequences. This is relevant for advanced melanoma as most patients receive multiple lines of therapy. Insight into (cost-) effectiveness of treatment sequences can be used to identify the most optimal order of treatments (both in terms of effectiveness and cost-effectiveness). Hence, (cost-)effectiveness of treatment sequences is another objective for future research. To inform cost-effectiveness analyses, 'real-world' quality of life (QoL) should also be an objective for future research. QoL has become an important outcome for assessing the benefits of cancer drugs, as most of these drugs cannot cure patients but may cause frequent and sometimes severe AEs. Although all immunotherapy/targeted therapy RCTs selected QoL as secondary or exploratory outcome (see Table 2), 'real-world' QoL may differ as patients who participated in the RCTs were not representative of patients in routine clinical practice.

Finally, while decision making on drug reimbursement is often focused on (relative) assessment of individual drugs, this may not be suitable for disease areas (such as advanced melanoma) in which the treatment landscape is changing rapidly and/or patients receive multiple lines of therapy. For such areas, it may be more suitable to assess the overall treatment landscape. In the Netherlands, this is part of the 'Zinnige Zorg' (appropriate care) program of the National Health Care Institute (ZIN). This program evaluates whether drugs are being used in a patient-oriented, effective, and cost-effective manner.[212] In this respect, real-world evidence can be used to inform

questions such as which patients should be eligible for novel drugs, how many lines of therapy may be prescribed to a patient, or should a patient start a new therapy near the end of life. Future research should aim to answer these types of questions, ideally by using data from nationwide population-based registries such as the DMTR.

To ensure the potential of using data from (nationwide population-based) registries for re-assessments and/or assessing appropriate care, several considerations should be taken into account. First, it is crucial to determine the objective(s) of the registry and to establish a governance structure (including a description of tasks and responsibilities). Decisions should be made regarding data ownership, access, and sharing.[213] For example, if the registry is funded by pharmaceutical companies, they may not be willing to share drug-specific data. This may hamper using such data for re-assessments and/or assessing appropriate care. Second, registries can be costly. It is, therefore, crucial to secure sufficient funding for all activities related to the registry. Potential sponsors are pharmaceutical companies, governmental bodies, health insurance companies, and patient organizations. Although multiple sponsors may be preferred because that may decrease the financial burden for each sponsor, it is important to realize that sponsors may have conflicting interests.[213] Third, data collection by specially-trained data managers can be very time-consuming. For example, in the DMTR, the registration of a patient record takes on average eight hours.[196] Therefore, it should be decided what data elements are required given the objective(s) of the registry and evaluated to what extent digital data collection can reduce the registration burden without negatively impacting the quality of the data.

CONCLUSION

This thesis showed that real-world evidence complements evidence from RCTs and, therefore, supports evidence-based decision making on drug reimbursement. Although RCTs provide the most reliable evidence regarding efficacy and safety, real-world data can provide additional evidence regarding accessibility, uptake, (cost-)effectiveness, 'real-world' safety, and (health care) costs. Nevertheless, it is crucial to recognize the challenges in collecting and analyzing real-world data.

Summary
Samenvatting

SUMMARY

General introduction

For many years, treatment options for patients with unresectable stage III and stage IV cutaneous melanoma (hereafter: advanced melanoma) were limited. Chemotherapy was the standard of care, but it never demonstrated to improve survival.[17] Advances in immunotherapy and targeted therapy drastically changed the treatment landscape for advanced melanoma. The first two novel drugs, ipilimumab (an immunotherapy) and vemurafenib (a targeted therapy), received a marketing authorization valid throughout the European Union in 2011 and 2012, respectively. Since then, multiple other drugs and combinations of drugs have been approved for advanced melanoma.[18]

To decide on reimbursement, national reimbursement authorities need valid evidence regarding a drug's (long-term) effects and costs. Although it is widely acknowledged that randomized controlled trials (RCTs) are the gold standard for assessing efficacy and safety, it is also well known that not all evidence can be obtained from RCTs. Therefore, in recent years, reimbursement authorities have become increasingly interested in real-world evidence (i.e., evidence obtained from real-world data).[8-10]

The aim of this thesis is to evaluate how and to what extent real-world evidence can complement evidence from RCTs in order to support evidence-based decision making on drug reimbursement in melanoma.

Trends in incidence and survival of cutaneous melanoma in the Netherlands (2003-2018)

In *Chapter 2*, we describe stage-specific trends in the incidence and survival of all patients diagnosed with primary cutaneous melanoma in the Netherlands between 2003 and 2018 (*n*=60,267). In addition, we report the annual proportion of patients who received chemotherapy, immunotherapy, or targeted therapy for their primary diagnosis during that period. Data were obtained from the Netherlands Cancer Registry.

Between 2003 and 2018, the age-standardized incidence rate (irrespective of stage at diagnosis) increased from 10.9 to 23.9 per 100,000 person-years for men and from 15.6 to 27.3 per 100,000 person-years for women. This increase reflected the increasing incidence rate of patients with stage I and III as the incidence rate of patients with other stages (II and IV) remained reasonably stable. During the same period, the five-year survival rate (irrespective of stage at diagnosis) increased from 81% to 92% for men and from 88% to 96% for women. This increase predominantly reflected the increasing five-year survival rate of patients with stage II and III. In recent years, a steep increase in the five-year survival rate was also observed for patients with stage IV. For

these patients, there was a shift from chemotherapy to immunotherapy and targeted therapy as from 2013.

Disease recurrence and survival in localized and regionally advanced cutaneous melanoma

Chapter 3 presents stage-specific survival from diagnosis, recurrence patterns, and post-recurrence survival of patients initially diagnosed with localized (i.e., stage I and II) or regionally advanced (i.e., stage III) cutaneous melanoma in six Dutch hospitals between 2003 and 2011 (*n*=3,093). Data on recurrence patterns were only collected for patients with stage IB to III as we assumed that disease recurrence would not be related to survival in patients with stage IA.

At a median follow-up of 5.4 years, median overall survival (OS) from diagnosis was not yet reached for patients with stage I, 9.5 years for patients with stage II, and 6.8 years for patients with stage III. Five-year survival rates were 94%, 66%, and 59% for patients with stage I, II, and III, respectively. In total, 8% of patients with stage IB, 29% of patients with stage II, and 47% of patients with stage III developed disease recurrence. Median time to first recurrence was 2.8, 1.5, and 1.0 years for patients with stage IB, II, and III, respectively. Of all patients with disease recurrence, most patients developed regional lymph node metastases (42%, 37%, and 31% of patients with stage IB, II, and III, respectively) or distant metastases (35%, 42%, and 48%, respectively) as first recurrence. Median post-recurrence OS was 2.8 for patients with intralymphatic metastases, 3.9 for patients with regional lymph node metastases, and 0.5 years for patients with distant metastases. Two-year post-recurrence survival rates were 57%, 65%, and 12% for patients with intralymphatic, regional lymph node, and distant metastases, respectively.

Health care costs of localized and regionally advanced cutaneous melanoma

Chapter 4 reports health care costs of patients initially diagnosed with localized or regionally advanced cutaneous melanoma in three Dutch hospitals between 2003 and 2011. Data were collected for a random selection of patients (*n*=296).

For the initial treatment episode (determined from the initial diagnosis until disease recurrence, death, or last follow-up), mean costs were €3,019 for patients with localized melanoma and €6,765 for patients with regionally advanced melanoma. Hospital visits were the main cost driver for patients with localized melanoma. Costs of patients with regionally advanced melanoma were mainly driven by the costs of hospital admissions. For patients with disease recurrence, mean episode costs (calculated from recurrence until the next recurrence, death, or last follow-up) were the highest for distant metastases (€10,393), followed by regional lymph node metastases (€8,129), intralymphatic metastases (€4,604), and a local recurrence (€4,414).

Efficacy and safety of immunotherapies and targeted therapies for advanced melanoma

In *Chapter 5*, we conducted a systemic literature review to identify all phase III RCTs involving patients with advanced melanoma that were published between January 2010 and March 2019. Data were retrieved on progression-free survival (PFS), OS, and grade 3/4 treatment-related adverse events (trAEs). A network meta-analysis (NMA) was used to assess the relative efficacy and safety of each therapy. Dacarbazine was selected as reference therapy.

The SLR identified 28 phase III RCTs of which 17 RCTs could be included in the NMA. The hazard ratio for PFS was most favorable for dabrafenib plus trametinib and vemurafenib plus cobimetinib (0.21 and 0.22, respectively). Five other therapies closely followed: dabrafenib (0.30), nivolumab plus ipilimumab (0.34), vemurafenib (0.38), nivolumab monotherapy (0.42), and pembrolizumab (0.46). The hazard ratio for OS was most favorable for nivolumab plus ipilimumab (0.39), followed by nivolumab monotherapy and pembrolizumab (0.46 and 0.50, respectively). In general, the relative risk for grade 3/4 trAEs was more favorable for immunotherapies than for targeted therapies.

Health care costs of advanced cutaneous melanoma

Chapter 6 reports health care costs of advanced cutaneous melanoma in the era of immunotherapies and targeted therapies. Data were obtained from the Dutch Melanoma Treatment Registry (DMTR) for all patients who were registered between July 2012 and December 2018 (n=4,806).

Mean total (calculated from the diagnosis of advanced melanoma until death or last follow-up) and monthly costs were €89,240 and €6,809, respectively. Costs substantially differed between patients who did not receive systemic therapy (total: €7,988; monthly: €2,483) and patients who received systemic therapy (total: €105,078; monthly: €7,652). This difference was largely owing to the costs of systemic therapy, which accounted for more than 80% of the costs. For patients who received systemic therapy, mean episode (calculated from the start of a systemic therapy until the start of a new systemic therapy, death, or last follow-up) and monthly costs were the highest for the second line (€59,701 and €11,939, respectively), as compared to the first line (€58,502 and €8,231, respectively) and the third line (€49,725 and €10,366, respectively). By drug, mean episode and monthly costs were the highest for nivolumab plus ipilimumab (€79,675 and €16,976, respectively), ipilimumab monotherapy (€79,110 and €17,252, respectively), and dabrafenib plus trametinib (€77,053 and €12,015, respectively).

Effectiveness, safety, and health care costs of ipilimumab

In *Chapter 7*, we present the time to first event (i.e., new therapy or death), OS, and grade 3/4 immune-related AEs (irAEs) of patients with advanced cutaneous melanoma who received ipilimumab in routine clinical practice. *Chapter 8* reports the health care costs of these patients.

For both chapters, data were obtained from the DMTR for patients who were registered between July 2012 and July 2015 (*n*=807).

At a median follow-up of 11.5 months for treatment-naive patients and 20.9 months for previously-treated patients, median time to first event was 5.4 months for treatment-naive patients and 4.4 months for previously-treated patients. The one-year cumulative incidence of a new therapy was 58% and 44% for treatment-naive and previously-treated patients, respectively. Median OS was 14.3 months for treatment-naive patients and 8.7 months for previously-treated patients. Two-year survival rates were 39% and 24% for treatment-naive and previously-treated patients, respectively. In total, 29% of treatment-naive patients and 21% of previously-treated patients experienced at least one grade 3/4 irAE. There were no treatment-related deaths.

Mean total costs (calculated from the start of ipilimumab until the start of a new systemic therapy, death, or last follow-up) were €81,484. Drug costs were by far the most important cost driver, accounting for 91% of the costs. Costs differed between treatment-naive patients (€85,081) and previously-treated patients (€78,811), and between patients without grade 3/4 irAEs (€81,480), patients with grade 3/4 colitis (€76,075), and patients with grade 3/4 irAEs other than colitis (€87,882).

General discussion

The final chapter of this thesis discusses the main findings and policy recommendations. The main findings were discussed on the basis of (1) the limitations of RCTs, (2) the challenges in using real-world data, and (3) the added value of real-world data.

Although RCTs provide the most reliable evidence regarding a drug's efficacy and safety, they also have important limitations. First, patients who participated in RCTs were not representative of patients in routine clinical practice. In addition, some RCTs choose an irrelevant comparator and/or used surrogate instead of final outcomes. Because of these limitations, reimbursement authorities are increasingly interested in evidence obtained from real-world data. There are, however, a number of challenges that complicate the use of such data, including missing data, the need for sufficient patient numbers and follow-up, and confounding. Despite these challenges, real-world data can provide valuable evidence regarding a drug's accessibility, uptake, (cost-) effectiveness, 'real-world' safety, and (health care) costs.

The findings of this thesis lead to several policy recommendations. First, real-world data can be used for re-assessments to answer questions that could not be answered at the moment of the initial reimbursement assessment. Further, if the treatment landscape is changing rapidly and/or patients receive multiple lines of therapy, real-world data can be used to assess whether drugs are being used in a patient-oriented, effective, and cost-effective manner.

In conclusion, this thesis showed that real-world evidence complements evidence from RCTs and, therefore, supports evidence-based decision making on drug reimbursement.

SAMENVATTING

Algemene introductie

Jarenlang waren de behandelmogelijkheden voor patiënten met inoperabel melanoom stadium III en stadium IV (hierna: gemetastaseerd melanoom) beperkt. Chemotherapie was de standaardbehandeling, maar leverde geen overlevingswinst op.[17] Ontwikkelingen op het gebied van immunotherapie en doelgerichte therapie hebben het behandellandschap van gemetastaseerd melanoom drastisch veranderd. De eerste twee nieuwe geneesmiddelen, ipilimumab (een immunotherapie) en vemurafenib (een doelgerichte therapie), ontvingen een handelsvergunning voor de Europese Unie in respectievelijk 2011 en 2012. Sindsdien zijn meerdere geneesmiddelen en combinaties van geneesmiddelen goedgekeurd voor de behandeling van gemetastaseerd melanoom.[18]

Om te bepalen of een geneesmiddel in aanmerking komt voor vergoeding hebben nationale vergoedingsautoriteiten bewijs nodig met betrekking tot de (lange termijn) effecten en kosten van het geneesmiddel. Ondanks dat het algemeen wordt erkend dat gerandomiseerde, gecontroleerde trials (RCT's) de gouden standaard zijn voor de beoordeling van werkzaamheid en veiligheid, is het ook bekend dat niet al het benodigde bewijs verkregen kan worden uit RCT's. Om die reden hebben vergoedingsautoriteiten de afgelopen jaren steeds meer interesse gekregen in bewijs uit de dagelijkse praktijk.[8-10]

Het doel van dit proefschrift is om te evalueren hoe en in welke mate bewijs uit de dagelijkse praktijk het bewijs uit RCT's kan aanvullen teneinde 'evidence-based' besluitvorming over de vergoeding van geneesmiddelen voor melanoom te ondersteunen.

Trends in incidentie en overleving van melanoom in Nederland (2003-2018)

In *Hoofdstuk 2* beschrijven we de stadiumspecifieke trends in de incidentie en overleving van alle patiënten gediagnosticeerd met primair melanoom in Nederland tussen 2003 en 2018 (n=60.267). Daarnaast rapporteren we het percentage patiënten dat per jaar is behandeld met chemotherapie, immunotherapie of doelgerichte therapie voor de primaire diagnose. Gegevens zijn verkregen uit de Nederlandse Kankerregistratie.

Tussen 2003 en 2018 steeg de gestandaardiseerde incidentie (ongeacht het stadium bij diagnose) van 10,9 tot 23,9 per 100.000 persoonsjaren voor mannen en van 15,6 tot 27,3 per 100.000 persoonsjaren voor vrouwen. Deze stijging weerspiegelt de stijgende incidentie van patiënten met stadium I en III, aangezien de incidentie van patiënten met andere stadia (II en IV) redelijk stabiel is gebleven. In dezelfde periode is de vijfjaarsoverleving (ongeacht het stadium bij diagnose) gestegen van 81% tot 92% voor mannen en van 88% tot 96% voor vrouwen. Deze stijging weerspiegelt met name de stijgende vijfjaarsoverleving van patiënten met stadium II en III. De

laatste jaren is ook een sterke stijging waargenomen in de vijfjaarsoverleving van patiënten met stadium IV. Voor deze patiënten was er vanaf 2013 een verschuiving van chemotherapie naar immunotherapie en doelgerichte therapie.

Terugkeer van ziekte en overleving van lokaal en regionaal gemetastaseerd melanoom

Hoofdstuk 3 presenteert de stadiumspecifieke overleving vanaf diagnose, recidiefpatronen en overleving na terugkeer van ziekte van patiënten primair gediagnosticeerd met lokaal (i.e., stadium I en II) of regionaal gemetastaseerd (i.e., stadium III) melanoom in zes Nederlandse ziekenhuizen tussen 2003 en 2011 (*n*=3.093). Gegevens over recidiefpatronen zijn alleen verzameld voor patiënten met stadium IB tot en met III, omdat we ervan zijn uitgegaan dat terugkeer van ziekte niet zou zijn gerelateerd aan de overleving van patiënten met stadium IA.

Bij een mediane follow-up van 5,4 jaar was de mediane algehele overleving vanaf diagnose nog niet bereikt voor patiënten met stadium I, 9,5 jaar voor patiënten met stadium II en 6,8 jaar voor patiënten met stadium III. De vijfjaarsoverleving bedroeg 94%, 66% en 59% voor patiënten met respectievelijk stadium I, II en III. In totaal ontwikkelde 8% van de patiënten met stadium IB, 29% van de patiënten met stadium II en 47% van de patiënten met stadium III een recidief. De mediane tijd tot het eerste recidief was 2,8, 1,5 en 1,0 jaar voor patiënten met respectievelijk stadium IB, II en III. Van alle patiënten bij wie de ziekte terugkeerde, ontwikkelden de meeste patiënten regionale lymfekliermetastasen (42%, 37% en 31% van de patiënten met respectievelijk stadium IB, II, en III) of afstandsmetastasen (respectievelijk 35%, 42% en 48%) als eerste recidief. De mediane algehele overleving na terugkeer van ziekte was 2,8 jaar voor patiënten met intralymfatische metastasen, 3,9 jaar voor patiënten met regionale lymfekliermetastasen en 0,5 jaar voor patiënten met afstandsmetastasen. De tweejaarsoverleving na terugkeer van ziekte was 57%, 65% en 12% voor patiënten met respectievelijk intralymfatische metastasen, regionale lymfekliermetastasen en afstandsmetastasen.

Ziekenhuiskosten van lokaal en regionaal gemetastaseerd melanoom

Hoofdstuk 4 rapporteert de ziekenhuiskosten van patiënten primair gediagnosticeerd met lokaal of regionaal gemetastaseerd melanoom in drie Nederlandse ziekenhuizen tussen 2003 en 2011. Gegevens zijn verzameld voor een willekeurige selectie van patiënten (*n*=296).

Voor de primaire behandelepisode (bepaald vanaf de primaire diagnose tot aan terugkeer van ziekte, overlijden of laatste follow-up) bedroegen de gemiddelde kosten €3.019 voor patiënten met lokaal melanoom en €6.765 voor patiënten met regionaal gemetastaseerd melanoom. Polikliniekbezoeken waren de belangrijkste kostenpost voor patiënten met lokaal melanoom. De kosten van patiënten met regionaal gemetastaseerd melanoom werden voornamelijk bepaald door de kosten van ziekenhuisopnames. Voor patiënten bij wie de ziekte terugkeerde, waren de

gemiddelde kosten per episode (berekend vanaf het recidief tot het volgende recidief, overlijden of laatste follow-up) het hoogst voor afstandsmetastasen (€10.393), gevolgd door regionale lymfekliermetastasen (€8.129), intralymfatische metastasen (€4.604) en een lokaal recidief (€4.414).

Werkzaamheid en veiligheid van immunotherapieën en doelgerichte therapieën voor gemetastaseerd melanoom

In *Hoofdstuk 5* hebben we een systematisch literatuuronderzoek uitgevoerd om alle fase III RCT's te identificeren die betrekking hadden op patiënten met gemetastaseerd melanoom en die zijn gepubliceerd tussen januari 2010 en maart 2019. Gegevens zijn verzameld met betrekking tot progressievrije overleving, algehele overleving en graad 3/4 behandelingsgerelateerde bijwerkingen. Een netwerk meta-analyse (NMA) is gebruikt om de relatieve werkzaamheid en veiligheid van elke therapie te evalueren. Dacarbazine is geselecteerd als referentietherapie.

Het literatuuronderzoek identificeerde 28 fase III RCT's waarvan 17 RCT's in de NMA konden worden opgenomen. De hazard ratio voor progressievrije overleving was het gunstigst voor dabrafenib plus trametinib en vemurafenib plus cobimetinib (respectievelijk 0,21 en 0,22). Vijf andere therapieën volgden kort daarop: dabrafenib (0,30), nivolumab plus ipilimumab (0,34), vemurafenib (0,38), nivolumab monotherapie (0,42) en pembrolizumab (0,46). De hazard ratio voor algehele overleving was het gunstigst voor nivolumab plus ipilimumab (0,39), gevolgd door nivolumab monotherapie en pembrolizumab (respectievelijk 0,46 en 0,50). Over het algemeen was het relatieve risico voor graad 3/4 behandelingsgerelateerde bijwerkingen gunstiger voor immunotherapieën dan voor doelgerichte therapieën.

Ziekenhuiskosten van gemetastaseerd melanoom

Hoofdstuk 6 rapporteert de ziekenhuiskosten van gemetastaseerd melanoom in het tijdperk van immunotherapieën en doelgerichte therapieën. Gegevens zijn verkregen uit de Dutch Melanoma Treatment Registry (DMTR) voor alle patiënten die zijn geregistreerd tussen juli 2012 en december 2018 (n=4.806).

De gemiddelde totale (berekend vanaf de diagnose van gemetastaseerd melanoom tot overlijden of laatste follow-up) en maandelijkse kosten bedroegen respectievelijk €89.240 en €6.809. Deze kosten werden voor meer dan 80% bepaald door de kosten van systemische therapie. Kosten verschilden aanzienlijk tussen patiënten die geen systemische therapie kregen (totaal: €7.988; maandelijks: €2.483) en patiënten die wel systemische therapie kregen (totaal: €105.078; maandelijks: €7.652). Voor patiënten die systemische therapie kregen, waren de gemiddelde episode (berekend vanaf het begin van een systemische therapie tot het begin van een nieuwe systemische therapie, overlijden of laatste follow-up) en maandelijkse kosten het hoogst voor de tweede lijn (respectievelijk €59.701 en €11.939) in vergelijking met de eerste lijn (respectievelijk €58.502 en €8.231) en de derde lijn (respectievelijk €49.725 en €10.366). De gemiddelde episode en

maandelijkse kosten per geneesmiddel waren het hoogst voor nivolumab plus ipilimumab (respectievelijk €79.675 en €16.976), ipilimumab monotherapie (respectievelijk €79.110 en €17.252 euro) en dabrafenib plus trametinib (respectievelijk €77.053 en €12.015).

Effectiviteit, veiligheid en ziekenhuiskosten van ipilimumab

In *Hoofdstuk 7* presenteren wij de tijd tot het eerste event (i.e., nieuwe therapie of overlijden), algehele overleving en graad 3/4 immuungerelateerde bijwerkingen van patiënten met gemetastaseerd melanoom die in de dagelijkse praktijk zijn behandeld met ipilimumab. *Hoofdstuk 8* rapporteert de ziekenhuiskosten van deze patiënten. Voor beide hoofdstukken zijn gegevens verkregen uit de DMTR voor patiënten die werden geregistreerd tussen juli 2012 en juli 2015 (n=807).

Bij een mediane follow-up van 11,5 maanden voor behandelingsnaïeve patiënten en 20,9 maanden voor eerder behandelde patiënten, was de mediane tijd tot eerste event 5,4 maanden voor behandelingsnaïeve patiënten en 4,4 maanden voor eerder behandelde patiënten. De één-jaars cumulatieve incidentie van een nieuwe therapie was 58% en 44% voor respectievelijk behandelingsnaïeve en eerder behandelde patiënten. De mediane algehele overleving was 14,3 maanden voor behandelingsnaïeve patiënten en 8,7 maanden voor eerder behandelde patiënten. De tweejaarsoverleving was 39% en 24% voor respectievelijk behandelingsnaïeve en eerder behandelde patiënten. In totaal ontwikkelde 29% van de behandelingsnaïeve patiënten en 21% van de eerder behandelde patiënten ten minste één graad 3/4 immuungerelateerde bijwerking. Er waren geen behandelingsgerelateerde sterfgevallen.

De gemiddelde totale kosten (berekend vanaf de start van ipilimumab tot de start van een nieuwe systemische therapie, overlijden of laatste follow-up) bedroegen €81.484. Deze kosten werden voor 91% bepaald door de kosten van systemische therapie. Kosten verschilden tussen behandelingsnaïeve patiënten (€85.081) en eerder behandelde patiënten (€78.811) en tussen patiënten zonder graad 3/4 immuungerelateerde bijwerkingen (€81.480), patiënten met graad 3/4 colitis (€76.075) en patiënten met graad 3/4 immuungerelateerde bijwerkingen anders dan colitis (€87.882).

Algemene discussie

Het laatste hoofdstuk van dit proefschrift bespreekt de belangrijkste bevindingen en beleidsaanbevelingen. De belangrijkste bevindingen zijn besproken op basis van (1) de beperkingen van RCT's, (2) de uitdagingen bij het gebruik van gegevens uit de dagelijkse praktijk en (3) de toegevoegde waarde van gegevens uit de dagelijkse praktijk.

Hoewel RCT's het meest betrouwbare bewijs leveren voor de werkzaamheid en veiligheid van een geneesmiddel, hebben ze ook belangrijke beperkingen. Ten eerste waren de patiënten die

deelnamen aan RCT's niet representatief voor patiënten in de dagelijkse praktijk. Bovendien kozen sommige RCT's een irrelevante comparator en/of gebruikten ze surrogaatresultaten in plaats van eindresultaten. Door deze beperkingen hebben vergoedingsautoriteiten steeds meer interesse gekregen in gegevens uit de dagelijkse praktijk. Er zijn echter een aantal uitdagingen die het gebruik van dergelijke gegevens bemoeilijken, waaronder ontbrekende gegevens, de noodzaak van voldoende patiënten en follow-up, en confounding. Ondanks deze uitdagingen kunnen gegevens uit de dagelijkse praktijk waardevol bewijs leveren met betrekking tot de toegankelijkheid, opname, (kosten-)effectiviteit, veiligheid (in de dagelijkse praktijk) en (ziekenhuis)kosten van een geneesmiddel.

De bevindingen van dit proefschrift leiden tot verschillende beleidsaanbevelingen. Ten eerste kunnen gegevens uit de dagelijkse praktijk worden gebruikt voor herbeoordelingen om antwoord te geven op vragen die niet konden worden beantwoord op het moment van de initiële vergoedingsbeslissing. Verder, als het behandelingslandschap snel verandert en/of patiënten meerdere behandellijnen krijgen, kunnen gegevens uit de dagelijkse praktijk worden gebruikt om te beoordelen of geneesmiddelen op een patiëntgerichte, effectieve en kosteneffectieve manier worden ingezet.

Concluderend kan worden gesteld dat dit proefschrift heeft aangetoond dat bewijs uit de dagelijkse praktijk het bewijs uit RCT's aanvult en daardoor 'evidence-based' besluitvorming over de vergoeding van geneesmiddelen ondersteunt.

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About the author
PhD portfolio
List of publications

ABOUT THE AUTHOR

Brenda Leeneman was born in Rotterdam on July 5, 1991. In 2009, she started the bachelor program Health Policy & Management at the Erasmus University Rotterdam. At the same university, she obtained a master's degree in Health Economics, Policy and Law (specialization: Health Technology Assessment) in 2013 and a master's degree in Health Sciences (specialization: Clinical Epidemiology) in 2016. In 2014, she started as a PhD candidate at the Erasmus School of Health Policy & Management under supervision of prof.dr. C.A. Uyl-de Groot, prof.dr. J.B.A.G. Haanen, and dr. M.G. Franken, which resulted in this thesis. Her research mainly focused on the epidemiological, clinical, and economic aspects of (advanced) melanoma. She has been involved in the Dutch Melanoma Treatment Registry from the start of her PhD trajectory. Besides her research, she works on an advisory project (Regie op Registers voor Dure Geneesmiddelen) for the National Health Care Institute.

PhD PORTFOLIO

PhD candidate:	Brenda Leeneman
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PhD period:	2014-2021
Supervisors:	prof.dr. C.A. Uyl-de Groot
	prof.dr. J.B.A.G. Haanen
Co-supervisor:	dr. M.G. Franken

PhD training

2014	Introduction to patient-reported outcome assessment: Instrument development and evaluation *ISPOR short courses. Amsterdam, the Netherlands*
2014	Discrete event simulation for economic analyses: Concepts and applications *ISPOR short courses. Amsterdam, the Netherlands*
2014-2016	Master of Science in Health Sciences, specialization: Clinical epidemiology *Faculty of Medicine and Health Sciences. Erasmus MC. Rotterdam, the Netherlands*
2015	Systematisch literatuuronderzoek in Pubmed en andere databases *Medical Library. Erasmus MC. Rotterdam, the Netherlands*
2015	Toetsing *RISBO. Erasmus University Rotterdam. Rotterdam, the Netherlands*
2015	Scriptiebegeleiding en -beoordeling *RISBO. Erasmus University Rotterdam. Rotterdam, the Netherlands*
2015	Nutritional epidemiology and physical activity *Institute of Public Health. University of Cambridge. Cambridge, United Kingdom*
2015	Geven van onderwijs *RISBO. Erasmus University Rotterdam. Rotterdam, the Netherlands*
2017	Patient-level modelling in R *Institute for Medical Technology Assessment. Erasmus University Rotterdam. Rotterdam, the Netherlands*

Teaching

2013	Patient preferences in the delivery of health care *Tutor. Health Economics, Policy & Law. Erasmus University Rotterdam. Rotterdam, the Netherlands*
2013	Thesis *Supervisor. Health Economics, Policy & Law. Erasmus University Rotterdam. Rotterdam, the Netherlands*

2014; 2017	Praktijkstage 'Werken in de zorg' *Tutor. Gezondheidswetenschappen, BMG. Erasmus University Rotterdam. Rotterdam, the Netherlands*
2014-2018	Scriptie *Supervisor. Gezondheidswetenschappen, BMG. Erasmus University Rotterdam. Rotterdam, the Netherlands*
2015	Health Economics *Tutor. Netherlands Institute for Health Sciences. Erasmus MC. Rotterdam, the Netherlands*
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2016	Introductie in de Gezondheidswetenschappen *Tutor. Gezondheidswetenschappen, BMG. Erasmus University Rotterdam. Rotterdam, the Netherlands*
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2017-2020	Health Technology Assessment *Tutor. Health Economics, Policy & Law. Erasmus University Rotterdam. Rotterdam, the Netherlands*
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Presentations

Podium

2018	The value of real-world data in reimbursement decisions of oncology drugs *FIGON Dutch Medicines Days. Ede, the Netherlands*

Poster

2014	The importance of long-term surveillance of stage IB melanomas: Low survival subsequent to recurrence *ISPOR 17th Annual European Congress. Amsterdam, the Netherlands*
2015	Improved survival with ipilimumab in patients with metastatic melanoma in real-world clinical practice: First results of the Dutch Melanoma Treatment Registry *ISPOR 18th Annual European Congress. Milan, Italy*

2015	Improved survival in patients with metastatic melanoma in real-world clinical practice: First results of the Dutch Melanoma Treatment Registry *ISPOR 18th Annual European Congress. Milan, Italy*
2016	Real-world outcomes of ipilimumab in patients with advanced cutaneous melanoma in the Netherlands *ISPOR 19th Annual European Congress. Vienna, Austria*
2016	Real-world treatment patterns and outcomes of novel treatments in patients with advanced cutaneous melanoma in the Netherlands *ISPOR 19th Annual European Congress. Vienna, Austria*
2016	Healthcare resource use alongside novel treatments for advanced cutaneous melanoma in the Netherlands *ISPOR 19th Annual European Congress. Vienna, Austria*
2018	End-of-life care in patients with metastatic cutaneous melanoma in the Netherlands *ISPOR 21st Annual European Congress. Barcelona, Spain*
2018	Reporting follow-up in survival analyses: Informative of not? *ISPOR 21st Annual European Congress. Barcelona, Spain*

LIST OF PUBLICATIONS

Included in this thesis

Leeneman B, Schreuder K, Uyl-de Groot CA, et al. Stage-specific trends in incidence and survival of cutaneous melanoma in the Netherlands (2003-2018): A nationwide population-based study. *Eur J Cancer.* 2021;154:111-119.

Leeneman B, Blommestein HM, Coupé VMH, et al. Real-world healthcare costs of localized and regionally advanced cutaneous melanoma in the Netherlands. *Melanoma Res.* 2021;31(3):249-257.

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Leeneman B, Franken MG, Coupé VMH, et al. Stage-specific disease recurrence and survival in localized and regionally advanced cutaneous melanoma. *Eur J Surg Oncol.* 2019;45(5):825-831.

Franken MG*, **Leeneman B***, Gheorghe M, Uyl-de Groot CA, Haanen JBAG, van Baal PHM. A systematic literature review and network meta-analysis of effectiveness and safety outcomes in advanced melanoma. *Eur J Cancer.* 2019;123:58-71.
*Both authors contributed equally.

Jochems A*, **Leeneman B***, Franken MG, et al. Real-world use, safety, and survival of ipilimumab in metastatic cutaneous melanoma in the Netherlands. *Anticancer Drugs.* 2018; 29(6):572-578.
*Both authors contributed equally.

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Not included in this thesis

Schouwenburg MG, Jochems A, **Leeneman B**, et al. Vemurafenib in BRAF-mutant metastatic melanoma patients in real-world clinical practice: prognostic factors associated with clinical outcomes. *Melanoma Res.* 2018;28(4):326-332.

Jochems A, Schouwenburg MG, **Leeneman B**, et al. Dutch Melanoma Treatment Registry: Quality assurance in the care of patients with metastatic melanoma in the Netherlands. *Eur J Cancer.* 2017;72:156-165.

De Groot S, van der Linden N, Franken MG, et al. Balancing the optimal and the feasible: A practical guide for setting up patient registries for the collection of real-world data for health care decision making based on Dutch experiences. *Value Health.* 2017;20(4):627-636.

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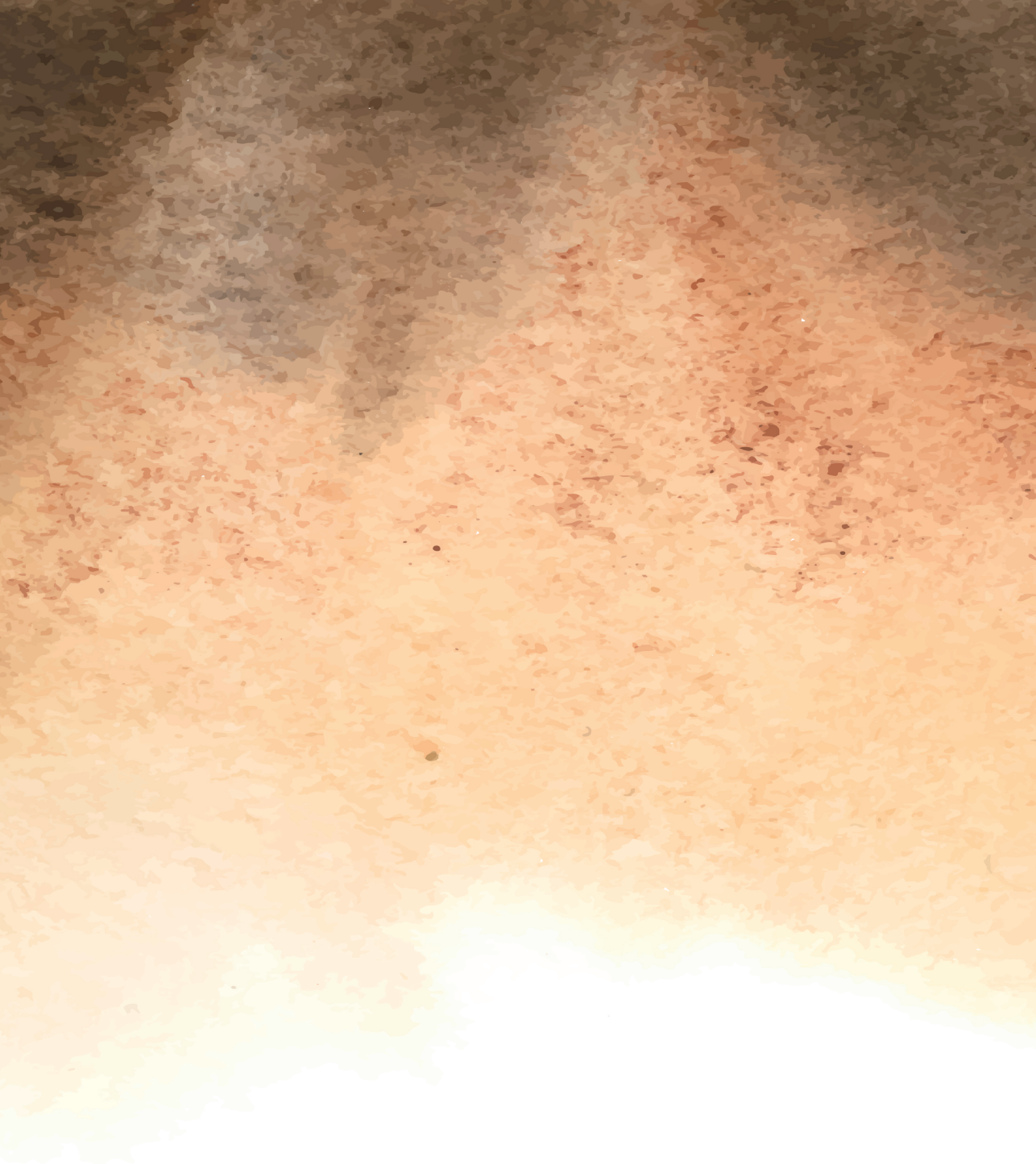

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