European Journal of Cancer 192 (2023) 113288

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Health care and socioeconomic costs for long-term survivors after implementation of checkpoint-inhibitors and targeted agents for metastatic melanoma

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Received 16 May 2023; Received in revised form 27 July 2023; Accepted 1 August 2023
Available online 19 August 2023

KEYWORDS
Metastatic melanoma;
Long-term survivors;
Health economic analysis;
Productivity costs;
Immune checkpoint-inhibitor;
Targeted therapy;
Nation-wide cohort

Abstract ***Background:*** Real-life data on health care costs and loss of productivity after implementing new agents for metastatic melanoma are important to supplement model-based economic data.
Materials and methods: All patients registered in the Danish Metastatic Melanoma Database (DAMMED) and the National Patient Registry in 2007–2011 were compared to 2012–2016 after the implementation of checkpoint inhibitors and targeted therapy. Health care costs, social transfer income (STI), and loss of productivity were calculated with a 2-step one model generalised linear regression (GLM) model. Medicine costs were calculated separately.
Results: In 2007–2011, 70 (15%) out of 464 patients were long-term survivors compared to 347 (32%) out of 1089 patients in 2012–2016. Total health care costs per patient year were significantly lower in the first treatment year (€41.457 versus €60.547, relative change (RC) 0.72, 95% confidence interval (CI) 0.56–0.94, p = 0.015) and without significant difference the second year in 2012–2016 compared to 2007–2011. Medicine costs per patient year increased the first (€85.464 versus €26.339, RC 3.39, 95% CI 2.61–4.41, p < 0.001) and the second (€26.464 versus €11.150, RC 2.59, 95% CI 1.98–3.40, p < 0.001) year in 2012–2016 compared

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https://doi.org/10.1016/j.ejca.2023.113288
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to 2007–2011. Productivity increased for long-term survivors in 2012–2016 in contrast to 2007–2011.

Conclusion: Implementation of targeted therapy and checkpoint-inhibitors has increased medicine costs more than three-fold for long-term survivors. Total health care costs excluding medicine costs were significantly lower for long-term survivors the first and without change the second treatment year in 2012–2016 compared to 2007–2011. However, the number of treated patients increased which leads to an increase in overall total health care costs. Importantly, productivity increased for long-term survivors in 2012–2016.

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1. Introduction

Malignant melanoma (MM) is an aggressive cancer disease with an increasing incidence-rate worldwide [1]. Up till 2011, only palliative chemotherapy or for selected patients cytokine-based immunotherapy was standard-of-care treatment resulting in a dismal median overall survival (OS) of 6 months [2]. The CTLA-4 inhibitor Ipilimumab was the first immune checkpoint-inhibitor (ICI) to be approved by the European Medical Agency and the United States Food and Drug Agency in 2011. Treatment with a PD-1 inhibitor was approved and implemented in routine practice in 2016 while the first BRAF-inhibitor was approved in 2011 and MEK-inhibitor in 2013. All drugs have shown efficacy in MM [3–9] but results cannot be completely transferred to real-life patient populations due to comorbidity and poor performance status (PS). Yet, we demonstrated in an earlier study that the implementation of ICI as standard-of-care treatment has led to improved outcomes in a nationwide cohort of real-life patients [10]. Median OS increased from 8.3 months in 2008–2011 to 11.3 months in 2012–2016 and the proportion of long-term survivors above 3 and 5 years doubled.

The downside is the medicine cost which challenges health care (HC) systems around the world. Medicine costs are estimated to account for 80–90% of total HC costs [11]. Most health economic cost analyses are model-based analyses generated from clinical trial data or selected patient populations. Cost-effectiveness calculation from prospective clinical studies is the norm but lacks long-term follow-up as the real benefit from ICI is the durability of response and potential long-term survival [12].

Many factors influence treatment choice in real-life patients such as PS, disease burden, and comorbidity, and as indicated in our previous study some patients obtain long-term survival in later treatment lines. This is not reflected in health economic analyses focusing on a single treatment line or agent. Other factors such as financial impact for the patient and the society or the ability to return to work are rarely reported. It is therefore critical to evaluate the economic influence on the whole treatment course to fully comprehend the socioeconomic consequences of implementing an expensive but effective new treatment paradigm for a nation-wide cohort of patients with MM. We analysed costs related to the patient's whole treatment course as well as socioeconomic costs related to loss of income.

2. Materials and methods

All Danish patients starting first-line treatment between 1st January 2007 to 31st December 2016 were identified in the nationwide Danish Metastatic Melanoma Database (DAMMED). The database covers more than 95% of patients with MM and contains data on baseline characteristics, treatment type, response, reason for treatment cessation, date of progression, and death.

Civil registration numbers were used to extract anonymous data from the National Patient Registry (NPR). NPR contains information on all inpatient and outpatient contact with somatic, psychiatric, and private hospitals in Denmark. All patients from the DAMMED database were included in this registry study if they were registered in NPR with an International Classification of Diseases 10 (ICD-10) diagnose code C43 for MM and a procedure code for systemic therapy with temozolomide, dacarbazine, interleukin-2, interferon-alpha, vemurafenib, dabrafenib, trametinib, encorafenib, cobimetinib, binimetinib, ipilimumab, pembrolizumab, nivolumab or dendritic cell vaccination.

A cut-off between 2007–2011 and 2012–2016 was chosen as ipilimumab was generally implemented in routine practice in 2012. Patients from 2007 to 2011 were excluded if they survived into 2012–2016 and received ICI or targeted therapy (TT). Patients surviving above 3 years after treatment initiation were registered as long-term survivors. Costs for all patients were also analysed.

A control cohort to each treatment cohort was established by randomly selecting persons from the civil registration system in a 1:4 patient-to-control ratio according to age, gender, civil status, and place of residence.

2.1. Costs estimates

Costs were divided in HC and productivity costs in 2007–2011 compared to 2012–2016. Costs were measured per patient year to avoid underestimation of costs

due to high mortality. A two-year follow-up period were chosen to approach a lifetime horizon and adjusted to 2018 prices. Costs were measured in Danish kroner (DKK) and converted to euros (€1: DKK 7.44). Analyses were made from a societal/government perspective. Discounting was omitted as median OS was less than a year.

2.2. Health care costs

HC costs represent the value of resources used on therapy, care, and rehabilitation in the primary and secondary HC sectors. The NPR is the basis for calculating HC costs through Diagnoses Related Group (DRG) and Danish Ambulatory Group System (DAGS) tariffs excluding detailed anti-neoplastic medicine costs. All tariffs are available through the Danish Health Authority´s homepage [13,14]. The calculated HC costs covers all costs in the primary HC sector, prescription medicine, outpatient and inpatient costs related to their cancer diagnosis and to all comorbid conditions. The hospital receives reimbursement from the government based on each patient´s individual combination of DRG and DAGS tariffs related to each patient diagnose and procedures performed under every out- and inpatient visit.

Anti-neoplastic medicine is provided free of charge for the patients and some medicine costs are therefore included in the DRG and DAGS tariffs. However, the DRG and DAGS tariffs cover an average out/inpatient visit with regards to diagnose, procedure, and visit but costs of TT or ICI are highly underestimated. Medicine costs were therefore calculated separately. Prices were obtained from the national procurement service (Amgros) if disclosed. Some anti-neoplastic treatment prices have not been disclosed and insights to these prices were given in discretion to do this analysis under the guarantee that they remained undisclosed.

Costs for prescription medicine were obtained from the pharmaceutical database registry (Lægemiddeldatabasen) [15] while primary care costs according to use and frequency were obtained through the registry for health insurance (Sygesikringsregisteret) [16].

2.3. Productivity costs

Productivity costs represent the value of resources lost due to disease-related work disability and premature mortality. We assessed income from employment status and loss of productivity due to disease-related work disability for patients between 18 and 64 (retirement age) years of age. Employment status, income, and social transfer income (STI) were extracted from the Danish income registry [17].

STI can be divided into temporary and permanent benefits. The temporary STI consists of unemployment benefits, social security benefits, and sick pay. The permanent STI consists of age-, disability-, and early retirement pension. All are registered in the Danish income registry. They are derived from public assets and represent financial support from the taxpayers to the recipient but they do not represent a net increase in society´s resources and were therefore not included in productivity costs.

3. Statistical analysis

In the total HC cost and income analyses for each treatment period we used a 2-step one model generalised linear regression (GLM) model with a gamma distribution and link=log to estimate the difference in cost and income between case and control groups. The same 2-step one model GLM regression model was used in the total HC cost and income analysis estimating the difference between the 2 treatment groups and in the detailed medicine cost analysis where patients were compared between 2012–2016 and 2007–2011 (reference in model). In the case versus case models, we also adjusted for age and gender. Estimates for age and gender are not reported. The 2-step one model regression was used since we are estimating cost (continuous variables) and also have null value in the response variable (no inpatient cost) [18].

OS was calculated with the Kaplan-Meier method and follow-up with the reverse Kaplan-Meier method. Survival was censored at end-of-study.

A significance level of 5% ($p < 0.05$) was chosen as statistically significant.

Statistical analysis was performed using SAS 9.4 TS Level 1M5 (SAS, Inc., Cary, NC, USA).

4. Results

Eighteen-hundred-and-seventy-seven patients were registered as receiving systemic therapy for MM in the DAMMED database between 1st January 2007 and 31st December 2016. However, 324 patients were omitted from the analyses as they were not sufficiently registered in the NPR (For flowsheet see Fig. 1). In 2007–2011, 464 patients received treatment compared to 1089 patients in 2012–2016 (Table 1). 70 (15%) and 347 (32%) patients were long-term survivors in 2007–2011 and 2012–2016, respectively. In 2012–2016 compared to 2007–2011, a higher number of patients received several lines of therapy both among long-term survivors and for all patients (for distribution see Fig. 2). Median OS and follow-up for all patients were 7 and 111 months in 2007–2011 and 11 and 52 months in 2012–2016, respectively.

4.1. Health care costs

For long-term survivors, medicine costs per patient year in 2012–2016 were more than three times higher

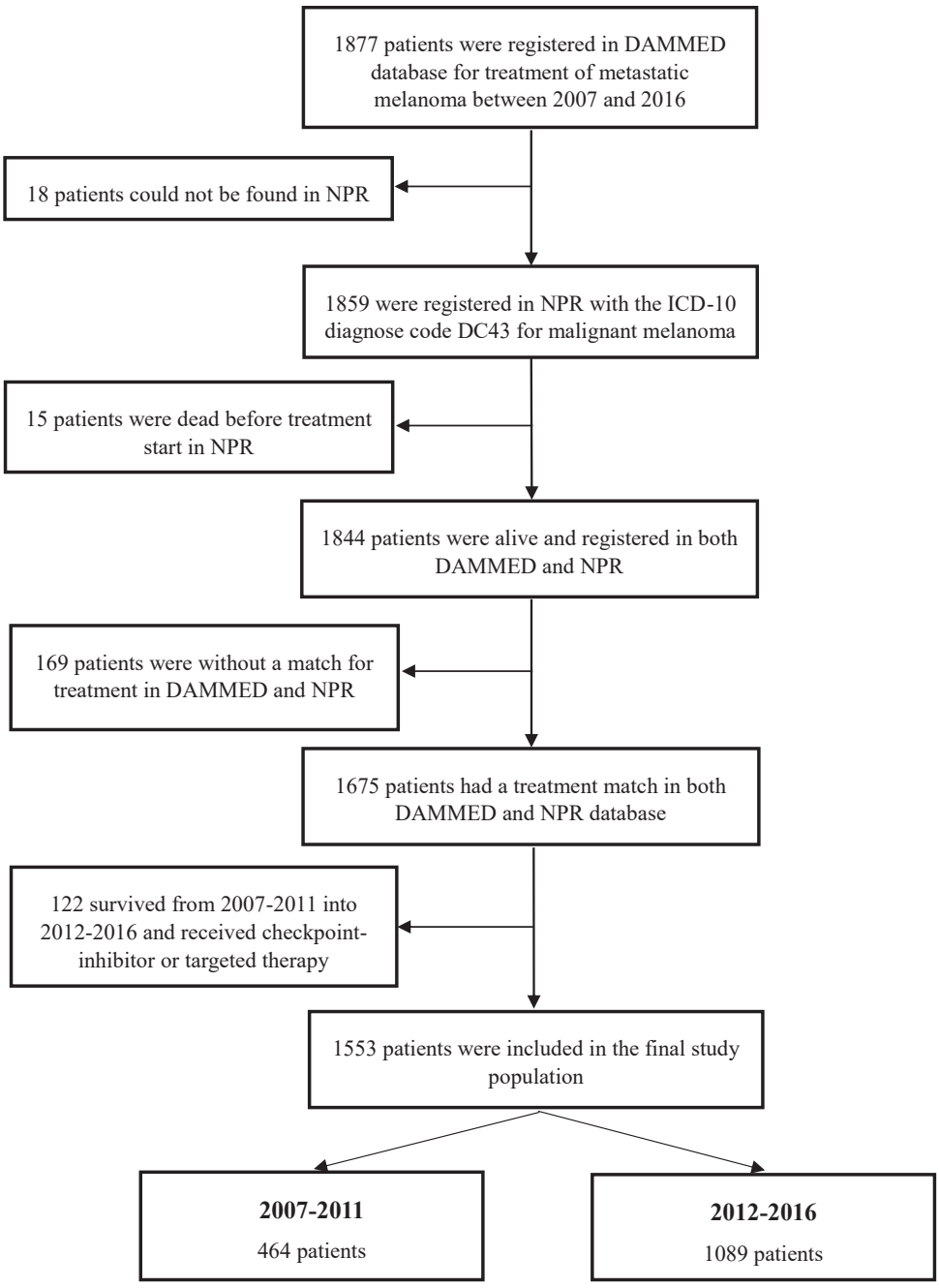


Fig. 1. Flowsheet. DAMMED = Danish Metastatic Melanoma Database; NPR = National Patient Registry.

(€85.464 versus €26.339, relative change (RC) 3.39, 95% confidence interval (CI) 2.61–4.41, $p < 0.001$) the first year and more than doubled (€26.464 versus €11.150, RC 2.59, 95% CI 1.98–3.40, $p < 0.001$) the second year after initiating treatment compared to 2007–2011 (Table 2a). In 2012–2016, separately calculated costs of TT and ICI the first treatment year were €10.379 and €67.109 per patient year, respectively. In the second year, costs of ICI dropped considerably to €14.350 while costs of TT remained at the same level. For all patients, costs followed a similar pattern with four- and three-times higher medicine costs in the first, and second year, respectively (Table 2b).

Total HC costs (excluding medicine costs) per patient year were significantly lower (€41.457 versus €60.547, RC 0.72, 95% CI 0.56–0.94, $p = 0.015$) the first year for long-term survivors in 2012–2016 compared to in 2007–2011 (Table 3). This was due to significantly lower inpatient costs (€11.965 versus €48.846, RC 0.29, 95% CI 0.22–0.38, $p < 0.001$) despite significantly higher outpatient costs (€28.557 versus €10.530, RC 2.74, 95% CI 2.11–3.54, $p < 0.001$) in 2012–2016 compared to 2007–2011. In the second year, total HC costs were not significantly different but fell to €26.645 per patient year in 2012–2016 compared to €24.584 in 2007–2011. There was no difference in total HC costs between the two

Table 1
Patient characteristics.

	Longterm survivors[a]			All patients		
	2007–2011	2012–2016	p value	2007–2011	2012–2016	p value
Number of patients (%)	70 (15%)	347 (32)		464	1089	
Male sex (%)	40 (57)	187 (54)	0.618	284 (61)	624 (57)	0.153
Married (%)	58 (83)	248 (72)	0.049	342 (74)	764 (70)	0.157
Mean age[b] (SD)	56 (11)	62 (13)		60 (13)	63 (13)	
Age[b] (%)			0.027			0.003
< 39	5 (7)	23 (7)		35 (8)	62 (6)	
40–49	17 (24)	43 (12)		54 (12)	134 (12)	
50–59	16 (23)	62 (18)		95 (21)	188 (17)	
60–69	21 (30)	113 (33)		167 (36)	342 (31)	
70–79	11 (16)	87 (25)		96 (21)	274 (25)	
> = 80	< 5	19 (6)		17 (4)	89 (8)	
M-stage			0.257			0.315
M1a	24 (34)	93 (27)		58 (13)	162 (15)	
M1b	12 (17)	63 (18)		55 (12)	130 (12)	
M1c	33 (47)	161 (46)		257 (55)	574 (53)	
M1d	< 5	27 (8)		89 (19)	197 (18)	
Treatment lines			0.002			< 0.001
1	40 (57)	115 (33)		368 (79)	522 (48)	
2	14 (20)	105 (30)		78 (17)	307 (28)	
3	9 (13)	59 (17)		11 (2)	159 (15)	
4	7 (10)	68 (20)		7 (2)	101 (9)	

SD - Standard deviation
[a] Overall survial > 3 years.
[b] At treatment start.

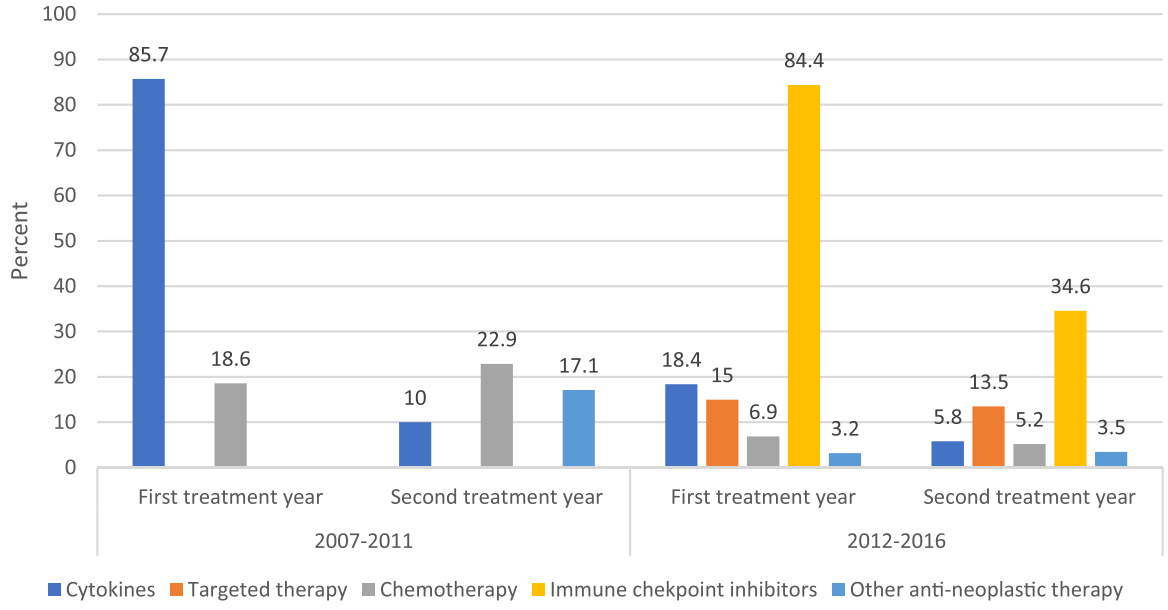


Fig. 2. Distribution of treatment regime.

periods prior to treatment start. A similar pattern was seen for all patients though costs were numerically higher (Supplementary table 1).

4.2. Productivity costs and social transfer income

Income was not significantly different from their control groups except for the second year of treatment in 2007–2011 where the income for long-term survivors were significantly lower (Table 4a,b). Between 2007–2011 and 2012–2016, income from employment for long-term survivors was not significantly different before treatment initiation (Table 3). Difference in income could not be estimated in the first treatment year as there were only few patients in the 2007–2011 cohort and many were without income from employment in

Table 2a
Mean medicine costs (euros) per patient year for longterm survivors (> 3 years) with metastatic melanoma.

	First treatment year					Second treatment year				
	2007–2011	2012–2016	RC[a]	95% CI	p value	2007–2011	2012–2016	RC[a]	95% CI	p value
Patient years	70	347				70	347			
Anti-neoplastic medicine										
Chemotherapy	1.112	305	0.43	0.32–0.57	< 0.001	683	114	0.17	0.13–0.22	< 0.001
Cytokines	23.214	6.333	0.32	0.25–0.41	< 0.001	1.013	816	0.93	0.70–1.22	0.577
Targeted therapy	0	10.379	n.a.			0	10.047	n.a.		
Immune checkpoint inhibitors		67.109	n.a.			0	14.350	n.a.		
Other anti-neoplastic therapy	2.013	1.338	0.67	0.52–0.87	0.002	9.455	1.136	0.04	0.03–0.05	< 0.001
Total medicine costs	26.339	85.464	3.39	2.61–4.41	< 0.001	11.150	26.464	2.59	1.98–3.40	< 0.001

RC=Relative change for 2007–2011 compared to 2012–2016; n.a.=not applicable; CI=Confidence interval.
[a] A 2-step generalised linear regression model with gamma distribution and link=log is used to control forage, gender and marital status.

Table 2b
Mean medicine costs (euros) per patient year for all patients with metastatic melanoma.

	First treatment year					Second treatment year				
	2007–2011	2012–2016	RC[a]	95% CI	p value*	2007–2011	2012–2016	RC[a]	95% CI	p value[a]
Patient years	282	779				97	419			
Anti-neoplastic medicine										
Chemotherapy	2.932	1.109	0.32	0.28–0.37	< 0.001	1011	301	0.31	0.25–0.38	< 0.001
Cytokines	14.838	5.431	0.37	0.32–0.42	< 0.001	748	778	1.23	0.97–1.55	0.083
Targeted therapy	0	19.938	n.a.			0	12.006	n.a.		
Immune checkpoint inhibitors	0	60.362	n.a.			0	14.002	n.a.		
Other anti-neoplastic therapy	2.473	1.513	0.58	0.50–0.66	< 0.001	7.407	1.285	0.06	0.05–0.08	< 0.001
Total medicine costs	20.243	88.353	4.64	4.04–5.32	< 0.001	9.166	28.373	3.39	2.69–4.27	< 0.001

RC=Relative change for 2007–2011 compared to 2012–2016; n.a.=not applicable; CI=Confidence interval.
[a] A 2-step generalised linear regression model with gamma distribution and link=log is used to control for age, gender and marital status.

that period but it was significantly higher in the second year in 2012–2016 compared to 2007–2011.

STI was not significantly different between long-term survivors and controls neither before nor after treatment initiation in 2012–2016 (Table 4a,b). Almost similar was observed in 2007–2011 except STI increased significantly for long-term survivors in the second treatment year. Over time in 2007–2011, long-term survivors got higher sick pay and disability pension explaining the increase in STI the second treatment year. In 2012–2016, a similar tendency was observed for long-term survivors though STI remained unchanged.

Between 2007–2011 and 2012–2016, there was no significant difference in STI after treatment initiation, but a significantly lower sick pay and early retirement pension was observed together with a tendency towards higher disability pension in the latter period (Table 3). Age pension was generally higher in 2012–2016 compared to 2007–2011 as long-term survivors were older in the 2012–2016 cohort. Some of the social transfer subsections could not be compared due to low numbers.

In 2007–2011, productivity cost (foregone earnings) per patient year kept increasing for long-term survivors from €509 before treatment start to €2.470 and €9.133 the first, and second treatment year, respectively (Table 2). In 2012–2016, productivity costs fell from €2.048 before treatment start to €1.328 and €856 the first, and second treatment year, respectively. This indicates a drop in productivity in 2007–2011 while productivity increased in 2012–2016 for long-term survivors. The same tendency was not observed for all patients in 2012–2016.

5. Discussion

In this present study, we are the first to report total HC and productivity costs of long-term survivors based on a national cohort of real-life patients with MM. We demonstrated that total HC costs per patient year were reduced significantly in the first and unchanged in the second treatment year after implementation of new anti-neoplastic medicine such as TT and ICI. Total HC costs for long-term survivors were numerically lower than for all patients which is expected as mean hospital admissions and length of admission have been higher for the post-progression-state as well as a higher number of patients gets admitted after progression as shown in the multinational study of ipilimumab-treated patients [19]. Even though total HC costs per patient year hasn´t increased a higher number of patients were treated in 2012–2016 compared to 2007–2011. The higher number of patients could be caused by an increase in incidence-rate but it is uncertain if it is followed by an increase in metastatic disease [20,21]. Possibly, better treatment

Table 3
Health care cost, income and productivity costs for longterm survivors (> 3 years) with metastatic melanoma. Prices are in euros per patient year.

	1 year before treatment start					First treatment year					Second treatment year				
	2007–2011	2012–2016	RC[a]	95% CI	p value	2007–2011	2012–2016	RC[a]	95% CI	p value	2007–2011	2012–2016	RC[a]	95% CI	p value
Patient years	**70**	**347**				**70**	**347**				**70**	**347**			
Health care cost															
Outpatient	6.553[b]	8.926[b]	1.38	1.06–1.80	**0.016**	10.530[b]	28.557[b]	2.74	2.11–3.54	**< 0.001**	11.400[b]	19.841[b]	1.79	1.38–2.33	**< 0.001**
Inpatient	13.987[b]	12.006[b]	0.90	0.69–1.17	0.416	48.846[b]	11.965[b]	0.29	0.22–0.38	**< 0.001**	11.739[b]	5.771[b]	0.55	0.43–0.72	**< 0.001**
Emergency room	23[b]	29[b]	1.09	0.84–1.42	0.506	26[b]	23[b]	0.87	0.68–1.13	0.307	18[b]	49[b]	2.20	1.66–2.91	**< 0.001**
Prescription medicine	576[b]	384	0.68	0.52–0.87	**0.003**	773[b]	470[b]	0.62	0.48–0.80	**< 0.001**	970[b]	548[b]	0.58	0.45–0.75	**< 0.001**
Primary health sector	426	452	0.97	0.75–1.27	0.849	372	442	1.10	0.85–1.42	0.491	457	436	0.86	0.66–1.11	0.251
Total health care cost	**21.565**[b]	**21.797**[b]	**1.04**	**0.80–1.35**	**0.781**	**60.547**[b]	**41.457**[b]	**0.72**	**0.56–0.94**	**0.015**	**24.584**[b]	**26.645**[b]	**1.14**	**0.88–1.48**	**0.333**
Income from employment	**35.679**	**25.743**	**0.99**	**0.76–1.29**	**0.934**	**32.557**	**24.298**	n.a.	n.a.	n.a.	**24.780**[b]	**23.206**	**1.49**	**1.13–1.95**	**0.004**
Foregone earnings	509	2.048				2.470	1.328				9.133	856			
Social transfer income															
Unemployment benefit (A-kasse)	941[b]	181[b]	n.a.	n.a.	n.a.	378	102[b]	n.a.	n.a.	n.a.	30[b]	104[b]	n.a.	n.a.	n.a.
Social security	237[b]	475[b]	n.a.	n.a.	n.a.	125	319[b]	n.a.	n.a.	n.a.	82[b]	435	n.a.	n.a.	n.a.
Sick pay (public funded)	487	593[b]	n.a.	n.a.	n.a.	1.722[b]	952[b]	0.22	0.16–0.30	**< 0.001**	3.306[b]	1.035[b]	0.40	0.30–0.53	**< 0.001**
Disability pension	460[b]	641[b]	n.a.	n.a.	n.a.	504[b]	829[b]	n.a.	n.a.	n.a.	1.297	1.024[b]	1.33	1.00–1.78	0.050
Early retirement	1.298	960	0.91	0.69–1.19	0.482	2.193[b]	909[b]	0.44	0.34–0.58	**< 0.001**	1.960	736[b]	0.38	0.29–0.49	**< 0.001**
Age pension	2.987	7.343	2.46	1.90–3.19	**< 0.001**	3.243	7.682	2.39	1.85–3.09	**< 0.001**	3.785	8.340	2.25	1.74–2.91	**< 0.001**
Total social transfer income	**6.409**	**10.193**	**1.39**	**1.08–1.80**	**0.012**	**8.166**	**10.793**	**1.12**	**0.87–1.46**	**0.372**	**10.460**[b]	**11.673**	**0.90**	**0.69–1.17**	**0.437**

RC=Relative change for 2007–2011 compared to 2012–2016; CI=Confidence interval; n.a.=not applicable.
[a] A generalised linear model with gamma link is used to control for age, gender and civil status between treated cohorts in 2007–2011 and 2012–2016.
[b] significant difference between treated and background control cohorts (bootstrapped t-test, p value < 0.05).

Table 4a
Productivity costs for longterm survivors (> 3 years) with metastatic melanoma in 2007–2011. Prices are in euros per patient year.

	1 year before treatment start			First treatment year			Second treatment year		
	Patients	Controls	p value	Patients	Controls	p value	Patients	Controls	p value
Income from employment	**35.679**	**36.188**	**0.916**	**32.557**	**35.027**	**0.586**	**24.780**	**33.913**	**0.02**
Foregone earnings	509			2.470			9.133		
Social transfer income									
Unemployment benefit (A-kasse)	941	553	**0.001**	378	391	0.684	30	543	**< 0.001**
Social security	237	122	**< 0.001**	125	139	0.482	82	263	**< 0.001**
Sick pay (public funded)	487	448	0.516	1.722	325	**< 0.001**	3.306	380	**< 0.001**
Disability pension	460	1.475	**< 0.001**	504	1.528	**< 0.001**	1.297	1.424	0.452
Early retirement	1.298	1.055	0.116	2.193	1.439	**0.002**	1.960	1.746	0.419
Age pension	2.987	2.536	0.212	3.243	2.829	0.270	3.785	3.242	0.270
Total social transfer income	**6.409**	**6.188**	**0.793**	**8.166**	**6.650**	**0.126**	**10.460**	**7.598**	**0.018**

Table 4b
Productivity costs for longterm survivors (> 3 years) with metastatic melanoma in 2012–2016. Prices are in euros per patient year.

	1 year before treatment start			First treatment year			Second treatment year		
	Patients	Controls	p value	Patients	Controls	p value	Patients	Controls	p value
Income from employment	**25.743**	**23.694**	**0.167**	**24.298**	**22.970**	**0.346**	**23.206**	**22.350**	**0.518**
Foregone earnings	2.048			1.328			856		
Social transfer income									
Unemployment benefit (A-kasse)	181	395	**< 0.001**	102	263	**< 0.001**	104	193	**< 0.001**
Social security	475	353	**< 0.001**	319	390	**0.001**	435	414	0.412
Sick pay (public funded)	593	261	**< 0.001**	952	242	**< 0.001**	1.035	141	**< 0.001**
Disability pension	641	1.052	**< 0.001**	829	989	**0.004**	1.024	908	**0.042**
Early retirement	960	1.069	0.075	909	1.268	**< 0.001**	736	1.097	**< 0.001**
Age pension	7.343	6.902	0.302	7.682	7.403	0.5	8.340	8.000	0.479
Total social transfer income	**10.193**	**10.032**	**0.793**	**10.793**	**10.556**	**0.713**	**11.673**	**10.753**	**0.175**

Income and public tra+A1:J28nsfers are stock variables on calendar years. Thus income and public transfers can be on both sides of the index date. 2-step one model GLM regression model with a gamma distribution and link=log to estimate the difference in cost or income between case and control.

options lead to more patients being referred for treatment. In either case it leads to a substantial increase in overall treatment cost for the HC providers. In Denmark, there is no defined limit of drug costs but cost-effectiveness/cost-per-quality-of-life studies together with expected number of patients and adverse events are taken into account by an independent medical counsel before implementing the treatment as a standard treatment option. With the anticipated change in demographic HC and medicine costs will continue to rise unless a global effort is made towards changing how drugs are reimbursed.

Separately calculated, costs of anti-neoplastic medicine for long-term survivors increased three-fold the first year after treatment initiation in 2012–2016 compared to 2007–2011. The decrease in medicine costs the second year in 2012–2016 caused by a drop in ICI costs is likely explained by ipilimumab being limited to 4 cycles. Some responding patients may even stop PD-1 blockage and remain in remission while TT needs continuedly dosing to be effective. Anti-neoplastic medicine especially ICI was the main driver of costs with a magnitude higher than the total HC costs.

To our knowledge, no other study has reported costs for long-term survivors but other extensive studies of real-life populations have been performed [11,22]. Due to heterogeneity in patient population and methodology (trial-based, modelling studies or retrospective cohorts) [23] it is difficult to compare costs across studies. Barbieri et al examined the intercountry variability between cost-effectiveness studies in Western Europe and found that variability was mostly due to varying parameters such as difference in efficacy, inpatient costs, medicine costs or resource use [24].

Most economic HC cost analyses are model-based which incorporate data from clinical trials. They provide a comparison often to standard-of-care treatment and an estimate for future costs or if available incremental cost per life year gained to HC providers prior to local use. However, treating real-life patients are often more complex as the majority of patients with MM do not resemble clinical trial patients [25] and real-life data are required to fully understand cost implications. In our study, we focused on a patient´s whole treatment course instead of only one treatment line or type. If focus is only on one treatment type or line, we risk omitting patients who obtain long-term survival on a subsequent treatment line or patients who had to change treatment regime due to serious adverse events.

Surprisingly, there was no difference in income or STI for long-term survivors in 2012–2016 compared to their control group. This indicated together with the drop in productivity costs over time that productivity increased for long-term survivors in 2012–2016. Same tendency was not observed for all patients in 2012–2016 (data not shown) as productivity costs increased after treatment initiation. A gap in income or an increase in STI before or after treatment initiation could have been expected anticipating that most patients wouldn´t be able to work due to adverse events or deteriorating PS. Instead, we found that controls had higher disability and early retirement pension before treatment initiation than patients. These findings could indicate an increased ability to remain affiliated with work and a difference in social status towards higher income despite their match for age, gender, marital status, and region of residence. These data are interesting but should be interpreted with caution as the patient populations are small.

In our study, emphasis should be put on assessing the changes measured as relative change instead of the actual costs which should be interpreted with caution. Even though this is one of the largest studies of health economic analyses of patients and long-term survivors with MM the patient numbers are general low for a register-based study. The strength of the study is the national-based cohort with long follow-up data, quality registries connected by personal security numbers which makes it possible to follow patients through their whole treatment course with surgeries, medical treatment, palliative care, and end of life support.

6. Conclusion

Implementation of TT and ICI has increased medicine costs more than three-fold for long-term survivors. Total HC costs per patient year excluding medicine costs were significantly lower for long-term survivors the first treatment year and without change the second treatment year in 2012–2016 compared to 2007–2011. However, the number of treated patients increased which leads to an increase in overall total HC costs. Importantly, productivity increased for long-term survivors in 2012–2016.

Funding

The study was funded by government funds through the Ministry of Finance. The Danish Metastatic Melanoma database received financial support from BMS, Roche, MSD and Novartis. The funders have no role in the design of the study; in the collection, analyses or interpretation of data; in the writing or in the decision to publish the results.

CRediT authorship contribution statement

Anne Vest Soerensen: Conceptualization, Formal analysis, Investigation, Data curation, Visualization, Writing – original draft preparation, Writing – review & editing, Project administration. **Jakob Kjellberg:** Formal analysis, Investigation, Supervision, Project administration. **Rikke Ibsen:** Formal analysis, Investigation, Data curation, Supervision, Project administration. **Lars Bastholt:** Investigation, Data curation. **Henrik Schmidt:** Investigation, Data curation. **Inge Marie Svane:** Conceptualization, Investigation, Data curation, Visualization, Supervision, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Inge Marie Svane has received honoraria for consultancies and lectures from IO Biotech, Novartis, MSD, Pierre Fabre, BMS, Novo Nordisk, TILT Bio; research grants from IO Biotech, BMS, Lytix, Adaptimmune, TILT Bio. A.V.S., J.K., R.I., L.B., and H.S. has no competing interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113288.

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