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Original Research

More than 5000 patients with metastatic melanoma in Europe per year do not have access to recommended first-line innovative treatments

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Abstract ***Background:*** Despite the efficacy of innovative treatments for metastatic melanoma, their high costs has led to disparities in cancer care among different European countries. We analysed the availability of these innovative therapies in Europe and estimated the number of patients without access to first-line recommended treatment per current guidelines of professional entities such as the European Society for Medical Oncology (ESMO), the European Organisation for Research and Treatment of Cancer (EORTC), the European Association of Dermato-Oncology (EADO), and European Dermatology Forum (EDF).
Materials and methods: Web-based online survey was conducted in 30 European countries with questions about the treatment schedules from 1st May 2015 to 1st May 2016: number of metastatic melanoma patients, registration and reimbursement of innovative medicines (updated data, as of 1st October 2016), percentage of patients treated and availability of clinical studies and compassionate-use programmes.
Results: The recommended BRAF inhibitor (BRAFi) + MEK inhibitor (MEKi) combination was both registered and fully reimbursed in 9/30 (30%) countries, and in 13/30 (43%) (all from Eastern Europe) not reimbursed. First-line immunotherapy with anti-PD1 antibodies was registered and fully reimbursed in 14/30 (47%) countries, while in 13/30 (43%) (all from Eastern Europe) not reimbursed. It was estimated that in Europe 19,600 patients with metastatic melanoma are treated, and 5238 (27%) do not have access to recommended first-line therapy. Significant correlation was found between human development index (HDI, UNDP report 2015), ($r = 0.662$; $p < 0.001$), health expenditure per capita ($r = 0.695$; $p < 0.001$) and the Mackenbach score of health policy performance ($r = 0.765$; $p < 0.001$) with the percentage of patients treated with innovative medicines and a number of reimbursed medicines.
Conclusions: Great discrepancy exists in metastatic melanoma treatment across Europe. It is crucial to increase the awareness of national and European policymakers, oncological societies, melanoma patients' associations and pharma industry.

1. Introduction

A tremendous breakthrough in the treatment of metastatic melanoma occurred in recent years with the targeted inhibition of RAF-MEK-ERK (i.e. the MAP kinase) pathway with the use of MAP kinase inhibitors on the one hand and immunotherapy using immune checkpoint inhibitors on the other that have an impressive effect on overall survival. Two-year survival rates have reached 50% with either anti-PD1 immunotherapy (immune checkpoint inhibitor) or the BRAF/MEK inhibitor combination (e.g. BRAF inhibitors, such as vemurafenib or dabrafenib and MEK inhibitors, such as cobimetinib or trametenib) compared to <10% with chemotherapy [1–4]. Early clinical trials showed a dramatic improvement of 34% in 5-year survival rate for nivolumab as the first PD1-antibody tested in melanoma [2–4]. To date, the longest follow-up suggests a 3-year survival rate as high as 44% with both immunotherapy and combined targeted therapies. If patients have normal values of lactate dehydrogenase (LDH), a 3-year survival of up to 60% appears to be realistic [2–4].

These agents have become first-line recommended treatments by major international melanoma guidelines including those by the European Society of Medical Oncology (ESMO), the European Dermatology Forum

(EDF), the European Organisation for Research and Treatment of Cancer (EORTC) and the European Association of Dermato-Oncology (EADO) [5–7]. However, their high cost has led to disparities in cancer care of metastatic melanoma patients in different European countries and different patient populations in the United States of America (USA) based on their insurance status [8–16]. These disparities were recorded previously for other types of cancer and have been shown to be associated with differences in overall survival [15–18].

The scientific assessment of innovative treatment, i.e. registration of medicines is harmonised in the European Union (EU), through the European Medicine Agency (EMA). Conversely, the degree and timing of reimbursement is decided at a national level and varies greatly among different national healthcare systems, driven mainly by socioeconomic and political factors [19]. Health expenditure is partly dependent on gross national income and is in relation to access to innovative medicines through a reimbursement process [19–23]. For example, after registration by EMA, reimbursement occurs within 30 days in Germany, whilst reimbursement delays may reach several years in some Eastern European countries [24–26].

The degree of inequality in access to innovative treatments for melanoma in Europe is largely unexplored. A recently published ESMO study [9] showed a large difference in the availability of innovative agents for cancer treatment, particularly for metastatic melanoma, renal cell cancer and non-small cell lung cancer where access to innovative drugs defines therapeutic outcome, classical oncological treatment being mostly ineffective [9]. However, due to the limitations of the survey period, immuno-oncological agents were not evaluated in this study [9].

A clear overview on the magnitude and configuration of the disparities in access to innovative melanoma treatments across Europe is essential as an evidence-based foundation for the development of strategies to harmonise quality of healthcare and health outcomes. As a step towards this aim, we analysed the availability of newly approved therapeutic agents for metastatic melanoma in Europe and estimated the number of patients without access to first-line recommended treatment options per current European guidelines. In order to better understand the possible causes in restricted access to treatment, data were correlated with relevant parameters of socioeconomic status, like human development index, national health expenditure per capita and Mackenbach score of health system efficiency in European countries [8,27–29].

2. Materials and methods

A web-based online expert survey (SurveyMonkey tool, SurveyMonkey Inc., Palo Alto, CA 94301, USA) was conducted in 35 oncology and/or dermato-oncology reference centres from 30 European countries under the auspices of the EADO, between the 1st of May, 2015 and the 1st of August, 2016 (Table S1, supplementary file). For registration and reimbursement, an update of data was obtained by direct contact between September 15th and October 1st, 2016. The survey questionnaire (Table S2, supplementary file) included multiple choice questions about the treatment regimens and the percentages of melanoma patients treated with recommended first-line treatment for metastatic melanoma of the current European (ESMO, EDF, EORTC, EADO) guidelines during the period 1st May 2015–1st May 2016.

The total number of metastatic melanoma patients per country and the percentage of patients treated with each therapy was estimated based on available epidemiological data, the medical records from the respective oncology centres and data from the current practice in the country (for 2 countries, data were not available). Online responses were grouped by country, and data cleaning was conducted to exclude empty entries, technical error entries or invalid answers. Human development indices (HDIs) for every country were obtained from the United Nations Development Programme (UNDP) 2015 report on human development; health expenditure per capita (HEPC) details were obtained from World Bank data, while data on Mackenbach score of healthcare policy performance were extracted from the original publication [27–29]. Descriptive statistics were used to analyse the data. Regression analysis for evaluation of correlation between data on access to innovative medicines and socioeconomic status (HDI, HEPC, Mackenbach score) was done. Statistically significant correlation was considered if $p < 0.05$.

3. Results

3.1. Registration and reimbursement of new treatments in Europe

Data on registration and reimbursement of innovative medicines are presented in Fig. 1.

As of 1st October 2016, in Europe, the recommended first-line therapy for BRAF-mutated metastatic melanoma was any BRAFi + MEKi combination (vemurafenib + cobimetinib, dabrafenib + trametinib), which was both registered and fully reimbursed in 9/30 (30%) countries, while in 8/30 (27%) countries it was available with administrative work needed to obtain the treatment. This usually implies that the physician is obliged to apply individually for reimbursement by sending detailed medical data to health insurance administrators in order to gain the approval of reimbursement. This process is time-consuming and time for approval is up to 30 days, causing delays in

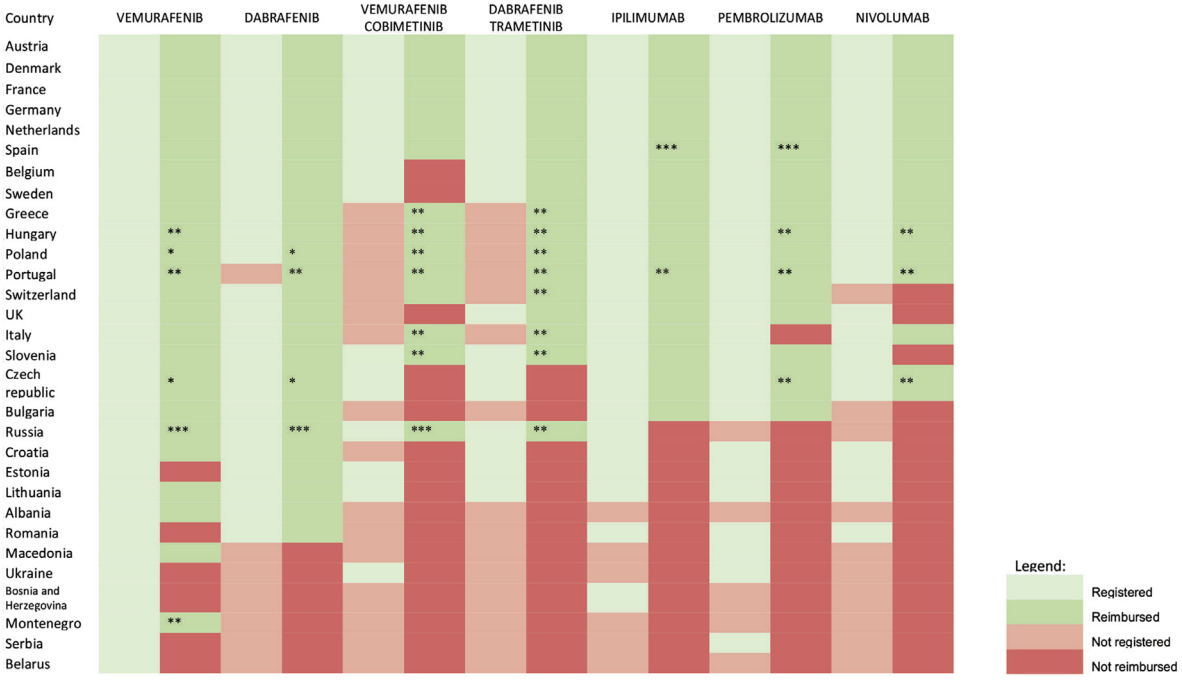

Fig. 1. Registration and reimbursement of innovative medicines in Europe on October 1, 2016. *Reimbursed, but only for first-line treatment; **Reimbursed, but with large and time-consuming administrative work needed to obtain the medicine for the patient; ***Reimbursed, but not fully available due to the restrictions in the hospital budget.

treatment. In 13/30 (43%) countries (all from Eastern Europe), BRAFi + MEKi combination was not available at all. In addition, BRAF inhibitor (BRAFi) was reimbursed in two countries (Poland, Czech Republic) only as first-line treatment. In the Russian federation, vemurafenib with or without cobimetinib and dabrafenib were not readily available because of hospital budget restrictions.

First-line immunotherapy with any of the approved anti-PD1 antibodies (pembrolizumab, nivolumab) was registered in 25/30 (83%) countries. It was fully reimbursed in 14/30 (47%) countries, in further 3/30 (10%) with individual applications to the national fund, while in 13/30 (43%) (again, all from Eastern Europe) it was not reimbursed. In Greece, nivolumab was reimbursed only as a second-line treatment in BRAF-positive patients, and not reimbursed after ipilimumab failure. In Spain, ipilimumab and pembrolizumab were not completely reimbursed due the hospital budget restrictions, and in Portugal reimbursement was possible with individual applications for reimbursement approval.

3.2. Percentage of patients treated with innovative medicines

Overall, in 50% of countries (92% are from Western Europe (WE)), chemotherapy with dacarbazine was employed in less than 10% of patients, and never as the first-line treatment. However, in 31% of countries, all from Eastern Europe (EE), dacarbazine was the only treatment available for 50–90% of patients (Table 1). Detailed data are available in the supplementary material (Figure S1).

3.3. Correlation of access to innovative agents to human development index, health expenditure per capita and Mackenbach score of health policy performance

From HDI, HEPC and Mackenbach score of health policy performance (Table 1, Fig. 2), highly significant correlation was found between human development index (HDI), ($r = 0.662$; $p < 0.001$), health expenditure ($r = 0.695$; $p < 0.001$) and the percentage of patients treated with innovative medicines. Also, highly significant correlation of medium strength was found between the number of reimbursed medicines, HDI ($r = 0.648$; $p < 0.001$) and health expenditure per capita ($r = 0.667$; $p < 0.001$) (Fig. 2). Strong, highly significant correlation was found between Mackenbach score of health policy performance and percentage of patients treated with innovative medicines ($r = 0.765$, $p < 0.001$), as well as with the number of reimbursed medicines ($r = 0.721$; $p < 0.001$) (not shown).

3.4. Availability of compassionate-use and expanded access programmes

Compassionate-use (CUPs) and expanded access programmes (EAPs) and clinical studies for metastatic

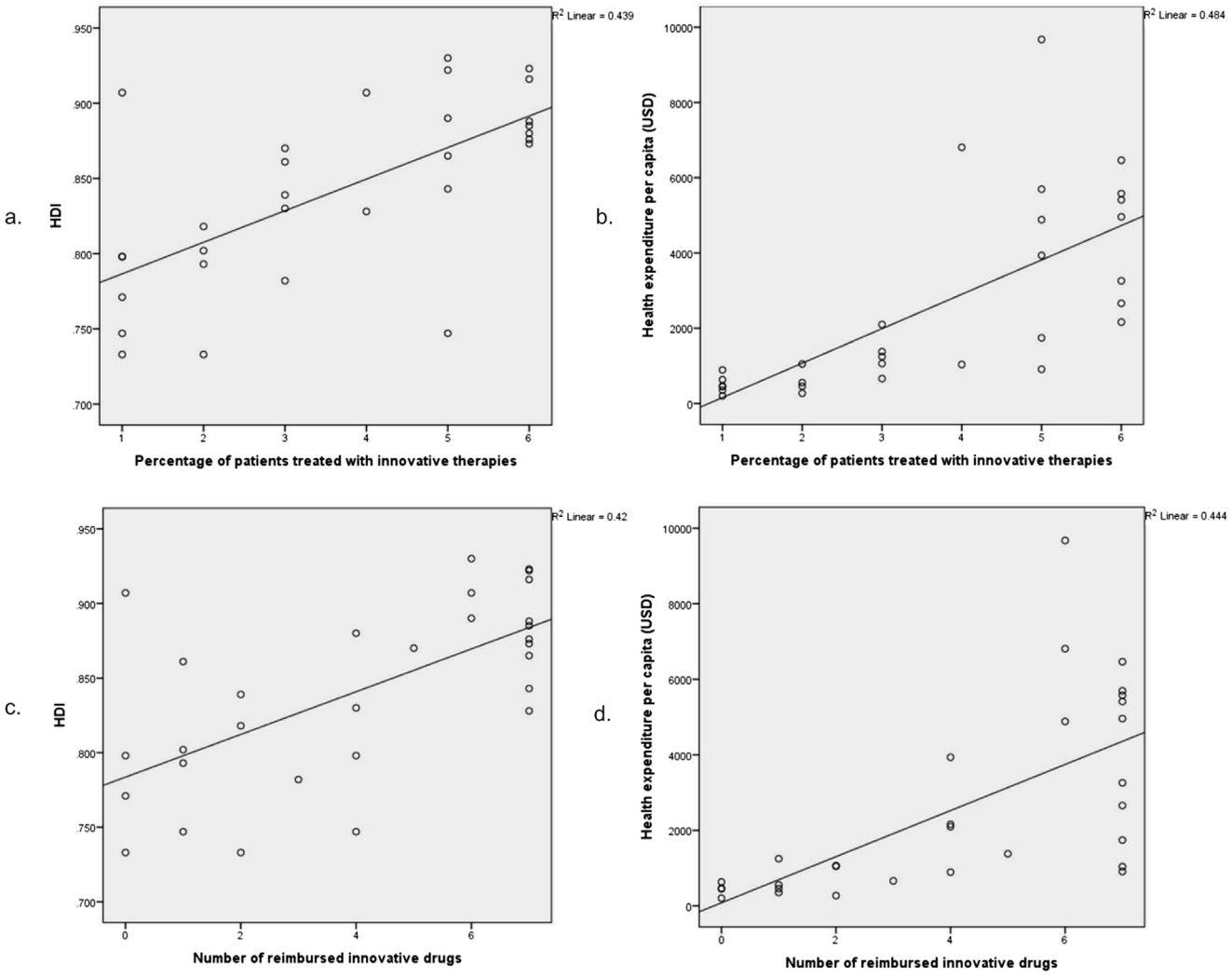

Fig. 2. Correlation of percentage of patients treated with innovative therapies and number of reimbursed innovative therapies with the human development index (HDI) and health expenditure per capita. A. A higher percentage of patients treated with innovative therapies correlates with higher HDI (r = 0.662; p < *0.001*), and B. higher health expenditure per capita (r = 0.695; *p < 0.001*) with significant correlation. C. A higher number of reimbursed medicines correlates with higher HDI (r = 0.648; *p < 0.001*), and D. higher health expenditure per capita (r = 0.667; *p < 0.001*), with significant correlation.

melanoma were available in 25/30 (83%) of countries (Table 2). In 8/30 (27%) of countries (all from Western Europe), 25–80% of patients were treated within these programmes. In 4/30 (13%) countries, although the programmes were available, the patients were not treated within these, and in 4 countries there were no programmes available at all. In most countries, the CUP/EAP programmes concerned BRAFi/MEKi, followed by pembrolizumab in 11/30 countries, nivolumab in 6/30 countries, and nivolumab/ipilimumab combination in 1 country.

At least one clinical study for stage IV melanoma was available in the survey period in 12/30 countries, 12/13 (92%) from Western, and 6/17 (35%) from Eastern Europe. In 10/30 (33%) countries, 3 or more studies were available. In 12/30 (40%) countries, no clinical studies for stage IV were available.

3.4.1. Estimated number of patients without access to innovative medicines

Experts' estimated numbers of metastatic melanoma cases for majority of countries were in line with the available data on estimated number of cancer deaths in European countries from the recent epidemiological analysis of International Agency for Research on Cancer (IARC), an intergovernmental agency under the World Health Organization of the United Nations [30]. Based on the results of our survey, it is estimated that 19,600 patients with metastatic melanoma are treated in Europe, and 5238 (26.7%), do not have access to recommended first-line therapy per European guidelines (ESMO, EORTC/EADO). These patients are, in majority, from the countries of Eastern Europe, where 7450/19,600 (39%) patients with metastatic melanoma are treated (Table 3).

Table 1
Access to innovative medicines and its correlation to human development index, health expenditure per capita and Mackenbach score of health policy performance.

	% Of patients treated with innovative therapies	Number of reimbursed innovative drugs	HDI	Health expenditure per capita (USD)	Mackenbach score of health policy performance
Switzerland	70–90%	6	0.93	9674	46
Sweden	70–90%	6	0.907	6808	89
Denmark	>90%	7	0.923	6463	43
Netherlands	70–90%	7	0.922	5694	56
Austria	>90%	7	0.885	5580	48
Germany	>90%	7	0.916	5411	35
France	>90%	7	0.888	4959	52
Belgium	70–90%	6	0.89	4884	17
United Kingdom	70–90%	4	0.747	3935	37
Italy	>90%	7	0.873	3258	31
Spain	>90%	7	0.876	2658	35
Slovenia	>90%	4	0.88	2161	15
Portugal	30–50%	4	0.83	2097	19
Greece	70–90%	7	0.865	1743	16
Czech Republic	30–50%	5	0.87	1379	12
Estonia	30–50%	1	0.861	1248	−32
Lithuania	30–50%	2	0.839	1063	−28
Croatia	10–30%	2	0.818	1050	−17
Hungary	50–70%	7	0.828	1037	−28
Poland	70–90%	7	0.843	910	−4
Russia	<10%	4	0.798	893	−69
Bulgaria	30–50%	3	0.782	662	−33
Serbia	<10%	0	0.771	633	−17
Romania	10–30%	1	0.793	557	−42
Bosnia and Herzegovina	<10%	0	0.733	464	−60
Montenegro	10–30%	1	0.802	458	−18
Belarus	<10%	0	0.798	450	−25
Macedonia	<10%	1	0.747	354	0
Albania	10–30%	2	0.733	272	−13
Ukraine	<10%	0	0.907	203	−73

HPI: human development index.

4. Discussion

In this study, large disparities in access to first-line recommended treatments for metastatic melanoma were found among countries of Europe. During the survey period, National Comprehensive Cancer Network (NCCN) guidelines as well as the ESMO guidelines recommended the combination of a BRAFi and MEK inhibitor (MEKi) for patients with a *BRAF* mutation or anti-PD1 therapy as first-line treatments [5,7]. However, BRAF + MEKi combination and anti-PD1 immunotherapy were not reimbursed until 1st October 2016 in 13/30 (43%) European countries.

It is well documented that the prices and the share of expenditure for oncology drugs are both rising [31]. This identifies the need for necessary adjustments to be made within different public health systems across Europe, which will be hard to achieve without the harmonisation of this process [31–33]. Considerable diversity within healthcare systems across EU countries regarding approval and reimbursement process of new pharmaceutical agents was documented recently [34]. Although different, most of the healthcare systems within Europe do declare universal access to healthcare, but their efficiency is largely dependent on economic parameters of the country, regardless whether it is financed from the national budget or various forms of health insurance (basic governmental, private or both) [17,19,20]. The largest population of 3600 patients with restricted access in this survey comes from the Russian federation, where oncology drugs are on the list of medicines with full coverage, and within this programme high-tech medicine care programme with innovative medicines is included [35]. However, regional budget and hospital budget restrictions lead to very restrictive inclusion of new medicines on this list, and even if the drug is declared to be reimbursed, the hospital has restricted budget to obtain it for the patients. A similar situation is evident in the many countries of Eastern and South-Eastern Europe where the budget restrictions lead to delayed inclusion of innovative medicine in the reimbursement list [11,36].

This trend of restriction in access is emerging also in other countries of Europe. The 2012 European Commission Transparency Directive 89/105/EEC recommends a limit of 120 days for national pricing and reimbursement decisions [25]. In reality, only the United Kingdom (UK) and Germany met this requirement and only for market access in 2014, while the average time

Table 2
Compassionate-use, expanded access programmes and clinical trials for metastatic melanoma in Europe.

	Compassionate-use and expanded access programmes			Clinical studies (number)	
	Availability	Percentage of patients treated	Agent*	Stage III	Stage IV
Austria	Yes	NA	DT, VC, P	1	1
Belgium	Yes	80%	DT, VC	2	0
Denmark	Yes	35%	DT, P	1	5
France	Yes	30%	DT	2	6
Germany	Yes	10%	DT, VC, P, N	3	2
Greece	Yes	60%	DT, VC, P, N	1	3
Italy	Yes	30%	DT, VC, P, N	1	4
Netherlands	Yes	12%	P	NA	5
Portugal	Yes	NA	DT, VC, P	1	2
Spain	Yes	5%	DT, P	6	6
Sweden	Yes	25%	DT, VC, P, N, IN	1	5
Switzerland	Yes	15%	DT, VC	1	4
United Kingdom	Yes	15%	DT, P	NA	NA
Albania	Yes	0	DT	0	0
Belarus	No	/	/	0	0
Bosnia and Herzegovina	No	/	/	0	1
Bulgaria	Yes	0	NA	0	0
Croatia	Yes	0	DT, VC, P, N	1	0
Czech Republic	Yes	20%	DT, VC, P	0	4
Estonia	Yes	50%	DT, N	1	0
Hungary	Yes	NA	P	2	2
Lithuania	Yes	0	DT, VC	0	0
Macedonia	Yes	1	VC	0	1
Montenegro	No	/	/	0	0
Poland	Yes	17.50%	DT	2	4
Romania	No	/	/	1	0
Russia	Yes	8%	DT, VC, N	5	5
Serbia	Yes	4%	DT, VC	1	0
Slovenia	Yes	33%	VC, P	0	0
Ukraine	Yes	1%	VC	0	0

NA: not available; *DT: dabrafenib trametinib; VC: vemurafenib cobimtinib; P: pembrolizumab; N: nivolumab; IN: ipilimumab/nivolumab.

from regulatory approval to full reimbursement access among the European Union Five (EU5) countries, which includes France, Germany, Italy, Spain and UK, is ranging between 14.9 and 18.1 months [26]. Reimbursement is, restricted in both WE and EE countries in similar ways: by time-consuming application processes for reimbursement, unscientific restrictions of use by line of therapy and by hospital budget restrictions. This implies that the new access models are the emerging need throughout entire Europe.

Overall, in accordance with previous studies, access to innovative medicines for metastatic melanoma correlated strongly with the human development index, healthcare budget expenditure per capita and health policy performance score. However, differences were evident in the number of reimbursed medicines among the countries with similar HDI and HEPC, which demonstrates the impact of political decisions in this process and points out to the necessity to overcome these differences at the national level. In some of the countries with medium-to-low healthcare expenditure per capita, the reimbursement of all medicines is evident, and these examples could lead the path for a next generation access models for the countries with restricted healthcare budgets.

CUPs and EAPs are provided by pharmaceutical companies in order to allow early access to medicines before the drug is registered in EU [31]. However, in a majority of countries, less than 25% of patients were treated within these programmes. Difficulties in implementing CU and EA programmes stem partly from unharmonised legislation in some countries. Furthermore, these programmes are often only active until EMA registration has been achieved, whilst reimbursement decisions often add significant delays [31].

Based on the data of this study, large differences exist in the availability of clinical trials across Europe that provide very early access to innovative medicines and are recommended in melanoma guidelines. This could be improved with the development of strategies for better cross-border patient participation in international clinical studies, the inclusion of more high-quality centres from all parts of Europe to future trials and the improvement of quality care in centres where this is yet to be achieved [31–33].

While this study provides a first view of access to novel melanoma drugs in Europe, its limitation is that it is a self-reported survey. However, the number provided by the experts corresponded to already published data from melanoma treatment registries [37,38]. Also,

Table 3
Estimation of number of patients without access to innovative medicines in Europe.

Country	Estimated total number of metastatic melanoma patients	Estimated number of cancer deaths in Europe, IARC, 2012[a]	Estimated % of patients treated with innovative medicines	Estimated % of patients without access to innovative medicines	Estimated number of patients without access to innovative medicines
Austria	200	350	>90%	10%**	/
Belgium	350	300	70–90%	10%**	/
Denmark	350	230	>90%	10%**	/
France	2000	1840	>90%	10%**	/
Germany	3000	2670	>90%	10%**	/
Greece	NA	200	70–90%	10%**	/
Italy	2000	1810	70–90%	10%**	/
Netherlands	800	870	70–90%	10%**	/
Portugal	200	220	30–50%	50%	100
Spain	400	970	70–90%	10%**	/
Sweden	500	570	70–90%	10%**	/
Switzerland	350	380	70–90%	10%**	/
UK	2000	2200	10–30%	10%**	/
Albania	30	20	10–30%	70%	21
Belarus	250	250	<10%	90%	225
Bosnia and Herzegovina	60	50	<10%	90%	54
Bulgaria	150	190	30–50%	50%	75
Croatia	100	210	10–30%	70%	70
Czech Republic	400	340	30–50%	50%	200
Estonia	50	60	30–50%	30%	25
Hungary	400	340	50–70%	30%	120
Lithuania	50	110	30–50%	50%	25
Macedonia	80	70	<10%	90%	72
Montenegro	30	20	10–30%	70%	21
Poland	1000	1350	70–90%	10%**	/
Romania	NA	370	10–30%	70%	NA
Russia	4000	3630	<10%	90%	3600
Serbia	200	340	<10%	90%	180
Slovenia	150	130	>90%	10%**	/
Ukraine	500	1120	<10%	90%	450
Total	19,600	21,210			5238

[a] Ferlay et al. International Agency for Research on Cancer [29], **never as the first-line of treatment; IARC: International Agency for Research on Cancer.

estimated number of 19,600 metastatic melanoma patients was comparable with the 21,210 deaths due to cutaneous malignant melanoma (CMM) estimated by the IARC [30]. The rate of financial toxicity in the countries without access should also be explored, but based on the available data from South-Eastern Europe, less than 1% of patients are treated out-of-pocket with innovative medicines in these countries [39]. Also, data derived from larger countries may not provide precise information on internal regional differences, which should be explored in future studies. Furthermore, the reimbursement process is dynamic and constant monitoring of data should be developed for better assessment.

The European network for Health Technology Assessment (HTA) is currently working on developing common procedures and standards in the field of relative effectiveness of medicines [22]. Also, European Commission Expert group on safe and timely access to medicines for patients (STAMP) and EMA developed a PRIME (priority medicines) scheme for the new medicines and in particular from the viewpoint of therapeutic innovation [40]. These initiatives could speed up the registration and pricing process within the EU, but whether will it improve access to medicines is uncertain given the lack of a common EU healthcare system. Public health and healthcare costs are organised at the national level, but initiatives may help to overcome the cross-national inequities within Europe. These initiatives must come from a dialogue among health professionals' organisations, patient advocacy organisations, national and European policy makers and the pharmaceutical industry.

Also, whilst pricing during the reimbursement process includes an element of governmental control in European countries, this is not the situation in the USA, and more sustainable pricing mechanisms will ultimately be necessary in a way that would not jeopardise the process of innovation [31,41]. Today, many pharmaceutical companies implement some form of affordability strategy such as differential pricing, patient assistance schemes and several models of risk-sharing agreements with national insurance funds, but improvements in these strategies are also needed.

In conclusion, it is estimated that more than 5000 patients from Europe do not have access to innovative medicines for metastatic melanoma, and this situation risks to highly aggravate the sharp differences in overall survival of these patients, across the Continent. Our data emphasise the need for reducing disparities in quality cancer care across European countries. Providing fair access to quality healthcare, including access to innovative medicines for all patients with metastatic melanoma is a fundamental human right, and it should be a commitment not only of EU Member states and candidate countries, but also of public healthcare systems outside of the EU [20,34].

Conflict of interest statement

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KP: advisory board member for Eli Lilly, LEO Pharma, MEDA and Roche.

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AS: Research support or honorariums: Roche, Novartis, MEDA, LEO, ABBVIE, MERCK.

JJG: Member of the advisory board for Roche, Novartis, BMS, MSD, Merck/Pfizer, Pierre Fabre, Amgen.

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HG: consultant or advisory role: BMS, MSD, Amgen, Novartis, Roche, travel expenses: Roche, BMS, research grants to the department: BMS, MSD, Roche, Novartis.

CL: Honoraria from Roche/BMS/Novartis/MSD/Amgen, Consulting or Advisory role Roche/BMS/Novartis/Amgen/MSD; Speakers' bureau BMS/Amgen/Roche/Novartis, Research funding Roche/BMS; travel and accommodation expenses Roche/BMS/Novartis/Amgen.

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Appendix A. Supplementary data

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References

[1] Eigentler TK, Caroli UM, Radny P, Garbe C. Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. Lancet Oncol 2003;4:748–59.

[2] Ugurel S, Röhmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies. Eur J Cancer 2015;53:125–34.

[3] Long GV, Grob JJ, Nathan P, Ribas A, Robert C, Schadendorf D, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. Lancet Oncol 2016;17(12):1743–54.

[4] Hodi S, Kluger H, Sznol M, Carvajal R, Lawrence D, Atkins M, et al. Durable, long-term survival in previously treated patients with advanced melanoma (MEL) who received nivolumab (NIVO) monotherapy in a phase I trial. In: AACR 2016 annual meeting New Orleans; 2016. abstract CT001.

[5] Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G, Keilholz U. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26:v126–32.

[6] Garbe C, Peris K, Hauschild A, Saiag P, Middleton M, Bastholt L, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – update 2016. Eur J Cancer 2016;63:201–17.
[7] NCCN guidelines: Melanoma. NCCN version v2. Available at: https://www.nccn.org; 2016.
[8] Arnold M, Rentería E, Conway DI, Bray F, Van Ourti T, Soerjomataram I. Inequalities in cancer incidence and mortality across medium to highly developed countries in the twenty-first century. Cancer Causes Control 2016;27:999–1007.
[9] Cherny N, Sullivan R, Torode J, Saar M, Eniu A. ESMO European Consortium Study on the availability, out-of-pocket costs and accessibility of antineoplastic medicines in Europe. Ann Oncol 2016;27:1423–43.
[10] Dawes SM, Tsai S, Gittleman H, Barnholtz-Sloan JS, Bordeaux JS. Racial disparities in melanoma survival. J Am Acad Dermatol 2016;75:983–91.
[11] Barbaric J, Sekerija M, Agius D, Coza D, Dimitrova N, Demetriou A, et al. Disparities in melanoma incidence and mortality in South-Eastern Europe: increasing incidence and divergent mortality patterns. Is progress around the corner? Eur J Cancer 2016;55:47–55.
[12] Strömberg U, Peterson S, Holmberg E, Holmén A, Persson B, Sandberg C, et al. Cutaneous malignant melanoma show geographic and socioeconomic disparities in stage at diagnosis and excess mortality. Acta Oncol 2016;55:993–1000.
[13] Forsea AM, Del Marmol V, Stratigos A, Geller AC. Melanoma prognosis in Europe: far from equal. Br J Dermatol 2014;171:179–82.
[14] De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE–5-a population-based study. Lancet Oncol 2014;15:23–34.
[15] Ades F, Senterre C, de Azambuja E, Sullivan R, Popescu R, Parent F, et al. Discrepancies in cancer incidence and mortality and its relationship to health expenditure in the 27 European Union member states. Ann Oncol 2013;24:2897–902.
[16] Amini A, Rusthoven CG, Waxweiler TV, Jones BL, Fisher CM, Karam SD, et al. Association of health insurance with outcomes in adults ages 18 to 64 years with melanoma in the United States. J Am Acad Dermatol 2016;74:309–16.
[17] Cylus J, Papanicolas I. An analysis of perceived access to health care in Europe: how universal is universal coverage? Health Policy 2015;119:1133–44.
[18] Williams CD, Salama JK, Moghanaki D, Karas TZ, Kelley MJ. Impact of race on treatment and survival among U.S. Veterans with early-stage lung cancer. J Thorac Oncol 2016;11:1672–81.
[19] Ades F, Senterre C, Zardavas D, de Azambuja E, Popescu R, Parent F, et al. An exploratory analysis of the factors leading to delays in cancer drug reimbursement in the European Union: the trastuzumab case. Eur J Cancer 2014;50:3089–97.
[20] WHO Europe: European observatory on Health Systems and Policies. Available at: http://www.euro.who.int/en/about-us/partners/observatory.
[21] Bergmann L, Enzmann H, Thirstrup S, et al. Access to innovative oncology medicines in Europe. Ann Oncol 2016;27:353–6.
[22] EUnetHTA JA2 Final Technical Report – EXECUTIVE SUMMARY. Available at: http://www.eunethta.eu/news/eunethta-ja2-final-technical-report-approved-be-submitted-european-commission.
[23] Hollingsworth SJ, Biankin AV. The challenges of precision oncology drug development and implementation. Public Health Genomics 2015;18:338–48.
[24] EFPIA W.A.I.T indicator. EFPIA market access delay Working Group. Available at: http://www.efpia.eu/documents/33/64/market-access-delays ; 2011.
[25] EU Directive relating to the transparency. Available at: http://europa.eu/rapid/press-release_MEMO-12-148_en.htm?locale=en.
[26] IMS Consulting Group. Pricing and access market outlook report 2015/2016. Available at: https://www.imshealth.com/files/web/Global/Services/P&MA_2015.pdf.
[27] Mackenbach JP, McKee M. A comparative analysis of health policy performance in 43 European countries. Eur J Public Health 2013;23:195–201.
[28] UNDP Human development report. Available at: http://hdr.undp.org/en/2015-report.
[29] World Bank Group. Available at: http://www.worldbank.org/.
[30] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1382.
[31] Leyens L, Brand A. Early patient access to medicines: health technology assessment bodies need to catch up with new marketing authorization methods. Public Health Genomics 2016;19:187–91.
[32] Groene O, Poletti P, Vallejo P, Cucic C, Klazinga N, Suñol R. Quality requirements for cross-border care in Europe: a qualitative study of patients', professionals' and healthcare financiers' views. Qual Saf Health Care 2009;18(Suppl. 1):i15–21. http://dx.doi.org/10.1136/qshc.2008.028837.
[33] Kerr DJ, Jani A, Gray SM. Strategies for sustainable cancer care. Am Soc Clin Oncol Educ Book 2016;35:e11–5.
[34] Wang T. Regulatory and reimbursement alas: a systematic comparison of Healthcare systems of 33 European jurisdictions process maps. Centre Innovation Regul Sci 2016. Available at: http://www.cirsci.org/hta-programme/regulatory-and-reimbursement-atlas/.
[35] Tobin H, Proctor R, Trocme-Latter J. Russia: planning for reimbursed future. In: Maroney M, Jennings E, editors. IMS Pharma Pricing and Reimbursement 2015;20:1. IMS Consulting Group 2015. Available at: https://www.hse.ru/pubs/share/direct/document/145079856.
[36] Mihajlović J, Dolk C, Tolley K, Simoens S, Postma MJ. Reimbursement of targeted cancer therapies within 3 different European health care systems. Clin Ther 2015 Feb 1;37(2):474–80.
[37] Jochems A, Schouwenburg MG, Leeneman B, Franken MG, van den Eertwegh AJ, Haanen JB, et al. Dutch Melanoma treatment registry: quality assurance in the care of patients with metastatic melanoma in the Netherlands. Eur J Cancer 2017;72:156–65.
[38] Li H, Pedersen L, Nørgaard M, Ulrichsen SP, Thygesen SK, Nelson JJ. The occurrence of non-melanoma malignant skin lesions and non-cutaneous squamous-cell carcinoma among metastatic melanoma patients: an observational cohort study in Denmark. BMC Cancer 2016;16:295.
[39] Kandolf-Sekulovic L, Babovic N, Nikolin B, Vrbic S, Vukanovic T, Ostojic N, et al. Treatment patterns and outcome of cutaneous melanoma in South-East Europe: first results from the nationalregistry of Serbian melanoma group. Melanoma Res 2016;26. e-Supplement 1:e16: P007.
[40] Enhanced early dialogue to facilitate accelerated assessment of PRIority MEdicines (PRIME). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2016/03/WC500202636.pdf.
[41] Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. JAMA 2016;316(8):858–71.