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Original Research

Access to innovative medicines for metastatic melanoma worldwide: Melanoma World Society and European Association of Dermato-oncology survey in 34 countries

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List of abbrevations: EADO, European Association of Dermato-oncology; MWS, Melanoma World Society; ASCO, American Society of Clinial Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Center Network; EORTC, European Organization for Research and Treatment of Cancer; EDF, European dermatology Forum; ASCO NBS 16, ASCO Framework Net Benefit Score 16; ESMO MCBS, ESMO Magnitude of clinical benefit scale; anti-PD-1, anti programmed cell death-1; PDL-1, programmed-cell death ligand-1; GDP, gross domestic product; DALY, disability-adjusted life year.

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Abstract According to data from recent studies from Europe, a large percentage of patients have restricted access to innovative medicines for metastatic melanoma. Melanoma World Society and European Association of Dermato-oncology conducted a Web-based survey on access to first-line recommended treatments for metastatic melanoma by current guidelines (National Comprehensive Center Network, European Society for Medical Oncology [ESMO] and European Organization for Research and Treatment of Cancer/European Association of Dermato-oncology/European dermatology Forum) among melanoma experts from 27 European countries, USA, China, Australia, Argentina, Brazil, Chile and Mexico from September 1st, 2017 to July 1st, 2018. Data on licencing and reimbursement of medicines and the number of patient treated were correlated with the data on health expenditure per capita (HEPC), Mackenbach score of health policy performance, health technology assessment (HTA), ASCO and ESMO Magnitude of clinical benefit scale (ESMO MCBS) scores of clinical benefit and market price of medicines. Regression analysis for evaluation of correlation between the parameters was carried out using SPSS software. The estimated number of patients without access in surveyed countries was 13768. The recommended BRAFi + MEKi combination and anti-PD1 immunotherapy were fully reimbursed/covered in 19 of 34 (55.8%) and 17 of 34 (50%) countries, and combination anti-CTLA4+anti-PD1 in was fully covered in 6 of 34 (17.6%) countries. Median delay in reimbursement was 991 days, and it was in significant correlation with ESMO MCBS ($p = 0.02$), median market price ($p = 0.001$), HEPC and Mackenbach scores ($p < 0.01$). Price negotiations or managed entry agreements (MEAs) with national authorities were necessary for reimbursement. In conclusion, great discrepancy exists in metastatic melanoma treatment globally. Access to innovative medicines is in correlation with economic parameters as well as with healthcare system performance parameters. Patient-oriented drug development, market access and reimbursement pathways must be urgently found.
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1. Introduction

Metastatic melanoma is a chemotherapy-resistant cancer with an expected median survival of 6–9 months before 2010. From 2011, major breakthrough was achieved with targeted therapy and immunotherapy, leading for the first time to significantly prolonged survival of this group of patients, with 28–34% of patients (nearly 50% in good prognostic groups) surviving 5 years based on the recent trials [1–9]. However, despite the high efficacy, their high costs have led to the restricted access to these treatments in parts of Europe [10–15].

Most innovative medicines are authorised first by the Food and Drug Administration (FDA) in the United States and subsequently in the European Union by the European Medicine Agency (EMA), typically with a delay of 6–12 months. However, the degree and timing of reimbursement in every European country is decided at the national level, and it varies greatly [15–19]. In the United States and in other countries with existing private insurance, availability of the medicines is also dependent on patients' insurance coverage [20–22]. Delays in reimbursement and different insurance coverage lead to different and rising out-of-pocket costs for the patient, indicating the challenges for healthcare systems in adapting to the rising costs of cancer care [10–22].

In this setting, there is a need for objective measurement of clinical benefit of every treatment and development of value-based pricing [23–25]. The major oncology organisations, American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO), developed scores of clinical benefit, ASCO Framework net clinical benefit 16 score (NBS 16) and ESMO Magnitude of clinical benefit score (MCBS), with an intention to be used for development of value-based pricing and prioritisation of medicines for reimbursement and/or insurance coverage [24,25].

The degree of inequality and major determinants of access to innovative treatments for metastatic melanoma are largely unexplored. Thus, the Melanoma World Society (MWS) and the European Association of Dermato-oncology (EADO) conducted a survey on access to first-line recommended treatments per current guidelines (National Comprehensive Center Network [NCCN], ESMO, European Organization for Research and Treatment of Cancer [EORTC]/EADO/European dermatology Forum [EDF]) in 34 countries worldwide and updated the results of European survey conducted in 2016. To further explore the patterns of access to innovative medicines for metastatic melanoma, data on access were correlated with their score of clinical benefit, i.e. ASCO NBS and ESMO MCBS, as well as economic parameters and parameters of health policy performance.

2. Materials and methods

A Web-based online survey (SurveyMonkey tool, SurveyMonkey Inc., Palo Alto, CA 94301, USA) was conducted among melanoma experts from 27 European countries, USA, China, Australia and countries of Latin America (Argentina, Brazil, Chile and Mexico) from September 1st to July 1st, 2018. Melanoma experts from each representative melanoma center were invited to use the Web link and completed the survey only once. For Russian Federation, Netherlands and Hungary, only the estimated number of patients and percentage of treated patients were collected based on the previous survey from October 2016 and data on access from personal communication. The survey questionnaire (Table S1, supplementary file) included multiple-choice questions about the number and percentages of melanoma patients treated with the first-line recommended treatments by current guidelines (NCCN, ESMO, EDF/EORTC/EADO), authorisation, reimbursement, type of health insurance, health technology assessment (HTA), budget impact, market price and governmental price control. Delay in reimbursement was measured in days from FDA authorisation and EMA authorisation for European countries to date of reimbursement or 01 July 2018. For chemotherapy, targeted therapy and immunotherapy, ASCO NBS 16 and ESMO MCBS scores were calculated from pivotal randomised controlled phase III trials based on overall survival or progression-free survival. For dacarbazine, ASCO NBS16 was calculated based on the response rate. Data were correlated with economic parameters and parameters of health policy performance: gross domestic product (GDP), health expenditure per capita (HEPC), human development index (HDI), Mackenbach score of health policy performance, HTA implementation and governmental price control mechanisms [26–28]. Descriptive statistics were used to analyse the data. Regression analysis for evaluation of correlation between data was carried out using SPSS software. Statistical significant correlation was considered if $p < 0.05$.

3. Results

3.1. Authorisation and reimbursement of new treatments worldwide

Data on authorisation and reimbursement of innovative medicines for metastatic melanoma in 34 countries are presented in Fig. 1.

On July 1st 2018, the recommended first-line therapy with any BRAFi + MEKi combination was both licenced and fully reimbursed in 19 of 34 (55.8%) countries and in 6 of 34 (17.6%) with restrictions in

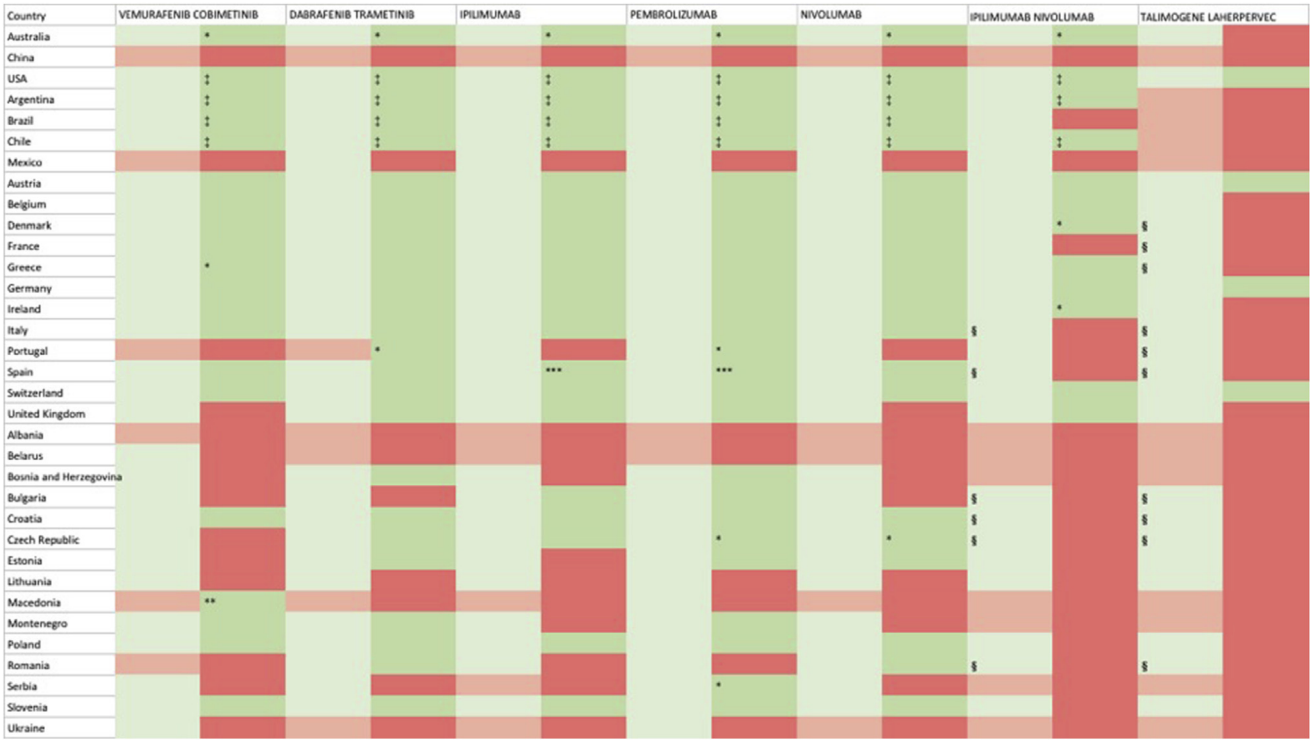

Fig. 1. Authorisation and reimbursement of innovative medicines for metastatic melanoma in 34 countries.

reimbursement or through compassionate use programs. First-line monotherapy with anti-PD1 antibodies was licenced and fully reimbursed in 17 of 34 (50%) countries, with restrictions in 9 of 34 (26.4%) of countries. Combination immunotherapy (anti-CTLA4 + anti-PD1) was licenced and fully reimbursed in 6 of 34 (17.6%) countries and with restrictions in 9 of 34 (26.4%) of countries. Talimogene laherparepvec was licenced in 21 of 34 (62%) countries, launched in 13 of 34 (38.2%) countries and reimbursed in 4 of 34 (11.7%) countries.

Reimbursement was restricted by indication (for the first-line or for the second-line treatment, based on PD-L1 expression for combination ipilimumab/nivolumab), hospital budget or prolonged administrative procedure. In countries of Latin America, reimbursed medicines were available only for patients with private health insurance. The only 4 countries with full reimbursement of all 9 drugs on July 1st, 2018 were the USA, Switzerland, Austria and Germany, in the USA with existing restrictions to reimbursement based on the type of insurance.

3.2. Estimated percentage and number of patients without access to innovative medicines

Of 38390 metastatic melanoma patients in surveyed countries with available data, 13768 (36%) patients per year do not have the access to the first-line recommended treatment for metastatic melanoma (Table 1).

3.3. Dynamics of reimbursement in Europe and worldwide

Data on reimbursement rates and delays for individual countries and individual medicines are presented in Tables S2 and S3 in Supplementary Appendix. Median delays for individual medicines ranged from 843 days for nivolumab/ipilimumab combination to 1425 days for ipilimumab. No delays were evident for the USA, Germany and Switzerland. In other countries, delays ranged from 185 days in Austria to 1523 days in Mexico, and greatest were in Eastern and Southeastern European countries, Latin America and China.

In comparison to the European study from October 2016 to July 2018, 10 of 18 countries reimbursed new drugs, whereas in other 8 of 18, there were no new reimbursements. During this time, new restrictions were introduced in a few countries, e.g. in Greece, where vemurafenib cobimetinib were previously reimbursed without restrictions, but from April 2018, it is reimbursed only for the second line [10].

3.4. Major determinants of access to innovative agents for metastatic melanoma (Table 2)

Significant correlation was found between GDP, HDI (UNDP report 2015), HEPC and score of health policy performance with the number of reimbursed medicines ($p < 0.001$) and delays in reimbursement ($p < 0.001$) (Table 2). There was no correlation found between the type of health insurance and access to

Table 1
Estimated number of patients without the access to innovative medicines in surveyed countries.

Country	Estimated number of metastatic melanoma patients	% of patients treated with innovative medicines	% of patients without the access to innovative medicines	Estimated number of patients without access
USA	9000	60%	40%	3600
China	4200	10–30%	70%	2940
Australia	3000	>90%	<10%	0
Latin America				
Argentina	600	70%	30%	200
Mexico	NA	NA	NA	NA
Chile	350	<10%	90%	315
Brazil	2000	10–30%	70%	1400
Europe				
Austria	200	>90%	<10%	0
Belgium	350	>90%	<10%	0
Denmark	350	>90%	<10%	0
France	2000	>90%	<10%	0
Germany	3000	>90%	<10%	0
Greece	NA	>90%	<10%	0
Ireland	140	>90%	<10%	0
Italy	2000	>90%	<10%	0
The Netherlands	800	>90%	<10%	0
Portugal	200	30–50%	50%	100
Spain	400	>90%	<10%	0
Switzerland	350	>90%	<10%	0
United Kingdom	2000	70–90%	<10%	200
Albania	30	10–30%	70%	21
Belarus	250	<10%	90%	225
Bosnia and Herzegovina	60	<10%	90%	60
Bulgaria	150	50–70%	30%	105
Croatia	100	>90%	<10%	0
Czech Republic	400	70–90%	10%	360
Estonia	50	>90%	<10%	0
Hungary	400	>90%	<10%	0
Lithuania	50	30–50%	50%	25
FYR Macedonia	80	30–50%	50%	40
Montenegro	30	>90%	<10%	27
Poland	1000	>90%	<10%	0
Romania	NA	50–70%	30%	NA
Russian Federation	4000	<10%	90%	3600
Serbia	200	30–50%	50%	100
Slovenia	150	>90%	<10%	0
Ukraine	500	<10%	90%	450
Total	38390			13768

innovative medicines ($p > 0.05$), except for the number of reimbursed medicines ($p = 0.034$) (Table 2).

The implementation of health technology assessment in the reimbursement process was evident in 21 of 34 (61.8%) countries and was inversely correlated with the delay in reimbursement. Countries without implemented HTA assessment were the ones with the greatest reimbursement delays (median 743 days vs. 1088 days, $p = 0.057$).

Governmental price control was evident in 16 of 20 (80%) of high-income countries and 7 of 14 (50%) of upper/lower middle-income countries. In 60% of countries with reimbursed first-line treatments, price negotiations after HTA assessment and risk-sharing agreements led to reimbursement (Table 3). Budget impact had an effect in reimbursement decisions in 27 of 33 (82%) countries, and in 15 of 34 (44.1%) countries, decisions made were also based on the list of reimbursed medicine in reference countries (countries in the region with similar economic parameters) (Table S2, Supplementary appendix).

Table 2
Determinants of delays in access to innovative medicines for metastatic melanoma.

Economic parameters and type of health insurance		Delay in reimbursement	Number of reimbursed medicines	% of patients treated with innovative medicines
GDP (World Bank 2015)	rho	−0.846	0.681	0.599
	p	<0.001	<0.001	<0.001
HDI	rho	−0.67	0.574	0.539
	p	<0.001	<0.001	0.001
HEPC 2016	rho	−0.854	0.768	0.634
	p	<0.001	<0.001	<0.001
Mackenbach score	rho	−0.799	0.72	0.482
	p	<0.001	<0.001	0.011
% Public healthcare insurance	rho	−0.087	−0.154	0.275
	p	0.641	0.384	0.116
% Private healthcare insurance	rho	−0.105	0.368	0.006
	p	0.573	0.032	0.973

HDI, human development index.

3.5. Correlation of access to innovative agents to scores of clinically meaningful benefit and market price of medicines

Delays in reimbursement were in correlation with ESMO scores of clinical benefit as well as the median market price (Table 4). The medicines with the highest scores of clinical benefits (and the one with the highest market prices) were the ones with the greatest delay in reimbursement (Table S3, Supplementary Appendix).

3.6. International availability of pre-approval clinical studies and compassionate use programs

The availability of international clinical studies and early access programs (EAPs) greatly varied between the countries (Table S4, Supplementary Appendix). The percentage of patients treated varies from 0 to 60%, with the highest numbers in China and Spain. In 20 of 34 (58.8%) countries, less than 10% of patients are treated within the clinical studies and EAP.

4. Discussion

The development of targeted therapy and immunotherapy have revolutionised the outcome for patients

Table 3
Governmental price control mechanisms in countries with reimbursed medicines.

Type of reimbursement	Vemurafenib cobimetinib	Dabrafenib trametinib	Pembrolizumab	Nivolumab	Ipilimumab	Nivolumab ipilimumab	T-Vec	median	%
No price control	6	7	9	8	8	7	4	7	35.0
Price negotiations[a]	9	13	17	15	12	6	2	12	60.0
Not known	2	3	0	1	2	0	0	1	5.0
Total	17	23	26	24	22	13	6	20	100.0

HTA, health technology assessment.
[a] Price negotiations based on HTA assessment, managed entry agreements.

Table 4
Correlation of access parameters, scores of clinically meaningful benefit and market price of medicines.

Reimbursement		Median price	ESMO MCBS	ASCO framework NHB 16
% full reimbursement	rho	−0,755	−0,488	−0,067
	P	0,012	0,152	0,853
% any reimbursement	rho	−0,578	−0,188	0,122
	p	0,080	0,603	0,738
Delay in reimbursement	rho	0,882	0,850	0,557
	p	0,001	0,002	0,095

with advanced melanoma, leading to five-year overall survival that reaches 50% in good prognostic group of patients [1–5,29,30]. Even patients with brain metastases with a median overall survival of 2–3 months in pre-innovation era can have intracranial response rates of 44%–58% with some patients achieving a long-term benefit [31,32].

These agents became standard-of-care first-line treatments recommended by international melanoma guidelines. However, their high costs have led to the restricted access to these treatments in Europe, with more than 5000 patients denying life-saving treatments for metastatic melanoma every year [7–10]. In the present study, disparities were recorded at the global level, with more than 13,000 patients in surveyed countries having no access. Thus, metastatic melanoma patients are frequently facing the situation that although the medicine is authorised and on the market, it is not available because of the delays in reimbursement or differential coverage by the insurance.

In Europe, after central marketing authorisation, there are further delays in product launch between countries due to the strategic launch sequences. The degree and timing of coverage of reimbursement of a licenced drug is decided at the national level, with significant restrictions in reimbursement in most Eastern and Southeastern countries [16,32,33]. In the United States and countries where private insurance is predominant, access to medicines is in correlation with insurance coverage of each patient. Based on the report from the Cancer Action Network of the American Cancer Society, 44% of US expenditures for cancer treatment were paid by private insurance, 33% by Medicare and 13% by Medicaid, other sources and as out-of-pocket costs of the patients [21,22]. Even with private insurance, cancer patients in the US often face unpredictable or unmanageable costs, needing a treatment that is not covered by their plan [21,22]. The US policymakers are trying to limit yearly out-of-pocket costs for privately insured patients, but access to health insurance that is adequate, available, affordable and easy to understand remains a major challenge [22].

In Argentina, three types of insurance exist (public, private and workers unions') with different coverage and access to medicines. Similar situation exists in other countries of Latin America, where most patients (80%) are treated within the public healthcare system without access to innovative medicines, whereas for minority (20%) with private insurance, full reimbursement is evident.

In public healthcare systems, even in countries with similar HEPC, the number of reimbursed medicines and percentage of patients treated could be quite different because of differences in health policy performance and HTA implementation [10]. In this study, HTA procedure was implemented in 11 of 15 (73.3%) countries where >90% of patients are treated with innovative medicines and in 2 of 9 (22.2%) countries where less than 30% of patients are treated with innovative medicines. Price negotiations after HTA assessment or managed entry agreements with pharmaceutical companies were evident in 53.5% of countries with reimbursed drugs. This is in concordance with previous studies that analysed differential access strategies in countries with different gross national income [34,37]. In some countries with medium-to-low healthcare expenditure per capita, the reimbursement of majority of medicines is evident, and these examples could lead the path for next-generation access models.

The issue of high prices of medicines has been a matter of global debate in recent years. The latest report of Goldstein *et al.* revealed that the drug prices are increasing at a significantly higher rate than inflation in the US [35,36]. Different strategies have been developed by pharmaceutical companies in the US which can make the medicines more affordable [38]. However, based on the present study, 36% of patients worldwide do not have the access to recommended medicines, pointing out

to the need for more patient-oriented drug development and access strategies in the future.

To facilitate price negotiations in public healthcare systems or insurance coverage in private healthcare systems, there is clearly a need for prioritisation of medicines for reimbursement/insurance coverage at the international level. ASCO Frameworks NBS16 and ESMO MCBS scores take into account markers of response, toxicity and, in its last versions, patient-reported outcomes to more objectively measure the clinically meaningful benefit of any medicine [24,25]. Based on the recent studies, a large number of FDA-approved drugs do not meet criteria for clinically meaningful benefit based on ASCO NBS 16 and ESMO MCBS scores [39]. For metastatic melanoma, the medicines with the highest scores of clinical benefits (and most costly) were the ones with the greatest delays in reimbursement (Table S2, 25). In a recent analysis on cost-effectiveness of recently approved anti-cancer medicines, the authors concluded that the global healthcare systems will approach the ceiling of being able to sustain high-quality cancer care in the near future [40]. The results of the present study confirm that health systems around the globe are already facing this situation and not providing optimum treatment to their citizens.

Compassionate use programs and pre-approval clinical studies are very important for an early access to innovative medicines before reimbursement/insurance coverage. However, in 58.8% countries, less than 10% of patients are treated within the clinical studies. For 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 the world to future trials is yet to be achieved [41–45].

The limitation of the present study is that it is a self-reported survey, but the data on number of cases provided by the experts (i.e. 38.390) are comparable with 43.473 deaths due to cutaneous metastatic melanoma (CMM) estimated by the International Agency for Research on Cancer [46]. Also, data derived from larger countries may not provide precise information on internal regional differences. Time from EMA registration to product launch was not collected, which could also add to delays in reimbursement in some countries, as was shown for talimogene laherparepvec in the present study.

In conclusion, great discrepancy exists in metastatic melanoma treatment globally. Access to innovative medicines is in correlation with economic parameters as well as with healthcare system performance parameters. Higher ASCO and ESMO clinical benefit scores for particular medicines are not in correlation with the better access, and their implementation could eventually lead to better prioritisation of medicines for reimbursement/insurance coverage on international level. Access to timely, acceptable and affordable healthcare is one of the fundamental human rights, so the development of patient-oriented research, development, market access and reimbursement/insurance coverage mechanisms in the future would be necessary to improve the current situation. It is the responsibility of all stakeholders in the process, including practising oncologists, policymakers, pharmaceutical companies, investors and patients' organisations.

Conflict of interest statement

L.K.S. had no conflict of interest to declare regarding this article and received relevant financial activities outside the submitted work such as speakers' fee from Roche, Novartis, BMS and MSD. S.A. received travel and accommodations expenses from MSD and Bristol-Myers Squibb.A.H. received clinical trial support, speaker's honoraria or consultancy fees from Amgen, BMS, Merck Serono, MSD, Novartis, Oncosec, Philogen, Pierre Fabre, Provectus, Regeneron and Roche.G.M. received research grants from Celgene, Genentech-Roche, BMS, Amgen, Merck and Array.G.C. received speaker's honoraria or consultancy fees from Novartis, MSD, BMS, Merck Serono and Roche. A.W. received travel and accommodation expenses from Roche, MSD and BMS.C.C. served consultant or advisory role in Lilly, BMS, MSD, Bayer and Astra Zeneca; was a part of the speakers' bureau of BMS, MSD, Bayer and Roche; received research funding from MSD, Boehringer Ingelheim, Glaxo Smith Kline, Bayer, Astra Zeneca, Medivation, Astellas Pharma and BMS and travel and accommodation expenses from Boehringer Ingelheim, MSD, BMS and Tecnofarma. P.L. served consulting or advisory role in Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, NeraCare GmbH, Novartis and Pierre Fabre; was a part of the speakers' bureau of Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis and Roche and received travel and accommodations expenses from Bristol-Myers Squibb and Merck Sharp & Dohme. H.G. served consultant or advisory role in BMS, MSD, Amgen, Novartis and Roche, received travel expenses from Roche and BMS and research grants to the department from BMS, MSD, Roche and Novartis.M.A. had no conflict of interest to declare regarding this article and received relevant financial activities outside the submitted work such as speakers' fee from Novartis, Pfizer, Asofarma, Janssen, Sanofi, Bayer, BMS and MSD.R.D. received honoraria from Roche, Novartis, Amgen, Celgene, Astellas and Tesaro and served consulting and advisory role in Roche, Novartis, Amgen, Celgene, Astellas and Tesaro.C.L. received honoraria from Roche, BMS, Novartis, Amgen and MSD, served consulting or advisory role in Roche, BMS, Novartis, Amgen and MSD, was a part of the speakers' bureau of BMS/Amgen/Roche/Novartis and received research funding from Roche/ BMS travel and accommodation expenses from Roche/BMS/Amgen. K.P. was an

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Appendix A. Supplementary data

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