An integrated view on assuring quality for multimodal therapy in oncologic care

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3 Dutch Melanoma Treatment Registry: quality assurance in the care of patients with metastatic melanoma in the Netherlands

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ABSTRACT

Background: In recent years, the treatment of metastatic melanoma has changed dramatically due to the development of immune checkpoint and mitogen-activated protein (MAP) kinase inhibitors. A population-based registry, the Dutch Melanoma Treatment Registry (DMTR), was set up in July 2013 to assure the safety and quality of melanoma care in the Netherlands. This article describes the design and objectives of the DMTR and presents some results of the first 2 years of registration.

Methods: The DMTR documents detailed information on all Dutch patients with unresectable stage IIIc or IV melanoma. This includes tumour and patient characteristics, treatment patterns, clinical outcomes, quality of life, healthcare utilisation, informal care and productivity losses. These data are used for clinical auditing, increasing the transparency of melanoma care, providing insights into real-world cost-effectiveness and creating a platform for research. Results: Within 1 year, all melanoma centres were participating in the DMTR. The quality performance indicators demonstrated that the BRAF inhibitors and ipilimumab have been safely introduced in the Netherlands with toxicity rates that were consistent with the phase trials conducted. The median overall survival of patients treated with systemic therapy was 10.1 months (95% confidence interval [CI] 9.1e11.1) in the first registration year and 12.7 months (95% CI 11.6e13.7) in the second year.

Conclusion: The DMTR is the first comprehensive multipurpose nationwide registry and its collaboration with all stakeholders involved in melanoma care reflects an integrative view of cancer management. In future, the DMTR will provide insights into challenging questions regarding the definition of possible subsets of patients who benefit most from the new drugs.

INTRODUCTION

Malignant melanoma is one of the most aggressive types of skin cancer. The incidence of melanoma has increased in Europe over the past few decades [1,2]. In the Netherlands, the number of new cases of invasive melanoma (all stages) more than doubled between 2000 and 2014 and it accounts for approximately 90% of skin-cancer-related mortality in 2014 [3]. The increased incidence accompanied by the high mortality rates made it one of the worst performing tumours in the Netherlands over recent years, especially for males [4].

The treatment of unresectable and metastatic melanoma has changed dramatically in recent years due to the development of immune checkpoint inhibitors (e.g. ipilimumab, nivolumab and pembrolizumab) and inhibitors of the mitogen-activated protein (MAP) kinase pathway (e.g. the BRAF inhibitors vemurafenib and dabrafenib and the MAP kinase (MEK) inhibitors trametinib and cobimetinib) [5-8]. These drugs create new opportunities to prolong progression-free and overall survival (OS) for patients with metastatic melanoma. However, the introduction of the new drugs poses several challenges. First, adequate selection of subsets of patients who may benefit from immune checkpoint inhibitors or MAP kinase inhibitors and sequencing these new drugs present a challenge. Second, experience in recognising and treating the potentially life-threatening side effects of immune checkpoint inhibitors is essential. Finally, the high costs of these new drugs raise questions about their cost-effectiveness in daily clinical practice.

The introduction of the new drugs to treat metastatic melanoma was approved by the Dutch Minister of Health subject to two firm conditions: I) the concentration of metastatic melanoma treatment in a limited number of designated centres and II) the recording of all patients with unresectable or metastatic melanoma (stage IIIc or stage IV melanoma) in a nationwide registry.

To achieve centralisation, the Dutch Society of Medical Oncologists (NVMO) selected 14 hospitals as melanoma centres in 2012. These centres were chosen on the basis of their expertise in the systemic treatment of melanoma, their infrastructure and their geographic distribution. At the same time, a set of multidisciplinary quality standards was established by the professional organisations involved in melanoma treatment, including a minimum volume standard of 20 new patients annually

receiving systemic treatment for meta-static melanoma [9]. This number of patients is based on safety reports in clinical trials [5,6]. In addition, it was assumed that this would allow the centres to have sufficient experience in treating patients with severe toxicity.
The Dutch Melanoma Treatment Registry (DMTR) was set up in July 2013. A unique consortium of organisations, including medical specialists, policymakers, healthcare researchers, patient advocates and pharmaceutical companies, was involved in establishing the registry.
This article describes the design and the objectives of the DMTR and presents some results of the first 2 years of registration.

MATERIALS AND METHODS

Objectives of the DMTR

The DMTR was designed to serve multiple objectives: I) clinical auditing, II) improving transparency concerning the quality of melanoma care, III) providing an insight into real-world outcomes on effects and costs and IV) to create a platform for research.

Clinical auditing: improving melanoma care
Clinical auditing has been recognised as an important tool for quality assessment and improvement [10,11]. The DMTR is used to provide melanoma treatment centres with benchmarked feedback on the number of patients treated, treatment patterns, toxicity rates and survival data on a weekly basis in relation to the national average and in relation to the results of other anonymised melanoma centres. All results are discussed at the quarterly meetings of the Medical Committee in which all centres participate to increase awareness of the quality of care delivered and to stimulate quality improvement initiatives.

Improving transparency of melanoma care: a set of quality standards
Healthcare professionals increasingly need to provide evidence of the quality of the care they deliver [12,13]. A set of well-defined, uniformly collected quality indicators evaluating melanoma care can be derived from data in the DMTR. These quality

indicators are established by the joint efforts of clinical professionals, patient advocates and the National Health Care Institute. These quality indicators at the level of melanoma centre will gradually be made publicly available to all stakeholders involved in melanoma care.

Real-world outcomes: cost-effectiveness of the new drugs
It is of great importance to assess the quality of life and cost-effectiveness of the new drugs in clinical practice. The DMTR, therefore, not only collects clinical data, but also data on quality of life, healthcare utilisation, informal care and productivity losses. These data will be used to develop a health economic disease model to evaluate the real-world cost-effectiveness of treatment for metastatic melanoma.

Platform for research
A population-based registry is a valuable resource for research as it provides real-world data, including information on patients often not eligible for clinical trials. Exploratory comparative effectiveness studies may be conducted with DMTR data if randomised controlled trials are not yet available.

Main structures of the DMTR

Funding
The initial costs of developing the DMTR database were funded through a grant from the Netherlands Organisation for Health Research and Development (ZonMw). The pharmaceutical companies (Roche Nederland B.V., Bristol-Myers Squibb, and GlaxoSmithKline/Novartis, participating from the establishment of the registry, and MSD, participating since 1 July 2015), which produce the newly approved drugs, funded the first 4 years of registration. Future funding will be created in collaboration with the pharmaceutical companies, health insurance companies and melanoma centres.

Organisational structure
The DMTR is a collaboration of multiple stakeholders involved in the treatment of metastatic melanoma. The NVMO is the official representative of all medical oncologists in the Netherlands. The NVMO is the initiator of the DMTR and together with the patient advocacy

(Stichting Melanoom) and the Working Group on Immunotherapy and Oncology (WIN-O), they form the Board of Directors.
The Dutch Institute for Clinical Auditing (DICA) facilitates the implementation of the DMTR and supervises data collection and management. The DICA is specialised in the uniform collection of data and in making appropriate adjustments to case-mix variations between hospitals to provide benchmarked feedback. The methods for case-mix adjustment are described in more detail elsewhere [14].
The Institute for Medical Technology Assessment (iMTA) cooperates with DICA and is responsible for reporting on the cost-effectiveness of the new drugs for advanced melanoma. The iMTA is a scientific institute for research in health economics [15].
Trained data managers at the Netherlands Comprehensive Cancer Organisation (IKNL) coordinate and perform data collection in the melanoma centres. IKNL is responsible for the Dutch Cancer Registry, which collects data concerning incidence, prevalence, survival and mortality of all malignancies in the Netherlands [16].

A diagram of the DMTR's organisational structure can be found in Figure 1.

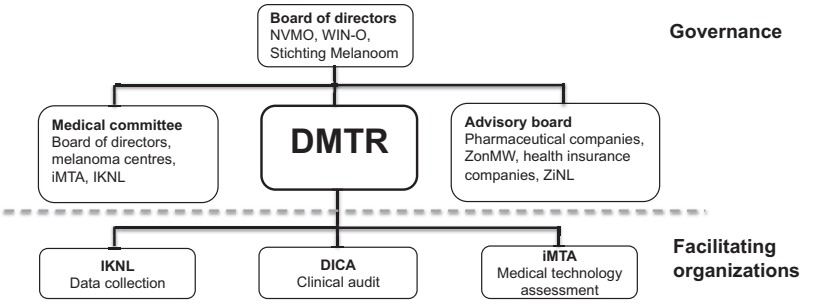

Figure 1. Organisational structure of the Dutch Melanoma Treatment Registry (DMTR). NVMO, Dutch Society of Medical Oncologists; WIN-O, the Working Group on Immunotherapy and Oncology; Stichting Melanoom, patient association; iMTA, Institute for Medical Technology Assessment; ZonMW, Netherlands Organisation for Health Research and Development; ZiNL, National Health Care Institute; DICA, Dutch Institute for Clinical Auditing and IKNL, the Netherlands Comprehensive Cancer Organisation.

Data collection

Dataset

Data collection started in September 2013, retrospectively registering data from patients with metastatic melanoma newly diagnosed (metastatic at first diagnosis) and metastatic upon progression or recurrence who were treated with ipilimumab and/or a BRAF inhibitor from July 2012 to June 2013. During this period, patients not receiving treatment with one of these drugs were not yet registered in the DMTR. From July 2013, all patients diagnosed with metastatic melanoma were prospectively registered irrespective of treatment modality.

An extensive entry in the register was performed for all patients who were referred to a melanoma centre. A concise entry in the register was carried out for patients for whom a melanoma centre was only consulted.

For all extensively monitored patients, the DMTR contains detailed clinical information on patient and tumour characteristics, diagnostics, treatment strategies, adverse events, time to progression and survival. In addition, data are collected on healthcare resource utilisation, informal care, productivity losses and patient-reported outcome measures (PROMs) (i.e. melanoma-specific and overall quality of life).

No ethical approval or informed consent was required under Dutch law to register this information. The clinical dataset is presented as a diagram in Appendix 1.

Web-based environment: data collection, processing and benchmarked feedback

The DMTR uses a web-based environment for data collection and data management including continuous benchmarked feedback to the participating healthcare professionals through a secure website. Pharmaceutical companies are provided with aggregated information regarding the use and performance of their drugs in clinical practice.

Internal and external data verification

Data quality is verified at several key time points along the registration process. Missing or potentially incorrect data are fed back directly to the data managers within the web-based environment. Furthermore, the IKNL data managers verify 10% of the registered data annually. Oncologists supervise the registration process and check all results at patient level. The administrative burden for participating physicians is roughly 30 min per patient record.

Statistical analysis

Descriptive statistics were used to assess patient, tumour and treatment characteristics. The OS was defined as the time from date of diagnosis of metastatic melanoma to death from any cause. Patients alive at time of analysis were censored. The OS with corresponding two-sided 95% confidence interval [CI] was analysed using the Kaplan Meier method. Follow-up time was calculated from first visit to a melanoma centre using the inverse Kaplan Meier method [17]. Performance on the quality indicators is presented in funnel plots using 99% confidence limits that vary in relation to the volume of patients per hospital [18]. All statistical analyses were performed in PASW Statistics version 20 (SPSS Inc., Chicago, IL).

RESULTS

Patient characteristics

From 1st July 2012 to 1st July 2014, 1472 patients with metastatic melanoma were registered in the DMTR. A total of 60 patients were not referred to a melanoma centre and therefore received only a concise entry mainly due to poor performance status or limited prognosis. Of all the patients referred to a melanoma centre (n =1412), 23 patients (1.6%) were excluded because of missing data on date of birth, date of first visit to a melanoma centre, date of diagnosis of disseminated disease and the type of treatment. These items of in-formation were considered to be the minimal requirements for analysis. Complete data was available for 1389 patients. Median follow-up was 18.8 months (95% CI 18.0-19.5) (data cut-off 14th September, 2015).

Baseline patient and tumour characteristics at the first visit to a melanoma centre are shown in Table 1 per registration year. Most patients had a World Health Organization performance score of 0e1 (83% first year and 77% second year), the median age was 59 and 62 years and over half of the patients were male (59% and 54%). Most of the patients had stage M1c disease (78% and 69%) and over a quarter had elevated serum lactate dehydrogenase (LDH) levels (35% and 26%). Furthermore, 23% of patients had brain metastases on radiographic imaging, with more than 10% of these patients having symptomatic brain metastases at first visit.

Table 1. Patient, tumour and treatment characteristics at first presentation in a melanoma centre

Characteristic	July 2012-July 2013 *N*=401 *N* (%)	July 2013- July 2014 *N*=988 *N* (%)
Patient characteristics		
Age, median (range), yrs	59 (20-90)	63 (18-92)
Age group		
< 50	108 (27)	191 (19)
50-59	97 (24)	210 (21)
60-69	118 (29)	291 (30)
=>70	78 (20)	296 (30)
Gender		
Female	163 (41)	453 (46)
Male	238 (59)	535 (54)
Median (range) time since primary diagnosis, yrs	2 (0-28)	2 (0-43)
ECOG performance score		
0	199 (50)	475 (48)
1	132 (33)	251 (25)
>/=2	44 (11)	102 (10)
Unknown	26 (7)	160 (16)
Elevated serum LDH level (>250 U/L)		
No	250 (62)	619 (63)
Yes	139 (35)	252 (26)
Unknown	12 (3)	117 (12)
Brain metastases		
No	290 (72)	664 (67)
Yes	92 (23)	224 (23)
Symptomatic brain metastasis	48 (12)	155 (16)
Unknown	19 (5)	100 (10)
Tumour characteristics		
Disease stage		
Unresectable stage IIIc	8 (2)	55 (6)
M1a	30 (8)	58 (6)
M1b	35 (9)	88 (9)

Table 1. Patient, tumour and treatment characteristics at first presentation in a melanoma centre (*continued*)

Characteristic	July 2012-July 2013 *N*=401 *N* (%)	July 2013- July 2014 *N*=988 *N* (%)
M1c	314 (78)	679 (69)
Unknown M stage	12 (3)	85 (9)
Unknown	2 (1)	23 (2)
Location of primary tumour		
Trunk	169 (42)	330 (33)
Extremities	106 (26)	292 (30)
Head and/or neck	50 (13)	119 (12)
Uveal	5 (1)	69 (7)
Acral	10 (3)	28 (3)
Mucosal	5 (1)	22 (2)
Primary unknown	50 (13)	121 (12)
Missing	6 (2)	7 (1)
Histology of primary tumour[a]		
Superficial spreading	171 (51)	374 (49)
Nodular	86 (26)	207 (27)
Acral lentiginous	5 (2)	16 (2)
Desmoplastic	4 (1)	5 (1)
Lentigo maligna	4 (1)	12 (2)
Other	19 (6)	55 (7)
Unknown	46 (14)	100 (13)
Mutation status		
No mutation status analysed	6 (2)	107 (11)
Mutation status analysed	395 (99)	879 (89)
Unknown	0 (0)	2 (0)
Type of mutation		
BRAF mutation	306 (76)	475 (48)
No BRAF mutation	89 (22)	404 (41)
NRAS mutation[b]	17	146
KIT mutation[b]	2	7
GNAQ mutation[b]	0	7

Table 1. Patient, tumour and treatment characteristics at first presentation in a melanoma centre (*continued*)

Characteristic	July 2012-July 2013 *N*=401 *N* (%)	July 2013- July 2014 *N*=988 *N* (%)
GN-11 mutation[b]	0	1
Wild type[b]	58	209
Type of mutation unknown[b]	12	34
Treatment characteristics		
Previous systemic treatment for metastatic disease		
Chemotherapy	78 (20)	41 (4)
BRAF inhibitor	13 (3)	13 (1)
Ipilimumab	0 (0)	2 (0)
Trial	26 (6)	30 (3)
Treatment in melanoma centre		
Systemic treatment	401 (100)	717 (73)
Only local treatment	N/A	151 (15)
RFA	N/A	2 (0)
Surgery	N/A	60 (6)
Radiotherapy	N/A	68 (7)
Surgery and radiotherapy	N/A	19 (2)
Other	N/A	2 (0)
No therapy	N/A	120 (12)

Yrs=years; ECOG = Eastern Cooperative Oncology Group; LDH= lactate dehydrogenase; RFA = radiofrequency ablation; N/A = not applicable.

[a] Histology is presented for patients with cutaneous melanoma (first registration year, *N*=335; second registration year, *N*=769).

[b] Type of mutation is presented for patients with BRAF, wild-type (first registration year, *N*=89; second registration year, *N*=404).

Treatment characteristics

Figure 2 demonstrates the type of drug administered to patients by line of treatment and by year of registration in the DMTR. In the first registration year, a BRAF inhibitor was most frequently administered in the first line of therapy (66%). Ipilimumab was mostly administered as second-line therapy (39%), but a shift towards first-line

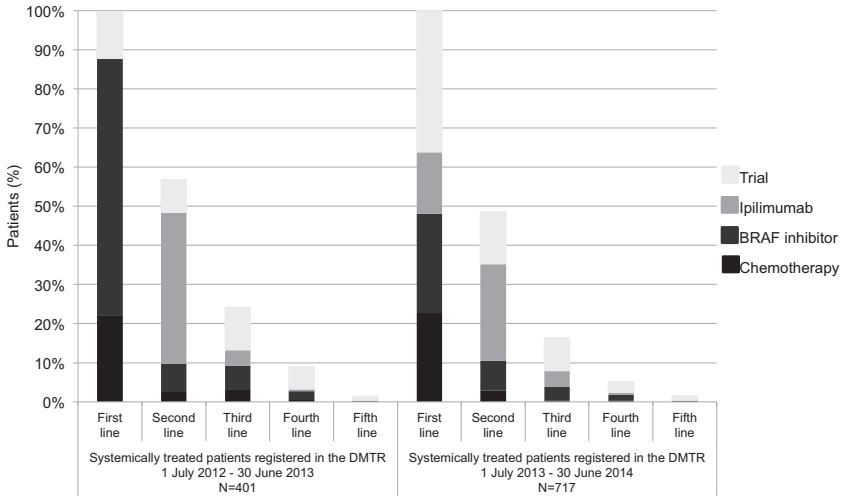

Figure 2. Treatment patterns of all systemically treated patients with metastatic melanoma, presented by line of systemic therapy and year of registration.

therapy (16%) was observed in the second registration year. This was probably due to the approval of ipilimumab as a first-line therapy at the beginning of 2014. More than one-third of the patients (36%) participated in a clinical trial or compassionate-use programme as first-line therapy in the second year.

Performance indicators of quality of metastatic melanoma care

Table 2 shows the indicators for quality of care in the first 2 registration years at national level.

Structure

Participation in the DMTR is obligatory for all 14 melanoma treatment centres and the full participation of all centres was achieved within the first registration year. Of all patients referred to a melanoma centre, 98-100% had sufficient quality of data to include for further analysis.

Outcome

Of all the patients treated with a BRAF inhibitor, almost 30% experienced at least one grade 3 or 4 adverse event. The grade 3/4 adverse events for patients treated with

Table 2. Results of the performance indicators on the quality of metastatic melanoma care

Indicator	2013			2014		
	Eligible patients (*N*)	Observed patients (*n*)	%	Eligible patients (*N*)	Observed patients (*n*)	%
Structure						
Hospitals participating in the Dutch Melanoma Treatment Registry	14[a]	14[a]	100	14[a]	14[a]	100
Patients referred to a melanoma center and eligible for analysis	401	401	100	1011	988	98
Process						
Patients without therapy	-	-		988	120	12
Patients with local therapy	-	-		988	151	15
Patients with systemic therapy	401	401	100	988	717	73
Patients with systemic therapy: chemotherapy[b]	401	34	8	988	156	16
Patients with systemic therapy: a BRAF inhibitor[b]	401	288	72	988	237	24
Patients with systemic therapy: ipilimumab[b]	401	174	43	988	320	32
Short term outcomes						
Patients with grade III-IV AE as a result of treatment with chemotherapy[b]	34	4	12	156	6	4
Patients with grade III-IV AE as a result of treatment with BRAF inhibitor[b]	288	89	31	237	67	28
Patients with grade III-IV AE as a result of treatment with ipilimumab[b]	174	34	20	320	75	23
Deaths associated with grade III-IV AE after treatment with chemotherapy[b]	34	0	0	156	0	0
Deaths associated with grade III-IV AE after treatment with BRAF inhibitor[b]	288	0	0	237	0	0
Deaths associated with grade III-IV AE after treatment with ipilimumab[b]	174	1	1	320	0	0

Table 2. Results of the performance indicators on the quality of metastatic melanoma care (*continued*)

Indicator	2013			2014		
Long term outcomes	Patients at risk (*N*)	Events[c] (*n*)		Patients at risk (*N*)	Events[c] (*n*)	
Overall survival and mortality rates of patients without therapy						
Median OS, months (95% CI)	-	-		120	77	4.5 (1.2-7.9)
6 months, % (95% CI)	-	-		47	62	45 (36-54)
12 months, % (95% CI)	-	-		31	73	34 (25-43)
18 months, % (95% CI)	-	-		17	77	29 (20-38)
Overall survival and mortality rates of patients with local therapy						
Median OS, months (95% CI)	-	-		151	87	10.3 (7.4-13.2)
6 months, % (95% CI)	-	-		83	58	60 (52-68)
12 months, % (95% CI)	-	-		46	78	44 (35-52)
18 months, % (95% CI)	-	-		NR	NR	NR
Overall survival and mortality rates of patients with systemic therapy						
Median OS, months (95% CI)	401	323	10.1 (9.1-11.1)	713	419	12.7 (11.6-13.7)
6 months, % (95% CI)	294	105	73 (68-77)	537	157	78 (75-81)
12 months, % (95% CI)	169	229	43 (38-48)	312	315	53 (49-57)
18 months, % (95% CI)	106	288	28 (23-32)	109	395	37 (32-41)

AE= adverse event, NR=not reached, OS = overall survival

[a] The number displayed corresponds to the number of hospitals

[b] Patients can be treated with more than one type of systemic therapy during the study period

[C] Event: number of deaths

ipilimumab were 20% and 23% in year 1 and 2, respectively. No deaths were related to the toxicity of treatment with a BRAF inhibitor. One death was associated with ipilimumab toxicity. The median OS of patients treated with systemic therapy was 10.1 months (95% CI 9.1- 11.1) in the first year and 12.7 months (95% CI 11.6- 13.7) in the second year. Figure 3 shows the hospital variation in percentage of patients with grade 3/4 adverse events during treatment with a BRAF inhibitor (3a) and ipilimumab (3b) in the first 2 years of registration. The funnel plots demonstrate that no melanoma centre performed significantly worse than average on toxicity rates for both ipilimumab and BRAF inhibitors. One melanoma centre performed significantly better than average on toxicity rates after treatment with a BRAF inhibitor.

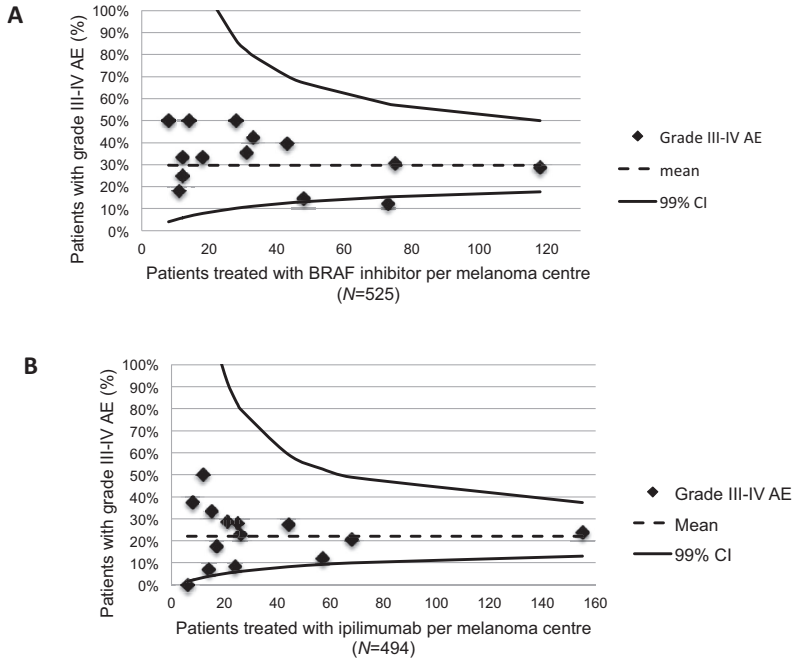

Figure 3. Variation between melanoma centres in the percentage of patients with grade III-IV AEs caused by a BRAF inhibitor (A) and/or ipilimumab (B). The dotted line presents the average percentage of patients who experienced grade III-IV AEs. AE = adverse event.

DISCUSSION

This article reports on the start-up and key elements of the DMTR. The DMTR is unique in its collaboration between all stakeholders involved in treating metastatic melanoma, and its multipurpose design. The active participation of the 14 dedicated melanoma centres led to the nationwide coverage of all patients with meta-static melanoma in the registry within the first year.

The results of the DMTR demonstrate that treatment with BRAF inhibitors and ipilimumab has been implemented as standard of care in the Netherlands. Monitoring these drugs in population-based registries is therefore highly relevant to the assessment of the extent to which results from clinical trials are achieved in clinical practice [19].

The first Dutch population-based registry in outcome research for cancer patients was PHAROS. This haematological registry started in 2010 and was created to serve multiple purposes, including evaluating the quality of care of three haematologic malignancies in daily practice and determining the clinical and cost-effectiveness of treatments used [20].

However, population-based registries are scarce in the field of metastatic melanoma. Existing registries generally have a retrospective design and do not have a nationwide coverage [21]. More importantly, these registries do not include information on patients treated with the new drugs; the reported results are, therefore, not applicable to current management of advanced melanoma [22].

Data from the DMTR demonstrates that BRAF inhibitors and ipilimumab have been safely introduced in the Netherlands. The toxicity rates were comparable with the results in clinical trials [5-8], although a relatively great number of patients registered in the DMTR have brain metastases and/or a poor performance status. These patients would have been ineligible for trial inclusion. Only one death was reported, due to an adverse event contributed to ipilimumab. This may indicate that adequate management of adverse events in specialised melanoma centres with experience in the treatment of patients with advanced melanoma can prevent life-threatening situations in daily practice. BRAF inhibitors and ipilimumab show a survival benefit compared with classic cytotoxic treatment [23,24]. In this study, the 12-month survival rate already improved during the second year of registration. This could be the effect

of the approval of ipilimumab as a first-line therapy and a large number of patients participating in clinical trials with an anti-PD1 antibody. With the rapid development of new drugs and the combination of drugs [25,26], we expect the survival of metastatic melanoma patients to improve.

Real-time feedback and transparency are essential to evaluating and anticipating the rapid advances in met-astatic melanoma treatment, but existing quality initiatives concerning melanoma care have mainly focused on surgical treatment [11,27]. The DMTR provides clinicians with benchmarked feedback with detailed information on both systemically and non-systemically treated patients. It has further agreed to make the results gradually publicly available to provide transparency to all stakeholders concerned. For instance, the funnel plots on toxicity rates of the new drugs increase awareness regarding safety issues in clinical practice. Although no melanoma centre performed significantly worse, the positive outlier (best practice) indicates areas for improvement.

Furthermore, the DMTR may provide information on optimal sequencing of various types of treatment in a real-world setting compared with phase III trials that only report on the investigational drug. This knowledge in combination with data on clinical effectiveness, quality of life, healthcare utilisation, informal care and productivity losses will be used to develop an advanced melanoma disease model. This may provide insight into real-world cost-effectiveness of treatments and treatment patterns, which is increasingly important to ensure the sustainability of the healthcare system. Effectiveness studies are important to both patients and healthcare providers as they determine whether interventions work in the real world, and therefore inform both clinical decision-making and health policy [20].

The DMTR also has its limitations. Population-based registers are generally more prone to registration bias because data are often self-reported and no standardised and uniform criteria are formulated as in clinical trials. This may have led unintentionally to adverse events being less strictly categorised. However, because of the prospective nature of the DMTR's long-term follow-up, patient records are updated every 3 months. To ensure high-quality data, data managers were extensively trained

and oncologists supervise the registration process and validate all data at patient level.
The multipurpose design makes the DMTR an extensive registry raising concerns on the financial and administrative burden and its sustainability in the future. The rough cost per patient in the DMTR is approximately V500, based on an average of 8 hours of registration per patient record, including data-entry (majority of the costs), validation, data-analyses, reporting and training of the data managers. This is a considerable amount; however, in comparison with the price of the drugs per patient, it is not more than 0.5e1% of the total costs per treated patient. Probably, this is an overestimation because costs of hospital resource use and informal care are not even included. It will be important to decision-makers whether securing a small percentage of the total treatment budget for obtaining quality information is acceptable.

Of course it is important to try to reduce the costs of the data registration. In the near future, the DMTR needs to discuss which items are essential to be collected on every patient and which items should be additional; for example, for evaluating cost-effectiveness.
Furthermore, integration with the electronic health record as well as data-linkage with existing sources and registries could reduce the administrative and financial burden even further.

To our knowledge, the DMTR is the first comprehensive population-based registry in advanced melanoma, since BRAF inhibitors and immune checkpoint inhibitors were introduced. The quality performance indicators demonstrated the safe introduction of the new drugs in the Netherlands with toxicity rates that were consistent with the phase III trials conducted. Bearing in mind the increasing number of expensive drugs for cancer coming on to the market, the unique design of the DMTR and the collaboration it represents can be used as a blueprint for future real-world data collection initiatives.

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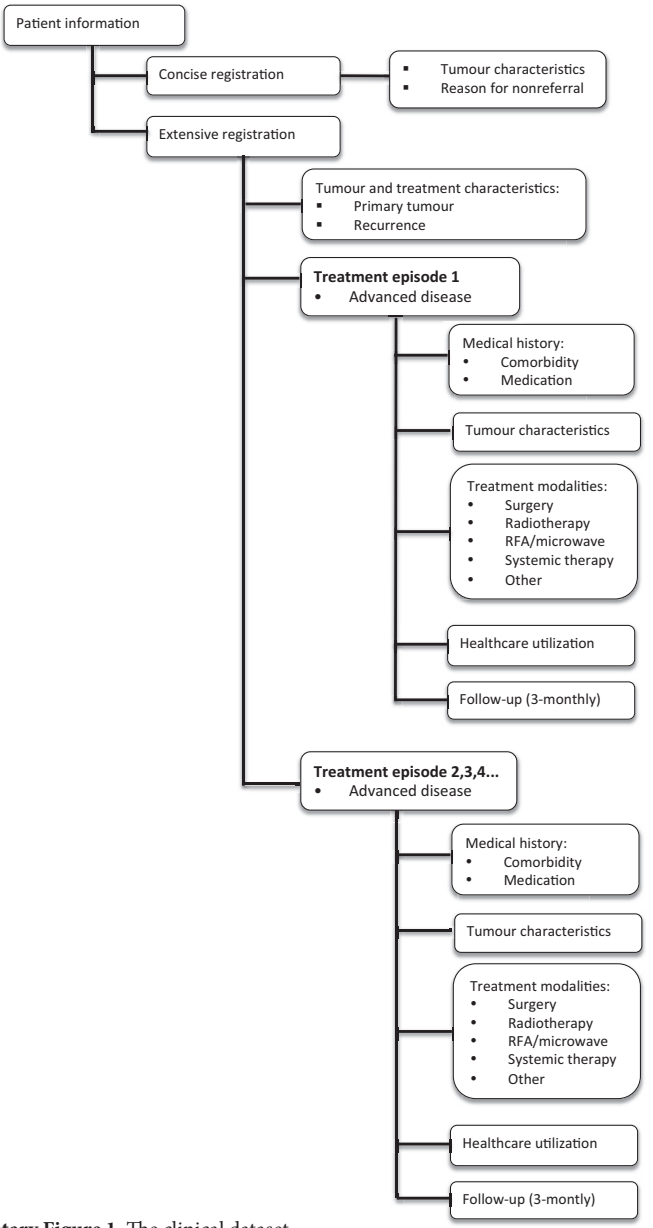
APPENDICES



Supplementary Figure 1. The clinical dataset