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Real-world outcomes of advanced melanoma patients not represented in phase III trials

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Abbreviations: ASCO, American Society of Clinical Oncology; BM, brain metastases; CIST, conditional inference survival tree; DMTR, Dutch Melanoma Treatment Registry; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ESMO, European Society of Medical Oncology; LDH, lactate dehydrogenase; MCBS, Magnitude of Clinical Benefit Scale; mOS, median OS; OS, overall survival; RCTs, randomized controlled trials.

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Abstract

The aim was to provide evidence on systemically treated patients with advanced melanoma not represented in phase III trials to support clinical decision-making. Analysis were performed on advanced melanoma patients diagnosed between 2014 and 2017 in the Netherlands, treated with immune- or targeted therapy, who met ≥1 trial exclusion criteria. These criteria were derived from the KEYNOTE-006 and CHECKMATE-067/-066 phase III trials. Prognostic importance of factors associated with overall survival (OS) was assessed with the Kaplan-Meier method, Cox models, predicted OS probabilities of prognostic subgroups and a conditional inference survival tree (CIST). A nationwide population-based registry was used as data source. Of 2536 systemically treated patients with advanced melanoma, 1004 (40%) patients were ineligible for phase IIII trials. Ineligible patients had a poorer median OS (mOS) compared to eligible patients (8.8 vs 23 months). Eligibility criteria strongly associated with OS in systemically treated ineligible patients were Eastern Cooperative Oncology Group Performance Score (ECOG PS) ≥2, brain metastases (BM) and lactate dehydrogenase (LDH) of >500 U/L. Patients with ECOG PS of ≥2 with or without symptomatic BM had a predicted mOS of 6.5 and 11.3 months and a 3-year survival probability of 9.3% and 23.6%, respectively. The CIST showed the strongest prognostic covariate for survival was LDH, followed by ECOG PS. The prognosis of patients with LDH of >500 U/L is poor, but long-term survival is possible. The prognosis of ineligible patients with advanced melanoma in real-world was very heterogeneous and highly dependent on LDH value, ECOG PS and symptomatic BM.

KEYWORDS
advanced melanoma, decision tree, ineligibility, real-world outcomes, survival

1 | INTRODUCTION

In recent years, treatment options for advanced melanoma have increased as immune- and targeted therapies became available. The randomized controlled trials (RCTs) used for marketing approval for these treatments showed major improvements in overall response rate, progression-free survival and overall survival (OS) compared to standard treatments.[1]

RCTs are considered the gold standard to determine efficacy of new treatments. Strict inclusion and exclusion criteria are applied to create a homogenous patient population. This improves the internal validity of clinical trials which enables estimation of valid treatment effects of new treatments. A large proportion of real-world patients with advanced melanoma are not represented in clinical trials.[2] Real-world patients not fulfilling the RCT inclusion criteria (ineligible patients) are being treated without evidence of the efficacy and safety in daily clinical practice. Donia et al[3] concluded that also ineligible patients might have benefited from the introduction of new treatments.

However, the ineligible patient population is heterogeneous. Additional information is needed to determine which subgroups of ineligible patients do not benefit from these new treatments. More efficient use of systemic treatment can spare patients severe adverse events[4,5] and perhaps reduce the financial burden for society.[6]

What's new?

By necessity, randomized controlled trials (RCTs) exclude many patients. However, these ineligible patients are often still treated with new systemic therapies on an individual basis. In this study, the authors examined how various subgroups of ineligible patients fared following treatment for advanced melanoma. They found that several criteria were strongly associated with prognosis in these patients, including lactate dehydrogenase (LDH) levels. These results should provide clinicians with a decision tree of prognostic factors to help guide treatment decisions.

In our study, the nationwide prospective population-based Dutch Melanoma Treatment Registry (DMTR) was used to report clinical outcomes of ineligible patients.[7] Our study aimed to identify prognostic factors for survival for systemically treated ineligible patients, to predict survival for prognostic subgroups of ineligible patients and to order the impact of prognostic factors with a decision tree to help guide clinical decision-making.

2 | METHODS

2.1 | Study design and patients

Patients of 18 years and older, diagnosed with unresectable stage IIIC or stage IV melanoma between January 1, 2014 and December 31, 2017, were included. Criteria to distinguish ineligible from eligible patients were derived from the KEYNOTE-006 and CHECKMATE-067/-066 phase III trials.[8-10] Patients were considered ineligible for potential trial participation if they met one or multiple of the following exclusion criteria:

- Brain metastasis or leptomeningeal metastasis
  - In the DMTR data no distinction could be made between active or not active brain metastasis
- Eastern Cooperative Oncology Group performance status (ECOG PS) of ≥2
- Active autoimmune disease(s)
  - Rheumatoid disease, systemic lupus erythematosus, vasculitis, inflammable bowel disease (Crohn's or colitis ulcerosa)
- Immune-modulating medication
  - Azathioprine or interferon
- Known history of Human Immunodeficiency Virus or AIDS
- Liver disease or failure or kidney failure
- Serious psychiatric disorder
  - Schizophrenia, severe depression or psychosis

Dataset cutoff date was June 1, 2019. The medical ethics committee judged that informed consent was not necessary for the DMTR and all patients were offered an opt-out possibility.

2.2 | Statistical analysis

Baseline patient and tumor characteristics of systemically treated ineligible and eligible patients were analyzed with descriptive statistics. OS estimates of these groups were estimated with the Kaplan-Meier method. Survival times were calculated from the start of systemic therapy until death or last follow-up. Median follow-up time was estimated with the reverse Kaplan-Meier method.[11] Within the systemically treated ineligible patient population, univariable and multivariable Cox proportional hazards regression models were used to estimate the association of exclusion criteria and other clinically relevant prognostic factors with OS.[12] Variables assessed were lactate dehydrogenase (LDH), Eastern Cooperative Oncology Group Performance Score (ECOG PS), age, gender, metastases in ≥3 organ sites, brain metastases, liver metastases, year of diagnosis, autoimmune disease, psychiatric disorder and BRAF mutation. We present the analyses of complete cases in Figure S1. The proportionality assumption in the Cox models was investigated by means of scaled Schoenfeld residuals.

For further analyses, we created prognostic subgroups of patients based on the most important factors from the multivariable Cox model. We used the full multivariable Cox model to predict the patient-specific probability of OS. For all subgroups the median OS (mOS) and 3-year OS probability were calculated based on these individual predicted probabilities.

To assess the potential benefit of systemic therapy in the absence of a historical cohort, we created a control group by selecting systemically treated and untreated ineligible patients diagnosed with advanced melanoma in 2013. We compared casemix-adjusted survival curves of this 2013 cohort with our study population. In the 2013 cohort of ineligible patients, 29% received no systemic treatment, 14% received chemotherapy, 37% ipilimumab or BRAF inhibitor monotherapy as first-line treatment and 21% of the patients received another systemic therapy (patients treated in named-patient or compassionate use programs or in trials).

We constructed a decision tree model using the recursive binary partitioning approach. The method of Hothorn et al[13] was used to create a conditional interference survival tree (CIST). The variables used in the model were gender, age, LDH, ECOG PS, number of organs with distant metastases, brain and liver metastases, year of diagnosis and BRAF-mutation. First, the model determines which variable is most strongly associated with OS. Second, a cut-off value in this variable is calculated that optimally splits the data creating two most prognostically different subpopulations. The model then repeats these two steps taking the two new nodes as the basis. The model stops if no variable significantly associated with OS is left and no prognostic difference is seen when partitioning the subpopulation further.[13]

Data handling and statistical analyses were performed using the R software system for statistical computing (version 3.6.1.; packages tidyverse, lubridate, car, survival, survminer, partykit).

3 | RESULTS

From 2014 to 2017, 3460 patients were diagnosed with unresectable stage IIIC and stage IV (advanced) melanoma prospectively registered in the DMTR. Patients diagnosed with uveal melanoma, age of <18 years and patients with missing values to determine eligibility or missing survival data were excluded from further analyses. Of the remaining 3009 patients, 1004 (40%) systemically treated patients with advanced melanoma were considered ineligible (Figure S2).

3.1 | Eligible vs ineligible patients

The main differences in characteristics between ineligible patients and eligible patients were related to the exclusion criteria, such as the

TABLE 1 Patient and tumor characteristics of systemically treated for phase III trials ineligible and eligible patients

	Ineligible (n = 1004)	Eligible (n = 1532)	*P* value
Median age, year (range)	62 (19, 94)	64 (19, 94)	.080
Age categories			.035
<50 years	176 (17.5)	273 (17.8)	
50-59 years	259 (25.8)	320 (20.9)	
60-69 years	274 (27.3)	452 (29.5)	
>70 years	295 (29.4)	487 (31.8)	
Female	422 (42.0)	607 (39.6)	.238
ECOG PS			
0	357 (38.3)	1028 (67.1)	
1	295 (31.6)	504 (32.9)	
2	204 (21.9)	—	
≥3	77 (8.3)	—	
Unknown	71	—	
LDH level			<.001
Normal	528 (54.0)	1052 (69.8)	
250-500 U/L	283 (28.9)	332 (22.0)	
>500 U/L	167 (17.1)	124 (8.2)	
Unknown	26	24	
Stage			<.001
IIIc	17 (1.7)	150 (9.8)	
IV-M1a	22 (2.2)	172 (11.2)	
IV-M1b	29 (2.9)	246 (16.1)	
IV-M1c	934 (93.2)	962 (62.9)	
Metastases in ≥3 organ sites	620 (61.9)	549 (35.8)	<.001
Brain metastasis			
No	308 (31.1)	1532 (100.0)	
Yes, asymptomatic	237 (23.9)	—	
Yes, symptomatic	445 (44.9)	—	
Unknown	14	—	
Liver metastasis	311 (31.7)	387 (25.4)	.001
Auto-immune disease[a]	141 (14.0)	—	
IM medication[b]	4 (0.4)	—	
HIV or AIDS	1 (0.1)	—	
Psychiatric disorder[c]	51 (5.1)	—	
BRAF mutant	671 (66.8)	833 (54.3)	<.001

Note: Values are n (%) unless otherwise indicated.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IM, immune modulating; LDH, lactate dehydrogenase.
[a]Rheumatoid disease, systemic lupus erythematosus, vasculitis, inflammable bowel disease (Crohn's or colitis ulcerosa).
[b]Azathioprine, interferon.
[c]Schizophrenia, major depression, psychosis and other psychiatric disorders.

presence of brain metastases (n = 682, 67.9%), ECOG PS of ≥2 (n = 281, 28.0%) and the presence of active autoimmune diseases (n = 141, 14.0%) in ineligible patients (Table 1). Besides these differences in exclusion criteria, other baseline characteristics were significantly more common in ineligible patients compared to eligible patients, such as elevated LDH level of ≥250 U/L, stage IVM1c disease, liver metastasis, metastasis in ≥3 organ sites and the presence of BRAF mutation (Table 1).

The mOS of systemically treated ineligible patients was shorter compared to systemically treated eligible patients (8.8 months (95%CI: 7.9-11.0) vs 23 months (95%CI: 21-27)). The 3-year OS probability was 22% (95%CI: 19-25) for ineligible patients and 41% (95%CI: 38-43) for eligible patients (Figure 1). The median follow-up of systemically treated ineligible patients was 38 months.

3.2 | Treatment and clinical outcomes of ineligible patients

The composition of the systemically treated ineligible patient group and the exclusion criteria are shown in Table S3. A total of 862 (85.9% of the ineligible patients) patients would have been excluded from trial participation, because of either brain metastases or ECOG PS ≥2, or both. The first- and second-line treatments of ineligible patients are shown in Figure 2.

In the multivariable Cox model, ECOG PS ≥2, elevated LDH ≥500 U/L and the presence of symptomatic brain metastases and liver metastases were negatively associated with OS. BRAF mutational status was not associated with OS (Table 3).

Comparison of the casemix-adjusted survival curves of the 2013 cohort with our study cohort of 2014 to 2017 indicated that OS for ineligible patients has increased when more systemic therapies were available (mOS of 5.7 months vs 8.8 months, respectively). The 3-year OS probability of the 2013 cohort was 7.5% vs 22% of our study cohort (Figure S4). The mOS of systemically untreated ineligible patients diagnosed with advanced melanoma from 2014 to 2017 (n = 327) was 2.4 (95% CI: 2.1-2.8) months (Figure S5).

We created 18 subgroups of systemically treated ineligible patients by combining the most important exclusion criteria from the multivariable Cox model, ECOG PS, and brain metastases with LDH level, as LDH level is an important prognostic factor for survival.[12,14] Each subgroup was assessed for the predicted mOS and 3-year survival probability (Table 2). The predicted survival curves of individual patients in the subgroups showed substantial prognostic variation in survival between patients in a subgroup (Figures S6 and S7). The covariates BRAF mutational status, LDH, ECOG PS and brain metastases violated the proportionality assumption. To keep interpretation easy and avoid overfitting, time-dependent effects of these risk factors were not modeled explicitly. The HRs have to be interpreted as averages over the follow-up time. The predicted probability curves also represent these averaged effects. The nonproportionality of BRAF mutation was further investigated in a Cox model in which this variable was entered as a stratification factor.

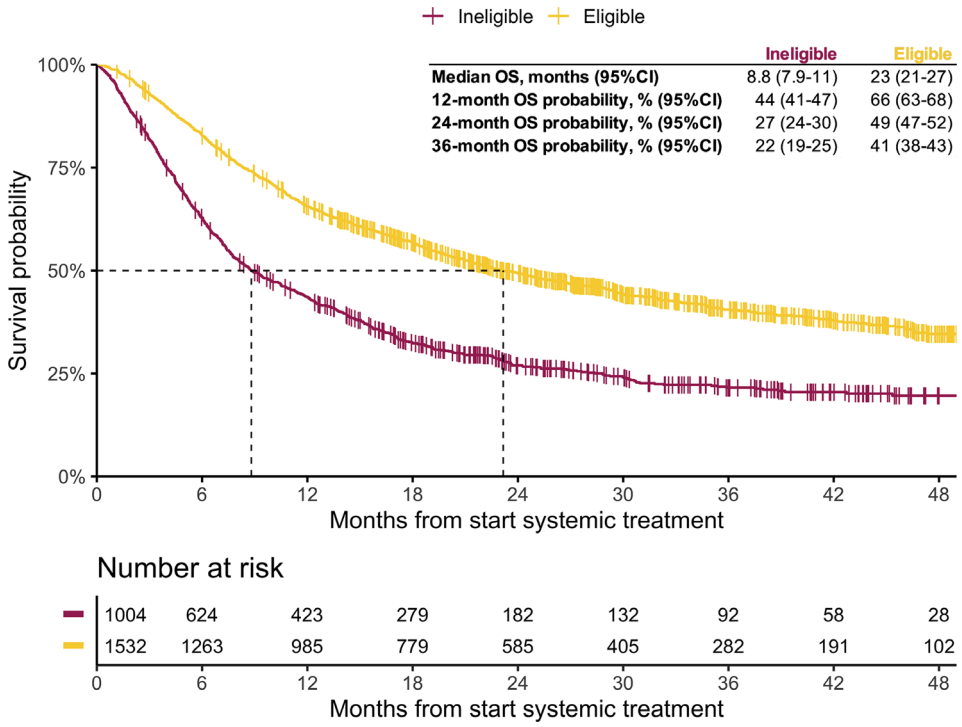

FIGURE 1 Overall survival of systemically treated ineligible and eligible patients estimated with the Kaplan-Meier method [Color figure can be viewed at wileyonlinelibrary.com]

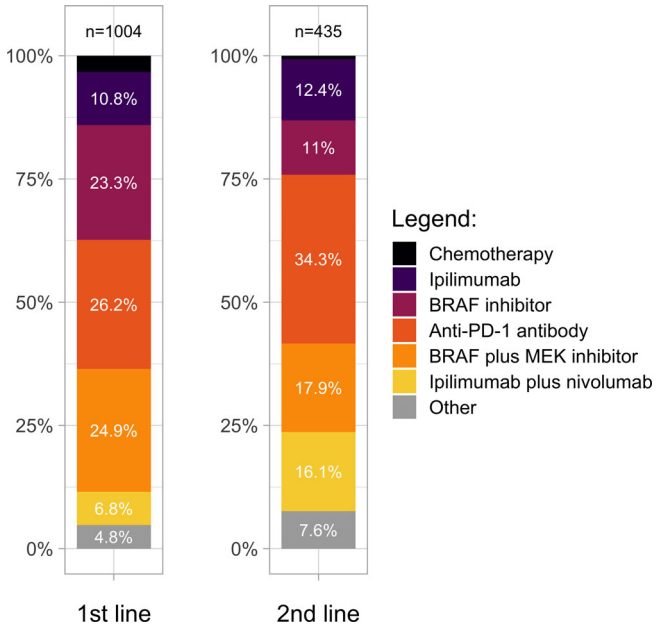

FIGURE 2 First- and second-line systemic treatment of ineligible patients [Color figure can be viewed at wileyonlinelibrary.com]

The conditional inference survival tree resulted in six subgroups (Figure 3). The covariate with the strongest association with survival was LDH. For patients with an LDH level of >500 U/L, other covariates did not significantly influence the OS. The most prognostic covariate in the subgroup of patients with a normal or LDH level of 250 to 500 U/L was ECOG PS followed by symptomatic brain metastases.

3.3 | BRAF mutational status

We performed an additional analysis of BRAF-mutant vs BRAF wild-type melanoma because BRAF mutational status was not associated with OS in the multivariable Cox model (Table 3). Baseline characteristics and the first-line systemic therapies of BRAF wild-type and BRAF-mutated melanoma patients are shown in Table S8 and Figure S9, respectively . The casemix-adjusted OS curves showed that the small survival benefit in favor of the BRAF mutated melanoma established in the first 6 months, disappeared after 10 months (Figure S10).

4 | DISCUSSION

Our study focused on clinical outcomes of ineligible advanced melanoma patients treated with systemic therapy in real-world. There is no RCT evidence to justify treatment in these patients, but our study fills this knowledge gap and provides guidance in shared decision-making. Forty percent of the systemically treated patients were considered ineligible following the exclusion criteria of phase III trials.[8-10] Although OS of systemically treated ineligible patients was significantly lower than the OS of systemically treated eligible patients, the 3-year OS probability of ineligible patients was still 22%. There was a high variation in (predicted) OS within the ineligible patient population, except for most subgroups with an LDH level of >500 U/L. The decision tree (CIST)[13] technique identified clinically interesting prognostic subgroups that can be used to prognostically stratify and inform ineligible patients in daily practice.

TABLE 2 Subgroups of ineligible patients with predicted median overall survival and median of predicted 3-year survival probability based on the multivariable Cox model

ECOG PS	Brain metastasis	LDH level	n	Predicted mOS (months)	3-year survival (%)
0-1	Absent	normal	82	22.7	44.5
0-1	Absent	250-500 U/L	32	15.4	33.1
0-1	Absent	>500 U/L	14	7.9	15.3
0-1	Asymptomatic	normal	119	16.4	35.1
0-1	Asymptomatic	250-500 U/L	63	9.9	21.0
0-1	Asymptomatic	>500 U/L	16	6.0	7.2
0-1	Symptomatic	normal	191	11.9	25.0
0-1	Symptomatic	250-500 U/L	94	7.2	12.4
0-1	Symptomatic	>500 U/L	21	5.0	3.7
≥2	Absent	normal	53	11.3	23.6
≥2	Absent	250-500 U/L	50	7.6	14.1
≥2	Absent	>500 U/L	65	4.8	3.2
≥2	Asymptomatic	normal	3	11.0	22.7
≥2	Asymptomatic	250-500 U/L	6	6.2	8.1
≥2	Asymptomatic	>500 U/L	10	4.8	3.1
≥2	Symptomatic	normal	37	6.5	9.3
≥2	Symptomatic	250-500 U/L	18	4.7	3.1
≥2	Symptomatic	>500 U/L	24	3.4	0.3

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; mOS, median overall survival.

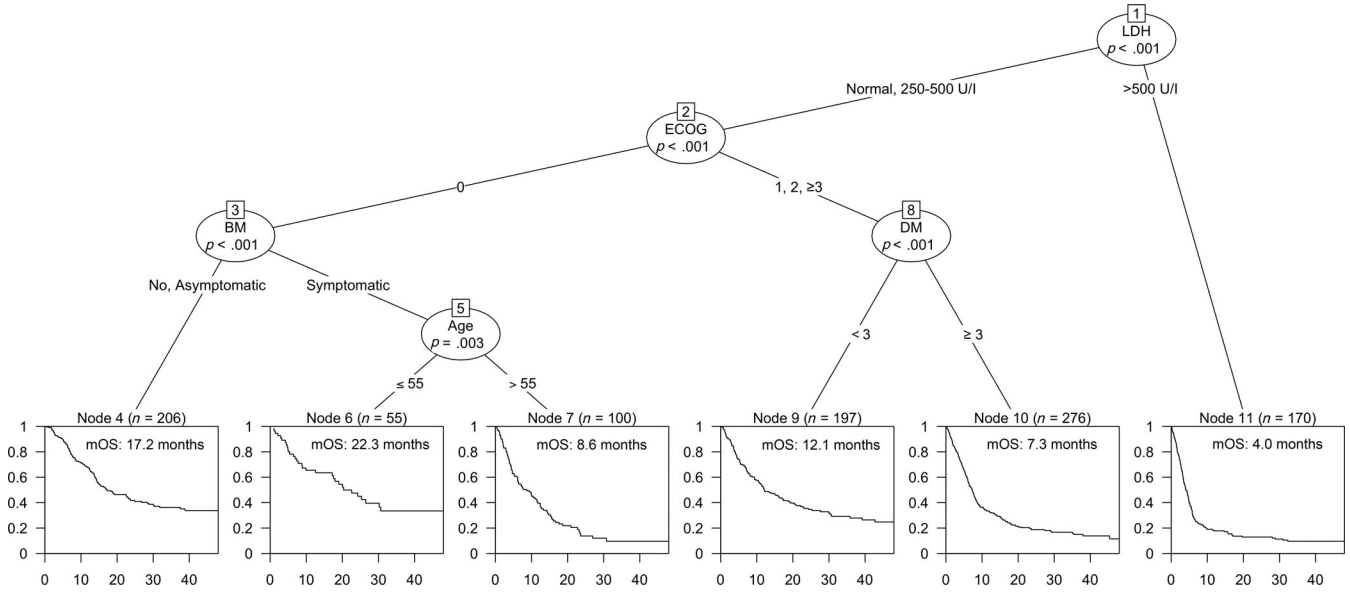

FIGURE 3 Conditional inference survival tree incorporating disease and patient variables into prognostic models for survival, based on year of diagnosis, age, gender, ECOG PS, LDH level, distant metastases, brain- and liver metastases and BRAF mutational status. P-values are from log-rank statistics

TABLE 3 Cox model of systemically treated ineligible patients for the association of prognostic factors with overall survival

	Univariable			Multivariable		
	n	HR (95% CI)	*P* value	n	HR (95% CI)	*P* value
Year of diagnosis						
2014	203	1		173	1	
2015	262	0.91 (0.75-1.12)	.383	226	0.84 (0.67-1.05)	.129
2016	244	0.76 (0.61-0.93)	.009	219	0.70 (0.56-0.87)	.002
2017	295	0.73 (0.59-0.91)	.004	264	0.61 (0.48-0.77)	<.001
Age						
≤50	176	0.70 (0.56-0.87)	.002	148	0.65 (0.51-0.84)	.001
50-59	259	0.84 (0.69-1.02)	.08	228	0.79 (0.64-0.98)	.032
60-69	274	1		245	1	
≥70	295	0.98 (0.81-1.18)	.792	261	1.02 (0.83-1.24)	.885
Gender						
Male	582	1		511	1	
Female	422	0.90 (0.78-1.04)	.149	371	0.91 (0.78-1.07)	.245
ECOG PS						
0	357	1		342	1	
1	295	1.46 (1.21-1.75)	<.001	278	1.35 (1.11-1.65)	.003
≥2	281	2.09 (1.75-2.51)	<.001	262	1.95 (1.52-2.5)	<.001
LDH						
Normal	528	1		475	1	
250-500 U/L	283	1.44 (1.21-1.7)	<.001	259	1.23 (1.02-1.49)	.03
>500 U/L	167	2.64 (2.17-3.2)	<.001	148	1.89 (1.49-2.41)	<.001
Metastases in ≥3 organ sites						
No	382	1		339	1	
Yes	620	1.57 (1.35-1.83)	<.001	543	1.25 (1.03-1.51)	.021
Brain metastasis						
Absent	308	1		295	1	
Asymptomatic	237	0.95 (0.78-1.16)	.614	208	1.31 (0.98-1.75)	.069
Symptomatic	445	1.25 (1.06-1.48)	.01	379	1.71 (1.34-2.18)	<.001
Liver metastasis						
No	671	1		602	1	
Yes	311	1.64 (1.4-1.9)	<.001	280	1.22 (1-1.48)	.049
Auto-immune disease						
No	863	1		754	1	
Yes	141	0.71 (0.57-0.89)	.003	128	1.02 (0.77-1.35)	.892
Psychiatric disorder						
No	953	1		835	1	
Yes	51	0.69 (0.49-0.99)	.044	47	0.93 (0.62-1.4)	.721
BRAF-mutant						
No	333	1		302	1	
Yes	671	1.06 (0.91-1.24)	.47	580	0.94 (0.79-1.12)	.474

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase.

In-depth postapproval research cannot replace RCTs, but it is necessary to try to substantiate the effectiveness of using new systemic treatments in real-world patients. The distinction in eligibility for trial participation is factitious. Eligibility depends on having one or multiple exclusion criteria that were once defined for phase III trials, but not all exclusion criteria are equally important with regard to

the prognosis and/or effect of treatment (ie, psychiatric disorder and immune-modulating medication). The ineligible patient population is heterogeneous in itself and with different statistical approaches, we attempted to provide in-depth evidence on what effect exclusion criteria have on survival in the real-world.

In our study, 86% of systemically treated ineligible patients had brain metastasis, ECOG PS of ≥2 or both. Brain metastases and ECOG PS were combined with LDH level, a nonexclusion criterion that is generally known for its prognostic and predictive importance, to create subgroups.[12,14] For subgroups of patients with (a)symptomatic brain metastases, the prognosis was relatively good, provided that ECOG PS was ≤1 and LDH level was normal. The decision tree (CIST) model also showed that ineligible patients with an LDH level of >500 U/L were a prognostic subgroup with poor survival. We previously showed the dismal prognosis in this group of patients and proposed switching to ICI upon response to BRAF(/MEK-)-inhibition with LDH normalization as a potential strategy to obtain long-term survival in these patients.[15] This information supports well-informed use of systemic therapy in this patient group.

4.1 | Clinical benefit

It is important to estimate the clinical benefit of systemic treatment in ineligible patients to decide whether possible treatment benefit is worth the risk of side-effects for individual patients and the financial burden for society. Donia et al[2,3] found that the (unadjusted) survival of ineligible patients improved over time and suggested that these patients might have benefited from systemic treatment. In the Netherlands, there are no guidelines for patients with advanced melanoma recommending systemic treatment for specific subgroups. Results from RCTs have to be extrapolated to the real-world population. For specific subgroups of patients, the choice to offer systemic therapy is, in most cases, based on the expertise of the medical team. In general, the interpretation of observational data for the effectiveness of treatment is complicated by the lack of a comparator. Moreover, a clear definition of significant clinical benefit is lacking. The American Society of Clinical Oncology (ASCO) Value Framework[16] and the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS)[17,18] were developed to assess the clinical benefit of new cancer therapies in clinical trials. However, lack of real-world comparison prohibits translation of these scales into daily practice.

We attempted to estimate the magnitude of the benefit from systemic treatment by comparing our study cohort to a surrogate control group from the DMTR. This surrogate control group was comprised of patients comprised of both systemically treated and untreated ineligible patients diagnosed in 2013 when only chemotherapy, ipilimumab and BRAF-inhibitors (dabrafenib and vemurafenib) monotherapy were available as standard treatments outside a trial setting. We observed a mOS benefit of 3.1 months and a 3-year survival probability increase of 14% to 22% of our study cohort (Figure 3). This suggests that ineligible patients have benefitted from systemic treatments. We are aware of the statistical limitations of the comparison with the artificially created "control group". However, HRs of year of diagnosis 2016 and 2017 from the Cox also indicate that with the availability of more effective immune and targeted therapies, OS has improved for systemically treated trial-ineligible patients with advanced melanoma in the Netherlands. Importantly, the full potential of ipilimumab plus nivolumab combination therapy may not have been achieved yet, because it only became available in the Netherlands in November 2016.

4.2 | BRAF mutational status

A high proportion of systemically treated ineligible patients had a BRAF-mutated melanoma. For patients who are in poor condition, which can be partly due to advanced melanoma, or patients with brain metastases (or both), the threshold to start with targeted therapy may be low. Targeted therapy for advanced melanoma is known for its potential dramatic antitumor activity and short time to first response.[19] A notable finding in our Cox model was that BRAF-mutational status was not associated with OS. The initial survival advantage of patients with BRAF-mutated melanoma did not persist. Our results do not appear to support an alleged synergy of (sequential) treatment with targeted- and immunotherapy in the ineligible patient population.[20]

4.3 | RCT recommendations

Currently, evidence on the effectiveness of systemic treatment in patients with melanoma brain metastases is being generated in phase II clinical trials.[21,22] In our study, 27% of all patients with advanced melanoma had (a)symptomatic brain metastases. We found that of the trial exclusion criteria, that having brain metastasis was one of the most important prognostic factors for survival. We observed, on the other hand, that some of these patients with brain metastasis could still reach long-term survival. Therefore, we advocate that patients with brain metastases should be included in RCTs. This will lead to a more representative casemix and an increase in evidence for effective systemic treatment of patients.[23]

4.4 | Limitations

There are limitations to our study. We used observational data of a nationwide population-based registry to analyze daily practice. Systemic treatment of ineligible patients was dependent on considerations of the medical team and patient. The mOS of untreated ineligible patients in the same period was less than 3 months (Figure S6). This indicates that the selection of ineligible patients suitable for treatment was justified. However, we were not able to estimate the influence of systemic treatment, because we do not

know what the outcomes would have been if untreated patients would have been treated and vice versa. The effectiveness of individual targeted or immunotherapies could not be investigated due to confounding by indication. We did not analyze safety of systemic treatment, and data on quality of life and exact treatment costs were not available, but these topics are important to further improve clinical decisions for starting systemic therapy in ineligible patients.

4.5 | Strengths

Although we used registry data, we argue the data are of high quality since trained data managers check electronic patient records every 3 months with quality control of data by medical oncologists. The DMTR has nationwide coverage and includes patients without treatment as well.[7]

Results from our study can be used to inform patients on probable prognosis to make well-informed shared-decision and set realistic treatment goals. In patients with (multiple) unfavorable prognostic factors refraining from systemic treatment should be seriously considered. Our real-world clinical results can be used in the treatment of future ineligible patients. The CIST method could also be used in future research for the entire patient population of advanced melanoma patients to further improve shared-decision making. Furthermore, if individual trial data would be publicly available, comparison of RCT data with real-world data could lead to a better understanding of clinical outcomes.

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CONFLICT OF INTEREST

A. J. M. v. d. E. has advisory relationships with Amgen, Bristol-Myers Squibb, Roche, Novartis, MSD, Pierre Fabre, Sanofi, Pfizer, Ipsen, Merck and has received research study grants not related to this article from Sanofi, Roche, Bristol-Myers Squibb, Idera and TEVA, travel expenses from MSD Oncology, Roche, Pfizer and Sanofi and received speaker honoraria from BMS and Novartis. M. J. B. S. has consultancy relationships with Pierre Fabre, MSD and Novartis. J. W. B. d. G. has advisory relationships with Bristol-Myers Squibb, Pierre Fabre, Servier, MSD, and Novartis. G. A. P. H. has consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Roche, MSD, Pfizer, Novartis, Pierre Fabre and has received research grants not related to this article from Bristol-Myers Squibb, Seerave. E. K. has consultancy/advisory relationships with Bristol-Myers Squibb, Novartis, Merck, Pierre Fabre and received research grants not related to this article from Bristol-Myers Squibb. K. P. M. S. has consultancy/advisory relationships with Bristol-Myers Squibb, Novartis, MSD, Pierre Fabre and received honoraria from Novartis, MSD and Roche. A. A. M. v. d. V. has consultancy/advisory relationships with Bristol-Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, Eisai, Merck. J. B. A. G. H. has advisory relationships with Aimm, Achilles Therapeutics, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Celsius Therapeutics, GSK, Immunocore, Ipsen, MSD, Merck Serono, Novartis, Neogene Thereapeutics, Neon Therapeutics, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics, Third Rock Ventures, Vaximm and has received research grants not related to this article from Bristol-Myers Squibb, MSD, Neon Therapeutics and Novartis. All grants were paid to the institutions. The funders had no role in the writing of this article or decision to submit it for publication. All remaining authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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