Bridging the gap between clinical trials and real-world for advanced melanoma: Results of the Dutch Melanoma Treatment Registry

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Survival outcomes of patients with advanced mucosal melanoma diagnosed from 2013 to 2017 in the Netherlands

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Abstract

Background Mucosal melanoma (MM) is rare and has a poor prognosis. Since 2011, new effective treatments are available for advanced melanoma. It is unclear whether patients with mucosal melanoma equally benefit from these new treatments compared with patients with cutaneous melanoma (CM).

Methods Patients with advanced MM and CM diagnosed between 2013 and 2017 were included from a nationwide population-based registry e the Dutch Melanoma Treatment Registry. Overall survival (OS) was estimated with the Kaplan-Meier method (also for a propensity score-matched cohort). A Cox model was used to analyse the association of possible prognostic factors with OS.

Results In total, 120 patients with MM and 2960 patients with CM were included. Median OS was 8.7 months and 14.5 months, respectively. Patients with MM were older (median age 70 versus 65 years) and more often female (60% versus 41%), compared with CM. In total, 77% and 2% of the MM patients were treated with first-line immunotherapy and targeted therapy, respectively, compared with 49% and 33% of the CM patients. In contrast to CM, OS for MM did not improve for patients diagnosed in 2015-2017, compared with 2013-2014. ECOG performance score ≥1 (HR = 1.99 (95% CI 1.26-3.15); p = 0.0030) and elevated LDH level (HR = 1.63 (95% CI 0.96-2.76); p = 0.069) in MM were associated with worse survival.

Conclusion(s) Within the era of immune and targeted therapies, prognosis for patients with advanced MM has not improved as much as for CM. Collaboration is necessary to enlarge sample size for research to improve immunotherapeutic strategies and identify targetable mutations.

Introduction

Primary mucosal melanoma (MM) is a rare type of cancer accounting for 1-2% of all melanomas.[1,2] In contrast to cutaneous melanoma (CM), the incidence of MM has not increased and lies between 0.2 and 0.4 cases per 100.000 people.[3,4] MM can originate from any mucosa-lined surface of the body, but the highest incidence is reported in the head and neck, vulvovaginal, anal and rectal region.[5,6] Because of the rareness of MM outcome data is scarce and mainly based on retrospective studies with the limited number of cases. MM is still a poorly understood disease.

In recent years, for advanced CM, effective immune and targeted therapies have improved overall survival (OS).[7] However, it is unclear whether the prognosis of patients with advanced MM has changed in the new era of immune and targeted therapy. Melanomas arising from mucosal sites differ from CM

in clinical characteristics and prognosis. From primary diagnosis of any stage melanoma, the 5-year overall survival probability for MM and CM are 37% and 92%, respectively [3]. Advanced stage of disease at presentation and high recurrence rates of mucosal melanoma are responsible for the low survival probability. Other possible explanations for poor prognosis of MM are the low tumour mutational burden (leading to a low response to checkpoint inhibitors), the absence of targetable oncogenic drivers, the alleged biological aggressiveness and the rich lymphatic and vascular supply of the mucosa.[6,8,9]

The aim of this study is to report real-world outcomes of patients with advanced MM and identify prognostic factors for OS. Furthermore, we aim to explore whether OS for patients with MM has improved after the introduction of immunotherapy. We used data from a nationwide population-based registry, in which all patients with unresectable stage IIIC and stage IV melanoma in the Netherlands are registered.

Materials and methods

Study design

We performed a retrospective observational study analysing patients aged ≥18 years with unresectable stage IIIC or stage IV (advanced) mucosal or cutaneous melanoma diagnosed between 2013 and 2017 from the Dutch Melanoma Treatment Registry (DMTR). The DMTR prospectively collects data from all advanced melanoma patients in the Netherlands and has been described in detail in a previous publication.[10] Electronic patient records were checked again to determine if patients had an MM. Characteristics and survival outcomes of patients with advanced MM were compared with a control group of patients with advanced CM. The stage for CM and MM were determined as per the American Joint Committee on Cancer version.[11] Patients with MM were analysed by location of the primary tumour, categorised as

head and neck region, upper gastrointestinal (oesophagus and stomach), lower gastrointestinal (anus and rectum) vulvovaginal, and other locations (location not further defined). Data-set cut-off date was 01-06-2019.

Statistical analysis

Baseline characteristics were analysed with descriptive statistics. Median follow-up was estimated with the reverse Kaplan-Meier method.[12] OS, estimated with the Kaplan-Meier method, was defined as time of diagnosis of advanced MM to death from any cause. OS of MM and CM was also compared by creating a propensity score-matched cohort. A matched CM cohort was created by using the propensity scores estimated based on the baseline variables age, gender, Eastern Cooperative Oncology Group Performance Score (ECOG PS), lactate dehydrogenase (LDH) level, distant metastases (<3 or ≥3 organ sites involved), brain and liver metastasis and BRAF mutational status. The algorithm of the nearest neighbour matching with 1:3 ratio was used. A Cox proportional hazards model was used to estimate the association of prognostic factors with OS; age, gender, ECOG PS, LDH level, brain and liver metastases and distant metastases (<3 or ≥3 organ sites involved) were included in the Cox models. We imputed missing covariates for the Cox model according to White and Royston (2009) using the multiple imputation by chained equation method and pooled coefficients as per Rubin's rules (100 imputations and 20 iterations).[13]. Statistical software used was R (version 3.6.1: packages car, lubridate, tidyverse, survival, MatchIt and mice).

Results

Patient characteristics

From 2013 to 2017, 3974 patients were diagnosed with advanced melanoma. After exclusion of 894 patients with uveal, acral or melanoma of unknown origin, a total of 120 (3.0%) patients with MM and 2960 (96%) patients with CM were included in the study (supplement Figure S1). Patients with MM were older, more often female, less often had stage IV-M1d disease and fewer distant metastases in ≥3 organ sites, but liver metastases were more frequent. The baseline characteristics of CM and MM are shown in Table 1.

Table 1 Patient characteristics of patients with mucosal and cutaneous melanoma at diagnosis of unresectable stage III or stage IV disease. Missing data <2.5% are not shown in this table. Values are *n* (%) unless otherwise indicated.

	Cutaneous	Mucosal	*P*-value*
Patients; *n*	2960	120	
Median age, year (IQR)	65 [54, 73]	70 [62, 76]	
Months to advanced melanoma			
Median (IQR)	35 [14, 75]	9 [0, 21]	<0.001
Female	1212 (41.0)	72 (60.0)	<0.001
ECOG PS			
0	1448 (53.7)	57 (52.3)	0.647
1	866 (32.1)	39 (35.8)	
≥2	384 (14.2)	13 (11.9)	
Unknown	262	11	
LDH level			
Normal	1788 (63.5)	76 (69.7)	0.277
1x ULN	3.5)	24 (22.0)	
>2x ULN	366 (13.0)	9 (8.3)	
Unknown	146	11	
Stage			
Unresectable IIIC	230 (7.8)	15 (12.5)	<0.001
IV-M1a	222 (7.5)	7 (5.8)	
IV-M1b	318 (10.7)	17 (14.2)	
IV-M1c	1387 (46.9)	70 (58.3)	
IV-M1d	791 (26.7)	11 (9.2)	
Metastases in ≥3 organ sites	1330 (45.0)	36 (30.0)	0.002
Mutations			
BRAF	1649 (55.7)	7 (5.8)	<0.001
NRAS	625 (21.1)	17 (14.2)	0.042
KIT	39 (1.3)	14 (11.7)	<0.001
GNAQ	18 (0.6)	2 (1.7)	0.001
GNA11	15 (0.5)	2 (1.7)	0.001

P-value of statistical tests comparing characteristics of patients with cutaneous and mucosal melanoma (excluding missing values). IQR - interquartile range, ECOG PS - Eastern Cooperative Oncology Group performance status, LDH - lactate dehydrogenase, ULN - upper limit of normal.

MM was located in the head and neck region in 39 (33%) patients, in the vulvovaginal region in 29 (24%) patients and in the upper and lower gastrointestinal tract in 7 (5.8%) and 38 (32%) patients, respectively.

Seven patients (5.8%) had MM located at other primary location(s). The LDH level, ECOG score and stage of disease were similar between the different locations of MM. Median time from initial diagnosis until confirmed advanced stage disease was shorter for MM located in the upper and lower gastrointestinal tract than that in the vulvovaginal region and the head and neck region (0 and 6 months compared with 9 and 15 months, respectively). Baseline characteristics of MM by location are shown in the supplement Table S1.

Oncogenic mutation(s) were less frequent for MM than for CM (Table 1). A BRAF mutation was found in 1649 (55.9%) patients with CM in seven of the 122 patients with MM (5.8%; five patients had V600E, one had V600R and one V600K, and one patient was classified as 'other' type BRAF mutation). NRAS and KIT mutations were found in 625 (21.1%) and 39 (1.3%)

patients with CM and in 17 (14.2%) and 15 (11.7%) patients with MM, respectively (Table 1). Patients with MM originating in the head and neck region most often had NRAS mutations (eight (20.5%) patients). The KIT gene was most often mutated in MM located in the lower gastrointestinal tract and vulvovaginal region, in eight (21.1%) and four (13.8%) patients, respectively.

Treatment characteristics

Fifteen (12.5%) patients with advanced MM were treated with local therapy alone (surgery, radiotherapy, hyperthermia therapy, radiofrequency or microwave ablation), 89 (74.2%) patients with systemic (and local) therapy and 16 (13.3%) patients did not receive any treatment. First-line systemic therapy for patients with MM mostly consisted of immunotherapy; 43 (48.3%) patients received an antiePD-1 antibody, 16 (18.0%) patients ipilimumab and nine (10.1%) patients ipilimumab plus nivolumab combination therapy. Best overall response (BOR) to immunotherapy was a complete response (CR) in four (5.9%) patients, partial response (PR) in 10 (14.7%) patients and stable disease (SD) in 16 (23.5%) patients. Of the patients with advanced CM, 271 (9.2%) patients received local therapy, 2440 (82.4%) patients were treated with systemic therapy and 249 (8.4%) patients received no treatment. First-line systemic therapy in CM consisted of antiePD-1 antibodies in 709 (29.1%) patients, ipilimumab in 356 (14.6%) patients and ipilimumab plus nivolumab combination therapy in 133 (5.5%) patients. BOR to immunotherapy for CM was a CR in 154 (12.9%) patients, PR in 298 (24.9%) patients and SD in 335 (28.0%) patients. First-line BRAF inhibitors were used in 409 (16.8%) patients and combined BRAF plus MEK inhibitors in 401 (16.4%) patients. Distribution of all first-line systemic therapies used in CM and MM are shown in the supplement Figure S3.

Overall survival

Median follow-up was 38 months for MM and 34 months for CM. Median OS of all patients with advanced MM and CM was 8.9 months (95% CI: 7.3-12.7) and 14.5 months (95% CI: 13.7-15.4), respectively. The 1- and 3-year OS probabilities of patients with MM were 42% (95% CI: 34-52) and 15% (95% CI: 9.0-24; Figure 1). For patients with CM, the 1- and 3-year OS probabilities were 55% (95% CI: 54-57) and 30% (95% CI: 29-32; Figure 1). OS of CM in the propensity score-matched cohort (supplement Table S2) was also associated with better OS in CM than MM (17.1 versus 10.8 months, *p* = 0.003; supplement Figure S2).
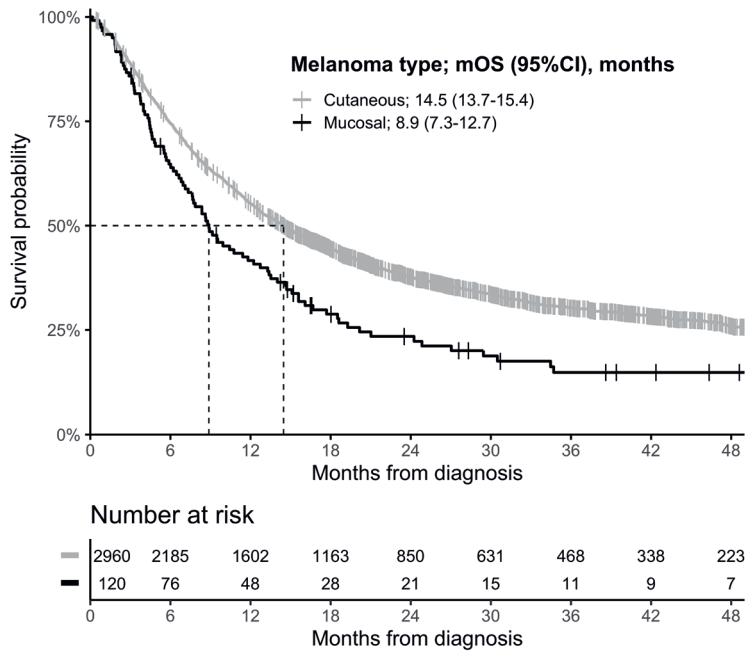
Figure 1 Kaplan-Meier curves of overall survival of patients with unresectable stage IIIC or stage IV mucosal versus cutaneous melanoma. OS - Overall survival, CI - confidence interval. (Log- rank test: p < 0.001).

Median OS of patients with MM diagnosed in 2013-2014 and in 2015-2017 was comparable (8.7 months (95% CI: 6.9-16.7) and 8.9 months (95% CI: 6.8-13.5), respectively), but median OS of patients with CM increased from 11.3 months (95% CI: 10.2-12.4) in 2013-2014 to 16.9 months (95% CI: 15.4-18.2) in 2015-2017 (Figure 2a). Median OS of patients treated with systemic therapy was 11.8 months (95% CI: 8.8-16.1) for MM and 17.9 months (95% CI: 16.6-18.9) for CM (Figure 2b). Median OS was 9.0 months (95% CI: 5.9-18.9) for lower gastrointestinal MM, 8.6 months (95% CI: 6.8-21) for vulvovaginal MM and 7.1 months (95% CI: 4.9-14) for head and neck MM (Figure 3).

At the 3-year landmark 11 patients with MM were alive and in the follow-up. All of these 'long-term' survivors had a baseline ECOG PS of 1; seven patients had a normal LDH level, and three patients had a LDH level of 1 upper limit of normal. No patient had stage IV-M1d disease, and two (18.2%) patients had distant metastases in ≥3 organ sites (supplement Table S3). Seven (63.6%) patients were treated with immunotherapy; three patients received an antiePD-1 antibody, and of the four patients who received first-line ipilimumab, three patients received an antiePD-1 antibody as second-line treatment. Of the remaining four patients, two patients were treated with local therapy and two patients with another systemic treatment.

Prognostic factors of survival

Distant metastases in ≥3 organ sites (hazard ratio (HR) = 1.56 [95% CI: 1.02-2.40; p = 0.041]), ECOG PS of ≥1 (HR = 1.79 (95% CI: 1.17-2.75); p = 0.007), elevated LDH level (HR = 1.53 (95% CI: 0.96-2.43); p = 0.073) and brain metastases (HR = 1.84 (95% CI: 0.94-3.59]; p = 0.073)) (although the association of the latter two was not statistically significant) were associated with death in the univariable Cox model for MM. ECOG PS of ≥1 (HR = 1.99 (95% CI: 1.26-3.15); p = 0.003) and elevated LDH level (HR = 1.63 (95% CI: 0.96-2.76); p = 0.069) were associated with death in the multivariable Cox model for MM. Age of 70 years and older was not significantly associated with death (HR = 1.43 (95% CI: 0.93-2.21); p = 0.11). The univariable and multivariable Cox models are shown in Table 2.
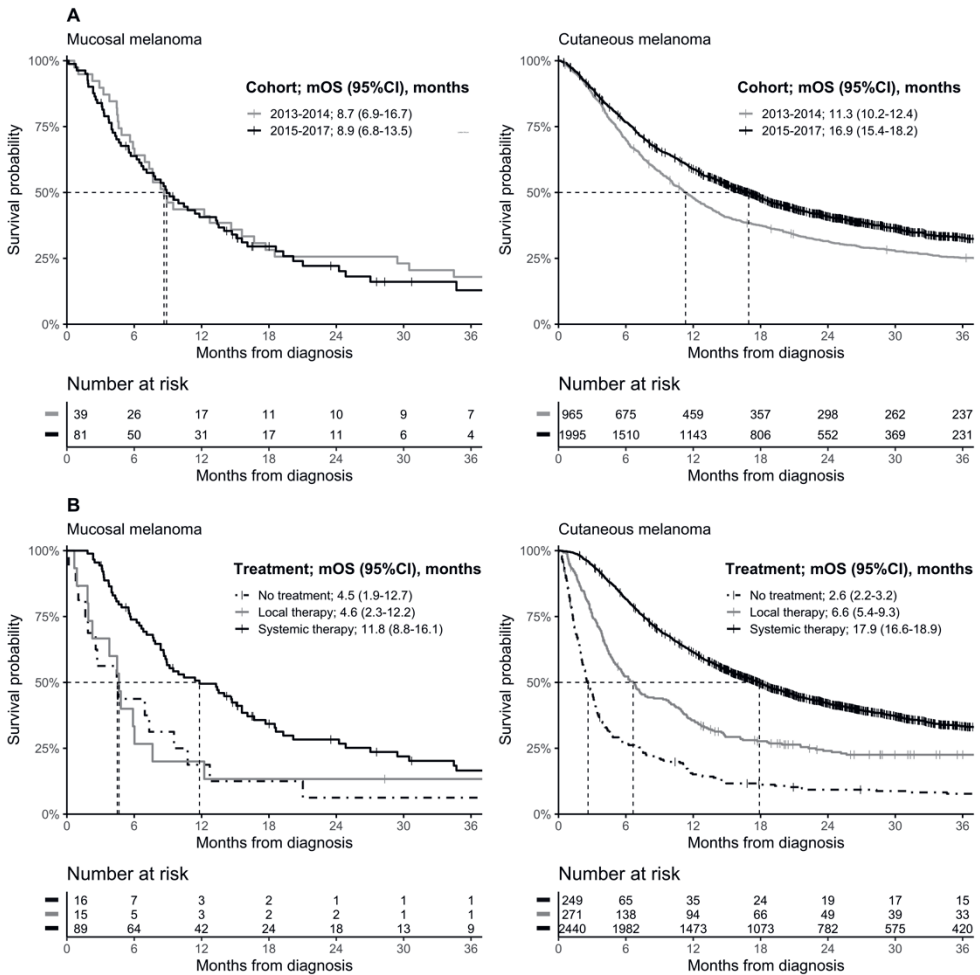
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Figure 2 Kaplan-Meier curves of overall survival for unresectable stage IIIC or stage IV mucosal and cutaneous melanoma of A) patients diagnosed in 2013 and 2014 versus 2015, 2016 and 2017 and B) stratified by treatment modality. OS - Overall survival, CI - confidence interval.
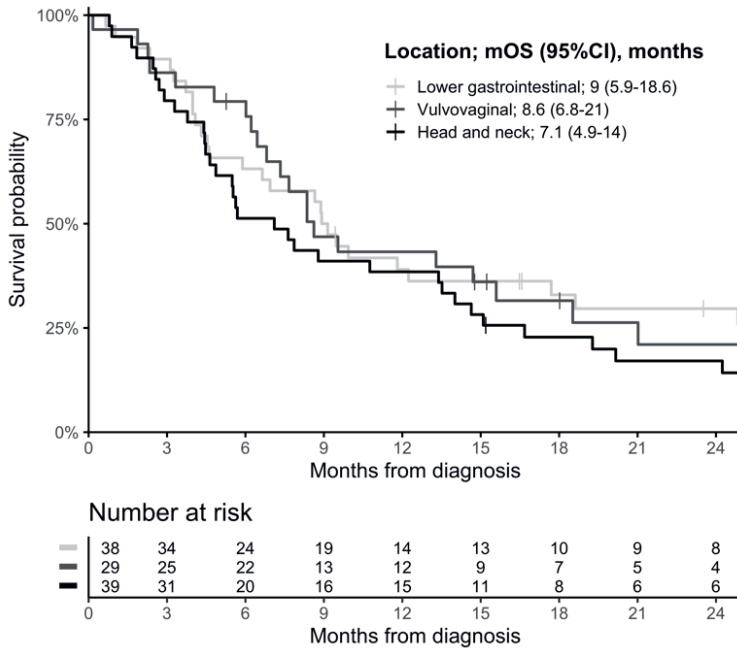
Figure 3 Kaplan-Meier curves of overall survival of patients with advanced mucosal melanoma stratified by location. Upper gastrointestinal (*n* = 7) and 'other' (*n* = 7) mucosal melanoma were excluded. mOS - median overall survival, CI - confidence interval.

Table 2 Univariable and multivariable Cox regression model for the association of prognostic factors with overall survival for mucosal melanoma. There was a total of 100 events.

		Univariable			Multivariable*		
	n	HR	95% CI	P-value	HR	95% CI	P-value
Age							
≤69 years	59	1.08	(0.73-1.61)	0.692	1.43	(0.93-2.21)	0.107
≥70 years	61	1			1		
Gender							
Male	48	1			1		
Female	72	0.80	(0.53-1.19)	0.267	0.88	(0.58-1.34)	0.548
ECOG PS							
0	57	1			1		
≥1	52	1.79	(1.17-2.75)	0.007	1.99	(1.26-3.15)	0.003
LDH level							
Normal	76	1			1		
>1x ULN	33	1.53	(0.96-2.43)	0.073	1.63	(0.96-2.76)	0.069
Distant metastases							
<3 organ sites	84	1			1		
≥3 organ sites	36	1.56	(1.02-2.40)	0.041	1.16	(0.68-1.99)	0.577
Liver metastasis							
No	58	1			1		
Yes	44	1.41	(0.91-2.19)	0.123	1.03	(0.63-1.70)	0.895
Brain metastasis							
Absent	91	1			1		
Present	11	1.84	(0.94-3.59)	0.073	1.43	(0.68-3.00)	0.346

HR - hazard ratio, CI - confidence interval, ECOG PS - ECOG performance score, LDH lactate dehydrogenase, ULN - upper limit of normal. *Multivariable model are pooled results after multiple imputation.

Discussion

To our knowledge, this is the first nationwide population-based cohort study of patients with advanced MM, reflecting the care and outcomes in the Netherlands of patients diagnosed from 2013 to 2017. Despite comparable baseline characteristics, the survival of patients with MM was worse than that of patients with CM. This also holds for the subgroup of patients who were treated with systemic therapy. In contrast to patients with CM, OS of patients with MM did not improve between 2013 and 2017, despite the introduction of novel therapies. Elevated LDH level and ECOG PS of ≥1 were independently associated with worse OS in MM. The prognosis of MM, originating from different types of primary locations appeared to be similar. NRAS (mainly in head and neck MM) and KIT mutations (mainly in gastrointestinal and vulvovaginal MM) were most common in MM. Results of our cohort of advanced MM and CM confirm that patients with advanced MM have a worse prognosis than patients with CM.[8,14] Despite that patients with advanced MM had favourable disease stage and similar ECOG PS and LDH levels compared with patients with advanced CM, outcomes for MM were worse. This suggests that MM has an inherent worse prognosis and it is hypothesised this may be due to a different, more aggressive, biological behaviour.[8] The clinical behaviour of MM and low tumour mutation burden with distinct driver mutations advocate that MM has a different pathogenesis than CM and should be seen as a unique entity of melanomas.[2,6,15,16] More studies found that MM less often metastasise to the brain and that lungs, liver and/or non-regional lymph nodes are involved most frequently.[17-21] Similar to CM and consistent with the literature for advanced MM, we found that the ECOG score of ≥1 and the elevated LDH level were independent prognostic factors for OS.[15,17,22]

From 2011 to 2016, immune and targeted therapies gradually became available for patients with advanced melanoma in the Netherlands.[23] Unlike for CM, we did not observe an increase in OS for MM when comparing the cohorts of 2013-2015 to 2016-2017. However, the median OS of patients with MM who received systemic therapy in our cohort is comparable with the median OS of post-hoc analysis of patients with MM in the pembrolizumab trials (respectively 11.8 months and 11.3 months), and it is higher than the historical median OS of 6-8 months for advanced melanoma in general.[11,24,25] It also resembles the median OS of 11.5 months in patients with MM treated with nivolumab after progression on or after ipilimumab, although OS was defined from start of nivolumab treatment.[26]

From currently available treatment options for advanced MM, immunotherapy has the potential to induce durable remissions, although much less frequently compared with advanced CM. Ipilimumab monotherapy has shown to have some antitumour activity in advanced MM, but overall response rates (ORRs) were lower than those in CM (<10%).[14,27,28] The post-hoc analysis of the KEYNOTE 001, 002, 006 trials showed an ORR of 19% and a median OS of 11.3 months for MM patients treated with pembrolizumab.[24] A median OS of 11.5 months was

found in the CHECKMATE-172 study, in which OS was defined from start of nivolumab on or after progression of ipilimumab.[26] Pooled analysis of the CheckMate studies compared effectiveness of ipilimumab, nivolumab and ipilimumab plus nivolumab in MM and observed the highest potential for the ipilimumab plus nivolumab, but no information on long-term outcomes is available (ORR of 8.3%, 23.3% and 37.1%, respectively).[29] An immunotherapeutic strategy that has shown the promising ORR in advanced cutaneous and uveal melanoma is adoptive cell therapy with tumour-infiltrating lymphocytes[30], but effectiveness data specifically for MM are lacking. MM-specific vaccine development will remain challenging given the low tumour neo-antigen burden.[31]

Patients with a BRAF-mutated MM can benefit from BRAF plus MEK inhibitors, but BRAF mutations are rare in MM.[32-35] KIT and NRAS mutations are more common, and additionally, we observed KIT mutation was more frequent in lower gastrointestinal and vulvovaginal MM.[34,35] KIT is a targetable driver mutation, and KIT inhibitors have demonstrated clinical activity in advanced melanoma, but ORR and survival benefit varied by the type of KIT alteration.[9] Within the DMTR, no data are captured on the use of imatinib or another c-KIT inhibitor for KIT mutated MM. It is clear that systemic treatment for MM is lagging behind its cutaneous counterpart. Research should be focused on identifying vulnerabilities specific for MM and attempt to target these with either immunotherapies or targeted therapies.

Some small studies on MM, in which all stages of MM were analysed, have found that localisation of MM was predictive of survival. Head, neck and gastrointestinal MM of any stage appeared to have inferior survival compared with other MM.[15,36] However, three large studies on prognostic factors for survival in MM found that location was not a prognostic factor for the early or advanced stage.[8,37,38] Cui et al.[37] even conclude that MM can be staged as a single group irrespective of location of MM. Our results endorse that survival between the subtypes of advanced MM is comparable, but imbalances in baseline characteristics of patients between the subtypes of advanced melanoma and low number of patients do not allow a fair comparison of OS.

A major limitation is the small sample size hampering analysis and adequate correction for confounding factors when comparing outcomes. Still, this is one of the largest real-world cohorts of MM that gives insight in the outcomes in recent years.

Conclusion

Survival of patients with advanced MM is worse than that in advanced CM. In the era of immune and targeted therapies, prognosis for patients with advanced MM has not improved as much as the prognosis of CM. The aim of future research should be to gain further knowledge on the vulnerabilities of MM to target these with novel strategies. We emphasise the need for

international collaboration allowing data exchange to increase sample size and research on this rare disease.

Conflict of interest

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Supplementary material
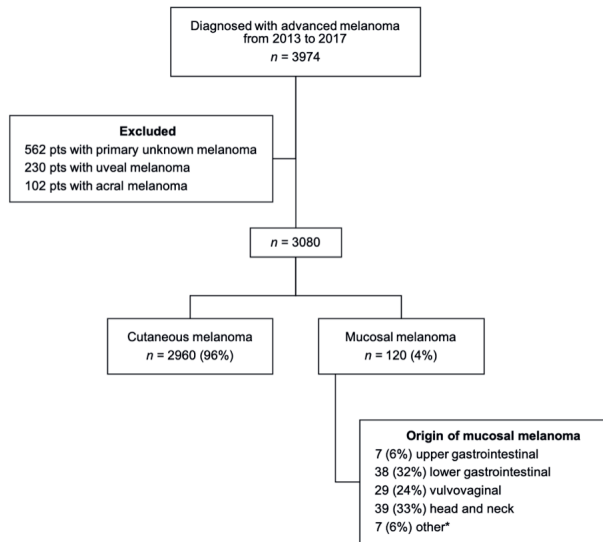
Figure S1 Flowchart of patient inclusion of this observational study. *Mucosal melanoma confirmed, but location was unknown or uncertain.
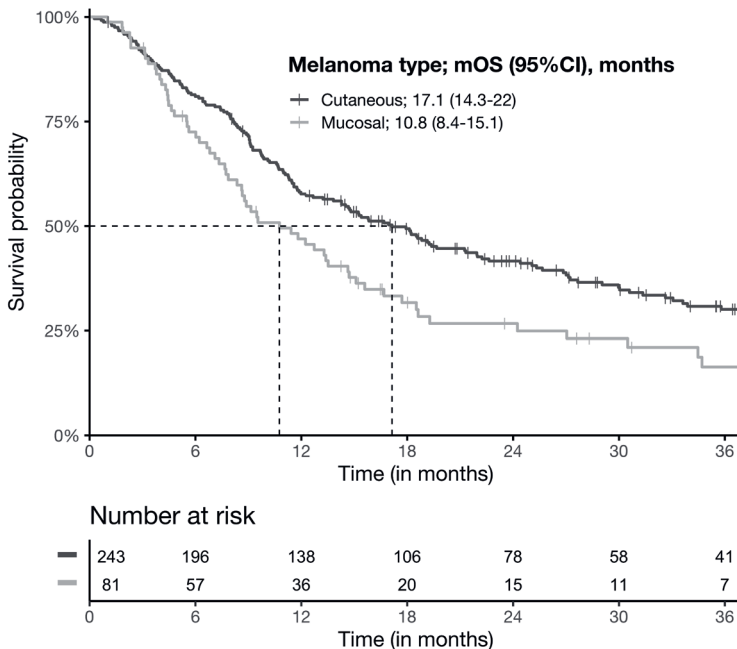
Figure S2 Kaplan Meier curves of overall survival of patients with unresectable stage IIIC or stage IV mucosal versus cutaneous melanoma in a propensity score matched cohort (Log-rank test: $p = 0.003$). Cases with missing data were omitted from this analysis, leading to $n = 81$ cases for mucosal melanoma. OS - Overall survival, CI - confidence interval. Baseline characteristics are shown in the supplement Table S2.

4
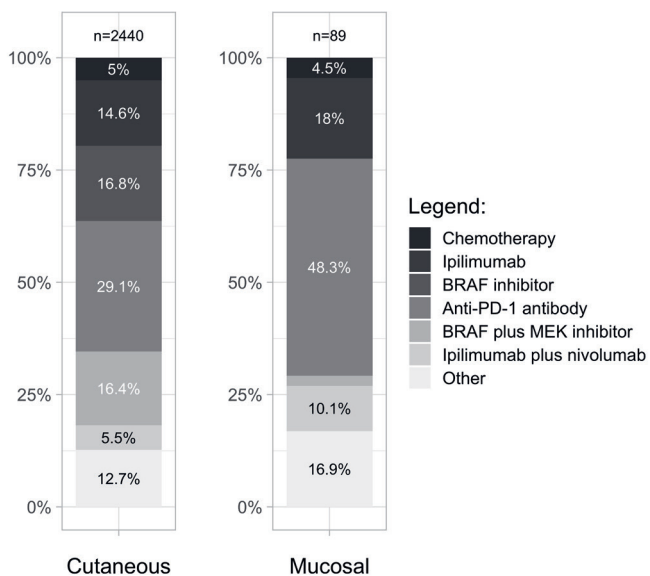
Figure S3 First-line systemic therapy of patients with cutaneous melanoma and mucosal melanoma. Category 'Other' also consists of systemic therapy given in trials. Data on KIT inhibitors were not available in the DMTR.

Table S1 Characteristics of patients with mucosal melanoma at diagnosis of unresectable stage III or stage IV disease stratified by location of primary site. Missing data of less than 2.5% are not shown in this table. Values are *n* (%) unless otherwise indicated.

	Upper GI	Lower GI	Vulvo-vaginal	Head and neck	Other	P-value
Patients; *n*	7	38	29	39	7	
Median age, year (IQR)	65 [54, 67]	72 [66, 76]	70 [63, 78]	64 [58, 73]	72 [66, 75]	
Median time to stage IIIC/IV						
Months (IQR)	0 [0, 0]	6 [0, 13]	9 [0, 15]	15 [4, 35]	9 [4, 25]	0.001
Female	2 (28.6)	17 (44.7)	29 (100.0)	20 (51.3)	4 (57.1)	<0.001
ECOG score						
0	0 (0.0)	22 (64.7)	15 (53.6)	15 (42.9)	5 (71.4)	0.113
1	4 (80.0)	11 (32.4)	8 (28.6)	15 (42.9)	1 (14.3)	
≥2	1 (20.0)	1 (2.9)	5 (17.9)	5 (14.3)	1 (14.3)	
Unknown	1	4	0	4	2	
LDH level						
Normal	5 (71.4)	21 (58.3)	17 (65.4)	27 (79.4)	6 (100.0)	0.091
1x ULN	2 (28.6)	10 (27.8)	9 (34.6)	3 (8.8)	0 (0.0)	
>2x ULN	0 (0.0)	5 (13.9)	0 (0.0)	4 (11.8)	0 (0.0)	
Unknown	0	2	2	5	2	
Stage						
Unresectable IIIC	0 (0.0)	4 (10.5)	4 (13.8)	6 (15.4)	1 (14.3)	0.360
IV-M1a	0 (0.0)	3 (7.9)	1 (3.4)	2 (5.1)	1 (14.3)	
IV-M1b	0 (0.0)	4 (10.5)	6 (20.7)	5 (12.8)	2 (28.6)	
IV-M1c	4 (57.1)	25 (65.8)	15 (51.7)	23 (59.0)	3 (42.9)	
IV-M1d	3 (42.9)	2 (5.3)	3 (10.3)	3 (7.7)	0 (0.0)	
Metastases in ≥3 organ sites	4 (57.1)	11 (28.9)	8 (27.6)	13 (33.3)	0 (0.0)	0.218
Mutations						
BRAF	2 (28.6)	2 (5.3)	0 (0.0)	2 (5.1)	1 (14.3)	0.032
NRAS	2 (28.6)	4 (10.5)	2 (6.9)	8 (20.5)	1 (14.3)	0.39
KIT	0 (0.0)	8 (21.1)	4 (13.8)	2 (5.1)	0 (0.0)	0.38
GNAQ	0 (0.0)	0 (0.0)	2 (6.9)	0 (0.0)	0 (0.0)	0.21
GNA11	0 (0.0)	0 (0.0)	1 (3.4)	1 (2.6)	0 (0.0)	0.68

*P-value of statistical tests comparing characteristics of patients by location of primary site of mucosal melanoma (excluding missing values). GI - gastrointestinal, IQR - interquartile range, ECOG PS - Eastern Cooperative Oncology Group performance status, LDH - lactate dehydrogenase, ULN - upper limit of normal.

Table S2 Characteristics at diagnosis of unresectable stage IIIC or stage IV disease of the propensity score matched cohort of patients with mucosal and cutaneous melanoma. *Cases with missing data were omitted from this analysis, leading to n = 81 cases for mucosal melanoma.

	Mucosal	Cutaneous	P-value
Patients; _n_	81*	243	
Median age, year (IQR)	67 [62, 74]	69 [60, 76]	0.903
Female	54 (66.7)	168 (69.1)	0.273
ECOG score			0.287
0	39 (48.1)	119 (49.0)	
1	33 (40.7)	98 (40.3)	
≥2	9 (11.1)	26 (10.7)	
LDH level			0.491
Normal	61 (75.3)	179 (73.7)	
1x ULN	16 (19.8)	53 (21.8)	
>2x ULN	4 (4.9)	11 (4.5)	
Stage			-
Unresectable IIIC	1 (1.2)	0 (0.0)	
IV-M1a	6 (7.4)	26 (10.7)	
IV-M1b	13 (16.0)	42 (17.3)	
IV-M1c	56 (69.1)	165 (67.9)	
IV-M1d	5 (6.2)	10 (4.1)	
Metastases in ≥3 organ sites	25 (30.9)	73 (30.0)	1.000
Brain metastasis			0.782
Absent	76 (93.8)	233 (95.9)	
Asymptomatic	2 (2.5)	3 (1.2)	
Symptomatic	3 (3.7)	7 (2.9)	
Liver metastasis	35 (43.2)	92 (37.9)	0.803
BRAF-mutant	5 (6.2)	19 (7.8)	0.351

*_P_-value of statistical tests comparing characteristics of the mucosal and cutaneous melanoma cohort. IQR - interquartile range, ECOG PS - Eastern Cooperative Oncology Group performance status, LDH - lactate dehydrogenase, ULN - upper limit of normal.

Table S3 Characteristics at diagnosis of unresectable stage IIIC or stage IV of patients with mucosal melanoma alive at the 3-year landmark.

	Alive at 3-year landmark
Patients; _n_	11
Median age, year (IQR)	66 [58, 73]
Median time to stage IIIC or IV	
Months (IQR)	4 [0, 44]
Female	7 (63.6)
ECOG score	
0	9 (81.8)
1	2 (18.2)
≥2	0 (0.0)
LDH level	
Normal	7 (70.0)
1x ULN	3 (30.0)
>2x ULN	0 (0.0)
Unknown	1
Stage	
Unresectable IIIC	1 (9.1)
IV-M1a	1 (9.1)
IV-M1b	2 (18.2)
IV-M1c	7 (63.6)
IV-M1d	0 (0.0)
Metastasis in ≥3 organ sites	2 (18.2)
Mutations:	
BRAF	1 (9.1)
NRAS	1 (9.1)
KIT	3 (27.3)
GNAQ	0 (0.0)
GNA11	0 (0.0)

IQR - interquartile range, ECOG PS - Eastern Cooperative Oncology Group performance status, LDH - lactate dehydrogenase, ULN - upper limit of normal.

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