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Characteristics and clinical outcomes of mucosal melanoma

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Clinical outcomes and toxicity of combined ipilimumab/nivolumab in rare melanomas – a nationwide population-based study and a review of the literature

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Simple summary

Mucosal and uveal melanomas (MM and UM) are rare melanomas with a poor prognosis. Whilst immune checkpoint inhibitors have improved overall survival in advanced cutaneous melanoma (CM), MM and UM appear less immunogenic, which is probably the reason for lower response rates. In this study we assessed efficacy, toxicity and predictors of survival in 46 advanced MM and 13 advanced UM treated with ipilimumab/nivolumab, and provided a review of the literature. We confirmed the lower efficacy of ipilimumab/nivolumab in MM and UM as compared to CM, but found that half of the MM and UM experienced clinical benefit. However, the prognosis of advanced MM and UM remains poor and toxicity rates of ipilimumab/nivolumab are high. Therefore, future research should focus on identifying the subgroup of patients with rare melanomas who may benefit from ipilimumab/ nivolumab including clinical trials testing novel therapeutic (combination) strategies.

Abstract

Background

Immune checkpoint inhibitors, and in particular combined anti-CTLA-4/anti-PD-1, have improved outcomes for patients with advanced cutaneous melanoma (CM). Mucosal and uveal melanoma (MM and UM) seem less immunogenic compared to CM, and the benefit of anti-CTLA-4/anti-PD-1 treatment is unclear. The aim of this study is to assess clinical outcomes and toxicity of combined ipilimumab/nivolumab treatment in advanced MM and UM, using nation-wide real-world data. Moreover, we aim to identify prognostic factors for outcomes and toxicity and provide a review of the literature.

Methods

All patients diagnosed with advanced MM and UM treated with ipilimumab/nivolumab between 2013 and 2021 in the Netherlands were included from the Dutch Melanoma Treatment Registry. Best overall response rate and grade ≥ 3 toxicity rates were calculated. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method. Independent predictors of OS in MM were assessed with Cox proportional hazards models.

Results

46 patients with MM and 13 patients with UM were included. Complete response, partial response or stable disease, as best overall response was achieved in 52% and 46% of the MM and UM, respectively. Median OS and PFS were 9.7 and 4.1 months for MM and 12.4 and 5.5 months for UM. One-year OS and two-year-OS for MM were 43% and 23%. Multivariable analysis showed LDH level of \geq two times upper limit of normal and the presence of liver metastasis to be associated with worse OS. Grade ≥ 3 toxicity occurred in 48% of MM and 38% of UM.

Conclusion

Our study shows that advanced MM and UM have a poor prognosis and that half of the patients with MM and UM experience clinical benefit of ipilimumab/nivolumab but that OS is short and toxicity rates are high. International collaboration and novel clinical trials are essential to improve outcomes for patients with advanced MM and UM.

Introduction

Immune-checkpoint inhibitors (ICI) have revolutionized outcomes for patients with advanced (irresectable stage III and stage IV) cutaneous melanoma (CM). ICIs block the immunologic inhibitory receptors CTLA-4 and PD-1 located on T-lymphocytes. Blockage of these receptors results in a boost of the immune response by T-cells attacking cancer cells. [1] At 6.5-year follow-up, the CheckMate 067 trial demonstrated a median overall survival (OS) and 6.5-year OS in advanced CM of ipilimumab, nivolumab and combined ipilimumab/nivolumab of 19.9, 36.9 and 72.1 months and 23%, 42%, and 49%, respectively. Combined ipilimumab/nivolumab also showed a higher response rate (RR) of 58% compared to ipilimumab monotherapy (19%) and nivolumab monotherapy (45%). [2] The favourable RR, along with long-term durable cancer control, have established the combined ICI and anti-PD1 monotherapy as the preferred treatments in advanced CM. [1, 3] However, an important problem of combining agents is the higher toxicity rate. In ipilimumab/nivolumab, grade ≥ 3 toxicity is experienced in 59% of the patients, leading to discontinuation of treatment in 31%, whilst toxicity rates in ipilimumab monotherapy and nivolumab monotherapy are lower (24% and 28%), and also less often lead to discontinuation of treatment (14% and 8%). [2, 4]

Mucosal melanoma (MM) and uveal melanoma (UM) represent small subgroups of melanoma. MM originates from the lining of any mucosal surface in the body and comprises 1-2% of all melanomas. [5] UM develops from the iris, ciliary body or choroid of the eye. [6, 7] Even though UM is the most common intraocular tumor, it comprises only 3-5% of all melanomas. [8, 9] Due to the unique clinical and biological characteristics and the low incidence of MM and UM, patients are often excluded from clinical trials, and the numbers of patients treated with ICI are low.

Although evidence is scarce, the limited data on the efficacy of ICI in MM and UM suggest that these may not be as promising as in CM. [10] Overall RR in MM are 0-17% for ipilimumab and 9-50% for nivolumab, respectively. [11] In UM, efficacy is even lower, with RR ranging from 0-6.5% for ipilimumab and 6-30% for nivolumab or pembrolizumab monotherapy. [12] The synergetic effect of combined ipilimumab/nivolumab treatment leading to a higher RR and better OS is evident in CM. In MM and UM, the limited data report overall RR ranging between 16-43% and 0-21%, respectively. In CM, the high tumor mutational burden (TMB) is associated with immunogenicity and therefore may in part, explain the high efficacy of ICI. It is likely that the lower TMB of both MM and UM contributes to the lower RR of ICI in these entities. [13-15]

The aim of this study is to assess efficacy and toxicity of ipilimumab/nivolumab in advanced MM and UM, using real-life data from a Dutch nationwide database in melanoma patients. In addition, we aim to identify prognostic factors for outcomes and toxicity and present a review of the literature covering anti-CTLA-4/anti-PD-1 treatment in MM and UM.

Materials and Results

Study design and data

Since 2013, systemic therapy for melanoma patients in the Netherlands is centralized in 14 melanoma centers. Data of these patients are prospectively collected in the Dutch Melanoma Treatment Registry (DMTR). We performed a retrospective observational study analyzing all patients registered in the DMTR between 2013 and 2021 with advanced (i.e. unresectable stage III or stage IV) MM or UM, treated with combined ipilimumab/nivolumab. [16] Registered information includes patient and tumor characteristics, treatment, clinical outcomes and toxicity data according to the Common Terminology Criteria for adverse events (CTCAE) 5.0. [17]

Exclusion criteria for this analysis were age under 18 years and less than six weeks of follow-up from the start of ipilimumab/nivolumab (a minimum of two courses ipilimumab/nivolumab). Patients were staged by the 8th edition of the American Joint Committee Cancer (AJCC) melanoma staging system. The data cut-off was October 2021. The study design was approved by the scientific board of the DMTR. In compliance with Dutch regulations, use of DMTR data for research was approved by the Medical Ethics Review Committee of Leiden University Medical Center.

Definitions of outcome

OS was defined as the time between start of treatment with ipilimumab/nivolumab until death. Patients not reaching the endpoint were right-censored at the date of the last contact. Progression-free survival (PFS) was calculated from start of ipilimumab/nivolumab until date of first progression according to the response evaluation, or death. In this real-world database, response is based on the evaluation by the RECIST (Response Evaluation Criteria in Solid Tumors) criteria of the treating physician at one of the melanoma expert centers. [18] Best overall response (BORR) was the best response evaluation that a patient had after initiation of treatment until start of a new melanoma therapy, last follow-up visit or death. The BOR rate was defined as the proportion of evaluable patients who achieved a complete or partial response. Based on the BOR rate at any moment during follow-up, clinical benefit was defined as either stable disease (SD), partial response (PR) or complete response (CR). One-year and two-year OS rates were calculated for MM, but due to a short median follow-up period, they were not calculated for UM.

Statistical analysis

The baseline characteristics at the start of treatment with combined ipilimumab/nivolumab were summarized using descriptive statistics. Categorical variables were summarized with counts and percentages. Age was presented as a median with a interquartile range (IQR) and was divided into two categories (<70 years or ≥70 years). Descriptive and survival

data were presented for MM and UM separately. Median follow-up was estimated with the reverse Kaplan-Meier method. [19] Median PFS and OS were estimated with the Kaplan-Meier method. For MM, a Cox proportional hazards model was used to estimate the association between prognostic factors with OS; age (<70 or ≥70) gender, WHO classification at baseline (0-1 or ≥2), number of metastatic sites at (<3 or ≥3 organ sites involved), LDH level, the presence of liver metastasis at baseline and presence of brain metastasis at baseline. Independent predictors for OS were evaluated by applying multivariable Cox proportional hazards regression models, following the selection of potential predictors based on a p-value is <0.1 in the univariable analyses. Due to the low number of patients, univariable and multivariable Cox regression analysis were not performed for UM. Statistical analyses were performed using SPSS (SPSS, version 25, IBM Corp. released 2017, Armonk, NY, USA). Values of p=0.05 or smaller were considered statistically significant and all tests were two sided.

Data sources

For the literature review, data on combined anti-CTLA-4/anti-PD-1 therapy in MM and UM were collected through the search engines PubMed, and Web of Science (date of last search June 15th, 2023). We included studies analyzing 5 or more cases, treated with any type of combined anti-CTLA-4/anti-PD-1 therapy.

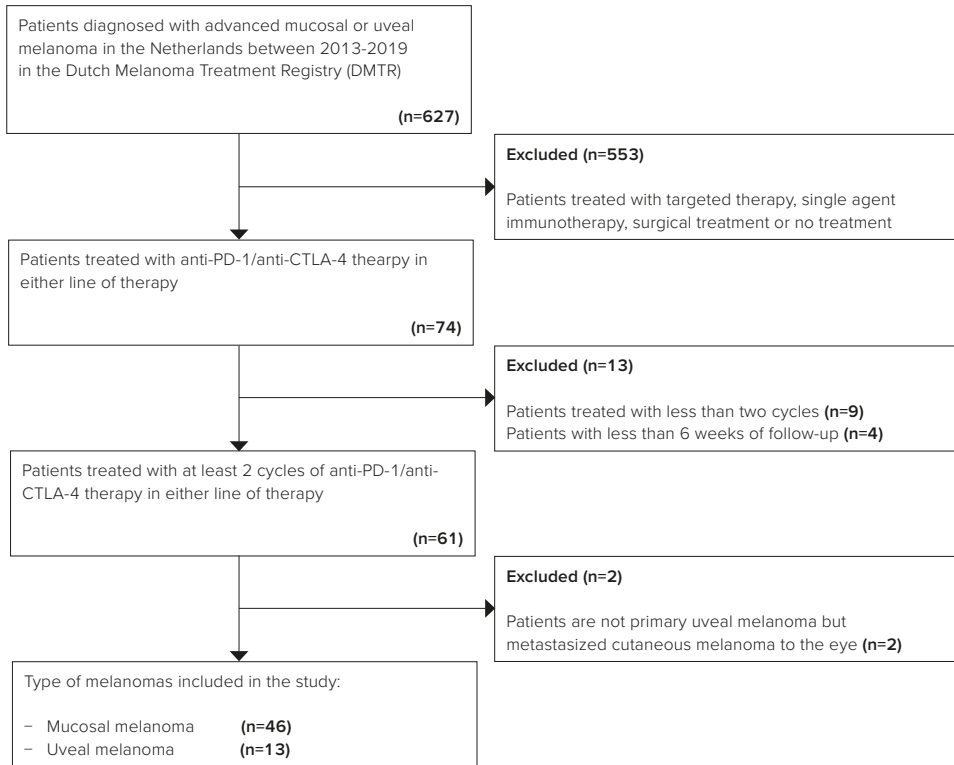
Results

Patient and treatment characteristics

From 2013 to 2021, 221 patients were diagnosed with advanced MM and 406 with advanced UM. In total, during this period, 46 patients with MM and 13 patients with UM were treated with ipilimumab/nivolumab and were included in this study (Figure 1). Thirteen patients were excluded, of which four due to inadequate follow-up, nine as they received less than two cycles of ipilimumab/nivolumab (Figure 1), and two as they were primary CM and not UM. The median follow-up was 15.2 months for MM and 4.9 months for UM.

Patients with MM had a median age of 66 years (IQR 59-73) and more often were female (n=34, 73.9%) (Table 1). Patients had stage IV M1c disease in 50% (n=20) and LDH level was elevated only in the minority of the patients (n=15, 32.6%). Treatment with ipilimumab/nivolumab was the first line of treatment in the majority of the patients (n=44, 95.7%) (Table 1). The two patients who received ipilimumab/nivolumab therapy as second-line treatment were treated with an anti-PD-1 inhibitor in the first line (n=2) (data not shown).

Figure 1. STROBE diagram for the study (STROBE: Strengthening the reporting of observational studies in epidemiology)



In UM, median age at diagnosis was 58 years (IQR 50-72) and females and males were equally affected (53.8% and 47.2%) (Table 1). Stage at diagnosis was IVc in 92.3% of the patients and liver metastasis were present in 76.9% of the patients. LDH levels were elevated in the greater part of the patients (n=9, 69.3%). In two patients, the disease had only spread to the liver (15.5%), in eight to both liver and other sites (61.3%) and three only had extra-hepatic metastasis (23.1%). Four cases (33.3% received ipilimumab/nivolumab as second-line treatment. As prior treatment strategy, one patient received radiofrequency ablation (RFA) and ipilimumab monotherapy, two patients were treated with liver perfusion and one patient underwent a surgical resection of a liver metastasis (data not shown). MM and UM both had low *BRAF*, *NRAS* and *KIT* mutation rates. Baseline characteristics are presented in Table 1.

Table 1. Baseline patient characteristics of patients with advanced mucosal melanoma and uveal melanoma

	Mucosal melanoma		Uveal melanoma	
	N= 46		N= 13	
	n	%	n	%
Median follow-up (months)	15.2		4.9	
Gender				
Male	12	26.1	6	46.2
Female	34	73.9	7	53.8
Age at diagnosis, years				
0–69	30	65.2	9	69.2
≥ 70	16	34.8	4	30.8
Median age at diagnosis (IQR)	66 (59-73)		58 (50-72)	
WHO performance status				
0-1	43	93.5	13	100.0
≥2	2	4.3	0	0.0
Unknown	1	2.2	0	0.0
Tumour stage				
Stage III (unresectable)	11	23.9	0	0.0
Stage IVa	1	2.2	0	0.0
Stage IVb	8	17.4	1	7.7
Stage IVc	23	50.0	12	92.3
Stage IVd	3	6.5	0	0.0
LDH level				
Normal	31	67.4	4	30.8
≥ 1x ULN – 2x ULN	8	17.4	6	46.2
≥ 2x ULN	7	15.2	3	23.1
Number of metastatic sites				
0	11	23.9	0	0.0
< 3	31	67.4	10	76.9
≥ 3	4	8.7	3	23.1
Brain metastasis				
No	36	78.3	13	100.0
Yes	3	6.5	0	0.0
Unknown	7	15.2	0	0.0
Liver metastasis				
No	34	73.9	3	23.1
Yes	12	26.1	10	76.9
Line of systemic treatment				
First line	44	95.7	8	66.6
Second line	2	4.3	4	33.3
BRAF mutation				
Yes	1	2.2	0	0.0
No	41	89.1	8	61.5
Not assessed	4	8.7	5	38.5

Table 1. (Continued.)

	Mucosal melanoma		Uveal melanoma	
	N= 46		N= 13	
	n	%	n	%
NRAS mutation				
Yes	7	15.2	0	0.0
No	32	69.6	8	61.5
Not assessed	7	15.2	5	38.5
KIT mutation				
Yes	2	4.3	0	0.0
No	35	76.1	8	61.5
Not assessed	9	19.6	5	38.5
Number of treatment cycles				
2	15	32.6	4	30.8
3	12	26.1	3	23.1
4	19	41.3	6	46.1

IQR, Interquartile range, LDH – lactate dehydrogenase, ULN Upper limit of normal

Treatment outcomes

In both MM and UM approximately half of the patients had clinical benefit from ipilimumab/nivolumab treatment (52.2% and 46.2%, Table 2). Of these patients, CR and PR was seen in 5/46 (10.9%) and 13/46 (28.3%) of the patients with MM. No patients with UM had a complete response, whilst partial response was seen in 4/13 (30.8%) patients. The median OS for all patients with clinical benefit in MM and UM were 10 and 12 months, respectively (Table 2).

Median OS for all patients with MM was 9.7 months [95% CI:5.9-13.5] and median PFS was 4.1 months [95% CI: 2.3-5.9] (Figure 2). For patients with UM, median OS was 12.4 months [95%CI: 1.4-23.4] and median PFS was 5.5 months [95% CI: 0.0-11.6] (Figure 3). Patients with MM had a 1- and 2- year OS of 43% [95%CI: 27.4-58.6] and 23% [95% CI: 5.4-40.6], respectively.

Table 2. Response rates based on best overall response and median OS in mucosal and uveal melanoma.

	Mucosal melanoma (n=46)		Uveal melanoma (n=13)	
	% of patients (n)	Median OS in months (IQR)	% of patients (n)	Median OS in months (IQR)
CR	10.9% (5)	15.5 (6.4-43.0)	0% (0)	-
PR	28.3% (13)	6.0 (3.6-17.3)	30.8% (4)	7.4 (3.0-14.8)
SD	13.0% (6)	10.0 (5.1-16.1)	15.4% (2)	13.9 (12.4-NR)
PD or death	47.8% (22)	3.3 (2.1-7.0)	38.5% (5)	4.1 (2.5-5.8)
Unknown	0.0% (0)	-	15.4% (2)	-
Clinical benefit	52.2% (24)	9.8 (4.1-17.4)	46.2% (6)	11.8 (3.3-15.6)
ORR	39.1% (18)	8.1 (3.9-19.2)	30.8% (4)	7.4 (3.0-14.8)

OS: overall survival, CR: complete response, PR partial response, SD Stable disease, PD progressive disease. Clinical benefit comprises CR, PR and SD. ORR: objective response rate comprises CR and PR. NR Not reached

Figure 2. Kaplan Meier curves of progression-free survival (A) and overall survival (B) of mucosal melanoma

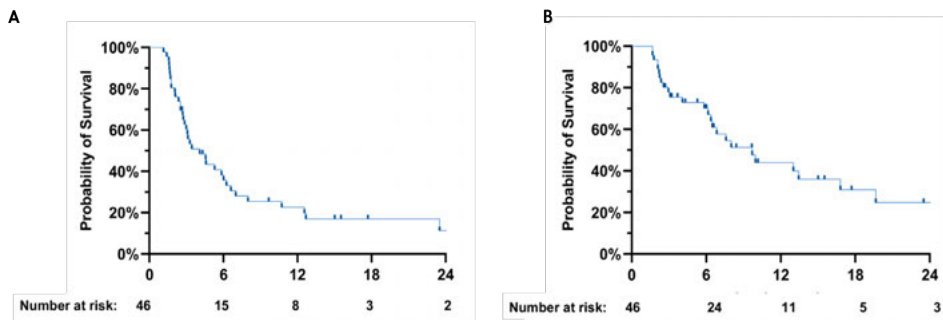
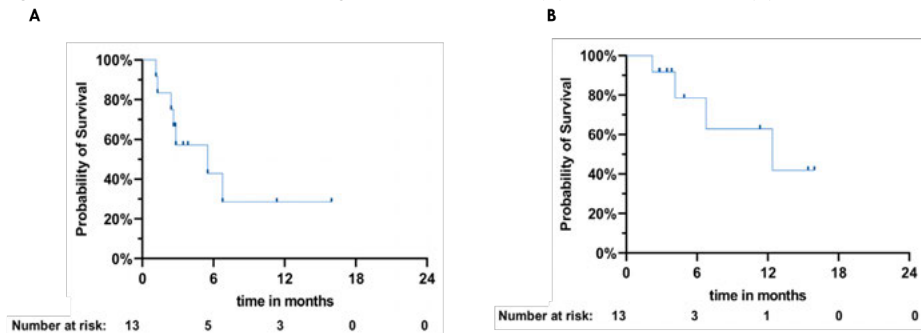


Figure 3. Kaplan Meier curves of progression-free survival (A) and overall survival (B) of uveal melanoma



Treatment toxicity

Grade ≥ 3 toxicity occurred in 47.8% ($n=22/46$) of the patients with MM and 38.4% ($n=5/13$) of the patients with UM, and led to hospital admission in 12/22 patients (54.5%) in MM and 2/5 (40.0%) patients in UM (Supplementary Table 1). Toxicity led to discontinuation of treatment in 18/22 (81.2%) patients with MM and in 5/5 (100%) patients with UM. No treatment-related deaths occurred during treatment or the observation period. The most frequent reported toxicities in MM were hepatitis (19.6%) and colitis (17.4%), and in UM colitis (20.0%), rash (6.7%), hepatitis (6.7%) and pneumonitis (6.7%) (Supplementary Table 1).

Predictors of overall survival

In MM, univariable analysis showed that LDH level ≥ 2 ULN, WHO status ≥ 2 , ≥ 3 metastatic sites, and the presence of liver metastasis were associated with worse survival (Table 3). The multivariable analysis showed that LDH level ≥ 2 ULN (HRadj: 6.57 95% CI:1.14-37.75) and the presence of liver metastasis (HRadj: 3.04 95% CI:1.13-8.16) were associated with worse survival (Table 3).

Table 3. Univariable and multivariable cox regression model for the association of determinants of overall survival for mucosal melanoma

	Mucosal melanoma					
	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age						
0-69	ref		ref			
≥ 70	0.84	0.36-1.93	0.68			
Gender						
Male	ref		ref			
Female	0.59	0.25-1.41	0.23			
Stage						
Stage III (unresectable)	ref					
Stage IVa	3.33	0.34-32.40	0.30			
Stage IVb	1.59	0.34-7.37	0.55			
Stage IVc	2.94	0.84-10.24	0.09			
Stage IVd	3.16	0.63-15.83	0.16			
LDH level						
Normal	ref		ref	ref		ref
≥ ULN – 2x ULN	0.39	0.11-1.37	0.14	0.31	0.08-1.16	0.08
≥ 2x ULN	3.50	1.22-10.01	0.02	2.88	0.78-10.7	0.11
WHO performance status						
0-1	ref		ref	ref		ref
2 or higher	5.13	1.09-24.14	0.04	0.26	0.03-2.48	0.24
Number of metastatic sites						
< 3	ref		ref	ref		ref
≥ 3	10.19	2.89-35.95	> 0.001	6.57	1.14-37.75	0.04
Brain metastasis						
Absent	ref		ref			
Present	1.51	0.44-5.19	0.50			
Liver metastasis						
Absent	ref					
Present						
Present	2.98	1.33-6.68	0.008	3.04	1.13-8.16	0.03

LDH – lactate dehydrogenase, ULN Upper limit of normal

Discussion

MM and UM are rare melanomas in which the optimal treatment strategy has not yet been established. In this retrospective study using real-world data from 2013-2021 we found that only the minority of the patients were treated with ipilimumab/nivolumab (Figure 1). Though, it is important to note that, as combined ipilimumab/nivolumab therapy was introduced in 2016, this therapy was not available in the first years of our cohort, partly explaining these figures. In both MM and UM, approximately half of the patients experienced clinical benefit of

ipilimumab/nivolumab and median OS was 9.7 months and 12.4 months, respectively. Grade ≥ 3 toxicity occurred in 47.8% of the MM and in 38.4% of the UM, leading to discontinuation of treatment in most of these patients. In MM, the presence of liver metastasis and an LDH level $\geq 2 \times$ ULN level were predictive for worse OS.

Next to our analyses, we present an overview of the studies assessing the efficacy of combined ipilimumab/nivolumab in both MM (7 studies) and UM (9 studies) (Table 4). [10, 20-23] In MM, a pooled analysis published by D'Angelo et al., a retrospective study including 197 patients by Dimitriou et al., and a phase II trial by Namikawa et al. demonstrated BORR of 37.1%, 36% and 31%, which are comparable with our findings (39.2% of the patients had CR of PR). [10, 20, 21] In all studies, including ours, only the minority responded completely. As compared to the other studies, Takahashi et al. presented a lower BORR of 16.7%. [22] However, in that study, half of the patients received ipilimumab/nivolumab as a second-line or higher treatment, whilst in the other studies this ranged between 0-7%. Moreover, when comparing the treatment-naïve group with the prior-treatment group, the BORR increased from 5.9% to 26.3%. Though not statistically significant, the lower efficacy of those receiving ipilimumab/nivolumab as second-line or higher treatment, was also reflected by lower OS and PFS (1-year OS 78% vs 43% and 1-year PFS 38.6% vs 17.6%). In CM, combined ipilimumab/nivolumab as second-line treatment is associated with lower RR, but still, Silva et al. found complete or partial response in 30% of the patients. [24-26] Our study population included only two patients (4.3%) with prior treatment (both anti-PD-1 monotherapy) hampering analysis between the treatment naïve group and the prior-treatment group.

As in CM, the pooled analysis of MM demonstrated that whilst combination therapy has a higher efficacy than anti-PD-1 monotherapy, this is at the expense of higher toxicity rates. [10, 27] ORR for nivolumab monotherapy and ipilimumab/nivolumab combination therapy were 23.3% and 37.1% and grade 3 toxicity or higher was seen in 8.1% and 40.0% of the patients. Interestingly, in CM treated with ipilimumab/nivolumab, grade 3 or higher toxicity occurred in 54.5%, whilst in MM this was only 40.0%, also leading to lower treatment discontinuation rates (31.0% vs 17.1%). [10] Yet, this pooled analysis is hampered by a short median follow-up. A post-hoc analysis of the Checkmate 067 trial has overcome this by presenting long-term outcomes of 79 MM patients with a minimum follow-up of 60 months. This study confirmed the higher efficacy of combined therapy when compared to ipilimumab or nivolumab monotherapy including more CR, respectively 14%, 4% and 0%. [28] In contrast, Dimitriou et al., Umeda et al., and Nakamura et al., concluded that anti-CTLA-4/anti-PD-1 treatment and anti-PD-1 had similar efficacy with an objective response rate (ORR) ranging between 26-29% vs 28-31%, respectively. Moreover, median PFS and median OS were similar between both treatment regimens. [20, 23, 29] Altogether, the evidence regarding the superior efficacy of combined nivolumab plus ipilimumab compared to ICI monotherapy for MM, based on non-randomized and retrospective studies, remains much less robust than in CM.

Table 4. Overview of studies describing efficacy and toxicity of combined anti-CTLA-4/ anti-PD-1 therapy in mucosal and uveal melanoma

Mucosal Melanoma							
Study (year)	Number of patients	Type of study	Type of ICI	OS (months)	PFS (months)	ORR (%)	Grade ≥3 toxicity (%)
D'Angelo et al (2017)	35	Pooled analysis	Ipi/Nivo	NA	5.9	37.1	40.0
	86		Nivolumab	NA	3.0	23.3	8.1
	36		Ipilimumab	NA	2.7	8.3	12.5
Namikawa et al (2020)	12	Phase II trial	Ipi/Nivo	NR	NR	36	NA
Shoustari et al (2020)	28	Phase III trial	Ipi/Nivo	22.7	5.8	43	54
	23		Nivolumab	20.2	3.0	30	26
	28		Ipilimumab	12.1	2.6	7	25
Umeda et al (2021)	42	Real world data	Anti CTLA-4/anti-PD-1, not specified	31.7	5.8	28	56.0
	171		<i>Anti-PD-1, not specified</i>	19.2	6.2	26	20.0
Nakamura et al (2021)	66	Retrospective study	Anti CTLA-4/anti-PD-1, not specified	20.1	6.8	29	53
	263		<i>Anti-PD-1, not specified</i>	20.4	5.9	26	17
Takahashi et al (2022)	36	Retrospective study	Ipi/Nivo	14	3.25	16.7	NA
Dimitriou et al (2022)	197	Retrospective study	Ipi/Anti-PD-1	21	4	31	NA
	348		Anti-PD-1, not specified	19	5	29	NA
Boer et al (2023)*	46	Real world data	Ipi/Nivo	9.7	4.1	39.1	47.8
Uveal Melanoma							
Study (year)	Number of patients	Type of study	Type of ICI	OS (months)	PFS (months)	ORR (%)	Grade ≥3 toxicity (%)
Shoustari et al (2016)	6	Expanded access program	Ipi/Nivo	15	2.5	0	NA
Heppt et al (2019)	64	Retrospective study	Ipi/Anti-PD-1	16.1	3.0	15.6	39.1
Bol et al (2019)	19	Retrospective study	Ipi/Nivo	18.9	3.7	21.1	NA
	24		Pembrolizumab	10.3	4.8	7.0	NA
	53		Ipilimumab	9.9	3.0	0.0	NA
Najjar et al (2020)	89	Retrospective study	Ipi/Nivo	15	2.7	11.6	NA
Peister et al (2021)	30	Phase II trial	Ipi/Nivo	19.1	5.5	18	40
Plulats et al (2021)	52	Phase II trial	Ipi/Nivo	12.7	3.0	11.5	75
Koch et al (2021)	109	Retrospective study	Anti CTLA-4/anti-PD-1, not specified	NA	NA	13.8	58.3
	53		<i>Anti-PD-1, not specified</i>	NA	NA	8.9	24.0
	15		Ipilimumab	NA	NA	0.0	NA
Salaun et al (2022)	47	Retrospective study	Ipi/Nivo	NA	2.9	4.3	15

Table 4. (Continued.)

Uveal Melanoma							
Study (year)	Number of patients	Type of study	Type of ICI	OS (months)	PFS (months)	ORR (%)	Grade ≥ 3 toxicity (%)
Van Aken et al (2022)	14	Retrospective study	Anti CTLA-4/anti-PD-1, not specified	NA	NA	14	NA
	27		Anti-PD-1, not specified	NA	NA	15	NA
	24		Ipilimumab	NA	NA	8	NA
Boer et al (2023)*	15	Real world data	Ipi/Nivo	12.4	5.5	30.8	38.4

ICI: Immune checkpoint inhibitor Ipi: Ipilimumab, Nivo: nivolumab, OS: Overall survival, PFS: Progression-free survival, ORR: Overall response rate, NA: not assessed, NR: not reached. For the studies assessing ipilimumab/nivolumab together with ipilimumab or nivolumab monotherapy, the outcomes for all treatment arms are presented.

* Results of the current study

Though our ORR in MM is comparable with other studies, median OS (9.7 months) fell below the range of 14.0-31.7 months, reported in the literature and presented in table 4. [10, 20-23, 29, 30] Whereas comparing baseline characteristics between studies is difficult, no large differences were found explaining the lower OS in our study. In line with the literature, in our study LDH level was elevated in 32.6% of the patients and stage at presentation most often was stage IV M1c. [23, 29] In our study, multivariable analysis demonstrates that higher LDH levels (HRadj:6.57 95% CI:1.14-37.75) and the presence of liver metastasis (HRadj:3.04 95% CI:1.13-8.16) were associated with worse OS. Yet the small sample size of our study restrains effective analysis of predictors of survival.

Toxicity is an important issue in patients treated with combined ipilimumab/nivolumab, as demonstrated in our study (grade ≥ 3 toxicity in 47.8%). Whilst grade ≥ 3 toxicity of MM is quite similar to CM, the high discontinuation rate in our study (80% of those experiencing toxicity discontinued treatment) is remarkable. [2, 31] Yet, the negative effect of discontinuing treatment is not evident, as Schadendorf et al. analysed pooled data of CM from the Checkmate 067 and 069 trials and could not link treatment discontinuation with worse outcomes. [32] Furthermore, the eleven patients with MM (15%) who started ipilimumab/nivolumab treatment, but were excluded from this study due to short follow-up, death or receiving less than two cycles, represent the aggressiveness of this disease. This should be taken into account when considering ICI on patient-level, as they may not derive benefit from these agents while they can face the potential harm of associated toxicities.

In UM, a total of nine studies evaluated safety and efficacy of anti-CTLA-4/anti-PD-1 of which all but three consisted of retrospective cohort studies. [30, 33-40] The two phase II studies including 30 and 52 patients found a median OS of 12.7 and 19.1 months and a BORR of 11.5% and 18%. [36, 39] In our study we observed an ORR of 30.8%, which is higher than the BORR of 12% calculated from all published studies in Table 4, but still is remarkably lower than in CM. [30, 33-40] Similar to the literature, no patients responded completely in our cohort. Unfortunately, the limited number of patients with UM in this study, impedes the ability to draw definitive and far-reaching conclusions.

UM is characterized by disease predominately spreading to the liver (90-95%). [41] Recent studies have suggested that UM which spreads exclusively to the liver has a worse prognosis than those with extra-hepatic disease (with or without liver metastasis). [40, 42] Moreover, response to dual ICI may be better in those with extra-hepatic disease when compared to patients with liver-only disease. Though not statistically significant, a study with 109 patients treated with combined anti CTLA-4/anti-PD-1 therapy of which 38 had liver only disease and 71 liver and extra-hepatic disease, reported worse ORR for those with liver-only disease (8.7% vs 16.7%, $p=0.45$). [40] Moreover, median OS was better for those with hepatic and extra-hepatic disease compared to liver-only spread disease (6 vs 18 months, $p=0.07$).

In the Netherlands, this has led to criteria for providing ipilimumab/nivolumab across the fourteen melanoma centers, in which patients are selected with a fairly good prognosis, characterized by limited tumor load, preferably extra-hepatic disease only, a good performance status and a normal LDH level. Due to these criteria, our study includes a selected population with relatively less liver metastasis as compared to the literature (73.3% vs 90-95%) and more patients with extra-hepatic disease only (26.7%). These patients, with a more favorable prognosis, may have affected our outcomes (median OS 12.4 months and 1-year OS 78%), which are promising as compared to data from a meta-analysis including 912 patients from 29 trials treated with various treatment regimens (median OS 10.2 months and 1-year OS 43%). [43] Due to the small numbers in our study, we could not compare outcomes of patients with liver-only disease compared to patients with extra-hepatic metastases. Still, the aggressive course of this disease is illustrated by the Kaplan-Meier curves (Figure 3). All deaths occurred within the first year and progression of disease occurred in 6/13 patients (46%), all within 6 months.

In CM, a thorough assessment of combined ipilimumab/nivolumab in 140 patients with in total 833 metastasis, found distinct heterogeneity in response patterns between different anatomical sites. [44] They observed that, when comparing nine locations of metastasis, site specific response of metastasis in the liver was the lowest (46%) whilst that of the lung was the highest (77%). [44] In multivariate analysis, those with liver metastasis had lower ORR, PFS and OS, whilst those with lung metastasis had better ORR and PFS. A hypothesis is that the liver possesses a distinct immunosuppressive tumor microenvironment (TME), which may hamper the function of tumor-infiltrating lymphocytes, explaining why UM has lower RR to ICI than CM. [45] In various cancer types, including CM, studies have demonstrated that the presence or abundance of specific T-cells and PD-L1 levels in the TME can strongly predict the response of ICI. [46, 47] In MM, the potential predictive value of the TME has not yet been analysed, but could be an important avenue for the future.

In this study, grade ≥ 3 toxicity occurred in 38.4% of the patients with UM. The six studies including 302 patients assessing toxicity in UM report grade ≥ 3 toxicity in 15-75% of the patients, with a calculated average of 46.4%. (Table 4). This is 15% lower than in CM, in which the largest clinical trial reported grade ≥ 3 toxicity in 59% the patients. [31] Bomze et al. and Kerepesi et al. found that tumours with a high TMB, such as CM and non-small cell lung cancer, are associated with a higher risk of immune-related adverse events (irAE), whilst lower TMB is associated with a lower risk of irAE. [48, 49] The comparatively low toxicity rates of UM and MM, which are characterized by a low TMB, fits this hypothesis.

A strength of this study is the use of real-world data, provided by a validated and detailed prospective registry in the Netherlands, which includes all patients since the era of immunotherapy. However, due to the low incidence of MM and UM combined with the

highly aggressive character resulting in only a minority of the patients receiving systemic therapy, we could only analyse 46 MM and 13 UM patients. Therefore our data should be seen in a larger context within the published evidence which we present in Table 4.

The lower efficacy of ICI, when compared with its cutaneous counterpart, suggests the lower immunogenicity of both MM and UM. [2] Still, in our study, approximately half of the patients with MM and UM experienced clinical benefit from ipilimumab/nivolumab. Yet, toxicity remains a constraining factor and the aggressive nature of the disease can catch up on time, diminishing the potential effect from ipilimumab/nivolumab, which can be seen in the low OS rates. Therefore, future studies should focus on identifying patients who have a high likelihood of benefitting from ipilimumab/nivolumab therapy. Moreover, studies assessing innovative (combination) treatment strategies for both MM and UM, and in particular clinical trials, are needed.

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Supplementary material

Supplementary Table 1. Overview of specific toxicities in mucosal and uveal melanoma

	Mucosal melanoma (n=46)	Uveal melanoma (n=13)
Total patients with grade ≥ 3 toxicity	22 (47.8)	5 (38.4)
Type of toxicity	N (%)	N (%)
Colitis	8 (17.4)	3 (23.1)
Hepatitis	9 (19.6)	1 (7.7)
Pneumonitis	0 (0)	1 (7.7)
Adrenal insufficiency	1 (2.2)	0 (0)
Hypopituitary insufficiency	1 (2.2)	0 (0)
Thyroiditis	1 (2.2)	0 (0)
Fatigue	3 (6.5)	0 (0)
Rash or pruritus	4 (8.7)	1 (7.7)

Supplementary Table 2. Toxicity determinants for mucosal and uveal melanoma

	Mucosal melanoma (n=46)				Uveal melanoma (n=13)			
	% of treated patients with toxicity	OR	95% CI	p-value	% of treated patients with toxicity	OR	95% CI	p-value
Age								
0-69	50 (15)	ref			44.4 (4)	ref		
≥ 70	43.8(7)	0.78	0.23-2.63	0.69	25.0 (1)	0.42	0.03-5.71	0.51
Gender								
Female	50.0 (6)	Ref			57.1(4)	ref		
Male	47.1(16)	0.90	0.24-3.32	0.86	16.7 (1)	6.6	0.49-91.3	0.16
Number of comorbidities								
0-2	41.9 (13)	ref			33.3 (3)	ref		
3 or more	57.1 (8)	1.9	0.52-6.62	0.35	50.0 (2)	2.0	0.18-22.1	0.57
WHO performance status								
0-1	46.5 (20)	Ref			5 (38.5)	Ref		
2 or higher	50.0 (1)	1.15	0.07-19.6	0.92	0 (0.0)	0.63	NA	0.41

In patients with MM there is 1 patient of which the number of comorbidities is unknown and 1 patient of which the WHO classification is not known. These patients are not presented in this table. NA: not assessable as 1 category does not include any patients.