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Original Research

# Response to immune checkpoint inhibitors in acral melanoma: A nationwide cohort study

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**Abstract** ***Background:*** Recent reports suggest the limited efficacy of immune checkpoints inhibitors in advanced acral melanoma (AM). This study aims to investigate the clinical outcomes of immune checkpoint inhibitors in patients with stage III and IV AM and compare them to cutaneous melanoma (CM).
***Methods:*** We included patients with advanced AM and CM treated with first-line anti-programmed cell death (PD)-1 monotherapy or ipilimumab-nivolumab registered in the prospective nationwide Dutch Melanoma Treatment Registry. Objective response rates, progression-free survival (PFS) and overall survival (OS) were calculated. A Cox proportional hazard model was used to assess the prognostic factors with PFS and OS.
***Results:*** In total, 2058 patients (88 AM and 1970 CM) with advanced melanoma were included. First-line objective response rates were 34% for AM versus 54% for CM in the advanced anti-PD-1 cohort and 33% for AM versus 53% for CM in the advanced ipilimumab-nivolumab cohort. The Median PFS was significantly shorter for anti-PD-1 treated AM patients (3.1 months; 95%CI: 2.8–5.6) than patients with CM (10.1 months; 95%CI: 8.5–12.2) ($P < 0.001$). In patients with advanced melanoma, AM was significantly associated with a higher risk of progression (HRadj 1.63; 95%CI: 1.26–2.11; $P < 0.001$) and death (HRadj 1.54; 95%CI: 1.15–2.06; $P = 0.004$) than CM.
***Conclusions:*** This study shows lower effectiveness of anti-PD -1 monotherapy and ipilimumab-nivolumab in AM, with lower response rates, PFS and OS than CM. This group of patients should be prioritised in the development of alternative treatment strategies.


## 1. Introduction

The introduction of immune checkpoint inhibitors (ICIs) has improved the survival of patients with advanced melanoma, especially for cutaneous melanoma (CM), in both trial and real-world settings [1–3]. The most frequently occurring melanoma type is CM, most commonly originating from the hair-bearing skin [4]. However, melanoma can also arise at other sites such as mucosal surfaces (mucosal melanoma), the uvea of the eye (uveal melanoma), or at the non-hair-bearing glabrous skin on the palms and soles and nail apparatus (acral melanomas; AM) [5]. AM are distinct from other CMs since they have a different genetic profile [6,7] and a lower tumour mutational burden (TMB) [8]. Previous studies have demonstrated a poor prognosis of patients diagnosed with advanced AM compared to non-acral CM. Still, data on the effectiveness of checkpoint inhibitors in the Western population is limited [9,10]. AM have a relatively low incidence in the Caucasian population [11], and studies investigating the response to ICIs in AM in Caucasians include limited sample sizes [12,13]. This nationwide study aimed to investigate the differences in objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) to ICIs in a large cohort of Dutch patients with advanced AM and CM. We hypothesise that patients with AM have a worse outcome compared to patients with CM and that the effectiveness of ICIs in patients with AM is lower in the advanced setting.

## 2. Materials and Methods

Data were retrieved from the Dutch Melanoma Treatment Registry (DMTR). The DMTR prospectively registers data of all patients with unresectable

stage III and IV melanoma in the Netherlands since 2012. Jochems *et al.* [14] have shown the high quality of this registry. The medical ethical committee approved research using DMTR data, and this research was not deemed subject to the Medical Research Involving Human Subjects Act in compliance with Dutch regulations. For this study, the dataset cut-off date was 2nd September 2021.

### 2.1. Patients

We included all patients with stage III and IV melanoma, 18 years or older, with AM or non-acral CM receiving first-line anti-PD-1 monotherapy or ipilimumab-nivolumab for irresectable stage III and IV. Patients that were treated on clinical trials and patients that received prior adjuvant treatment were excluded. All melanomas registered as acral lentiginous melanoma in the DMTR, and melanomas located on the glabrous skin of the hand and feet or subungual melanomas were considered AMs.

### 2.2. Characteristics

The following patient and tumour characteristics at diagnosis were registered for all patients: age at diagnosis, gender, Eastern cooperative oncology group performance status (ECOG PS), lactate dehydrogenase levels (LDH), primary melanoma location, type of melanoma, Breslow thickness, ulceration, mutation (*BRAF*, *NRAS*, *KIT*, *GNAQ*, *GNA11*, other or wild type), liver metastasis, brain metastasis, number of organ sites with metastases, median time from primary melanoma to metastatic disease and AJCC staging system 8th edition [15].

### 2.3. Outcomes

For patients with advanced melanoma who received systemic therapy, outcomes were calculated for anti-PD-1 monotherapy and ipilimumab-nivolumab separately. Patients who did not have a response evaluation were excluded from the analysis. First-line ORR and ORR in any treatment line were calculated separately. The treating physicians determined response evaluation in line with Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 [16]. PFS and OS were calculated for first-line treated patients only. A Cox proportional hazards model was used to perform a multivariate regression analysis to assess individual factors associated with PFS and OS.

### 2.4. Statistical analysis

Baseline characteristics were analysed using descriptive statistics. Pearson's chi-squared test was used to compare categorical variables and the t-test for continuous variables. The median follow-up time was estimated from the first visit to the melanoma centre using the reversed Kaplan–Meier method [17]. Covariates used in the multivariable regression analysis for patients with advanced melanoma were age, gender, ECOG PS, LDH level, liver metastasis, brain metastasis, number of organ sites with metastasis and type of systemic therapy. The ORR was defined as the proportion of evaluable patients who were tumour-free or achieved a complete response or partial response. Patients were deemed not evaluable if they died from a non-melanoma-related cause before their first evaluation of response or did not have a response registered in the DMTR. The median PFS and OS were calculated using the Kaplan–Meier method. PFS was calculated from the start of systemic therapy until progression, death or the last moment of follow-up. OS was calculated from the start of systemic therapy until death by any cause or the last moment of follow-up. Patients not reaching the end-point were right-censored at the date of the last contact. A Cox proportional hazards model was used to perform a multivariable regression analysis to assess factors associated with PFS and OS. Comparisons were considered statistically significant for two-sided P-values $\leq 0.05$. Data handling and statistical analyses were performed using R studio (version 4.0.2) [18], packages tidyverse [19], tableone [20], survival [21], and survminer [22].

## 3. Results

From 2013 to 2021, 2580 patients with advanced melanoma (unresectable stage III-IV) were registered in the DMTR who received ICIs as their first-line treatment. We excluded 374 patients with melanoma of unknown primary, 26 patients with uveal melanoma, 101 patients with mucosal melanoma and 21 patients because information regarding the location of their primary melanoma was lacking. In total, 2058 patients treated with first-line ICIs met the inclusion criteria. Eighty-eight patients treated with ICIswere diagnosed with AM, of which 70 received anti-PD-1 monotherapy and 18 ipilimumab-nivolumab. Of the 1970 patients with CM treated with ICIs, 1402 patients received anti-PD-1 monotherapy and 568 patients received ipilimumab-nivolumab. The median follow-up was 32.2 months for patients treated with anti-PD-1 and 23.9 months for patients treated with ipilimumab-nivolumab.

### 3.1. Patient and tumour characteristics

Patients with AM had higher Breslow thickness, more ulcerated melanomas but lower AJCC metastatic stage and higher T-stage at primary diagnosis. *BRAF* mutations were less frequent in the AM group than in the CM group (10% versus 42%; $P < 0.001$) and *KIT* mutations were seen more often in patients with AM (7% versus 2%; $P = 0.001$). All baseline characteristics are shown in

Table 1
**Patient characteristics**. Comparison of baseline characteristics of advanced first-line treated melanoma patients stratified by melanoma type: acral melanoma and cutaneous melanoma.

| | | Acral | Cutaneous | P-value |
|---|---|---|---|---|
| | | 88 | 1970 | |
| Age categories[a] | <70 years | 46 (52.3) | 1134 (57.6) | 0.383 |
| | ≥70 years | 42 (47.7) | 836 (42.4) | |
| Median age [IQR][a] | | 69.0 [60.8,77.0] | 66.0 [56.0,74.0] | 0.109 |
| Gender | Male | 46 (52.3) | 1233 (62.6) | 0.146 |
| | Female | 42 (47.7) | 737 (37.4) | |
| ECOG PS[a] | 0 | 41 (46.6) | 1092 (55.4) | 0.277 |
| | 1 | 33 (37.5) | 664 (33.7) | |
| | ≥2 | 7 (8.0) | 122 (6.2) | |
| | Unknown | 7 (8.0) | 92 (4.7) | |
| Melanoma location[b] | Head-Neck | 0 (0.0) | 382 (19.4) | <0.001 |
| | Trunk | 0 (0.0) | 886 (45.0) | |
| | Extremities | 0 (0.0) | 702 (35.6) | |
| | Acral | 88 (100.0) | 0 (0.0) | |
| Melanoma type[b] | Superficial spreading | 14 (15.9) | 936 (47.5) | <0.001 |
| | Nodular | 7 (8.0) | 498 (25.3) | |
| | Acral lentiginous | 53 (60.2) | 0 (0.0) | |
| | Lentigo maligna | 0 (0.0) | 58 (2.9) | |
| | Desmoplastic | 0 (0.0) | 17 (0.9) | |
| | Other | 5 (5.7) | 58 (2.9) | |
| | Unknown | 9 (10.2) | 403 (20.5) | |
| Breslow thickness[b] | <1.01 mm | 4 (4.5) | 220 (11.2) | <0.001 |
| | 1.01–2.00 mm | 11 (12.5) | 486 (24.7) | |
| | 2.01–4.00 mm | 24 (27.3) | 562 (28.5) | |
| | >4.00 mm | 40 (45.5) | 479 (24.3) | |
| | Unknown | 9 (10.2) | 223 (11.3) | |
| Median Breslow thickness [IQR][b] | | 4.2 [2.5,6.0] | 2.5 [1.5,4.3] | <0.001 |
| Ulceration[b] | No | 28 (31.8) | 953 (48.4) | <0.001 |
| | Yes | 52 (59.1) | 609 (30.9) | |
| | Unknown | 8 (9.1) | 408 (20.8) | |
| LDH levels[a] | Normal | 60 (68.2) | 1345 (68.3) | 0.850 |
| | 250–500 | 21 (23.9) | 446 (22.6) | |
| | >500 | 7 (8.0) | 150 (7.6) | |
| | Unknown | 0 (0.0) | 29 (1.5) | |
| AJCC stage (8th edition)[a] | IIIc unresectable | 17 (19.3) | 176 (8.9) | 0.004 |
| | IV-M1a | 12 (13.6) | 166 (8.4) | |
| | IV-M1b | 16 (18.2) | 315 (16.0) | |
| | IV-M1c | 32 (36.4) | 874 (44.4) | |
| | IV-M1d | 11 (12.5) | 436 (22.1) | |
| | Unknown | 0 (0.0) | 3 (0.2) | |
| Liver metastases[a] | No | 67 (76.1) | 1441 (73.1) | 0.581 |
| | Yes | 21 (23.9) | 510 (25.9) | |
| | Unknown | 0 (0.0) | 19 (1.0) | |
| Brain metastases[a] | No | 77 (87.5) | 1531 (77.7) | 0.173 |
| | Yes, asymptomatic | 8 (9.1) | 278 (14.1) | |
| | Yes, symptomatic | 3 (3.4) | 158 (8.0) | |
| | Unknown | 0 (0.0) | 3 (0.2) | |
| Organ sites[a] | <3 | 56 (63.6) | 1133 (57.5) | 0.379 |
| | ≥3 | 31 (35.2) | 826 (41.9) | |
| | Unknown | 1 (1.1) | 11 (0.6) | |
| Median time from primary melanoma to metastatic disease (months)[IQR] | | 27.5 [11.0–64.5] | 27.0 [10.5–45.3] | 0.326 |
| Mutations[a] | *BRAF* | 9 (10.2) | 829 (42.1) | <0.001 |
| | *NRAS* | 24 (27.3) | 579 (29.4) | |
| | *KIT* | 6 (6.8) | 30 (1.5) | |
| | *GNAQ* | 0 (0.0) | 12 (0.6) | |
| | *GNA11* | 0 (0.0) | 8 (0.4) | |
| | Wild type[c] | 25 (28.4) | 279 (14.2) | |
| Therapy type | Anti-PD1 antibody | 70 (79.5) | 1402 (71.2) | 0.113 |
| | Ipilimumab-nivolumab | 18 (20.5) | 568 (28.8) | |

[a] Determined at the start of systemic therapy.
[b] Determined at the diagnosis of primary melanoma.
[c] Wild type for BRAF, NRAS, KIT, GNAQ and GNA11.

[Table 1]. Except for mutation status, no significant differences at baseline existed between the acral and cutaneous ipilimumab-nivolumab patients.

### 3.2. ORR

ORR on first-line anti-PD-1 was 34% for AM and 54% for CM. In any treatment line, ORR was 31% for AM and 52% for CM. For ipilimumab-nivolumab, first-line ORR was 31% for AM and 52% for CM and 23% for AM and 43% for CM in any treatment line [Table 2].

### 3.3. PFS

The median PFS was significantly longer for patients with CM than for patients with AM receiving anti-PD-1 monotherapy. The median PFS was 3.1 months (95%CI: 2.8–5.6) for AM and 10.1 months (95%CI: 8.5–12.2) for CM ($P < 0.0001$) [Fig. 1a]. In the ipilimumab-nivolumab cohort, PFS was 3.0 months for AM (95%CI: 2.5-NR) and 6.7 months for CM (95%CI: 5.4–9.3) ($P = 0.23$) [Fig. 1b].In multivariable analysis including both anti-PD-1 and ipilimumab-nivolumab treated patients, AM was significantly associated with a higher hazard of progression or death ($HR_{adj}$ 1.63; 95%CI: 1.26–2.11; $P < 0.001$) [Fig. 2].

### 3.4. Overall survival

The median OS was significantly lower for patients with AM than for CM in both treatment cohorts [Fig. 3a and b]. For patients treated with anti-PD-1, median OS was 18.6 months (95%CI: 11.7–27.2) for patients with AM versus 32.3 months (95%CI: 29.0–35.8) for patients with CM ($P = 0.00016$). Patients with AM and treated with ipilimumab-nivolumab had a median OS of 7.6 months (95% CI: 6.1-NR) and patients with CM of 30.9 months (95%CI: 22.3-NR) ($P = 0.0097$). After correction in multivariable analysis, being diagnosed with AM remained significantly associated with a higher hazard of death ($HR_{adj}$ 1.54; 95% CI: 1.15–2.06; $P = 0.004$) [Fig. 4].

### 3.5. Subsequent treatment

Of the 88 AM patients receiving first-line checkpoint inhibitors, 35 received a second treatment line. Thirteen of these patients received ipilimumab, eight received anti-PD-1 monotherapy and five received BRAF/MEK inhibitors. All subsequent treatment lines can be seen in [Supplementary Tables 1a and 1b].

## 4. Discussion

To our knowledge, this real-world, population-based study is the largest study to demonstrate the lower effectiveness of ICIs in patients with AM in direct comparison to patients with CM. ORR, median PFS and median OS were all significantly lower in the advanced AM group, despite relatively lower AJCC stages. The acral subtype was significantly associated with a higher hazard for progression and death in multivariable analysis. Although we describe the largest ipilimumab-nivolumab-treated cohort of patients with advanced AM thus far, the number of ipilimumab-nivolumab-treated patients is still small. Moreover, a direct comparison of anti-PD-1 and ipilimumab-nivolumab-treated patients is potentially hampered by selection bias. In both the AM and CM cohorts, patients with AM and CM treated with ipilimumab-nivolumab had higher LDH levels and more often had liver and brain metastases than patients with anti-PD-1 (data were not shown), which possibly explains limited response rates in this treatment group. Therefore, even though one might tend towards using dual checkpoint inhibition in advanced AM patients based on the limited effectiveness of anti-PD-1 monotherapy, our data do not provide conclusive evidence to support or discourage this.

The lower effectiveness of ICIs in AM than in CM might be due to the lower TMB which can be explained by its non-UV-related pathogenesis. Furney *et al.* [23] demonstrated a lower TMB in AM than in CM. Furthermore, the frequency of tumour-infiltrating lymphocytes, a known predictive factor for ICI-response, has been shown to be lower in AM [24].

Table 2
Objective response rate in first and any treatment line in advanced melanoma stratified by melanoma location.

| Objective Response Rate | First treatment line | | | | | | Any treatment line | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Anti-PD-1 monotherapy | | | Ipilimumab-Nivolumab | | | Anti-PD-1 monotherapy | | | Ipilimumab-Nivolumab | | |
| | AM | CM | Total | AM | CM | Total | AM | CM | Total | AM | CM | Total |
| CR | 13% | 23% | 22% | 6% | 14% | 13% | 11% | 21% | 21% | 3% | 11% | 11% |
| PR | 21% | 32% | 31% | 28% | 40% | 39% | 20% | 30% | 30% | 19% | 32% | 31% |
| SD | 21% | 19% | 19% | 17% | 11% | 11% | 20% | 18% | 18% | 13% | 11% | 11% |
| PD or death | 45% | 27% | 28% | 50% | 36% | 36% | 48% | 30% | 31% | 65% | 46% | 46% |
| ORR | 34% | 54% | 53% | 33% | 53% | 53% | 31% | 52% | 51% | 23% | 43% | 42% |
| Total (n) | 67 | 1346 | 1413 | 18 | 524 | 542 | 99 | 2073 | 2172 | 31 | 973 | 1004 |

CR: complete response PR: partial response SD: stable disease PD: progressive disease ORR: objective response rate.

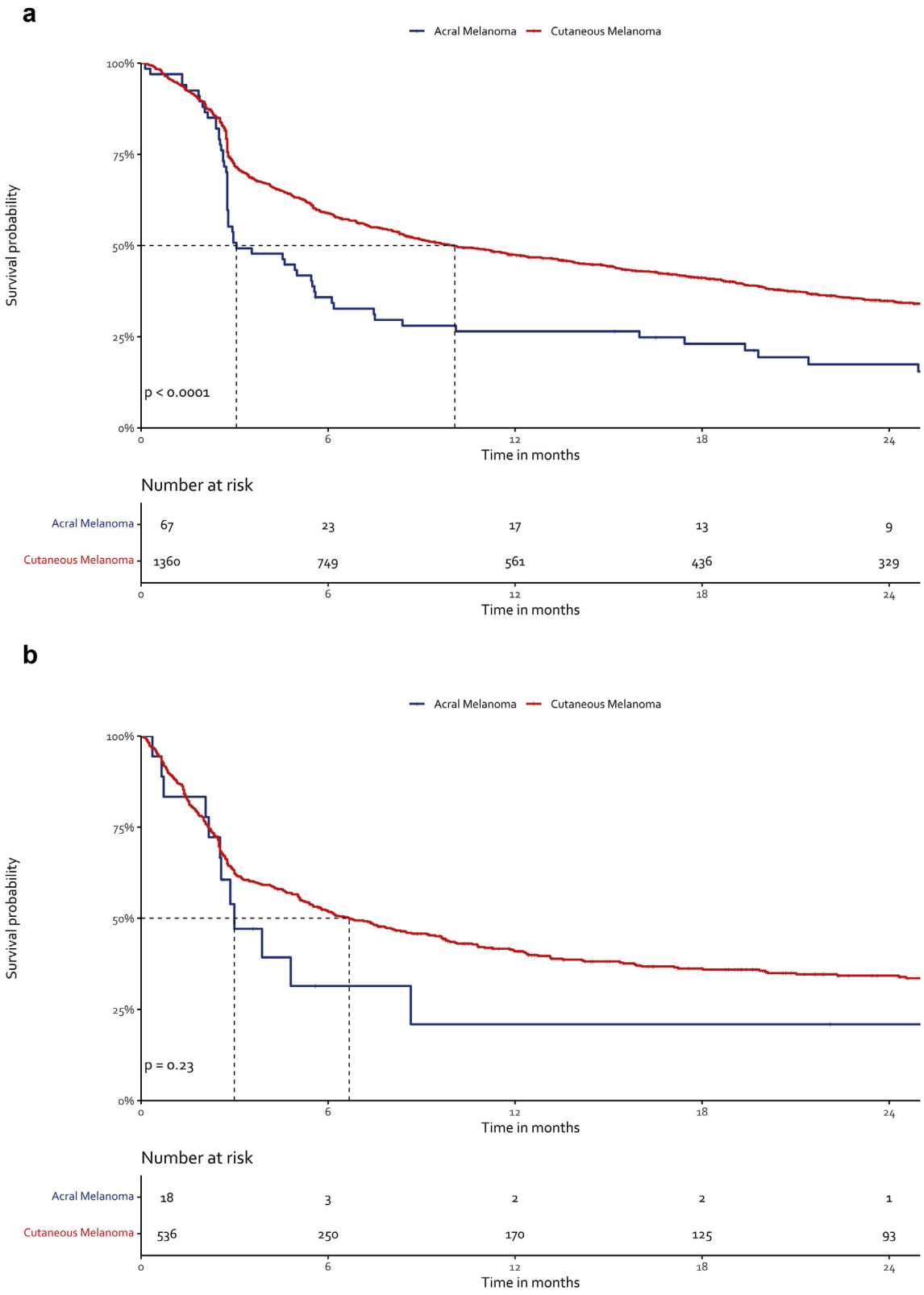


Fig. 1. **(a)** Kaplan–Meier estimate of PFS in anti-PD-1-treated patients with advanced melanoma. **(b)** Kaplan–Meier estimate of PFS in ipilimumab-nivolumab-treated patients with advanced melanoma. PFS, progression-free survival.

Compared to CM, AM patients harboured fewer *BRAF* mutations and more *KIT* mutations. The higher incidence of *BRAF* mutations in patients with CM partially explains the higher OS in this group since *BRAF* mutated patients are eligible for BRAF or BRAF/MEK inhibitors after progressing on ICI

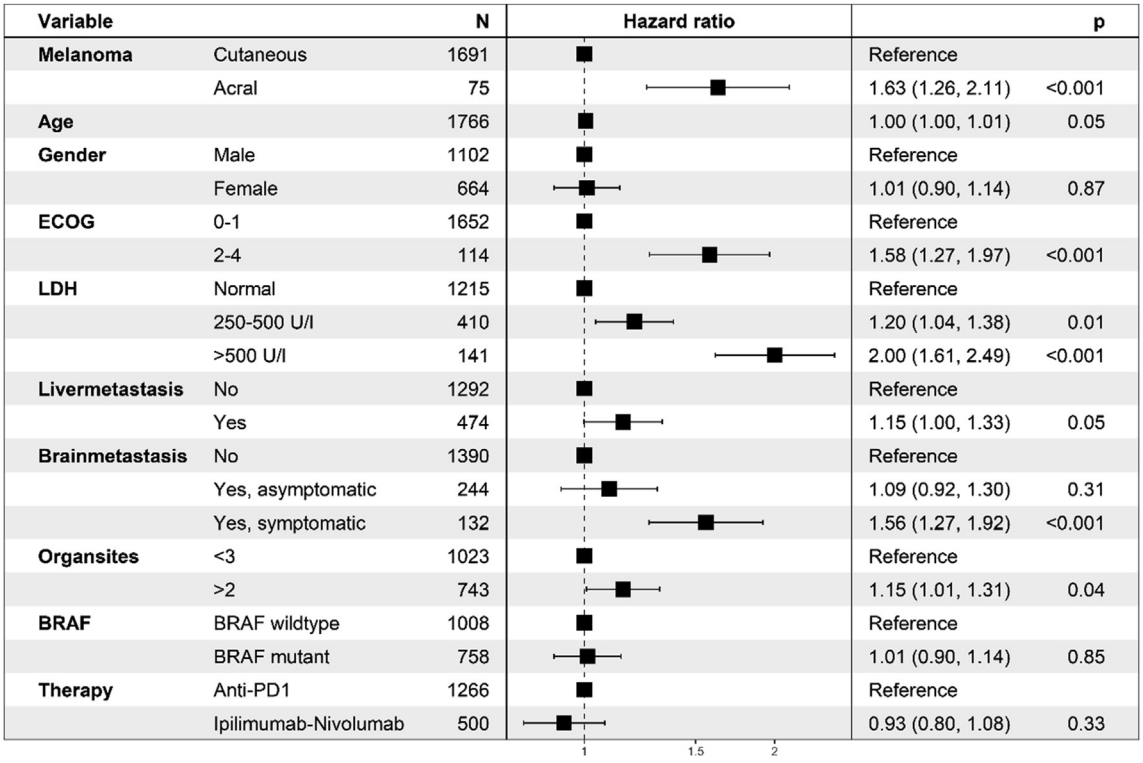


Fig. 2. Multivariate Cox proportional hazard model of PFS in ICI-treated patients with advanced melanoma.ICI, immune checkpoint inhibitor; PFS, progression-free survival.

treatment [25]. Fifty percent of patients with CM receiving a second treatment line were treated with either BRAF or BRAF/MEK inhibitors versus fourteen percent of patients with AM. Earlier studies have reported a higher incidence of *KIT* mutations in AM [26]. Hode *et al.* [27] did not find a response to KIT-inhibitors in AM, but a systematic review by Steeb *et al.* [28] found an ORR of 22% for AM. In the DMTR, KIT-inhibitors are listed as other systemic therapy. Therefore, we could not retrieve the exact number of patients treated with KIT-inhibitors.

Our data are in contrast to the results of the phase II CheckMate 172 study by Nathan *et al.* [29] which included 55 patients with AM treated with nivolumab after progression on ipilimumab. In this study, a median OS of 25.8 months for patients with AM was reported, which was similar to patients with CM (25.3 months) and compares very favourably to our results. A recent study by Nakamura *et al.* [10] investigated the response to anti-PD-1 in any line in 193 Japanese patients. They reported an ORR of 16.6%, which is lower than the ORR we found in our cohort. They found a PFS of 3.5 months and an OS of 18.2 months, comparable to the PFS of 3.1 months and OS of 18.6 months for anti-PD-1 monotherapy in our study. The variation in response could be due to differences in the study design but are more likely to reflect differences in ICI effectiveness in Asian and Caucasian populations. Shoushtari *et al.* [30] investigated the effectiveness of ICIs in acral and mucosal melanoma in patients with advanced melanoma, of which most already received prior treatment. This study included 25 patients with AM treated with nivolumab or pembrolizumab. Patients with AM had an ORR of 32%, a median PFS of 4.1 months and a median OS of 31.7 months. The reported ORR and PFS of AM were comparable to our cohort. However, we found a shorter median OS of 18.6 months for anti-PD-1 treated patients. A single-centre cohort study by Rose *et al.* [31] included 230 patients with advanced melanoma treated with anti-PD-1 ± anti-CTLA4. Their cohort included 18 AM patients, of whom 11 were treated with anti-PD-1 monotherapy and 7 with ipilimumab-nivolumab. They found a median PFS of 3.5 months and a median OS of 14.6 months, similar to our findings. Zheng *et al.* [32] recently published a systematic review, including mostly Asian studies, investigating anti-PD-1 monotherapy in advanced melanoma. They included 12 studies with a total of 494 patients with AM treated with anti-PD-1, reporting an ORR ranging from 14 to 40%. The median PFS ranged from 3.2 to 9.2 months, and the median OS was over 14 months.

The present study does have some limitations. The use of observational data can cause bias by indication. Additionally, due to the retrospective analysis of our study, we cannot rule out the presence of residual confounding. The DMTR does not contain information

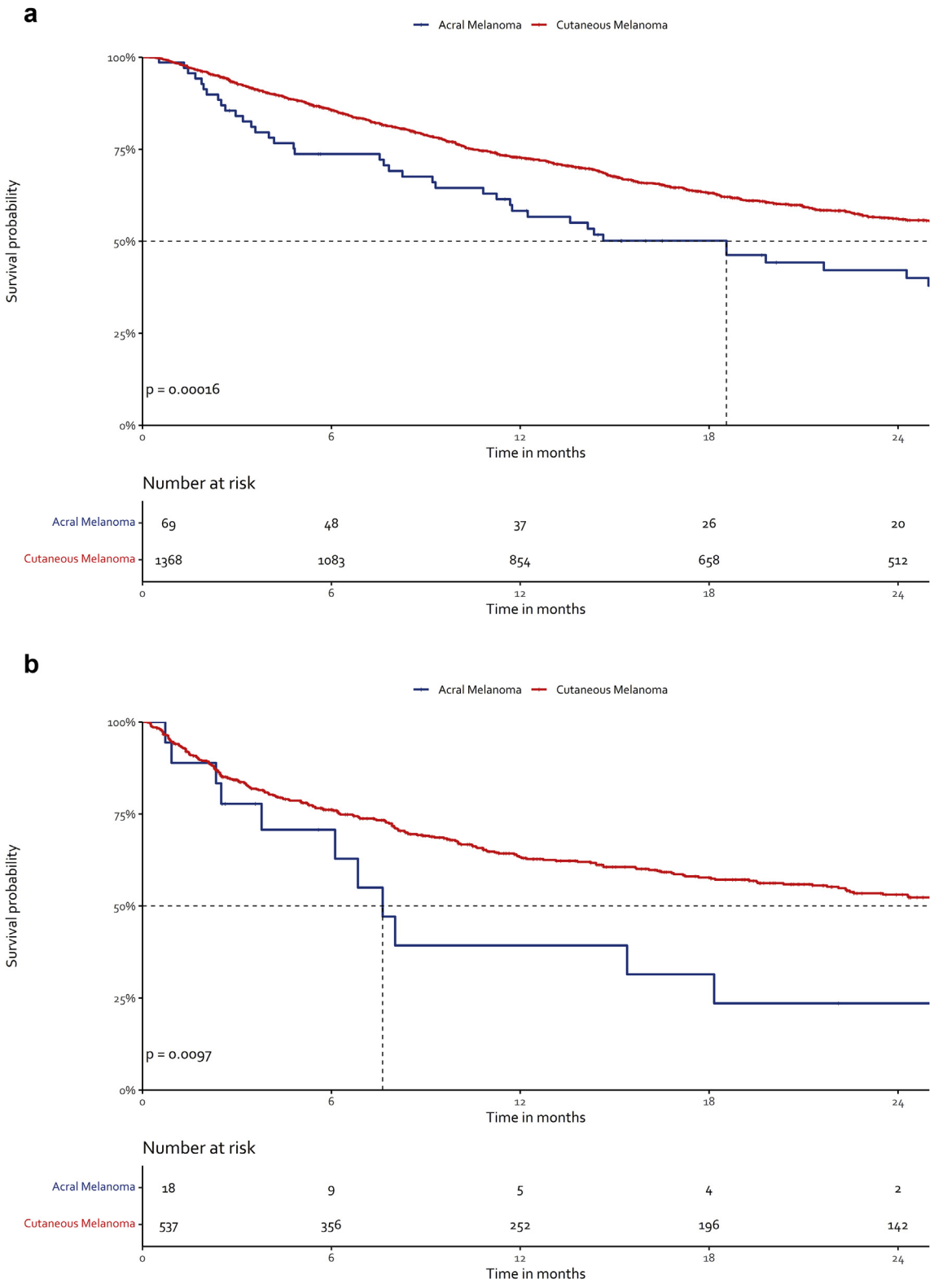


Fig. 3. **(a)** Kaplan–Meier estimate of OS in anti-PD-1-treated patients with advanced melanoma. **(b)** – Kaplan–Meier estimate of OS in ipilimumab-nivolumab-treated patients with advanced melanoma. OS, overall survival.

about the ethnic background of patients, so it is unknown what proportion of our treatment cohort consists of patients with a non-Caucasian background.

A strength of our study is that we report on the largest nationwide cohort of Western AM patients. DMTR data registration is performed by independent data managers

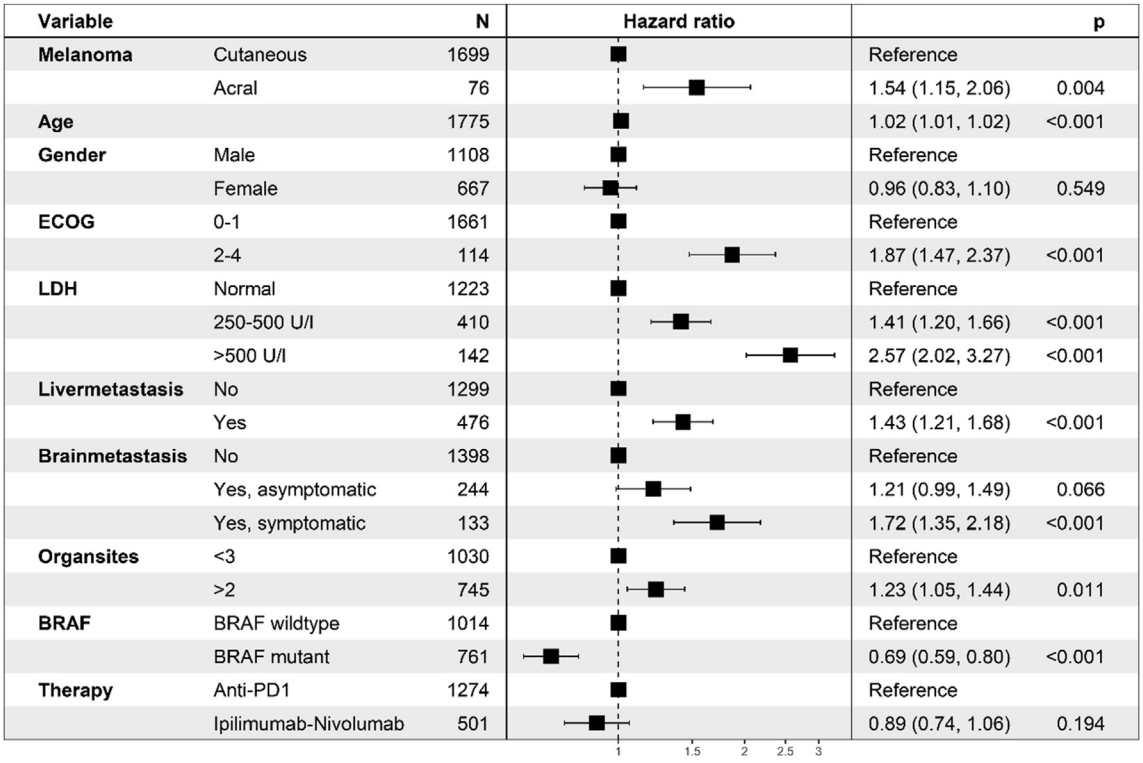


Fig. 4. – Multivariate Cox proportional hazard model of OS in ICI-treated patients with advanced melanoma. ICI, immune checkpoint inhibitor; OS, overall survival.

who are annually trained. The patients' treating oncologist checks the registered data to ensure data quality. The online registry in which patients are registered also includes warnings on inconsistent or missing data. Our study confirms decreased effectiveness of anti-PD-1 monotherapy as well as ipilimumab-nivolumab for advanced AM. Future studies should focus on alternative treatment strategies for this subgroup of patients with melanoma.

## Author contributions section

Van Not: Conceptualisation, Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing. De Meza: Conceptualisation, Writing – Review & Editing. Van den Eertwegh: Writing - Review & Editing. Haanen: Writing - Review & Editing Blank: Writing - Review & Editing. Aarts: Writing - Review & Editing. Van den Berkmortel: Writing - Review & Editing. Van Breeschoten: Writing - Review & Editing. De Groot: Writing - Review & Editing. Hospers: Writing - Review & Editing. Ismail: Writing - Review & Editing. Kapiteijn: Writing - Review & Editing. Piersma: Writing - Review & Editing Van Rijn: Writing - Review & Editing Stevenseden Boer: Writing - Review & Editing Van der Veldt: Writing - Review & Editing Vreugdenhil: Writing - Review & Editing Bonenkamp: Writing - Review & Editing Boers-Sonderen: Writing - Review & Editing Blokx: Conceptualisation, Writing - Review & Editing, Supervision Wouters: Conceptualisation, Writing - Review & Editing, Supervision Suijkerbuijk: Conceptualisation, Writing - Review & Editing, Supervision.

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## Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AvdE 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 paper from Sanofi, Roche, Bristol Myers Squibb, Idera and TEVA and has received travel expenses from MSD Oncology, Roche, Pfizer and Sanofi and has received speaker honoraria from BMS and Novartis.

JH has advisory relationships with Achilles Therapeutics, AstraZeneca, Bristol Myers Squibb, BioNTech, Immunocore, Iovance Biotherapeutics, Ipsen, MSD, Merck Serono, Molecular Partners, Novartis, Neogene Therapeutics, Pfizer, PokeAcel, Roche/Genentech, Sanofi, Third Rock Ventures, T-Knife and has received research grants not related to this paper from Asher Bio, Amgen, Bristol Myers Squibb, MSD, BioNTech, Neogene Therapeutics and Novartis. All grants were paid to the institutions.

CB has received commercial research grants from Novartis, BristolMyers Squibb, and NanoString; is a paid advisory board member for Bristol Myers Squibb, MSD, Roche, Novartis, GlaxoSmithKline, AstraZeneca, Pfizer, Lilly, GenMab, and Pierre Fabre; and holds ownership interest in Uniti Cars, Neon Therapeutics, and Forty Seven.

MA has advisory board/consultancy honoraria from Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas, Bayer. Research grants Merck-Pfizer. Not related to current work and paid to institute.

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GH consultancy/advisory relationships with Amgen, Bristol Myers Squibb, Roche, MSD, Pfizer, Novartis, Pierre Fabre and has received research grants not related to this paper from Bristol Myers Squibb, Seerave and were paid to the institution.

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MBS has consultancy/advisory relationships with Pierre Fabre, MSD and Novartis.

KS has advisory relationships with Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, AbbVie and received honoraria from Novartis, MSD and Roche.

All remaining authors have declared no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.02.026.

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