European Journal of Cancer 220 (2025) 115356

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

First-line checkpoint inhibitor therapy in metastatic acral lentiginous melanoma compared to other types of cutaneous melanoma: A multicenter study from the prospective skin cancer registry ADOREG

Sören Reinhard [a], Jochen Sven Utikal [b,c], Anne Zaremba [d], Georg Lodde [d], Imke von Wasielewski [e], Kai Christian Klespe [e], Friedegund Meier [f], Sebastian Haferkamp [g], Katharina C. Kähler [h], Rudolf Herbst [i], Christoffer Gebhardt [j], Anca Sindrilaru [k], Edgar Dippel [l], Yenny Angela [m], Peter Mohr [n], Claudia Pfoehler [o], Andrea Forschner [p], Martin Kaatz [q], Beatrice Schell [r], Anja Gesierich [s], Carmen Loquai [t], Jessica C. Hassel [u], Jens Ulrich [v], Frank Meiss [w], Gaston Schley [x], Lucie M. Heinzerling [y], Michael Sachse [z], Julia Welzel [aa], Carsten Weishaupt [ab], Cord Sunderkötter [ac], Christiane Michl [ac], Harm-Henning Lindhof [ad], Alexander Kreuter [ae], Markus V. Heppt [af], Saskia Wenk [ag], Cornelia Mauch [ah], Carola Berking [af], Annekathrin Silvia Nedwed [ai], Ralf Gutzmer [m], Ulrike Leiter [p], Dirk Schadendorf [c], Selma Ugurel [c], Michael Weichenthal [h], Maximilian Haist [a], Maria Isabel Fleischer [a], Berenice Lang [a], Stephan Grabbe [a], Henner Stege [a,*]

[a] Department of Dermatology, University Medical Center Mainz, Mainz 55131, Germany
[b] Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany
[c] Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, Ruprecht-Karl University of Heidelberg, Mannheim, Germany
[d] Department of Dermatology, Venereology and Allergology, University Hospital Essen and German Cancer Consortium (DKTK), Partner Site Essen/Düsseldorf, Essen, Germany
[e] Skin Cancer Center Hannover, Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany
[f] Department of Dermatology, University Hospital Carl Gustav Carus, Dresden, Germany
[g] Department of Dermatology, University Hospital Regensburg, Regensburg, Germany
[h] Department of Dermatology, Skin Cancer Center, University Hospital Schleswig-Holstein - Campus Kiel, Kiel, Germany
[i] Department of Dermatology, HELIOS Hospital Erfurt, Erfurt, Germany
[j] Department of Dermatology and Venerology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[k] Department of Dermatology, University Hospital of Ulm, Ulm, Germany
[l] Department of Dermatology, Ludwigshafen City Hospital, Ludwigshafen, Germany
[m] Department of Dermatology, Muehlenkreiskliniken Minden and Ruhr University Bochum, Minden, Germany
[n] Department of Dermatology, Elbe Kliniken Buxtehude, Buxtehude, Germany
[o] Department of Dermatology, Saarland University Hospital and Saarland University Faculty of Medicine, Homburg, Germany
[p] Center for Dermatooncology, Department of Dermatology, Eberhard-Karls University of Tübingen, Tubingen, Germany
[q] Department of Dermatology, DRK Hospital Chemnitz-Rabenstein, Rabenstein, Germany
[r] Department of Dermatology, Wald-Klinikum Gera, Gera 07546, Germany
[s] Department of Dermatology, University Hospital Würzburg, Würzburg, Germany
[t] Department of Dermatology, Klinikum Bremen-Ost, Gesundheit Nord gGmbH, Bremen, Germany
[u] Heidelberg University, Medical Faculty Heidelberg, Department of Dermatology and National Center for Tumor Diseases (NCT), NCT Heidelberg, a partnership between DKFZ and University Hospital Heidelberg, Heidelberg, Germany
[v] Department of Dermatology and Allergy, Harzklinikum Dorothea Christiane Erxleben GmbH, Quedlinburg, Germany
[w] Department of Dermatology, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany
[x] Department of Dermatology, HELIOS Hospital Schwerin, Schwerin, Germany
[y] Department of Dermatology and Allergy, University Hospital, Ludwig-Maximilian Universität Munich, München, Germany
[z] Department of Dermatology, Hospital Bremerhaven Reinkenheide, Bremerhaven, Germany
[aa] Department of Dermatology, University Hospital Augsburg, Augsburg, Germany
[ab] Department of Dermatology, University Hospital of Muenster, Muenster, Germany
[ac] Department of Dermatology and Venereology, Martin Luther University Halle-Wittenberg, Halle, Germany
[ad] Department of Dermatology, Universitätsklinikum Düsseldorf, Dusseldorf, Germany

* Corresponding author.
E-mail address: Henner.Stege@unimedizin-mainz.de (H. Stege).

https://doi.org/10.1016/j.ejca.2025.115356
Received 24 February 2025; Accepted 5 March 2025
Available online 15 March 2025

[ae] Department of Dermatology, Venerology and Allergology, Helios St. Elisabeth Klinik Oberhausen, University Witten-Herdecke, Oberhausen, Germany
[af] Department of Dermatology, Uniklinikum Erlangen, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Comprehensive Cancer Center Erlangen-European Metropolitan Area of Nuremberg (CCC ER-EMN) and CCC Alliance WERA, Bavarian Cancer Research Center (BZKF), Erlangen 91052, Germany
[ag] Department of Dermatology, Medical Center Klinikum Darmstadt, Teaching Hospital Goethe-University Frankfurt, Darmstadt, Germany
[ah] Department of Dermatology, Ruhr-Universität Bochum, Bochum, Germany
[ai] Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), University Medical Center Mainz, Mainz, Germany

ARTICLE INFO

Keywords:
Melanoma
Checkpoint inhibition
Response

ABSTRACT

Background: Melanoma is the main cause of skin cancer-related death. Treatment with immune checkpoint inhibitors (CPI) has improved the prognosis in recent years. However, subtypes of melanoma differ in their response. Acral lentiginous melanoma (ALM) has a worse prognosis compared to cutaneous melanoma other than ALM (CM) and is therefore of particular relevance.
Aims: To evaluate the efficacy of CPI in first-line treatment of patients with advanced ALM compared CM.
Methods: Retrospective analysis of patients with metastatic ALM (n = 45) or CM (n = 328) who received first-line CPI therapy from the multicenter prospective skin cancer registry ADOREG. Study endpoints were best overall response (BOR), progression-free survival (PFS) and overall survival (OS).
Results: ALM patients had significantly higher rates of ulcerated tumors, loco regional metastases and fewer BRAF-mutated tumors compared to CM patients. Combined CPI was administered in 48.9 % ALM patients and 39.3 % of CM patients, while the remaining patients received PD-1 monotherapy. OS trended to be shorter in patients with ALM (18.1 vs. 43.8 months, p = 0.10) with no significant differences in PFS (7.0 vs. 11.5 months, p = 0.21). In patients with CM, median OS with combined CPI was not reached, whereas the median OS after PD-1 monotherapy was 37.8 months (p = 0.22). Conversely, in patients with ALM, OS with combined CPI was 17.8 months, compared to 26 months with PD-1 monotherapy (p = 0.15). There were no significant differences in BOR between patients with ALM or CM.
Conclusion: Analysis of this real-world cohort of patients with metastatic melanoma showed a trend towards poorer survival outcomes upon first-line treatment with CPI in ALM compared to cutaneous melanoma of other subtypes.

1. Introduction

Melanoma is an aggressive tumor that develops from pigment cells (melanocytes) in the skin [1]. Although less frequent than basal cell carcinoma and squamous cell carcinoma, melanoma is responsible for the majority of skin cancer-related deaths [2]. The most common histological variant defined by the WHO classification of cutaneous melanoma is the superficial spreading melanoma. Other common variants are nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma (ALM) [3].

The various subtypes of cutaneous melanoma can differ in their prognosis [3]. ALM occurs on the palms, soles and subungual and has a lower prevalence than cutaneous melanoma other than ALM (CM), particularly in Caucasian populations. It represents a significant proportion of cutaneous melanomas in people of color [4]. The prognosis for ALM tends to be poorer compared to CM. Possible reasons for this include later stages at diagnosis due to the less visible locations of ALM and potentially different biological tumor behavior as well as difficulty of primary surgery and safety margins at acral localisations [5]. ALM occurs in areas not typically exposed to UV radiation, suggesting different pathomechanisms compared to CM. The genetic and molecular profiles of ALM, including the prevalence of certain driver mutations, differs from those commonly seen in CM, with implications for the efficacy of targeted therapies and immunotherapies [5–8].

Checkpoint inhibitor (CPI) immunotherapies such as ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (both anti-PD-1) have emerged as promising treatment options for melanoma patients in recent years and have significantly improved the prognosis of metastatic melanoma [9–15]. For example, in a phase III randomized clinical trial (*CheckMate 067*), efficacy and safety outcomes of a combination therapy with ipilimumab + nivolumab (IpiNivo) were compared with monotherapies of either ipilimumab or nivolumab in untreated unresectable stage III or stage IV cutaneous melanoma patients. A report 10 years after the start of the study showed an impressive success of the IpiNivo combination therapy with a median OS of 71.9 months compared to 36.9 and 19.9 months in the nivolumab and ipilimumab groups, respectively [15]. Pembrolizumab is another PD-1-inhibitor (PD-1-i) that is used as a monotherapy for the treatment of inoperable or metastatic melanoma or in adjuvant therapy [16]. The majority of studies, however, investigated the effect of CPI in CM rather than ALM. ALM are often underrepresented in clinical studies, especially since the different tumor characteristics suggest that the efficacy of immunotherapies may differ between the subtypes.

In addition, despite their promising efficacy, immunotherapeutic drugs can be associated with serious side effects that require careful consideration of the therapeutic benefits versus the potential risks [17].

A critical comparison of the efficacy of combination therapy of ipilimumab and nivolumab or PD-1-inhibitor monotherapy in metastatic ALM versus CM is therefore of great clinical interest. Understanding the differences in response of these melanoma subtypes to CPI immunotherapies may lead to improved treatment strategies and more individualized patient care.

In this study, we analyzed a real-world cohort of patients from the multicenter prospective skin cancer registry ADOREG with metastatic ALM or CM who received first-line therapy with CPI, either combination therapy with IpiNivo, or PD-1-i monotherapy.

2. Methods

2.1. Study design and data source

This study analyses data from patients with acral lentiginous melanoma (ALM) or cutaneous melanoma other than ALM (CM), who received first-line therapy with PD-1-based CPI, either combined ipilimumab + nivolumab (IpiNivo) or PD-1 monotherapy (PD-1-i), for advanced, unresectable disease and were enrolled into the prospective multicenter skin cancer registry ADOREG. ADOREG is a nationwide prospective skin cancer registry of the German Dermatologic Cooperative Oncology Group (DeCOG), with data on more than 9000 patients from 67 study centers as of July 01, 2023. Patient data were provided for analysis in a pseudonymized form. The ADOREG was approved by the Medical Ethics Committee of the University Duisburg-Essen (14–5921-

BO), and written informed consent for participation was obtained from all patients.

2.2. Patient cohort and study endpoints

At the cut-off date (July 01, 2023), patient data from 485 patients with advanced, unresectable melanoma who received either CPI therapy or targeted therapy (TT) were provided from the ADOREG database. Of these, 415 patients received any line of CPI and had the diagnosis of CM (n = 370) or ALM (45). Only patients who received a first-line CPI regimen (328 patients with CM and 45 patients with ALM) were analyzed (Figure 1). First-line CPI regimens included combination therapy with ipilimumab + nivolumab or PD-1 inhibitor monotherapy with either nivolumab or pembrolizumab. Study endpoints were best overall response (BOR), progression-free survival (PFS) and overall survival (OS).

2.3. Statistical analysis

The classification of patients into combination therapy with ipilimumab + nivolumab versus PD-1 monotherapy was based on the first-line CPI regimen, regardless of whether other treatment modalities were used in subsequent lines of therapy. Patients not reaching a progression or survival event were censored at the last documented follow-up. Baseline characteristics were analyzed using descriptive statistics. Objective response rate (ORR) was defined as partial response (PR) or complete response (CR) versus stable disease (SD) or progressive disease (PD) according to standard RECIST criteria. Disease control was defined as SD, PR or CR versus PD. CPI treatment duration was calculated as the period during which patients received first-line treatment. Serious treatment-related adverse events (trAE) were defined as grade 3 or higher adverse events. The median follow-up duration was calculated using the reverse Kaplan–Meier method. OS was calculated from the start of first-line CPI treatment to the date of death or censoring. PFS was calculated as the time from when patients received first-line treatment to the first documented progression or censoring. Kaplan-Meier plots were used to calculate the probabilities of OS and PFS for the groups studied. Survival curves were compared using the log-rank test. Univariate and multivariate Cox regression analyses were used to assess the impact of specific clinical characteristics on OS and PFS. Hazard ratios (HR) with 95 % confidence intervals (CI) were used to quantify the effect on OS and PFS. In all cases, two-tailed p-values were calculated and considered significant at $p < 0.05$. SPSS (version 27, IBM, Ehningen, Germany) was used for all analyses.

3. Results

3.1. Demographic and clinical baseline data

A total of 328 patients with CM and 45 patients with ALM who received first-line CPI therapy were analyzed. Patients with CM were younger at the start of CPI with a median age of 67 years versus 73 years

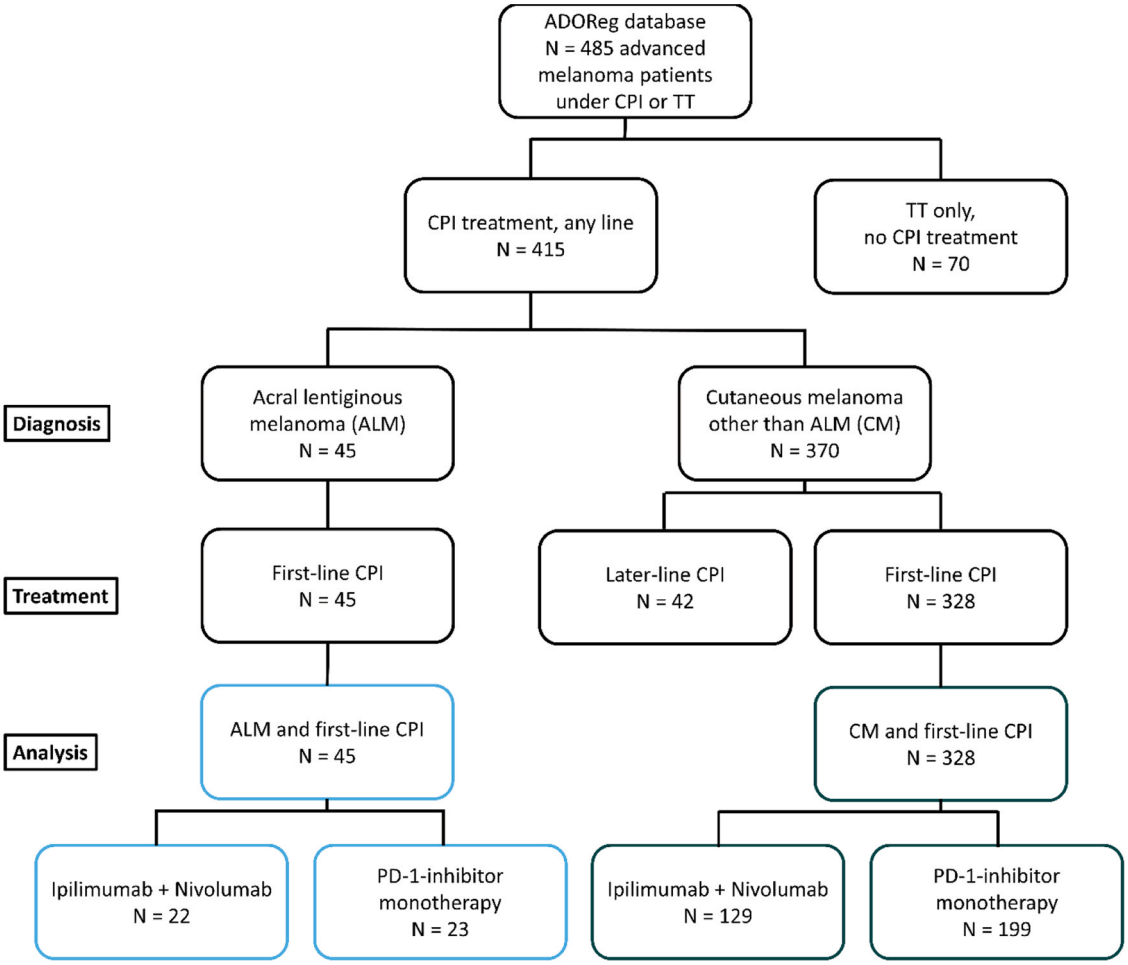

Fig. 1. Flow chart illustrating the selection criteria for this multicenter analysis with patient data from the prospective ADOREG skin cancer registry. We analyzed the outcome of patients with advanced acral lentiginous melanoma (ALM) or cutaneous melanoma other than ALM (CM) treated with first-line checkpoint inhibitors (CPI). TT: targeted therapy.

(p = 0.06) for ALM (Table 1A). The majority of patients in both groups were male (62.8 % with CM versus 68.9 % with ALM). More than half of the patients had an ECOG performance status of ≤ 1) at the start of CPI therapy with 55.8 % in patients with CM versus 68.9 % with ALM. At the time of diagnosis, the Breslow vertical tumor penetration depth in mm was similar in patients with CM (3.20 mm) versus ALM (3.85 mm, p = 0.68). However, the tumors were significantly more frequently ulcerated in patients with ALM (35.7 % CM versus 57.8 % ALM, p = 0.017). The prevalence of metastases at the time of diagnosis was analyzed by anatomic site. Significant differences were found for metastases in lymphatic tissue (40.9 % in CM versus 62.2 % in ALM, p = 0.007) and skin (23.8 % in CM versus 40.0 % in ALM, p = 0.001). No significant differences in the prevalence of bone, lung, liver and brain metastases or metastases at other sites were found. The mutation status (any mutation) was analyzed for BRAF, NRAS and CKIT genes. BRAF mutations were significantly more frequent in patients with CM (30.8 % for CM versus 8.9 % for ALM, p < 0.001), whereas there were no significant differences for NRAS, but a trend towards more CKIT mutations in patients with ALM (1.5 % in CM versus 8.9 % in ALM, p = 0.23). Less than half of the patients had normal baseline LDH levels (defined as LDH <245 U/l) at initiation of CPI therapy, with no significant differences between the two groups (41.5 % in CM versus 44.4 % in ALM, p = 0.80).

3.2. Treatment modalities, response and adverse events

First-line CPI regimens were divided into two groups. Patients received either a combination therapy with IpiNivo or monotherapy with a PD-1-inhibitor, either nivolumab or pembrolizumab (Table 1B). Patients with CM more frequently received PD-1-i monotherapy (60.7 % PD-1-i versus 39.3 % IpiNivo) than ALM patients, while treatment distribution was more balanced in patients with ALM (48.9 % IpiNivo versus 51.1 % PD-1-i). There were no significant differences in the best overall response (BOR) to the first-line CPI between the two groups. In each group, nearly half of the patients had progressive disease (PD) as their best response (45.7 % for CM versus 46.7 % for ALM). A complete response was observed in 11.3 % of patients with CM versus 15.6 % of patients with ALM. Objective response rates (ORR) were found to be similar in both groups (25.6 % in patients with CM versus 24.4 % in patients with ALM, p = 0.94). Stratified by first-line treatment, the ORR for CM was 20.9 % for IpiNivo versus 28.6 % for PD-1-i (p = 0.46) and 18.2 % for IpiNivo versus 30.4 % for PD-1-i in patients with ALM (p = 0.33). Disease control, defined as stable disease or better versus PD, was achieved by 47.9 % of patients with CM versus 43.2 % of patients with ALM (p = 0.59). The median duration of CPI treatment was slightly longer in patients with ALM (5.2 months for CM versus 7.0 months for ALM, p = 0.12).

3.3. Survival outcomes and follow-up

Overall survival and progression-free survival were initially evaluated stratified by diagnosis only, without factoring in the regiment of first-line treatment. The analysis was carried out using Kaplan-Meier plots and the groups were compared using the log-rank test (Fig. 2).

Patients with ALM showed a trend to shorter median OS compared to patients with CM, although the differences were not significant (43.8 months, 95 % CI: 19.1–68.6 months for CM versus 18.1 months, 95 % CI: 12.8–23.4 months for ALM, p = 0.10). Median PFS followed a similar trend (11.5 months, 95 % CI: 8.2–14.9 months for CM versus 7.0 months, 95 % CI: 3.4–10.6 months for ALM, p = 0.21). One year after initiating CPI treatment, 58.2 % of patients with CM were still alive, compared to 46.7 % of patients with ALM (Table 1C). As of the cut-off date (July 01, 2023), deaths were reported in 37.2 % of patients with CM and 44.4 % of patients with ALM. The median follow-up duration was significantly longer in patients with CM (30.5 months, 95 % CI: 25.1–35.9 months for CM versus 27.0 months, 95 % CI: 0.0–55.8 months for ALM, p = 0.046). OS and PFS were also analyzed stratified by first-

Table 1
Baseline patient characteristics, treatment modalities, response, adverse events and survival outcomes. Abbreviations: ALM: acral lentiginous melanoma; CI: confidence interval; CM: cutaneous melanoma other than ALM; CPI: checkpoint inhibitors; CR: complete response; ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; ORR: Objective response rate; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial response; SD: stable disease; trAE: treatment-related adverse events.

Clinicopathological Characteristics	CM	ALM	*p* Value
Number of patients	328	45	
A) Demographic and Clinical Baseline Data			
Age at CPI initiation, y (median, range)	67.0 (19–94)	73.0 (21–88)	0.06§
Sex			
Female	122 (37.2 %)	14 (31.1 %)	0.43$
Male	206 (62.8 %)	31 (68.9 %)	
Baseline ECOG performance status[a]			
Good performance status (ECOG ≤ 1)	183 (55.8 %)	31 (68.9 %)	0.21$
Poor performance status (ECOG > 1)	15 (4.6 %)	5 (11.1 %)	
High-risk features			
Breslow thickness (median, range) [mm]	3.20 (0.00–28.00)	3.85 (0.90–17.00)	0.68§
Ulceration[b]	117 (35.7 %)	26 (57.8 %)	**0.017$**
Anatomic sites of metastases			
Lymphatic tissue	134 (40.9 %)	28 (62.2 %)	**0.007$**
Skin	78 (23.8 %)	18 (40.0 %)	**0.001$**
Bone	79 (24.1 %)	6 (13.3 %)	0.11$
Lung	185 (56.4 %)	25 (55.6 %)	0.91$
Liver	110 (33.5 %)	12 (26.7 %)	0.36$
Brain	109 (33.2 %)	10 (22.2 %)	0.14$
Other	124 (37.8 %)	11 (24.4 %)	0.08$
Mutation status, any mutation[c]			
BRAF pos	101 (30.8 %)	4 (8.9 %)	**< 0.001&**
NRAS pos	52 (15.9 %)	7 (15.6 %)	0.17$
CKIT pos	5 (1.5 %)	4 (8.9 %)	0.23&
Baseline LDH levels[d]			
Normal (<245 U/l)	136 (41.5 %)	20 (44.4 %)	0.80$
Elevated (≥245 U/l)	119 (36.3 %)	16 (35.6 %)	
B) Treatment, Response and Adverse Events			
CPI regimen first-line			
Ipilimumab + Nivolumab	129 (39.3 %)	22 (48.9 %)	0.22$
PD−1-inhibitor monotherapy[e]	199 (60.7 %)	23 (51.1 %)	
Best overall response (BOR)[f]			
Progressive disease, PD	150 (45.7 %)	21 (46.7 %)	
Stable disease, SD	54 (16.5 %)	5 (11.1 %)	
Partial response, PR	47 (14.3 %)	4 (8.9 %)	0.54$
Complete response, CR	37 (11.3 %)	7 (15.6 %)	
ORR vs SD/PD	84 (25.6 %)	11 (24.4 %)	0.94$
Disease control vs PD	138 (47.9 %)	16 (43.2 %)	0.59$
Median CPI treatment duration, months (range)	5.2 (0–76.0)	7.0 (0–46.0)	0.12§
Treatment-related adverse events (trAE)[g]			
Any trAE	159 (48.5 %)	12 (26.7 %)	**< 0.001$**
Serious trAE	88 (26.8 %)	5 (11.1 %)	**0.022$**
Discontinuation due to trAE	80 (24.4 %)	3 (6.7 %)	**0.007&**
C) Survival Outcomes and Follow-Up			
Median OS, months (95 % CI)	43.8 (19.1–68.6)	18.1 (12.8–23.4)	0.10#
1-year OS	191 (58.2 %)	21 (46.7 %)	0.14$
Deceased	122 (37.2 %)	20 (44.4 %)	0.35$
Median PFS, months (95 % CI)	11.5 (8.2–14.9)	7.0 (3.4–10.6)	0.21#
Median follow-up duration, months (95 % CI)	30.5 (25.1–35.9)	27.0 (0.0–55.8)	**0.046#**

[a] ECOG performance status was unknown for 139 patients;
[b] ulceration status was unknown for 98 patients;
[c] BRAF, NRAS and CKIT mutation status was unknown for 67, 185 and 255 patients, respectively;
[d] Baseline LDH levels were not reported for 60 patients;

[e] Patients on PD-1-inhibitor monotherapy received either nivolumab or pembrolizumab;
[f] Best overall response was not evaluated for 48 patients;
[g] Treatment-related adverse events were not evaluated for 151 patients; [§] Mann-Whitney U Test; [$] Chi-square test for independence, statistics apply for patients with documented categorial variable; [&] Fisher's exact test, statistics apply for patients with documented categorial variable; [#] Log Rank test

line CPI regimen (Figure 3).

When only patients with first-line combination therapy of IpiNivo were compared, there was a significant advantage in OS for patients with CM versus ALM (not reached for CM versus 17.8 months, 95 % CI: 5.0–30.5 months for ALM, p = 0.018). The same trend in the IpiNivo group was also observed for PFS (13.0 months, 95 % CI: 0–28.8 months for CM versus 6.3 months, 95 % CI: 1.2–11.4 months for ALM, p = 0.10). In contrast, when analyzing patients with PD-1-i monotherapy as the first CPI regimen, there were no significant differences in either OS (37.8 months, 95 % CI 24.2–51.4 months for CM versus 26.0 months, 95 % CI: 0–78.5 months for ALM, p = 0.83) or PFS (10.3 months, 6.4–14.3 months for CM versus 7.0 months, 95 % CI: 4.1–9.9 months for ALM, p = 0.79). In patients with ALM, overall survival trended to be shorter with first-line IpiNivo combination therapy than with PD-1-i monotherapy (17.8 months, 95 % CI: 5.0–30.5 months for IpiNivo versus 26.0 months, 95 % CI: 0–78.5 months for PD-1-i, p = 0.15). Conversely, in patients with CM, overall survival trended to be longer under IpiNivo combination therapy (not reached for IpiNivo versus 37.8 months, 95 % CI: 24.2–51.4 months for PD-1-i, p = 0.22), even though the differences were not statistically significant (Figure S1). When comparing the demographic and clinical baseline data, response rates and adverse events of patients with ALM receiving first-line IpiNivo (n = 22) with those of patients with ALM receiving PD-1-i monotherapy (n = 23), there were no significant differences (Table S1). Only a trend towards significant differences in sex distribution was observed between ALM patients treated with IpiNivo and those treated with PD-1-i (18.2 % female for ALM+IpiNivo vs 43.5 % for ALM+PD-1-i, p = 0.07). It is noteworthy that the median follow-up time in the ALM group with PD-1-i was non-significantly longer then observed in the IpiNivo therapy group (15.0 months, 95 % CI: 10.4–19.6 months for ALM+IpiNivo vs. 42.0 months, 95 % CI: 13.9–70.1 months for ALM+PD-1-i, p = 0.11).

3.4. Predictors of overall survival and progression-free survival

Univariate and multivariate Cox regression analysis was used to identify potential predictors of OS and PFS irrespective of the diagnosis of ALM or CM. In univariate Cox regression analysis, the following variables were found to have a significant influence on OS (Table S2): Age at first-line CPI, CPI duration, baseline ECOG status (poor vs good), baseline LDH (lower than 245 U/I versus ≥ 245 U/l) and disease control (PD vs CR/PR/SD). No significant influence on OS was found for sex, tumor ulceration status, Breslow thickness, mutation status of BRAF, NRAS or CKIT, and first-line CPI treatment regimen. Variables that showed a potentially significant influence on OS in univariate Cox regression analysis were analyzed using multivariate Cox regression analysis (Fig. 4). Significant effects on OS were found for the following variables: Age at first-line CPI (HR: 1.015, 95 % CI: 1.001–1.029, per 1 year increase, p = 0.031), CPI duration (HR: 0.921, 95 % CI 0.898–0.945, per 1 month increase, p < 0.001), baseline ECOG status (HR: 2.603, 95 % CI: 1.393–4.866, poor vs good (≤ 1), p = 0.003) and disease control (HR: 0.214, 95 % CI: 0.142 – 0.322, CR/PR/SD vs PD, p < 0.001).

The following variables were found to have a significant influence on PFS in univariate Cox regression analysis (Table S3): Sex, CPI duration, baseline ECOG status (poor vs good), baseline LDH (lower than 245 U/I versus ≥ 245 U/l) and disease control (PD vs CR/PR/SD). In multivariate Cox regression analysis, significant effects on PFS were found for the following variables (Figure 5): CPI duration (HR: 0.948, 95 % CI: 0.930–0.967, per 1 month increase, p < 0.001), baseline ECOG status (HR: 1.989, 95 % CI: 1.079 – 3.666, poor vs good (≤ 1), p = 0.028), baseline LDH status (HR: 0.546, 95 % CI: 0.387 – 0.771, lower than 245 U/I versus ≥ 245 U/l, p = 0.001) and disease control (HR: 0.061, 95 % CI: 0.040 – 0.093, CR/PR/SD vs PD, p < 0.001).

4. Discussion

In this study, we analyzed real-world efficacy data in a cohort of patients with metastatic ALM or other types of cutaneous melanoma who received first-line CPI therapy. We categorized the treatment modalities into two groups, combination therapy with IpiNivo or PD-1-i monotherapy.

A similar analysis of a Dutch melanoma registry by van Not *et al.* published in 2022 provides a good basis for comparison with our results [18]. Consistent with the literature [4,5,18], the ALM population in our analysis was older than the CM population, suggesting either later development or delayed diagnosis due to less apparent localization. According to the literature and in line with the theory of later diagnosis of ALM, a greater Breslow tumor thickness and a higher proportion of ulcerations at the time of diagnosis were to be expected in this cohort [5,6,18,19]. Although in our analysis vertical tumor thickness was only

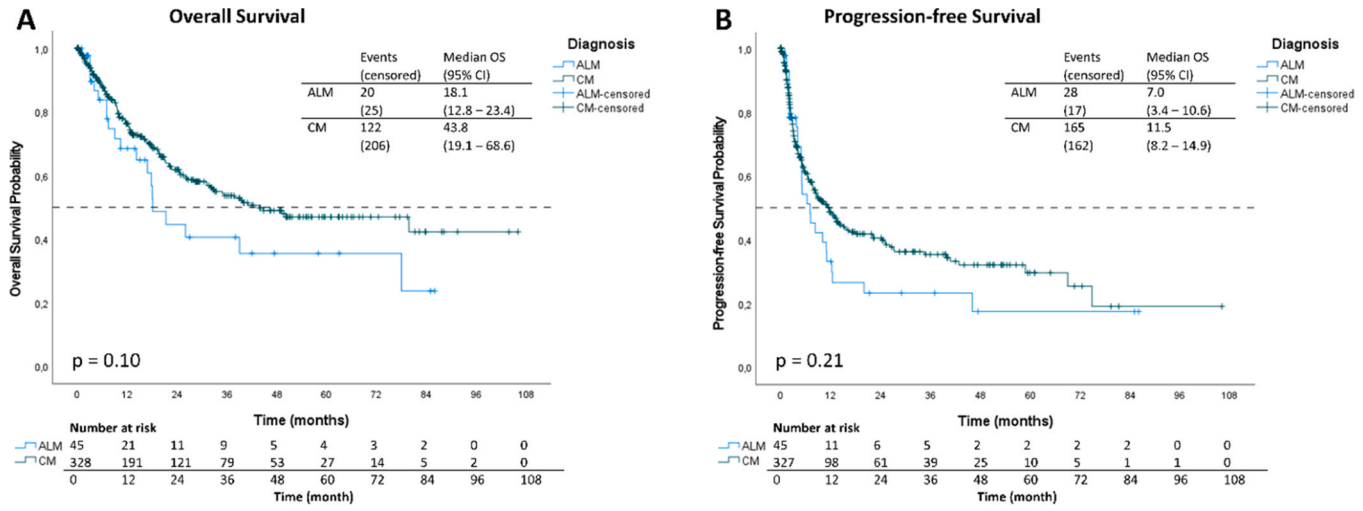

Fig. 2. (A) Overall survival (OS) and (B) progression-free survival (PFS) stratified by diagnosis. Patients with acral lentiginous melanoma (ALM) had a shorter PFS and OS compared to patients with cutaneous melanoma other than ALM (CM).

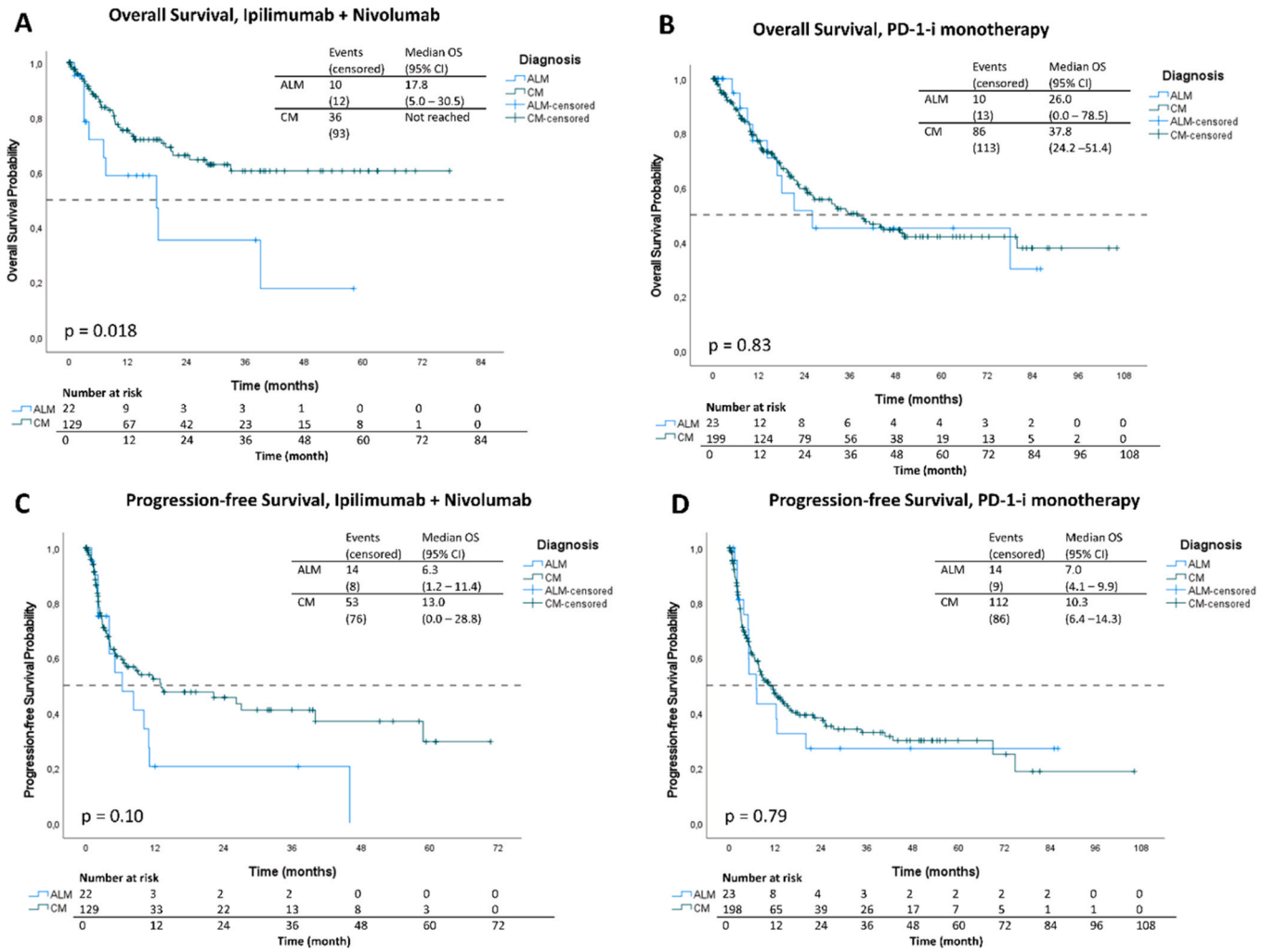

Fig. 3. Overall survival (OS) with (A) ipilimumab + nivolumab (IpiNivo) combination therapy or (B) PD-1-inhibitor monotherapy (PD-1-i) and progression-free survival (PFS) with (C) IpiNivo combination therapy or (D) PD-1-i monotherapy stratified by diagnosis. The differences in overall survival and progression-free survival between patients with cutaneous melanoma other than ALM (CM) and acral lentiginous melanoma (ALM) trended to be greater in patients receiving ipilimumab + nivolumab than in patients receiving PD-1-i monotherapy.

slightly and not significantly increased in the ALM cohort, the proportion of ulcerated tumors was significantly higher in patients with ALM (57.8 %) than in patients with CM (35.7 %). Different distribution patterns of melanoma metastases between ALM and CM have already been reported in literature, with bone metastases occurring more frequently in ALM patients and brain metastases less frequently [20]. In our cohort, we found more brain metastases in numbers than in CM patients, but significantly more metastases in lymphatic tissue and skin in ALM patients. This supports the assumption that the two subgroups may differ in the distribution patterns of the metastases. There is also evidence in the literature suggesting that CM is associated with more BRAF driver mutations than ALM, but fewer CKIT mutations [5,18]. In agreement with this, we found significantly fewer BRAF mutations in the ALM cohort and a trend towards more CKI mutations. NRAS mutation status was similar in both groups. Since ultraviolet (UV) radiation does not appear to play a significant pathogenetic role in ALM, an overall lower tumor mutation burden (TMB) is expected in ALM compared to CM [5,7,8]. In melanoma, as well as in various other types of cancer, it has been shown that tumors with a higher mutational burden are more likely to respond to immunotherapy. This effect has been demonstrated for anti-CTLA-4 treatments such as ipilimumab, PD-1/PD-L-1 inhibitors and combination therapy of those [21–23]. Differences in TMB, with an overall lower mutational burden in ALM versus CM, may provide an explanation for a poorer response to immunotherapy and the resulting reduction in OS and PFS in the ALM population.

As we categorized the first-line CPI regimens in our analysis into combination therapy with ipilimumab + nivolumab versus PD-1 inhibitor monotherapy, it is important to note that the ratio was more evenly balanced in ALM with 48.9 % IpiNivo versus 51.1 % PD-1-i monotherapy than in CM (39.3 % IpiNivo versus 60.7 % PD-1-i). This is in contrast to the Dutch cohort study by van Not *et al.*, in which 79.5 % of ALM patients and 71.2 % of CM patients received PD-1-i monotherapy (while only 20.5 % and 28.8 % of ALM and CM patients, respectively, received combination therapy) [18]. In clinical trials, ORRs in patients with stage III or IV CM treated with IpiNivo combination therapy or nivolumab monotherapy, defined as partial or complete response, were reported to be up to 58 % and 45 %, respectively [14]. The Dutch cohort study reported first-line objective response rates of 34 % for ALM versus 54 % for CM in the PD-1-i monotherapy cohort and 33 % for ALM versus 53 % for CM in the IpiNivo combination therapy cohort [18]. A multicenter study by Nakamura *et al.* of 193 Japanese patients with ALM receiving any-line PD-1-i monotherapy reported an ORR of 16.6 % [24]. A large international cohort study of 325 patients with ALM receiving any-line CPI therapy by Bhave et al. reported ORRs of 43 % with combination therapy of ipilimumab plus a PD-1 inhibitor and 26 % with PD-1-i monotherapy [25]. Our analysis showed ORRs of 25.6 % in

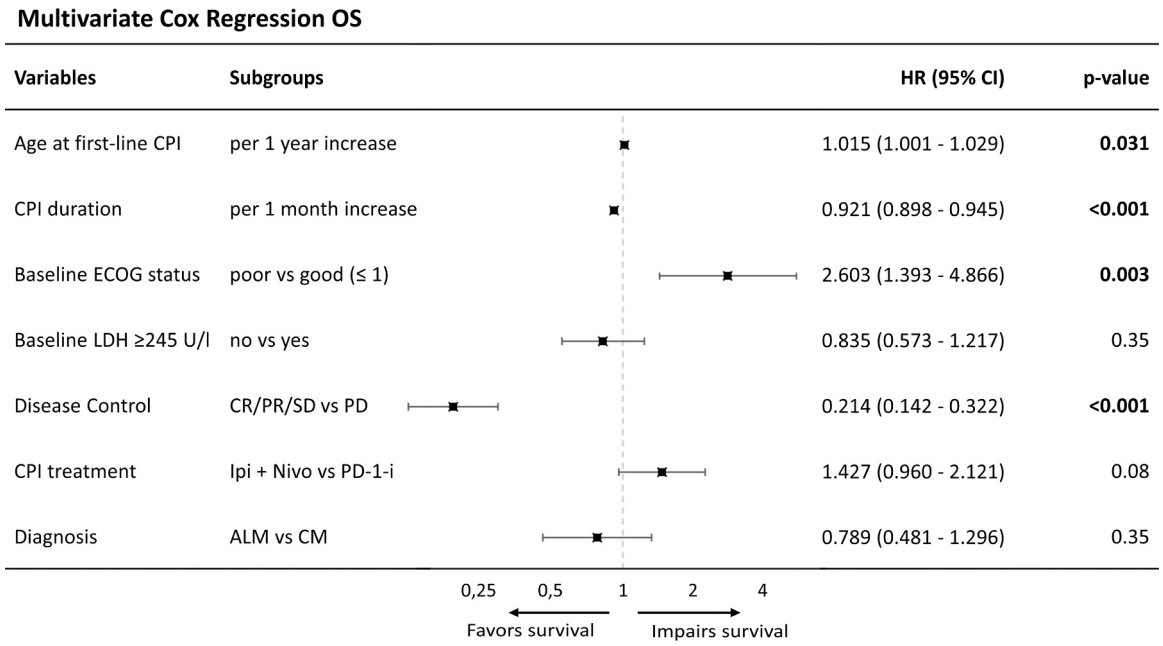

Fig. 4. Forest plot of the multivariate Cox regression analysis of potential predictors of overall survival (OS). Abbreviations: ALM: acral lentiginous melanoma; CI: confidence interval; CM: cutaneous melanoma other than ALM; CPI: checkpoint inhibitors; CR: complete response; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; LDH: lactate dehydrogenase; PD: progressive disease; PR: partial response; SD: stable disease. The box for age at first-line CPI overlaps with the line for HR = 1 only due to the way of presentation.

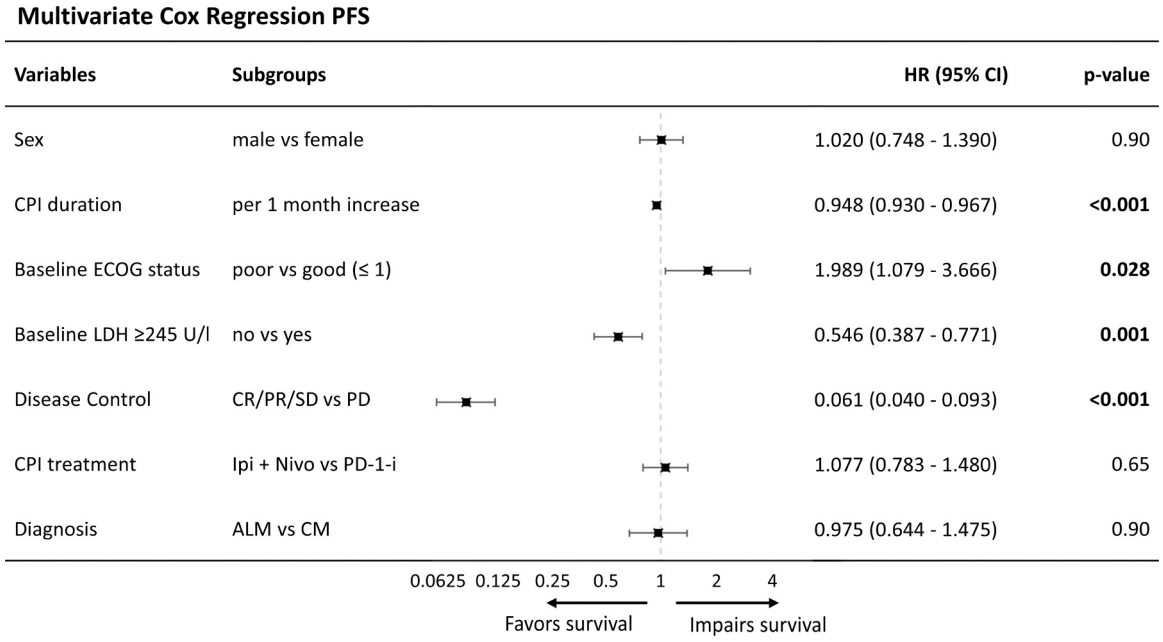

Fig. 5. Forest plot of the multivariate Cox regression analysis of potential predictors of progression-free survival (PFS). Abbreviations: ALM: acral lentiginous melanoma; CI: confidence interval; CM: cutaneous melanoma other than ALM; CPI: checkpoint inhibitors; CR: complete response; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; LDH: lactate dehydrogenase; PD: progressive disease; PR: partial response; SD: stable disease.

patients with CM (20.9 % for IpiNivo versus 28.6 % for PD-1-i monotherapy) and 24.4 % in patients with ALM (18.2 % for IpiNivo versus 30.4 % for PD-1-i monotherapy), and thus in between the ORRs found in the Japanese and Dutch cohort studies. The ORR in our analysis corresponds well with the ORR of 32 % in patients with ALM in a US cohort study by Shoushtari *et al.* who received nivolumab or pembrolizumab, although in most cases with prior systemic treatment [26]. Disease control rates (SD, PR or CR vs PD) were slightly higher in CM (47.9 %) than in ALM (43.2 %) in our analysis.

In our analysis of OS, which was stratified by diagnosis only, regardless of first-line IpiNivo or PD-1-i treatment regimen, patients with CM achieved an OS of 43.8 months versus 18.1 months for patients with ALM. The OS in our ALM cohort corresponds very well with the results of the Japanese cohort study by Nakamura *et al.,* which also reported an OS of 18.1 months [24]. Stratified by first-line treatment modality, we found an OS in patients with ALM of 17.8 months with IpiNivo combination therapy and 26.0 months with PD-1-i monotherapy. In patients with CM, median survival was not reached with

IpiNivo and was 37.8 months with PD-1-i monotherapy. The US cohort study by Shoushtari *et al.*, which included mostly pre-treated patients, reported a slightly longer median OS for ALM patients of 31.7 months receiving PD-1-i monotherapy [26]. Similar to our results, Nathan *et al.* (*CheckMate 172*) reported an OS of 25.8 months (95 % CI: 15.1–30.6) at a minimum follow-up of 18 months in patients with ALM receiving nivolumab after ipilimumab pre-treatment [27]. In the Dutch cohort study by van Not *et al.*, patients with ALM treated with PD-1-i monotherapy had a median OS of 18.6 months, compared to 32.3 months for patients with CM. For patients receiving combination therapy with IpiNivo, van Not *et al.* reported a median OS of 7.6 months for ALM patients compared to 30.9 months for CM patients [18]. The international cohort study of ALM patients receiving any-line CPI therapy by Bhave *et al.* reported a median OS of 1.9 years (≈ 23 months) for PD-1-i monotherapy and 1.3 years (≈ 16 months) for PD-1-i/ipilimumab combination therapy [25]. Thus, the cohort studies by van Not *et al.* and Bhave *et al.* as well as our study report a longer OS in patients with ALM receiving PD-1-i monotherapy compared to a combination therapy with ipilimumab, although the two groups were not directly compared by van Not *et al.* or the differences were not significant (Bhave *et al.* and our analysis). An important limitation of our study is the low number of patients in the ALM group when considering the treatment modalities separately ($n = 22$ for ALM+IpiNivo and $n = 23$ for ALM+PD-1-i). Additionally, our analysis revealed a trend towards a longer median follow-up time in the ALM+PD-1-i group (42.0 months) compared to the ALM+IpiNivo group (15.0 months, $p = 0.11$), which makes a comparison of survival times less conclusive. A direct comparison of patients treated with PD-1-i monotherapy and IpiNivo combination therapy may also be affected by selection bias, as in clinical practice dual CPI therapy may be preferred over monotherapy in patients with advanced disease and poorer prognosis. Nevertheless, in patients with CM, we found a survival benefit in the IpiNivo combination therapy group compared to PD-1-i monotherapy, while the Dutch cohort study found a slightly shorter OS with IpiNivo therapy. One possible explanation could be that in our cohort 39.3 % of patients with CM received IpiNivo combination therapy (compared to 28.8 % in the Dutch study [18]) and therefore more patients with an initially better prognosis may have received combination therapy already as a first-line therapy in Germany. Of note, the OS in CM patients in our real-world analysis are in good agreement with the phase III *CheckMate 067* study, which found an OS of 71.9 months with IpiNivo combination therapy at a minimum follow-up of 10 years (in our analysis: not reached at a median follow-up of 30.5 months) and 36.9 months (37.8 months in our analysis) with PD-1-i monotherapy [15].

In our analysis, the PFS of patients with CM treated with PD-1-i monotherapy was similar to the PFS reported by van Not *et al.* (10.3 months in our study versus 10.1 months in the Dutch study) [18]. However, patients with ALM in our study had a longer PFS compared to the PFS reported in the Dutch cohort study. Specifically, ALM patients treated with IpiNivo combination therapy and PD-1-i monotherapy showed a PFS of 6.3 months and 7.0 months, respectively, compared to 3.0 months and 3.1 months reported by van Not *et al.* [18] Given that almost half of the patients in our ALM population were treated with first-line IpiNivo, this also suggests that combination therapy was given at earlier stages of the disease, which may have resulted in a shorter PFS compared to PD-1-i due to selection bias, but a longer PFS overall. However, it should be noted that our cohort of patients with ALM treated with PD-1-i monotherapy included significantly fewer patients - 23 patients versus 70 patients in the Dutch study [18] - which could potentially lead to more inaccurate results.

Consistent with literature, our multivariate Cox regression analysis showed significant effects on OS for age at first-line CPI and baseline ECOG status [18]. However, in contrast to van Not *et al.* we found no significant influence of baseline LDH levels or BRAF mutations [18]. As expected, we also found a negative impact on OS with shorter CPI duration and significantly prolonged OS if disease control was achieved. Similar to van Not *et al.*, our multivariate Cox regression showed a significant influence of baseline LDH levels on PFS [18]. We also found a negative effect on PFS with shorter CPI duration while disease control led to a significantly prolonged PFS.

Limitations of our study include all the limitations associated with cohort studies, such as 1) inconsistencies, missing data and registry errors. In our case, safety data were unavailable for many patients in the database, which limits the interpretation of treatment-related adverse events. 2) selection bias as patients are not randomly assigned to treatment groups, which can potentially be very important in our study as we are comparing patients with either CPI combination therapy or monotherapy. Clinicians may be more likely to consider combination therapy in patients with advanced disease and poorer prognosis. 3) Confounding variables that often cannot be fully accounted for in cohort studies 4) Time bias, for example due to changes in treatment practice over time. While the first patients in our analysis received CPI therapy in 2013, our analysis also includes patients who started therapy shortly before the cut-off date (July 01, 2023). 5) Retrospective cohort studies are limited in their ability to establish causality. 6) Generalizability: The results of a specific registry, such as the German skin cancer registry ADOREG, may not be generalizable to other populations due to differences in healthcare systems, patient demographics and treatment availability. ADOREG does not provide information on the ethnicity of patients, which could be critical as it is known that some ethnic groups, such as people of color, are more affected by ALM than Caucasians. 7) Due to the low prevalence of ALM and the corresponding small sample size in our study population, we combined the PD-1 inhibitor treatments, pembrolizumab and nivolumab, into a single analysis group. Overall, we analyzed only 45 patients with ALM undergoing first-line CPI therapy, which is why comparisons between the treatment regimens IpiNivo and PD-1-i monotherapy, particularly the comparison between ALM+IpiNivo and ALM+PD-1-i, should be interpreted with caution.

Strengths of our study include the extensive database and nationwide representation through access to ADOREG, the largest nationwide prospective clinical registry of skin cancer in Germany with data on more than 9000 patients from 67 study centers. We analyzed the predictors of OS and PFS, which contributes to a deeper understanding of the factors that influence patient outcomes. This may help to identify potential prognostic indicators and develop personalized treatment strategies.

5. Conclusion

Analysis of this real-world cohort of patients from the German prospective multicenter skin cancer registry ADOREG with metastatic melanoma treated with first-line CPI showed shorter OS and PFS in patients with ALM compared to CM. This discrepancy highlights the need for improved therapeutic approaches that address the specific biological and clinical features of ALM. Consistent with randomized controlled clinical trials [15], we found that first-line combination therapy with IpiNivo had a positive impact on survival in patients with CM compared to PD-1-i monotherapy, which has not previously been shown in similar cohort studies [18].

First-line treatment with IpiNivo was associated with shorter, but not significant, OS compared to PD-1-i monotherapy in patients with ALM, although this result should be interpreted with caution due to the small number of patients with ALM and possible selection bias. Multivariate Cox regression analysis revealed that age at first-line CPI, duration of CPI, occurrence of treatment-related adverse events, baseline ECOG status and disease control had a significant impact on OS.

Funding

none

CRediT authorship contribution statement

Wenk Saskia: Data curation, Writing – review & editing. **Dippel Edgar:** Data curation, Writing – review & editing. **Mauch Cornelia:** Data curation, Writing – review & editing. **Angela Yenny:** Data curation, Writing – review & editing. **Mohr Peter:** Data curation, Writing – review & editing. **Pfoehler Claudia:** Data curation, Writing – review & editing. **Kähler Katharina C:** Data curation, Writing – review & editing. **Michl Christiane:** Data curation, Writing – review & editing. **Lindhof Harm-Henning:** Data curation, Writing – review & editing. **Herbst Rudolf:** Data curation, Writing – review & editing. **Kreuter Alexander:** Data curation, Writing – review & editing. **Gebhardt Christoffer:** Conceptualization, Data curation, Writing – review & editing. **Heppt Markus V:** Data curation, Writing – review & editing. **Sindrilaru Anca:** Data curation, Writing – review & editing. **Nedwed Annekathrin Silvia:** Data curation, Writing – review & editing. **Forschner Andrea:** Data curation, Writing – review & editing. **Gutzmer Ralf:** Data curation, Writing – review & editing. **Kaatz Martin:** Data curation, Writing – review & editing. **Leiter Ulrike:** Data curation, Writing – review & editing. **Schell Beatrice:** Data curation, Writing – review & editing. **Schadendorf Dirk:** Data curation, Writing – review & editing. **Berking Carola:** Data curation, Writing – review & editing. **Klespe Kai Christian:** Data curation, Writing – review & editing. **Lang Berenice:** Data curation, Writing – review & editing. **Meiss Frank:** Data curation, Writing – review & editing. **Utikal Jochen Sven:** Data curation, Writing – review & editing. **Schley Gaston:** Data curation, Writing – review & editing. **Zaremba Anne:** Data curation, Writing – review & editing. **Lodde Georg:** Data curation, Writing – review & editing. **Heinzerling Lucie M:** Data curation, Writing – review & editing. **von Wasielewski Imke:** Data curation, Writing – review & editing. **Gesierich Anja:** Data curation, Writing – review & editing. **Ugurel Selma:** Data curation, Writing – review & editing. **Loquai Carmen:** Data curation, Writing – review & editing. **Weichenthal Michael:** Data curation, Writing – review & editing. **Hassel Jessica C:** Data curation, Writing – review & editing. **Haist Maximilian:** Conceptualization, Data curation, Writing – review & editing. **Stege Henner:** Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. **Fleischer Maria Isabel:** Data curation, Writing – review & editing. **Ulrich Jens:** Data curation, Writing – review & editing. **Reinhard Sören:** Conceptualization, Data curation, Methodology, Project administration, Visualization, Writing – original draft. **Sachse Michael:** Data curation, Writing – review & editing. **Welzel Julia:** Data curation, Writing – review & editing. **Weishaupt Carsten:** Data curation, Writing – review & editing. **Meier Friedegund:** Data curation, Writing – review & editing. **Haferkamp Sebastian:** Data curation, Writing – review & editing. **Sunderkötter Cord:** Data curation, Writing – review & editing. **Grabbe Stephan:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

SR, JSU, AZ, GL, IvW, KCK, FM, SH, RH, CG, AS, ED, YA, PM, AF, MK, BS, AG, GS, LMH, MS, CW, CS, CM, HHL, AK, SW, CMau, ASN, RG, UL, DS, MW, MH, MIF, BL, SG, HS declare no conflict of interest

JCH received honoraria from BMS, Delcath, Immunocore, MSD, Novartis, Pierre Fabre, Sanofi and Sunpharma for talks and from Sunpharma for advisory board participation, travel support from BMS, Iovance and Sunpharma outside the submitted work.

JU is on the advisory board or has received honoraria and travel support from Amgen, Bristol Myers Squibb, GSK, Immunocore, LeoPharma, Merck Sharp and Dohme, Novartis, Pierre Fabre, Rheacell, Roche and Sanofi outside the submitted work.

MVH received honoraria from MSD, BMS, Roche, Novartis, Sun Pharma, Sanofi, Almirall, Biofrontera, Galderma, Immunocore, InfectoPharm.

CB received speaker's fees and/or honoraria for consultancy (advisory board) from BMS, Delcath, InflaRx, Immunocore, MSD, Novartis, Pierre Fabre, Regeneron, and Sanofi, outside the submitted work.

FM served as consultant and/or has received honoraria from Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, Sanofi Genzyme, Sun Pharma and travel support from Novartis, Sun Pharma, Roche, Pierre Fabre and Merck Sharp & Dohme, outside the submitted work.

KCK served as consultant and/or has received honoraria from Bristol-Myers Squibb, Kyowa Kirin, Novartis, Recordati Rare Diseases, Vetter Pharma, Pierre Fabre, Sun Pharma

SU declares research support from Bristol Myers Squibb and Merck Serono; speakers and advisory board honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, and Novartis; and meeting and travel support from Almirall, Bristol-Myers Squibb, IGEA Clinical Biophysics, Merck Sharp & Dohme, Novartis, Pierre Fabre, and Sun Pharma; outside the submitted work.

CL declares speakers and advisory board honoraria from BMS, MSD, Merck, Roche, Immunocore, Novartis, Pierre Fabre, Sanofi, Sun Pharma, Almirall Hermal, Kyowa Kirin, Biontech, Boehriner Ingelheim, Merck, Roche, Almirall Hermal, Kyowa Kirin, Biontech, Lilly and travel support from BMS, MSD, Merck, Roche, Immunocore, Novartis, Pierre Fabre, Sanofi, Sun Pharma, Almirall Hermal, Kyowa Kirin, Biontech, Pfizer outside the submitted work.

CP declares speakers, advisory board honoraria and travel support from MSD, BMS, Roche, Novartis, AbbVie, Sanofi, Merck Serono, Sun Pharma, Pierre Fabre, LEO, AMGEN and Allery Therapeutics outside the submitted work.

JW received speaker fees and travel expenses support from BMS, MSD, Almirall, Abbvie, Sanofi, Leo Pharma, Novartis, Janssen, Boehringer Ingelheim and Lilly.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115356.

References

[1] Schadendorf D, van Akkooi ACJ, Berking C, et al. Melanoma. 2018/09/15/ Lancet 2018;392(10151):971–84. https://doi.org/10.1016/S0140-6736(18)31559-9.
[2] Leiter U, Keim U, Garbe C. Epidemiology of Skin Cancer: Update 2019. Adv Exp Med Biol 2020;1268:123–39. https://doi.org/10.1007/978-3-030-46227-7_6.
[3] Tímár J, Ladányi A. Molecular pathology of skin melanoma: epidemiology, differential diagnostics, prognosis and therapy prediction. Int J Mol Sci May 11 2022;23(10). https://doi.org/10.3390/ijms23105384.
[4] Bradford PT, Goldstein AM, McMaster ML, Tucker MA. Acral Lentiginous Melanoma: Incidence and Survival Patterns in the United States, 1986-2005. Arch Dermatol 2009;145(4):427–34. https://doi.org/10.1001/archdermatol.2008.609.
[5] Häfliger EM, Ramelyte E, Mangana J, et al. Metastatic acral lentiginous melanoma in a tertiary referral center in Switzerland: a systematic analysis. Melanoma Res Oct 2018;28(5):442–50. https://doi.org/10.1097/cmr.0000000000000465.
[6] Kuchelmeister C, Schaumburg-Lever G, Garbe C. Acral cutaneous melanoma in caucasians: clinical features, histopathology and prognosis in 112 patients. Br J Dermatol 2000;143(2):275–80. https://doi.org/10.1046/j.1365-2133.2000.03651.x.
[7] Si L, Kong Y, Xu X, et al. Prevalence of BRAF V600E mutation in Chinese melanoma patients: large scale analysis of BRAF and NRAS mutations in a 432-case cohort. Eur J Cancer Jan 2012;48(1):94–100. https://doi.org/10.1016/j.ejca.2011.06.056.
[8] Zhou QM, Li W, Zhang X, et al. The mutation profiles of common oncogenes involved in melanoma in southern China. J Invest Dermatol Jul 2012;132(7):1935–7. https://doi.org/10.1038/jid.2012.64.
[9] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med Jul 2 2015;373(1):23–34. https://doi.org/10.1056/NEJMoa1504030.
[10] Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med Oct 5 2017;377(14):1345–56. https://doi.org/10.1056/NEJMoa1709684.
[11] Tawbi HA, Forsyth PA, Algazi A, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med Aug 23 2018;379(8):722–30. https://doi.org/10.1056/NEJMoa1805453.

[12] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med Oct 17 2019; 381(16):1535–46. https://doi.org/10.1056/NEJMoa1910836.
[13] Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. Lancet Oncol Jun 2021; 22(6):836–47. https://doi.org/10.1016/s1470-2045(21)00097-8.
[14] Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol Jan 10 2022;40(2):127–37. https://doi.org/10.1200/jco.21.02229.
[15] Wolchok JD, Chiarion-Sileni V, Rutkowski P, et al. Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma. N Engl J Med Sep 15 2024. https://doi.org/10.1056/NEJMoa2407417.
[16] Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol Sep 2019;20(9): 1239–51. https://doi.org/10.1016/s1470-2045(19)30388-2.
[17] Darnell EP, Mooradian MJ, Baruch EN, Yilmaz M, Reynolds KL. Immune-Related Adverse Events (irAEs): Diagnosis, Management, and Clinical Pearls. Curr Oncol Rep Mar 21 2020;22(4):39. https://doi.org/10.1007/s11912-020-0897-9.
[18] van Not OJ, de Meza MM, van den Eertwegh AJM, et al. Response to immune checkpoint inhibitors in acral melanoma: A nationwide cohort study. /05/01/ 2022 Eur J Cancer 2022;167:70–80. https://doi.org/10.1016/j.ejca.2022.02.026.
[19] Teramoto Y, Keim U, Gesierich A, et al. Acral lentiginous melanoma: a skin cancer with unfavourable prognostic features. A study of the German central malignant melanoma registry (CMMR) in 2050 patients. Br J Dermatol 2018;178(2):443–51. https://doi.org/10.1111/bjd.15803.
[20] Schoenewolf NL, Belloni B, Simcock M, et al. Clinical implications of distinct metastasizing preferences of different melanoma subtypes. Eur J Dermatol Mar-Apr 2014;24(2):236–41. https://doi.org/10.1684/ejd.2014.2292.
[21] Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med Dec 4 2014;371(23):2189–99. https://doi.org/10.1056/NEJMoa1406498.
[22] Van Allen EM, Miao D, Schilling B, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science Oct 9 2015;350(6257):207–11. https://doi.org/10.1126/science.aad0095.
[23] Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet Feb 2019;51 (2):202–6. https://doi.org/10.1038/s41588-018-0312-8.
[24] Nakamura Y, Namikawa K, Yoshino K, et al. Anti-PD1 checkpoint inhibitor therapy in acral melanoma: a multicenter study of 193 Japanese patients. /09/01/ 2020 Ann Oncol 2020;31(9):1198–206. https://doi.org/10.1016/j.annonc.2020.05.031.
[25] Bhave P, Ahmed T, Lo SN, et al. Efficacy of anti-PD-1 and ipilimumab alone or in combination in acral melanoma. J Immunother Cancer Jul 2022;10(7). https://doi.org/10.1136/jitc-2022-004668.
[26] Shoushtari AN, Munhoz RR, Kuk D, et al. The efficacy of anti-PD-1 agents in acral and mucosal melanoma. Cancer 2016;122(21):3354–62. https://doi.org/10.1002/cncr.30259.
[27] Nathan P, Ascierto PA, Haanen J, et al. Safety and efficacy of nivolumab in patients with rare melanoma subtypes who progressed on or after ipilimumab treatment: a single-arm, open-label, phase II study (CheckMate 172). /09/01/ 2019 Eur J Cancer 2019;119:168–78. https://doi.org/10.1016/j.ejca.2019.07.010.