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Efficacy of anti-PD-1 and ipilimumab alone or in combination in acral melanoma

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ABSTRACT

Background Acral melanoma is a rare melanoma subtype with poor prognosis. Importantly, these patients were not identified as a specific subgroup in the landmark melanoma trials involving ipilimumab and the anti-programmed cell death protein-1 (PD-1) agents nivolumab and pembrolizumab. There is therefore an absence of prospective clinical trial evidence regarding the efficacy of checkpoint inhibitors (CPIs) in this population. Acral melanoma has lower tumor mutation burden (TMB) than other cutaneous sites, and primary site is associated with differences in TMB. However the impact of this on the effectiveness of immune CPIs is unknown. We examined the efficacy of CPIs in acral melanoma, including by primary site.

Methods Patients with unresectable stage III/IV acral melanoma treated with CPI (anti-PD-1 and/or ipilimumab) were studied. Multivariable logistic and Cox regression analyses were conducted. Primary outcome was objective response rate (ORR); secondary outcomes were progression-free survival (PFS) and overall survival (OS).

Results In total, 325 patients were included: 234 (72%) plantar, 69 (21%) subungual and 22 (7%) palmar primary sites. First CPI included: 184 (57%) anti-PD-1, 59 (18%) anti-PD-1/ipilimumab combination and 82 (25%) ipilimumab. ORR was significantly higher with initial anti-PD-1/ipilimumab compared with anti-PD-1 (43% vs 26%, HR 2.14, p=0.0004) and significantly lower with ipilimumab (15% vs 26%, HR 0.49, p=0.0016). Landmark PFS at 1 year was highest for anti-PD-1/ipilimumab at 34% (95% CI 24% to 49%), compared with 26% (95% CI 20% to 33%) with anti-PD-1 and 10% (95% CI 5% to 19%) with ipilimumab. Despite a trend for increased PFS, anti-PD-1/ipilimumab combination did not significantly improve PFS (HR 0.85, p=0.35) or OS over anti-PD-1 (HR 1.30, p=0.16), potentially due to subsequent therapies and high rates of acquired resistance. No outcome differences were found between primary sites.

Conclusion While the ORR to anti-PD-1/ipilimumab was significantly higher than anti-PD-1 and PFS numerically higher, in this retrospective cohort this benefit did not translate to improved OS. Future trials should specifically

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is an absence of prospective clinical trial data on the efficacy of immune checkpoint inhibitors (CPIs), particularly anti-programmed cell death protein-1 (PD-1)/ipilimumab combination, in acral melanoma as these patients were not identified as a specific subgroup in the landmark melanoma immunotherapy trials.

WHAT THIS STUDY ADDS

⇒ This study presents data on one of the largest acral melanoma cohorts to be reported to date, and demonstrates that the objective response rate (ORR) to anti-PD1/ipilimumab combination was significantly higher than single agent anti-PD-1. However this increased ORR did not lead to improved overall survival in this retrospective analysis. Acquired resistance (progression after initial response) was common.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ This study provides preliminary data on the efficacy of CPIs in acral melanoma, and highlights the importance of the need for further prospective clinical trials to be conducted in this subgroup.

include patients with acral melanoma, to help determine the optimal management of this important melanoma subtype.

INTRODUCTION

Acral melanoma is a rare subtype of melanoma originating from glabrous (non-hair bearing) skin melanocytes located in the palms, soles and nail beds (nail apparatus or subungual). Acral melanoma accounts for approximately 1%–3% of melanomas in the Caucasian population. While the incidence between Caucasians and non-Caucasians is similar, non-acral cutaneous melanomas are infrequently diagnosed in non-Caucasians and therefore acral melanoma is the more commonly diagnosed subtype in this population.[1 2] Acral melanoma is etiologically, genetically and molecularly distinct from non-acral cutaneous melanoma. It is not typically associated with ultraviolet exposure, which partially accounts for its lower tumor mutational burden (TMB).[3 4] The single-nucleotide variant and indel frequencies have been found to be over 18 times higher in cutaneous melanoma than in acral melanoma.[5] Acral melanoma also has a distinct association with specific oncogenic drivers, including a higher rate of KIT mutations (15%–20% vs 2%–3%), CCND1 and CDK4 amplification, and fewer BRAF (10%–23% vs ~50%) and NRAS mutations.[1 2 6]

Importantly, patients with acral melanoma were not identified as a specific subgroup in the landmark clinical trials of ipilimumab and the anti-programmed cell death protein-1 (PD-1) agents nivolumab and pembrolizumab, and as a result there is an absence of prospective clinical trial evidence regarding the efficacy of immune checkpoint inhibitors (CPIs) in this specific patient population. Retrospective studies have examined the activity of single agent anti-PD-1 inhibitors in patients with acral melanoma, suggesting lower response rates than seen in clinical trial populations, however there are no published data regarding the comparable efficacy of combination anti-PD-1/ipilimumab blockade in acral melanoma.[2 7–10] Furthermore, whole genome sequencing has shown variability in the genomic makeup of acral melanoma based on primary site of origin, with subungual acral melanoma demonstrating higher rates of TMB.[5 11] The impact of this on the effectiveness of CPIs is unknown.

We present data on the largest cohort of patients with acral melanoma to be reported to date, from multiple institutions worldwide. The aim of our study was to examine the efficacy of combination CPIs (anti-PD-1 with ipilimumab) compared with single agent CPIs in acral melanoma, and to determine if site of primary acral melanoma affected response and patient outcomes. We also explore the safety profile of CPIs in acral melanoma.

METHODS

Patients and study design

Following institutional ethics review board approval, patients with unresectable stage III/IV acral melanoma who received at least one dose of CPI therapy in the advanced setting were identified retrospectively. Patient, disease and treatment characteristics were collected, including; patient demographics, baseline and advanced acral melanoma characteristics, number and characteristics of systemic therapy received, toxicity and grade (per Common Terminology Criteria for Adverse Events (CTCAE) V.5.0) and treatment outcomes. Patients who received experimental treatment combinations with anti-PD-1 and/or ipilimumab backbone were categorized based on anti-PD-1/ipilimumab therapy received. For example, patients who received anti-PD-1 with talimogene laherparepvec (TVEC), lenvatinib, indoleamine 2,3-dioxygenase (IDO) or interleukin were combined with those having received anti-PD-1 monotherapy (online supplemental 1). Importantly, no patients received other drug therapy combinations that have been shown to have substantial efficacy, such as anti-PD-1±BRAF +/− MEK inhibitor combinations or LAG3 antibodies. No distinction was made between differences in ipilimumab dosing. Patients were followed until death or data censorship date, whichever occurred first.

Efficacy assessment

The primary outcome measured was objective response rate (ORR) to first CPI exposure, with secondary outcome measures of progression-free survival (PFS) to first CPI exposure and overall survival (OS). Radiological response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST V.1.1). ORR was defined as the proportion of patients achieving a partial response (PR) or complete response (CR). PFS was calculated from the date of initiation of systemic therapy to the date of radiological or clinical progression, death or last follow-up. OS was calculated from the date of initiation of systemic therapy to the date of death from any cause or last follow-up.

Statistical analysis

Categorical variables are summarized as frequencies and percentages, continuous variables are described using median and range. Pearson's χ^2 test and/or Fisher's exact test was used for comparisons between categorical variables as appropriate. For continuous variables, Wilcoxon rank test was used. Univariable and multivariable logistic regression analysis were conducted to investigate factors associated with ORR. PFS and OS was analyzed using univariable and multivariable Cox proportional hazard regression. PFS and OS were described using the Kaplan-Meier method. Median survival time and its 95% CI were reported. Differences between survival curves were assessed using log-rank test. A p value<0.05 was considered statistically significant. All statistical analyses were conducted using SAS V.9.4 and R V.3.6.0.

RESULTS

Patient and disease characteristics at first exposure to CPI

A total of 369 patients were identified from 26 centers in Australia, Asia, Europe and the USA. After exclusion

of 40 patients who received adjuvant CPI therapy and 4 patients who received their first CPI as fourth line systemic therapy or later, the final analysis included 325 patients. Of these, 256 (79%) received CPI therapy as first line treatment, while 69 (21%) patients were first exposed to CPI therapy as second or third line treatment. Primary site distribution was 22 (7%) palmar, 234 (72%) plantar and 69 (21%) subungual. Of the total, 171 (53%) were men and 252 (76%) were Caucasian. Median age at diagnosis of advanced disease was 66 years (23–90). The most commonly mutated oncogenes were NRAS (n=54/264, 21%) and BRAF (n=38/312, 12%). At commencement of first CPI therapy, lactate dehydrogenase (LDH) concentration was above the upper limited of normal (ULN) in 34% (69/204) of patients tested, 52% had an Eastern Cooperative Oncology Group (ECOG) of 0, and 76% had stage IV disease (table 1, online supplemental 2). Median follow-up from primary acral melanoma diagnosis was 8.1 years (95% CI 7.7 to 10.7 years), and from commencement of first line therapy was 3.9 years (95% CI 3.6 to 4.5 years).

Treatment characteristics

Of the total, 184 (57%) patients received anti-PD-1 as their first CPI therapy (henceforth referred to as first exposure CPI), 59 (18%) received anti-PD-1/ipilimumab combination and 82 (25%) received ipilimumab. The groups were well balanced for most characteristics at commencement of first exposure CPI, however, those treated with combination therapy or ipilimumab were more likely to be younger or have M1c or M1d disease than those treated with anti-PD-1 monotherapy (table 1). Median duration of first exposure CPI was 2.5 months [range, 0–36 months]: 3.7 months [0–36] for anti-PD-1 monotherapy, 2.2 months [0–23] for combination CPI and 2.1 months [0–5] for ipilimumab monotherapy. A total of one line of systemic therapy for advanced disease was received by 95 (29%) patients, while 138 (42%) received three or more lines.

Efficacy analysis

Of the 325 patients, 5 patients were not evaluable for response to first exposure CPI: two died from COVID-19, two died with unknown cause and one electively ceased CPI prior to first response evaluation. Thus, 320 patients were evaluable for ORR to first exposure CPI.

ORR to first exposure CPI was 26% (47/180) to anti-PD-1, 43% (25/58) to anti-PD-1/ipilimumab and 15% (12/82) to ipilimumab (table 2). Univariable logistic regression analysis demonstrated that compared with anti-PD-1, combination therapy with anti-PD-1/ipilimumab was associated with significantly improved ORR (OR 2.14, p=0.0004), while ipilimumab monotherapy was associated with significantly poorer ORR (OR 0.49, p=0.0016). ORR was not significantly associated with sex, ethnicity (non-Caucasian vs Caucasian), LDH or ECOG (table 3).

Progression free survival (PFS)

A total of 286/325 (88%) patients progressed on first exposure CPI. Median PFS for all patients from commencement of first exposure CPI was 4.0 months (95% CI 3.6 to 4.8; figure 1A). Landmark PFS was 23.3% (95% CI 19.1% to 28.4%) at 1 year and 6.4% (95% CI 3.7% to 11.0%) at 5 years. PFS was significantly associated with type of first CPI (p=0.0022, figure 1). Median PFS was highest for anti-PD-1/ipilimumab combination at 5.4 months (95% CI, 3.4 to 11.7), compared with 4.1 months (95% CI 3.7 to 5.9) with anti-PD-1 and 3.5 months (95% CI 2.9 to 4.1) with ipilimumab. Landmark PFS at 1, 2 and 5 years was highest for anti-PD-1/ipilimumab combination at 34% (95% CI 24% to 49%), 22% (95% CI 13% to 37%) and 18% (95% CI 10% to 32%) respectively, compared with 26% (95% CI 20% to 33%), 18% (95% CI 13% to 25%) and 7% (95% CI 4% to 14%) with anti-PD-1 and 10% (95% CI 5% to 19%), 6% (95% CI 3% to 14%) and not evaluable with ipilimumab. Univariable and multivariable Cox regression analysis demonstrated that ipilimumab monotherapy was associated with significantly worse PFS compared with anti-PD-1 monotherapy (HR 1.50, p=0.0032 and HR 1.48, p=0.01, respectively, table 4). However PFS did not significantly differ between anti-PD-1/ipilimumab combination and anti-PD-1 monotherapy on both univariable and multivariable Cox regression analysis (HR 0.85, p=0.35 and HR 0.77, p=0.15, respectively), though there was a trend favoring combination CPI. PFS was significantly shorter in patients with stage M1d disease on both univariable and multivariable Cox regression analysis (HR 2.81, p=0.02 and HR 2.75, p=0.03, respectively). PFS was significantly shorter in patients with ECOG ≥1 on univariable (HR 1.35, p=0.02) but not multivariable analysis (table 4).

Of the 84 patients that responded to first exposure CPI, 34 (40%) achieved CR and 50 (60%) achieved PR. PFS for responders at 1 year was 73% (95% CI 64% to 83%) and at 2 years was 53% (95% CI 42% to 86%, online supplemental 3a). PFS according to best RECIST response demonstrated significantly higher survival in those who achieved CR as best response compared with those who achieved PR (online supplemental 3b). PFS for responders was highest for those who were first exposed to anti-PD-1 compared with those who were exposed to anti-PD-1/ipilimumab combination and ipilimumab monotherapy (online supplemental 3c–e)

Post progression therapy

ORR to second line therapy immediately subsequent to first CPI exposure was explored (online supplementary 4). ORR was 24% (5/21) to anti-PD-1/ipilimumab after anti-PD-1, 14% (5/37) to ipilimumab after anti-PD-1, 75% (6/8) to targeted therapy after anti-PD-1 and 67% (2/3) to targeted therapy after anti-PD-1/ipilimumab.

Overall Survival (OS)

At the time of data cut-off, a total of 216/325 (66%) patients had died. Median OS for all patients from

Table 1 Patient and disease characteristics at first exposure to CPI

Patient and disease characteristic	Total (N=325)	Anti-PD-1 (N=184)	Anti-PD-1 +ipilimumab (N=59)	Ipilimumab (N=82)	P value*
Primary site - no. (%)					0.55
Palmar	22 (7)	13 (7)	3 (5)	6 (7)	
Plantar	234 (72)	138 (75)	41 (70)	55 (67)	
Weight bearing	141	84	26	31	
Non-weight bearing	46	28	8	10	
Subungual	69 (21)	33 (18)	15 (25)	21 (26)	
Toenail	39	19	9	11	
Fingernail	30	14	6	10	
Median age at diagnosis of advanced acral melanoma, years (range)	66 (23–90)	69 (31–90)	64 (23–82)	65 (31–85)	**0.002**
Sex - no. (%)					0.47
Female	154 (47)	82 (45)	29 (49)	43 (52)	
Male	171 (53)	102 (55)	30 (51)	39 (48)	
Ethnicity - no. (%)					**0.0003**
Caucasian	252 (76)	131 (71)	46 (78)	75 (92)	
Non-Caucasian†	64 (20)	50 (27)	9 (15)	5 (6)	
Unknown	9 (3)	3 (2)	4 (7)	2 (2)	
Mutation - positive/tested (% of tested)					0.07
BRAF	38/312 (12)	21/179 (12)	10/55 (18)	7/78 (9)	
KIT	23/235 (10)	19/140 (14)	1/45 (2)	3/50 (6)	
NRAS	54/264 (21)	29/153 (19)	11/49 (22)	14/62 (23)	
ECOG (%)					0.13
0	170 (52)	99 (54)	27 (46)	44 (54)	
≥1	110 (34)	59 (32)	28 (47)	23 (28)	
Unknown	45 (14)	26 (14)	4 (7)	15 (18)	
LDH					**0.01**
Normal (≤ULN)	135 (42)	86 (47)	19 (32)	30 (37)	
Elevated (>ULN)	69 (21)	31 (17)	20 (34)	18 (22)	
Unknown	121 (37)	67 (36)	20 (34)	34 (42)	
Stage (AJCC 8th edition) - no (%)					**<0.0001**
Unresectable III	79 (24)	57 (31)	10 (17)	12 (15)	
IV	246 (76)	127 (69)	49 (83)	70 (85)	
M1a	53 (16)	33 (18)	6 (10)	14 (17)	
M1	66 (20)	43 (23)	6 (10)	17 (21)	
M1c	103 (32)	45 (25)	25 (42)	33 (40)	
M1d	24 (7)	6 (3)	12 (20)	6 (7)	
De-novo metastatic disease - no (%)	33 (10)	20 (11)	7 (12)	6 (8)	0.66
Time from primary diagnosis to advanced disease, months (range)	21 (0–261)	18 (0–261)	23 (0–131)	24 (0–246)	0.27
Number of treatment lines for advanced disease prior to first CPI exposure					**0.0003**
0	256 (79)	151 (82)	54 (92)	51 (62)	
1	62 (19)	29 (16)	5 (9)	28 (34)	
2	7 (2)	4 (2)	0	3 (4)	

Bold values indicate significant results (P<0.05).
*Pearson's χ^2 test; Fisher's exact test.
†Non-Caucasian includes: East Asian, South East Asian, Middle Eastern, Hispanic and black.
AJCC, American Joint Committee on Cancer; CPI, checkpoint inhibitor; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-1, programmed cell death protein-1; ULN, upper limited of normal.

Table 2 Objective response rate (ORR) to first exposure checkpoint inhibitors

N (%)	Anti-PD-1 (N=180)	Anti-PD-1 +Ipilimumab (N=58)	Ipilimumab (N=82)
ORR, %	26	43	15
CR	22 (12)	8 (14)	4 (5)
PR	25 (14)	17 (29)	8 (10)
SD	31 (17)	7 (12)	14 (17)
PD	102 (57)	26 (45)	56 (68)
OR (95% CI)	1	2.14 (1.16 to 3.97)	0.49 (0.24 to 0.97)
P value	–	0.0004	0.0016

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3 Univariable Logistic regression for objective response rate to first exposure CPI

	Univariable	
Variable	**OR (95% CI)**	**P value**
First CPI exposure		
Anti-PD-1	1	
Anti-PD-1/ipilimumab	2.14 (1.16 to 3.97)	**0.0004**
Ipilimumab	0.49 (0.24 to 0.97)	**0.0016**
Primary acral melanoma site		
Subungual	1	
Plantar	1.51 (0.77 to 2.97)	0.62
Palmar	3.12 (1.08 to 8.95)	0.05
Sex		
Female	1	
Male	0.63 (0.38 to 1.04)	0.07
Ethnicity		
Non-Caucasian	1	
Caucasian	1.30 (0.67 to 2.50)	0.44
Stage of advanced disease		
Unresectable IIIB	1	
Unresectable IIIC	3.41 (0.38 to 30.24)	**0.03**
Unresectable IIID	2.67 (0.24 to 30.07)	0.40
M1a	1.65 (0.17 to 14.81)	0.92
M1b	1.80 (0.20 to 16.15)	0.82
M1c	2.45 (0.29 to 21.97)	0.15
M1d	0.55 (0.04 to 7.09)	0.09
LDH		
Normal (≤ULN)	1	
Elevated (>ULN)	1.03 (0.53 to 2.00)	0.93
ECOG		
0	1	
≥1	0.68 (0.39 to 1.21)	0.19

CPI, immune checkpoint inhibitor; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-1, programmed cell death protein-1; ULN, upper limited of normal .

commencement of first exposure CPI was 1.9 years (95% CI 1.4 to 2.3; figure 1). Landmark OS was 68.2% (95% CI 63.3% to 73.6%) at 1 year and 22.4% (95% CI 17.0% to 29.5%) at 5 years. OS was not significantly associated with type of first CPI (p=0.36, figure 1). Median OS was 1.9 years (95% CI 1.4% to 2.6%) for anti-PD-1, 1.3 years (95% CI 1.2 to 2.7) for anti-PD-1/ipilimumab and 1.9 years (95% CI 1.3 to 2.6) for ipilimumab. Landmark OS at 1, 2 and 5 years was 69% (95% CI 62% to 76%), 49% (95% CI 42% to 58%) and 28% (95% CI 20% to 39%) respectively, with anti-PD-1, 66% (95% CI 55% to 80%), 43% (95% CI 31% to 59%) and 16% (95% CI 7% to 37%) with anti-PD-1/ipilimumab and 68% (95% CI 59% to 79%), 48% (95% CI 38% to 60%) and 21% (95% CI 13% to 32%) with ipilimumab. On both univariable and multivariable Cox regression analysis, OS was significantly shorter in patients with stage M1d disease (HR 4.49, p=0.002 and HR 2.96, p=0.04, respectively) and ECOG ≥1 (HR 2.11, p<0.0001 and HR 1.75, p=0.0006, respectively). OS was significantly shorter in patients with elevated LDH on univariable (HR 1.45, p=0.04) analysis (Supplement 5).

Primary site

To determine if primary site of acral melanoma affected ORR and survival outcomes, a separate analysis was conducted. Patient and disease characteristics by primary site were well matched between the three groups and are summarized in online supplemental 6. Palmar acral melanoma had the highest ORR to first exposure CPI of 43% (9/21), compared with 27% (62/232) for plantar and 19% (13/67) subungual (online supplemental 7). Although not statistically significant on univariable analysis, there was a trend favoring palmar acral melanoma (OR 3.12, p=0.05) (table 3). PFS and OS were not significantly associated with primary acral melanoma site (p=0.13 and p=0.25, respectively, figure 2).

Efficacy—first line CPI

To mitigate the potential influence of non-CPI therapy received prior to first exposure to CPI on outcomes; a separate analysis was conducted based on patients treated with pure first line CPI (vs first exposure) CPI therapy (online supplemental 8). Results regarding ORR, PFS and OS were consistent with the results of the entire

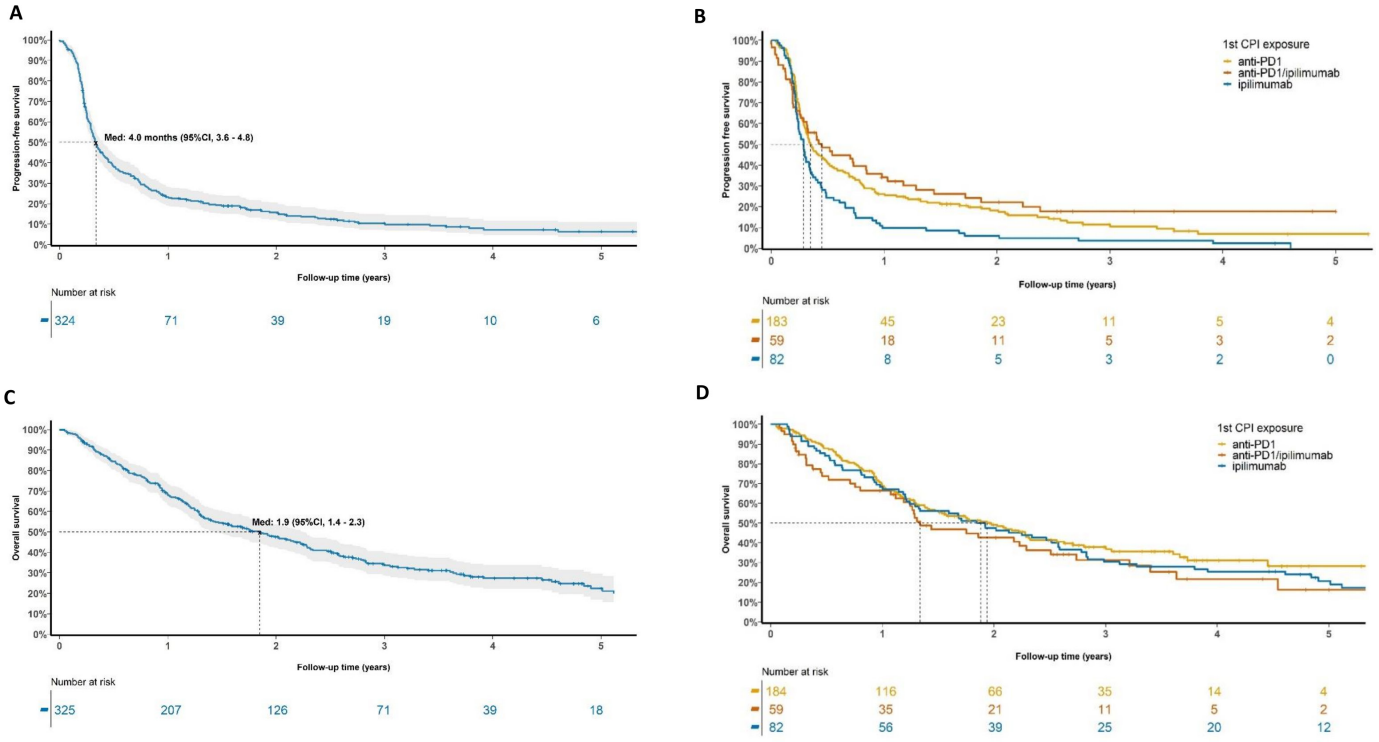

Figure 1 Kaplan-Meier curve for (A) PFS for all patients from commencement of first CPI exposure, one patient was not evaluable for PFS as they were lost to follow-up. (B) PFS by first CPI exposure (p=0.0022). Landmark PFS for anti-PD-1/ipilimumab versus anti-PD-1 versus ipilimumab at 1 year: 34% (95% CI 24% to 49%) versus 26% (95% CI 20% to 33%) versus 10% (95% 5% to 19%); 2 years: 22% (95% CI 13% to 37%) versus 18% (95% CI 13% to 25%) versus 6% (95% 3% to 14%); at 5 years: 18% (95% CI 10% to 32%) versus 7% (95% CI 4% to 14%) versus NR; (C) OS for all patients from commencement of first CPI exposure; (D) OS by first CPI exposure (p=0.36). Landmark OS for anti-PD-1/ipilimumab versus anti-PD-1 versus ipilimumab at 1 year: 66% (95% CI 55% to 80%) versus 69% (95% CI 62% to 76%) versus 68% (95% 59% to 79%); 2 years: 43% (95% CI 31% to 59%) versus 49% (95% CI 42% to 58%) versus 48% (95% 38% to 60%); at 5 years: 16% (95% CI 7% to 37%) versus 28% (95% CI 20% to 39%) versus 21% (95% CI 13% to 32%). CPI, checkpoint inhibitors; OS, overall survival; PD-1, programmed cell death protein-1; PFS, progression-free survival.

population. In particular, ORR to first line CPI was 26% (39/149) to anti-PD-1, 45% (24/54) to anti-PD-1/ipilimumab and 12% (6/51) to ipilimumab. Univariable and multivariable logistic regression analyses demonstrated that compared with anti-PD-1, combination therapy with anti-PD-1/ipilimumab was associated with significantly improved ORR (OR 2.33, p=0.0002 for both), while ipilimumab monotherapy was associated with significantly poorer ORR (OR 0.38, p=0.0026 and OR 0.36, p=0.0019, respectively) (online supplemental 9).

PFS was significantly associated with first line CPI (p=0.017, online supplemental 10a). Median PFS was highest for first line anti-PD-1/ipilimumab combination at 6.2 months (95% CI 3.8 to 14.0), compared with 4.1 months (95% CI 3.6 to 5.9) with first line anti-PD-1 and 3.5 months (95% CI 2.6 to 5.2) with first line ipilimumab. Univariable and multivariable Cox regression analyses demonstrated that ipilimumab monotherapy was associated with significantly worse PFS compared with anti-PD-1 monotherapy (HR 1.43, p=0.03 and HR 1.58, p=0.02, respectively). However PFS did not significantly differ between first line anti-PD-1/ipilimumab combination and anti-PD-1 monotherapy on both univariable and multivariable Cox regression analyses (HR 0.81, p=0.23 and HR 0.78, p=0.19, respectively, online supplemental 10b). OS was not significantly associated with first line CPI (p=0.68, online supplemental 10c,d).

Propensity score matching

To further explore differences in outcomes between anti-PD-1 monotherapy and anti-PD-1/ipilimumab combination, we performed a propensity score analysis to mitigate the effect of variables that may have differed between these two treatment groups. A population of 51 patients was identified after matching for LDH, stage and BRAF status (online supplemental 11). After matching, the OR for ORR for anti-PD-1/ipilimumab compared with anti-PD-1 was 2.30 (p=0.05), with no difference in PFS and OS. (online supplemental file 12–14).

BRAF mutant patients

Of the 38 BRAF mutant (BRAFm) patients in the total cohort, 27 (71%) received first line CPI, 9 (24%) received BRAF/MEK inhibitors and 2 (5%) received chemotherapy. ORR to first line therapy was 31% (5/16) to anti-PD-1, 63% (5/8) to anti-PD-1/ipilimumab, 67% (2/3) to ipilimumab and 67% (6/9) to BRAF/MEK inhibitors (online supplemental 15a) with no factors significantly

Table 4 Univariable and multivariable Cox regression for progression-free survival to first exposure CPI

	Univariable		Multivariable	
Variable	HR (95% CI)	P value	HR (95% CI)	P value
First CPI exposure				
Anti-PD-1	1		1	
Anti-PD-1/ipilimumab	0.85 (0.61 to 1.19)	0.35	0.77 (0.55 to 1.10)	0.15
Ipilimumab	1.50 (1.15 to 1.97)	**0.0032**	1.48 (1.09 to 1.99)	**0.01**
Stage of advanced disease				
Unresectable IIIB	1		1	
Unresectable IIIC	0.68 (0.29 to 1.59)	0.37	0.74 (0.31 to 1.77)	0.50
Unresectable IIID	0.81 (0.31 to 2.14)	0.67	0.94 (0.35 to 2.52)	0.91
M1a	1.08 (0.47 to 2.57)	0.83	1.22 (0.51 to 2.87)	0.66
M1b	0.90 (0.39 to 2.09)	0.80	0.89 (0.38 to 2.09)	0.79
M1c	0.87 (0.38 to 2.01)	0.75	0.86 (0.37 to 1.99)	0.72
M1d	2.81 (1.17 to 7.05)	**0.02**	2.75 (1.08 to 6.99)	**0.03**
Primary acral melanoma site				
Subungual	1			
Plantar	0.76 (0.57 to 1.01)	0.05	–	–
Palmar	0.69 (0.41 to 1.19)	0.18	–	–
Sex				
Female	1			
Male	1.04 (0.82 to 1.31)	0.74	–	–
Ethnicity				
Non-Caucasian	1			
Caucasian	0.98 (0.73 to 1.32)	0.89	–	–
LDH				
Normal (≤ULN)	1			
Elevated (>ULN)	1.26 (0.93 to 1.73)	0.14	–	–
ECOG				
0	1		1	
≥1	1.35 (1.04 to 1.74)	**0.02**	1.28 (0.97 to 1.67)	0.08

CPI, checkpoint inhibitor; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-1, programmed cell death protein-1; ULN, upper limited of normal .

associated with ORR (online supplemental 15b). Median PFS was 5.1 months (95% CI 3.0 to 15.4, online supplemental 15c) and median OS was 4.5 years (95% CI 1.9 to NA, online supplemental 15d).

Toxicity

Immune-related adverse events (IRAEs) were reported in 157 of 325 (48%) patients to first exposure CPI. Of these, 19% (30/157) of patients were affected by multiple IRAEs and 31% (48/157) were affected by CTCAE grade 3 or 4 IRAEs. The most common severe IRAE was gastrointestinal (colitis, enteritis, gastritis). Of the 48 patients with grade 3 or 4 IRAEs, 13 (24%) received anti-PD-1, 21 (49%) received anti-PD-1/ipilimumab combination and 14 (28%) received ipilimumab as first exposure CPI. No treatment-related deaths occurred. Toxicity was not impacted by primary site of acral melanoma (data not shown).

DISCUSSION

To our knowledge, this is the largest study to explore the efficacy and safety of CPIs in acral melanoma to date, and the first to report on the efficacy of anti-PD-1/ipilimumab combination immunotherapy in a significant population of acral melanoma. Furthermore, this is the first study to systematically investigate the effect of primary acral melanoma site on CPI efficacy and survival.[8–12]

We found a significantly higher ORR with anti-PD-1/ipilimumab combination compared with anti-PD-1 monotherapy. This benefit was seen with both first exposure

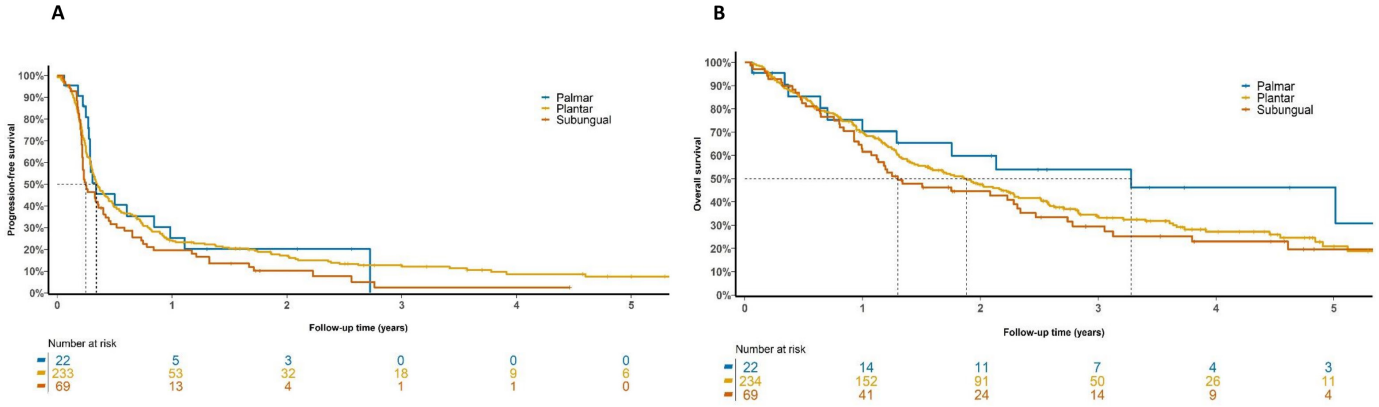

Figure 2 Kaplan-Meier curve for (A) PFS from commencement of first CPI exposure by primary site of acral melanoma (p=0.13). Median PFS 4.0 months for palmar (95% CI 3.4 to 13.3), 4.1 months (95% CI 3.7 to 5.4) for plantar, 3.0 months (95% CI 2.7 to 4.8) for subungual melanoma; (B) OS from commencement of first CPI exposure by primary site of acral melanoma (p=0.25). Median OS 3.3 years for palmar (95% CI 1.9 to NA), 1.9 years (95% CI 1.4 to 2.3) for plantar and 1.3 years (95% CI 1.1 to 2.3) for subungual melanoma. CPI, checkpoint inhibitor; OS, overall survival; PFS, progression-free survival.

CPI, including patients who received non-CPI agents prior to CPI therapy, and in first line CPI. We also found that PFS was significantly associated with type of CPI, with ipilimumab being inferior to anti-PD-1 and anti-PD-1/ipilimumab. Landmark PFS was higher for anti-PD-1/ipilimumab over anti-PD-1 at 1, 2 and 5 years for the entire cohort, and the multivariable HR of 0.77 in our study is comparable to the HR for PFS of 0.79 (95% CI 0.64 to 0.96) seen in CheckMate-067 for nivolumab/ipilimumab versus nivolumab, though we acknowledge that our study did not include a cohort of patients with non-acral cutaneous melanoma to allow for direct comparison.[13] Notably, however, the numerical difference in PFS between anti-PD-1/ipilimumab and anti-PD-1 monotherapy was not statistically significant, even after multivariable and propensity score analysis attempting to adjust for potential selection bias. These results suggest that in acral melanoma, the addition of ipilimumab to anti-PD-1 therapy improves response; however this does not seem to translate to a statistically significant PFS benefit over anti-PD-1 alone.[14]

The differences in ORR and PFS observed between first exposure CPI agents did not translate to significant differences in OS. The heterogeneity of subsequent treatment often seen in retrospective analyses may have impacted this. Indeed, our cohort demonstrated significant variability in treatment subsequent to first CPI exposure, and clinically meaningful ORRs were seen with some subsequent CPIs: both ipilimumab and anti-PD-1/ipilimumab were interestingly associated with significant activity after progression on anti-PD-1 monotherapy. Furthermore, duration of response to CPIs was relatively short, which may have further impacted OS results. In our cohort, of the patients that initially responded to first exposure CPI, PFS was only 53% at 2 years, demonstrating a short duration of response and a high rate of acquired resistance to CPI therapy. While cross study comparisons should be made with caution, when these results are compared with CheckMate-067 where the median duration of response for those treated with nivolumab alone or in combination with ipilimumab has not been reached at 6.5 years, our data suggest acquired resistance is more common in acral compared with non-acral cutaneous melanoma.[15] Interestingly, we found that acquired resistance was more common/earlier in those treated with combination CPI or ipilimumab than for anti-PD-1 monotherapy. This may have contributed to the lack of improvement in PFS and OS seen in patients receiving combination CPI compared with anti-PD-1 monotherapy, despite increased response rates.

The observed ORR to anti-PD-1 therapy of 26% in our study is better than the ORR of 16%–19% observed in Japanese cohorts.[2 13] The median PFS of 4.1 months to anti-PD-1 therapy is also somewhat better than that reported in other studies, including the multicenter Japanese study which reported a median PFS of 3.5 months 2, but similar to a US study where a median PFS of 4.1 months was seen.[7] Overall, our cohort was comparable to the Japanese cohort with respect to patient and disease characteristics: median age at first CPI exposure 66 versus 70 years; males 53% versus 59%, BRAFm 12% versus 8%; brain metastasis 7% versus 6%. While our study had a smaller proportion of patients with elevated LDH at commencement of first CPI exposure (21% vs 47%), a significant proportion (37%) of our cohort did not have LDH data available. Thus, the difference in ORR and PFS to anti-PD-1 monotherapy suggests that there may be distinctions in disease characteristics and/or tumor biology between Caucasian and Asian populations.

Our results are consistent with findings from the Japanese cohort in that acral melanoma seems to have a lower ORR to CPIs when compared with cutaneous melanoma. For example, the CheckMate-067 trial demonstrated an ORR of 58% to combination CPIs and 45% to single agent anti-PD-1 therapy.[16] Mucosal melanoma has also been shown to have lower ORRs to CPIs.[17 18] Recognizing the limitations of a retrospective analysis and indirect comparisons between retrospective data sets and prospective

clinical trials, the differing results raise the question of what biological mechanisms influence response. One of the proposed reasons for this reduced response rate is the lower TMB at acral and mucosal primary sites. Furthermore, other factors may have pre-disposed our cohort to have a lower ORR, such as high disease burden and site of metastases. Our study did not investigate TMB or sites of disease, but this would be important to include in future studies.

In our study, the BRAFm population had an ORR to targeted therapy of 67% which is similar to the ORR of 68% seen in cutaneous melanoma,[19] suggesting that in BRAFm acral melanoma, combination BRAF/MEK inhibition is a viable treatment option in appropriately selected cases. Furthermore, in this population, there was a suggestion of a larger benefit of anti-PD-1/ipilimumab over single agent CPI with respect to ORR.

We also explored the impact of primary acral melanoma site on ORR and survival. Whole genome sequencing has revealed that subungual, particularly fingernail, melanoma has a higher TMB than other sites and it could therefore be hypothesized that subungual acral melanoma may have a higher ORR to CPI therapy.[5 20–22] Our study did not however demonstrate an association between ORR and primary site. The multicenter Japanese study similarly did not find an association between subungual acral melanoma and higher ORR to CPIs, and, in fact, found that ORR was significantly lower in the subungual group compared with palmar or plantar sites (8.6% vs 21.1%, p=0.026).[2] Indeed, in our propensity score matched population, palmar and plantar acral melanoma was associated with improved OS compared with subungual. This suggests that more complicated mechanisms beyond site of origin and TMB may contribute to immune responses, such as tumor microenvironment characteristics including tumor infiltrating lymphocytes, programmed death ligand-1 expression and T cell receptor clonal expansion.[23 24]

Limitations of this study include the retrospective nature of data collection and associated biases. Heterogeneity of the population including variations in local practice and access to drug may have impacted results.[25 26] Also, we grouped patients who received experimental treatment combinations with anti-PD-1 and/or ipilimumab backbone into either anti-PD-1 or ipilimumab categories. While we acknowledge the potential impact of experimental therapy on our results (eg, one patient received pembrolizumab and lenvatinib combination), patient numbers were too low in each of these categories to have had any meaningful impact (online supplemental 1). Importantly, we excluded patients who received other drug therapy combinations that have been shown to have substantial efficacy. A number of patients had data missing on baseline ECOG and LDH, as is not uncommonly seen in retrospective analysis. Strengths of this study include its large sample size, long follow-up and inclusion of patients from a variety of countries. As a result, 20% of the study population was non-Caucasian, allowing examination of the impact of ethnicity on ORR and patient outcomes; no association was found.

While the ORR to CPIs demonstrated in this study represents a significant improvement over historical treatments such as chemotherapy, additional work is needed to improve the outcomes of this generally young and otherwise healthy population. For example, median OS was only 1.9 years in our large cohort, significantly less than the median OS of over 5 years seen in melanoma clinical trials.[18] With the advent of novel therapies such as LAG3 inhibitors, as well as clinical trials exploring new combinations such as CPIs with tyrosine kinase inhibitors, it would be ideal for dedicated clinical trials in acral melanoma to be undertaken. However, given the rarity of the disease subtype, this may not be practical and failing this, it is vital to ensure that patients with acral melanoma are included in 'general' melanoma studies.[27] Importantly, prospective collection of detailed primary characteristics in prognostic clinical trials will assist in determining the optimal treatment for acral and other melanoma subtypes. This includes determining when combination immunotherapy is indicated over single agent checkpoint inhibition, such as in those with a high volume of disease who are not candidates for targeted therapy.[28] Novel paradigms and treatment sequencing approaches, such as the utilization of neoadjuvant therapy, also need to be validated in patients with acral melanoma.[29] Furthermore, novel translational science approaches such as genomic sequencing and spatial transcriptomics will help elucidate more information on the relationship between the primary tumor and surrounding tumor microenvironment.[30] Dedicated trials including early phase drugs in development should be specifically designed to include patients with acral melanoma.[31] This will also allow prospective data collection and subsequent pooled analyses to be conducted, which is of particular importance in this rare cancer type.

CONCLUSION

Patients with acral melanoma demonstrate response rates to CPIs which seem to be lower than that seen in the landmark clinical trials of non-acral cutaneous melanoma. While the highest ORR was obtained with anti-PD-1/ipilimumab combination, the difference in PFS between anti-PD-1/ipilimumab and anti-PD-1 monotherapy was not statistically significant, and no difference in OS was observed, possibly due to the influence of subsequent therapies and acquired resistance. The relationship between primary acral melanoma site, TMB and response to CPIs remains unclear. As such, future trials should specifically include and identify patients with acral melanoma, to help gather evidence to answer these important scientific questions.

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