ORIGINAL RESEARCH

Impact on Survival with Immunotherapy and Evaluation of Biomarkers in Peruvian Patients with Advanced Melanoma

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Introduction: Advanced malignant melanoma is a very aggressive disease, historically with poor prognosis before the new advances with immunotherapy and targeted therapies that have changed the standard of care, especially in cutaneous melanoma. Peru has aggressive features such as higher rates of acral lentiginous melanoma (ALM) subtype with historically shorter survival.

Methods: This study describes Peruvian patients with advanced melanoma treated with immunotherapy (nivolumab) in two oncological institutions (public and private), including the discussion of the impact on overall survival (OS) divided by subtype (with incidence in ALM histology) and potential biomarkers that could be related to prognosis.

Results: We found that immunotherapy is safe, and improves progression-free survival (PFS), OS and objective response rate (ORR) in our patients, with lower benefit in ALM histology. No prognostic blood inflammatory biomarkers were detected.

Discussion: There is very limited data of Peruvian patients with metastatic melanoma treated with immunotherapy, especially the outcomes in ALM histology. Our goal is to share an example of the impact of immunotherapy in a Latin American (LATAM) population considered as an unsatisfied group with an enormous need of novel treatments and biomarkers.

Keywords: advanced melanoma, immunotherapy, overall survival, biomarkers, Peru

Introduction

Malignant melanoma is an aggressive disease, and incidence continues to increase (ranked 5th in incidence in the United States in 2024). American Cancer Society estimates 100640 news cases (both sexes) and 8290 deaths (both sexes) in American patients with melanoma of the skin in 2024, with 4% of patients with distant metastatic disease.[1] In Peru, GLOBOCAN 2022 showed that melanoma ranked 13th in incidence (1360 new cases) and 16th in mortality (443 deaths).[2] A report of Instituto Nacional de Enfermedades Neoplásicas (INEN) (cancer center reference in Lima, Peru) mentioned that melanoma ranked 21st place in incidence (2310 new cases) with 14% patients in stage IV between years 2000–2020.[3]

Outcomes in melanoma depend on the stage at presentation and other factors such as ulceration, or lactate dehydrogenase (LDH) levels, among others. Survival in patients with metastatic melanoma was historically less than 10% at 1 year, with a median progression-free survival (PFS) of 2 months and overall survival (OS) of 6 months before the use of novel systemic treatments such as immunotherapy[4–6] and target therapies.[7–9] These treatments increased OS, including a proportion of long-term responders and have changed the standard of care.

Chemotherapy was historically used for treatment for advanced melanoma with limited outcomes: dacarbazine obtained a median OS of 5.6 to 7.8 months[10] and remains used especially in countries with no access to immunotherapy or targeted therapies.

Melanoma is genetically heterogeneous, and includes many subtypes: cutaneous, mucosal, uveal and unknown primary (UP).[11] Cutaneous melanoma is histologically categorized into superficial spreading, nodular, lentigo maligna (LM) and acral lentiginous melanoma (ALM). According to World Health Organization (WHO) 2018 Classification of Cutaneous Melanocytes, ALM is categorized as pathway number 5, harboring genetic hallmarks as multiple amplifications of KIT, BRAF and NRAS.[12] In advanced disease, molecular biology examination is added. ALM harbors a lower proportion of BRAF mutations (10–15%).[13,14] The efficacy of immunotherapy is expected to be lower in ALM than non-acral melanoma histologies due to lower tumor mutational burden (TMB) than non-acral melanomas.[15–17] Some trials showed that the use of immunotherapy (anti-PD-1 monotherapy or combination of anti-PD-1 with anti-CTLA-4) provides antitumor activity on ALM or mucosal melanoma. Small trials of advanced melanoma with ALM and mucosal subtypes in Chinese population reported an objective response rate (ORR) of 18–20% when anti-PD-1 was used in monotherapy, and the ORR could increase to 50% when using a combination of anti-PD-1 plus axitinib.[18,19] However, the data of immunotherapy efficacy in ALM histology is scarce in Latin America (LATAM) populations. This study evaluates the effectiveness and safety of immunotherapy (nivolumab) for Peruvian patients with advanced melanoma, including ALM.

Material and Methods
Patients
Peruvian treatment-naïve patients aged ≥ 18 years with histologically confirmed stage IV, unresectable or recurrent melanoma (n = 81) were included. Patients were treated in two oncological institutions [public: Instituto Nacional de Enfermedades Neoplásicas (INEN) (n = 72), private: Oncosalud (n = 9)].

Study Design and Treatment
A retrospective study based on medical case data evaluated the efficacy of immunotherapy. Eligible patients were metastatic, recurrent or unresectable malignant melanoma undergoing treatment with anti-PD-1 (nivolumab 240 mg intravenous (IV) every 2-week or 480 mg IV every 4-week per cycle until progressive disease or unacceptable toxicity) as first line (1L) for at least 3 consecutive months between 2020 and January 2024 in two institutions (INEN, Oncosalud). Clinical pathologic features and immune inflammatory blood markers [neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and prognostic nutritional index (PNI)] were evaluated before the start of immunotherapy. Efficacy was measured as progression-free survival (PFS), objective response rate (ORR) and OS. Estimates of OS and PFS were made with Kaplan–Meier method, and differences in survival according to characteristics of interest were evaluated with the log rank test.

Possible associations of features under study with objective response were evaluated with Chi-square test. A $p < 0.05$ value (SPSS) will be considered for a significant difference. Software R was used, version 4.3.2, manufactured by R Development Core Team (2023). Vienna, Austria.

Adverse event (AE) severity was graded in accordance with Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

The Cox regression model was used to evaluate the association between clinic pathologic variables with OS and PFS.

The patient consent to review their medical records was not required by the Institutional Review Board (IRB) called "Review committee of Instituto Nacional de Enfermedades Neoplásicas (INEN)" due to the retrospective nature of this study. Moreover, all patients treated signed an institutional written consent recorded in medical files. Authors understand the importance of covering patient data confidentiality and compliance with the Declaration of Helsinki. Authors declare that they follow ethical principles for medical research involving human subjects according to the Declaration of Helsinki. Follow-up was obtained from patient files and survival status was verified from Peruvian government web

page (RENIEC) when there was not any clear follow-up. Personal data was protected with a code in an Excel table As a retrospective trial there was no contact with patients.

Results

Patients

A total of 81 patients who received immunotherapy (nivolumab) were enrolled from two institutions in Peru. Demographic features are shown in Table 1. The median age of diagnosis was 61 years (range 27–83), with 50% of patients under the median age. 54.3% were female. The territorial distribution of births shows that Lima (the most populated region of Peru) is the region where the largest number of patients are born and refer to as their place of origin, followed by northern Peru (coastal region). Clinic and pathological features are shown in Table 2. At baseline, the

Table 1 Demographic Features of Peruvian Patients with Advanced Melanoma

Features	N = 81
Age at diagnosis, year	
Median [Min-Max]	61.4 (27–83)
Sex	
Male	37 (45.7%)
Woman	44 (54.3%)
Region of birth	
Lima	25 (30.9%)
Piura	8 (9.9%)
Cajamarca	6 (7.4%)
Cusco	6 (7.4%)
Apurímac	5 (6.2%)
Ancash	4 (4.9%)
Huánuco	4 (4.9%)
Junín	4 (4.9%)
Lambayeque	3 (3.7%)
Ayacucho	3 (3.7%)
Huancavelica	3 (3.7%)
Amazonas	1 (1.2%)
Callao	1 (1.2%)
Ica	1 (1.2%)
La Libertad	1 (1.2%)
Tacna	1 (1.2%)
Region of origin	
Lima	40 (49.4%)
Cusco	6 (7.4%)
Piura	6 (7.4%)
Callao	5 (6.2%)
Cajamarca	4 (4.9%)
Apurímac	3 (3.7%)
Ayacucho	3 (3.7%)
Junín	3 (3.7%)
Ancash	2 (2.5%)
Huánuco	2 (2.5%)
Ica	2 (2.5%)
Amazonas	1 (1.2%)
La Libertad	1 (1.2%)
Lambayeque	1 (1.2%)

Table 2 Clinic and Pathological Features of Peruvian Patients with Advanced Melanoma

Features	N = 81
ECOG	
0–1	66 (81.5%)
2	15 (18.5%)
Primary site	
Lower extremity	38 (46.9%)
Head and neck	13 (16.0%)
Trunk	8 (9.9%)
Upper extremity	6 (7.4%)
Anus rectum	5 (6.2%)
Genital	4 (4.9%)
Primary unknown	7 (8.6%)
Histology	
Non acral	33 (40.7%)
Acral lentiginous melanoma (ALM)	26 (32.1%)
Mucosal	13 (16.0%)
Not determined	9 (11.1%)
Non acral histology (N=33)	
Epithelioid	15 (45.5%)
Fusocellular	4 (12.1%)
Nodular	3 (9.1%)
Melanotic	2 (6.1%)
Amelanotic	1 (3.0%)
Epithelioid-sarcomatoid	1 (3.0%)
Lentiginous	1 (3.0%)
Sarcomatoid	1 (3.0%)
Clinical stage at diagnosis	
I	3 (3.7%)
II	8 (9.9%)
III	31 (38.3%)
IV	32 (39.5%)
Metastatic site	
Systemic	52 (64.2%)
Local	29 (35.8%)
Lymphovascular invasion	
No	37 (45.7%)
Yes	14 (17.3%)
Not registered	30 (37.0%)
Perineural invasion	
No	33 (40.7%)
Yes	13 (16.0%)
Not registered	35 (43.2%)
BRAF mutation	
Detected	13 (13.6%)
No detected	52 (64.2%)
Not realized	18 (22.2%)
KIT gene mutation	
No detected	2 (2.5%)
Not realized	74 (91.4%)
Not determined	5 (6.2%)

(*Continued*)

Table 2 (Continued).

Features	N = 81
PD-L1 protein expression	
Not detected	2 (2.5%)
Not realized	74 (91.4%)
Not determined	5 (6.2%)

Table 3 Laboratory Features of Peruvian Patients with Advanced Melanoma

Features	N	Average	Median	Minimum	Maximum
Leucocytes, x 10⁹/L	81	7.354	6.91	3.93	16.9
Neutrophils, absolute value	81	4.502	4.26	1.63	10.69
Lymphocytes, absolute value	81	2.079	1.952	0.68	4.56
Hemoglobin, g/L	81	137.519	137	92	182
Platelets, x 10⁹/L	81	295.642	276	129	1021
Albumin, g/L	79	38.432	42.3	3.6	51.3
LDH, U/L	80	244.075	205.5	130	1281
NLR	81	2.485	2.188	0.766	9.481
PLR	81	171.282	131.646	39.34	1014.97
NPI	79	48.865	52.6	7.039	69.2

Eastern Cooperative Oncology Group (ECOG) performance status was 0–1 in 77.2%. The most frequent primary site was the lower extremities (54.4%). Regarding histology, 40.7% (n = 33) had non-acral, 32.1% (n =26) had ALM subtype, 16% (n = 13) mucosal and 11.1% (n=9) unknown primary (UP). 64.2% had negative BRAF mutation status, and the median lactate dehydrogenase (LDH, normal values 120–246 U/L) level was 257 U/L (130–1281). Of the total patients included in the analysis, 63.2% had visceral metastasis, the most common site being lung (42%) and liver (9%). A 5% of patients had central nervous system (CNS) metastases. 25% of patients who received radiotherapy (RT), with the CNS accounting for 8.3% of RT sites.

Table 3 shows the laboratory features. In relation to leukocytes a mean of 7.35×10^9/L (3.93–16.9) was obtained. For neutrophils (absolute value) the mean was 4.50 mL (1.63–10.69). For lymphocytes (absolute value) the mean was 2.07 uL (0.68–4.56). The mean hemoglobin level was 13.75 g/L (92–182), in 12 (14.8%) patients the diagnosis of anemia was made. The mean platelet count was 295.6×10^9/L (129–1021). Respect to albumin, a mean of 38.4 g/L (3.6–51.3 g/L) was found. About LDH, the mean level was 244.07 U/L (130–1281). The mean neutrophil-lymphocyte rate (NLR) was 2.48 (0.76–9.48), the mean platelet-lymphocyte rate (PLR) was 171.28 (39.34–1014.98). Regarding nutritional prognostic index (NPI), a mean of 52.6 (7.03–69.2) was obtained.

Progression-Free Survival

Forty-eight (56.8%) patients with progression were documented. With a median follow-up of 9 months (1–41), PFS rates at 12, 24 and 36 months were estimated at 51%, 34% and 34%, respectively (Table 4), the median PFS in total population was 13 months (Figure 1). Table 4 also shows PFS according to features; significant differences were found in PFS related to histology. Figure 2 shows that PFS in non-acral patients was longer than ALM histology (16 vs 5 months, p = 0.026) and cannot be estimated for mucosal histology. There is a significantly increased risk of progression for ALM histology compared to non-acral subtypes (HR 2.49, 95% CI, 1.25–4.99, p = 0.0096).
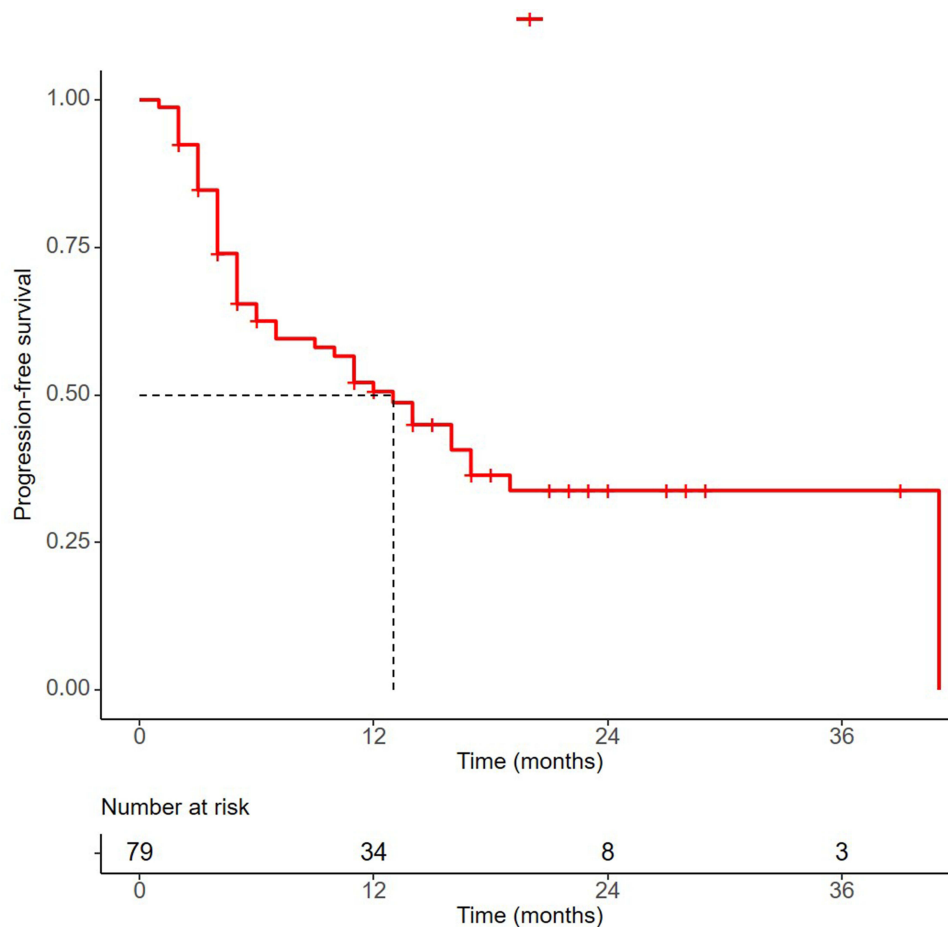
Overall Survival

After a median follow-up was 22 months (1–71), 39 (48.1%) deaths were documented; Table 5 shows that OS rates at 12, 36 and 60 months were estimated at 79%, 48%, and 32%, respectively. The median OS reported was 30 months

Table 4 Estimates of PFS According to Study Features

	N (Events)	PFS			P Value
		12 Months	24 Months	36 Months	
All patients	81 (48)	51%	34%	34%	
Age groups					
< 65	43 (21)	64%	42%	42%	
> 65	38 (25)	36%	24%	24%	0.054
Sex					
Male	37 (21)	56%	41%	41%	
Woman	44 (25)	46%	27%	27%	0.22
ECOG					
0–1	65 (37)	55%	36%	36%	
2	16 (9)	27%	—	—	0.26
Histology					
ALM	24 (17)	26%	19%	19%	
Mucosal	14 (6)	51%	51%	—	
Non-acral	34 (18)	67%	40%	40%	**0.026**
Clinical stage at diagnosis					
I	3 (3)	33%	33%	33%	
II	8 (5)	50%	38%	38%	
III	31 (16)	58%	34%	—	
IV	33 (19)	49%	31%	31%	0.96
Metastases site					
Local	30 (15)	54%	31%	—	
Systemic	51 (31)	49%	35%	35%	0.83
Lymphovascular invasion					
No	38 (22)	45%	34%	—	
Yes	13 (5)	62%	—	—	0.44
Perineural invasion					
No	34 (19)	51%	31%	—	
Yes	12 (7)	24%	—	—	0.57
Anemia					
No	68 (37)	51%	32%	32%	
Yes	13 (9)	50%	40%	40%	0.78
LDH, U/L					
> 246	22 (15)	38%	19%	19%	
120–246	58 (31)	54%	37%	37%	0.17
Radiotherapy*					
No	49 (30)	40%	18%	18%	
Yes	18 (10)	59%	47%	47%	0.056
NLR					
≤ 2.5	51 (29)	46%	32%	—	
> 2.5	30 (17)	57%	37%	37%	0.49
PLR					
≤ 150	48 (26)	42%	36%	—	
> 150	33 (20)	61%	29%	29%	0.59
NPI					
≤ 45	15 (13)	40%	27%	27%	
> 45	62 (31)	56%	37%	—	0.34

Notes: * Patients who received RT to brain metastases were not considered. The bold value is to emphasize that result is positive (statistically significant).

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Figure 1 Estimated progression-free survival (PFS) in Peruvian patients with advanced melanoma treated with immunotherapy.

(Figure 3). Tables 5 and 6 shows that a significant difference was founded in OS between non-acral and ALM histology: median OS was longer for non-acral (61 months, HR: 0.23, p = 0.0001) and mucosal (HR: 0.28, p = 0.011) than ALM histology (14 months) (Figure 4).

Subsequent Treatment

Among patients treated with immunotherapy, 44.3% had received subsequent therapy, 32% was chemotherapy (most frequent dacarbazine) followed by 12.3% which received palliative radiotherapy (CNS, local progression). 24.6% of patients received best supportive care after 1L immunotherapy.

Response to Treatment

According to response to treatment, objective response rates (ORR) were observed in 29.6% of patients: 8.6% had complete response (CR), 21% had partial response (PR). 34.6% achieved stable disease (SD) and 35.8% presented progressive disease (PD). Divided by histology, ORR were 33.3%, 30.7% and 19.2% in non-acral, mucosal and ALM histology, respectively. No significant differences were found between study features and ORR.

Safety

Table 7 shows treatment-related adverse events (AEs), these were reported in 59.6% of patients, the majority were mild (grade I and II), only 3% were grade 3 (rash grade 3) and no grade 4 AEs were reported. About immune-related adverse events (irAEs), the most frequent were skin reactions (29%), followed by asthenia (22%) and hypothyroidism (11%). The
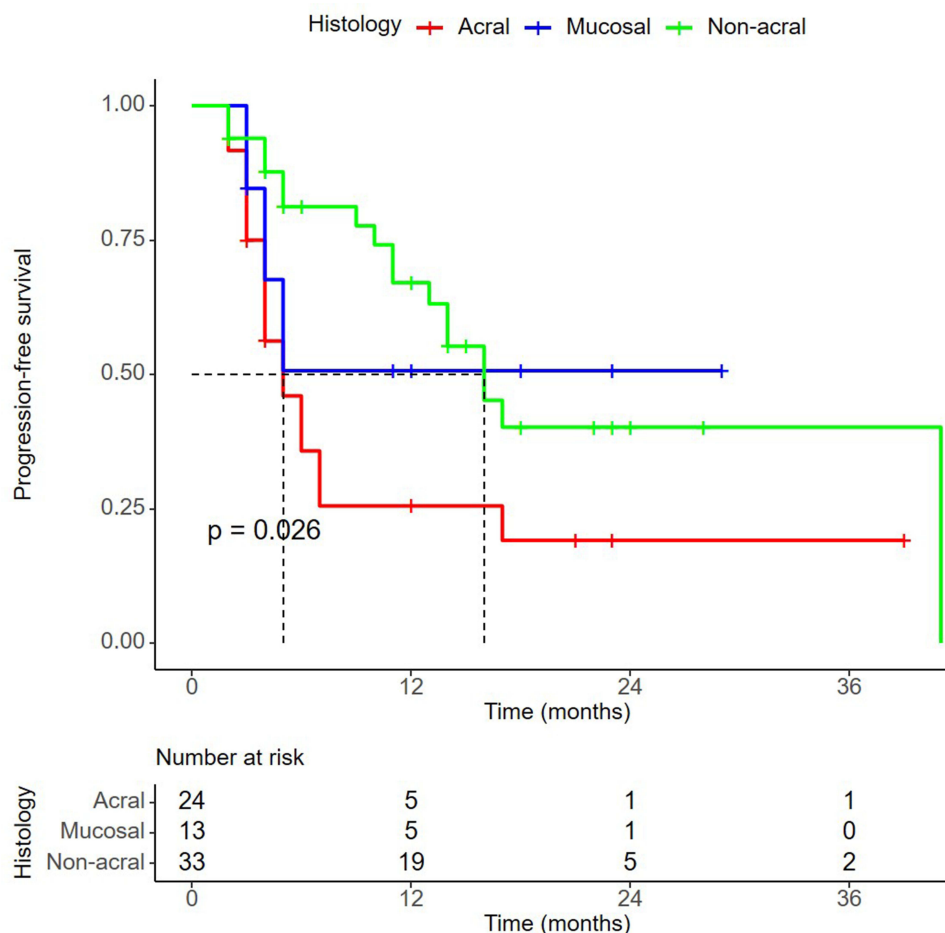
Figure 2 Estimated progression-free survival (PFS) according to histology.

percentage of patients who discontinued the treatment owing to AEs was 7%. No deaths were attributed to immunotherapy.

Biomarkers

Regarding immune inflammatory blood biomarkers, no association between PFS with NLR (p = 0.49), PLR (p = 0.3) and PNI (p = 0.71) were found.

Discussion
Efficacy

Immunotherapy (anti-PD-1 monotherapy and combinations) reported antitumor efficacy in pivotal studies with advanced melanoma; most of these patients had non-acral histologies. This Peruvian study enrolled more ALM cases than pivotal studies. Is known that responses and OS for ALM and mucosal subtypes are worse than non-acral subtypes,[20] and this was confirmed in our trial. Despite immunotherapy efficacy being expected to be lower, our ALM patients had a manageable safety profile using nivolumab as 1L treatment. Although the efficacy seems to be lower in ALM histology, it is not well documented as this subtype has been excluded in pivotal trials. In Caucasians population, non-acral is the most common subtype (<10% is acral subtype),[21] whereas Asian populations have higher prevalence of acral (>40%)[22,23] and 20% in Latin America (LATAM) countries.[24]

Significant differences were found in OS and PFS with histology, confirming lower response to immunotherapy in ALM histology in our cases. Whereas PFS and OS were lower than non-acral histology, outcomes with immunotherapy

Table 5 Overall Survival Estimates According to Study Features

	N (Events)	OS			p Value
		12 Months	36 Months	60 Months	
All patients	81 (39)	79%	48%	32%	
Age groups, years					
< 65	44 (19)	82%	53%	53%	
≥ 65	37 (20)	74%	43%	—	0.37
Sex					
Male	37 (16)	80%	56%	56%	
Woman	44 (23)	78%	43%	—	0.27
ECOG					
0–1	66 (30)	80%	51%	34%	
2	15 (9)	72%	36%	—	0.19
Histology					
ALM	26 (21)	59%	14%	—	
Mucosal	13 (5)	85%	62%	—	
Non-acral	33 (11)	87%	65%	65%	**< 0.0001**
Clinical stage at diagnosis					
I	3 (3)	100%	33%	33%	
II	8 (6)	50%	38%	—	
III	31 (15)	82%	42%	—	
IV	32 (12)	83%	59%	59%	0.28
Metastases site					
Local	29 (13)	83%	42%	—	
Systemic	52 (26)	76%	52%	35%	0.77
Lymphovascular invasion					
No	37 (20)	74%	41%	—	
Yes	14 (6)	77%	—	—	0.55
Perineural invasion					
No	33 (17)	83%	40%	—	
Yes	13 (8)	43%	32%	—	0.28
Anemia					
No	69 (32)	81%	48%	—	
Yes	12 (7)	67%	50%	50%	0.92
LDH, U/L					
> 246	22 (11)	76%	45%	45%	
120–246	58 (28)	79%	48%	24%	0.87
Radiotherapy*					
No	49 (23)	74%	46%	—	
Yes	17 (7)	82%	58%	58%	0.33
Neutrophil-lymphocyte rate (NLR)					
≤ 2.5	51 (24)	78%	45%	—	
> 2.5	30 (15)	79%	54%	36%	0.72
Platelet-lymphocyte rate (PLR)					
≤ 150	49 (22)	77%	47%	—	
> 150	32 (17)	80%	50%	33%	0.86
Nutritional prognostic index (NPI)					
≤ 45	15 (9)	80%	53%	35%	
> 45	64 (28)	79%	50%	—	0.76

Notes: * Patients who received RT to brain metastases were not considered. The bold value is to emphasize that result is positive (statistically significant).
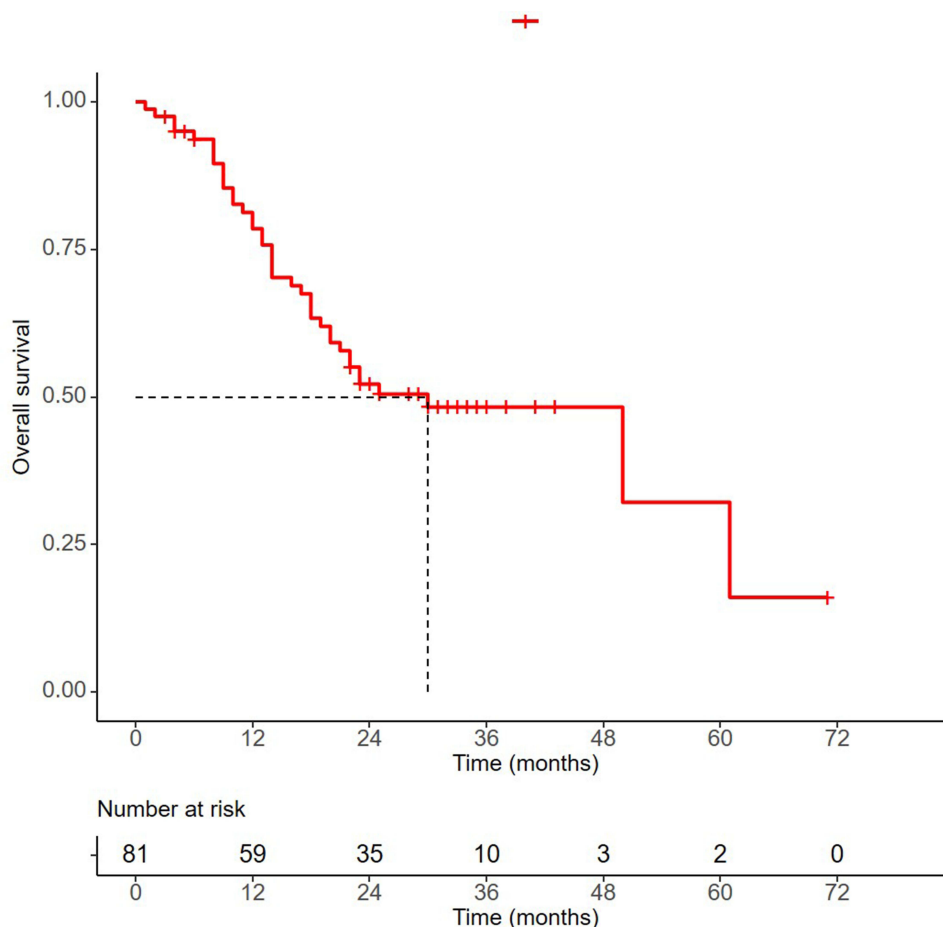
Figure 3 Estimated first line (1L) overall survival (OS) in Peruvian patients with advanced melanoma treated with immunotherapy.

are better than historical chemotherapy. These results can be useful for possible treatment profile decisions in a population with more patients with ALM histology.

The 5-year OS rate in Peruvian patients was compared with rates reported in pivotal trials (CheckMate 066, CheckMate 067 nivolumab group) and small Asian trials. Although 5-year OS rate of Peruvian patients in this study was lower than CheckMate 066 and CheckMate 067 (32%, 39% and 44%, respectively), probably due to a higher proportion of ALM histology patients.[25] Compared with Asian trials, Peruvian patients with ALM histology achieved lower OS rates. Although a Japanese trial with ALM and mucosal advanced melanoma patients treated with immunotherapy (n = 30) showed 1-year and 2-year OS rates of 83.3% and 65.6%, respectively; our study (ALM n = 26) reported 1-year and 3-year OS rates of 59% and 14%, respectively.[26] Regarding PFS for all subtypes in our study was

Table 6 Estimation of the Effect of Features Under Study on the Risk of Death

	HR	**95% CI**	**p Value**
Histology			
ALM	Ref.		
Mucosal	0.28	0.10–0.75	**0.011**
Non-acral	0.23	0.10–0.48	**0.0001**

Notes: The bold value is to emphasize that result is positive (statistically significant).
Abbreviations: HR, hazard ratio; CI, confidence interval; Ref., reference.
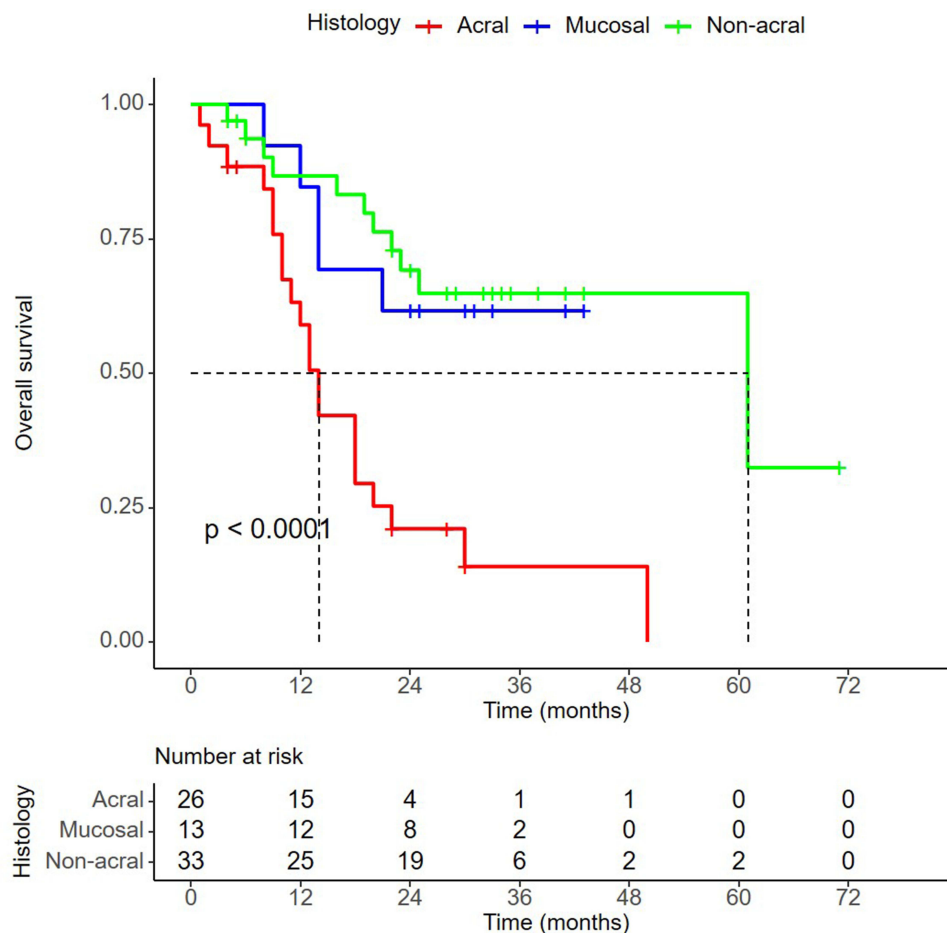
Figure 4 Estimated OS in Peruvian patients with advanced melanoma according to histology.

longer than median PFS for nivolumab group in CheckMate 067 and CheckMate 066 trials (13 vs 6.9 vs 5.1 months, respectively). In fact, our PFS was similar to the nivolumab + ipilimumab group in CheckMate 067 (13 vs 11.5 months, respectively). However, the median PFS for ALM histology was modest (5 months). These results could have some explanations, mainly due to small samples for analysis between subgroups, and the high burden of disease in Peruvian patients (almost 40% metastatic de novo, with average LDH levels above normal). Another point to consider that can affect survival outcomes is the regularity of treatment: 14% of total patients had a delay of 1 week at most 2 weeks in receiving monthly therapy due access issues. After progression, most of our patients received chemotherapy as subsequent therapy (more accessible for the majority of patients in LATAM countries and public institutions), whereas in high-income countries there are more novel treatment options.

Peruvian patients achieved an ORR of 29.6%, while patients in CheckMate066 trial obtained an ORR of 42%. As expected, the ORR in mucosal and especially ALM population were lower compared with non-acral subtypes. It is important to point out that the ORR in Peruvian ALM subpopulation was 19.2%, very similar to that reported in Asian populations (18%). Recently, a Peruvian trial which evaluated immunotherapy (nivolumab) in patients with advanced melanoma (n = 57) including ALM (37%, n = 21) reported a median OS of 28.9 months for ALM histology, with a similar ORR of 19% in these patients.[27] Despite a small percentage of irregular treatment, we obtained a high clinical benefit rate (CBR) of 64.2%, ensuring a maintained response in our patients using immunotherapy.

The rate of BRAF mutation in our study was 13.6% (the Asia population reported rates of BRAF mutation about of 30%).[28,29] However, we must consider that BRAF mutation was not performed in 22.2% of patients. Also, few patients were tested for KIT and PD-L1. Biomarking is necessary in all patients with advanced melanoma. A benefit of

Table 7 Treatment-Related Adverse Events of Peruvian Patients with Advanced Melanoma

Adverse Events	Nivolumab, N=81			
	Number and Percentage (%) of Patients			
	Grade 1	Grade 2	Grade 3	Grade 4
	23 (68)	10 (29)	1 (3)	0 (0)
General disorders and administration site conditions				
Asthenia[a]	4 (11)	4 (11)	0 (0)	0 (0)
Infusion reaction	1 (3)	0 (0)	0 (0)	0 (0)
Edema	2 (6)	0 (0)	0 (0)	0 (0)
Hematological disorders				
Anemia	1 (3)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders				
Emesis	0 (0)	1 (3)	0 (0)	0 (0)
Transaminitis[b]	0 (0)	2 (5)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders				
Pruritus	0 (0)	1 (3)	0 (0)	0 (0)
Vitiligo like	7 (20)	0 (0)	0 (0)	0 (0)
Rash[c]	1 (3)	1 (3)	1 (3)	0 (0)
Metabolism and nutrition disorders				
Hypothyroidism	4 (11)	1 (3)	0 (0)	0 (0)
Musculoskeletal and neurological disorders				
Paresthesia	2 (6)	0 (0)	0 (0)	0 (0)
Renal disorders				
Creatinine increased	1 (3)	0 (0)	0 (0)	0 (0)

Notes: Severity of adverse events was graded according with Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. a. Includes asthenia, decreased activity, fatigue and malaise. b. Includes AST and/or ALT elevated. c. Includes dermatitis, dermatitis acneiform, erythematous rash, macular rash, papular rash, pruritic rash, erythema and erythema multiforme.

immunotherapy in Peruvian patients was found independent of BRAF status as shown in pivotal trials of immunotherapy for advanced melanoma.

In Peru, patients with melanoma have different clinic-pathological features than patients included in pivotal trials (mostly non-acral subtype). A Peruvian study of patients with malignant melanoma (n=488) was realized at INEN (2009–2011) and concluded that, despite its low incidence rate in the country, it is one of the most aggressive tumors, with a mean age at diagnosis of 63 years. Of the cases, 83% were cutaneous melanoma, 7% mucosal, 5% ocular and 5% indeterminate. Of the total cases with cutaneous melanoma, 58.4% were located on the lower limbs, 21.6% on the upper limbs and 9.4% on the trunk. Regarding staging, 77.2% had stage I–III and 22.8% had stage IV. The distribution of histologic subtypes was as follows: 62.2% ALM, 33.1% nodular, 2.9% superficial extension and 1.7% lentigo maligna (LM). The presence of ulceration and lymph node involvement were independent prognostic factors for survival in patients with cutaneous melanoma stage I–III.[30] Another Peruvian trial evaluated patients with cutaneous melanoma (n = 824), included ALM (n = 537) showing that older age (p = 0.022), higher Breslow (p = 0.008) and ulceration (p < 0.001) were found to be more common in ALM. Moreover, ALM had worse OS compared with total number of patients. Lower

tumor-infiltrating lymphocytes (TILs) were associated with poor outcomes in ALM subtype.[31] Recently, a Peruvian trial describing clinic-pathological characteristics of patients with melanoma during 20 years (n = 584) showed a mean Breslow thickness of 7.4 mm (T4), the most common location being lower extremity (72%), most patients had metastases at time of presentation (36% with stage III and 19% in stage IV), and stage II and III had a lower 3-year OS, reflecting a higher incidence of late-stages due to the fact that half of the populations lives in regions with limited oncological access.[32]

Other Asian populations showed similar trends as Peru. A Chinese trial showed that 41.8% of melanomas occur on the extremities (hands, feet, subungual acral melanoma) and 22.6% were located in mucosal membranes of the rectum, anus, vulva, mouth, nasopharynx (mucosal melanoma). It has been observed that in the Chinese population, melanoma has 2 main characteristics: younger age at diagnosis and advanced disease. The BRAF mutation incidence was 25.5% in these population.[22]

Safety

Immunotherapy was safe and well tolerated in our patients with advanced melanoma. The incidence of treatment-related AEs grade 3/4 with nivolumab in Peruvian patients were less comparable with CheckMate 066 trial and CheckMate 067 (3%, 11.7% and 23%, respectively). Only rash grade 3 was reported, no AEs grade 4 events occurred in our trial, allowing more patients to continue immunotherapy without permanent discontinuation. The discontinuation rate was similar to CheckMate 066 (7% and 6.8%, respectively). AEs were manageable and resolved with careful management. One fact that draws attention is the appearance of vitiligo-like in 20% of Peruvian patients treated with nivolumab (in CheckMate 066 the incidence of vitiligo was 10.7% in any grades, grade 3/4 vitiligo was 0%); this could explain the benefit in survival (mainly for non-acral subtype), knowing that the dermatological events with immunotherapy has been associated with better survival outcomes.[33,34]

Biomarkers

Regarding biomarkers, no one has been identified yet as prognostic in acral and mucosal melanoma in our study. A Chinese study evaluated factors influencing the efficacy of anti-PD-1 treatment in patients with advanced ALM and mucosal subtype melanoma (both with high frequency in this population) (n=51) and compared the use of anti-PD-1 immunotherapy in 3 cohorts (nivolumab vs pembrolizumab vs nivolumab/ipilimumab). Thirty-eight patients received monotherapy, and 13 received the combination. 31.4% were acral melanomas, 34.3% were mucosal melanoma. The total population obtained an ORR of 17.6% and a median time to progression (TTP) of 5.2 months. The ORR was 18.8% and 17.6% in patients with acral and mucosal melanoma, respectively. In subgroup analysis, patients who received combination therapy (nivolumab/ipilimumab) achieved an ORR of 35.7%, and those without liver metastases and without elevated C-reactive protein (CRP) levels before dual blockade had a higher ORR than those who did not meet these features. Univariate analysis showed that some clinical characteristics such as ECOG ≥ 2, liver metastasis, elevated LDH and elevated CRP before anti-PD-1 therapy were factors affecting time to progression (TTP). In our report no clinical or laboratory characteristics were associated with better results.

Additionally, blood biomarkers (NLR, PLR, PNI) were not associated with better outcomes in Peruvian melanoma patients. The reason of evaluating biochemical markers is for the connection between chronic inflammation and cancer, mediated by immune system cells.[35] Activated lymphocytes are necessary for tumor surveillance and destruction, while neutrophils play a role in suppressing lymphocyte proliferation and in inducing lymphocyte apoptosis.[36,37] Some trials report that in high-risk localized melanoma, a high NLR (>3) correlates with worse OS and disease-free survival (DFS).[38] Likewise, in a trial of metastatic melanoma treated with surgery (metastasectomy) and immunotherapy, a high NLR of (> 5) predicts worse OS and PFS.[39,40] A trial that evaluated the association between NLR and clinical stage at initial melanoma diagnosis (through biopsies) showed a correlation with NLR > 2.7 and advanced stages; however, it was not statistically significant due to small sample size (n = 63). Authors concluded NLR is an accessible biochemical tool with low cost that could provide prognostic information for advanced melanoma.[41] A Peruvian study showed that high NLR is a risk factor for mortality and should be monitored in every patient who is diagnosed with melanoma during their first blood count.[42]

Several studies demonstrated the prognostic benefit of NLR in patients receiving immunotherapy (checkpoint inhibitors). For example, a trial that evaluated metastatic melanoma patients receiving anti-PD-1 monotherapy (nivolumab and pembrolizumab) (n = 224) mentioned that an NLR > 5 was an independent factor of poorer OS and PFS. Patients with high NLR had more disease burden and poorer performance status.[43] More blood biomarkers are necessary to incorporate in metastatic melanoma (NLR is a potential biomarker in high risk non metastatic melanoma although the cut-off is variable in trials)[44] especially in ALM.

Nutritional prognostic index (NPI) reflects poor immune dietary status and has shown prognostic value in some diseases related with inflammation (such as myocardial infarction) and cancer; a trial reported that a lower NPI was associated with reduced tolerance to chemoradiotherapy and more AEs in head and neck cancer patients.[45] Also, NPI was evaluated as a biomarker in cancer patients who received immunotherapy (immune checkpoint inhibitors): a trial which included gastric cancer patients treated with immunotherapy and used NPI as prognostic for PFS and OS reported that a low NPI was associated with shorter PFS and OS in all patients (HR: 2.33, p = 0.013). The authors of this trial conclude that NPI could be used as a biomarker for immunotherapy to identify patients who might be sensitive to immune checkpoint inhibitors.[46] In our trial, the NPI score (as an inflammatory and nutritional biomarker) was not associated with better survival results.

Our study has potential limitations. First, it is based on retrospective analysis of medical records. Second, the sample size is small and this could affect outcomes. Also, is a real-world-data report (usually, real-world-data reports different results from pivotal studies that include highly selected populations).

Conclusion

Immunotherapy (anti-PD-1 monotherapy) showed efficacy in improving OS, PFS, ORR and CBR in Peruvian patients with advanced melanoma, with a manageable safety profile. These results confirm the significant benefit of nivolumab monotherapy, also survival can be maintained after treatment discontinuation, even using chemotherapy or radiotherapy. Acral lentiginous melanoma (ALM) histology had shorter PFS, OS and ORR compared with other non-acral subtypes. A significant difference was found in OS and PFS with histology: patients with non-acral subtype had better outcomes than ALM patients. These results are valuable for deciding profile treatments in our patients who are diagnosed with a high incidence of metastatic de novo disease and high burden disease. The ORR in Peruvian patients with ALM histology was very similar as reported in small Asian populations, and they developed more mild vitiligo-like AEs than reported in pivotal trials with immunotherapy.

No potential prognostic clinical or blood biomarkers were identified, emphasizing the need of novel biomarkers in advanced melanoma, particularly in ALM.

Acknowledgments

Disclosure

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