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IMMUNO-ONCOLOGY AND TECHNOLOGY

ORIGINAL ARTICLE

The MELimmune score—prognostic factors for overall survival in advanced melanoma and anti-PD-1 monotherapy—a multicentre, retrospective cohort study

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Background: Immunotherapy has revolutionized advanced melanoma treatment. Several prognostic factors have been studied to predict survival in this setting. We aimed to develop a prognostic score.

Materials and methods: A multicentre, retrospective cohort study was conducted including patients with advanced melanoma who started anti-programmed cell death protein 1 (PD-1) monotherapy between January 2016 and October 2019 with $\leq$2 prior treatment lines. The study endpoint was overall survival (OS). Univariate and multivariate Cox regression identified independent prognostic factors, with 95% confidence intervals (CIs). The predictive accuracy of the model was evaluated by the receiver operating characteristic (ROC) curve model.

Results: We identified 147 patients with a median follow-up of 28.9 months (95% CI 22.5-33.5 months). The median OS (mOS) for the whole cohort was 14.8 months (95% CI 10.8-18.7 months). Overall, 43 and 104 patients were treated with nivolumab and pembrolizumab, respectively. We identified four prognostic factors at baseline: $\geq$3 metastatic sites [hazard ratio (HR) 1.90, 95% CI 1.21-2.97], performance status by Eastern Cooperative Oncology Group $\geq$1 (HR 2.02, 95% CI 1.28-3.18), lymphopenia (HR 2.85, 95% CI 1.54-5.27) or increased lactate dehydrogenase (HR 2.08, 95% CI 1.19-3.63). The MELimmune score grouped patients into three risk categories: favourable prognosis (no risk factors; $n = 34$), intermediate prognosis (one risk factor; $n = 65$) and poor prognosis (two or more risk factors; $n = 48$). The mOS was 43.4 (95% CI 32.1-54.7), 14.4 (95% CI 6.8-22.0) and 6.5 (95% CI 3.6-9.4) months for favourable, intermediate and poor prognosis groups, respectively ($P < 0.001$). The area under the ROC curve was 0.74 (95% CI 0.66-0.82).

Conclusion: Using easily accessible variables from daily practice, the MELimmune prognostic score for patients with advanced melanoma treated with anti-PD-1 monotherapy holds potential to be used in clinical practice and prospectively validated in clinical trials.

Key words: melanoma, MELimmune score, anti-PD-1, prognostic factors

INTRODUCTION

Melanoma is the fifth most frequent cancer in males and females and remains one of the deadliest forms of cancer.[1-5] For >30 years, the standard of care for advanced melanoma was dacarbazine, with an overall survival (OS) at 5 years of 10%.[1,6] The treatment landscape has significantly improved with the introduction of immune checkpoint inhibitors (ICIs).[1,3] Anti-programmed cell death protein 1 (PD-1) monotherapy increased median OS (mOS) to 33-38 months, surpassing the first improvement with ipilimumab.[7-13] Long-term data from KEYNOTE-006 have demonstrated durable survival benefits, with 40% of patients achieving a 10-year OS.[13] Despite these results, the overall efficacy rates for anti-PD-1 monotherapy are still low,[14] with innate resistance in 40%-50% of patients[15] and response rates of 30%-40% in the first line.[6,16] This highlights the importance of better understanding prognostic factors of patients treated with immunotherapy, particularly when its toxicity is not negligible.[1,3,17]

Established biomarkers, such as lactate dehydrogenase (LDH), performance status (PS) by Eastern Cooperative Oncology Group (ECOG) and metastatic burden provide

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valuable prognostic information, but their individual use may be insufficient to fully stratify patients.[1,5,17-19] Emerging biomarkers, including systemic inflammatory response, like albumin, C reactive protein and neutrophil-to-lymphocyte ratio (NLR), have shown promise but lack validation for routine clinical use.[20-25] We have previously demonstrated the prognostic impact of NLR, platelet-to-lymphocyte and lymphocyte-to-monocyte ratio in patients with advanced melanoma treated with anti-PD-1.[26] Despite the utility of these biomarkers, a need persists for a more comprehensive and practical prognostic score.[5,27] An optimal model should ideally be simple and easy to use, inexpensive and readily available.[20,22] Combining various biomarkers into a prognostic score tool may be more precise and representative of true prognosis, simultaneously assessing patient's biological reserve and tumour burden/aggressiveness.[14] Such models may better stratify patients in clinical trials and provide relevant prognostic information to clinical practice.

Real-world data (RWD) provide a broader patient representation than clinical trials, capturing diverse demographic and clinical characteristics. Prognostic models developed using RWD can offer enhanced generalizability, aiding clinicians in making informed decisions tailored to real-world patient needs. In this study, our aim is to develop a simple and practical prognosis score for patients with advanced melanoma undergoing anti-PD-1 monotherapy, by incorporating clinical and laboratory variables reflective of patient status, tumour aggressiveness/burden and systemic inflammatory status.

MATERIALS AND METHODS

Study design, objective and eligibility criteria

This is a multicentre, retrospective cohort study conducted in two Portuguese centres (one general teaching hospital and one cancer centre), including patients with advanced melanoma [stage III unresectable or stage IV as per the American Joint Committee on Cancer (AJCC) eighth edition[5]] who started treatment with anti-PD-1 monotherapy (nivolumab or pembrolizumab) between January 2016 and July 2019, as first, second or third line. This is an analytical study with the objective of developing a prognostic score for survival.

Patient inclusion criteria consisted of diagnosis of advanced melanoma of the skin, conjunctive or unknown primary, regardless of the *BRAF*^{V600} mutational status, with no more than two previous treatment lines. We excluded patients who did not start systemic treatment due to clinical deterioration, or who started anti-PD-1 but had choroidal or mucosal melanoma, nonmelanoma primary cancer of the skin, other active cancer, no available whole blood count data at baseline (i.e. start date of anti-PD-1), previous exposure to anti-PD-1 or treatment with combination of anti-PD-1 and anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4). We also excluded from this study patients who died within the first 30 days of therapy start or who were exposed to less than two cycles of treatment.

Data source and variables

Important prognostic variables are not captured in the national cancer registry or other available routine database; therefore, we retrospectively assessed the patients' health records for eligibility and extraction of detailed study variables. Uniform database templates were used to ensure consistent data collection between participating sites.

Variables on demographic, clinical and pathological data at the time of diagnosis were collected, including, but not limited to, tumour location, stage as per AJCC eighth edition[5] and *BRAF*^{V600}mutational status. Clinical, laboratory and treatment characteristics at baseline were also collected [e.g. presence of central nervous system (CNS) metastases, number of metastatic sites, ECOG-PS, lymphocyte count and LDH at start date of anti-PD-1 and number and type of previous lines]. Disease progression was considered whenever reported by the physician based on clinical, laboratory or radiological/metabolic assessment. No variables in this study were coded or derived; all variables were used as originally recorded. Supplementary Annex S1, available at https://doi.org/10.1016/j.iotech.2025.101043, describes a list of all variables collected for this study.

Study endpoints and statistical analysis

Study baseline was defined as the start date of anti-PD-1. Due to the exploratory nature of the study, no pre-planned sample size and study power were calculated.

Patient, disease and treatment characteristics at diagnosis and at baseline were summarized as frequencies and percentages for categorical data and as medians and interquartile ranges for continuous data. Categorical data were compared using the χ^2 test; continuous variables were compared using the Mann—Whitney or the Kruskal—Wallis tests.

The study endpoint was OS, defined as the time from the start date of treatment with anti-PD-1 until the date of death from any cause. Patients were censored at the date of the last follow-up whenever they were lost to follow-up or death was not reported. We calculated mOS and 1-/2-year OS rates. In addition to OS, real-world progression-free survival (rwPFS) was analysed and defined as the time from the start date of anti-PD-1 therapy to either documented disease progression or death, whichever occurred first. Patients were censored at the date of the last follow-up if neither progression nor death was reported.

Median OS and rwPFS were obtained using the Kaplan—Meier product-limit method, and the log-rank test was used to compare group outcomes, with study baseline considered as the index date. The impact of individual independent variables on OS and rwPFS was analysed using a univariate Cox proportional hazards model. We subsequently used Cox proportional hazards model for multivariate analysis (stepwise procedure with a significance level of 0.05 for entering and removing variables). The model included clinically relevant criteria regardless of statistical significance in the univariate analysis (LDH, ECOG-PS) and statistically significant or notoriously unbalanced variables.

The proportionality assumption was assessed graphically by using plots of log [−log(survival)] versus log of survival time. The case deletion method was used to handle missing values in all explanatory variables.

Once the prognostic factors were identified and the final model designed, a risk-group variable was created by dividing patients according to the number of risk factors present (favourable prognosis if no risk factors, intermediate if one risk factor and high risk if two or more risk factors)—the MELimmune score. The predictive accuracy of the model was evaluated by the receiver operating characteristic (ROC) curve method. All statistical tests were two-tailed and statistical significance was assumed when $P < 0.05$. Analyses were carried out using SPSS statistics v.24 (IBM, Armonk, NY).

General considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and was reported following the European Society for Medical Oncology (ESMO) Guidelines for Reporting Oncology Real-World Evidence.[28] The study protocol and the request for exemption from informed consent were approved by the ethics committee from both participating centres.

RESULTS

Population characteristics

We included 147 patients and the patients' flow diagram is presented in Supplementary Figure S1, available at https://doi.org/10.1016/j.iotech.2025.101043. Demographic and clinicopathological characteristics at diagnosis, clinical and laboratory characteristics at baseline and systemic treatment characteristics are presented in Table 1.

In the overall cohort, most patients had skin as the primary location of melanoma (87.8%) and no *BRAF*^{V600} mutations were detected (78.9%). Significant differences among the MELimmune groups included: (i) a higher proportion of patients in the intermediate group with no metastases at diagnosis and older at baseline; (ii) a significantly higher proportion of patients in the poor prognostic group with CNS metastases, ≥3 metastatic sites, higher ECOG-PS, lymphopenia and excessively high LDH at baseline. Overall, 43 (29.3%) and 104 (70.7%) patients were treated with nivolumab and pembrolizumab, respectively, used for the first-line setting in 107 (72.8%) patients. Forty patients were treated in the second- ($n = 35$; 23.8%) or third-line ($n = 5$; 3.5%) context. At the time of the analysis, 122 (83.0%) patients had discontinued anti-PD-1, mainly due to disease progression (59.9%), and 99 (67.3%) had died. Of those who progressed, while on anti-PD-1 or after stopping for other reason than progression ($n = 106$), 80 (75.5%) patients went on to receive subsequent systemic therapy, with a significant lower proportion of patients in the poor prognostic group receiving subsequent treatment.

Clinical outcomes

With a median follow-up time after anti-PD-1 treatment initiation of 28.0 months [95% confidence interval (CI) 22.5-33.5 months], the median rwPFS for the entire cohort of 147 patients was 7.5 months (95% CI 5.9-9.2 months, Supplementary Figure S2, available at https://doi.org/10.1016/j.iotech.2025.101043) and mOS was 14.8 months (95% CI 10.8-18.7 months, Figure 1). The 1- and 2-year OS for the whole cohort was 49.0% and 21.1%, respectively.

Univariate analyses. Univariate analyses of all potential prognostic variables with OS are presented in Table 2. Baseline clinical features significantly associated with poor OS were the presence of CNS metastatic disease, both asymptomatic and symptomatic (HR 2.09, 95% CI 1.16-3.78 and HR 5.49, 95% CI 1.66-17.59, respectively), three or more metastatic sites (HR 2.29, 95% CI 1.51-3.47) and ECOG-PS ≥1 (HR 2.58, 95% CI 1.68-3.96). Baseline laboratory findings associated with worse OS included the presence of anaemia [haemoglobin (Hb) <12.0 g/dl; HR 2.13, 95% CI 1.41-3.20], lymphopenia (<1.0 × 10^9/l; HR 2.51, 95% CI 1.38-4.57), thrombocytosis (>450 × 10^9/l; HR 2.26, 95% CI 1.21-4.26) and excessively high LDH (>2× upper limit of normal; HR 3.96, 95% CI 2.33-6.75). Similar findings for univariate analyses for rwPFS are presented in Supplementary Table S1, available at https://doi.org/10.1016/j.iotech.2025.101043.

Multivariate analysis. Table 3 presents the final multivariate model for OS, including four adverse prognostic factors at baseline—three or more metastatic sites (HR 1.90, 95% CI 1.21-2.97), ECOG-PS of ≥1 (HR 2.02, 95% CI 1.28-3.18), presence of lymphopenia (HR 2.85, 95% CI 1.54-5.27) and excessively high LDH (HR 2.08, 95% CI 1.19-3.63). None of the four variables violated the proportional hazards assumption. Similar model was conducted for rwPFS (Supplementary Table S2, available at https://doi.org/10.1016/j.iotech.2025.101043).

Considering the aforementioned criteria, patients were categorized according to the number of risk factors present at baseline: favourable (no risk factors, $n = 34$), intermediate (one risk factor, $n = 65$) and poor prognosis (two or more risk factors, $n = 48$)—the MELimmune score. The mOS was 43.4 months (95% CI 32.1-54.7 months), 14.8 months (95% CI 8.5-21.0 months) and 6.5 months (95% CI 3.3-9.7 months) for favourable, intermediate and poor prognosis, respectively ($P < 0.001$; Figure 2). One- and two-year OS rates were 88.2% and 52.9%; 47.7% and 18.5%; and 22.9% and 2.1% for favourable, intermediate and poor prognosis, respectively. The rwPFS per prognosis group is described in Supplementary Figure S3, available at https://doi.org/10.1016/j.iotech.2025.101043.

To evaluate the value of the MELimmune score as a prognostic model, we used the ROC curve method, showing an area under the curve (AUC) of 0.74 (95% CI 0.66-0.82, $P < 0.001$) (Supplementary Figure S4, available at https://doi.org/10.1016/j.iotech.2025.101043).

Table 1. Patient, disease and treatment characteristics ($n = 147$)

Variable list	Overall cohort	MELimmune score			*P* value
		Favourable	Intermediate	Poor	
Number of patients (%)	147 (100)	34 (23.1)	64 (43.5)	49 (33.3)	—
Demographic and clinicopathological characteristics at diagnosis					
Gender, *n* (%)					
Female	74 (50.3)	12 (35.3)	36 (56.3)	26 (53.1)	0.128
Primary location, *n* (%)					
Skin	129 (87.8)	29 (85.3)	60 (93.8)	40 (81.6)	0.191
Conjunctive	4 (2.7)	2 (5.9)	1 (1.6)	1 (2.0)	
Unknown	14 (9.5)	3 (8.8)	3 (4.7)	8 (16.3)	
BRAF status, *n* (%)					
Wild type	116 (78.9)	27 (79.4)	53 (82.8)	36 (73.5)	0.481
Metastatic status, *n* (%)[a]					
M0	119 (81.0)	25 (73.5)	59 (92.2)	35 (71.4)	**0.002**
M1a	11 (7.5)	6 (17.6)	3 (4.7)	2 (4.1)	
M1b	4 (2.7)	2 (5.9)	1 (1.6)	1 (2.0)	
M1c	10 (6.8)	1 (2.9)	1 (1.6)	8 (16.3)	
M1d	3 (2.0)	0 (0)	0 (0)	3 (6.1)	
Clinical and laboratory characteristics at baseline					
Age, years					
Median	68	61	71	66	**0.025**
IQR	55-77	53-69	60-80	52-76	
CNS metastases, *n* (%)					
No	127 (86.4)	34 (100)	59 (92.2)	34 (69.4)	**<0.001**
Yes, and asymptomatic	16 (10.9)	0 (0)	5 (7.8)	12 (24.5)	
Yes, and symptomatic	4 (2.7)	0 (0)	0 (0)	3 (6.1)	
Metastatic sites, *n* (%)					
0	7 (4.8)	2 (5.9)	5 (7.8)	0 (0)	**<0.001**
1-2	68 (46.3)	32 (94.1)	30 (46.9)	6 (12.2)	
≥3	72 (49.0)	0 (0)	29 (45.3)	43 (87.8)	
ECOG-PS, *n* (%)					
0	73 (49.7)	34 (100)	34 (53.1)	5 (10.4)	**<0.001**
≥1	74 (50.3)	0 (0)	30 (46.9)	44 (89.8)	
Haemoglobin, *n* (%)					
No anaemia	98 (66.7)	28 (82.4)	47 (72.3)	23 (47.9)	**0.001**
Anaemia	49 (33.3)	6 (17.6)	17 (26.2)	26 (54.2)	
Neutrophils, *n* (%)					
No neutrophilia	127 (86.4)	32 (94.1)	58 (90.6)	37 (75.5)	**0.022**
Neutrophilia	20 (13.6)	2 (5.9)	6 (9.4)	12 (24.5)	
Lymphocytes, *n* (%)					
No lymphopenia	131 (89.1)	34 (100)	59 (92.2)	38 (77.6)	**0.003**
Lymphopenia	16 (10.9)	0 (0)	5 (7.8)	11 (22.4)	
Platelets, *n* (%)					
No thrombocytosis	134 (91.2)	32 (94.1)	60 (93.8)	42 (85.7)	0.259
Thrombocytosis	13 (8.8)	2 (5.9)	4 (6.3)	7 (14.3)	
LDH, U/l					
Median	224	228	254	576	**<0.001**
IQR	185-333	178-293	176-286	219-763	
LDH, *n* (%)					
Normal (≤ULN)	72 (49.0)	21 (61.8)	39 (60.9)	12 (24.5)	**<0.001**
High (1-2× ULN)	51 (34.7)	13 (38.2)	22 (34.4)	16 (32.7)	
Excessively high (>2× ULN)	24 (16.3)	0 (0)	3 (4.7)	21 (42.9)	
Treatment characteristics					
Number of previous lines					
Median	0	0	0	0	0.348
IQR	0-1	0-1	0-0	0-1	
Previous lines, *n* (%)					
0	107 (72.8)	25 (73.5)	50 (78.1)	32 (65.3)	0.355
1	35 (23.8)	9 (26.5)	11 (17.2)	15 (30.6)	
2	5 (3.4)	0 (0)	3 (4.7)	2 (4.1)	
Anti-PD-1, *n* (%)					
Nivolumab	43 (29.3)	10 (29.4)	30 (31.3)	13 (26.5)	0.861
Pembrolizumab	104 (70.7)	24 (70.6)	44 (68.8)	36 (73.5)	
Number of anti-PD-1 cycles received, *n*					
Median	10	27	14	10	
IQR	5-21	15-36	5-18	3-13	**<0.001**
Anti-PD-1 status, *n* (%)					
Stopped after 2 years of therapy	9 (6.1)	6 (17.6)	2 (3.1)	1 (2.0)	**0.001**
Stopped	113 (76.9)	19 (55.9)	49 (76.6)	45 (91.8)	
Ongoing	25 (17.0)	9 (26.5)	13 (20.3)	3 (6.1)	

Continued

Table 1. Continued

Variable list	Overall cohort	MELimmune score			*P* value
		Favourable	Intermediate	Poor	
Reason for stopping anti-PD-1, *n* (%)					
Toxicity	17 (11.6)[b]	4 (21.1)[b]	9 (18.4)	4 (8.9)	**0.006**
Progressive disease	88 (59.9)[b]	15 (78.9)[b]	36 (73.5)	37 (82.2)	
Other	8 (5.4)[b]	0 (0)[b]	4 (8.2)	4 (8.9)	
Subsequent systemic treatment received, *n* (%)					**0.042**
No	26 (24.5)	1 (6.3)	9 (20.0)	16 (35.6)	
Yes	80 (75.5)	15 (93.7)	36 (80.0)	29 (64.4)	

Bold values indicate statistically significant *P*-values (<0.05).
Anaemia, Hb <12 g/dl; lymphopenia, lymphocyte count $<1.0 \times 10^9$/l; neutrophilia, neutrophil count $>7.5 \times 10^9$/l; thrombocytosis, platelets $>450 \times 10^9$/l.
AJCC, American Joint Committee on Cancer; CNS, central nervous system; ECOG-PS, performance status by Eastern Cooperative Oncology Group; Hb, haemoglobin; IQR, interquartile range; LDH, lactate dehydrogenase; M1, metastatic disease; PD-1, programmed cell death protein 1; ULN, upper limit of normal.
[a]Staging by AJCC eighth edition.[5]
[b]Percentage of patients who stopped immunotherapy.

DISCUSSION

Our study aimed to develop a simple and practical prognostic model, the MELimmune score, tailored to patients undergoing anti-PD-1 monotherapy for advanced melanoma. Our findings confirm that several key independent prognostic factors significantly impact OS in this population: baseline ECOG-PS, number of metastatic sites, lymphopenia and excessively high LDH. By integrating these factors into the MELimmune score, we were able to stratify patients into three prognostic groups: favourable, intermediate and poor, with significant differences observed in OS among them. This score is associated with an AUC of the ROC curve of 0.74.

Several other scores merging different biological factors have been evaluated for patients treated with immunotherapy based on ICI.[16] For example, for patients with BRAF-mutant advanced melanoma, Schadendorf et al. conducted a retrospective pooled analysis of phase III trials of dabrafenib plus trametinib (COMBI-d and COMBI-v),[17] where high baseline LDH levels and a higher number of metastatic sites were both associated with worse OS. Combining these two factors with the sum of lesion diameters, patients were categorized into five prognostic groups.[17] Also, Diem et al. obtained similar results using ECOG-PS, LDH and number of metastatic sites as factors.[29] More recently, Pires da Silva et al. built a model based on a nomogram to predict overall

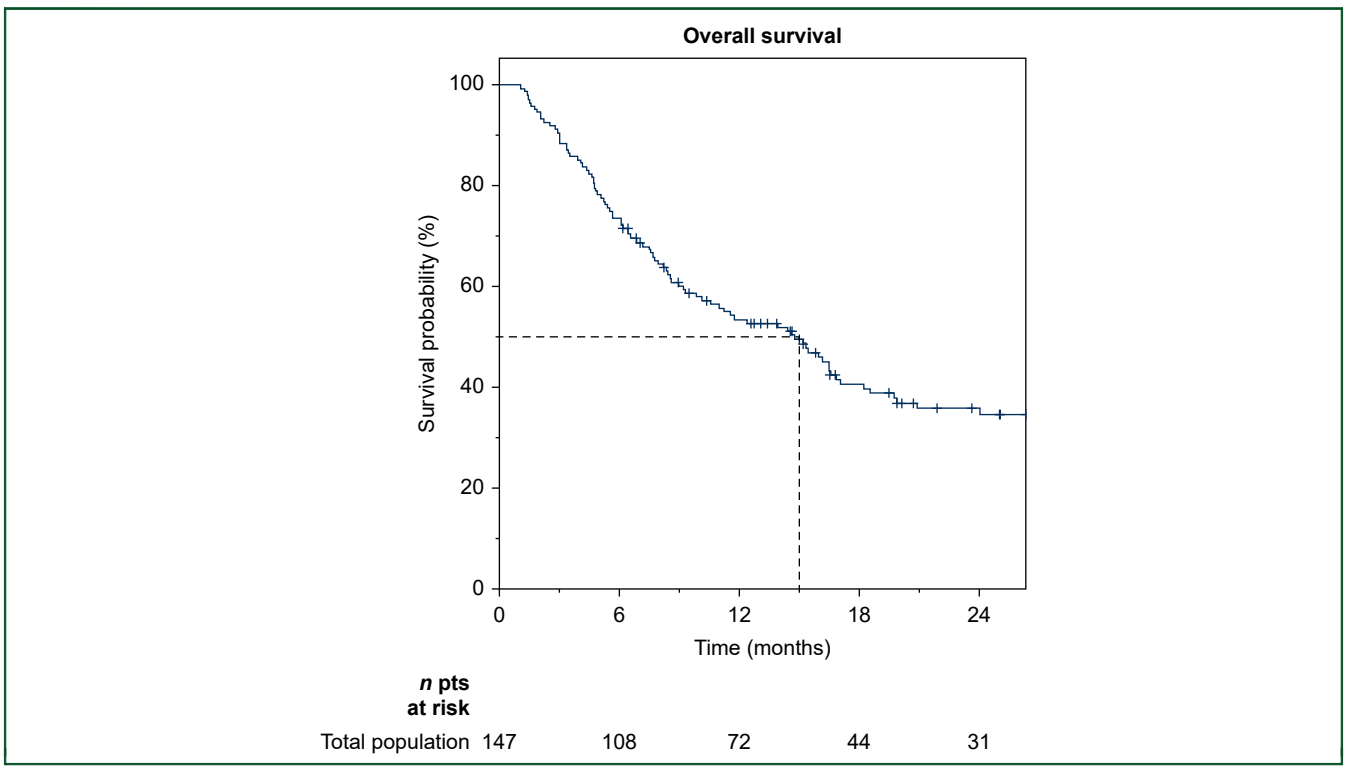

Figure 1. OS probability for patients treated with anti-PD-1. The mOS for the entire cohort of 147 patients was 14.8 months (95% CI 10.8-18.7 months). The 1- and 2-year OS for the whole cohort was 49.0% and 21.1%, respectively.
CI, confidence interval; mOS, median overall survival; OS, overall survival; PD-1, programmed cell death protein 1; pts, patients.

Table 2. Overall survival—univariate analyses of patient demographic and clinical characteristics

Variable list	Overall survival		
	HR	95% CI	*P* value
Univariate analyses			
Demographic and clinicopathological characteristics at diagnosis			
Sex			
Female	Reference	Reference	0.242
Male	0.79	0.52-1.18	
Primary tumour location			
Skin	Reference	Reference	
Conjunctive	0.29	0.04-2.06	0.214
Unknown	0.63	0.28-1.45	0.280
BRAF status			
Wild type	Reference	Reference	0.915
Mutated	1.03	0.63-1.6	
Metastatic status[a]			
M0	Reference	Reference	
M1a	0.51	0.12-2.08	0.346
M1b	<0.001	<0.001-1.23[271]	0.969
M1c	0.16	0.01-1.74	0.131
M1d	0.49	0.10-2.44	0.382
Clinical and laboratory characteristics at baseline			
Age			
≤70 years	Reference	Reference	0.116
>70 years	1.39	0.92-2.09	
CNS metastases			
No	Reference	Reference	
Yes, and asymptomatic	2.09	1.16-3.78	**0.014**
Yes, and symptomatic	5.40	1.66-17.59	**0.005**
Metastatic sites			
0-2	Reference	Reference	**<0.001**
≥3	2.29	1.51-3.47	
ECOG-PS			
0	Reference	Reference	**<0.001**
≥1	2.58	1.68-3.96	
Haemoglobin			
No anaemia	Reference	Reference	**<0.001**
Anaemia	2.13	1.41-3.20	
Neutrophils			
No neutrophilia	Reference	Reference	0.135
Neutrophilia	1.54	0.87-2.72	
Lymphocytes			
No lymphopenia	Reference	Reference	**0.003**
Lymphopenia	2.51	1.38-4.57	
Platelets			
No thrombocytosis	Reference	Reference	**0.011**
Thrombocytosis	2.26	1.21-4.26	
LDH			
Normal (≤ULN)	Reference	Reference	
High (1-2× ULN)	1.33	0.84-2.11	0.228
Excessively high (>2× ULN)	3.96	2.33-6.75	**<0.001**
Number of previous lines			
0	Reference	Reference	
1	1.05	0.66-1.68	0.843
2	1.40	0.50-3.90	0.518

Bold values indicate statistically significant *P*-values (<0.05).
Anaemia, Hb <12 g/dl; lymphopenia, lymphocyte count <1.0 × 10^9/l; neutrophilia, neutrophil count >7.5 × 10^9/l; thrombocytosis, platelets >450 × 10^9/l.
AJCC, American Joint Committee on Cancer; CI, confidence interval; CNS, central nervous system; ECOG-PS, performance status by Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; M1, metastatic disease; ULN, upper limit of normal.
[a]Staging by AJCC eighth edition.[5]

Table 3. Overall survival—multivariate analysis and final model

Variable list (all at baseline)	Overall survival		
	HR	95% CI	*P* value
Multivariate model with multiple imputation			
Number of metastatic sites			
0-2	Reference	Reference	**0.005**
≥3	1.90	1.21-2.97	
ECOG-PS			
0	Reference	Reference	**0.002**
≥1	2.02	1.28-3.18	
Lymphocytes			
No lymphopenia (≥1.0 × 10^9/l)	Reference	Reference	**<0.001**
Lymphopenia (<1.0 × 10^9/l)	2.85	1.54-5.27	
LDH			
Normal to high (≤2× ULN)	Reference	Reference	**0.010**
Excessively high (>2× ULN)	2.08	1.19-3.63	

Bold values indicate statistically significant *P*-values (<0.05).
CI, confidence interval; CNS, central nervous system; ECOG-PS, performance status by Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal.

response rate, PFS and OS.[30] The nomogram for OS assesses ECOG-PS, laboratory values (such as Hb, NLR and LDH), presence of brain and/or liver metastases, line of treatment and treatment based on anti-PD-1 monotherapy or combination with ipilimumab. Similarly to our score, the nomogram categorizes patients into three groups of OS (good, intermediate and poor) and an AUC of 0.77.[30]

Combining various biomarkers into a prognostic score would be more precise and representative of true prognosis, rather than assessing them individually.[14] By using the MELimmune score with these four factors, we can evaluate the triad patient—tumour—inflammation interaction (ECOG-PS as a surrogate for biological reserve and functional status; number of metastatic sites and LDH for tumour's aggressiveness/burden; and lymphopenia for systemic inflammatory status).[1,17-19] Additionally, such biomarkers are readily available and not associated with practice-changing methods or costly tests.

Limitations to this study include its retrospective nature and associated problems of potential selection bias and missing data. Consecutive patient sampling from two different participating centre types (general teaching hospital and cancer centre) was used to reduce selection bias, and several efforts were made to obtain the complete patient information (only four patients were excluded due to missing data). ICI responses are not expected as shortly after treatment start as with BRAF/MEK inhibitor combination because the immune system stimulation takes weeks to act. Consequently, patients who died within 30 days were excluded from this analysis, as they were less likely to benefit from the therapy, effectively introducing additional bias. Furthermore, this study is limited for its population heterogeneity. Distinct settings (first, second or even third line) were allowed, which contribute for different prognosis: for untreated patients, an mOS of 33-38 months is expected,[9-13] and for patients previously exposed to ipilimumab, an mOS of 13-16 months is expected.[31,32] However, this variable was well balanced at baseline and there were no differences between the three prognostic categories, decreasing the likelihood of bias. Finally, although melanomas of different primaries were included, literature shows similar prognosis between melanoma of skin, conjunctive

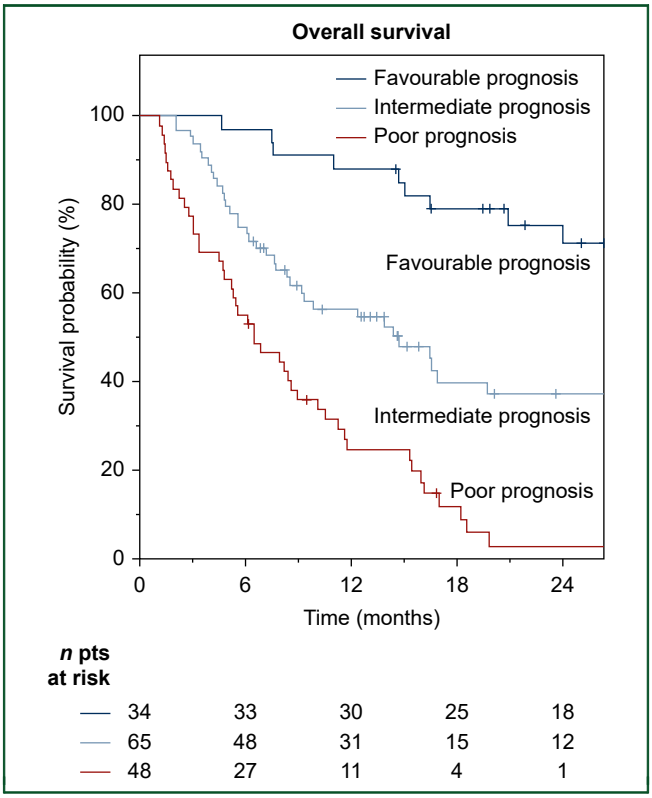

Figure 2. OS probability for patients treated with anti-PD-1 by prognostic group according to the MELimmune score. The mOS was 43.4 months (95% CI 32.1-54.7 months), 14.8 months (95% CI 8.5-21.0 months) and 6.5 months (95% CI 3.3-9.7 months) for favourable, intermediate and poor prognosis, respectively ($P < 0.001$). The 1- and 2-year OS rates were 88.2% and 52.9%; 47.7% and 18.5%; and 22.9% and 2.1% for favourable, intermediate and poor prognosis, respectively.
CI, confidence interval; mOS, median overall survival; OS, overall survival; PD-1, programmed cell death protein 1; pts, patients.

and unknown primary. We carefully excluded patients with choroidal or mucosal melanoma with substantial worse prognosis.[33,34] Moreover, despite the unbalance with more unknown primaries in the poor prognostic group, there were no differences found regarding these three groups in the univariate and multivariate analyses for OS.

The MELimmune score could hold significant clinical utility in guiding treatment management and prognostic assessment for patients with advanced melanoma undergoing anti-PD-1. Further validation of this tool in an independent larger sample may confirm its clinical validity. Future studies should aim to include a diverse, multicentric cohort to evaluate the score's generalizability across various health care settings and patient populations. Additionally, given the increasing use of combination immunotherapy with ipilimumab and nivolumab in advanced melanoma, it will be crucial to assess the prognostic value of the MELimmune score in this context. Evaluating the score's applicability in patients receiving dual checkpoint blockade may provide important insights into optimizing treatment selection and better identifying those most likely to benefit from combination therapy. ESMO has suggested the use of several clinical parameters as biomarkers to better select patients with the highest benefit from combination immunotherapy (anti-CTLA-4 plus anti-PD-1), although the evidence for some of these factors comes from unplanned analysis.[1] Thus, combining these biomarkers into a score, like the MELimmune, enables clinicians to identify individuals at a higher risk of disease progression and death, better selecting patients in need for the synergistically improved antitumour responses provided by the dual blockade or new clinical trials.

Overall, the integration of the MELimmune score into clinical practice and trials has the potential to improve patient care and optimize resource allocation in the management of advanced melanoma.

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