Acral lentiginous melanoma shows a poorer response to immune checkpoint inhibition in the unresectable or metastatic setting – a EUMelaReg real world outcome study.

Michael Weichenthal[1], Iván Márquez Rodas[2], Johanna Mangana[3], Lidija Kandolf[4], Nethanel Asher[5], Marc Bender[6], Iva Gavrilova[7], Amina Jalovčić-Suljevic[8], Laura Mazilu[9], Selma Ugurel[10], Paolo Antonio Ascierto[11], Lars Bastholt[12], Helen Gogas[13], Ralf Gutzmer[14], John Haanen[15], Peter Mohr[16], Piotr Rutkowski[17], Reinhard Dummer[3], Dirk Schadendorf[10], Enrique Espinosa[18]

[1]Christian-Albrechts-Universität Kiel, Kiel, Germany, [2]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [3]University Hospital of Zurich, Zurich, Switzerland; [4]Military Medical Academy Belgrad, Belgrad, Serbia; [5]The Ella Lemelbaum Institute for Immuno-Oncology Sheba Medical Center, Ramat-Gan, Israel; [6]EuMelaReg gGmbH, Berlin, Germany; [7]National Oncology Hospital Sofia, Sofia, Bulgaria; [8]Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina ; [9]Ovidius Clinical Hospital OCH, Ovidiu, Romania; [10]Universitätsklinikum Essen, Essen, Germany; [11]Instituto Nazionale Tumori - IRCCS - Fondazione Pascale, Napoli, Italy; [12]Odense University Hospital, Odense, Denmark; [13]Laiko Hospital Athens, Athens, Greece; [14]Mühlenkreiskliniken, Minden, Germany; [15]Netherlands Cancer Institut Antoni van Leeuwenhoek, Amsterdam, The Netherlands; [16]Elbe Klinikum Buxtehude, Buxtehude, Germany; [17]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [18]Hospital Universitario La Paz, Madrid-CIBERONC, Spain

Background

Melanoma and other skin cancers are prone to respond to immune checkpoint inhibition (ICI), due to a high tumor mutational burden (TMB), mainly caused by ultraviolet (UV) induced somatic mutations. The TMB of metastatic disease may therefore be related to the extent of mutagenic UV radiation the primary has been exposed to. Acral lentiginous melanoma (ALM) is a clinico-pathological subtype of cutaneous melanoma, usually localised at the palms of the hand or the foot, fingers, toes, or the nail apparatus. The existing evidence is not finally settled as to whether these patients would benefit from ICI immunotherapies like patients with other cutaneous subtypes.

Methods and patients

The EUMelaReg melanoma treatment registry (EMR) is a European initiative combining real world data on the treatment and outcome of melanoma patients all across Europe. We extracted cases with ALM and from these, we analysed cases with unresectable stage III or stage IV metastatic melanoma having been treated with systemic treatment.

First-line treatments were categorized for ICI-, BRAF V600 targeted, and other treatments and analysed for outcome parameters adjusted for prognostic factors. As a reference group, cases with superficial spreading or nodal subtype of cutaneous sites other than acral served as controls.

Results

A total of 229 cases with ALM and non-resectable or metastatic disease receiving first-line systemic treatment were identified in the registry. Among these, 172 patients received ICI, either anti-PD1 antibody or combined anti-CTLA4/anti-PD1 therapy. These were analysed in comparison to n = 1,295 cases with advanced disease from other subtypes.

The overall survival (OS) outcome comparison was adjusted for relevant prognostic covariates such as age, sex ECOG performance status, serum LDH levels, AJCC substage, number of metastatic sites, and treatment category. In a fully adjusted Cox regression model ALM patients had a significantly increased risk for death (HR 1.47; p=0.033) and disease progression (HR 1.32; p=0.043) as compared to the reference group

Figure 1: OS grouped by Subtype

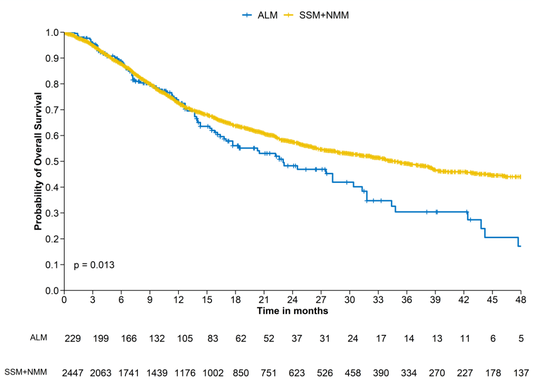


Figure 2: PFS grouped by Subtype

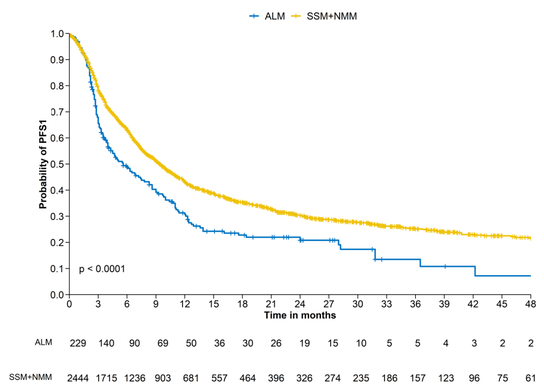


Table 1: Baseline patient characteristics

	ALM (N=229)	SSM+NMM (N=2,451)	P-value
Gender			
Female	107 (46.7%)	967 (39.5%)	0.0378
Male	122 (53.3%)	1,484 (60.5%)	
Age at start of 1st line (years)			
< 70	104 (45.4%)	1,532 (62.5%)	<0.001
70-80	84 (36.7%)	665 (27.1%)	
> 80	41 (17.9%)	253 (10.3%)	
ECOG at start of 1st line			
0	118 (51.5%)	1,313 (53.6%)	0.228
1	41 (17.9%)	527 (21.5%)	
≥ 2	11 (4.8%)	110 (4.5%)	
Missing/Unknown	59 (25.8%)	501 (20.4%)	
Charlson comorbidity score*			
< 9	86 (37.6%)	1,324 (54.0%)	<0.001
≥ 9	87 (38.0%)	760 (31.0%)	
Adjuvant therapy prior to 1st line treatment	67 (29.3%)	578 (23.6%)	

Table 2: Baseline tumor characteristics

	ALM (N=229)	SSM+NMM (N=2,451)	P-value
BRAF			
Wildtype	178 (77.7%)	897 (36.6%)	<0.001
Mutated	33 (14.4%)	1,377 (56.2%)	
Unknown	18 (7.9%)	177 (7.2%)	
AJCC stage at start of 1st line			
Stage III, non-resectable	63 (27.5%)	340 (13.9%)	<0.001
Stage IV M1a	40 (17.5%)	405 (16.5%)	
Stage IV M1b	43 (18.8%)	370 (15.1%)	
Stage IV M1c	68 (29.7%)	916 (37.4%)	
Stage IV M1d	15 (6.6%)	420 (17.1%)	
LDH at start of 1st line			
Normal	111 (48.5%)	1,170 (47.7%)	0.705
Elevated	56 (24.5%)	658 (26.8%)	
Missing	62 (27.1%)	623 (25.4%)	
Number of metastatic sites at start of 1st line			
1	90 (39.3%)	889 (36.3%)	0.00204
2	81 (35.4%)	672 (27.4%)	
≥ 3	58 (25.3%)	890 (36.3%)	
Type of 1st line therapy			
BRAFi+MEKi	15 (6.6%)	707 (28.8%)	<0.001
PD1 blockade	135 (59.0%)	955 (39.0%)	
Ipi/Nivo	37 (16.2%)	340 (13.9%)	
Other	42 (18.3%)	449 (18.3%)	

Table 3: Multivariable cox regression (OS) for the interaction between Subtype and Treatment

	HR	Lower 95% CI	Upper 95% CI
Subtype (ref: SSM+NMM)			
SubtypeALM	1.43	0.97	2.10
Treatment (ref: PD1 blockade)			
PD1 blockade	1.64	1.34	2.01
Ipi/Nivo	0.80	0.60	1.06
Other	1.10	0.85	1.42
Subtype:Treatment (ref: ALM:PD1 blockade)			
ALM:BRAFi+MEKi	0.94	0.43	2.05
ALM:Ipi/Nivo	1.59	0.67	3.80
ALM:Other	1.41	0.77	2.80

Results have been adjusted for age, ECOG, gender, LDH, Stage and Metastatic sites.

Table 4: Treatment outcomes

	ALM (N = 229)	SSM+NMM (N = 2,451)	P-value
Best response			
CR	29 (12.7%)	402 (16.4%)	< 0.0001
PR	44 (19.2%)	620 (25.3%)	
SD	50 (21.8%)	586 (23.9%)	
PD	82 (35.8%)	518 (21.1%)	
Unknown	24 (10.5%)	325 (13.3%)	
ORR	73 (31.9%)	1,022 (41.7%)	0.004
DCR	123 (53.7%)	1,608 (65.6%)	0.0004
Survival			
Median PFS from start of 1st line (95% CI)	5.6 (4.1-8.3)	9.5 (8.8-10.1)	< 0.0001
Median OS (95% CI) from start of 1st line	23 (17.7-31.3)	34.7 (31-38.8)	0.013

Table 5: Treatment outcomes (IO only)

	ALM (N = 172)	SSM+NMM (N = 1,295)	P-value
Best response			
CR	26 (15.1%)	217 (16.8%)	0.012
PR	29 (16.9%)	264 (20.4%)	
SD	33 (19.2%)	292 (22.5%)	
PD	66 (38.4%)	328 (25.3%)	
Unknown	18 (10.5%)	194 (15.0%)	
ORR	55 (32.0%)	481 (37.1%)	0.21
DCR	88 (51.2%)	773 (59.7%)	0.039
Survival			
Median PFS from start of 1st line (95% CI)	4.7 (3.7-8.6)	11.5 (9.5-13.7)	< 0.0001
Median OS (95% CI) from start of 1st line	27.5 (17-34.4)	46.4 (37.3-65.5)	0.001

Figure 3: Multivariable cox regression for OS

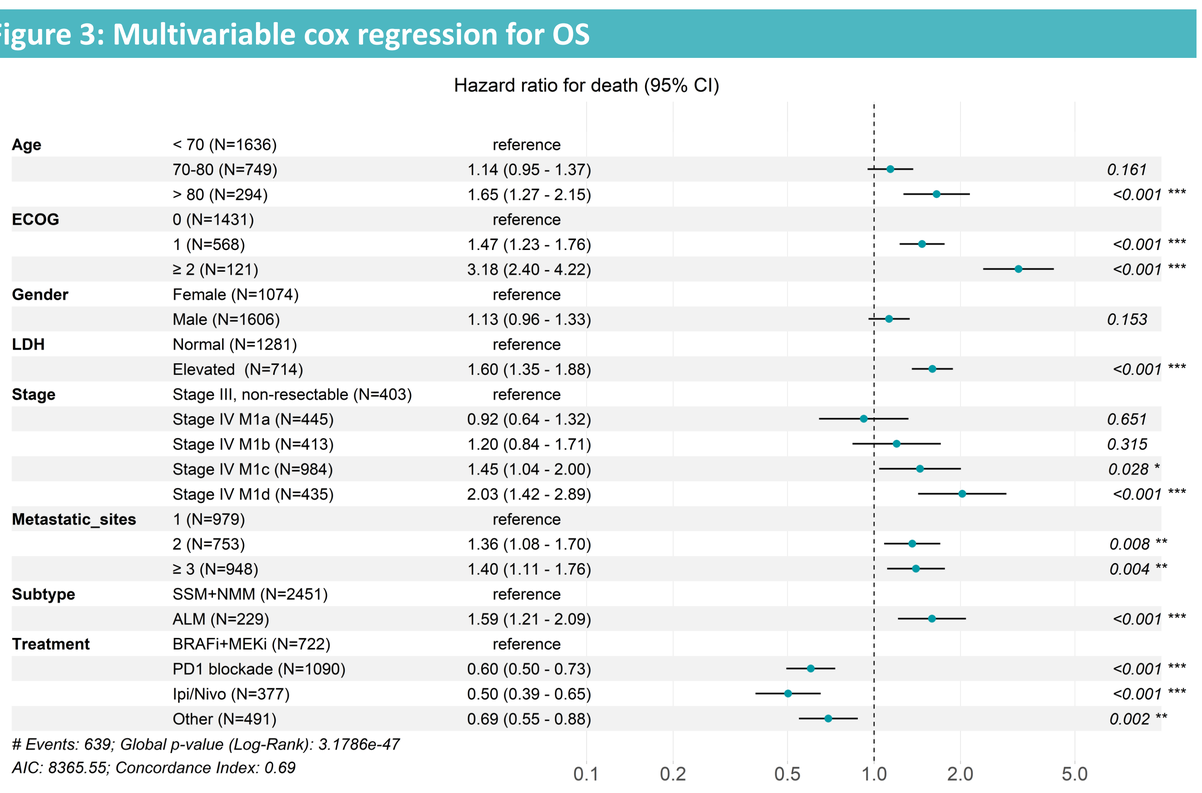


Figure 4: Multivariable cox regression for PFS

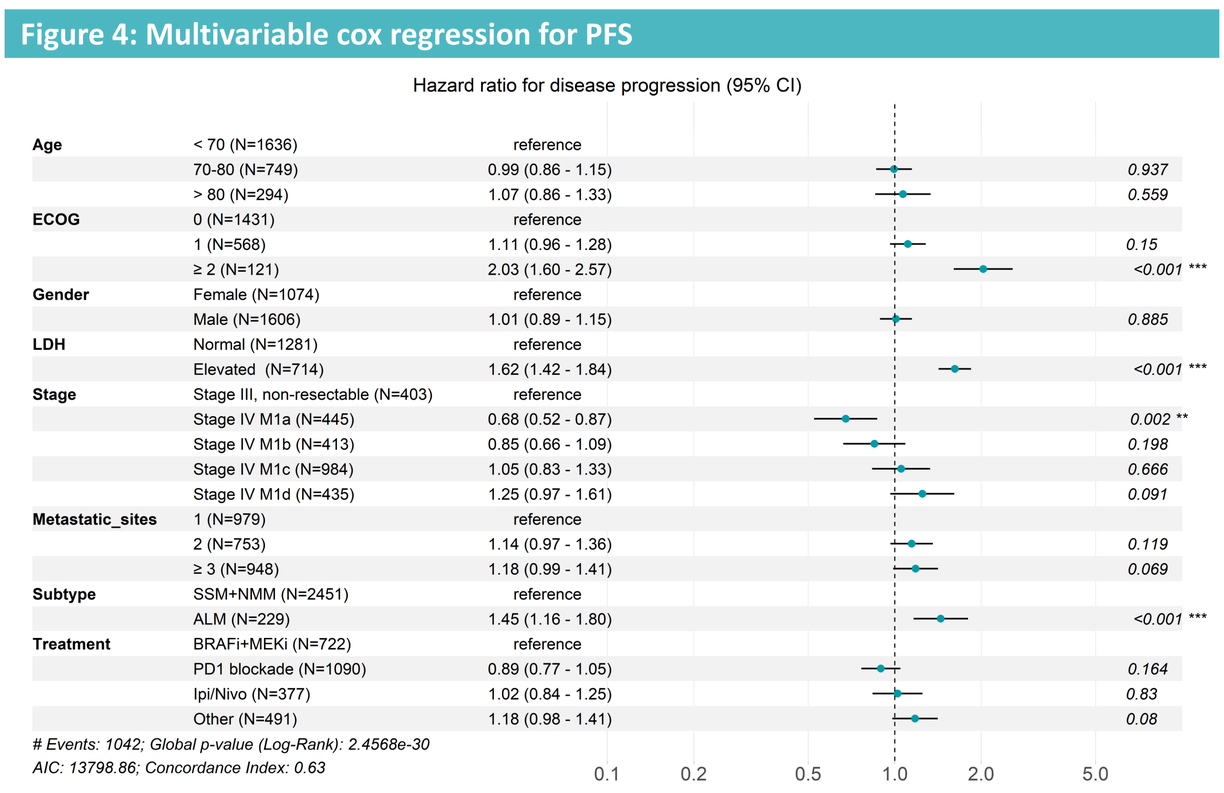


Figure 5: Multivariable cox regression for OS (IO only)

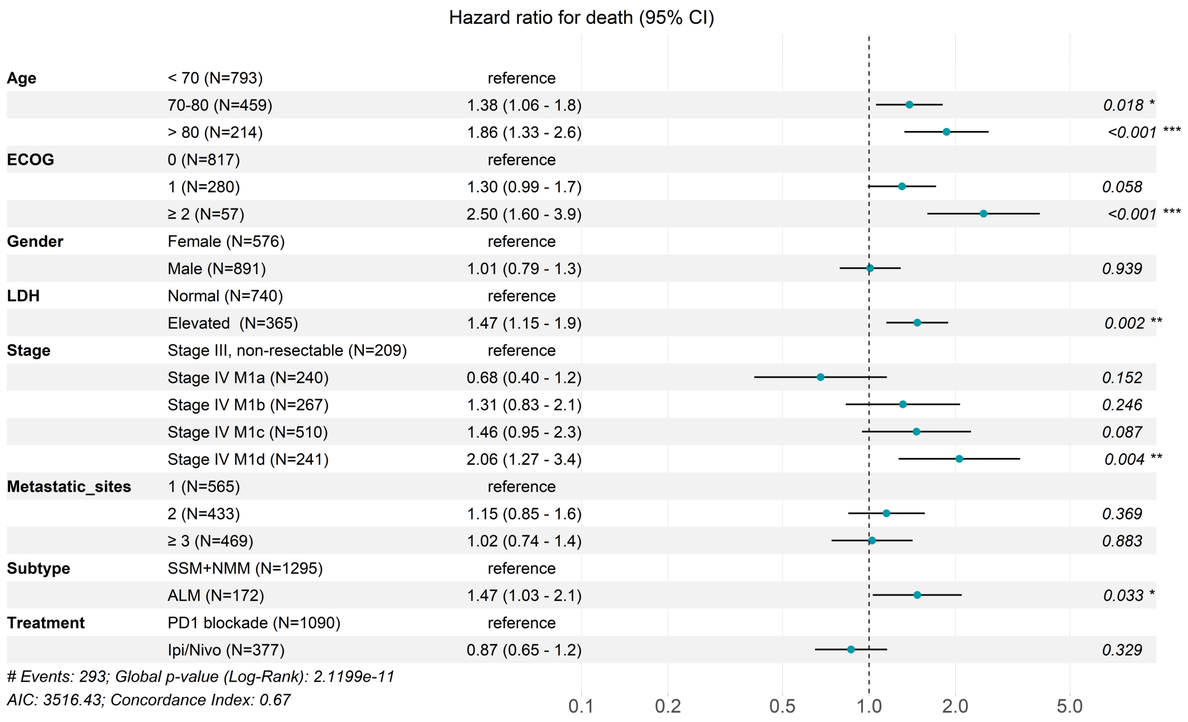
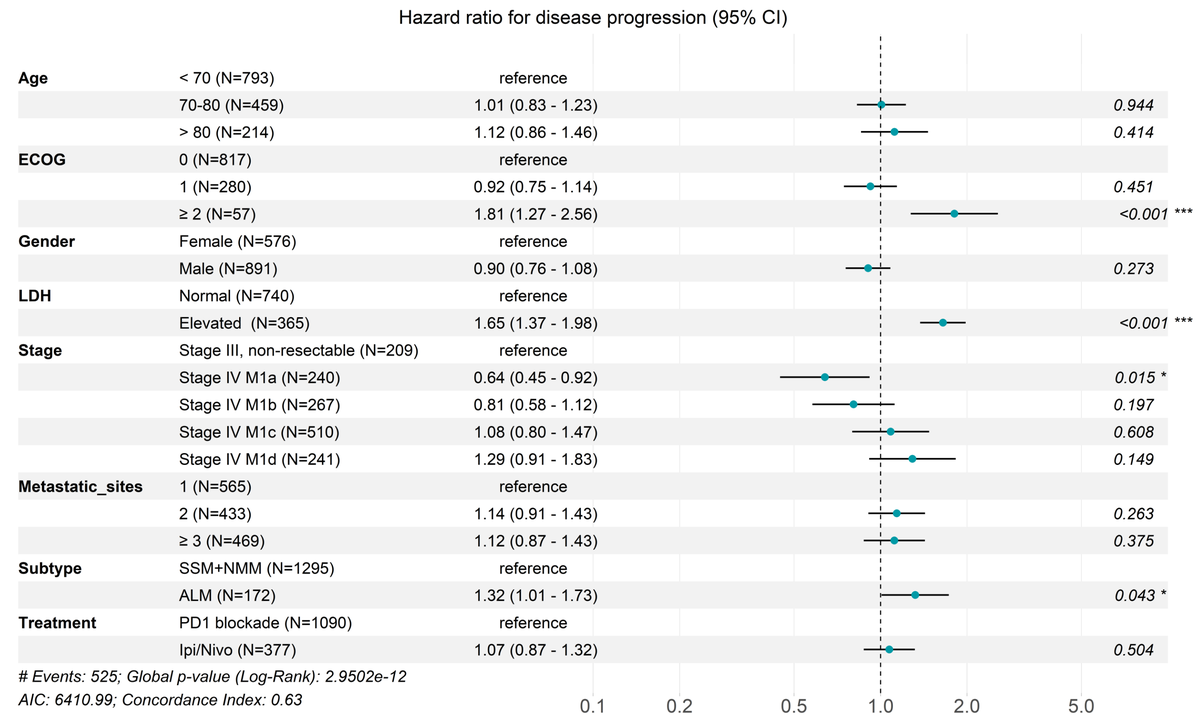


Figure 6: Multivariable cox regression for PFS (IO only)



ALM: Acral lentiginous melanoma. CR: Complete response. DCR: Disease control rate. ECOG: Eastern Cooperative Oncology Group. LDH: Lactate dehydrogenase. NMM: Nodular malignant melanoma. ORR: Objective response rate. OS: overall survival. PD: Progressive disease PFS: Progression-free surivval. PR: Partial response. SD: Stable disease SSM: Superficial spreading melanoma.

Conclusions

Our study confirms that ALM is a melanoma subtype that responds less well to ICI treatment than other cutaneous melanoma subtypes. Given the fact that treatment alternatives are sparse, in particular since BRAF V600 mutations are rare in ALM, new treatment approaches are urgently needed for patients with advanced ALM.

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