MELASITE: UV Exposure Pattern as a Clinical Surrogate for Immunotherapy Response in Advanced Melanoma

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BACKGROUND

- Cutaneous melanoma (CM) arise in anatomical sites with markedly different patterns of ultraviolet (UV) exposure, resulting in distinct mutational landscapes and clinical behavior.
- Melanoma from chronically sun-exposed skin harbor a higher tumor mutational burden (TMB) and may therefore be more immunogenic, suggesting greater sensitivity to immune checkpoint inhibitors (ICIs).
- We hypothesized that the UV exposure pattern of the primary melanoma (PM) could serve as a simple, clinically accessible surrogate for tumor immunogenicity and independently predict immunotherapy outcomes.

OBJECTIVES

- To determine whether the UV exposure pattern of the PM independently predicts response and survival following immune checkpoint inhibition in advanced CM.
- We also explored the biological basis of this association by evaluating its interaction with BRAF status and TMB.

METHODS

- We performed a retrospective analysis of the multinational **European Melanoma Registry (EUMelaReg)** including 3,897 patients with advanced CM treated with ICIs. Patients were classified according to the UV exposure pattern of the primary tumor into chronically sun-exposed (CSE), intermittently sun-exposed (ISE), and sun-protected (SP) groups.
- Study endpoints included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).
- Multivariable Cox and logistic regression models were used to adjust for relevant clinicopathologic covariates. TMB data was available for a subset of 126 patients.

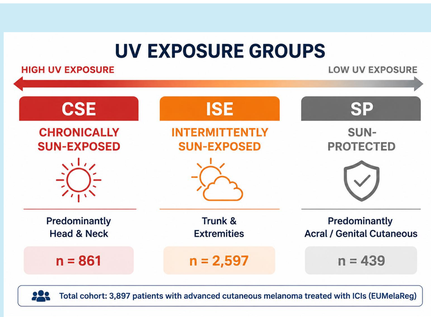


Figure 1. Patients were classified by primary melanoma site as chronically sun-exposed (**CSE**; n=861; 90.1% head/neck, 9.9% back of hand), intermittently sun-exposed (**ISE**; n=2,597; 51.9% trunk, 48.1% non-acral extremities), or sun-protected (**SP**; n=439; 79% acral, 15.3% genital, 5.7% buttocks) sites. The final cohort included 3,897 patients. Figure was created with ChatGPT.

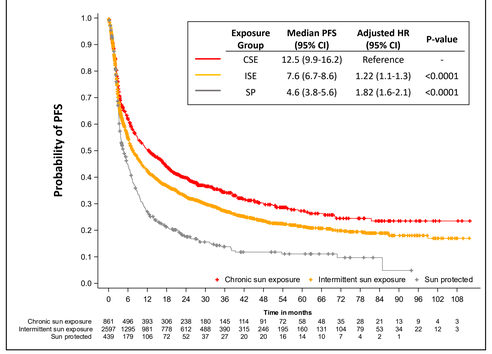
RESULTS - UV EXPOSURE GRADIENT IN ICI OUTCOMES

Table 1. Baseline patient and tumor characteristics at 1L according to primary melanoma UV exposure group

	Chronic sun exposure (CSE) N = 861	Intermittent sun exposure (ISE) N = 2,597	Sun protected (SP) N = 439	P-Value CSE vs. ISE	P-Value CSE vs. SP	P-Value ISE vs. SP	Total N = 3,897
Age, years				**0.014**	0.987	**0.041**	
Median (Min-Max)	71 (17-99)	68 (12-97)	69 (29-95)				69 (12-99)
Gender				**<.0001**	**<.0001**	**<.0001**	
Male	615 (71.4%)	1,598 (61.5%)	226 (51.5%)				2,439 (62.6%)
Female	246 (28.6%)	999 (38.5%)	213 (48.5%)				1,458 (37.4%)
BRAF status				0.071	**<.0001**	**<.0001**	
Positive	287 (33.3%)	976 (37.6%)	59 (13.4%)				1,322 (33.9%)
Wild type	504 (58.6%)	1,434 (55.2%)	358 (81.6%)				2,296 (58.9%)
Missing/Unknown	70 (8.1%)	187 (7.2%)	22 (5.0%)				279 (7.2%)
Localization of primary				**<.0001**	**<.0001**	**<.0001**	
Acral	-	-	347 (79.0%)				347 (8.9%)
Cutaneous genitalia	-	-	67 (15.3%)				67 (1.7%)
Trunk and buttocks	-	1,348 (51.9%)	25 (5.7%)				1,373 (35.2%)
Extremities	85 (9.9%)	1,249 (48.1%)	-				1,334 (34.3%)
Head/Neck skin	776 (90.1%)	-	-				776 (19.9%)
Ulceration				**0.002**	**<.0001**	**<.0001**	
Yes	361 (41.9%)	1,269 (48.9%)	257 (58.5%)				1,887 (48.4%)
No	370 (43.0%)	975 (37.5%)	118 (26.9%)				1,463 (37.5%)
Unknown	130 (15.1%)	353 (13.6%)	64 (14.6%)				547 (14.0%)
TMB				**0.0005**	**<.0001**	**<.0001**	
N	36	75	15				126
Median (Min-Max)	36.9 (4.7-107.7)	20.0 (3.1-132.0)	12.3 (1.6-28.6)				20.6 (1.6-132.0)
Breslow thickness*				0.957	**0.014**	**0.010**	
N	770	2,350	372				3,492
Median (Min-Max)	3.6 (0.0-30.0)	3.4 (0.0-50.0)	4.0 (0.0-110.0)				3.5 (0.0-110.0)
State at prim. diagnosis				**<.0001**	**<.0001**	**<.0001**	
Distant mets	112 (13.0%)	249 (9.6%)	71 (16.2%)				432 (11.1%)
Locoregional mets	252 (29.3%)	966 (37.2%)	186 (42.3%)				1,404 (36.0%)
Non-metastatic	423 (49.1%)	1,196 (46.0%)	164 (37.4%)				1,783 (45.8%)
Unknown	74 (8.6%)	186 (7.2%)	18 (4.1%)				278 (7.1%)
Brain metastases				0.922	**<.0001**	**<.0001**	
Yes	176 (20.4%)	526 (20.3%)	33 (7.5%)				735 (18.9%)
ECOG				0.609	0.972	0.519	
0	537 (62.4%)	1,679 (64.7%)	270 (61.5%)				2,486 (63.8%)
1	199 (23.1%)	578 (22.3%)	102 (23.2%)				879 (22.6%)
≥2	49 (5.7%)	131 (5.0%)	25 (5.7%)				205 (5.2%)
Missing/Unknown	76 (8.8%)	209 (8.0%)	42 (9.6%)				327 (8.4%)
LDH				0.086	0.969	0.355	
Normal	502 (58.3%)	1,440 (55.5%)	253 (57.6%)				2,195 (56.3%)
Elevated	265 (30.8%)	903 (34.8%)	138 (31.5%)				1,306 (33.5%)
Missing/Unknown	94 (10.9%)	254 (9.8%)	48 (10.9%)				396 (10.2%)
No. of metastatic sites				0.316	**0.018**	**0.0005**	
≤3	745 (86.5%)	2,209 (85.1%)	400 (91.1%)				3,354 (86.1%)
>3	116 (13.5%)	388 (14.9%)	39 (8.9%)				543 (13.9%)
Prior adjuvant therapy				**<.0001**	**<.0001**	**0.011**	
Yes	178 (20.7%)	763 (29.4%)	156 (35.5%)				1,097 (28.2%)
No	683 (79.3%)	1,834 (70.6%)	283 (64.5%)				2,800 (71.8%)
Type 1L ICI				**0.010**	0.351	0.805	
Anti-PD1 monotherapy	564 (65.5%)	1,583 (61.0%)	274 (62.4%)				2,421 (62.1%)
Anti-PD1/Anti-CTLA4	289 (33.6%)	1,002 (38.6%)	163 (37.1%)				1,454 (37.3%)
Anti-PD1/Anti-LAG3	8 (0.9%)	12 (0.5%)	2 (0.5%)				22 (0.6%)
TNM-M				0.109	**<.0001**	**<.0001**	
M0/M1a	214 (24.9%)	714 (27.5%)	179 (40.8%)				1,107 (28.4%)
M1b	211 (24.5%)	540 (20.8%)	113 (25.7%)				864 (22.2%)
M1c	260 (30.2%)	817 (31.5%)	114 (26.0%)				1,191 (30.5%)
M1d	176 (20.4%)	526 (20.3%)	33 (7.5%)				735 (18.9%)

N, number of patients; TMB, tumour mutational burden; prim, primary; mets, metastases; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; ICI, immune checkpoint inhibition; No, number; 1L, first line. *Median values were calculated only among patients with available data.

PFS - CSE/ISE/SP



- Kaplan-Meier analyses shows a clear UV exposure-dependent survival gradient. Patients with CSE melanoma achieved the most favorable PFS and OS, ISE melanoma showed intermediate outcomes, and SP melanoma had the poorest survival (**Figure 2**).
- This association remained significant after multivariable adjustment for PFS, while for OS only the SP group remained independently associated with inferior survival (**Figure 3**).

Figure 2. Progression-free survival (PFS) according to primary melanoma UV exposure group. CSE, chronic sun exposure (red line); ISE, intermittent sun exposure (orange line); SP, sun protected (grey line); HR, hazard ratio; CI, confidence interval.

OS - CSE/ISE/SP

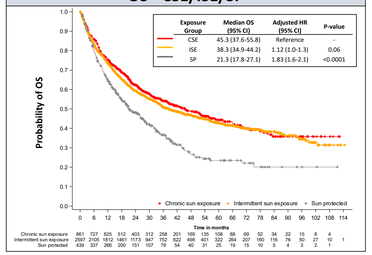


Figure 3. Overall survival (OS) according to primary melanoma UV exposure group. CSE, chronic sun exposure (red line); ISE, intermittent sun exposure (orange line); SP, sun protected (grey line); HR, hazard ratio; CI, confidence interval.

ORR - CSE/ISE/SP

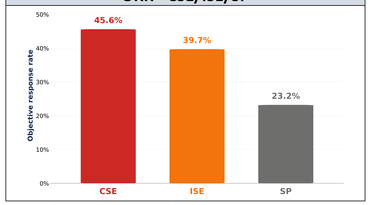
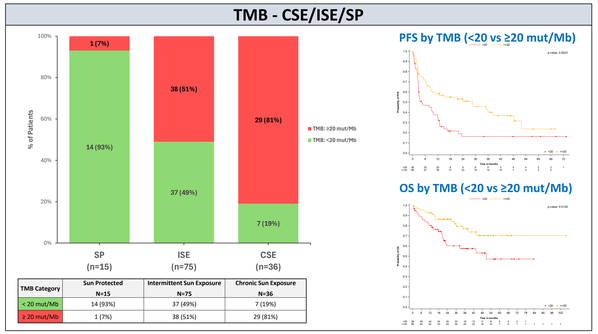


Figure 4. Overall Response Rate (ORR) according to primary melanoma UV exposure group. CSE, chronic sun exposure (red bar); ISE, intermittent sun exposure (orange bar); SP, sun protected (grey bar).

In multivariable logistic regression analysis, ISE was associated with a 21% lower likelihood of response compared with CSE melanoma [OR 0.79 (0.67-0.93; p=0.004)], while SP was associated with a 67% lower likelihood of response [OR 0.34 (0.26-0.44; p<0.0001)].

TMB - CSE/ISE/SP

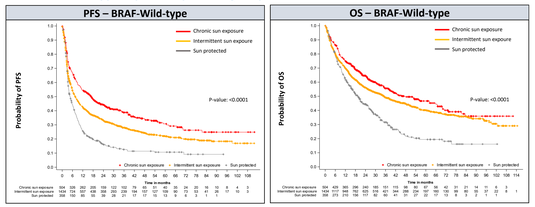


TMB Category	Sun Protected N=15	Intermittent Sun Exposure N=75	Chronic Sun Exposure N=36
< 20 mut/Mb	14 (93%)	37 (49%)	7 (19%)
≥ 20 mut/Mb	1 (7%)	38 (51%)	29 (81%)

Figure 5. Tumor Mutational Burden (TMB) according to primary melanoma UV exposure group and association with outcome (n=126). CSE, chronic sun exposure; ISE, intermittent sun exposure; SP, sun protected; PFS, progression-free survival; OS, overall survival; mut/Mb, mutations per megabase.

- TMB showed a marked UV exposure gradient, with median TMB of **36.9, 20.0**, and **12.3** mut/Mb in CSE, ISE, and SP melanoma, respectively.
- **High TMB** (>25 mut/Mb) was present in **72% of CSE** compared with 31% of ISE and 7% of SP tumors.
- Using a TMB cutoff of 20 mut/Mb, higher TMB was associated with a **higher ORR** (76.5% vs 46.6%) and significantly **longer PFS and OS** (log-rank p=0.0022 and p=0.014, respectively).

A. BRAF wild-type by UV exposure group



B. BRAF mutant by UV exposure group

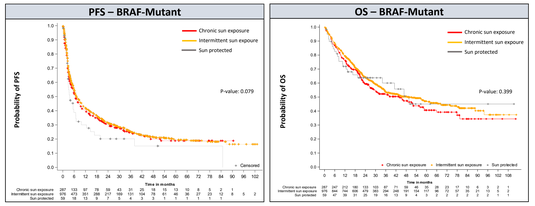


Figure 6. Progression-free survival (PFS, left) and overall survival (OS, right) according to UV exposure group stratified by BRAF status: A: BRAF wildtype, B: BRAF mutant. CSE, chronic sun exposure (red line); ISE, intermittent sun exposure (orange line); SP, sun protected (grey line).

- Among patients with BRAF wild-type melanoma, a pronounced UV exposure gradient was observed for both PFS and OS (log-rank p<0.0001 for both). Median PFS was 16.8, 7.6, and 4.6 months, and median OS was 47.6, 34.9, and 19.4 months for CSE, ISE, and SP, respectively.
- In contrast, among patients with BRAF-mutant melanoma, outcomes did not significantly differ by UV exposure group (PFS p=0.08; OS p=0.40).

SUMMARY AND CONCLUSIONS

- In this large EUMelaReg cohort of 3,897 patients, primary melanoma UV exposure pattern was strongly and independently associated with immunotherapy outcomes: CSE, ISE and SP melanoma showed a clear gradient in ORR, PFS and OS.
- A corresponding TMB gradient was observed across UV exposure groups, supporting a biological basis for the differences in ICI sensitivity.
- The UV exposure gradient in PFS and OS was pronounced among BRAF wild-type patients but was absent in BRAF-mutant melanoma. We hypothesize that BRAF signaling may partly override the immunogenic advantage associated with UV-induced mutational burden.
- Primary melanoma UV exposure groups define biologically and clinically distinct diseases and may serve as a clinically accessible surrogate for tumor immunogenicity, particularly in BRAF wild-type.

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European Melanoma Registry (EUMelaReg): www.eumelareg.org/i This registry is a multi-center database run by a cross-national consortium of academic groups in Europe collecting and evaluating real-world melanoma cases with non-resectable stage III or metastatic stage IV melanoma. Data has been captured since 2018 entered voluntarily into the system by participating centers.