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29 **MANUSCRIPT TEXT**30 *To the Editor:*

31 Anti-programmed cell death-1 (anti-PD-1) agents have demonstrated their efficacy in the treatment of
32 advanced melanoma with reasonable toxicities [1]. Although anti-PD-1 related adverse events (AEs), especially
33 vitiligo, have been reported as associated with higher response rates and prolonged survival, this association
34 remains controversial due to conflicting results [2]. Consequently, the impact of AEs under anti-PD-1 on survival
35 in patients treated for advanced melanoma in the setting of daily practice was investigated.

36 All patients treated with anti-PD-1 agents for stage III-IV melanoma between 2011 and 2018 were
37 retrospectively reviewed. Type and severity of AEs according to the CTCAE v5.0 and interval from anti-PD-1
38 initiation to AEs occurrence were collected. Using Cox-regression models, the prognostic impact of clinical
39 factors including AEs on progression free survival (PFS) and overall survival (OS) was investigated. Additionally,
40 a landmark analysis at 3 time points to address lead-time bias inherent to the time dependence of the
41 occurrence of AEs was performed.

42 Overall, 111 patients treated with anti-PD-1 were evaluated. Patients' characteristics are listed in Table 1. Over
43 a median follow-up of 438 days (range 8-1687), 61 patients experienced AEs (55%) after a median time of 51
44 days (range, 1-758). Cutaneous (n=32, 29%) including vitiligo (n=15, 13.5%), endocrine (n=35, 32%), and gastro-
45 intestinal (n=17, 15%) AEs were the most frequent. Specifically, vitiligo occurred at a median time of 256 days
46 (range, 30-758). Severe AEs occurred in 12 patients (11%) leading to therapy discontinuation in 8 patients (7%).
47 Median OS was 22.5 months (CI95% 14.9-30.1). Median OS in patients experiencing vitiligo, other AEs and no
48 AE were not reached, 28 months (CI95% 11.1-46.9) and 12 months (CI95% 4.7-20.3, p<0.001) respectively. Upon
49 multivariable analysis, experiencing vitiligo (HR=0.099, CI95% 0.013-0.737, p=0,024) and serum LDH level
50 (HR=3.514, CI95% 1.787-6.962, p<0.001) were independently associated with OS. Median PFS was 8.9 months
51 (CI95% 9.2-11.6). Upon multivariable analysis, experiencing vitiligo (HR=0.109, CI95% 0.025-0.471, p=0.003)
52 and serum LDH level (HR=3.077, CI95% 1.702-5.561, p<0.001) were independently associated with PFS. Using a
53 landmark analysis, we confirmed that vitiligo was associated with prolonged OS as compared to patients
54 experiencing other AEs or no AEs (Figure 1).

55 In daily practice, AEs under anti-PD-1 are frequent with a predominance of endocrine, cutaneous and
56 gastrointestinal AEs as previously described [1]. Regarding vitiligo, while its occurrence varies among series it

57 has been correlated with disease response [1,3,4]. Yet, its association with survival remains disputed [4-5]. In
58 the current study, patients who developed vitiligo under anti-PD-1 experienced longer survival. However,
59 analyzing the correlation between AEs such as vitiligo should take into account the lead-time-bias due to the
60 fact that patients dying of disease especially early after anti-PD-1 initiation will not develop AEs. This issue has
61 been addressed using a landmark analysis. Further, the occurrence of any AEs other than vitiligo was not
62 associated with any survival benefit as compared to patients experiencing no AEs. This observation highlighted
63 the relevance of monitoring vitiligo under anti-PD-1 therapy.

64 While inherently limited by its retrospective nature and single-center design, the current study showed that the
65 occurrence of vitiligo under anti-PD-1 therapy seems relevant as a surrogate of treatment efficacy and
66 prolonged survival in daily practice.

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100 **Abbreviations and acronyms:**

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102 AE: adverse event

103 AJCC: American Joint Committee on Cancer

104 Anti-CTLA-4: anti-cytotoxic T lymphocyte antigen-4 antibodies

105 Anti-PD-1: anti-programmed cell death-1 monoclonal antibodies

106 BMI: body mass index

107 CI: confidence interval

108 CTCAE: Common Terminology Criteria for Adverse Events

109 HR: hazard ratio

110 ICI: immune checkpoint inhibitor

111 IPI: ipilimumab

112 LDH: Lactate Dehydrogenase

113 NIVO: nivolumab

114 OR: Odds ratio

115 PBZ: pembrolizumab

116 SG: severe grade

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139 **Figure legends**

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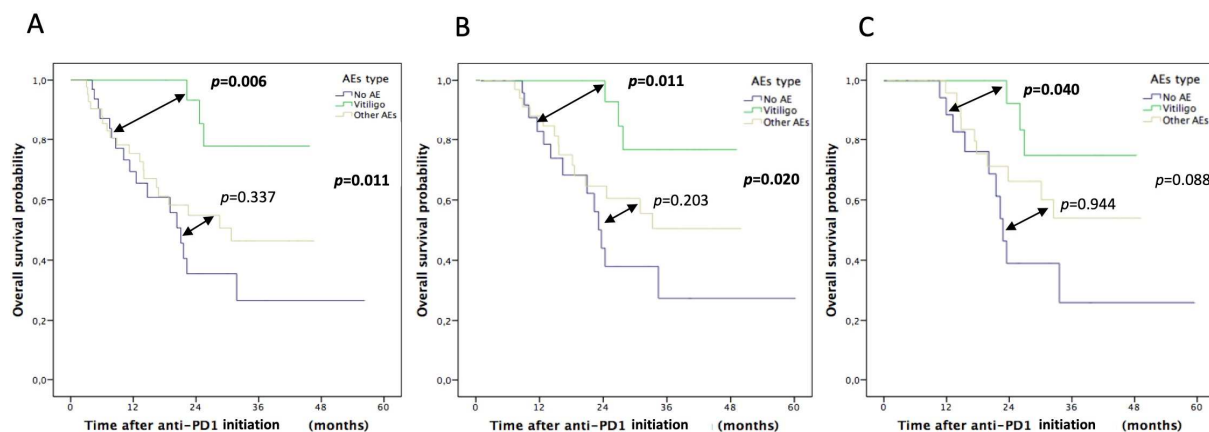
142 **Figure 1. Overall survival (OS) in patients treated with anti-PD-1 with vitiligo, other adverse events (AEs) and**143 **without AE of alive patients after 3 time points (n=111). Kaplan-Meier product-limit curves show overall**144 **survival after 3 time points (3 (A), 6 (B) and 12 (C) months) after anti-PD-1 initiation to avoid the lead-time bias.**

Figure 1. Overall survival (OS) in patients treated with anti-PD-1 with vitiligo, other adverse events (AEs) and without AE of alive patients after 3 time points (n=111). Kaplan-Meier product-limit curves show overall survival after 3 time points (3 (A), 6 (B) and 12 (C) months) after anti-PD-1 initiation to avoid the lead-time bias.

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156 **Table**157 **Table 1 Characteristics of patients with or without adverse events (AE).-**

158 ¹Percentages of total patients (111), ²percentages of patients with AEs (61), ³percentages of patients without
 159 AEs (50), ⁴ Patients who previously received a targeted therapy were either in treatment failure or experienced a
 160 toxicity contraindicating targeted therapies. ⁵Patients who previously received ipilimumab. AID: autoimmune
 161 disease; BMI: body mass index; ICI: checkpoint inhibitor; IPI: ipilimumab; LDH: lactate dehydrogenase; NIVO:
 162 nivolumab; n = number ; OR: Odds Ratio and confidence interval at 95% ; PBZ: pembrolizumab.

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	Total ¹ n=111(100%)	Patients with AE ² n=61 (55%)	Patients without AE ³ n=50 (45%)	Univariable
				p-value
Age Median age, [range] (years)	67 [25-89]	66 [32-89]	68 [25-88]	0.585
Sex ratio Male (%) Female (%)	58 (52) 53 (48)	33 28	25 25	0.667
BMI Median, [range], (kg/m ²)	25.5 [15.7-45.4]	27.0 [15.7-45.5]	25.4[18.3-39.5]	0.229
History of AID (%) Yes No	9 (8) 102 (92)	5 56	4 46	0.970
Use of steroids Yes No	15 (14) 96 (86)	10 51	5 45	0.327
AJCC Stage III (%) IV (%)	30 (27) 81(73)	14 47	16 34	0.285
Brain metastases (%) Yes No	35(32) 76 (68)	17 44	18 32	0.359
LDH level (UI/L) Median, [range] (UI/L)	250 [139-2367]	242 [139-2367]	250 [156-1876]	0.092
BRAF^{V600} mutation (%) Yes No	37 (21) 74 (79)	18 43	19 31	0.345
Targeted therapies⁴ (%) Yes No	30 (17) 81 (73)	15 46	15 35	0.523
IPI monotherapy⁵ (%) Yes No	44 (24) 67 (76)	26 35	18 32	0.478
Anti-PD-1 monotherapy (%) PBZ monotherapy NIVO monotherapy	85 26	47 14	38 12	0.897

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