Vitiligo under anti–programmed cell death-1 therapy is associated with increased survival in melanoma patients

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MANUSCRIPT TEXT

To the Editor:

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

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

Overall, 111 patients treated with anti-PD-1 were evaluated. Patients' characteristics are listed in Table 1. Over a median follow-up of 438 days (range 8-1687), 61 patients experienced AEs (55%) after a median time of 51 days (range, 1-758). Cutaneous (n=32, 29%) including vitiligo (n=15, 13.5%), endocrine (n=35, 32%), and gastro-intestinal (n=17, 15%) AEs were the most frequent. Specifically, vitiligo occurred at a median time of 256 days (range, 30-758). Severe AEs occurred in 12 patients (11%) leading to therapy discontinuation in 8 patients (7%).

Median OS was 22.5 months (CI95% 14.9-30.1). Median OS in patients experiencing vitiligo, other AEs and no AE were not reached, 28 months (CI95% 11.1-46.9) and 12 months (CI95% 4.7-20.3, p<001) respectively. Upon multivariable analysis, experiencing vitiligo (HR=0.099, CI95% 0.013-0.737, p=0,024) and serum LDH level (HR=3.514, CI95% 1.787-6.962, p<0.001) were independently associated with OS. Median PFS was 8.9 months (CI95% 9.2-11.6). Upon multivariable analysis, experiencing vitiligo (HR=0.109, CI95% 0.025-0.471, p=0.003) and serum LDH level (HR=3.077, CI95% 1.702-5.561, p<0.001) were independently associated with PFS. Using a landmark analysis, we confirmed that vitiligo was associated with prolonged OS as compared to patients experiencing other AEs or no AEs (Figure 1).

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

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

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

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Abbreviations and acronyms:

AE: adverse event

AJCC: American Joint Committee on Cancer

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

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

BMI: body mass index

CI: confidence interval

CTCAE: Common Terminology Criteria for Adverse Events

HR: hazard ratio

ICI: immune checkpoint inhibitor

IPI: ipilimumab

LDH: Lactate Dehydrogenase

NIVO: nivolumab

OR: Odds ratio

PBZ: pembrolizumab

SG: severe grade

Figure legends

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.

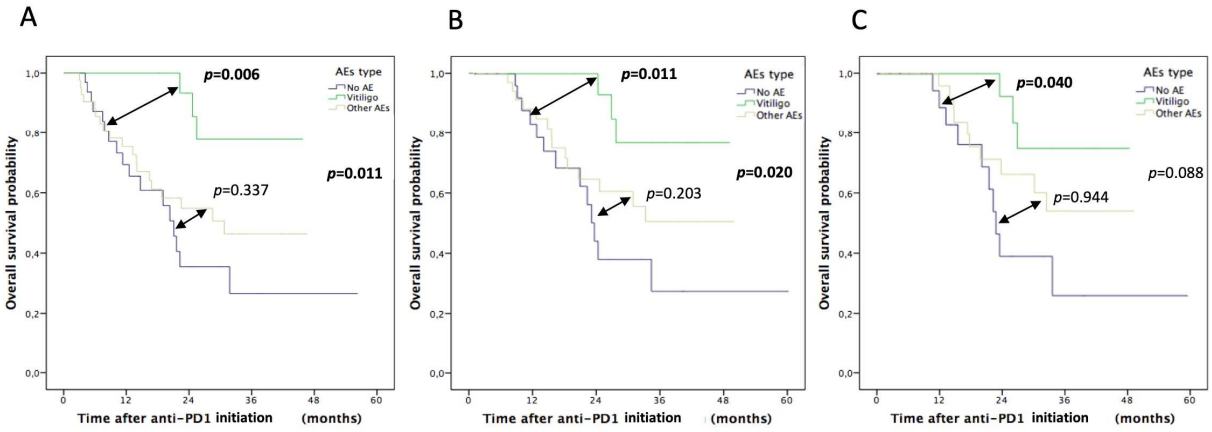

Figure 1. Overall survival (OS) in patients treated with anti-PD-1 with vitiligo, other adverse events (AEs) and without AE of alive patients after 3 time points (n=111). Kaplan-Meier product-limit curves show overall survival after 3 time points (3 (A), 6 (B) and 12 (C) months) after anti-PD-1 initiation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

Table

Table 1 Characteristics of patients with or without adverse events (AE).

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

	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 (%)	58 (52)	33	25	0.667
Female (%)	53 (48)	28	25	
BMI				
Median, [range], (kg/m²)	25.5 [15.7-45.4]	27.0 [15.7-45.5]	25.4[18.3-39.5]	0.229
History of AID (%)				
Yes	9 (8)	5	4	0.970
No	102 (92)	56	46	
Use of steroids				
Yes	15 (14)	10	5	0.327
No	96 (86)	51	45	
AJCC Stage				
III (%)	30 (27)	14	16	0.285
IV (%)	81(73)	47	34	
Brain metastases (%)				
Yes	35(32)	17	18	0.359
No	76 (68)	44	32	
LDH level (UI/L)				
Median, [range] (UI/L)	250 [139-2367]	242 [139-2367]	250 [156-1876]	0.092
$BRAF^{V600}$ mutation (%)				
Yes	37 (21)	18	19	0.345
No	74 (79)	43	31	
Targeted therapies[4] (%)				
Yes	30 (17)	15	15	0.523
No	81 (73)	46	35	
IPI monotherapy[5] (%)				
Yes	44 (24)	26	18	0.478
No	67 (76)	35	32	
Anti-PD-1 monotherapy (%)				
PBZ monotherapy	85	47	38	0.897
NIVO monotherapy	26	14	12	