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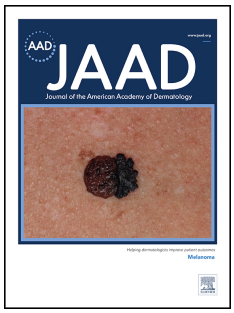

Late-onset adverse events under anti-PD1 therapy in melanoma patients: an observational study from MELBASE, a nationwide prospective cohort

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Late-onset adverse events under anti-PD1 therapy in melanoma patients: an observational study from MELBASE, a nationwide prospective cohort

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Key message

- Late-onset adverse events (AEs) of anti-PD1 antibodies (occurring after two years of treatment) are scarcely reported.
- In a prospective cohort of melanoma patients (MelBase), late-onset AEs were observed in 43% of patients and were mostly mild or moderate. Early-onset AEs and prolonged anti-PD1 treatment increased the risk of late-onset AEs.

Abstract

Late-onset adverse events (AEs) of anti-programmed cell death 1 (anti-PD1) antibodies have not been systematically described.

The purpose was to evaluate late-onset AEs in melanoma patients treated with anti-PD1 administered at least 2 years in a real-life setting.

Patients were screened from MelBase (NCT02828202), a French multicentric biobank dedicated to the prospective follow-up of unresectable stage III or IV melanoma. 119 patients who received anti-PD1 during at least 2 years from January 2013 to November 2019 were included. Median follow-up was 41.7 months (25.2-57.5). Patients received nivolumab (n=53) or pembrolizumab (n=66). AEs occurred in 99 patients (83%) with a median time of 13.3 months (0-53.9), including severe AEs (grade 3 or 4) in 30 patients (30%). Late-onset AEs, mostly grade 1-2, occurred in 51 (43%) patients and led to 5 (4%) hospitalizations of which 4 were severe. Factors associated with late-onset AEs in multivariate analysis were early-onset AEs (within the first two years of treatment) and treatment duration (p=0,02 and p=0,03 respectively).

Our data demonstrate the possibility of late-onset AEs occurring after 2 years of anti-PD1 therapy. Late-onset AEs appear frequent and mostly mild or moderate. Early-onset AEs and prolonged anti-PD1 treatment may increase the risk of late-onset AEs.

Keywords: immunotherapy, immune checkpoint inhibitor, nivolumab, pembrolizumab, anti-PD1, late-onset adverse events, adverse event, toxicities, melanoma.

Introduction

Immune checkpoint inhibitors, anti-PD1 and anti-CTLA-4, by activating the patient's immune system against tumor cells, are associated with specific adverse events (AEs), including immune-related adverse events (irAEs) (1–8). AEs and irAEs mostly occur early, within weeks from immunotherapy initiation (5,9,10). However they can occur later (11,12).

In most clinical trials, patients with advanced melanoma have been treated with anti-PD1 for up to two years (11–14). In clinical practice, anti-PD1 are commonly maintained longer than two years, because treatment interruption is not mandatory. The optimal duration of anti-PD1 treatment is not established for melanoma patients. The maintenance of anti-PD1 efficacy after their discontinuation is partially explained by the pharmacokinetics of anti-PD1 with a persistent drug exposure until approximately one year after stopping pembrolizumab and nivolumab, based on the study of Fukudo et al. (15).

Beside their antitumor effect due to a shift from an exhausted T-cell phenotype to an active T-cell effector phenotype, anti-PD1 treatments are associated with expansion of the T cell repertoire, changes in B cells responses, autoantibody production and induction of an immunological memory against tumor cells, and against normal tissues which may contribute to the pathogenesis of AEs even later after the discontinuation of anti-PD1 (16).

Altogether, this suggests that anti-PD1 may induce late-onset AEs.

Finally, real-world data of late-onset AEs, occurring after two years of anti-PD1 treatment, are lacking in melanoma patients (17).

90 This study aimed to describe late-onset AEs of anti-PD1 agents (nivolumab and
91 pembrolizumab) in advanced melanoma patients treated for at least two years in a real-
92 life setting.
93

Materials and methods

Data were extracted from MelBase, a prospective cohort enrolling adults with melanoma at diagnosis of advanced disease (de novo or at recurrence of a previous localized disease), who never received systemic therapy, from 26 French hospitals [NCT02828202]. Patients with unresectable stage III or stage IV melanoma, who had been treated with anti-PD1 (pembrolizumab and/or nivolumab) monotherapy for at least 24 months, between January 2013 and November 2019, were included. A switch from anti-PD1 (nivolumab to pembrolizumab or inversely) was possible. Previous treatment with ipilimumab was allowed. Patients with an interruption of the anti-PD1 immunotherapy exceeding 3 months were excluded. In the case of repeated interruptions in the same patient, a maximum of 3 months for each interruption was allowed. Baseline patients' features were reported as follows: age, gender, Eastern Cooperative Oncology Group performance status (ECOG-PS), primary tumor, autoimmune disease, Breslow index, ulceration, BRAF mutation, AJCC stage, LDH level, number of AEs before two years, best overall response rate (BORR) (complete response [CR], partial response [PR] and stable disease [SD]), treatment duration, number of metastatic targets, line of treatment, anti-PD1 agent and use of steroids at anti-PD1 initiation.

AEs induced by anti-PD1, including early-onset AEs (defined as AEs before two years of treatment) and late-onset AEs (defined as occurring after two years of the anti-PD1 treatment either under treatment or after treatment discontinuation) were noticed from the first day of treatment to the end of patient follow-up. AEs were categorized on the basis of the organ/system involved and their severity in accordance with the National Cancer Institute Common Toxicity Criteria for Adverse Events.

The primary endpoint was to describe the incidence and characteristics of late-onset AEs (excluding AEs that had started before two years and continue after two years of anti-PD1 treatment); the secondary endpoint was to further investigate factors associated with late-onset AEs occurrence using univariate logistic regression. AEs were stratified before and after 2 years. Factors significantly associated with the occurrence of late-onset AEs in univariate analysis were then evaluated in multivariate analysis. Statistical analyses were performed using R software version 3.5.2. Characteristics were presented for all patients using descriptive statistics. Odds ratios and 95% confidence intervals (95% CIs) are presented. *p*-value <0.05 was considered to be statistically significant.

Results

Among 1849 patients included in the MELBASE cohort, 119 patients with advanced melanoma treated with anti-PD1 for at least two years were included.

Median follow-up was 41.7 months (25.2-57.5).

Patient characteristics

Patient characteristics were: male sex (61%), median age of 64 years, history of autoimmune disease (11%), BRAF V600E mutation (25%), AJCC stage IV (84%), brain metastases (22%), ECOG-PS 0 or 1 (88%) and elevated LDH levels (18%). 41 patients (34%) had previously received ipilimumab and 27 patients (23 %) had experienced AEs under ipilimumab (Table 1). A switch of anti-PD-1 therapy was noticed in 20 patients (17 %). Anti-PD1 agents were temporarily interrupted in 22 patients (18 %). The median duration of anti-PD1 treatment was 33.4 months (range, 24.7-56.9). Four patients (3%) died during follow-up, including 2 from disease progression. The BORR to anti-PD1 therapy was as follows: 70 patients had CR, 41 patients had PR, 8 patients had SD. 49 patients remained in CR until the end of follow-up, and 21 subsequently experienced progression disease (PD) while they were still treated by anti-PD1 treatment.

Adverse events characteristics

99 patients (83%) experienced 618 AEs of any grade after a median duration of anti-PD1 therapy of 13.3 months (range 0-53.9). Among them, thirty patients (30%) presented 47 severe AEs (grade 3 or 4). 19 patients (16%) were hospitalized due to

their AE, including 1 in intensive care. Supplemental Table 1 summarizes all AEs by types and grades.

51 patients (43%) experienced 140 late-onset AEs. Among them, 49 patients (96 % patients) experienced 120 late-onset AEs (86 % events) while still being treated, whereas 8 patients (16 % patients) experienced 20 late-onset AEs (14 % events) after treatment discontinuation. The median duration of treatment was 39 months (range, 26.4-54.9) for patients with late-onset AEs under treatment (n=49) and 26.6 months (range, 24.4-34.5) for patients with late-onset AEs after discontinuation (n=8).

Treatment was temporarily interrupted in 4 (4 %) and permanently discontinued in 8 patients (8 %) for late-onset AEs. Supplemental Table 2 presents late-onset AEs that led to permanent discontinuation of the anti-PD1 therapy.

Late-onset AEs were mostly low-grade (mild and moderate) cutaneous, general and gastrointestinal. 23 patients had a single AE, 8 patients had two AEs, 8 patients had three AEs, and 12 patients had more than three AEs. 4 patients (8%) presented one severe late-onset AE and 5 (10%) were hospitalized corresponding to 3 % and 4% respectively in the entire cohort. Among 51 patients with late-onset AEs, 6 (12 %) had a previous autoimmune disease. 45 patients (88%) had already had an early-onset AE, and 29 (57%) had already had multiple early-onset AEs (at least two).

Supplemental Table 3 presents early-onset and late-onset AEs of anti-PD1 treatment.

Concerning the dermatological adverse events, there were 56 (60 %) early-onset AEs: 5 (4 %) grade 3-4 AEs and 51 (43 %) grade 1-2 AEs; there were 28 (55 %) late-onset AES including 1 (1 %) grade 3-4 AE and 27 (23 %) grade 1-2 AEs. Grade 3-4 AEs were acneiform rash, erythroderma, pruritus and purpura and grade 1-2 AEs were pruritus, vitiligo, dry skin, rash, bullous dermatitis, nail infection, skin induration, skin infection, purpura and skin ulceration.

Among 49 patients with maintained CR, 25 (51 %) experienced AEs, including 16 (33 %) late-onset AEs.

Factors associated with late-onset AEs

Table 3 presents the evaluation of factors associated with late-onset AEs. The duration of anti-PD1 treatment and the occurrence of early-onset AE were significantly associated with the occurrence of late-onset AEs in multivariate analysis (p = 0.03 and p = 0.02 respectively). The type of response to anti-PD1, the type of early-onset AE and toxicity to ipilimumab were not associated with late-onset AEs under anti-PD1 (Table 3).

Discussion

Late-onset AEs have scarcely been reported in the literature (11,12,17–19).

Our study demonstrates the possibility of late-onset AEs in a real-life prospective cohort of melanoma patients treated with anti-PD1 therapy during at least 24 months for advanced disease.

Although the overall safety profile of anti-PD1 agents was similar to that reported (11,12,17,20–25), late-onset AEs (occurring after two years of anti-PD1 treatment) were more frequent (43%) than reported in a previous study (30%) (17). The difference may be explained by a longer follow-up (median follow-up of 41.7 months [min-max 25.2-57.5] in the current study as compared to 23.3 months [min-max 21.8-25.2] in the study of Nigro et al) and the prospective collection of data which ensure better AEs reporting (17).

Late-onset AEs were less frequent than early-onset AEs (78 % and 43 % respectively in our study) as previously reported (17,25).

Late-onset AEs were mostly low-grade toxicities (grades 1 and 2) (97 %). Indeed, severe late-onset AEs were rare (3 %) similarly to that reported by Nigro et al. (4.8 %) (17). The four types of severe late-onset AEs observed were arthralgia, type 1 diabetes mellitus, immune system disorder and cutaneous rash.

The risk of late-onset AEs increased with the duration of anti-PD1 treatment in multivariate analysis. However, the number of infusions of anti-PD1 treatment was not associated with increased late-onset AEs in multivariate analysis. Even if previous studies were not focused on late-onset AEs, the association between the duration and the dose of anti-PD1 treatment has been studied with conflicting results (13,22,26,27). Indeed, a significant association between the number of infusions and irAEs have been

demonstrated in patients treated with pembrolizumab (OR 1.15, 95%CI 1.08-1.22, $p < 0.001$) (26). This suggests that the benefit/risk balance should be taken into account to establish recommendations for the optimal duration of anti-PD1 treatment in responder patients, who have an excellent prognosis (28).

Late-onset AEs were also more frequent in patients who experienced at least one early-onset AE (within the first two years of treatment). To our knowledge, this has never been reported in the literature.

The type of response to anti-PD1 treatment (CR, PR, SD) was not significantly associated with the occurrence of late-onset AEs. The association between AEs of anti-PD1 and improved outcomes is still discussed and has not been specifically evaluated with late-onset AEs (17,29,30).

It has been reported that patients with a history of autoimmune disease may have a flare-up of their autoimmune disease and more AEs than other patients (23,31,32). In this cohort, a history of autoimmune disease does not appear to be a risk factor for early or late-onset AEs (10 % and 12 % respectively) or their severity (15 % of grade 3-4 early-onset AEs and no grade 3-4 late-onset AEs). It was remarkable to note that auto-immune cutaneous AEs such as vitiligo were not observed as late-onset AEs.

In addition, we observed late-onset AEs occurring after anti-PD1 discontinuation (8% of all AEs and 16% of late-onset AEs) as already described (33–35). The median time to onset of these AEs was 21 days (range 0.9-401.1 days) after the last infusion of anti-PD1. Couey et al. reported a median time to onset of delayed immune–related events of six months (range 3-28) after treatment discontinuation in a review of 23 cases. However, these delayed immune–related events occurred following a brief course of anti-PD-1 treatment with a median number of 4 doses of anti-PD1 antibodies administered (range 3-42 months) contrary to the current cohort (33). Couey et al suggested that late-onset AEs after discontinuation may be underestimated due to wrong diagnoses, use of

243 treatments with overlapping toxicities, and reduced vigilance after the interruption of
244 anti-PD1 treatment. Altogether our data confirm the possibility of late-onset AEs even
245 after anti-PD1 discontinuation.
246
247 This study has several limitations. The selective bias of patients (patients included are
248 responders to anti-PD1 treatment treated for at least two years) may impact the types
249 and grades of AEs, as recently reported by Nigro el al. (17). Late-onset AEs were defined
250 as occurring after two years of anti-PD1 treatment, which is variable between studies.
251 Thus, the comparison between studies remains difficult. Late-onset AEs occurring
252 within the first month after anti-PD1 discontinuation may be due to the last infusion of
253 monoclonal anti-PD1 antibodies, which are still circulating in the plasma due to their
254 half life of 21-28 days. The MELBASE cohort includes only melanoma patients. Thus,
255 further investigations are needed to evaluate late-onset AEs of anti-PD1 in other cancers
256
257

Conclusion

The long-term use of anti-PD-1 treatment (beyond two years) is frequently associated with late-onset AEs, which are mostly low-grade toxicities. Early-onset AEs (AE occurring within the first two years of treatment) and the duration of anti-PD1 therapy were independently associated with the occurrence of late-onset AEs. This study highlights the need to monitor late-onset AEs even after prolonged anti-PD1 treatment (more than 2 years) including the period after their discontinuation. Physicians should consider the benefit-risk balance when choosing to maintain or discontinue anti-PD1 therapy in patients with advanced melanoma. In the future, the identification of predictive factors of AEs, including late-onset AEs, with auto-antibodies as previously proposed, may prompt clinicians to adjust the duration of anti-PD1 therapy based on patient profile (36).

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Acquisition, analysis, or interpretation of data: Carlet, Nardin.

Drafting of the manuscript: Carlet, Nardin

Critical revision of the manuscript for important intellectual content: Dalle, Leccia, Mortier, Dalac-Rat, Dutriaux, Legoupil, Montaudie, Dereure, De Quatrebarbes, Granel-Brocard, Le-Bouar, Charles, Brunet-Possenti, Dreno, Lebbe.

Statistical analysis: Lefevre.

Administrative, technical, or material support: Allayous.

Supervision: Allayous and Nardin.

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426 # Tables

427 **Table 1: Characteristics of patients.**

	Total n=119 (100 %)
Age (years) Median, [range]	64 [26-90]
Gender	
Male n (%)	73 (61)
Female n (%)	46 (39)
ECOG performance status	
0/1 n (%)	105 (88)
>1 n (%)	3 (3)
N/A n (%)	11 (9)
Primary tumor	
Known n (%)	104 (87)
Unknown n (%)	15 (13)
Autoimmune disease	
Yes n (%)	13 (11)
No n (%)	106 (89)
Breslow index (mm) Median, [range]	3.3 [0.15-18]
Ulceration	
Yes n (%)	45 (38)
No n (%)	48 (40)
N/A n (%)	11 (9)
Unknown primary tumor n (%)	15 (13)
$BRAF^{V600}$ mutation	
Yes n (%)	30 (25)
No n (%)	86 (72)
N/A n (%)	3 (3)
AJCC stage	
III n (%)	17 (15)
IV n (%)	101 (85)
N/A n (%)	1 (1)
Number of metastatic targets	
At least 3 n (%)	48 (40)
< 3 n (%)	70 (59)
N/A n (%)	1 (1)
Elevated LDH level	
Yes n (%)	21 (18)
No n (%)	67 (56)
N/A n (%)	31 (26)
Anti-PD1	
Pembrolizumab n (%)	66 (55)
Nivolumab n (%)	53 (45)
Line of therapy	
1 n (%)	48 (40)
2 n (%)	52 (44)
>= 3 n (%)	19 (16)
Duration of anti-PD1 Median, [range]	33.4 [24.7-56.9]
Best overall response rate	
Complete response n (%)	70 (59)
Partial response n (%)	41 (34)
Stable disease n (%)	8 (7)
Use of steroids at anti-PD1 initiation	
Yes n (%)	9 (8)
No n (%)	110 (92)

Abbreviations: AJCC, American Joint Committee on Cancer ; LDH: lactate dehydrogenase ; anti-PD1, anti-programmed cell death 1 antibodies.

Supplemental Table 1: All adverse events under anti-PD1.

	All grades AEs n=99 (83 %)	Grades 1 and 2 n=99 (83%)	Grades 3 and 4 n=30 (25%)
Cutaneous AEs - No. (%)	67 (56)	66 (55)	6 (5)
Endocrine AEs - No. (%)	29 (24)	25 (21)	8 (7)
Gastrointestinal AEs - No. (%)	48 (40)	48 (40)	2 (2)
Hepatic AEs - No. (%)	12 (10)	11 (9)	3 (3)
Pulmonary AEs - No. (%)	9 (8)	9 (8)	1 (1)
Cardiac AEs - No. (%)	2 (2)	2 (2)	0 (0)
Neurologic AEs - No. (%)	15 (13)	15 (13)	0 (0)
Rheumatologic AEs - No. (%)	10 (8)	10 (8)	1 (1)
General AEs - No. (%)	52 (44)	51 (43)	2 (2)
Hematologic AEs - No. (%)	8 (7)	8 (7)	1 (1)
ENT AEs - No. (%)	8 (7)	8 (7)	1 (1)
Ocular AEs - No. (%)	8 (7)	8 (7)	0 (0)
Others - No. (%)	28 (24)	27 (23)	7 (6)
Single AE - No. (%)	13 (11)	16 (13)	20 (17)
Multiple AEs - No. (%)	86 (72)	83 (70)	10 (8)

Abbreviations: AEs, Adverse events ; ENT, ear, nose and throat.

Supplemental Table 2: adverse events leading to the permanent discontinuation of anti-PD1.

Adverse events - No.(%)	**8 (7)[a]**
Grades 3-4	
Rheumatologic AEs - No. (%)	1 (1)
Others - No. (%)	1 (1)
Grades 1-2	
General AEs - No. (%)	2 (2)
Cutaneous AEs - No. (%)	2 (2)
Ocular AEs - No. (%)	1 (1)
Gastrointestinal AEs - No. (%)	1 (1)
Neurologic AEs - No. (%)	1 (1)
Pulmonary AEs - No. (%)	1 (1)

Abbreviations: AEs, adverse events. [a] Patients may have several adverse events.

Table 2: Late-onset adverse events (after two years of treatment) of anti-PD1.

Late-onset adverse events No. (%)	All grades n=51 (43 %)	Grades 1-2 n=50 (42 %)	Grades 3-4 n=4 (3 %)
Cutaneous - No. (%)	28 (24)	27 (23)	1 (1)
Endocrine - No. (%)	3 (3)	2 (2)	1 (1)
Gastrointestinal - No. (%)	15 (13)	15 (13)	0 (0)
Hepatic - No. (%)	4 (3)	4 (3)	0 (0)
Pulmonary - No. (%)	3 (3)	3 (3)	0 (0)
Cardiac - No. (%)	0 (0)	0 (0)	0 (0)
Neurologic - No. (%)	2 (2)	2 (2)	0 (0)
Rheumatologic - No. (%)	4 (3)	4 (3)	1 (1)
General - No. (%)	17 (14)	17 (14)	0 (0)
Hematologic - No. (%)	3 (3)	3 (3)	0 (0)
ENT - No. (%)	1 (1)	1 (1)	0 (0)
Ocular - No. (%)	4 (3)	4 (3)	0 (0)
Others - No. (%)	7 (6)	7 (6)	1 (1)
Single - No. (%)	23 (19)	23 (19)	4 (3)
Multiple - No. (%)	28 (24)	27 (23)	0 (0)

Abbreviations: AEs: adverse events, ENT: ear, nose and throat

Supplemental Table 3: Adverse events during the first two years and after two years of antiPD1.

Adverse Events - No. (%)	Before 2 years 93 (78)	After 2 years 51 (43)
Grades 3-4 - No. (%)		
Cutaneous AEs	5 (4)	1 (1)
Endocrine AEs	9 (8)	1 (1)
Gastrointestinal AEs	2 (2)	0 (0)
Hepatic AEs	1 (1)	0 (0)
Pulmonary AEs	1 (1)	0 (0)
Cardiac AEs	0 (0)	0 (0)
Neurologic AEs	0 (0)	0 (0)
Rheumatologic AEs	0 (0)	1 (1)
General AEs	2 (2)	0 (0)
Hematologic AEs	1 (1)	0 (0)
ENT AEs	0 (0)	0 (0)
Ocular AEs	0 (0)	0 (0)
Others	2 (2)	1 (1)
Grades 1-2 - No. (%)		
Cutaneous AEs	51 (43)	27 (23)
Endocrine AEs	25 (21)	2 (2)
Gastrointestinal AEs	43 (36)	15 (13)
Hepatic AEs	8 (7)	4 (3)
Pulmonary AEs	7 (6)	3 (3)
Cardiac AEs	2 (2)	0 (0)
Neurologic AEs	14 (12)	2 (2)
Rheumatologic AEs	8 (7)	4 (3)
General AEs	46 (39)	17 (14)
Hematologic AEs	7 (6)	3 (3)
ENT AEs	8 (7)	1 (1)
Ocular AEs	5 (4)	4 (3)
Others	22 (18)	7 (6)
Single AEs - No. (%)	12 (10)	23 (19)
Multiple AEs - No. (%)	81 (68)	28 (24)

Abbreviations: AEs, adverse events ; ENT, ear, nose and throat.

Table 3: Univariate and multivariate analyses of factors associated with late-onset adverse events.

	Univariate analysis			Multivariate analysis		
Characteristics	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.00	0.98-1.03	0.81			
Sex	1.73	0.83-3.67	0.15			
ECOG PS	1.46	0.47-5.02	0.52			
Auto-immune disease	1.58	0.49-5.22	0.44			
Breslow index	0.93	0.8-1.06	0.3			
Ulceration	0.68	0.31-1.43	0.31			
BRAF mutation	0.68	0.28-1.57	0.37			
AJCC	1.83	0.88-3.91	0.11			
LDH level	1.44	0.54-3.91	0.47			
Number of metastatic targets	1.73	0.83-3.67	0.15	0.76	0.26-2.09	0.59
CR	1,00	0,30-3,69	1.00			
Number of infusions	1.04	1.02-1.07	< 0.001	1.01	0.98-1.05	0.43
Treatment duration	1.01	1.001-1.020	< 0.001	1.01	1.001-1.020	0.03
Number of AEs before 2 years	1.07	0.98-1.2	0.17			
At least 1 AE before 2 years	3.26	1.26-9.59	0.02	3.64	1.28-11.85	0.02
Ipilimumab AEs before treatment	1.26	0.53-3.00	0.60			
CR+PR vs SD	2.46	0.54-17.28	0.28			
CR vs PR+SD	0.92	0.44-1.93	0.82			
Cutaneous AEs before 2 years	1.83	0.88-3.86	0.10			
Hepatic AEs before 2 years	1.03	0.24-4.11	0.96			
Endocrine AEs before 2 years	1.68	0.71-4.00	0.23			
Gastrointestinal AEs before 2 years	1.86	0.87-4.00	0.11			
Neurologic AEs before 2 years	1.84	0.60-5.98	0.28			
Severe AEs before 2 years	*2.06*	*0.86--5.09*	0.1			

P <0,05 statistically significant.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status ; AEs, adverse events ; AJCC, American Joint Committee of Cancer ; LDH, lactate dehydrogenase ; CR, complete response ; OR, odds ratio ; 95% CI, confidence interval at 95 %.

- Late-onset adverse events (AEs) of anti-PD1 antibodies (occurring after two years of treatment) are scarcely reported.
- In a prospective cohort of melanoma patients (MelBase), late-onset AEs were observed in 43% of patients and were mostly mild or moderate. Early-onset AEs and prolonged anti-PD1 treatment increased the risk of late-onset AEs.