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

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

3
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34

Key message

35

- Late-onset adverse events (AEs) of anti-PD1 antibodies (occurring after two years of treatment) are scarcely reported.

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- 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.

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Abstract

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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.

66 **Introduction**

67

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

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

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

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

88 Finally, real-world data of late-onset AEs, occurring after two years of anti-PD1
89 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

94 **Materials and methods**

95

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

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

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

129

130

131 **Results**

132

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

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

136

137 **Patient characteristics**

138 Patient characteristics were: male sex (61%), median age of 64 years, history of
139 autoimmune disease (11%), BRAF V600E mutation (25%), AJCC stage IV (84%), brain
140 metastases (22%), ECOG-PS 0 or 1 (88%) and elevated LDH levels (18%). 41 patients
141 (34%) had previously received ipilimumab and 27 patients (23 %) had experienced AEs
142 under ipilimumab (Table 1). A switch of anti-PD-1 therapy was noticed in 20 patients
143 (17 %). Anti-PD1 agents were temporarily interrupted in 22 patients (18 %). The
144 median duration of anti-PD1 treatment was 33.4 months (range, 24.7-56.9). Four
145 patients (3%) died during follow-up, including 2 from disease progression. The BORR to
146 anti-PD1 therapy was as follows: 70 patients had CR, 41 patients had PR, 8 patients had
147 SD. 49 patients remained in CR until the end of follow-up, and 21 subsequently
148 experienced progression disease (PD) while they were still treated by anti-PD1
149 treatment.

150

151 **Adverse events characteristics**

152 99 patients (83%) experienced 618 AEs of any grade after a median duration of anti-
153 PD1 therapy of 13.3 months (range 0-53.9). Among them, thirty patients (30%)
154 presented 47 severe AEs (grade 3 or 4). 19 patients (16%) were hospitalized due to

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

157 51 patients (43%) experienced 140 late-onset AEs. Among them, 49 patients (96 %
158 patients) experienced 120 late-onset AEs (86 % events) while still being treated,
159 whereas 8 patients (16 % patients) experienced 20 late-onset AEs (14 % events) after
160 treatment discontinuation. The median duration of treatment was 39 months (range,
161 26.4-54.9) for patients with late-onset AEs under treatment (n=49) and 26.6 months
162 (range, 24.4-34.5) for patients with late-onset AEs after discontinuation (n=8).

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

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

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

174 Concerning the dermatological adverse events, there were 56 (60 %) early-onset AEs: 5
175 (4 %) grade 3-4 AEs and 51 (43 %) grade 1-2 AEs; there were 28 (55 %) late-onset AEs
176 including 1 (1 %) grade 3-4 AE and 27 (23 %) grade 1-2 AEs. Grade 3-4 AEs were
177 acneiform rash, erythroderma, pruritus and purpura and grade 1-2 AEs were pruritus,
178 vitiligo, dry skin, rash, bullous dermatitis, nail infection, skin induration, skin infection,
179 purpura and skin ulceration.

180

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

183

184 **Factors associated with late-onset AEs**

185 Table 3 presents the evaluation of factors associated with late-onset AEs. The duration
186 of anti-PD1 treatment and the occurrence of early-onset AE were significantly
187 associated with the occurrence of late-onset AEs in multivariate analysis ($p = 0.03$ and p
188 $= 0.02$ respectively). The type of response to anti-PD1, the type of early-onset AE and
189 toxicity to ipilimumab were not associated with late-onset AEs under anti-PD1 (Table 3).

190

191

192 **Discussion**

193

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

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

198 Although the overall safety profile of anti-PD1 agents was similar to that reported
199 (11,12,17,20–25), late-onset AEs (occurring after two years of anti-PD1 treatment) were
200 more frequent (43%) than reported in a previous study (30%) (17). The difference may
201 be explained by a longer follow-up (median follow-up of 41.7 months [min-max 25.2-
202 57.5] in the current study as compared to 23.3 months [min-max 21.8-25.2] in the study
203 of Nigro et al) and the prospective collection of data which ensure better AEs reporting
204 (17).

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

207 Late-onset AEs were mostly low-grade toxicities (grades 1 and 2) (97 %). Indeed, severe
208 late-onset AEs were rare (3 %) similarly to that reported by Nigro et al. (4.8 %) (17).

209 The four types of severe late-onset AEs observed were arthralgia, type 1 diabetes
210 mellitus, immune system disorder and cutaneous rash.

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

216 Indeed, a significant association between the number of infusions and irAEs have been

217 demonstrated in patients treated with pembrolizumab (OR 1.15, 95%CI 1.08-1.22, $p <$
218 0.001) (26). This suggests that the benefit/risk balance should be taken into account to
219 establish recommendations for the optimal duration of anti-PD1 treatment in responder
220 patients, who have an excellent prognosis (28).

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

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

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

234 In addition, we observed late-onset AEs occurring after anti-PD1 discontinuation (8% of
235 all AEs and 16% of late-onset AEs) as already described (33–35). The median time to
236 onset of these AEs was 21 days (range 0.9-401.1 days) after the last infusion of anti-PD1.

237 Couey et al. reported a median time to onset of delayed immune-related events of six
238 months (range 3-28) after treatment discontinuation in a review of 23 cases. However,
239 these delayed immune-related events occurred following a brief course of anti-PD-1
240 treatment with a median number of 4 doses of anti-PD1 antibodies administered (range
241 3-42 months) contrary to the current cohort (33). Couey et al suggested that late-onset
242 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 et 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

258 **Conclusion**

259

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

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273

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278 **Authors contributions :**

279 Concept and design: Nardin.

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

281 Drafting of the manuscript: Carlet, Nardin

282 Critical revision of the manuscript for important intellectual content: Dalle, Leccia,

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284 Brocard, Le-Bouar, Charles, Brunet-Possenti, Dreno, Lebbe.

285 Statistical analysis: Lefevre.

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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)

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429 Abbreviations: AJCC, American Joint Committee on Cancer ; LDH: lactate dehydrogenase ; anti-PD1, anti-

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

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Late-onset adverse events	All grades	Grades 1-2	Grades 3-4
No. (%)	n=51 (43 %)	n=50 (42 %)	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)

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

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

Characteristics	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
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			

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445 *P* <0,05 statistically significant.

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

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