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## Rheumatic and musculoskeletal disorders induced by immune checkpoint inhibitors: Consequences on overall survival

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1 **Effect of immune checkpoint inhibitor-induced rheumatic and**  
2 **musculoskeletal disorders on overall survival**

3  
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28 **ABSTRACT**

29

30 **Objectives:** Immune checkpoint inhibitors (ICIs) frequently induce immune related adverse  
31 events (irAEs) that may be associated with more favorable clinical outcomes. We aimed to  
32 evaluate the impact of all types of rheumatic adverse events (AEs) on overall survival (OS)  
33 and tumor response in patients treated with ICIs.

34 **Methods:** We performed a single-center retrospective observational study to analyze the OS  
35 and tumor response in patients receiving ICIs who experienced a rheumatic AE compared to  
36 those who did not experience any AE.

37 **Results:** From December 2010 to September 2018, 264 patients with any cancer type were  
38 included. Forty-three patients (16.3%) presented with at least one rheumatic AE. The  
39 median OS of patients with rheumatic AEs was significantly higher than that of patients  
40 without AEs, with 132 weeks (95% CI [69.3-not reached]) and 42.7 weeks (95% CI [25.6-not  
41 reached]), respectively ( $P<0.01$ ). This result remained significant after multivariate analysis  
42 (HR 0.54, 95% CI [0.30-0.97],  $P<0.05$ ). Also, tumor response was better in patients with  
43 rheumatic AEs.

44 **Conclusion:** The occurrence of rheumatic AEs in patients treated with ICIs is associated with  
45 better survival and tumor response. Therefore, it seems essential to detect rheumatic AEs as  
46 early as possible to allow rapid and optimal management, given the long-term response  
47 potential of these patients.

48

49

50 **Keywords:** Arthritis; Autoimmunity; Biomarkers; Immunotherapy; T Lymphocytes

## 51 1. INTRODUCTION

52 Under normal physiological conditions, immune checkpoints function as a negative feedback  
53 to regulate inflammatory responses following T-cell activation. However, tumor cells are  
54 able to evade the host immune system response through activation of immune checkpoints  
55 [1]. The immune checkpoints cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) with its  
56 ligand CD80-CD86 and programmed cell death 1 (PD-1) with its ligands PD-L1 and PD-L2, are  
57 currently used as therapeutic targets in oncology. Immune checkpoint inhibitors (ICIs), such  
58 as anti-CTLA-4 (ipilimumab), anti-PD-1 (nivolumab and pembrolizumab), and anti-PD-L1  
59 (avelumab, atezolizumab and durvalumab) have been approved by the Food and Drug  
60 Administration (FDA) for the treatment of melanoma, non-small cell lung cancer (NSCLC),  
61 renal cell carcinoma (RCC), head and neck cancer, Hodgkin lymphoma, and urothelial cancer.  
62 These agents have significantly improved the prognosis of many patients with advanced  
63 cancer. However, by removing the natural brakes of T-cell activation, ICIs can disrupt the  
64 immunological self-tolerance, leading to immune mediated damage to healthy tissues, also  
65 called immune-related adverse events (irAEs). Various organs can be affected, mainly skin,  
66 gastrointestinal tract, endocrine glands, liver and lung. The frequency of adverse events  
67 (AEs) due to ICIs varies between 61 and 86% of patients treated with anti-CTLA-4 [2,3] and  
68 38 to 82% of patients treated with anti-PD-1 [2,4]. Rheumatic and musculoskeletal AEs have  
69 been described in previous studies. Two recent prospective studies reported an incidence of  
70 6.6% [5] and 3.5% [6] for these events. A variety of clinical presentations have been  
71 observed. Arthralgia and myalgia are the most commonly reported symptoms, with a  
72 frequency of up to 26% and 12% under anti-PD-1 treatment [7], and 17% and 13% under  
73 anti-CTLA-4 treatment [8], respectively. Case series dedicated to rheumatic manifestations  
74 under ICIs reported clinical presentations related to inflammatory rheumatism, such as  
75 rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), psoriatic arthritis (PA) and other  
76 non-classified inflammatory arthritis [8–10]. These rheumatic manifestations are mostly mild  
77 to moderate, even if particularly severe forms of myositis have been reported [11,12].

78 According to several studies, the occurrence of irAEs due to ICIs appears to be associated  
79 with improved response rate and overall survival (OS). In melanoma [13] or NSCLC [14]  
80 patients treated with anti-PD-1, irAEs have been associated with a higher tumor response  
81 rate. Improved OS associated to irAEs was also observed in patients with melanoma [15–17],

82 NSCLC [18–20], RCC [21] and gastric cancer [22]. Moreover, some types of irAEs seem to be  
83 particularly associated with these better prognoses. Cutaneous irAEs, like vitiligo in  
84 melanoma ~~was~~ ~~were~~ associated with a better response rate [13] and better OS [15,16].  
85 Likewise, better OS has been observed in patients with NSCLC who developed thyroid  
86 toxicity [23]. The same has been observed with rheumatic irAEs, which have been associated  
87 with a higher tumor response rate, compared to patients without irAEs [5,24]. Moreover, in  
88 a retrospective study, patients with arthralgia showed a better treatment response and  
89 improved progression-free survival (PFS) and OS [25]. Nevertheless, this question remains  
90 controversial, as some studies concluded that there was no association between the  
91 appearance of irAEs and OS [26], or an associations between the appearance of irAEs and  
92 the tumor response, without improved OS [27].

93 In this context we conducted a single-center retrospective study to analyze the association  
94 between the appearance of rheumatic AEs induced by anti-PD-1 or anti-CTLA-4 and OS and  
95 tumour response in patients with any type of cancer. We also studied the association  
96 between OS and dermatologic AEs, endocrine AEs or any type of AE, to find out if their  
97 appearance had a similar effect on survival in our population as the rheumatic AEs.

98

99

## 100 2. METHODS

### 101 2.1 Study design

102 Patients aged 18 years and older ~~treated that started treatment~~ with anti-CTLA-4  
103 (ipilimumab), anti-PD-1 (nivolumab and pembrolizumab) and anti-PD-L1 agents (avelumab,  
104 atezolizumab and durvalumab) alone or in combination, in routine clinical practice in the  
105 departments of oncology, dermatology, pulmonology, hematology and gastro-enterology  
106 from December 2010 to ~~May 2019~~ ~~September 2018~~ were included in this retrospective  
107 observational study. ~~Patients were followed up until May 2019. All patients receiving ICI~~  
108 ~~were identified using oncological pharmacy dispensing records.~~ Patients enrolled in clinical  
109 trials or receiving concurrent chemotherapy/targeted therapy or with joint or bone pain due  
110 to metastatic disease were not included. ~~The baseline patient characteristics were assessed~~  
111 ~~from electronic medical records.~~

112 The study was approved by the French National Data Protection Commission (Commission  
113 Nationale de l'Informatique et des Libertés (Paris, France); registration number:  
114 PI2018\_843\_0062). Patients were provided with information about the study, and were free  
115 to refuse to participate. In line with the French legislation on non-interventional studies,  
116 approval by an investigational review board was neither required nor sought.

117

## 118 **2.2. Collection of baseline patient characteristics**

119 Demographic characteristics (age and sex), body-mass index, and comorbidities were  
120 retrospectively collected from electronic medical records: smoking status (defined as  
121 “never” or “current/past”), alcohol consumption (defined as daily consumption or not,  
122 regardless of the dose), a history of cardiovascular disease (including myocardial infarction,  
123 stroke, obliterating arteriopathy of the lower limbs, and deep vein thrombosis, the presence  
124 or absence of diabetes mellitus (regardless of the severity), the presence or absence of high  
125 blood pressure, the presence or absence of dyslipidemia), a history of cancer and a history of  
126 other auto-immune diseases. The type of current cancer, its metastatic status, and the  
127 Eastern Cooperative Oncology Group (ECOG) performance status were collected.

128

## 129 **2.3 Evaluation of AEs, tumor response and OS**

130 AEs were defined as adverse events which were considered to be treatment-related. All AEs  
131 related to ICI were identified from electronic medical records, by clinical or biological  
132 diagnosis established by the treating clinician, with or without clinical intervention (e.g.  
133 treatment, complementary examinations). Rheumatic AEs were assessed if they were  
134 recurrent (mentioned in at least two medical reports) or if medication or additional medical  
135 examination were required. Patients were included regardless of the fact that they had a  
136 history of rheumatic disease. Rheumatic AEs were systematically validated by two  
137 rheumatologists (AS and BB), in particular to ensure that joint or bone pain due to  
138 metastasis were excluded, and to classify rheumatic AEs as arthritis or arthralgia/myalgia.  
139 Cases of arthritis were either clinically confirmed by medical examination or by  
140 complementary examinations (e.g. echography). Acute and subacute joint or muscle pain  
141 with no other symptoms following ICI initiation were classified as arthralgia/myalgia. For

142 patients with history of similar symptoms, we ensured that they were free of similar  
143 symptoms during the months preceding ICI initiation. If the onset of arthralgia was clearly  
144 associated with osteoarthritis in the medical records, it was not considered as a rheumatic  
145 AE. All AEs were graded using the Common Terminology Criteria for Adverse Events, version  
146 5.0 [28].

147 Tumor response was defined according to RECIST criteria version 1.1 and gathered from the  
148 conclusions of the Multidisciplinary Collaborative Meetings (MCM) and from Control Imaging  
149 results. Good response to treatment included complete response, partial response and  
150 stable disease, as opposed to dissociated response (defined as the concomitant decrease in  
151 certain tumoral elements and increase in other sites) or progression of disease. OS was  
152 calculated from the date of the initiation of the ICI to death from any cause or the date of  
153 the last follow-up examination.

154

## 155 **2.4 Statistics**

156 In our descriptive analysis, categorical variables were expressed as the number (percentage),  
157 and continuous variables were expressed as the mean  $\pm$  standard deviation (SD) or the  
158 median (range), depending on the data distribution. The Shapiro-Wilk test was used to  
159 determine whether or not the data were normally distributed.

160 In bivariate analysis comparing rheumatic AEs and no AE groups, continuous variables were  
161 compared using Student's *t* test or a Wilcoxon's rank sum test (depending on the data  
162 distribution), and categorical variables were compared using a chi-square test or Fisher's  
163 exact test. Kaplan Meier curves and a log-rank test were performed to compare the OS  
164 between rheumatic AEs and non-rheumatic AEs groups. In multivariate analysis, a Cox  
165 proportional-hazards model was used. Significant variables ( $P < 0.05$ ) from the bivariate  
166 analysis, as well as the most common predictors of death (i.e. age, sex, body-mass index,  
167 smoking, alcohol consumption, history of cardiovascular disease, cancer duration and ECOG  
168 performance status), were included in the Cox model. If a patient had multiple rheumatic  
169 AEs, the event (occurrence of an AE) was the first rheumatic AE.

170 The same methodology was performed to compare the OS between rheumatic AEs and (i)  
171 dermatologic AEs and (ii) endocrine AEs groups.

172 In order to compare our population with the literature data, the same methodology was  
173 performed to compare the OS between AEs and no AE groups.

174 In order to determine the predictors of the occurrence of rheumatic AEs when using  
175 immunotherapy and to determine whether the occurrence of a rheumatic AE was predictive  
176 of tumor response, continuous variables were compared using Student's *t* test or a  
177 Wilcoxon's rank sum test (depending on the data distribution), and categorical variables  
178 were compared using a chi-square test or Fisher's exact test. In multivariate analysis, a  
179 logistic regression was performed. Variables significantly associated with rheumatic AEs  
180 ( $P<0.05$ ) in the previous analysis were included in the model.

181 All analyses were performed using R software (version 3.6.0, R Foundation for Statistical  
182 Computing, Vienna, Austria).

183

184

## 185 **3. RESULTS**

### 186 **3.1 Patient characteristics**

187 Two hundred and sixty-six patients started treatment with ipilimumab, nivolumab or  
188 pembrolizumab, monotherapy or combination therapy, between December 1, 2010 and  
189 September 1, 2018. Two patients were excluded because of lack of data. A total of 264  
190 patients were included in the analysis. The average age was  $65.3 \pm 12.5$  years. The most  
191 prescribed ICI was nivolumab, with 153 patients (58%). **Five patients received a combination**  
192 **therapy (nivolumab + ipilimumab).** There was no patient treated with anti-PD-L1 therapy.  
193 The majority of cancers were pleuro-pulmonary (46.2%) and melanomas (33.7%). Detailed  
194 demographic data are listed in **table 1**.

195

### 196 **3.2 Description of AEs**

#### 197 *3.2.1 Global description*

198 A total of 50 rheumatic AEs and 324 non-rheumatic AEs were identified, for a total of 374  
199 AEs. Of the 264 patients, 39.8% had no AEs. Among the 374 AEs, the most commonly  
200 reported ones were cutaneous (27.0%), gastrointestinal (18.4%), general (15.8%), rheumatic

201 (13.4%) and endocrine (11.2%). The earliest effects were gastrointestinal (median onset at  
202 8.1 weeks) and cutaneous (median onset at 12 weeks); the latest ones were hepatic (median  
203 onset at 20.9 weeks).

204

### 205 3.2.2 Rheumatic AEs

206 Forty-three patients (16.3%) developed at least one rheumatic AE due to ICI. Thirty-seven **of**  
207 **the patients** (86.1%) had only one rheumatic AE, but six patients presented several separate  
208 rheumatic AEs: 5 patients had 2 rheumatic AEs, 1 patient had 3 rheumatic AEs, for a total of  
209 50 rheumatic AEs ~~in 43 patients~~.

210 Three patients (7%) had a history of **autoimmune or** inflammatory rheumatism (1  
211 rheumatoid arthritis (RA), 1 polymyalgia rheumatica (PMR), 1 ankylosing spondylitis (AS)), 5  
212 patients (11,6%) had a history of **crystal-induced** arthritis and 12 patients (27.9%) had a  
213 history of non-inflammatory rheumatic disease. Regarding the 50 rheumatic AEs reported,  
214 36 (72%) were arthralgia/myalgia and 14 (28%) were arthritis, of which 7 were **crystal-**  
215 **induced** arthritis cases (5 *de novo* and 2 flares) and 7 cases of inflammatory rheumatism.  
216 Among the inflammatory rheumatic AEs, there were 4 (1.5%) *de novo* cases (2 PMR, 1 RA  
217 and 1 RS3PE syndrome) and 3 (1.1%) flares of preexisting rheumatic disease (1 PMR, 1 RA  
218 and 1 AS). Among the cases of arthralgia/myalgia, 6 (16.7%) were flare ups of an existing  
219 rheumatic **disease condition**.

220 ~~The severity was classified as grade 1 in 50% of the cases, grade 2 in 40% of the cases and~~  
221 ~~grade 3 in 10% of the cases.~~ The median time of occurrence of rheumatic AEs was at 18  
222 weeks after the start of treatment, with extreme values ranging from 0.1 to 133 weeks.  
223 Among the 43 patients with a rheumatic AE, 39 (90%) experienced at least one other type of  
224 AE. **Among these, the most frequent types were cutaneous (experienced by 47% of**  
225 **patients), gastro-intestinal (35%) and endocrine (23%) adverse events.**

226 **The severity was classified as grade 1 in 50% of the cases (n = 25), grade 2 in 40% of the**  
227 **cases (n = 20) and grade 3 in 10% of the cases (n = 5: 1 PMR *de novo*, 1 RS3PE syndrome, 1**  
228 **crystal-induced arthritis with knee swelling, 1 case of worsening of RA, 1 case of arthralgia).**  
229 Most rheumatic AEs were resolved using grade I or grade II analgesics and NSAIDs. Grade III  
230 analgesics were necessary for ~~two~~ **three** patients: **one with crystal-induced arthritis (grade**

231 3), one with a worsening of RA (grade 3) and one with shoulder arthralgia (grade 2). Crystal-  
232 induced arthritis cases were treated either by colchicine or by increasing the dose of  
233 allopurinol. The use of immunosuppressants (corticosteroids and methotrexate) was  
234 required for 9 patients (21%), including 5 patients with grade 3 rheumatic AEs. Eighteen  
235 patients (41.9%) received a medical consultation or advice from a rheumatology specialist.

236

### 237 3.3 Effect of rheumatic AEs vs. no AE on overall survival and tumor response

238 Of the 43 patients experiencing at least one rheumatic AE and the 105 patients without any  
239 AEs (no AE group), 17 patients and 51 patients died, respectively. The median OS in the no  
240 AEs group was 42.7 weeks (95% CI [25.6-not reached]) versus 132 weeks (95% CI [69.3-not  
241 reached]) in the rheumatic AEs group (log-rank,  $P<0.01$ ) (**Figure 1**).

242 In multivariate analysis, the OS was significantly improved in the rheumatic AEs group  
243 compared to the no AE group (HR 0.54, 95% CI [0.30-0.97],  $P<0.05$ ). In addition, in this  
244 population, the higher the ECOG performance status, the poorer was the survival (**Table 2**).

245 There were more responders in the rheumatic AEs group compared to the no AE group  
246 (76.8% vs. 21.0% respectively,  $P<0.001$ , **Table 3**). In multivariate analysis, the occurrence of a  
247 rheumatic AE was strongly associated with better tumor response (OR = 10.5, 95% CI [3.96-  
248 230],  $P<0.001$ , **Table 4**).

249

### 250 3.4 Effect of rheumatic AEs vs. dermatologic AEs on OS

251 OS did not differ significantly in dermatologic AEs and rheumatic AEs groups (log-rank,  $P=NS$ ,  
252 **supplementary, figure S1**). In this population (n = 97, **supplementary, table S1**), 17 patients  
253 in the rheumatic AEs group and 15 in the dermatologic AEs group died. The median survival  
254 in the dermatologic AEs group was not reached and it was 132 weeks (95% CI [69.3 – not  
255 reached]) in the rheumatic AEs group.

256

### 257 3.5 Effect of rheumatic AEs vs. endocrinologic AEs on OS

258 OS did not differ significantly in endocrinologic AEs and rheumatic AEs groups (log-rank,  
259  $P=NS$ , **supplementary, figure S2**). In this population (n = 74, **supplementary, table S2**), 17

260 patients in **the** rheumatic AEs group and 9 in **the** endocrinologic AEs group died. The median  
261 survival in the endocrinologic AEs group was not reached.

262

### 263 **3.6 Effect of overall AEs vs. no AE on OS**

264 We investigated whether the occurrence of overall AEs (OAEs) was associated with better  
265 tumor response and survival compared to patients without AEs. In this population (n = 264,  
266 **supplementary, table S3**), 56 patients in the OAEs group and 51 patients in the no AE group  
267 died. The median survival in the OAE group was not reached while it was 42.7 weeks (95% CI  
268 [25.6 – not reached]) in the no AE group (log-rank,  $P < 0.001$ , **supplementary, figure S3**). In  
269 multivariate analysis, the OS was significantly higher in the OAEs group compared to the no  
270 AE group (HR: 0.44, 95% CI [0.29-0, 68],  $P < 0.001$ , **supplementary, figure S4**). In addition, a  
271 high ECOG performance score at the start of treatment with ICIs was associated with poorer  
272 survival.

273

274

## 275 **4. DISCUSSION**

276 In this study, we showed that ICI-induced rheumatic AEs improve OS. The median survival in  
277 the rheumatic AEs group was significantly higher compared to the no AE group, reaching 132  
278 weeks and 42.7 weeks, respectively. Multivariate analysis confirmed these results. Our  
279 observations are in line with those obtained in studies comparing overall survival in patients  
280 without AEs to patients with arthralgia [25], at least one irAE [15,17–22], a thyroid irAE [18],  
281 or a dermatologic irAE [15,16]. In addition, we observed a better tumor response in the  
282 rheumatic AEs group, with 76.8% responders, compared to the no AE group, with 21%  
283 responders. Our results also confirm the recent findings of the study by Kostine M. *et al.* [5],  
284 in which patients with rheumatic irAEs had a tumor response rate of 85.7% vs 35.3% for  
285 patients without irAEs, and the study by Liew DFL. *et al.* [24], in which rheumatic irAEs were  
286 more common in patients with a good oncological response to therapy (relative risk of 11.2).  
287 Therefore, the occurrence of a rheumatic AE could be a potential predictor of better survival  
288 in patients treated with ICIs. One possible hypothesis is that the occurrence of  
289 immunological toxicity induced by ICIs reflects the effective T cell response, directed against

290 tumor antigens, leading to anti-tumor activity in tumor tissues, as well as side effects in  
291 normal tissues [29]. Tumor cell lysis by CD8+ cytotoxic activated T lymphocytes releases  
292 tumor antigens and neo-antigens which can lead to cross-reactivity with healthy tissues. This  
293 phenomenon, called “epitope spreading”, ~~as well as bystander activation of T lymphocytes,~~  
294 ~~could be a~~ provide hypotheses to explain the development of irAEs [29–31], including  
295 rheumatic and musculoskeletal disorders. In addition to rheumatic AEs, we identified  
296 another factor that influences OS, the ECOG performance score. In a multivariate analysis,  
297 patients with an ECOG performance score of 0 ~~at the introduction of~~ ~~at the start of~~  
298 ~~treatment with~~ immunotherapy showed better OS than patients with an ECOG performance  
299 score of 1, 2 or 3. According to the literature, patients suffering from melanoma have a  
300 better tumor response rate compared to patients with other types of cancer (NSCLC, renal  
301 cell carcinoma and head and neck carcinoma) [32]. However, in our population, we did not  
302 find any association between melanoma and OS in a multivariate analysis: compared to  
303 other types of cancer, melanoma was not associated either with better OS or better tumor  
304 response.

305 The study of factors associated with efficacy of ICI is particularly interesting because a  
306 limited proportion of patients respond to treatment [32]. Thus, the identification of  
307 predictive response markers for ICIs is a major research area in the field of anti-tumor  
308 immunotherapy. The hypothesis that the occurrence of rheumatic AEs could be an early  
309 marker of tumor response remains difficult to use in clinical practice. In our study, the  
310 median time of onset of rheumatic AEs was at 18 weeks, whereas the first radiological  
311 evaluation occurred earlier, usually between 9 and 12 weeks after the beginning of  
312 treatment. Furthermore, this median time of 18 weeks was consistent with data in the  
313 literature and was within the range of extreme median values reported, from 4 to 45 weeks  
314 [6,10,33].

315 In our population, the OS did not differ significantly between the dermatologic AEs, the  
316 endocrinologic AEs and the rheumatic AEs groups. In the literature, the occurrence of a  
317 dermatologic AE [14,15] or an endocrinologic AE [18,23] has been identified as a predictor of  
318 better OS. Therefore, in addition to dermatologic or endocrinologic AEs, the occurrence of  
319 rheumatic AEs is another factor that could be considered to be associated with a better OS.  
320 We also investigated whether the occurrence of overall AEs was associated with better

321 tumor response and survival compared to patients without any AEs. The median survival in  
322 the no AEs group was 42.7 weeks, while it was not reached in the OAEs group. Multivariate  
323 analysis confirmed that survival, as well as tumor response, were significantly higher in the  
324 AEs patient group compared to the group of patients without any AEs. Our results are  
325 therefore similar in this regard to those obtained in previous studies, in various cancer types  
326 [15,17–22].

327 The use of immunosuppressants (corticosteroids and methotrexate) was required in a  
328 minority of patients (21%). Current data suggest that they should be used with caution,  
329 especially at the beginning of treatment, because of their deleterious impact on OS [34,35].  
330 Our observations indicated that their use was decided on collegially, between the referring  
331 oncologist and a rheumatologist in most cases (6 cases out of 9 cases). As only a few patients  
332 received immunosuppressive therapy, we were not able to study their impact on OS in our  
333 population. Therefore, this could involve interpretation bias, since the use of  
334 immunosuppressive treatment, that might reduce ICIs efficacy, was limited. The majority of  
335 rheumatic AEs observed in this study were mild (90% were grade 1 and 2). No temporary or  
336 permanent interruption of ICIs was necessary. This is particularly interesting because, as  
337 shown in this study, since patients with rheumatic AEs are more likely to be good responders  
338 to ICIs, premature discontinuation of therapy due to severe toxicity would not be  
339 beneficial. In addition, except for two patients, all rheumatic AEs were resolved by the end  
340 of the follow up. The grade of severity of the rheumatic disorders described in the literature  
341 has rarely been reported. This might be explained by the fact that CTCAE grading used by  
342 oncologists in ICI trials does not appear to be totally appropriate for rheumatic AEs, due to  
343 their heterogeneity, especially regarding rare rheumatic manifestations. Moreover, when  
344 the grading of rheumatic AE is made by rheumatologists, there might be some confusion as  
345 it differs from their usual evaluation systems, such as Disease Activity Score or the  
346 Rheumatology Common Toxicity Criteria used in rheumatological clinical trials [36].  
347 Nevertheless, with the exception of rare reported cases [10], relatively few rheumatic AEs  
348 appear to be at the origin of an interruption of treatment. In this study, less than half of the  
349 patients (41.9%) who experienced a rheumatic AE were examined by a rheumatologist. This  
350 could indicate that, during the first years following ICI initiation, oncologists were not alerted  
351 enough about rheumatic AE screening. Moreover, after reviewing medical reports, we

352 noticed that some patients would have required further rheumatological investigations or an  
353 optimized management of rheumatic AEs. Therefore, we recommend a consultation with a  
354 rheumatologist upon first clinical symptoms in ICI treated-patients. In our center, this study  
355 raised awareness among oncologists and the number of rheumatology consultations  
356 increased.

357 Combination of ICI (nivolumab + ipilimumab) has been described to be associated with a  
358 higher rate of AEs [37], which was not the case in this study, probably because of a lack of  
359 statistical power (n = 5 patients).

360 Our study had several limitations. First, two patients were excluded due to lack of data.  
361 Then, because of the retrospective nature of the study, information about rheumatic AEs  
362 was collected through medical reports and was not systematically evaluated by a  
363 rheumatologist. We have collected all rheumatic AEs attributable to the ICIs, even the milder  
364 ones, insofar as they appeared under ICI treatment. In the same way, we chose to collect all  
365 AEs following ICI initiation, even if their immune character was uncertain. However, it seems  
366 difficult to exclude any immune implication in arthralgia/myalgia manifestations, especially  
367 since, in some patients, subclinical inflammation could not be verified in the absence of  
368 additional examinations (e.g. medical imaging or biological tests). This could explain the  
369 relatively high incidence of rheumatic AEs in this study, compared to other prospective [5,6]  
370 or retrospective [24] studies. That said, if we consider only new inflammatory rheumatisms,  
371 their incidence was low (1.5%), which is closer to previously published data [6,24]. On the  
372 other hand, However, some patients suffered from severe comorbidities related to cancer  
373 (deterioration of the general state, pain related to metastases, etc.), or even related to the  
374 ICI (mainly digestive or pulmonary disorders). In such a context, the inquiry about rheumatic  
375 symptoms may have been relegated to the background, or have been more complex,  
376 especially in patients with ~~low mobility~~ a poorer ECOG status or those treated with powerful  
377 analgesics masking possible joint or muscle pain. This could explain the difference in ECOG  
378 status between the rheumatic AEs and no AEs groups.

379 In conclusion, Immune checkpoint inhibitor-induced rheumatic and musculoskeletal  
380 disorders are associated with improved OS and a better tumor response. Their occurrence  
381 could be a predictor of better OS. Afflicting 16.3% of patients treated with ICIs, they were  
382 generally mild and manageable without any temporary or permanent cessation of ICIs.

383 These results are encouraging given the long-term response potential of these patients. In  
384 this context, the careful detection of rheumatic AEs and their early management seem to be  
385 essential, in order to maintain the quality of life of these patients as satisfactory as possible.

386 **Contributors**

387 LA, BB and AS contributed to the conception and design of the study and were involved in  
388 the acquisition of data; LA, BB, ZS, BC and AS contributed to the analysis and interpretation  
389 of data. All authors contributed to drafting and/or revising the manuscript.

390

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394

395 **Competing interests**

396 The authors declare that they have no conflict of interest to disclose for this work.

397

398 **Ethics approval and consent to participate**

399 The study was approved by the French National Data Protection Commission (Commission  
400 Nationale de l'Informatique et des Libertés (Paris, France); registration number:  
401 PI2018\_843\_0062). Patients were provided with information about the study, and were free  
402 to refuse to participate. In line with the French legislation on non-interventional studies,  
403 approval by an investigational review board was neither required nor sought.

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- 522
- 523

524 **Tables**

525

526 **Table 1: Characteristics of the study population and comparisons between the RAEs and no AEs groups**

	Population n = 264	No AEs group n = 105	RAEs group n = 43
<b>Age (years), <i>m ± sd</i></b>	65.3 ± 12.5	65.1 ± 11.8	65.1 ± 10.4
<b>Sex</b>			
Male, <i>n (%)</i>	171 (64.8)	73 (69.5)	29 (67.4)
Female, <i>n (%)</i>	93 (35.2)	32 (30.5)	14 (32.6)
<b>Body mass index (kg/m<sup>2</sup>), <i>m ± sd</i></b>	25.4 ± 5.8	24.5 ± 5.38	27.0 ± 4.85**
<b>ECOG performance status</b>			
0, <i>n (%)</i>	92 (34.8)	20 (19.0)	21 (48.8)
1, <i>n (%)</i>	111 (42.0)	45 (42.9)	16 (37.2)
2, <i>n (%)</i>	41 (15.5)	23 (21.9)	5 (11.6)**
3, <i>n (%)</i>	14 (5.3)	12 (11.4)	1 (2.3)
4, <i>n (%)</i>	6 (2.3)	5 (4.8)	0
<b>Smoking (current or past), <i>n (%)</i></b>	180 (68.2)	80 (76.1)	27 (62.8)*
<b>Alcohol consumption</b>	71 (26.9)	33 (31.4)	9 (20.9)
<b>History of rheumatic disease</b>	65 (24.6)	28 (26.7)	20 (39.5)
Non-inflammatory, <i>n (%)</i>	52 (19.7)	23 (21.9)	12 (27.9)
Auto-immune, <i>n (%)</i>	1 (0.4)	0	1 (2.3)
Inflammatory, <i>n (%)</i>	2 (0.8)	1 (1.0)	2 (2.3)
Crystal-induced, <i>n (%)</i>	12 (4.5)	5 (4.8)	5 (11.6)
<b>History of other auto-immune diseases<sup>1</sup>, <i>n (%)</i></b>	24 (9.1)	10 (9.5)	3 (7.0)
<b>Tumor type</b>			
Lung, <i>n (%)</i>	123 (46.2)	57 (54.3)	18 (41.9)
Melanoma, <i>n (%)</i>	89 (33.7)	18 (17.1)	20 (46.5)***
Renal, <i>n (%)</i>	23 (8.7)	12 (11.4)	4 (9.3)
Urothelial, <i>n (%)</i>	1 (0.4)	0	0
Head and neck, <i>n (%)</i>	12 (4.5)	9 (8.6)	1 (2.3)
Hodgkin lymphoma, <i>n (%)</i>	4 (1.5)	1 (1.0)	0
Digestive, <i>n (%)</i>	2 (0.8)	0	0
Cutaneous squamous-cell carcinoma, <i>n (%)</i>	1 (0.4)	1 (1.0)	0
Adenocarcinomas of unknown primary, <i>n (%)</i>	5 (1.9)	3 (2.9)	0
Squamous-cell carcinoma of unknown primary, <i>n (%)</i>	4 (1.5)	3 (2.9)	0
<b>Metastatic cancer, <i>n (%)</i></b>	209 (79.1)	82 (78.1)	33 (76.7)
<b>Cancer duration (months), <i>med [min – max]</i></b>	15.7 [0.4 – 236]	12.5 [0.8 – 145]	15.7 [0.4 – 214]
<b>ICIs</b>			
Nivolumab, <i>n (%)</i>	158 (59.8)	78 (74.3)	23 (53.5)*
Pembrolizumab, <i>n (%)</i>	91 (34.5)	26 (24.8)	17 (39.5)
Ipilimumab, <i>n (%)</i>	15 (5.7)	2 (1.9)	4 (9.3)
<b>Nivolumab + ipilimumab, <i>n (%)</i></b>	<b>5 (1.9)</b>	<b>1 (1.0)</b>	<b>1 (2.3)</b>

527 <sup>1</sup>Thyroid disorders, Basedow disease, psoriasis, eczema, hepatitis, inflammatory bowel diseases

528

529 *AEs, adverse events; ICIs, immune checkpoint inhibitors; RAEs, rheumatic adverse events; m, mean; max, maximum; med,*530 *median; min, minimum; sd, standard deviation*

531

532 \**P*<0.05; \*\**P*<0.01; \*\*\**P*<0.001

533 **Table 2: Effect of predictors on overall survival**

	N (%)	Crude model	Adjusted model
		HR (95% CI)	HR (95% CI)
<b>Age</b>	148 (100)	0.99 (0.97 – 1.02)	1.00 (0.97 – 1.02)
<b>Body mass index</b>	148 (100)	0.95 (0.91 – 1.00)	1.01 (0.95 – 1.07)
<b>Cancer duration</b>	148 (100)	0.99 (0.98 – 1.00)	0.99 (0.98 – 1.00)
<b>Sex</b>			
Male	102 (68.9)	Reference	Reference
Female	46 (31.1)	0.81 (0.47 – 1.39)	0.79 (0.44 – 1.41)
<b>History of cardiovascular disease</b>			
Absence of cardiovascular disease	52 (35.1)	Reference	Reference
Presence of cardiovascular disease	96 (64.9)	0.87 (0.53 – 1.42)	0.69 (0.40 – 1.19)
<b>ECOG performance status</b>			
0	41 (27.7)	Reference	Reference
1	61 (41.2)	2.02 (1.02 – 4.01)*	2.39 (1.04 – 5.49)*
2	28 (18.9)	6.14 (2.90 – 13.0)***	7.85 (3.09 – 20.0)***
> 3	18 (12.2)	5.80 (2.56 – 13.1)***	5.51 (2.08 – 14.6)***
<b>Smoking</b>			
Never	41 (27.7)	Reference	Reference
Current or past	107 (72.3)	1.85 (1.02 – 3.34)*	1.06 (0.51 – 2.23)
<b>Alcohol consumption</b>			
No	106 (71.2)	Reference	Reference
Yes	42 (28.8)	1.47 (0.89 – 2.46)	0.99 (0.98 – 1.00)
<b>Tumor type</b>			
Other	110 (74.3)	Reference	Reference
Melanoma	38 (25.7)	0.47 (0.26 – 0.87)**	1.26 (0.55 – 2.91)
<b>Rheumatic AE</b>			
No	105 (70.9)	Reference	Reference
Yes	43 (29.1)	0.45 (0.26 – 0.79)**	0.54 (0.30 – 0.97)*

534  
535 \*P<0.05; \*\*P<0.01; \*\*\*P<0.001

536

**Table 3: Description of best tumor responses (according to RECIST criteria) in the no AEs and RAEs groups**

	<b>No AEs group n = 105</b>	<b>RAEs group n = 43</b>
<b>Responders, n (%)</b>	22 (21.0)	33 (76.8)***
Complete response, n (%)	4 (3.8)	4 (9.3)
Partial response, n (%)	4 (3.8)	8 (18.6)**
Stability, n (%)	14 (13.3)	21 (48.8)***
<b>Non-responders, n (%)</b>	71 (67.6)	9 (20.9)***
<b>Dissociated response</b>	2 (1.9)	1 (2.3)
<b>Unknown, n (%)</b>	10 (9.5)	0
<b>Response time (week), med [min – max] (n' = 138<sup>1</sup>)</b>	n' = 95, 9.2 [3.6 – 71]	n' = 43, 12.7 [6.4 – 121]***

537

<sup>1</sup> Unknown response for 10 patients

538

539

RAEs, rheumatic adverse events

540

541

\*\*p&lt;0.01; \*\*\*p&lt;0.001

Table 4: Multivariate analysis of the association of different parameters to the occurrence of rheumatic AEs

	N (%)	Crude model	Adjusted model
		OR (95% CI)	OR (95% CI)
<b>Body mass index</b>	138 (100)	1.09 (1.02 – 1.17)*	1.02 (0.92 – 1.13)
<b>ICIs duration</b>	138 (100)	1.02 (1.00 – 1.05)*	0.98 (0.95 – 1.01)
<b>ECOG performance status</b>			
0	39 (28.3)	Reference	Reference
1	56 (40.6)	0.34 (0.14 – 0.77)*	4.68 (0.62 – 98.1)
2	27 (19.6)	0.21 (0.06 – 0.61)**	3.48 (0.51 – 74.5)
> 3	16 (11.5)	0.06 (0.00 – 0.31)**	3.01 (0.36 – 66.9)
<b>Smoking</b>			
Never	38 (27.5)	Reference	Reference
Current or past	100 (72.5)	0.53 (0.25 – 1.14)	1.16 (0.39 – 3.64)
<b>Tumor type</b>			
Other	102 (73.9)	Reference	Reference
Melanoma	36 (26.1)	4.2 (1.93 – 9.34)***	2.49 (0.58 – 11.24)
<b>Nivolumab</b>			
No	45 (32.6)	Reference	Reference
Yes	93 (67.4)	0.40 (0.19 – 0.83)*	1.14 (0.39 – 3.53)
<b>Responders</b>			
No	83 (60.1)	Reference	Reference
Yes	55 (39.9)	10.95 (4.82 – 26.8)***	9.67 (3.59 – 23.3)***

543

544

\*P&lt;0.05; \*\*P&lt;0.01; \*\*\*P&lt;0.001

545 **FIGURE LEGENDS**

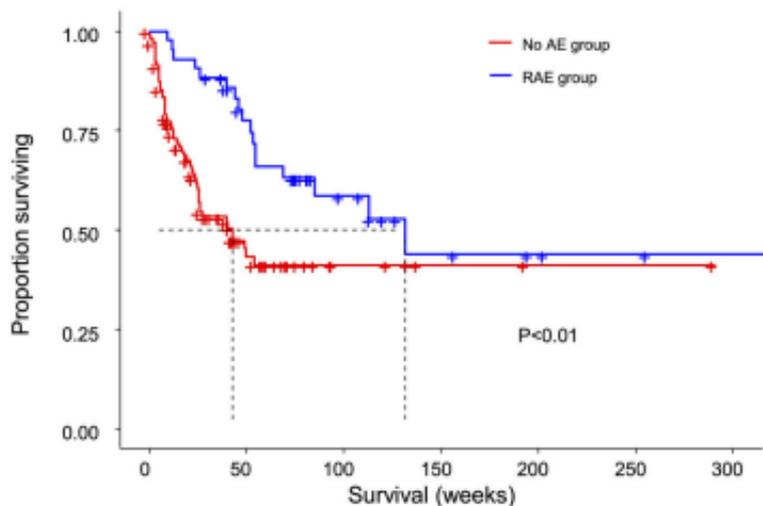
546

547 **Figure 1: Overall survival in rheumatic AE and no AE groups**

548 Kaplan-Meier analysis comparing the OS in cancer patients treated with ICI with rheumatic  
549 adverse events (RAE group, n=43) or without rheumatic adverse events (no AE-group,  
550 n=105).

551 No AE, no adverse event; RAEs, rheumatic adverse events

### Overall survival



### Number at risk

	0	50	100	150	200	250	300
No AE group	105	22	5	2	1	1	0
RAE group	43	27	11	5	3	2	1

Survival (weeks)