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1 **Title: Diabetes and blood glucose disorders under anti-PD1**

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29

30

31 **Abstract**

32

33 Acute type 1 diabetes (AD1) is a rare but definitive immune related adverse event
34 associated with anti-PD1. Most of reported cases are close to what has been described
35 as “fulminant type 1 diabetes”. We **sought** to determine **whether** anti-PD1 could
36 impair glycoregulation and whether occurrence of AD1 could be anticipated by prior
37 glycemic changes. Fasting glycaemia collected before, under and after treatment in
38 melanoma patients treated with anti-PD1 over a period of 36 months were
39 retrospectively analyzed. Glycemic trend analyses was performed using linear
40 regression analysis. 1470 **glucose values** were monitored in 163 patients treated for
41 a mean duration of 5.96 months. Three patients developed an AD1 (1, 84%). Two other
42 cases were observed in the same period in a still blinded trial of anti-PD1 vs
43 Ipilimumab. All cases of AD1 occurred in patients with a normal pretreatment glycaemia
44 and there was no detectable drift of glycaemia prior to ketoacidosis onset. In 4 of the
45 5 cases of AD1, HLA subgroups were DRB1* 03 or 04 known to increase type 1
46 diabetes risk in general population. In the 28 patients with preexisting type 2 diabetes,
47 there was a slight trend for glycaemia increase with anti-PD1 infusions (0.05
48 mmol/L/infusion p=0.004). In the 132 patients with normal pretreatment glycaemia,
49 there was a slight trend for a decrease of glycaemia with anti-PD1 infusions (-
50 0.012/mmol/L/infusion p=0.026). **These data suggest that the monitoring of**
51 **glycaemia under anti-PD1 cannot help to anticipate AD1, and there is no general**
52 **tendency to glycemic disorder.** HLA-genotyping before treatment may help to focus
53 surveillance in patients with the HLA DRB1*03/04 group.

54

55 **Key words:** anti-PD1, melanoma, diabetes, glycaemia, immune related adverse
56 event, HLA

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65 **INTRODUCTION**

66 The development of new immunotherapies with check point inhibitors including anti-
67 CTLA4 antibodies and more recently anti-PD1 antibodies has dramatically improved
68 the **prognosis** of metastatic melanoma [1–5]. Anti-PD1 have also demonstrated
69 efficacy in many other malignancies like non-small cell lung cancer, renal cell
70 carcinoma, head and neck squamous cell carcinoma and relapsing Hodgkin
71 lymphoma.

72 Many immune-related adverse events (IRAE) have been reported with checkpoint-
73 inhibitors including dermatitis, enterocolitis, hepatitis, thyroiditis, hypophysitis **as well**
74 **as some less frequent but potentially life threatening rare AEs** [6,7]. In the
75 context of an increasing number of patients exposed to these drugs, management of
76 these IRAEs has become a priority and specific guidelines have been established [6].
77 While no warning signal for diabetes induced by checkpoint inhibitors has been
78 detected during the clinical trials, several cases of acute insulin-dependent type 1
79 diabetes (AD1) have been recently reported under anti-PD1, and anti- PDL1 antibodies
80 [8–10], and more recently under **the anti-CTLA4 and anti-PD1 combination** [11].

81 The exact mechanisms of these acute insulin-dependent diabetes under anti-PD1
82 therapies is currently unknown. Evidence that blockade of PD1-PDL1 checkpoint can
83 accelerate the emergence of autoimmune diabetes in the non-obese diabetic mouse-
84 model [12] suggests it may play a role in protecting against the development of
85 autoimmune diabetes. **Anti-Glutamic Acid Decarboxylase (GAD) autoantibodies**
86 **or Insulin auto antibodies (IAA)** have been identified in approximately half of the
87 anti-PD1 induced AD1 [7,8,11,17–21]. Several reported cases share close similarities
88 with the “fulminant type 1 diabetes” frequent in East Asia [22]: i) abrupt onset of
89 ketoacidosis, ii) low HbA1c value despite a high plasma glucose level iii) absence of
90 insulin secretion capacity after glucagon test. This brutal onset suggests a drastic
91 immune reaction against β -cell.

92 **Apart from “fulminant diabetes”, a case of diabetic ketoacidosis with insulin**
93 **requirement has also been reported in a patient who had preexisting type 2**
94 **diabetes controlled with metformin [17], suggesting that some patients with**
95 **preexisting type 2 diabetes might become more difficult to equilibrate under anti-**
96 **PD1.**

97

98 In order to determine whether anti-PD1 could impair glycoregulation in more patients
99 than expected, especially in those with preexisting type 2 diabetes, and whether AD1
100 could be anticipated by prior glycaemic changes we retrospectively analyzed blood
101 glucose samples of a series of 163 consecutive patients treated by anti-PD1 antibodies
102 for melanoma.

103

104 **PATIENTS AND METHODS**

105

106 We performed a **single institution**, descriptive study of consecutive patients treated
107 with anti-PD1 for melanoma in the department of dermatology of CHU Timone in
108 Marseille, FRANCE **since September 2013**. Each patient gave is written consent.
109 Data were recorded for each patient between the first anti-PD1 infusion and the date
110 of final analysis on May 2016. Available fasting blood glucose values were collected
111 from the hospital files and retrieved from external laboratories before (in the year
112 preceding the treatment with anti-PD1), **under** (usually 24-72h before each infusion),
113 and within the year after anti-PD1 discontinuation for those in whom it was
114 discontinued. The following variables were also collected: initial and per-treatment
115 weight changes, BMI (body mass index); personal or familial history of type 1 or type
116 2 diabetes; personal history and history of autoimmune disease; previous treatment
117 with Ipilimumab (yes or no), type of anti-PD1 administered (Nivolumab or
118 Pembrolizumab), dosage, number of infusions, and cumulative dose of **exposure**;
119 treatment efficacy (partial or complete response, stable disease or disease
120 progression); date and cause of anti-PD1 discontinuation. The World Health
121 Organization (WHO) definition was used for the diagnosis of diabetes i.e. fasting
122 plasma glucose ≥ 7.0 mmol/L [23].

123

124 **Statistical analysis**

125

126 Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM SPSS
127 Inc., Chicago, IL, USA). Continuous variables are expressed as means \pm SD or as
128 median with range (min, max), and categorical variables are reported as count and
129 percentages. When the distribution of differences between pairs was non-normally
130 distributed, the Wilcoxon signed-rank test was used to compare pre and post **glycaemia**
131 measurements. Glycemic trend analyses were performed using linear regression

132 analysis. All the tests were two-sided. The statistical significance was defined as
133 $p < 0.05$.

134

135

136

137 **RESULTS**

138 **Population and treatment**

139 The characteristics of the 163 consecutive patients treated with anti-PD1 over a period
140 of 36 months are presented in table 1. **Twenty-eight patients (17.2%) had at least**
141 **one elevated pre-treatment glycaemia. Twelve of these 28 patients had a known**
142 **history of type 2 diabetes whereas 16 were not known to be diabetic.** No patient
143 had a previous history of type 1 diabetes. Ninety-five patients (64%) were treated with
144 Nivolumab and 68 (36%) with Pembrolizumab, 27 of which in the context of therapeutic
145 trials. All patients, but 3 (1.8%) who were treated in the adjuvant setting, had a
146 metastatic melanoma. Treatment was first-line in 109 (66.9%) patients. Fifty-four
147 (32.9%) had previously been treated with ipilimumab. A total of 1920 infusions (1146
148 Nivolumab and 774 Pembrolizumab) were **administered** over the study period. The
149 mean duration of the anti-PD1 treatment was 4.5 (0.5-40) months. Mean number of
150 anti-PD1 infusions was 12.1 (1-53).

151 At the time of datalock, study treatment had been discontinued in 97 (59.5%) patients
152 for disease-related death in 34 (35.1%), disease progression in 44 (45.4 %), complete
153 response in 8 patients (8.2%), IRAEs in 7 patients (7.2%), and other adverse events
154 non considered as IRAEs in 4 patients (4.1%) (Bilateral lower-limb ischemia in 1,
155 dyspnea worsening in 1, intestinal ischemia in 1, and septic shock in 1 patient).

156

157 **Fasting glycaemia in the whole cohort**

158 Blood glucose samples were available in 160 of the 163 patients, and a total of 1470
159 **before, under and after**-treatment glycaemia were collected. There was a non-
160 significant trend toward a decrease of glycaemia with anti-PD1 infusions (-0.012
161 mmol/L/infusions $p=0.656$). The median of the glycaemia did not change over the time
162 of anti-PD1 exposure. The evolution of the median (min, max) glycaemia according to
163 the number of anti-PD1 infusion is presented in figure1.

164 The patients weight did not significantly change under treatment (71.8 kg +/- 15.1 vs
165 71.6 kg +/- 15.1, p = 0.429, for mean pre-treatment and last available weight,
166 respectively).

167 There was no difference in mean fasting glycaemia values according to the anti-PD1
168 molecule administered (Nivolumab or Pembrolizumab) nor to the fact that they had
169 received ipilimumab before (data not shown).

170

171 **Patients with normal glycaemia before-treatment**

172 Among the 132 patients without known preexisting type 2 diabetes, and having normal
173 glycaemia **before treatment**, 3 (2.22%) developed an AD1, all fulfilling the “fulminant
174 diabetes” criteria. Figure 2 represents the evolution of median (min, max) glycaemia
175 with successive anti-PD1 infusion in this population.

176 Apart from these 3 AD1, only one patient had one isolated increased glycaemia
177 (8.7mmol/L) under anti-PD1 therapy, which may correspond to inadequate non-fasting
178 sampling. In the 132 patients with normal glycaemia **before treatment**, there was a
179 **statistically** significant negative but very low trend toward a decrease of glycaemia (-
180 0.012/mmol/L/infusion (p=0.026)). **Five patients received systemic corticosteroids**
181 **(1mg/kg), for IRAE management (colitis n=2, 1 skin rash n=1) or for symptomatic**
182 **reason (2 cerebral edema).**

183

184 **Patients with abnormal glycaemia before treatment**

185 Twelve patients had a preexisting treated type 2 diabetes, and 16 others had pre-
186 treatment fasting glycaemia compatible with type 2 diabetes definition (table 2). Out of
187 the 16 who were previously untreated, only one patient required the introduction of
188 repaglinide, whereas dietetic measures were sufficient to maintain glycaemia within
189 the normal range in the 15 others. The 12 patients with a diagnosis of type 2 diabetes
190 **before treatment** were respectively treated with insulin (n=5), oral hypoglycemic
191 agents (n=15) (metformine (4), repaglinide (4), gliclazide (3), vildagliptine-metformine
192 (1), sitagliptine-metformine (1), sitagliptine (1), glimepiride (1)). Among these 28
193 patients, 8 (28.6%) had at least one elevated glycaemia (>10mmol/L) under anti-PD1
194 therapy. Evolution of median glycaemia in this population is represented in figure 3.

195 Hemoglobin A1c (HbA1c) values were available only in 7 of these 28 patients. An
196 HbA1c >7% was found in 2 patients during anti-PD1 treatment course, while their
197 weight remained stable. **No type 2 patient not requiring insulin at baseline**

198 **subsequently required insulin to manage hyperglycemia.** Glycemic trend analysis
199 by linear regression analysis suggested a slight increase of blood glucose values along
200 with increasing number of infusions (0.05 mmol/L/infusion p=0.004). **Three patients**
201 **received systemic corticosteroids for IRAE management (1 colitis) or**
202 **symptomatic reason (2 cerebral edema).**

203

204 **New onset AD1 under anti-PD1**

205 Three cases (1.84%) of AD1 were diagnosed in the cohort: one after 2 **doses** of
206 Pembrolizumab, and the two others after 4 and 11 doses of Nivolumab respectively.
207 Two additional cases (n° 4 and 5) were diagnosed in patient receiving immunotherapy
208 in blinded therapeutic trials (Ipilimumab versus Anti-PD1). **One of them (n°4) have**
209 **since been unblinded and confirmed having received nivolumab.** As patient 5 is
210 still blinded, we are not certain that he received anti-PD1. A summary of these 5 cases
211 is provided in Table 3. **Briefly, all of them presented a cardinal syndrome with**
212 **diabetic ketoacidosis, normal or subnormal HbA1C levels (range 6.4 to 7.6%),**
213 **and collapsed C-peptide secretion.** Two patients had slightly positive anti islet
214 **antigen-2 antibodies. Four patients carried a predisposition HLA DRB1*03 or**
215 **HLA DRB1*04 haplotypes. Insulin therapy was initiated insulin therapy upon**
216 **presentation for all patients, and they all remained insulin-dependent at this**
217 **time.**

218

219

220 **DISCUSSION**

221 This is the first systematic study of glycaemia in patients treated by anti-PD1 in the real
222 life setting. It does not support the idea that anti-PD1 could systematically induce
223 glycemic disorders or make preexisting diabetes more difficult to manage despite a
224 small trend for an increase of glycaemia along with anti-PD1 infusions. However, our
225 data confirm the possibility of anti-PD1-induced AD1, and suggest that incidence of
226 AD1 (1.8% in this series) could be underestimated. The glycaemia monitoring shows
227 that AD1 cannot be anticipated by any preliminary drift in glucose metabolism. Our
228 data also suggest that some HLA group (HLA DRB1*03/04) may be a risk marker for
229 anti-PD1 induced AD1 in the Caucasian population.

230

231 More than 25 cases of type 1 acute diabetes, most of them diagnosed in patients
232 treated for a melanoma, have been reported so far in the literature, 22 under anti-PD1,
233 1 under anti-CTLA4 and anti-PD1 combination and 3 under anti-PDL1 [7–9,11,17–
234 21,24–30]. (Table 4). Among these reported cases, 3 patients had a personal history
235 of autoimmune thyroiditis, like 2 of our patients, and 8 had previously been treated with
236 ipilimumab [7,17,18,20,29,31].

237
238 The five cases of AD1 described herein fulfill the criteria of “ fulminant diabetes”[22]: a
239 sudden onset of hyperglycemia with ketoacidosis, normal or subnormal HbA1C levels
240 and collapsed **C-peptide** secretion reflecting an absence of insulin-secreting capacity.
241 In the Japanese population where fulminant diabetes was described, it was suspected
242 to result from a rapid destruction of β -pancreatic cells secondary to a viral pancreatic
243 infection [32,33] on a genetic predisposed background (DRB1 * 0405-DQB1 * 0401),
244 [34,35]. In the present study, no previous change in glycaemia was predictive, making
245 the anticipation of this complication impossible, a characteristic that justifies the term
246 **fulminant**.

247
248 In the general population the annual incidence of AD1 is estimated 0.1 to 36/ 100.000
249 [36–38]. In our cohort, 2% of patients developed an AD1 under a mean period under
250 treatment of 4 months, which suggests a huge incidence increase 100 to 1000 times
251 higher compared to basic risk.

252
253 Our anti-PD1 AD1 cases lack the HLA haplotypes identified in the fulminant diabetes
254 described **in the** Asian population. However, it is noteworthy that 4 of our 5 pts carried
255 a HLA DRB1*03 or HLA DRB1*04 haplotypes known to be associated with a life-time
256 risk of AD1 3 to 5 times higher than in the general population and even 20 to 40 times
257 higher in patients carrying both the HLA DR3 and DR4 haplotypes [39]. As these
258 haplotypes were mentioned in several other **Caucasian** cases of AD1 under anti-PD1,
259 HLA DRB1*03 and 04 genotyping can be suspected to be a risk marker for AD1 in
260 patients treated by anti-PD1. These data are compatible with the hypothesis that anti-
261 PD1 could trigger AD1 in genetically predisposed patients, who would have been
262 natural candidate to AD1 later on. The delay between the introduction of
263 immunotherapy and the onset of AD1 ranged from one week to 12 months, suggesting
264 that, when the genetic background is there, anti-PD1 can trigger the disease very fast.

265 It is noteworthy that developing an AD1 under anti-PD1 does not seem to be in itself a
266 guarantee of successful treatment, although some results suggest some link between
267 response to anti-PD1 and occurrence of irAE [40]. Tumor response was documented
268 in only 10 of the previous published cases. Some degree of response was observed in
269 8 of these 10 patients, as well as in 4 of our 5 cases.

270

271

272 When focusing on patients with a known preexisting diabetes, or at least pretreatment
273 increased glycaemia compatible with a type 2 diabetes, we found a estimated pre-
274 treatment prevalence of diabetes at 17.1% for a mean age of 65.2 years, which is quite
275 similar to the prevalence in the French epidemiological study OBEPI [41]. Linear
276 regression analysis in these patients suggests a slight increase (0.05mmol/L per
277 infusion) along with increasing anti-PD1 infusions, but only one patient required the
278 introduction of a new antidiabetic treatment. It should be noticed that the weight of
279 patients did not either change significantly under anti-PD1 treatment. All these
280 observations are not suggestive of a direct effect of anti-PD1 on glucose metabolism.
281 The slight trend for an increasing glycaemia in patients with a preexisting glycemic
282 disorder might result from a lower ability to control glycemic changes induced by many
283 factors other than anti-PD1 treatment: impact of the tumor load on the general
284 metabolism, indirect consequences of other immune-related complication, differences
285 in dietary behavior, supportive treatments including steroids, etc.

286

287 In patients with normal pretreatment glycaemia, the trend is so low that it can be
288 considered negligible.

289

290 The limit of our work is related to its retrospective character, and the fact that we did
291 not have systematically access to HbA1c results. Nevertheless, no case of AD1 could
292 be missed, and the study of blood glucose values does not suggest that we could find
293 different results with a prospective study or prospective HbA1c collection. The
294 advantage of this cohort is that it is not biased by any selection on disease severity,
295 age and general status. **As steroids can potentially affect glycemic levels, it is
296 important to notice that only eight patients were treated with systemic steroids
297 to manage irAE or symptomatic cerebral oedema.**

298

299 **Better determining the monitoring of asymptomatic individuals under anti-PD1**
300 **therapy has crucial cost and care implications. When investigating the**
301 **relationship between asymptomatic grade 3 or higher increases in amylase**
302 **and/or lipase and pancreatitis in melanoma patients who received a**
303 **combination of nivolumab + Ipilimumab, Friedman and colleagues [42] found**
304 **only two cases of pancreatitis, representing roughly 20% of patients with grade**
305 **3 or higher amylase, or amylase lipase elevations.** Our data suggest that close
306 monitoring of glycaemia in all patients treated by anti-PD1 is useless since there was
307 no general tendency to glycemic disorder and since AD1 cannot be anticipated from
308 blood glucose monitoring. Furthermore, for type 2 diabetic patients, there is no
309 reason to change the regular monitoring of their diabetes under anti-PD1 therapy.
310 From the practical point of view, it is important to sensitize practitioners to the risk of a
311 sudden severe ketotic decompensation in patients treated with anti-PD1, but also to
312 inform patients on the usual symptoms, since misdiagnosis or delayed management
313 can be fatal. HLA-genotyping before treatment may be useful to focus surveillance in
314 patients with the HLA DRB1*03/04 group. Conversely, it would not be sensible to
315 contraindicate anti-PD1 for these patients in the context of a deadly metastatic disease,
316 but it may be cautious to exclude these groups from adjuvant treatment with anti-PD1.
317
318 The occurrence of IRAE under anti-PD1 being potentiated by use of immunotherapy
319 such as anti-CTLA4 antibodies, it will therefore be necessary to be particularly vigilant
320 and reactive in patients receiving combination or sequence of anti-PD1 and other
321 immune-active agents.

322 323 **REFERENCES**

- 324
325 [1] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in
326 previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320–
327 30. doi:10.1056/NEJMoa1412082.
328 [2] Weber JS, D’Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab
329 versus chemotherapy in patients with advanced melanoma who progressed after anti-
330 CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial.
331 *The Lancet Oncology* 2015;16:375–84. doi:10.1016/S1470-2045(15)70076-8.
332 [3] Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab
333 versus Ipilimumab in Advanced Melanoma. *New England Journal of Medicine*
334 2015;372:2521–32. doi:10.1056/NEJMoa1503093.
335 [4] Bowyer S, Lorigan P. The place of PD-1 inhibitors in melanoma management. *The*
336 *Lancet Oncology* 2015;16:873–4. doi:10.1016/S1470-2045(15)00094-7.

- 337 [5] Hamid O, Robert C, Daud A, Hodi FS, Hwu W-J, Kefford R, et al. Safety and Tumor
338 Responses with Lambrolizumab (Anti-PD-1) in Melanoma. *New England Journal of*
339 *Medicine* 2013;369:134–44. doi:10.1056/NEJMoa1305133.
- 340 [6] Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the Immune-Related
341 Adverse Effects of Immune Checkpoint Inhibitors: A Review. *JAMA Oncol* 2016;2:1346–
342 53. doi:10.1001/jamaoncol.2016.1051.
- 343 [7] Hofmann L, Forschner A, Loquai C, Goldinger SM, Zimmer L, Ugurel S, et al.
344 Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1
345 therapy. *Eur J Cancer* 2016;60:190–209. doi:10.1016/j.ejca.2016.02.025.
- 346 [8] Mellati M, Eaton KD, Brooks-Worrell BM, Hagopian WA, Martins R, Palmer JP, et
347 al. Anti-PD-1 and Anti-PDL-1 Monoclonal Antibodies Causing Type 1 Diabetes. *Diabetes*
348 *Care* 2015;38:e137–8. doi:10.2337/dc15-0889.
- 349 [9] Hickmott L, Peña HDL, Turner H, Ahmed F, Protheroe A, Grossman A, et al. Anti-
350 PD-L1 atezolimumab-Induced Autoimmune Diabetes: a Case Report and Review of the
351 Literature. *Targ Oncol* 2017;1–7. doi:10.1007/s11523-017-0480-y.
- 352 [10] Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. Safety and
353 Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer. *New England Journal*
354 *of Medicine* 2012;366:2455–65. doi:10.1056/NEJMoa1200694.
- 355 [11] Lowe JR, Perry DJ, Salama AKS, Mathews CE, Moss LG, Hanks BA. Genetic risk
356 analysis of a patient with fulminant autoimmune type 1 diabetes mellitus secondary to
357 combination ipilimumab and nivolumab immunotherapy. *J Immunother Cancer* 2016;4.
358 doi:10.1186/s40425-016-0196-z.
- 359 [12] Ansari MJI, Salama AD, Chitnis T, Smith RN, Yagita H, Akiba H, et al. The
360 programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese
361 diabetic (NOD) mice. *J Exp Med* 2003;198:63–9. doi:10.1084/jem.20022125.
- 362 [13] Kochupurakkal NM, Kruger AJ, Tripathi S, Zhu B, Adams LT, Rainbow DB, et al.
363 Blockade of the Programmed Death-1 (PD1) Pathway Undermines Potent Genetic
364 Protection from Type 1 Diabetes. *PLOS ONE* 2014;9:e89561.
365 doi:10.1371/journal.pone.0089561.
- 366 [14] Wang J, Yoshida T, Nakaki F, Hiai H, Okazaki T, Honjo T. Establishment of NOD-
367 *Pdcd1*^{-/-} mice as an efficient animal model of type I diabetes. *Proc Natl Acad Sci USA*
368 2005;102:11823–8. doi:10.1073/pnas.0505497102.
- 369 [15] Cernea S, Herold KC. Monitoring of antigen-specific CD8 T cells in patients with
370 type 1 diabetes treated with antiCD3 monoclonal antibodies. *Clin Immunol*
371 2010;134:121–9. doi:10.1016/j.clim.2009.09.005.
- 372 [16] Ansari MJI, Salama AD, Chitnis T, Smith RN, Yagita H, Akiba H, et al. The
373 programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese
374 diabetic (NOD) mice. *J Exp Med* 2003;198:63–9. doi:10.1084/jem.20022125.
- 375 [17] Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, et al. Precipitation of
376 Autoimmune Diabetes With Anti-PD-1 Immunotherapy. *Diabetes Care* 2015;38:e55–7.
377 doi:10.2337/dc14-2349.
- 378 [18] Martin-Liberal J, Furness AJ, Joshi K, Peggs KS, Quezada SA, Larkin J. Anti-
379 programmed cell death-1 therapy and insulin-dependent diabetes: a case report. *Cancer*
380 *Immunol Immunother* 2015;64:765–7. doi:10.1007/s00262-015-1689-1.
- 381 [19] Chae YK, Chiec L, Mohindra N, Gentzler R, Patel J, Giles F. A case of
382 pembrolizumab-induced type-1 diabetes mellitus and discussion of immune checkpoint
383 inhibitor-induced type 1 diabetes. *Cancer Immunol Immunother* 2017;66:25–32.
384 doi:10.1007/s00262-016-1913-7.
- 385 [20] Hansen E, Sahasrabudhe D, Sievert L. A case report of insulin-dependent diabetes

386 as immune-related toxicity of pembrolizumab: presentation, management and outcome.
387 *Cancer Immunol Immunother* 2016;65:765–7. doi:10.1007/s00262-016-1835-4.

388 [21] Usui Y, Udagawa H, Matsumoto S, Imai K, Ohashi K, Ishibashi M, et al. Association
389 of Serum Anti-GAD Antibody and HLA Haplotypes with Type 1 Diabetes Mellitus
390 Triggered by Nivolumab in Patients with Non-Small Cell Lung Cancer. *Journal of*
391 *Thoracic Oncology* 2016;0. doi:10.1016/j.jtho.2016.12.015.

392 [22] Hanafusa T, Imagawa A. Fulminant type 1 diabetes: a novel clinical entity
393 requiring special attention by all medical practitioners. *Nat Clin Pract Endocrinol Metab*
394 2007;3:36–45; quiz 2p following 69. doi:10.1038/ncpendmet0351.

395 [23] Surveillance WHOD of ND. Definition, diagnosis and classification of diabetes
396 mellitus and its complications : report of a WHO consultation. Part 1, Diagnosis and
397 classification of diabetes mellitus 1999.

398 [24] Ishikawa K, Shono-Saito T, Yamate T, Kai Y, Sakai T, Shimizu F, et al. A case of
399 fulminant type 1 diabetes mellitus, with a precipitous decrease in pancreatic volume,
400 induced by nivolumab for malignant melanoma: analysis of HLA and CTLA-4
401 polymorphisms. *European Journal of Dermatology* 2200;1. doi:10.1684/ejd.2016.2923.

402 [25] Teramoto Y, Nakamura Y, Asami Y, Imamura T, Takahira S, Nemoto M, et al. Case
403 of type 1 diabetes associated with less-dose nivolumab therapy in a melanoma patient. *J*
404 *Dermatol* 2016;n/a – n/a. doi:10.1111/1346-8138.13486.

405 [26] Okamoto M, Okamoto M, Gotoh K, Masaki T, Ozeki Y, Ando H, et al. Fulminant
406 type 1 diabetes mellitus with anti-programmed cell death-1 therapy. *J Diabetes Investig*
407 2016;n/a – n/a. doi:10.1111/jdi.12531.

408 [27] Munakata W, Ohashi K, Yamauchi N, Tobinai K. Fulminant type I diabetes mellitus
409 associated with nivolumab in a patient with relapsed classical Hodgkin lymphoma. *Int J*
410 *Hematol* 2017;105:383–6. doi:10.1007/s12185-016-2101-4.

411 [28] Miyoshi Y, Ogawa O, Oyama Y. Nivolumab, an Anti-Programmed Cell Death-1
412 Antibody, Induces Fulminant Type 1 Diabetes. *The Tohoku Journal of Experimental*
413 *Medicine* 2016;239:155–8. doi:10.1620/tjem.239.155.

414 [29] Gaudy C, Clévy C, Monestier S, Dubois N, Préau Y, Mallet S, et al. Anti-PD1
415 Pembrolizumab Can Induce Exceptional Fulminant Type 1 Diabetes. *Diabetes Care*
416 2015;38:e182–3. doi:10.2337/dc15-1331.

417 [30] Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. Safety and
418 Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer. *N Engl J Med*
419 2012;366:2455–65. doi:10.1056/NEJMoa1200694.

420 [31] Aleksova J, Lau PKH, Soldatos G, McArthur G. Glucocorticoids did not reverse type
421 1 diabetes mellitus secondary to pembrolizumab in a patient with metastatic melanoma.
422 *BMJ Case Reports* 2016;2016:bcr2016217454. doi:10.1136/bcr-2016-217454.

423 [32] Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. A novel subtype of type 1
424 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related
425 antibodies. Osaka IDDM Study Group. *N Engl J Med* 2000;342:301–7.
426 doi:10.1056/NEJM200002033420501.

427 [33] Imagawa A, Hanafusa T. Fulminant type 1 diabetes—an important subtype in
428 East Asia. *Diabetes Metab Res Rev* 2011;27:959–64. doi:10.1002/dmrr.1236.

429 [34] Fujisawa R, Haseda F, Tsutsumi C, Hiromine Y, Noso S, Kawabata Y, et al. Low
430 programmed cell death-1 (PD-1) expression in peripheral CD4+ T cells in Japanese
431 patients with autoimmune type 1 diabetes. *Clin Exp Immunol* 2015;180:452–7.
432 doi:10.1111/cei.12603.

433 [35] Moreau C, Drui D, Arnault-Ouary G, Charbonnel B, Chaillous L, Cariou B.
434 Fulminant type 1 diabetes in Caucasians: A report of three cases. *Diabetes & Metabolism*

435 2008;34:529–32. doi:10.1016/j.diabet.2008.05.003.
436 [36] Lévy-Marchal C, Patterson CC, Green A, EURODIAB ACE Study Group. Europe and
437 Diabetes. Geographical variation of presentation at diagnosis of type I diabetes in
438 children: the EURODIAB study. *European and Diabetes. Diabetologia* 2001;44 Suppl
439 3:B75–80.
440 [37] DIAMOND Project Group. Incidence and trends of childhood Type 1 diabetes
441 worldwide 1990-1999. *Diabet Med* 2006;23:857–66. doi:10.1111/j.1464-
442 5491.2006.01925.x.
443 [38] Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J.
444 Incidence of childhood type 1 diabetes worldwide. *Diabetes Mondiale (DiaMond) Project*
445 *Group. Diabetes Care* 2000;23:1516–26.
446 [39] Erlich H, Valdes AM, Noble J, Carlson JA, Varney M, Concannon P, et al. HLA DR-DQ
447 haplotypes and genotypes and type 1 diabetes risk: analysis of the type 1 diabetes
448 genetics consortium families. *Diabetes* 2008;57:1084–92. doi:10.2337/db07-1331.
449 [40] Hua C, Boussemart L, Mateus C, et al. Association of vitiligo with tumor response
450 in patients with metastatic melanoma treated with pembrolizumab. *JAMA Dermatol*
451 2016;152:45–51. doi:10.1001/jamadermatol.2015.2707.
452 [41] Eschwege E, Basdevant A, Crine A, Moisan C, Charles M-A. Type 2 diabetes
453 mellitus in France in 2012: results from the ObEpi survey. *Diabetes Metab* 2015;41:55–
454 61. doi:10.1016/j.diabet.2014.11.007.
455 [42] Friedman CF, Clark V, Raikhel AV, Barz T, Shoushtari AN, Momtaz P, et al.
456 Thinking Critically About Classifying Adverse Events: Incidence of Pancreatitis in
457 Patients Treated With Nivolumab + Ipilimumab. *J Natl Cancer Inst* 2017;109.
458 doi:10.1093/jnci/djw260.
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462 **Figure legends**

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464 Figure 1: Whole population (n=160): Median (min, max) glycaemia with successive
465 anti-PD1 infusions

466

467 Figure 2: Patients with normal glycaemia before treatment (n=132): evolution of
468 median (min, max) glycaemia with successive anti-PD1 infusions.

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470 Figure 3: Patients with abnormal glycaemia before treatment (n=28): evolution of
471 median (min, max) glycaemia with successive anti-PD1 infusions.

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