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# Risk of irAEs in patients with autoimmune diseases treated by immune checkpoint inhibitors for stage III or IV melanoma: results from a matched case–control study

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## ABSTRACT

**Objective** To quantify the risk of immune-related adverse events (irAEs) in patients with pre-existing autoimmune disease (pAID) treated by immune checkpoint inhibitors (ICIs) for stage III or IV melanoma.

**Methods** Case–control study performed on a French multicentric prospective cohort of patients with melanoma, matched for irAE risk factors and oncological staging. Risk of irAE was assessed by logistic regression.

**Results** 110 patients with pAID were included and matched with 330 controls, from March 2013 to October 2020. Over a median follow-up period of 7.2 months for cases and 6.9 months for controls, the ORs of developing all-grade and grade  $\geq 3$  irAEs among cases compared with controls were 1.91 (95% CI (1.56 to 2.27)) and 1.44 (95% CI (1.08 to 1.82)), respectively. Patients with pAID had an increased risk of multiple irAEs (OR 1.46, 95% CI (1.15 to 2.67)) and a shorter time to irAE onset. In contrast, there were no difference in irAE-related mortality nor in the rate of treatment discontinuation, and a landmark analysis revealed a better survival at 24 months among cases ( $p=0.02$ ). Thirty per cent of cases experienced a pAID flare during follow-up, and baseline immunosuppression did not prevent irAE occurrence. Last, we report associations between the pAID clinical subsets and organ-specific irAEs.

**Conclusion** In our study, patients with pAID were at greater risk of all-grade, severe and multiple irAEs, yet had a better 24-month survival than controls. Thus, patients with pAID should be eligible for ICI therapy but benefit from a close monitoring for irAE occurrence, especially during the first months of therapy.

## INTRODUCTION

Immune checkpoint inhibitors (ICIs) are one of the major therapeutic advances in oncology in the past 10 years. Since their first approval in metastatic melanoma<sup>1</sup> and non-small cell lung cancer (NSCLC),<sup>2</sup> ICI indications have broadened and now extend to more than 50 different cancer types.<sup>3</sup> The most prescribed ICIs are anti-PD-1/PD-L1 (programmed cell death protein 1/programmed cell death

## WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Patients with pre-existing autoimmune diseases (pAID) are thought to be at greater risk of immune-related adverse events (irAEs), but previously published data are discordant.
- ⇒ Precise quantification of this risk, independently of the other known risk-factors of irAEs is lacking.

## WHAT THIS STUDY ADDS

- ⇒ - Patients with pAID had a higher risk of developing both all-grade and grade  $\geq 3$  irAEs, but also of multiple irAEs, occurring in a shorter time than controls, but contrasting with a better overall survival at 24 months. Subsetting pAID into clinical subgroups highlighted distinct associations with organ-specific irAEs.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Patients with pAID benefit from ICI but should be closely monitored for irAEs, especially during the first months of therapy. The knowledge of distinct associations between pAID subsets and organ-specific irAEs can improve the early detection of irAEs.

ligand 1) agents, and their prescription is likely to increase with up to 2975 active clinical trials of September 2019.<sup>4</sup> ICI restore anticancer immunity by targeting tumour-driven expression of immune checkpoints to mount an effective antitumoral immune response. However, as these pathways are physiologically involved in the downregulation of T cell responses and act as gatekeepers to prevent excessive T-cell activation, ICIs subsequently expose to the risk of T-cell-driven autoimmunity.<sup>5</sup> ICIs' side effects include a large range of autoimmune manifestations (immune-related adverse events, referred to as irAEs),<sup>6</sup> estimated to occur in 54%–76% of the patients.<sup>7</sup> Management depends on the severity

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grade: while most CTCAE (Common Terminology Criteria for Adverse Events) grade 1 irAEs do not require therapeutic intervention; grade 2 irAEs may require ICI temporary interruption and patients with grade  $\geq 3$  should receive corticosteroids.<sup>5</sup> Lethal irAEs occur in 0.3%–1.3% of cases,<sup>8</sup> and symptoms may persist after ICI cessation and cause long-term sequelae.<sup>9,10</sup> Thus, identifying patients at higher risk of developing irAEs is crucial to early diagnosis and improved care

Autoimmune diseases (AIDs) are frequent, with an estimated prevalence of 4.5%,<sup>11</sup> and co-occurrence with cancer is not uncommon, as recent studies reported a 14%–25% frequency of pre-existing AID (pAID) in 210 509 patients with lung cancer,<sup>12</sup> and of 1.6% in 311 patients treated by anti-PD-1 agents.<sup>13</sup> As irAEs often mimic AID manifestations,<sup>14–17</sup> patients with pAID were thought to be at higher risk of irAEs and excluded from the first clinical trials of ICI.<sup>18–20</sup> Several studies described the safety and oncological outcomes of ICI therapy in patients with pAID. Overall, they reported a frequency of pAID flare of 23%–47%, a frequency of irAEs of 29%–44% and a frequency of grades 3–4 irAEs of 10%–44%. Most pAID flares and irAEs were managed by corticosteroid therapy, leading the authors to conclude that ICI therapy in pAID patients was safe but required close monitoring.<sup>21–25</sup> In a recent study published by Tison *et al*,<sup>25</sup> of 112 patients with pAID treated by ICI, 71% presented with an immune toxicity (pAID flare, irAE or both), and ICI was permanently withdrawn for 21%. Moreover, treatment of immune toxicities with immunosuppressive drugs was associated with a lower progression-free survival. In contrast, in a recent study from a prospective Dutch nationwide melanoma registry, the incidence of grade  $\geq 3$  irAEs did not differ between 415 patients with pAID and controls.<sup>26</sup> These results pinpoint the need for a precise evaluation of the risk of irAEs in patients with pAID.

We present the results of a large case–control matched study of patients included in a prospective cohort, evaluating the risk of irAEs among patients with pAID compared with patients without pAID matched for irAEs' risk factors and disease stage.

## Study design

This study was conducted using the French multicentric prospective and longitudinal cohort MelBase (registered NCT02828202), which is dedicated to the prospective follow-up in 26 participating centres of adults with unresectable stage III or IV melanoma at the time of declaration of metastasis. MelBase prospectively records data regarding oncological progression and survival, treatment introduction and discontinuation, adverse events, and their management, as well as demographic data including age, sex and medical history. Inclusion criteria require an age of over 18 years old, the availability of a tumour sample for histological confirmation of advanced primary melanoma (unresectable stage III or stage IV) and the absence of prior systemic treatment other than adjuvant treatment. Additional data regarding baseline immunosuppressive therapy and pAID flares in cases were collected retrospectively through a questionnaire sent to all recruiting centres.

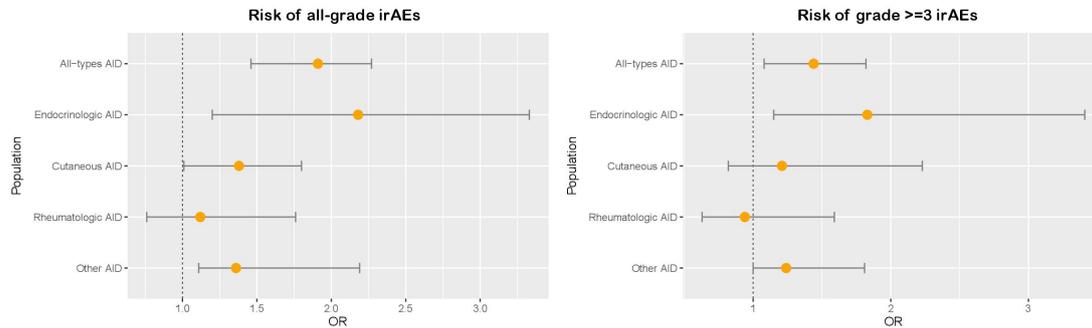
## Cases and controls

Cases were defined as patients treated by anti-PD-1 and/or anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) antibodies for metastatic melanoma with a history of AID prior to immunotherapy, prospectively recorded at inclusion and were referred to as pAID. Specifically, during the inclusion process of the MelBase cohort, the dermatologist in charge of

**Table 1** Cases and controls characteristics

	Cases (N=110)	Controls (N=330)	P value
Age (years old, mean (SD))	65 (14)	65 (18)	1
>65 years old (no (%))	n=65 (59)	n=195 (59)	1
Gender (no (%))			1
Female	n=58 (53)	n=174 (53)	
Male	n=52 (47)	n=156 (47)	
Body mass index (kg/m <sup>2</sup> , mean (SD))	26 (21)	25 (20)	0.8
Melanoma stage			0.3
M1a	n=9 (8%)	n=51 (15%)	
M1b	n=22 (20%)	n=55 (17%)	
M1c	n=59 (54%)	n=172 (52%)	
IIIB	n=5 (5%)	n=8 (2%)	
IIIC	n=15 (14%)	n=44 (13%)	
BRAF status (no (%))			0.8
Wild type	n=67 (61)	n=195 (59)	
Mutated	n=43 (39)	n=135 (41)	
LDH at baseline			
>1x ULN	n=29 (26%)	n=87 (26%)	1
>2x ULN	n=4 (4%)	n=17 (5%)	0.7
ECOG status at baseline			0.02*
0–1	n=84 (76%)	n=285 (86%)	
>1	n=26 (24%)	n=45 (14%)	
Number of metastases (no (%))			1
<3	n=16 (15)	n=48 (15)	
$\geq 3$	n=94 (85)	n=282 (85)	
Hepatic metastases			1
Yes	n=30 (27%)	n=90 (27%)	
Cerebral metastases			1
Yes	n=28 (25%)	n=84 (25%)	
First-line immunotherapy			1
Yes	n=81 (74%)	n=243 (74%)	
No	n=29 (26%)	n=87 (26%)	
Number of previous therapeutic lines			1
0	n=81 (74%)	n=243 (74%)	
1	n=19 (17%)	n=57 (17%)	
$\geq 2$	n=10 (9%)	n=30 (9%)	
Immunotherapy regimen			1
Anti-PD-1 monotherapy	n=86 (78%)	n=258 (78%)	
Pembrolizumab	n=40 (36%)	n=120 (36%)	
Nivolumab	n=46 (42%)	n=138 (42%)	
Anti-CTLA-4 monotherapy	n=15 (14%)	n=45 (14%)	
Anti-PD-1+anti-CTLA-4 combination	n=9 (8%)	n=27 (8%)	
* p<0.05			
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; ULN, upper limit of normal.			

the patient declared if his/her patient had an history of an AID (detailed in the online supplemental annex). For most of these patients, the decision of initiating an ICI therapy was taken collegially by multidisciplinary boards specialised in the management of immunotoxicities due to their history of AIDs and weighted while considering the diagnostic criteria and AID activity. All cases of pAID were centrally reviewed by the authors at the conception of the study.



**Figure 1** Risk of all-grade irAEs and risk of grade  $\geq 3$  irAEs in patients with pre-existing autoimmune diseases matched to controls. AID, autoimmune disease; irAEs, immune-related adverse events.

### Definitions and classification of irAEs

irAEs were defined as an event or laboratory test abnormality, considered to be possibly, probably or certainly linked to the immunotherapy, following the WHO-UMC (WHO-Uppsala Monitoring Centre) causality assessment guidelines, and recorded prospectively during the follow-up. Severity was determined using the CTCAE v4.0. The clinical subtypes of irAEs were regrouped as follows: cardiovascular, endocrinological, rheumatological, cutaneous, pulmonary, haematological, neurological, psychiatric, renal, ophthalmological, musculoskeletal and general symptoms.

### Statistical analysis and case-control matching

Baseline demographic and disease characteristics were summarised as numbers and percentages for categorical variables, and as mean, SD, median, IQR and range for continuous variables, as appropriate. Case-control matching was performed on R statistical software V4.0.4, on a 3-controls-for-1-case ratio, using the following criteria: age (by 2-year range classes), sex, immunotherapy regimen (anti-PD-1 monotherapy, anti-CTLA-4 monotherapy, or anti-PD-1 and anti-CTLA-4 associated therapy), number of previous therapeutic lines, baseline lactate dehydrogenase (LDH) values (by quartiles), existence of liver metastasis and of cerebral metastasis and number of metastasis ( $<$  or  $\geq 3$  sites). Comparison of variable distribution between cases and controls was performed using either  $\chi^2$ , Fisher's exact test and Kruskal-Wallis's test when appropriate. Logistic regression was used to calculate OR of developing irAEs. Patients censored before 12 months were patients lost to follow-up (most commonly patients who had completed their follow-up). Missing data were handled by multiple imputation using chained equations. Twenty datasets were imputed and analysed separately, and results were then pooled into a final estimate. Survival analysis was performed using log-rank test and Kaplan-Meier method with associated 95% CI was used to generate survival curves and estimate overall survival and time-to-first-irAE. Data analyses were conducted using R statistical software V4.0.4 and the R MICE (Multivariate Imputation by Chained Equations) package to address missing data (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set to  $p < 0.05$ .

### Patient's consent

The French Ethics Committee approved MelBase protocol (Comité de protection des personnes Ile-de-france XI, no 12027, 2012). MelBase is registered in the National Institute of Health clinical trials database (NCT02828202). Written informed consent was obtained from all patients.

### Patient's and public involvement

None.

## RESULTS

### Patient's characteristics

One hundred and ten patients with pAID were identified among the 2227 patients included in the prospective cohort MelBase from March 2013 to October 2020, and matched with 330 controls, on a 1-case-for-3-controls ratio. The median duration of follow-up was 7.24 months (IQR (3.67–23.41)) for cases and 6.86 months (IQR (3.62–20.83)) ( $p = 0.30$ ) (online supplemental figure).

The mean age was 65 years old for cases and controls. There was no difference for the gender repartition, nor for the mean body mass index (table 1). Thirty-nine per cent of the cases harboured a BRAF mutation, and 41% of the controls ( $p = 0.8$ ). The proportion of patients with an ECOG (Eastern Cooperative Oncology Group) performance status score  $> 1$  was higher in cases than in controls (24% vs 14%,  $p = 0.02$ ) (table 1).

Seventy-eight per cent of the patients were treated by anti-PD-1 monotherapy (42% by nivolumab, 36% by pembrolizumab), 14% by anti-CTLA-4 monotherapy and 8% by the association of anti-PD-1 and anti-CTLA-4 therapy (combination therapy). Seventy-four per cent received ICI as first-line immunotherapy.

### Pre-existing autoimmune diseases

Of the 110 cases, 47 (43%) had a history of autoimmune thyroiditis, 18 (16%) of psoriasis, 11 (10%) of rheumatoid arthritis, 8 (7%) of vitiligo, 3 (3%) of sarcoidosis, 3 of Raynaud disease, 3 of spondyloarthritis, 3 of multiple sclerosis, 2 (2%) of Crohn's disease, 2 of thrombopenic idiopathic purpura, 2 of giant cell arteritis, 2 of myasthenia, 1 (1%) of Guillain-Barré syndrome, 1 of systemic sclerosis, 1 of polymyositis, 1 of dermatomyositis, 1 of autoimmune hepatitis and 1 of IgA nephropathy. The median time from AID diagnosis to first ICI infusion was 103 months (IQR (37–241)). Seventy cases (63%) were treated for their pAID in the 3 months before ICI initiation, and 19 (17%) by immunosuppressive or immunomodulatory agents (13 by systemic corticosteroid therapy and 8 by methotrexate). We separated pAID into four subgroups: endocrinological pAID (autoimmune thyroiditis), cutaneous pAID (psoriasis and vitiligo), rheumatological pAID (rheumatoid arthritis and spondyloarthritis) and others. Endocrinological and cutaneous pAID were more often treated by anti-CTLA-4 monotherapy or combination therapy, and rheumatological and other pAID were more often treated by immunosuppressive agents at baseline (online supplemental table).

**Table 2** Characteristics of the irAEs presented by cases and controls

	Cases (N=110)	Controls (N=330)	P value
Duration of follow-up from first infusion (months, median (IQR))	7.24 (3.67–23.41)	6.86 (3.62–20.83)	0.3
Number of cures before first irAEs (mean, SD)	1.4 (0.76)	1.3 (0.49)	0.1
Time between first infusion and first irAEs (months, mean (SD))			
All-grade	4.8 (12.1)	4.3 (11.2)	0.12
Grade ≥3 irAEs	8.3 (16.4)	8.9 (17.4)	0.16
Immunotherapy interruption due to irAEs			
Temporarily	15 (14%)	36 (11%)	0.6
Definitively	8 (7%)	14 (4%)	0.3
Number of irAEs per patient (mean, SD)	7.2 (1.2)	5.1 (1.1)	<b>0.04*</b>
Number of grade ≥3 irAEs per patient (mean, SD)	1.04 (0.3)	0.40 (0.10)	0.05
Death due to irAEs (no. (%))	n=2 (1.8)	n=6 (1.8)	1
Total number of irAEs	n=794	n=1683	0.56
Type of irAEs (no (%)):			
Cardiological	16 (2.0)	30 (1.8)	
Cutaneous	94 (11.8)	184 (10.9)	
Digestive tract	166 (20.9)	402 (23.9)	
Endocrinological	48 (5.6)	56 (3.3)	
Haematological	33 (4.2)	69 (4.1)	
Neurological	47 (5.9)	106 (6.3)	
Pulmonary	33 (4.2)	76 (4.5)	
Rheumatological	21 (2.6)	23 (1.4)	
Renal	17 (2.1)	29 (1.7)	
Psychiatric	15 (1.9)	31 (1.8)	
Musculoskeletal	22 (2.8)	53 (3.1)	
Ophthalmological	17 (2.1)	32 (1.9)	
General symptoms	265 (33.4)	592 (35.2)	
Total number of grade ≥3 irAEs	n=114	n=132	0.74
Type of grade ≥3 irAEs (no (%))			
Cardiological	4 (3.5)	6 (4.5)	
Cutaneous	6 (5.3)	9 (6.8)	
Digestive tract	32 (28.0)	42 (31.8)	
Endocrinological	12 (10.5)	10 (7.6)	
Haematological	8 (7.0)	10 (7.6)	
Neurological	3 (2.6)	4 (3.0)	
Pulmonary	8 (7.0)	10 (7.6)	
Rheumatological*	2 (1.8)	3 (2.3)	
Renal	5 (4.4)	2 (1.5)	
Psychiatric	5 (4.4)	2 (1.5)	
Musculoskeletal*	1 (0.9)	4 (3.0)	
Ophthalmological	3 (2.6)	3 (2.3)	
General symptoms	25 (21.9)	27 (20.4)	

\*Rheumatological irAEs included arthralgia and arthritis. Musculoskeletal irAEs included myalgia, myositis, muscle weakness, CPK (Creatinine phosphokinase) increase and bone pain.  
irAEs, immune-related adverse events.

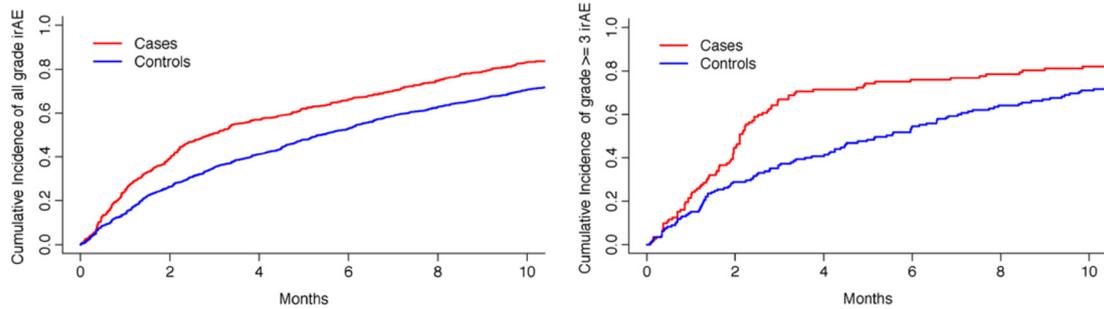
**Risk of irAEs and severe irAEs**

Overall, 72% of the 118 cases and 77% of the 354 controls presented with at least one irAE of all-grades, and 57% and 37% with at least one irAE of grade ≥3. There was no difference for the number of immunotherapy cures before irAEs between cases and controls (1.4 vs 1.3, p=0.1). The mean time from first infusion of immunotherapy to first irAEs was 4.5 months (SD 3.0) in the whole population, 4.8 months for cases and 4.3 months for controls (SD 2.8 and SD 2.6, respectively, p=0.12).

Cases had a higher risk of all-grade irAE occurrence (OR 1.91, 95% CI (1.56 to 2.27), p=0.03), along with a higher risk of

grade ≥3 irAEs (OR 1.44, 95% CI (1.08 to 1.82), p=0.04) when compared with matched controls (figure 1). When considering only organ-specific irAEs (ie, after exclusion of general symptoms of irAEs), cases still had a higher risk of all-grade irAE occurrence (OR 2.26, 95% CI (1.22 to 4.39), p=0.03) and of grade ≥3 irAEs (OR 1.71, 95% CI (1.09 to 2.34), p=0.05).

The risk of multiple irAEs was also higher among cases (OR 1.46, 95% CI (1.15 to 2.67)) with a mean number of irAEs per patient of 7.2 (SD 1.2) versus 5.1 for controls (SD 1.1) (p=0.04, table 2). Both all-grade and grade ≥3 irAEs occurred earlier in cases (log-rank test, p=0.002 and p=0.01, respectively;



**Figure 2** Cumulative incidence of all-grade irAE and grade  $\geq 3$  irAE among patients with pre-existing autoimmune diseases and matched controls. Cases: patients with pre-existing autoimmune disease, controls: patients without pre-existing autoimmune disease. The x axis represents the percentage of patients who developed 100% of their irAEs at a given follow-up time, represented on the y axis. Both cases and controls curves will reach a plateau at 1.0 at the end of follow-up. irAE, immune-related adverse event.

figure 2). No difference was seen for irAEs-related mortality, and the proportion of patients requiring definitive immunotherapy cessation after irAEs was not higher in cases than in controls (7% vs 4%,  $p=0.30$ , table 2). The existence of a baseline immunosuppressive therapy in cases was not associated with a significant protective effect on all-grade or grade  $\geq 3$  irAEs (OR 1.18, 95% CI (0.66 to 2.13),  $p=0.57$  and OR 0.91, 95% CI (0.38 to 2.21),  $p=0.85$ , respectively).

#### Risk of irAEs depending on the ICI regimen

The higher risk of all-grade irAEs in patients with pAID was consistent in patients treated by anti-PD-1 monotherapy (OR 2.47, 95% CI (1.40 to 4.92),  $p=0.03$ ), anti-CTLA-4 monotherapy (OR 1.82, 95% CI (1.02 to 4.51),  $p=0.05$ ), combination therapy (OR 2.31, 95% CI (1.18 to 5.10),  $p=0.04$ ), as well as the higher risk of grade  $\geq 3$  irAEs in patients treated by anti-PD-1 monotherapy (OR 1.80, 95% CI (1.19 to 2.47),  $p=0.04$ ), anti-CTLA-4 monotherapy (OR 1.50, 95% CI (1.03 to 2.42)  $p=0.05$ ) and combination therapy (OR 1.49, 95% CI (1.07 to 2.46),  $p=0.05$ ).

#### Risk of irAEs and pAID flares among pAID subgroups

When considering pAID subgroups (online supplemental table), endocrinological pAID were associated with a higher risk of all-grade irAEs (OR 2.18, 95% CI (1.20 to 3.33)  $p=0.03$ ) and of grade  $\geq 3$  irAEs (OR 1.83, 95% CI (1.15 to 3.41),  $p=0.04$ ) (figure 1). Neither cutaneous nor rheumatological pAID were associated with a higher risk of all-grade irAEs (OR 1.38, 95% CI (1.01 to 1.80),  $p=0.05$ , and OR 1.12, 95% CI (0.76 to 1.76),  $p=0.16$ , respectively) nor with a higher risk of grade  $\geq 3$  irAEs (OR 1.21, 95% CI (0.82 to 2.23),  $p=0.10$ , and OR 0.94, 95% CI (0.63 to 1.59),  $p=0.13$ ). The subgroup of 'others' pAID was associated with a higher risk of all-grade irAEs and of grade  $\geq 3$  irAEs (OR 1.36, 95% CI (1.11 to 2.04),  $p=0.04$ , and OR 1.24, 95% CI (1.09 to 1.81),  $p=0.04$ , respectively). Overall, 33 (30%) cases experienced a flare of their pAID: 12 (25%) with endocrinological pAID, 8 (31%) in patients with cutaneous pAID, 7 (50%) in patients with rheumatological pAID and 6 (26%) in patients with others pAID.

#### Clinical subtypes of irAEs

The distribution of the clinical irAE subtypes did not differ between cases and controls, neither for all-grade irAEs nor for grade  $\geq 3$  irAEs (table 2). The most frequent grade  $\geq 3$  irAEs were digestive tract, endocrinological, haematological and pulmonary (table 2).

#### Distribution of irAE subtypes depending on pAID subgroup

We compared the distribution of the irAE clinical subtypes between patients with endocrinological, cutaneous, rheumatological and others pAID. The overall distribution of all-grade (but not grade  $\geq 3$ ) irAE clinical subtypes was significantly different between pAID subgroups ( $p=0.04$ ) (table 3). Patients with rheumatological pAID had a higher frequency of gastrointestinal tract and rheumatological all-grade irAEs ( $p=0.04$  and  $p<0.0001$ , respectively) as well as of severe irAEs ( $p=0.002$ ). Patients with endocrinological pAID had the higher frequency of all-grade neurological irAEs ( $p<0.0001$ ) but not of severe neurological irAEs. Musculoskeletal irAEs were more frequent among patients with others pAID ( $p=0.02$ ) (table 3).

#### Survival analysis

Cases had an increased overall survival when compared with controls (log-rank test,  $p=0.02$ ; figure 3). However, many of the survival data were censored due to restricted follow-up duration. The estimated landmark overall survival at 24 months was 64.8% (IQR (56.2–74.7)) for cases and 45.9% (IQR (40.4–52.1)) for controls. We compared cases treated with immunosuppressive agents or not and did not find a difference in survival (log-rank test,  $p=0.68$ ).

#### DISCUSSION

While previous studies reported a high risk of irAEs and/or AID flare in patients with pAID treated by ICI, this study is to our knowledge the first to compare these patients with matched controls for irAE risk factors and oncological status, in a prospective cohort of patients treated for metastatic melanoma. The strengths of our study are the prospective collection of data and the case–control design allowing for precise quantification of the risk of irAEs depending on the existence of a history of AID.

The main limitations are the absence of data on the irAEs' therapeutic management apart from checkpoint inhibitor therapy discontinuation, and the limited follow-up duration which might have underestimated the risk of delayed irAEs. Another potential limitation is the absence of a systematic set of diagnostic criteria fulfilment at the inclusion of a patient with pAID in the MelBase cohort. This could restrict the interpretation of our observations in small groups of complex AIDs. The theoretical risk of misclassification of a control as a case, despite central reviewing, would result in negative bias and thus does not prevent the extrapolation of our results.

In our study, patients with pAID had two times higher risk of developing both all-grade irAEs than controls, independently of

**Table 3** Distribution of the clinical subtypes of irAEs depending on the subgroup of pre-existing autoimmune disease

irAE subtype	Endocrinological AID	Cutaneous AID	Rheumatological AID	Others AID	P value for the distribution
Median number of all-grade irAEs (IQR)	4.1 (0–13)	1.5 (0–8)	3 (1–6)	4(1–13)	<b>0.04*</b>
Median number of grade 3+ irAEs (IQR)	1 (0–1)	1 (0–1)	1 (0–1)	2 (0–4)	0.16
Endocrinological irAEs (no (%))					
All-grade	19 (5.2)	8 (5.4)	6 (7.3)	15 (7.5)	0.65
Grade 3+	2 (5.6)	1 (3.8)	1 (7.1)	8 (20.5)	0.12
Digestive tract irAEs (no(%))					
All-grade	65 (17.9)	32 (21.8)	22 (26.9)	47 (23.4)	<b>0.04*</b>
Grade 3+	12 (33.3)	6 (23.1)	4 (28.6)	10 (25.6)	0.83
Cutaneous irAEs (no (%))					
All-grade	53 (14.6)	16 (10.9)	7 (8.5)	18 (9.0)	0.16
Grade 3+	2 (5.6)	2 (7.7)	0 (0)	3 (7.7)	0.86
Haematological irAEs (no (%))					
All-grade	12 (3.3)	6 (4.1)	8 (9.8)	7 (3.5)	0.09
Grade 3+	5 (13.9)	2 (7.7)	0 (0)	1 (2.6)	0.21
Neurological irAEs (no (%))					
All-grade	33 (9.1)	3 (2.0)	0 (0)	11 (5.5)	<b>&lt;0.001*</b>
Grade 3+	1 (2.8)	1 (3.8)	0 (0)	1 (2.6)	1.0
Pulmonary irAEs (no (%))					
All-grade	18 (4.9)	7 (4.8)	1 (1.2)	7 (3.5)	0.47
Grade 3+	2 (5.6)	2 (7.7)	1 (7.1)	3 (7.7)	1.0
Cardiovascular irAEs (no (%))					
All-grade	7 (1.9)	3 (2.0)	0 (0)	6 (3.0)	0.50
Grade 3+	1 (2.8)	2 (7.7)	0 (0)	1 (2.6)	0.67
Rheumatological irAEs* (no (%))					
All-grade	7 (1.9)	6 (4.1)	8 (9.8)	0 (0)	<b>&lt;0.001*</b>
Grade 3+	0 (0)	0 (0)	2 (14.2)	0 (0)	<b>0.002*</b>
Renal irAEs (no (%))					
All-grade	9 (2.)	5 (3.4)	1 (1.2)	2 (1.0)	0.43
Grade 3+	2 (5.6)	2 (7.7)	0 (0)	1 (2.6)	0.69
Psychiatric irAEs (no (%))					
All-grade	3 (0.8)	4 (2.7)	1 (1.2)	7 (3.5)	0.09
Grade 3+	1 (2.8)	1 (3.8)	1 (7.1)	2 (5.1)	0.92
Musculoskeletal irAEs* (no (%))					
All-grade	5 (1.4)	4 (2.7)	1 (1.2)	12 (6.0)	<b>0.02*</b>
Grade 3+	0 (0)	1 (3.8)	0 (0)	0 (0)	0.35
Ophthalmological irAEs (no (%))					
All-grade	8 (2.2)	1 (0.7)	3 (3.7)	5 (2.5)	0.42
Grade 3+	2 (5.6)	0 (0)	1 (7.1)	0 (0)	0.13
General symptom irAEs (no (%))					
All-grade	125 (34.3)	52 (35.4)	24 (29.3)	64 (31.8)	0.74
Grade 3+	6 (16.7)	6 (23.1)	4 (28.6)	9 (23.1)	0.77

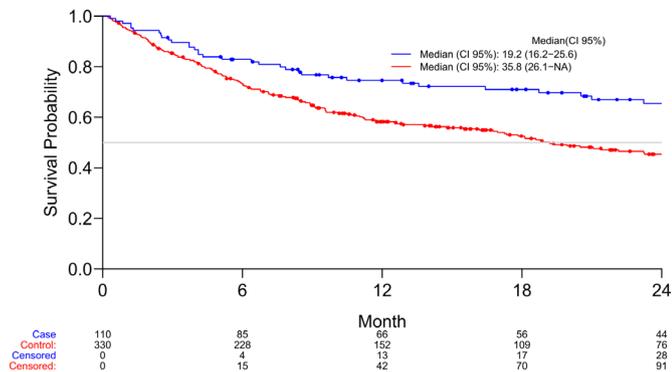
\*: p&lt;0.05

\*Rheumatological irAEs included arthralgia and arthritis. Musculoskeletal irAEs included myalgia, myositis, muscle weakness, CPK increase and bone pain. AID, autoimmune disease; irAEs, immune-related adverse events.

known risk factors of irAEs, such as age, sex,<sup>27 28</sup> the immunotherapy regimen<sup>29</sup> and/or of disease status, such as the melanoma stage, the existence of hepatic or cerebral metastasis, the number of metastasis and the LDH values at baseline.<sup>30 31</sup> Additionally, there were no difference between cases and controls for the body mass index values.<sup>32</sup> We were not able to perform a matching of the ECOG status because of a higher proportion of ECOG 0 patients among control candidates. Thus, cases were more often classified as ECOG >1 than controls, which could, however, have undermined our results, as low ECOG has been associated with an increased risk of irAEs and of multisystem irAEs.<sup>33 34</sup> We

also reported a higher risk of multiple irAEs, and a shorter time to both all-grade and grade  $\geq 3$  irAE onset in patients with pAID, as previously reported.<sup>22</sup>

The most frequently represented AID among cases were autoimmune thyroiditis, psoriasis, rheumatoid arthritis and vitiligo, in a relative proportion close to the one described in the general population.<sup>35</sup> We regrouped the cases into four pAID subgroups based on their clinical expression, a choice that might not reflect common disease pathogenesis but rather help categorise patients in the real-world practice. Patients with endocrinological and others pAID had an increased risk of all-grade and grade  $\geq 3$



**Figure 3** Overall survival among patients with pre-existing autoimmune diseases and matched controls. Cases: patients with pre-existing autoimmune disease, controls: patients without pre-existing autoimmune disease. NA, not applicable.

irAEs, but not patients with cutaneous or rheumatological pAIDs. This difference could be explained by the high proportion of immunosuppressive treatment at baseline in patients with rheumatological pAID or be the testament of physiopathological differences. Thirty per cent of the cases experienced a pAID flare during follow-up. As the pAID flares were all declared as irAEs, this might have overestimated the number of irAEs in cases—however, they only represent a small fraction of the irAEs developed over follow-up in this group ( $n=794$ ) and were the most frequent in patients with rheumatological irAEs, whose risk of irAEs was not increased when compared with controls in the subgroup analysis. Importantly, we noticed a difference in the clinical subtypes of all-grade irAEs depending on the subgroup of pAID, suggesting a predisposition for certain irAEs. These patterns of irAE clinical subtypes' susceptibility could help monitoring patients with pAID treated by ICI and improve the screening for irAEs in this population.

Both cases and controls presented with a rather high number of irAEs compared with previously published data. This might be explained by the systematic and prospective recording of all-grade irAEs and by the inclusion of general symptom irAEs, which were declared as linked to the immunotherapy but might also reflect cancer evolution. Importantly, after exclusion of general symptom irAEs, the ORs of developing all-grade and grade  $\geq 3$  irAEs in cases compared with controls were even greater. Despite of a higher risk of grade  $\geq 3$  irAEs, the proportion of lethal irAEs did not differ between cases and controls, and cases had an increased overall survival rate. This result could possibly be linked to the increased occurrence of multiple irAEs, which have reportedly been associated with increased survival in patients with NSCLC.<sup>34</sup> Moreover, in patients treated for metastatic melanoma or NSCLC, the occurrence of irAEs seems to be associated with an increased oncological survival.<sup>36,37</sup>

Our findings are in line with previously published data from retrospective case-series and prospective cohorts. Menzies *et al* were the first to address the risk of irAEs in patients with pAID and found an incidence of 29% of all-grade irAEs among 51 patients with pAID followed for a median of 4.7 months and a 8% ICI discontinuation rate.<sup>21</sup> Danlos *et al* reported a grade  $\geq 2$  irAE incidence of 44% over a 5.1-month period of follow-up, along with an ICI discontinuation rate of 11.1%, in 45 patients with pAID compared with 352 patients without pAID from the REISAMIC prospective registry.<sup>22</sup> The higher incidence of all-grade irAEs in our study can be explained by the prospective design and systematic recording of all-grade irAEs, the differences in ICI regimen<sup>6,38</sup> and longer follow-up. In a large multicentric

retrospective study, Cortellini *et al* found a 65.9% incidence of all-grade irAEs in 85 patients with pAID followed for a median of 14.7 months, along with an ICI discontinuation rate of 7%.<sup>33</sup> Interestingly, both inactive and active pAID were associated with a higher risk of all-grade irAEs. Moreover, in accordance with our results, the risk of all-grade irAEs was greater in patients with endocrinological pAID and lower in patients with rheumatological pAID. In a large multicentric retrospective study, Tison *et al* reported a 71% incidence of all-grade irAEs and/or autoimmune flares in 112 patients with pAID followed for a median of 8 months. The ICI discontinuation rate (21%) was greater than in our study, possibly reflecting a higher proportion of potentially severe AIDs, such as inflammatory bowel disease.<sup>25</sup> Our results however contrast with those of a recent prospective cohort study published by Van der Kooij *et al*, which did not find an increase in the risk of grade  $\geq 3$  irAEs among patients with pAID treated by checkpoint inhibitors for advanced melanoma, a difference possibly explained by the absence of a matched case-control design for irAEs risk factors and by the high proportion of patients with AID treated by corticosteroids at inclusion.<sup>26</sup>

Overall, while our results pinpoint an increased risk of irAEs and severe irAEs in patients with pAID, we did not find an increased risk of lethal irAEs and reported an increased overall survival when compared with controls, further confirming they should be considered for ICI therapy. Patients with pAID should, however, be closely monitored for irAEs, which are more frequent and occur earlier. As the risk of irAEs differs depending on the nature of the pAID, specific guidelines for autoimmune flares and irAEs should be considered.<sup>39</sup> Ongoing clinical trials will provide valuable data to confirm the safety and efficacy of ICI in patients with pAID.<sup>40</sup>

## CONCLUSION

In this case-control study, the existence of a history of AID was associated with an increased risk of all-grade irAEs, severe irAEs and multiple irAEs, yet was associated with an increase in overall survival. Patients with a history of AID should be closely monitored during checkpoint inhibitor therapy.

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