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Original Research

Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease

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Abstract ***Objective:*** Patients with autoimmune or inflammatory disease (AID) are susceptible to immune-related adverse events (irAEs) when treated with immune check-point inhibitors (ICIs). We decided to analyse the safety and effectiveness of anti-PD-1 antibodies in AID patients and look for an association between the presence of pre-existing AID and the clinical outcome.
Methods: In a prospective study of the REISAMIC registry of grade ≥2 irAEs occurring in ICI-treated patients, we studied the associations between pre-existing AID on one hand and irAE-free survival, overall survival and best objective response rate on the other.
Results: We identified 45 patients with 53 AIDs in REISAMIC. The cancer diagnoses included melanoma (n = 36), non–small-cell lung cancer (n = 6) and others (n = 3). The most frequent pre-existing AIDs were vitiligo (n = 17), psoriasis (n = 12), thyroiditis (n = 7), Sjögren syndrome (n = 4) and rheumatoid arthritis (n = 2). Twenty patients (44.4%) presented with at least one irAE: eleven of these were associated with a pre-existing AID ('AID flare'). Treatment with anti-PD-1 antibodies was maintained in 15 of the 20 patients with an irAE. The IrAE-free survival time was significantly shorter in AID patients (median: 5.4 months) than in AID-free patients (median: 13 months, $p = 2.1 \times 10^{-4}$). The AID and AID-free groups did not differ significantly with regard to the overall survival time and objective response rate (p = 0.38 and 0.098, respectively).
Conclusion: In patients treated with anti-PD-1 antibody, pre-existing AID was associated with a significantly increased risk of irAEs. Our results indicate that cancer treatments with anti-PD-1 antibodies are just as effective in AID patients as they are in AID-free patients.

1. Introduction

The immune check-point inhibitors (ICIs, i.e. antibodies against cytotoxic T-lymphocyte–associated protein 4 [CTLA-4] or programmed death 1 [PD-1]) are effective in the treatment of several types of cancer [1–5]. The clinical success of this immunotherapeutic strategy has confirmed the immune system's role weight in controlling cancer and that the ability of neoplastic cells to hide from the immune system is one of the hallmarks of cancer [6,7].

With anti-CTLA-4 and anti-PD-1 antibodies, oncologists have been confronted with the occurrence of immune-related adverse events (irAEs) [9,8,10,11]. Interestingly, the occurrence of irAE has been linked to greater anti-tumour effectiveness of anti-PD-1 treatment in patients with advanced melanoma and non–small-cell lung cancer (NSCLC) [16–18]. Patients with pre-existing autoimmune and/or inflammatory disease (AID) were initially excluded from clinical trials of ICI because of the possible increase of irAE [12]. Despite this initial reluctance, patients with mild-to-moderate pre-existing AID are now often treated with ICI. Recent studies have shown that both anti-CTLA-4 and anti-PD-1 antibodies can be effective AID patients [13–15]. However, all the data published to date were collected in retrospective studies of small numbers of patients.

Using data from a prospective multicenter registry, we therefore decided to describe and analyse the safety and effectiveness of anti-PD-1 antibodies in patients with a pre-existing AID.

2. Patients and methods

2.1. Patients

We described ICI-treated patients with pre-existing AID and compared them with AID-free patient groups in terms of the occurrence of toxicity, overall survival (OS) and the best overall response rate (ORR). The patients had been included in the prospective REISAMIC registry ('Registry of Severe Adverse Events of Immunomodulating Monoclonal Antibodies in Oncology') between June 1st, 2014, and December 31st, 2016. REISAMIC includes all patients treated with anti-PD-1 antibodies following marketing authorisation, as part of patient access programs for unlicensed medications, or during compassionate use at Gustave Roussy. Exclusion criteria were malignant haematologic disease, a second advanced cancer or a chronic viral infection. The end date for the analysis was set to December 31st, 2016.

Pre-existing AIDs were defined according to the standard diagnostic criteria [19–32]. Diseases not included as AID in the study were atopic diseases, metabolic inflammatory diseases and AIDs caused by infectious diseases or drugs.

2.2. Data collection

We collected data at baseline on demographic characteristics, pre-existing manifestations of AID, AID treatments, the patient's cancer status and previous cancer treatments.

2.3. Outcome and treatment response

For each patient, we recorded the date of the last infusion of anti-PD-1, whether the treatment had been maintained or discontinued, and the reason for discontinuation of the anti-PD-1. We defined an irAE as an immune-mediated disease occurring after anti-PD-1 administration. We distinguished an irAE due to the worsening of the pre-existing AID (i.e. a 'flare') and an irAE that did not have a clear causal link with the pre-existing AID. Each irAE was diagnosed and notified prospectively by the clinicians in charge of patient care and a panel of experts (OL, JMM, ALV, and SC) independently reviewed all diagnoses. All irAEs were classified and graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). For each patient, we considered all irAEs with a CTCAE grade of 2 or higher. Grade 1 vitiligo events were considered as irAE. The best response during anti-PD1 treatment was defined with reference to the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1; PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response). The ORR was defined as the proportion of patients who achieved either a CR or a PR. To analyse OS, we recorded the date of death, the date of last follow-up, and the analysis end date (defined as December 31st, 2016).

2.4. Statistical analysis

All recorded data were described for each patient group at baseline. Categorical variables were described as the number, percentage, and the number of missing data. Continuous variables were described as the number, mean ± standard deviation, and median (interquartile range [IQR]).

To study the putative association between pre-existing AID and outcomes (safety and survival) in patients receiving anti-PD-1 antibodies, we defined irAE-free survival and OS as endpoints. IrAE-free survival was defined by the time interval between the first administration of anti-PD-1 and (i) the date of occurrence of the irAE, (ii) the date of last post-treatment follow-up in irAE-free patients or (iii) the date of last follow-up. OS was defined by the time interval between the first administration of anti-PD-1 and (i) the occurrence of death (due to any cause), (ii) the date of last follow-up in alive patients, (iii) the date of last follow-up or (iv) the analysis end date. Patients lost to follow-up before the primary endpoint who could be evaluated were excluded from the safety analysis. IrAE-free survival and OS in the two groups were estimated using the Kaplan–Meier method and compared using a log-rank test. A univariate logistic regression was used for inter-group comparisons of the ORR. The threshold for statistical significance was set to $p < 0.05$ for all endpoints. The study was conducted in compliance with good clinical practice and the tenets of the Declaration of Helsinki. Constitution of the REISAMIC registry had been authorised by the French National Data Protection Commission (*Commission Nationale de l'Informatique et des Libertés*).

3. Results

A total of 45 patients enrolled in REISAMIC were assessed (median [IQR] age: 63.3 (56.6–70.7); males: 46.7%; Fig. 1). We then compared the 45 patients enrolled in REISAMIC with 352 AID-free patients included in REISAMIC over the same period.

3.1. Characteristics of the pre-existing AID in REISAMIC

Thirty-seven patients had a single pre-existing AID, and eight (17.8%) had two concomitant AIDs. The median [IQR] time since diagnosis of the AID was 2.5 [0.4–16.1] years when considering all 45 patients and 14.1 [2–24.6] years when excluding those with vitiligo. The ICI used, and the baseline characteristics of the 53 pre-existing AID are summarised in Tables 1 and 2.

Thirty-six patients had a pre-existing AID other than vitiligo: cutaneous psoriasis (n = 12, including one case with psoriatic arthritis), autoimmune thyroiditis (Hashimoto disease or Grave's disease; n = 7), primary Sjögren's syndrome (n = 4), rheumatoid arthritis (n = 2), immune thrombocytopenic purpura (n = 1), spondyloarthritis (n = 1), multiple sclerosis (n = 2), hidradenitis suppurativa (n = 1), myasthenia gravis (n = 1), polymyalgia rheumatica (n = 1), polyarteritis nodosa (n = 1), sarcoidosis (n = 1), chronic cutaneous lupus (n = 1) and type 1 diabetes (n = 1). The patients had received a median [IQR] of 1 (0–2) previous treatments for the pre-existing AID, with systemic corticosteroids in 6 cases (19.4%), hydroxychloroquine in 2 cases (6.5%) and immunosuppressive drugs in 4 cases (35.1%; methotrexate in 3 cases and cyclophosphamide in one case). One patient had been treated with intravenous immunoglobulins and another had received interferon beta. None had received rituximab or an anti-TNFα agent. Seventeen patients (31.4%) had vitiligo. Three patients with vitiligo also had an AID (17.6%: myasthenia gravis, thyroiditis and sarcoidosis).

To manage pre-existing AID before the initiation of the ICI, a specific multidisciplinary meeting was held in 3 cases (6.7%), and 19 patients (42.2%) had consulted a specialist physician. In 2015, one treatment by methotrexate, used by a patient during 8 months for a polymyalgia rheumatica as sparing-corticosteroids agents, was stopped before anti-PD-1 infusion for a metastatic melanoma. The patient did not develop an irAE but

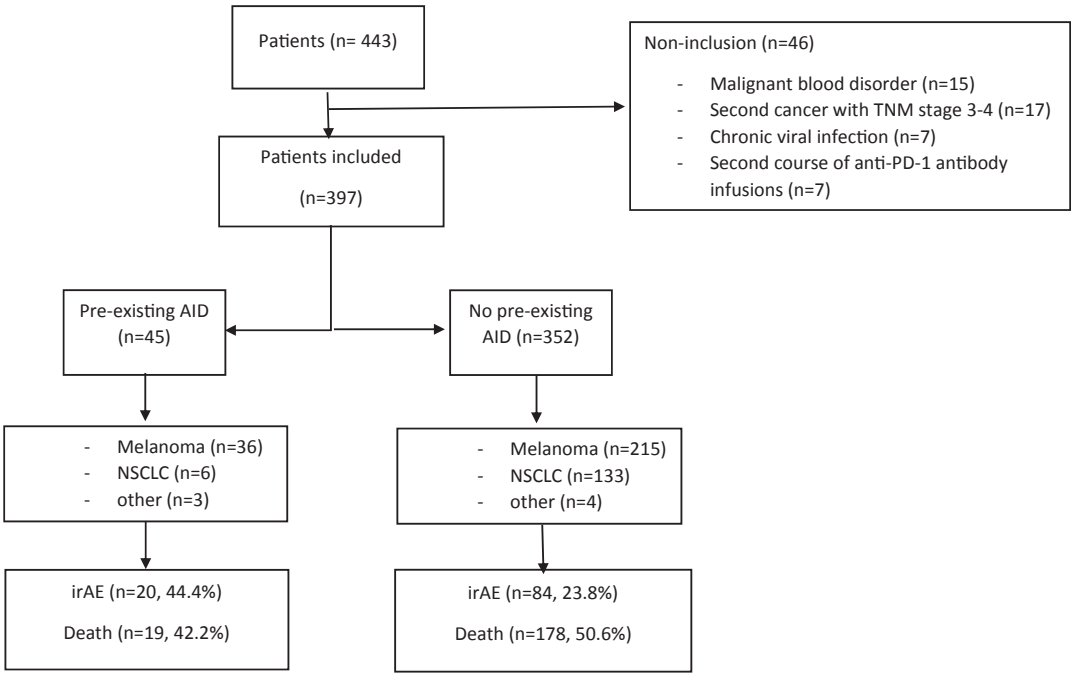

Fig. 1. Flow-chart for analysis of the REISAMIC patients. AID, autoimmune or inflammatory disease; NSCLC, non–small-cell lung cancer; irAE, immune-related adverse event.

died by cancer progression. No patient received preventive corticosteroids or DMARD. Forty-four patients had received an anti-PD-1 antibody, and one had received the anti-PD-L1 agent avelumab. At the time of ICI initiation, 25 of the AID patients (55.6%) were symptomatic, 22 had stable disease and three had flares (extension of vitiligo, in all three cases). Seven patients (15.6%) were taking one or more AID-specific medications: corticosteroids (n = 3), hydroxychloroquine (n = 2), methotrexate (n = 1), antithyroid drugs (n = 1) and a cholinesterase inhibitor drug (n = 1).

3.2. Cancer characteristics and previous treatments

The diagnosed cancer was melanoma (n = 36, 80%), NSCLC (n = 6, 16.3%) and other cancers (n = 3, 6.7%; renal cancer, penile epidermoid cancer and Merkel carcinoma). The TNM or AJCC stage was three in 3 patients (6.7%), and four in 42 patients (93.3%). The median [IQR] number of previous cancer treatments was 1 (1–2). The median [IQR] time interval between the initiation of cancer treatment and the initiation of treatment with an ICI was 4.3 (0–12.3) months.

3.3. Previous treatment with ICI and irAE

Nine patients had received at least one previous course of an ICI: an anti-CTLA-4 antibody in 8 cases (17.8%) and an anti-PD-1 antibody in 2 cases (4.4%). All 9 were being treated for metastatic melanoma. Six patients (66.7%) had already experienced an irAE: acute colitis in 3 cases, and thyroiditis with hyperthyroidism, hypophysitis, and acute tubulointerstitial nephritis revealing Sjögren's syndrome in one case each. The ICI was discontinued as a result of melanoma progression in 5 cases (55.6%). The median [IQR] time interval between discontinuation of the previous ICI treatment and initiation of the ICI of interest was 4.8 [2.8–8] months. Three patients (two having received an anti-PD-1 antibody previously and one received an anti-CTLA-4 antibody previously) developed an irAE after initiation of treatment with an anti-PD-1 antibody; this included the recurrence of earlier immune-related acute colitis in one case. However, 7 patients (77.8%) in this group died. The median [IQR] time interval between the last initiation of the ICI of interest and death was 6.9 [5.3–7.3] months.

3.4. IrAE

Twenty of the 45 patients (44.4%) presented with an irAE or more (a grade 2 event in 14 cases, a grade 3 event in 5 cases, and no grade 4 or 5 events). We considered that 11 of the 20 irAEs (55%) were associated with a pre-existing AID (i.e. a flare). The exacerbation of psoriasis was observed in 4 of the 13 patients with pre-existing psoriasis. One of them developed psoriatic arthritis and pustular psoriasis. Extension of vitiligo was

Table 1
Characteristics of cancer and pre-existing AID in REISAMIC patients.

Features	AID patients (n = 45)
Patient characteristics	
Age, median [IQR]	62.3 (23–88)
Males (%)	46.7%
Cancer diagnosis	
Type of cancer	
Melanoma, n (%)	36 (80%)
NSCLC, n (%)	6 (13.3%)
Other cancers, n (%)	3 (6.7%)
TNM stage	
3, n (%)	3 (6.7%)
4, n (%)	51 (93.3%)
Previous courses of treatment, median [IQR]	1 (0–1)
Previous treatment with ICIs	
Anti-CTLA-4, n (%)	8 (17.8%)
Anti-PD-1, n (%)	2 (4.4%)
Previous irAEs, n (%)	6 (13.3%)
Pre-existing AIDs	
Autoimmune disease, n (%)	36 (67.9%)
Inflammatory disease, n (%)	17 (32.1%)
Systemic disease, n (%)	11 (20.8%)
Organ-specific disease, n (%)	42 (79.2%)
Rheumatic disease, n (%)	7 (13.2%)
Dermatologic disease, n (%)	33 (62.3%)
Endocrine disease, n (%)	9 (17%)
Neurologic disease, n (%)	3 (5.7%)
Haematologic disease, n (%)	1 (1.9%)
Delay between the diagnosis of AID and cancer (years), median [IQR]	2.5 (0.4–16.1)
Previous immunomodulatory drugs for AID	
Corticosteroids, n (%); median max. dose [IQR] (mg/d)	6 (13.3%); 25 mg/d [5–60]
Immunosuppressive drugs, n (%)	4 (8.9%)

AID, autoimmune or inflammatory disease; NSCLC, non–small-cell lung cancer; TNM, tumour node metastasis, CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD-1, programmed death 1.

Table 2
Treatments and clinical characteristics of AID patients in the REISAMIC registry.

Features	AID patients (n = 45)
ICIs	
Pembrolizumab, n (%)	34 (75.6%)
Nivolumab, n (%)	10 (22.2%)
Avelumab, n (%)	1 (2.2%)
Time interval (months) between the cancer diagnosis and initiation of an ICI, median [IQR]	4.3 (0–12.3)
Characteristics of the AID (n = 53) at the time of ICI initiation	
Asymptomatic disease, n (%)	
- Less than 1 year, n (%)	5 (9.4%)
- For 1–5 years, n (%)	10 (18.9%)
- More than 5 years, n (%)	8 (15.1%)
Symptomatic disease, n (%)	
- Stable disease, n (%)	27 (50.9%)
- Flare, n (%)	3 (5.7%)
Treatment of the AID, n (%)	7 (15.6%)
CTCs	
- Systemic, n (%); median dose (mg/d)	3 (6,7%); 5 mg [2,5–40]
- Topical, n (%)	0
Hydroxychloroquine, n (%); dose (mg/d)	2 (4.4%); 200 mg
Methotrexate, n (%); dose (mg/w)	1 (2.2%); 20 mg
Antithyroid drugs, n (%)	1 (2.2%)
Cholinesterase inhibitors, n (%)	1 (2.2%)
AID management during cancer treatment	
Multidisciplinary team meeting on AID, n (%)	3 (6.7%)
Consultation with an AID specialist, n (%)	19 (42.2%)
Active surveillance, n (%)	9 (20%)
Introduction of preventive CTC, n (%)	0
Stop of CTC or IS, n (%)	1 (2.2%)

AID, autoimmune or inflammatory disease; ICI, immune check-point inhibitor; NSAID, nonsteroid anti-inflammatory drug; CTC, corticosteroid; IS, immunosuppressive drug.

observed in 4 of the 17 patients. One of eight patients with pre-existing thyroiditis experienced hyperthyroidism. One patient developed symptoms of a pre-existing Sjögren syndrome (acute dermatitis and sicca syndrome), and one experienced ophthalmologic manifestations of myasthenia gravis.

Ten patients developed irAE who were not associated with the pre-existing AID: thyroiditis in 5 cases, and one case each of acute colitis, microscopic colitis, severe gastritis, acute tubulointerstitial nephritis associated with *de novo* Sjögren's syndrome and grade 2 hyperlipasemia.

Despite the occurrence of an irAE, anti-PD-1 antibody infusions were maintained in 15 of the 20 cases (75%). Twelve patients received specific treatment for the irAE: topical corticosteroids or calcipotriol (n = 3), systemic corticosteroids (n = 6), levothyroxine (n = 4), and a cholinesterase inhibitor (n = 1). The irAE resolved completely in 9 cases (40.9%), after a median [IQR] time interval of 2.1 [0.9–5.6] months. The anti-PD-1 agent was temporarily discontinued in 1 case and definitively discontinued in 4 cases (due to acute colitis, microscopic colitis, acute tubulointerstitial nephritis associated with Sjögren's syndrome, and a flare of myasthenia gravis). Excluding the patients with vitiligo, 16 patients (51.6%) with a pre-existing AID did not develop an irAE after a median [IQR] follow-up period of 5.1 [3.9–7] months). In these cases, the pre-existing AID was multiple sclerosis, autoimmune cytopenia, sarcoidosis, hidradenitis suppurativa, polymyalgia rheumatica, polyarteritis nodosa, chronic cutaneous lupus or type 1 diabetes.

3.5. OS and cancer status

The clinical outcomes for the 45 patients enrolled in REISAMIC are summarised in Table 3. Twenty-six patients (57.8%) were alive, and 17 patients (37.8%) were still being treated with an ICI at last follow-up (after a median time interval of 6.3 [4–9.1] months). At last follow-up, four of the alive patients (8.9%) displayed a CR, 12 (26.7%) displayed a PR, 6 (13.3%) displayed SD, 3 displayed PD (6.7%) and 1 was lost of follow-up. Nineteen patients were dead (42.2%) and

Table 3
Outcomes for REISAMIC patients: IrAEs, survival and the ORR.

Features	AID patients (n = 45)
IrAEs	
Patients with IrAE, n (%)	20 (44.4%)
CTCAE grade, median [IQR]	2 (1–5)
Time (months) between ICI initiation and the irAE, median [IQR]	2.1 (0.7–3.1)
IrAE not associated with pre-existing AID, n (%)	10 (22.2%)
Flare of pre-existing AID, n (%)	11 (24.4%)
Anti-PD-1 antibody discontinued due to irAE, n (%)	5 (11.1%)
Treatment of the irAE	6 (13.3%); 40 [30–80]
- Corticosteroids, n (%); median dose [IQR] (mg/d)	0
- Immunosuppressive drugs, n (%)	10 (43.5%)
Complete resolution of the irAE, n (%)	2.8 (1.3–13.2)
Time (months) between diagnosis and resolution of the irAE, median [IQR]	1 (33.3%)
Re-introduction of anti-PD-1 antibody after resolution of the irAE, n (%)	
Survival and death	
Survival at last follow-up, n (%)	26 (57.8%)
Cancer status at last follow-up	
- Complete response, n (%)	4 (9%)
- Partial response, n (%)	13 (29%)
- Stable disease, n (%)	6 (13%)
- Progressive disease, n (%)	21 (47%)
Lost to follow-up, n (%)	1 (2%)
Death, n (%)	
- Due to cancer progression, n (%)	18 (40%)
- Due to the irAE, n (%)	0
- Due to unknown causes, n (%)	1 (2.2%)

AID, autoimmune or inflammatory disease; irAE, immune-related adverse event; CTCAE, Common Terminology Criteria for Adverse Events; PD-1, programmed death 1.

causes were mainly cancer progression (n = 18) and unknown in one case.

3.6. IrAE-free survival, OS and the best ORR in patients enrolled in REISAMIC

We compared 45 AID patients with 352 AID-free patients enrolled in REISAMIC over the same period (Fig. 1 and Table 4). Among AID patients, 20/45 (44.4%) developed an irAE (median CTCAE grade 2 [IQR 2-2]) instead of 102/352 (29%) for non-AID patients (median CTCAE grade 2 [IQR 2–3]). The irAE-free survival time was significantly shorter in AID patients (median: 5.4 months) than in AID-free patients (median: 13 months; $p = 2.1 \times 10^{-4}$; Fig. 2A). There was no difference in OS between AID and AID-free patients (p = 0.38; Fig. 2B). The best ORR was 38% (9% with a CR and 29% with a PR) in AID patients and 28% (7% with a CR and 21% with a PR) in AID-free patients. The intergroup difference in the ORR was not significant (odds ratio [95% confidence interval] = 0.51 [−1.54–0.077]; p = 0.098).

4. Discussion

Our results highlighted at least three important points. First, pre-existing AID of mild-to-moderate severity was associated with an elevated risk of an irAE which can occur earlier than in non-AID patients. However, more than half of the patients with AID did not experience a flare of their disease. Second, anti-PD-1 had to be stopped only in 25% of the cases of irAEs and steroids were required in only 6 patients. These results are in accordance with retrospective studies [13,14]. This suggests that we could treat patients with quiescent AID as non-AID patients. However, a close monitoring of these patients by a multidisciplinary team is necessary to identify these predicable flares and to counsel the patients. Third, we did not observe any differences in OS between AID and AID-free patients; cancer treatment with anti-PD-1 antibodies seems to provide similar levels of benefit in the two groups.

Recent retrospective studies have provided additional information on the safety of anti-PD-1 antibodies in patients with pre-existing AID (particularly those with melanoma) [14,15]. Our study's main strength is its confirmation of the elevated risk of ICI toxicity in AID patients, thanks to a prospective comparison with AID-free patients. The incidence of grade ≥ 2 irAEs in the present study was in line with the literature data (38% in the study by Menzies *et al.*, and 42% in the study by Gutzmer *et al.*).

The study has some limitations. The observed difference in irAE between AID and AID-free patients might be due to monitoring bias. Mild irAEs might be reported more frequently in AID patients than in AID-free patients. To decrease this possible source of bias, we excluded (i) grade 1 CTCAE irAEs and (ii) adverse events that did not have a clear immune aetiology. These measures may have led to the underestimation of the true incidence of irAEs. Patients with a symptomatic active AID were rare. In these patients, administration of ICI should be cautiously discussed.

Multidisciplinary meetings can help to improve the care of patients with metastatic cancer and AID. This is a need for more information and data on the management of patients with symptomatic disease and/or severe previous manifestations pre-existing AID. Assessment of the impact of corticosteroids, hydroxychloroquine, biologics, and immunosuppressive drugs on patients treated with ICI may increase safety levels without decreasing the effectiveness of this approach [33,34].

5. Conclusion

When treated with anti-PD-1 antibodies, patients with pre-existing AID were found to have an elevated risk of irAE and flares. However, with appropriate management, anti-PD-1 antibodies seem to be just as safe and

Table 4
Characteristics of the REISAMIC patients at baseline.

Features	AID patients (n = 45)	AID-free patients (n = 352)
Patient characteristics		
Age in year, median [IQR]	62.3 (23–88)	62.4 (20–92)
Sex ratio (H/F)	0.88	1.23
Type of cancer		
Melanoma, n (%)	36 (80.0%)	215 (61.1%)
NSCLC, n (%)	6 (13.3%)	133 (37.8%)
Other cancers, n (%)	3 (6.7%)	4 (1.1%)
TNM stage		
2, n (%)	0 (0%)	1 (0.3%)
3, n (%)	3 (6.7%)	46 (13.1%)
4, n (%)	42 (93.3%)	304 (86.4%)
Metastatic sites		
Median [IQR]	2 (0–5)	2 (0–9)
Previous treatment		
Number of previous drug treatments for cancer, median [IQR]	1 (0–1)	1 (1–2)
Previous ICI treatment		
None, n (%)	36 (80.0%)	290 (82.4%)
Anti-CTLA-4, n (%)	8 (17.8%)	57 (16.2%)
Anti-PD-1, n (%)	2 (4.4%)	12 (3.4%)
Previous irAE ≥ CTCAE grade 2		
n (%)	6 (13.3%)	29 (8.2%)
Baseline prognostic factors		
CRP mg/L, mean (range)	26.7 (0.2–162.2)	39.2 (0.2–256.7)
Albumin g/L, mean (range)	40 (24–46)	38 (20–50)
LDH IU/L, mean (range)	304 (127–1647)	305 (89–1896)
Lymphocyte count/mm^3, mean (range)	1376 (400–2800)	1507 (200–6500)
ICI received		
Pembrolizumab, n (%)	34 (75.6%)	196 (55.7%)
Nivolumab, n (%)	10 (22.2%)	155 (44.0%)
Avelumab, n (%)	1 (2.2%)	0 (0%)
Nivolumab + ipilimumab, n (%)	0 (0%)	1 (0.3%)

AID, autoimmune or inflammatory disease, NSCLC, non–small-cell lung cancer; TNM, tumour node metastasis; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; PD-1, programmed death 1; CTCAE, common terminology criteria for adverse events; CRP, protein C-reactive; LDH, lactate dehydrogenase.

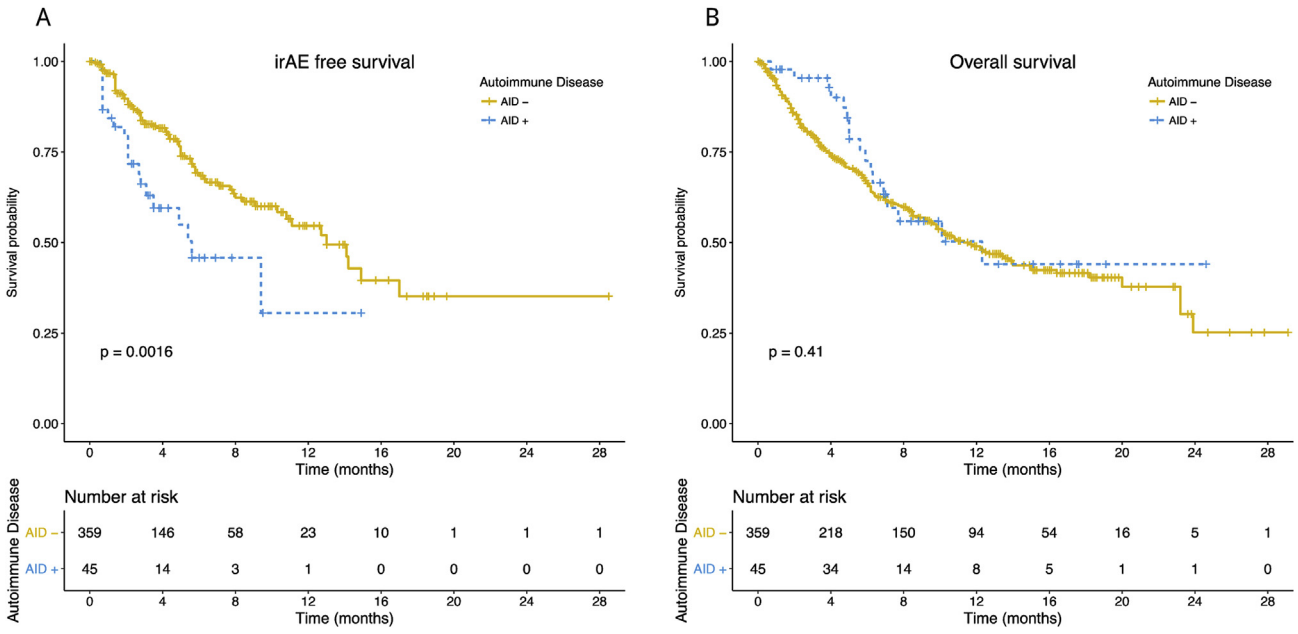

Fig. 2. **Outcomes in REISAMIC patients: irAE-free survival and OS**. A. Kaplan–Meier plots for irAE-free survival, which was shorter in AID patients (median: 5.4 months) than in AID-free patients (median: 13 months; $p = 2.1 \times 10^{-4}$ in a log-rank test). B. Kaplan–Meier plots for OS: the difference between AID and AID-free patients was not significant ($p = 0.38$ in a log-rank test).

effective in AID patients as in AID-free patients. Our observations highlight the importance of collaboration between oncologists, organ specialists, internists and clinical immunologists for improving patient care.

Conflict of interest statement

JMM is a member of BMS Board consultancy. ER is sub-investigator for BMS, Roche, Novartis, Merk and Amgen. SC received paid expert testimony for AstraZeneca, BMS, Janssen, MSD and Roche. CM acknowledges his participation to advisory boards and is speaker or investigator for Amgen, Astellas, AstraZeneca, Bayer, Celgene, Genentech, Ipsen, Jansen, Lilly, Novartis, Pfizer, Roche, Sanofi and Orion. NG received paid expert testimony for BMS, MSD, AstraZeneca, Merck and Roche. SD received paid expert testimony for Roche, Amgen, MSD, Merck and BMS. JCS: received consultancy fees from AstraZeneca, Astex, Clovis, GSK, Gammamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, PharmaMar, Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen, Takeda. CM is investigator for Merck, BMS, Pfizer. CR received consultancy fees from AMGEN, BMS, Merck, MSD, Roche and Novartis. OL received paid expert testimony and consultancy fees from BMS France, MSD, Aztra Zeneca; consultancy fees from Genzyme. The remaining authors declare no conflict of interest.

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References

[1] Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320–30. https://doi.org/10.1056/NEJMoa1412082.

[2] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer. N Engl J Med 2015;373:1627–39. https://doi.org/10.1056/NEJMoa1507643.

[3] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018–28. https://doi.org/10.1056/NEJMoa1501824.

[4] Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet Lond Engl 2016. https://doi.org/10.1016/S0140-6736(16)32455-2.

[5] Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311–9. https://doi.org/10.1056/NEJMoa1411087.

[6] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74. https://doi.org/10.1016/j.cell.2011.02.013.

[7] Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1–10. https://doi.org/10.1016/j.immuni.2013.07.012.

[8] Michot JM, Bigenwald C, Champiat S, Collins M, Carbonnel F, Postel-Vinay S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer Oxf Engl 1990 2016;54:139–48. https://doi.org/10.1016/j.ejca.2015.11.016.

[9] Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol 2016. https://doi.org/10.1038/nrclinonc.2016.58.

[10] June CH, Warshauer JT, Bluestone JA. Is autoimmunity the Achilles' heel of cancer immunotherapy? Nat Med 2017;23:540–7. https://doi.org/10.1038/nm.4321.

[11] Le Burel S, Champiat S, Routier E, Aspeslagh S, Albiges L, Szwebel T-A, et al. Onset of connective tissue disease following anti-PD1/PD-L1 cancer immunotherapy. Ann Rheum Dis 2017. https://doi.org/10.1136/annrheumdis-2016-210820.

[12] Calabrese L, Velcheti V. Checkpoint immunotherapy: good for cancer therapy, bad for rheumatic diseases. Ann Rheum Dis 2017;76:1–3. https://doi.org/10.1136/annrheumdis-2016-209782.

[13] Johnson DB, Sullivan RJ, Ott PA, Carlino MS, Khushalani NI, Ye F, et al. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol 2016;2:234–40. https://doi.org/10.1001/jamaoncol.2015.4368.

[14] Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong ANM, Park JJ, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol Off J Eur Soc Med Oncol 2016. https://doi.org/10.1093/annonc/mdw443.

[15] Gutzmer R, Koop A, Meier F, Hassel JC, Terheyden P, Zimmer L, et al. Programmed cell death protein-1 (PD-1) inhibitor therapy in patients with advanced melanoma and preexisting autoimmunity or ipilimumab-triggered autoimmunity. Eur J Cancer Oxf Engl 1990 2017;75:24–32. https://doi.org/10.1016/j.ejca.2016.12.038.

[16] Freeman-Keller M, Kim Y, Cronin H, Richards A, Gibney G, Weber JS. Nivolumab in resected and unresectable metastatic melanoma: characteristics of immune-related adverse events and association with outcomes. Clin Cancer Res Off J Am Assoc Cancer Res 2016;22:886–94. https://doi.org/10.1158/1078-0432.CCR-15-1136.

[17] Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol Off J Am Soc Clin Oncol 2017;35:785–92. https://doi.org/10.1200/JCO.2015.66.1389.

[18] Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol 2017. https://doi.org/10.1001/jamaoncol.2017.2925.

[19] Lebwohl M. Psoriasis. Lancet Lond Engl 2003;361:1197–204. https://doi.org/10.1016/S0140-6736(03)12954-6.

[20] Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73. https://doi.org/10.1002/art.21972.

[21] Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CCE, et al. Revised classification/nomenclature of vitiligo and related issues: the vitiligo global issues consensus conference. Pigment Cell Melanoma Res 2012;25:E1–13. https://doi.org/10.1111/j.1755-148X.2012.00997.x.

[22] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League

Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81. https://doi.org/10.1002/art.27584.

[23] Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol Hoboken NJ 2017;69:35–45. https://doi.org/10.1002/art.39859.

[24] Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011; 70:25–31. https://doi.org/10.1136/ard.2010.133645.

[25] Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med 2003;348:2646–55. https://doi.org/10.1056/NEJMra021194.

[26] Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292–302. https://doi.org/10.1002/ana.22366.

[27] Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386–93. https://doi.org/10.1182/blood-2008-07-162503.

[28] Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol 2002;69:258–71.

[29] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013;65: 1–11. https://doi.org/10.1002/art.37715.

[30] Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other granulomatous disorders. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG 1999;16:149–73.

[31] American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care 2015;38(Suppl):S8–16. https://doi.org/10.2337/dc15-S005.

[32] Dasgupta B, Cimmino MA, Kremers HM, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Arthritis Rheum 2012;64:943–54. https://doi.org/10.1002/art.34356.

[33] Esfahani K, Miller WH. Reversal of autoimmune toxicity and loss of tumor response by interleukin-17 blockade. N Engl J Med 2017;376:1989–91. https://doi.org/10.1056/NEJMc1703047.

[34] Uemura M, Trinh VA, Haymaker C, Jackson N, Kim DW, Allison JP, et al. Selective inhibition of autoimmune exacerbation while preserving the anti-tumor clinical benefit using IL-6 blockade in a patient with advanced melanoma and Crohn's disease: a case report. J Hematol Oncol 2016;9(1):81.