

Prevalence, therapy and tumour response in patients with rheumatic immune-related adverse events following immune checkpoint inhibitor therapy: a single-centre analysis

Sophia H. Verspohl, Tobias Holderried, Charlotte Behning, Peter Brossart and Valentin S. Schäfer 

Ther Adv Musculoskel Dis

2021, Vol. 13: 1–14

DOI: 10.1177/
1759720X211006963

© The Author(s), 2021.
Article reuse guidelines:
sagepub.com/journals-
permissions

Abstract

Background: Immune checkpoint inhibitors (ICIs) improved cancer therapy by inducing a higher immune system activity. This effect can cause rheumatic immune-related adverse events (rh-irAEs), which have not yet been extensively studied.

Methods: We analysed 437 patients between 2014 and 2019, treated with ipilimumab (anti-CTLA-4) and/or nivolumab (anti-PD-1) or pembrolizumab (anti-PD-1) at the Clinic for Internal Medicine III, Oncology, Haematology and Rheumatology at the University Hospital Bonn, Germany.

Results: Of the 437 patients 60% were males. Patients were mainly treated for melanoma, lung cancer, head and neck tumour and urothelial carcinoma. At least one immune-related adverse event (irAE) was observed in 163 patients (37.3%), including rh-irAE. Most common side effects were rash, colitis and hepatitis. We identified 19 patients (4.3%) with a minimum of one rh-irAE due to ICI therapy; three of those had a pre-existing rheumatic disease.

Arthralgia developed most frequently in eight patients (42.1%). Other rh-irAEs were: arthritis ($n=7$; distinguished in rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis and undifferentiated arthritis), myalgia ($n=2$) and myositis ($n=3$). Most rh-irAEs were classified as moderately severe (Common Terminology Criteria of Adverse Events grade 2: 68.4%). Median time between starting ICI therapy and the occurrence of rh-irAE was 109 days (interquartile range 40–420 days). Fifteen patients (78.9%) were treated with glucocorticosteroids. In four cases additional therapy with methotrexate or tocilizumab was required. Even though patients benefited from ICI treatment, therapy had to be discontinued in six of the participants due to rh-irAE. Interestingly, patients with rh-irAE had a significantly higher tumour response compared with patients without rh-irAE (94.4% versus 43.5%; $p < 0.0001$).

Conclusion: Rh-irAEs occur under ICI therapy, especially in patients with higher tumour response. However, they are not the most frequent irAE after ICI exposure: 9.3% of all irAEs were rheumatic (20 rh-irAE cases in 19 patients of a total of 215 irAE cases in 163 patients).

Keywords: anti-CTLA-4, anti-PD-1, arthralgia, arthritis, immune checkpoint inhibitor therapy, immune-related adverse events, immunotherapy, myositis, rheumatic

Received: 7 February 2021; revised manuscript accepted: 10 March 2021.

Introduction

Immune checkpoint inhibitors (ICIs) have accelerated the immunotherapy revolution in cancer therapy and improved clinical outcomes for oncological patients.¹ ICIs are newly developed

monoclonal antibodies and play a crucial role in immune system activity.

The mechanism of ICI therapy is complex. The adaptive immune system plays an important role

Correspondence to:
Valentin S. Schäfer
MD, PhD, Clinic for
Internal Medicine
III, Department of
Oncology, Haematology,
Rheumatology and Clinical
Immunology, University
Hospital of Bonn,
Germany, Venusberg
Campus 1, Bonn 53127,
Germany
valentin.s.schaefer@hotmail.de

Sophia H. Verspohl
Tobias Holderried
Peter Brossart
Clinic for Internal
Medicine III, Department
of Oncology, Haematology,
Rheumatology and Clinical
Immunology, University
Hospital of Bonn, Bonn,
Germany

Charlotte Behning
Institute for Medical
Biometry, Informatics and
Epidemiology, University
Hospital of Bonn, Bonn,
Germany

in the surveillance of the organism. Costimulatory and coinhibitory immune checkpoints (ICs) are provided for the regulation of the adaptive immune system. Stimulating ICs enables immune reactions and tumour cell elimination. The inhibitory function is important to prevent excessive immune response and autoimmunity.² However, many malignancies escape the immune response directed against them by expressing receptors and activating inhibitory ICs. This immune evasion of tumour cells is mainly the therapeutic starting point of ICI therapy. With the help of ICIs, T-cells can attack the tumour cells.

Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) have been most extensively evaluated in clinical practice. Ipilimumab (anti-CLTA-4) can be used in the treatment of patients with melanoma.³ Pembrolizumab and nivolumab are antibodies against PD-1. Both are approved for several cancer entities, including melanoma, non-small-cell lung cancer, Hodgkin's lymphoma, head and neck carcinoma, urothelial carcinoma and renal cell cancer.⁴ Besides the option of ICI monotherapy, patients with melanoma or renal cell cancer have the opportunity to be treated with a combination therapy of ipilimumab and nivolumab. This dual blockade shows an increased antitumour effect.⁵

Due to the suppression of inhibitory function and subsequent increasing immune response, ICI treatment is associated with various adverse effects, known as immune-related adverse events (irAEs), affecting nearly every organ system.^{6–8} Colitis and rash occur most frequently.⁹ Rheumatic irAEs (rh-irAEs) are also described and have not been extensively studied and characterized yet. Arthralgias have been described in 1–43%¹⁰ of patients receiving either single ICI or combination therapy. Despite this high frequency, the classification of rh-irAEs remains limited.^{10–14} Several institutions have reported the occurrence of rh-irAEs in a small number of patients.¹⁵ Despite these reports, gaps in our understanding of this entity remain.

In this single centre study, we aimed to add important information regarding prevalence and type of rh-irAEs, as well as duration, therapy, laboratory findings, description of differences between patients with and without pre-existing rheumatic diseases and correlation between

tumour response rate compared with patients with or without rh-irAEs.

Patients and methods

Patients

In this retrospective study, all patients were >18 years old and were treated for a malignancy with ICIs at the University Hospital Bonn, Germany. We analysed 437 patients treated with ipilimumab (anti-CTLA-4) and/or nivolumab (anti-PD-1) or pembrolizumab (anti-PD-1). We selected these three ICIs as they were already approved in Germany when our data collection started and were used in our clinic to treat various cancer entities. Our study focused on both PD-1 and CLTA-4 antibodies, despite their different mechanisms, in order to provide a realistic overview of ICIs used in clinical practice.

Patients were included between 1 January 2014 and 31 December 2018. Follow-up was conducted until 31 October 2019. Patients with pre-existing rheumatic diseases were included in this study.

Medical records of patients were reviewed and irAEs as well as rh-irAEs related to ICI therapy were identified. We examined the following rheumatic diseases or rheumatic symptoms: arthralgia, myalgia, arthritis, tenosynovitis, myositis, vasculitis, Sicca syndrome, Sjogren's syndrome, polymyalgia rheumatica (PMR), systemic lupus erythematosus, sarcoidosis, dermatomyositis, polymyositis, eosinophilic fasciitis and giant cell arteritis. Below, we will only mention the rheumatic diseases that occurred in our patients. We did not investigate the occurrence of osteoarthritis. Severity of irAEs was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.¹⁹ Prednisolone doses were graded according to Buttgerit *et al.*,²⁰ low dose ≤ 7.5 mg, medium dose > 7.5 mg to ≤ 30 mg, high dose > 30 mg to ≤ 100 mg, very high dose > 100 mg and pulse therapy ≥ 250 mg prednisolone. The Karnofsky Performance Score (KPS) was defined by Karnofsky and Burchenal.²¹ The tumour stage of melanoma skin cancer was classified according to the American Joint Committee on Cancer (AJCC).²²

We investigated 437 patients with first-line, 58 patients with second-line and 11 patients with

third-line ICI therapy. Unless otherwise stated, all information refers to first-line therapy.

All patients with rh-irAEs were seen by a rheumatologist at the time of event occurrence. All cases were again reviewed by a rheumatologist (VSS) to confirm the presence of a rh-irAE.

Patient and disease related characteristics, type of cancer, previous treatment, occurrence of other irAEs and tumour response rate according to ICI therapy were also recorded for every patient. Tumour response, defined by RECIST version 1.1,²³ was classified as: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). In general CR, PR and SD were noted as tumour response. Non-responders suffered from PD.

Local ethics committee approval was obtained from the University Hospital Bonn, Germany (Lfd.Nr.010/19). Due to the retrospective study design, no consent form was needed, as advised by the local ethics committee.

The data underlying this article are available in the article and in its Supplemental Material online.

Statistical analysis

Statistical analyses were performed using SPSS version 26 (IBM). Descriptive data evaluation and explorative data analysis were used. Comparison among groups with different variables was assessed by Chi-square test. *p* values <0.05 were considered statistically significant, whereby *p* values are only reported in an explorative analysis and are therefore not corrected for multiple testing. Progression-free survival (PFS) in different cohorts [patients without irAEs, with non-rheumatic irAEs (non-rh-irAE) and with rh-irAEs] was compared with the Kaplan–Meier method. To evaluate a distinction of these cohorts, log rank test was applied. A Cox proportional hazards regression model with time-dependent covariates was used to examine associations between the occurrence of adverse events (rh-irAEs and non-rh-irAEs) and PFS. The time-dependent covariates had an initial value of 0 and were set to 1 after the first occurrence of rh-irAEs or rather non-rh-irAEs. This analysis was conducted in R (Version 4.0.3)²⁴ with the survival package by Therneau.²⁵

Results

Patient characteristics

We included 437 patients treated with ICIs. Demographic data, type of cancer, cancer therapy, previous treatment, tumour response and other non-rh-irAEs for all patients and for patients with rh-irAEs are listed in Table 1.

Median ICI treatment time was 69 days [interquartile range (IQR) 28.5–187 days]. Most common reasons for discontinuation of ICI therapy were: progressive disease in 164 patients (37.5%), any irAE in 52 patients (11.9%) and stable disease or complete response in 19 patients (4.3%). Death occurred in 51 patients (11.7%) during ICI therapy; 20 patients (4.6%) continued the therapy beyond the follow-up time. Other reasons for discontinuing ICI therapy were: deterioration of general condition, change of location, end of therapy, change of therapy or patient's request. In 66 patients (15.1%) the reason for discontinuing ICI therapy remained unknown as some patients were treated in different clinics.

Adjunctive radiotherapy was administered to 46 patients (10.5%) and 23 patients (5.3%) were treated with chemotherapy at the same time of ICI treatment. Five patients received additional radiotherapy and chemotherapy. Fifteen patients (3.4%) who were treated with additional chemotherapy received a fixed therapy scheme with pembrolizumab, pemetrexed and cisplatin.

In addition, we recorded pre-existing diseases and complaints of every patient. An overview is displayed in the Supplemental Material (Supplemental Table S1).

Characteristics of rh-irAEs

We identified 19 patients (4.3%) in first-line ICI therapy with a minimum of one rh-irAE due to ICI therapy, with a total of 20 rh-irAE cases (Table 1). The median time between first exposure to ICIs and the occurrence of rh-irAEs was 109 days (IQR 40–420 days).

In first-line ICI therapy one in 38 patients (2.6%) treated with ipilimumab, 10 in 188 patients (5.3%) treated with nivolumab and eight in 159 patients (5.0%) treated with pembrolizumab were affected by at least one rh-irAE. We observed rh-irAEs only in first-line ICI monotherapy. In second-line

Table 1. Demographic data and characteristics of all patients and of patients with rheumatic immune-related adverse events (rh-irAEs).

	All patients <i>n</i> = 437 (%)	Patients with rh-irAEs <i>n</i> = 19 (%)
Age, median, years	66 (IQR 56–75)	69 (IQR 48–72)
Gender		
Male	260 (59.5)	11 (57.9)
Female	177 (40.5)	8 (42.1)
Tumour type		
Melanoma	210 (48.1)	13 (68.4)
Lung	78 (17.8)	3 (15.8)
Head and neck	34 (7.8)	2 (10.5)
Gastrointestinal	12 (2.7)	1 (5.3)
Liver	17 (3.9)	–
Renal	21 (4.8)	–
Urothelial	20 (4.6)	–
Others	45 (10.3)	–
Initial cancer therapy		
Ipilimumab	38 (8.7)	1 (5.3)
Nivolumab	188 (43.0)	10 (52.6)
Pembrolizumab	159 (36.4)	8 (42.1)
Ipilimumab + nivolumab	52 (11.9)	–
Previous treatment		
Radiotherapy	160 (36.6)	6 (31.6)
Chemotherapy	170 (38.9)	5 (26.3)
Biologics	117 (26.8)	1 (5.3)
Tumour response		
Non-responders	<i>n</i> = 377 ^a 204 (54.1)	<i>n</i> = 18 ^a 1 (5.6)
Responders	173 (45.9)	17 (94.4)
Stable disease	95 (25.2)	7 (38.9)
Partial response	63 (16.7)	8 (44.4)
Complete response	15 (4.0)	2 (11.1)
Discontinuation		
Due to rh-irAEs	<i>n</i> = 371 ^a 6 (1.6)	<i>n</i> = 18 ^a 6 (33.3)
Due to non-rh-irAEs	46 (12.4)	2 (11.1)
Pre-existing rheumatic disease	11 (2.5)	3 (15.8)

(Continued)

Table 1. (Continued)

	All patients <i>n</i> = 437 (%)	Patients with rh-irAEs <i>n</i> = 19 (%)
Non-rh-irAEs	<i>n</i> = 195 cases in 153 patients	<i>n</i> = 10 cases in nine patients
Rash	61 (31.3)	3 (30)
Colitis	35 (17.9)	1 (10)
Hepatitis	20 (10.3)	2 (20)
Pneumonitis	13 (6.7)	–
Thyroiditis	12 (6.2)	1 (10)
Vitiligo	9 (4.6)	–
Nephritis	8 (4.1)	1 (10)
Hypophysitis	7 (3.6)	–
Hyperthyroidism	7 (3.6)	1 (10)
Hypothyroidism	6 (3.1)	–
Psoriasis vulgaris	3 (1.5)	1 (10)
Others	14 (7.2)	–

^aPatients with available full data set.
IQR, interquartile range; non-rh-irAEs, non-rheumatic immune-related adverse events.

therapy four out of five patients with rh-irAEs received a combination therapy with ipilimumab and nivolumab. Rh-irAEs were observed in 19% of patients with second-line combination ICI therapy. In the other patient, rh-irAE occurred under pembrolizumab as second-line therapy. In third-line ICI therapy none of the 11 patients developed rh-irAEs.

Arthralgia developed most frequently in eight of the 19 patients (42.1%), arthritis in seven (36.8%), myalgia in two (10.5%) and myositis in three patients (15.8%). Further information and clinical characteristics of rh-irAEs are displayed in Table 2. All rh-irAEs were reviewed by a rheumatologist to confirm the occurrence of a rh-irAE. Myositis as a severe rh-irAE was diagnosed in the synopsis of the clinical presentation, a muscle biopsy was performed in one case, electromyography performed in two cases and myositis-associated and specific antibodies tested in two cases.

Individual treatment and detailed information on every patient with rh-irAE in first- and second-line ICI therapy are listed in Table 3.

Most rh-irAEs were classified as moderately severe: in first-line ICI therapy two out of 19 patients (10.5%) reported CTCAE grade 1, 13 patients (68.4%) CTCAE grade 2 and four patients (21.1%) CTCAE grade 3.

In 13 of the 19 patients, rheumatological laboratory parameters were ordered. Nine patients were tested for anti-citrullinated peptide-antibodies (CCP) and 10 patients for rheumatoid factor (RF). One patient (number 6 in Table 3) was found to be positive for both parameters. He was diagnosed with RF- and CCP-antibody-positive rheumatoid arthritis (RA). In eight patients presence of anti-nuclear antibodies was examined and found to be elevated in one patient with myositis (1:1280) and one patient with arthralgia (1:320), both with granular fluorescence pattern. Out of four patients tested for anti-neutrophil cytoplasmic antibodies, no one was found to be positive.

Patients were most frequently treated with glucocorticosteroids (GCs). The majority of these patients received prednisolone therapy, with a median maximum dose of 25 mg (range 15–80 mg). No patient received a low GC dose, seven

Table 2. Clinical characteristics of rheumatic immune-related adverse events (rh-irAEs).

	Number of patients (%)
Patients with rh-irAEs	19 (100)
Median onset time of rh-irAEs	109 days (IQR 40–420 days)
Types of rh-irAEs	
Arthralgia only ^a	8 (42.1)
Arthritis	7 (36.8)
Rheumatoid arthritis	3
Psoriatic arthritis	2
Juvenile idiopathic arthritis	1
Undifferentiated arthritis	1
Myalgia	2 (10.5)
Myositis	3 (15.8)
Immunosuppressive treatment	
Glucocorticosteroids (GC) only	11 (57.9)
GC plus MTX	3 (15.8)
GC plus tocilizumab	1 (5.3)
Other treatments	
NSAIDs	6 (31.6)
Opioids	1 (5.3)
Rh-irAE treatment response	
Complete resolution	4 (22.2)
Partial resolution	14 (77.8)
Discontinuation of ICI therapy due to:	
Arthralgia	1/8
Arthritis	3/7
Myalgia	0/2
Myositis	2/3

^aExcluding patients with arthritis.
^bPatients with available full data set.
ICI, immune checkpoint inhibitor; IQR: interquartile range; MTX: methotrexate;
NSAID: non-steroidal anti-inflammatory drug.

patients received a medium dose, five patients received a high dose and no patient received a very high dose. Two patients underwent intravenous

steroid pulse therapy with either 250 mg or 500 mg, while in one patient the maximum GC dose remained unknown. The median duration of GC therapy (including tapering) was 92.5 days (range 41–189 days). In a few cases methotrexate (MTX) or tocilizumab was administered. Different treatment options and outcomes of rh-irAEs are displayed in Table 2.

Six of the 19 patients had to discontinue ICI therapy as a consequence of rh-irAE (Table 2). Other patients discontinued ICI therapy later because of tumour progression ($n=3$), CR ($n=1$), SD ($n=1$), a non-rh-irAE ($n=2$), end of therapy ($n=2$) or change of therapy location ($n=1$). Two patients continued ICI therapy beyond the follow-up time of this study. In one patient the reason for the end of ICI therapy remained unknown.

Pre-existing rheumatic diseases

Of all 437 patients, 11 patients (2.5%) had a minimum of one pre-existing rheumatic disease. Five patients out of 11 (45.5%) were diagnosed with RA, two patients (18.2%) with ankylosing spondylitis. Other rheumatic diseases, such as juvenile idiopathic arthritis (JIA), polymyositis, polymyalgia rheumatica, psoriatic arthritis and systemic lupus erythematosus occurred once each. Of these 11 patients, three patients (27.3%) developed a rh-irAE.

Three out of 19 rh-irAE patients (15.8%) had a pre-existing rheumatic disease. Two patients with RA experienced a disease flare. One patient with JIA suffered from an arthritis flare. In none of the three patients did ICI therapy have to be terminated due to disease flare. Four patients with rh-irAE suffered from psoriasis. Two of them developed a psoriatic arthritis under ICI therapy.

The median time between first exposure to ICIs and the occurrence of rh-irAEs in patients with pre-existing rheumatic disease was 30 days (range 15–365 days).

Relation to other irAEs

Overall, 153 of all 437 patients (35%) displayed at least one non-rh-irAEs, 35 of them suffered from a second irAE and seven of them displayed three irAEs. In total, there were 195 cases of non-rh-irAEs in 153 patients. Rh-irAEs occurred less frequently compared with other non-rh-irAEs: 9.3% of all irAEs were rheumatic (20 rh-irAE

Table 3. Characteristics of patients with rheumatic immune-related adverse events (rh-irAEs).

Patient ID	Age/sex	Type of malignancy	Immunotherapy	Rh-irAE	CTCAE grade	Onset-time (months)	New occurrence of autoantibody positivity	Systemic therapy	Clinical response
1	46/M	Head and neck tumour	Nivolumab	Juvenile idiopathic arthritis	2	12	-	GCs	Resolution
2	69/F	Melanoma	Ipilimumab	Undifferentiated arthritis	2	3	-	GCs	Partial
3	69/F	Melanoma	Nivolumab	Myositis	2	5	ANA	GCs, NSAIDs	Partial
4	55/M	Lung tumour	Nivolumab	Arthralgia	2	17	-	GCs	Not observed
5	68/M	Lung tumour	Nivolumab	Arthralgia	2	0,5	-	NSAIDs	Partial
6	69/F	Gastrointestinal tumour	Nivolumab	Rheumatoid arthritis	2	0,5	Anti-CCP, RF	GCs, MTX	Partial
7	43/M	Melanoma	Pembrolizumab	Myositis	2	14	-	GCs	Resolution
8	76/F	Melanoma	Pembrolizumab	Myositis	3	4	-	GCs	Partial
9	80/F	Melanoma	Pembrolizumab	Myalgia	2	0,2	-	Opioids	Partial
10	46/M	Melanoma	Pembrolizumab	Arthralgia	2	20	-	NSAIDs	Partial
11	73/M	Lung tumour	Pembrolizumab	Arthralgia and myalgia	1	14	-	GCs	Resolution
12	72/M	Melanoma	Pembrolizumab	Rheumatoid arthritis	3	21	-	GCs, MTX	Partial
13	64/F	Head and neck tumour	Nivolumab	Arthralgia	2	6	-	GCs, NSAIDs	Partial
14	71/F	Melanoma	Pembrolizumab	Rheumatoid arthritis	2	1	-	GCs, tocilizumab	Partial
15	77/M	Melanoma	Pembrolizumab	Arthralgia	2	6	ANA	GCs, NSAIDs	Partial
16	45/M	Melanoma	Nivolumab	Arthralgia	2	3	-	GCs	Partial
17	48/F	Melanoma	Nivolumab	Arthralgia	1	2	-	NSAIDs	Resolution
18	59/M	Melanoma	Nivolumab	Psoriatic arthritis	3	2	-	GCs, MTX	Partial
19	71/M	Melanoma	Nivolumab	Psoriatic arthritis	3	1	-	GCs	Partial
20	47/M	Melanoma	Ipilimumab + nivolumab	Sicca syndrome	2	0,5	-	GCs	Not observed
21	69/F	Melanoma	Pembrolizumab	Myalgia	1	2	-	NSAIDs	No
22	88/M	Melanoma	Ipilimumab + nivolumab	Myalgia	2	1	-	-	-
23	63/M	Melanoma	Ipilimumab + nivolumab	Myositis	3	3	-	GCs	Partial
24	79/M	Melanoma	Ipilimumab + nivolumab	Arthralgia and myalgia	1	2	-	GCs	Resolution

Patients 1 to 19: first-line ICI therapy, patients 20 to 24: second-line ICI therapy. (In only 13 patients were laboratory values examined).

ANA: anti-nuclear antibodies; anti-CCP: anti-citrullinated peptide; CTCAE: Common Terminology Criteria for Adverse Events; F, female; GC: glucocorticosteroid; MTX: methotrexate; M, male; NSAID: non-steroidal anti-inflammatory drug; RF: rheumatoid factor.

Table 4. Comparison of best tumour response to immune checkpoint inhibitors in patients without immune-related adverse events (irAEs), patients with non-rheumatic irAEs (non-rh-irAEs) and in patients with rheumatic irAEs (rh-irAEs).

	Patients without irAEs <i>n</i> =218 (%)	Patients with non-rh-irAEs <i>n</i> =141 (%)	Patients with rh-irAEs <i>n</i> =18 (%)
Responders ^a	68 (31.2)	88 (62.4)	17 (94.4)
Non-responders ^a	150 (68.8)	53 (37.6)	1 (5.6)

^aResponse to immune checkpoint inhibitor therapy includes complete response, partial response and stable disease. Non-responders were affected by progressive disease.

cases in 19 patients of a total of 215 irAE cases in 163 patients). Most common irAEs were rash, colitis and hepatitis (Table 1). More detailed information of all non-rh-irAEs can be found in the Supplemental Material (Supplemental Table S2). Median time to development of a non-rh-irAE was 60 days (IQR 30–145 days). Non-rh-irAEs were observed in nine patients with rh-irAE (47.4%). Patients without rh-irAE suffered from non-rh-irAE in 34.4% of patients. We did not observe a significant correlation between the occurrence of rh-irAEs and non-rh-irAEs in general ($p=0.248$).

The severity of non-rh-irAEs was distributed as follows: CTCAE grade 1 in 32.5% of patients, CTCAE grade 2 in 40.8%, CTCAE grade 3 in 25.1%, while three patients (1.6%) were affected by CTCAE grade 4.

Tumour response according to rh-irAEs

Exact data on tumour response to ICI therapy were reported in 377 patients out of 437 patients. For 60 patients we lacked the exact data because the patients came from other clinics within the University Hospital Bonn. A summary of tumour response in all patients and in patients with rh-irAE is given in Table 1. In general, a treatment response was observed in 173 patients (45.9%), including CR ($n=15$, 4.0%), PR ($n=63$, 16.7%) and SD ($n=95$, 25.2%). PD (non-responders) was observed in 204 patients (54.1%). Rh-irAEs were found in 17 patients (9.8%) of responders and in one patient (0.5%) of non-responders.

Patients with rh-irAEs had a significantly higher tumour response rate compared with patients without rh-irAEs (94.4% versus 43.5%; $p<0.0001$). In addition, patients with rh-irAEs had a better tumour response than patients with non-rh-irAEs (94.4% versus 62.4%; $p=0.007$). The comparison of tumour response in different

cohorts (patients without irAEs, with non-rh-irAEs and with rh-irAEs) is listed in Table 4.

In order to calculate PFS, we performed a Kaplan–Meier analysis (Figure 1) and compared PFS in three cohorts: patients without irAEs, patients with non-rh-irAEs and patients with rh-irAEs. Patients who suffered from rh-irAEs and non-rh-irAE were classified as rh-irAE cohort. This results in a median PFS of 3 months (range 0–43 months) for all patients with available data included in this calculation. For patients without any irAE the median PFS was 2 months [95% confidence interval (CI) 1.7–2.3]. The non-rh-irAE cohort showed a median PFS of 5 months (95% CI 2.4–7.6) and the rh-irAE cohort displayed a median PFS of 20 months (95% CI 9.1–30.9). The 95% CIs of these cohorts do not overlap and therefore differ considerably. To investigate the distribution of PFS of the three cohorts a Kaplan–Meier graph was constructed (Figure 1). Using the log-rank test, a significant difference in PFS was found in these three cohorts ($p<0.0001$).

To investigate the impact of rh-irAEs and non-rh-irAEs on PFS in a time-dependent manner and to account for immortal time bias, we conducted a Cox proportional hazards regression model. Please note that this modelling approach also considers the impact of non-rh-irAEs on the PFS in patients of the rh-irAEs cohort. When adjusting for age at baseline, sex and body mass index (BMI) at baseline, the occurrence of non-rh-irAEs showed a reduced hazard ratio (HR) (HR=0.47, 95% CI 0.36–0.63, $p<0.0001$), indicating a significant association with PFS. The occurrence of rh-irAEs also displayed a reduced HR concerning PFS; however, this was not found to be statistically significant (HR=0.52, 95% CI 0.23–1.20, $p=0.128$). PFS was not significantly affected by age (HR=1.00, 95% CI 0.99–1.01, $p=0.816$), sex (female: HR=1.10, 95% CI

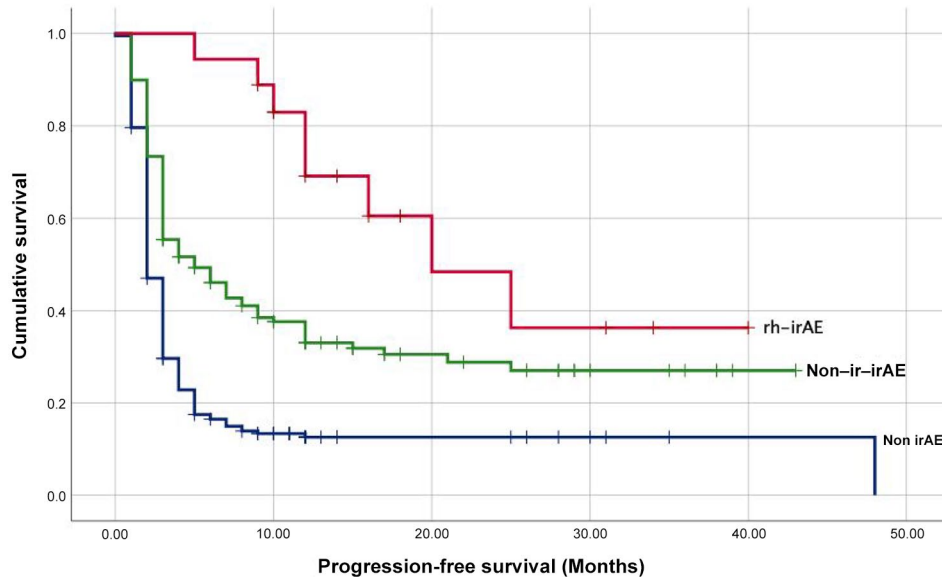


Figure 1. Kaplan–Meier analysis estimated progression-free survival after immune checkpoint inhibitor therapy.

Compared were patients with no side effects (no irAEs), patients with other non-rh-irAEs and patients with rh-irAEs. Log rank test: $p < 0.0001$; +: censored.

irAEs, immune-related adverse events; non-rh-irAEs, non-rheumatic immune-related adverse events; rh-irAEs, rheumatic immune-related adverse events

0.84–1.44, $p = 0.465$) or BMI at baseline (HR = 0.99, 95% CI 0.99–1.00, $p = 0.574$).

An additional model was adjusted for the different tumour types. Considering the different malignancies, the HR was not significantly affected in the groups clearly defined by tumour type.

We fitted additional models adjusting for the KPS and AJCC staging system for melanoma, as these variables were not available on the whole dataset. For the 178 patients with KPS data, the occurrence of non-rh-irAEs and the KPS at baseline showed a significant association with PFS (non-rh-irAEs: HR = 0.58, 95% CI 0.40–0.84, $p = 0.004$; KPS: HR = 0.84, 95% CI 0.75–0.95, $p = 0.00425$; rh-irAEs: HR = 0.47, 95% CI 0.14–1.53, $p = 0.212$). For the 178 patients with AJCC data in melanoma skin cancer, the occurrence of non-rh-irAEs and AJCC showed a significant association with PFS (non-rh-irAEs: HR = 0.56, 95% CI 0.39–0.81, $p = 0.0021$; stage III: HR = 0.30, 95% CI 0.17–0.53, $p < 0.0001$; rh-irAEs: HR = 0.62 95% CI 0.22–1.73, $p = 0.3681$). Of melanoma patients, 77.5% were identified as stage IV tumour patients. The remaining patients with melanoma were listed as stage III.

In 12 out of 15 patients (80%) who were treated with GC, PFS persisted after GC administration. Three patients who received GC were found to have disease progression at the next staging after starting GC therapy. One in six patients (16.7%) with a medium GC dose experienced progression after GC administration, as did two in five patients (40%) with high GC doses. In the two patients with steroid pulse therapy, PFS remained after GC therapy.

Discussion

The aim of this study was to determine the prevalence of rh-irAEs under ICI therapy. Due to widespread use of ICIs in many malignant diseases, the burden of irAEs as well as rh-irAEs has increased. A detailed description and investigation of rh-irAEs is therefore essential.

In our study, 4.3% of all patients with ICI therapy suffered from at least one rh-irAE. In the four publications available, the prevalence of rh-irAEs varied between 2.3%²⁶ and 6.6%.¹⁷ This difference might be explained by different study designs: in the retrospective study by Le Burel *et al.*,²⁶ 21 of 908 patients (2.3%) were affected by rh-irAEs. Patients were selected *via* a French register

(REISAMIC), which contains only rh-irAEs of CTCAE grade ≥ 2 . Applied to our study, this results in an adjusted prevalence of rh-irAEs of 3.9%. Kostine *et al.*¹⁷ published a rather high prevalence of 35 rh-irAEs patients in 524 patients (6.6%) investigated in their prospective study, including all CTCAE grades. All patients were actively asked about symptoms such as arthralgia, which is a common complaint in general and might explain the higher prevalence published. In the other studies available, rh-irAEs occurred in 3%²⁷ and in 3.5%.²⁸ These results are comparable to ours.

Concerning the occurrence of new antibodies, in our cohort in only three out of 19 rh-irAE patients new antibodies were detected. Our results are in line with previous published studies.^{17,18,29}

The most common previously reported rh-irAE is arthralgia, which occurs in 1%–43% of patients.¹⁰ In our study, a total of 15 out of 437 (3.4%) patients complained of arthralgia. A much higher result was published in a study by Buder-Bakhaya *et al.*,³⁰ where arthralgia was described in 13.3%. Authors in this study included also osteoarthritis as rh-irAE, which is a degenerative disease and, rather, not ICI related. In addition, 17 of the 26 patients complained of arthralgia of CTCAE grade 1 and only nine patients of CTCAE grade 2. Especially these mild and common symptoms are in our opinion difficult to classify in the context of rh-irAEs.

Rather rare previously described rh-irAEs such as PMR,²⁶ vasculitis,^{31,32} sarcoidosis,^{26,28,31} Sjögren's syndrome²⁶ and systemic lupus erythematosus³¹ did not occur in our cohort. This raises the question of whether these diseases are rh-irAEs or occurred by chance under ICI therapy. Le Burel *et al.*²⁶ investigated 908 patients: PMR and sarcoidosis occurred in two patients each. Three patients were affected by Sjögren's syndrome. Considering that the number of patients examined was about twice as large as in our study, it is not surprising that these rare diseases did not occur in our study. Vasculitis was also observed very rarely (in 0.27% with anti-PD-1/anti-PD-L1 monotherapy and in 0.22% with anti-CTLA-4 monotherapy).³² Systemic lupus erythematosus was reported in only one patient out of 524 patients (0.2%) receiving ipilimumab therapy.³¹ In order to investigate the correlation between the described diseases and ICI therapy, a much larger patient population would be necessary.

Roberts *et al.*³³ examined 117 patients with rh-irAEs in a nationwide multi-centre cohort study. Although these data cannot be used to make conclusions about the prevalence of rh-irAEs, the large number of patients allows a good representation of the different rh-irAE types. In contrast to our data, the most common rh-irAEs in this study were symmetric polyarthritides ($n=45$, 33.1%) and PMR-like syndrome ($n=17$, 12.5%). In comparison, arthralgia and myalgia occurred in only 15 patients (11%). In our study, 10 patients (52.6%) complained of arthralgia and myalgia and no patient presented with PMR-like syndromes. This distinction could be interpreted by different reporting behaviour of the centres, or different evaluations of arthralgia as rh-irAE.

Some studies reported a general increase of irAEs¹⁴ as well as rh-irAEs^{34,35} under ICI combination therapy with ipilimumab and nivolumab. We did not observe rh-irAEs under a combination first-line ICI therapy. However, in second-line ICI combination therapy the occurrence of rh-irAEs was 19%. This significant difference between first- and second-line ICI combination therapy raises the question of whether ICI combination therapy leads to an increase of rh-irAEs or whether this increase is related to second-line therapy. We also found rh-irAEs to occur more frequent under therapy with PD-1-inhibitors nivolumab (5.3%) or pembrolizumab (5.7%) compared with therapy with CTLA-4-inhibitor ipilimumab (2.6%). Kostine *et al.*¹⁷ came to a similar observation in their prospective study, where all except one patient with rh-irAEs received anti-PD-1 or anti-PD-L1 treatment. This difference could result from the varying impact mechanism of PD-1 and CTLA-4 antibodies.^{36,37} In addition, a different spectrum of irAEs regarding anti-CTLA-4 *versus* anti-PD-1/anti-PD-L1 therapy has been reported.⁹ Thereby, arthralgia and myalgia occur more frequently under anti-PD-1/anti-PD-L1 therapy compared with anti-CTLA-4 therapy and consequently support our observation.

In therapy of rh-irAEs the cooperation between the treating oncologist and rheumatologist is of particular importance. The severity, classified by CTCAE grades, drives the therapy decision.³⁸ Patients with mild symptoms received non-steroidal anti-inflammatory drugs. If more severe symptoms occurred, GCs were administered. In our study, every patient with rh-irAE \geq CTCAE grade 3 received GC and three patients required additional therapy with MTX. In some case reports,

successful treatment of arthritis with tocilizumab was reported.³⁹ In our cohort only one patient with arthritis received tocilizumab and responded only partially to the treatment, indicating that IL-6 receptor inhibition might not work in every patient. In addition, EULAR recommendations on the diagnosis and therapy of rh-irAEs were published by Kostine *et al.*⁴⁰ in April 2020. Thereby, three treatment escalations were defined: (1) local/systemic glucocorticoids if symptoms are not controlled by symptomatic treatment, then tapered to the lowest efficient dose, (2) conventional synthetic disease-modifying antirheumatic drugs, in the case of inadequate response to glucocorticoids or for steroid sparing and (3) biological disease-modifying antirheumatic drugs, for severe or refractory irAEs.⁴⁰ In general, a similar procedure was followed for our patients. We achieved a good outcome with this therapy procedure in our patients with rh-irAEs, so that our study confirms the recommendations.

Another interesting aspect is whether GC therapy affects tumour response and PFS. In our study, PFS persisted in the majority of patients (80%) even after GC administration was initiated. Therefore, we hypothesize that the use of GC to control rh-irAEs is often associated with no negative PFS-related impact. This hypothesis is supported by Petrelli *et al.*,⁴¹ where the use of GC (to treat irAEs) does not appear to reduce overall survival in cancer patients treated with ICIs. Furthermore, our data suggest that there is no clear correlation between a high steroid dose and the occurrence of progression. This is because progression was indeed observed more frequently in patients with high GC doses than in patients with medium GC doses. Nevertheless, the two patients with steroid pulse therapy were among the majority of patients where PFS persisted. This observation demonstrates the importance of the adequate treatment of rh-irAEs.

Six of 18 patients (33.3%) with rh-irAE and available full data set discontinued ICI therapy as a consequence of rh-irAE. In the study by Richter *et al.*²⁷ ICI therapy was terminated in 13 of 61 patients with rh-irAE (21.3%). In general, the decision to discontinue ICI therapy prematurely depends on the severity.³⁸ In our study ICI therapy was discontinued in four rh-irAE patients with CTCAE grade 3 and two with CTCAE grade 2. In addition to the severity of rh-irAE, the response to therapy and other reasons, including personal reasons, always play a role in the

decision to discontinue ICI therapy. Especially in myositis patients, the decision to discontinue ICI therapy should consider that continuation of ICI therapy could lead to potentially life-threatening myositis.⁴⁰ As a result, ICI therapy was also discontinued in two of our three patients with myositis as rh-irAE.

The remarkable aspect of this study was the investigation of rh-irAEs and irAEs in general. Rh-irAEs occurred less frequently compared with other irAEs (9.3% of all irAEs were rheumatic). In our study, no significant difference in the occurrence of non-rh-irAEs in patients with or without rh-irAEs was observed. Based on our results, we have established that various side effects occur independently of each other. In a publication by Cappelli *et al.*³⁵ the authors observed in 68.7% of patients with immune-related inflammatory arthritis the occurrence of another irAE. In that study, only patients with inflammatory arthritis due to ICI therapy were examined, so that no information about the overall occurrence of irAEs and no general data about all rh-irAEs are available. The study by Kostine *et al.*¹⁷ is the only study available investigating the prevalence of rh-irAEs as well as non-rh-irAEs in all patients. Of the 35 patients with rh-irAEs, 16 patients (45.7%) were also affected by a non-rh-irAE. Our study yielded very similar results as we observed non-rh-irAEs in 47.4% of patients with rh-irAE. Despite a possible similar autoimmune pathogenesis, non-rh-irAEs were observed in only about half of patients with rh-irAEs.

Median onset of rh-irAEs in our cohort was 109 days, which is comparable to previous studies, where 70 days¹⁷ to 100 days³⁰ were observed. However, in some patients, symptoms occurred months later, possibly partially due to diagnostic delay. Based on our results, it can be confirmed that rh-irAEs seem to have a later onset than non-rh-irAEs (median onset time of rh-irAEs: 109 days *versus* non-rh-irAEs 60 days). This result confirms the observation of Smith and Bass.⁴²

In most other studies on irAEs, patients with pre-existing rheumatic diseases were excluded.^{18,30} We decided deliberately to include all patients with pre-existing rheumatic diseases, as the aim of this study is to show a realistic prevalence also on the number of flares of a pre-existing rheumatic disease. In a study by Menzies *et al.*,⁴³ 52 patients with pre-existing autoimmune diseases were included, 27 of whom suffered from a

rheumatological pre-existing condition. The authors concluded that, although irAEs occur frequently in these predisposed patients, they are usually mild and easy to manage and do not require discontinuation of therapy. Our results show that one-third (27.3%) of patients with pre-existing rheumatic disease experienced a disease flare, but in none of them did ICI therapy have to be terminated. It is important to notice that no new rheumatological diseases occurred in these patients. This result confirms the statement of Menzies *et al.*,⁴³ that patients with pre-existing rheumatic diseases should not be deprived of ICI therapy. The observation that patients with pre-existing rheumatic diseases tend to have mild and reversible rh-irAEs is also supported by Sebastiani *et al.*⁴⁴ However, it is of great importance to pay attention to these patients in order to diagnose a disease flare in time. Differentiation of an ICI mediated flare of disease and a flare which would have occurred without ICI therapy remains a bias which can hardly be eliminated.

In our study, rh-irAEs occurred considerably earlier in patients with pre-existing rheumatic disease than in patients with *de novo* disease (median: 30 days *versus* 109 days). This observation confirms the thesis published in 2019 by Mooradian *et al.*,⁴⁵ where the median time to the occurrence of *de novo* toxicity was 38 weeks and 4.6 weeks in patients with pre-existing rheumatic disease.

The role of rh-irAEs as predictor for response to ICIs is of particular interest. A correlation between irAEs (including rh-irAEs) and tumour response (CR, PR and SD) was observed in various studies.^{17,46,47} In our cohort, this association was also found; 17 of all 18 patients (94.4%) with rh-irAEs and available full data to therapy response responded strongly to ICI therapy. Moreover, patients with rh-irAEs had a higher rate of responders to ICIs compared with the non-rh-irAEs cohort. This result is different from the study published by Kostine *et al.*,¹⁷ where the authors did not find a difference between patients with rh-irAEs and with non-rh-irAEs concerning response to ICI therapy.

In the study by Buder-Bakhaya *et al.*³⁰ a significantly improved PFS in patients with arthralgia was reported. Our study comes to a similar conclusion, as a significant difference was observed between patients without irAEs, patients with non-rh-irAEs and patients with rh-irAEs. In the above-mentioned study³⁰ the number of patients

was less than half of our study (195 patients *versus* 437 patients in our study). Furthermore, our study includes PFS of patients with all rh-irAE (not only patients with arthralgia) and patients with non-rh-irAE were also examined. Using the Kaplan–Meier analysis, our study showed significantly longer median PFS, especially in patients with rh-irAE than in patients without irAE or in patients with non-rh-irAE. In addition, we observed a strong association between the occurrence of non-rh-irAEs and a reduced risk of progression in the Cox proportional hazards regression model with time-dependent covariates. No significant reduction was observed concerning rh-irAEs. This might be due to the rather low number of rh-irAE patients compared with the non-rh-irAE cohort. Even though approximately 50% of patients with rh-irAEs were also affected by non-rh-irAEs, the effect on PFS reduction cannot be estimated precisely.

Conclusion

Rh-irAEs occur under ICIs and with the increasing use, related side effects will also become more frequent. We observed a prevalence of rh-irAEs of 4.3%. Most commonly observed was arthralgia, followed by arthritis, myositis and myalgia in line with current literature. Therapy of rh-irAEs requires close cooperation between the treating oncologist and rheumatologist. Best therapy for each patient has to be found in an interdisciplinary way according to CTCAE grade. ICI therapy termination has to be decided individually. The observed significantly improved tumour response in patients with rh-irAE (94.4% of patients with rh-irAE were responders to ICI therapy) should be kept in mind, considering termination of ICI therapy. Further prospective studies are necessary to define rh-irAEs more precisely and to derive treatment algorithms.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Valentin S. Schäfer  <https://orcid.org/0000-0002-6591-5936>

Supplemental material

Supplemental material for this article is available online.

References

- Ribas A and Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science* 2018; 359: 1350–1355.
- Suarez-Almazor ME, Kim ST, Abdel-Wahab N, *et al.* Review: immune-related adverse events with use of checkpoint inhibitors for immunotherapy of cancer. *Arthritis Rheumatol* 2017; 69: 687–699.
- Hodi FS, O'Day SJ, McDermott DF, *et al.* Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363: 711–723.
- Hargadon KM, Johnson CE and Williams CJ. Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. *Int Immunopharmacol* 2018; 62: 29–39.
- Buchbinder EI and Desai A. CTLA-4 and PD-1 Pathways. *Am J Clin Oncol* 2016; 39: 98–106.
- Postow MA, Sidlow R and Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018; 378: 158–168.
- June CH, Warshauer JT and Bluestone JA. Is autoimmunity the Achilles' heel of cancer immunotherapy? *Nat Med* 2017; 23: 540–547.
- Weinmann SC and Pisetsky DS. Mechanisms of immune-related adverse events during the treatment of cancer with immune checkpoint inhibitors. *Rheumatology* 2019; 58: vii59–vii67.
- Spain L, Diem S and Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev* 2016; 44: 51–60.
- Cappelli LC, Gutierrez AK, Bingham CO, *et al.* Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. *Arthritis Care Res* 2017; 69: 1751–1763.
- Weber JS, Gibney G, Sullivan RJ, *et al.* Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. *Lancet Oncol* 2016; 17: 943–955.
- Robert C, Long GV, Brady B, *et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; 372: 320–330.
- Borghaei H, Paz-Ares L, Horn L, *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; 373: 1627–1639.
- Larkin J, Chiarion-Sileni V, Gonzalez R, *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015; 373: 23–34.
- Bronstein Y, Ng C, Hwu P, *et al.* Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy. *AJR Am J Roentgenol* 2011; 197: W992–W1000.
- Chan MMK, Kefford RF, Carlino M, *et al.* Arthritis and tenosynovitis associated with the anti-PD1 antibody pembrolizumab in metastatic melanoma. *J Immunother* 2015; 38: 37–39.
- Kostine M, Rouxel L, Barnetche T, *et al.* Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer: clinical aspects and relationship with tumour response: a single-centre prospective cohort study. *Ann Rheum Dis* 2018; 77: 393–398.
- Belkhir R, Burel SL, Dunogean L, *et al.* Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment. *Ann Rheum Dis* 2017; 76: 1747–1750.
- Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf (2017, accessed 02 March 2020).
- Buttgereit F, Silva JAPD, Boers M, *et al.* Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002; 61: 718–722.
- Karnofsky D and Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM (ed.) *Evaluation of chemotherapeutic agents*. New York, NY: Columbia University Press, 1949, pp.191–205.
- Amin MB, Greene FL, Edge SB, *et al.* The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin* 2017; 67: 93–99.
- Eisenhauer EA, Therasse P, Bogaerts J, *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45: 228–247.
- Team RC. *R: a language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing, <https://www.r-project.org/> (2020, accessed 29 January 2021).

25. Therneau T. A package for survival analysis in R. R package version 3.2-3, <https://CRAN.R-project.org/package=survival> (2020, accessed 29 January 2021).
26. Le Burel S, Champiat S, Mateus C, *et al.* Prevalence of immune-related systemic adverse events in patients treated with anti-programmed cell death 1/anti-programmed cell death-ligand 1 agents: a single-centre pharmacovigilance database analysis. *Eur J Cancer* 2017; 82: 34–44.
27. Richter MD, Crowson C, Kottschade LA, *et al.* Rheumatic syndromes associated with immune checkpoint inhibitors: a single-center cohort of sixty-one patients. *Arthritis Rheumatol* 2019; 71: 468–475.
28. Lidar M, Giat E, Garelick D, *et al.* Rheumatic manifestations among cancer patients treated with immune checkpoint inhibitors. *Autoimmun Rev* 2018; 17: 284–289.
29. Cappelli LC, Gutierrez AK, Baer AN, *et al.* Inflammatory arthritis and Sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis* 2017; 76: 43–50.
30. Buder-Bakhaya K, Benesova K, Schulz C, *et al.* Characterization of arthralgia induced by PD-1 antibody treatment in patients with metastasized cutaneous malignancies. *Cancer Immunol Immunother* 2018; 67: 175–182.
31. Pérez-De-Lis M, Retamozo S, Flores-Chávez A, *et al.* Autoimmune diseases induced by biological agents. A review of 12,731 cases (BIOGEAS Registry). *Expert Opin Drug Saf* 2017; 16: 1255–1271.
32. Salem J-E, Manouchehri A, Moey M, *et al.* Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018; 19: 1579–1589.
33. Roberts J, Ennis D, Hudson M, *et al.* Rheumatic immune-related adverse events associated with cancer immunotherapy: a nationwide multi-center cohort. *Autoimmun Rev* 2020; 19: 102595.
34. Hao C, Tian J, Liu H, *et al.* Efficacy and safety of anti-PD-1 and anti-PD-1 combined with anti-CTLA-4 immunotherapy to advanced melanoma: a systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2017; 96: e7325.
35. Cappelli LC, Brahmer JR, Forde PM, *et al.* Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen. *Semin Arthritis Rheum* 2018; 48: 553–557.
36. Boutros C, Tarhini A, Routier E, *et al.* Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol* 2016; 13: 473–486.
37. Parry RV, Chemnitz JM, Frauwirth KA, *et al.* CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol Cell Biol* 2005; 25: 9543–9553.
38. Brahmer JR, Lacchetti C, Schneider BJ, *et al.* Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018; 36: 1714–1768.
39. Kim ST, Tayar J, Trinh VA, *et al.* Successful treatment of arthritis induced by checkpoint inhibitors with tocilizumab: a case series. *Ann Rheum Dis* 2017; 76: 2061–2064.
40. Kostine M, Finckh A, Bingham CO, *et al.* EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. *Ann Rheum Dis* 2021; 80: 36–48.
41. Petrelli F, Signorelli D, Ghidini M, *et al.* Association of steroids use with survival in patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *Cancers* 2020; 12: 546.
42. Smith MH and Bass AR. Arthritis after cancer immunotherapy: symptom duration and treatment response. *Arthritis Care Res* 2019; 71: 362–366.
43. Menzies AM, Johnson DB, Ramanujam S, *et al.* Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol* 2017; 28: 368–376.
44. Sebastiani GD, Scirocco C and Galeazzi M. Rheumatic immune related adverse events in patients treated with checkpoint inhibitors for immunotherapy of cancer. *Autoimmun Rev* 2019; 18: 805–813.
45. Mooradian MJ, Nasrallah M, Gainor JF, *et al.* Musculoskeletal rheumatic complications of immune checkpoint inhibitor therapy: a single center experience. *Semin Arthritis Rheum* 2019; 48: 1127–1132.
46. Liew DFL, Leung JLY, Liu B, *et al.* Association of good oncological response to therapy with the development of rheumatic immune-related adverse events following PD-1 inhibitor therapy. *Int J Rheum Dis* 2019; 22: 297–302.
47. Petrelli F, Grizzi G, Ghidini M, *et al.* Immune-related adverse events and survival in solid tumours treated with immune checkpoint inhibitors: a systematic review and meta-analysis. *J Immunother* 2020; 43: 1–7.