Sicca/Sjögren's syndrome triggered by PD-1/PD-L1 checkpoint inhibitors. Data from the International ImmunoCancer Registry (ICIR)

M. Ramos-Casals[1-3], A. Maria[4], M.E. Suárez-Almazor[5], O. Lambotte[6,7], B.A. Fisher[8], G. Hernández-Molina[9], P. Guilpain[4], X. Pundole[5], A. Flores-Chávez[1], C. Baldini[10], C.O. Bingham III[11], P. Brito-Zerón[1,12], J.-E. Gottenberg[13], M. Kostine[14], T.R.D. Radstake[15], T. Schaeverbeke[14], H. Schulze-Koops[16], L. Calabrese[17], M.A. Khamashta[18], X. Mariette[19], on behalf of the ICIR

Affiliations: see page S-120.
Manuel Ramos-Casals, MD, PhD
Alexandre Maria, MD, PhD
Maria E. Suárez-Almazor, MD, PhD
Olivier Lambotte, MD, PhD
Benjamin A. Fisher, MD, PhD
Gabriela Hernández-Molina, MD, PhD
Philippe Guilpain, MD, PhD
Xerxes Pundole, MD, PhD
Alejandra Flores-Chávez, LN, PhD
Chiara Baldini, MD, PhD
Clifton O. Bingham III, MD, PhD
Pilar Brito-Zerón, MD, PhD
Jacques-Eric Gottenberg, MD, PhD
Marie Kostine, MD, PhD
Timothy R.D. Radstake, MD, PhD
Thierry Schaeverbeke, MD, PhD
Hendrik Schulze-Koops, MD, PhD
Leonard Calabrese, MD, PhD
Munther A. Khamashta, MD, PhD
Xavier Mariette, MD, PhD

The members of the International Immuno Cancer Registry (ICIR) are listed in the Appendix.

Please address correspondence to:
Dr Manuel Ramos-Casals,
Servei de Malalties Autoimmunes
Sistèmiques, Hospital Clínic,
C/Villarroel 170,
08036-Barcelona, Spain.
E-mail: mramos@clinic.ub.es

ABSTRACT

Objective. To analyse the worldwide occurrence of sicca/Sjögren's (SS) syndrome associated with the use of immune checkpoint inhibitors (ICI) in patients with cancer.

Methods. The ImmunoCancer International Registry (ICIR) is a Big Data-Sharing multidisciplinary network composed by 40 specialists in Rheumatology, Internal Medicine, Immunology and Oncology from 18 countries focused on the clinical and basic research of the immune-related adverse events (irAEs) related to cancer immunotherapies. For this study, patients who were investigated for a clinical suspicion of SS after being exposed to ICI were included.

Results. We identified 26 patients (11 women and 15 men, with a mean age at diagnosis of 63.57 years). Underlying cancer included lung (n=12), renal (n=7), melanoma (n=4), and other (n=3) neoplasia. Cancer immunotherapies consisted of monotherapy (77%) and combined regimens (23%). In those patients receiving monotherapy, all patients were treated with PD-1/PD-L1 inhibitors (nivolumab in 9, pembrolizumab in 7 and durvalumab in 4); no cases associated with CTLA-4 inhibitors were identified. The main SS-related features consisted of dry mouth in 25 (96%) patients, dry eye in 17 (65%), abnormal ocular tests in 10/16 (62%) and abnormal oral diagnostic tests in 12/14 (86%) patients. Minor salivary gland biopsy was carried out in 15 patients: histopathological findings consisted of mild chronic sialadenitis in 8 (53%) patients and focal lymphocytic sialadenitis in the remaining 7 (47%); a focus score was measured in 5 of the 6 patients (mean of 1.8, range 1–4). Immunological markers included positive ANA in 13/25 (52%), anti-Ro/SS-A in 5/25 (20%), RF in 2/22 (9%), anti-La/SS-B in 2/25 (8%), low C3/C4 levels in 1/17 (6%) and positive cryoglobulins in 1/10 (10%). Classification criteria for SS were fulfilled by 10 (62%) out of 16 patients in whom the two key classificatory features were carried out. Among the 26 patients, there were only 3 (11%) who presented exclusively with sicca syndrome without organ-specific autoimmune manifestations. Therapeutic management included measures directed to treat sicca symptoms and therapies against autoimmune-mediated manifestations (glucocorticoids in 42%, second/third-line therapies in 31%); therapeutic response for systemic features was observed in 8/11 (73%). No patient died due to autoimmune involvement.

Conclusion. Patients with Sjögren's syndrome triggered by ICI display a very specific profile different from that reported in idiopathic primary SS, including more frequent occurrence in men, a higher mean age, a predominant immunonegative serological profile, and a notable development of organ-specific autoimmune involvement in spite of the poor immunological profile. The close association found between sicca/Sjögren's syndrome and primarily PD-1 blockade requires further specific investigation.

Introduction

Immunotherapies are a group of drugs designed to target specific molecules of the immune system. These therapies use different pharmacoimmunological approaches that may include not only the use of specific drugs (monoclonal antibodies, small proteins, fusion pro-

teins) targeting proteins located on the surface of cancer or immune cells, but also the use of other non-specific therapies including cytokines, oncolytic virus therapies, cancer vaccines, or CAR T-cell therapies (1). Among monoclonal antibodies, immune checkpoint inhibitors (ICIs) target different pathways that harbour immunosuppressive functions used by cancer cells to evade immunosurveillance, and among the ICIs, PD-1/PD-L1 and CTLA-4 inhibitors have showed promising therapeutic outcomes (2).

However, with the increasing use of ICIs the occurrence of a group of side effects referred to as immune-related adverse events (irAEs) is also increasingly recognised. Many of these side effects are driven by the same immunologic mechanisms responsible for the drugs' therapeutic effects, namely the blockade of the inhibitory mechanisms that suppress the immune system and protect body tissues from autoimmune damage. These irAEs are unique and different than those associated with cytotoxic chemotherapy, radiotherapy, or targeted therapies (3). Immunotherapy-related irAEs typically have a delayed onset and prolonged duration compared to adverse events from chemotherapy (4). Clinical features are important in providing evidence that helps with diagnosis, including, where possible, histological confirmation through biopsy-proven autoimmune related damage. Moreover, serological confirmation of the presence of positive autoantibody testing should be sought to clarify the nature of the autoimmune process, although the results may be negative in a significant number of patients. Most irAEs consisted of organ-specific autoimmune diseases, and less frequently, systemic and rheumatic diseases (3). The first case of Sjögren's syndrome (SS) triggered by cancer immunotherapies has been recently reported by Cappelli *et al.* (5), with an increasing number of additional cases reported since then (6).

The objective of this study was to analyse the worldwide scenario of SS associated with the use of cancer immunotherapies through the development of an international real-life registry of patients with cancer diagnosed with rheumatic and systemic autoimmune diseases using a big data network approach (International Immunocancer Registry Project).

Methodology

The International ImmunoCancer Registry (ICIR) is a Big Data-Sharing multidisciplinary network composed by 40 specialists in Rheumatology, Internal Medicine, Immunology and Oncology from 18 countries focused on the clinical and basic research of the irAEs related to cancer immunotherapies. The two starting objectives of the Project consisted of:

a) A retrospective study of rheumatic and systemic autoimmune diseases triggered by cancer immunotherapies seen in daily practice by the ICIR members, following a descriptive, non-interventional, data-sharing international network database design. Data were obtained by retrospective evaluation of medical charts by the physician on charge of the patient included into ongoing research projects involving local registries of irAEs (each validated for the corresponding local IRB). For this study, we selected patients presenting with a clinical suspicion of SS after being exposed to cancer immunotherapies. Exclusion criteria included the concomitant use of standard chemotherapy/radiotherapy or other aetiologies directly related to the development of sicca symptoms.

b) A systematic literature review (SLR) performed until April 15, 2019. We selected biologics from the main groups of cancer immunotherapies, which were crossed with rheumatic and systemic autoimmune diseases using the terms included in the Medical Dictionary for Regulatory Activities terminology (MedDRAVR 15.0). Data were extracted by MRC and AFC. The following information was recorded for each study: first author's name, title, year of publication, study design, underlying cancer, biologic drug and combinations, treatment arms, number of patients available for analysis, number of autoimmune events, grade of toxicity according to the Common Termi-

nology Criteria for Adverse Events (CTCAE) defined by the National Cancer Institute, histopathological analysis, immunophenotyping analysis, therapeutic management and outcomes (7). We selected reported cases fulfilling the same inclusion criteria and exclusion criteria used in the ICIR Registry.

The following variables were collected: age, gender, ethnicity, country of residence, fulfilment of the 2002/2016 criteria items (8, 9), antinuclear antibodies (ANA >1/40), rheumatoid factor (RF), C3 and C4 levels, cryoglobulins, and an estimation of systemic damage using the EULAR Sjögren's syndrome disease activity index (ESSDAI). Diagnostic tests for SS (ocular tests, oral tests and salivary gland biopsy) were evaluated according to the recommendations of the European Community Study Group (10). Disease diagnosis was defined as the time when the attending physician confirmed sicca syndrome or the fulfilment of the 2002/2016 criteria. Organ-specific autoimmune manifestations (irAEs) concomitant to sicca symptoms and developed after the initiation of cancer immunotherapies were also collected, and were classified in two groups: those who fit into the definitions included in the ESSDAI index (11), which evaluates 12 domains or organ systems, and those involved organs not included in the ESSDAI. Descriptive data are presented as mean and range for continuous variables and number and percentage for categorical variables.

Results

We identified in the ICIR Registry a total of 29 patients who were studied for a clinical suspicion of SS after being treated with cancer immunotherapies. Three patients who received cancer immunotherapies other than ICI (trastuzumab in 2 cases, vemurafenib in 1 case) were excluded for the analysis.

The baseline characteristics of the 26 patients treated with ICI are summarised in Table I. There were 11 (42%) women and 15 (58%) men, with a mean age at diagnosis of sicca/SS of 63.57 years (range 39–79 years, all but one classified as White ethnicity). A previ-

Table I. Baseline characteristics of 26 patients treated with ICI who developed sicca/SS included in the ICIR Registry.

Patient	Gender	Age at diagnosis	Previous autoimmune diseases	Underlying cancer	Checkpoint inhibitor	Months	ICI stopped	Specific sicca therapy	Systemic therapy (organ involved)
1	F	61	None	Lung	Nivolumab	10	No	Topical	No
2	F	72	None	Lung	Nivolumab + ipilimumab	7	No	Topical	GC, IFX (colitis)
3	M	39	None	Melanoma	Nivolumab + ipilimumab	1	No	Topical	GC, MMF (CRS)
4	F	52	None	Colon	Nivolumab + ipilimumab	1	No	Topical	GC (hep)
5	F	79	None	Lung	Pembrolizumab	1	No	Topical	GC, ivIG (systemic)
6	F	71	PHEWS	Melanoma	Nivolumab	6	Yes	Topical	GC, TAC (hep)
7	M	64	PM	Lung	Durvalumab	1	Yes	Topical	GC, MMF, IVIG, PeX (musc)
8	M	71	None	Lung	Pembrolizumab	7	Yes	Topical + GC	No
9	M	79	None	Melanoma	Pembrolizumab	28	Yes	Topical + GC	No
10	F	50	None	Lung	Pembrolizumab	5	No	Topical	GC, HCQ (art)
11	M	74	None	Renal	Nivolumab	11,2	No	Topical	GC, TCZ (art)
12	M	77	None	Renal	Nivolumab	5,7	No	Topical + cevimeline	No
13	M	72	None	Lung	Pembrolizumab	2	No	None	No
14	M	70	None	Lung	Nivolumab	18	Yes	Ocular GC/CyA	No
15	F	51	None	Chordoma	Durvalumab	3,7	No	Topical	No
16	M	71	None	Lung	Nivolumab	2	No	Topical	No
17	M	58	None	Lung	Pembrolizumab	6	No	Topical	No
18	M	60	None	Melanoma	Durvalumab	2	No	Topical	GC (art)
19	M	71	Uveitis	Renal	Nivolumab + pegIL10	8,3	No	Topical	GC (iridocyclitis)
20	F	68	None	Lung	Nivolumab	6	Yes	Topical	No
21	M	51	None	Lung	Durvalumab	3	No	Topical	No
22	M	49	None	Renal	Nivolumab + ipilimumab	4,6	No	Topical	No
23	F	56	SpA	Renal	Nivolumab + ipilimumab	2,4	No	None	No
24	F	58	None	Cervix	Nivolumab	2,6	No	None	No
25	M	67	None	Renal	Pembrolizumab	14	No	None	No
26	F	62	None	Renal	Nivolumab	10,5	No	Topical + pilocarpine	GC, HCQ (art)

ous history of autoimmune diseases was recorded in 4 (15%) cases, and a family history of autoimmune disease in 2 (7%). Underlying cancer included lung (n=12), renal (n=7), melanoma (n=4), and other (n=3) neoplasia. Cancer immunotherapies consisted of monotherapy (77%) and combined regimens (23%). In those patients receiving monotherapy, all patients were treated with PD-1/PD-L1 inhibitors (nivolumab in 9, pembrolizumab in 7 and durvalumab in 4); no cases associated with CTLA-4 inhibitors were identified. Combined therapies included nivolumab combined with ipilimumab (6 cases) or pergIL10 (1 case). The median interval between onset of ICI treatment and sicca/SS diagnosis was 6.5 months (range 1–28 months).

The main SS-related features are summarised in Table II and consisted of dry mouth in 25 (96%) patients, dry eye in 17 (65%), abnormal ocular tests in 10/16 (62%) and abnormal oral diagnostic tests in 12/14 (86%) patients. Minor salivary gland biopsy was carried out in 15 patients: histopathological findings consisted of mild chronic sialadenitis in 8 (53%) patients and focal lymphocytic sialadenitis (Chisholm-Mason classification ≥3) in the remaining 7 (47%); a focus score was measured in 5 of the 6 patients (mean of 1.8, range 1–4). Immunological markers included positive ANA in 13/25 (52%), anti-Ro/SS-A in 5/25 (20%), RF in 2/22 (9%), anti-La/SS-B in 2/25 (8%), low C3/C4 levels in 1/17 (6%) and positive cryoglobulins in 1/10 (10%). Classification criteria for SS were fulfilled by 10 (62%) out of 16 patients in whom the two key classificatory features (salivary gland biopsy and Ro autoantibodies) were carried out; 5 (50%) of the 10 patients fulfilled the criteria due to the histopathological findings in the absence of anti-Ro autoantibodies.

Among the 26 patients, there were only 3 (11%) who presented exclusively sicca syndrome without organ-specific autoimmune manifestations. Among those with systemic features, 10 (43%) presented with features included in the ESSDAI classification, 7 (30%) with non-ESSDAI features, and the remaining 6 (27%) presented with both ESSDAI and non-ESSDAI features. The estimated mean total ESSDAI score was 10.26 (ranging between 0 and 48) and 11.68 (ranging between 0 and 56) for clinESSDAI. The involved organs following the ESSDAI classification consisted of features included in the cutaneous (n=10), articular (n=8), glandular (n=5), peripheral nerve system (n=5), constitutional (n=4), muscular (n=4), pulmonary (n=1), renal (n=1) and central nervous system (n=1) domains. Non-ESSDAI organ-specific autoimmune features included thyroiditis (n=10), enterocolitis (n=5), hepatitis (n=5), vitiligo (n=2), myocarditis (n=1), hypophysitis (n=1), adrenal insufficiency (n=1) and cytokine-release syndrome (n=1).

Therapeutic management included measures directed to treat sicca symptoms and therapies against autoimmune-mediated manifestations. In most patients, sicca symptoms were managed with topical measures, including oral pilocarpine in two cases presenting with severe oral dryness, and topical CyA drops in one case with severe ocular dryness; two patients received systemic corticosteroids. Sicca

Table II. The main SS-related features of 26 patients treated with ICI who developed sicca/SS included in the ICIR Registry.

Patient	Dry mouth/oral tests results	Dry eye/ocular tests results	Minor salivary gland biopsy (focus score)	Autoantibodies (ANA/RF/Ro/La)	Complement levels/ cryoglobulins	SjS criteria	ESSDAI (clinESSDAI)	Systemic features	Other irAEs
1	Yes/abnormal	Yes/abnormal	NA	Neg/neg/neg/neg	NA/NA	NA	9 (10)	Cut. Musc	Col
2	Yes/abnormal	Yes/normal	MCS	Neg/neg/neg/neg	Normal/negative	No	8 (9)	Cut, pulm	Col, thyr
3	Yes/na	Yes/na	MCS	Neg/neg/neg/neg	Normal/NA	No	0 (0)	None	CRS, hep
4	Yes/abnormal	Yes/abnormal	NA	Pos/NA/neg/neg	Normal/NA	NA	3 (3)	Cut	Hep
5	Yes/abnormal	Yes/normal	MCS	Pos/neg/pos/neg	Normal/negative	Yes	48 (56)	Const, gland, art, renal, musc, PNS, CNS	Hep
6	Yes/na	Yes/na	NA	Pos/neg/neg/neg	Normal/NA	NA	0 (0)	None	Hep, col
7	No/normal	Yes/abnormal	MCS	Pos/neg/neg/neg	NA/NA	No	18 (21)	Musc	Myoc, col, thyr
8	Yes/abnormal	No/normal	MCS	Pos/neg/neg/neg	Normal/negative	No	0 (0)	None	None
9	Yes/abnormal	No/normal	FLS (1.8)	Neg/neg/neg/neg	Normal/NA	Yes	5 (5)	Const, gland	None
10	Yes/abnormal	Yes/abnormal	FLS (2)	Pos/neg/neg/neg	Normal/negative	Yes	9 (12)	Art, cut	None
11	Yes/na	Yes/na	NA	Neg/neg/neg/neg	NA/NA	NA	4 (6)	Art	None
12	Yes/na	No/na	NA	Neg/neg/neg/neg	Normal/NA	NA	2 (3)	Art	None
13	Yes/abnormal	Yes/abnormal	MCS	Pos/neg/neg/neg	NA/negative	No	23 (26)	Const, cut, musc, PNS	None
14	Yes/abnormal	Yes/abnormal	MCS	Pos/neg/neg/neg	Normal/negative	No	3 (3)	Cut	None
15	Yes/na	No/na	NA	Neg/neg/neg/neg	NA/NA	NA	0 (0)	None	None
16	Yes/abnormal	Yes/na	NA	Pos/neg/neg/neg	Normal/NA	NA	0 (0)	None	None
17	Yes/na	No/normal	NA	NA/NA/NA/NA	NA/NA	NA	5 (5)	PNS	None
18	Yes/na	No/normal	NA	Pos/neg/pos/neg	Low/pos	Yes	28 (30)	Art, cut, pulm, PNS	Pneum, vitil
19	Yes/na	No/na	FLS (1)	neg/NA/neg/neg	NA/NA	Yes	0 (0)	None	Thyr, iridocyclitis
20	Yes/abnormal	Yes/abnormal	FLS (1)	Pos/neg/neg/neg	Normal/negative	Yes	3 (3)	Cut	Thyr
21	Yes/abnormal	No/abnormal	FLS (4)	Pos/neg/pos/pos	Normal/NA	Yes	3 (3)	Cut	Thyr
22	Yes/na	No/na	NA	Neg/neg/neg/neg	NA/NA	NA	0 (0)	None	Thyr, adren
23	Yes/na	Yes/normal	FLS (nd)	Pos/pos/pos/pos	Normal/NA	Yes	5 (6)	Gland, art	Thyr, col
24	Yes/na	Yes/abnormal	MCS	Neg/neg/pos/neg	Normal/NA	Yes	4 (5)	Gland, art	Thyr, hep, vitil
25	Yes/normal	Yes/abnormal	FLS (1)	neg/NA/neg/neg	NA/negative	Yes	11 (11)	Const, cut, PNS	Thyr, hypoph
26	Yes/na	Yes/na	NA	Neg/pos/neg/neg	Normal/negative	NA	4 (5)	Gland, art	Thyr, pneum

NA: not available/not performed; MCS: mild chronic sialadenitis; FLS: focal lymphocytic sialadenitis; Neg: negative; Pos: positive; Cut: cutaneious; Musc: muscular; Pulm: pulmonary; Const: constitutional; gland: glandular; art: articular; PNS: peripheral nervous system; CNS: central nervous system; Col: colitis; thyr: thyroiditis; hep: hepatitis; myoc: myocarditis; pneum: pneumonitis; vitil: vitiligo; adrenal: adrenal failure; hypoph: hypophysitis.

Table III. Dryness reported as irAE in patients with cancer treated with ICI included in RCTs (17–21).

Authors (year)	Checkpoint inhibitor	Combination therapy	Type of study	Population studied	Sicca cases	%
Hodi et al. (2018)	Ipilimumab		Phase III	311	7	2.25
Robert et al. (2015)	Ipilimumab		Phase III	256	1	0.39
Hodi et al. (2018)	Nivolumab	Ipilimumab	Phase III	313	19	6.07
Hodi et al. (2018)	Nivolumab		Phase III	313	13	4.15
Motzer et al. (2015)	Nivolumab		Phase II	167	11	6.59
Giaccone et al. (2018)	Pembrolizumab		Phase II	40	2	5.00
Long et al. (2017)	Pembrolizumab	Ipilimumab	Phase I	154	25	16.23
Robert et al. (2015)	Pembrolizumab		Phase III	278	20	7.19
Total				1832	98	5.35

symptoms persisted in spite of using these therapies. Systemic therapy was used in 11 (42%) patients using first-line therapy with glucocorticoids (including methylprednisolone pulses in 2 cases, plus second-line therapies including hydroxychloroquine (arthritis in 2 cases) or immunosuppressive agents (myositis and hepatitis, respectively), and rescue therapies including intravenous immunoglobulins/plasma exchanges (myositis, cytokine-release syndrome), infliximab (enterocolitis) and tocilizumab (arthritis); therapeutic response for systemic features was observed in 8/11 (73%). No patient died due to autoimmune involvement.

Discussion

Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands. This leads to dryness of the main mucosal surfaces, such as the mouth, eyes, nose, pharynx, larynx and vagina (12). In the aetiopathogenesis of SS, a specific combination of individual genetic predisposition (intrinsic factors) and environmental agents (extrinsic factors) may be central to the development of the disease (13). The key SS symptoms (oral and ocular dryness) have been also linked to a large list of systemic and topical drugs, mainly through their impact on lachrymal and salivary gland secretion (14-16). Until the arrival of cancer immunotherapies, no association between sicca/Sjögren's syndrome and the use of monoclonal antibodies was reported.

Oral/ocular dryness are reported as irAE in 98/1832 (5.3%) patients with cancer treated with immunotherapies included in RCTs (17-21) (Table III); the frequency was higher for patients who received combination therapy of checkpoint inhibitors (9.4%) and lower for patients treated with CTLA-4 inhibitors (1.4%). No information about specific SS evaluations was reported, and all cases but one were classified as CTCAE grade I-II. The ICIR Reg-
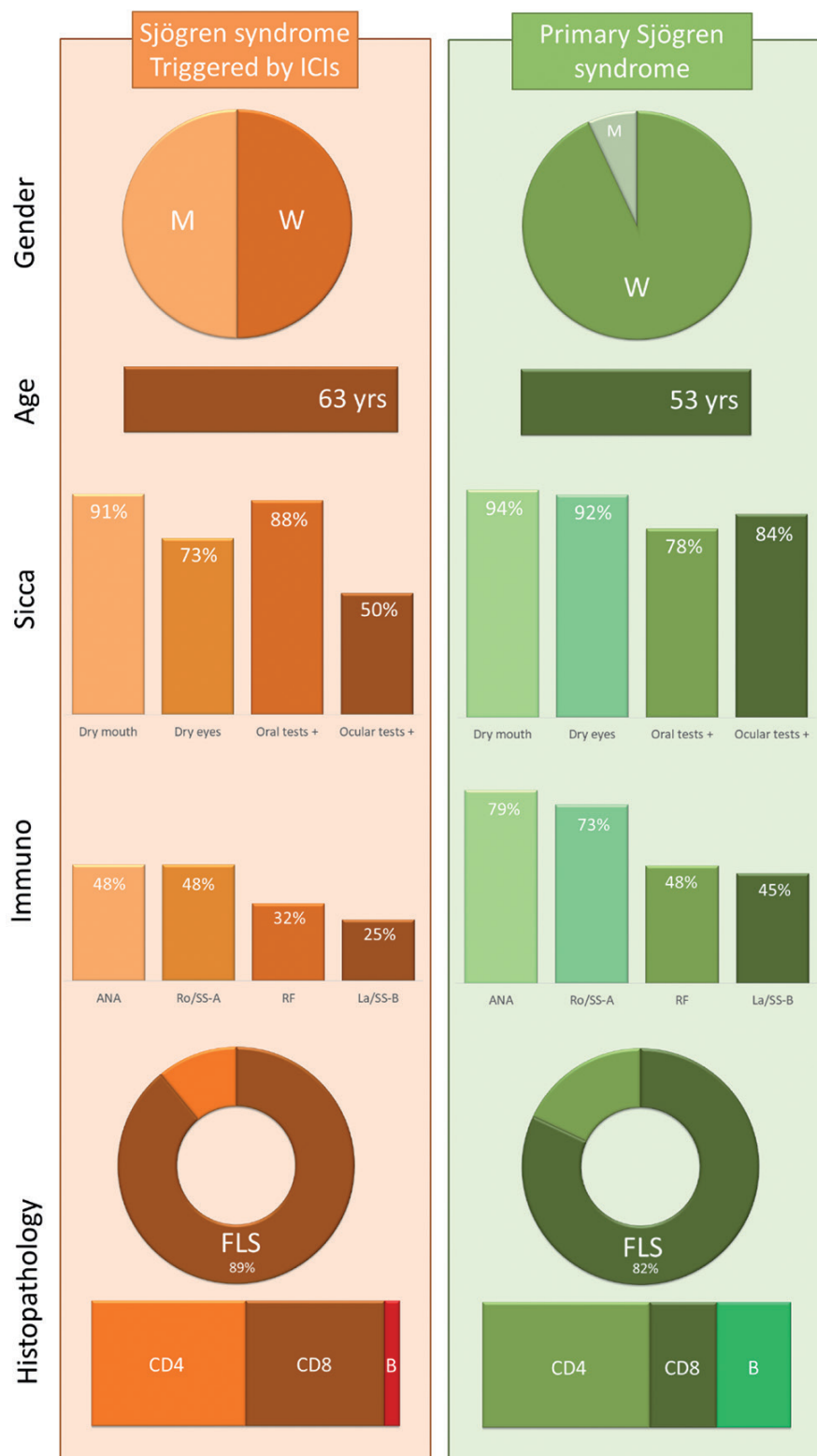
Fig. 1. Phenotype of 22 cases of SS triggered by ICIs that fulfilled the current classification criteria for SS in comparison with patients with primsary SS (ref. 37).

istry has identified 60 cases of sicca/Sjögren's syndrome triggered by ICIs in patients with cancer, 34 from the SLR (5, 6, 22-32) and the 26 unpublished cases collected among ICIR centres. Among them, the 22 patients (10 from the ICIR Registry and 12 from the SLR) who fulfilled the current classification criteria of SS had a very specific phenotype, clearly different from that observed in the idiopathic Sjögren's syndrome (33) (Fig. 1):

The epidemiological and clinical profile seem to be quite different from primary SS, with half cases being men (only 5% in primary), a mean age at diagnosis ten years older, a lower frequency of both oral and ocular dryness and a lower frequency of abnormal ocular tests in comparison with the data reported in the "idiopathic" primary SS (33). In addition, nearly 20% of cases had a history of previous autoimmune diseases (personal or familial), suggesting a potential predisposing immunogenetic background in some patients.

The histopathological profile consisted of the typical focal lymphocytic sialadenitis of the primary form in half the cases biopsied (34). In primary SS, the median % of T-cells is around 70% (50% CD4^{+}, 20% CD8^{+}) and of B cells around 22% (35, 36). By immunohistochemistry, Warner et al. (6) have recently reported a predominant T-lymphocytic infiltrate, with a slight majority of CD4^{+} over CD8^{+} T cells and few CD20^{+} B cells. This pattern is different from characteristic SS infiltrates where B cells may represent 20–62% of all lymphocytes and FS directly correlating with B-cell ratios (37). The study also reported scattered infiltrating PD-1-positive T cells and epithelial PD-L1 positivity only in the most severely infiltrated cases. Some patients reported by Warner et al. (6) were treated with ICI for thymic epithelial neoplasms; the significance of this finding is intriguing but may reflect underlying thymic dysfunction-related autoimmunity, which was exacerbated by an ICI-augmented immune response (38).

There was a much lower prevalence of SS-associated serum autoantibodies (52% ANA, 20% Ro/SS-A, 9% RF, 8% La/SS-B) in comparison with idiopathic primary SS. The predominant seronegative immunological pattern is similar to that reported for other irAEs related to cancer immunotherapies (31, 39-41).

These patients required a more intense therapeutic management than primary SS patients (42): 20% of patients re-

quired specific therapies for severe dryness, 42% of cases required systemic corticosteroids, and 31% second/third line therapies for non-sicca systemic disease.

The aetiopathogenesis of immunotherapy-induced SS/sicca syndrome is unknown. Probably, a specific genetic background that predisposes to their development could play a role. This could also contribute to explain the exacerbations of pre-existing SS, reported in several patients exposed to cancer immunotherapies. Danlos *et al.* (43) reported one patient who developed a relapse consisting of acute dermatitis and sicca syndrome, Menzies *et al.* (44) reported a relapse in 2 patients with SS (no further details), and Warner *et al.* (6) reported dry eye or dry mouth prior to ICI treatment in 5 patients. Furthermore, it seems reasonable to hypothesise that patients with pre-treatment positive immunological markers could be more prone to develop autoimmune processes, as has been reported in patients with autoimmune diseases developed after TNF-targeting therapies (45). From a pathogenic view, two findings should be highlighted from our results: the enhanced risk in patients receiving combined regimens as has been reported for other irAEs (46), and the remarkable association with the use of PD-1 blockers (95% of reported cases of triggered SS were exposed to these immunotherapies). In fact, PD-1 deficiency results in the development of fatal myocarditis in MRL mice due to a massive infiltration of lymphocytes in heart, with additional inflammatory foci being found in the liver, lung, stomach and salivary glands (47). The close association we found between sicca/SS and treatment with anti-PD-1/PD-L1 antibodies may help to better understanding pathophysiology of SS. Like other systemic autoimmune diseases, SS is an heterogeneous disease and a better stratification of patients is necessary (48). A first effort of stratification may be to divide patients between those with a type 1 interferon/BAFF/ B-cell signature from those with a T-cell /NK-cell/ type 2 IFN signature. Of note these patients cannot be separated based on

the transcriptomic IFN signature since it overlaps between type 1 and type 2 IFN. The pattern of sicca/SS presented by these patients with cancer treated with ICI suggest that the PD-1/PD-L1 pathway could play a role in the SS patients with the T-cell/NK-cell/type 2 IFN signature.

We also found a significant overlap between some organ-specific irAEs and the clinical domains included into the score that measures systemic activity in primary SS (ESSDAI), making difficult to consider these organ-specific features either as independent irAEs (unrelated to SS) or as forming part of the triggered SS (systemic form of the disease). This may be even more difficult when the patient develop ESSDAI features highly characteristic of the disease (parotid enlargement, articular or cutaneous features, autoimmune neuropathies). It is unclear whether the ESSDAI can be used in scoring systemic activity in patients with SS triggered by ICI, a clinical scenario for which this score was not specifically designed for. Another key message is that nearly 60% of patients in whom a SS was clinically suspected and that were fully evaluated for the disease (including both immunological and histopathological studies) fulfilled the current classification criteria for SS. This significant percentage raises two questions: a) whether a history of ICI use should be included as a new exclusion criterion in a future review of SS criteria, and b) whether the fulfilment or not of the current criteria could modify the therapeutic approach of the triggered SS, especially in cases presenting with systemic involvement.

The retrospective design of the study means that our results need to be interpreted cautiously. The level of association between a drug and the induced autoimmune disease cannot be evaluated by a retrospective analysis of individual reported cases and should always be studied according to the estimated total population exposed to this agent. We cannot rule out the possibility that some cases may have a latent SS, especially in women of middle-age in whom the cancer diagnosis (and the corresponding treatment) was coinci-

dental with the initial development of a SS, with the frequent medical visits and the enhanced medical follow-up favouring the discovery of an underlying SS. Indeed, the overwhelming majority of reported cases defined the induced autoimmune disease as newly diagnosed, although in some cases this was not clearly stated. More importantly, a complete study for confirming the fulfilment of the current classification criteria for SS (salivary biopsy + anti-Ro determination) was carried out in only 36 cases, of whom 61% fulfilled the criteria; in nearly half the confirmed cases, the diagnosis was achieved with salivary biopsy in immunonegative patients.

In spite of these limitations and the scarce quality of the available data, most of the previously reported recommendations for the management of patients with autoimmune diseases triggered by biological agents would seem to remain valid when applied to patients initiating cancer immunotherapy (49). Before initiating the biological therapy, a careful pre-therapeutic evaluation paying special attention to pre-existing clinical or immunological autoimmune features is recommended. Discontinuation of biological therapy is mandatory in patients with severe involvement of internal organs, while in patients with sicca features, continuation could be considered (always with a closer follow-up). If they are diagnosed timely, most irAEs, except endocrine and some inflammatory arthritis cases, are reversible, requiring the use of immunosuppressive agents only in very limited cases (50). This does not appear to be the case for sicca/Sjogren syndrome, whose triggered sicca symptoms overwhelmingly became chronic, following the same pattern of the idiopathic form of the disease. Therefore, corticosteroids are not recommended to treat exclusively sicca features as is recommended for primary SS, and should be carefully used in patients with cancer (51, 52). Corticosteroids and/or immunosuppressive agents may be required in severe cases to control the induced systemic manifestations of SS despite the withdrawal of the immunotherapy.

In summary, immune checkpoint inhibitors should be included in the large list of drugs causing sicca symptoms; 60% of cases fulfil the current classification criteria for primary SS, and this triggered SS should be considered a new emerging immunotherapy-triggered form of the disease. These patients display a very-specific profile different from that reported in idiopathic SS, including an enhanced involvement of men, a higher mean age at diagnosis, a predominant immunonegative serological profile, and a notable development of systemic disease in spite of the poor immunological profile. The close association found between sicca/Sjögren's syndrome and cancer immunotherapy, primarily PD-1 blockade, requires further specific investigation.

Affiliations
[1]Department of Autoimmune Diseases, ICMiD, Barcelona, Spain; [2]Sjögren Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, IDIBAPS-CELLEX, Barcelona, Spain; [3]Department of Medicine, University of Barcelona, Hospital Clínic, Barcelona, Spain; [4]Department of Internal Medicine Multi-Organic Diseases, Local Referral Center for Autoimmune Diseases, Saint Eloi Hospital, Montpellier University Hospital, France; [5]Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]APHP Médecine Interne/Immunologie Clinique, Hôpital Bicêtre, Paris, France; [7]Université Paris Sud - INSERM U1184 - CEA, Immunology of Viral Infections and Autoimmune Diseases, IDMIT Department, IBFJ, Fontenay-aux-Roses & Le Kremlin-Bicêtre, France; [8]Institute of Inflammation and Ageing, University of Birmingham; and National Institute of Health Research Birmingham Biomedical Research Centre and Department of Rheumatology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [9]Immunology and Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. México City, Mexico; [10]Rheumatology Unit, University of Pisa, Italy; [11]Department of Rheumatology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA; [12]Department of Internal Medicine, Hospital CIMA-Sanitas, Barcelona, Spain; [13]Department of Rheumatology, Strasbourg University Hospital, National Centre For Rare Systemic Autoimmune Diseases, CNRS, Institut de Biologie Moléculaire et Cellulaire, Immunologie, Immunopathologie et Chimie Thérapeutique, Strasbourg University, Strasbourg, France; [14]Department of Rheumatology, Centre Hospitalier Universitaire, Bordeaux, France; [15]Department of Rheumatology/Clinical Immunology, University Medical Center Utrecht, The Netherlands; [16]Department of Rheumatology/Clinical Immunology, Ludwig-Maximilians-University Munich, Germany; [17]Department of Rheumatic/Immunologic Diseases, Cleveland Clinic University, OH, USA; [18]Lupus Clinic, Rheumatology Department, Dubai Hospital, UAE; [19]Center for Immunology of Viral Infections and Autoimmune Diseases, Assistance Publique - Hôpitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, Université Paris Sud, INSERM, Paris, France.

Appendix
List of investigators
Coordination
- Manuel Ramos-Casals, *Autoimmune Diseases, Hospital Clínic, Barcelona, Spain*.
- Xavier Mariette, *Rheumatology, Paris-Sud University, Le Kremlin Bicêtre, France*.

Co-Convenors
- Olivier Lambotte, *Médecine Interne/Immunologie Clinique, Hôpital Bicêtre, Paris, France*.
- Marie Kostine, *Rheumatology, Centre Hospitalier Universitaire, Bordeaux, France*.
- Munther A. Khamashta, *Lupus Research Unit, St Thomas' Hospital, London, UK*.

Steering Committee
- Leonard Calabrese, *Rheumatic/Immunologic Diseases, Cleveland Clinic University, Cleveland, OH, USA*.
- Maria Suárez-Almazor, *Rheumatology/Clinical Immunology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*.
- Chiara Baldini, *Rheumatology Unit, University of Pisa, Italy*.
- Clifton O. Bingham III, *Rheumatology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA*.
- Jacques-Eric Gottenberg, *Department of Rheumatology, Strasbourg University Hospital, National Centre For Rare Systemic Autoimmune Diseases, CNRS, Institut de Biologie Moléculaire et Cellulaire, Immunologie, Immunopathologie et Chimie Thérapeutique, Strasbourg University, Strasbourg, France*.
- Timothy R.D. Radstake, *Rheumatology/Clinical Immunology, University Medical Center Utrecht, The Netherlands*.
- Thierry Schaeverbeke, *Rheumatology, Centre Hospitalier Universitaire, Bordeaux, France*.
- Hendrik Schulze-Koops, Jan Leipe, *Rheumatology/Clinical Immunology, Ludwig-Maximilians-University Munich, Germany*.

Research Fellows
Pilar Brito-Zerón, Internal Medicine, Hospital CIMA-Sanitas, Barcelona, Spain, mpbrito@sanitas.es
Alejandra Flores-Chávez, Department of Autoimmune Diseases, Hospital Clínic, Barcelona, Spain, ale.floreschavez@hotmail.com

Data Scientist
Belchin Kostov, Primary Healthcare Transversal Research Group, IDIBAPS, Barcelona, Spain, BADRIYAN@clinic.cat

International Coordinators
Cassandra Calabrese, Department of Rheumatic and Immunologic Diseases, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland Clinic Foundation, Cleveland, OH, USA, CALABRC@ccf.org
Soledad Retamozo, Gustavo Citera, Argentinian Registry, Argentina, soleretamozo@hotmail.com
Eva Mª Aguilar, GEAS-SEMI Spanish Registry, Spain, eva.aguilar@quironsalud.es
Michael David Richter, Department of Internal Medicine, Mayo School of Graduate Medical Education, Rochester, MN, USA richter.michael@mayo.edu
Merav Lidar, Rheumatology Unit, Sheba Medical Center, Israel; Sackler Faculty of

Medicine, Tel Aviv University, Tel Aviv, Israel, Merav.Lidar@sheba.health.gov.il

Ben Fisher, Rheumatology Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK, B.Fisher@bham.ac.uk

Jean Marie Michot, Département des Innovations Thérapeutiques et Essais Précoces, Gustave Roussy, Université Paris-Saclay, Villejuif, France; Service de Médecine Interne and Immunologie Clinique, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France, jean-marie.michot@gustaveroussy.fr

David Liew, Melbourne EpiCentre, Royal Melbourne Hospital, and the University of Melbourne, Parkville, Victoria, Australia, david.liew@austin.org.au

Marte Schrumpf Heiberg, Diakonhjemmet Hospital, Oslo, Sweden, Marte.Schrumpf@diakonsyk.no

Philippe Guilpain, Alexandre Maria, Department of Internal Medicine, Multi-Organic Diseases, Montpellier University Hospital, Montpellier, France, p-guilpain@chu-montpellier.fr

Debashish Danda, Professor & Head Clinical Immunology & RheumatologyChristian Medical College & Hospital, Vellore, India, debashisdandacmc@hotmail.com

Peter Olsson, Department of Rheumatology, Skåne University Hospital Malmö, Malmö, Sweden, (peter.a.olsson@gmail.com).

Yasunori Suzuki, Mitsuhiro Kawano, Kanazawa university, Kanazawa, Japan, zukitechno@yahoo.co.jp

Saadettin Kılıçkap, Hacettepe University Institute of Cancer, Turkey, skilickap@yahoo.com

Gabriela Hernández-Molina, Immunology and Rheumatology Department, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. México City, Mexico, gabyhm@yahoo.com

Oscar Arrieta, Thoracic Oncology Unit, Instituto Nacional de Cancerología, Mexico City, Mexico

Virginia Fernandes Moça Trevisani, Federal University of São Paulo, Sao Paulo, Brazil, vmoca@uol.com.br

Sonja Praprotnik, Department of Rheumatology, University Medical Centre, Ljubljana, Slovenia, sonja.praprotnik@kclj.si

Ildiko Fanny Horváth, Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, fanny.horvath@gmail.com

Naoto Azuma, Division of Rheumatology, Department of Internal Medicine, Hyogo College of Medicine, Mukogawa-cho, Nishinomiya, Hyogo, Japan, naoazuuh@hyo-med.ac.jp

Xerxes Pundole, Rheumatology/Clinical Immunology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, XNPundole@mdanderson.org

References

1. PAPAIOANNOU NE, BENIATA O V, VITSOS P, TSITSILONIS O, SAMARA P: Harnessing the immune system to improve cancer therapy. *Ann Transl Med* 2016; 4: 261.
2. DARVIN P, TOOR SM, SASIDHARAN NAIR V, ELKORD E: Immune checkpoint inhibitors: recent progress and potential biomarkers. *Exp Mol Med* 2018; 50: 165.
3. CALABRESE LH, CALABRESE C, CAPPELLI LC: Rheumatic immune-related adverse events from cancer immunotherapy. *Nat Rev Rheumatol* 2018; 14: 569-79.
4. PUZANOV I, DIAB A, ABDALLAH K *et al.*: Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017; 5: 95.
5. 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.
6. WARNER BM, BAER AN, LIPSON EJ *et al.*: Sicca syndrome associated with immune checkpoint inhibitor therapy. *Oncologist* 2019 Apr 17 [Epub ahead of print].
7. RAMOS-CASALS M, LAMBOTTE O, KOSTINE M *et al.*: Immune-related adverse events induced by cancer immunotherapies. Big Data analysis of 13,051 cases (ImmunoCancer International Registry). *Ann Rheum Dis* 2019.
8. VITALI C, BOMBARDIERI S, JONSSON R *et al.*: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
9. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al.*: 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome. *Ann Rheum Dis* 2017; 76: 9-16.
10. VITALI C, BOMBARDIERI S, MOUTSOPOULOS HM *et al.*: Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993; 36: 340-7.
11. SEROR R, RAVAUD P, BOWMAN SJ *et al.*: EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010; 69: 1103-9.
12. BRITO-ZERÓN P, BALDINI C, BOOTSMA H *et al.*: Sjögren syndrome. *Nat Rev Dis Prim* 2016; 2: 16047.
13. MARIETTE X, CRISWELL LA: Primary Sjögren's Syndrome. *N Engl J Med* 2018; 378: 931-9.
14. CORNEC D, SARAUX A, JOUSSE-JOULIN S *et al.*: The differential diagnosis of dry eyes, dry mouth, and parotidomegaly: a comprehensive review. *Clin Rev Allergy Immunol* 2015; 49: 278-87.
15. FRAUNFELDER FT, SCIUBBA JJ, MATHERS WD: The role of medications in causing dry eye. *J Ophthalmol* 2012; 2012: 285851.
16. MIRANDA-RIUS J, BRUNET-LLOBET L, LAHOR-SOLER E, FARRE M: Salivary secretory disorders, inducing drugs, and clinical management. *Int J Med Sci* 2015; 12: 811-24.
17. HODI FS, O'DAY SJ, McDERMOTT DF *et al.*: Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363: 711-23.
18. ROBERT C, SCHACHTER J, LONG GV *et al.*: Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015; 372: 2521-32.
19. MOTZER RJ, RINI BI, McDERMOTT DF *et al.*: Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol* 2015; 33: 1430-7.
20. GIACCONE G, KIM C, THOMPSON J *et al.*: Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. *Lancet Oncol* 2018; 19: 347-55.
21. LONG GV, ATKINSON V, CEBON JS *et al.*: Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. *Lancet Oncol* 2017; 18: 1202-10.
22. PAPAVASILEIOU E, PRASAD S, FREITAG SK, SOBRIN L, LOBO A-M: Ipilimumab-induced ocular and orbital inflammation – a case series and review of the literature. *Ocul Immunol Inflamm* 2016; 24: 140-6.
23. ZIMMER L, GOLDINGER SM, HOFMANN L *et al.*: Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016; 60: 210-25.
24. RICHTER MD, CROWSON C, KOTTSCHADE LA, FINNES HD, MARKOVIC SN, THANARAJASINGAM U: Rheumatic syndromes associated with immune checkpoint inhibitors: a single-center cohort of sixty-one patients. *Arthritis Rheumatol* 2019; 71: 468-75.
25. GHOSN J, VICINO A, MICHIELIN O, COUKOS G, KUNTZER T, OBEID M: A severe case of neuro-Sjögren's syndrome induced by pembrolizumab. *J Immunother Cancer* 2018; 6: 110.
26. LEIPE J, CHRIST LA, ARNOLDI AP *et al.*: Characteristics and treatment of new-onset arthritis after checkpoint inhibitor therapy. *RMD Open* 2018; 4: e000714.
27. NARVAEZ J, JUAREZ-LOPEZ P, LLUCH J, NARVAEZ JA *et al.*: Rheumatic immune-related adverse events in patients on anti-PD-1 inhibitors: Fasciitis with myositis syndrome as a new complication of immunotherapy. *Autoimmun Rev* 2018; 17: 1040-5.
28. CORTAZAR FB, MARRONE KA, TROXELL ML *et al.*: Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int* 2016; 90: 638-47.
29. BEN-BETZALEL G, BARUCH EN, BOURSI B *et al.*: Possible immune adverse events as predictors of durable response to BRAF inhibitors in patients with BRAF V600-mutant metastatic melanoma. *Eur J Cancer* 2018; 101: 229-35.
30. HOFMANN L, FORSCHNER A, LOQUAI C *et al.*: Cutaneous, gastrointestinal, hepatic, en-

docrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016; 60: 190-209.

31. 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.

32. ORLANDI A, FASCIANI R, CASSANO A *et al.*: Trastuzumab-induced corneal ulceration: successful no-drug treatment of a "blind" side effect in a case report. *BMC Cancer* 2015; 15: 973.

33. BRITO-ZERON P, ACAR-DENIZLI N, NG W-F *et al.*: How immunological profile drives clinical phenotype of primary Sjögren's syndrome at diagnosis: analysis of 10,500 patients (Sjögren Big Data Project). *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S102-12.

34. KROESE FGM, HAACKE EA, BOMBARDIERI M: The role of salivary gland histopathology in primary Sjögren's syndrome: promises and pitfalls. *Clin Exp Rheumatol* 2018; 36 (Suppl. 112): S222–33.

35. COSTA S, SCHUTZ S, CORNEC D *et al.*: B-cell and T-cell quantification in minor salivary glands in primary Sjögren's syndrome: development and validation of a pixel-based digital procedure. *Arthritis Res Ther* 2016; 18: 21.

36. ALESSANDRI C, CICCIA F, PRIORI R *et al.*: CD4 T lymphocyte autophagy is upregulated in the salivary glands of primary Sjögren's syndrome patients and correlates with focus score and disease activity. *Arthritis Res Ther* 2017; 19: 178.

37. CHRISTODOULOU MI, KAPSOGEORGOU EK, MOUTSOPOULOS HM: Characteristics of the minor salivary gland infiltrates in Sjögren's syndrome. *J Autoimmun* 2010; 34: 400-7.

38. SHELLY S, AGMON-LEVIN N, ALTMAN A, SHOENFELD Y: Thymoma and autoimmunity. *Cell Mol Immunol* 2011; 8: 199-202.

39. 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: 553-7.

40. PUNDOLE X, ABDEL-WAHAB N, SUAREZ-ALMAZOR ME: Arthritis risk with immune checkpoint inhibitor therapy for cancer. *Curr Opin Rheumatol* 2019; 31: 293-9.

41. CALABRESE C, KIRCHNER E, KONTZIAS K, VELCHETI V, CALABRESE LH: Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. *RMD Open* 2017; 3: e000412.

42. GHEITASI H, KOSTOV B, SOLANS R *et al.*: How are we treating our systemic patients with primary Sjögren syndrome? Analysis of 1120 patients. *Int Immunopharmacol* 2015; 27: 194-9.

43. DANLOS F-X, VOISIN A-L, DYEVRE V *et al.*: Safety and efficacy of anti-programmed death 1 antibodies in patients with cancer and pre-existing autoimmune or inflammatory disease. *Eur J Cancer* 2018; 91: 21-9.

44. 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: 368-76.

45. COUTZAC C, CHAPUIS J, POULLENOT F *et al.*: Association between infliximab trough levels and the occurrence of paradoxical manifestations in patients with inflammatory bowel disease: a case-control study. *J Crohns Colitis* 2015; 9: 982-7.

46. HASSEL JC, HEINZERLING L, ABERLE J *et al.*: Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): Evaluation and management of adverse drug reactions. *Cancer Treat Rev* 2017; 57: 36-49.

47. WANG J, OKAZAKI I-M, YOSHIDA T *et al.*: PD-1 deficiency results in the development of fatal myocarditis in MRL mice. *Int Immunol* 2010; 22: 443-52.

48. MINGUENEAU M, BOUDAOUD S, HASKETT S *et al.*: Cytometry by time-of-flight immunophenotyping identifies a blood Sjögren's signature correlating with disease activity and glandular inflammation. *J Allergy Clin Immunol* 2016; 137: 1809-1821.e12.

49. RAMOS-CASALS M, ROBERTO-PEREZ-ALVAREZ, DIAZ-LAGARES C, CUADRADO M-J, KHAMASHTA MA: Autoimmune diseases induced by biological agents. A double-edged sword? *Autoimmun Rev* 2010; 9: 188-93.

50. KUMAR V, CHAUDHARY N, GARG M, FLOUDAS CS, SONI P, CHANDRA AB: Current diagnosis and management of immune related adverse events (irAEs) Induced by immune checkpoint inhibitor therapy. *Front Pharmacol* 2017; 8: 49.

51. DRAGHI A, BORCH TH, RADIC HD *et al.*: Differential effects of corticosteroids and anti-TNF on tumor-specific immune responses: implications for the management of irAEs. *Int J Cancer* 2018 Dec 21 [Epub ahead of print].

52. OBRADOVIC MMS, HAMELIN B, MANEVSKI N *et al.*: Glucocorticoids promote breast cancer metastasis. *Nature* 2019; 567: 540-4.