Opportunistic autoimmunity secondary to cancer immunotherapy (OASI): An emerging challenge

M. Kostine[a], L. Chiche[b,*], E. Lazaro[c], P. Halfon[b], C. Charpin[b,d], D. Arniaud[d], F. Retornaz[b], P. Blanco[e], N. Jourde-Chiche[f], C. Richez[a], C. Stavris[b]

[a] *Département de rhumatologie, hôpital Pellegrin, place Amélie-Raba-Léon, Bordeaux, France*
[b] *Service de médecine interne, département de médecine interne et infectiologie, hôpital européen de Marseille, 6, rue Désirée-Clary, Marseille, 13003 France*
[c] *Département de médecine interne, hôpital du Haut-Lévêque, Pessac, France*
[d] *Département de rhumatologie, hôpital Saint-Joseph, Marseille, France*
[e] *Département d'immunologie, hôpital Pellegrin, Bordeaux, France*
[f] *Département de néphrologie, hôpital de la conception, AP–HM, Marseille, France*

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A B S T R A C T

With "checkpoint inhibitors" targeting PD1/PD-1-ligands or CTLA-4/CD28 pathways, immunotherapy has profoundly modified therapeutic strategies in oncology. First approved in refractory metastatic neoplasms (melanoma and lung adenocarcinoma), it is now being tested broadly in other cancers and/or as adjuvant treatment. For a significant proportion of patients, immunotherapy is responsible for "immunological" events, identified as Immune-Related Adverse Events (irAEs). Owing to the increasing number of prescriptions, identification and management of specific immunological side effects is crucial and requires close collaboration between oncologists and internists and/or other organ specialists. Within irAEs, we propose to individualize the induced autoimmunity by the term "Opportunistic Autoimmunity Secondary to Cancer Immunotherapy" (OASI). The aims of this article are (1) to present the different available checkpoint inhibitors and the OASIs reported with these treatments and (2) to propose practical recommendations for diagnosis, pre-therapeutic assessment and management of OASIs. The need for predictive biomarkers of OASIs occurrence will also be discussed.

1. Opportunistic autoimmunity secondary to cancer immunotherapy

1.1. Background

Recently, immunotherapy has completely modified the management of cancer patients. Of note, sustained remissions have been obtained in patients with cancers refractory to conventional approaches, such as metastatic melanoma [1–4]. After an initial use restricted to melanoma and lung adenocarcinoma [2–20], immunotherapy is now being tested in patients with many other types of cancers, as well as in first-line therapy for patients naive to chemotherapy. While the concept of immunotherapy in cancer is far from new, the monoclonal antibodies "checkpoint inhibitors" clearly marked a turning point in the success of this approach. The molecules currently available target CTLA-4 and PD-1 receptors or their ligands, but several other immunomodulatory agents are under development [21,22] (Fig. 1). So far, the results available (Table 1) indicate a broadening of indications to come; therefore, it is crucial to become familiar with these new molecules and with the management of their specific side effects.

Indeed, cancer immunotherapy is responsible for autoimmune manifestations in a significant proportion of patients (70 to 90% of patients receiving anti-PD-1 and anti-CTLA-4 respectively), potentially severe (≤10% and 20% respectively). Diagnosis and management of these autoimmune events require a close collaboration between oncologists and internists and/or other organ specialists. In addition to their expertise for diagnosis, these specialists have experience using biologics such anti-TNF to manage induced/paradoxical autoimmunity and monitoring patients during and after immunotherapy to detect potential short- and long-term side effects. In the context of cancer immunotherapy, notably checkpoint inhibitors, T-cell activation is induced by releasing the PD-1/PD-1 ligands or CTLA-4/CD28 co-inhibitory signals, leading to a cytotoxic attack of tumor cells. However, this T-cell activation may also promote the emergence of autoimmunity

* Corresponding author.
E-mail address: l.chiche@hopital-europeen.fr (L. Chiche).

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Table 1
OASIs reported in anti-PD1 trials.

Studies	Phase *n*	Molecule/Dosage/± Association	Cancer/Stage	Oncologic response
Hamanishi et al., 2015 [5]	II *n* = 20	Nivolumab 1 or 3 mg/kg/2 W	Ovarian platines R	CR 2 (10%) PR 1 (5%)
Patnaik et al., 2015 [6]	I *n* = 30	Pembrolizumab Escalade dose	Solid (MM, NSCLC. . .)	CR 2 (7%) PR 3 (10%)
Rizvi et al., 2015 [7]	II *n* = 117	Nivolumab 3 mg/kg/2 W	NSCLC M+ multi-R	CR 0 (0%) PR 17 (15%)
Hamid et al., 2013 [4]	I *n* = 135	Pembrolizumab 10 mg/kg/2 or 3 W Or 2 mg/kg/3 W ± Ipilimumab	MM M+ or unresectable	GR 44 (38%)
Garon et al., 2015 [8]	I *n* = 495	Pemprolizumab 2 mg or 10 mg/kg/3 W Or 10 mg/kg/2 W	NSCLC Advanced or M+	ORR 19.4%
Larkin et al., 2015 [3]	III *n* = 945	Nivolumab Variable dosage± Ipilimumab N *n* = 316 N + I *n* = 314	MM III or IV	CR 4 (1%) PR 255 (40%)
Brahmer et al., 2015 [9]	III *n* = 272	Nivolumab 3 mg/kg/2 W N *n* = 135	NSCLC M+	CR 1 (1%) PR 26 (19%)
Gettinger et al., 2015 [10]	I *n* = 129	Nivolumab 1 or 3 or 10 mg/kg/2 W Escalade dose	NSCLC M+	ORR 22 (17%)
McDermott et al., 2015 [11]	I *n* = 34	Nivolumab 1 or 10 mg/kg/2 W	Renal advanced	ORR 10 (29%)
Robert et al., 2015 [12]	III *n* = 210	Nivolumab 3 g/kg/2 W (*n* = 210)	MM M+	CR 16 (8%) PR 68 (32%)
Topalian et al., 2014 [13]	I *n* = 107	Nivolumab 1 or 3 or 10 mg/kg/2 W Escalade dose	MM advanced	ORR 33 (31%)
Ansell et al., 2015 [14]	I *n* = 23	Nivolumab 3 mg/kg/2 W Escalade dose	Hodgkin Relapsing or R	CR 4 (17%) PR 16 (70%)
Motzer et al., 2015 [15]	II *n* = 168	Nivolumab 0,3 or 2 or 10 mg/kg/3 W	Renal M+	CR 2 (1%) PR 33 (20%)
Le et al., 2015 [16]	II *n* = 41	Pembrolizumab 10 mg/kg/2 W	Solid (colorectal, endometrial, small bowel, gastric)	CR 1 (3%) PR 8 (23%)
Postow et al., 2015 [17]	I *n* = 142	Nivolumab Dose escalade ± Ipilimumab (*n* = 95)	MM M+	*n* + I CR 21 (22%) PR 37 (39%)
Robert et al., 2014 [2]	I *n* = 173	Pembrolizumab 2 or10 mg/kg/3 W + Ipilimumab	MM Advanced	CR 2 (1%) PR 39 (25%)
Robert et al., 2015 [18]	III *n* = 834	Pembrolizumab 10 mg/kg/2 or 3 W P2 W *n* = 279 P3 W *n* = 277	MM Advanced III or IV	GR/CR P2 W 34%/5% P3 W 33%/6%
Wolchok et al., 2013 [19]	I *n* = 86	Nivolumab Dose Escalade + Ipilimumab N + I *n* = 53 I then N *n* = 33	MM Advanced III or IV	CR 5 (9%) PR 16 (30%)
Borghae et al., 2015 [20]	III *n* = 292	Nivolumab 3 mg/kg/2 W *n* = 292	NSCLC IIIB or IV or relapsing	CR 4 (1%) PR 52 (18%)

Table 1 (*Continued*)

Studies	OASI									
	Median age	Type and incidence *n* (%)[a]						Severity		
	Gender Male (%)	Digestive	Hepatic	Endocrine	PNP	Cutaneous	Others	Grade 3-4	Death related to OASI	IT discontinuation
Hamanishi et al., 2015 [5]	60 0%	Frequent	ASAT 8 (40%) ALAT 5 (25%)	HypoT 8 (40%) hyperT 1 (5%)	NA	Rash 5 (5%)	Anemia 4 (20%) arthralgia 5 (25%)	ALAT 1 (5%) anemia 3 (15%) Rash 1 (5%)	0	Thyroiditis 2 (11%)
Patnaik et al., 2015 [6]	66.5 77%	Diarrhea 2 (7%)	0 (0%)	HypoT 2 (7%)	1 (3%)	Erythema1 (3%) Pruritus 5 (17%) Vitiligo 1 (3%)	Myalgia 1 (3%)	0	0	1 (3%)
Rizvi et al., 2015 [7]	65 73%	Diarrhea 12 (10%)	Frequent	NA	6 (5%)	Rash 13 (11%) Pruritus 7 (6%)	Anemia 7 (6%) Myalgia 6 (5%) Nephritis 4 (3%) Xerostomia 7 (6%)	Anemia 1 (≤1%) Diarrhea 3 (3%) Rash 1 (≤1%); Prurit 1 (≤1%) Myalgia 1 (≤1%) PNP 4 (3%)	1 (PNP)	PNP 5 (4%) Adrenal1 (≤1%) Diarrhea 1 (≤1%) NRP 2 (2%) Rash 1 (≤1%)
Hamid et al., 2013 [4]	60 59%	Diarrhea 27 (20%)	ASAT 13 (10%) ALAT 11 (8%)	HypoT 1 (≤1%) HyperT 1 (≤1%) Adrenal 1 (≤1%)	6 (4%)	Rash 28 (21%) Pruritus 28 (21%) Vitiligo 12 (9%)	Nephritis 3 (2%)	hypoT 1 (≤1%) hyperT 1 (≤1%) diarrhea 1 (≤1%) ASAT 2 (≤1%) Nephritis 2 (≤1%) Rash 3 (2%) Pruritus1 (≤1%)	1 (PNP)	NA
Garon et al., 2015 [8]	NA	Diarrhea 40 (8%)	ASAT 15 (3%) ALAT 11 (2%)	HypoT 34 (7%)	18 (4%)	Rash 48 (10%) Pruritus 53 (11%)	Anemia 21 (4%) Arthralgia 45 (9%) Myalgia 13 (3%)	Rash 1 (≤1%) Arthralgia 2 (≤1%) Diarrhea 3 (≤1%) hypoT 1 (≤1%) PNP 9 (2%) ASAT 3 (≤1%); ALAT 2 (≤1%)	1 (PNP)	Yes
Larkin et al., 2015 [3]	59 65%	Diarrhea 198 (32%) Colitis 41 (7%)	ASAT 60 (10%) ALAT 67 (11%)	HypoT 74 (12%)	Frequent	Pruritus 163 (26%) Rash 207 (33%)	Arthralgia 57 (9%)	Diarrhea 36 (6%) Colitis 26 (4%) ALAT 30 (5%); ASAT 22 (4%) hypoT 1 (≤1%) Pruritus 6 (≤1%); Rash 17 (3%) Arthralgia 1 (≤1%)	1 (neutropenia)	NA
Brahmer et al., 2015 [9]	62 82%	Diarrhea 10 (8%)	0	HypoT (4%)	6 (5%)	Rash 5 (4%)	Anemia 2 (2%) Arthralgia 7 (5%) Myalgia 2 (2%) Nephritis (3%) Neutropenia 1 (≤1%) NRP 1 (≤1%)	Diarrhea 1 (≤1%) PNP 1 (≤1%) Renal 1 (≤1%)	0	3%
Gettinger et al., 2015 [10]	65 61%	15 (12%)	6 (5%)	8 (6%)	9 (7%)	20 (15%)	Nephritis 4 (3%)	Digestive 1 (≤1%) PNP 3 (2%) Hepatic 1 (≤1%)	3 (PNP)	Yes (grades 3-4)
McDermott et al., 2015 [11]	58 76%	Diarrhea 6 (18%)	ASAT 2 (6%) ALAT 4 (12%)	HypoT 3 (9%)	1 (3%)	Rash 9 (26%) Pruritus 6 (18%)	Anemia 2 (6%) Arthralgia 3 (9%) NRP 2 (6%) Xerostomia 2 (6%)	Pruritus 1 (3%)	0	Definitive 5 (15%) Temporary 2 (6%)
Robert et al., 2015 [12]	64 58%	Diarrhea 33 (16%)	Frequent	NA	NA	Pruritus 35 (17%) Rash 31 (15%) Vitiligo 22 (11%)	ND	Pruritus 1 (≤1%); rash 1 (≤1%) Diarrhea 2 (≤1%) ALAT 2 (≤1%)	0	NA
Topalian et al., 2014 [13]	NA	Diarrhea 19 (18%) Colitis 2 (2%)	ASAT 4 (4%) ALAT 5 (5%)	HypoT 6 (6%) Hypophysitis 1 (≤1%)	2 (2%)	Rash 25 (23%) Pruritus 14 (13%) Vitiligo 10 (9%)	Anemia 5 (5%) Arthralgia 7 (7%) Myalgia 4 (4%) Nephritis 3 (3%) Thrombocytopenia 5 (5%) Uveitis1 (≤1%) Xerostomia 7 (7%)	Diarrhea 2 (2%) Xerostomia 1 (≤1%) Anemia 1 (1%) Thrombocytopenia 1(≤1%) hypoT 1 (≤1%)	0	NA

Table 1 (*Continued*)

Studies	OASI									
	Median age	Type and incidence *n* (%)[a]						Severity		
	Gender Male (%)	Digestive	Hepatic	Endocrine	PNP	Cutaneous	Others	Grade 3-4	Death related to OASI	IT discontinuation
Ansell et al., 2015 [14]	35 52%	Diarrhea 3 (13%)	Frequent	HypoT 2 (9%)	NA	Rash 5 (22%) Pruritus 3 (13%)	Pancreatitis 1 (4%) Thrombocytopenia 4 (17%)	Pancreatitis 1 (4%) Digestive 2 (9%) Thrombocytopenia 1 (4%)	0	9%
Motzer et al., 2015 [15]	61 72%	Diarrhea 16 (10%)	ASAT 8 (5%) ALAT 7 (4%)	HypoT 10 (6%)	8 (5%)	Pruritus 17 (10%) Rash 16 (10%)	Arthralgia 13 (8%) Nephritis 2 (≤1%)	Arthralgia 1 (≤1%) Pruritus 1 (≤1%) hypoT 1 (≤1%) ASAT 2 (≤1%); ALAT 2 (≤1%)	0	ASAT 2 (≤1%) Endocrine 2 (≤1%) Neurologic/ Pulmonary 2 (≤1%)
Le et al., 2015 [16]	NA 58%	Diarrhea 10 (24%)	ALAT 3 (7%)	HypoT/hypophysitis 4 (10%)	1 (2%)	Rash/pruritus 10 (24%)	Anemia 8 (20%) Arthralgia 7 (17%) Myalgia 6 (15%) Pancreatitis 6 (15%)	Anemia 7 (17%) Diarrhea 2 (5%) ALAT 2 (5%)	0	NA
Postow et al., 2015 [17]	*N*+I 64 66%	Diarrhea 42 (45%) Colitis 22 (23%)	ASAT 20 (21%) ALAT 21 (22%)	HypoT 15 (16%) hypophysitis 11 (12%)	10 (11%)	Rash 57 (60%) Pruritus 33 (35%) Vitiligo 10 (11%)	Arthralgia 10 (11%) Myalgia 9 (10%)	Diarrhea 10 (11%); Colitis 16 (17%) Rash 8 (9%); Pruritus 1 (≤1%) ALAT 10 (11%); ASAT 7 (7%) Hypophysitis 2 (2%) PNP 2 (2%)	1 (PNP)	NA
Robert et al., 2014 [2]	59 61%	NA	NA	NA	NA	NA	NA	Hepatitis 1 (≤1%) Rash 1 (≤1%) Pancreatitis 1 (≤1%) PNP 1 (≤1%) Diarrhea 1 (≤1%) Hypophysitis 1 (≤1%)	0	4 (2%)
Robert et al., 2015 [18]	P2 W 61 58% P3 W 63 63%	Diarrhea 87 (16%) Colitis 15 (3%)	8 (≤1%)	HypoT 52 (9%) hyperT 27 (5%) Hypophysitis 3 (≤1%) Diabetes 2 (≤1%)	6 (≤1%)	Rash 78 (14%) Pruritus 79 (14%) Vitiligo 56 (10%)	Arthralgia 58 (10%) Myositis2 (≤1%) Nephritis 1 (≤1%) Uveitis4 (≤1%)	Diarrhea 10 (2%); colitis 11 (2%) Arthralgia 1 (≤1%) HypoT 1 (≤1%) Hypophysitis 2 (≤1%); diabetes 2 (2%) Hepatitis 8 (≤1%) PNP 1 (≤1%)	0	NA
Wolchok et al., 2013 [19]	*N*+I 58 60% I then N 64 55%	Diarrhea 18 (34%) Colitis 5 (9%)	ASAT 11 (21%) ALAT 11 (21%)	HypoT 2 (4%) HyperT 2 (4%) Hypophysitis 2 (4%) Adrenal 2 (4%)	3 (6%)	Rash 37 (70%) Pruritus 29 (55%) Urticaria 1 (2%) Bullous dermatosis1 (2%)	nephritis 3 (6%)	PNP 1 (2%) hypophysitis 1 (2%) ASAT 7 (13%); ALAT 6 (11%) Diarrhea 3 (6%); colitis 2 (4%) Nephritis 3 (6%) Rash 2 (4%)	0	NA
Borghae et al., 2015 [20]	61 52%	Diarrhea 22 (8%)	ASAT 3% ALAT 3%	HypoT (7%)	(3%)	Rash (9%) pruritus (8%) erythema (≤1%)	Anemia 6 (2%) Myalgia 7 (2%) Neutropenia 1 (≤1%)	Diarrhea 2 (≤1%) Myalgia 1 (≤1%) Anemia 1 (≤1%)	1 (encephalitis)	PNP (≤1%)

A systematic review of the literature was conducted over the period 2013-2016, using the following key words: safety; Side effects; Adverse events; anti-pd1; anti-pd-1; Pembrolizumab; Lambrolizumab; Nivolumab. Original articles (clinical trials) in the English language with full-text accessibility were selected; Journal articles and metaanalyses excluded; as well as trials that studied immunotherapy in combination with conventional treatment. Adrenal: adrenal insufficiency; HypoT: hypothyroidism; HyperT: hyperthyroidism; I: ipilimumab; M+: metastasis; MM: multiple melanoma; N: nivolumab; NA: not available; NRP: neuropathy; NSCLC: non-small cell lung cancer; ORR: objective response rate; PNP: pneumopathy; R: refractory;CR: complete response; GR: global response = CR + PR; PR: partial response; W: every x week.

[a] The incidence of OASIs is provided with the number (*n*) when available and/or% of patients but in some trials only "frequent" was reported; Corresponding to an incidence> 3 to 5%.

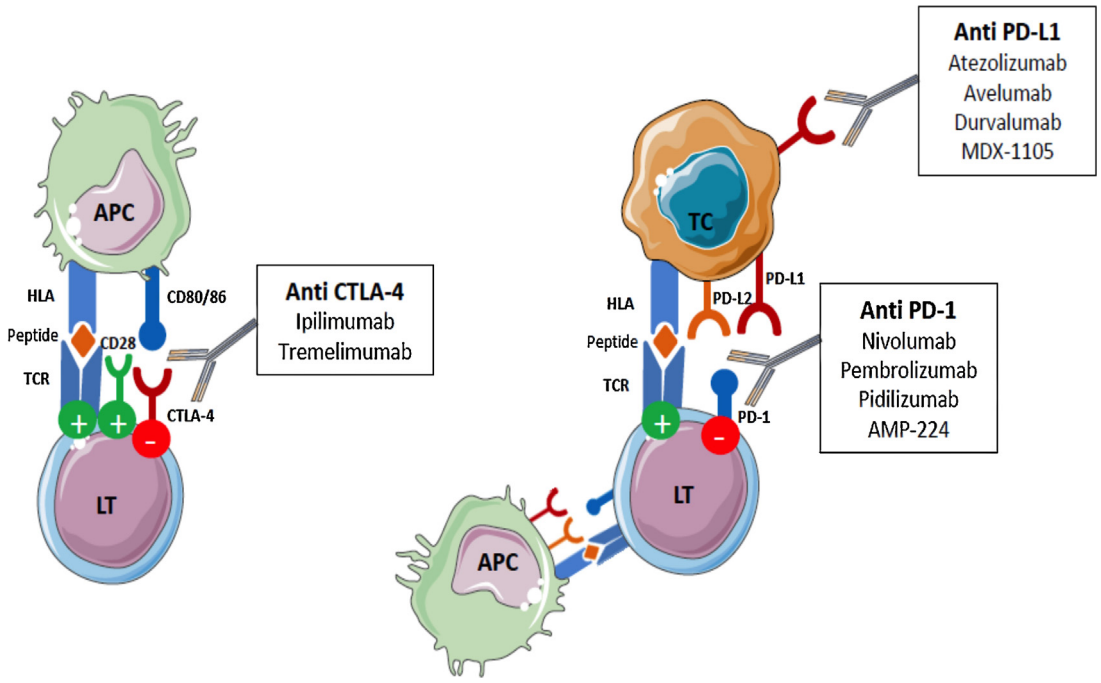

Fig. 1. Checkpoint inhibitors. In some cancers, tumoral microenvironment partially inhibits the targeted immune response generated by the tumor antigen, normally presented by the major histocompatibility complex (HLA) and recognized via TCR. This inhibition of T lymphocyte activation involves the expression of "checkpoint inhibitors" such as CTLA-4, induced on the surface of the T lymphocyte after recognition of the tumor antigen. Another mechanism is the expression of PD-L1 and/or PD-L2 by tumor cells and antigen-presenting cells, which interact with the PD-1 receptor expressed on the lymphocytes. This results in T cell apoptosis, inhibition of cytokine production and immunosuppression that will facilitate tumor survival and growth [21,22]. The therapeutic monoclonal antibodies that bind to the T-cell CTLA-4 or PD-1 receptors therefore block their interaction with the CD80/86 or PD-L1/-L2 ligands and potentiate the anti-tumor cytotoxic T lymphocyte response. Anti-PD-L1 monoclonal antibodies are also in clinical development. APC: Antigen Presenting Cell; CTLA-4: Cytotoxic T-Lymphocyte Associated Protein 4; HLA: Human Leukocyte Antigen; LT: T lymphocyte; PD-1: Programmed Death receptor; PD-L1/L2: Programmed Death-Ligand; TC: Tumoral Cell; TCR: T Cell Receptor.

by loss of peripheral tolerance. Recently, mechanisms of cancer immunotherapy have been developed in the journal and will not be discussed in detail (Fig. 1) [23]. The purpose of this article is to present an update on these opportunistic autoimmune manifestations secondary to cancer immunotherapy by specialists using immunotherapy for the treatment of severe autoimmune diseases.

1.2. Terminology

In literature, the side effects of immunotherapy have been reported with different terminology (e.g. adverse effects of special interest) but with a recent consensus on the term "Immune-Related Adverse Events" (irAEs) [24,25]. While using a common terminology makes sense, reported irAEs include both induced autoimmune manifestations and other "immunological" effects such as tumor progression or paradoxical worsening of opportunistic infections, similarly observed during an immune reconstitution syndrome. Therefore, identifying the manifestations of "Opportunistic Autoimmunity Secondary to Cancer Immunotherapy" (OASI) within irAEs will be worthwhile, in order to use a specific term referring to the pathogenesis of this new type of side effects.

2. OASIs: reported autoimmune manifestations

2.1. Background

The use of checkpoint inhibitors in trials and now in clinical practice gives us a more accurate picture of the broad spectrum of OASIs. Regarding the incidence rate, we must keep in mind biases related to exclusion of patients with pre-existing autoimmune diseases for clinical trials and the use of monotherapy in most trials. A systematic literature review was conducted to identify OASIs occurring with PD-1 pathway inhibitors (see Methods, Tables 1 and 2) to complete the one with anti-CTLA4 recently published by our group [26]. OASIs reported during clinical trials mainly concerned gastrointestinal tract, skin, endocrine glands, liver and lung (Table 1), but can affect nearly all organs, as reported in "real life" series (out of trial setting).

Both systemic and organ-specific autoimmune manifestations have been reported. Recently, rare and various OASIs are being reported with the growing use of checkpoint inhibitors [27–44] (Table 2). Fortunately, occurrence of severe OASIs, mainly gastrointestinal and defined by grade 3 and 4 according to the Common Terminology Criteria for Adverse Events (CTCAE) is not common, especially for patients receiving anti-PD1 monotherapy ($\leq 10\%$). Indeed, OASIs are usually graded 1 or 2 according the CTCAE criteria, involving skin or digestive tract. While incidence of OASIs differed between trials, a recent meta-analysis provided better estimates of severe OASIs. For example, severe pneumonitis occurs in slightly less than 1% of patients [45]. Once again, these data have to be analyzed by taking into consideration the inclusion/exclusion criteria of the corresponding studies.

2.2. OASIs by organs

Dermatological OASIs are by far the most frequent OASIs in melanoma patients receiving checkpoint inhibitors. Vitiligo, erythema, psoriasis, bullous pemphigoid, DRESS syndrome and toxic epidermal necrolysis or Stevens-Johnson syndrome have been described [30,46–48]. Mucosal involvement with sicca syndrome has also been reported, especially with anti-PD-1, with sometimes positivity of antinuclear or La/SSB antibodies [43]. Gastrointestinal OASIs range from diarrhea (frequent with anti-CTLA-4) to inflammatory colitis mimicking both endoscopic and histological aspects of Crohn's disease. Pancreatitis, gastritis and celiac disease have also been reported. The endocrine OASIs observed with anti-PD-1

Table 2
Case reports of OASIs with anti-PD1 (out of trials).

Cases	*n*	Molecule + association	Cancer/stage	Age/gender	Organ involved	Severity NCICTCAE	Delay of onset	Risk Factor for AI	Oncologic response	Stop IT	Treatment of the OASI	Evolution of the OASI
Polat et Donofrio, 2016 [27]	1	N 292 mg/2 W	NSCLC stage IV	65/M	Myasthenia Ab anti-AChR – MuSK –	3	10 days	NA	NA	Yes	Pyridostigmine	+
Lau et al., 2016 [28]	1	P	MM M+	75/M	Myasthenia Ab anti AChR+	4	5 weeks	Myasthenia	Stability	No	NIV CT IVIg	+
Loochtan et al., 2015 [29]	1	N + I	SCLC	70/M	Myasthenia Ab anti-AChR +	5	16 days	NA	NA	Yes	CT PE IVIg	Death
Jour et al., 2016 [30]	5	N 3 mg/kg	Tongue Carcinoma M+	63/M	Bullous Pemphigoïd	2	96 days	0	NA	Yes	CT	+
		P 2 mg/kg	MM	68/M		2	113 days	Psoriasis	TP	Yes	CT	+
		N 3 mg/kg/2W + I	Urothelial cancer M+	74/F		2	112 days	0	PR	Yes	CT	+
		N 3 mg/kg	NSCLC	73/F		2	49 days	0	TP	Yes	CT	-
		N 3 mg/kg	MM	59/M		2	21 days	0	TP	Yes	CT	+
Vandiver et al., 2016 [31]	1	N 3 mg/kg	MM M+	58/F	Nephritis	3	4 days	Hypothyroidism	TP	Yes	CT	+
Hansen et al., 2016 [32]	1	P 2 mg/kg/3W + I*	MM	58/M	Type 1 Diabetes Ab anti-GAD +	3	12 months	NA	PR	Yes	Insuline	+
Alabed et al., 2015 [33]	1	P + I*	MM	57/M	Asymptomatic pancreatitis	2	3 cycles	Previous colitis with I	NA	NA	NA	NA
Danlos et al., 2016 [34]	1	N 3 mg/kg/2 W	Unresectable MM	57/M	Cutaneous and ganglionic granulomatosis	2	10 months	NA	CR	Yes	0	+
Koelzer et al., 2016 [35]	1	N 3 mg/kg/2W + I*	MM	35/F	Pulmonary granulomatosis, meningitis, myocarditis	4	2 months	NA	TP	Yes	CT	-
Läubli et al., 2015 [36]	1	P 2 mg/kg/3W + I*	MM	73/F	Myocarditis with left ventricular dysfunction	4	15 weeks	0	NA	Yes	CT	+
Garel et al., 2016 [37]	2	P 2 mg/kg	MM	88/F	PMR	3	1 day	NA	PR	Temporary	CT	+
		P	MM	79/M		2	3 cycles	NA	PR	No	CT	+
Chan et al., 2015 [38]	2	P 2 mg/kg/3 W	MM M+	60/M	Polyarthritis, seronegative, non-erosive	2	14 months	0	CR	Temporary	SLZ	+

Table 2 (*Continued*)

Cases	*n*	Molecule + association	Cancer/stage	Age/gender	Organ involved	Severity NCICTCAE	Delay of onset	Risk Factor for AI	Oncologic response	Stop IT	Treatment of the OASI	Evolution of the OASI
		P 10 mg/kg/3 W	MM M+	68/F		2	11 months	0	CR	Yes	NSAID HCQ	+ partial
Salmon et al., 2016 [39]	1	P	MM	69/M	Polyarthritis, seronegative	2	NA	NA	NA	Temporary	CT MTX	+
Nair et al., 2016 [40]	1	P + I*	MM M+	52/F	AIHA, Erythroblastopenia	4	3 cycles	Previous hepatitis with I	TP	NA	CT IVIg	+
Kong et al., 2016 [41]	1	N 3 mg/kg/2W + I*	MM	85/M	AIHA	3	2 months	Coombs +	NA	Yes	CT	+
Kanameishi et al., 2015 [42]	1	N 2 mg/kg/3 W	MM	79/F	Immune Thrombocytopenia Ab anti-platelet +	4	6 weeks	NA	NA	NA	CT IVIg romiplostim	+
Cappelli et al., 2016 [43]	12	N	NSCLC	61/M	Sjögren RF+	2	2 months	NA	Stability	No	Pilocarpine	+
		N + I	MM	57/M	Sjögren	2	2 months	NA	TP	No	CT cevimeline	-
		N	MM	74/F	Sjögren (parotitis) Ab anti-SSB+	2	8 months	NA	PR	No	CT cevimeline	+
		N + I	Renal cell carcinoma	58/M	Polyarthritis, seronegative	3	12 months	Previous colitis with IT	Stability	Yes	CT MTX adalimumab	+
		N + I	MM	46/F	Polyarthritis, seronegative, erosive	3	13 months	Previous colitis with I	PR	Yes	CT MTX infliximab etanercept	+
		N + I	NSCLC	62/M	Polyarthritis, seronegative, erosive	2	9 months	NA	Stability	Yes	CT	+ partial
		N + I	MM	35/M	Polyarthritis, seronegative	3	3 months	Previous colitis with IT	Stability	No	CT adalimumab	+
		N	NSCLC	56/M	Polyarthritis Ab anti-SSA+	2	2 months	NA	Stability	No	CT	+
		N + I	MM	66/M	Polyarthritis, seronegative	3	23 months	Previous colitis with IT	PR	No	CT infliximab adalimumab	+
		N + I	SCLC	57/M	Spondyloarthritis HLAB27-	2	8 months	NA	PR	No	CT colchicine	+
		N + I	NSCLC	42/M	Polyarthritis, seronegative	2	3 months	NA	PR	No	Dexamethasone (M+ cerebral)	+
		N	NSCLC	75/F	Polyarthritis, seronegative	NA	5 months	NA	PR	No	NSAID	NA
Ishikawa et Oashi, 2016 [44]	1	N 2 mg/kg/3 W	Advanced MM	55/M	Hypophysitis	3	84 days	NA	Stability	No	Hydrocortisone	+

For clinical cases (excluding trials), a critical review of the literature was conducted (see Table 1) but only the best documented and/or most illustrative of less frequent OASI events and/or non-recommended treatments were selected. Ab: antibody; AI: autoimmunity; AIHA: auto-immune hemolytic anemia; SCLC: small cell lung cancer; CR: complete response; CT: corticosteroid therapy; HCQ: hydroxycholoroquine; I: Ipilimumab (I *: ipilimumab previously administered); IT: immunotherapy (agent not specified); IVIg: intravenous polyvalent immunoglobulins; M + metastasis; MM: multiple melanoma; MTX: methotrexate; N: Nivolumab; NA: not available; NIV: non-invasive ventilation; NSAID: non-steroidal anti-inflammatory drug; NSCLC: non-small cell lung cancer; P: Pembrolizumab; PE: Plasma exchange; PMR: Polymyalgia Rheumatica PR: partial response; RF: rheumatoid factor; SLZ: salazopirin; TP: tumor progression; NCICTCAE: common terminology criteria for adverse events.

affect mainly the thyroid gland with hypothyroidism or, less frequently, hyperthyroidism with usually a spontaneous regression or secondary hypothyroidism. Hypophysitis, (commonly with anti-CTLA-4, rarely reversible [49] and mainly associated with central hypothyroidism), adrenal insufficiency or type 1 diabetes can also occur [32,50,51]. Pulmonary OASIs are represented by inflammatory lung diseases, including sarcoidosis and BOOPs, with various radiological and histological aspects [52], and more rarely pleural effusions. Finally, hepatic OASIs are mostly biological (elevated transaminases) but authentic autoimmune hepatitis are possible, requiring histological documentation.

Less frequent OASIs have also been reported (Table 2), including neurological (peripheral neuropathy, aseptic meningitis, Guillain-Barre syndrome, myelitis, encephalitis, myasthenia gravis), renal (lupus-like glomerulonephritis, granulomatous interstitial nephritis), hematological (hemolytic anemia, thrombocytopenia, neutropenia, aplastic anemia, acquired hemophilia), articular (giant-cell arteritis (GCA)/polymyalgia rheumatica (PMR), lupus, rheumatoid arthritis (RA) (which one treatment option is based on a selective CD28/CD80-86 blockade via CTLA4 molecule), muscular (myositis), cardiac (pericarditis, myocarditis) and ophthalmological (episcleritis, uveitis, retinitis) manifestations.

3. OASIs: risk factors and diagnostic workup

3.1. Risk factors

To date, there is no predictive biomarker (clinical or biological) for OASIs occurrence. However, the optimal management of OASIs is based on their early recognition and some clinical parameters might help to optimize this monitoring. OASIs occur mostly 3 to 6 months after treatment initiation [53]. The median delay also varies according to OASIs nature: dermatological (5 weeks), digestive (7 weeks), hepatic (8 weeks), pulmonary (9 weeks) or endocrine (10 weeks). However, they can occur after a longer period (sometimes more than a year), and even after treatment discontinuation, highlighting the need for prolonged monitoring. Some OASIs seem more specific to the type of cancer, such as vitiligo and melanoma [54], or to the type of molecule (anti CTLA-4 versus PD-1) [55]. Patients receiving combination therapy develop more OASIs than those treated with monotherapy [3]. While a dose effect has been suggested with anti-CTLA-4 [26], no cumulative toxicity has been observed with anti-PD-1 [8]. Finally, identification of patients at highest risk of autoimmunity is important, based on personal and/or familial history of autoimmunity or ongoing active autoimmune disease, but other characteristics such as age or presence of renal/hepatic impairment do not seem to favor OASIs occurrence. So far, screening for OASIs occurrence should be offered similarly to all treated patients.

3.2. Diagnostic workup

In theory, OASIs presentation can mimic any known autoimmune disease (see above). Therefore, the purpose is not to list exhaustively all the clinical manifestations (Tables 1 and 2) or the corresponding diagnostic tests which are well known by internists and other organ specialists, but rather to point out the specificities of OASIs as compared to corresponding autoimmune diseases (Table 3). Indeed, autoantibodies are often missing in OASIs, challenging the differential diagnostic approach (cancer evolution, opportunistic and nosocomial infections, thrombosis.). Moreover, there is no specific radiological presentation and sometimes biopsy is required [56,57]. Referring patients with OASI to an organ specialist or internist has been recommended but only for severe OASIs (grades 3 and 4) [25]. Ideally, we consider that these specialists should be involved also for mild and moderate OASIs when possible, first because these OASIs can progress to more severe manifestations, and second to allow the different specialists in each center to become familiar and gain experience with the entire spectrum of OASIs.

4. OASIs: treatment

4.1. Pre-treatment assessment

The optimal management of OASIs depends on pre-treatment evaluation. This assessment has two aims: to identify risk factors of autoimmunity and to establish baseline (or reference) clinical and paraclinical evaluation before treatment initiation in order to facilitate the distinction between some abnormalities induced by the treatment and those that were pre-existing. The questioning should seek to identify personal or familial history of autoimmunity and suggestive symptoms (e.g. joint pain, digestive disorders), which will be a reference when monitoring treatment. Similarly, laboratory tests including liver, renal, endocrine, as well as electrocardiogram and chest imaging are essential. A pre-immunotherapy workup has been proposed by some expert cancer centers [25]. Apart from screening for thyroid dysfunction, common in the general population, the value of other hormonal measurements before or during follow-up is questionable in the absence of suggestive symptoms. The search for antinuclear antibodies, except for defining a reference value, has no impact on treatment decision. So far, no data demonstrated that their presence could identify a group at higher risk of OASIs. Conversely, it seems interesting to associate this pre-therapeutic assessment with the one proposed before initiation of anti-TNF, since some of these patients may require this biologic agent in case of severe OASIs. In this respect, we propose a minimum pre-therapeutic assessment (Table 4), while recognizing the value of collecting additional parameters in a biological resource center as part of research programs assessing predictive biomarkers.

4.2. Patients with previous autoimmune condition

Pre-therapeutic assessment is even more important for patients already suffering from an autoimmune disease. Owing to a theoretical risk of worsening of the pre-existing autoimmune disease, these patients have been excluded from clinical trials and there are few safety data with checkpoint inhibitors in such patients. Some case reports have been published regarding patients with pre-existing RA, ulcerative colitis (UC), or Behçet's disease successfully treated with ipilimumab (anti CTLA-4) [58]. No worsening of the autoimmune condition was observed and the anticancer effect of immunotherapy was preserved. Conversely, severe relapses of multiple sclerosis or UC were observed in two patients treated with ipilimumab, while improving the outcome of their metastatic melanoma [59,60]. So far, the largest retrospective series of patients with pre-existing autoimmune diseases treated with ipilimumab ($n = 30$) revealed that 50% of patients developed either OASIs or exacerbation of the pre-existing autoimmune disease, which were usually controlled with corticosteroids or increased immunomodulatory treatments [61]. The occurrence of severe OASIs seems less common with the anti-PD-1 in clinical trials comparing pembrolizumab or nivolumab versus ipilimumab in melanoma patients [3,18]. Therefore, anti-PD-1 should probably be preferred for patients with pre-existing autoimmune disease. Recently, pembrolizumab was prescribed successfully in two patients with metastatic melanoma with active autoimmune disease, namely pulmonary vasculitis (Churg-Strauss) and bullous pemphigoid [48,62]. Thus, currently available data do not suggest that a

Table 3
OASIs: diagnostic and therapeutic aspects.

Manifestations	Management				
	Severity Place Immunotherapy Diagnostic tools	Grade 1 Outpatient Continuation	Grade 2 Outpatient Temporary stop[a]	Grade 3 Hospitalisation Stop ± definitive[a]	Grade 4 Hospitalisation
Gastrointestinal Diarrhea Colitis (“Crohn like”)	Stool Calprotectin	Diet + Loperamide Budesonide	Colonoscopy? CT oral 0.5–1 mg/kg[b]	Scanner: perforation? Colonoscopy ++ CT 1–2 mg/kg iv then at D3 CT 1 mg/kg CTR: Infliximab 5 mg/kg (/2 weeks) CTD: AZA	
		< 4 stools/d	4–6 stools/d	> 6 stools/d, ileus, peritoneal irritation	
Hepatic	Auto-Abs often missing		CT oral 0.5–1 mg/kg[b]	CT 1–2 mg/kg then at D3 CT 1 mg/kg CTD: AZA, MMF (500 mg x 2/d)	
		Transaminases < 2.5 N And/or Bilirubin < 1.5 N	Transaminases > 2.5 N and/or Bilirubin > 1.5 N	Transaminases > 5 N and/or Bilirubin > 3 N	
Dermatologic Rash (lupus) Dryness (Sjögren)	Histology (skin, salivary gland) Complement Proteinuria	Anti-histaminics Dermocortisone	CT oral 0.5–1 mg/kg[b] ± HCQ	CT 1–2 mg/kg then at D3 CT 1 mg/kg CTD: AZA, MMF ± HCQ	
		<10% BS	10–30% BS	> 30% BS, surinfections	
Articular	Lupus, RA, Sjögren, GCA/PMR, ANCA.	Analgesics	CT oral 0.2–0.5 mg/kg[b] HCQ	CT 0.5–1 mg/kg CTD: MTX, AZA, anti-TNF	
Pulmonary	Sarcoidosis BOOP		BAL? CT oral 0.5–1 mg/kg[b]	CT 1–2 mg/kg iv then at D3 CT 1 mg/kg CTR: Infliximab 5 mg/kg (/2 weeks)	
		–	Dyspnea	Oxygenotherapy	Intubation
Endocrine Thyroiditis Hypophysitis	Hypothyroidism +++ Hyperthyroidism hypophysary MRIOther hormones	Hormonotherapy ± CT oral 1 mg/kg Treatment of hyperthyroidism ± CT 1 mg/kg		CT 1 mg/kg + Hormonotherapy then at 4 weeks, hydrocortisone 30 mg/j	

AZA: azathioprine; BAL: bronchoalveolar lavage; BS: body surface; CT: corticotherapy; CTR: corticosteroid resistance; CTD: corticosteroid dependence; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; MTX: methotrexate. Therapeutic suggestions based on manufacturers' recommendations (63,64), data from the literature and personal experience of the authors that can be adapted on a case-by-case basis in the absence of prospective data.

[a] Non-mandatory stop for immunotherapy if endocrinopathy, but definitive stop in case of recurrent grade 3 or grade 4.

[b] CT after 1 week, if no improvement after discontinuation of immunotherapy.

Table 4
Pretreatment workup and biological monitoring under immunotherapy.

Before treatment	Specificities	During treatment[a]	After treatment[a]
Complete Blood Count[b]		+	/3 months
Plasmatic proteins electrophoresis[b]		NS	NS
Liver tests[b]		+	/3 months
Serologies HBV, HCV, HIV[b]		NS	NS
Anti-nuclear antibodies ± anti-dsDNA and anti-nuclear antigens[b,c]		NS	NS
Chest X ray[b]	A CT scan is often available during neoplasia evaluation	NS	NS
Tuberculosis test[b]		NS	NS
TSH, T4, anti-thyroid antibodies[d]	Other hormonal testing can be proposed	/1 to 2 months	/3 months
C-reactive protein[d]		+	NS
Blood glucose[d]		+	/3 months
Coagulation tests[d]		+	/3 months
Na, K, HCO3, Ca, serum creatinin, urinary labstick or sample proteinuria/creatininuria ratio[d]		+/1 to 2 months	/3 months

+: at each infusion; NS: no systematic reevaluation.

[a] After treatment initiation, clinical and biological monitoring focuses on the most frequent OASIs, “A.B.C.D.E.” Asat-alat; Breath (Bronchopulmonary); Cutaneous; Digestive (Diarrhea); Endocrine manifestations.

[b] Some patients receiving immunotherapy will develop an OASI and/or relapse of a pre-existingautoimmune disease. They are likely to receive corticosteroid therapy and in some cases, anti-TNF biotherapy. It seems advisable to carry out a pre-therapeutic assessment inspired of the one carried out before anti-TNF treatment.

[c] Some elements of this assessment do not yet have any decisional impact on the implementation of immunotherapy or any predictive value of the occurrence of an OASI and are therefore debatable or carried out for research purposes.

[d] Finally, other parameters are specific to the OASIs encountered under immunotherapy.

pre-existing autoimmune disease should be a systematic exclusion criteria for immunotherapy but estimation of the benefit/risk ratio should be carefully discussed with the patient and the oncologist. Combination therapy should probably be avoided in first line therapy for such patients.

4.3. Treatment of OASIs

The optimal management is based on the earliest possible identification of OASI. The therapeutic challenge is to manage opportunistic autoimmunity while preserving antitumor activity of immunotherapy. There are no prospective studies evaluating the treatment modalities of OASIs. Some recommendations developed by the manufacturers [63,64] as well as by experts [65,66] are available. These resources also provide for each organ the precise definition of OASIs severity based on CTCAE criteria. Indeed, this severity determines the nature and intensity of immunomodulatory treatments to be initiated and the decision to resume (or not) immunotherapy [67]. Overall, grade 1 OASIs are treated symptomatically and do not require discontinuation of immunotherapy. For grade 2 OASIs (moderate toxicity), oral corticosteroids (0.5 to 1 mg/kg) may be proposed if the OASI persists after one week of symptomatic treatment and immunotherapy discontinuation. Finally, for grades 3 or 4 OASIs (severe or life-threatening toxicity), the permanent immunotherapy discontinuation is discussed (except for skin and endocrine OASIs), and treatment with high dose of intravenous corticosteroids ($\geq$ 1–2 mg/kg) is initiated. Patients sensitive to corticosteroids often respond within few days. In this case, after OASI improvement to an equivalent of grade 1, corticosteroid therapy is gradually tapered over one month. Conversely, in case of non-response or worsening, an immunomodulatory treatment with anti-TNF or other immunosuppressant should be initiated according to the affected organ (Table 3). There is no data showing that patients who received such treatments for OASI have a lower tumor response [68,69]. However, the long-term impact of biological or other immunosuppressive drugs on cancer outcome has to be more thoroughly investigated. The decision of outpatient or inpatient treatment (sometimes intensive care unit required) depends on OASI severity together with patient comorbidities and/or the need to rule out a differential diagnosis (e.g. infection, neoplasia progression). Like the need of strong immunosuppressive therapy in the setting of conventional autoimmune pathologies, the issue of opportunistic infections prophylaxis arises. For *Pneumocystis carinii* pneumonia (PCP), prophylactic sulfamethoxazole-trimethoprim administration should be discussed considering past anti-cancer treatments. Some groups suggest systematic prophylaxis but these recommendations are not evidence-based and may still allow a more individualized approach to avoid sulfamethoxazole-trimethoprim toxicities (cutaneous, digestive, hematological). Some oncologists rely on US guidelines suggesting prophylaxis (sulfamethoxazole trimethoprim-, atovaquone or pentamidine) for patients treated with corticosteroids > 20 mg/day for 4 weeks [70,71]. Corticosteroid treatment should be as short as possible and in regard to endocrine manifestations may even be questionable owing to the effectiveness of hormone replacement therapy and the very low probability that steroids will avoid the use of hormone therapy. There are no recommendations for fungal or viral prophylaxis. TNF antagonists should be reserved for severe manifestations but they have the advantage of faster immunosuppressive action. Infliximab is initiated at 5 mg/kg in case of no improvement, sometimes after only 3 days of intravenous high-dose corticosteroids, and a second dose of 5 mg/kg may be administered after 2 weeks if necessary. For some OASIs of mild/moderate severity and for which manifestations suggest a potential benefit of hydroxychloroquine (HCQ) in addition to corticosteroids (e.g. arthralgia, arthritis), such association can be proposed, especially with the "favorable" benefit/risk profile of HCQ from a neoplastic perspective [72]. Regarding the resuming of immunotherapy, it is conditioned by the improvement of severe manifestations to grade 1 or less, a significant decrease of corticosteroids (< 10 mg/day) and the absence of permanent immunosuppression. In practice, some patients have been retreated after severe pneumonia without relapses, while, more rarely, some patients relapsed when corticosteroids were stopped even if immunotherapy had not been resumed [45,52]. Preliminary data suggest that a patient who developed OASI under anti-CTLA-4 can be treated with anti-PD-1 without occurrence of a new OASI [73].

5. OASIs: perspectives

5.1. New therapeutic approaches

Despite the sustainable tumor response observed with checkpoint inhibitors, a significant proportion of patients do not respond to these treatments. Several new strategies should allow better clinical outcomes in these non-responder patients. Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) showed a higher response rate and more sustained response than either agent alone. However, such a combination also tends to increase the OASIs severity, especially diarrhea, colitis and hepatitis. In the landmark study, the need for immunomodulatory agents was reported for 83% of patients with OASIs in the combination group versus only half of patients treated with ipilimumab or nivolumab alone [3]. Most of these OASIs were manageable and no manifestation seemed specifically related to the combination strategy. The combination of a checkpoint inhibitor with conventional chemotherapy or targeted therapy such as BRAF, MEK or other small molecule inhibitors is also being studied [74–77]. Radiation therapy is another attractive synergistic, by inducing multiple immunomodulatory effects on both the tumor and its microenvironment [78].

Finally, new immunomodulatory monoclonal antibodies are being developed to overcome the resistance to the first generation of checkpoint inhibitors. Of note, promising preclinical anti-OX40 antibody agonists, which activate the costimulatory signal on T cells, and are being tested in early-stage clinical trials [79]. Some of these new therapeutic strategies will likely be validated in the near future for a wide range of cancers, with the common goal of enhancing the anti-tumor immunity but thereby the occurrence of OASIs. There are potentially so many combinations to test that using mathematical modelling tools will be valuable to guide the selection and timing of future combinations [80].

5.2. Predictive biomarkers for OASIs

Given that a significant proportion of patients receiving immunotherapy will develop OASI, research on the identification of predictive biomarkers of severe autoimmune toxicity is needed. [81] Indeed, early identification of patients who may be predisposed to develop OASIs could promote their early detection or even the development of preventive strategies. To date, most studies have focused on tumor biomarkers predictive of treatment response [82]. Regarding OASI biomarkers, some studies assessed the genetic variants of CTLA-4. Some variants appear to influence treatment response with improved overall survival and without evidence of autoimmunity [83,84]. PD-1 and CTLA-4 polymorphisms are also associated with various autoimmune diseases such as RA, lupus, diabetes, thyroiditis [85]. Some OASIs clearly share the clinical features of these diseases and further

research should focus on these possible genetic predisposition [86]. Recent findings also showed that microbiota-associated biomarkers correlated with lower occurrence of anti-CTLA-4-induced colitis [87]. An increased proportion of *Bacteroidetes phylum* was found in the patients "resistant" to the onset of colitis, possibly related to an immunomodulatory role of these bacteria through stimulation of Treg differentiation. If validated in larger series, this data could help to identify a subgroup of patients at higher or lower risk of colitis, with the possible evaluation of preventive interventions. Other biological markers associated with the occurrence of OASIs, especially digestive, have been identified in peripheral blood such as increased eosinophils [88,89], IL-17 [90], CD177 expression and CEACAM1 genes and a high infiltration of the lamina propria by neutrophils in the colon during treatment [91]. Another group assessed blood transcriptome of patients with melanoma and identified differential gene expression in patients prone to develop gastrointestinal OASIs [92]. Finally, some studies correlated the immune tumor phenotype with treatment response, but these data were not used in regard to OASIs occurrence.

5.3. Registries and multidisciplinary approach

The spectrum of OASIs is extremely broad and its incidence is probably higher than suspected clinically. An autopsy study of a patient with melanoma treated with ipilimumab and nivolumab identified asymptomatic lymphocytic myocarditis, and inflammatory lesions of the central nervous system, liver and bone marrow [35]. This observation highlights for the first time the potential presence of sub-clinical and diffuse inflammation induced by these agents. Thus, physicians of all specialties can be confronted to OASIs. Oncologists are encouraged to develop a local network with organ specialists trained to manage OASIs, as a collaborative approach will help to reduce morbidity and to guide therapeutic interruptions [25]. Multidisciplinary meetings dedicated to OASIs management might be developed in the future. Immunotherapy including the use of the checkpoint inhibitors is now entering routine practice and the number of patients developing OASIs will rapidly increase. National registries set up to collect cases of malignancies and opportunistic infections in patients receiving biologics in RA and other autoimmune diseases could be an example to follow [93]. Moreover, the establishment of a biological collection/database seems essential. This would provide additional real life data to those from clinical trials and can be the basis for translational research. In addition, long-term monitoring of these patients would answer some clinical questions, such as the impact of immunosuppressive drugs/biologics on cancer and pre-existing autoimmune disease evolution under immunotherapy. In France, the national pharmacovigilance registry Registry of Severe Adverse Effects of Monoclonal Antibodies in Cancer Immunomodulators (REISAMIC) is now available to report serious adverse events related to immunotherapy [25].

6. Conclusion

OASIs are relatively common, usually benign and easily managed, therefore not compromising the oncologic benefit obtained for some patients with extensive and/or refractory neoplasms. However, potential severity justifies an early OASIs detection, which can be facilitated by a pre-treatment workup and a close/systematic clinical and laboratory monitoring. Collaboration between oncologists, internists and organ specialists for the diagnosis and treatment of these induced autoimmune manifestations is worthwhile. Development of validated therapeutic algorithms and predictive biomarkers for the onset of OASIs represents future research priorities.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.revmed.2017.01.004.

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