Le manifestazioni reumatologiche da Checkpoint inibitori

Enrico Fusaro

S.C. Reumatologia AO Città della Salute e della Scienza di Torino

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

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APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

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Immune checkpoint inhibitors Immunotherapy has emerged as a new pillar in the treatment of cancer and has transformed outcomes of patients with previously untreatable malignancies.

Khalil DN et Al. Nat Rev Clin Oncol 2016;13:394
Horn L et Al. , J Clin Oncol Conf 2016;34:15_suppl.

Unlike traditional chemotherapy, which commonly has the secondary effect of immunosuppression, modern immunotherapy aims at up-regulating the immune system to augment antitumor responses.

Immune checkpoint inhibitors (ICI) have emerged as one of the most promising forms of immunotherapy

Topalian SL et Al. Cancer Cell 2015;27:450-61

Table 1 | **FDA-approved checkpoint inhibitors for cancer immunotherapy**

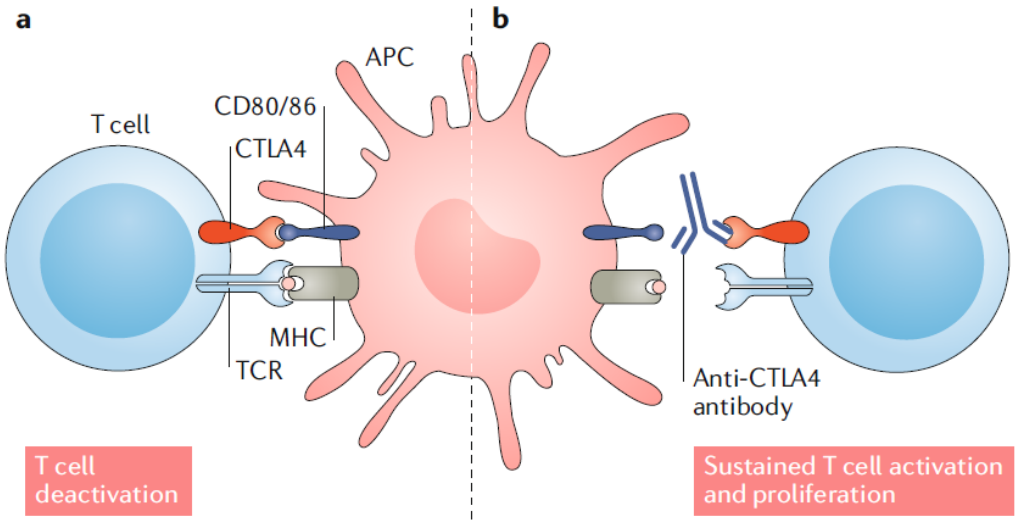
Therapeutic	Molecular target	Indication	Year of FDA approval[110]
Nivolumab	PD-1	Melanoma	2013
		NSCLC	2014
		Renal cell carcinoma	2015
		Hodgkin lymphoma	2016
		Head and neck cancer	2016
		Urothelial carcinoma	2017
		Hepatocellular carcinoma	2017
		Microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer	2017
Pembrolizumab	PD-1	Melanoma	2014
		NSCLC	2015
		Hodgkin lymphoma	2017
		Urothelial carcinoma	2017
		Head and neck cancer	2017
		PD-L1$^+$ gastric and gastroesophageal junction adenocarcinoma	2017
		Microsatellite instability-high or mismatch repair-deficient solid tumours	2017
Atezolizumab	PD-L1	Urothelial carcinoma	2016
		NSCLC	2016
Durvalumab	PD-L1	Urothelial carcinoma	2017
Avelumab	PD-L1	Merkel cell carcinoma	2017
		Urothelial carcinoma	2017
Ipilimumab	CTLA4	Melanoma	2011
		Melanoma in combination with nivolumab	2014

Rheumatic immune-related adverse events from cancer immunotherapy

Leonard H. Calabrese[1], Cassandra Calabrese[1] and Laura C. Cappelli[2]*

Immune checkpoint inhibitors increase antitumor activity by blocking intrinsic down-regulators of the immune system, including **cytotoxic T-lymphocyte-associated antigen 4** (**CTLA-4**), **programmed death protein-1** (**PD-1**) and **programmed death ligand-1** (**PD-L1**)

CTLA-4

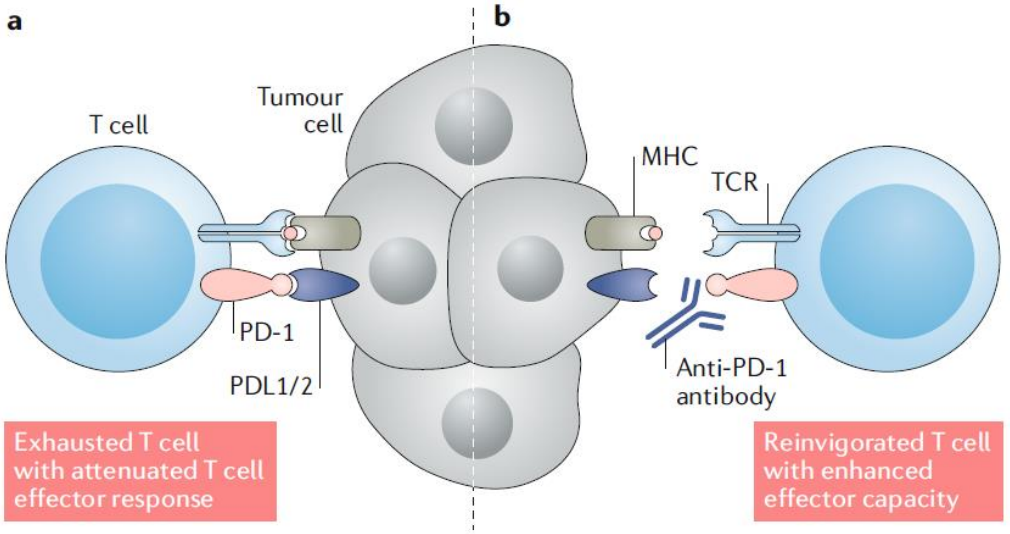


inhibitory signal to activated T-cells at a proximal step in the immune response, by preferentially binding to CD80/86 expressed by antigen presenting cells (APCs), thereby blocking the second signal required for T cell activation.

CTLA-4 Blockers

Reduction of the suppression of effector T cells (CD8+)

Immune checkpoint inhibitors increase antitumor activity by blocking intrinsic down-regulators of the immune system, including **cytotoxic T-lymphocyte-associated antigen 4** (**CTLA-4**), **programmed death protein-1** (**PD-1**) and **programmed death ligand-1** (**PD-L1**)



chronic infection or cancer

↓

enhanced expression of PD-1

↓

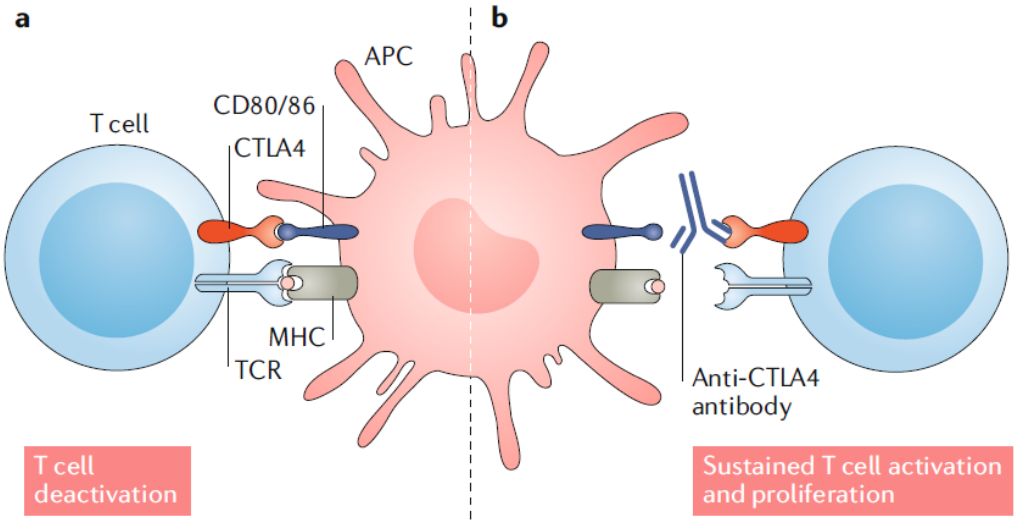
T cell inhibition in the peripheral Tissues

↓

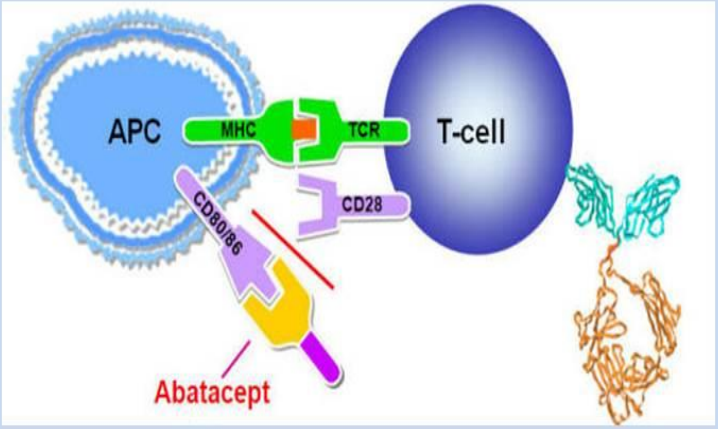
T cell exhaustion

The binding of PD-1 to its ligands, PD-L1 and PD-L2 (which are expressed by many tumor cells) interferes with downstream signalling and can lead to T cell exhaustion.

Antibodies that block the interaction of PD-1 with PD-L1/PD-L2 serve to neutralize this checkpoint, restoring T cell effector function



Abatacept Mechanism of Action



Abatacept modulates the immune response by bonding to CD80/CD86 on an antigen-presenting cell (APC), such as a dendritic cell, thus preventing costimulatory binding of CD28 on naïve T cells and attenuating T-cell activation.

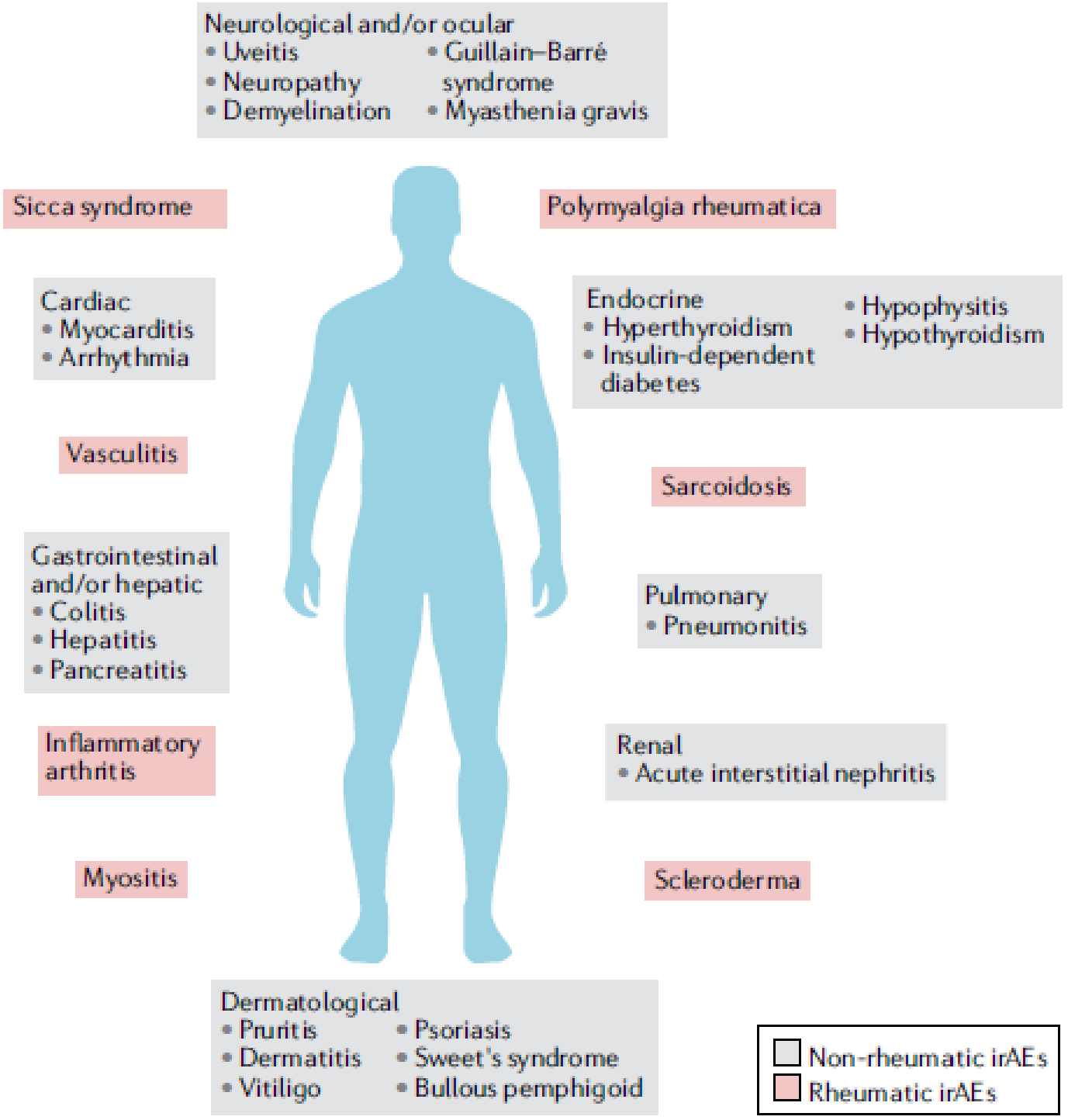

Neurological and/or ocular
• Uveitis
• Neuropathy
• Demyelination
• Guillain–Barré syndrome
• Myasthenia gravis
Sicca syndrome
Polymyalgia rheumatica
Cardiac
• Myocarditis
• Arrhythmia
Endocrine
• Hyperthyroidism
• Insulin-dependent diabetes
• Hypophysitis
• Hypothyroidism
Vasculitis
Sarcoidosis
Gastrointestinal and/or hepatic
• Colitis
• Hepatitis
• Pancreatitis
Pulmonary
• Pneumonitis
Inflammatory arthritis
Renal
• Acute interstitial nephritis
Myositis
Scleroderma
Dermatological
• Pruritis
• Dermatitis
• Vitiligo
• Psoriasis
• Sweet's syndrome
• Bullous pemphigoid
Non-rheumatic irAEs
Rheumatic irAEs

Table 1. Summary of Safety During the Overall Study Period

AE	Nivolumab Plus Ipilimumab (N = 448), No. (%)	
	Any Grade	Grade 3/4
Any treatment-related AE	425 (94.9)	248 (55.4)
Any AE in ≥ 10% of patients		
Diarrhea	197 (44.0)	44 (9.8)
Fatigue	164 (36.6)	18 (4.0)
Pruritus	158 (35.3)	7 (1.6)
Rash	155 (34.6)	17 (3.8)
Nausea	111 (24.8)	8 (1.8)
Pyrexia	85 (19.0)	5 (1.1)
Increased ALT	82 (18.3)	40 (8.9)
Increased AST	76 (17.0)	27 (6.0)
Decreased appetite	68 (15.2)	4 (0.9)
Hypothyroidism	69 (15.4)	1 (0.2)
Vomiting	63 (14.1)	9 (2.0)
Colitis	57 (12.7)	39 (8.7)
Arthralgia	53 (11.8)	1 (0.2)
Maculopapular rash	53 (11.8)	9 (2.0)
Increased lipase	55 (12.3)	38 (8.5)
Headache	50 (11.2)	4 (0.9)
Any AE that led to discontinuation	160 (35.7)	126 (28.1)
Any AE in ≥ 1% of patients		
Colitis	37 (8.3)	30 (6.7)
Diarrhea	31 (6.9)	25 (5.6)
Increased ALT	22 (4.9)	20 (4.5)
Increased AST	19 (4.2)	17 (3.8)
Increased transaminases	7 (1.6)	6 (1.3)
Pneumonitis	10 (2.2)	5 (1.1)
Hepatotoxicity	6 (1.3)	4 (0.9)
Any treatment-related select AE	392 (87.5)	186 (41.5)
Select AE by category and any AE in ≥ 10% patients		
Skin	288 (64.3)	33 (7.4)
Pruritus	158 (35.3)	7 (1.6)
Rash	155 (34.6)	17 (3.8)
Maculopapular rash	53 (11.8)	9 (2.0)
Vitiligo	38 (8.5)	0
GI	209 (46.7)	73 (16.3)
Diarrhea	197 (44.0)	44 (9.8)
Colitis	57 (12.7)	39 (8.7)
Endocrine	133 (29.7)	21 (4.7)
Hypothyroidism	69 (15.4)	1 (0.2)
Hypophysitis	38 (8.5)	8 (1.8)
Hyperthyroidism	37 (8.3)	3 (0.7)
Hepatic	129 (28.8)	76 (17.0)
Increased ALT	82 (18.3)	40 (8.9)
Increased AST	76 (17.0)	27 (6.0)
Pulmonary	34 (7.6)	6 (1.3)
Pneumonitis	31 (6.9)	6 (1.3)
Renal	20 (4.5)	7 (1.6)

NOTE. Select AEs are defined as having a potential immunologic cause that needs frequent monitoring and potential intervention with immune suppression and/or endocrine treatment.
Abbreviation: AE, adverse event.

Sznol M et Al. J Clin Oncol 2017; 35:1-11

Table 2 | **Comparison of major rheumatic irAEs with corresponding rheumatic diseases**

Rheumatic irAE	Rheumatic disease comparator	Similarities to rheumatic disease	Differences from rheumatic disease
Inflammatory arthritis	RA	• Can cause erosive disease • Many patients with similar joint distribution (MCPs, PIJs, wrists and knees)	• Tendon involvement more prominent early in course of disease • Early erosions • RF and CCP often negative • Not female-predominant
	SpA and PsA	• SpA features such as inflammatory back pain, enthesitis and dactylitis • Sterile urethritis and conjunctivitis with oligoarthritis (reactive arthritis-like)	• Concomitant psoriasis rarely reported • HLA-B27-positivity not reported • Early erosions
Polymyalgia rheumatica and/or GCA	Polymyalgia rheumatica and/or GCA	• Biopsy findings in GCA-like irAEs similar to the rheumatic disease comparator • Patients aged >50 years	• Patients with polymyalgia rheumatica-like disease do not always have elevated inflammatory markers • Some patients with polymyalgia rheumatica-like disease not responsive to low-dose prednisone
Inflammatory myopathy	Dermatomyositis, polymyositis and immune-mediated necrotizing myopathy	• Range of creatine kinase is 10–100 IU/l (upper limit of normal) • Biopsy results are consistent with dermatomyositis, polymyositis or immune-mediated necrotizing myopathy • Can have myasthenia with myositis	• Classic dermatomyositis rash rare • Response to intravenous immunoglobulin may be less effective in irAE
Sicca syndrome	Sjogren syndrome	• Dry mouth responds to treatment with sialagogues • Dry mouth and eyes common	• anti-Ro and anti-La antibodies rare • Rare parotitis

Clinical Trials
Arthralgias 1-43%
Myalgias 2-20%

PMRlike (shoulder and pelvic girdle stiffness)

Small joint symmetric inflammatory arthritis (predominantly hand) with diffuse tenosynovitis

Large joint, asymmetric oligoarthritis, predominantly involving the knees.

Reactive arthritis-like triad (urethritis, conjunctivitis, and arthritis)

Psoriatic arthritis

no gender predilection reported

- Seronegative

can often become chronic, despite stopping immunotherapy, unlike other irAE, such as colitis and pneumonitis

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journal homepage: www.elsevier.com/locate/semarthrit

Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen

Laura C. Cappelli, MD[a,*], Julie R. Brahmer, MD[b], Patrick M. Forde, MBBCh[b], Dung T. Le, MD[b], Evan J. Lipson, MD[b], Jarushka Naidoo, MBBCh[b], Lei Zheng, MD, PhD[b], Clifton O. Bingham III, MD[a,1], Ami A. Shah, MD[a,1]

Demographic and clinical variables at initial evaluation

	All patients (n = 30)	PD-1/PD-L1 monotherapy (n = 16)	Combination CTLA-4/PD-1 therapy (n = 14)	p Value[a]
Age: median (IQR)	59 (54–68)	65 (55–73)	57.5 (45–59)	**0.01**
Female sex: N (%)	12 (40%)	9 (56.3%)	3 (21.4%)	0.07
Tumor type: N (%)	Melanoma: 7 (23.3%) NSCLC: 12 (40%) Other: 11 (36.7%)	Melanoma: 1 (6.3%) NSCLC: 9 (50%) Other: 6 (37.5%)	Melanoma: 6 (42.9%) NSCLC: 3 (21.4%) Other: 5 (35.7%)	0.04
Complete tumor response[c]: N (%) N = 29	Yes: 10 (34.5%)	Yes: 6 (40%)	Yes: 4 (26.7%)	0.70
First joint/s affected: N (%)	Knee: 17 (56.7%) Other large: 7 (23.3%) Small joint/s: 6 (20%)	Knee: 7 (43.8%) Other large: 3 (18.8%) Small joint/s: 6 (37.5%)	Knee: 10 (71.4%) Other large: 4 (28.6%) Small joint/s: 0 (0%)	**0.03**
# Swollen joints: median (IQR)	7 (4–10)	8.5 (5–10.5)	6 (4–10)	0.50
Reactive arthritis triad: N (%)	Yes: 3 (10%)	Yes: 0 (0%)	Yes: 3 (23.0%)	0.08
CRP (mg/dL) median (IQR)	2.6 (0.2–7.2)	0.5 (0.2–3.5)	4 (0.5–9.2)	**0.03**
Additional irAE present: N (%)	None: 10 (33.3%) 1 irAE: 12 (40%) $>$1 irAE: 8 (26.7%)	None: 7 (43.8%) 1 irAE: 7 (43.8%) $>$1 irAE: 2 (12.5%)	None: 3 (21.4%) 1 irAE: 5 (35.7%) $>$1 irAE: 6 (42.9%)	0.18
Types of additional irAE[b]	Colitis: 10 Thyroid disease[d]: 5 Pneumonitis: 4 Hypophysitis: 2 Rash: 4 Sicca: 3	Colitis: 2 Thyroid disease: 2 Pneumonitis: 3 Rash: 2 Sicca: 1 Pancreatitis: 1	Colitis: 8 Thyroid disease: 3 Pneumonitis: 1 Hypophysitis: 2 Rash: 2 Sicca: 2 Myocarditis: 1	
Time to first irAE Dx (months): median (IQR) Total, N = 22	3 (1.3–12)	10 (3–16)	2 (1–4.25)	0.20
Time to IA Sx (months): median (IQR)	5 (2–8)	3.5 (1.5–7)	5.75 (5–8)	0.20
Time to IA Dx (months): median (IQR)	9 (4–17)	7 (3.5–19)	9.5 (6–16)	0.72
IA as 1st IRAE: n (%)	16 (53.3%)	12 (75%)	4 (28.6%)	**0.03**
CCP positive: n (%)	1 (3.3%)	1 (6.3%)	0 (0%)	1.0
RF positive: n (%)	1 (3.3%)	1 (6.3%)	0 (0%)	1.0
ANA positive: n (%)	2 (6.7%)	2 (12.5%)	0 (0%)	0.49

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Rheumatic & Musculoskeletal Diseases

CLINICAL CASE

Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity

C Calabrese,[1,2] E Kirchner,[1,2] A Kontzias,[1,2] V Velcheti,[1,3] L H Calabrese[1,2]

Table 3 Clinical phenotypes of inflammatory arthritis

Patient	Joint pattern	Symmetrical	Tenosynovitis
1	PIPs, MCPs, wrists, elbows, knees	Yes	
2	Generalised involvement of small hand joints	Yes	Yes
3	PIPs, MCPs, PIPs, elbows, knees, ankles, feet, toes	Yes	
4	PIPs, MCPs, ankles, knees	Yes	
5	PIPs, MCPs, wrists, knees	Yes	
6	Generalised involvement of small hand joints, wrists	Yes	
7	Generalised involvement of small hand joints, left knee	No	Yes

MCP, metacarpal phalangeal joints; PIP, proximal interphalangeal joint.

OP0335

A PROSPECTIVE CLINICAL AND MRI STUDY OF IMMUNE CHECKPOINT INHIBITOR (ICI)-INDUCED MUSCULOSKELETAL MANIFESTATIONS MYO-FASCIITIS AND NOT SYNOVITIS IS THE PROMINENT IMAGING FINDING

Dimitrios Daoussis[1], Alexandra Filippopoulou*[1], Pantelis Kraniotis[2], Spyridoula Theodoraki[3], Rafaella Argiriadi[3], Thomas Makatsoris[3], Angelos Koutras[3], Aikaterini Solomou[2], Haralampos Kalofonos[3], Stamatis-Nick Liossis[1]. [1]*Patras University Hospital, University of Patras Medical School, Rheumatology, Patras, Greece;* [2]*Patras University Hospital, University of Patras Medical School, Radiology, Patras, Greece;* [3]*Patras University Hospital, University of Patras Medical School, Oncology, Patras, Greece*

eular EUROPEAN CONGRESS OF RHEUMATOLOGY 2019 | 12–15 JUNE MADRID

Annual European Congress of
RHEUMATOLOGY
EULAR 2019
Madrid, 12-15 June 2019
Abstracts

Results: During the study period a total of 130 patients were treated with ICI. Of those, 10 (7.7%) developed ICI-induced musculoskeletal manifestations. They suffered from lung (n=4), bladder (n=3), renal cancer (n=2) or melanoma (n=1) and received treatment with nivolumab (n=7), pembrolizumab (n=1), durvalumab (n=1) and atezolizumab (n=1). They were mostly male (n=8) with a mean ± SEM age of 66.7 ± 2.6 years. The median (range) time from ICI treatment since development of symptoms was 2.5 (1-22) months. Autoantibodies (RF/ACPA/ANA) were negative in all patients and only 3/10 had a mild/moderate increase of inflammatory markers at disease onset. Three different pattems of musculoskeletal manifestations were found: i) Prominent joint involvement (n=3). Areas involved were the small joints of the hands (n=2) and knee/ankle (n=1). The MRI

Conclusion: In our cohort ICI-induced musculoskeletal manifestations were not uncommon and developed in 7.7% of patients. Imaging evidence of myo-fasciitis was found in all patients indicating that the muscle/fascia is more frequently involved than the synovium. Our clinical and imaging data point to the direction that ICI-induced musculoskeletal manifestations mostly involve periarticular structures and associate mainly with myo-fasciitis and not synovium based pathology

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.5029

CONCISE COMMUNICATION

DOI 10.1002/art.38282

Drug-associated polymyalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of CTLA-4

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 3, March 2014, pp 768–769

CASE REPORT

MAYO CLINIC

CrossMark

Scleroderma Induced by Pembrolizumab: A Case Series

Naiara S. Barbosa, MD; David A. Wetter, MD; Carilyn N. Wieland, MD; Niraj K. Shenoy, MBBS; Svetomir N. Markovic, MD, PhD; and Uma Thanarajasingam, MD, PhD

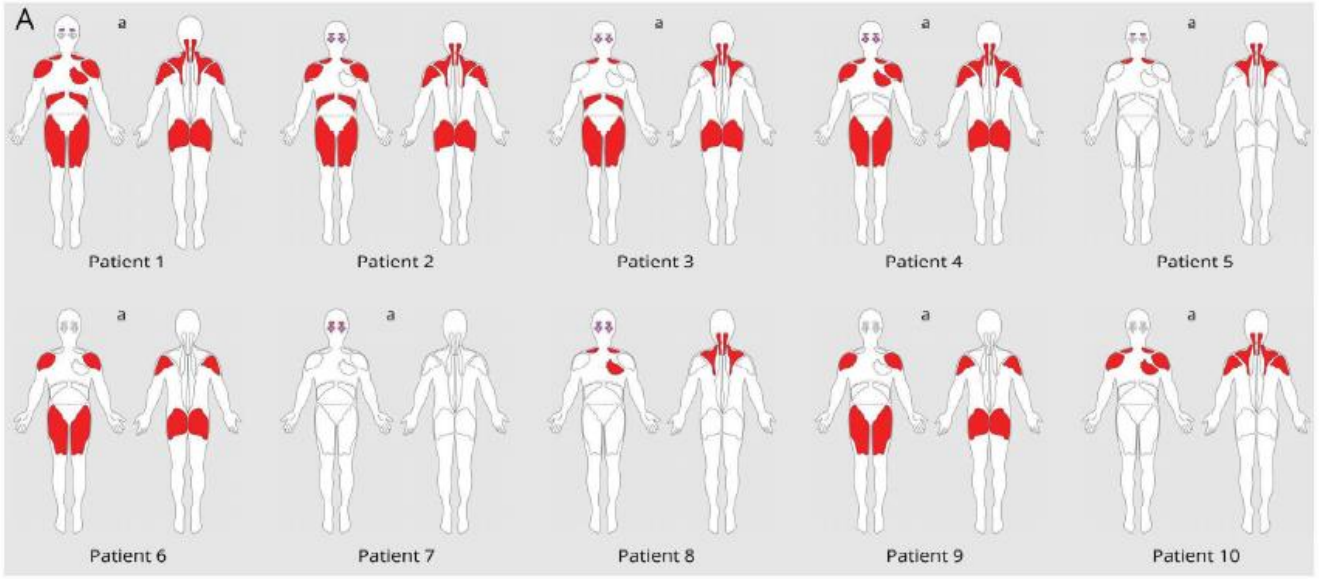
ARTICLE

Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer

Mehdi Touat, MD, Thierry Maisonobe, MD, Samuel Knauss, MD, Omar Ben Hadj Salem, MD, Baptiste Hervier, MD, PhD, Karine Auré, MD, PhD, Tali-Anne Szwebel, MD, Nora Kramkimel, MD, Claire Lethrosne, MD, Jean-Frédéric Bruch, MD, Pauline Laly, MD, Jacques Cadranel, MD, PhD, Nicolas Weiss, MD, PhD, Anthony Béhin, MD, Yves Allenbach, MD, PhD, Olivier Benveniste, MD, PhD, Timothée Lenglet, MD, Dimitri Psimaras, MD, Werner Stenzel, MD, PhD,* and Sarah Léonard-Louis, MD*

Correspondence
Dr. Touat
mehdi.touat@gmail.com
or Dr. Stenzel
werner.stenzel@charite.de
or Dr. Leonard-Louis
sarah.leonard-louis@aphp.fr

Neurology® 2018;91:e985-e994. doi:10.1212/WNL.0000000000006124



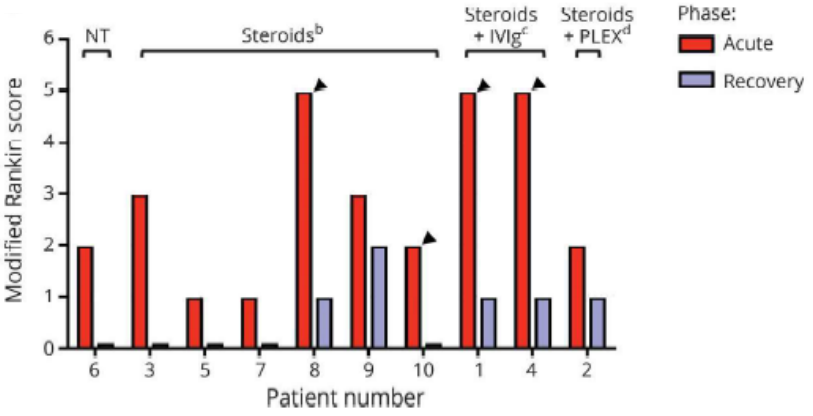


Table 2. Ten Questions Relevant to the Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Blockade.

Questions about Immune-Related Adverse Events	Comments
Why do they occur?	The precise pathophysiology is unknown. Translational studies in patients with immune-related adverse events have shown that T-cell, antibody, and cytokine responses may be involved.
How are they generally treated?	No prospective trials have defined the best treatment approaches, and recommendations are based on consensus opinion. Immunosuppression is used to reduce the excessive state of temporary inflammation. Glucocorticoids are usually the first-line immunosuppressive agent. Additional immunosuppressive agents can be used if glucocorticoids are not initially effective.
When do they occur?	Immune-related adverse events usually start within the first few weeks to months after treatment but can occur anytime, even after treatment discontinuation. Dermatologic adverse events are usually the first to appear.
Why do they occur in some patients and not others?	The reason for the occurrence of immune-related adverse events only in certain patients is unknown. Some studies are investigating whether such factors as germline genetics and the composition of host microbiota are related to risk.
Are they associated with the efficacy of immune checkpoint blockade?	Conflicting data are available regarding whether the occurrence of immune-related adverse events is associated with improved treatment efficacy. The development of immune-related adverse events is not required for treatment benefit. Specific adverse events (e.g., vitiligo) may be more clearly associated with treatment efficacy.
Does immunosuppression to treat such adverse events reduce the antitumor efficacy of treatment?	Clinical outcomes are similar in patients who require immunosuppression to treat immune-related adverse events and in those who do not require such treatment. Beneficial responses can persist despite the use of immunosuppression to treat immune-related adverse events.
Are there unintended effects of immunosuppression to treat adverse events?	Side effects of glucocorticoid use (e.g., hyperglycemia, edema, anxiety, and iatrogenic adrenal insufficiency) can occur. Immunosuppression is a risk factor for subsequent opportunistic infections.
Is it safe to restart treatment after a major adverse event?	Retrospective studies have shown that immune-related adverse events associated with one class of agent (e.g., anti–CTLA-4) may not necessarily recur during subsequent treatment with another agent (e.g., anti–PD-1). The safety of retreatment probably depends on the severity of the initial immune-related adverse event.
Is it necessary to restart treatment after resolution of an adverse event?	Retrospective data suggest that patients who have had a favorable response to immune checkpoint blockade and then discontinue treatment because of immune-related adverse events generally maintain responses. Prospective data are needed to address whether restarting immunotherapy is necessary.
Is it safe to treat patients at potentially increased risk for such adverse events?	Patients at increased risk for immune-related adverse events (e.g., preexisting autoimmune disease) may still benefit from immune checkpoint blockade. Age alone should not be used to exclude patients from treatment, since benefit appears to be similar regardless of age.

Postow MA et Al. N Engl J Med 2018;378:158-68.

Perché?

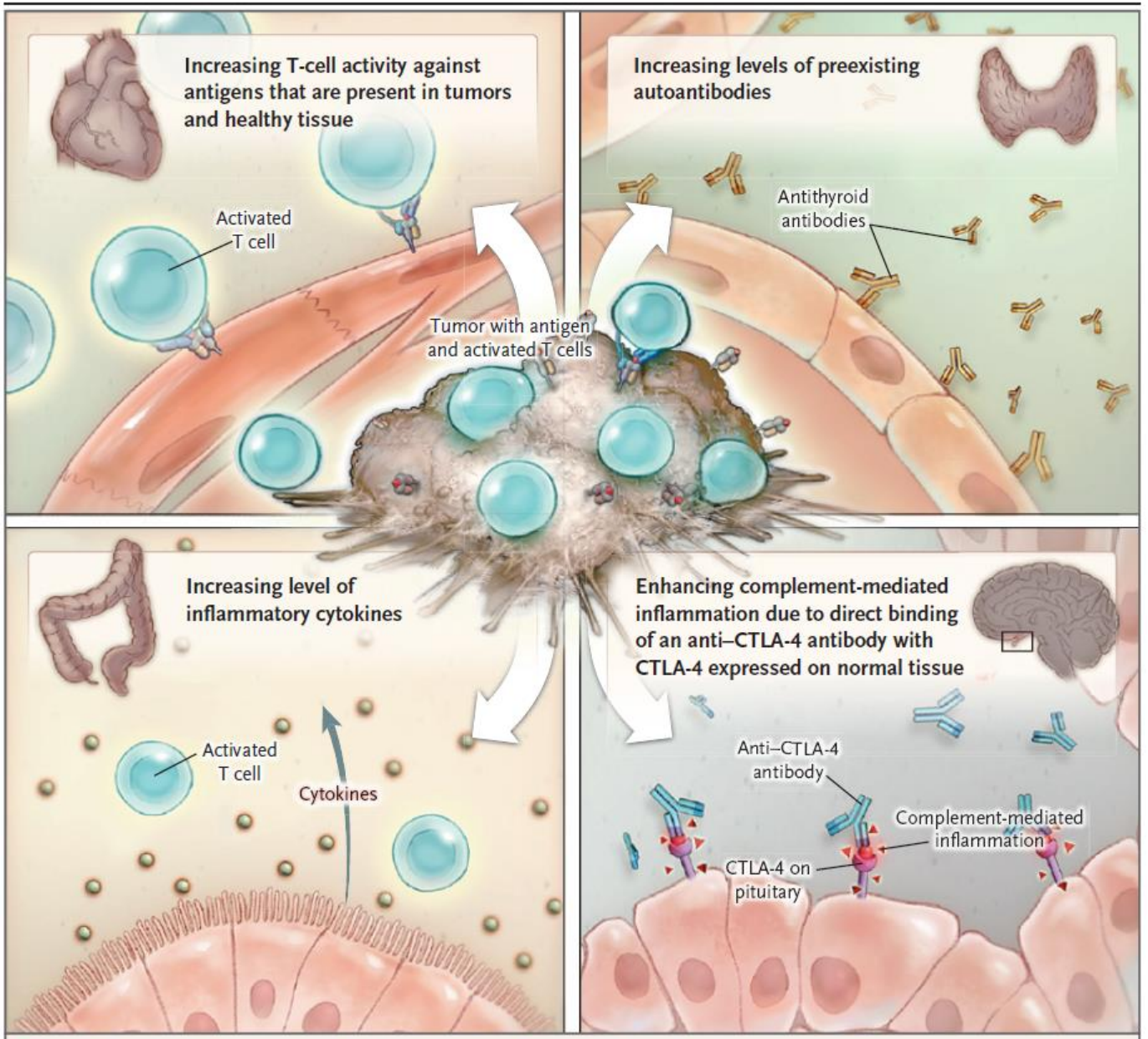


Figure 2. Possible Mechanisms Underlying Immune-Related Adverse Events.

The mechanisms that result in immune-related adverse events are still being elucidated. Some potential mechanisms include increasing T-cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies, an increase in the level of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue, such as the pituitary gland.

Postow MA et Al. N Engl J Med 2018;378:158-68.

Quale è il trattamento?

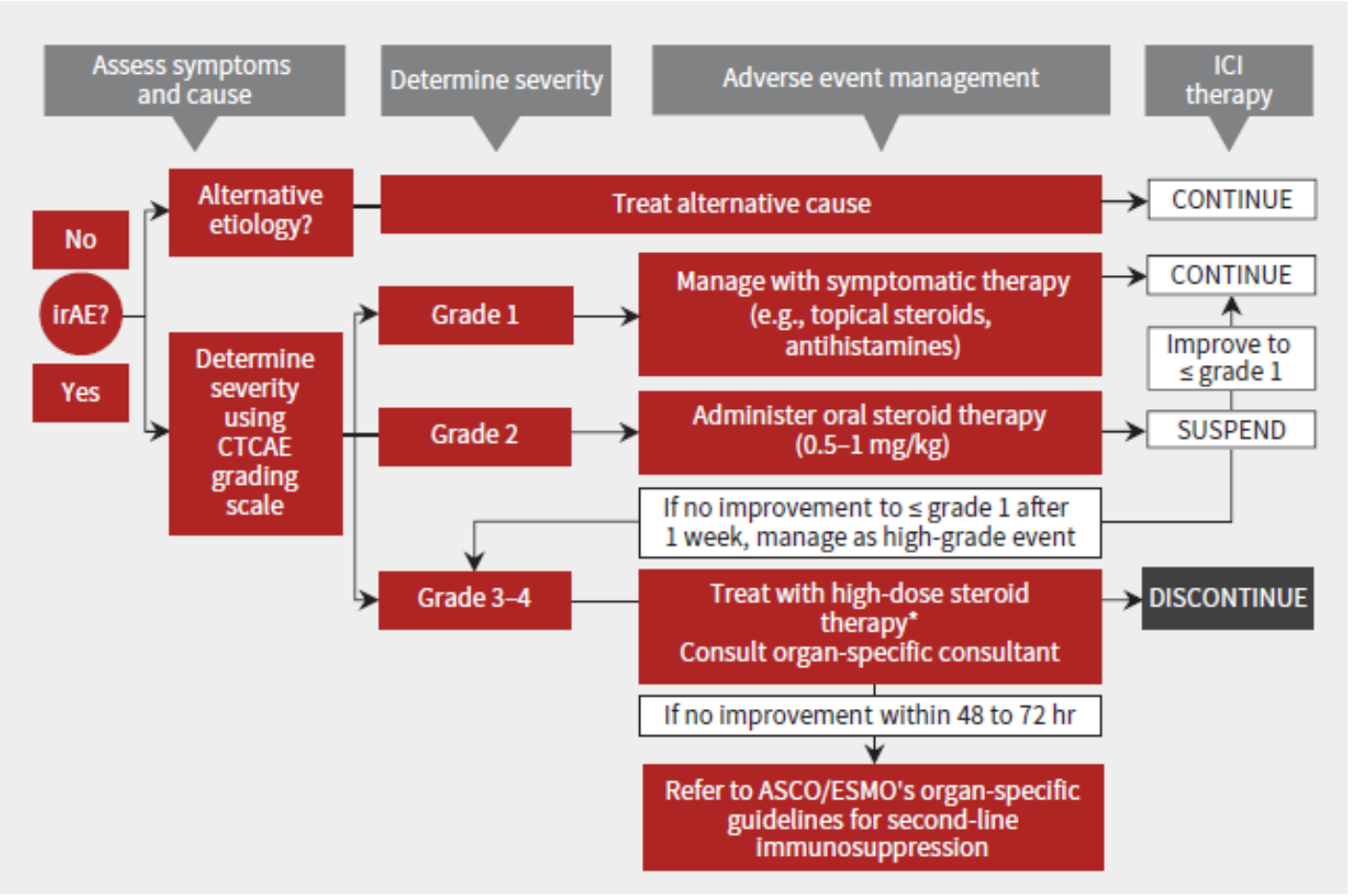
Sospensione temporanea?
Sospensione definitiva?
Riduzione del dosaggio?
Immunosoppressione?

Postow MA et Al. N Engl J Med 2018;378:158-68.

Table 3: General grading guidelines from the Common Terminology Criteria for Adverse Events*[12]

CTCAE grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activity of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalization indicated; disabling; limiting self care.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event.

Note: CTCAE = Common Terminology Criteria for Adverse Events.
*CTCAE provides general grading guidelines as described within this table. For each specific organ affected, the CTCAE also provides descriptive organ-specific grading.[12]



Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
Washington (DC): US Department of Health and Human Services; 2017.
Available: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Quale è il trattamento?

ESMO
Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225
CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

Arthralgia: Pain in the joints without associated swelling; may be found in conjunction with myalgia (muscle pain), a common AE

DDx to consider:
- Arthritis (see Figure 14 for further tests and management)
- Polymyalgia rheumatica (see arthritis as may present with small joint synovitis)
- Myositis (characterised by tenderness to palpation of muscle)

Due to the paucity of literature on management of this AE, this algorithm serves as a general guide only; seek rheumatology advice if severe symptoms not responding to steroids

Symptom Grade	Management escalation pathway	Assessment and Investigations
Grade 1: Mild pain with inflammation, erythema or joint swelling	Initiate analgesia with paracetamol and ibuprofen Continue ICPi	Complete rheumatological history regarding DDx above and examination of all joints and skin Consider plain X ray/imaging to exclude metastases if appropriate Autoimmune blood panel (as above)
Grade 2: Moderate pain associated with the above, limits instrumental ADL	Escalate analgesia and use diclofenac or naproxen or etoricoxib If inadequately controlled, initiate prednisolone 10-20 mg or consider intra-articular steroid injections for large joints Consider withholding ICPi and resuming upon symptom control, prednisolone < 10 mg; if worsens treat as per Grade 3	Complete history and examination as above; autoimmune blood panel US +/- MRI imaging of affected joints Consider early referral to a rheumatologist
Grade 3: Severe pain; irreversible joint damage; disabling; limits self-care ADL	Withhold ICPi Initiate prednisolone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime – refer patient to rheumatologist (consider anti-TNFα therapy)	As for Grade 2 Seek rheumatologist advice and review

Rheumatological toxicity

- For mild arthralgia, start NSAIDs, and in the case of no improvement, consider low dose steroids (10–20 mg prednisone). In the case of severe polyarthritis, refer patient to or consult a rheumatologist and start prednisone 1 mg/kg. Sometimes infliximab or another anti-TNFα drug is required for improvement of arthritis [V, B].

Postow MA et Al. N Engl J Med 2018;378:158-68.

Table 2 Characteristics of musculoskeletal IRAEs, laboratory and imaging results

Quando si sviluppano gli IR-AEs?

Patient	Pattern of arthritis	PMR-like disease	Other MS IRAEs	Latency of MS IRAEs after ICI start (days)	CRP at onset of MS IRAEs (mg/L)	RF/anti-CCP	ANA/ENA	HLA-B27	Synovial fluid cell counts (cells/µL)	Proof of MSI on imaging: US (1), PET-CT (2), CT (3), MRI (4)
1	Oligo	+ve	–ve	174	9.9	–ve /–ve	–ve / –ve	–ve	12 300	1
2	Mono	–ve	–ve	121	≤5.0	–ve /–ve	1:100/ ND	ND	ND	3, 4
3	Mono	+ve	Sicca	289	5.5	–ve /–ve	–ve / ND	–ve	ND	1, 4
4	Poly	+ve	–ve	1	9.8	+ve/+ve	1:400/ –ve	ND	ND	1,2,3
5	Poly	+ve	–ve	48	38.6	–ve /–ve	1:3200/ –ve	–ve	ND	1
6	Oligo	–ve	–ve	143	38.2	–ve /–ve	1:1600/ –ve	ND	ND	1
7	Oligo	–ve	Sicca	43	71.3	–ve /–ve	–ve / ND	–ve	2600	1
8	Mono	–ve	–ve	31	21.2	–ve /–ve	1:800/ –ve	–ve	ND	2
9	Mono	–ve	–ve	716	≤5.0	–ve/–ve	1:200/ –ve	–ve	ND	2, 3, 4
10	Mono	–ve	–ve	253	≤5.0	+ve/ ve	1:100/ ND	ND	ND	1, 4
11	Oligo	–ve	Myositis	76	≤5.0	–ve/–ve	–ve / ND	–ve	20 000	1, 2, 3
12	Mono	–ve	–ve	139	6.8	+ve/–ve	1:400/ –ve	–ve	ND	4
13	Oligo	–ve	–ve	116	48	+ve/–ve	1:12800/ SSA	–ve	6000	1, 2, 3
14	Mono	+ve	–ve	394	114	+ve/–ve	–ve / –ve	–ve	ND	1
	7 M 5 O 2 P	**5 +**		**1-715**	**4 – 10 +**	**FR 5 APCA 2**	**3 +**			

Leipe J, *et al. RMD Open* 2018;**4**:e000714. doi:10.1136/rmdopen-2018-000714

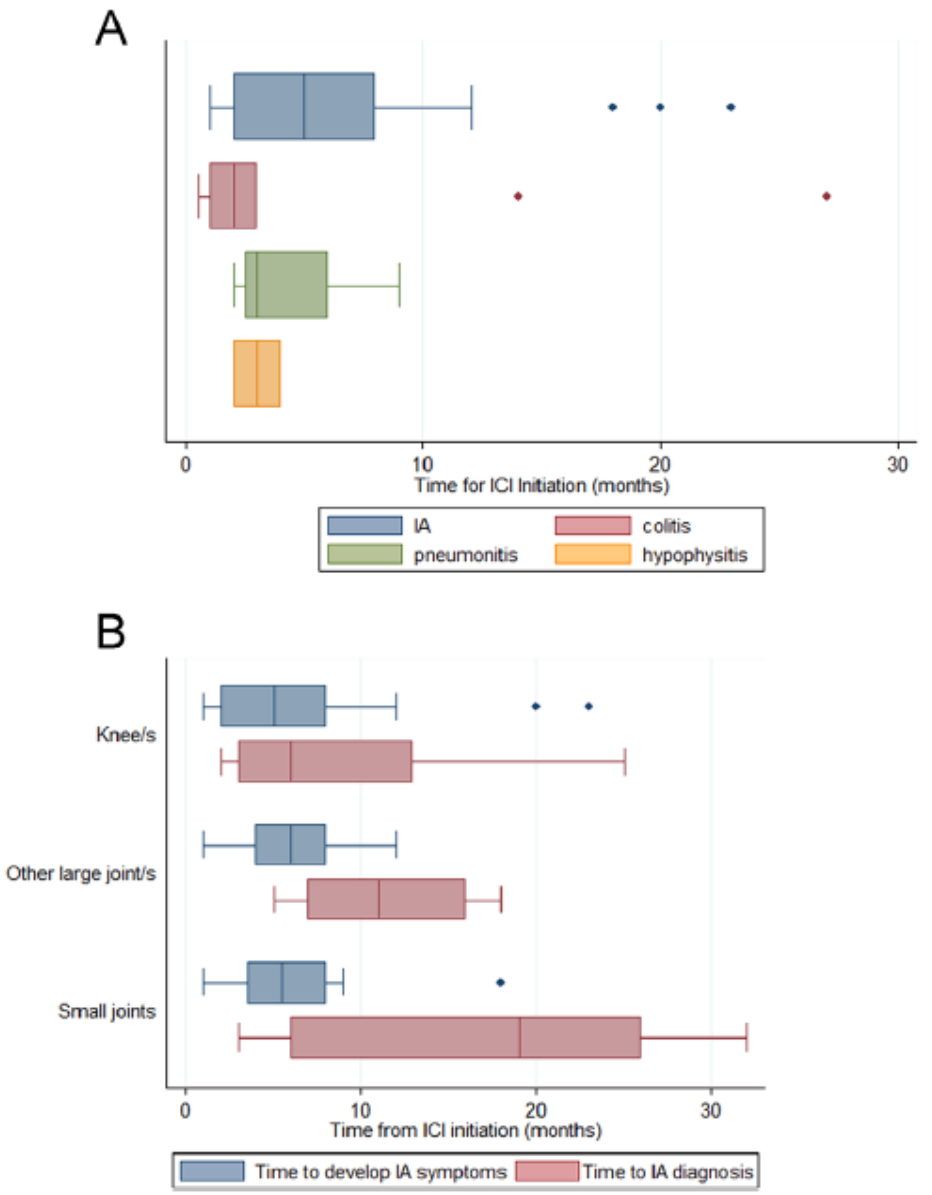


Fig. 1. (A) Time to develop irAE after ICI initiation (time to symptoms for IA, time to diagnosis for others). (B) Time to develop IA symptoms and for IA diagnosis in groups by first joint involvement.

Perché in alcuni e non in altri?

Predisposizione genetica, al pari di alcune malattie autoimmuni «spontanee»?

Non sembra….

(Wolchok JD, Weber JS, Hamid O, et al. Ipilimumab efficacy and safety in patients with advanced melanoma: a retrospective analysis of HLA subtype from four trials. Cancer Immun 2010; 10: 9)

Ruolo del microbioma intestinale?

Si sull'efficacia

(Chaput N, Lepage P, Coutzac C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol 2017; 28: 1368-79).

Predominanza di Bacteriodes Phylum riduce la comparsa di coliti

Dubin K, Callahan MK, Ren B, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpointblockade-induced colitis. Nat Commun 2016; 7: 10391.

C’è una relazione tra IRAEs ed efficacia della terapia?

La severità degli IRAEs è una misura della risposta antitumorale?

SI

Attia P, Phan GQ, Maker AV, et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4.
J Clin Oncol 2005; 23:6043-53.

SI (Vitiligo)

Teulings HE, Limpens J, Jansen SN, et al. Vitiligo-like depigmentation in patients with stage III-IV melanoma receiving immunotherapy and its association with survival: a systematic review and metaanalysis. J Clin Oncol 2015; 33: 773-81.

NO

Downey SG, Klapper JA, Smith FO, et al. Prognostic factors related to clinical response in patients with metastatic melanoma treated by CTL-associated antigen-4 blockade. Clin Cancer Res 2007; 13: 6681-8.

NI

Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. J Clin Oncol 2015; 33: 3193-8.

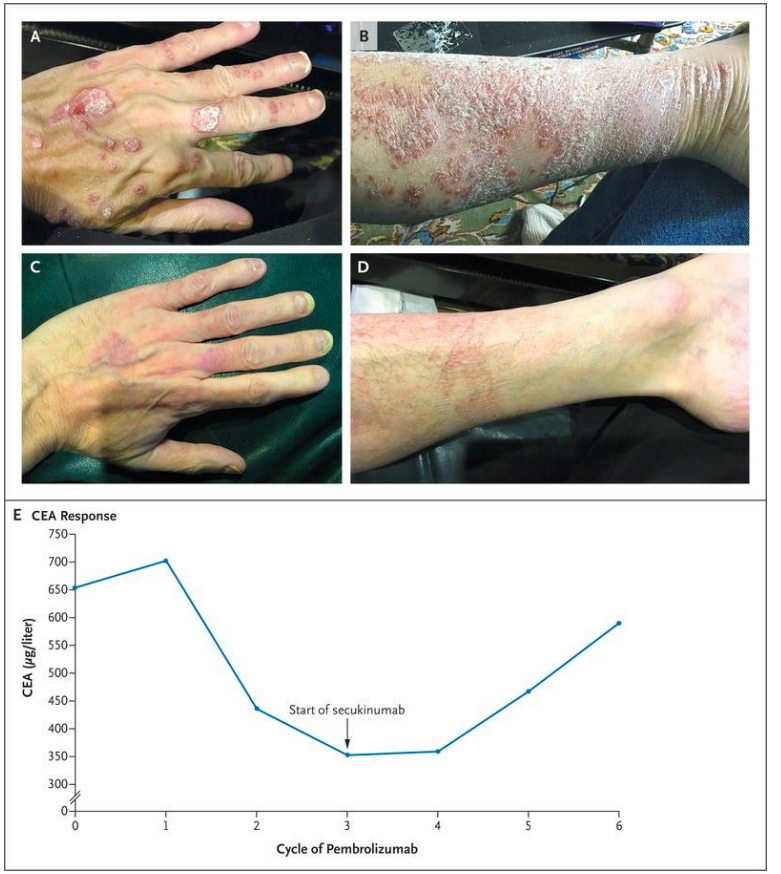
L'immunosoppressione riduce l'efficacia dell'immunoterapia?

NO

Horvat TZ, Adel NG, Dang TO, et al. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center.
J Clin Oncol 2015; 33: 3193-8.

SI

Esfahani K, Miller WH Jr. Reversal of autoimmune toxicity and loss of tumor response by interleukin-17 blockade.
N Engl J Med 2017; 376: 1989-91.



ARTICLE IN PRESS

Seminars in Arthritis and Rheumatism ▮ (2018) ▮▮–▮▮

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Clinical presentation of immune checkpoint inhibitor-induced inflammatory arthritis differs by immunotherapy regimen

Laura C. Cappelli, MD[a,*], Julie R. Brahmer, MD[b], Patrick M. Forde, MBBCh[b], Dung T. Le, MD[b], Evan J. Lipson, MD[b], Jarushka Naidoo, MBBCh[b], Lei Zheng, MD, PhD[b], Clifton O. Bingham III, MD[a,1], Ami A. Shah, MD[a,1]

***TNF-inhibitors(TNFi), with or without methotrexate**, were required for **7** patients, and **Methotrexate (MTX) monotherapy** was used in **3** patients.*

*The duration of TNF use range **from 2 to 1 6 months**.*

*All **TNFi-treated patients** had clinical improvement in their arthritis.*
Of those receiving TNFi, 4 had a complete tumor response at the time of TNFi initiation, with none having tumor progression onTNFi (duration:3–16months).

*Of the **MTX monotherapy-treated patients**, 3 had a complete or sustained partial tumor response to ICI therapy, and did not develop progressive cancer during the 2–12 monts of IA management follow up.*

L’immunosoppressione ha effetti avversi?

SI

STEROIDI:

Effetti ormonali

TUTTI:

Aumentato rischio infettivo

Del Castillo M, Romero FA, Arguello E, Kyi C, Postow MA, Redelman-Sidi G. The spectrum of serious infections among patients receiving immune checkpoint blockade for the treatment of melanoma. Clin Infect Dis 2016; 63: 1490-3.

L'immunosoppressione ha effetti avversi?

Table 1. Patient Characteristics and Risk Factors for Serious Infection

Characteristic (n = 740 Patients)	Overall	Serious Infection? Yes (n = 54)	No (n = 686)	*P* Value	OR (95% CI)
Age, y, mean (range)	63 (4–93)	61.6 ± 2.0	63.0 ± 0.5	.47	
Male sex	469 (63)	40 (74)	430 (63)	.11	1.70 (.90–3.09)
Prior chemotherapy	229 (31)	20 (37)	209 (30)	.36	1.34 (.76–2.39)
Prior temozolomide	142 (19)	12 (22)	130 (19)	.59	1.22 (.64–2.36)
Corticosteroid use	339 (46)	46 (85)	293 (43)	<.0001	7.71 (3.71–16.18)
Infliximab use	54 (7)	13 (24)	41 (6)	<.0001	4.74 (2.27–9.45)

Treatment (n = 898 Treatment Courses)	Overall	Serious Infection? Yes (n = 54)	Yes (n = 844)	*P* Value	OR (95% CI)
Ipilimumab	658 (73)	40 (74)	618 (73)	.99	1.05 (.55–1.90)
Nivolumab	52 (5.7)	1 (1.9)	51 (6)	.36	0.29 (.03–1.68)
Pembrolizumab	83 (9.2)	0 (0)	83 (9.8)	.0069	0 (0–.63)
Ipilimumab + nivolumab	80 (8.9)	12 (22)	68 (8)	.0017	3.26 (1.70–6.27)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 2. Specific Infection Types

Infection Type	No. of Cases
Bacterial	46
Pneumonia	13
Intra-abdominal infection	7
Craniofacial infection	3
Bacterial bloodstream infection	13
Clostridium difficile–associated diarrhea	10
Fungal	6
Invasive pulmonary aspergillosis	2
Pneumocystis pneumonia	3
Candida bloodstream infection	1
Viral	5
Zoster (disseminated or facial)	3
CMV enterocolitis	1
EBV reactivation causing facial nerve paralysis	1
Parasitic	1
Strongyloides hyperinfection	1
Total[a]	58

«when patients require 20 mg of prednisone daily or the equivalent for at least 4 weeks, Pneumocystis jirovecii prophylaxis with trimethoprim–sulfamethoxazole, atovaquone, or pentamidine should be considered»

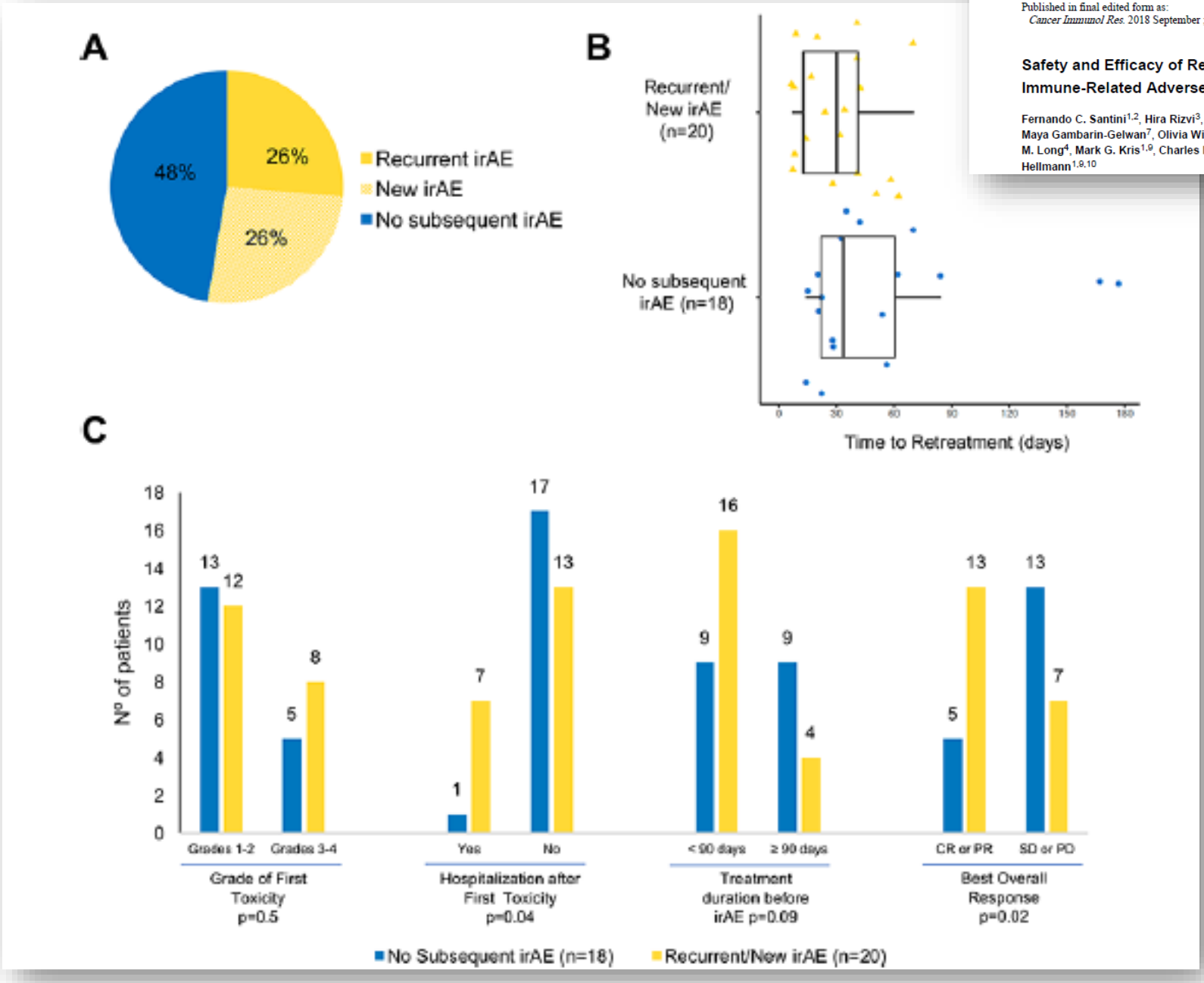
National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections, version 1.2018, December 1, 2017 (http://www .nccn .org/professionals/ physician_gls/ pdf/ infections.pdf)

E’ sicuro riprendere un Checkpoint inibitore dopo un evento avverso serio?

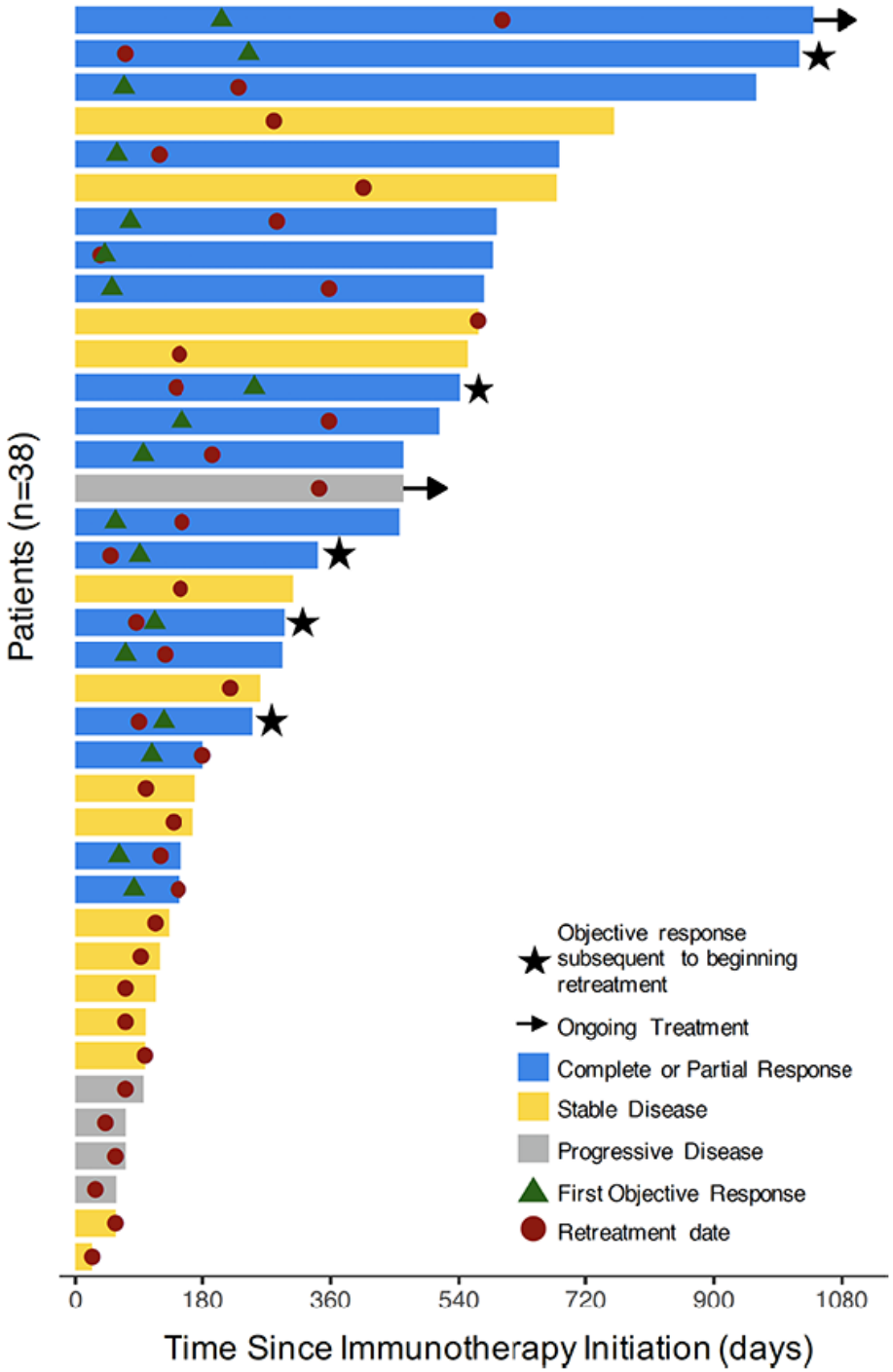
Published in final edited form as:
Cancer Immunol Res. 2018 September ; 6(9): 1093–1099. doi:10.1158/2326-6066.CIR-17-0755.

Safety and Efficacy of Retreating with Immunotherapy After Immune-Related Adverse Events in Patients with NSCLC

Fernando C. Santini[1,2], Hira Rizvi[3], Andrew J. Plodkowski[4], Andy Ni[5], Mario E. Lacouture[6], Maya Gambarin-Gelwan[7], Olivia Wilkins[1], Elizabeth Panora[8], Darragh F. Halpenny[4], Niamh M. Long[4], Mark G. Kris[1,9], Charles M. Rudin[1,3,9], Jamie E. Chaft[1,9], and Matthew D. Hellmann[1,9,10]



E’ necessario riprendere un Checkpoint inibitore dopo un evento avverso serio?



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E’ sicuro trattare pazienti a rischio?
Es. con pre-esistente malattia autoimmune

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 368–376, 2017
doi:10.1093/annonc/mdw443
Published online 29 September 2016

ORIGINAL ARTICLE

Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab

A. M. Menzies[1,2*], D. B. Johnson[3], S. Ramanujam[1], V. G. Atkinson[4], A. N. M. Wong[5], J. J. Park[6], J. L. McQuade[7], A. N. Shoushtari[8], K. K. Tsai[9], Z. Eroglu[10], O. Klein[11], J. C. Hassel[12], J. A. Sosman[3], A. Guminski[1,2], R. J. Sullivan[13], A. Ribas[14], M. S. Carlino[1,6], M. A. Davies[7], S. K. Sandhu[5] & G. V. Long[1,2]

Table 2. Toxicity of anti-PD-1 antibodies in patients with autoimmune disorders

	Number (%) ($N = 52$)	Details
Flare AD on PD1		
No	32 (62%)	
Yes	20 (38%)	
Time to flare, median (range), d	38 (8–161)	
Grade of flare		
G1-2	17 (33%)	
G3	3 (6%)	
G4	0 (0%)	
Flare by AD subtype		
Rheumatologic	14 of 27 (52%)	7/13 RA, 3/3 PMR, 1/2 scleroderma, 2/2 Sjogren's, 1/2 psoriatic arthritis
Dermatologic	3 of 8 (38%)	3/6 psoriasis
Gastrointestinal	0 of 6 (0%)	
Neurologic	0 of 5 (0%)	
Endocrine	1 of 4 (25%)	1/4 Graves
Respiratory	0 of 2 (0%)	
Hematologic	2 of 2 (100%)	2/2 ITP

Annals of Internal Medicine REVIEW

Use of Immune Checkpoint Inhibitors in the Treatment of Patients With Cancer and Preexisting Autoimmune Disease

A Systematic Review

Noha Abdel-Wahab, MD, PhD; Mohsin Shah, MD; Maria A. Lopez-Olivo, MD, PhD; and Maria E. Suarez-Almazor, MD, PhD

Ann Intern Med. 2018;168:121-130. doi:10.7326/M17-2073

119 casi:

- 39 case reports
- 4 case series
- 6 pubblicazioni con 5 studi osservazionali retrospettivi

92 pazienti (75%) hanno avuto eventi avversi

40 pazienti (41%) hanno avuto una riacutizzazione della loro pre-esistente malattia autoimmune

31 (25%) pazienti hanno avuto un nuovo irAEs

11 (9%) hanno avuto entrambi

Table 3. CPI-Related Adverse Events Reported in the Literature According to the Disease Activity of the Preexisting Autoimmune Disease and the CPI Therapy Used

Variable	Patients, *n*	Adverse Event, *n (%)**		
		Any	Exacerbation of Autoimmune Disease	De Novo irAE
Status of autoimmune disease at start of CPI therapy†				
Active	49	33 (67)	23 (47)	16 (33)
Inactive or stable	57	43 (75)	30 (53)	14 (25)
Receiving any therapy for autoimmune disease at start of CPI therapy‡				
Yes	44	26 (59)	17 (39)	10 (23)
No	57	47 (83)	33 (58)	20 (35)
Receiving immunosuppressive therapy for autoimmune disease at start of CPI therapy				
Yes	27	18 (67)	13 (48)	5 (19)
No	74	55 (74)	37 (50)	25 (34)
CPI used				
Ipilimumab	55	36 (66)	20 (36)	23 (42)
Anti–PD-1 or anti–PD-L1 agent	65	53 (82)	40 (62)	17 (26)
Combination of ipilimumab and nivolumab	3	3 (100)	1 (33)	2 (67)

Che fare?

OP0165

EULAR RECOMMENDATIONS FOR THE DIAGNOSIS AND THE MANAGEMENT OF RHEUMATIC IMMUNE-RELATED ADVERSE EVENTS DUE TO CANCER IMMUNOTHERAPY

Results: 4 overarching principles and 10 recommendations were developed. The overarching principles define the role of rheumatologists and highlight the shared decision-making process between patients, oncologists and rheumatologists. One recommendation addresses the referral process, two address the diagnosis, and five address the therapeutic strategy of cancer patients experiencing rheumatic, musculoskeletal, and systemic signs or symptoms while receiving immunotherapy. An additional recommendation was included to address pre-existing rheumatic conditions and the last focuses on the diagnostic approach before immunotherapy.

Conclusion: These recommendations provide the basis of a EULAR consensus on the diagnosis and the management of rheumatic irAEs.

Che fare?

Kestin M et Al. June 2019 Volume 78 Supplement 2

Che fare?

Pre-terapia:

- Anamnesi relativamente a patologie autoimmuni pre-esistenti

Durante la terapia:

- Grading dell'AE
- Sede del dolore
- Presenza dei segni dell'infiammazione
- Presenza di rigidità mattutina
- Necessità di assumere FANS o analgesici per sintomatologia articolare?

VISITA REUMATOLOGICA

Valutazione stato autoanticorpale al basale ?!

Conclusioni

- Gli irAEs reumatici dei Check Points inibitori sono prevalentemente di tipo articolare con carattere di sinovite e con impegno mono-oligo o poliarticolare.
- Il trattamento è steroideo e nei casi refrattari con MTX e quindi con Anti-TNF alfa
- Nei casi di mono-oligoartiti può essere utile il trattamento steroideo locale.
- Nei pazienti con pre-esistenti malattie autoimmuni sistemiche è necessaria una valutazione collegiale per la valutazione del rapporto rischi/benefici
- In questi casi è determinante il coinvolgimento del paziente
- La collaborazione oncologo-reumatologo deve svilupparsi maggiormente per affrontare nel modo migliore questa nuova sfida

Conclusioni

- Gli irAEs reumatici dei Check Points inibitori sono prevalentemente di tipo articolare con carattere di[illegible]e e con impegno mono-oligo o poliarticolare.
- Il trattamento è steroideo e nei casi [illegible]uindi con Anti-TNF alfa
- Nei casi di mono-oligoa[illegible]ento steroideo locale.
- Nei pazient[illegible]atoimmuni sistemiche è neces[illegible]ale per la valutazione del rap[illegible]
- In [illegible]minante il coinvolgimento del pa[illegible]
- La co[illegible]borazione oncologo-reumatologo deve svilupparsi maggiormente per affrontare nel modo migliore questa nuova sfida

IL REUMATOLOGO DEVE CONTRIBUIRE AD OFFRIRE AL PAZIENTE LE MIGLIORI OPPORTUNITA' PER LA CURA DEL TUMORE

Abbiamo tutti dentro un mondo di cose: ciascuno un suo mondo di cose! E come possiamo intenderci, signore, se nelle parole ch'io dico metto il senso e il valore delle cose come sono dentro di me; mentre chi le ascolta, inevitabilmente le assume col senso e col valore che hanno per sé, del mondo com'egli l'ha dentro?

(Luigi Pirandello, Sei personaggi in cerca d'autore)

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«IMMUNOSOPPRESSIONE» / «IMMUNOSTIMOLAZIONE»

«ARTRALGIA» / «ARTRITE»

«SINDROME SICCA» / «SINDROME DI SJOGREN»

«

Le manifestazioni reumatologiche da Checkpoint inibitori

Enrico Fusaro

S.C. Reumatologia AO Città della Salute e della Scienza di Torino

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino