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Toxicité des immunothérapies

A.P. Meert

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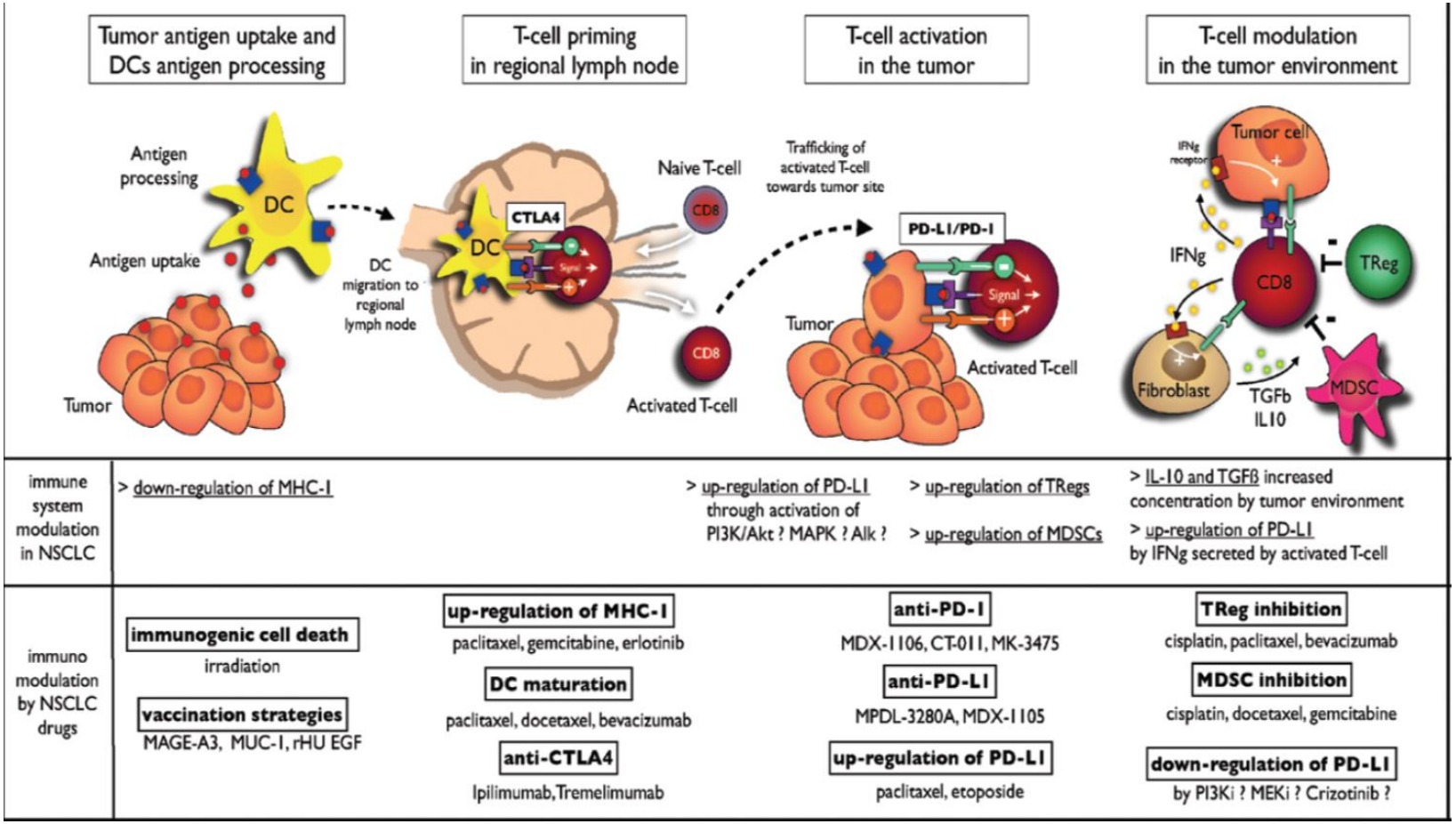
Inhibiteurs des points de contrôle



Champiat et al, J Thorac Oncol 2014

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Indications

- Mélanome
- Cancer bronchique
- Cancer rein
- Cancer vessie
- Tumeur ORL
- Lymphome…

Cas clinique 1

- Mr CR 61 ans

Apparition depuis 10j d'un « flou visuel » évoluant rapidement vers une diplopie

Asthénie progressive avec dyspnée à l'effort

Myalgies et lombalgies

Difficulté à tenir la tête droite

Antécédents

- hypertrophie prostatique bénigne R/ tamsulosine
- polypectomie colique
- diverticulose compliquée de diverticulite
- hypertension artérielle R/ Préterax
- obésité compliquée d'un syndrome d'apnée du sommeil traité par C-PAP
- hypertension artérielle
- syndrome métabolique
- psoriasis

Affection néoplasique

- 12.2018: autopalpation d'une masse cervicale droite
- Adénopathie para-jugulaire droite.
- Curage cervical: métastase d'un mélanome (mutation B-RAF V600E et PIC3CA E545K)
- Le primitif n'a pas été retrouvé.
- R/ Pembrolizumab 24.05.2019 et 14.06.2019

Examen physique

- Param: 37°C - 92/mn - 98%AA - 126/89mmHg
- Tête et cou: JNT, cicatrice jug D propre, pas d'ADP palpées, pupilles isocores réflectiques, ptose palpébrale D
- Co-Po: sp
- Abdo: SDIP+, pas d'organomégalie, PCL -/-
- MI: OMI -/-
- Tég: psoriasis, léger rash érythémateux au niveau du tronc
- Neuro: force MS à 4.5/5, MI 5/5, pas de trouble de la sensibilité (autre que au niveau cervical post op), RCP indifférent, réflexes rotuliens et achiléens absents bilat, paralysie abduction oeil G, pas de nystagmus, marche sp

RMN cérébrale

- **Conclusion**
- Absence de signe de complication hémorragique ou d'effet de masse ou dilatation du système ventriculaire.
  Pas d'évidence d'infiltration métastatique intracrânienne.
  Pas d'argument radiologique en faveur d'une toxoplasmose ou d'une autre infection opportuniste.

- EMG: décrément significatif à la stimulation du nerf facial G

- Echographie cardiaque: FEVG normale

Myasthenia gravis: An emerging toxicity of immune checkpoint inhibitors

D. Makarious [a], K. Horwood [b], J.I.G. Coward [b,c,d,*]

Table 1
Cases of immune checkpoint inhibitor-induced myasthenia gravis.

Reference	Patient	Pre-existing	AChR status	Onset (weeks)	Cycles completed	Intervention	Elevated serum CK	Myasthenia-associated mortality
Anti-PD-1 inhibitor-induced MG								
Case report	85-year-old female with metastatic melanoma treated with pembrolizumab	No	Negative	4.5	2	• IVIG, 450 mg/kg for 5 d • Prednisone, 100 mg o.d. for 7 d • Pyridostigmine, 90 mg o.d.	No	No
Zimmer *et al.* [6]	69-year-old female with metastatic melanoma treated with pembrolizumab	No	Negative	9	3	• 1 g of methylprednisolone (i.v.), for 3 d then tapered to 60 mg daily • 30 mg of pyridostigmine b.d. p.o. • Five cycles of plasmaphaeresis	Yes	Yes
March *et al.* [1]	63-year-old male with metastatic melanoma treated with pembrolizumab	No	Negative	2	1	• Prednisone, 60 mg o.d. for 2 d escalated to 1 g methylprednisolone (i.v.) for 9 d • 120 mg of pyridostigmine q.i.d., for 11 d • Five treatments of IVIG at 400 mg/kg/d • Four cycles of plasmaphaeresis	Yes	Yes
Gonzalez *et al.* [2]	71-year-old female with uterine carcinosarcoma treated with pembrolizumab	No	Negative	12	4	• Pyridostigmine, 60 mg t.d.s. • Prednisone, 20 mg o.d.	Yes	No
Nugyen *et al.* [3]	81-year-old male with metastatic melanoma treated with pembrolizumab	No	Negative	11	3 before the event and 5 post the event	• Prednisone, 25 mg o.d. p.o.	No	No
Nugyen *et al.* [3]	86-year-old female with metastatic melanoma treated with pembrolizumab	No	Negative	7	2	• 500 mg of i.v. methylprednisolone for 5 d, which was switched to prednisone on the 6th day.	No	No
Alnahhas *et al.* [7]	84-year-old female with metastatic melanoma treated with pembrolizumab	No	Positive	4	2	• Prednisone, 60 mg p.o. o.d. • Pyridostigmine, 60 mg t.d.s. • IVIG, 400 mg/kg 5 d	No	No
Polat *et al.* [8]	65-year-old male with stage IV NSCLC treated with nivolumab	No	Negative	8	3	• 45 mg q.i.d. of pyridostigmine	No	No
Sciacca *et al.* [9]	81-year-old male with stage IV NSCLC treated with nivolumab	No	Positive	6	3	• Prednisone, 50 mg o.d. p.o.	No	No
Chang *et al.* [10]	75-year-old male with squamous cell carcinoma of the bladder treated with nivolumab	No	Positive	6	2	• Pyridostigmine 90 mg q.i.d. • IVIG, 400 mg/kg for 5 d	Yes	No
Lopez *et al.* [11]	65-year-old male with renal cell carcinoma treated with nivolumab	No	Positive	3	2	• High-dose steroids (no further details) • IVIG for 5 d (no dose details)	Yes	Yes
Shirai *et al.* [4]	81-year-old female with metastatic melanoma treated with nivolumab	Subclinical	Positive	2	1	• i.v. hydration for rhabdomyolysis. • 2 mg/kg of methylprednisolone for hepatitis. • Nil directed therapy for MG	Yes	Yes
Kimura *et al.* [5]	80-year-old male with metastatic melanoma treated with nivolumab	Subclinical	Positive	2	1	• Three days of steroid pulse therapy 100 mg/d followed by oral prednisolone at 1 mg/kg	Yes	No

European Journal of Cancer 82 (2017) 128–136

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Anti-CTLA-4 inhibitor-induced MG								
Liao *et al.* [12]	70-year-old female with metastatic melanoma treated with ipilimumab	No	Positive	4	2	• Plasmaphaeresis for 3 d • 125 mg of methylprednisolone (i.v.)	Yes	No
Johnson *et al.* [13]	69-year-old woman with metastatic melanoma treated with ipilimumab	No	Positive	6	3	• Pyridostigmine, 30 mg t.d.s. • Methylprednisolone, 2 mg/kg • Plasmaphaeresis	No	No
Johnson *et al.* [13]	73-year-old woman with metastatic melanoma treated with ipilimumab	No	Positive	3	2	• Corticosteroids • Pyridostigmine	No	No
Montes *et al.* [14]	74-year-old woman with advanced melanoma treated with ipilimumab	No	Negative	6	3	• Pyridostigmine • Prednisone	No	No
Combination immune checkpoint inhibitor therapy-induced MG								
Antonia *et al.* [15]	Patient with advanced NSCLC treated with durvalumab + tremelimumab	Unknown	Unknown	2	1	Unknown	Unknown	Yes
Loochtan *et al.* [16]	70-year-old male with extensive stage SCLC treated with nivolumab + ipilimumab	No	Positive	2	2	• 1 mg/kg of prednisone escalated to 80 mg of methylprednisolone • Six cycles of plasmaphaeresis • IVIG, 500 mg/kg	No	Yes
PD-1 inhibitor exacerbation of MG								
Lau *et al.* [18]	75-year-old male with metastatic melanoma treated with pembrolizumab	Yes	Positive	5	2	• 1 g of methylprednisolone (i.v.) for 5 d • IVIG, 500 mg/kg for 4 d	No	No
Zhu *et al.* [21]	59-year-old with metastatic melanoma treated with pembrolizumab	Yes	Negative	9	3	• Plasmaphaeresis (cycles unknown) • IVIG (dose unknown) • Prednisone, 40 mg o.d.	No	No
Phadke *et al.* [20]	75-year-old male with metastatic melanoma treated with pembrolizumab	Yes	Positive	6	2	• Seven plasma exchanges (dose unknown) • Two doses of IVIG (dose unknown) • Four doses of rituximab (dose unknown) • Pyridostigmine was up titrated to 180 mg t.d.s. • Prednisone, 30 mg o.d.	No	No
Maeda *et al.* [19]	79-year-old male with metastatic melanoma treated with nivolumab	Yes	Positive	9	3 before the event and 7 post the event	• The patient did not receive any 'rescue' therapy and was maintained on their usual dose of 3 mg of oral corticosteroids every 2nd day.	Yes	Yes

Fatal adverse events in two thymoma patients treated with anti-PD-1 immune check point inhibitor and literature review

Thomopoulou Konstantina[a,1], Rounis Konstantinos[a,1], Koutsopoulos Anastasios[b], Mala Anastasia[a], Lagoudaki Eleni[b], Sougklakos Ioannis[a], Agelaki Sofia[a], Mavroudis Dimitris[a,*]

[a] *Department of Medical Oncology, University General Hospital of Heraklion, Heraklion, Greece*
[b] *Laboratory of Pathology, University General Hospital of Heraklion, Heraklion, Greece*

A B S T R A C T

Objectives: Thymomas, as well as thymic carcinomas, are extremely rare tumors that arise from the thymus. The management of these tumors is primarily the complete surgical resection, however when there is tumor progression or metastatic unresectable disease, palliative platinum-based chemotherapy is the standard of care. On this setting, alternative options are emerging including immune checkpoints inhibitors. Based on that, PDL-1 expression was measured in thymic tumors as a potential predictive biomarker of response to anti-PD1 and anti-PDL1 immune inhibitors. Our objective is to report the first two cases of fatal toxicity due to anti- PD1 therapy in thymoma patients.

Materials and Methods: Here, we report two cases of metastatic B2/B3 thymomas refractory to initial standard chemotherapy treatment, with high PDL1 expression (> 50%), that were treated with the anti-PD1 agent, pembrolizumab.

Results: The administration of anti- PD1 immune check point inhibitor resulted in a storm of immune related adverse events including myositis, myocarditis and myasthenia gravis and death after administration of the first treatment cycle.

Conclusion: In thymomas, the administration of PD1 inhibitors seems to be associated with a high percentage of severe immune related adverse events, thus requiring special caution on the usage of these agents in thymomas.

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Lung Cancer 135 (2019) 29–32

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Cas clinique 2

- Mme BC, 70 ans
- Adénocarcinome bronchique métastatique au niveau cérébral
- R/ Cisplatine – pemetrexed

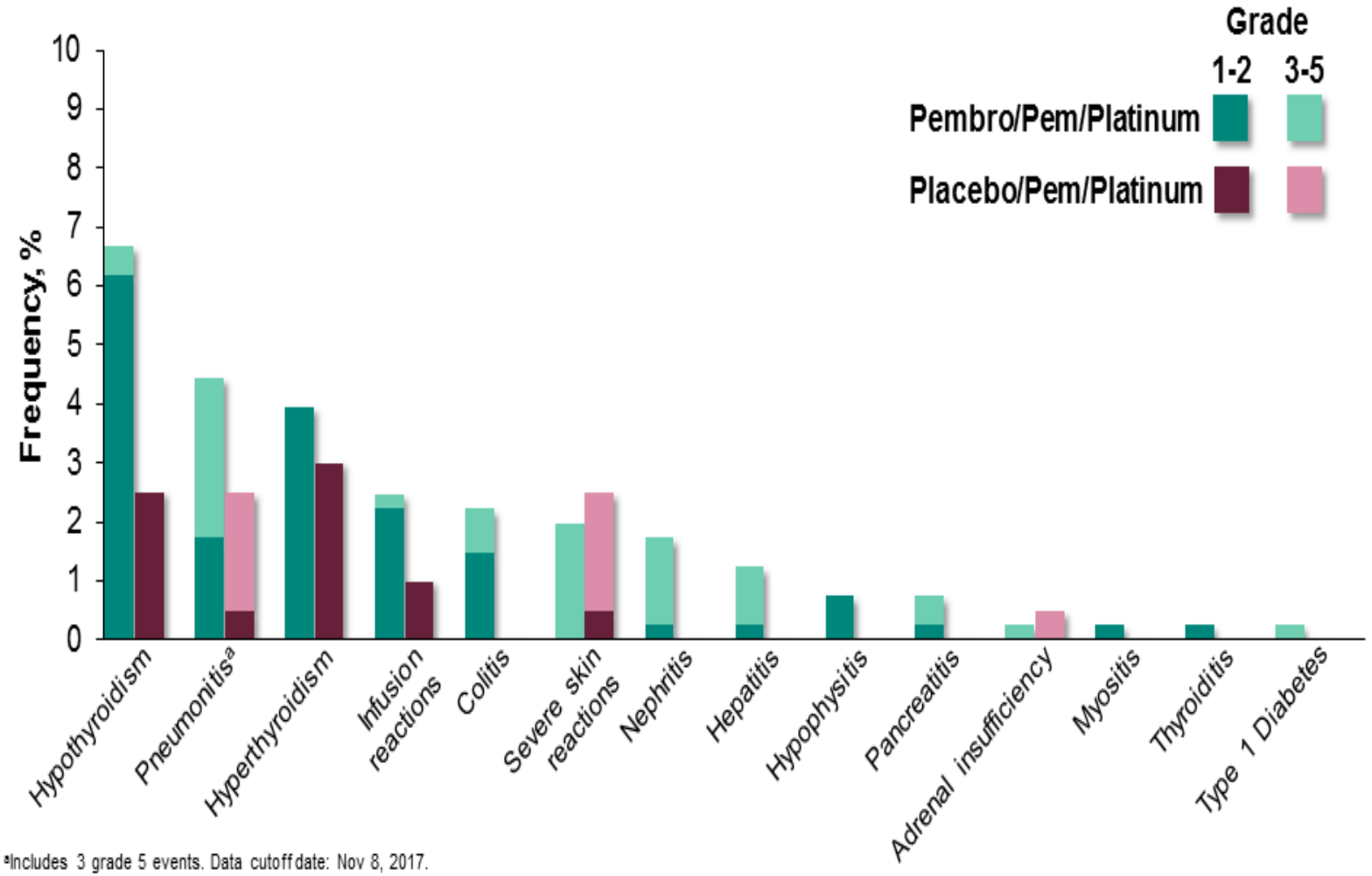
  Radiothérapie cérébrale stéréotaxique

  Nivolumab (2/2018)

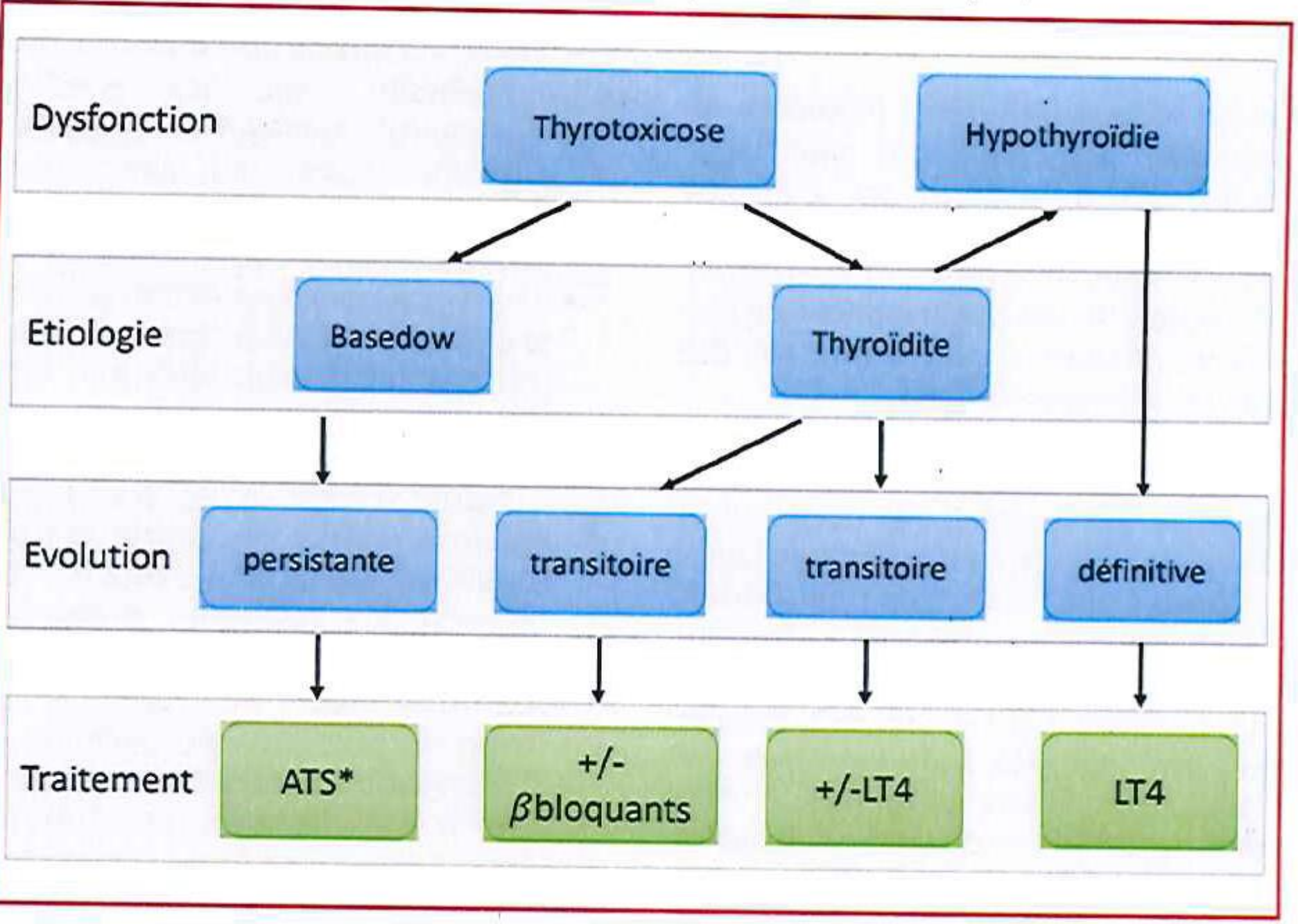
07/2018: fatigue

- TSH 72 mU/L; T4 9,9 pmol/L

Immune-Mediated Adverse Events



[a]Includes 3 grade 5 events. Data cutoff date: Nov 8, 2017.



charge de la toxicité thyroïdienne. *ATS : antithyroïdien de synthèse. Delaunay. Rev Mal Respir 2019

08/2018: lésions cutanées érythémateuses xérostomie

Fragment cutané fixé non orienté mesurant 0.3 cm de diamètre.
A01. In toto

COMPTE RENDU : MV

Prélèvement cutané dont l'épiderme ne montre pas de particulairté.
En particulier, on n'observe pas d'atteinte lichenoïde.
Au niveau du derme superficiel, on observe un discret œdème et un infiltrat périvasculaire minime, formé de quelques polynucléaires éosinophiles.

CONCLUSION :

Altérations très discrètes: discret infiltrat périvasculaire à éosinophiles, pouvant cadrer avec une réaction médicamenteuse.

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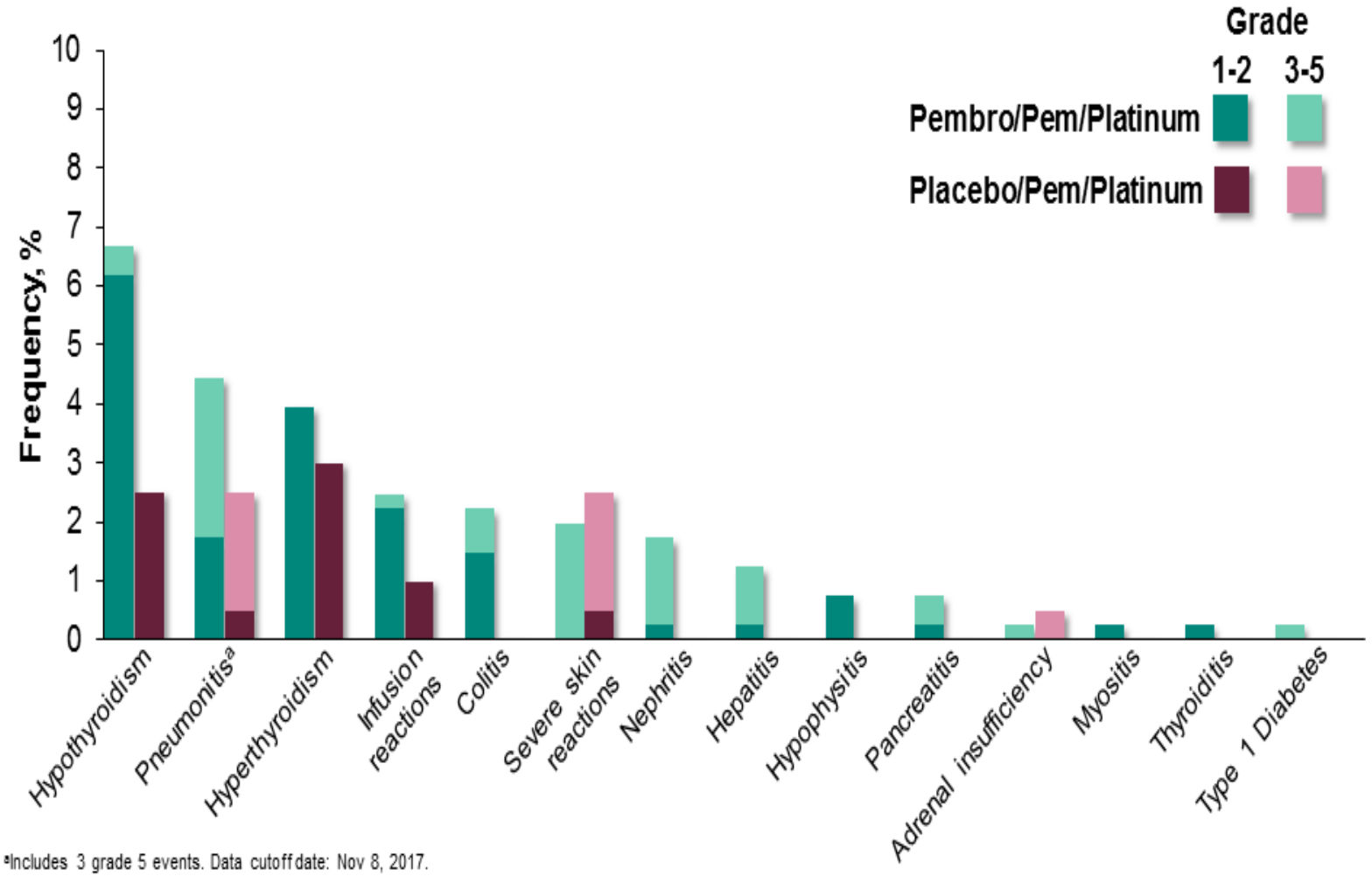
Immune-Mediated Adverse Events



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Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies

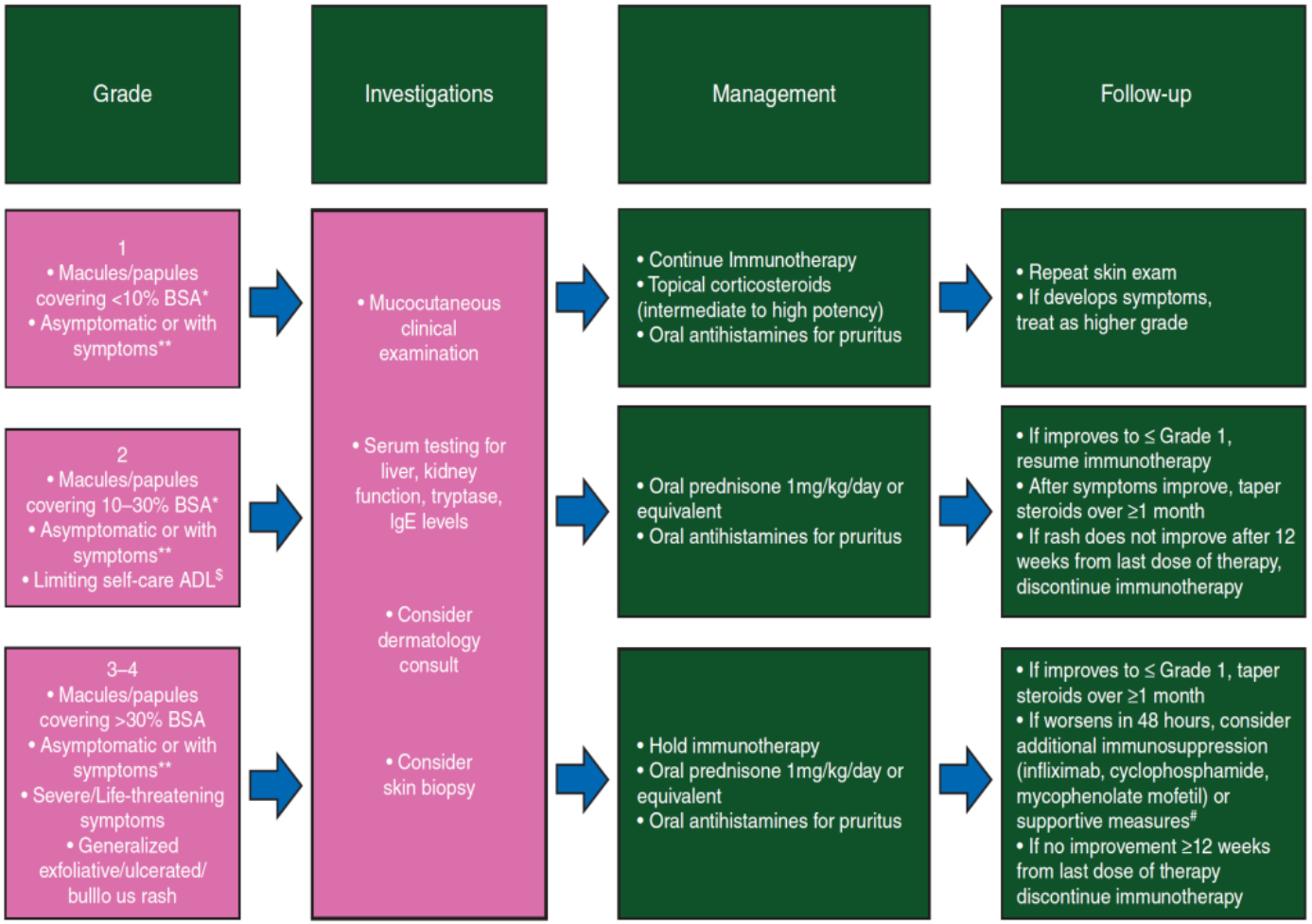

Figure 1. Adapted management algorithm for skin rash with immune checkpoint blockade. *BSA, body surface area, **Symptoms as per CTCAE version 4.0. For example: pruritus, burning and skin tightness. $Additional supportive measures: this denotes the use of, for example, prophylatic antibiotics and management in the burns unit.

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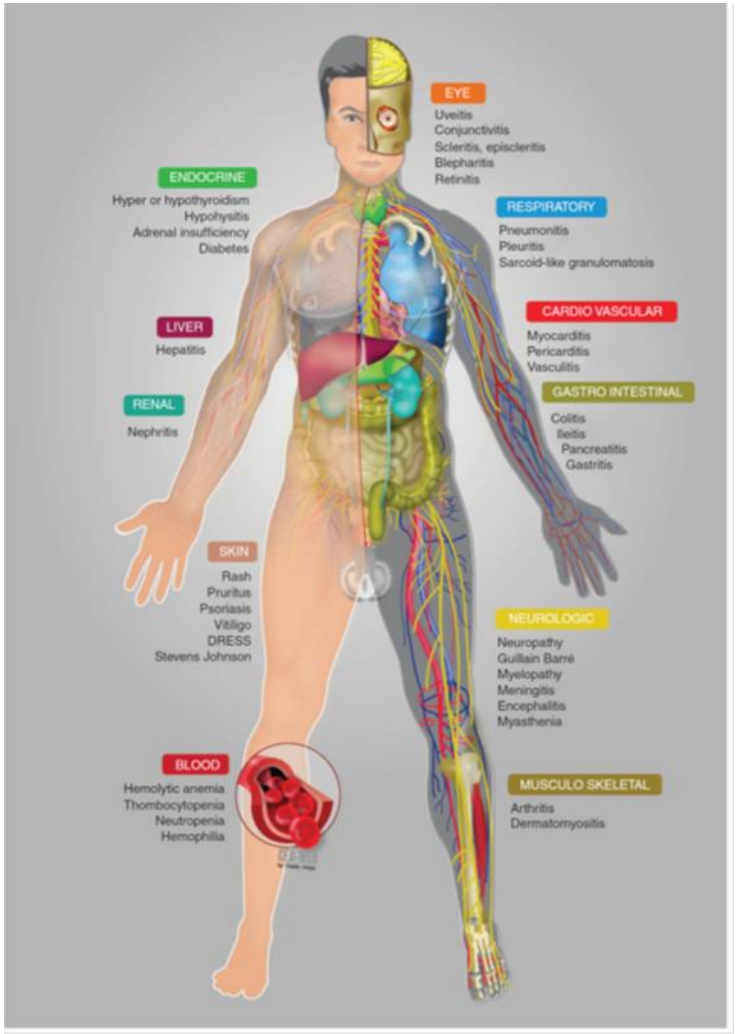
- Conjonctivite
- Gonalgies



02/2019: Diarrhée

Pet CT: hypermétabolisme modéré et diffus au niveau colique (côlon gauche) d'allure inflammatoire: colite sous immunothérapie

Examen: Tractus digestif selles
Aspect macroscopique selles
Examen macroscopique: Liquide
Cocci Gram négatif selles
Négatif

Culture aérobie selles
:
Absence de Salmonella, Shigella, Yersinia, Aeromonas
Culture Campylobacter selles
Négatif
Culture Clostridium difficile selles
GDH (Ag Clostridium difficile) Négatif
Toxine C. diff. A&B/selles: Négatif
Négatif

CONCLUSION :
Colite chronique légèrement active.
Recoupe et immunomarquage en cours.

Un immunomarquage CD 3 été réalisé. Absence d'augmentation significative des lymphocytes intraépithéliaux.
Un immunomarquage a été réalisé à la recherche de CMV. Il est négatif.
La coloration spéciale de trichrome ne montre pas d'épaississement de la membrane basale sous épithéliale.

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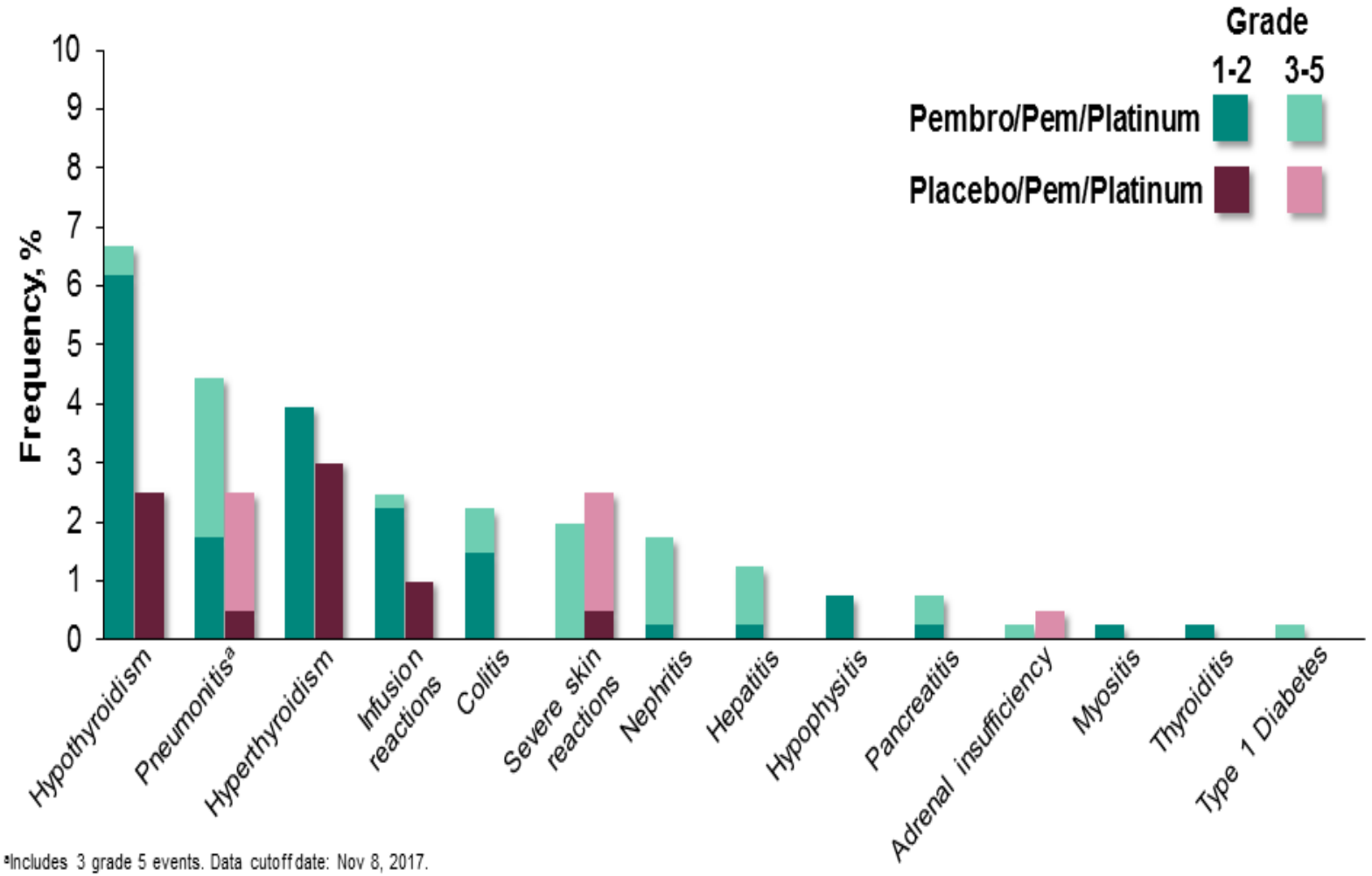
Immune-Mediated Adverse Events



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Management of toxicities of immune checkpoint inhibitors

Lavinia Spain, Stefan Diem, James Larkin *

Management of immune-related diarrhoea, colitis and hepatitis.

	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
Diarrhoea and Enterocolitis	*<4 bowel actions per day over baseline; mild:* supportive measures such as increasing oral fluid, anti-motility agents such as loperamide	*4–6 bowel actions per day over baseline; moderate:* withhold ICPI. As per Grade 1 if patient is well. If no improvement in 5 days, or if worsening of symptoms, commence steroids at a dose of 0.5–1 mg/kg per day of prednisolone (or IV equivalent) and continue until symptoms improve to G1. If no improvement occurs, manage as per G3. Steroids can be tapered over 2–4 weeks. Sigmoidoscopy and biopsy can be considered and may assist in determining the duration of steroid taper based on the macroscopic and microscopic inflammation evident	*⩾7 bowel actions per day over baseline; severe symptoms:* admit patient to hospital for intravenous hydration and clinical observation as appropriate. Commence steroids at 1–2 mg/kg prednisolone or IV equivalent. If no improvement in 2–3 days, commence infliximab 5 mg/kg and continue steroids. Infliximab is contraindicated in patients with sepsis or a perforation. Sigmoidoscopy and biopsy recommended to exclude other causes. Once symptoms resolve to G1, taper steroids over minimum 1 month (up to 3 months for severe cases). Infliximab may be re-administered at 2 and 6 weeks if symptoms persist or recur. Dietician input recommended	*Life threatening consequences, urgent intervention indicated:* management as per G3. Involve gastroenterologist and surgeon in management. Permanently discontinue ICPI
Hepatitis	*ALT/AST up to 3 times ULN:* continue ICPI. Send viral serology looking for hepatitis A, B C and CMV and iron studies to look for underlying haemochromatosis. Advise against excessive alcohol intake	*3 to 5 times ULN:* withhold ICPI. Product information (Ipi, Nivo, Pembro) recommends initiation of steroids with prednisolone 1–2 mg/kg/day or IV equivalent. If patient is well, it is reasonable to re-check liver function every 2 days and initiate steroids if no improvement or worsening. Taper steroids over 4 weeks once liver function G1 or at baseline	*5 to 20 times ULN:* as per Grade 2 except that steroids should be initiated immediately. Ipilimumab should be permanently discontinued. Consider permanent discontinuation of anti-PD-1 drugs	>20 times ULN: as per Grade 3. Permanently discontinue ICPI

Cancer Treatment Reviews 44 (2016) 51–60

09/2019: Dyspnée

Examen: Lavage broncho-alvéolaire
RENSEIGNEMENTS CLINIQUES
Symptômes pulmonaires.:Symptômes pulmonaires
Tests diagnostiques rapides
I.F. Pneumocystis jiroveci: Négatif
Examen direct
Leucocytes 1 - 5 /champ
Eosinophiles 1 - 5 /champ
Cellules épithéliales 1 - 5 /champ
Erythrocytes 6 -10 /champ
Macrophages 1 - 5 /champ
Cellules bronchiques 1 - 5 /champ
Cocci Gram positif
diplocoques en chaînettes 1 - 5 /champ
Culture aérobie
20.000 col/ml Flore salivaire
Culture anaérobie
Négatif

Examen direct mycologie
Culture moisissures: Négatif
Culture levures: Négatif

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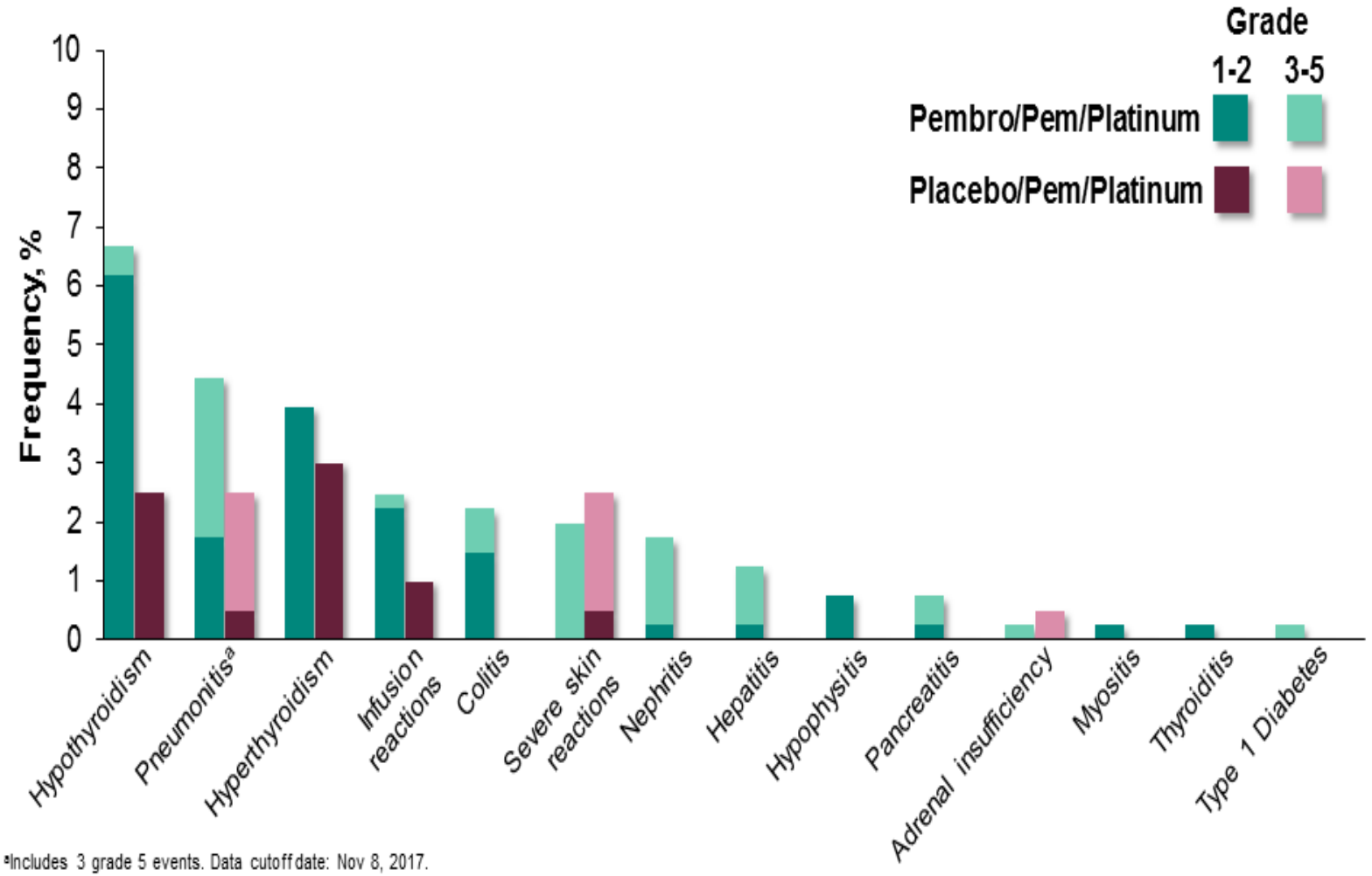
Immune-Mediated Adverse Events



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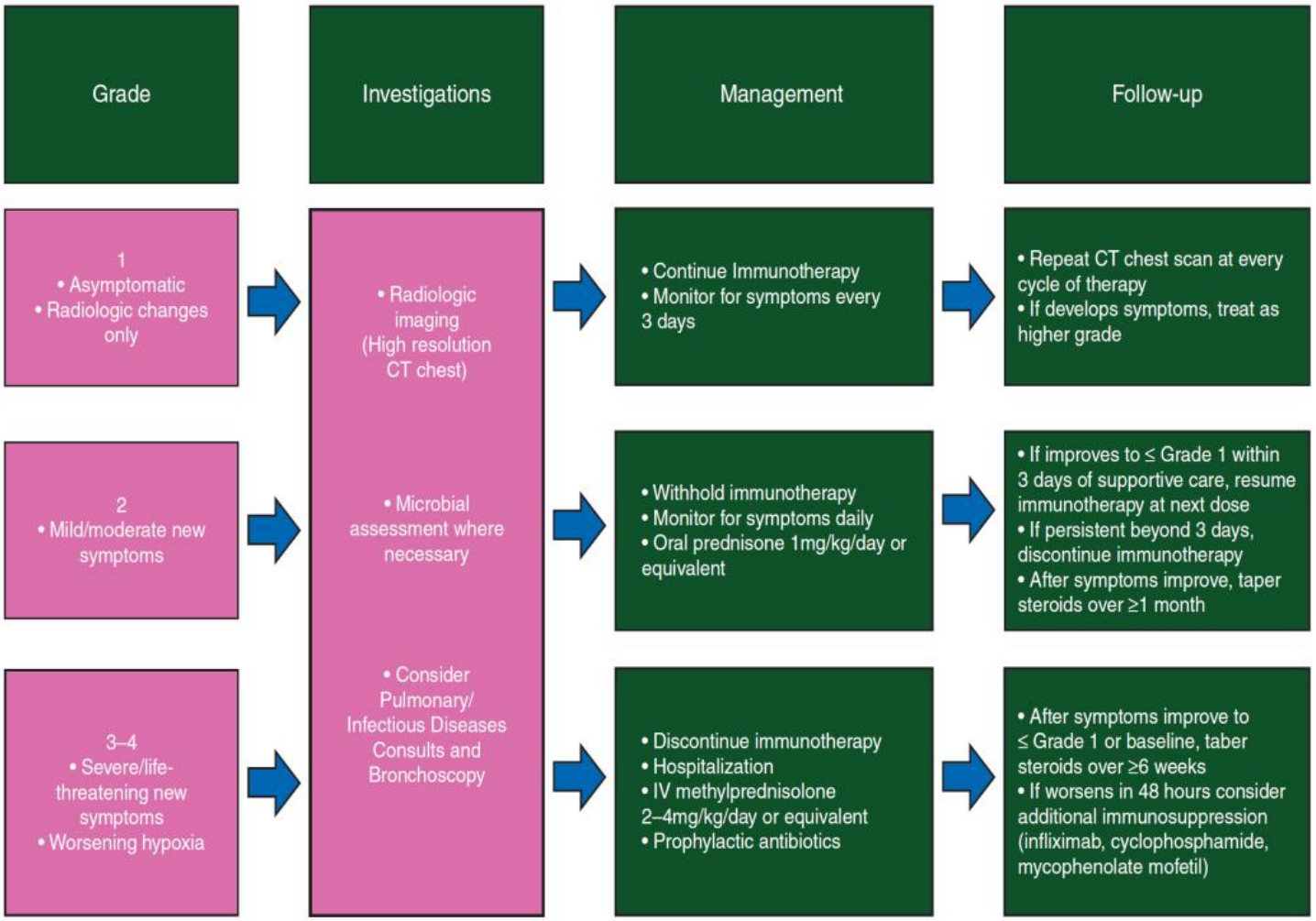

Figure 3. Adapted management algorithm for pneumonitis with immune checkpoint blockade.

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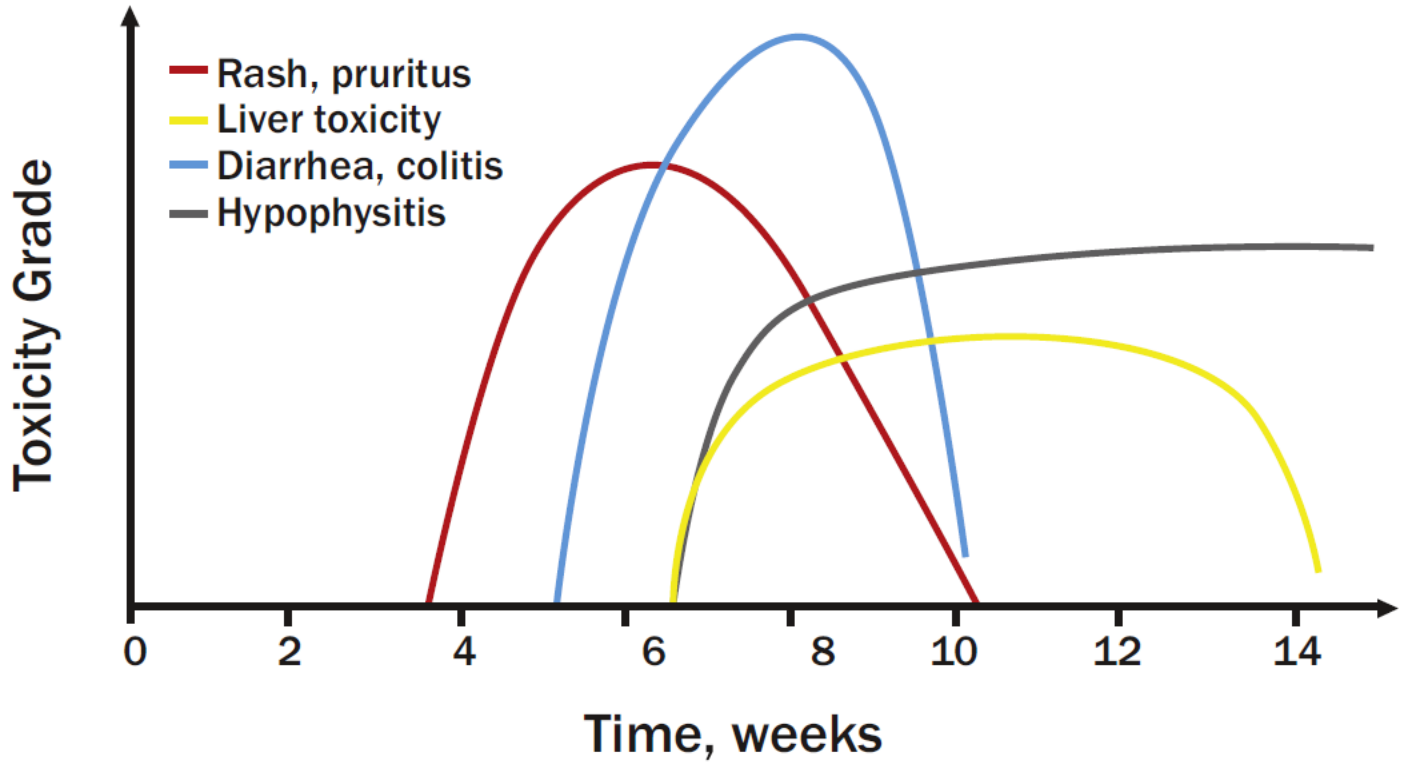
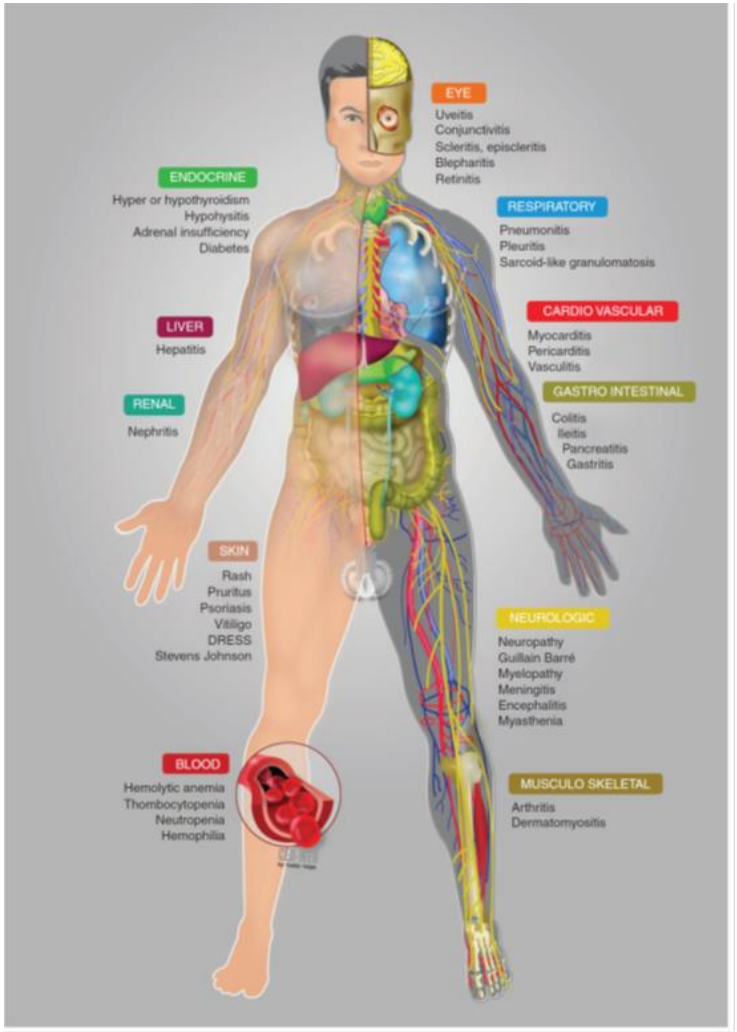


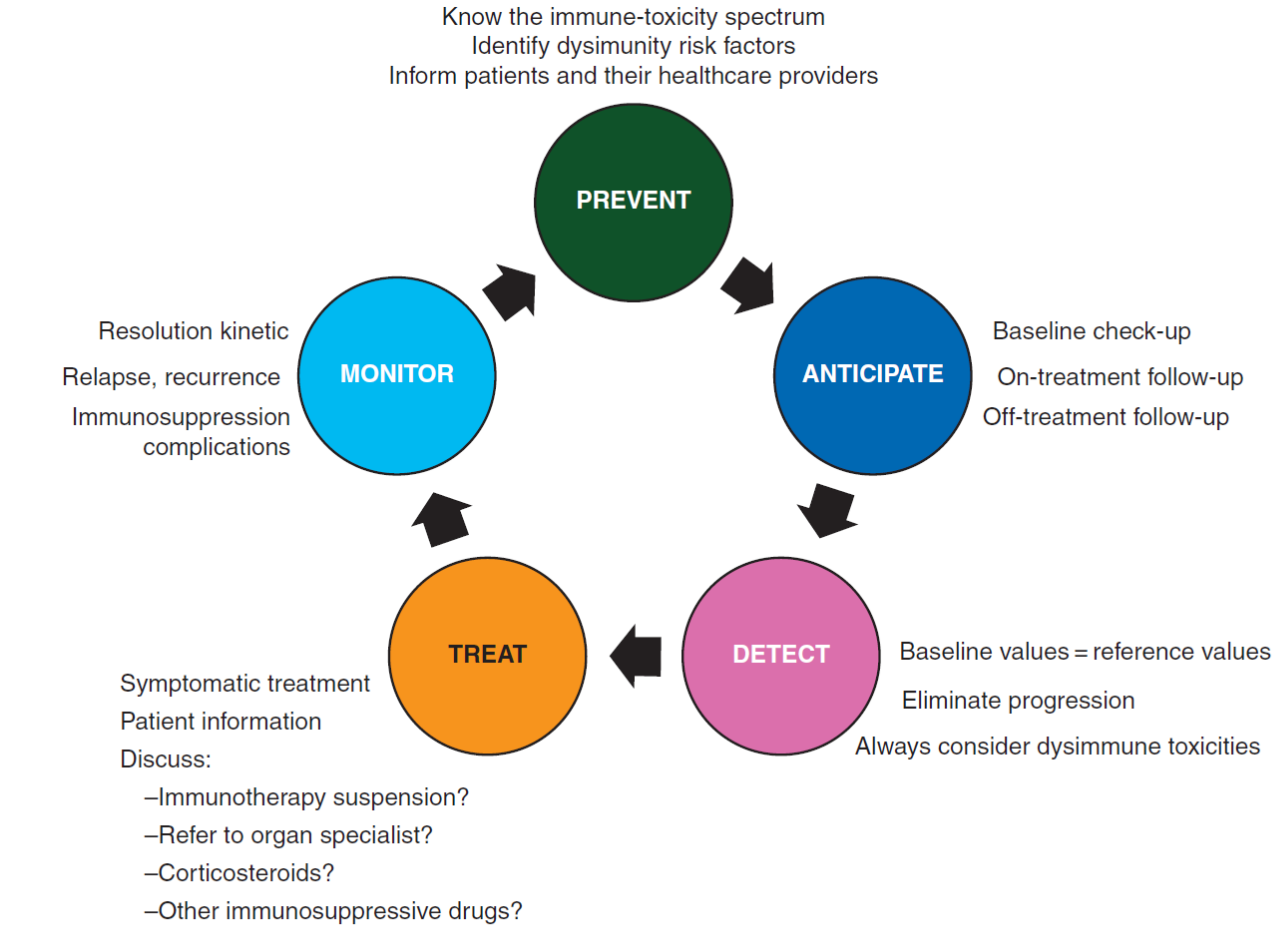
Figure 1. Kinetics of the onset of immune-related adverse events. Reprinted with permission from Weber JS, Kähler KC, Hauschild A. J Clin Oncol. 2012;30:2691-2697. Copyright © 2012 American Society of Clinical Oncology.[40]

Types de toxicités



Annals of Oncology 27: 559–574, 2016

Quand y penser?



I. The five pillars of immunotherapy toxicity management.

Annals of Oncology 27: 559–574, 2016

Table 2. Immunotherapy baseline checklist

- Physical examination
  - Performance status
  - Weight, size, body mass index
  - Heart rate and blood pressure
  - General symptoms such as asthenia or appetite should be evaluated as they are frequently affected
  - Particularly pay attention to pre-existing symptoms regarding: intestinal transit, dyspnea and coughing, rash, nausea, headaches, signs of motor or sensory neuropathy and arthralgia
  - History of fever or recent infection must be checked and investigated appropriately
  - Baseline electrocardiogram
  - Ongoing treatment
- Laboratory test
  - Complete CBC
  - Serum electrolytes: Na, K, alkaline reserve, calcium, phosphorus, uric acid, urea, creatinine with estimated GFR (MDRD or CKD EPI)
  - Glycemia
  - Total bilirubin, AST, ALT, GGT, PAL
  - Albuminemia, CRP
  - TSH, T4
  - Cortisol and ACTH at 8 am
  - LH FSH estradiol testosterone
  - Proteinuria: morning sample, fasting if possible (g/l with concomitant dosing creatinine in mmol/l)—better than an urine dipstick to detect low levels of proteinuria and tubular proteinuria
  - Urinary sediment
  - Quantiferon tuberculosis or TST in case of anterior exposure
  - Virology: HIV, HCV and HBV serology
  - Antibody: ANA, TPO Ab, Tg Ab
  - If doable, we recommend a plasma/serum biobanking before the beginning of immunotherapy to retrospectively titrate at baseline any other factor of interest in case of development of toxicity with biological marker.
- Imaging
  - X-ray chest imaging reference is recommended at baseline
  - The conventional pretherapeutic thoracic CT scan should be performed with thin sections with and without injection to have a baseline reference in case a pulmonary toxicity occurs.

Annals of Oncology 27: 559–574, 2016

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

Background: Cancer immunotherapy with checkpoint inhibitors (CPIs) is associated with frequent immune-related adverse events (irAEs) and is often not recommended for patients with concomitant autoimmune disease.

Purpose: To summarize the evidence on adverse events associated with CPIs in patients with cancer and preexisting autoimmune disease.

Data Sources: MEDLINE, EMBASE, Web of Science, PubMed ePubs, and the Cochrane Central Register of Controlled Trials through September 2017 with no language restrictions.

Study Selection: Original case reports, case series, and observational studies describing patients with cancer and autoimmune disease who were receiving CPIs.

Data Extraction: 2 reviewers independently extracted data and assessed the quality of reporting.

Data Synthesis: 123 patients in 49 publications were identified; 92 (75%) had exacerbation of preexisting autoimmune disease, irAEs, or both. No differences in adverse events were observed in patients with active versus inactive disease. Patients receiving immunosuppressive therapy at initiation of CPI therapy seemed to have fewer adverse events than those not receiving treatment. Most flares and irAEs were managed with corticosteroids; 16% required other immunosuppressive therapies. Adverse events improved in more than half of patients without discontinuation of CPI therapy. Three patients died of adverse events.

Limitations: The quality and quantity of data were limited. Case reports typically describe unique manifestations and are not generalizable to the population at large. Because there were no prospective observational studies, incidence could not be determined.

Conclusion: Flares and irAEs in patients with autoimmune disease who are receiving CPIs can often be managed without discontinuing therapy, although some events may be severe and fatal. Prospective longitudinal studies are needed to establish incidence of adverse events and evaluate risk–benefit ratios and patient preferences in this population.

Primary Funding Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Ann Intern Med. doi:10.7326/M17-2073 **Annals.org**

For author affiliations, see end of text.

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Table 1. Patient Demographic and Baseline Characteristics

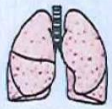
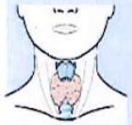
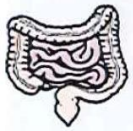
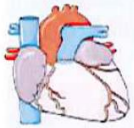
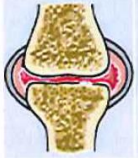
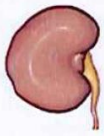
Characteristic	Value
Median age (range), y*	61.4 (26-87)
Sex, *n* (%)†	
Male	68 (57.1)
Female	51 (42.9)
Current cancer, *n* (%)	
Metastatic melanoma	103 (83.7)
Lung cancer	16 (13.0)
Renal cell cancer	3 (2.4)
Merkel cell carcinoma	1 (0.8)
Preexisting autoimmune disease, *n* (%)	
Psoriatic arthritis and/or psoriasis	28 (22.8)‡
Rheumatoid arthritis	20 (16.3)
Autoimmune thyroid disease	11 (8.9)§
Ulcerative colitis	8 (6.5)
Crohn disease	5 (4.1)
Multiple sclerosis	6 (4.9)
Sarcoidosis	5 (4.1)
Myasthenia gravis	4 (3.3)
Eosinophilic granulomatosis with polyangiitis	2 (1.6)
Inflammatory arthritis	2 (1.6)
Psoriasis and autoimmune thyroid disease	2 (1.6)‖
Spondyloarthropathy	2 (1.6)
Systemic lupus erythematosus	2 (1.6)
Vitiligo	2 (1.6)
Ankylosing spondylitis	1 (0.8)
Ankylosing spondylitis and psoriasis	1 (0.8)
Behçet disease	1 (0.8)
Celiac disease	1 (0.8)
Cold agglutinin	1 (0.8)
Crohn disease and sarcoidosis	1 (0.8)
Crohn disease and psoriasis	1 (0.8)
Granulomatosis with polyangiitis (sinus-limited)	1 (0.8)
Guillain-Barrė syndrome	1 (0.8)
Idiopathic thrombocytopenic purpura	1 (0.8)
IgA nephropathy	1 (0.8)
IgM nephropathy	1 (0.8)
Melanoma-associated retinopathy	1 (0.8)
Melanoma-associated retinopathy and vitiligo	1 (0.8)
Myositis	1 (0.8)
Polymyalgia rheumatica	1 (0.8)
Rheumatoid arthritis and polymyalgia rheumatica	1 (0.8)
Rheumatoid arthritis and myasthenia gravis	1 (0.8)
Reactive arthritis	1 (0.8)
Rheumatic fever	1 (0.8)
Sjögren syndrome	1 (0.8)
Seronegative rheumatoid spondyloarthritis and autoimmune thyroid disease	1 (0.8)
Transverse myelitis	1 (0.8)
Type 1 diabetes	1 (0.8)

Incidence

Table 1. Immune checkpoint blockade (ICB) toxicities

Frequent (>10%) ICB toxicities
- Ipilimumab (anti-CTLA4): diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite and abdominal pain
- Nivolumab (anti-PD1): fatigue, rash, pruritus, diarrhea and nausea
- Pembrolizumab (anti-PD1): diarrhea, nausea, pruritus, rash, arthralgia and fatigue

Rare (<10%) life-threatening ICB toxicities
- Colitis and risk of gastrointestinal perforation
- Pneumonitis including acute interstitial pneumonia/acute respiratory distress syndrome
- Infusion reaction and anaphylactic shock
- Type 1 diabetes and risk of diabetic ketoacidosis
- Severe skin reactions, DRESS, Stevens Johnson syndrome
- Hemolytic anemia or immune thrombocytopenia and hemorrhagic risk
- Neutropenia and sepsis risk
- Encephalopathy and neurological sequelae
- Guillain–Barré syndrome and respiratory risk
- Myelitis and motor sequelae
- Myocarditis and cardiac insufficiency
- Acute adrenal insufficiency and hypovolemic shock
- Pleural and pericardial effusion
- Nephritis

Organe	Étiologies des toxicités	Incidence en monothérapie par anti-PD-1/PD-L1	Incidence en monothérapie par anti-CTLA-4	Incidence en bithérapie par anti CTLA4 et antiPD-1/L-1
	Pneumopathie interstitielle diffuse	De 1% à 5%	Peu décrit	6,6%
	Exanthème maculo-papuleux Exacerbation de psoriasis Réactions lichenoïdes Vitiligo Atteinte muqueuse buccale	De 37,4 à 41,9%	De 43,7 à 58,7%,	Jusqu'à 71,3%
	Hypophysite Dysthyroïdie Diabète type 1 Insuffisance surrénalienne	Hypophysite : <1% Dysthyroïdies: 6-18%	Hypophysite : 1-17% Dysthyroidies : 6%	Hypophysite : 8% Dysthyroïdies : 22%
	Diarrhées Entérocolites	15%	30%	35 à 40%
	Hépatite auto-immune	5 à 10 %	<4%	10 à20%
	Myocardite	0,09%	Plusieurs cas rapportés	0,027%
	Arthralgies Polyarthrite	5%	5 à 10%	Jusqu'à 10%
	Néphrite interstitielle Néphrite granulomateuse	1%	1%	Jusqu'à 6%

Delaunay, Rev Mal Respir 2018,

Diagnostic différentiel

Table 3. Symptoms and laboratory abnormalities associated with immune-related toxicities

	Symptoms	Frequently associated diagnosis in oncology	Immune-related adverse events to be suspected
General	Headache	Intracranial hypertension	Febrile headache: dysimmune meningitis
		Leptomeningeal metastasis	Non-febrile headache: dysimmune hypothyroidism
		Cerebral hemorrhage	Progressive: hypophysitis
		Meningitis due to carcinomatous meningitis or opportunistic infection	Acute/subacute: stroke due to vasculitis
		Other drug-related	
	Acute confusion	Metastatic brain evolution, carcinomatous meningitis	Febrile confusion: dysimmune meningoencephalitis
		Sepsis	Afebrile confusion: encephalitis, hypophysitis
		Metabolic: hypercalcemia, dysnatremia	Acute/subacute: stroke due to vasculitis
		Encephalopathy: hypoxic/hypercapnic/liver/uremic	Hyperosmolar coma linked to dysimmune diabetes
		Iatrogeny: new drug, pain	
		Urinary globe, fecal impaction	
		Toxic	
	Chest pain	Pulmonary embolism	Dysimmune pericarditis
		Pneumonia /pleurisy infectious	Dysimmune myocarditis
		Tumor pleurisy	Dysimmune pleurisy
		Parietal tumor invasion	Dysimmune gastritis
		Rib fractures	
		Pneumothorax	
		Shingles	
		Anxiety	
	Asthenia	Brain tumor progression	Endocrine: dysimmune hypothyroidism, dysimmune hypophysitis with antipituitary insufficiency, adrenal acute failure, dysimmune diabetes
		Sepsis	
		Chronic pain	Metabolic: renal failure on dysimmune nephropathy,
		Iatrogenic: opiates, psychotropic, antiepileptics, …	Neurological and muscular: dysimmune encephalitis, acute polyradiculoneuropathy, dysimmune myositis, dysimmune myasthenia
		Metabolic: dysnatremia, anemia, hypercalcemia (paraneoplastic, bone metastases …)	Blood: dysimmune hemolytic anemia
		Iatrogenic: corticosteroids: steroid myopathy or adrenal insufficiency id steroids stopped	Induced connective tissue disease
		Toxicities of previous treatments: surgery, radiotherapy and cerebral postradiation encephalopathy, …	
		Depression	
		Decompensation of chronic organ failure: renal, cardiac, respiratory, liver	
	Peripheral edema	Vein thrombosis	Nephro: dysimmune nephropathy with glomerulonephritis
		Compression venous or lymphatic tumor	Cardio: dysimmune pericarditis, dysimmune myocarditis
		Sodium retention with corticosteroids	Endoc: dysimmune hypothyroidism
		Malnutrition	Systemic: dysimmune vasculitis, APLS with thrombosis
		Venous stasis-related movement disorders or sensory (brain tumor, spinal cord compression, neuropathy)	Neuro: dysimmune neuropathy

	Symptoms	Frequently associated diagnosis in oncology	Immune-related adverse events to be suspected
	Weight loss	Tumor progression	Dysimmune gastritis
		Mechanical obstruction digestive tumor/ENT	Dysimmune enterocolitis
		Oral thrush, bad dental status	Celiac disease
		Digestive surgery: derivation/short bowel syndrome	Dysimmune hyperthyroidism
		Radiation-induced esophagitis	Dysimmune hypophysitis
		Mucositis in chemotherapy	Dysimmune adrenal insufficiency
		Long-term corticosteroid	Dysimmune diabetes
		Toxic: nausea/vomiting in opiates	Induced systemic diseases
		Pain	
		Depression	
		Hypercatabolism related to inflammatory syndrome	
		Loss of autonomy for food	
	Influenza syndrome, fever	Sepsis: infection of the catheter, pneumonia, urinary tract infection, cholangitis, erysipelas, deep infection	ILI reaction to immunotherapy
			Dysimmune colitis
		Thrombosis phlebitis	Hyperthyroidism
		Tumor-specific inflammation (elimination diagnosis)	Thrombosis
		Paraneoplastic	Vasculitis
Neurologic	Sensory loss	Medullary compression/metastatic evolution	Dysimmune mononeuritis
		Carcinomatous meningitis	Dysimmune Polyradiculoneuritis/Guillain–Barré
		Neurotoxicity previous treatments	Encephalitis
		Paraneoplastic	Myelitis
			Vasculitis
	Motor deficit	Medullary compression/metastatic evolution	Dysimmune mononeuritis
		Carcinomatous meningitis	Dysimmune polyradiculoneuritis/Guillain–Barré
		Neurotoxicity previous treatments	Encephalitis
		Paraneoplastic	Myelitis
			Vasculitis
			Myasthenia
			Myositis
	Seizure	Brain metastasis and carcinomatous meningitis	Dysimmune encephalitis
		Infectious encephalitis	
		Neurotoxicity previous treatment	
		Paraneoplastic	
Cutaneous	Rash	Anaphylactic or anaphylactoid urticarial (off target effects of conventional drugs)	Immune-related hives, eczema (on-target off tumor effects of immune-targeted drugs)
			Pemphigus
	Pruritus	Cholestasis secondary to liver/pancreatic metastasis	Dysimmune hypo/hyperthyroidism
			Immune-related hives, eczema

Respiratory	Acute dyspnea/desaturation	Pneumonia/pleurisy infectious, aspiration pneumonia	Dysimmune interstitial lung disease
		Thoracic tumor invasion	Hydrops, pleurisy autoimmune
		Bronchial tumor compression/	Dysimmune pericarditis
		specific pleurisy/lymphangitis carcinomatosis	Dysimmune myocarditis
		Rib fractures on bone metastases	Dysimmune myasthenia
		Tumoral hemoptysis	Acute autoimmune polyradiculoneuropathy
		Pneumothorax	
		Anemia	
		Overdose of morphine, benzodiazepines	
		Anxiety	
Rheumatic	Arthralgia	Bone metastasis	Dysimmune arthritis
		Referred pain of visceral metastasis	
		Thrombosis	
		pathological fracture	
Digestive	Abdominal pain	Tumor compression of the biliary tract, urinary tract, pancreatic ducts	Dysimmune enterocolitis
		Peritoneal tumor invasion	Dysimmune pancreatitis
		Tumor or iatrogenic bowel obstruction	Dysimmune gastritis
		Intra-abdominal infection (cholecystis …)	Dysimmune pericarditis
		Hypercalcemia	Dysimmune myocarditis
		Pancreatitis (lithiasis, alcohol …)	Dysimmune pleurisy
		Thrombosis	Occlusive syndrome of enteric neuropathy
			Occlusive syndrome in dysimmune hypothyroidism
			Acute adrenal insufficiency
			Ketoacidosis due to dysimmune diabetes
	Diarrhea	Secondary to antibiotic use	Dysimmune enterocolitis
		Enteropathy due to cancer	Celiac disease
		Clostridium difficile	Dysimmune hyperthyroidism
		Exocrine pancreatic insufficiency on tumor compression	
	Nausea vomiting	Bowel obstruction by the tumor	Dysimmune meningitis
		Carcinomatous peritonitis	Dysimmune enterocolitis
		Carcinomatous meningitis	Ketoacidosis due to dysimmune diabetes
		Intracranial hypertension	Dysimmune adrenal insufficiency
		Hypercalcemia	Dysimmune nephropathy
		Hyponatremia	Dysimmune pancreatitis
			Dysimmune hepatitis
Hepatic	Liver Enzymes Elevation	Hepatic cancer progression	Dysimmune hepatitis
		Sepsis	Dysimmune myocarditis (AST)
		Concurrent medication	Dysimmune myositis (AST)
			Dysimmune hemolytic anemia (AST)
	Jaundice, bilirubin elevation GGT and ALP elevation	Intrinsic liver cancer progression, gall, locoregional tumor or extrinsic compression	Dysimmune hepatitis
			Sclerosing cholangitis
		Sepsis	Primary biliary cirrhosis
		Medication, parenteral nutrition	Dysimmune granulomatosis
			Dysimmune hemolytic anemia (unconjugated bilirubin)

Sévérité et traitement

Table 4. Typical management of irAEs

Severity—CTCAE grade	Ambulatory versus inpatient care	Corticosteroids	Other immunosuppressive drugs	Immunotherapy
1	Ambulatory	Not recommended	Not recommended	Continue
2	Ambulatory	Topical steroids or Systemic steroids oral 0.5–1 mg/kg/day	Not recommended	Suspend temporarily[a]
3	Hospitalization	Systemic steroids Oral or i.v. 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ Specialist referral advised	Suspend and discuss resumption based on risk/benefit ratio with patient
4	Hospitalization consider intensive care unit	Systemic steroids i.v. methylprednisolone 1–2 mg/kg/day for 3 days then reduce to 1 mg/kg/day	To be considered for patients with unresolved symptoms after 3–5 days of steroid course Organ specialist referral advised	Discontinue permanently

Some dysimmune toxicities may follow a specific management: this has to be discussed with the organ specialist.
[a]Outside skin or endocrine disorders where immunotherapy can be maintained.

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in

Methods

A multidisciplinary, multi-organizational panel of experts in medical oncology, dermatology, gastroenterology, rheumatology, pulmonology, endocrinology, urology, neurology, hematology, emergency medicine, nursing, trialist, and advocacy was convened to develop the clinical practice guideline. Guideline development involved a systematic review of the literature and an informal consensus process. The systematic review focused on guidelines, systematic reviews and meta-analyses, randomized controlled trials, and case series published from 2000 through 2017.

Results

The systematic review identified 204 eligible publications. Much of the evidence consisted of systematic reviews of observational data, consensus guidelines, case series, and case reports. Due to the paucity of high-quality evidence on management of immune-related adverse events, recommendations are based on expert consensus.

Recommendations

Recommendations for specific organ system–based toxicity diagnosis and management are presented. While management varies according to organ system affected, in general, ICPi therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities. ICPi therapy may be suspended for most grade 2 toxicities, with consideration of resuming when symptoms revert to grade 1 or less. Corticosteroids may be administered. Grade 3 toxicities generally warrant suspension of ICPis and the initiation of high-dose corticosteroids (prednisone 1 to 2 mg/kg/d or methylprednisolone 1 to 2 mg/kg/d). Corticosteroids should be tapered over the course of at least 4 to 6 weeks. Some refractory cases may require infliximab or other immunosuppressive therapy. In general, permanent discontinuation of ICPis is recommended with grade 4 toxicities, with the exception of endocrinopathies that have been controlled by hormone replacement. Additional information is available at

Home » Immunomanager » **Immune-related Adverse Events (irAE)**

Immune-related Adverse Events (irAE)

In case of preexisting autoimmune disorder, discussion with the organ specialist (eg. rheumatologist) is indicated.

Immune CheckPoint Inhibition (ICPI)

- Joint pathology →
- Colitis →
- Skin toxicity →
- Hepatitis →
- Nephritis →
- Neurologic →
- Pneumonitis →
- Endocrine →
- Muscle pathology →

Immune Checkpoint Inhibition in combination with TKI

- Axitinib + anti-PD-(L)1 →

https://www.bsmo.be/immunomanager/

Myastenia gravis

Polymyalgia rheumatica →

Myositis →

Myastenia gravis →

Management escalation pathway

- Steroids indicated (oral or i.v.)
- Pyridostigmine initial dose 30 mg
- Neurological consult If no improvement, or worsening, plasmapheresis or IVIG may be considered
- Avoid certain medications, that may precipitate cholinergic crisis (e.g. ciprofloxacin, beta blockers, amikacin, benzodiazepines and above all curares during general anesthesia)')

Assessment and Investigations

- Check for ocular muscle and proximal muscle fatigability AChr and MuSK antibodies
- Bedsides tests, e.g. Tensilon test or ice pack test with neurological input
- Repetitive nerve stimulation and single fibre EMG
- Exclude myocarditis with cardiac enzymes (and cardiac MRI in case of doubt) (cave pseudo myasthenic myositis)

Emergency presentations in patients treated with immune checkpoint inhibitors

Tim Cooksley*, Avinash Gupta, Tamer Al-Sayed, Paul Lorigan

Table 4
Frequency and nature of immune-mediated toxicities in emergency presentations in patients treated with ICIs.

Diagnosis	Number
Immune-mediated	98 (32.7%)
Colitis	38 (12.7%)
Hepatitis	19 (6.3%)
Pneumonitis	14 (4.7%)
Nephritis	7 (2.3%)
Hypophysitis	6 (2.0%)
Dermatitis	6 (2.0%)
Cerebral vasculitis	1 (0.3%)
DKA	1 (0.3%)
Gastritis	1 (0.3%)
Meningoencephalitis	1 (0.3%)
Myocarditis	1 (0.3%)
Pancreatitis	1 (0.3%)
Pruritus	1 (0.3%)
Thrombocytopaenia	1 (0.3%)
Non-immune-mediated presentation	202 (67.3%)

2% de mortalité liée

European Journal of Cancer 130 (2020) 193–197

Immune checkpoint blockade toxicity among patients with cancer presenting to the emergency department

Olivier Peyrony,[1] Yoann Tieghem,[1] Jessica Franchitti,[1] Sami Ellouze,[1] Ivonne Morra,[1] Isabelle Madelaine-Chambrin,[2] Remi Flicoteaux,[3] Barouyr Baroudjian,[4,5] Elie Azoulay,[6,7] Sylvie Chevret,[3,7] Jean-Paul Fontaine[1]

139 ED/409 (34%) ICB treated

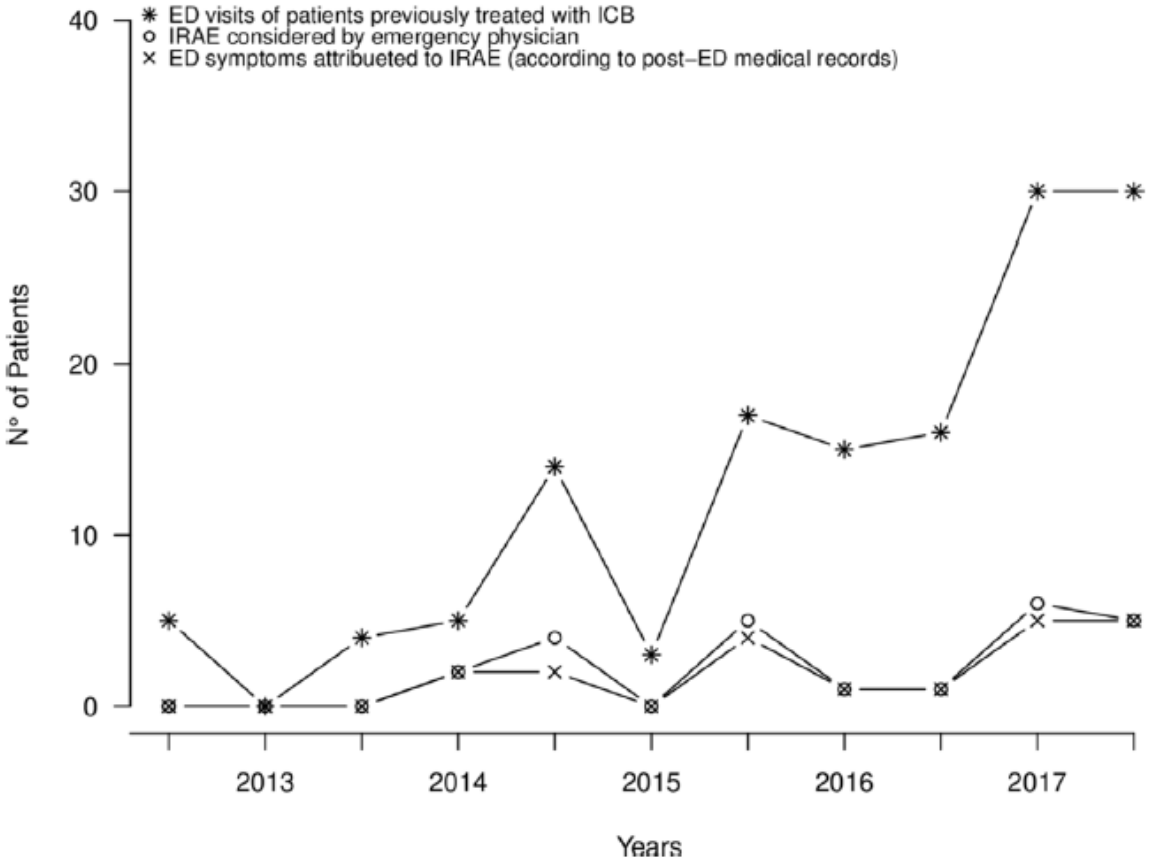


Figure 1 Number of ED visits, IRAE and consideration of IRAE by emergency physician over the years. ED, emergency department; ICB, immune checkpoint blockade; IRAE, immune-related adverse event.

Table 1 Characteristics of the patients treated with ICB presenting to the ED

			IRAE (according to referring oncologist opinion in post-ED medical records)			
	Whole sample		No		Yes	
N	139		119		20	
Age, median IQR	60	49–69	60	49–68	67	48–75
Female, n %	61	43.9	53	44.5	8	40.0
Cancer type, n %						
Melanoma	91	65.5	73	61.4	18	90.0
Lung cancer	34	24.5	33	27.7	1	5.0
Other	14	10.0	13	10.9	1	5.0
Cancer status, n %						
Remission or newly diagnosed	22	15.8	17	14.3	5	25,0
Progression	117	84.2	102	85.7	15	75.0
Number of distinct ICB courses, n %						
1	114	82.0	102	85.7	12	60.0
2	25	18.0	17	14.3	8	40.0
Number of ICB medications n %						
1	105	75.5	95	79.8	10	50.0
>1	34	24.5	24	20.2	10	50.0
Number of ICB cycles, median IQR	4	2–7	4	2–7	4	3–11
ICB medication, n %						
Nivolumab	68	48.9	62	52.1	6	30.0
Ipilimumab	58	41.7	44	37.0	14	70.0
Pembrolizumab	22	15.8	17	14.3	5	25.0
Atezolizumab	3	2.2	3	2.5	0	0.0
Ipilimumab–nivolumab	12	8.6	9	7.6	3	15.0
History of prior IRAE, n %	21	15.1	17	14.3	4	20.0
Days since last infusion of ICB, median IQR	15	7–46	15	7–60	12	11–24
Chief complaint, n %						
Fatigue	35	25.2	29	24.4	6	30.0
Fever	32	23.0	27	22.7	5	25.0
Vomiting	19	13.7	15	12.6	4	20.0
Diarrhoea	19	13.7	9	7.5	10	50.0
Dyspnoea	17	12.2	16	13.4	1	5.0
Abdominal pain	16	11.5	12	10.1	4	20.0
Confusion/altered mental status	12	8.6	11	9.2	1	5.0
Headache	11	7.9	8	6.7	3	15.0
Biological or radiological signs	24	17.3	19	16.0	5	25.0
Emergency physician contacted patient's referring oncologist	71	51.1	59	49.6	12	60.0
Consideration of IRAE according to ED medical record, n %	24	17.3	11	9.2	13	65.0
Final diagnosis according to ED medical record, n %						
Malignancy progression	68	48.9	67	56.3	1	5.0
Infection	22	15.8	19	16.0	3	15.0
IRAE	15	10.8	5	4.2	10	50.0
Other cause	34	24.5	28	23.5	6	30.0
Hospital admission, n %	95	68.3	81	68.1	14	70.0
ICU admission during hospitalisation, n %	7	5.0	3	3.7	4	20.0
Length of stay (days), median IQR	10	4–15	9	4–14	11	6–17
Hospital death, n %	14	10.1	13	10.9	1	5.0

ED, emergency department; ICB, immune checkpoint blockade; ICU, intensive care unit; IRAE, immune-related adverse event.

14.4% des présentations aux urgences sont dues à un IRAE

Table 2 Characteristics of IRAEs

N	20	%
Type of IRAE		
Colitis	8	40.0
Endocrine toxicity	6	30.0
Hypophysitis	2	10.0
Hypothyroidism	2	10.0
Diabetes mellitus	1	10.0
Hypopituitarism	1	10.0
Hepatitis	5	25.0
Pulmonary	1	5.0
Myocarditis	1	5.0
Ototoxicity	1	5.0
Fever	1	5.0
Patients with 1 IRAE	17	85.0
Patients with 2 IRAE	3	15.0
Days since last ICB infusion		
Median	12	
IQR	11–24	
Max	86	

ICB, immune checkpoint blockade; IRAE, immune-related adverse event.

Adverse Effects of Immune Checkpoint Therapy in Cancer Patients Visiting the Emergency Department of a Comprehensive Cancer Center

Imad El Majzoub, MD; Aiham Qdaisat, MD; Kyaw Z. Thein, MD; Myint A. Win, MD; Myat M. Han, MD; Kalen Jacobson, MD; Patrick S. Chaftari, MD; Michael Prejean, RN; Cielito Reyes-Gibby, PhD; Sai-Ching J. Yeung, MD, PhD*

Table 3. Adverse effects of immune checkpoint therapy reported by ED patients with cancer.

Adverse Effect	Ipilimumab	Nivolumab	Pembrolizumab	>1 Medicatior
Total	186 (29.6)	154 (24.5)	109 (17.4)	179 (28.5)
Diarrhea	27 (14.5)	13 (8.4)	7 (6.4)	33(18.4)
Colitis	13 (7.0)	4 (2.6)	2 (1.8)	13 (7.3)
Pneumonitis	6 (3.2)	11 (7.1)	5 (4.6)	8 (4.5)
Dermatitis	8 (4.3)	7 (4.5)	5 (4.6)	14 (7.8)
Hypophysitis	8 (4.3)	1 (0.6)	0	9 (5.0)
Hepatitis	2 (1.1)	11 (6.1)	2 (1.3)	1 (0.9)
Thyroiditis	3 (1.6)	1 (0.6)	0	9 (5.0)
Pancreatitis	2 (1.1)	3 (1.9)	1 (0.9)	9 (5.0)
Adrenalitis	1 (0.5)	2 (1.3)	0	2 (1.1)
Nephritis	0	0	1 (0.9)	1 (0.6)
Hematologic effects	0	0	0	2 (1.1)
Myocarditis	0	0	0	1 (0.6)
Vasculitis	0	1 (0.6)	0	0
Eye effects	0	0	0	1 (0.6)

Data are presented as No. (%).

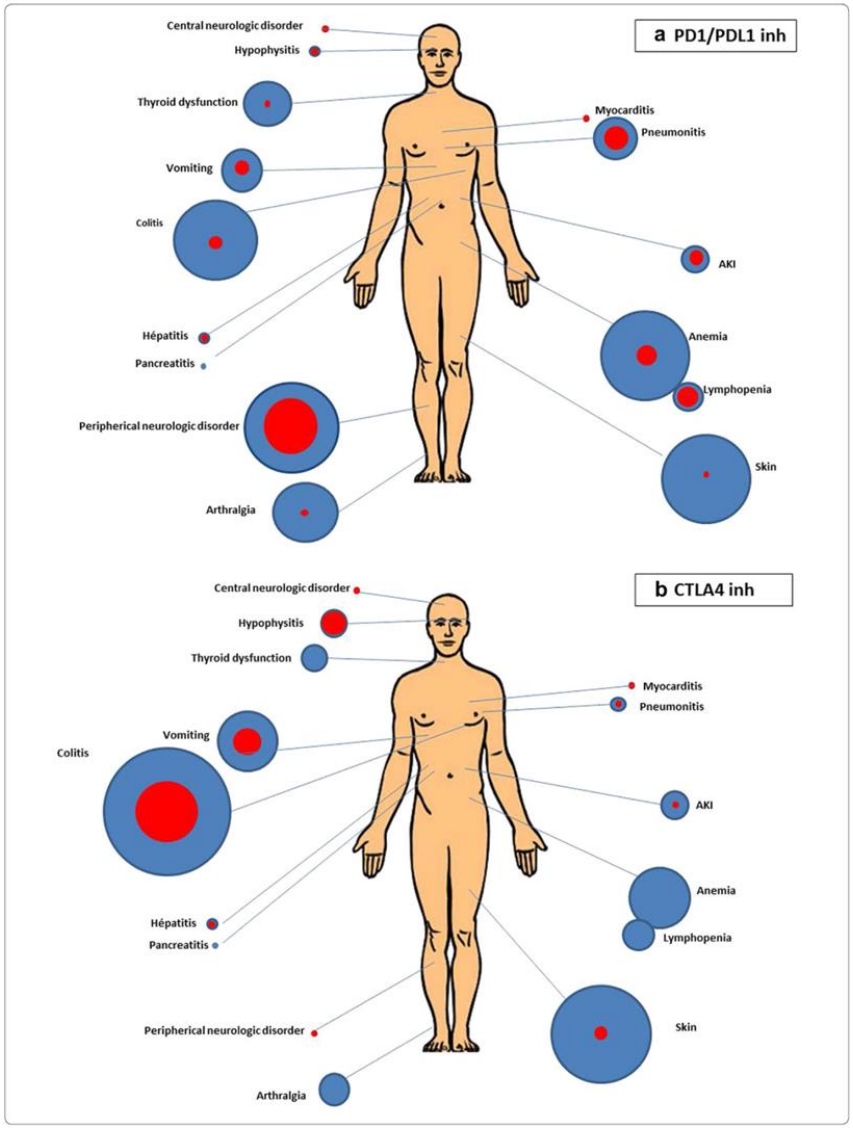
Table 4. Univariable and multivariable Cox regression analysis for overall survival for each immune-related adverse effect.

Adverse Effect	Univariable, HR (95% CI)	Multivariable, All Patients (N = 628), HR* (95% CI)	Multivariable, Patients Without Preexisting Autoimmune Disease (N = 529), HR† (95% CI)
Diarrhea	0.79 (0.53–1.17)	0.80 (0.54–1.20)	0.81 (0.53–1.23)
Colitis	0.45 (0.21–0.95)	0.46 (0.21–0.98)	0.49 (0.23–1.04)
Pneumonitis	1.64 (1.00– 2.69)	1.72 (1.03–2.87)	1.95 (1.09–3.47)
Dermatitis	0.57 (0.29–1.10)	0.60 (0.30–1.17)	0.67 (0.31–1.42)
Hypophysitis	0.54 (0.22–1.30)	0.59 (0.24–1.43)	0.56 (0.21–1.51)
Hepatitis	1.03 (0.42–2.50)	0.91 (0.37–2.24)	1.00 (0.40–2.46)
Thyroiditis	1.01 (0.42–2.46)	1.16 (0.47–2.88)	1.95 (0.78–4.85)
Pancreatitis	0.79 (0.33–1.92)	0.87 (0.36–2.13)	1.05 (0.43–2.60)
Adrenalitis	0.65 (0.16–2.61)	0.72 (0.18–2.96)	0.66 (0.09–4.75)
Myocarditis	4.66 (0.65–33.32)	5.23 (0.70–39.31)	6.05 (0.79–46.07)

*HR adjusted for age, sex, race, Charlson comorbidity index, cancer type, preexisting autoimmune disease, and presence of allergy.
†HR adjusted for age, sex, race, Charlson comorbidity index, cancer type, and presence of allergy.

Severe toxicity from checkpoint protein inhibitors: What intensive care physicians need to know?

Virginie Lemiale[1*], Anne-Pascale Meert[2], François Vincent[3], Michael Darmon[1,4], Philippe R. Bauer[5], Andry Van de Louw[6], Elie Azoulay[1,4] and Groupe de Recherche en Reanimation Respiratoire du patient d'Onco-Hématologie (Grrr-OH)



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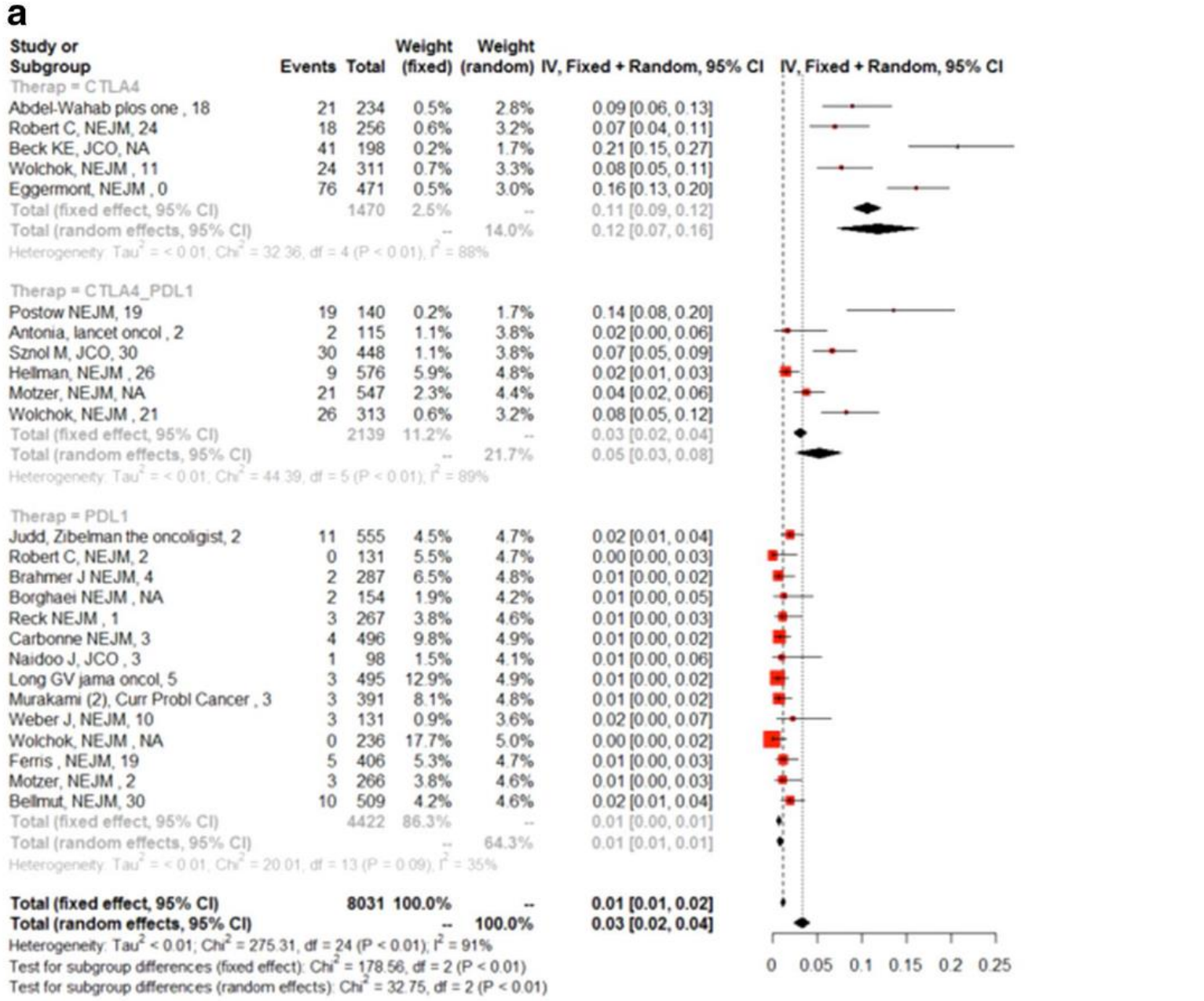
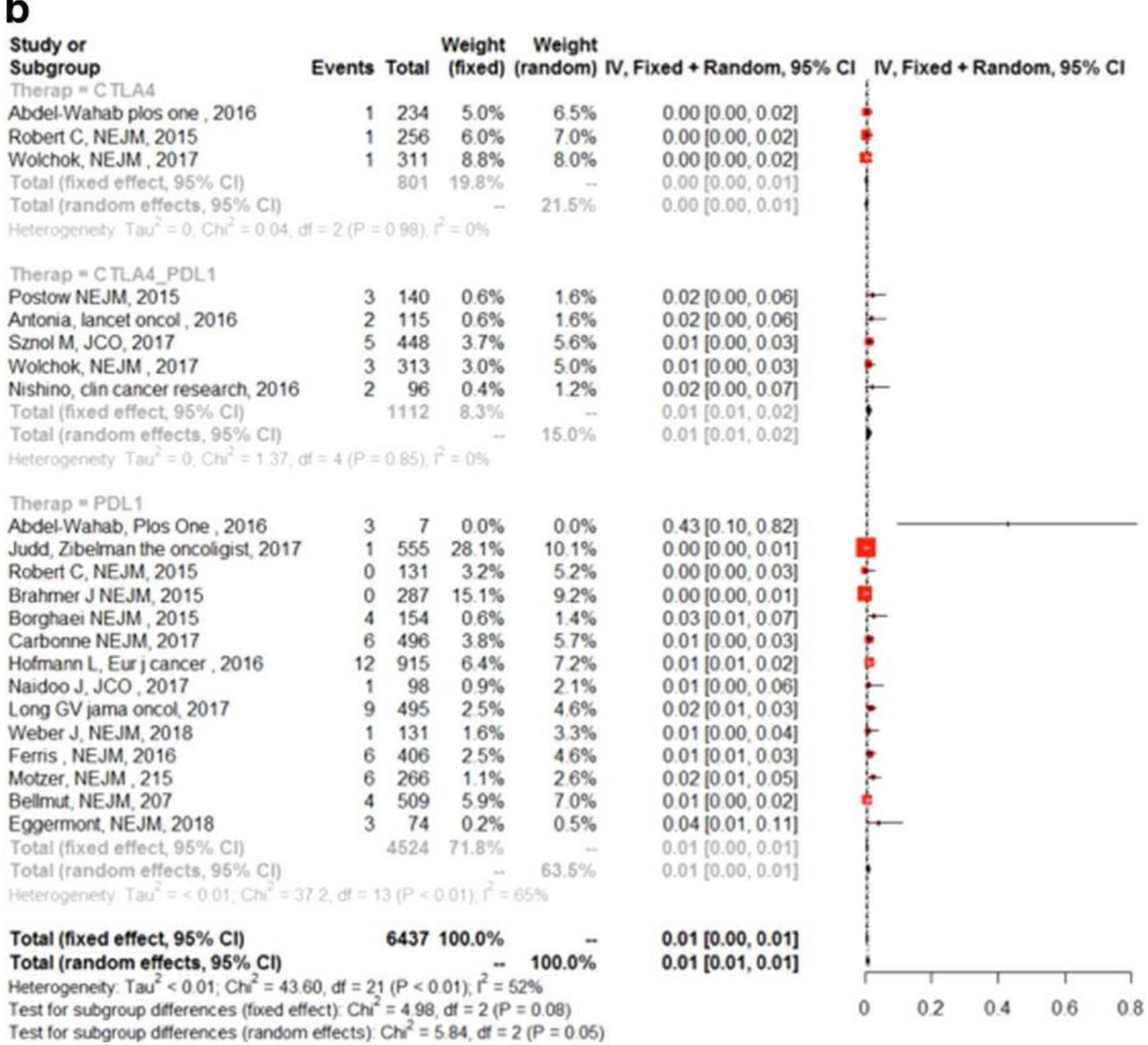


Fig. 3 Frequencies of grade III and IV IrAEIrAE in studies. Meta-analysis of randomized control trials including CTLA4i (upper plot), CTLA4i + PD1i/PDL1i (middle plot) or PD1i/PDL1i (lower plot). The forest plots represent the frequencies of IrAEIrAE organ by organ. **a** Severe gastrointestinal irEA; **b** severe lung IrAE. References: [3–5, 13, 16–18, 24, 33, 34, 40, 60, 71, 75, 88–95]

b



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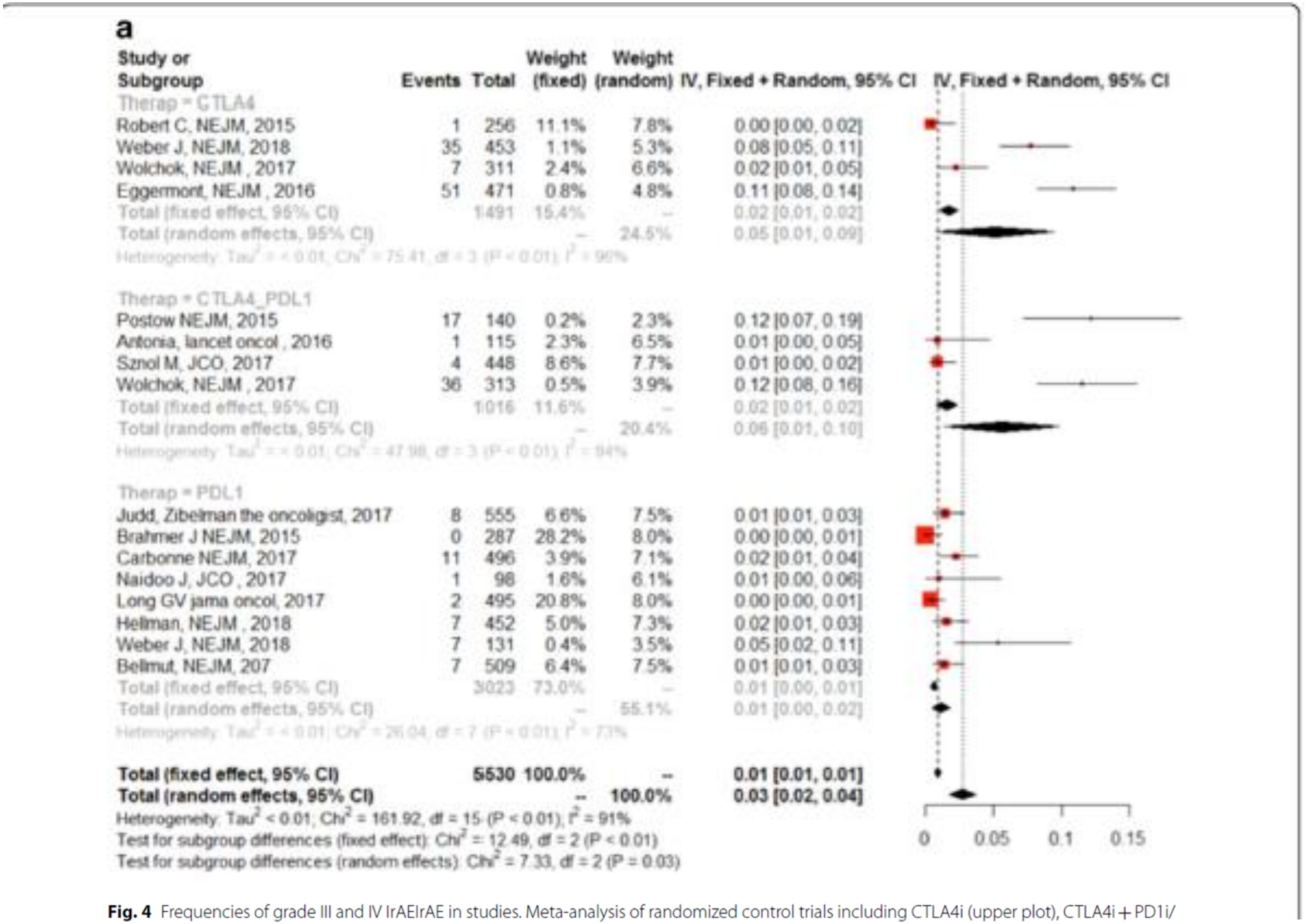
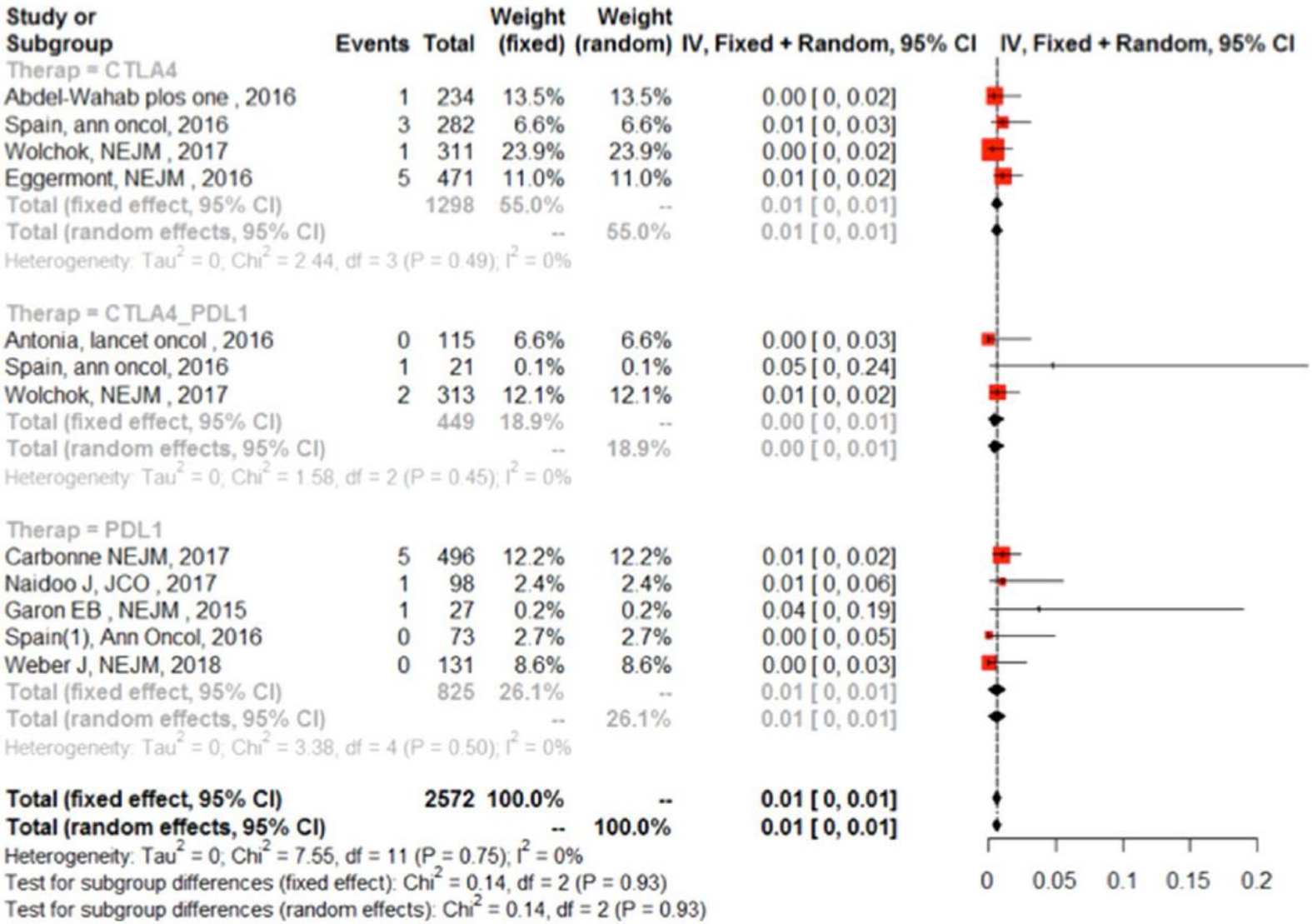


Fig. 4 Frequencies of grade III and IV IrAEIrAE in studies. Meta-analysis of randomized control trials including CTLA4i (upper plot), CTLA4i + PD1i/PDL1i (middle plot) or PD1i/PDL1i (lower plot). The forest plots represent the frequencies of IrAEIrAE organ by organ. **a** Severe liver IrAE; **b** severe neurological IrAE. References: [3–5, 13, 16–18, 24, 33, 34, 40, 60, 71, 75, 88–95]

b



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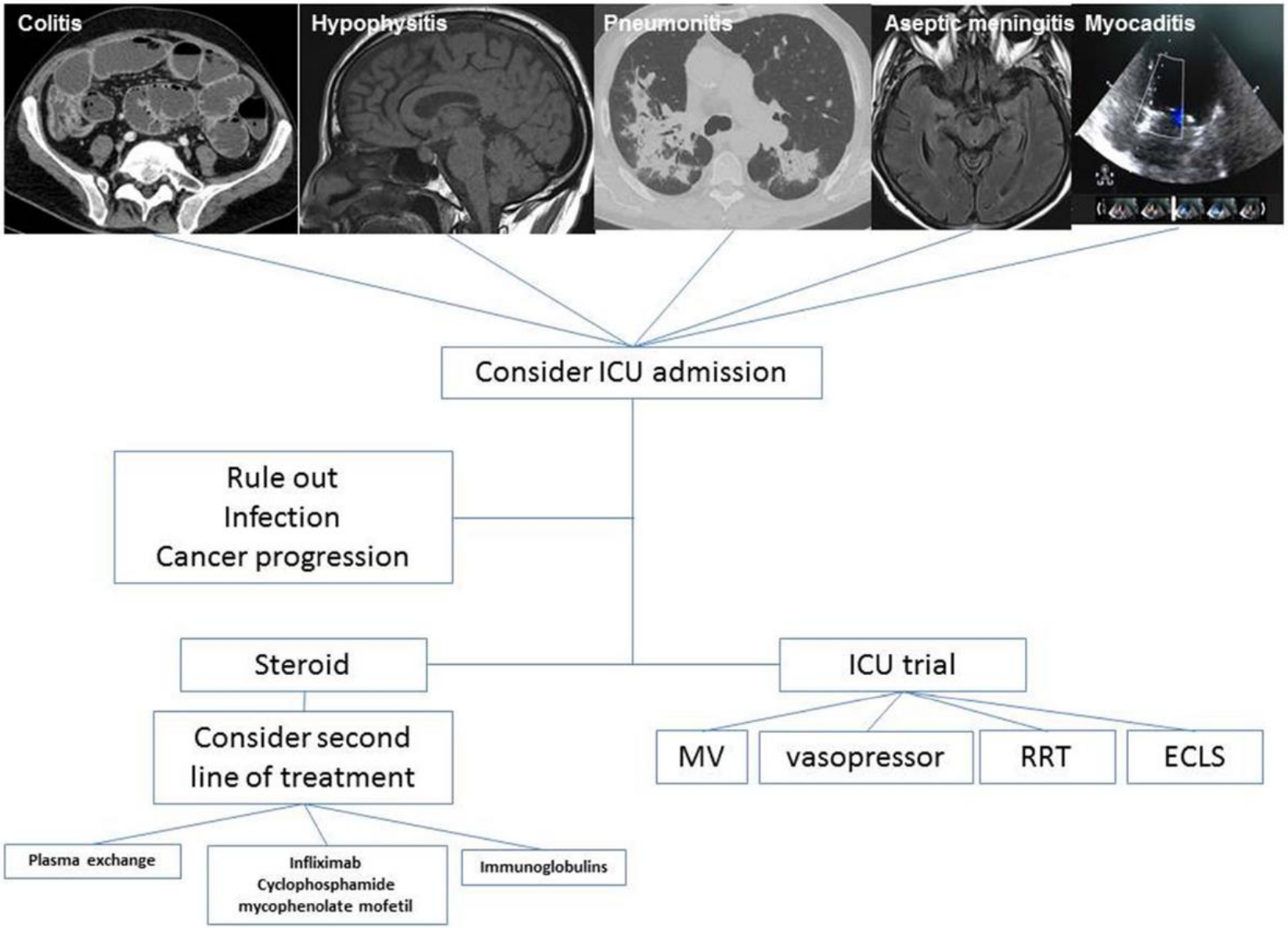

Fig. 6 Management of the most frequent IrAEs in the ICU. *ICU* intensive care unit, *MV* mechanical ventilation, *RRT* renal replacement therapy, *ECLS* extracorporeal life support

Table 2 Management of immune-related adverse events according to severity [85]. Guidelines from American Society of Clinical Oncology (www.asco.org)

Immune-related adverse events	Definitions of severe IrAE	Diagnostic workup before treatment	Steroid and other treatment
Gastrointestinal Colitis: disorder with inflammation of colon	Grade III: > 7 stools/day or increase in ostomy output, incontinence, need for hospitalization, limited self-care/ADL Grade IV: life-threatening consequences	Metabolic and hematologic panel TSH *Clostridium difficile*, CMV, parasite CT scan abdomen and pelvis Endoscopy with biopsy	Consider permanently discontinuing CTAL4i. PD/PDL1 agent may be restarted if patient recovered. Consider MP 1–2 mg/kg/day and other immunosuppressive drugs after 3–5 days symptoms
Lung Pneumonitis: focal or diffuse inflammation of lung parenchyma (no pathognomonic pattern)	Grade III: severe symptoms, need for hospitalization, more than 50% of parenchyma involved, limited self-care/ADL, need for oxygenation Grade IV: acute respiratory failure with life-threatening consequences	Chest X-ray Thoracic CT Nasal swab, sputum culture, blood and urine culture Bronchoscopy and BAL ± biopsy	Permanently discontinue CPI Empirical antibiotics and 1–2 mg/kg/MP Consider other immunosuppressive drugs after 2 days
Heart Myocarditis, pericarditis, arrhythmia, impaired ventricular function, and vasculitis	Grade III: moderate abnormal testing or symptoms occurring with mild activity Grade IV: moderate to severe decompensation, life-threatening consequences	ECG, troponin, BNP Echocardiogram, chest X-ray Cardiac MRI Cardiac catheterization	Permanently discontinue CPI MP 1–2 mg/kg/day Consider other immunosuppressive agent or MP 1 g/day if no improvement
Neurological Myasthenia gravis	Grade III–IV: limited self-care, aids warranted, weakness limiting walking, any dysphagia, facial or respiratory weakness or rapidly progressive symptoms	Anti-striated muscle antibody in blood, muscle specific kinase Pulmonary function assessment CPK, CRP ± MRI of spine or brain, EMG	Permanently discontinue CPI Consider MP 2 mg/kg/day MP and plasmapheresis and IVIg 2 g/kg over 5 days
Guillain–Barré syndrome or peripheral neuropathy	Grade III–IV: severe symptoms, limited self-care, aids warranted, weakness limiting walking, any dysphagia, facial or respiratory weakness or rapidly progressive symptoms	Neurological consultation MRI spine Lumbar puncture EMG Pulmonary function testing	Discontinue CPI Consider MP 1–2 mg/kg/day and plasmapheresis
Aseptic meningitis	Grade III–IV: severe symptoms, limited self-care, aids warranted	MRI with pituitary protocol Cortisol and ACTH test Lumbar puncture with measurement of opening pressure	Hold CPI until patient stabilization Consider restarting after risk/benefit analysis. MP 0.5–1 mg/kg
Encephalitis	Grade III–IV: severe symptoms, limited self-care, aids warranted	Neurologic consultation Brain MRI Lumbar puncture EEG CRP, ±, ANCA, TPO, thyroglobulin	Hold CPI until patient stabilization Consider restarting after risk/benefit analysis. Steroid 1–2 mg/kg MP Consider pulse steroids 1 g IV 3–5 days
Hepatitis	Grade III: symptomatic liver dysfunction, fibrosis by biopsy, cirrhosis, reactivation of chronic hepatitis, ASAT or ALAT 5–20 N, bilirubin 3–10 N Grade IV: decompensated liver function, ASAT or ALAT > 20 N, bilirubin > 10 N	Viral hepatitis, alcohol history, iron study, thromboembolic event Liver ultrasound (metastasis) ± antinuclear antibody, anti-smooth-muscle antibody, ANCA	Permanently discontinue CPI Steroids 1–2 mg/kg/day MP Consider other immunosuppressive agent after 3 days Avoid using Infliximab
Endocrine Hypothyroidism Hyperthyroidism	Grade III–IV: severe symptoms, unable to perform ADL, life-threatening consequences	TSH and T4 dosage	Hold CPI until patient is stabilized Hormone replacement therapy
Adrenal insufficiency	Grade III–IV: severe symptoms, unable to perform ADL, life-threatening consequences	ACTH dosage, cortisol level ± ACTH stimulation test	Hold CPI until patient is stabilized Hormone replacement therapy

Immune-related adverse events	Definitions of severe IrAE	Diagnostic workup before treatment	Steroid and other treatment
Hypophysitis	Grade III–IV: severe symptoms, unable to perform ADL, life-threatening consequences	ACTH dosage, cortisol level +/-ACTH stimulation test TSH and T4 dosage, LH, FSH Brain MRI	Hold CPI until patient has stabilized Hormone replacement therapy
Diabetes mellitus	Grade III–IV: severe symptoms, unable to perform ADL, life-threatening consequences Grade III: blood sugar 13.9–27.8 mmol/l Grade IV: blood sugar > 27.8 mmol/l	Anti-insulin antibody, anti-islet antibody C peptide levels	Hold CPI until glucose control Initiate Insulin therapy
Kidney Nephritis	Grade III: creatinine level > 3 × baseline or > 350 µmol/l Grade IV: life-threatening complication, dialysis required	Rule out other causes of AKI Urinary tract infection	Permanently discontinue CPI MP 1–2 mg/kg/day
Hematologic Autoimmune hemolytic anemia	Grade III: Hb < 8 g/dl, transfusion indicated Grade IV: life-threatening complication	Drug history, insect bites LDH, haptoglobin, bilirubin, reticulocyte count, autoimmune serology PNH Viral or bacterial infection Protein electrophoresis, cryoglobulin analysis G6PD, methemoglobinemia B12, folate, parvovirus, thyroid ± ADAMTS 13	Permanently discontinue CPI MP 1–2 mg/kg/day Consider other immunosuppressive agent if no improvement.
Immune thrombocytopenia	Grade III: platelet count < 50/mm^3 Grade IV: platelet count < 25/mm^3	HIV, hepatitis B or C, *Helicobacter pylori* Reticulocyte count, blood smear ± bone marrow	Hold CPI until improvement Steroid oral 1–2 mg/kg/day Consider IVIg Consider permanently discontinue CPI if no improvement
Skin Rash Bullous dermatoses	Grade III: affects quality of life if no response to treatment (rash) Over 30% of body surface (bullous dermatoses) affected, with pain Over 10% of body surface or mucosal involvement (DRESS, pustulosis) Grade IV: > 30% body surface with electrolyte abnormalities (bullous dermatoses) >10% body surface with blood abnormality (liver function)	Whole body examination Assessment for drug, infection Skin biopsy	Permanently discontinue CPI MP 1–2 mg/kg/day Consider other immunosuppressive agent if no improvement

ADL activities of daily living, *TSH* thyroid-stimulating hormone, *CMV* cytomegalovirus, *BAL* bronchoalveolar lavage, *MRI* magnetic resonance imaging, *BNP* Brain natriuretic peptide, *CPK* creatine phosphokinase, *CRP* C-reactive protein, *MP* methylprednisolone or equivalent, *EMG* electromyogram, *ANCA* Antineutrophil cytoplasmic *antibodies*, *TPO* thyroid peroxidase, AKI acute kidney failure, *PHN Paroxysmal nocturnal hemoglobinuria*, *ADAMTS 13* a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, *DRESS* drug reaction with eosinophilia and systemic symptoms, *HIV* human immunodeficiency virus

Conclusions: toxicité des immunothérapies

- A tout moment (prédominance dans les 3 premiers mois)
- « Contre-indications » si maladie auto-immune préexistante
- Diagnostic délicat (symptômes non spécifiques, diagnostic différentiel)
- Les plus fréquentes: cutanée, digestive, endocrinienne, (pulmonaire, hépatique)
- Doivent être reconnues et traitées tôt (potentiellement mortelles)
- Corticoïdes +/- interruption de l'immunothérapie
- Collaboration internistes, oncologues, spécialistes d'organes, radiologues

Newsletter IMMUNOREA N°5

Caractéristiques et prise en charge des patients atteints d'une tumeur solide traités par immunothérapie admis en réanimation

OBJECTIF PRINCIPAL

Evaluer la fréquence de l'imputabilité de l'immunothérapie dans le motif d'admission en réanimation des patients souffrant d'une tumeur solide traités par immunothérapie.

OBJECTIFS SECONDAIRE

Description des traitements immunosuppresseurs mis en place lors du séjour en réanimation pour la prise en charge du patient (notamment la corticothérapie).
Description de la survie en réanimation et à l'hôpital.

DEMARCHES REGLEMENTAIRES

Promoteur : Institut Jules Bordet, Bruxelles
Leclercq Nathalie (nathalie.leclercq@bordet.be)

Comité d'éthique de l'institut Jules Bordet: 10/08/2018
Début de l'étude: septembre 2018

Pour les centres français, il s'agit d'un projet de collaboration institutionnel n'entrant pas dans le cadre de la Loi Jardé et n'entrainant pas de surcoût, il n'apparait pas nécessaire d'établir de convention
DRCI CHU Grenoble Alpes, ametz@chu-grenoble.fr, bportal@chu-grenoble.fr

CONTACTS : n'hésitez pas à nous contacter pour tout besoin

ARC, Juliette Meyzenc : JMeyzenc@chu-grenoble.fr Tel : +33 4 76 76 94 81

Investigateurs :

Dr Anne Claire Toffart — **Mail : AToffart@chu-grenoble.fr**
Dr Anne-Pascale Meert — **Mail : ap.meert@bordet.be**
Dr Virginie Lemiale — **Mail : virginie.lemiale@aphp.fr**

Qui inclure ?

Critères d'inclusion :

- **patient âgé de plus de 18 ans**
- **porteur d'une tumeur solide**
- **traité par anti-CTL-A4 et/ou anti-PD-1/PDL-1 que le traitement soit en cours ou jusqu'à 6 mois après son arrêt**
- **admis en réanimation ou soins continus de manière non programmée, quel qu'en soit le motif.**

Comment inclure ?

Recueil de données prospectif, selon le fichier de recueil de données fourni.
L'investigateur envoie un mail d'inclusion à Juliette Meyzenc (JMeyzenc@chu-grenoble.fr) à chaque nouveau patient inclus.
L'investigateur recueille les données de survie à l'hôpital.
Les cahiers d'observation **ANONYMISES** sont envoyés au fur et à mesure à Juliette Meyzenc (JMeyzenc@chu-grenoble.fr)
L'investigateur du centre garde une copie du cahier et un fichier de correspondance cahier/nom pour d'éventuels compléments d'information à distance.

A notre connaissance, 102 patients ont été inclus à ce jour et 72 CRF récupérés
Nous avons atteint l'objectif ! Merci pour votre implication dans le projet !
Les inclusions se termineront donc au 1er mars 2020.
Notre priorité est maintenant de récupérer l'ensemble des CRF.