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# Le patient atteint d'un cancer en réanimation : qui admettre en 2022 ? Le patient sous immunothérapie.

A.P. Meert

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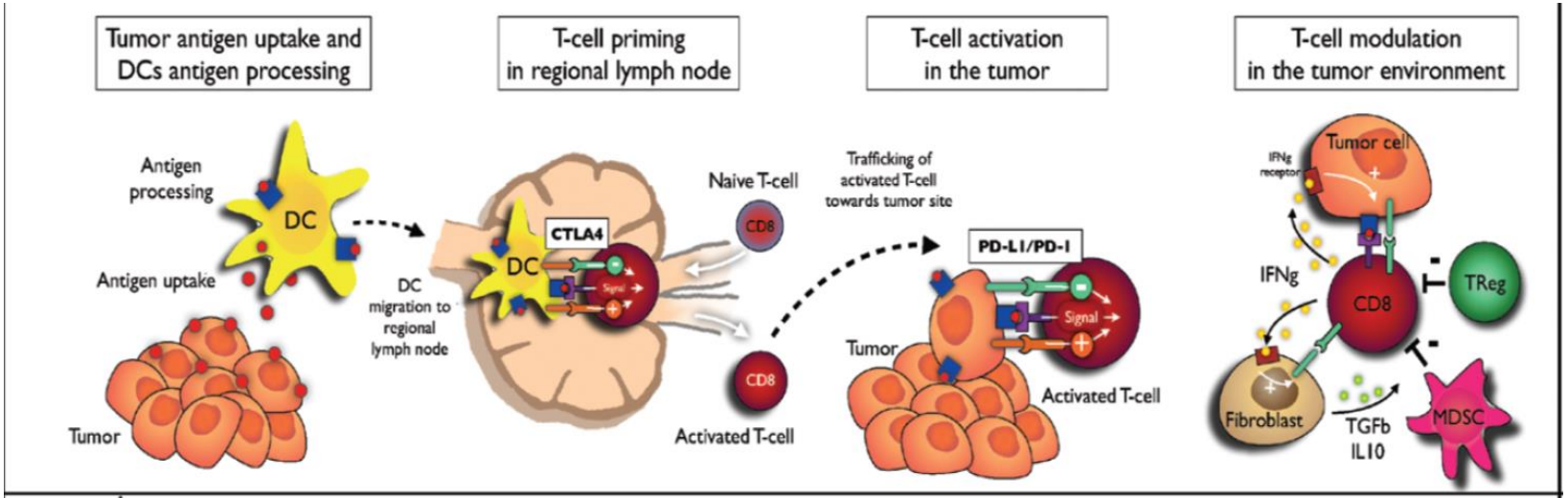
# Inhibiteurs des points de contrôle




| | | | | |
|---|---|---|---|---|
| immune system modulation in NSCLC | > down-regulation of MHC-I | | > up-regulation of PD-L1 through activation of PI3K/Akt ? MAPK ? Alk ?<br>> up-regulation of TRegs<br>> up-regulation of MDSCs | > IL-10 and TGFß increased concentration by tumor environment<br>> up-regulation of PD-L1 by IFNg secreted by activated T-cell |
| immuno modulation by NSCLC drugs | **immunogenic cell death**<br>irradiation<br>**vaccination strategies**<br>MAGE-A3, MUC-1, rHU EGF | **up-regulation of MHC-I**<br>paclitaxel, gemcitabine, erlotinib<br>**DC maturation**<br>paclitaxel, docetaxel, bevacizumab<br>**anti-CTLA4**<br>Ipilimumab, Tremelimumab | **anti-PD-1**<br>MDX-1106, CT-011, MK-3475<br>**anti-PD-L1**<br>MPDL-3280A, MDX-1105<br>**up-regulation of PD-L1**<br>paclitaxel, etoposide | **TReg inhibition**<br>cisplatin, paclitaxel, bevacizumab<br>**MDSC inhibition**<br>cisplatin, docetaxel, gemcitabine<br>**down-regulation of PD-L1**<br>by PI3Ki ? MEKi ? Crizotinib ? |

Champiat et al, J Thorac Oncol 2014

**Table 1. List of Current ICIs and Their Indications***

| Drug Class | Drug Name | Indications and Status | Most Common Toxicity of Any Grade (1–4) | Most Common High-Grade (3 or 4) Toxicity |
|---|---|---|---|---|
| CTLA-4 Inhibitor | Ipilimumab† (1) | Approved melanoma after surgery<br>Late stage melanoma | Dermatologic (43.5%)<br>Gastrointestinal (29.0%)<br>Hepatic (3.8%)<br>Endocrine (7.6%) | Gastrointestinal (7.6%) |
| | Tremelimumab (2) | Mesothelioma | Diarrhea (30–40%)<br>Rash/pruritis (30–34%) | Diarrhea (5–10%) |
| PD-1 Inhibitor | Nivolumab (5) | Hodgkin's lymphoma<br>HNSCC<br>Advanced lung cancer<br>Metastatic renal cell carcinoma<br>Advanced melanoma<br>High microsatellite instability tumors<br>Merkel cell carcinoma | Dermatologic (29.1%)<br>Gastrointestinal (11.2%)<br>Endocrine (7.8%) | Hepatitis (2–3%) |
| | Pidilizumab | Under trial | NR | NR |
| | Pembrolizumab† (6) | Recurrent or metastatic HNSCC<br>Metastatic NSCLC<br>Advanced melanoma<br>Renal cell carcinoma<br>Merkel cell carcinoma | Dermatologic (10.7%)<br>Gastrointestinal (8.1%)<br>Endocrine (6.9%) | Pneumonitis (1.8%) |
| | Atezolizumab (2) | Melanoma<br>HNSCC<br>Renal cell carcinoma<br>Classical Hodgkin's lymphoma<br>High microsatellite instability tumors<br>Merkel cell carcinoma<br>Metastatic NSCLC<br>Urothelial carcinoma | Diarrhea (18–20%) | Diarrhea (1–2%) |
| | Durvalumab (2) | Melanoma<br>HNSCC<br>Renal cell carcinoma<br>Classical Hodgkin's lymphoma<br>High microsatellite instability tumors<br>Merkel cell carcinoma | Diarrhea (9–10%) | NR |
| | Avelumab | Melanoma<br>HNSCC<br>Renal cell carcinoma<br>Classical Hodgkin's lymphoma<br>High microsatellite instability tumors | NR | NR |

# Indications

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

# Cas clinique 1

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

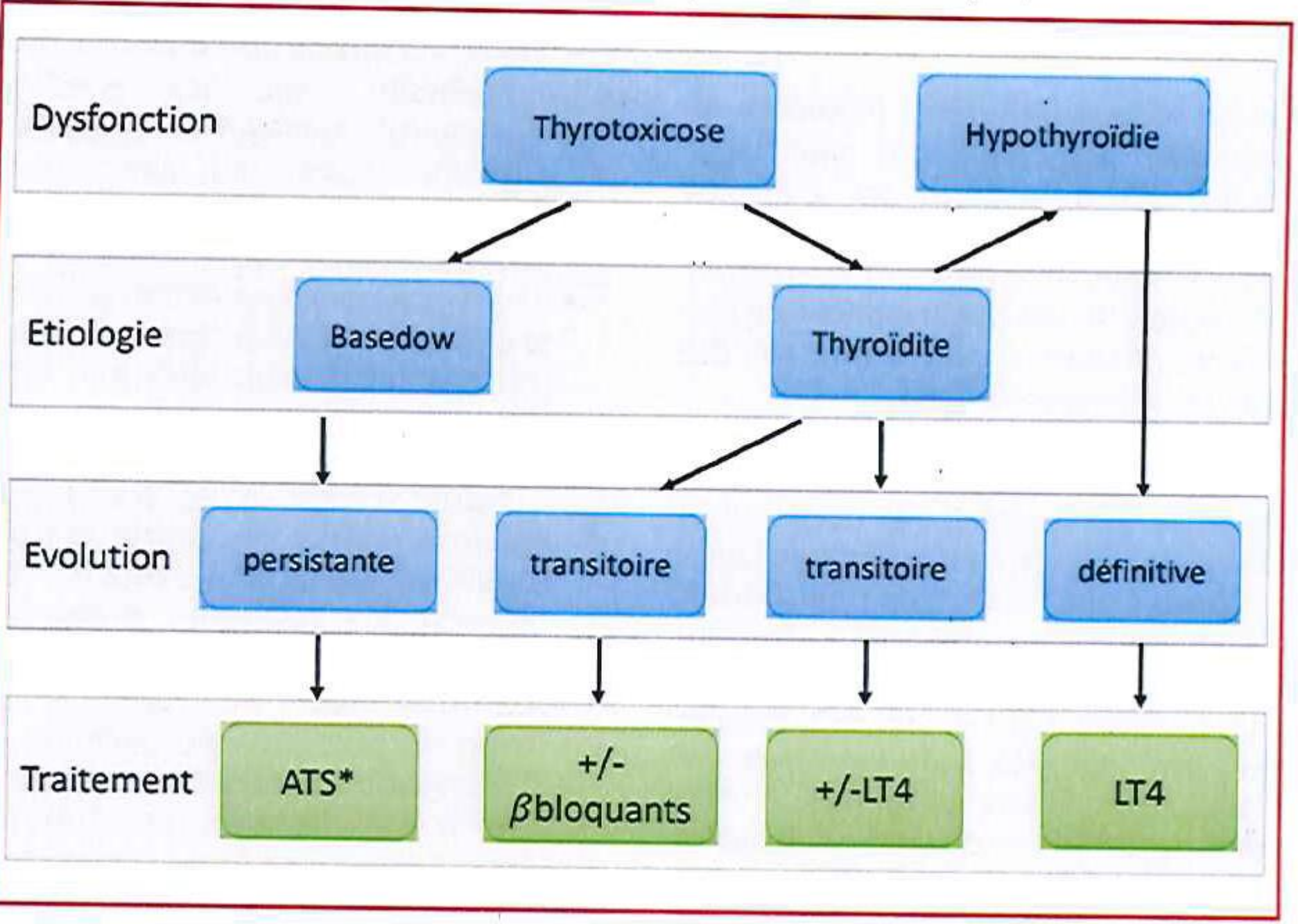
  Radiothérapie cérébrale stéréotaxique

  Nivolumab (2/2018)

# 07/2018: fatigue

# 07/2018: fatigue

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




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 particularité.
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.

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

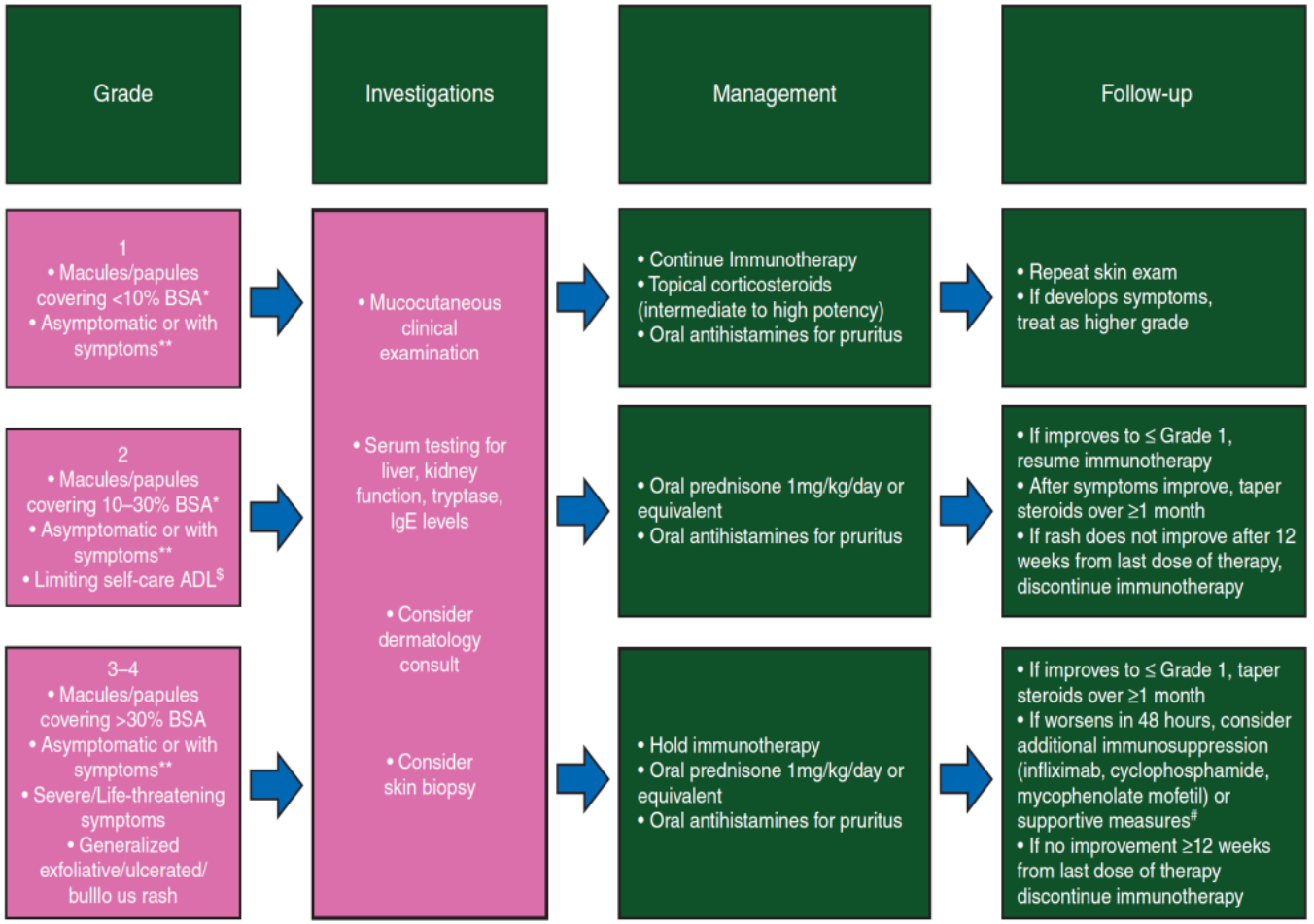



**Figure 1.** Adapted management algorithm for skin rash with immune checkpoint blockade. *BSA, body surface area, **Symptoms as per CTCAE version 4.0. For example: pruritus, burning and skin tightness. $Additional supportive measures: this denotes the use of, for example, prophylatic antibiotics and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

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Ann Oncol 2015 Naidoo et al

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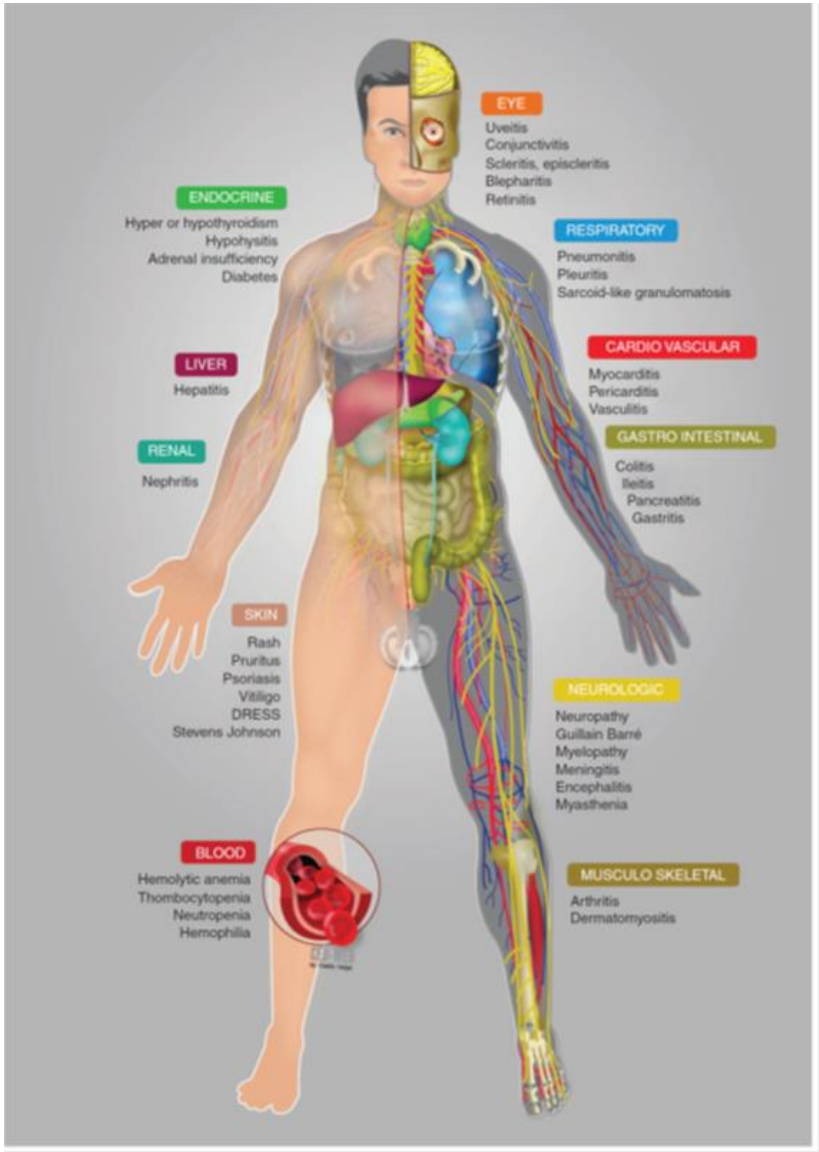
- Conjonctivite
- Gonalgies

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

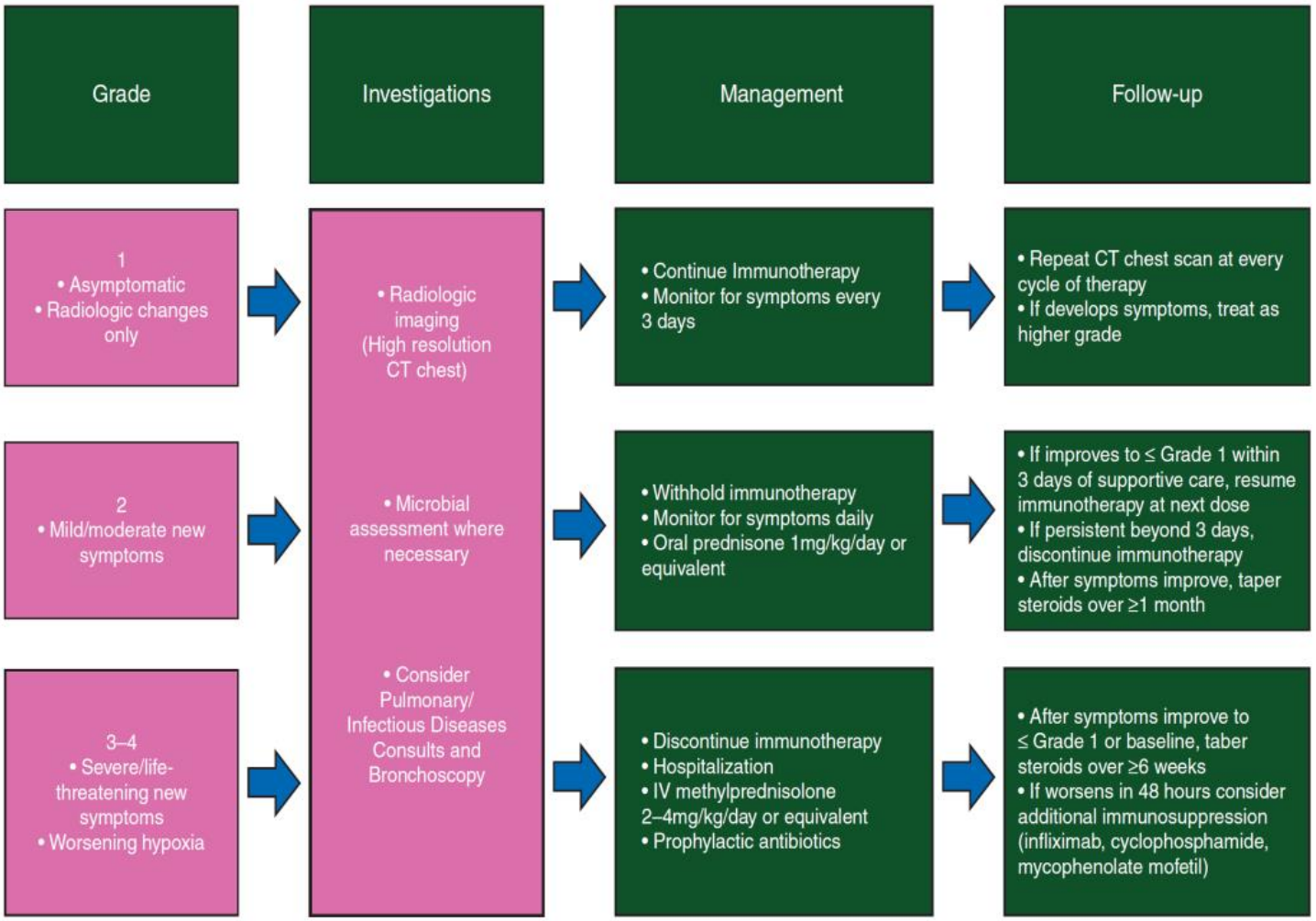


**Figure 3.** Adapted management algorithm for pneumonitis with immune checkpoint blockade.

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Ann Oncol 2015 Naidoo et al

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# Cas clinique 2

- Mr CR 61 ans
- - Mélanome (mutation B-RAF V600E et PIC3CA E545K)
- R/ Pembrolizumab 2cures
- - 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

# 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<br>• Prednisone, 100 mg o.d. for 7 d<br>• 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<br>• 30 mg of pyridostigmine b.d. p.o.<br>• 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<br>• 120 mg of pyridostigmine q.i.d., for 11 d<br>• Five treatments of IVIG at 400 mg/kg/d<br>• 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.<br>• 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.<br>• Pyridostigmine, 60 mg t.d.s.<br>• 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.<br>• 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)<br>• 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.<br>• 2 mg/kg of methylprednisolone for hepatitis.<br>• 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

# 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

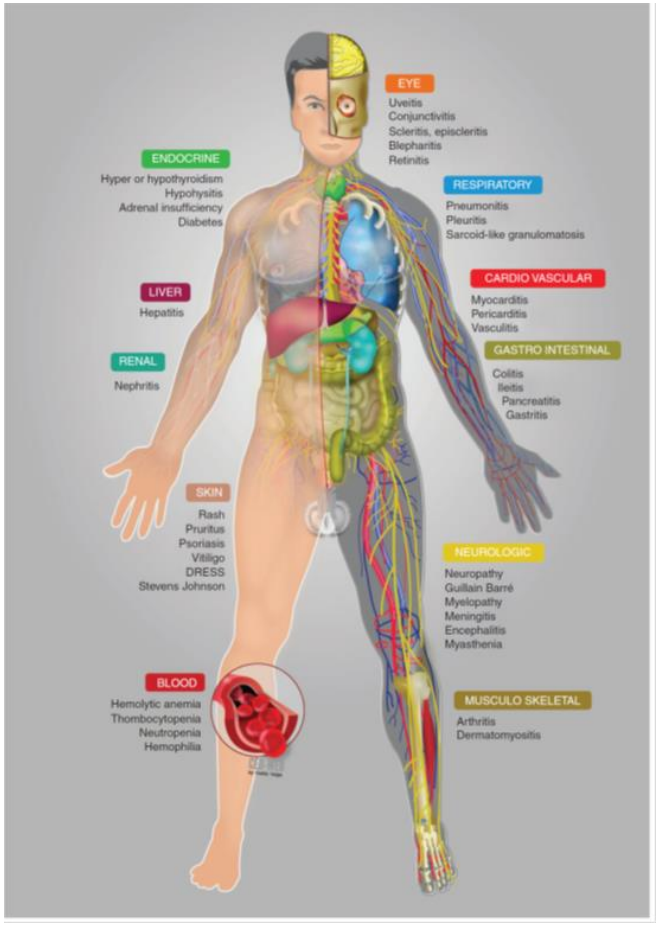
*Objectives:* Thymomas, as well as thymic carcinomas, are extremely rare tumors that arise from the thymus. The management of these tumors is primarily the complete surgical resection, however when there is tumor progression or metastatic unresectable disease, palliative platinum-based chemotherapy is 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.

# Types de toxicités




*Annals of Oncology* 27: 559–574, 2016

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# Incidence

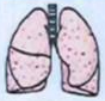
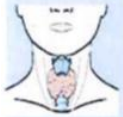
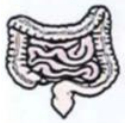
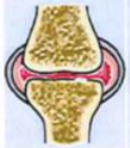
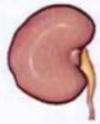
**Table 1.** Immune checkpoint blockade (ICB) toxicities

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



*Annals of Oncology* 27: 559–574, 2016

| 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<br>Exacerbation de psoriasis<br>Réactions lichenoïdes<br>Vitiligo<br>Atteinte muqueuse buccale | De 37,4 à 41,9% | De 43,7 à 58,7%, | Jusqu'à 71,3% |
|  | Hypophysite<br>Dysthyroïdie<br>Diabète type 1<br>Insuffisance surrénalienne | Hypophysite : <1%<br>Dysthyroïdies: 6-18% | Hypophysite : 1-17%<br>Dysthyroïdies : 6% | Hypophysite : 8%<br>Dysthyroïdies : 22% |
|  | Diarrhées<br>Entérocolites | 15% | 30% | 35 à 40% |
|  | Hépatite auto-immune | 5 à 10 % | <4% | 10 à20% |
|  | Myocardite | 0,09% | Plusieurs cas rapportés | 0,027% |
|  | Arthralgies<br>Polyarthrite | 5% | 5 à 10% | Jusqu'à 10% |
|  | Néphrite interstitielle<br>Néphrite granulomateuse | 1% | 1% | Jusqu'à 6% |

Delaunay, Rev Mal Respir 2018,

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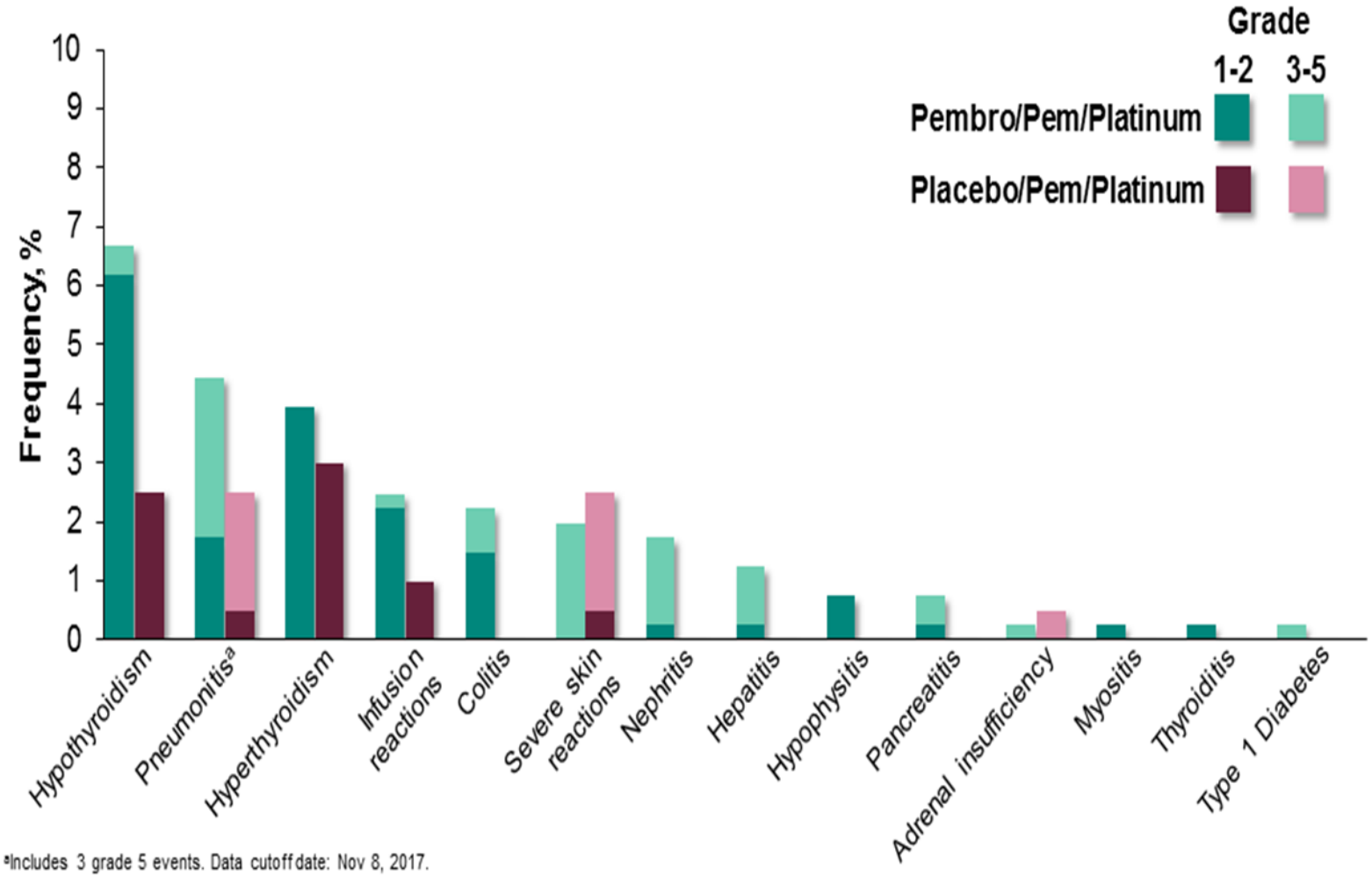
Gandhi KN189
AACR 2018

# Immune-Mediated Adverse Events




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

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# 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<br>or<br>Systemic steroids<br>oral<br>0.5–1 mg/kg/day | Not recommended | Suspend temporarily[a] |
| 3 | Hospitalization | Systemic steroids<br>Oral or i.v.<br>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<br>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<br>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<br>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 collaboration with the National Comprehensive Cancer Network*

**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/

# 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

# 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

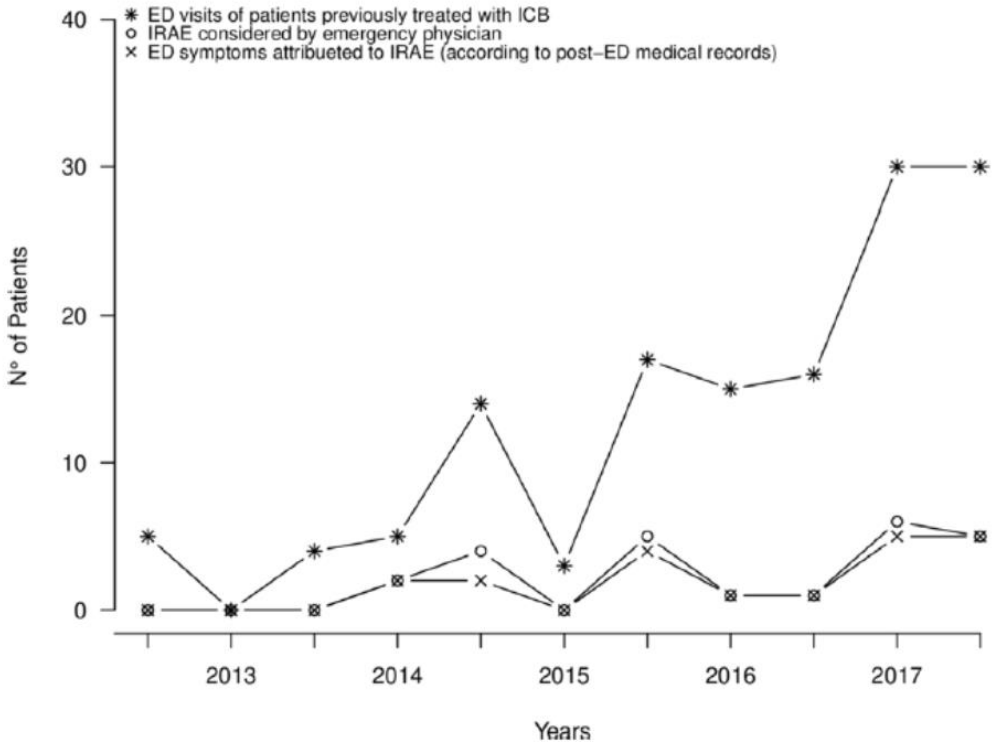


**Figure 1** Number of ED visits, IRAE and consideration of IRAE by emergency physician over the years. ED, emergency department; ICB, immune checkpoint blockade; IRAE, immune-related adverse event.

14.4% des présentations aux urgences sont dues à un IRAE

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**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.

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

| | Whole sample | | IRAE (according to referring oncologist opinion in post-ED medical records) | | | |
|---|---|---|---|---|---|---|
| | | | 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.

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# 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. (%).

25%

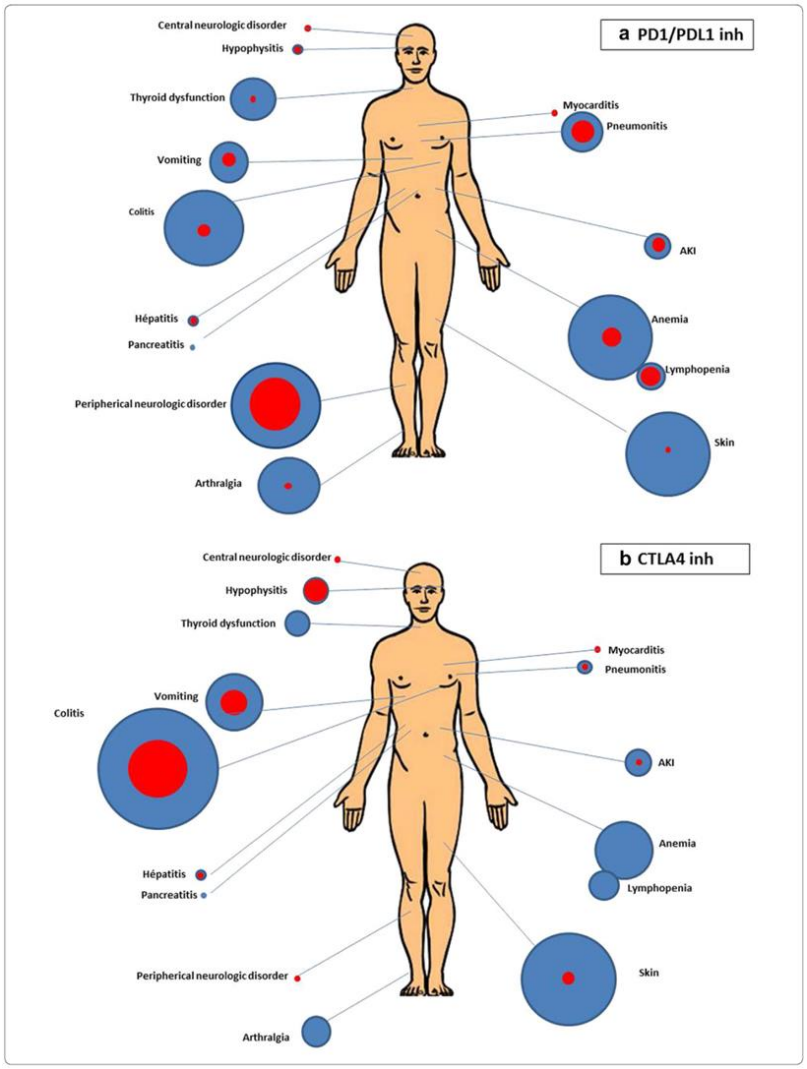
**Table 4.** Univariable and multivariable Cox regression analysis for overall survival for each immune-related adverse effect.

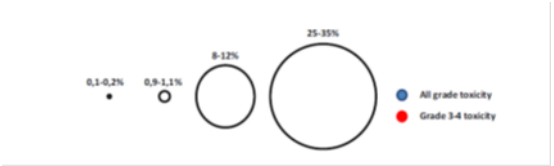
| Adverse Effect | Univariable, HR (95% CI) | Multivariable, All Patients (N=628), HR* (95% CI) | Multivariable, Patients Without Preexisting Autoimmune Disease (N=529), HR† (95% CI) |
|---|---|---|---|
| Diarrhea | 0.79 (0.53–1.17) | 0.80 (0.54–1.20) | 0.81 (0.53–1.23) |
| Colitis | 0.45 (0.21–0.95) | 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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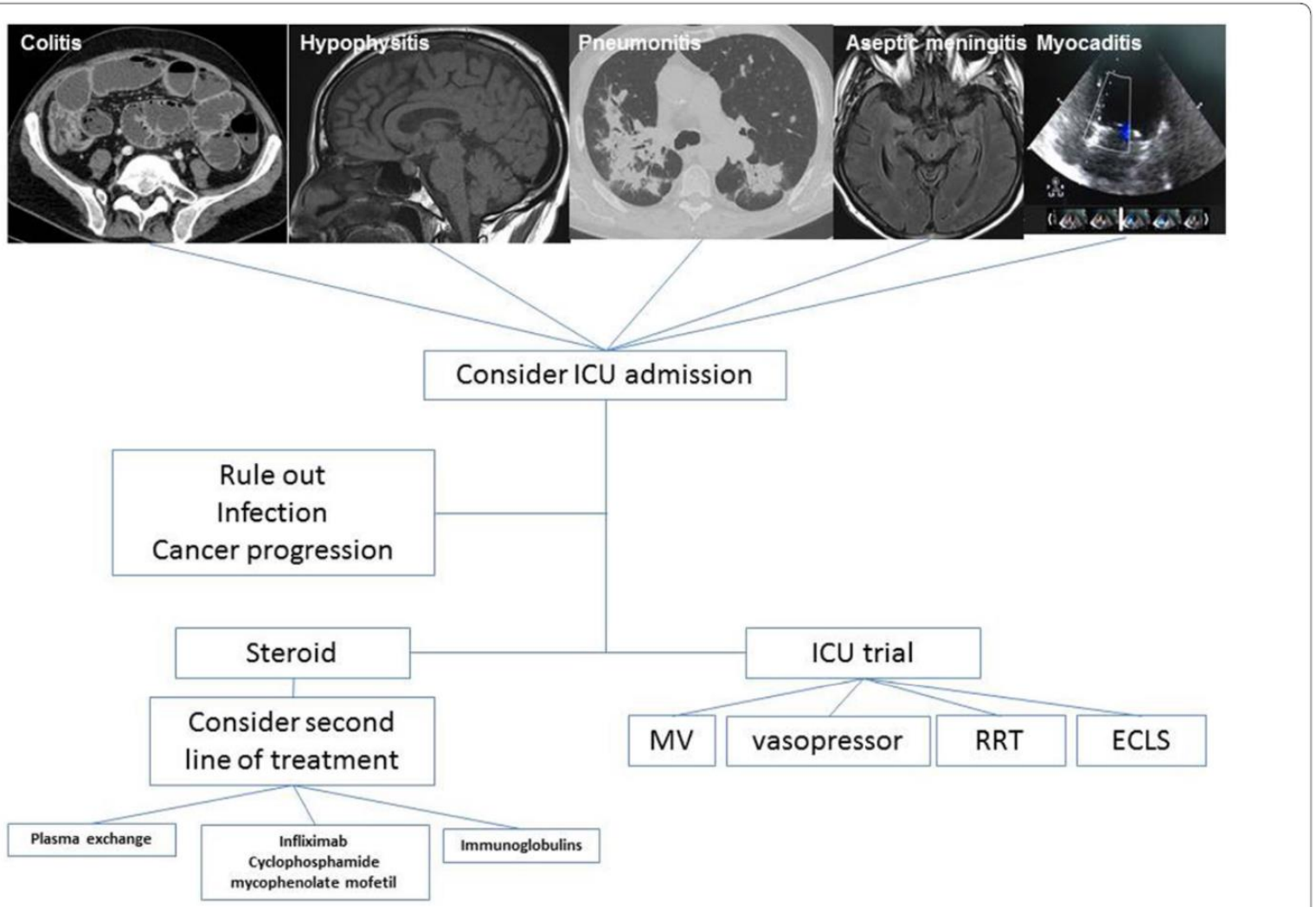


**Fig. 6** Management of the most frequent IrAEs in the ICU. *ICU* intensive care unit, *MV* mechanical ventilation, *RRT* renal replacement therapy, *ECLS* extracorporeal life support

# Immune-related adverse events: a retrospective look into the future of oncology in the intensive care unit

Adrien Joseph[1,2,3,10*], Audrey Simonaggio[4,5], Annabelle Stoclin[6], Antoine Vieillard-Baron[7,8,9], Guillaume Geri[7,8,9], Stéphane Oudard[4,5], Jean-Marie Michot[11], Olivier Lambotte[10,12,13], Elie Azoulay[3,14] and Virginie Lemiale[3]

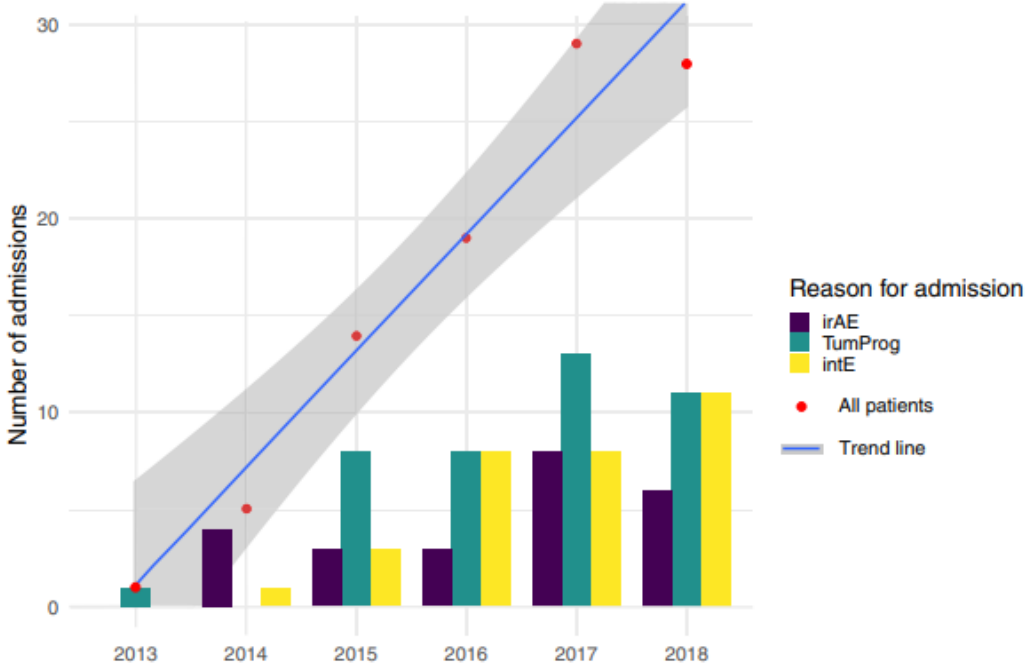


**Fig. 1** Bar plots of the number and reasons for admission over the study period ($p < 0.001$). *irAE* immune-related adverse event, *TumProg* complication related to tumor progression, *intE* intercurrent event

26% admissions dues à un IRAE

Joseph *et al. Ann. Intensive Care* (2020) 10:143

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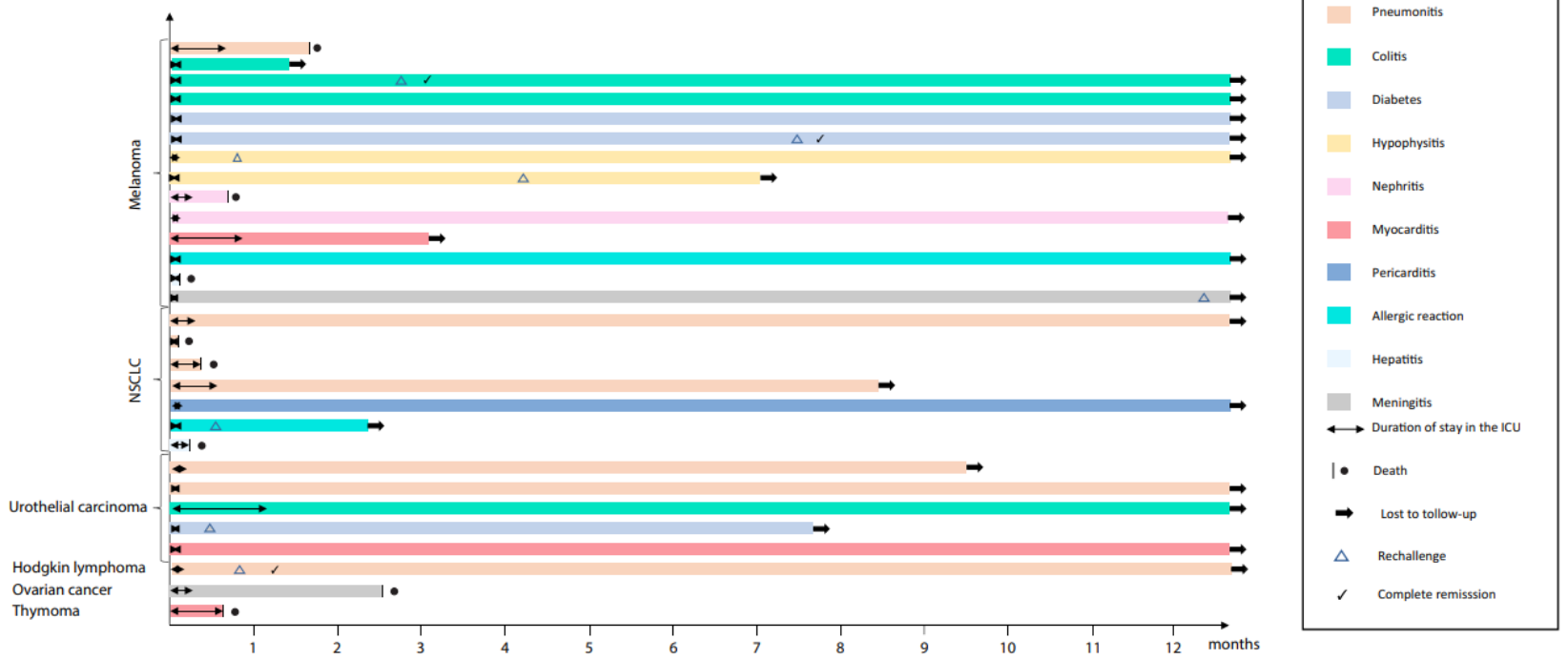



**Fig. 2** Swimmer plot of patients admitted for immune-related adverse events and evolution after discharge from ICU. An arrow represents the moment when the patient is lost to follow-up, a dot represents the moment of death. *NSCLC* non-small cell lung cancer, *ICU* intensive care unit

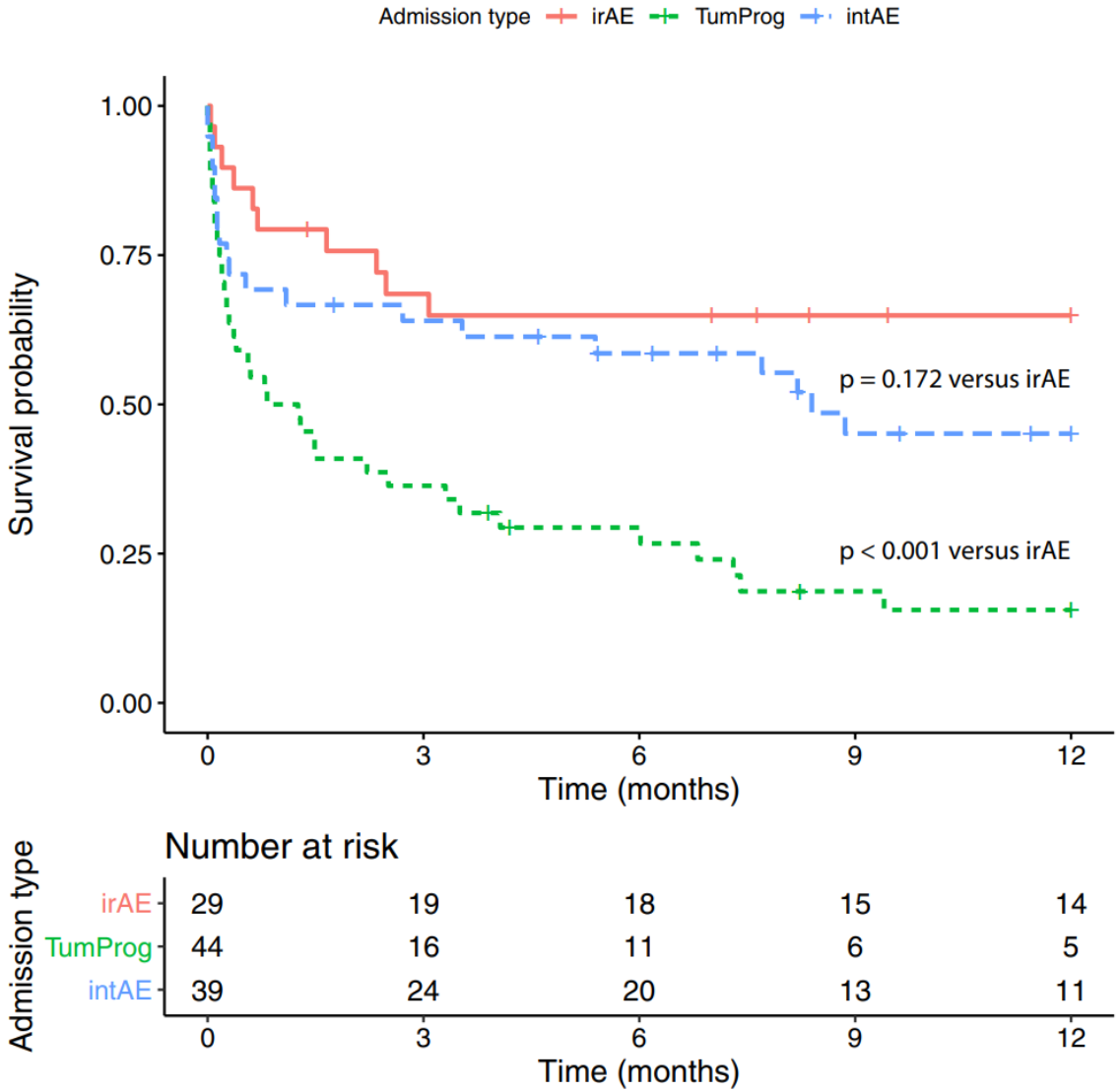


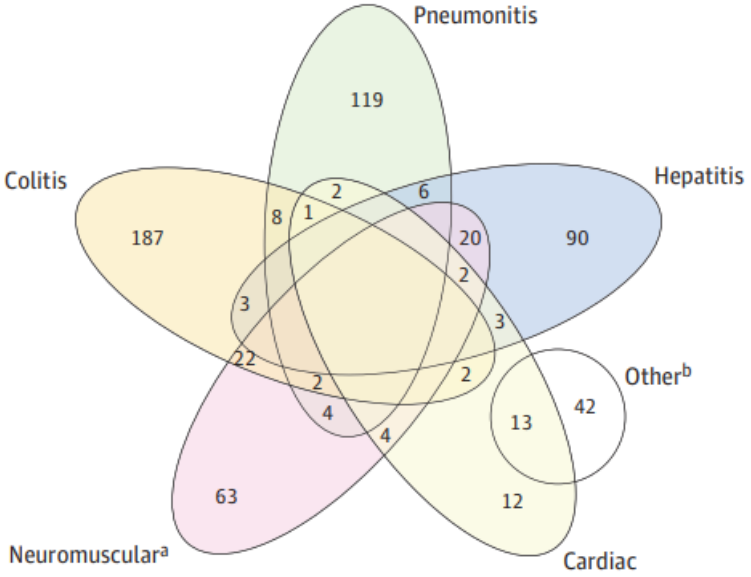

**Fig. 3** Kaplan–Meier curves for overall survival of patients admitted for irAE compared to intE ($p = 0.172$) and TumProg patients ($p < 0.001$) (irAE versus others $p = 0.004$). *irAE* immune-related adverse event, *TumProg* complication related to tumor progression, *intE* intercurrent event

# Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors
## A Systematic Review and Meta-analysis

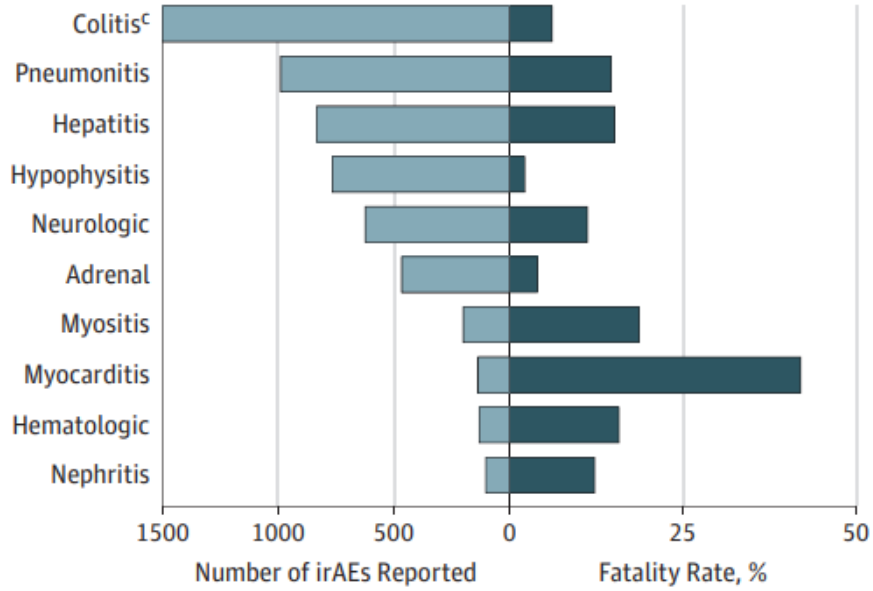
Daniel Y. Wang, MD; Joe-Elie Salem, MD; Justine V. Cohen, MD; Sunandana Chandra, MD; Christian Menzer, MD; Fei Ye, PhD; Shilin Zhao, PhD; Satya Das, MD; Kathryn E. Beckermann, MD, PhD; Lisa Ha, MSN; W. Kimryn Rathmell, MD, PhD; Kristin K. Ancell, MD; Justin M. Balko, PharmD, PhD; Caitlin Bowman, PharmD; Elizabeth J. Davis, MD; David D. Chism, MD; Leora Horn, MD; Georgina V. Long, MBBS, PhD; Matteo S. Carlino, MBBS; Benedicte Lebrun-Vignes, MD; Zeynep Eroglu, MD; Jessica C. Hassel, MD; Alexander M. Menzies, MBBS, PhD; Jeffrey A. Sosman, MD; Ryan J. Sullivan, MD; Javid J. Moslehi, MD; Douglas B. Johnson, MD

**Figure 1. Clinical Characteristics of Fatal Immune-Related Adverse Events (irAEs)**

A Co-occurring fatal irAEs




C Cases and fatality rates

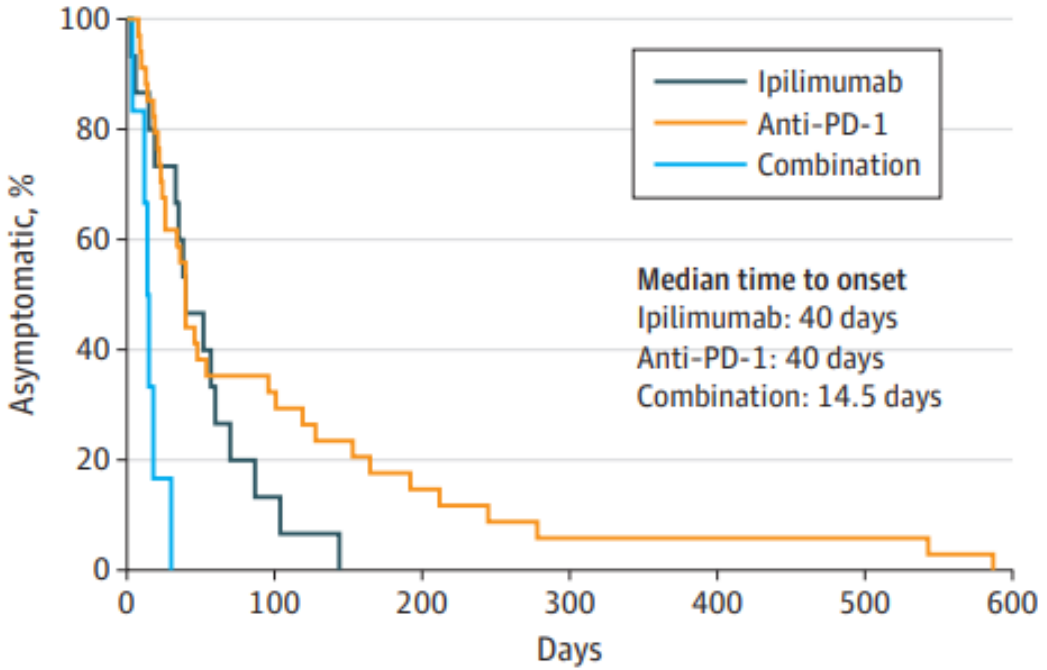



*JAMA Oncol*. 2018;4(12):1721-1728. doi:10.1001/jamaoncol.2018.3923

**Table 2. Incidence and Types of Immune Checkpoint Inhibitor-Related Fatalities From Systematic Review and Meta-analysis**

| Variable | Anti-CTLA-4 (n = 5368) | Anti-PD-1 (n = 9136) | Anti-PD-L1 (n = 3164) | Anti-PD-1/PD-L1 Plus CTLA-4 (n = 1549) |
|---|---|---|---|---|
| Deaths, No. (%) | 58 (1.08) | 33 (0.36) | 12 (0.38) | 19 (1.23) |
| Type of fatal toxic effect | | | | |
| Colitis | 23 (40) | 2 (6) | 0 | 2 (11) |
| Pneumonitis | 3 (5) | 14 (42) | 5 (42) | 4 (21) |
| Hepatitis | 5 (9) | 0 | 1 (8) | 2 (11) |
| Cardiac | 9 (16) | 4 (12) | 3 (25) | 4 (21) |
| Neurologic | 1 (2) | 1 (3) | 0 | 3 (16) |
| Nephritis | 1 (2) | 0 | 0 | 1 (5) |
| Hematologic | 2 (4) | 2 (6) | 0 | 2 (11) |
| Infectious | 8 (14) | 5 (15) | 2 (18) | 3 (16) |
| Hemorrhagic/thrombotic | 2 (4) | 1 (3) | 0 | 1 (5) |
| Electrolyte imbalance | 1 (2) | 2 (6) | 0 | 0 |
| Multiorgan failure | 3 (5) | 0 | 0 | 0 |
| Other | 1 (2) | 2 (6) | 1 (8) | 0 |

## Figure 2. Time to Symptom Onset of Fatal Toxic Effects by ICI Regimen




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ipilimumab | 15 | 2 | 0 | 0 | 0 | 0 | 0 |
| Anti-PD-1 | 34 | 11 | 5 | 2 | 2 | 2 | 0 |
| Combination | 6 | 0 | 0 | 0 | 0 | 0 | 0 |

Anti–PD-1 indicates anti–programmed death-1.

# Conclusions

- Toxicités graves peu fréquentes, précoces
- Pneumonies, colites, hépatites, myocardites
- Diagnostic délicat (symptômes non spécifiques, diagnostic différentiel)
- Doivent être reconnues et traitées tôt (potentiellement mortelles)
- Traitement par corticoïdes
- Bon pronostic
- Collaboration internistes, oncologues, spécialistes d'organes, radiologues

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*Samedi 26 novembre 2022*

# 21ème Rencontre sur les Urgences et Complications sévères chez le Patient Cancéreux

*Auditoire Tagnon New Bordet (route 2980)*

E.L.C.W.P.