Gestion des effets secondaires en immunologie anti-tumorale

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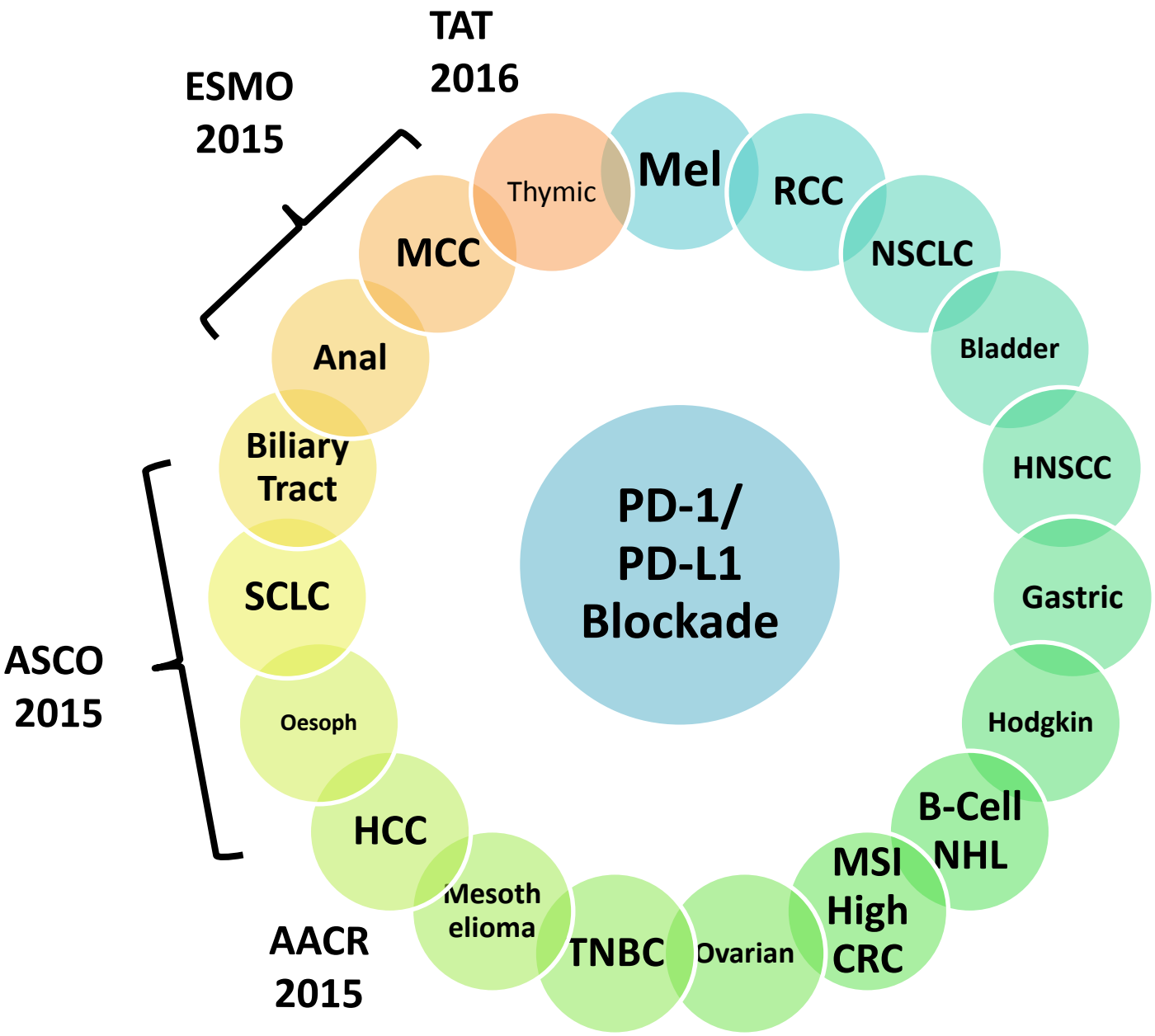
Spectrum of activity PD1/PDL1 Ab



Anti-CTLA-4	Anti-PD-1	Anti-PD-L1
Ipilimumab (BMS) **Tremelimumab** (AZ)	**Nivolumab** (BMS) **Pembrolizumab (MSD)**	**Atezolizumab** (MPDL3280A) **Durvalumab** (MEDI4736) **Avelumab** (PF-06834635 /MSB0010718C)
Approved	**Approved**	
YERVOY™	OPDIVO™	
	KEYTRUDA®	

Anti PD1 + anti CTLA4 combination

Nivo alone or combined with Ipi vs Ipi alone
phase III trial in advanced melanoma

Patients Reporting Event, %	NIVO + IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

- 67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response

Anti PD-1 vs chemotherapy

Nivolumab vs docetaxel in NSCLC

	Nivolumab n = 287	Docetaxel n = 268
All Grade AEs, any cause	98%	99%
Treatment-related AEs	69%	88%
Grade 3-4 AEs, any cause	46%	67%
Treatment-related Grade 3-4 AEs	10%	54%
Grade 5 AEs, any cause	8%	5%
Patients withdrawing from treatment due to AEs	5%	15%

Treatment-related Grade 5 events

- Nivolumab (n = 1): encephalitis (causality was changed after the database lock)
- Docetaxel (n = 1): febrile neutropenia

Borghaei et al. (2015). Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. ***NEJM***

Anti PD-1 vs chemotherapy

Nivolumab vs docetaxel in NSCLC

Table 3. Treatment-Related Adverse Events Reported in at Least 10% of the Patients Treated with Nivolumab or Docetaxel.*

Event	Nivolumab (N = 287)		Docetaxel (N = 268)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	199 (69)	30 (10)	236 (88)	144 (54)
Fatigue	46 (16)	3 (1)	78 (29)	13 (5)
Nausea	34 (12)	2 (1)	70 (26)	2 (1)
Decreased appetite	30 (10)	0	42 (16)	3 (1)
Asthenia	29 (10)	1 (<1)	47 (18)	6 (2)
Diarrhea	22 (8)	2 (1)	62 (23)	3 (1)
Peripheral edema	8 (3)	0	28 (10)	1 (<1)
Myalgia	7 (2)	1 (<1)	30 (11)	0
Anemia	6 (2)	1 (<1)	53 (20)	7 (3)
Alopecia	1 (<1)	0	67 (25)	0
Neutropenia	1 (<1)	0	83 (31)	73 (27)
Febrile neutropenia	0	0	27 (10)	26 (10)
Leukopenia	0	0	27 (10)	22 (8)

Borghaei et al. (2015). Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. *NEJM*

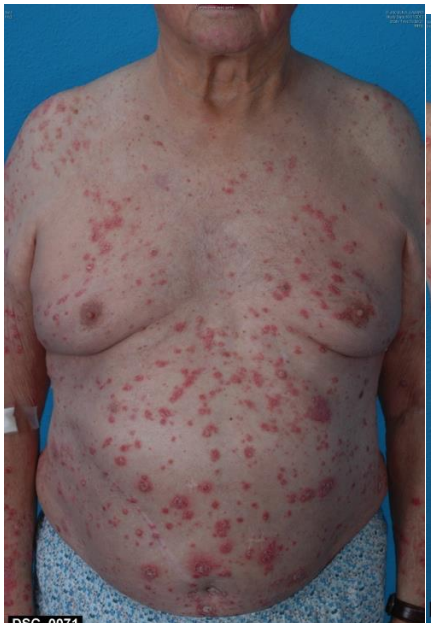
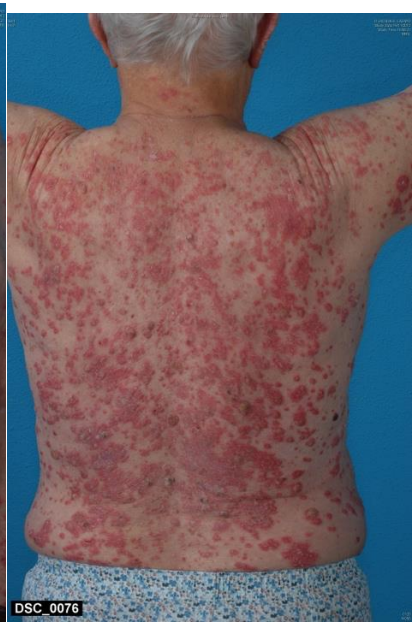
The “1% toxicities”

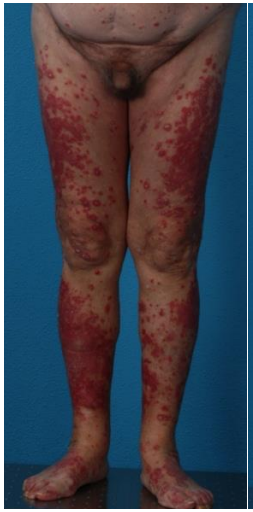
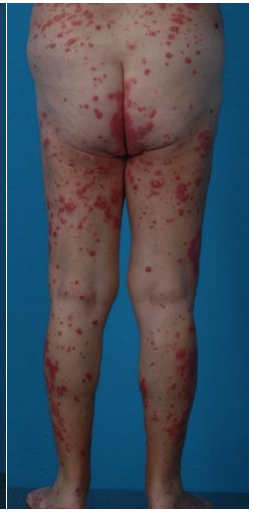
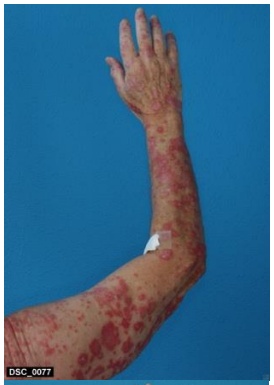
Table S9. Treatment-related Serious Adverse Events Reported in Patients Treated with Nivolumab or Docetaxel.[a]

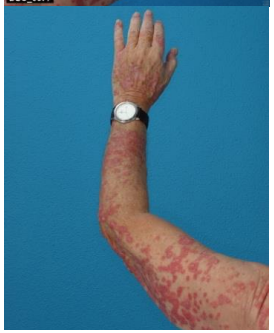
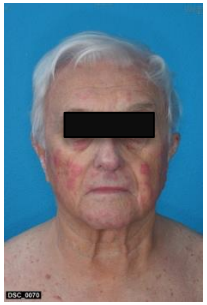
Event	Nivolumab n = 287		Docetaxel n = 268	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	Number of patients with an event (%)			
Any event	21 (7)	15 (5)	53 (20)	48 (18)
Pneumonitis	4 (1)	3 (1)	0	0
Interstitial lung disease	2 (1)	1 (<1)	0	0
Infusion related reaction	2 (1)	0	0	0
Nausea	2 (1)	1 (<1)	1 (<1)	1 (<1)
Colitis	2 (1)	1 (<1)	0	0
Diarrhea	1 (<1)	1 (<1)	1 (<1)	0
Dyspnea	1 (<1)	1 (<1)	0	0
Hypoxia	1 (<1)	1 (<1)	0	0
Pulmonary embolism	1 (<1)	1 (<1)	0	0
Cardiac tamponade	1 (<1)	1 (<1)	0	0
Pericardial effusion	1 (<1)	1 (<1)	0	0
Blood creatinine increased	1 (<1)	0	0	0
Transaminases increased	1 (<1)	1 (<1)	0	0
Osteonecrosis	1 (<1)	1 (<1)	0	0
Polymyalgia rheumatica	1 (<1)	1 (<1)	0	0
Hepatotoxicity	1 (<1)	0	0	0
Cerebrovascular accident	1 (<1)	1 (<1)	0	0
Encephalitis	1 (<1)	1 (<1)	0	0

Borghaei et al. (2015). Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. *NEJM*

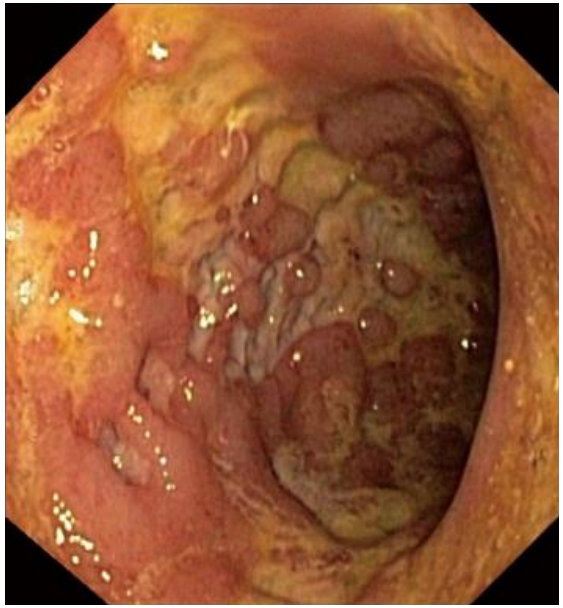
PD1-induced psoriasis

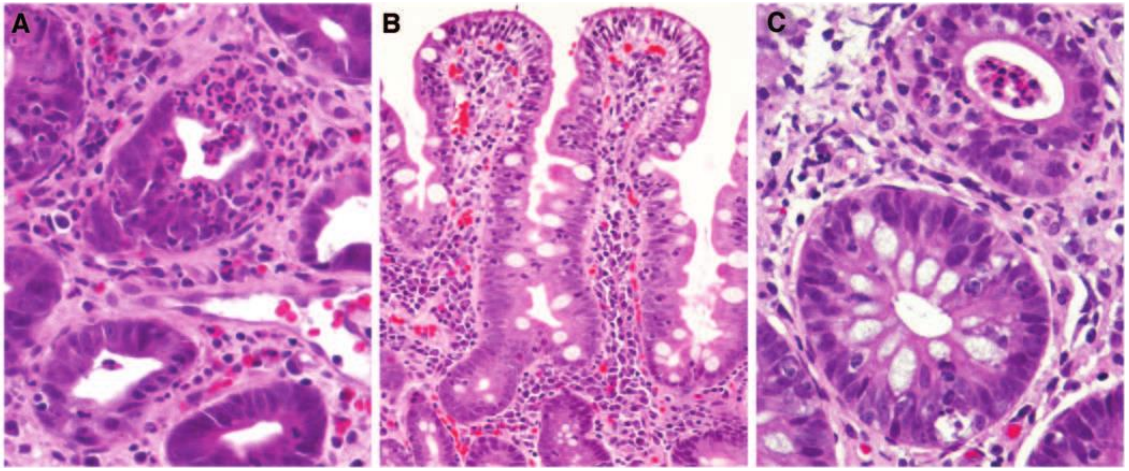




Dysimmune colitis

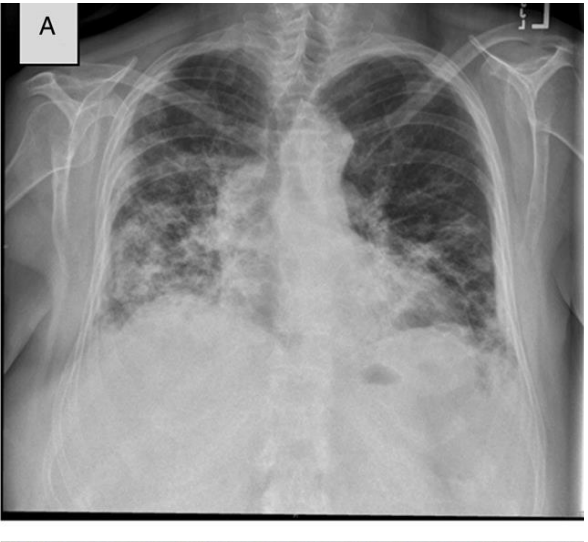


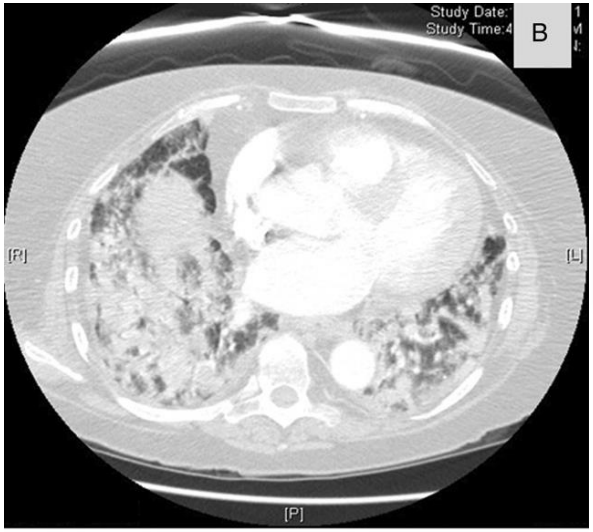
Slangen et al., (2013). Diarrhoea in a patient with metastatic melanoma: Ipilimumab ileocolitis treated with infliximab. *World Journal of Gastrointestinal Pharmacology and Therapeutics*

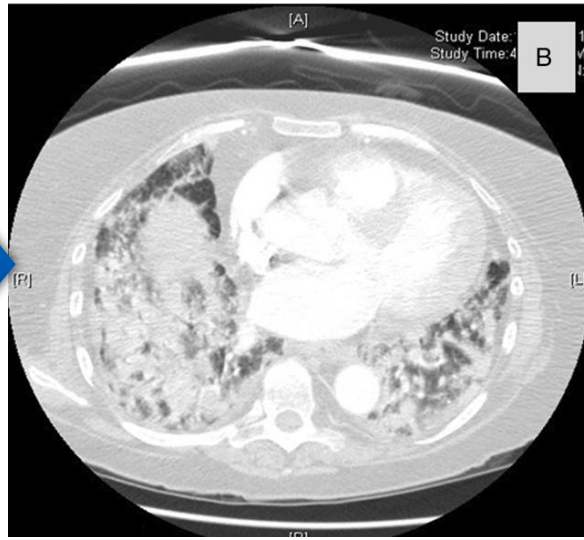


Beck et al. (2006). Enterocolitis in Patients With Cancer After Antibody Blockade of Cytotoxic T-Lymphocyte-Associated Antigen 4. *Journal of Clinical Oncology*

Pneumonitis







Cough+dyspnea
No fever

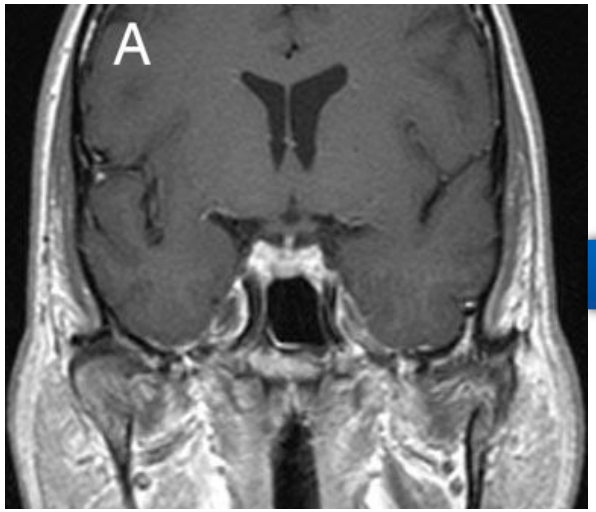
2 months after
last ipi infusion

BAL :
lymphocytic alveolitis

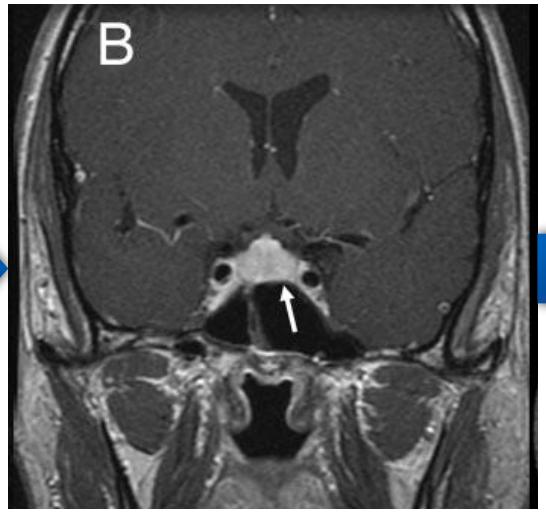
6 weeks after
Methylprednisolone IV 2mg/kg
Broad spectrum antibiotics

Barjaktarevic, I. Z., Qadir, N., Suri, A., Santamauro, J. T., & Stover, D. (2013). Organizing pneumonia as a side effect of ipilimumab treatment of melanoma. *Chest*

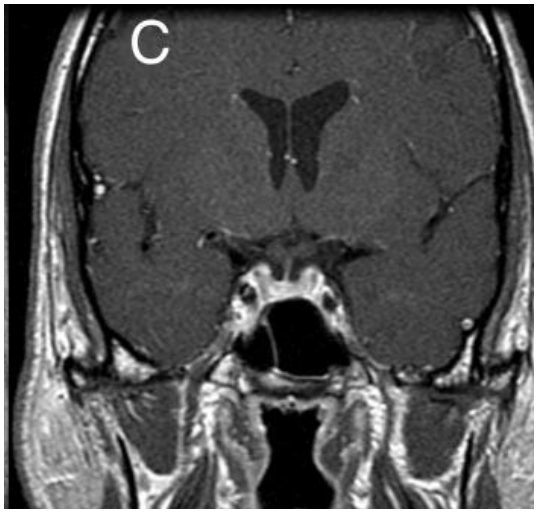
Hypophysitis



baseline



3 months
after anti CTLA4

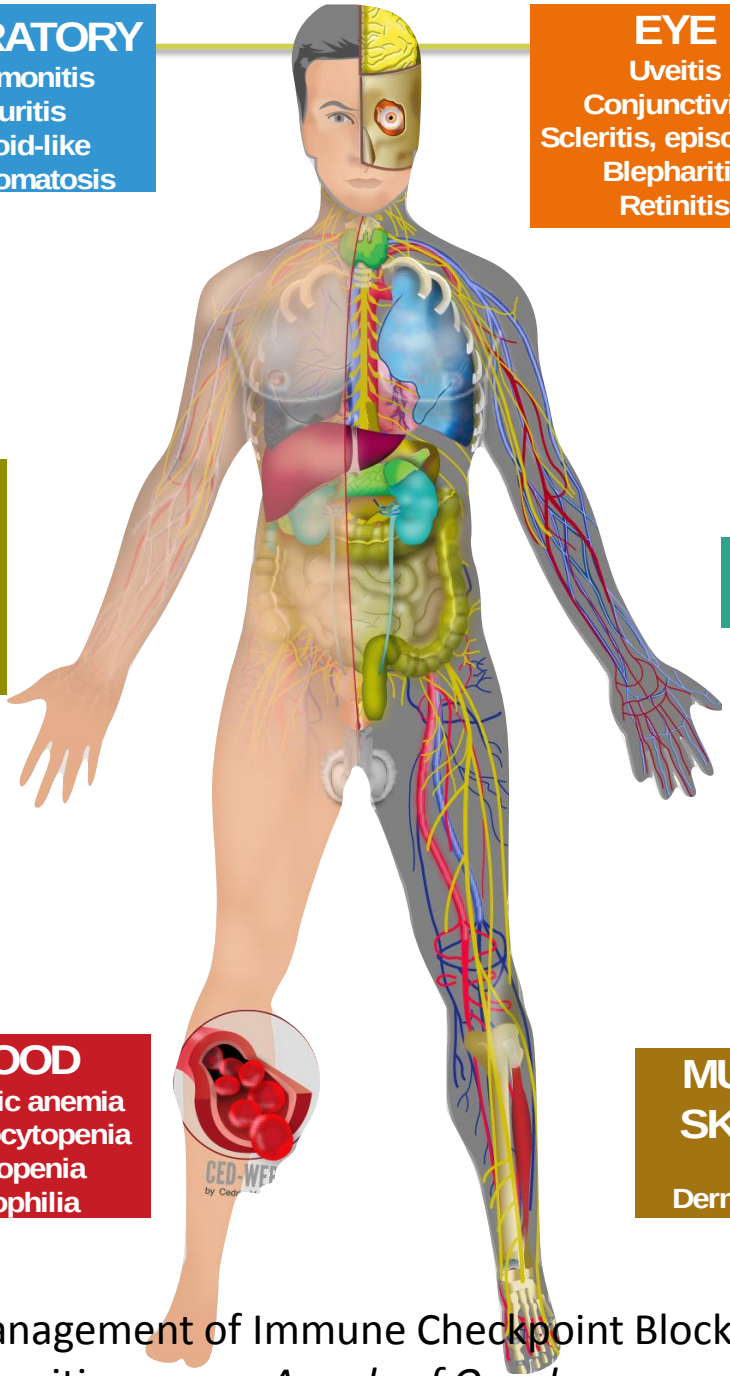


6 months
after anti CTLA4

Headaches, asthenia

anterior pituitary hormone deficiencies

Shaw, S. A., Camacho, L. H., McCutcheon, I. E., & Waguespack, S. G. (2007). Transient hypophysitis after cytotoxic T lymphocyte-associated antigen 4 (CTLA4) blockade. *The Journal of Clinical Endocrinology and Metabolism*,



REPIRATORY
Pneumonitis
Pleuritis
Sarcoid-like granulomatosis

EYE
Uveitis
Conjunctivitis
Scleritis, episcleritis
Blepharitis
Retinitis

ENDOCRINE
Hyper or hypothyroidism
Hypophysitis
Adrenal insufficiency
Diabetes

CARDIO VASCULAR
Myocarditis
Pericarditis
Vasculitis

GASTRO INTESTINAL
Colitis
Ileitis
Pancreatitis
Gastritis

RENAL
Nephritis

LIVER
Hepatitis

NEUROLOGIC
Neuropathy
Guillain Barré
Myelopathy
Meningitis
Encephalitis
Myasthenia

SKIN
Rash
Pruritus
Psoriasis
Vitiligo
DRESS
Stevens Johnson

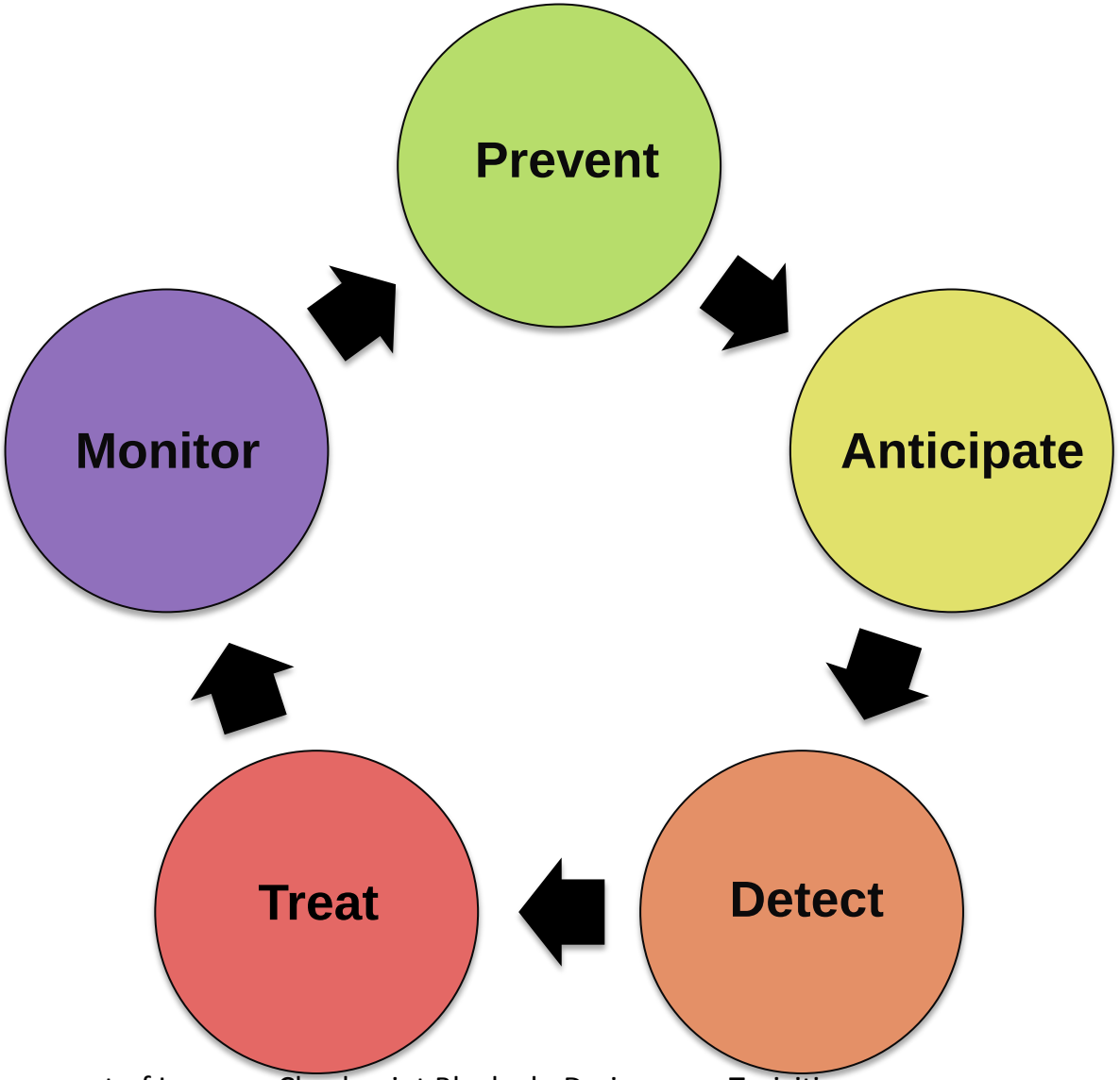
BLOOD
Hemolytic anemia
Thrombocytopenia
Neutropenia
Hemophilia

MUSCULO SKELETAL
Arthritis
Dermatomyositis

Champiat et al. (2015). Management of Immune Checkpoint Blockade Dysimmune Toxicities: a collaborative position paper. *Annals of Oncology*

Comment gérer les toxicités dysimmunitaires

Immunotherapy toxicity management



Champiat et al. (2015). Management of Immune Checkpoint Blockade Dysimmune Toxicities: a collaborative position paper. *Annals of Oncology*

Prevent

Inform patient
& the whole health care team

Report quickly
any new, persitent or worsening of pre-existing symptom

Early recognition and management
may limit worsening or toxicity severity

Prevent

Risk factors

> *Personal and family history*

-autoimmune diseases, systemic diseases, chronic inflammatory diseases
(Crohn, polyarthritis, lupus, …)

-**respiratory, cardiovascular, hepatic, … chronic diseases**

-**recent infections, chronic viral infections**

> *Co-medications*

Anticipate

Baseline lab tests :

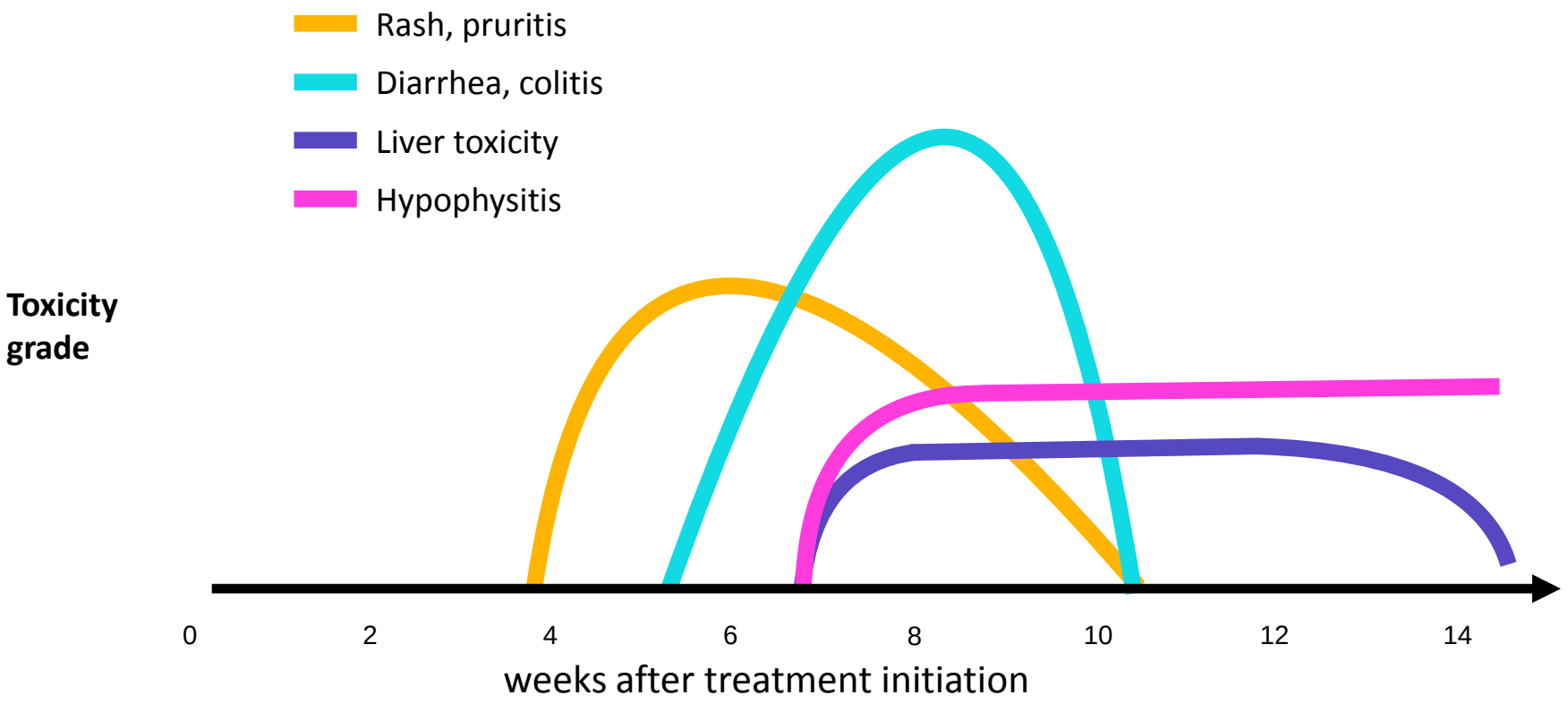
Complete CBC
Serum electrolytes, creatinine
Liver tests
Thyroid function
Chest imaging reference

During treatment course :

Complete CBC
Serum electrolytes, creatinine
Liver tests

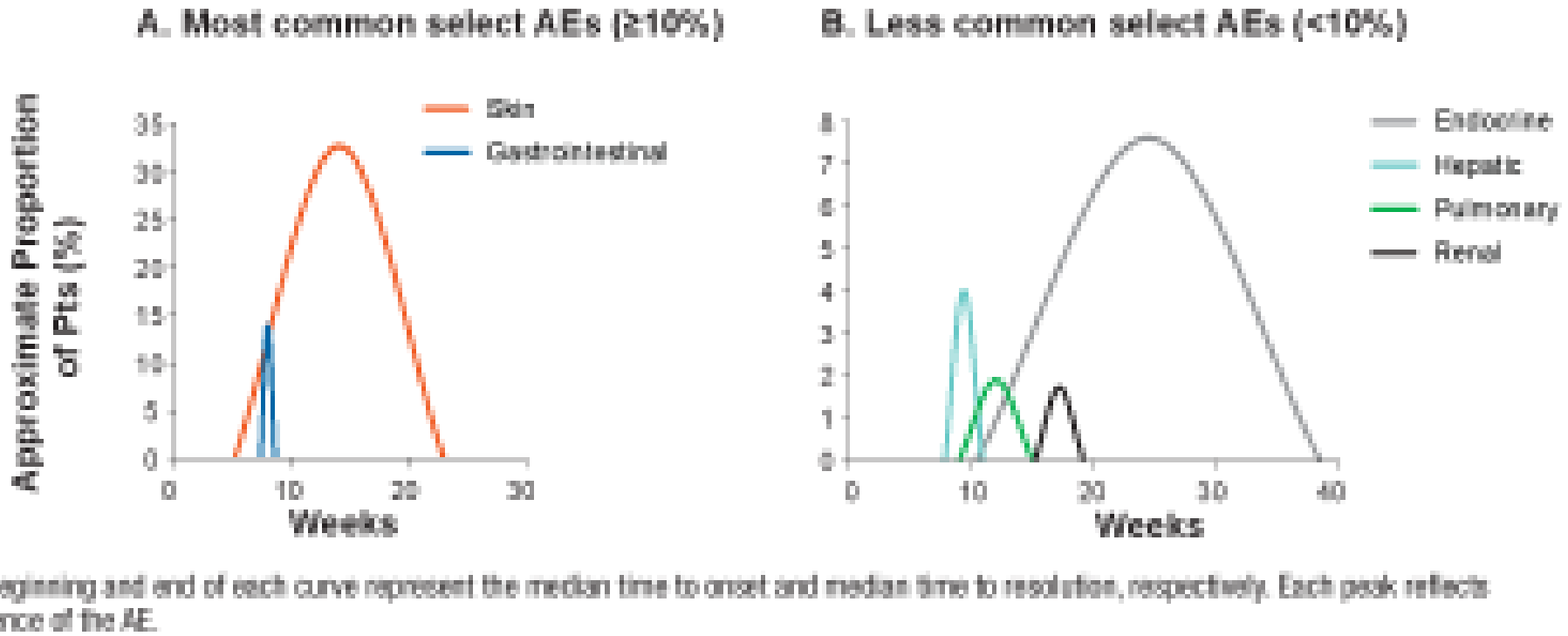
Thyroid function every 2-3 courses

Kinetics of appearance of immune-related adverse events (CTLA4)



adapted from Weber, et al., Management of immune-related adverse events and kinetics of response with ipilimumab. Journal of Clinical Oncology, 2012.

PD1 AE kinetic profile



The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE.

Weber et al., Poster, ASCO 2015.
Safety profile of nivolumab in patients with advanced melanoma: A pooled analysis.

Detect

Most frequent irAEs (≥ 10%) :

Anti-CTLA4 : diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased apetite, abdominal pain

Anti-PD1: fatigue, rash, pruritus, diarrhea, nausea, arthralgia

Focus on life threatening irAEs :

Infusion reaction

Colitis

Pneumonitis

Pleural & pericardial effusion, myocarditis

Skin (DRESS)

Neuro : Guillain-Barré, myélitis, encephalopathy

Hemato : hemolytic anemia, immune thrombocytopenia, neutropenia

Endoc : type 1 diabetes, acute adrenal insufficiency

Treat

Symptomatic treatment

Guidelines

Patient information

Suspend/ discontinue immunotherapy ?

Corticosteroids ?
taper slowly
Other **immunosuppressive drugs ?** (anti-TNF, etc)

Refer to organ specialist ?

Managing immune-related toxicities

A team work

Oncologist

Dermatologist
Caroline ROBERT

Internal Medicine
Olivier LAMBOTTE
Kremlin Bicêtre

Nephrologist
Hélène FRANÇOIS
Kremlin Bicêtre

Endocrinologist
Philippe CHANSON
Kremlin Bicêtre

Gastro Enterologist
Franck CARBONNEL
Kremlin Bicêtre

Chest Specialist
Jérôme LE PAVEC
Marie Lannelongue

Cardiologist
Stéphane EDERHY
Saint Antoine

Hematologist
Julien LAZAROVICI

Rhumatologist
Rakiba BELKHIR
Kremlin Bicêtre

Hepatologist
Didier SAMUEL
Paul Brousse

Neurologist
Cécile CAUQUIL
Kremlin Bicêtre

Ophtalmologist
Emmanuel BARREAU
Kremlin Bicêtre

Application mobile Gustave Roussy

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Principes généraux

Bilan pré-thérapeutique

Bilan au cours de l'immunothérapie

Symptômes d'appel et diagnostics à évoquer

CAT devant une anomalie biologique

CAT devant un symptôme

Pathologies dysimmunitaires

Signes associés aux maladies systémiques

Auto-anticorps

Immunosuppresseurs

Coordonnées des référents

Pharmacovigilance

Scores

Annexes

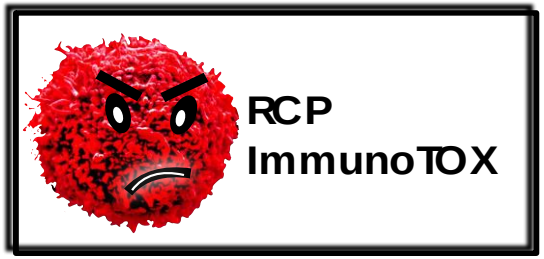
Disponible sur App Store

Available on the Android App Store

Mise en place d'une RCP ImmunoTOX

Pharmacovigilance
nouvelles toxicités,
fréquences rapportées via REISAMIC

Rapport de cas particuliers
pour discussion prise en charge diagnostique/thérapeutique



Avis de référent
sollicité via un formulaire de RCP
Décision d'arrêt de l'immunothérapie
Toxicités résistantes
Décision de mise sous immunothérapie

Translationnel
Physiopathologie
Mise en place d'études cliniques/biologiques

Adaptation des guidelines

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UNIVERSITÉ PARIS SUD

MOLECULAR ANALYSIS FOR PERSONALISED THERAPY

CONFERENCE

MAP

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2016
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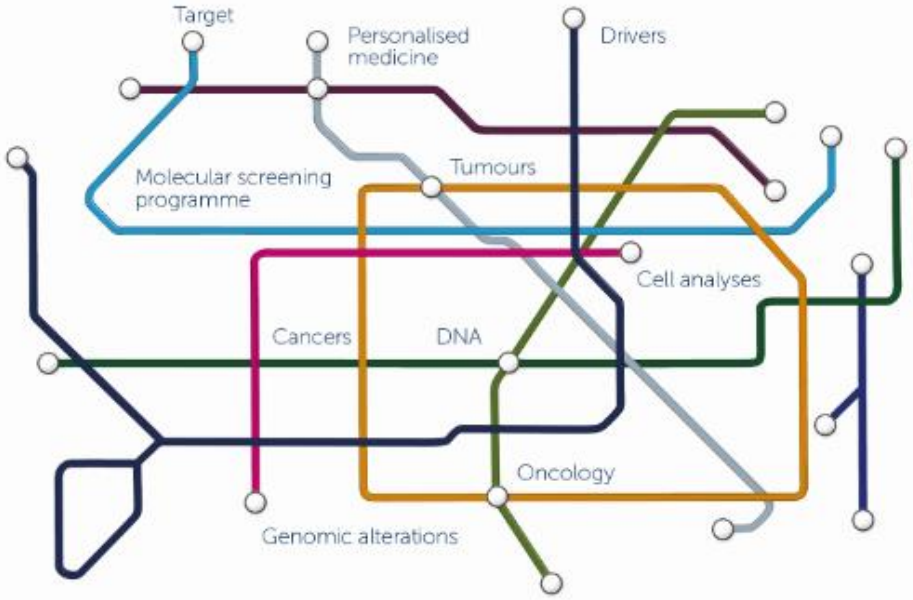
London

INTERPRETING MOLECULAR ALTERATIONS FOR CLINICAL PRACTICE



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