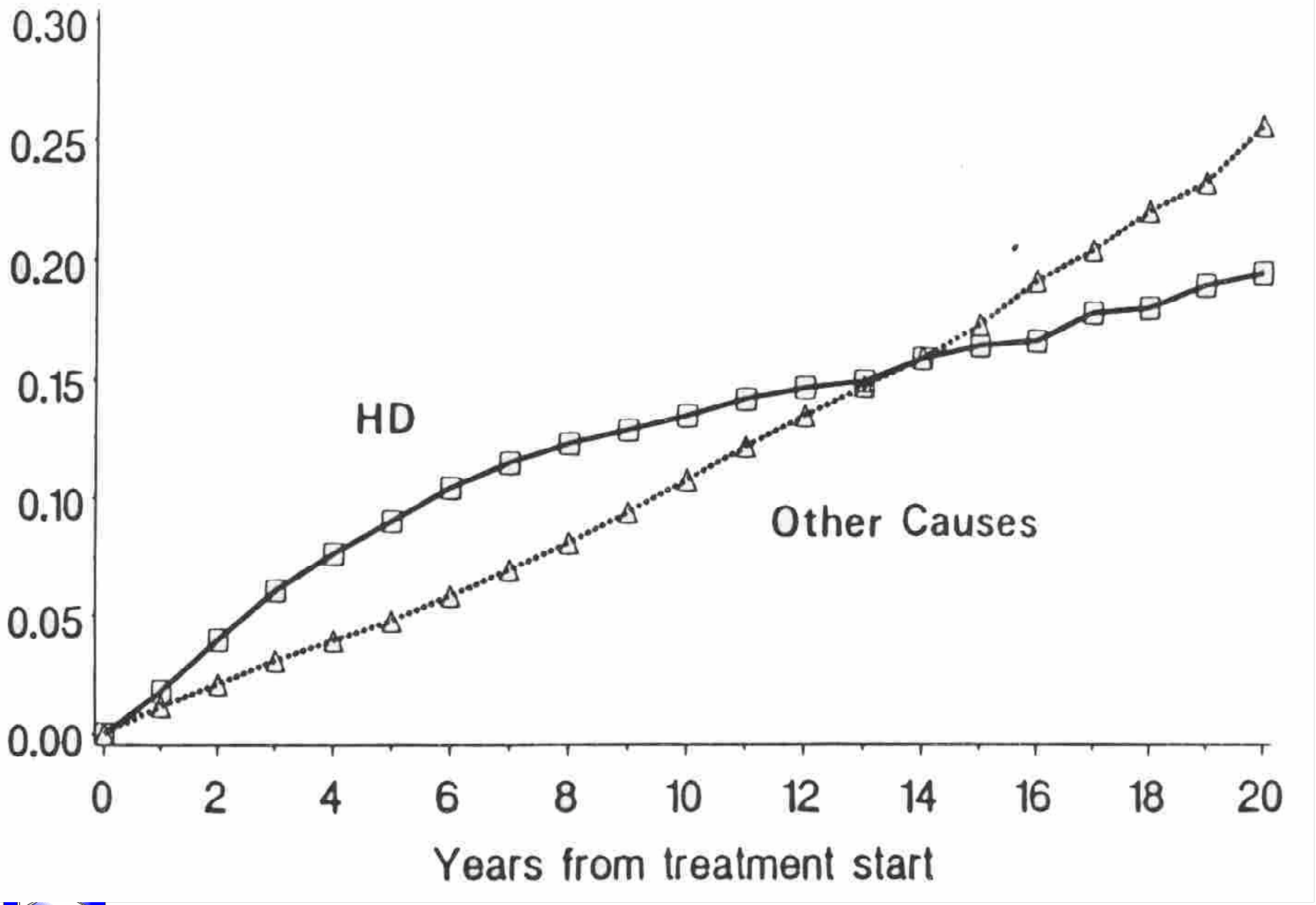
GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Effets indésirables des anti-PD1/PD-L1, anti-CTLA4

Pr. Patrice CARDE *tél. 33 (0)1 42 11 45 14*
email dr.pcarde@gmail.com

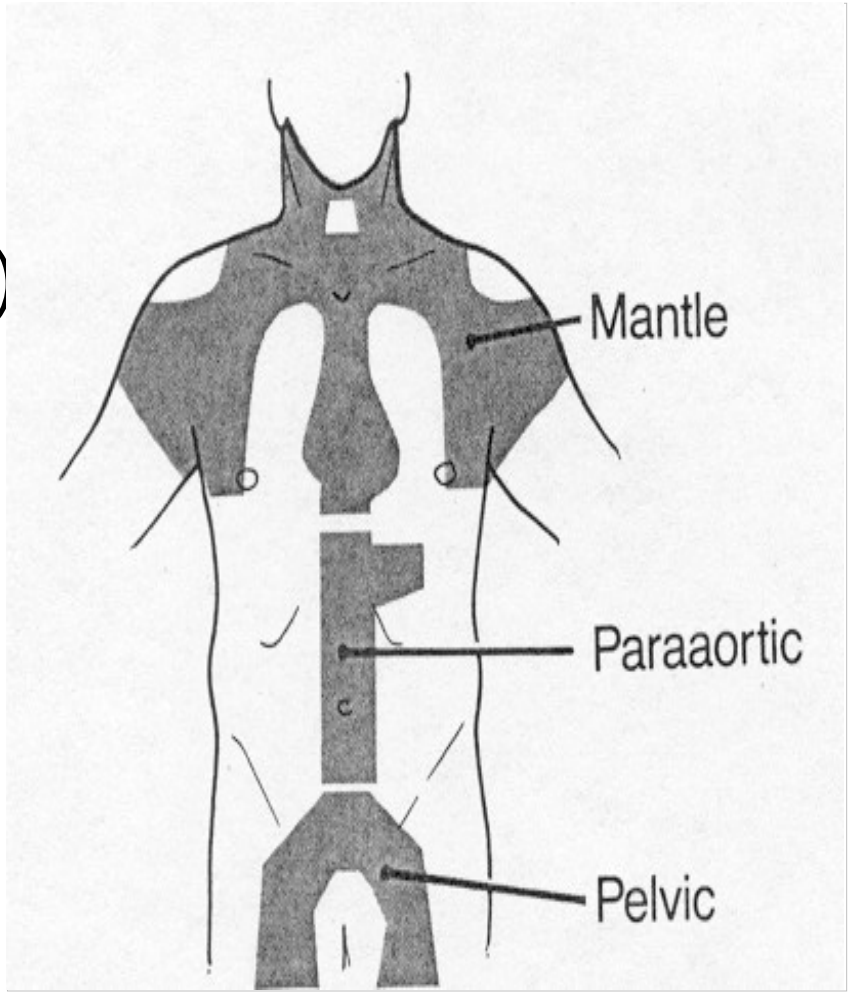
Dr Stéphane CHAMPIAT MD, PhDc
Gustave Roussy



Henry - Amar, Paris workshop: 1989

IRRADIATION SEULE => guérison des LH

- irradiation lymphoïde totale ou subtotale (TLI, TNI, STLI, STNI)
- pleine dose (> 40 Gy)
- staging maximum
  - lymphographie
  - laparotomie exploratrice
  - splénectomie



MOPP

agent	jour	dosage
Méchloréthamine	1, 8	6 mg/m²
Oncovin (vincristine)	1, 8	1,4 mg/m² (max. 2 mg)
Procarbazine	1 - 14	100 mg/m²/j
Prednisone	1 - 14	40 mg/m²/j

cycle suivant au j29

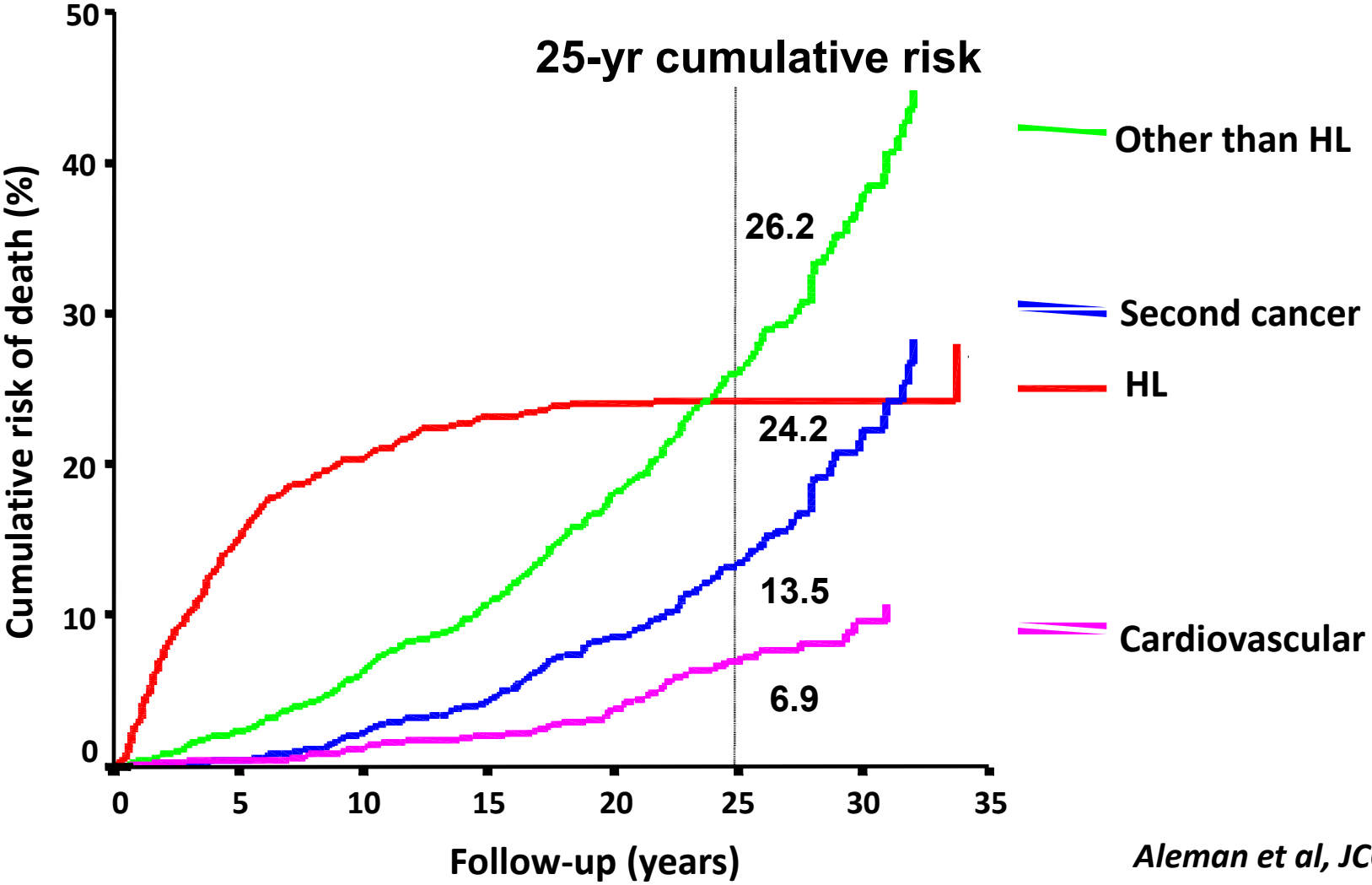
ABVD, ou bien ….

Adriamycine	1, 15	25 mg/m²
Bléomycine	1, 15	10 mg/m²
Vinblastine	1, 15	6 mg/m²
Dacarbazine (DTIC)	1, 15	375 mg/m²

cycle suivant au j29 *8 cycles total dans les stades étendus*

causes of death in HL patients

competing mortality



Aleman et al, JCO 2003

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%

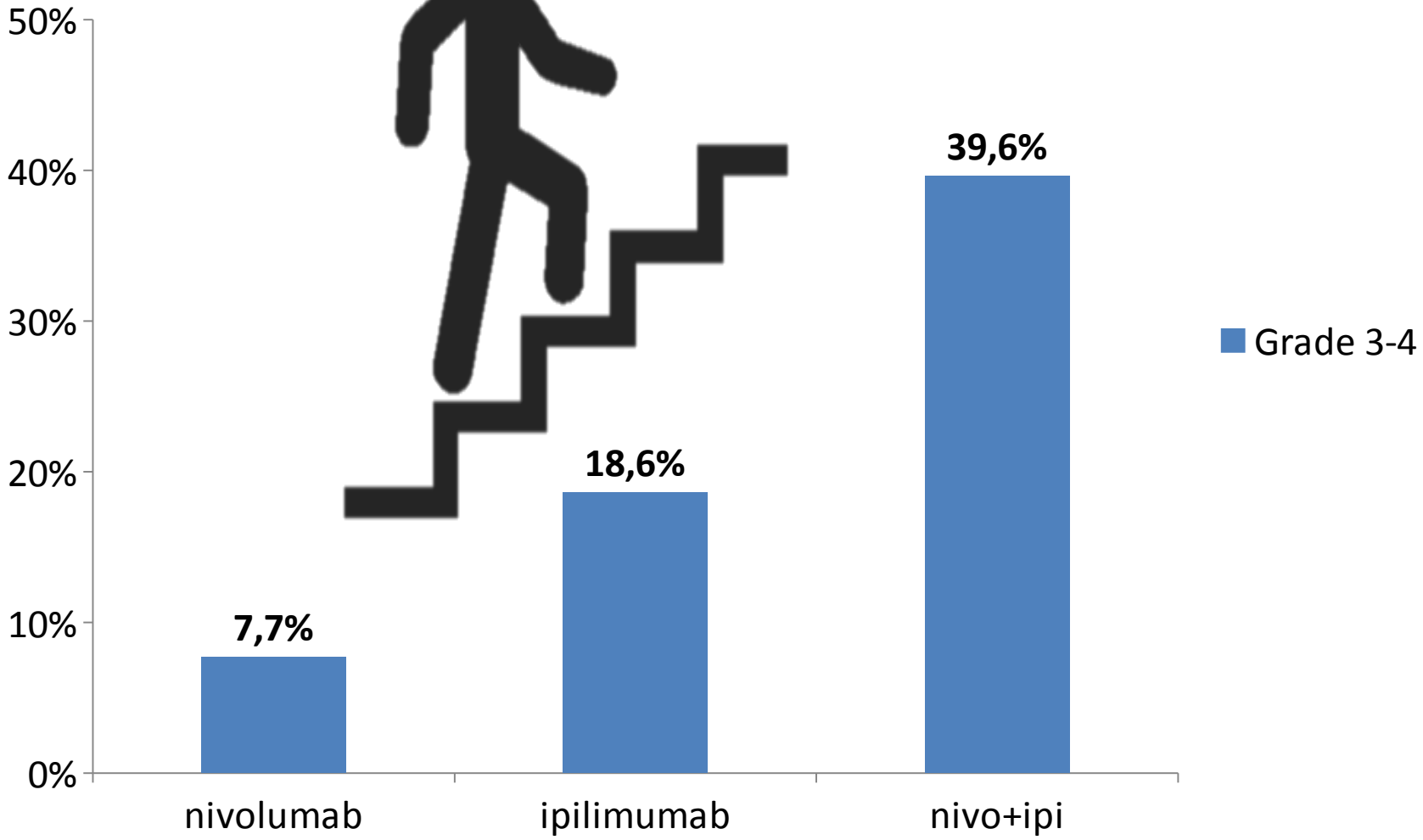
Treatment-related Grade 5 events

- 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*

irAEs are NOT so rare when used in combination

Grade 3-4 immune related Adverse Events with anti-CTLA4 + anti-PD-1

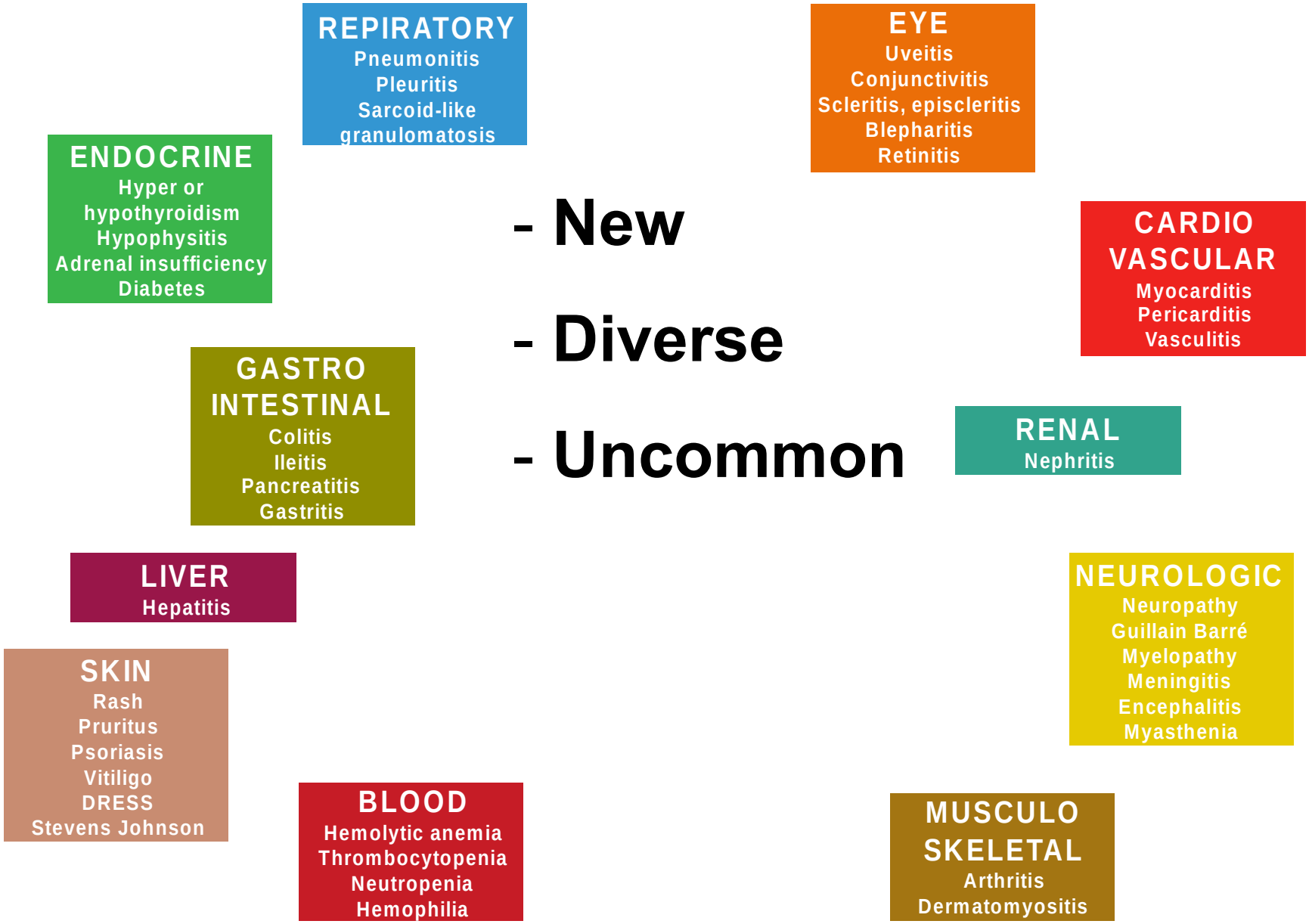


Larkin et al, N Engl J Med 2015.

Current IO agents (anti-PD1/PD-L1, anti-CTLA4) are NOT specific immunotherapies

Mr. anti-tumor Lymphocyte

Current IO agents (anti-PD1/PD-L1, anti-CTLA4) are NOT specific immunotherapies



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

Un nouveau spectre de toxicités

1 - 5 %

Digestives
Colites inflammatoires perforées

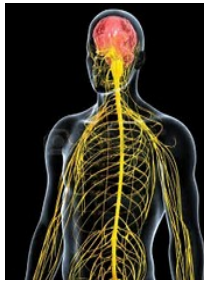
Pulmonaires
Pneumopathie inflammatoire
Epanchement pleuro/péricardique

Hépatiques
Hépatites cytolytiques

Toxicités rares mais potentiellement mortelles

< 1 %

Cardio
Myocardite fulminante



Neurologiques
Guillain Barré
Encéphalite

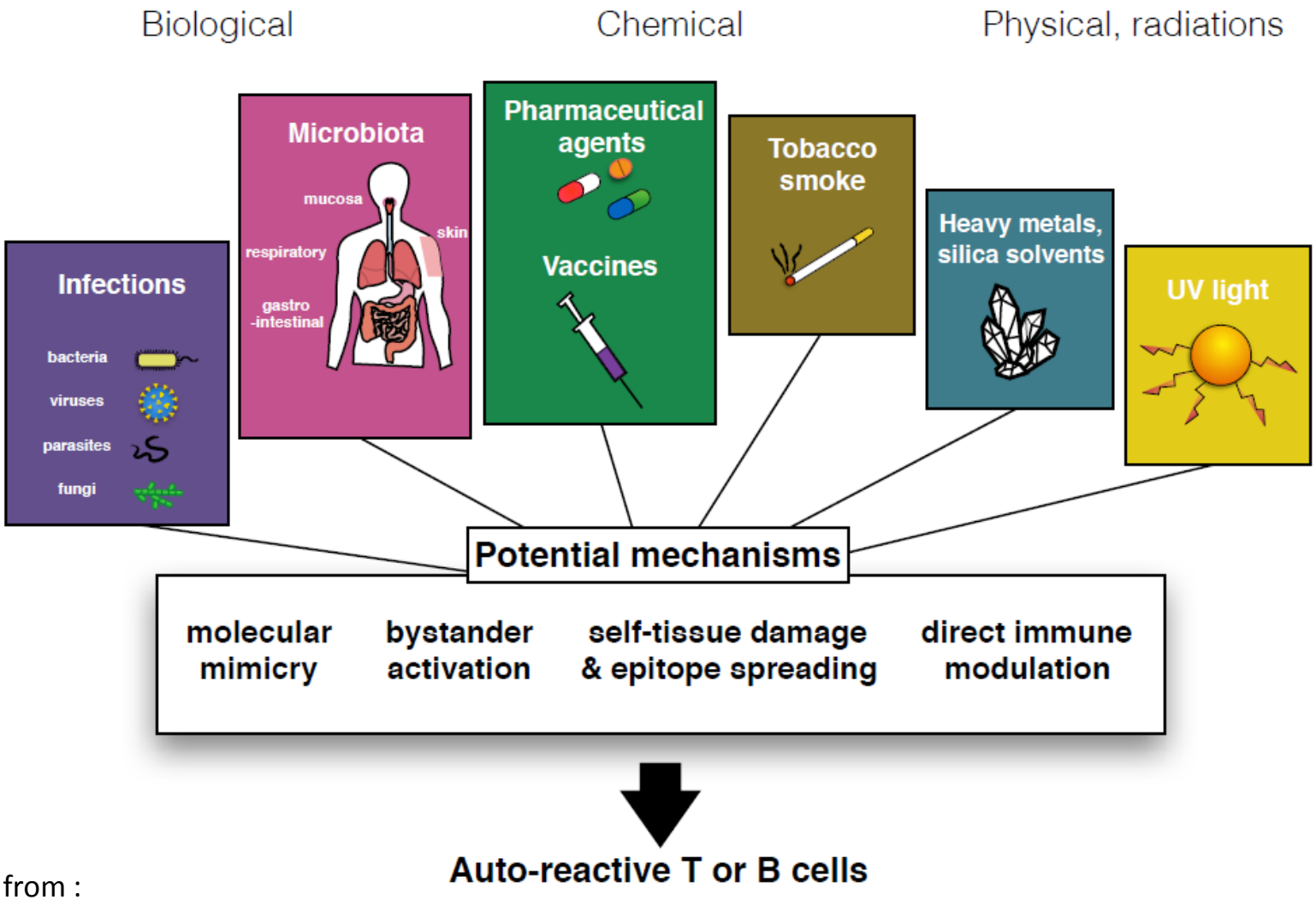
Endocriniennes
Insuffisance surrénalienne
Acidocétose diabétique

Hématologiques
Anémie
Thrombopénie
Neutropénie

Cutanées
DRESS
Steven Johnson

Rénales
Néphrite

Environmental Factors associated with autoimmunity



Adapted from :
Wang et al., (2015). *Journal of Internal Medicine*
Vanderlugt, et al., (2002). *Nature Reviews Immunology*

Application mobile Gustave Roussy

Une aide au diagnostic et à la prise en charge des toxicités des immunothérapies

IMMUNOTHERAPIE

Bilan pré-thérapeutique

Symptômes d'appel et diagnostics à évoquer

CAT devant une anomalie biologique ou symptôme

Pathologies dysimmunitaires

Auto-anticorps

Immunosuppresseurs

Coordonnées des référents

Disponible sur App Store

Available on the Android App Store

Discussion de cas complexes

Pharmacovigilance
Nouvelles toxicités
Rapports REISAMIC

Discuter d'une contre-indication à l'immunothérapie

RCP
Immuno TOX

Discuter de la CAT pour un terrain particulier

Discuter de l'arrêt définitif ou de la reprise de l'immunothérapie

RCP.iTOX@gustaveroussy.fr

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Stéphane CHAMPIAT MD, PhDc
Gustave Roussy
stephane.champiat@gustaveroussy.fr

Jean-Charles Soria
Aurélien Marabelle
Olivier Lambotte
Jean-Marie Michot
Delphine Loirat

Une aide au diagnostic et à la prise en charge des toxicités des immunothérapies

Disponible sur App Store

Available on the Android App Store

Actualité publications sur les toxicités des immunothérapies :

@iTOXreport

conclusion

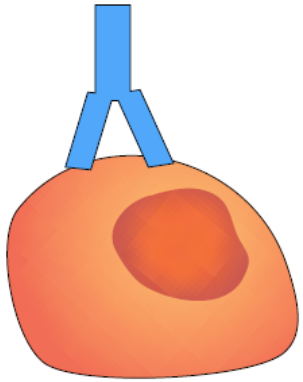
- espoirs thérapeutiques « bio » & « ciblés » antiPD1 +++
- intensité effets secondaires +/- proportionnelle qualité réponse
- même en l'absence de rechute, inégalité devant le risque de complication: rien n'est joué pour le patient, bilan initial & surveillance adaptés au patient & ses antécédents, environnement & habitus (cœur, vaisseaux, poumons, tabac, obésité)
- surveillance à long terme, nous l'espérons..

références

- Byun DJ et al. Cancer Imunotherapy – immune checkpoint blockade and associated endocrinopathies - Nature Reviews 11: 195-205, 2017 (April)
- Weber J et al. Safety profile of nivolumab monotherapy:a pooled analysis of patients with advanced melanoma – J Clin Oncol 35: 785-791, 2016 (April 1)
- Brahmer J et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer – N Engl J Med 373: 123-135, 2015 (July 9)
- Burstein HJ et al. Clinical Cancer Advances 2017: annual report on progress against cancer from the american Society of Clinical Oncology - – J Clin Oncol 35: 1-27, 2017 (February 1)

Immunothérapies & **Immunothérapies**

Cibler la cellule tumorale

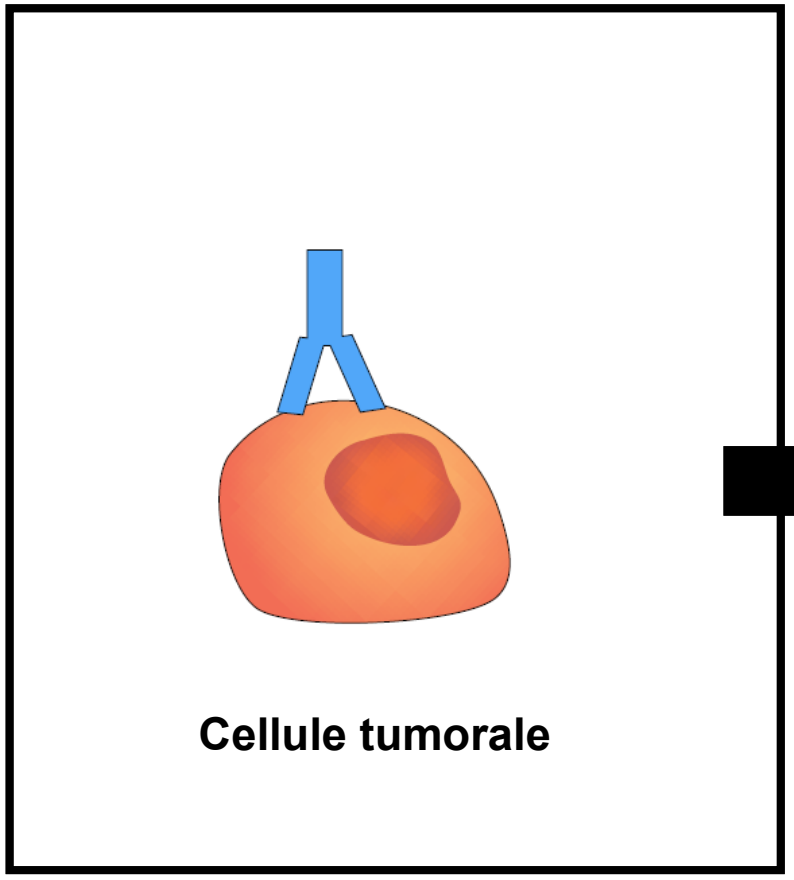


Cellule tumorale

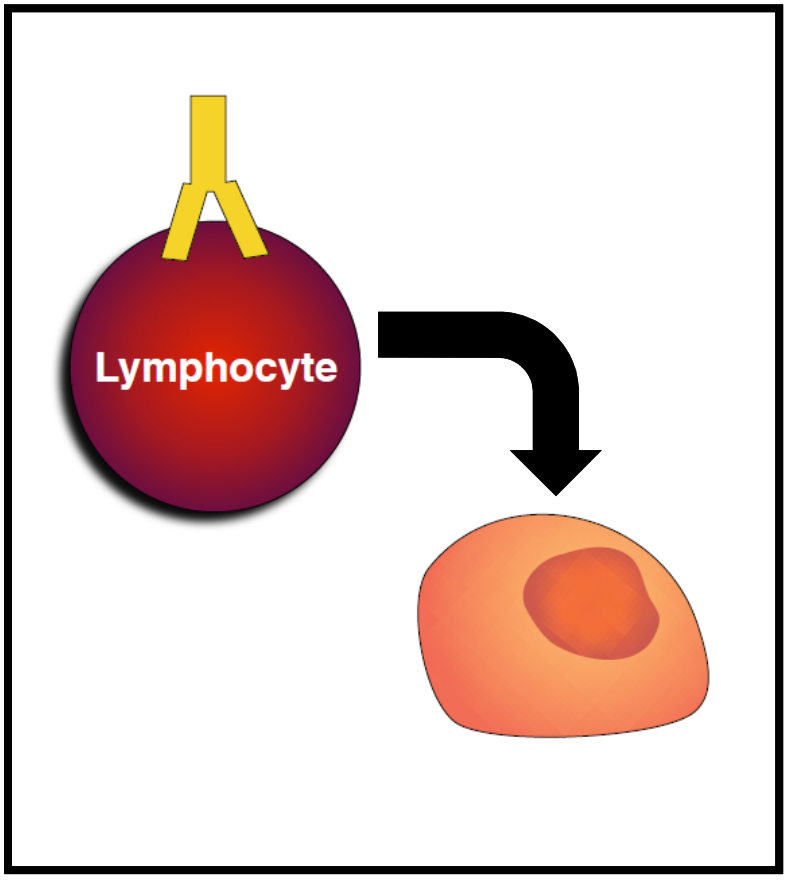
Immunothérapies & **Immunothérapies**

Nouvelles immunothérapies anti-cancéreuses

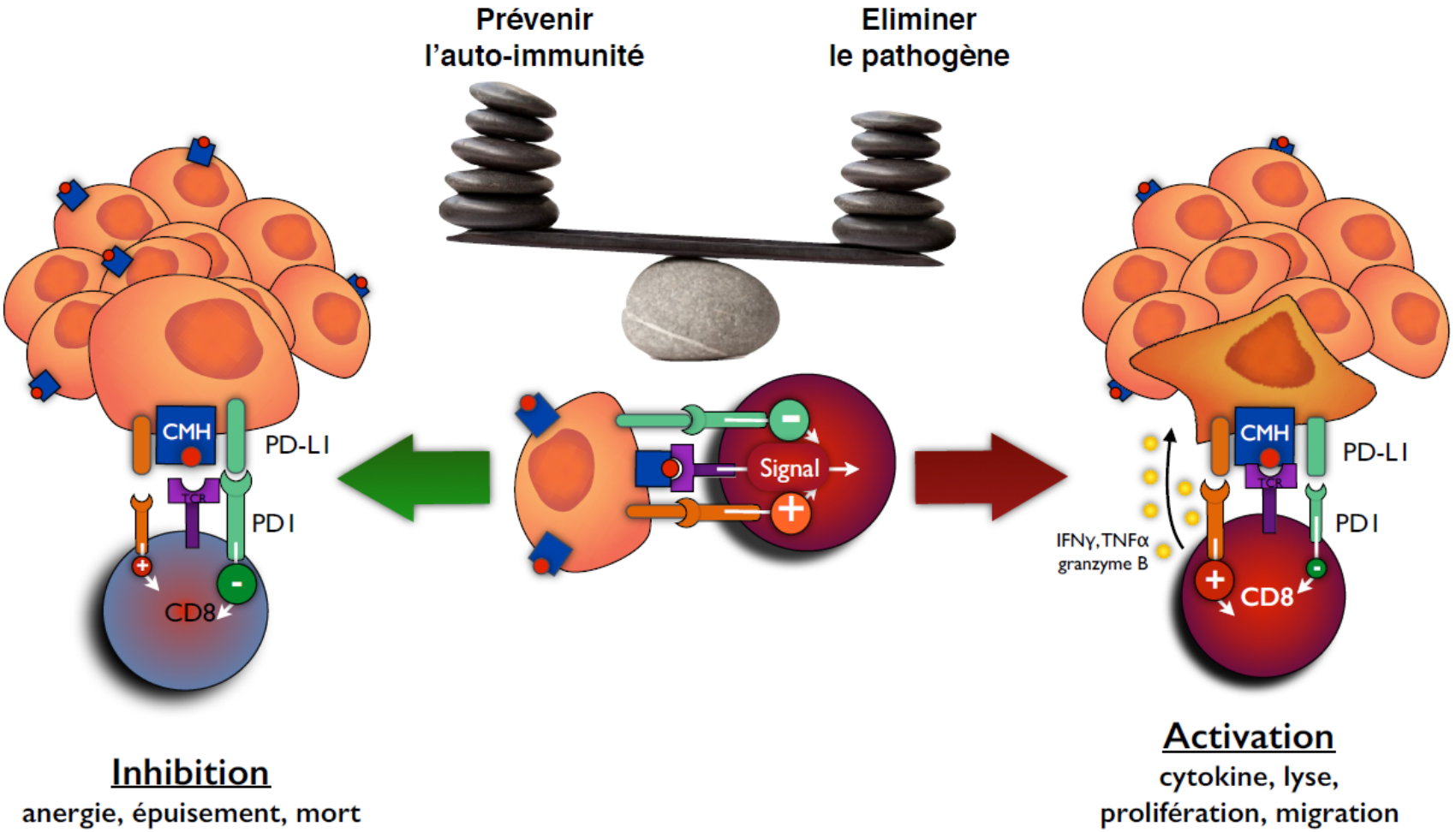
Cibler la cellule tumorale



Cibler la cellule immunitaire



Les points de contrôle du système immunitaire
“immune checkpoints”



Contrôle de l’intensité et de la durée de la réponse immunitaire

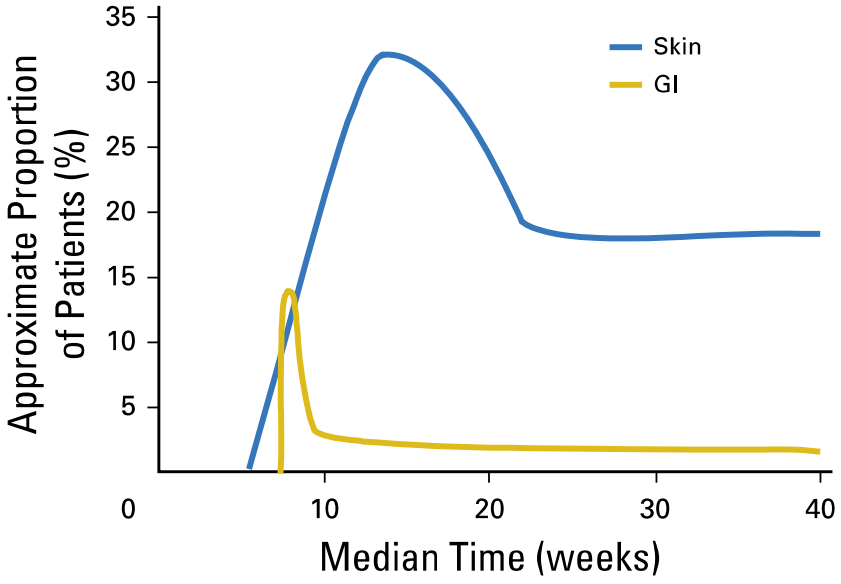
It’s not about the frequency…**it’s about diversity !**

It’s not about the frequency…**it’s about diversity !**

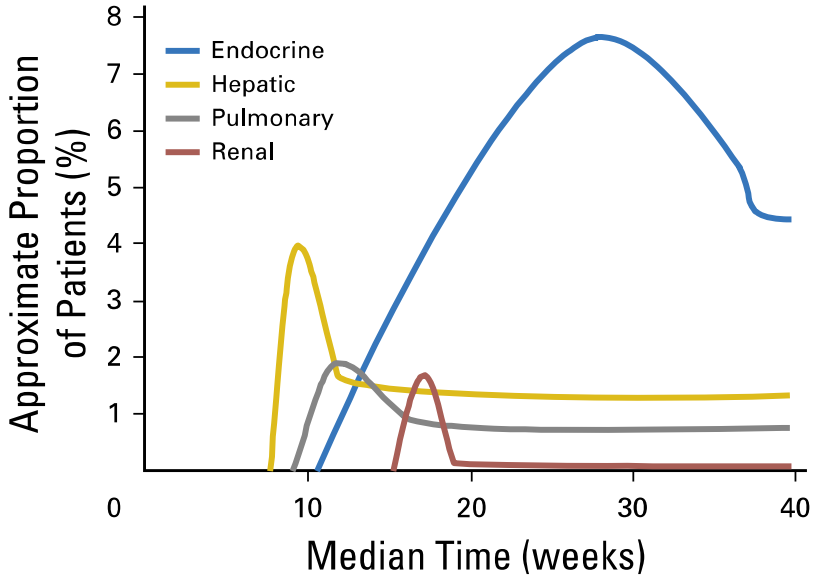
Kinetics of onset and resolution of anti-PD1 irAEs

Safety Profile of Nivolumab Monotherapy:
A Pooled Analysis of Patients With Advanced Melanoma (N=576)
Weber et al. JCO 2016

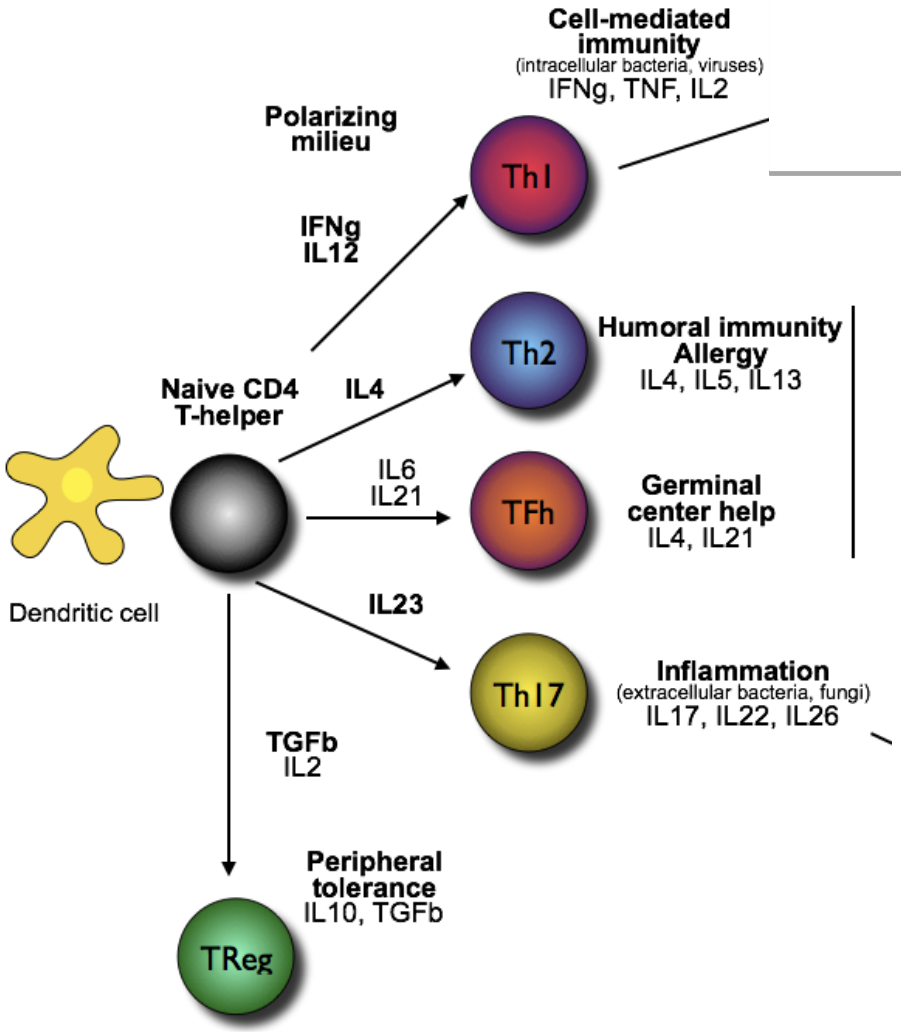
Most common irAEs (≥ 10%)



Less common irAEs (<10%)



Immuno-pathogenesis



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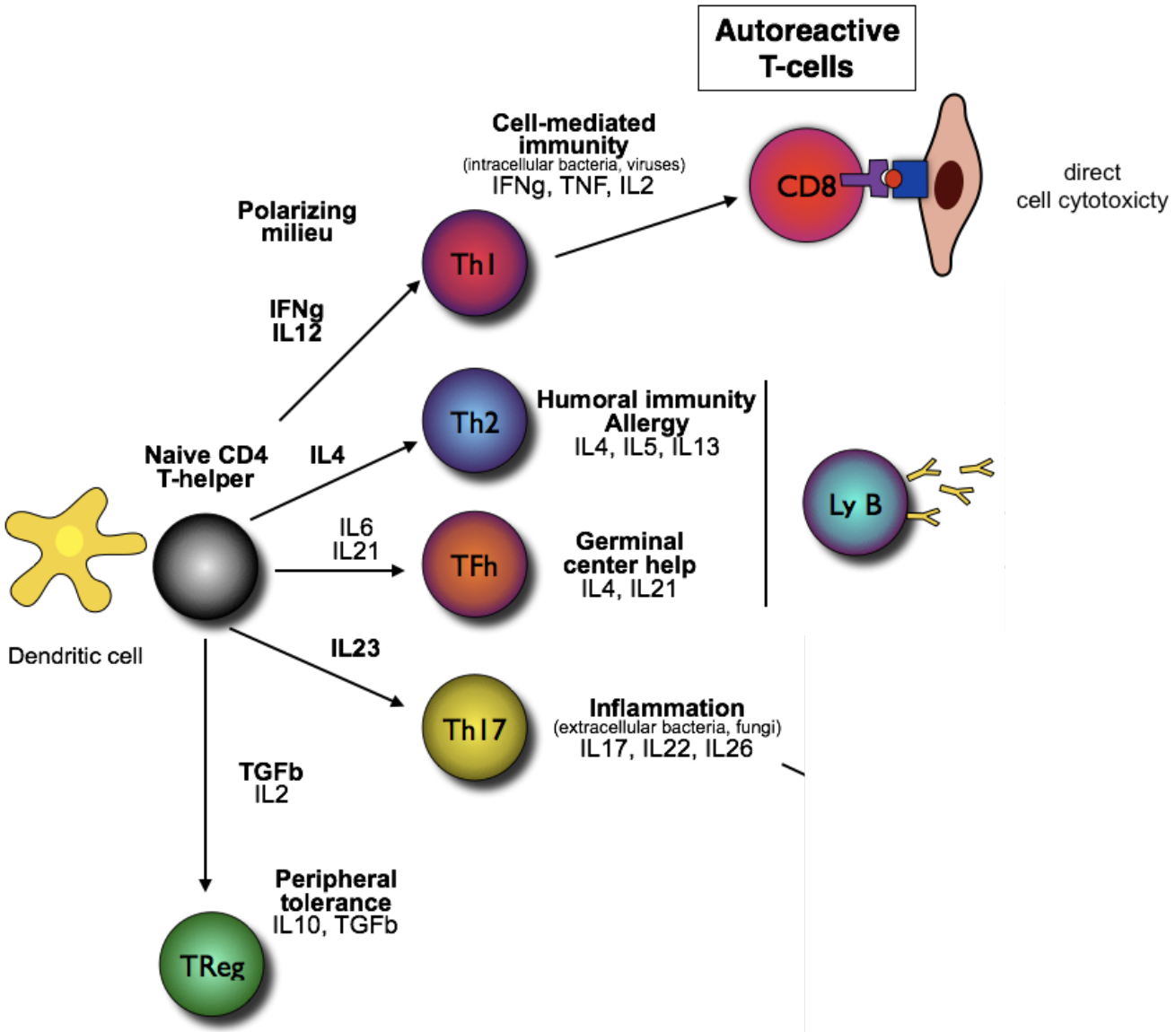

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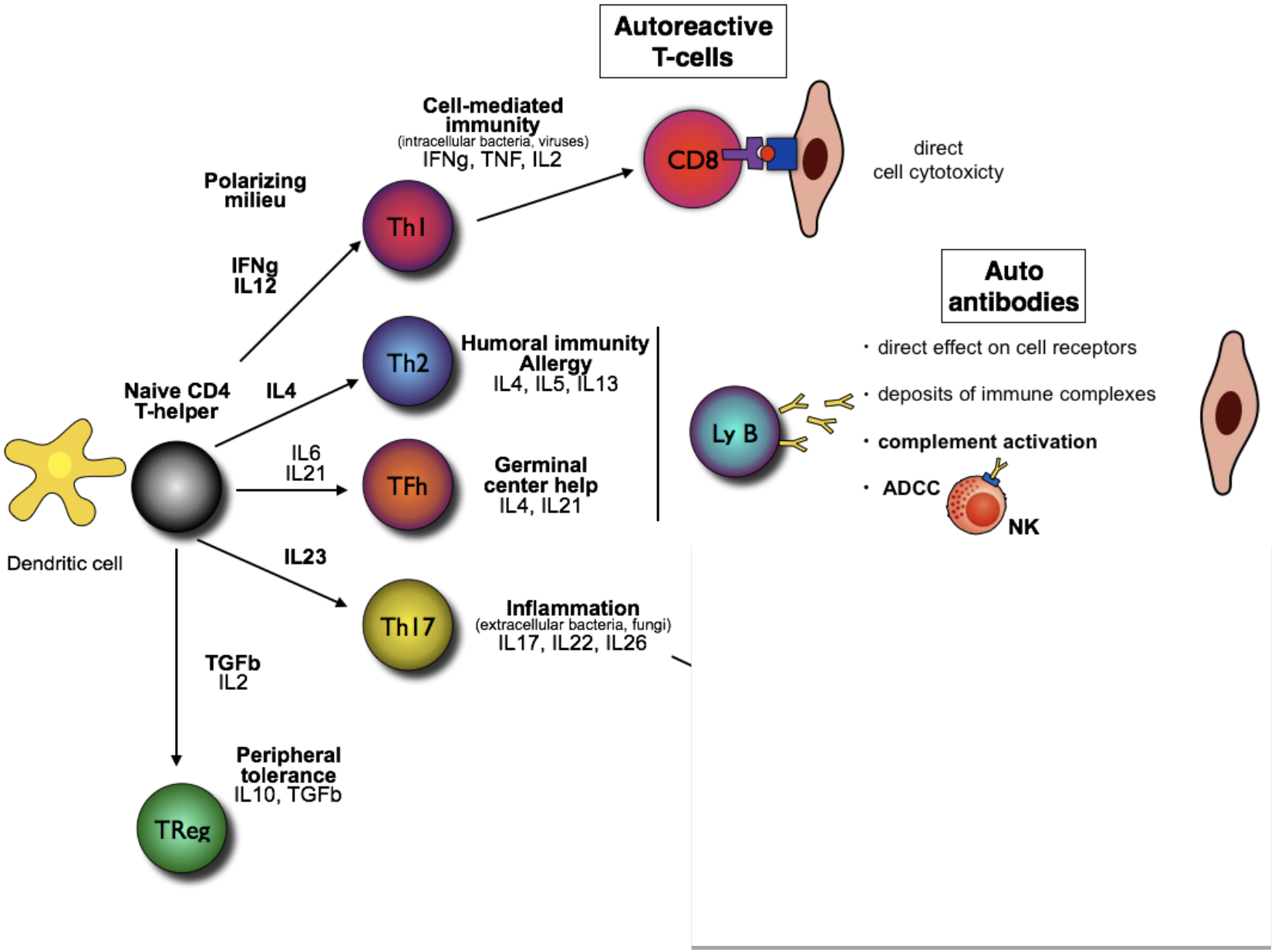

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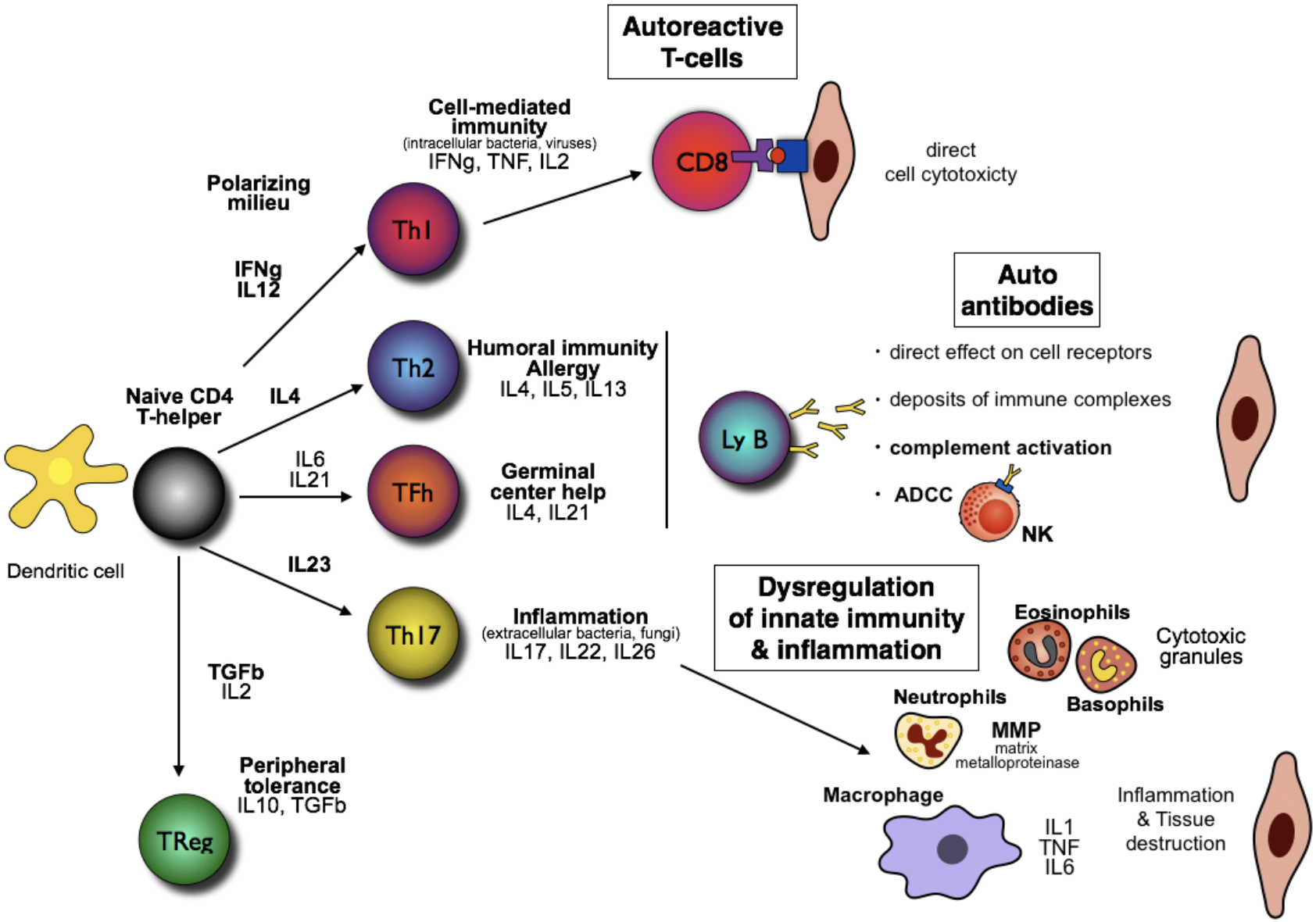
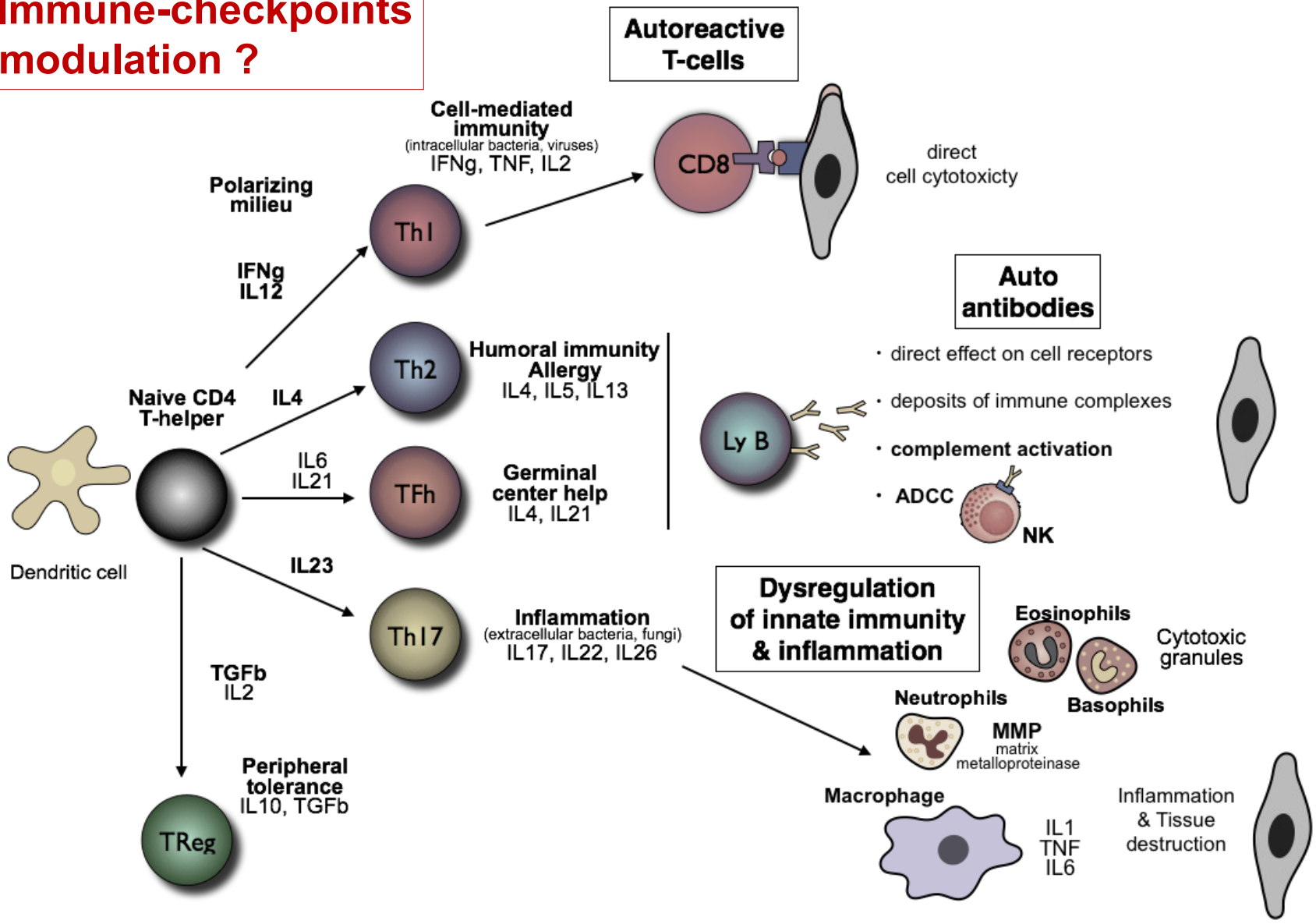


Immuno-pathogenesis

Role of Immune-checkpoints modulation ?



Immuno-pathogenesis

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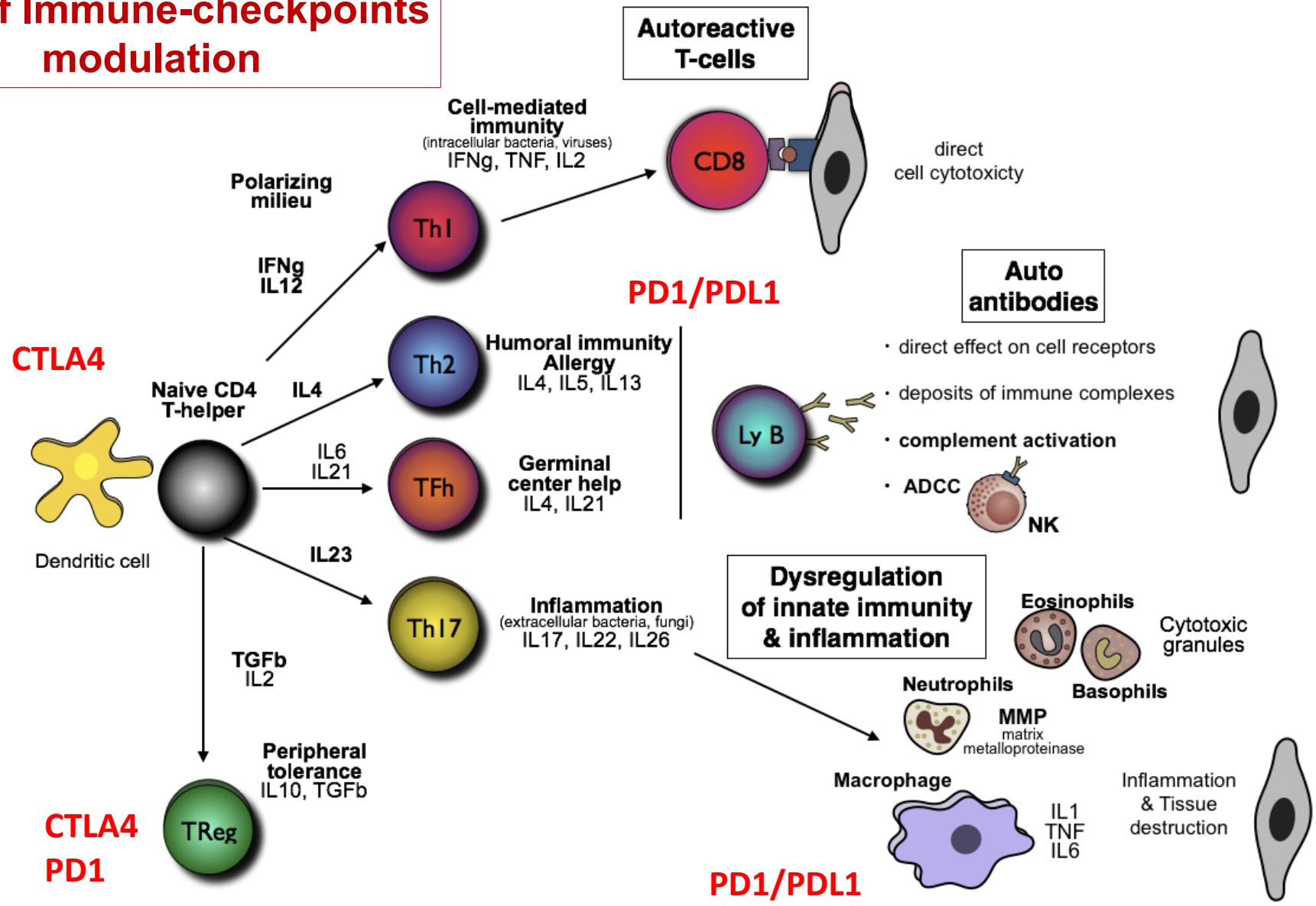

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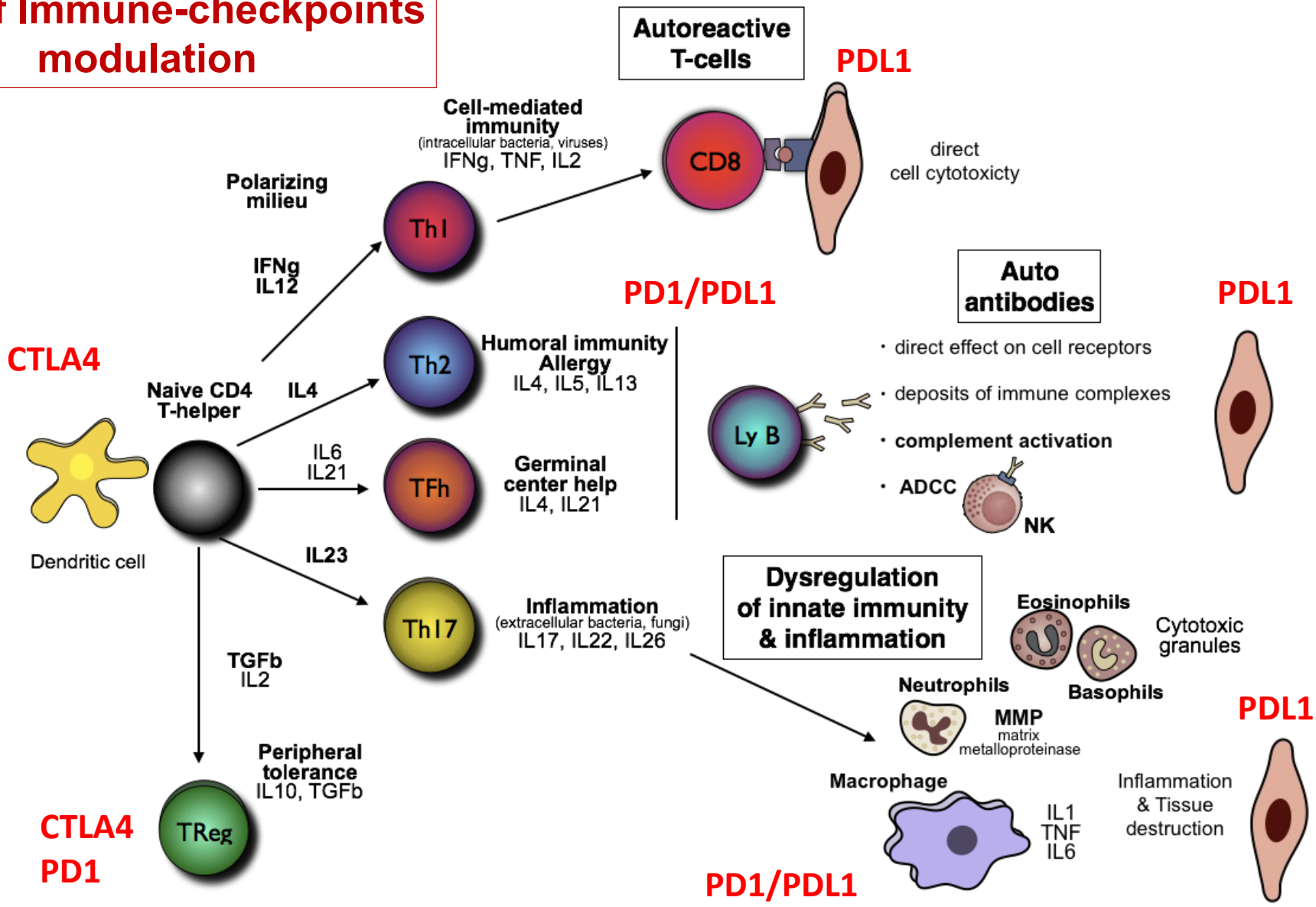
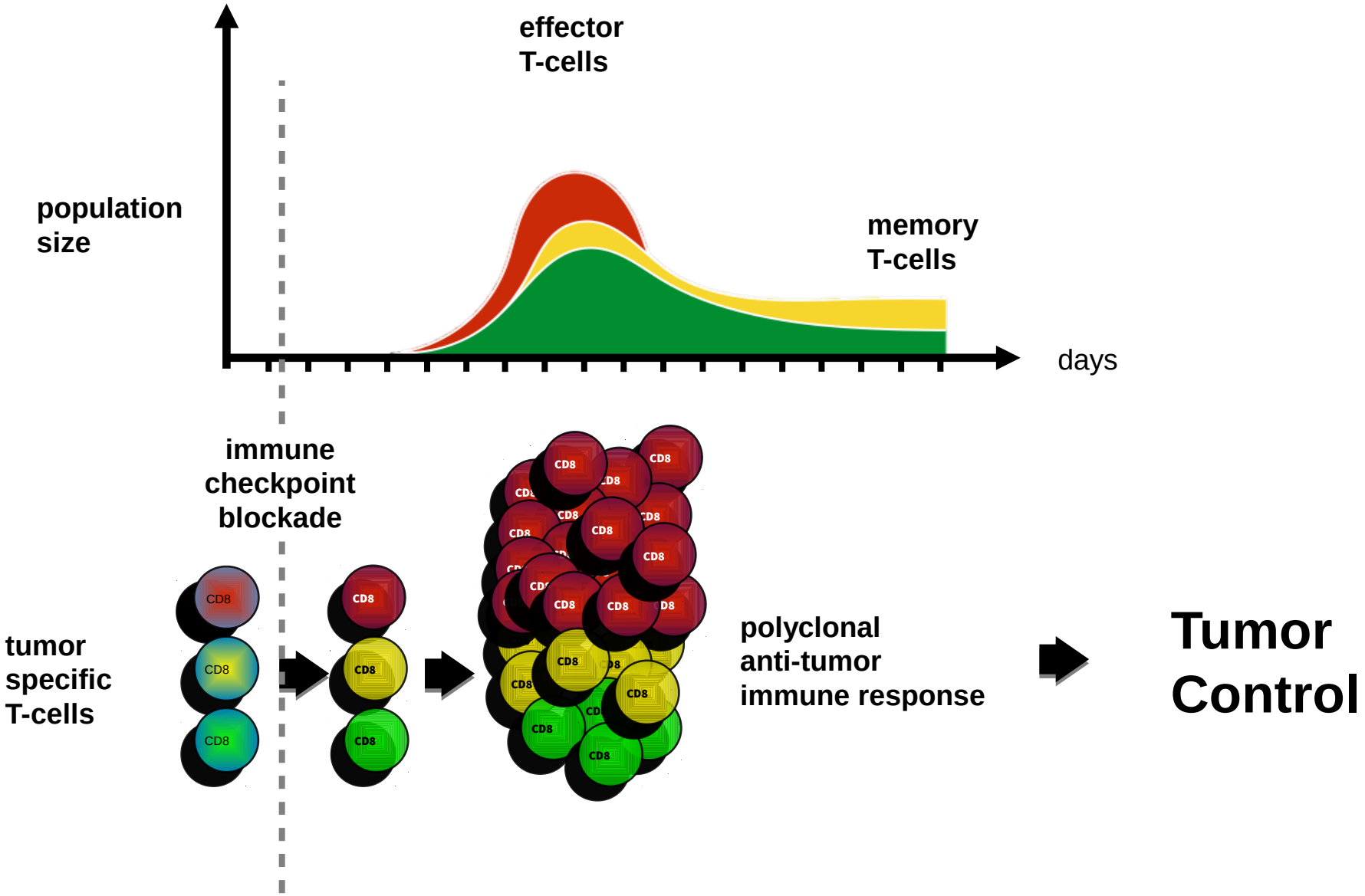


Kinetic of T-cell responses



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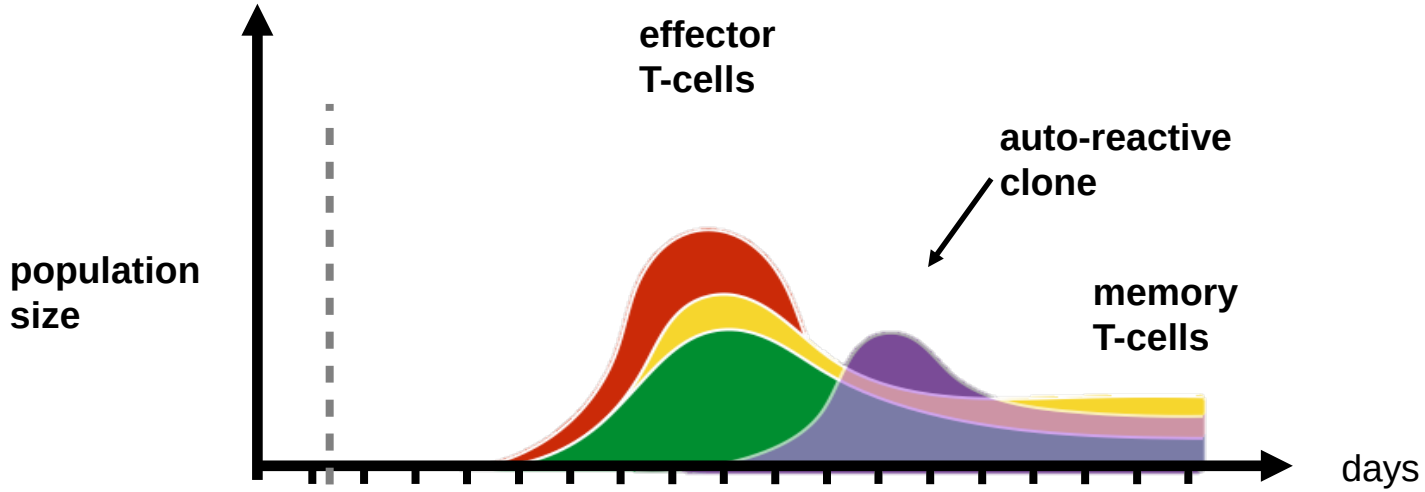

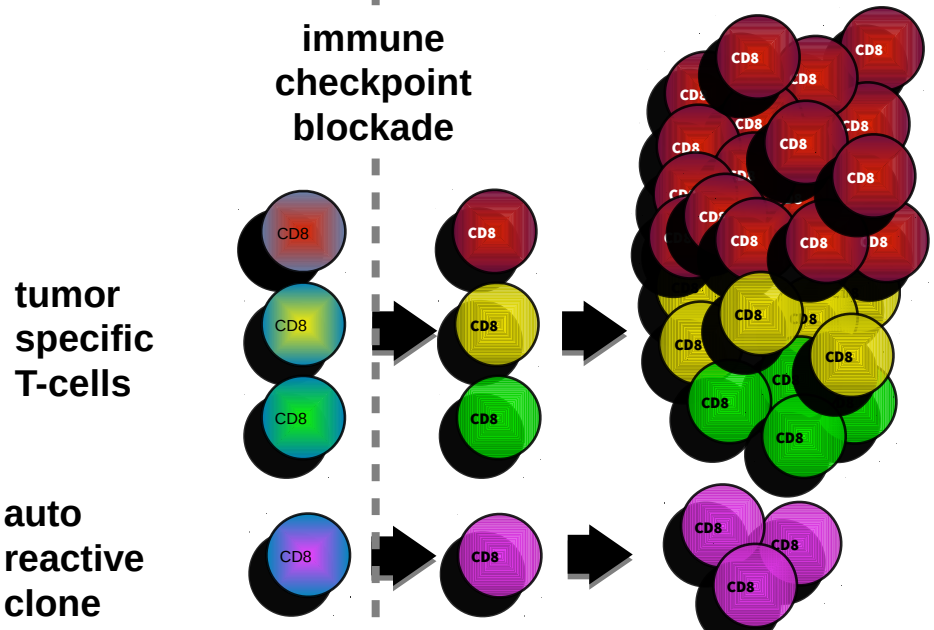

Tumor Control

Auto Immunity

Prevalence of Autoimmune Disease

- **3-5 % in general population**
  more frequent in women

- **Strongest genetic factor : MHC**

- Autoimmune disease concordance in monozygotic tweens
  75-83% coeliac disease
  12-30% rheumatoid arthritis

Role of the environment +++

Jacobson et al. , (1997). *Clin Immunol Immunopathol*
Eaton et al., (2007). *J Autoimmun*
Sollid et al., (2014) *Curr Opin Immunol*
Bogdanos et al., (2012) *J Autoimmun*

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Bogdanos et al., (2012) *J Autoimmun*

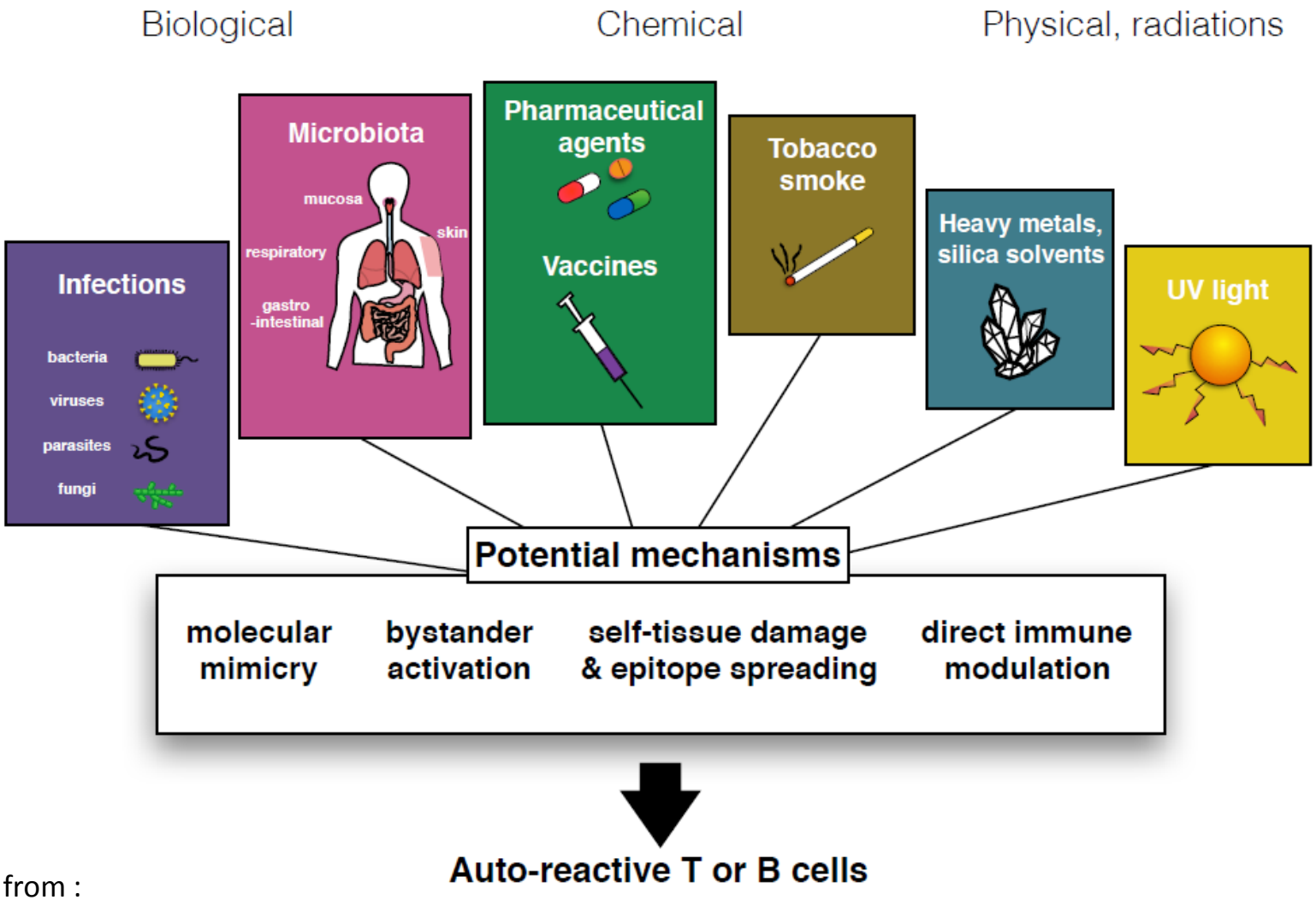
Prevalence of Autoimmune Disease Among Patients With Lung Cancer

Table 2. Prevalence of the 10 Most Common Individual Autoimmune Diseases Among 210 509 Patients With Lung Cancer

Autoimmune Disease	Prevalence, %
Rheumatoid arthritis	5.9
Psoriasis	2.8
Polymyalgia rheumatic	1.8
Addison disease	1.0
Systemic lupus erythematosus	0.9
Ulcerative colitis	0.8
Giant cell arteritis	0.8
Sicca syndrome	0.6
Regional enteritis	0.5
Ménière disease, unspecified	0.5
Total (any autoimmune disease)	13.5

Khan et al. , (2016). Prevalence of Autoimmune Disease Among Patients With Lung Cancer. *JAMA Oncology*

Environmental Factors associated with autoimmunity



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Vanderlugt, et al., (2002). *Nature Reviews Immunology*

Immunopathogenic mechanisms of systemic autoimmune disease

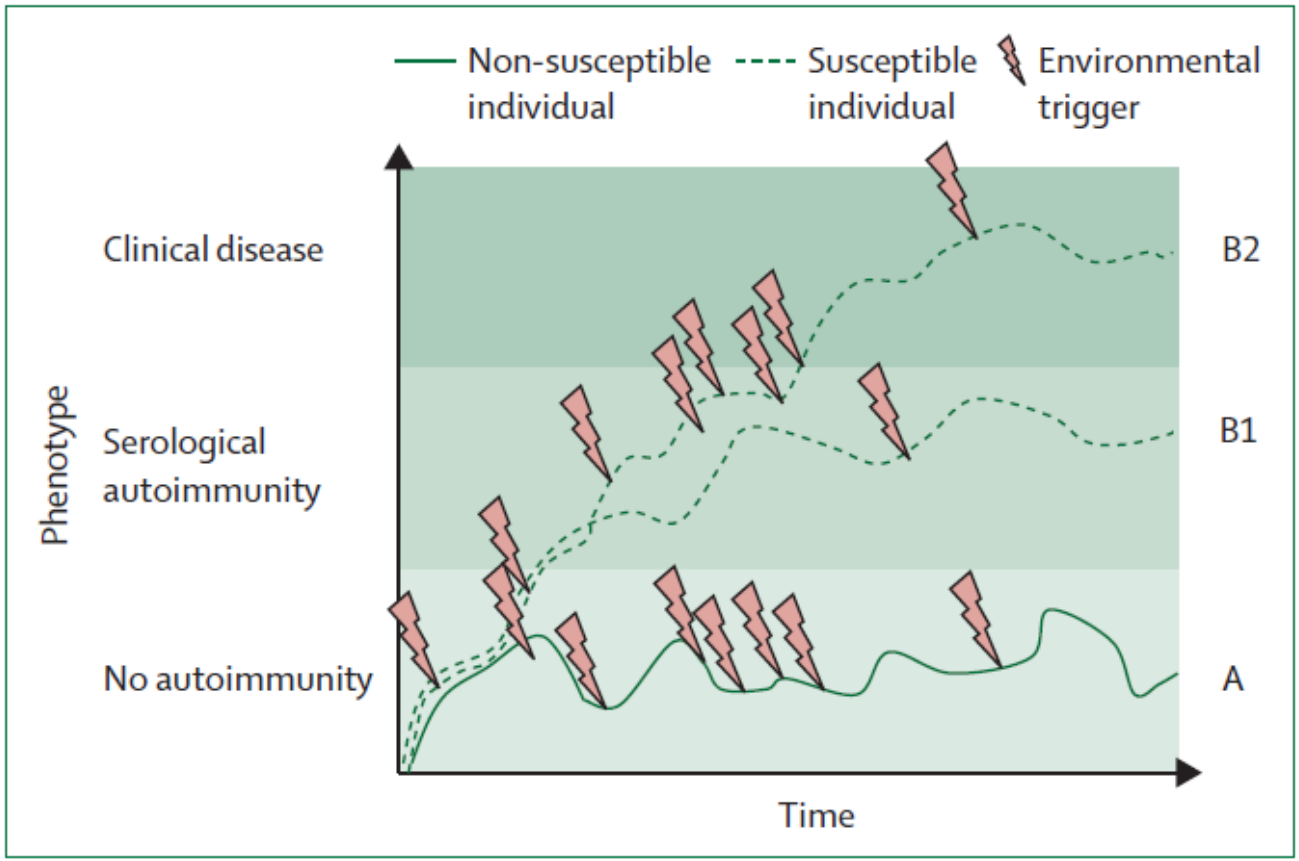
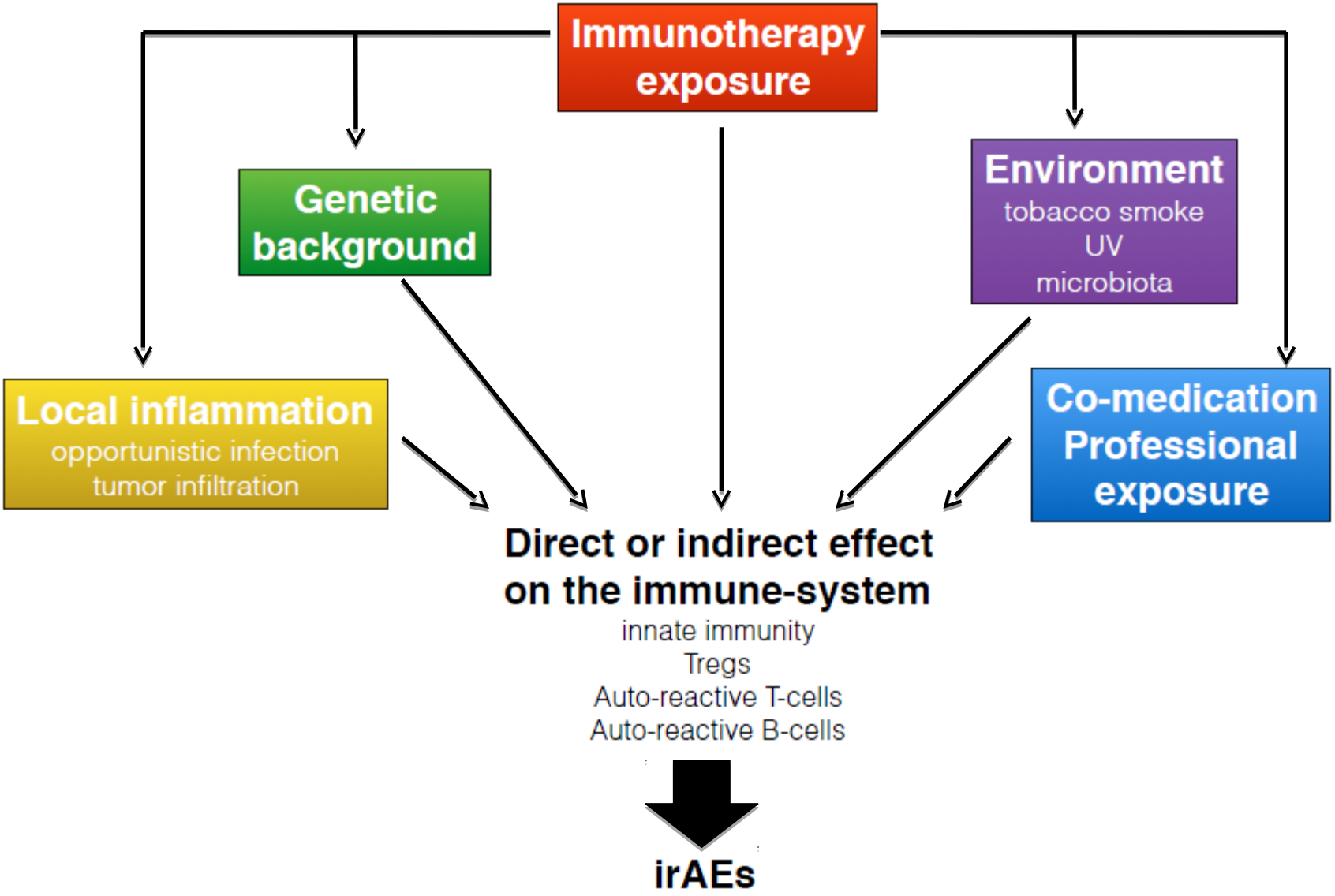


Figure 2: Time to clinical manifestation

Immunopathogenic mechanisms of systemic autoimmune disease Lancet 2013

Immunotherapy irAEs

Immunopathogenesis hypothetical model



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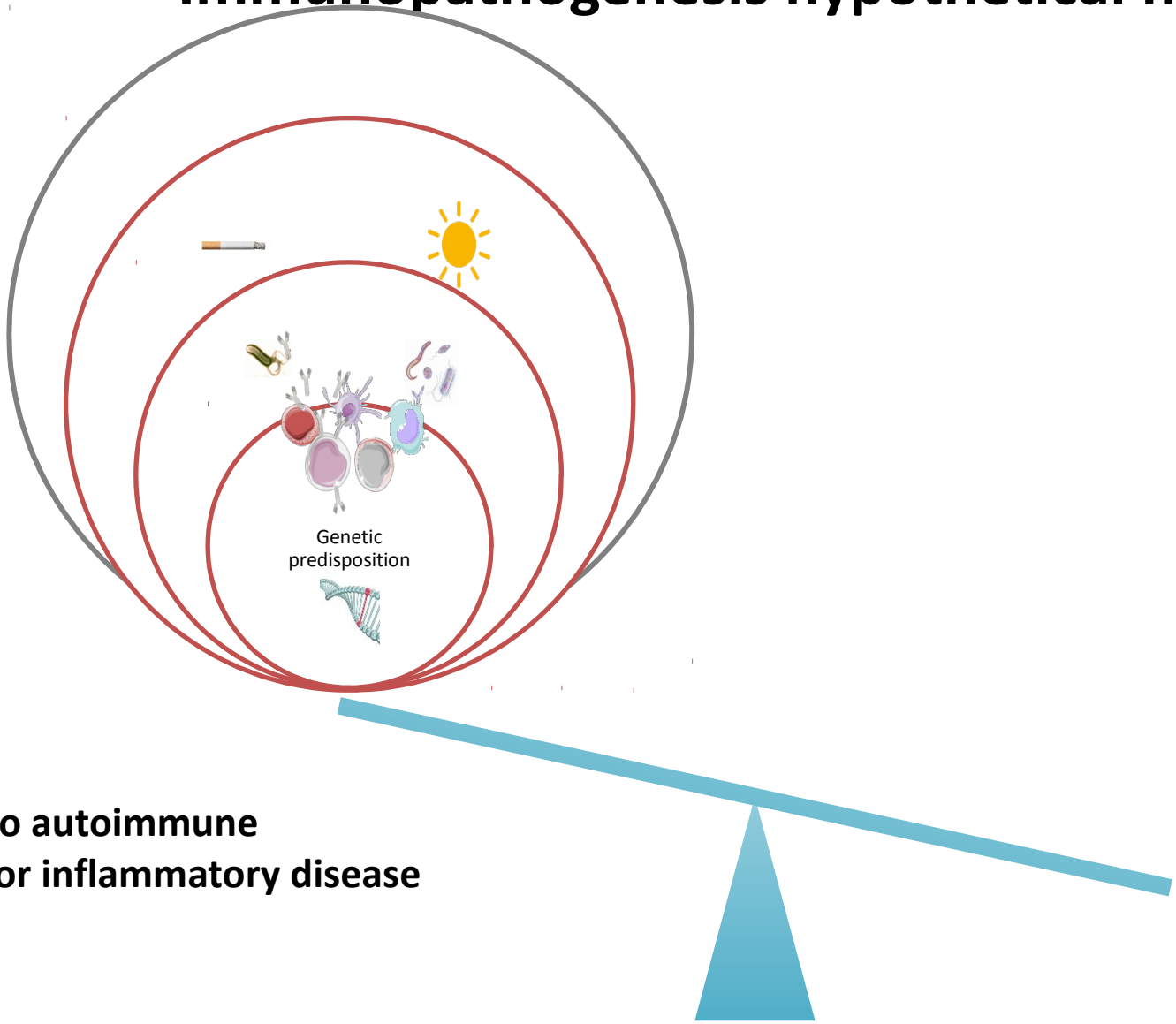
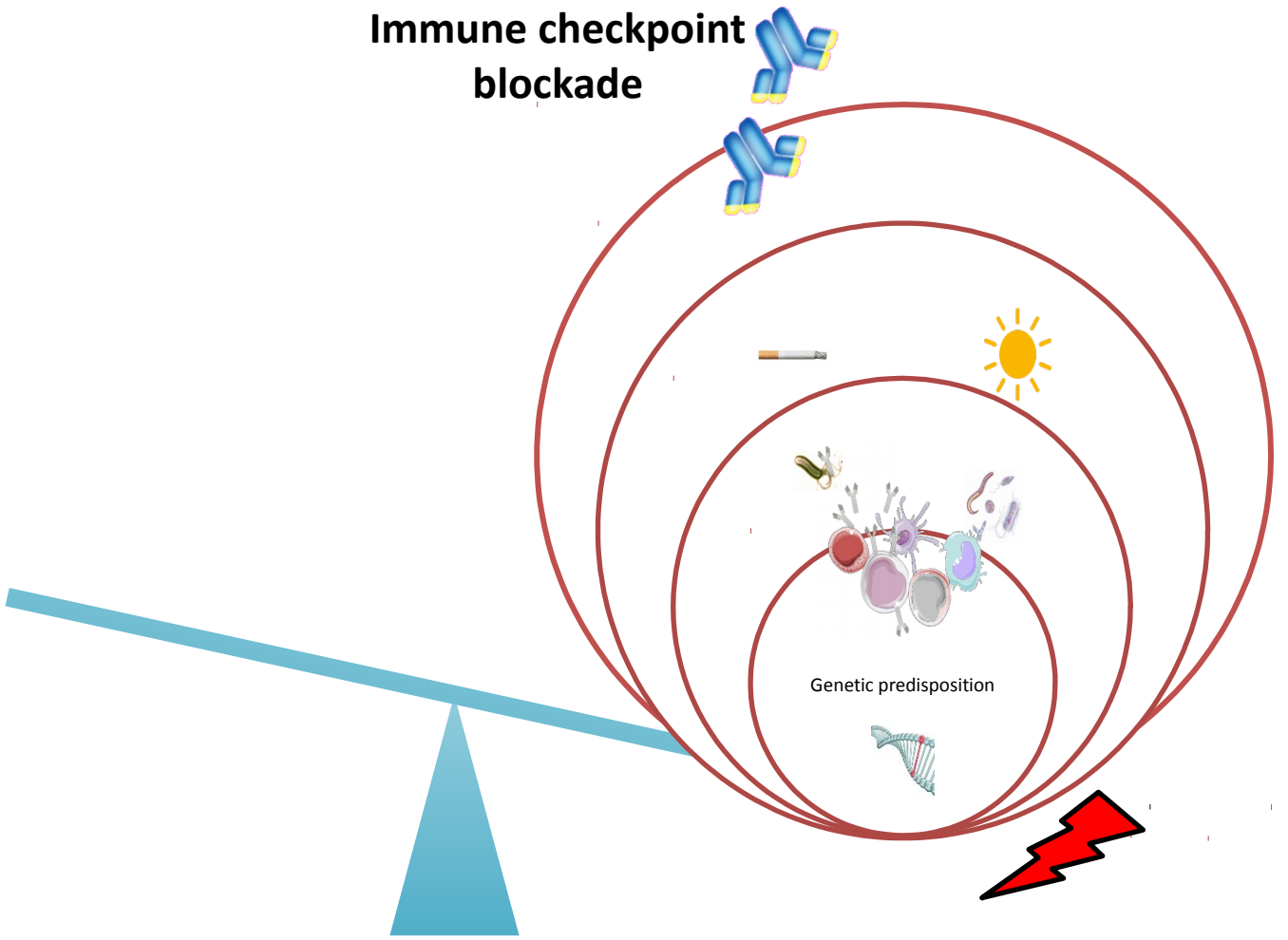


No autoimmune
nor inflammatory disease

Courtesy FX DANLOS

Immunotherapy irAEs

Immunopathogenesis hypothetical model



Courtesy FX DANLOS

CAS CLINIQUE N°1

Madame M.

Histoire de la maladie

- **Mme M., 53ans, Tabac 30 PA sevré depuis 5 ans**
  - **Antécédents : asthme, allergie aux pollens, poils de chat**
  - **Traitement habituel : budésonide160/formotérol 4,5 x2/j , desloratadine 5 mg SB, salbutamol SB, paracétamol**
- **Adénocarcinome LSD métastatique surrénalien**

  EGFR, ALK et ROS1 négatif; **PDL1+**

  L1 : Carboplatine-Alimta

  après 3 cures : **progression hépatique et ganglionnaire**

  => 2ème ligne de traitement par anti-PD1

Question

Vous recevez la patiente en consultation, avec un bilan biologique (NFS, ionogramme et créatinine sans anomalie) pour initier le traitement

1. Vous contre-indiquez l'immunothérapie en raison des antécédents médicaux de la patiente

2. Vous complétez le bilan pré-thérapeutique

3. Vous prescrivez d'emblée le traitement et envoyez la patiente à l'hôpital de jour

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Bilan pré-thérapeutique

- **NFS, ionogramme, créatinine, urée, bilan hépatique (ASAT, ALAT, gGT, bilirubine)**
- **TSH, T3, T4**
- **Bilan infectieux : VHB, VHC, VIH1-2**
- **Glycémie**
- **ECG**
- **Radio thorax/imagerie de référence**

Bilan pré-thérapeutique

- NFS, ionogramme, créatinine, urée, bilan hépatique (ASAT, ALAT, gGT, bilirubine)
- TSH, T3, T4
- Bilan infectieux : VHB, VHC, VIH1-2
- Glycémie
- Radio thorax/ imagerie thoracique de référence
- +/- CRP, LDH
- TP/TCA
- Lipase
- Sédiment urinaire, BU

- **Bilan selon le terrain : EFR …**

Bilan avant chaque injection

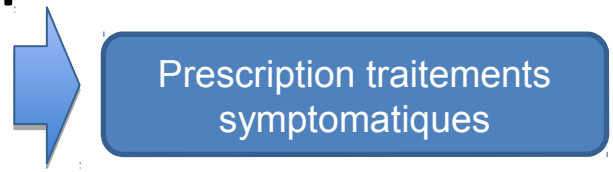
- NFS
- ionogramme, créatinine, urée
- bilan hépatique (ASAT, ALAT, gGT, bilirubine)
- TSH, T3, T4 toutes les 2 cures

Contre-indication

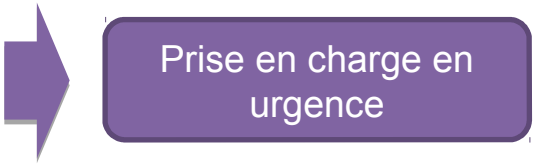
- **Maladie auto-immune active ou en poussée** à l'exception : vitiligo, diabète type 1, asthme, hypothyroïdie équilibrée
- **Infection active**, hépatite B, C chronique et VIH
- Contre-indication relative : **corticoïdes systémiques**
- **Toxicité sévère lors d'une précédente immunothérapie**

Education thérapeutique

- Bilan pré-thérapeutique
- **Gestion des toxicités fréquentes**
  - Cutanée
  - Digestive



- **Conduite à tenir si**
  - Diarrhées +/- douleurs abdominales +/- rectorragies
  - Toux ou dyspnée
  - Autres symptômes intenses



- A J30, pour une troisième perfusion, la patiente va bien cliniquement, mais se plaint principalement d'une **éruption cutanée** et d'un **prurit**

- **A l'examen clinique :**
  - **Eruption maculo-papuleuse du tronc**
  - **Xérose** grade 1, **lésions de prurigo** non infectées
  - Le reste de l'examen clinique est sans anomalie

- Le bilan biologique est normal mis à part :
  - TSH = 5,2 microU/ml (N=0,29-4,2 mU/L) et T4 non dosée

?

Vous décidez de :

1. Suspendre le traitement devant la toxicité cutanée
2. Diminuer la dose d'anti-PD1
3. Poursuivre le traitement à la même dose
4. Suspendre le traitement devant la toxicité endocrinienne

Vous décidez de :

1. Suspendre le traitement devant la toxicité cutanée
2. Diminuer la dose d'anti-PD1
3. Poursuivre le traitement à la même dose
4. Suspendre le traitement devant la toxicité endocrinienne

?

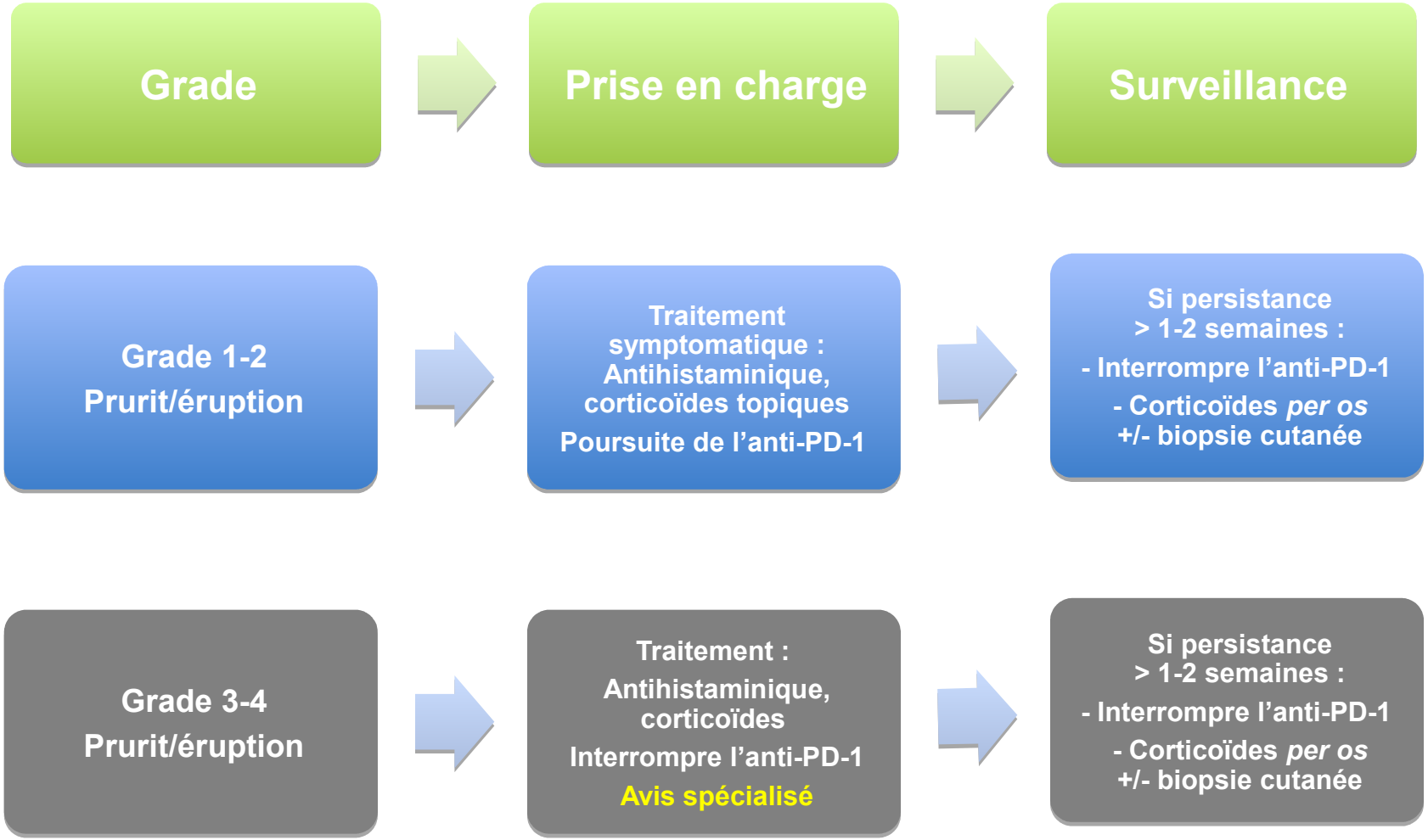
Vous faites une ordonnance ce jour

1. Renforcement des anti-histaminiques
2. Prednisolone 20 mg /j
3. Dermocorticoïdes x1 /j
4. Emollients
5. L-thyroxine 25 ug/J

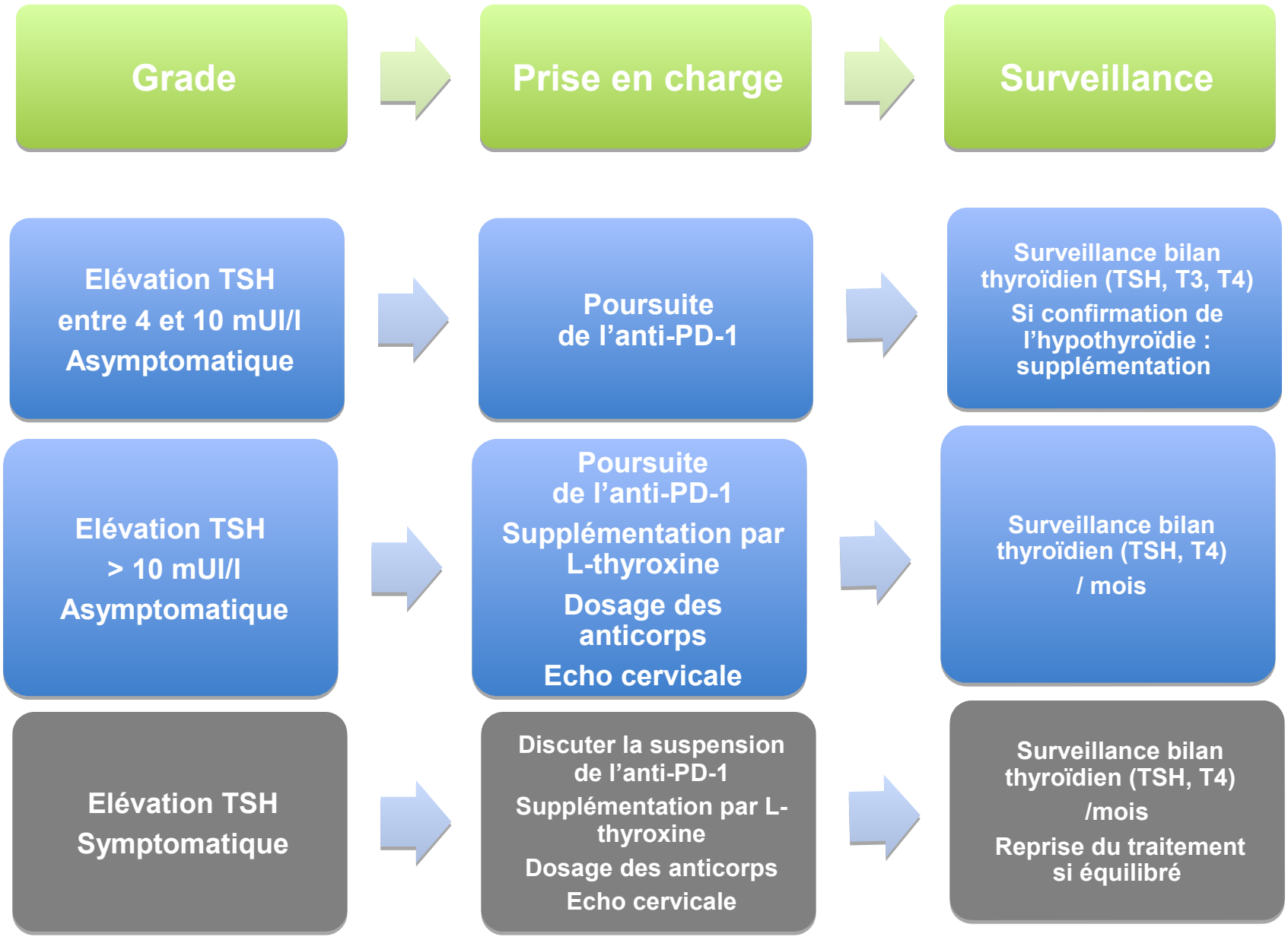
Vous faites une ordonnance ce jour

1. **Renforcement des anti-histaminiques**
2. Prednisolone 20 mg /j
3. **Dermocorticoïdes x1 /j**
4. **Emollients**
5. L-thyroxine 25 ug/J

Gestion toxicité cutanée

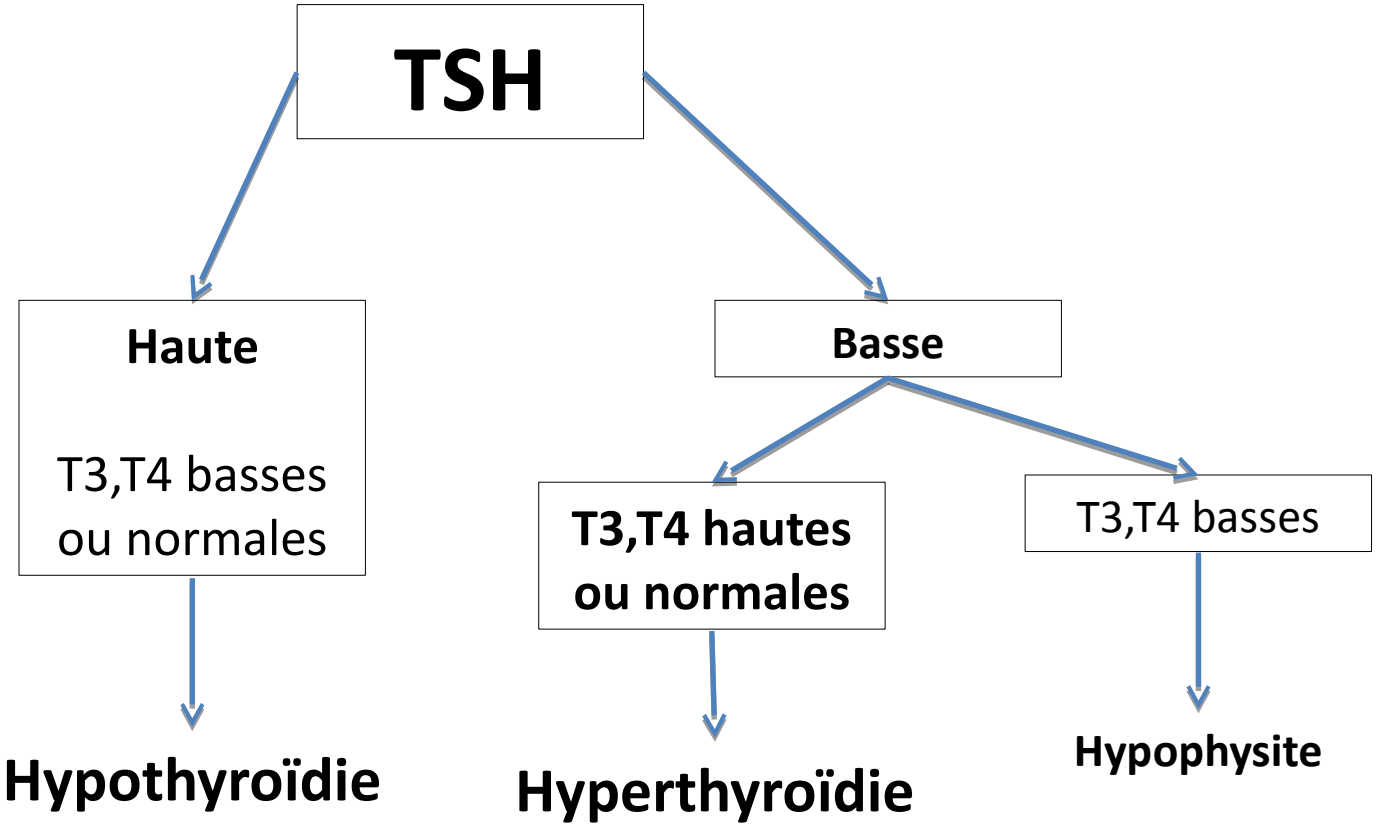


Gestion hypothyroïdie



Dysthyroïdies sous immunothérapies

généralités



Dysthyroïdies sous immunothérapies
généralités

Quels auto-anticorps doser ?

En cas d'hypothyroïdie :

Anti TPO : Thyroperoxydase = enzyme de la synthèse des hormones thyroïdiennes => thyroïdite de Hashimoto

Anti TG : Thyroglobuline = précurseur des hormones thyroïdiennes T4 et T3

En cas d'hyperthyroïdie : doser en plus

Anti R-TSH/TRAK : auto-anticorps stimulant les récepteurs de la TSH => hyperthyroïdie autoimmune de Basedow

Echographie thyroïdienne : recherche de nodules associés, d'un goitre (Hashimoto), d'une hypervascularisation (Basedow)

Gestion hyperthyroïdie

Grade	Prise en charge	Exploration
TSH basse Asymptomatique	Poursuite de l'anti-PD-1	Dosage des anticorps Echo cervicale Avis ENDOC systématique
TSH basse Symptomatique	Discuter suspension de l'anti-PD-1 Ttt symptomatique si besoin : anxiolytiques si anxiété, propanolol si FC > 90	Dosage des anticorps Echo cervicale Avis ENDOC systématique
Cardiothyréose Trbles du rythme, insuffisance cardiaque ou coronarienne	Suspendre l'anti-PD-1 URGENCE AVIS REA	

- Après deux mois et demi de traitement vous revoyez madame L, qui est très inquiète car elle présente une fatigue de grade 2, n'arrive plus à se lever pour accompagner son fils à la maternelle

- Elle n'a pas fait de bilan biologique, ni son imagerie d'évaluation

Vous suspectez

1. Progression
2. Hypothyroïdie
3. Insuffisance surrénale
4. Une pathologie auto-immune : myosite, myasthénie, anémie hémolytique, diabète type 1…

Vous suspectez

1. Progression
2. Hypothyroïdie
3. Insuffisance surrénale
4. Une pathologie auto-immune : myosite, myasthénie, anémie hémolytique, diabète type 1…

Bilan de l'asthénie

- **Bilan clinique : précisez les symptômes +++**
  - Dyspnée ?
  - Faiblesse musculaire ?
  - Douleurs musculaires ou articulaires ?
  - Fatigabilité ?
  - Ralentissement psychomoteur/confusion ?
- **Modification récente des traitements :** antalgiques, psychotropes, corticothérapie
- **Éléménts pour un sepsis**
- **BU**
- **ECG**

Bilan de l'asthénie

- **Bilan biologique extensif :**
  - NFS, Ionogramme, urée, créatininémie,
  - Bilan hépatique (ASAT/ALAT, bilirubine, GGT, PAL)
  - CPK
  - Ca/Ph, albumine, CRP
  - Glycémie
  - TSH, T3, T4
  - Cortisol à 8h
  - Electrophorèse des protéines

- **Imagerie d'évaluation : TDM**

A l’interrogatoire, la patiente vous décrit des vertiges lorsqu’elle se lève trop brutalement ainsi que des douleurs abdominales et 2 épisodes de vomissements survenus la veille

Vous craignez une insuffisance surrénalienne aigüe, que faites vous ?(il est 14h15)

1. Corticothérapie 1 mg/kg jour IV en urgence
2. Cortisolémie puis Corticothérapie 1mg/kg IV
3. Hydrocortisone en urgence
4. Hydratation en urgence

A l’interrogatoire, la patiente vous décrit des vertiges lorsqu’elle se lève trop brutalement ainsi que des douleurs abdominales et 2 épisodes de vomissements survenus la veille

Vous craignez une insuffisance surrénalienne aigüe, que faites vous ?(il est 14h15)

1. Corticothérapie 1 mg/kg jour IV en urgence

2. Cortisolémie puis Corticothérapie 1mg/kg IV

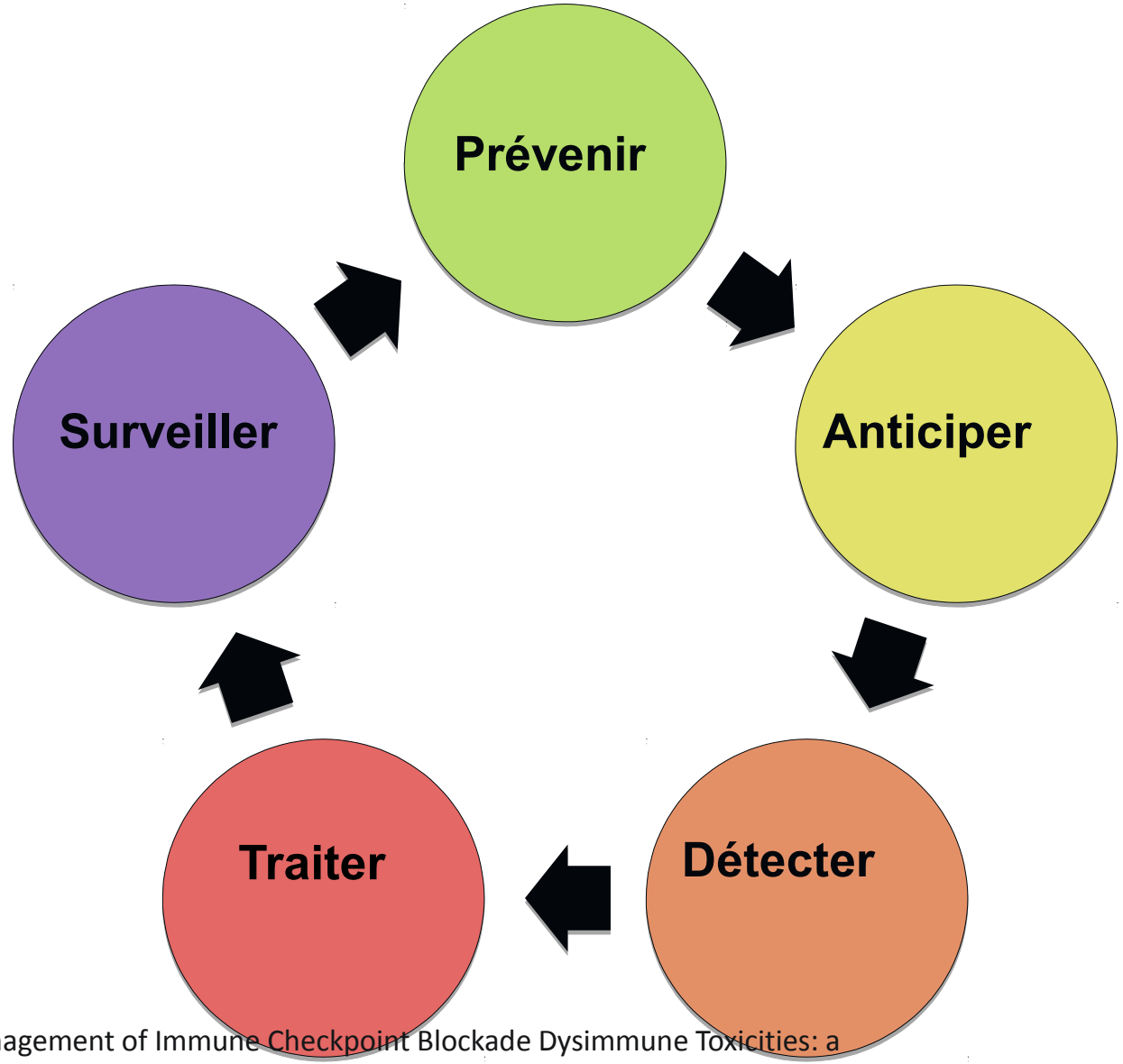
3. **Hydrocortisone en urgence**

4. **Hydratation en urgence**

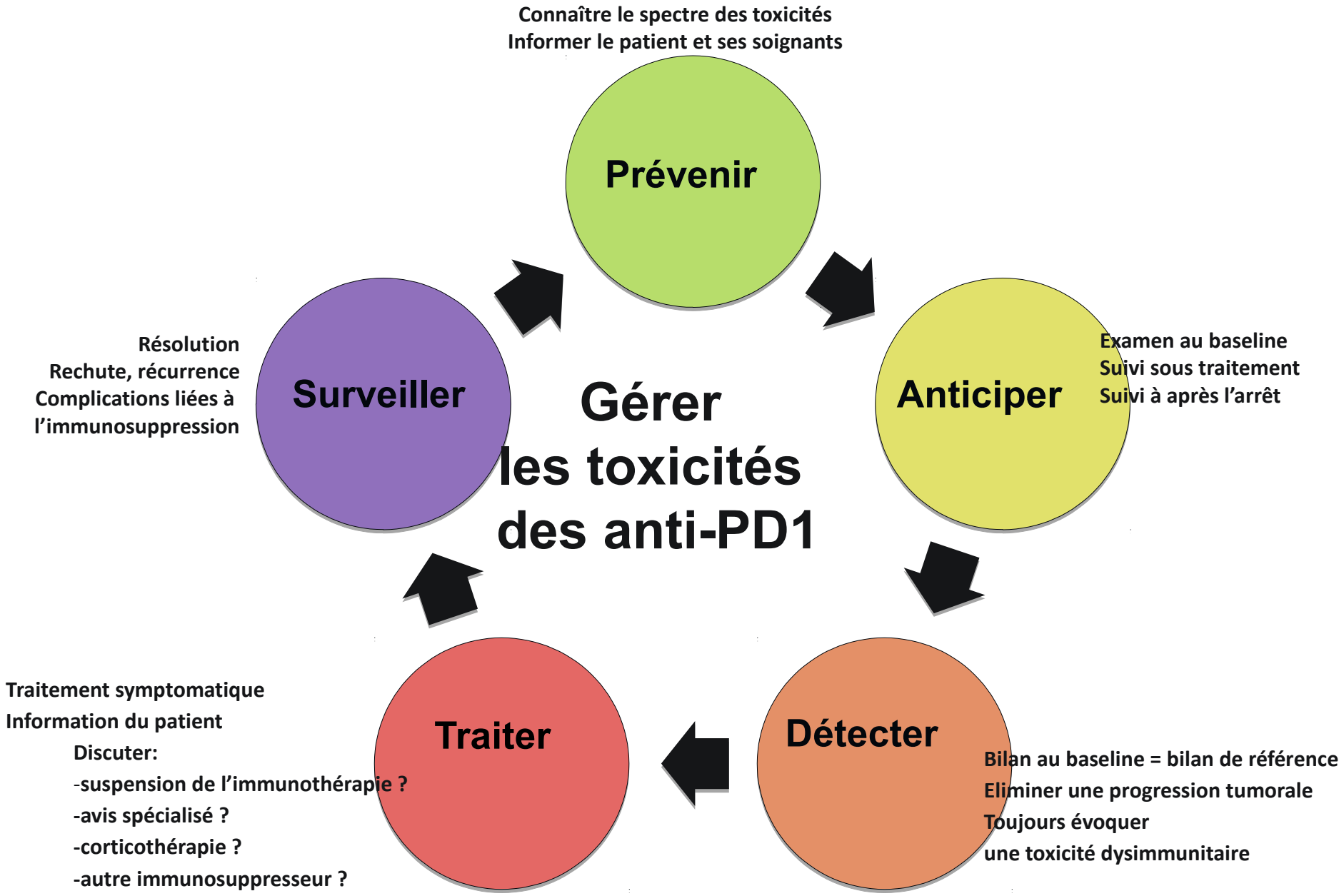
Insuffisance surrénalienne aigüe

- **URGENCE thérapeutique +++**
- **Clinique NON SPECIFIQUE** : asthénie, anorexie, hypotension orthostatique, douleurs abdominales, nausées, vomissements, hypoglycémie, hyponatrémie
- **Signes de gravité = avis REA**
  - **hypotension/choc hypovolémique**
  - **Douleurs abdominales, vomissements**
  - **Troubles neurologiques**
  - **ECG : signes d'hyperkaliémie**
- **Diagnostic : cortisol à 8h +++**
- **Thérapeutique : ne pas attendre le diagnostic pour débuter l'hydrocortisone 100 mg IM/SC puis 200 mg/24h IVSE + HYDRATATION**
- **Avis spécialisé systématique**

Gérer les toxicités des immunothérapies



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



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

Un nouveau spectre de toxicités

Toxicités les plus fréquentes *des immunothérapies*

Cutanées

15%

Asthénie

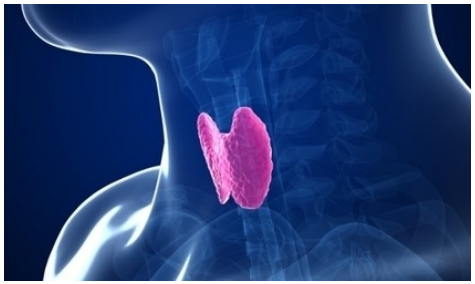
20%

Digestives

10-15%

Dysthyroïdies

5-10%



Hépatiques

5%

Pulmonaires

<5%

Sibaud V, Delord JP. Dermatologic complications of anti-PD-1 / PD-L1 immune checkpoint antibodies. ***Curr Opin Oncol 2016; 28: 254-63.***
Boutros C et al. Nature Reviews Clinical Oncology CR 2016

Lutter contre les anciens réflexes

Quelques exemples …

« Le principal traitement de la diarrhée sous anticancéreux sont les ralentisseurs du transit »

=> En cas de colite inflammatoire, risque de perforation !

« En cas d'anémie/thrombopénie : transfusion selon les seuils transfusionnels »

=> Les transfusions sont à éviter en cas d'anémie/thrombopénie autoimmunes !

!valeurs baseline = valeurs de référence!

« Toute dégradation est liée à une progression tumorale»

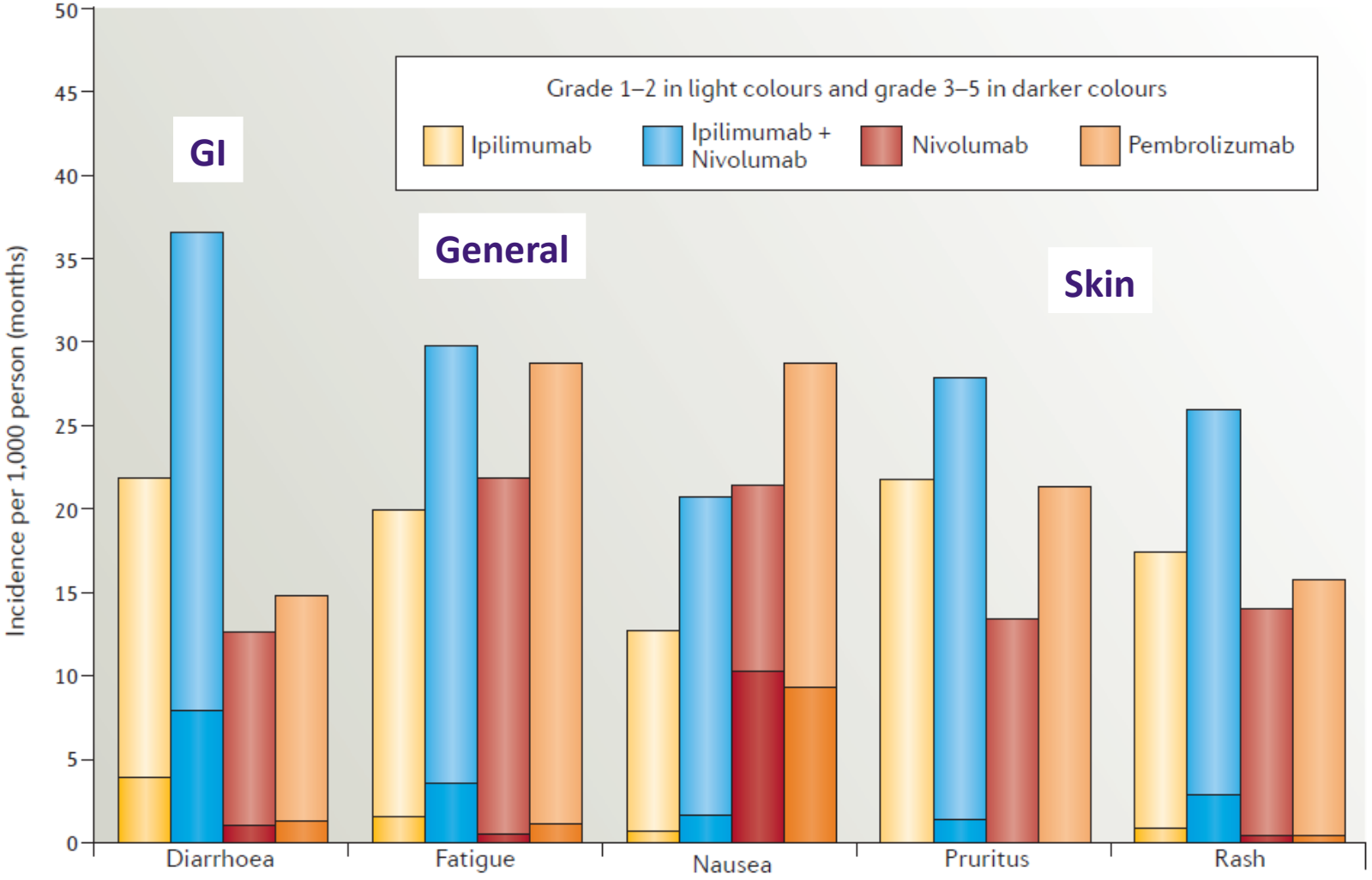
=> AEG : insuffisance surrénale? hypothyoïdie ?...

=> Dyspnée : pneumopathie inflammatoire ? myocardite ? anémie hémolytique ?...

=> Troubles neurologiques : encéphalite autoimmune? polyradiculonévrite aigüe? …

Prevent

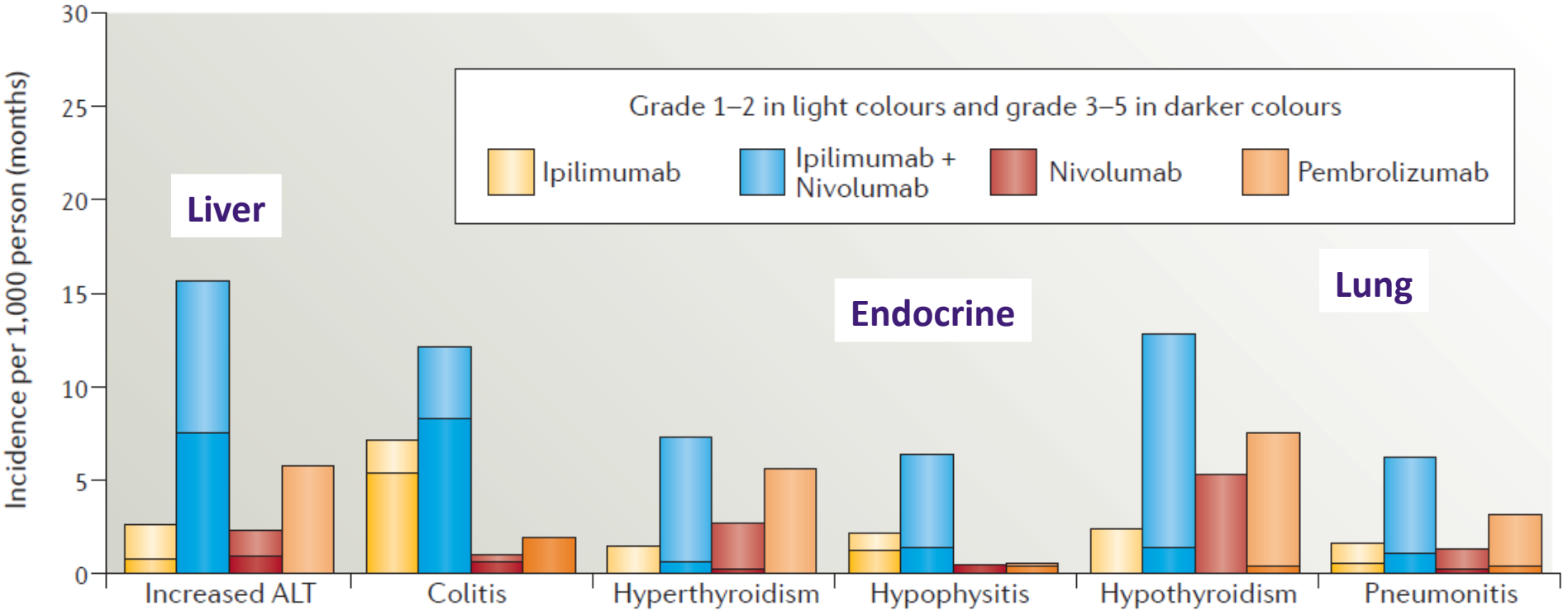
Most frequent irAEs



Boutros C et al. Nature Reviews Clinical Oncology CR 2016

Prevent

Most frequent irAEs



Boutros C et al. Nature Reviews Clinical Oncology CR 2016

Prevent

Patient card

Name, Family name:
Immunotherapy drug(s):
I am currently receiving an immunotherapy which may increase the risk of occurrence of autoimmune diseases and in particular:

- pneumonitis (inflammation of the lungs)
- colitis (inflammation of the gut)
- hepatitis (inflammation of the liver)
- nephritis (inflammation of the kidneys)
- endocrinopathy: hypophysitis, thyroid dysfunction, diabetes, adrenal insufficiency (inflammation of the hormone producing organs)
- cutaneous rash (inflammation of the skin)

as well as other immune-related adverse events: neurological, hematological, ophthalmological,… **The management of these dysimmune adverse events is specific and sometimes urgent. It absolutely requires coordination with the health care team which has prescribed the treatment:**

Prescriber Contact Information

Medical information letter

Dear Colleague,

Mr/Mrs *Name, Family name*:

has been put under the following Immunotherapy drug(s):

-
-

I wanted to raise your attention on the fact that this immunotherapy may increase the risk of occurrence of autoimmune symptoms such as:

- ✓ pneumonitis (inflammation of the lungs)
- ✓ colitis (inflammation of the gut)
- ✓ hepatitis (inflammation of the liver)
- ✓ nephritis (inflammation of the kidneys)
- ✓ endocrinopathy: hypophysitis, thyroid dysfunction, diabetes, adrenal insufficiency (inflammation of the hormone producing organs)
- ✓ cutaneous rash (inflammation of the skin)

as well as other immune-related adverse events: neurological, hematological, ophthalmological,…

The management of these dysimmune toxicities requires specific care and can be organ or life threatening. It absolutely necessitates coordination with the health care team which has prescribed the therapy.

Please contact the following contact for any further information you may need or in case of emergence of symptoms which may be related to an organ inflammation:

Prescriber ID:
Contact information :

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 check-up is KEY

Physical exam

-Performance status

-Weight, size

-Heart rate and blood pressure, baseline electrocardiogram

-General symptoms : asthenia, appetite

-**Pre-existing symptoms** :

intestinal transit, dyspnea and coughing, rash, nausea, headaches

signs of motor or sensory neuropathy and arthralgia

-History of fever or recent infection

-Ongoing treatment

Anticipate

Baseline check-up is KEY

Laboratory test

General	Complete CBC Serum electrolytes Liver tests
Endocrine	TSH, T4, T3
Urine	Urine dipstick
Infectious	Virology: HIV, HCV, HBV and CMV serology Quantiferon tuberculosis or TST in case of anterior exposure
Auto-Abs	Antibody: ANA, TPO Ab, Tg Ab, TRAK Ab

Anticipate

Baseline lab tests :

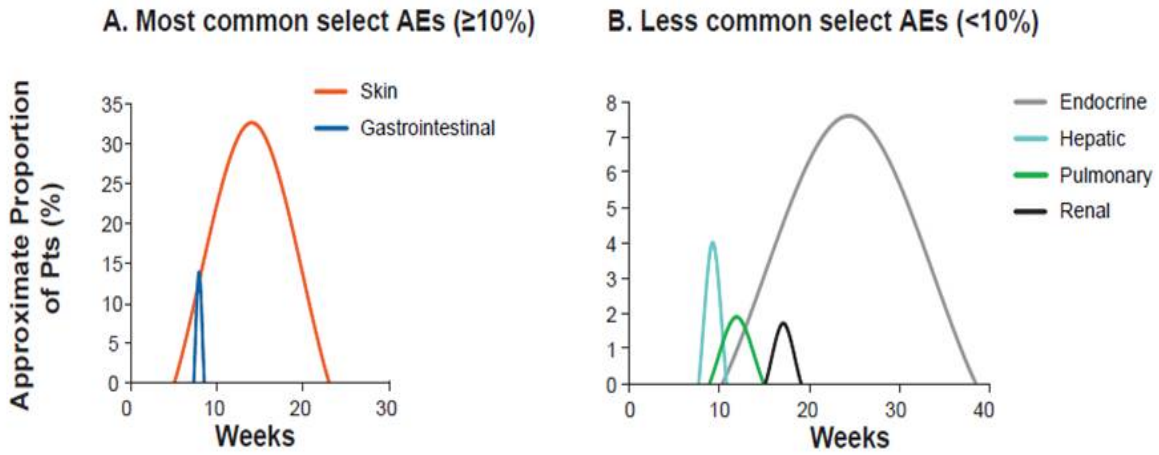
Complete CBC
Serum electrolytes, creatinine
Liver tests
Thyroid function
Chest imaging reference

During treatment course :

Complete CBC
Serum electrolytes, creatinine
Liver tests
Thyroid function every 2-3 courses

Anticipate

Kinetics of Onset and Resolution of Select Nivolumab Treatment-related AEs (Any Grade)



- Select AEs generally resolved within several weeks, apart from endocrinopathies, as some events were not considered resolved due to the continuing need for hormone replacement therapy

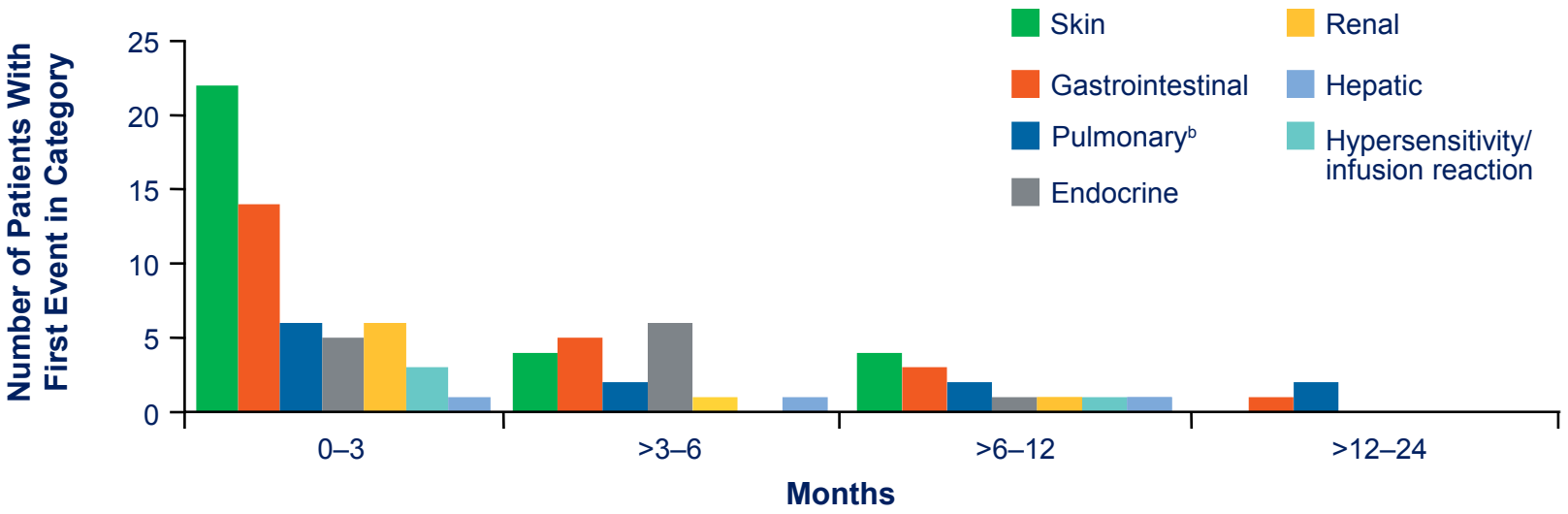
The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE.

Weber et al. ASCO 2015

Anticipate

Time to onset of Treatment-related select AE

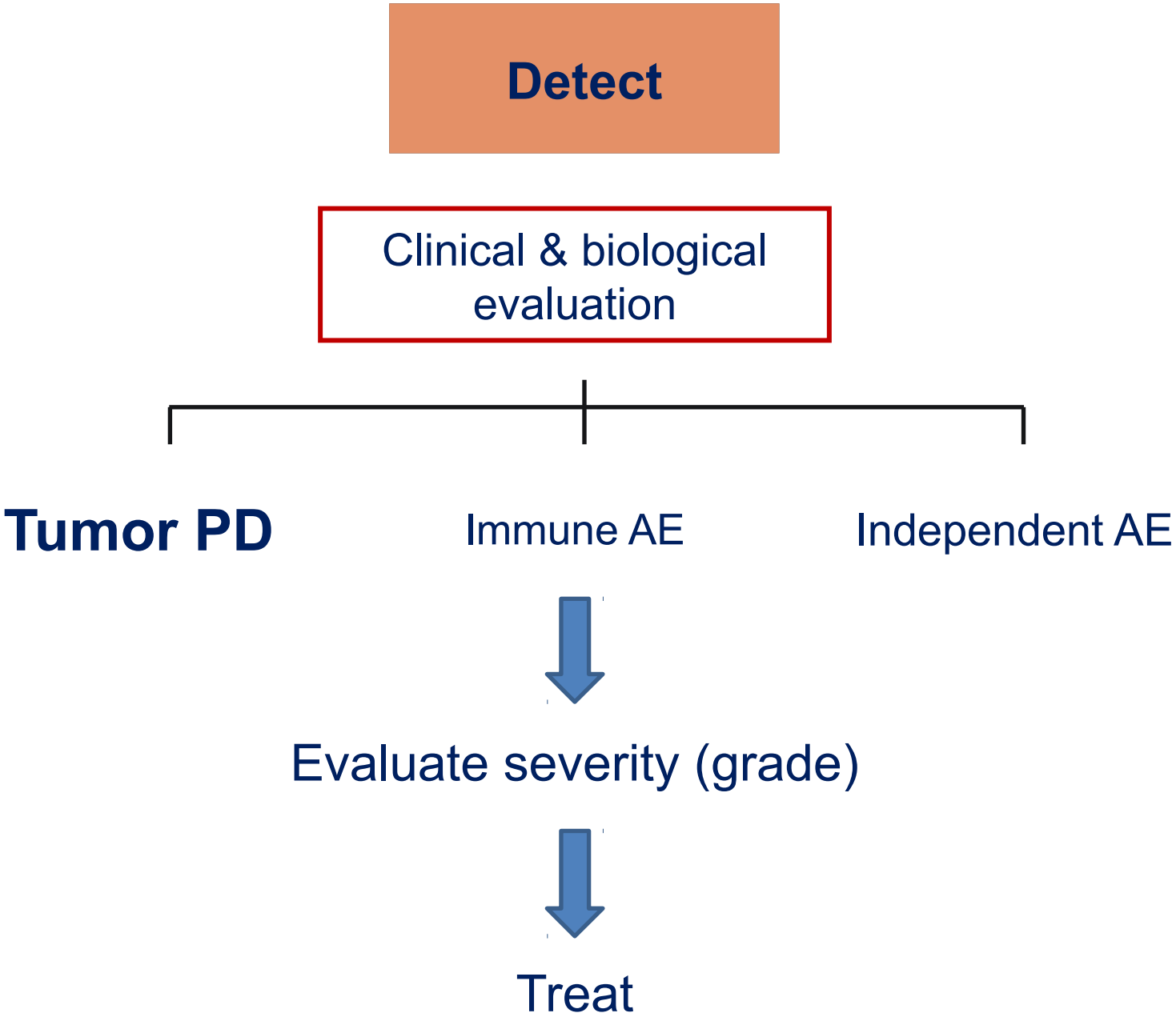
Example: Nivolumab in SCC (pooled analysis from CM-063 & CM-017)



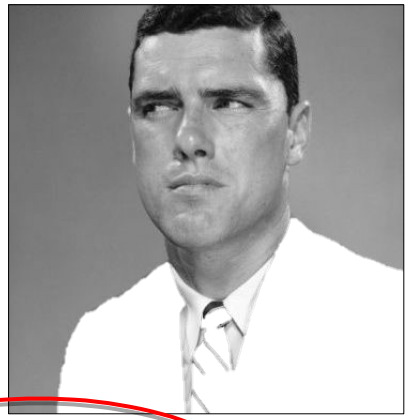
	0–3	>3–6	>6–12	>12–24
Pts still on study, n	248	206	153	84
Pts still on treatment, n	248	134	85	38
Total pts with a first event,[a] n	49	14	10	2

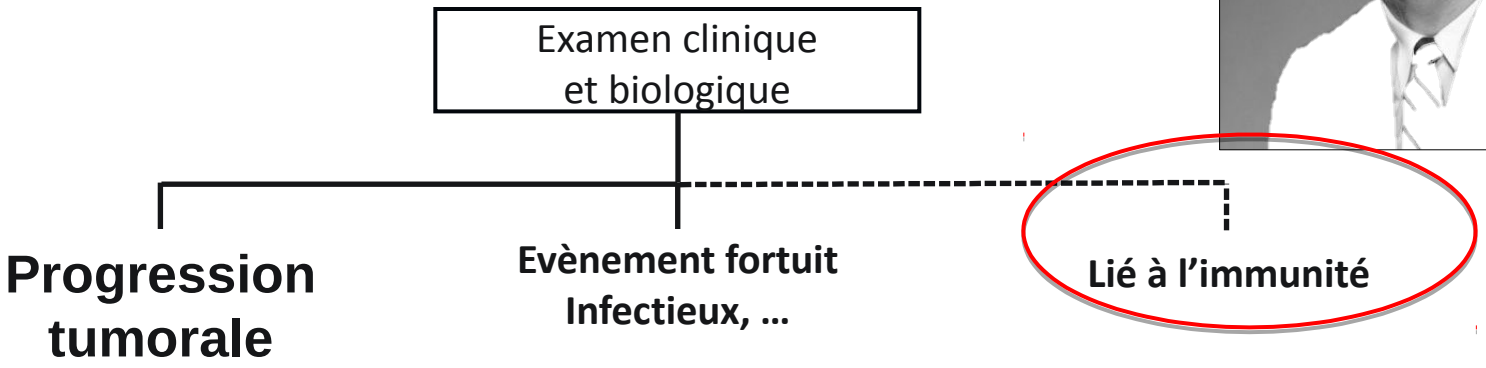
Longest time to onset: Hepatic and Endocrine IRAEs

Antonia S, ESMO 2015, abstract: 346


Detect
Clinical & biological evaluation
Tumor PD
Immune AE
Independent AE
Evaluate severity (grade)
Treat

Intégrer les toxicités autoimmunes dans l'algorithme diagnostique





<u>Risque de survenue à distance</u> !

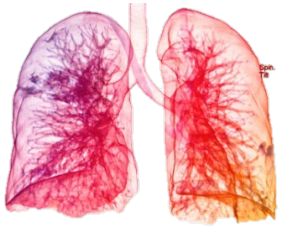
- **même si bonne tolérance initiale**
- parfois **après l'arrêt de l'immunothérapie** (6 mois, 1 an, …)

Un nouveau spectre de toxicités

Toxicités rares mais potentiellement mortelles

1 - 5 %

Digestives
Colites inflammatoires perforées



Pulmonaires
Pneumopathie inflammatoire
Epanchement pleuro/péricardique

Hépatiques
Hépatites cytolytiques

Toxicités le plus souvent réversible à l'arrêt de l'immunothérapie +/- corticoïdes

Un nouveau spectre de toxicités

1 - 5 %

Digestives
Colites inflammatoires perforées

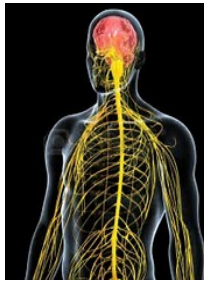
Pulmonaires
Pneumopathie inflammatoire
Epanchement pleuro/péricardique

Hépatiques
Hépatites cytolytiques

Toxicités rares mais potentiellement mortelles

< 1 %

Cardio
Myocardite fulminante



Neurologiques
Guillain Barré
Encéphalite

Endocriniennes
Insuffisance surrénalienne
Acidocétose diabétique

Hématologiques
Anémie
Thrombopénie
Neutropénie

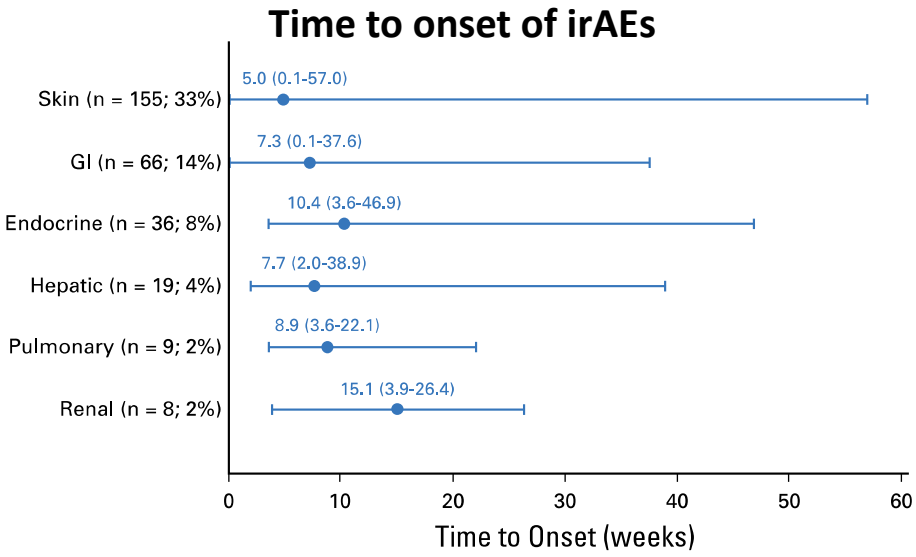
Cutanées
DRESS
Steven Johnson

Rénales
Néphrite

Time to onset of irAEs

Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma (N=576)

Weber et al. , JCO 2016



Time to onset of irAEs

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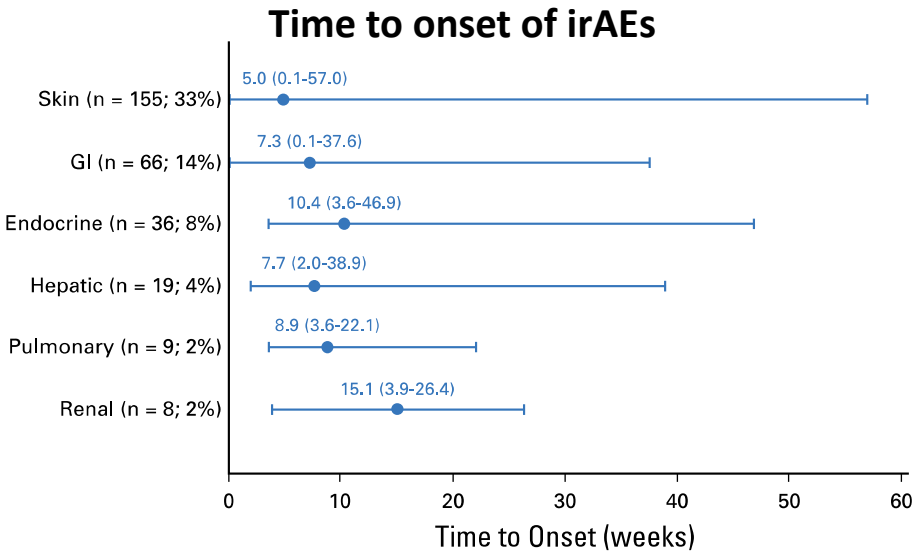
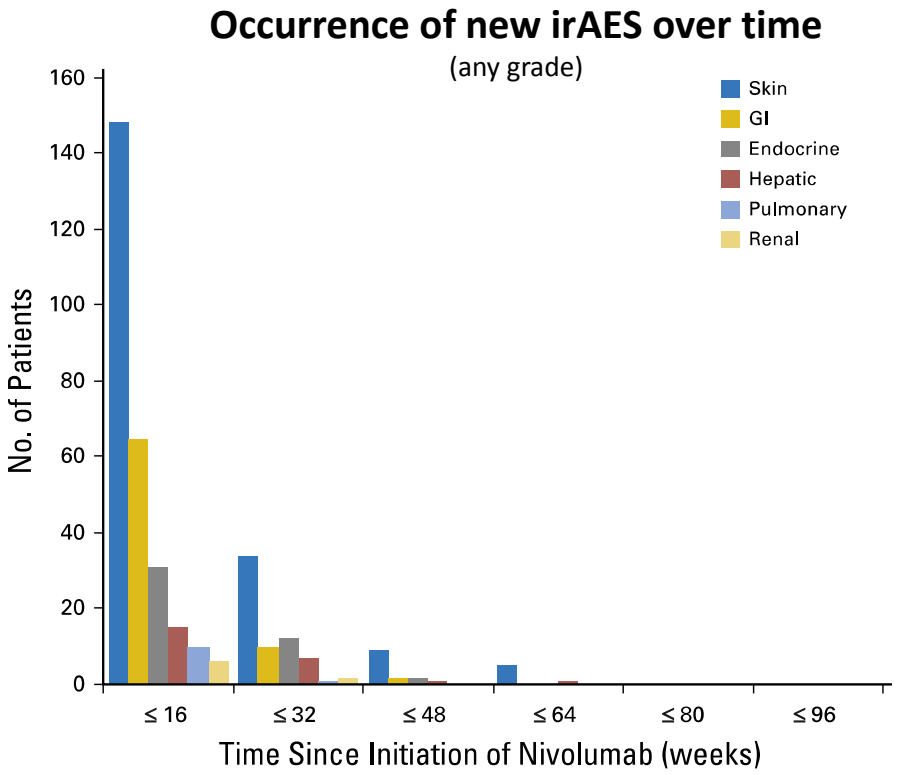


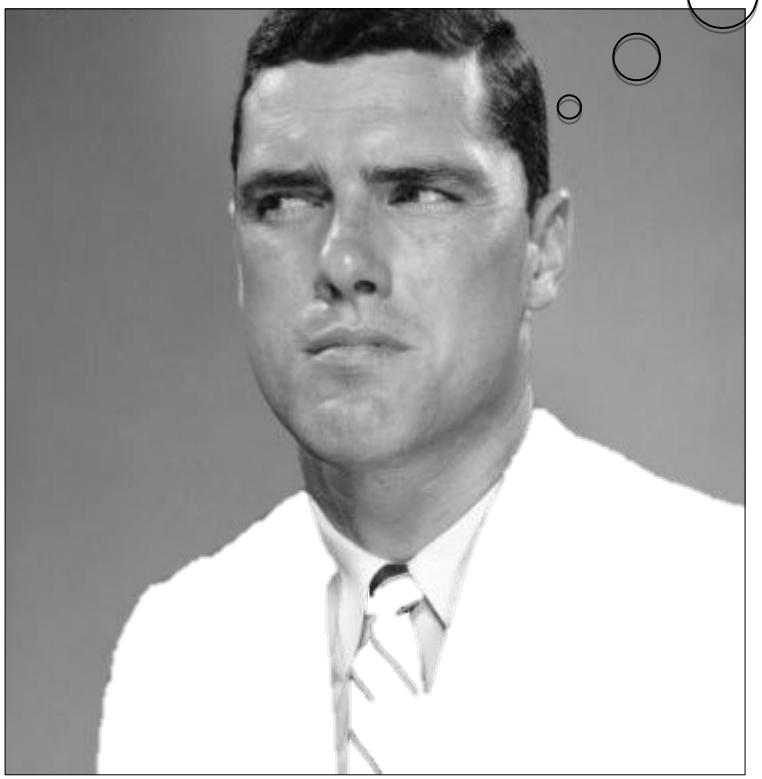


No. of patients						
Still in study	453	281	138	26	10	9
Still receiving treatment	298	172	76	11	3	0
Total with new event	239	34	4	5	0	0
Still in study with new event, %	53	12	3	19	0	0

En cas de toxicité liée à l'immunité

Avoir le réflexe corticoïdes

On y pense trop tard
…On les arrête trop tôt



- **Diagnostics différentiels** ?
  Infectieux : attention CRP/PCT/..peu discriminant
- Evaluation **gravité** ?
  Si gravité, ne pas retarder la corticothérapie
- **Avis spécialisé** ?
  Pathologie complexe, autres immunosuppresseurs

En cas de toxicité liée à l'immunité

Des guidelines généraux…parfois non applicables aux cas particuliers

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.

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

Traiter

Points clés

- **Surveillance rapprochée**
- **Information du patient**
- **Traitement symptomatique**
- **Suspension de l'immunothérapie ou arrêt définitif**
- **Discuter corticothérapie**
- **Avis spécialisé**
- **Autres immunosuppresseurs**

Traiter

Corticothérapie

On y pense trop tard

On les arrête trop tôt

- **Avant l'initiation : éliminer une infection**
- **Antibio-prophylaxie: prise orale de trimethoprime/sulfamethoxazole**
- **Décroissance progressive: ≥ 1 mois**

Traiter

CAT // immunothérapie

> **Suspendre** +/- **Reprendre** lorsque l'EILI redevienttGrade 0-1

> **Arrêter définitivement** pour

- ✔ **tout EILI avec menace vitale**
- ✔ **impossibilité de réduire la corticothérapie**
- ✔ **Grade 2 ou 3 persistant**
- ✔ **Toute toxicité sévère ou grade 3 qui récidive**

Time to resolution of irAEs

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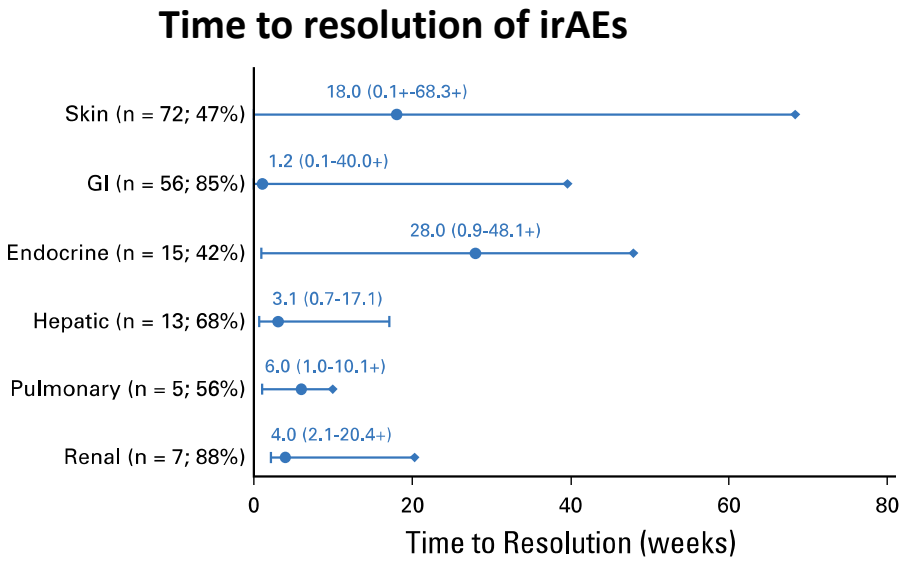

Time to resolution of irAEs

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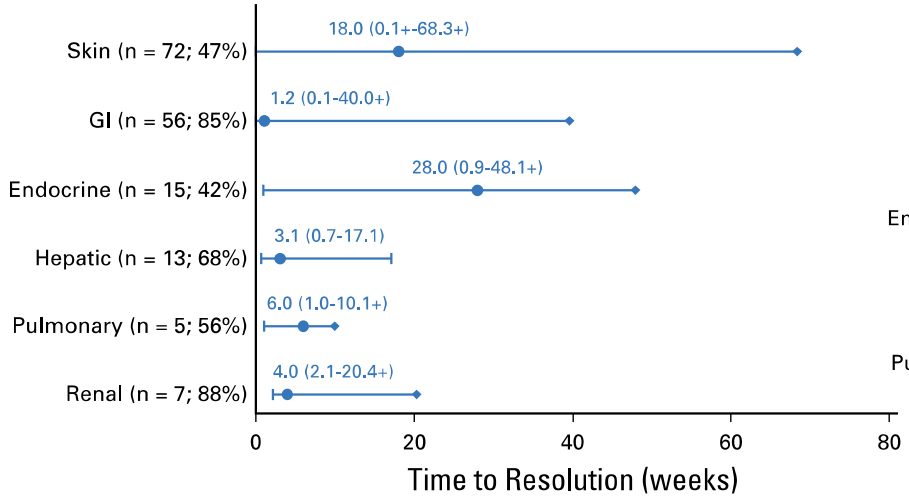
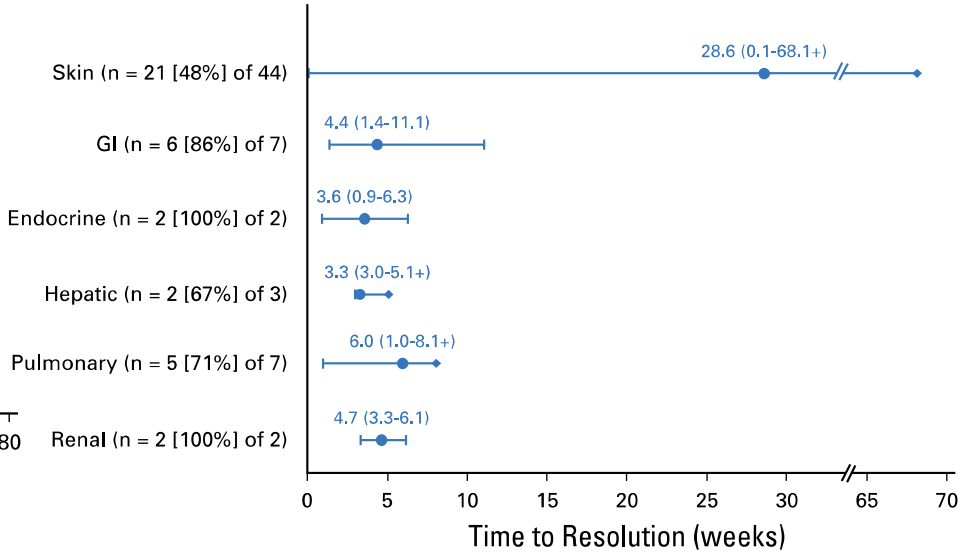
Time to resolution of irAEs



Time to resolution of irAEs with immune-modulating agent



Medication	N of patients (%)
Any immune-modulating agent	166 (35%)
Corticosteroid, systemic	114 (24%)
Corticosteroid, topical	76 (16%)
Corticosteroid, inhaled	5 (1%)
Nonsteroidal systemic suppressive agents Infliximab Mycophenolic acid	5 (1%) 2 1
Immunoglobulin	1 (0,2%)

Monitor

- Close monitoring of **response to irAE treatment**
- Risk of **relapse**
- The occurrence of dysimmune toxicity
  does not prevent the **occurrence of other toxicities**
- **Complications of immunosuppression**

Impact of irAEs and IM use on ORR

Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma (N=576)

Weber et al. , JCO 2016

Table 2. Impact of Treatment-Related Select AEs and IM Use on Response to Nivolumab Therapy

		Any-Grade Treatment-Related Select AEs*				Grade 3 to 4 Treatment-Related Select AEs		Patients Receiving Systemic IM	
	All Patients (N = 576)	Any (n = 255)	None (n = 321)	1-2 (n = 242)	≥ 3 (n = 13)	Yes (n = 18)	No (n = 558)	Yes (n = 114)	No (n = 462)
ORR, No. of patients (%)	181 (31.4)	124 (48.6)	57 (17.8)	113 (46.7)	11 (84.6)	5 (27.8)	176 (31.5)	34 (29.8)	147 (31.8)
95% CI	27.6 to 35.4	42.3 to 54.9	13.7 to 22.4	40.3 to 53.2	54.6 to 98.1	9.7 to 53.5	27.7 to 35.6	21.6 to 39.1	27.6 to 36.3
P		< .001		< .0001†	< .001†	1.00		.736	

Abbreviations: AE, adverse event; IM, immune-modulating agent; ORR, objective response rate.
*Data in these columns are for patients with the indicated numbers of any-grade treatment-related select AEs: any AE, no AEs, 1-2 AEs, and ≥ 3 AEs.
†Versus no treatment-related select AEs.

irAEs are associated with higher ORR

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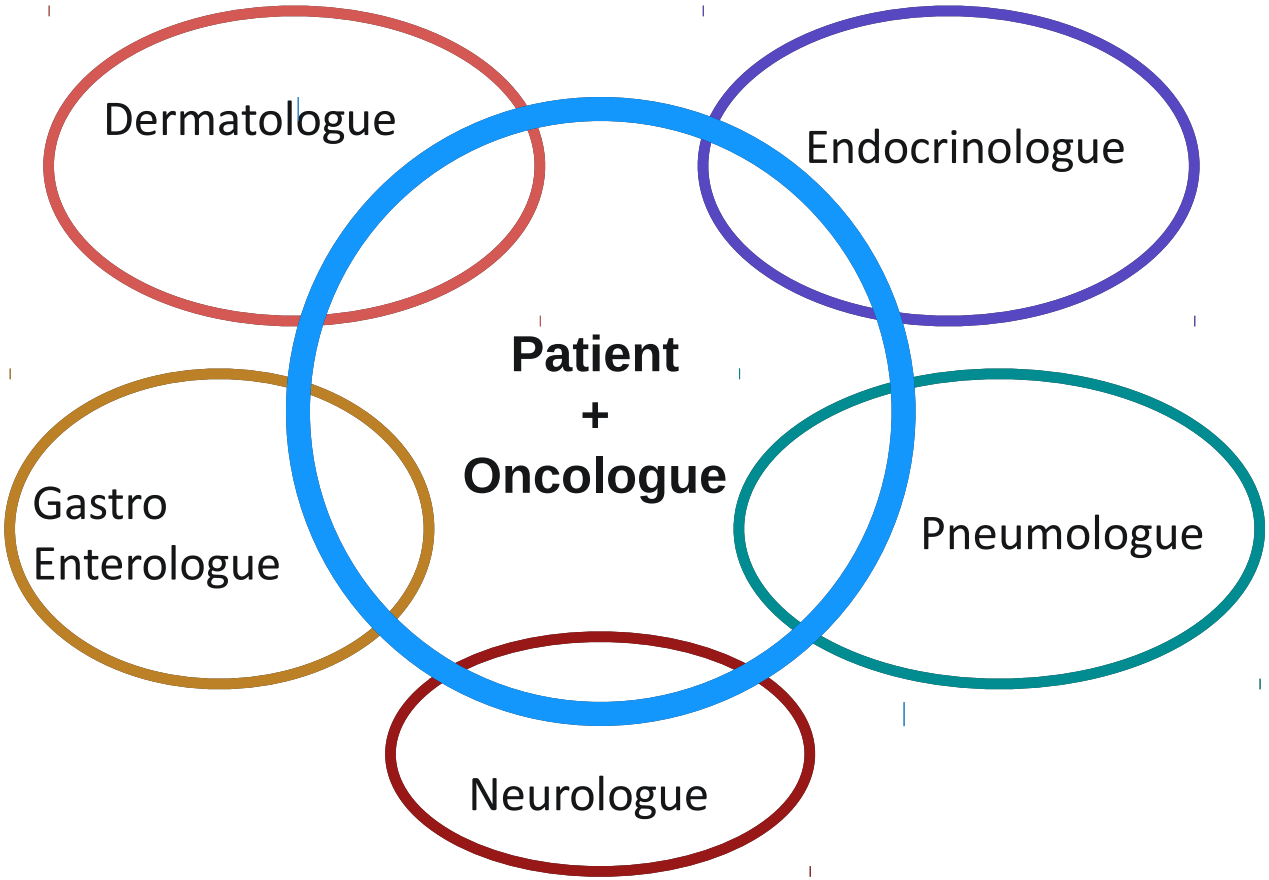
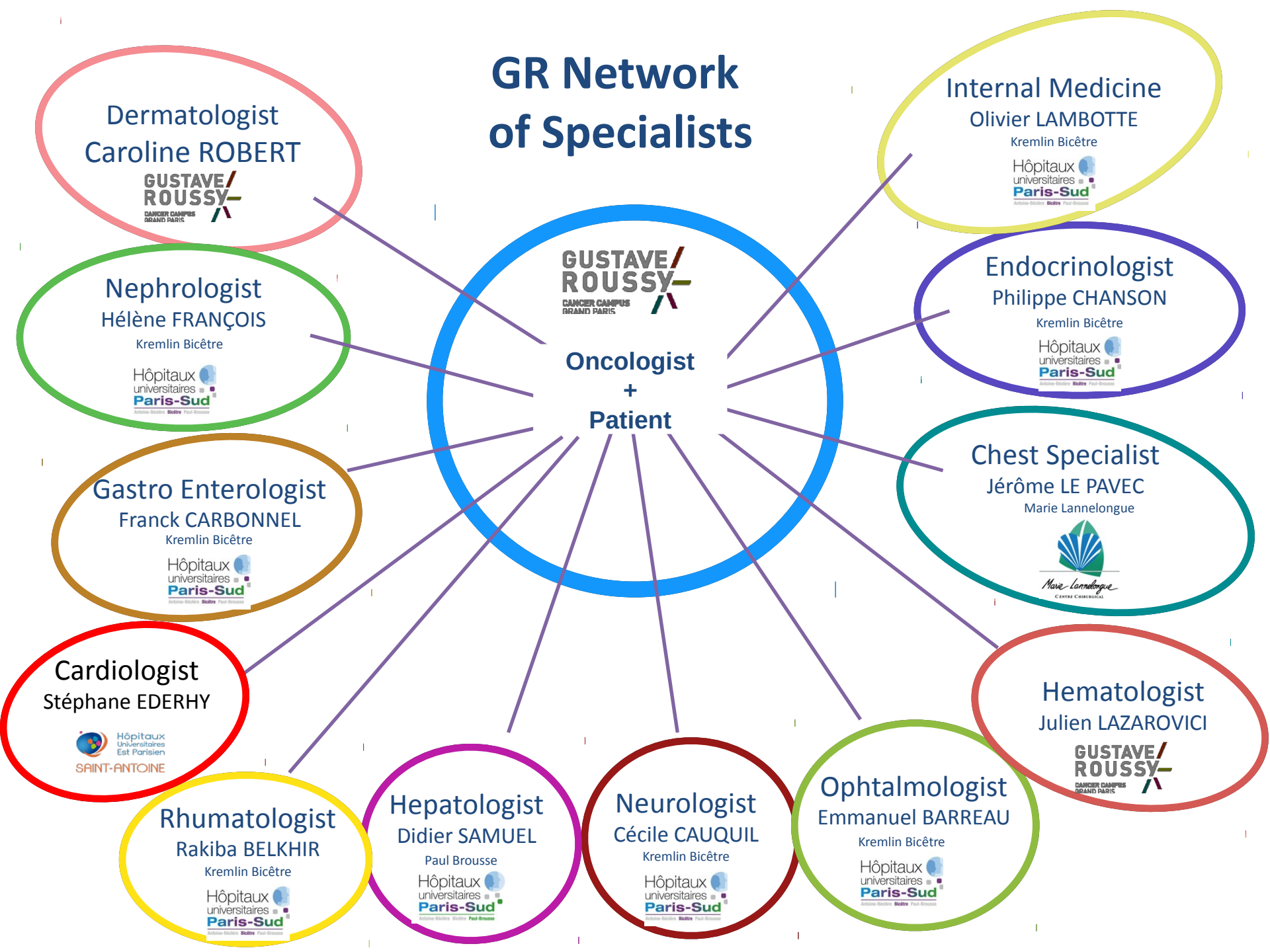
irAEs are associated with higher ORR

IM use does not affect ORR

Traiter

Définir sa dream team

une approche multidisciplinaire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