Complications des Immunothérapies

V. Gounant

Service d'Oncologie Thoracique
et essais précoces
CIC 1425-CLIP2 Paris-Nord

Hôpital Bichat

Liens d’intérêt

Astra Zeneca, BMS, Boehringer-Ingelheim,
Lilly, Novartis, Pfizer, Roche

Plan

- Introduction
- Indications des immunothérapies en cancérologie
- Principales complications
- Facteurs prédictifs de complications
- Complications infectieuses
- Immunothérapies anti K chez le patient porteur du VIH et/ ou hépatites virales
- Conclusion

thebmj

Surgical Section.

July 13, 1909.

Mr. J. WARRINGTON HAWARD, President of the Section, in the Chair.

The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus erysipelas and the Bacillus prodigiosus).

By WILLIAM B. COLEY, M.D. (New York.)[1]

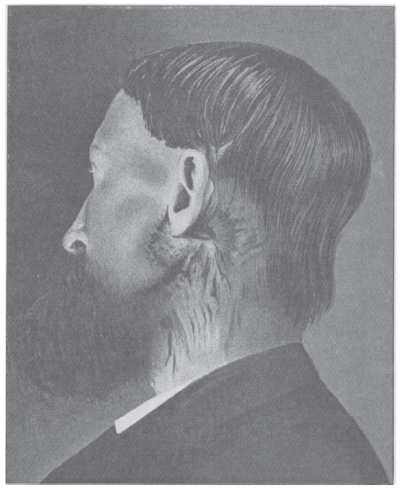


FIG. 1.

Recurrent round-celled sarcoma. Spontaneous recovery following accidental erysipelas. Photograph taken seven years after the cure.

The Journal of Urology
Volume 116, Issue 2, August 1976, Pages 180-182

Intracavitary Bacillus Calmette-guerin in the Treatment of Superficial Bladder Tumors

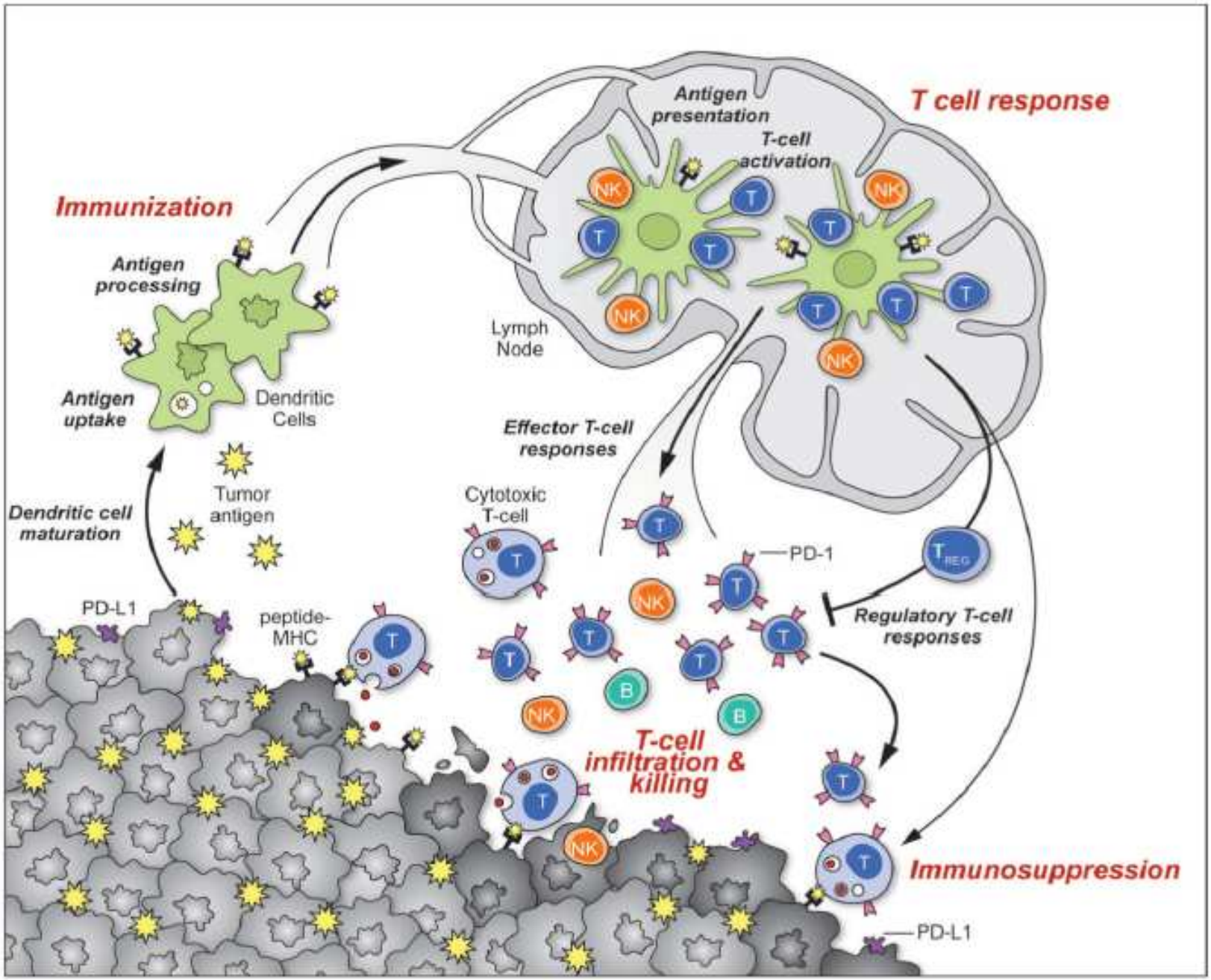
A. Morales *, D. Eidinger, A.W. Bruce

Predicting Response to Intravesical Bacillus Calmette-Guérin Immunotherapy: Are We There Yet? A Systematic Review

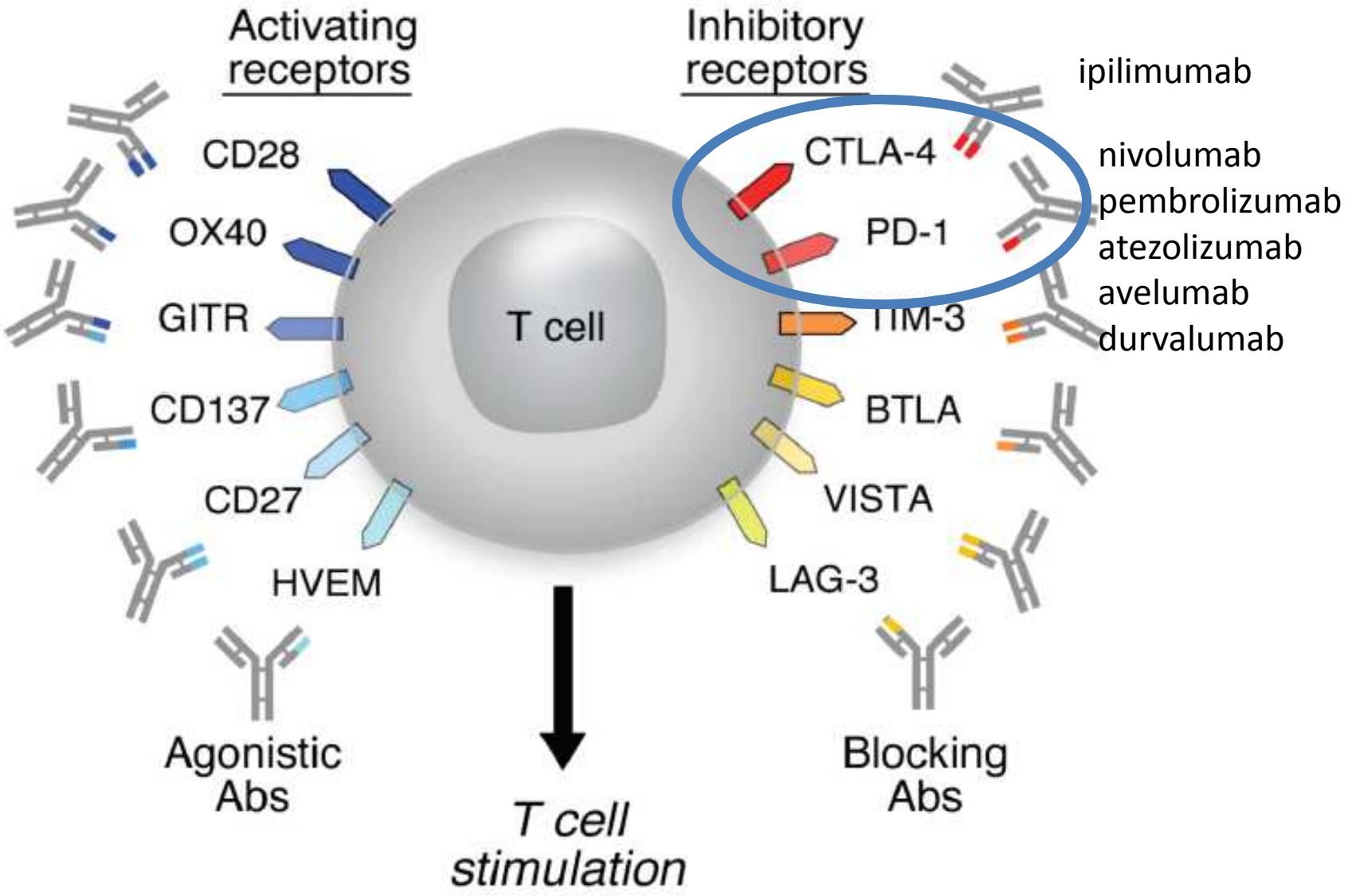
Ashish M. Kamat[a,*], *Roger Li*[a], *Michael A. O'Donnell*[b], *Peter C. Black*[c], *Morgan Roupret*[d], *James W. Catto*[e], *Eva Comperat*[f], *Molly A. Ingersoll*[g], *Wim P. Witjes*[h], *David J. McConkey*[i], *J. Alfred Witjes*[j]

In press

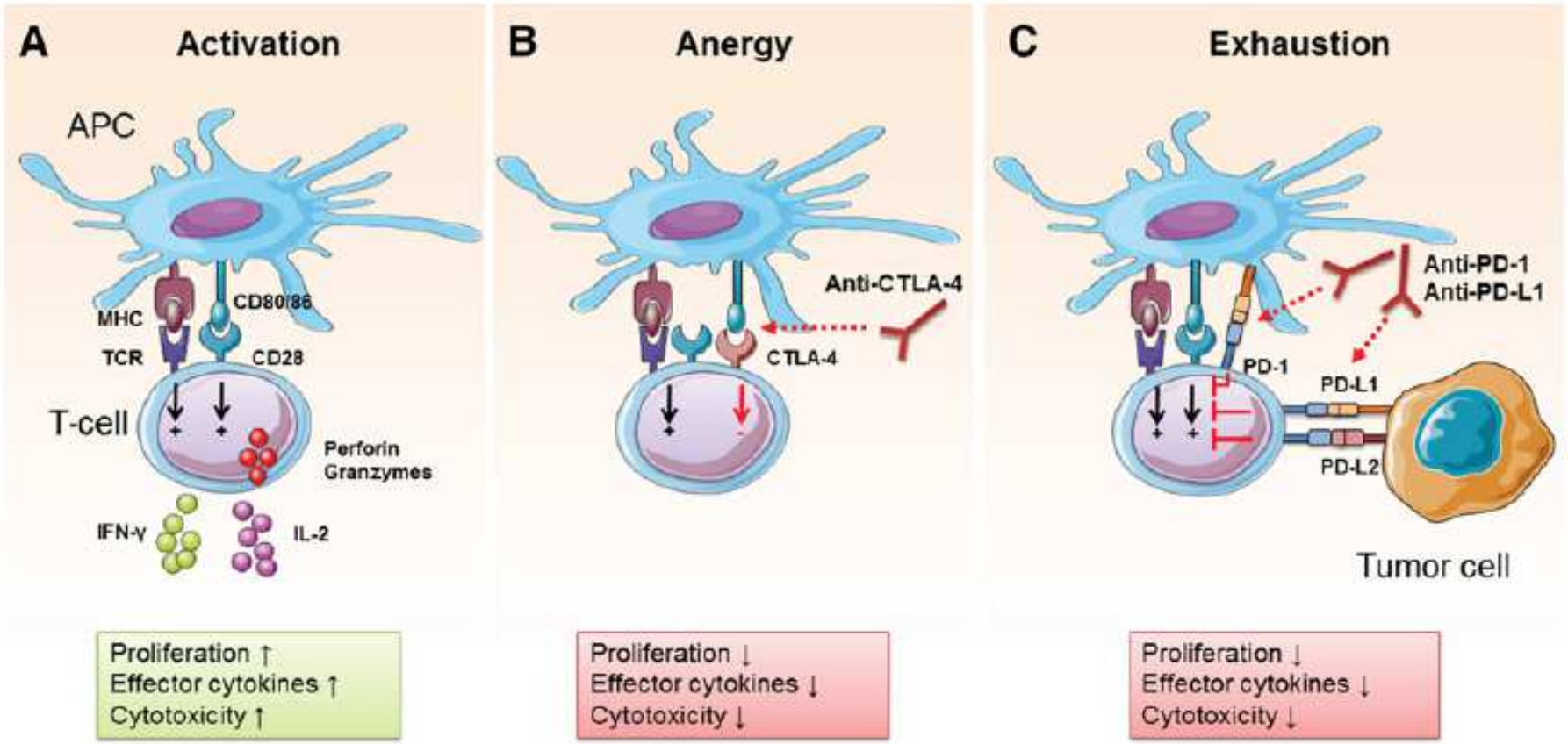
Nivolumab et Pembrolizumab approuvés par la FDA en L2



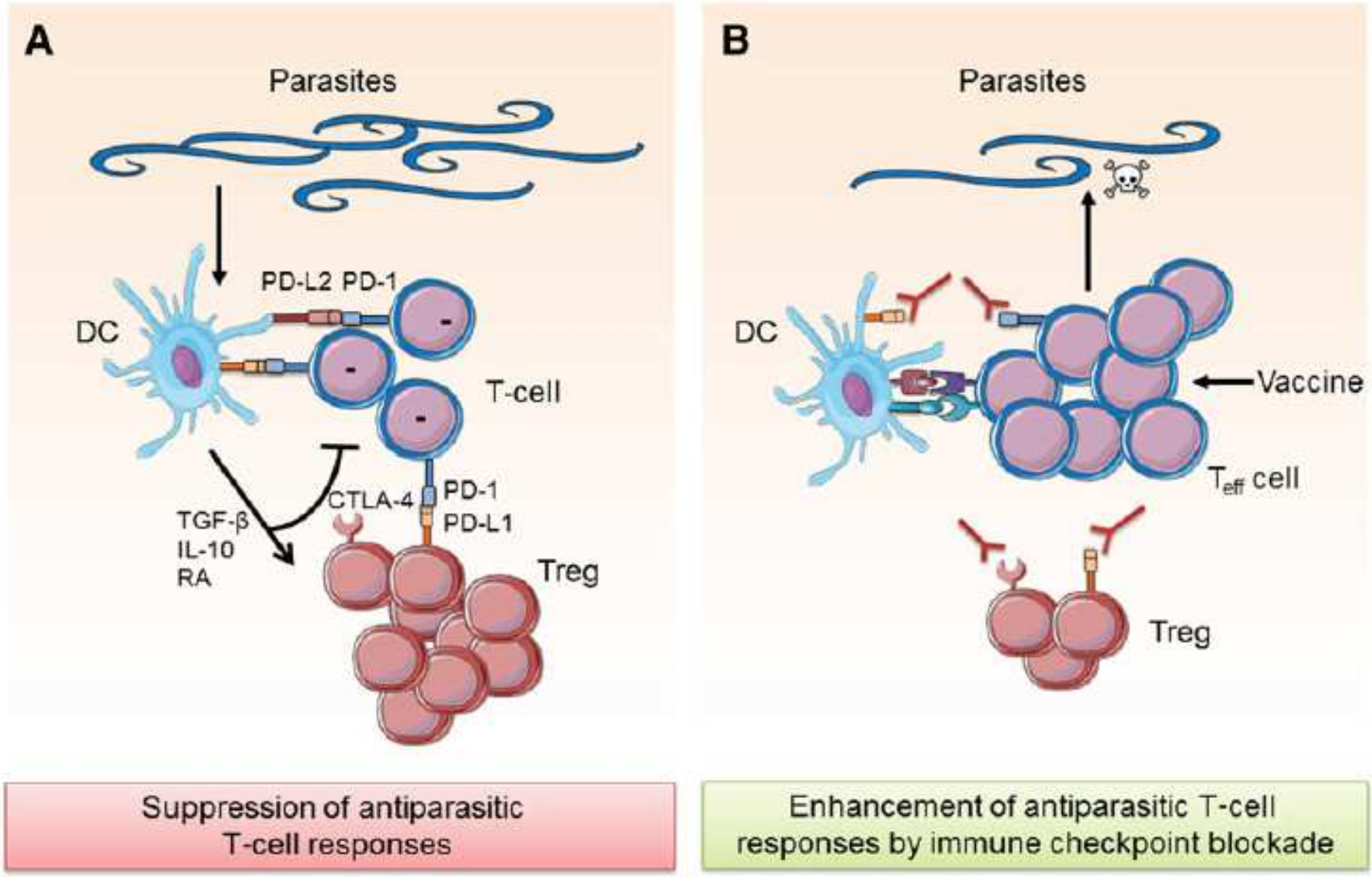
Mellman, Nature, 2011



Mellman, Nature, 2011



Dyck, Eur J Immunol, 2017



Dyck, Eur J Immunol, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 19, 2010 VOL. 363 NO. 8

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

L2 ou +

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D., Jessica C. Hassel, M.D., Wallace Akerley, M.D., Alfons J.M. van den Eertwegh, M.D., Ph.D., Jose Lutzky, M.D., Paul Lorigan, M.D., Julia M. Vaubel, M.D., Gerald P. Linette, M.D., Ph.D., David Hogg, M.D., Christian H. Ottensmeier, M.D., Ph.D., Celeste Lebbé, M.D., Christian Peschel, M.D., Ian Quirt, M.D., Joseph I. Clark, M.D., Jedd D. Wolchok, M.D., Ph.D., Jeffrey S. Weber, M.D., Ph.D., Jason Tian, Ph.D., Michael J. Yellin, M.D., Geoffrey M. Nichol, M.B., Ch.B., Axel Hoos, M.D., Ph.D., and Walter J. Urba, M.D., Ph.D.

ORIGINAL ARTICLE

2011

Ipilimumab plus Dacarbazine for Previously Untreated Metastatic Melanoma

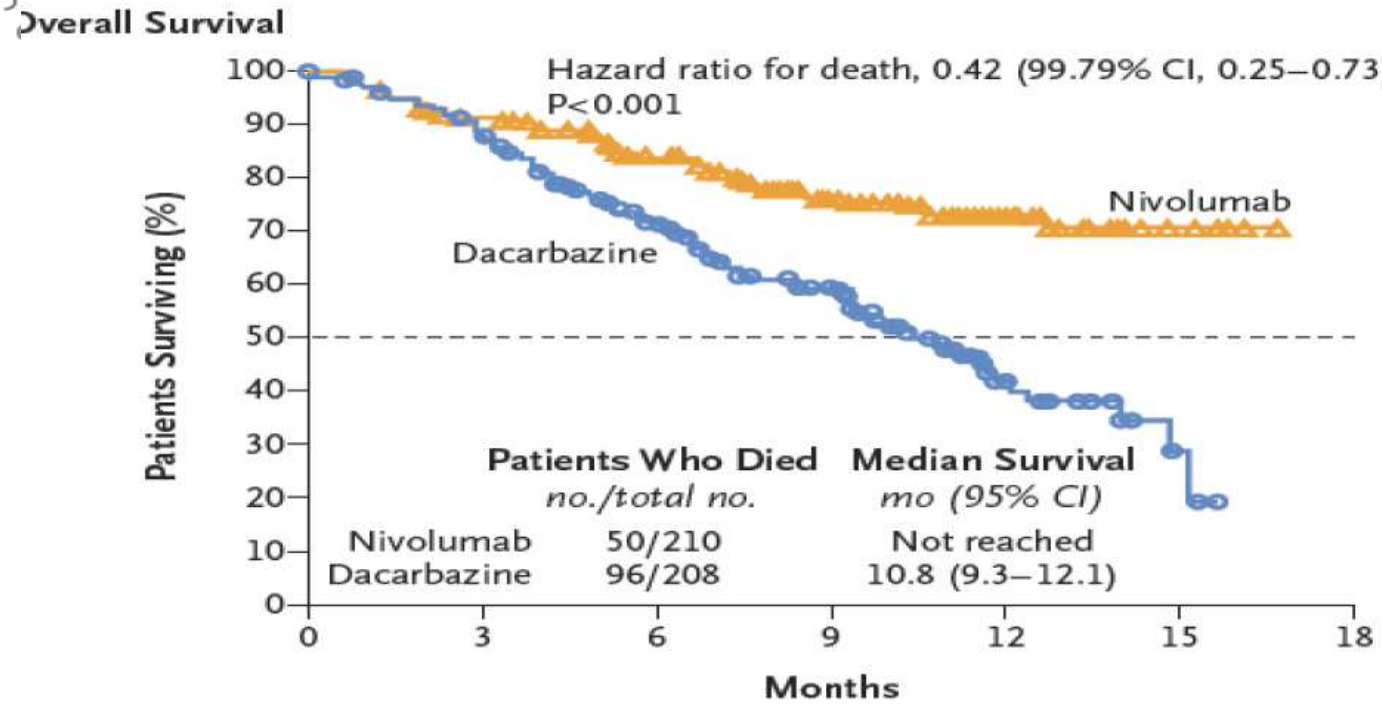
Caroline Robert, M.D., Ph.D., Luc Thomas, M.D., Ph.D.,

The NEW ENGLAND JOURNAL of MEDICINE 2015

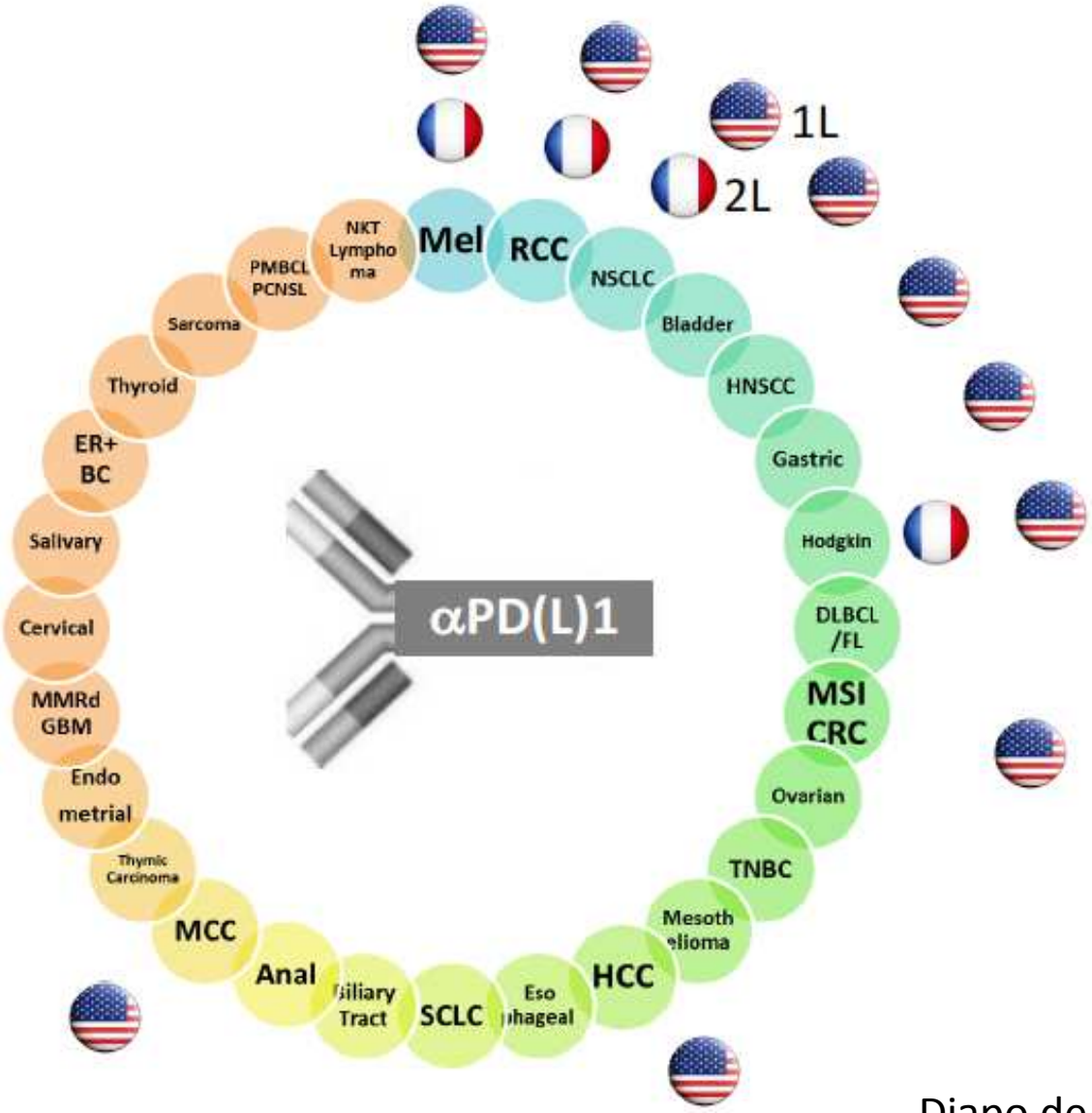
ORIGINAL ARTICLE

Nivolumab in Previously Untreated Melanoma without *BRAF* Mutation

Caroline Robert, M.D., Ph.D., Georgina V. Long, M.D., Ph.D., Benjamin Brady, M.D., Caroline Dutriaux, M.D., Michele Maio, M.D., Laurent Mortier, M.D., Jessica C. Hassel, M.D., Piotr Rutkowski, M.D., Ph.D., Catriona McNeil, M.D., Ph.D., Ewa Kalinka-Warzocha, M.D., Ph.D., Kerry J. Savage, M.D., Micaela M. Hernberg, M.D., Ph.D., Celeste Lebbé, M.D., Ph.D.,



Approvals



Diapo de A. Marabelle

The NEW ENGLAND JOURNAL of MEDICINE

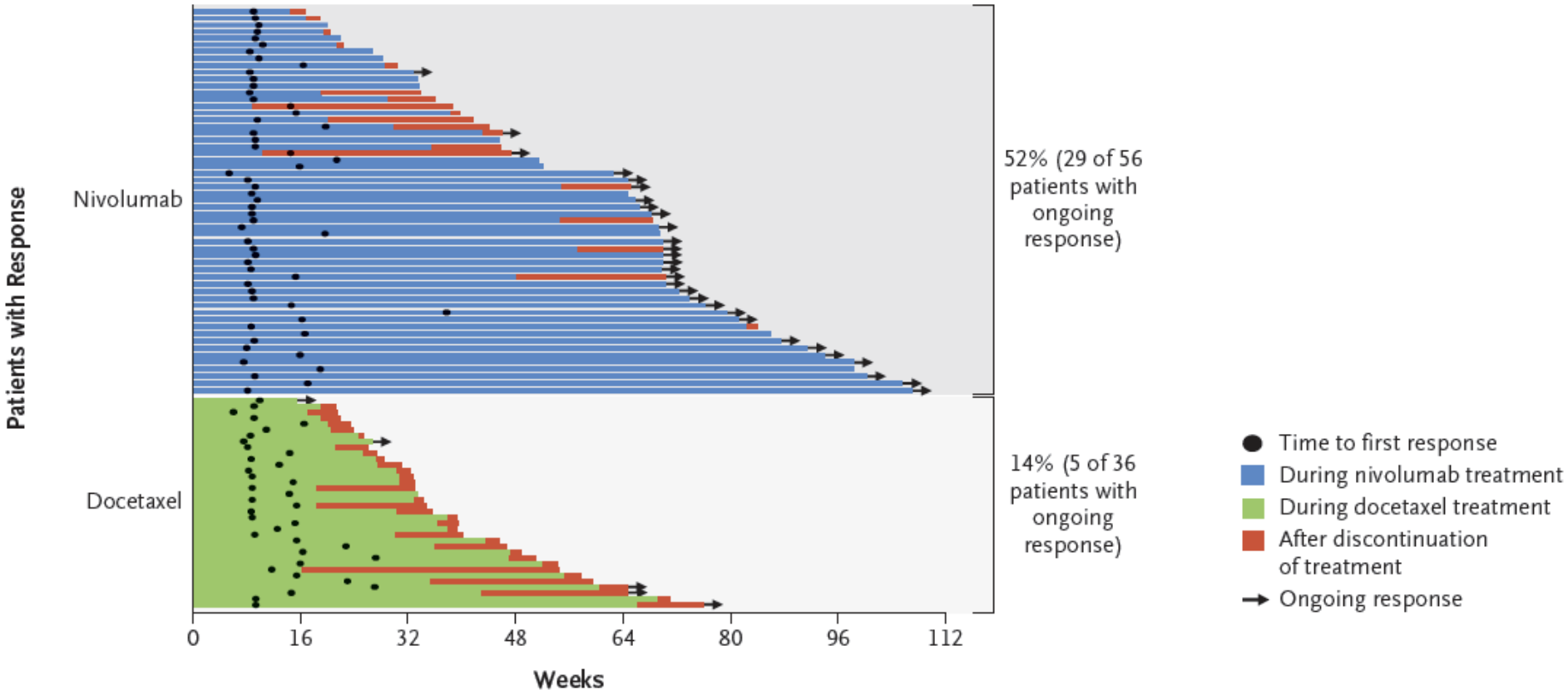
ORIGINAL ARTICLE

2015

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow,

B Duration of Response



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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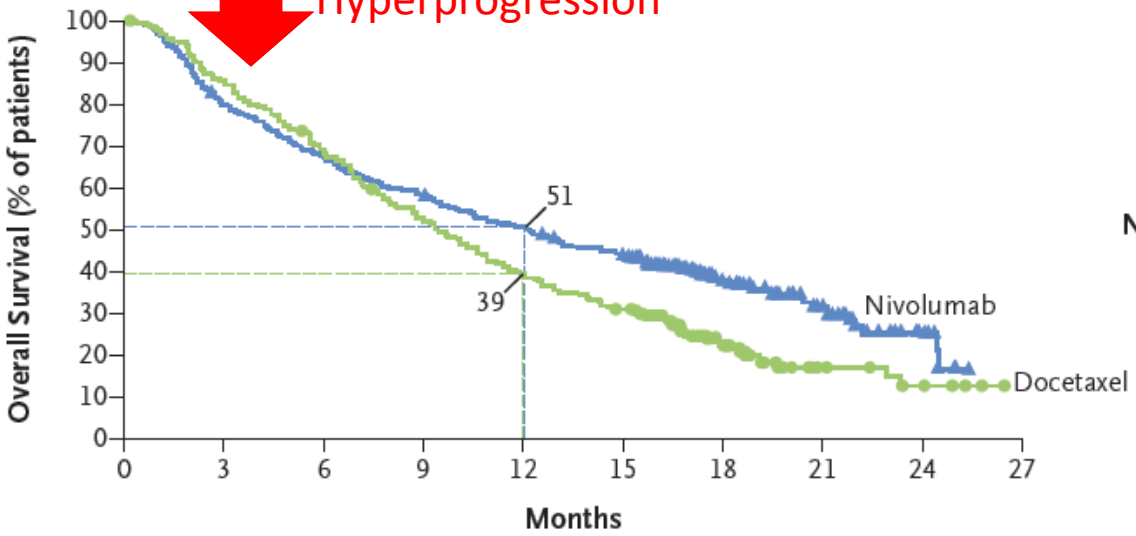
H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow,

A Overall Survival

Hyperprogression



No. at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

Cancer Therapy: Clinical

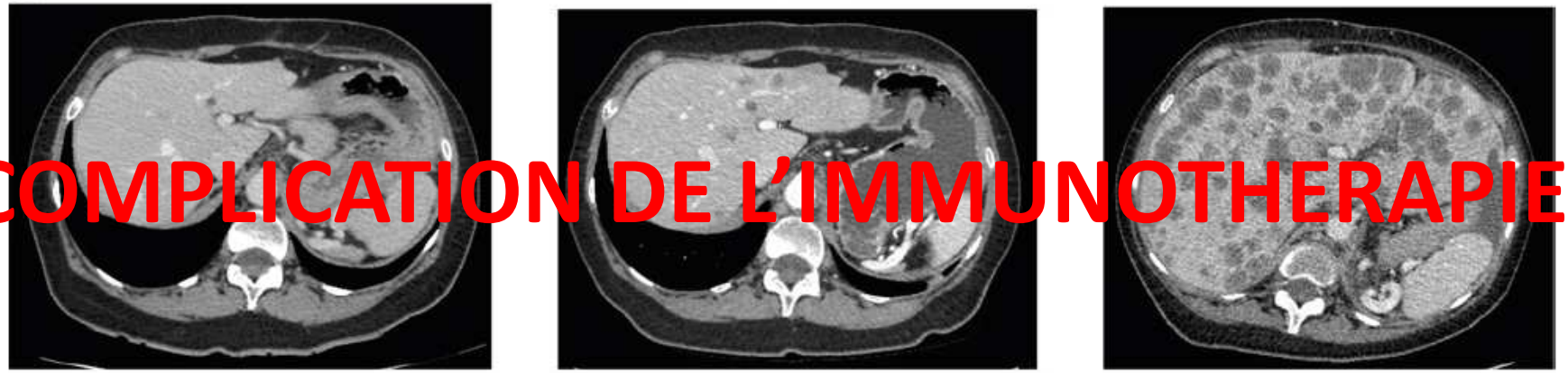
Clinical Cancer Research

Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1

Champiat et al 2016

COMPLICATION DE L'IMMUNOTHERAPIE

A



B

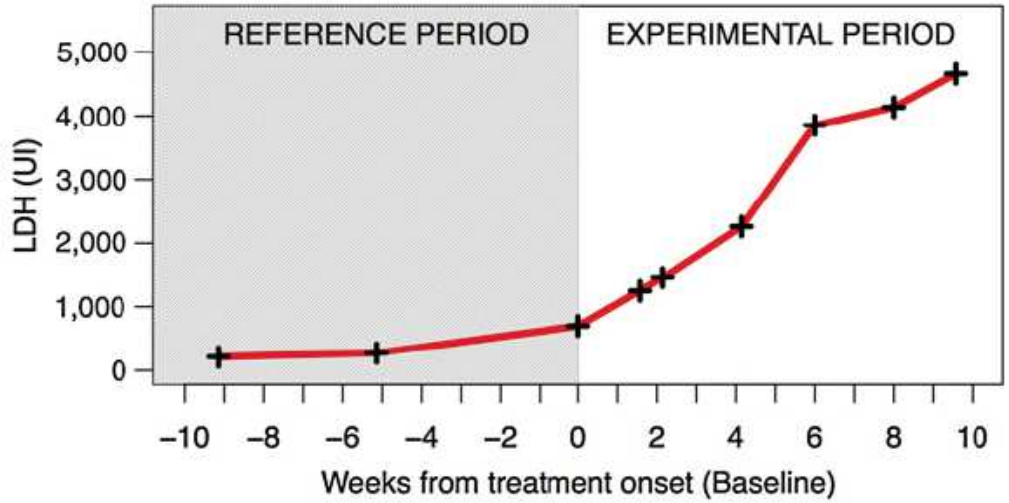


Table 3. Treatment-Related Adverse Events Reported in at Least 10% of the Patients Treated with Nivolumab or Docetaxel.*

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)

Anti PD-1 vs chemotherapy

Nivolumab vs docetaxel in NSCLC

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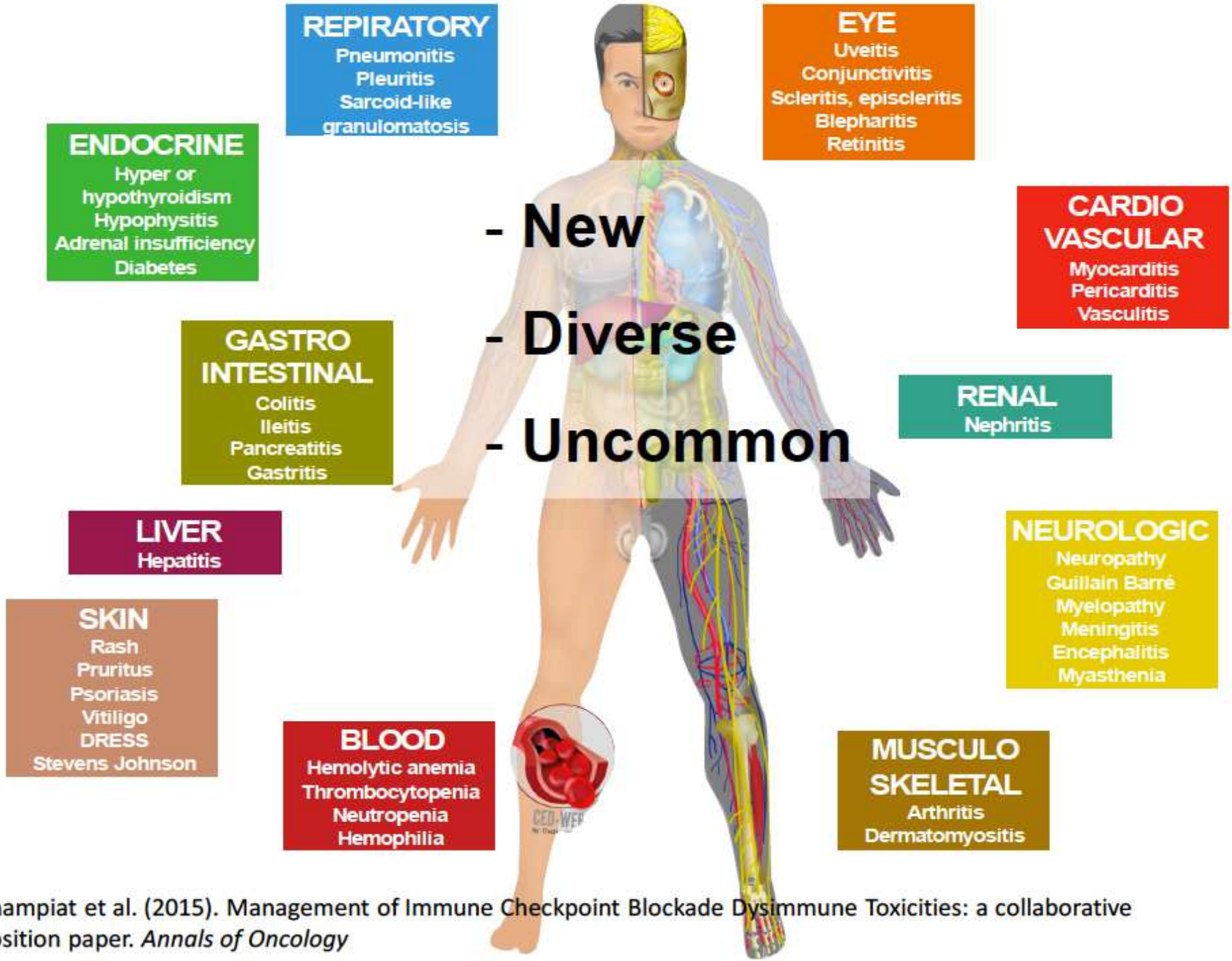
The "1% toxicities"

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*

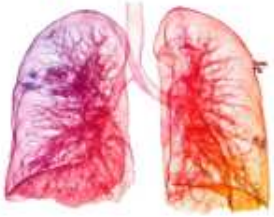


Champiat et al. (2015). Management of Immune Checkpoint Blockade Dysimmune Toxicities: a collaborative position paper. *Annals of Oncology*

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

Diapo S Champiat

Toxicités rares mais potentiellement mortelles

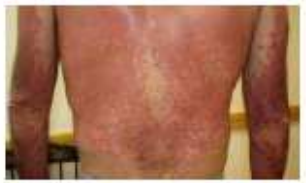
< 1 %

Cardio
Myocardite fulminante

Neurologiques
Guillain Barré
Encéphalite

Endocriniennes
Insuffisance surrénalienne
Acidocétose diabétique

Hématologiques
Anémie
Thrombopénie
Neutropénie



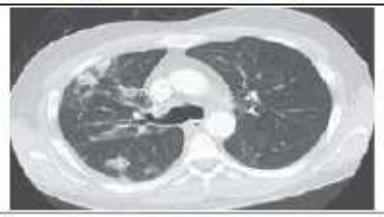
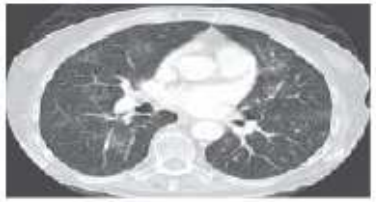
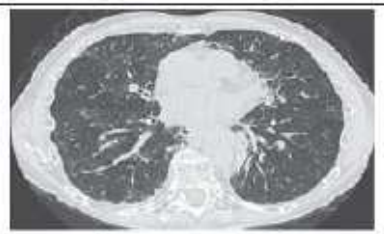
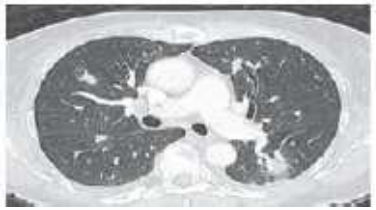
Cutanées
DRESS
Steven Johnson

Rénales
Néphrite

Diapo S Champiat

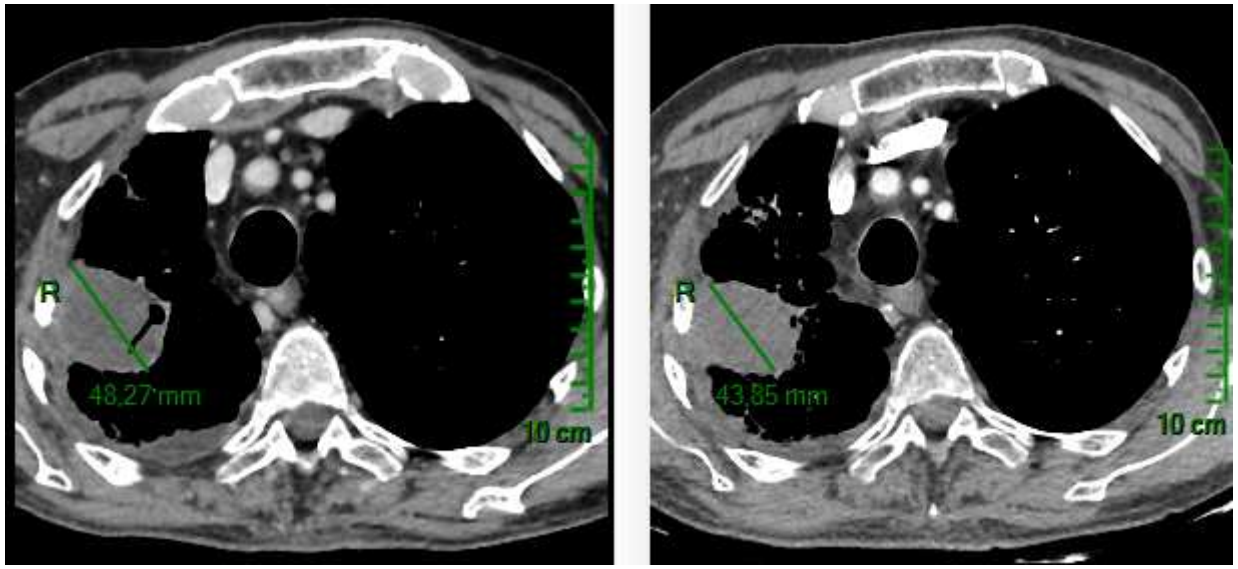
Wide spectrum of radiological presentation

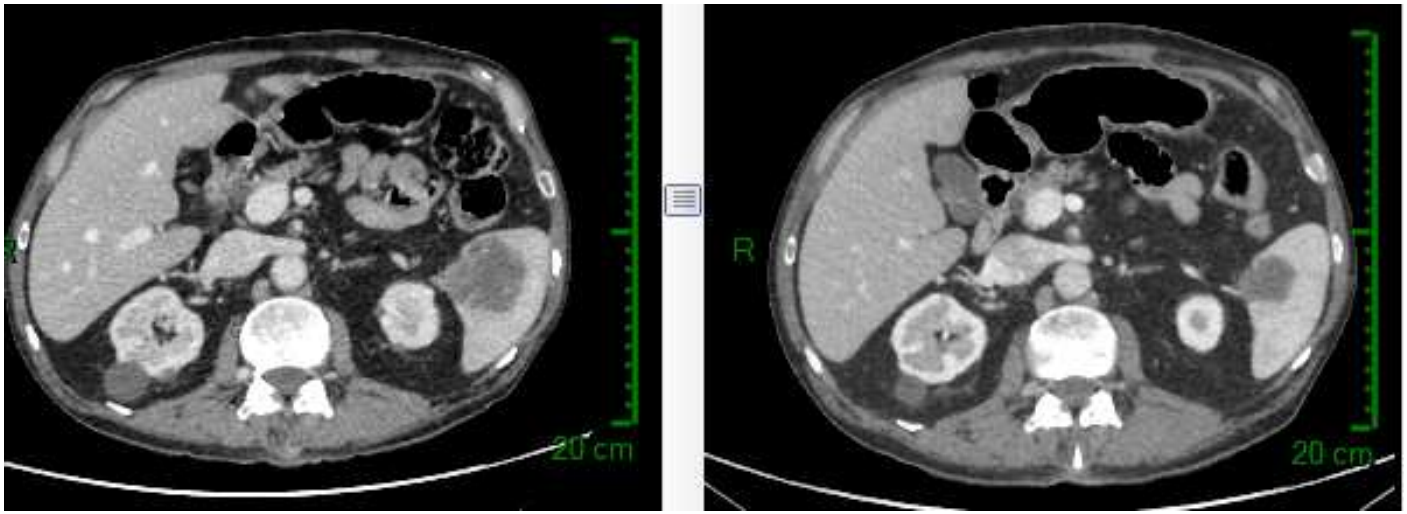
Radiologic features

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

Naidoo et al. , JCO 2016

M. B, 67 ans, Tabac 60 PA, K epidermoide bronchique stade IV (os, rate)
Nivolumab débuté le 13/03/2015 en L3



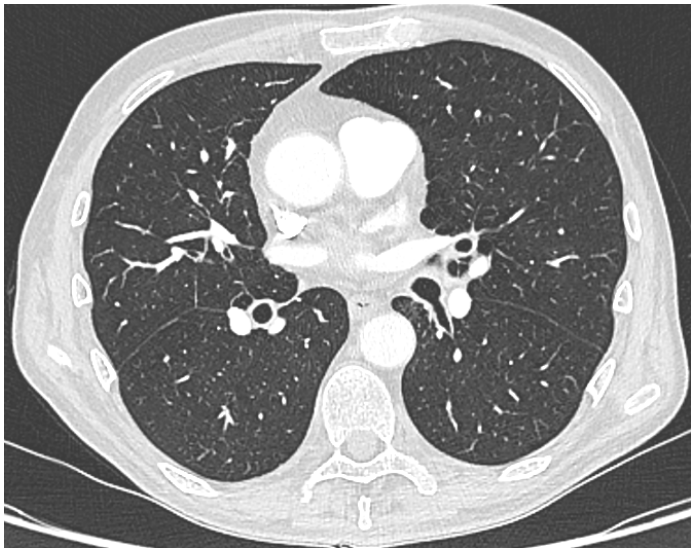


26/02/2015

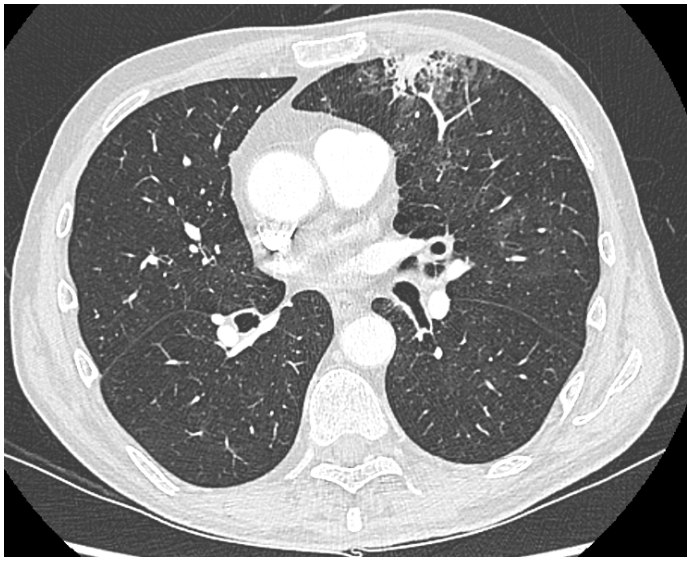
22/04/2015

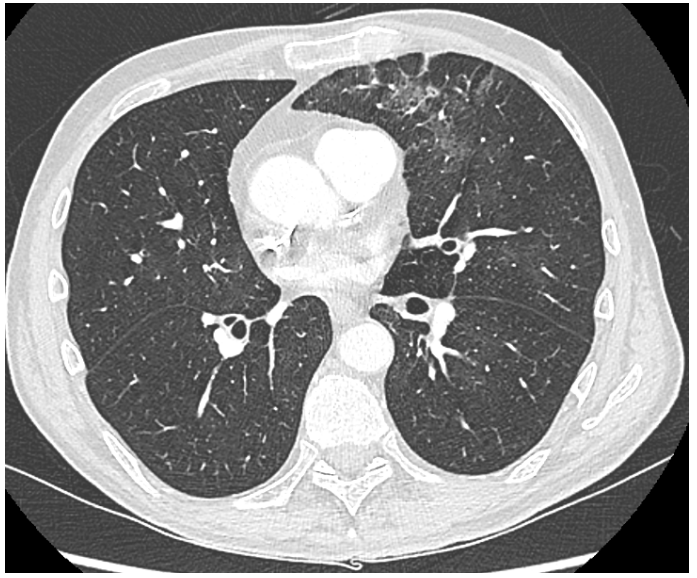
- A M2 : thyroidite grade 2
- A M3 : minime dyspnée

TDM 22/04/2015



TDM 17/06/2015 **(M3)**





- Pas de fièvre, Pas de S. inflammatoire
- EFR

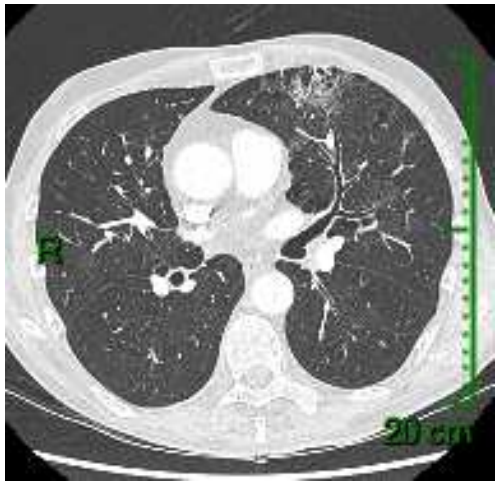
  CPT 94%; CV 74%; VEMS 70%; VEMS/CV 71%; DLCO 51%

- Fibroscopie avec LBA

  - 60 ml récupérés / 150 ml injectés
  - 1 170 000 cellules/ml dont 65% M; 32,5% L; 2% PNN; 0,5% PNE
  - 30% CD4, 67% CD8
  - Stérile

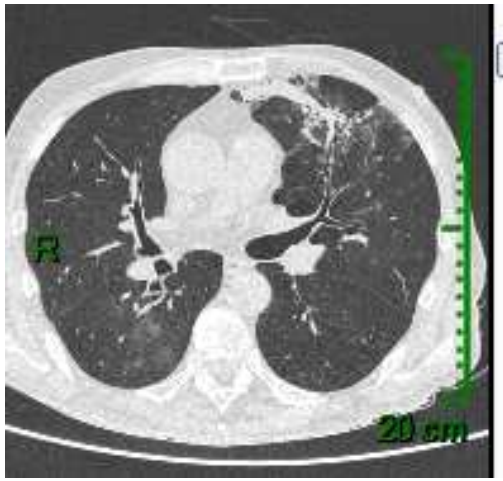
- Pneumopathie au nivolumab grade 2
- Stop nivolumab
- Corticoides 1 mg/kg + Bactrim

Nivo débuté le 13/03/2015



17/06/2015

Stop nivolumab

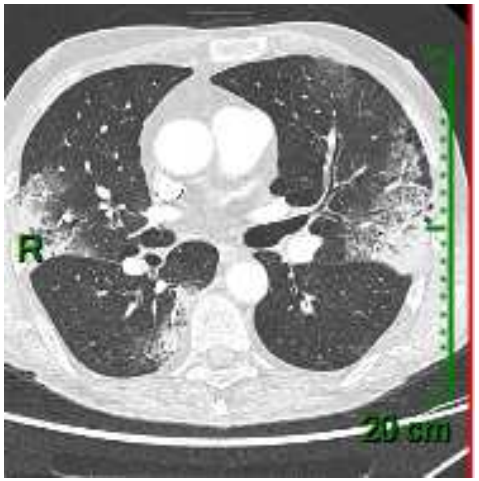


2/07/2015

J1 CT

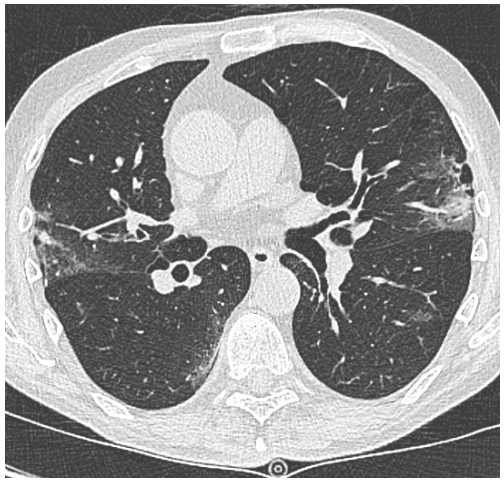
23/09/2015

Stop CT

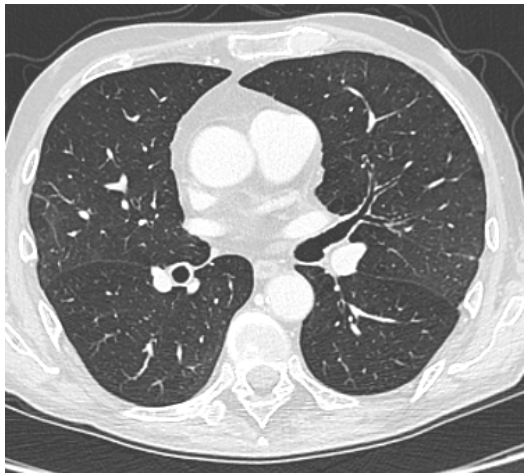


18/11/2015

Fibro LBA J1 CT



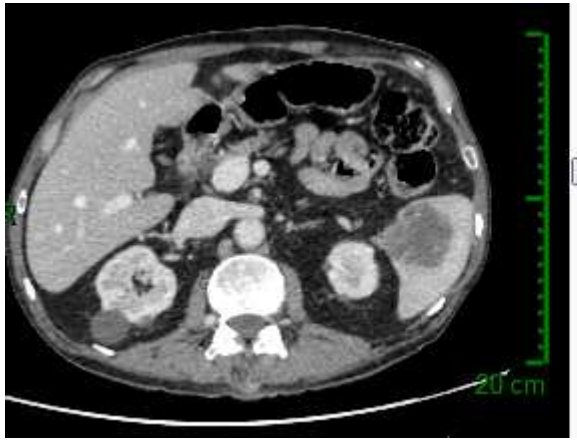
09/12/2015



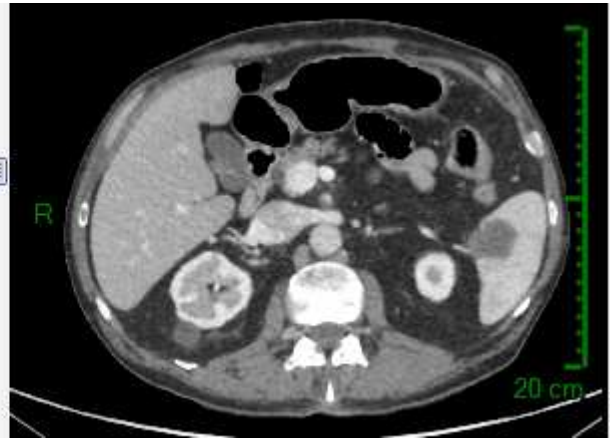
10/02/2016

CT=7,5 mg

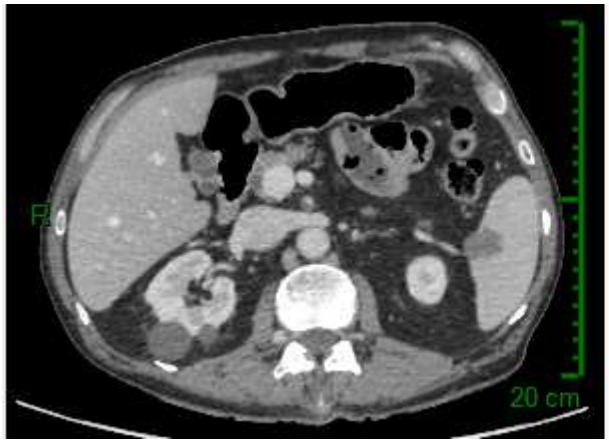
Nivolumab débuté le 13/03/2015 et arrêté en juin 2015



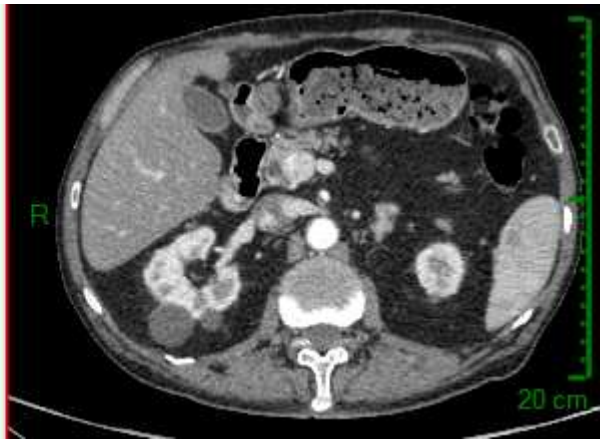
26/02/2015



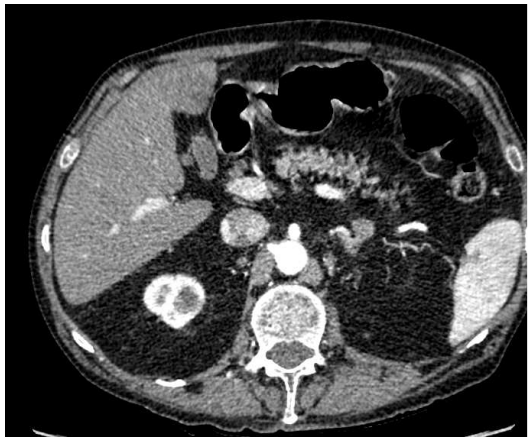
22/04/2015



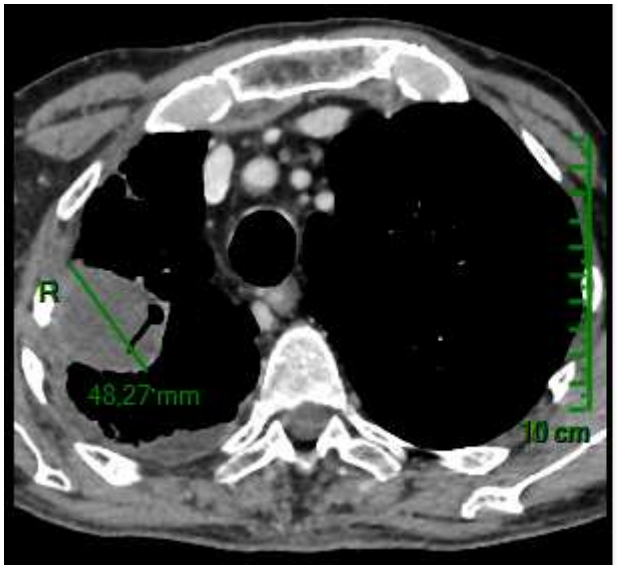
17/06/2015



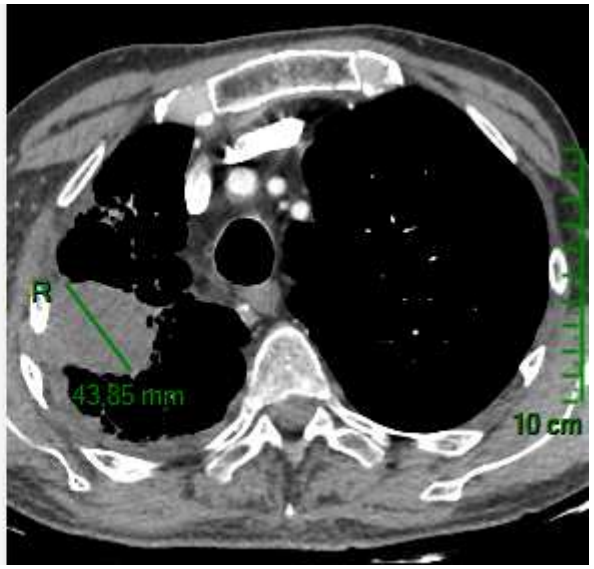
18/11/2015



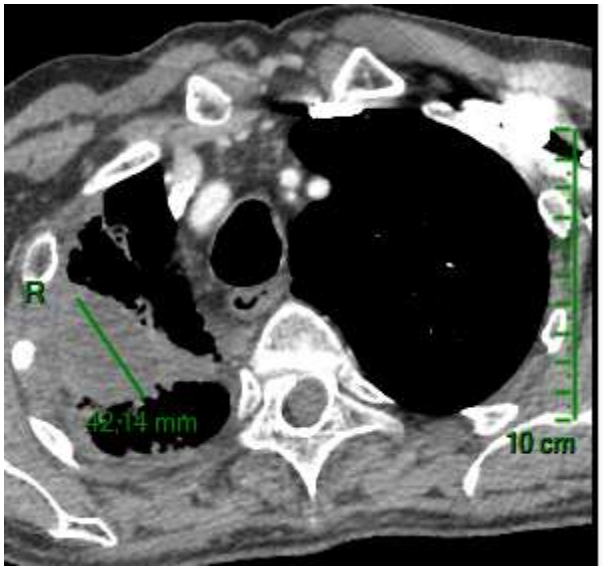
05/09/2017



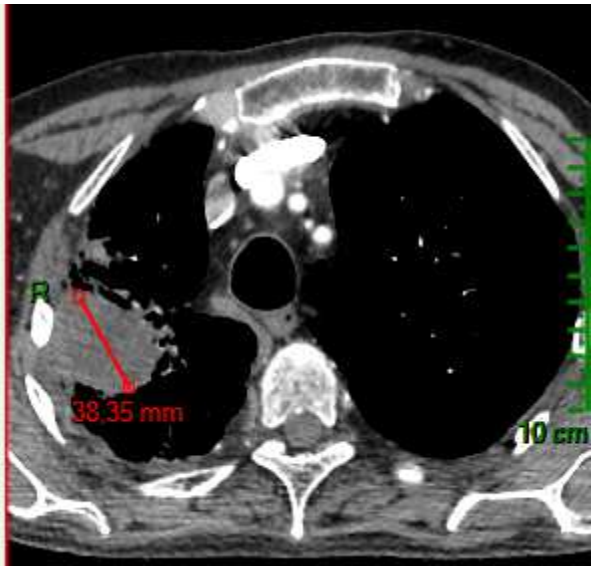
26/02/2015



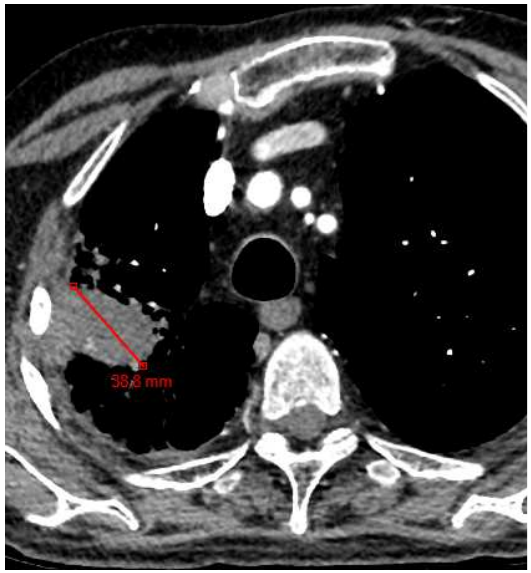
22/04/2015



17/06/2015

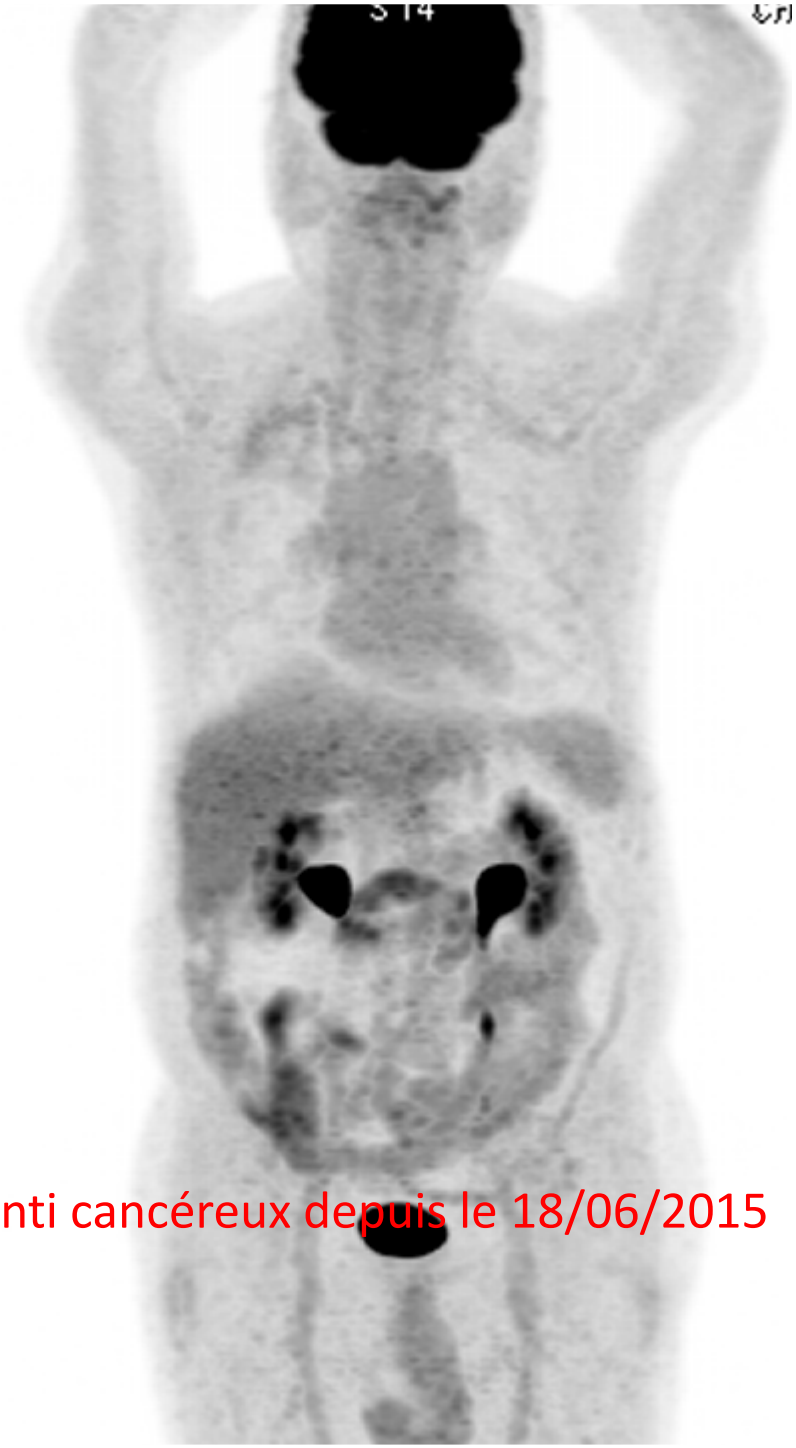


18/11/2015



05/09/2017

TEP-TDM 25/04/2017

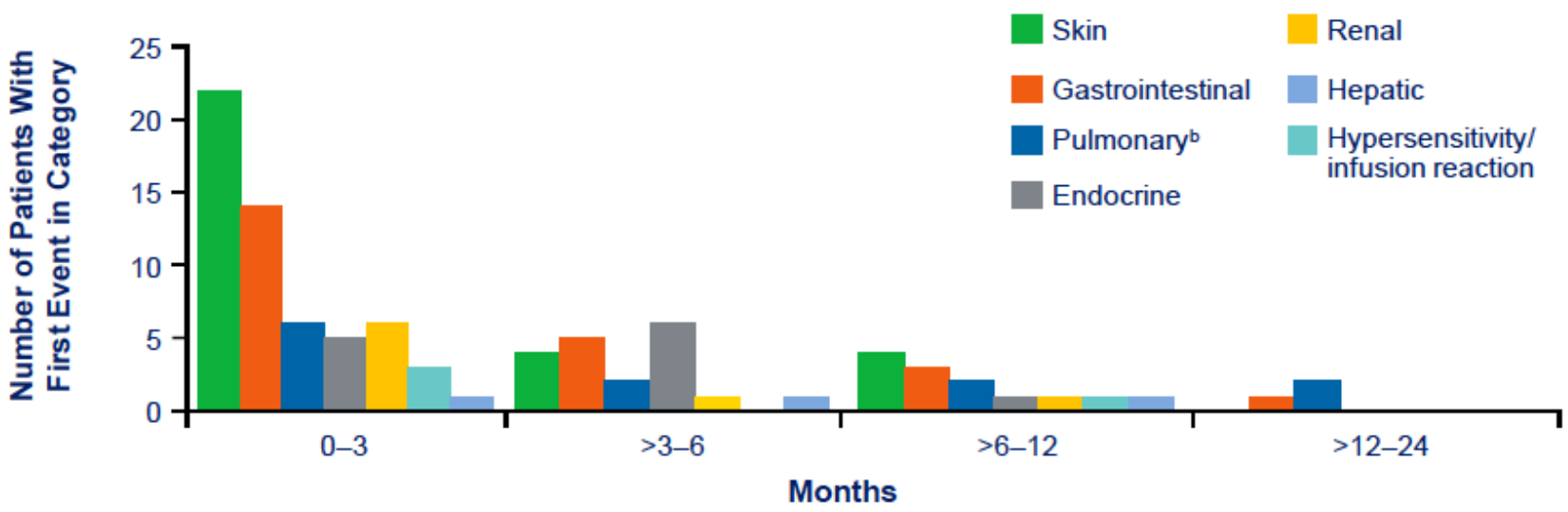


Le patient n’a reçu aucun traitement anti cancéreux depuis le 18/06/2015

Efficacité prolongée … toxicité potentielle prolongée

Time to onset of Treatment-related select AE

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

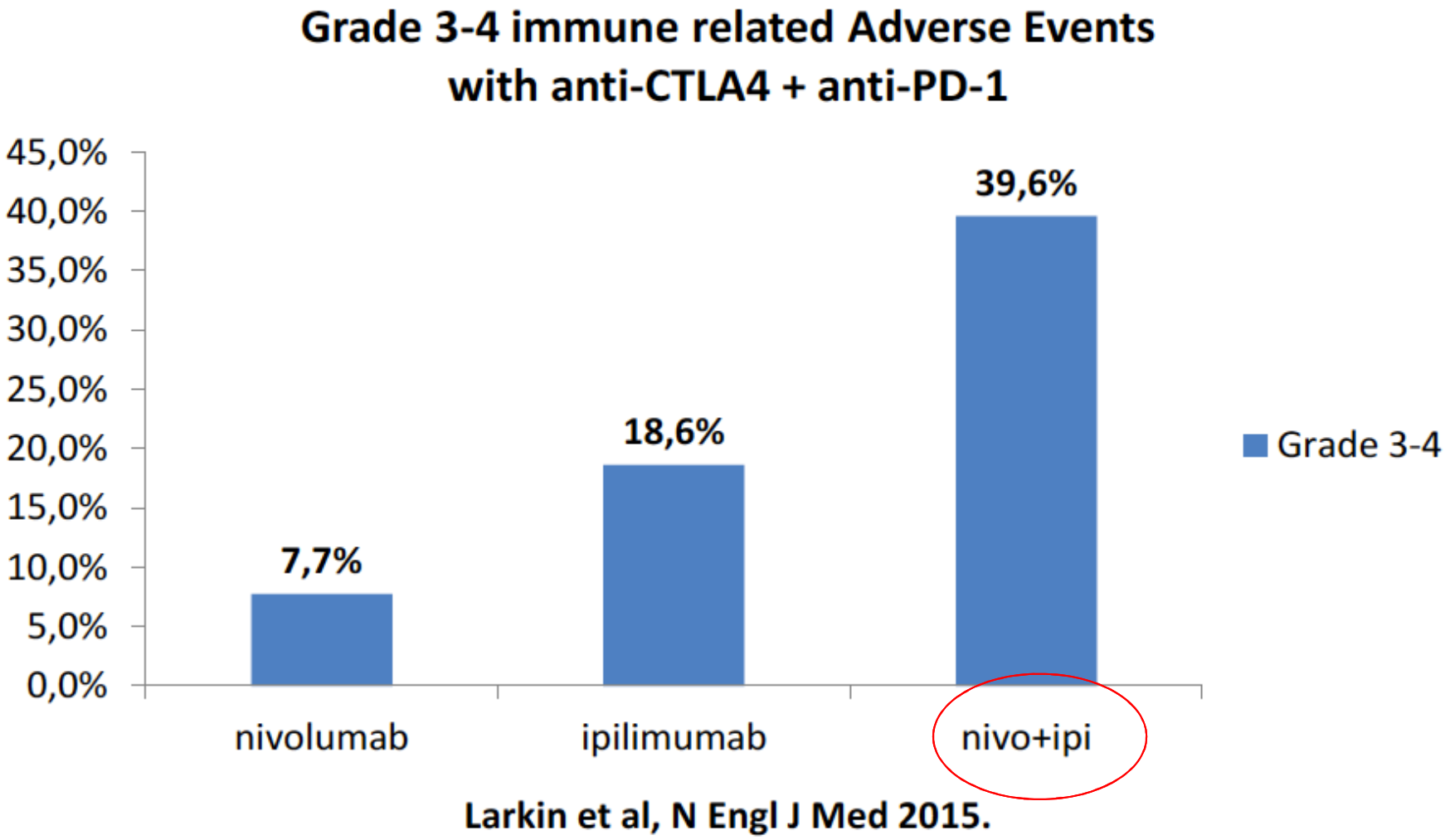


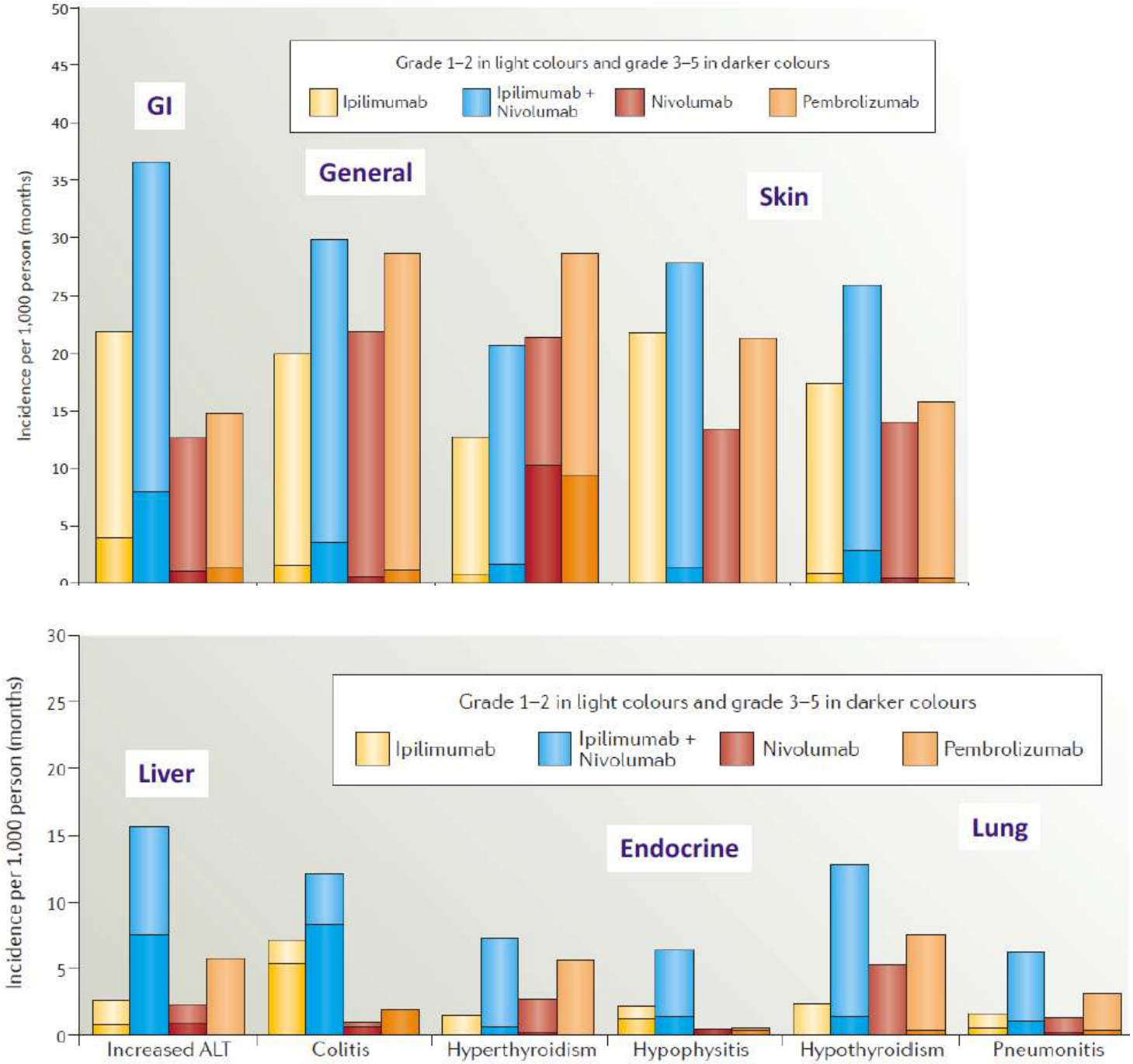
Pts still on study, n	248	206	153	84
Pts still on treatment, n	248	134	85	38
Total pts with a first event,[a] n	49	14	10	2

Longest time to onset: Hepatic and Endocrine IRAEs

Antonia S, ESMO 2015, abstract: 346

Facteurs prédictifs de toxicité





Boutros, Nature Rev Clinical Oncol 2016

Facteurs prédictifs de toxicité

le terrain

- ATCD personnel et familial de maladie auto immune augmente le risque d'EI d'origine immunologique

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, JAMA, 2016

Facteurs prédictifs de toxicité
le terrain

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

	Number (%) (*N* = 52)	Details
Flare AD on PD1		
No	32 (62%)	
Yes	20 (38%)	
Time to flare, median (range), d	38 (8–161)	
Grade of flare		
G1-2	17 (33%)	
G3	3 (6%)	
G4	0 (0%)	
Flare by AD subtype		
Rheumatologic	14 of 27 (52%)	7/13 RA, 3/3 PMR, 1/2 scleroderma, 2/2 Sjogren's, 1/2 psoriatic arthritis
Dermatologic	3 of 8 (38%)	3/6 psoriasis
Gastrointestinal	0 of 6 (0%)	
Neurologic	0 of 5 (0%)	
Endocrine	1 of 4 (25%)	1/4 Graves
Respiratory	0 of 2 (0%)	
Hematologic	2 of 2 (100%)	2/2 ITP
Flare by AD stability at start of PD1		
Clinically active	9 of 15 (60%)	
Clinically inactive	11 of 37 (30%)	
On immunosuppression	10 of 20 (50%)	
Not on immunosuppression	10 of 32 (31%)	

Menzies, Ann Oncol 2017

Facteurs prédictifs de toxicité

l'environnement ?

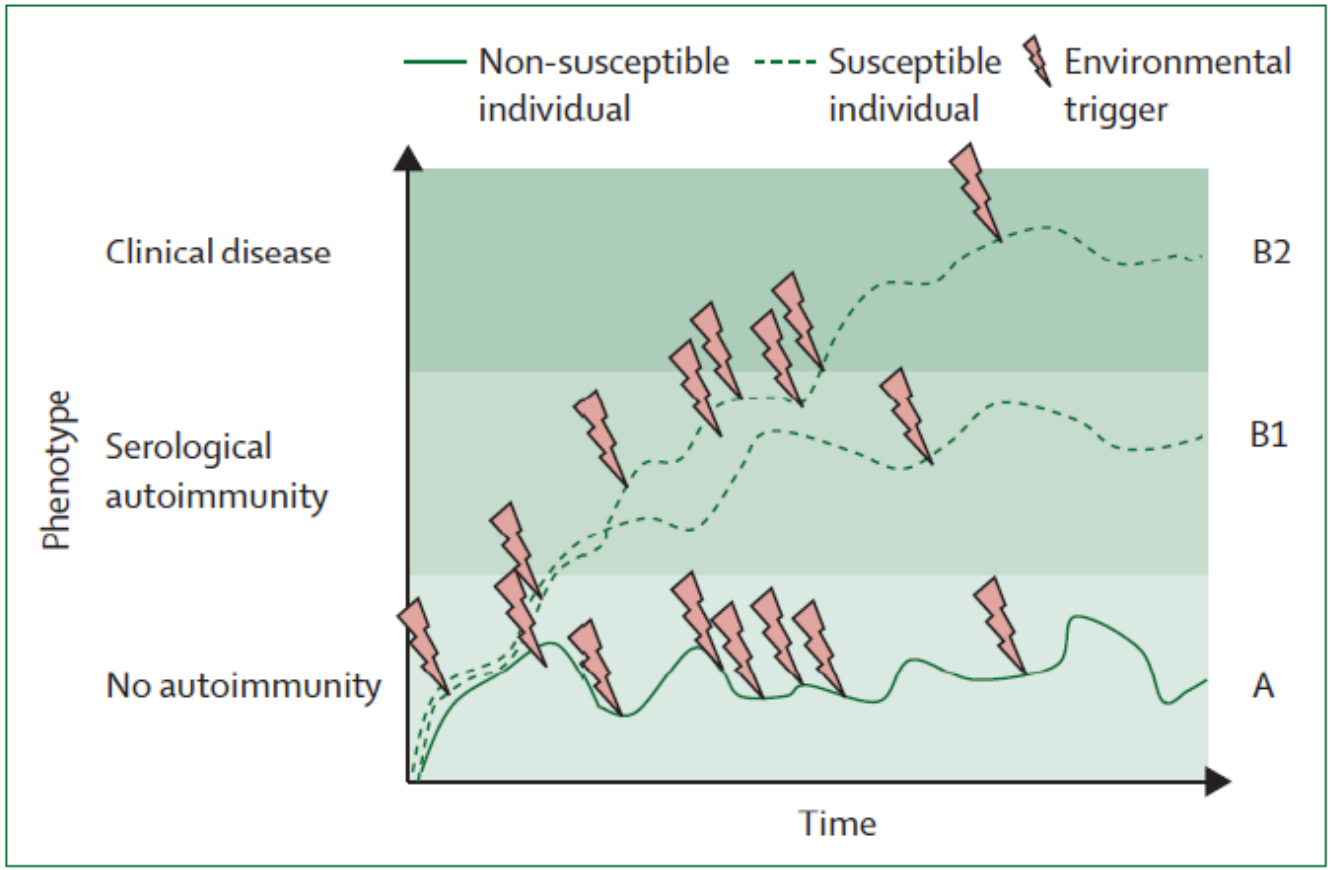
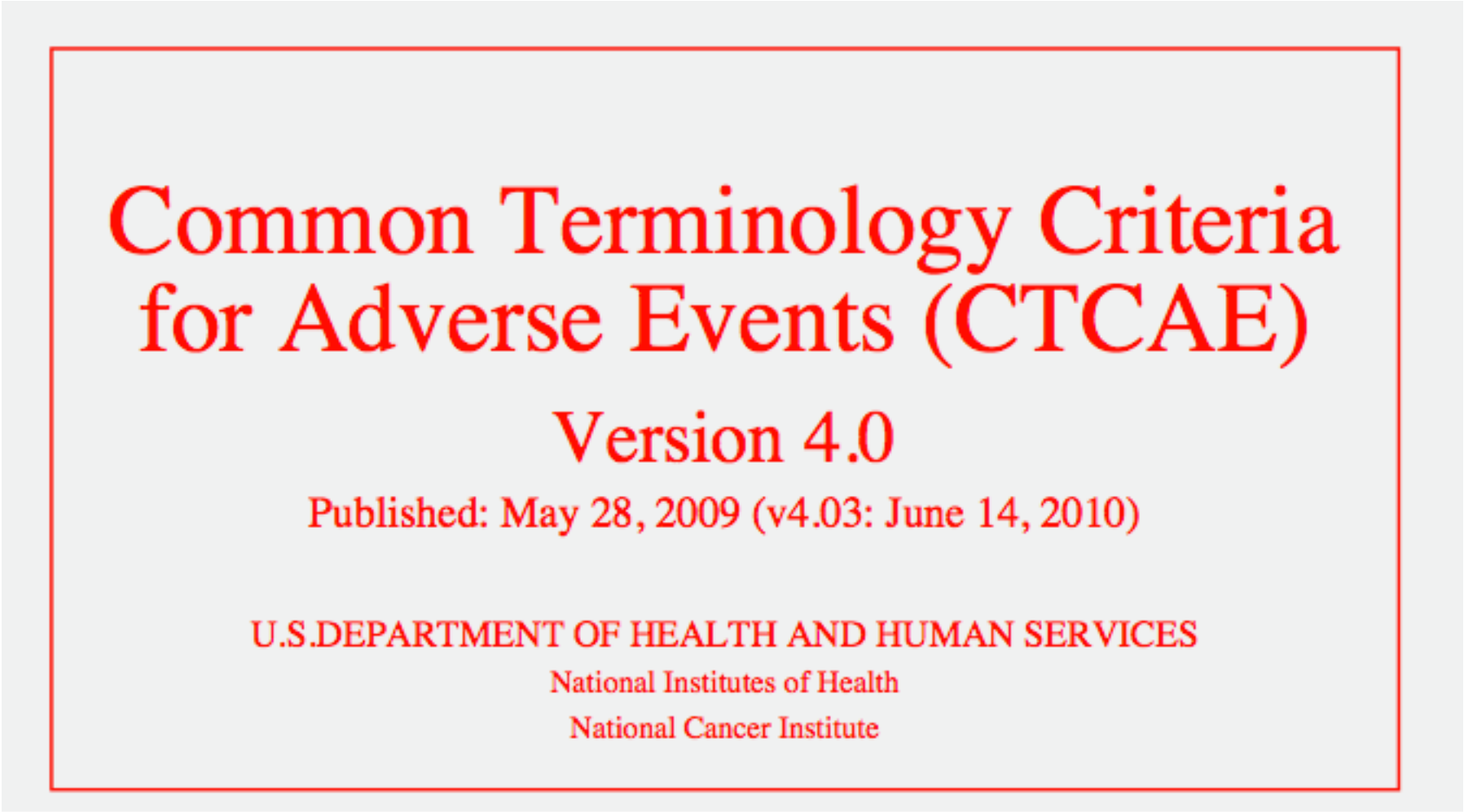


Figure 2: **Time to clinical manifestation**

Wahren-Herlenius, Lancet 2013

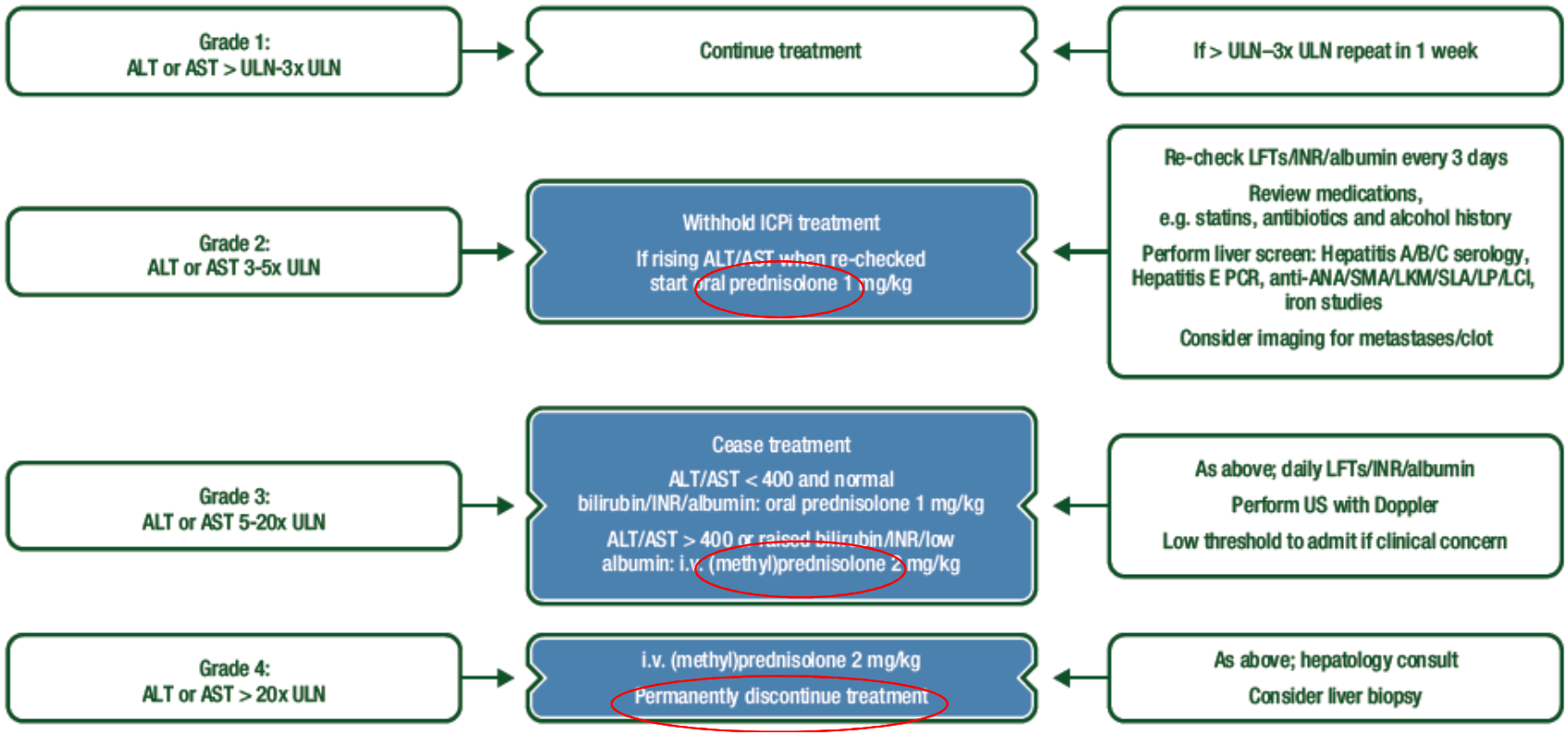
Gestion de la toxicité



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

CLINICAL PRACTICE GUIDELINES

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



Complications infectieuses en rapport avec les ttt immunosuppresseurs

Étude rétrospective MSKCC
2010-14
N= 740 mélanomes traités par ICI
-> 54 soit 7% ont présenté une infection requérant hospitalisation ou AB IV pendant le TTT ICI ou l'année suivant l'arrêt

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

Del Castillo, CID 2016

Complications infectieuses en rapport avec les ttt immunosuppresseurs

Table 2. Specific Infection Types

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

Del castillo, CID 2016

Complications infectieuses en rapport avec les ttt immunosuppresseurs ?

Étude rétrospective
National Hospital Organization Kyoto Medical Center and Kyoto University Hospital
2015-16
N= 84 NSCLC ayant reçu du nivolumab durant cette période

20 / 84 soit 24% ont présenté une pathologie infectieuse (dont 10 étaient sous corticoides)

N= 15 infections bactériennes

- 9 pneumonies
- 1 abcès pulmonaire
- 2 bactériémies
- 2 infections cutanées
- 1 tuberculose

N= 2 infections fongiques (Aspergillus, Trichophyton)

N= 3 infections virales (1 VZV, 2 Influenza)

Pas de différence en terme de chimiothérapies antérieures ni de corticothérapie entre les patients avec ou sans infections (PA ? VEMS ?)

Fujita, ERS 2017

Complications infectieuses ?

72 ans
K epidermoide bronchique
Nov 2014 : L1 carboplatine docetaxel X 4
Mai 2015 : L2 carboplatine gemzar x 4
Dec 2015 : nivolumab x 8

-> apparition de micronodules pulmonaires
-> interferon gamma positif
-> LBA : BAAR +; culture : M. tuberculosis
-> BTB : infiltration lymphocytaire

-> arrêt du nivolumab et TTT anti tuberculeux

Anti-PD1 antibody treatment and the development of acute pulmonary tuberculosis

IMPUTABILITE ?

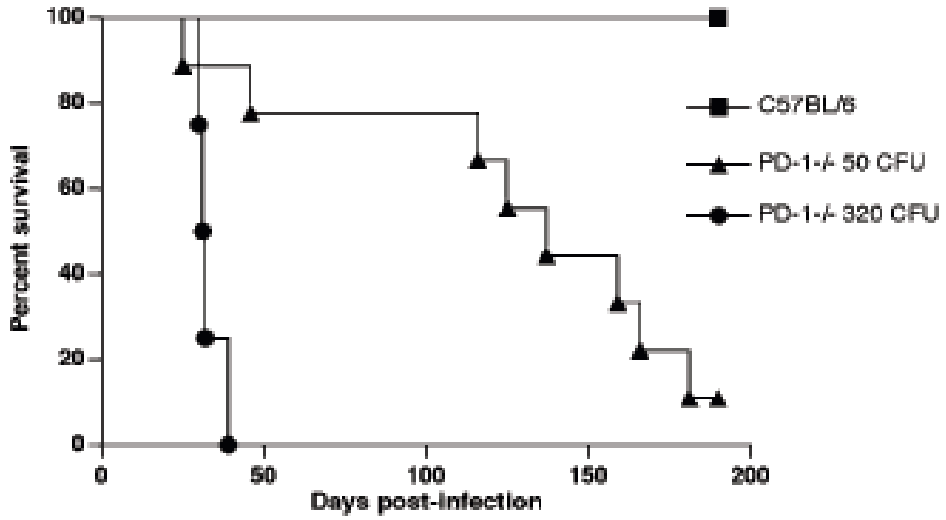
Fujita, JTO 2016

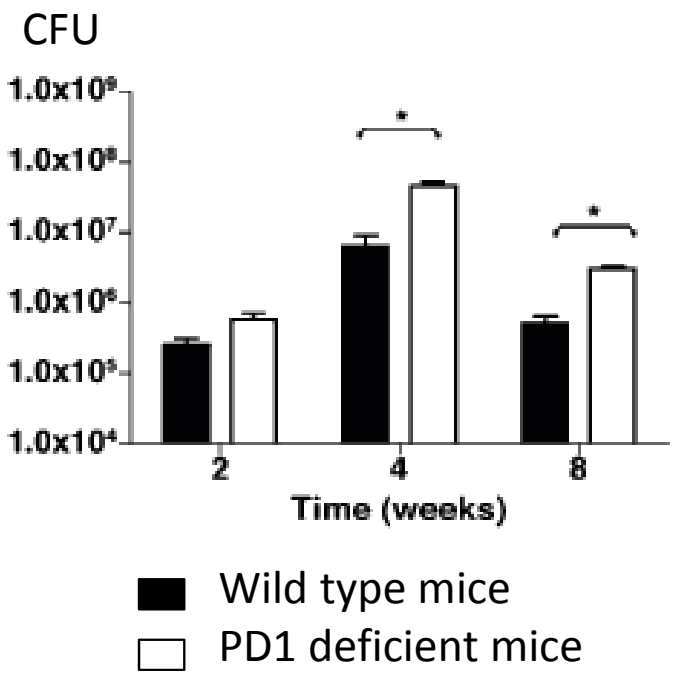
M. tuberculosis et PD1

PD1 et PDL1 up-régulés sur les Lymphocytes T des sujets infectés / BK et diminue sous TTT efficace

Shen, Tuberculosis 2016
Singh, Tuberculosis 2014

Survie réduite chez les souris PD1 -/- après aérosol de M. tuberculosis
Augmentation du nombre de colonies à 4 et 8 semaines post aérosol chez souris PD1 -/-
Augmentation des cytokines pro-inflammatoires (inflammation aberrante)





Trinath, JID 2012

Lazar-Molnar, PNAS 2010

Sepsis et PD1

Zhang *et al. Critical Care* 2010, **14**:R220
http://ccforum.com/content/14/6/R220

CRITICAL CARE

RESEARCH Open Access

PD-L1 blockade improves survival in experimental sepsis by inhibiting lymphocyte apoptosis and reversing monocyte dysfunction

JLB

Highlighted Article

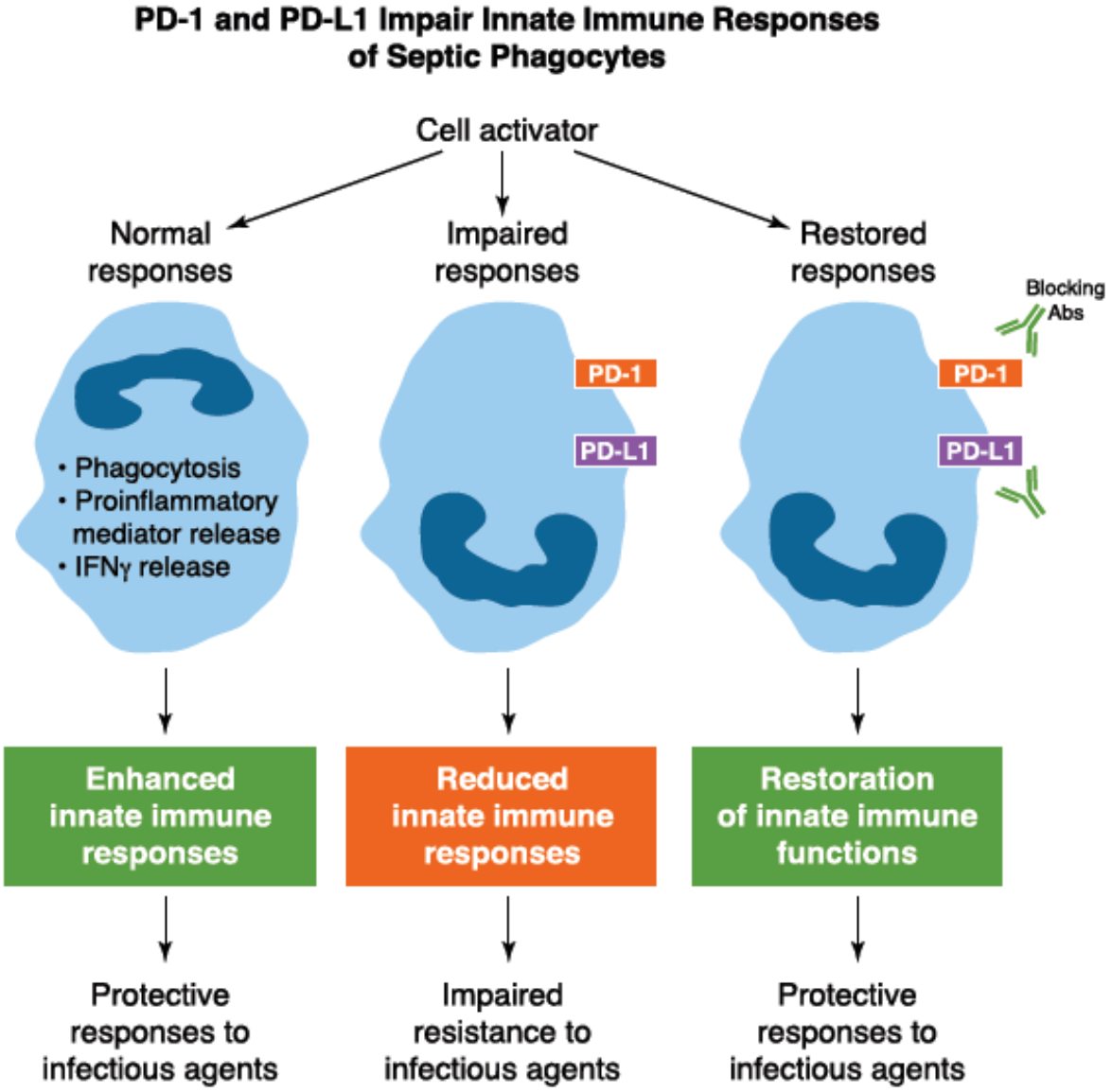
Frontline Science: Defects in immune function in patients with sepsis are associated with PD-1 or PD-L1 expression and can be restored by antibodies targeting PD-1 or PD-L1

Andriani C. Patera,[*1] Anne M. Drewry,[‡] Katherine Chang,[‡] Evan R. Beiter,[‡] Dale Osborne,[‡] and Richard S. Hotchkiss[‡]*

*Infectious Disease and Vaccines Department, MedImmune LLC, Gaithersburg, Maryland, USA; and [†]Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri, USA

RECEIVED JUNE 6, 2016; REVISED AUGUST 1, 2016; ACCEPTED AUGUST 26, 2016. DOI: 10.1189/jlb.4HI0616-255R

Sepsis et PD1



Ward, JLB 2017

Immunothérapie chez le patient porteur du VIH atteint d'un cancer

Exclu des essais thérapeutiques donc peu de données

Case report

Etude rétrospective CBNPC / HIV / immunothérapie en cours de publication

Etude rétrospective internationale (16 centres)

N= 42 patients dont 29 mélanomes

5 patients transplantés d'organe

11 patients HIV+ (2 RC, 1 RP, 4 SD, 4 PD)

14 patients HCV+ (2 RC, 9 SD, 4 PD)

12 patients HBV + (1 RC, 1 RP, 8 SD, 2 PD)

-> pas d'hépatite reliée au TTT, pas de réactivation du virus

Rai, ESMO 2017

Immunothérapie chez le patient porteur du VIH atteint d'un cancer

Mais AMM non restreintes sur statut HIV

RCP onco VIH

Essai Spanish Lung Cancer Group phase II durvalumab tumeur solide HIV+

Essai IFCT phase II CHIVA2 nivolumab L2 pour CBNPC stade IV HIV +

IFCT Intergroupe Francophone de Cancérologie Thoracique

VIH et PD1 / PDL1

- Stimulation antigénique chronique / HIV uprégule PD1 et PDL1

-> « immune exhaustion »

- Surexpression PD1 sur Lymphocytes = F pronostique chez patients HIV + non traités
- TTT anti rétroviral réduit l'expression de PDL1

- Données d'efficacité de BMS 936559 (Ac anti PDL1) chez le macaque

Clinical Trial of the Anti-PD-L1 Antibody BMS-936559 in HIV-1 Infected Participants on Suppressive Antiretroviral Therapy

Juin 2017

Cynthia L. Gay,[1] Ronald J Bosch,[2] Justin Ritz,[2] Jason M. Hataye,[3] Evgenia Aga,[2] Randall L. Tressler,[4,5] Stephen W. Mason,[6] Carey K. Hwang,[7] Dennis M. Grasela,[7] Neelanjana Ray,[7] Josh C. Cyktor,[8] John M. Coffin,[9] Edward P. Acosta,[10] Richard A. Koup,[3] John W. Mellors,[8] Joseph J. Eron[1]; for the AIDS Clinical Trials 5326 Study Team

Phase I randomisée en double aveugle
N= 6 patients HIV+ traités > 350 CD4
4 reçoivent 1 seule perfusion de BMS-936559
2 reçoivent un placebo
Toxicité : hypophysite grade 1
diarrhée grade 2

Immunothérapie chez le patient porteur d'une hépatite virale atteint d'un cancer

Peu de données

Case report

Etude rétrospective

Hepatitis B virus reactivation in patients with solid tumors receiving systemic anticancer treatment

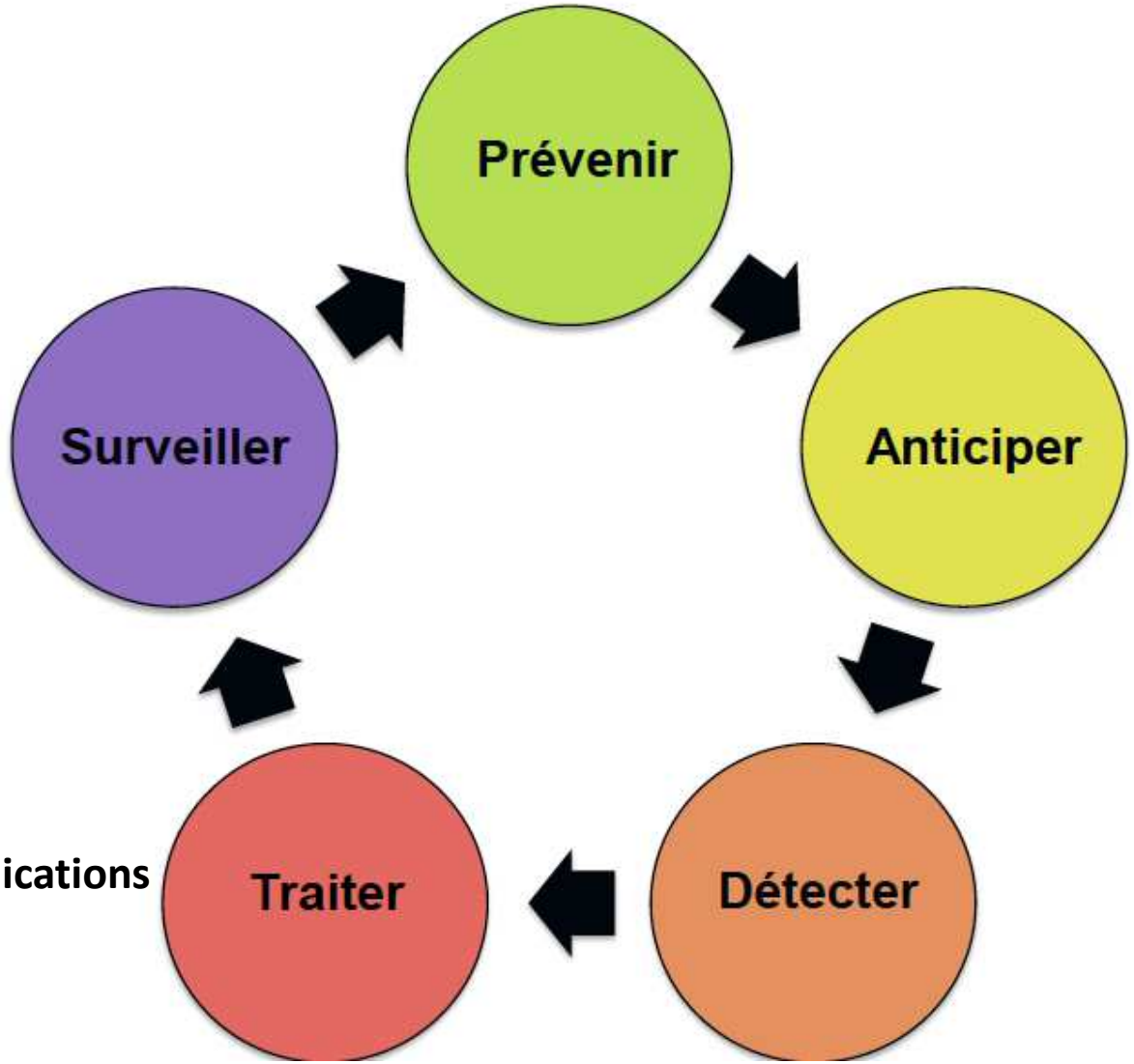
C. S. Voican[1], O. Mir[2*], P. Loulergue[3], M. Dhooge[1], C. Brezault[1], J. Dréanic[1], S. Chaussade[1], S. Pol[4,5] & R. Coriat[1]

Ann Oncol 2016

monoclonal antibodies and immunotherapy

To date, no case of HBV reactivation was documented with those recent agents.

Complications des Immunothérapies



Et prévenir les complications des TTT -> Bactrim

Champiat, Ann Oncol 2015

11 décembre - 12 décembre