Complications infectieuses des nouveaux traitements du cancer (thérapies ciblées et immunothérapie)

Luis Teixeira
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Service d'Oncologie Médicale
Hôpital Saint Louis
Paris

Plan

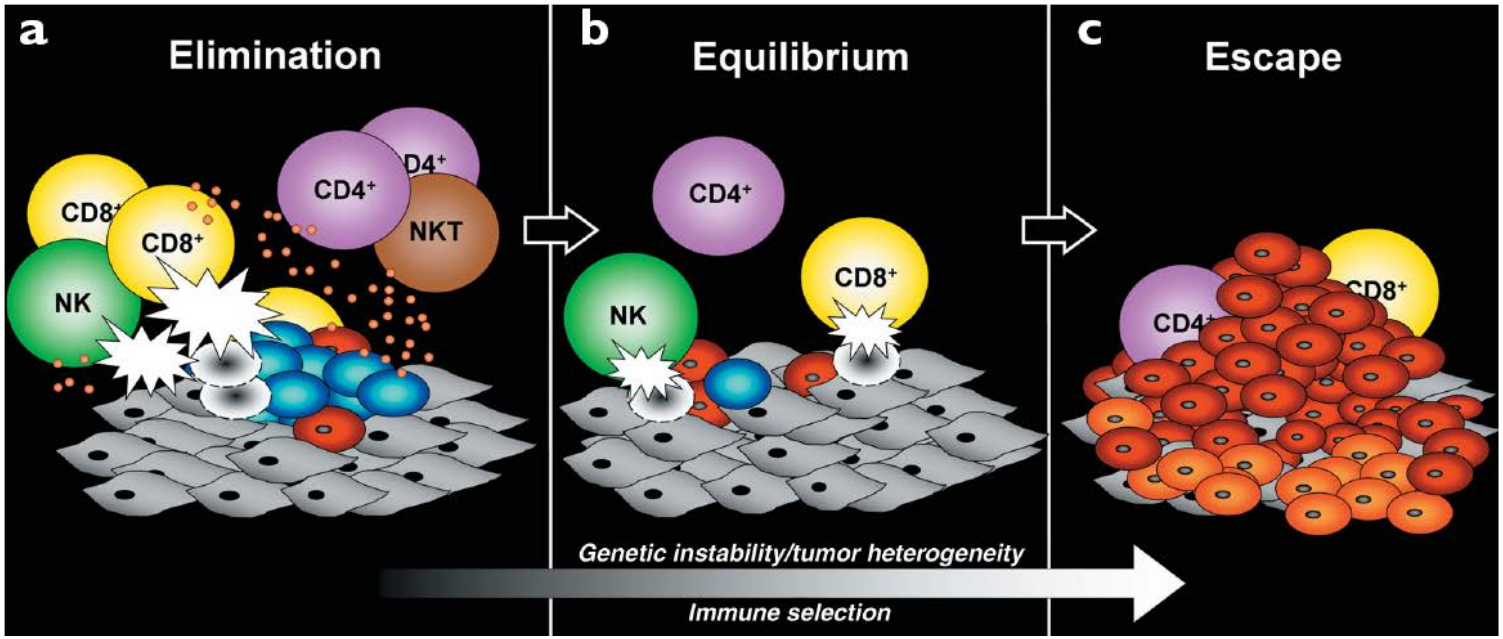
- Concept d'immunothérapie dans les cancers solides

- Les « check-point inhibiteurs »
  - Complications non infectieuses
  - Complications infectieuses
  - recommandations

- Perspectives à venir avec les combinaisons d'immunothérapie

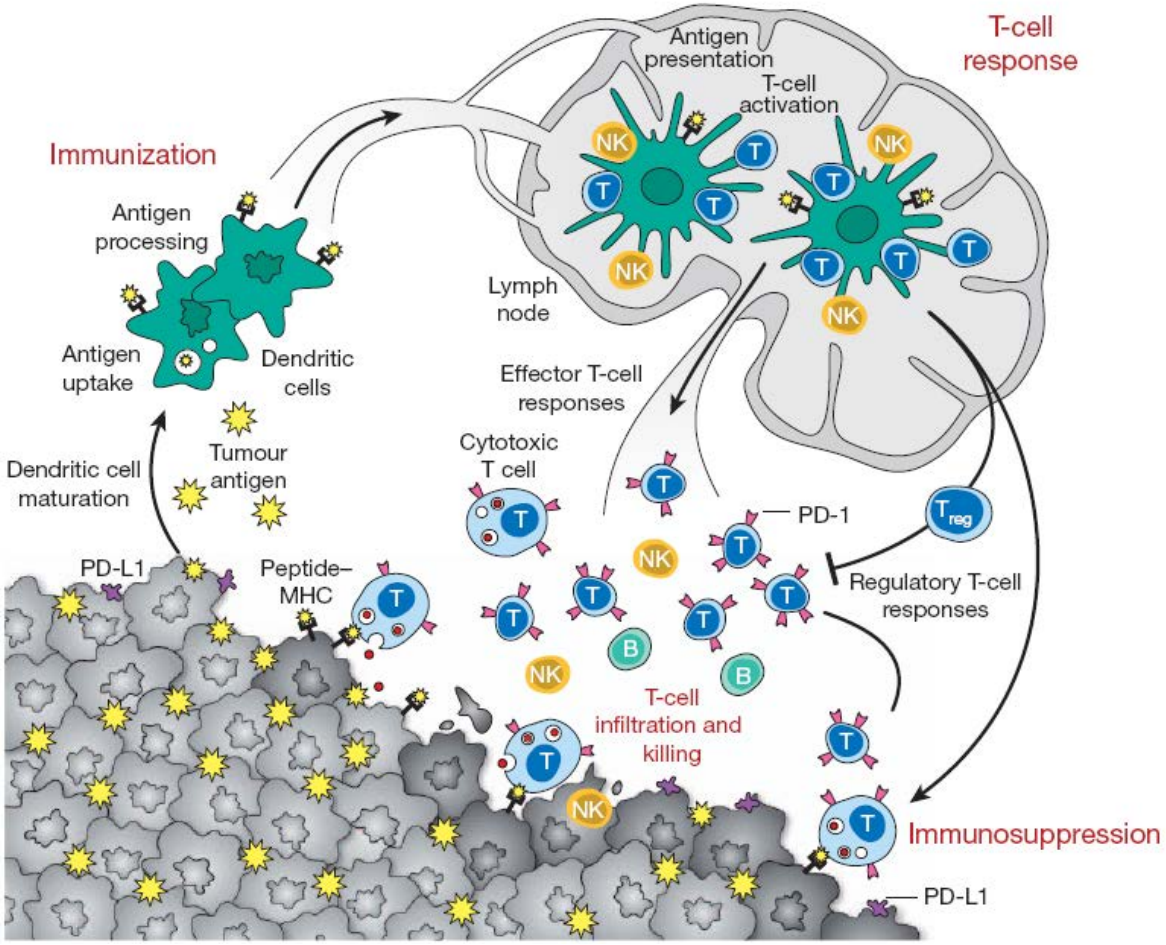
Rationnel

Concept d'immunosurveillance et d'immunoediting: les 3E



Rationnel

Intervention de l'immunité innée et acquise



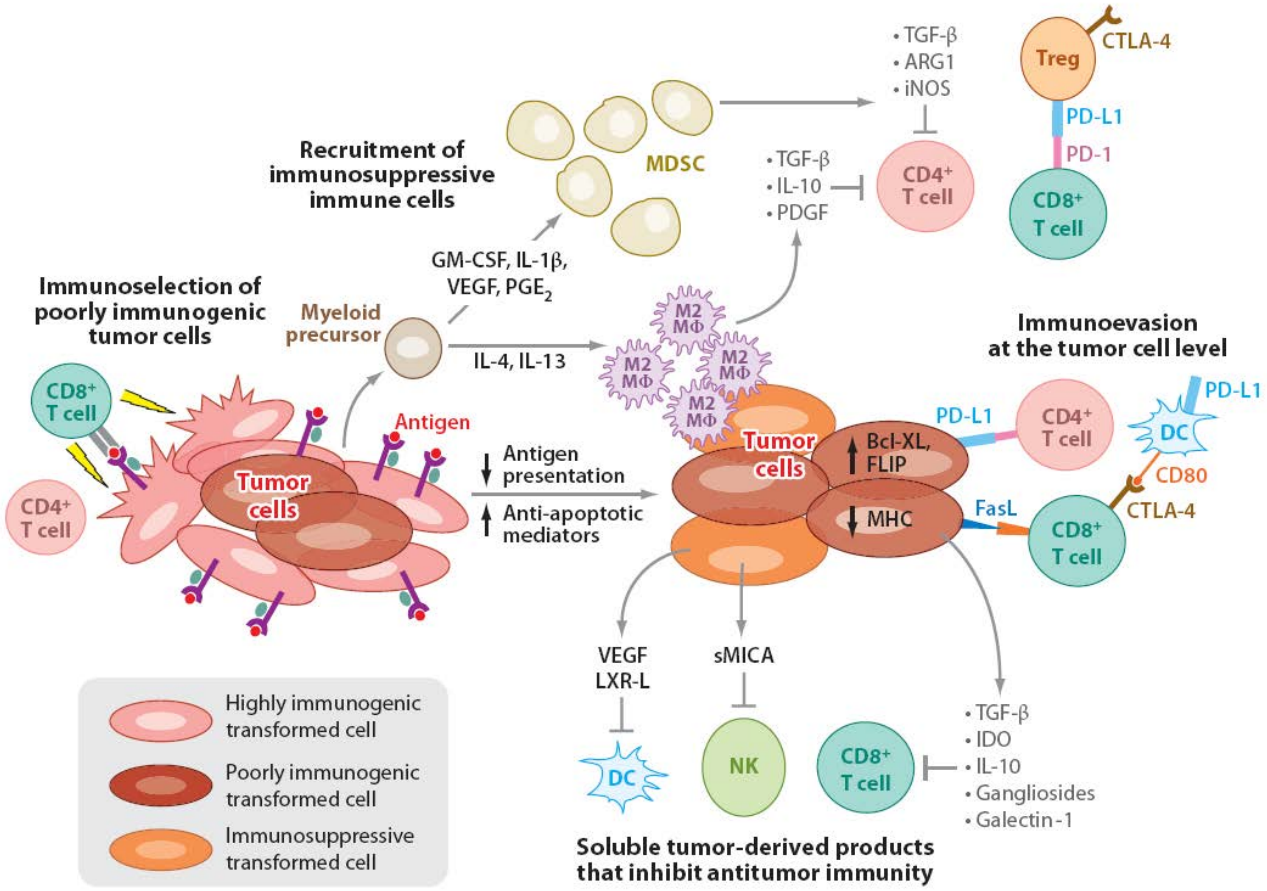
Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Mellman I, Nature 2011

GREPI

3es JOURNÉES du GREPI

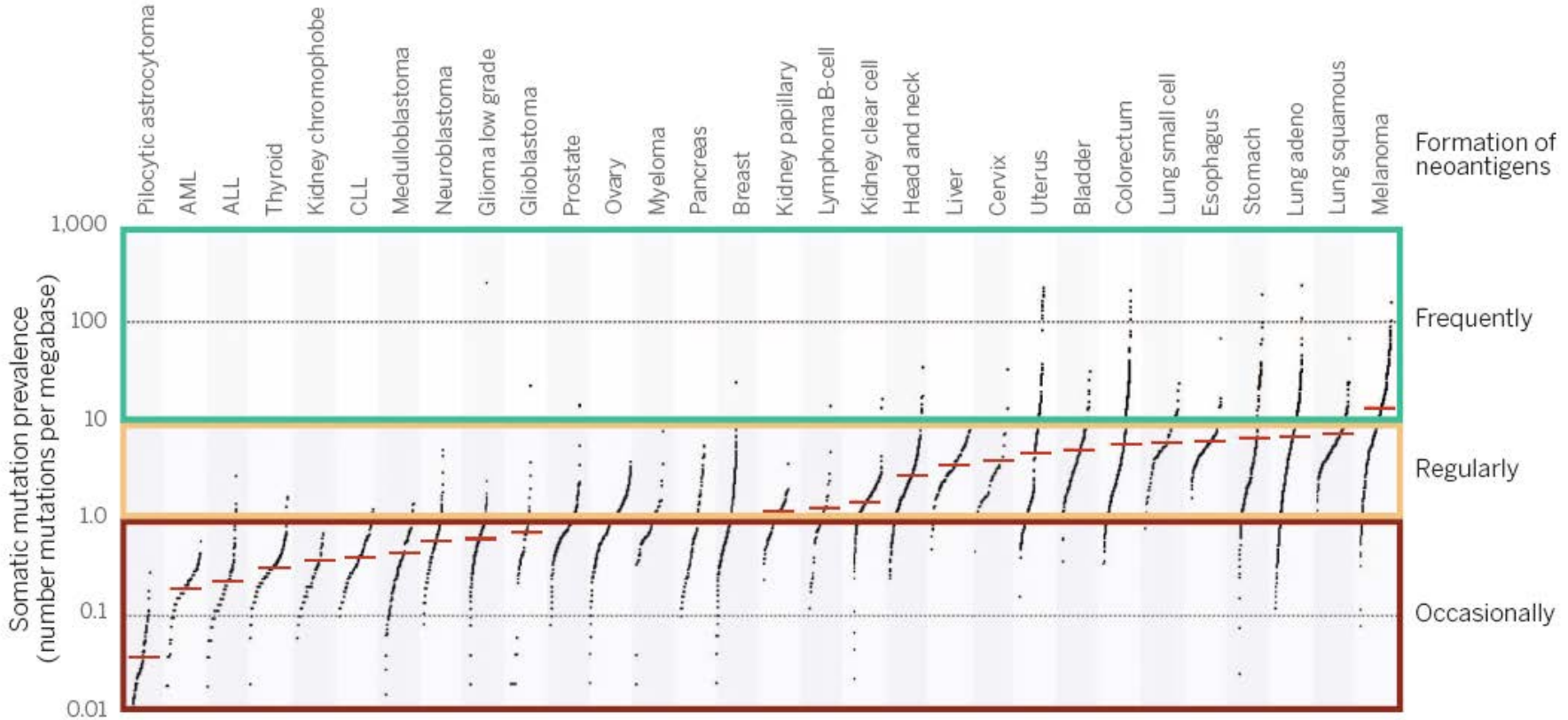
Principaux mécanismes d'échappement



Vesely M.D. et al Ann Rev Immunol 2011

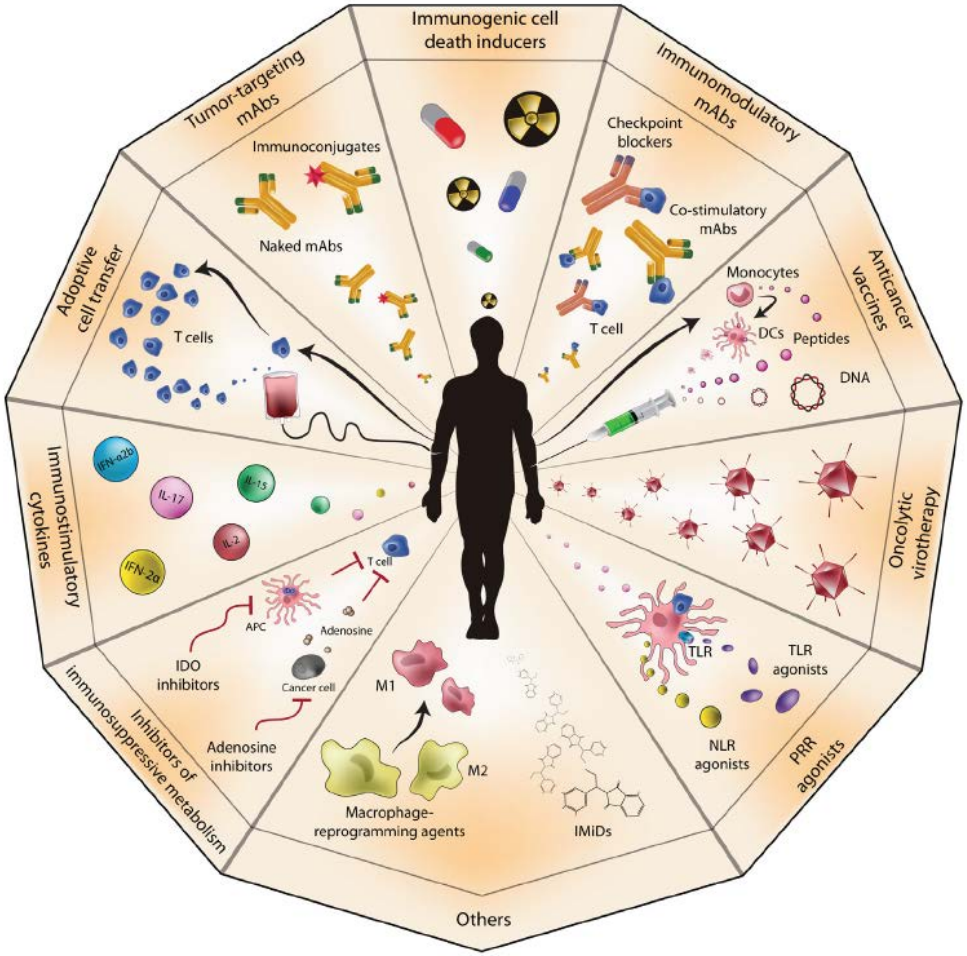
Rationnel

Théorie des Néoantigènes



Adapté de Lawrence et al, Nature 2013

Différents types d'immunothérapies dans le traitement du cancer



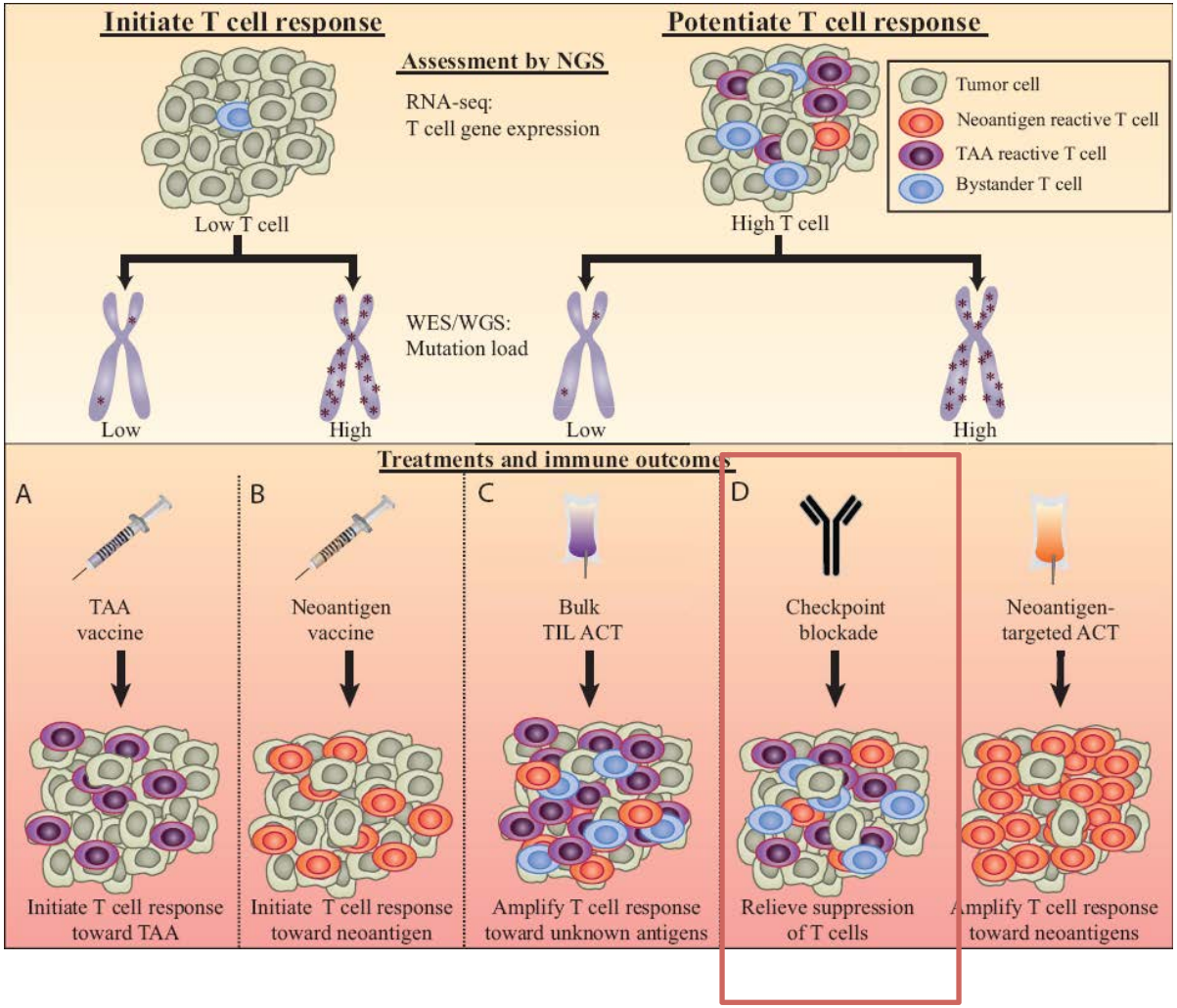
Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Galuzzi et al Oncotarget 2014

GREPI

3es JOURNÉES du GREPI

Différentes approches en immunothérapie ciblant les Ly T

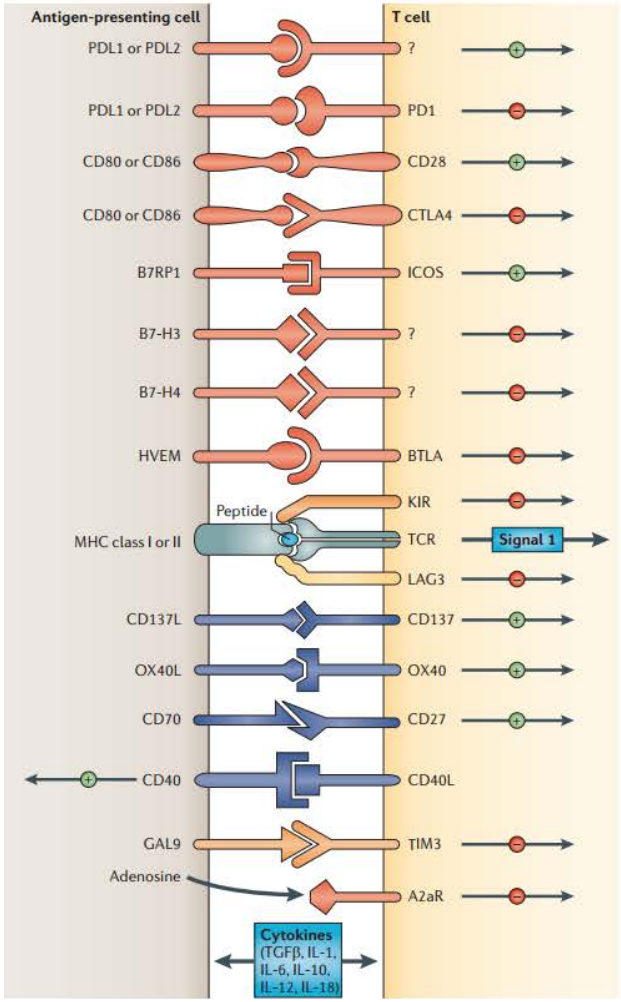


Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Martin SD et al Ann Oncol sous presse

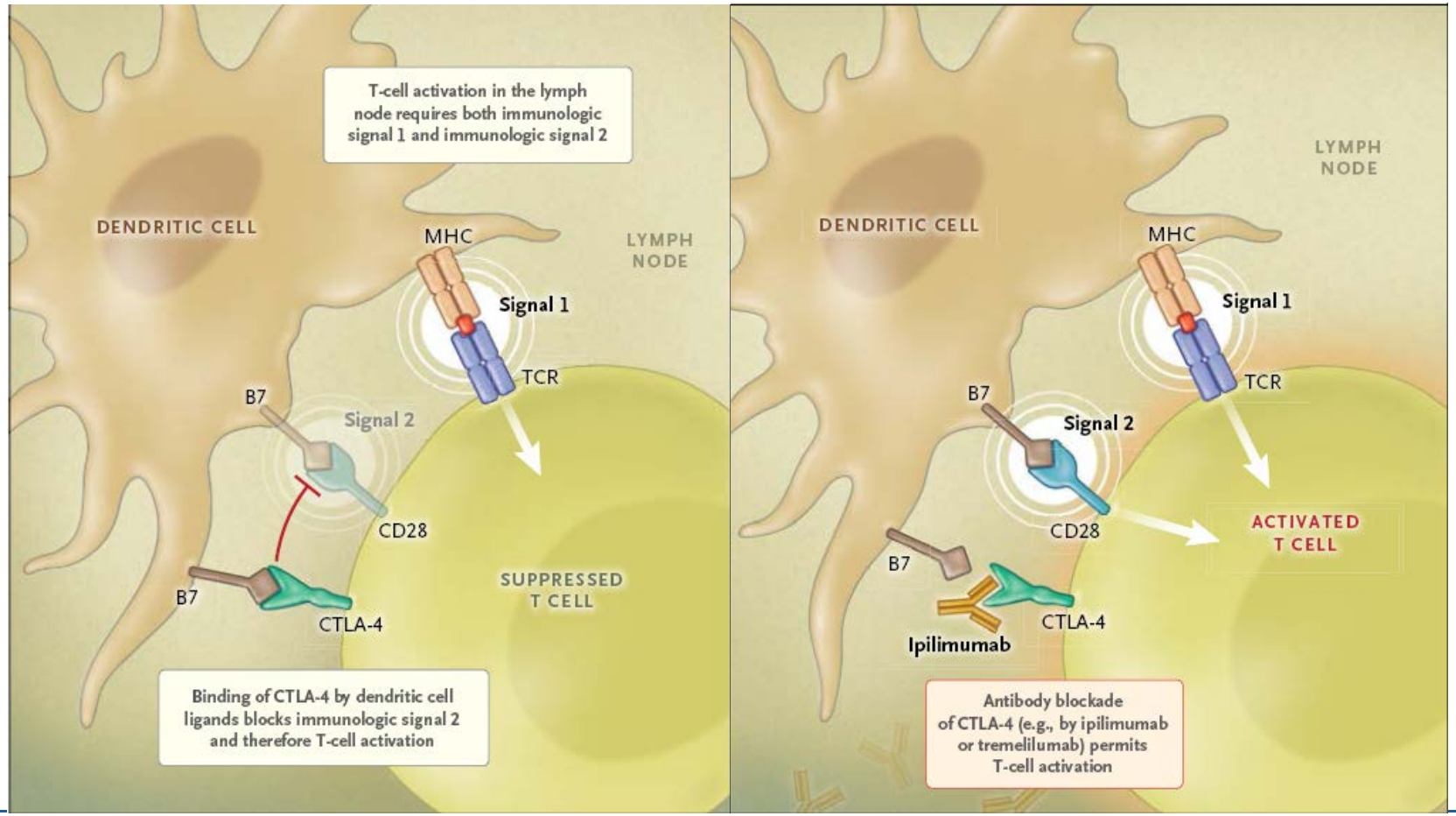
GREPI 3es JOURNÉES du GREPI

Activation des lymphocytes T: Synapse Immunologique



Pardoll et al Nat Rev Cancer 2012

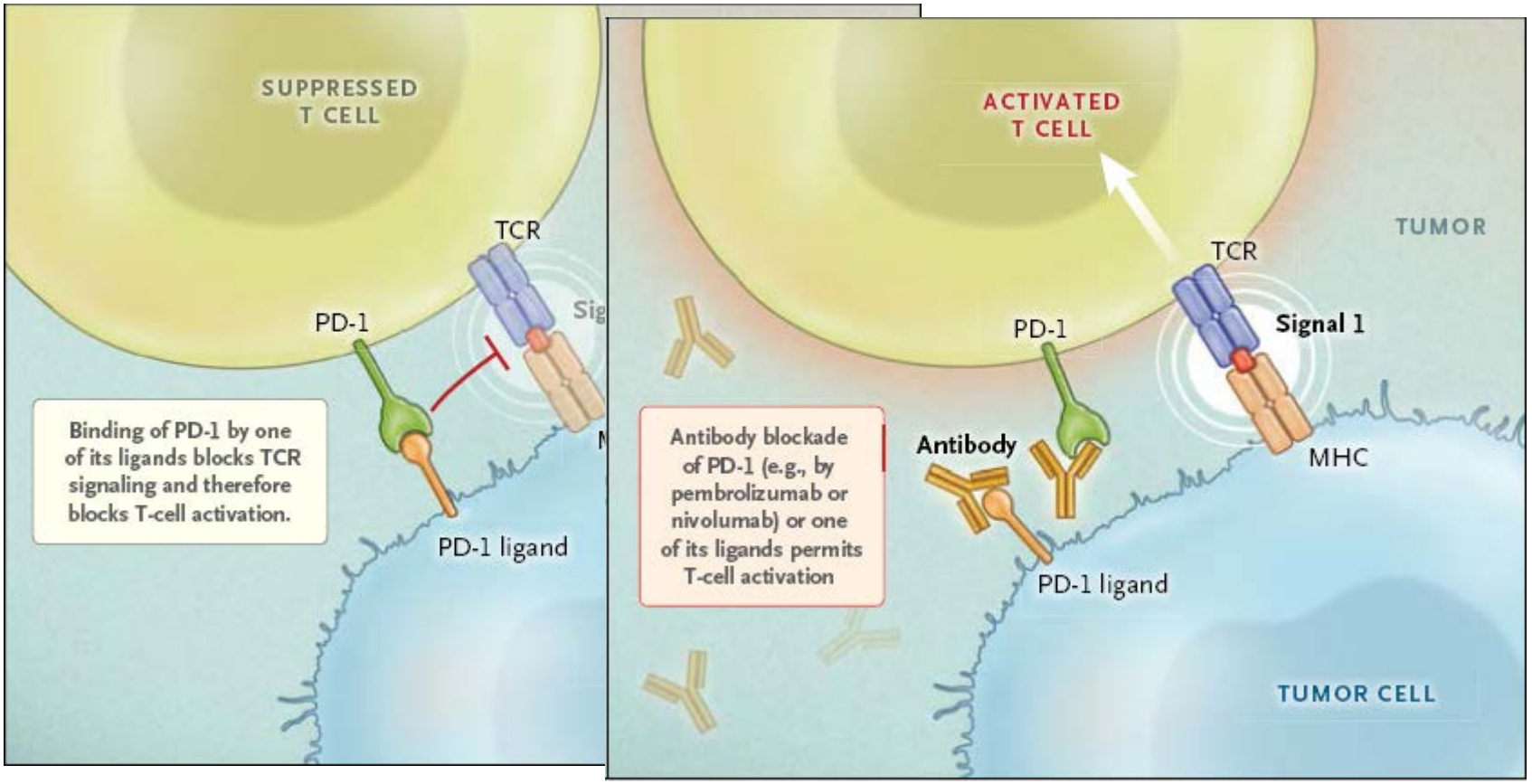
Activation des lymphocytes T: « priming »



Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Ribas A NEJM 2015

Activation des Lymphocytes T: phase effectrice



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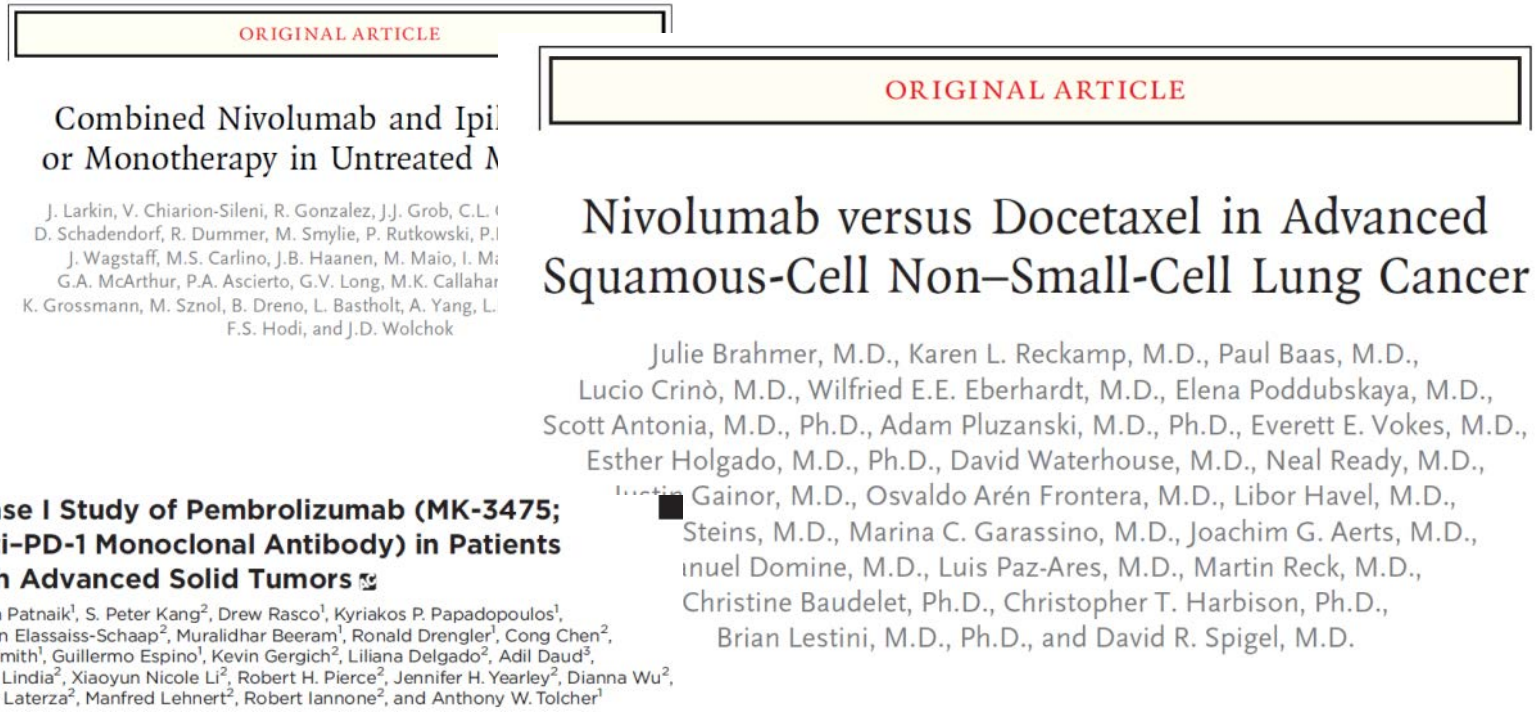
Ribas A NEJM 2015

Multiples études positives



ORIGINAL ARTICLE

Combined Nivolumab and Ipi
or Monotherapy in Untreated M

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L.
D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.
J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Ma
G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahar
K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.
F.S. Hodi, and J.D. Wolchok

ORIGINAL ARTICLE

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

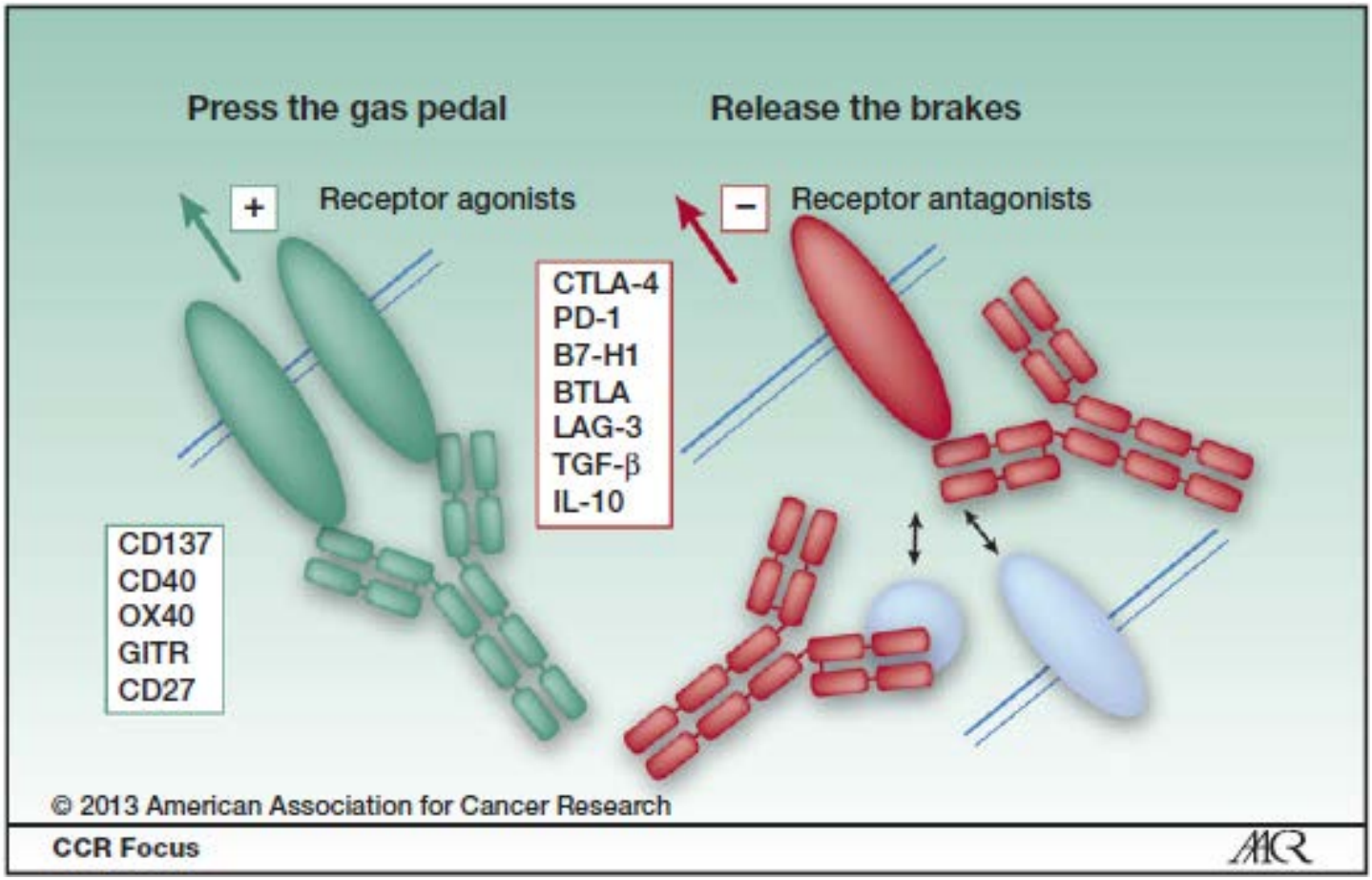
Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D.,
Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D.,
Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D.,
Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D.,
Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D.,
Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D.,
nuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D.,
Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D.,
Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

Phase I Study of Pembrolizumab (MK-3475; Anti–PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors

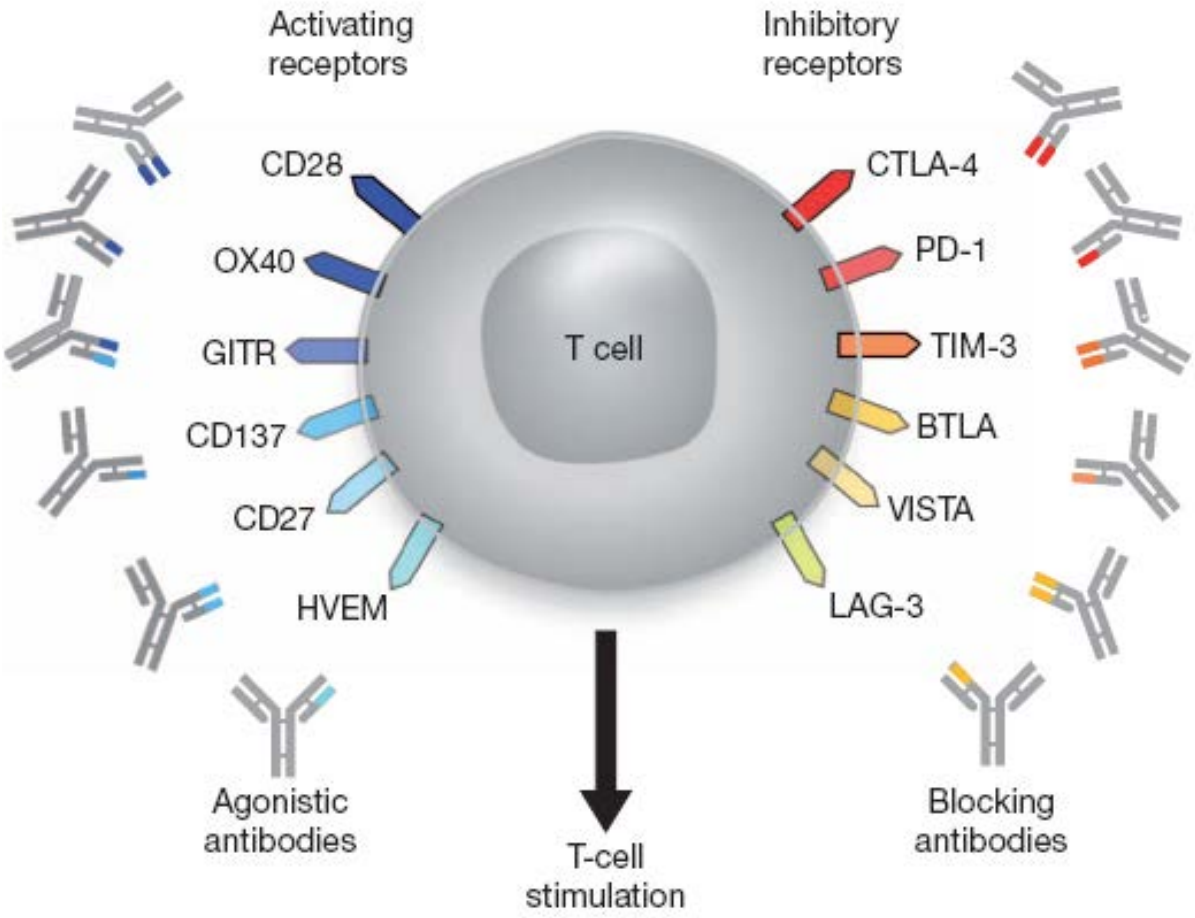
Amita Patnaik[1], S. Peter Kang[2], Drew Rasco[1], Kyriakos P. Papadopoulos[1], Jeroen Elassaiss-Schaap[2], Muralidhar Beeram[1], Ronald Drengler[1], Cong Chen[2], Lon Smith[1], Guillermo Espino[1], Kevin Gergich[2], Liliana Delgado[2], Adil Daud[3], Jill A. Lindia[2], Xiaoyun Nicole Li[2], Robert H. Pierce[2], Jennifer H. Yearley[2], Dianna Wu[2], Omar Laterza[2], Manfred Lehnert[2], Robert Iannone[2], and Anthony W. Tolcher[1]

Efficacité dans de multiples types tumoraux;
Cancer de la vessie, rein, NSLC, SCLC, Cancer MSI-High, Maladie de Hodgkin
Testés en pratique dans tous les types tumoraux

Stratégies d'activation des Ly T effecteurs



Agonistes sur les activateurs
Anticorps bloquants sur les inhibiteurs



Hôpitaux Universitaires SAINT-LOUIS LARIBOISIÈRE FERNAND-WIDAL

Mellman I, Nature 2011

Molécules actuellement en développement

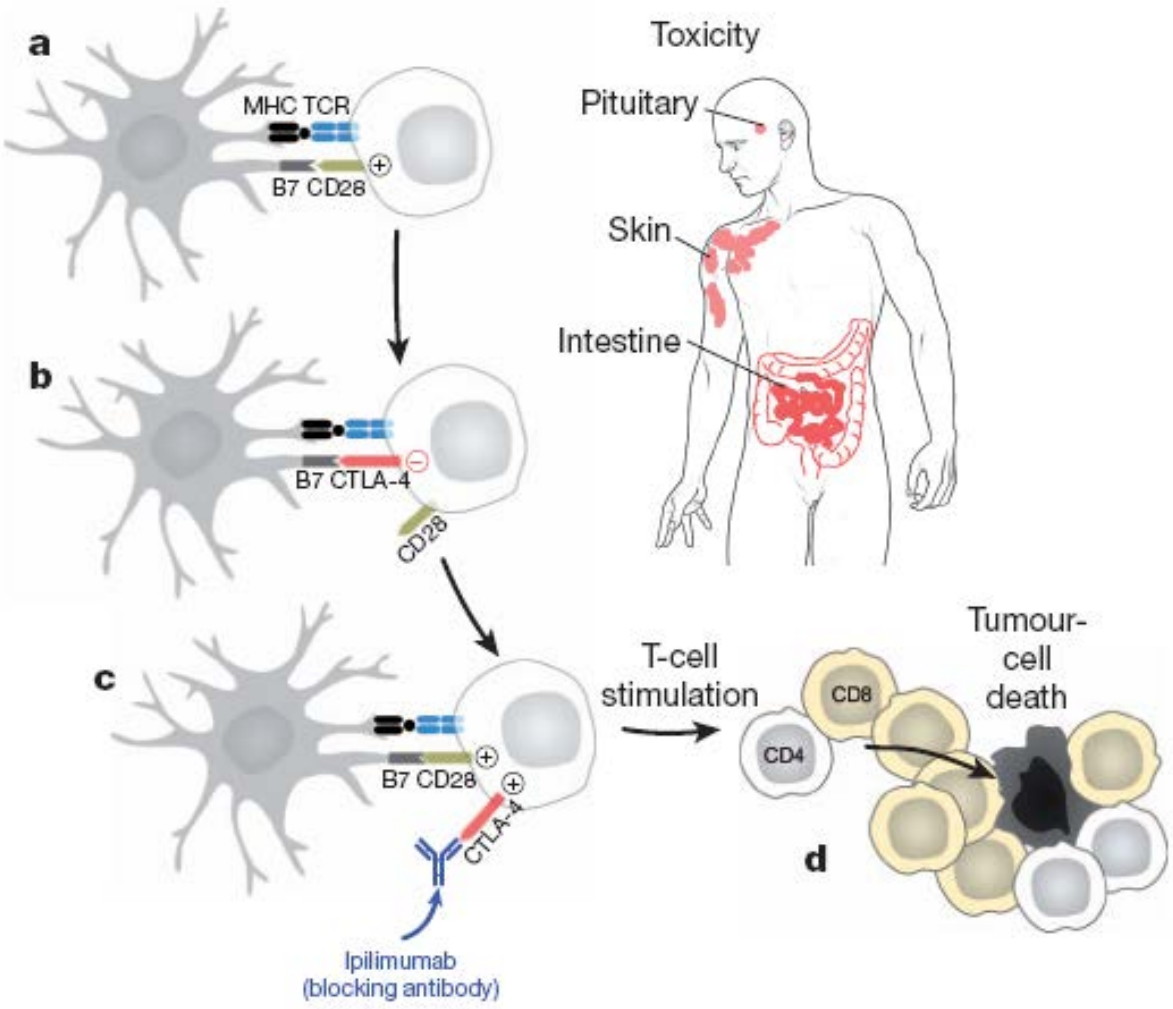
Table 1. Drugs in Clinical Development that Block PD-1 or PD-L1

Target	Drug Name	Other Names	Source	Isotype and Characteristics	Clinical Testing Phase
PD-1	MEDI0680	AMP-514	MedImmune/ AstraZeneca	information not available	phase I
	nivolumab	Opdivo, BMS-936558, MDX-1106, ONO-4538	Bristol-Myers Squibb, Ono Pharmaceuticals	fully human IgG4[a]	approved, treatment-refractory unresectable melanoma (Japan, United States) and squamous NSCLC (United States)
	pembrolizumab	Keytruda, MK-3475, lambrolizumab	Merck	humanized IgG4	approved, treatment-refractory unresectable melanoma (United States)
	pidilizumab	CT-011	CureTech	humanized IgG1	phase I-II
PD-L1	BMS-936559	MDX-1105	Bristol-Myers Squibb	fully human IgG4[a]	phase I
	MEDI4736	none	MedImmune/ AstraZeneca	Fc-modified human IgG1[b]	phase I-III
	MPDL3280A	RG7446	Genentech/ Roche	Fc-modified human IgG1[b]	phase I-III
	MSB0010718C	none	EMD Serono	fully human IgG1[a]	phase I-II

[a]Fully human mAbs were produced in genetically engineered mice.
[b]Fc-modified mAbs were engineered to abrogate ADCC and complement-dependent cytotoxicity (CDC).

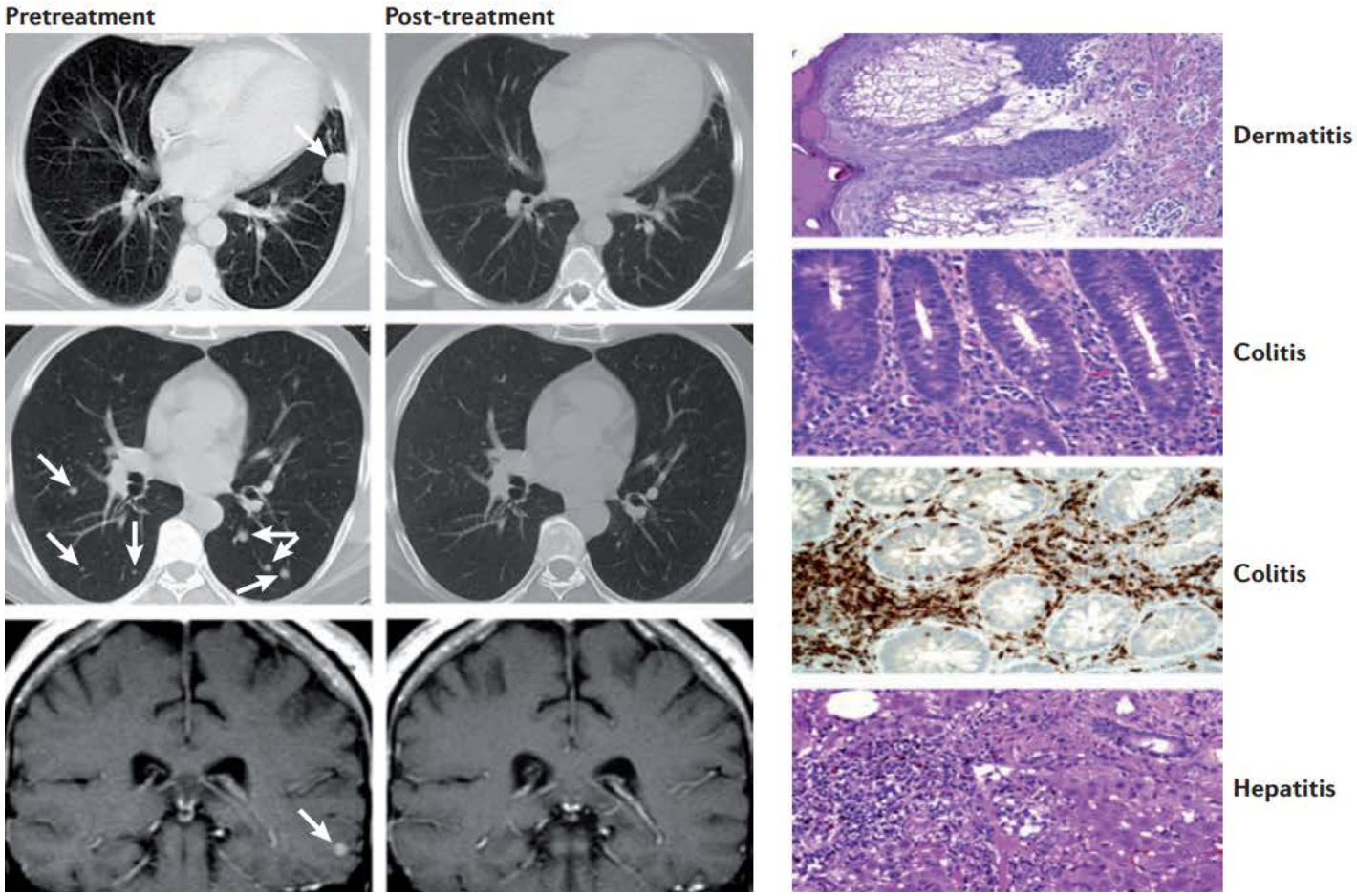
Topalian et al, Cancer cell 2015

Toxicités des « check-point inhibiteurs »



Mellman I et , Nature 2011

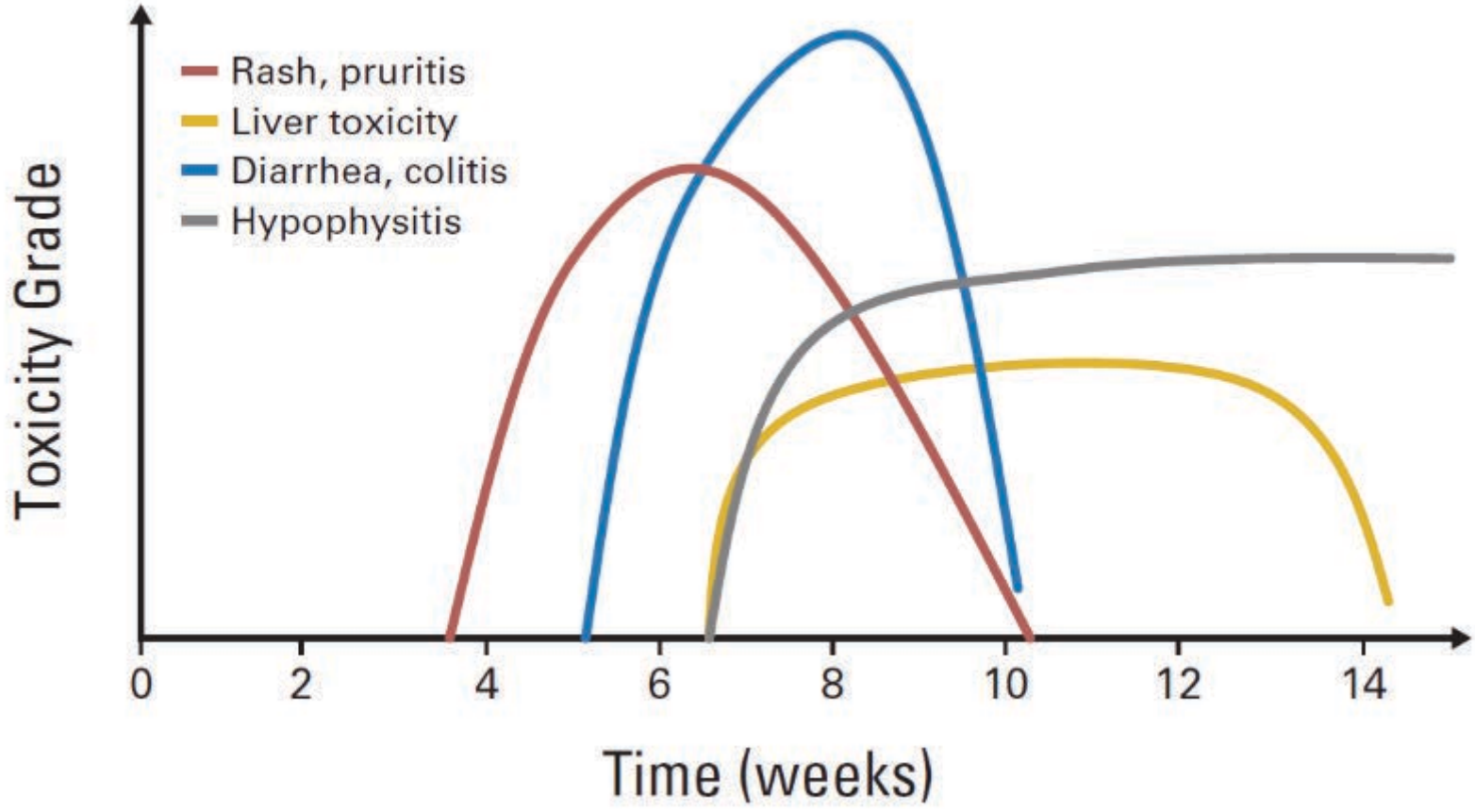
Toxicités des « check-point inhibiteurs »



Toxicités IPILIMUMAB

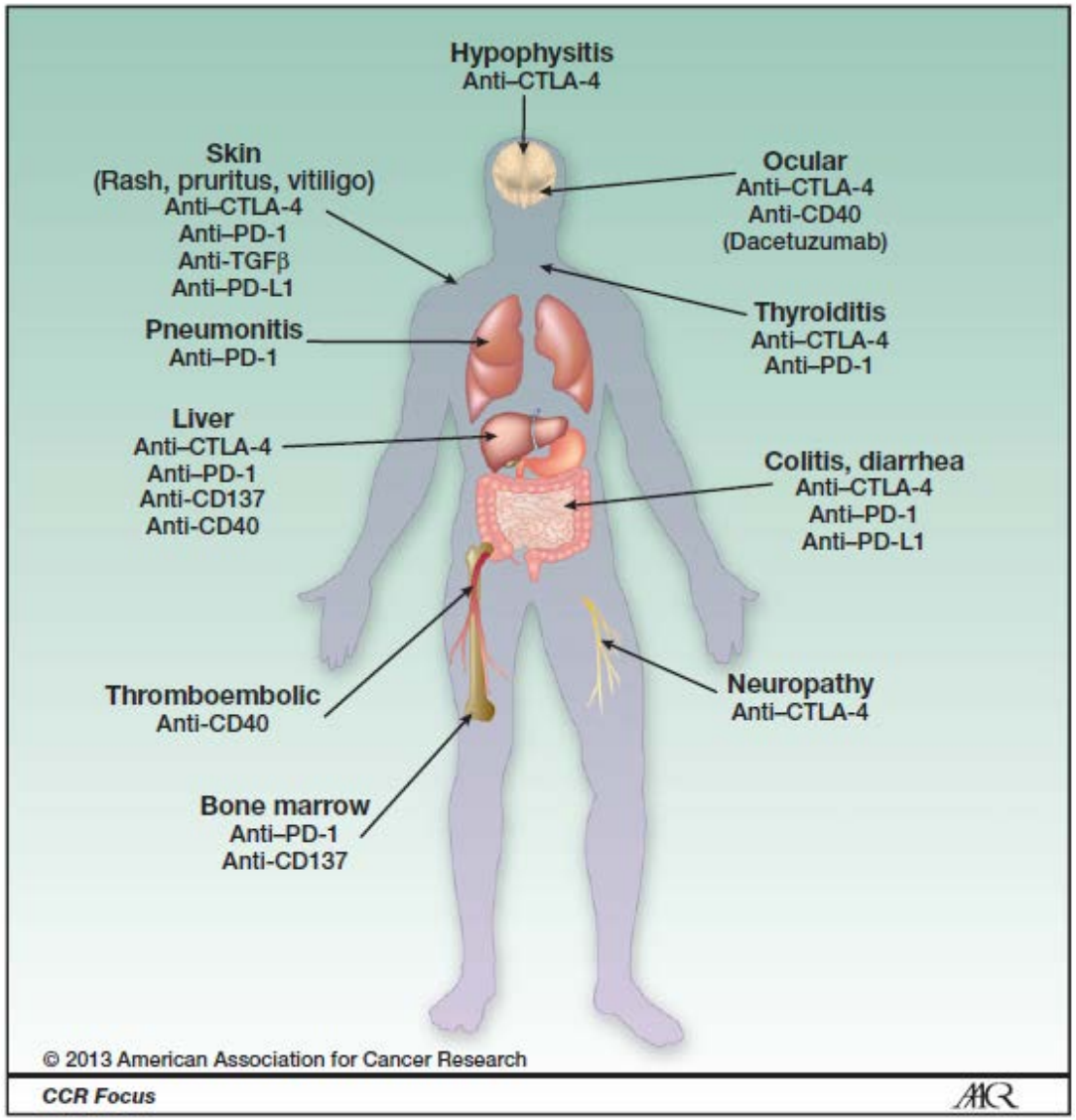
Pardoll et al , Nature Rev Cancer 2012

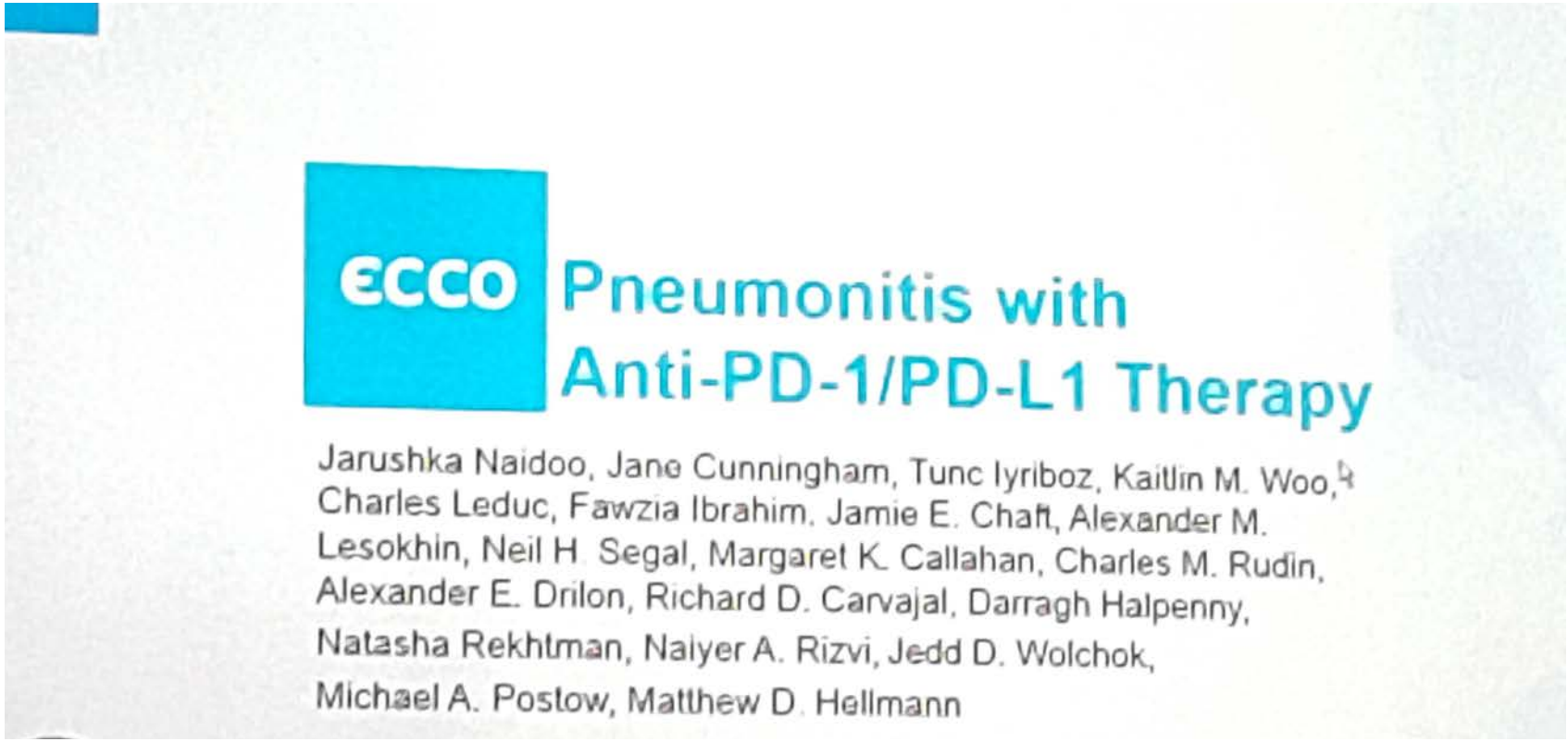
Cinétique de survenue des effets secondaires immuns (IrAEs)



Ipilmumab atteinte pulmonaires de type pseudo-sarcoidosiques

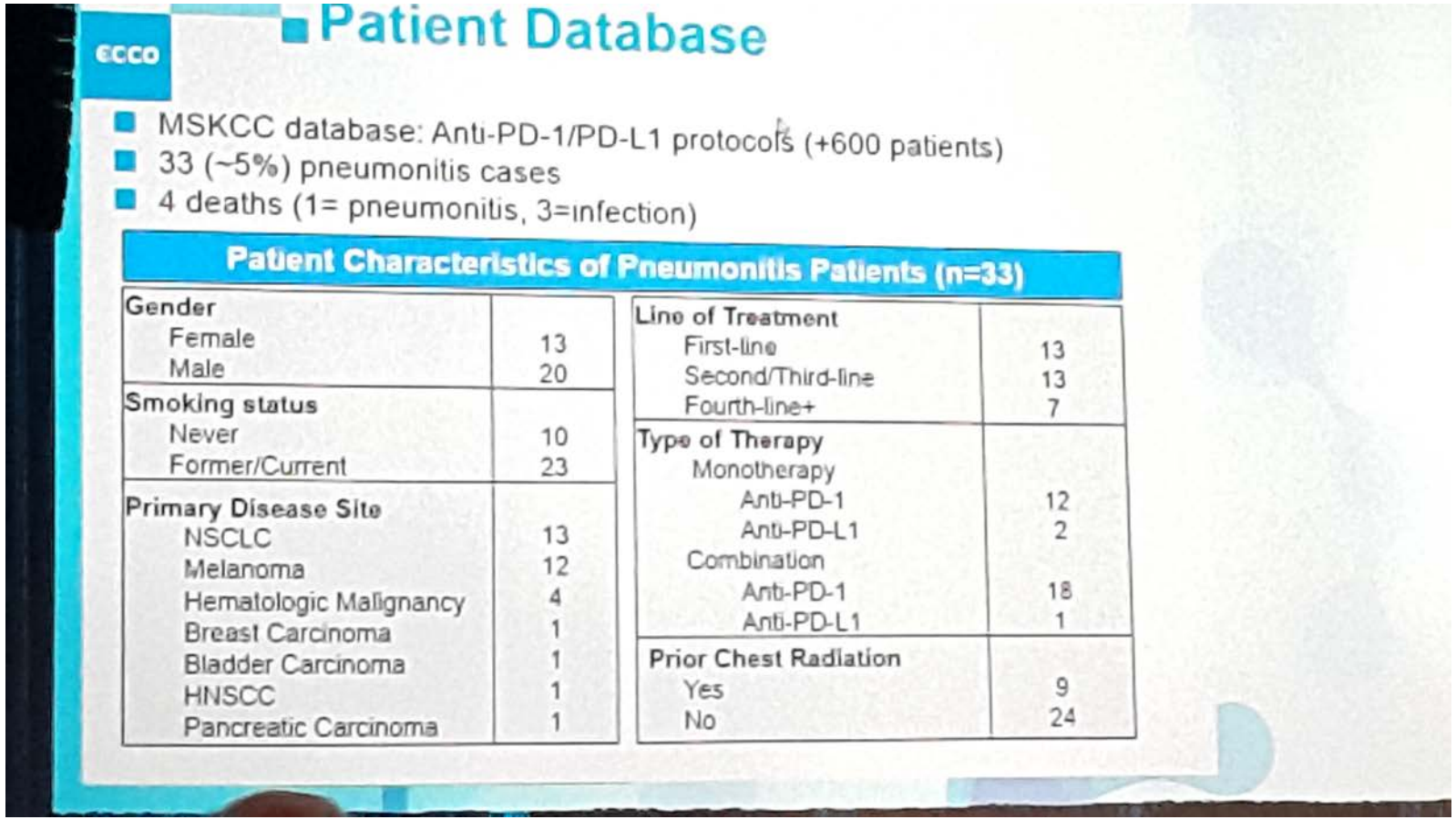
Toxicités de classe: Maladies auto-immunes





Naidoo J et al abstract ESMO2015

Plus de pneumopathies dans le cancer du poumon



ecco

Patient Database

- MSKCC database: Anti-PD-1/PD-L1 protocols (+600 patients)
- 33 (~5%) pneumonitis cases
- 4 deaths (1= pneumonitis, 3=infection)

Patient Characteristics of Pneumonitis Patients (n=33)

Gender	
Female	13
Male	20
Smoking status	
Never	10
Former/Current	23
Primary Disease Site	
NSCLC	13
Melanoma	12
Hematologic Malignancy	4
Breast Carcinoma	1
Bladder Carcinoma	1
HNSCC	1
Pancreatic Carcinoma	1

Line of Treatment	
First-line	13
Second/Third-line	13
Fourth-line+	7
Type of Therapy	
Monotherapy	
Anti-PD-1	12
Anti-PD-L1	2
Combination	
Anti-PD-1	18
Anti-PD-L1	1
Prior Chest Radiation	
Yes	9
No	24

Naidoo J et al abstract ESMO2015

Anomalies Radiologiques

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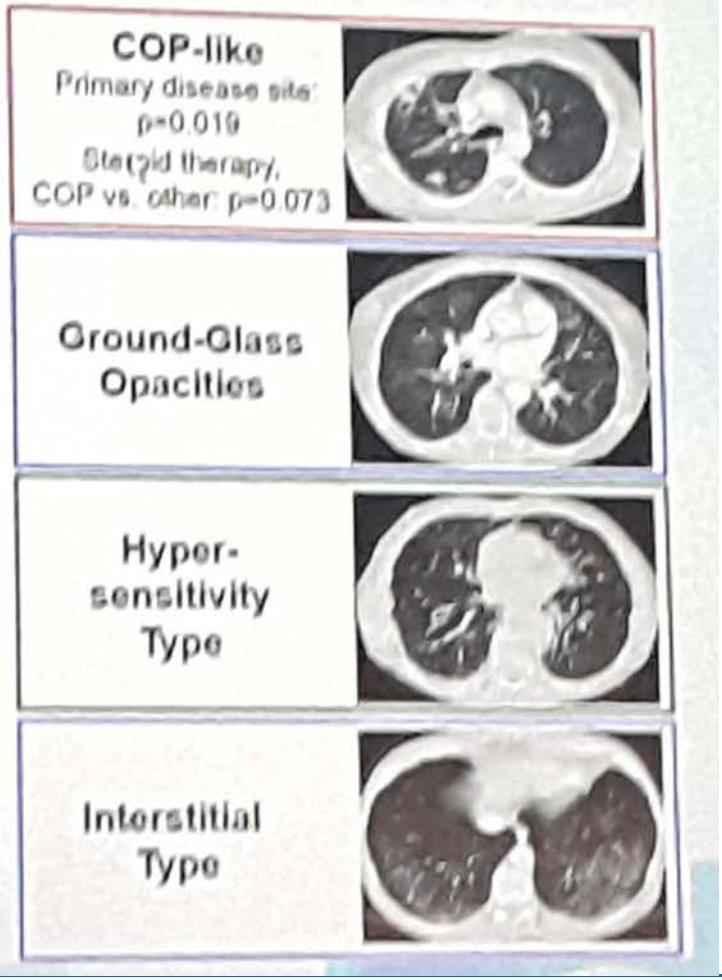
Radiologic Features

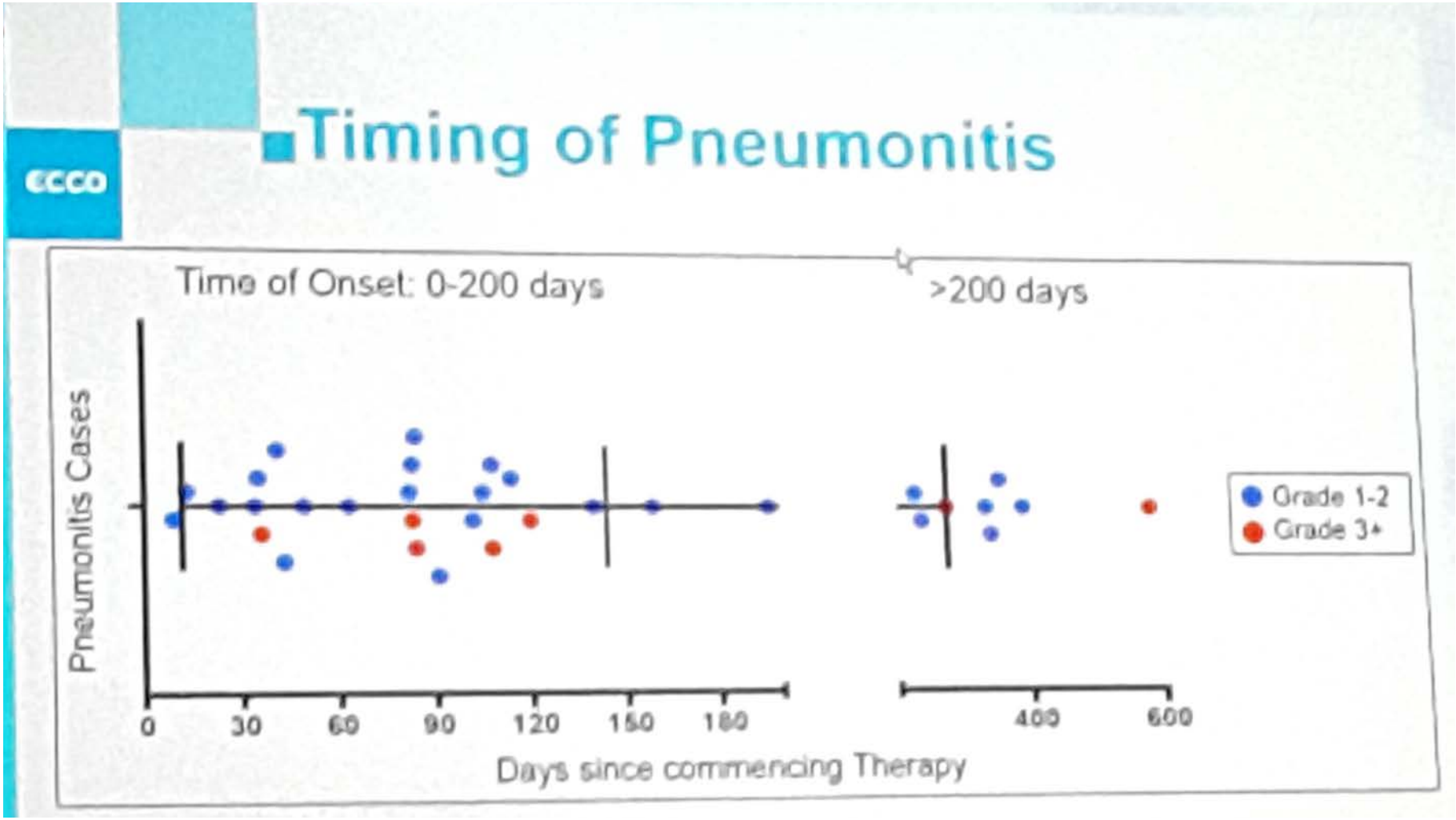
- 5 subtypes of pneumonitis identified[1]

Subtype	Description
COP-like* (n=7)	• Discrete areas of consolidation • Peripheral distribution
Ground Glass Opacities (n=12)	• Discrete areas attenuation • Preserved bronchovascular markings
Hypersensitivity Type (n=6)	• 'Tree-in-bud' micronodularity • Centrilobular distribution
Interstitial Type (n=4)	• Interlobular septal thickening • Subpleural reticulations • Increased interstitial markings
Pneumonitis NOS (n=4)	• Does not clearly fit into other subtypes

*Cryptogenic organizing pneumonia **Not otherwise specified

et al. Eur J Radiol 2015





Naidoo J et al abstract ESMO2015

Pathologic Features

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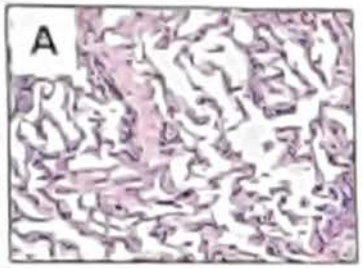
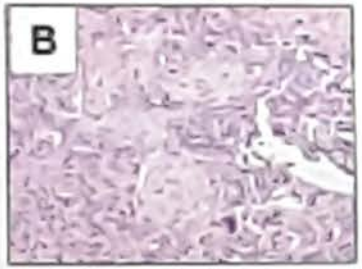
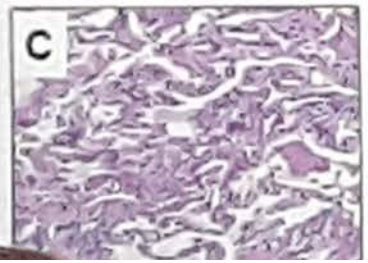
- 18/33 patients had bronchoscopy
- 7 patients had lung biopsy findings



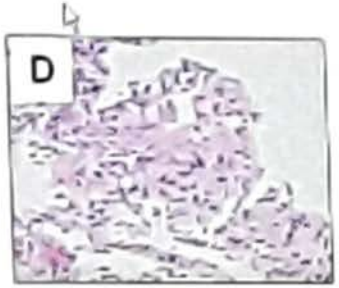
Cellular interstitial Pneumonitis (n=4)



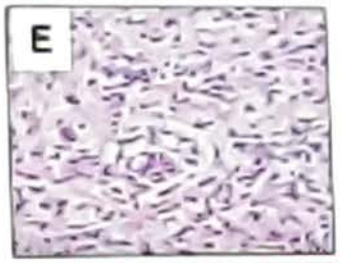
Organizing Pneumonia (n=2)



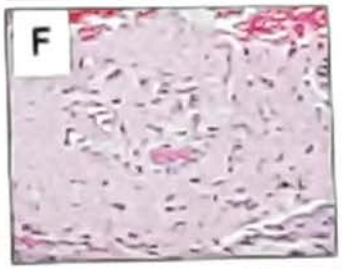
Diffuse Alveolar Damage (n=1)



Granulomas (n=2)



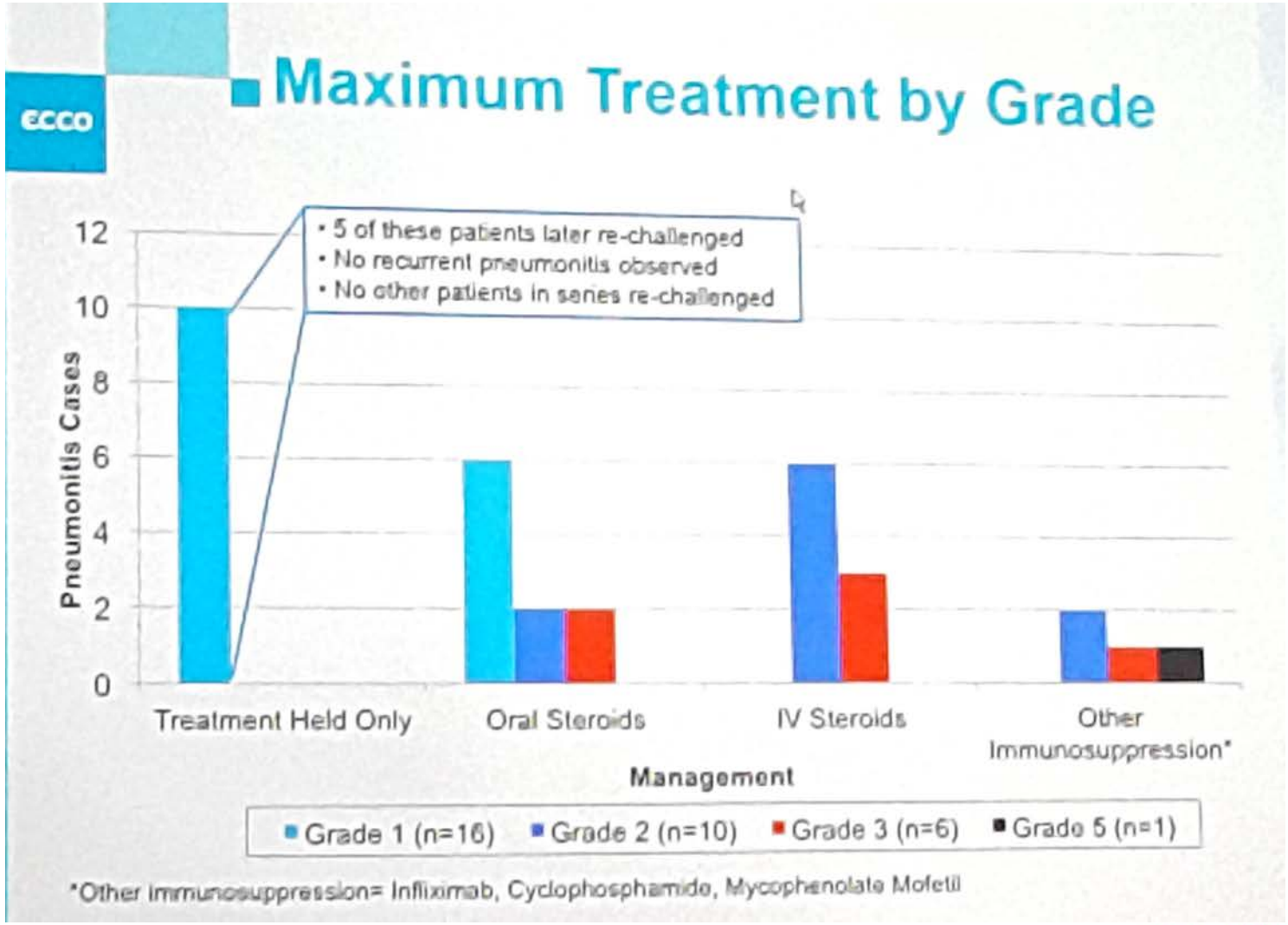
Eosinophils (n=3)



Vascular recanalization (n=1)

Naidoo J et al abstract ESMO2015

80 % de grade 1-2, 20% de grade 3

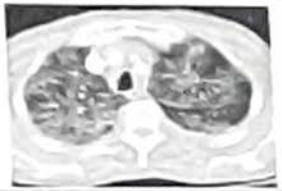


Infection and Immunosuppression

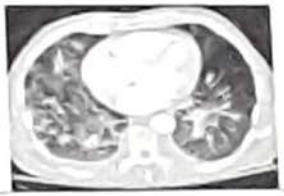
ECCO

- 3 deaths from infection, in the context of immunosuppression

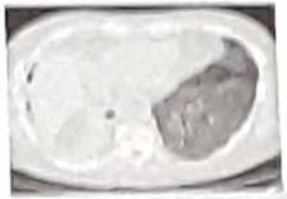
Case 1:
64 year old male, Melanoma
4 doses anti-PD-1+anti-CTLA-4 therapy (1st-line)
2 months of oral, then IV steroids
Died Pseudomonas Infection



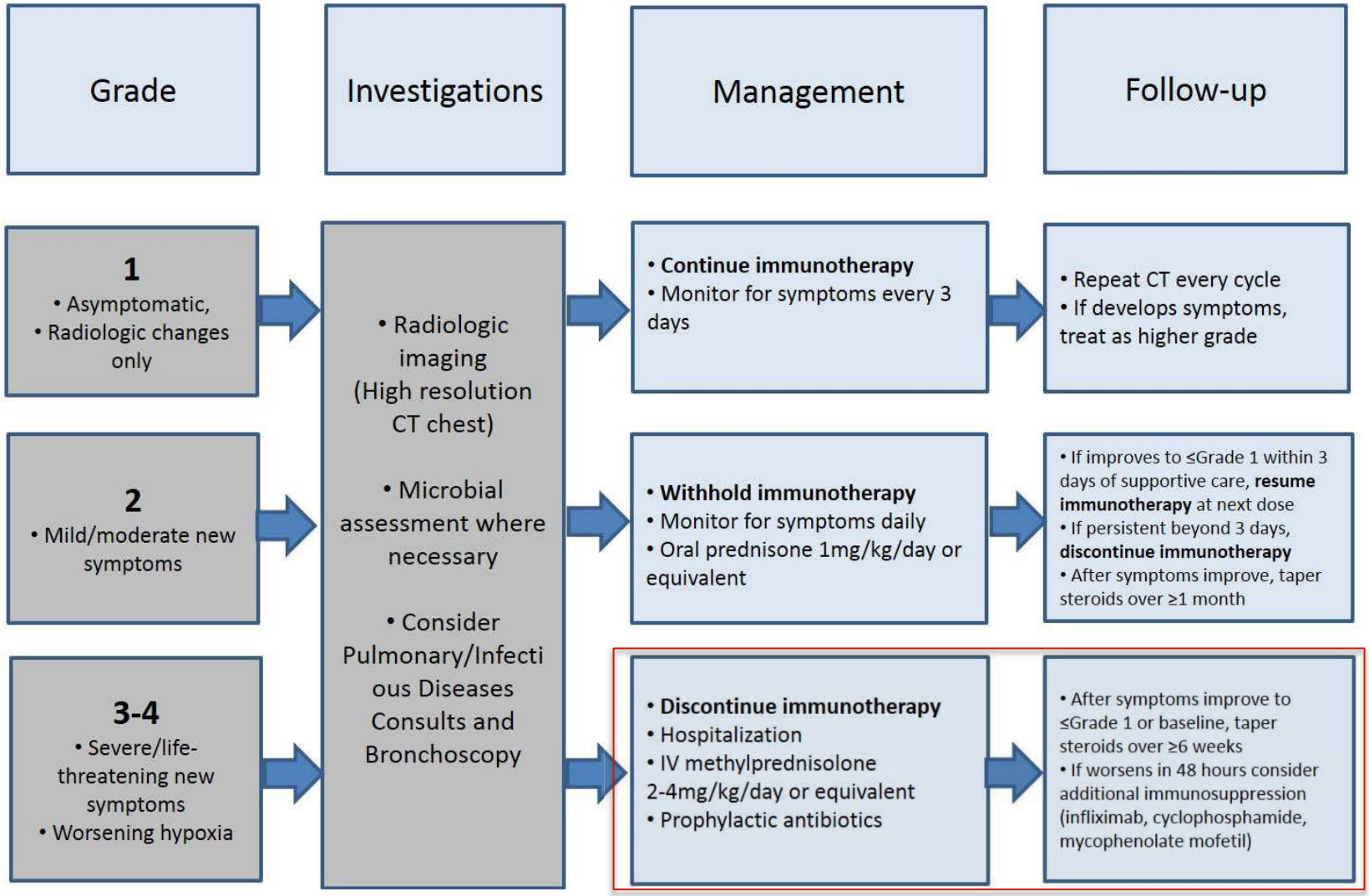
Case 2:
78 year old male, NSCLC
2 doses anti-PD-1 therapy alone (2nd-line)
Acutely dyspneic, IV steroids + Infliximab
Died from HSV-1 sepsis



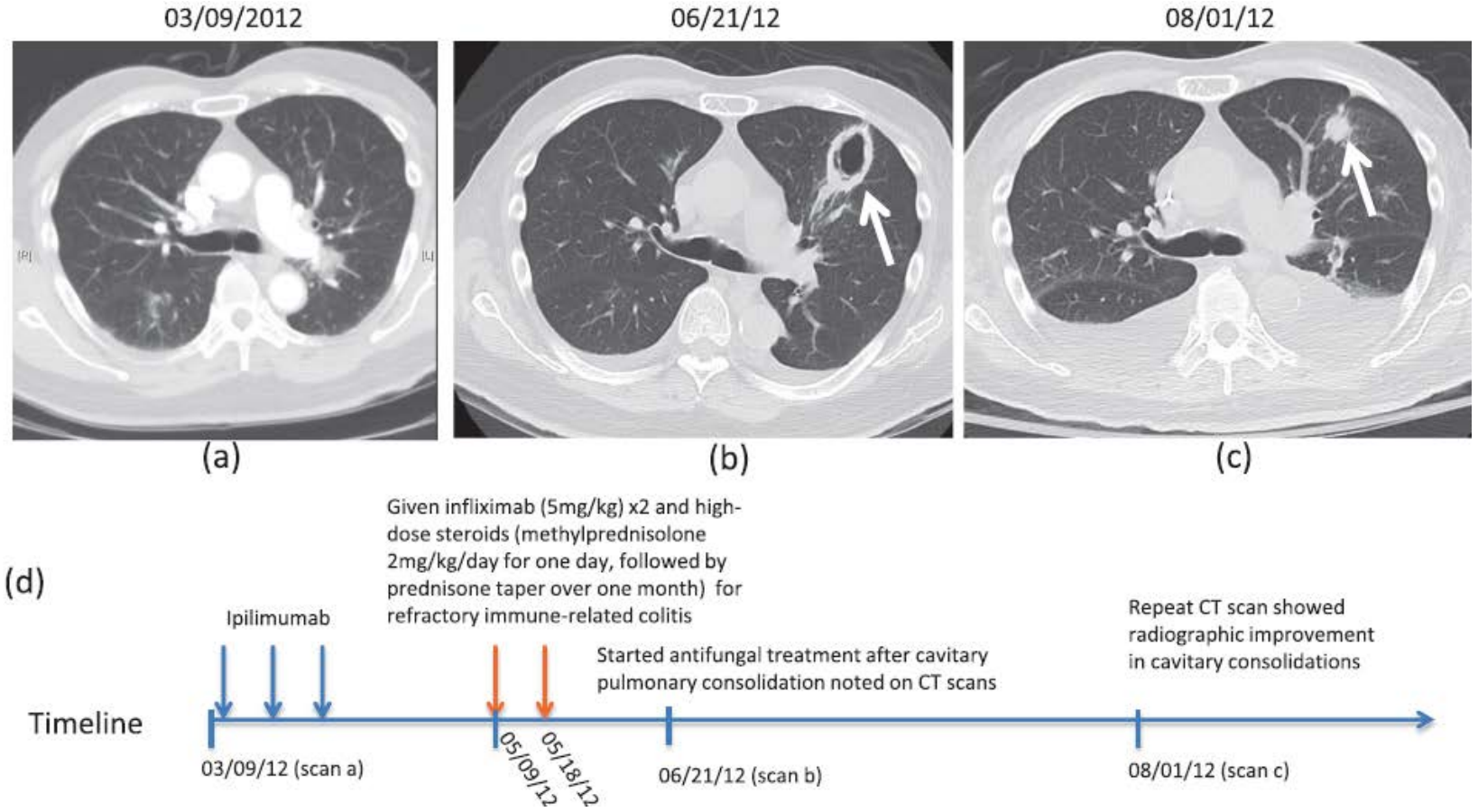
Case 3:
52 year old male, NSCLC
38 doses anti-PD-1 therapy alone (2nd-line)
Oral steroids (6 months) Infliximab, Cyclophosphamide
Died of angio-invasive mucormycosis



Algorithme décisionnel: atteinte pulmonaire et check-point inhibiteurs



Aspergillose sous corticothérapie et infliximab



Kyi et al. Journal for ImmunoTherapy of Cancer 2014

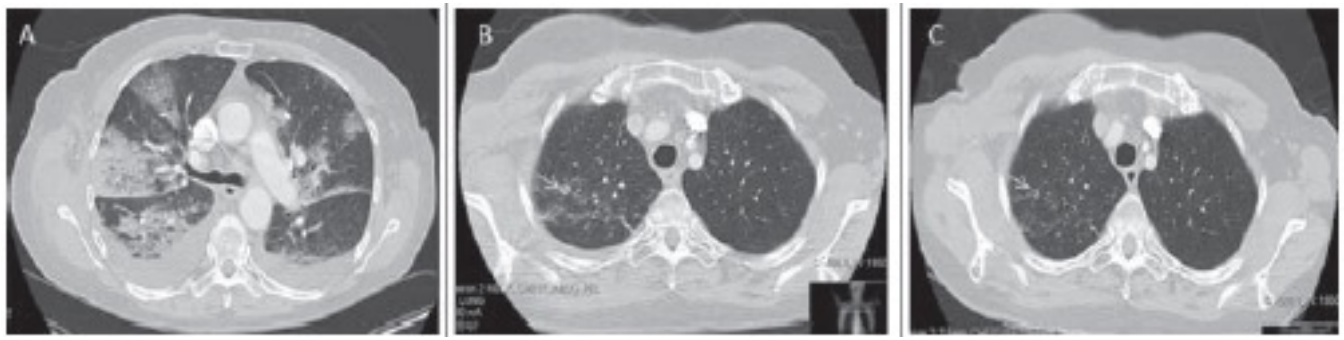
Sous corticothérapie et infliximab

- Autres cas décris
  - Gangrène de Fournier
  - « Virémie à CMV »

Kyi et al. Journal for ImmunoTherapy of Cancer 2014

Pneumocystose

- 2 cas/150 patients traités par Ipilimumab pour mélanome métastatique et sous corticoides + infliximab.
- Un des patients avait par ailleurs une LLC



Arriola et al, Oncoimmunology 2015

Immunosuppréssion liée à la prise en charge de IrAEs

- Corticoides
- Infliximab
- Cyclophosphamide
- Mycophénolate mofetil/Azathioprine
- Autres exceptionnellement discutés

- Indication à une prophylaxie?
  - Dès lors qu'il y a nécessité d'introduire des traitements par corticoides ou immunosuppresseurs?
  - Discuté, actuellement pas de recommandations en ce sens
  - Essais de combinaison en cours : IDR tuberculine demandée

Moins de risques infectieux que pour les chimiothérapies classiques

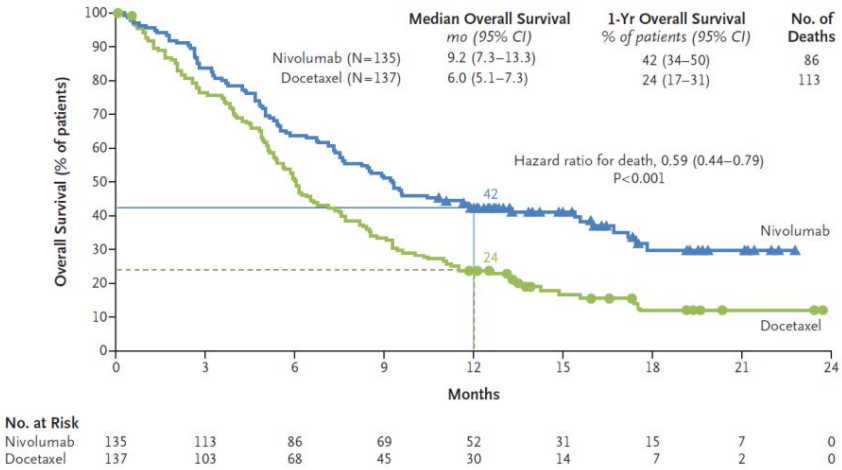


Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N=131)		Docetaxel (N=129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

Evolution vers de combinaisons

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

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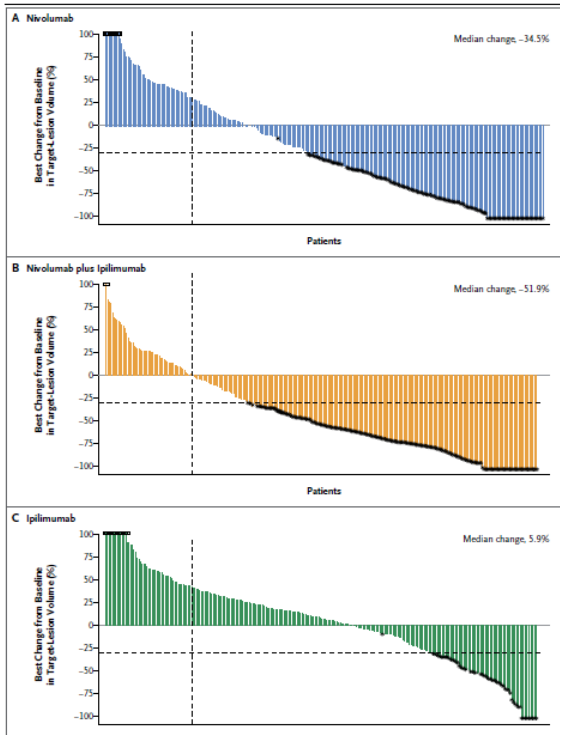
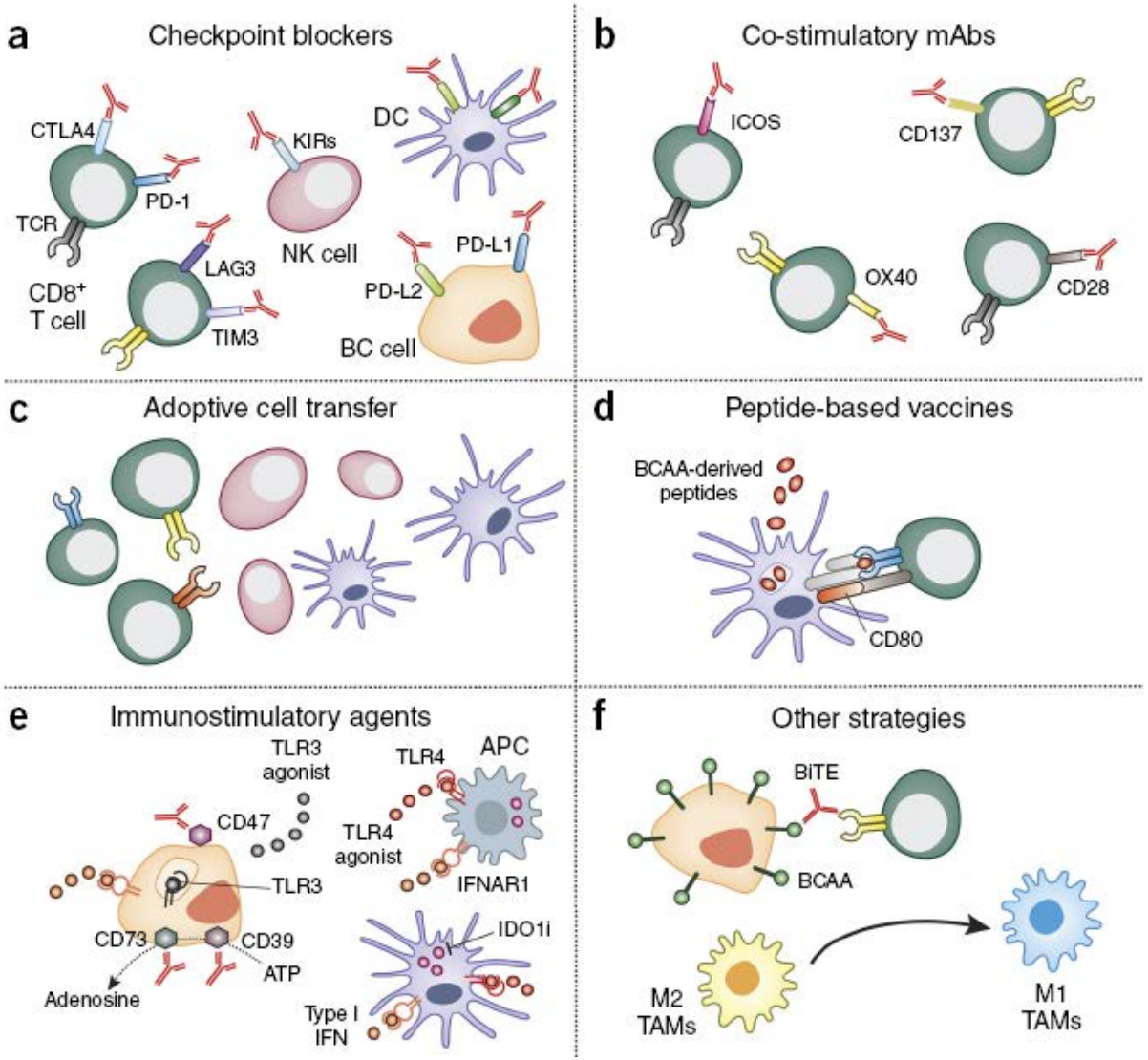


Evolution vers de combinaisons

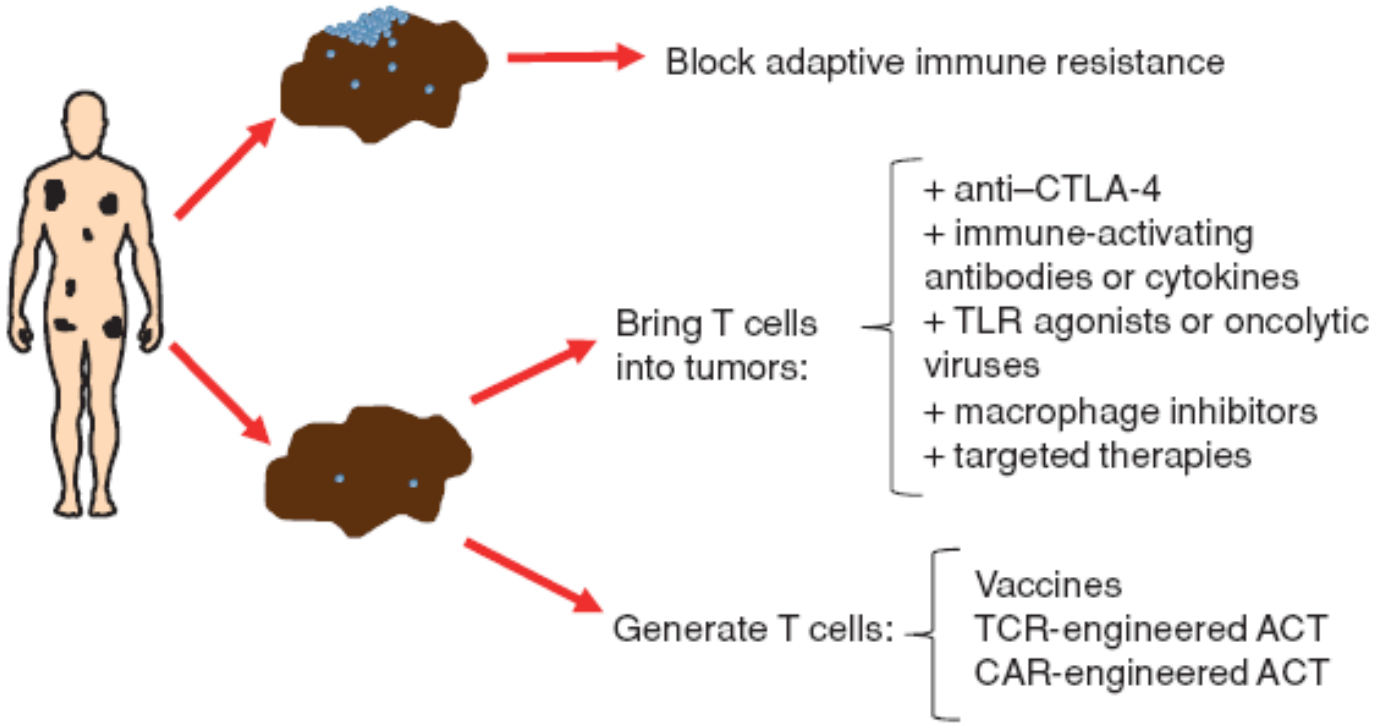
Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine amino-transferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate amino-transferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

Ce qui arrive et qui pourrait augmenter le risque



Kroemer et al, Nat Med 2015

Stratégies pour contourner les mécanismes de résistance à l'immunité adaptative



Les Vaccins

invectys
THERAPEUTIC CANCER VACCINE

INV_18301_INVAC-1
Anti-Cancer hTERT DNA Immunotherapy

A FIRST-IN-HUMAN PHASE I STUDY OF INVAC-1 AS A SINGLE AGENT IN PATIENTS WITH ADVANCED CANCER

Mise en place du 14 novembre 2014 – Hôpital Saint-Louis

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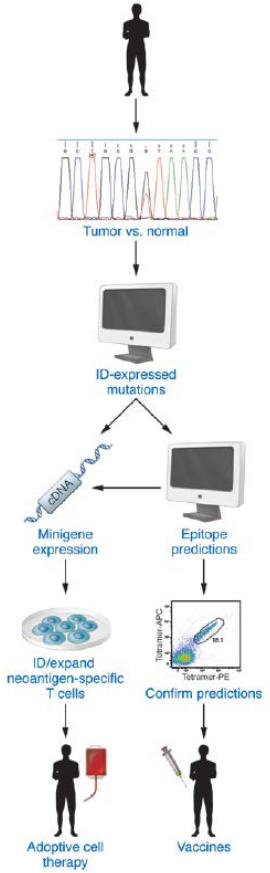
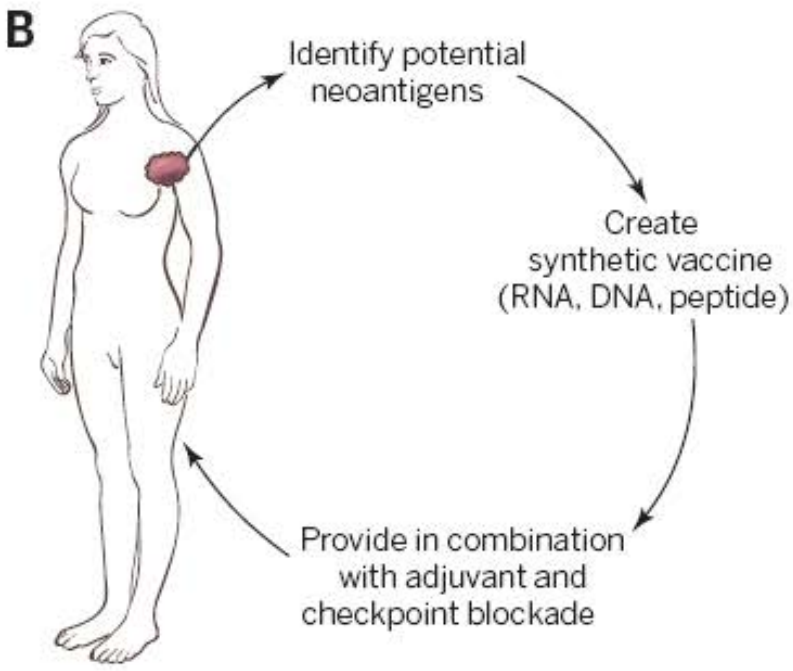
Keyrus BIOPHARMA

GREPI

3es JOURNÉES du GREPI

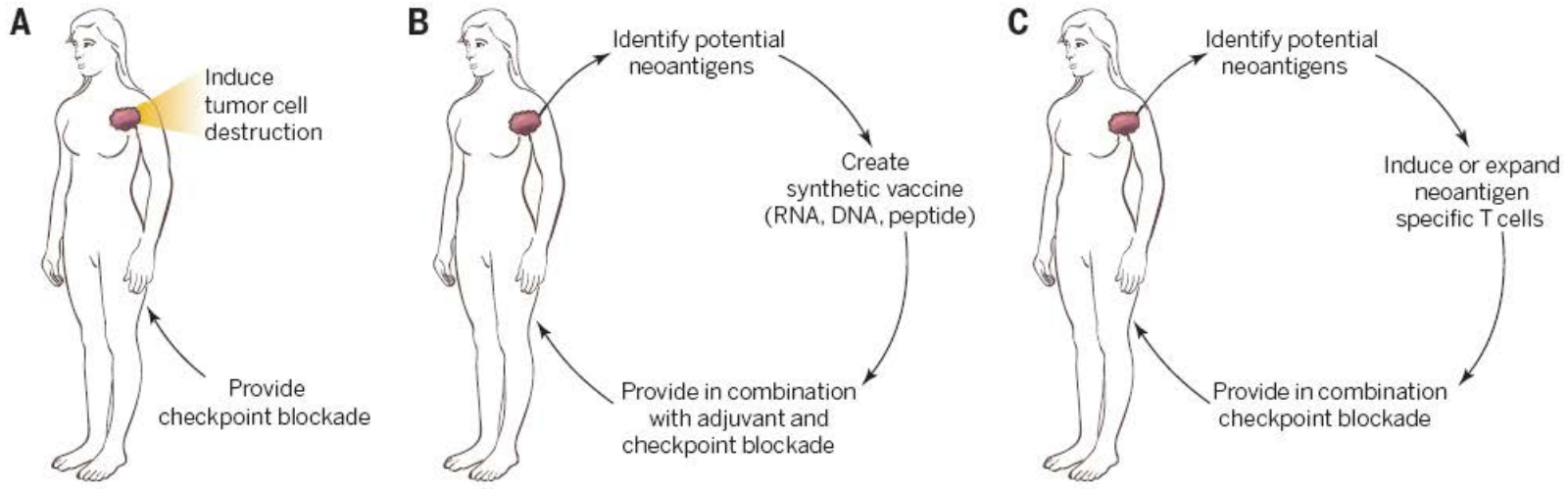
Stratégies pour les vaccins thérapeutiques





Schumacher T.N., Schreiber R.D., Science 2015

Différentes approches vaccination+ « check-point » inhibiteurs



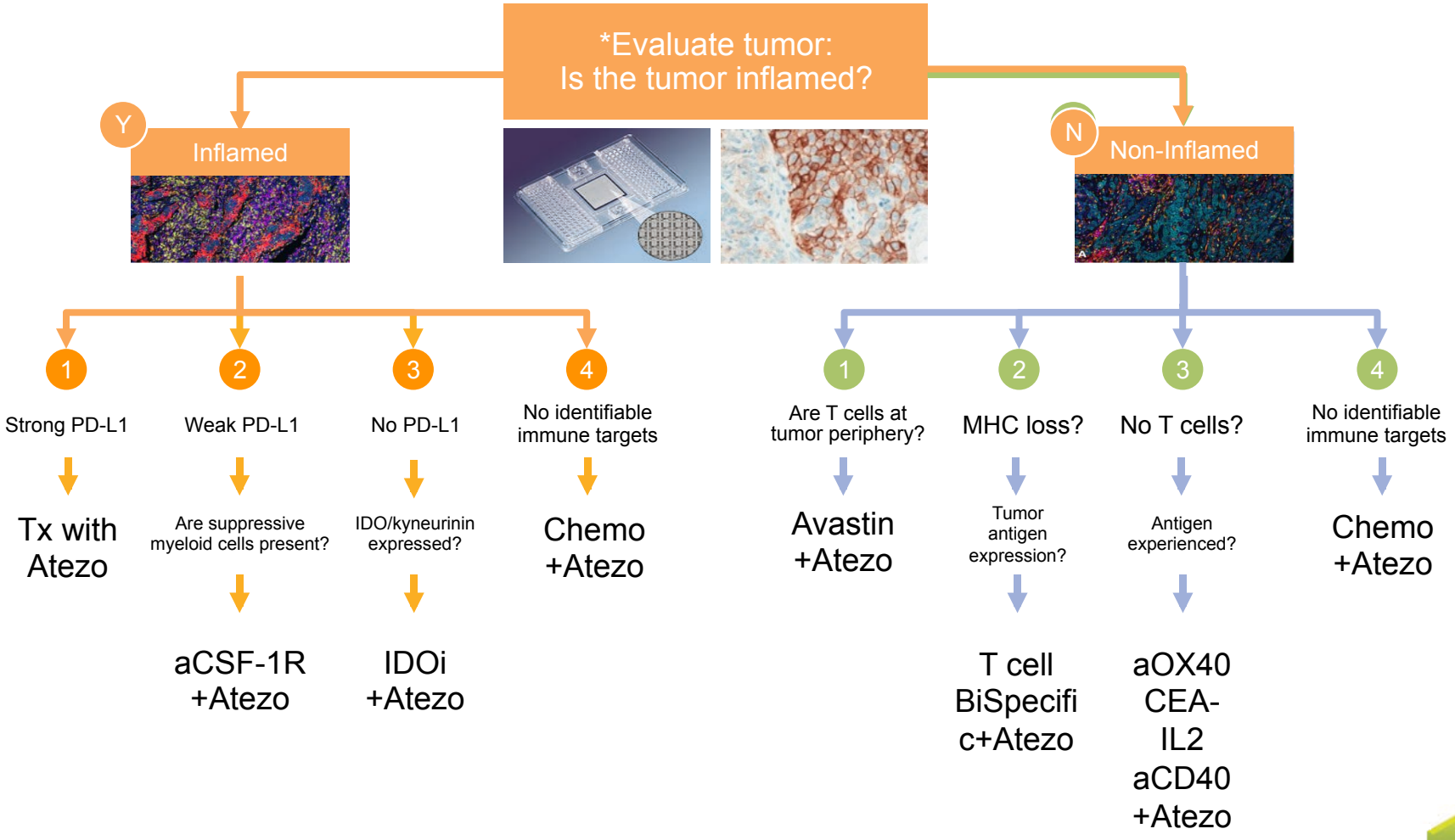
Certains vaccins sont des vaccins oncolytiques

Schumacher T.N., Schreiber R.D., Science 2015

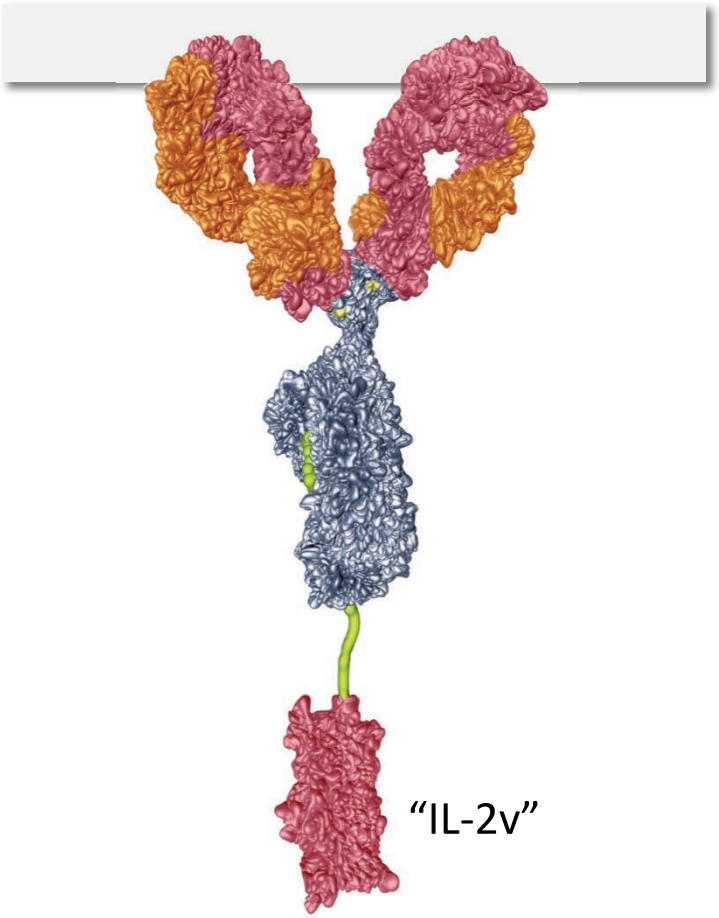
Exemples d'immunotherapies en développement

Cancer immunotherapy
Atezolizumab (Anti-PDL1 MAb, RG7446) Phase I/Ib/II/III
Emactuzumab (Anti–CSF-1R MAb, RG7155) Phase I/II
Anti-CD40 MAb (RG7876) Phase Ib
Anti–CEA-IL2v MAb (RG7813)* Phase I
MOXR0916 (Anti-OX40 MAb, RG7888)* Phase I
CEA CD3 T-cell bispecific (TCB) Ab (RG7802)* Phase I
IDO inhibitor (GDC-0919, NLG919, RG6078)* Phase I

Vision: Towards a personalized cancer immunotherapy paradigm



CEA-IL-2 Variant Cytokine Fusion (RG7813)
Designed to amplify immune response

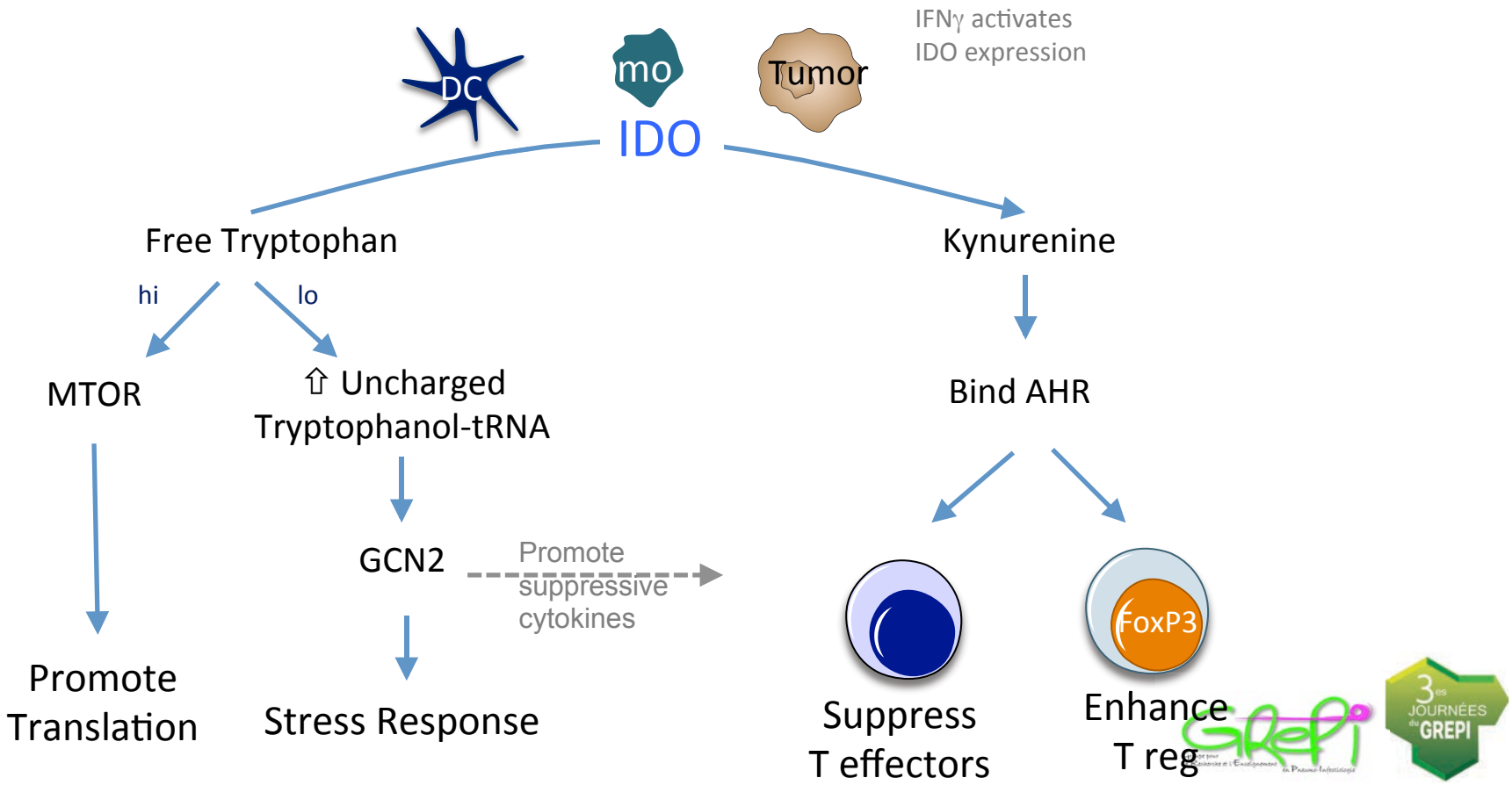


- The AB binds to tumor overexpressing carcinoembryonic antigen (CEA) to deliver a novel variant of IL-2 to the tumor
- IL-2 modified by abolishing the CD25 binding leading to reduced activity on Tregs
- The IL-2v is brought close to the tumor by the Ab, minimizing a systemic exposure
- The IL-2v recruits T and Natural Killer (NK) cells to the tumor
- Compared to standard IL-2-based therapy, it shows:
  - Superior expansion of immune effectors, NK and effector Tcells
  - Less activation of suppressive T-cells
  - Better tolerability
  - Better tumor targeting
- **Phase 1 and Atezolizumab combo study ongoing**

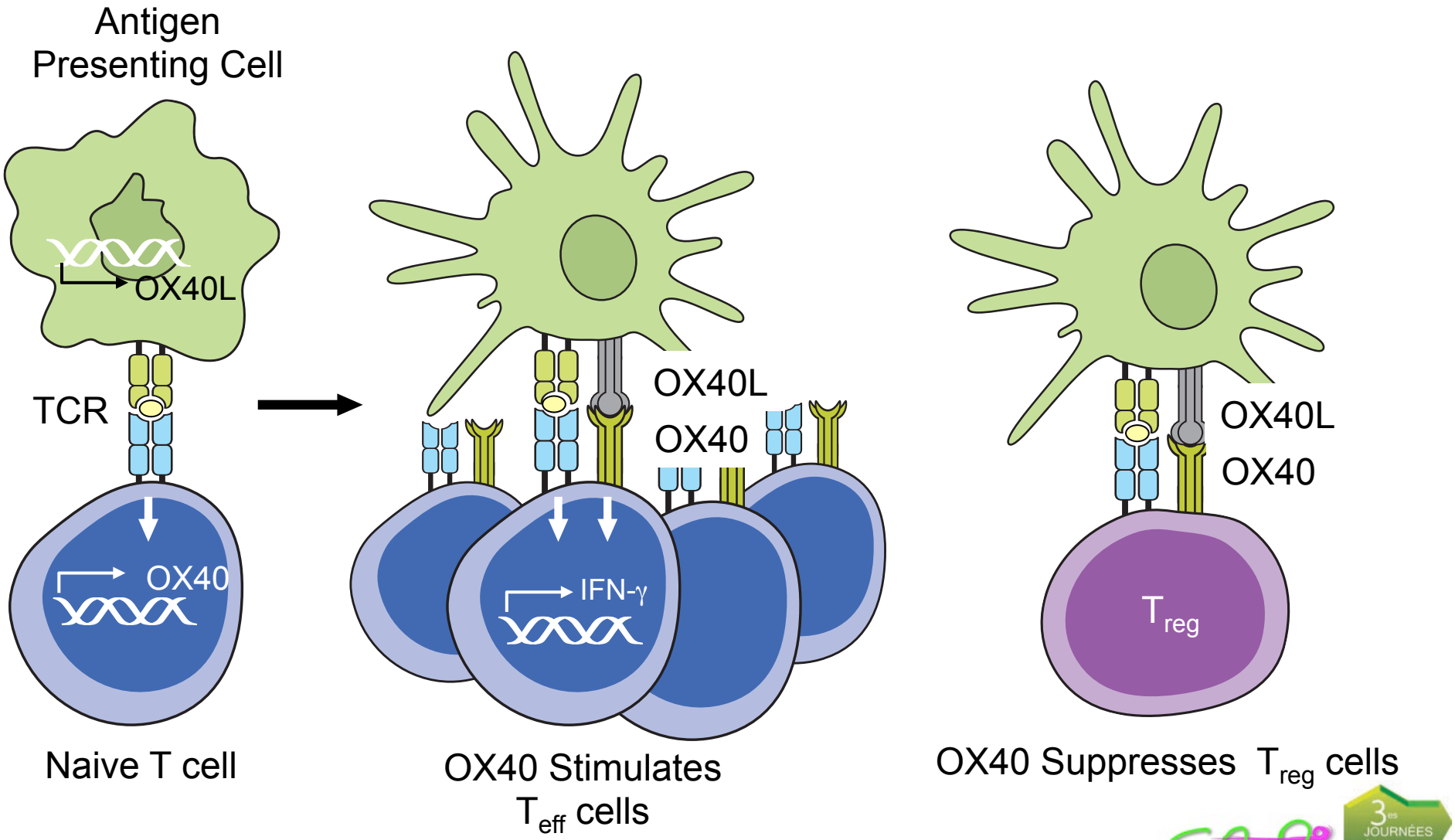
IDO Contributes to Local Immune Tolerance

Role of IDO (*Indoleamine-pyrrole 2,3-dioxygenase*) in the immune system:

- Endogenous regulator of local immune responses: “metabolic immune regulation”
- Critical for mucosal immune tolerance and fetal-maternal tolerance
- Catabolizes tryptophan to metabolites including Kynurenine
- Kyn binds AHR to suppress effector T cells and hyperactivate Tregs



OX40 Function: Promote Antigen Dependent Effector T cell Activation and Treg Cell Inhibition



OX40 et maladies auto-immunes

- OX40 Rôle important dans la physiopathologie des maladies Auto-immunes
- A risque de pathologies Auto-immunes et à l'utilisation d'immunosuppresseurs

Croft et al., Immunol Rev 2009

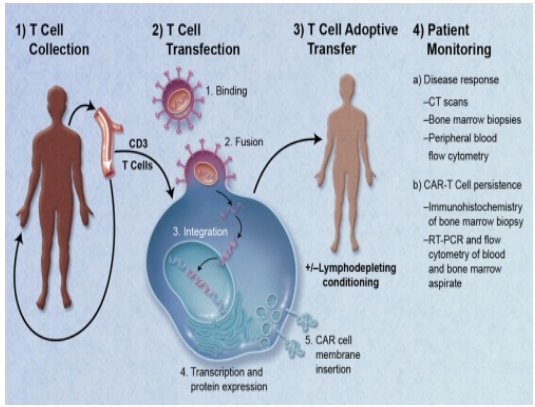
Requirement for OX40-OX40L in Inflammatory and Autoimmune Disease

Disease	Mice or Reagent	Clinical Phenotype	Immune Phenotype
EAE	Anti-OX40-toxin	Strong inhibition	↓ CD4+ T cells
	OX40.Ig	Strong inhibition	↓ CD4+ T cells
	Anti-OX40L	Strong inhibition	↓ CD4+ T cells
	OX40-/-	Strong inhibition	↓ CD4+ T cells
	OX40L-/-	Strong inhibition	↓ IFNγ, IL-2, and IL-6
Colitis/IBD	OX40.Ig	Strong inhibition	↓ CD4+ T cells, CD8+ T cells
	Anti-OX40L	Strong inhibition	↓ α4β7 CD4+ T cells, CD11c+ DC
Asthma/Atopy	OX40-/-	Strong inhibition	↓ IL-4, IL-5, IgE
	OX40L-/-	Strong inhibition	↓ IL-13, IL-4, TNF, IFNγ
	Anti-OX40L	Strong inhibition	↓ CD4+ T cells, IL-4, IL-5, IL-13, IgE, CD11c+ DC
Diabetes	OX40L-/-	Strong inhibition	—
	Anti-OX40L	Strong inhibition	—
Arthritis (CIA/adjuvant)	Anti-OX40L	Strong inhibition	↓ IFNγ, IgG2a
	Anti-OX40-toxin	Partial inhibition	↓ CD4+ T cells

Activity expected in colorectal, breast, sarcoma…

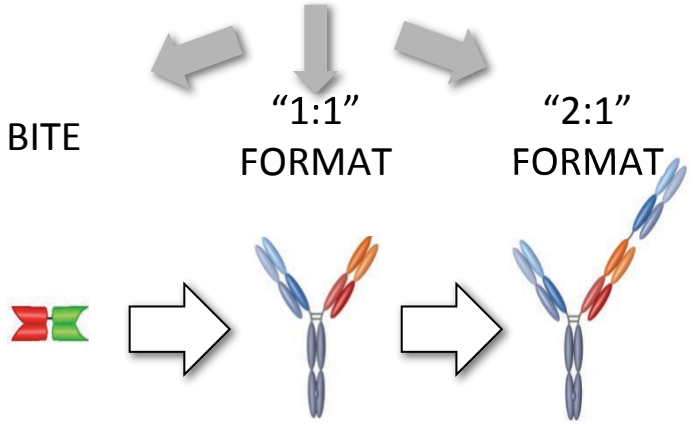
T-Cell Engaging Therapies
Competitive landscape

ENGINEERED T-CELLS (CARs)



+	High interest, outstanding clinical efficacy with CD19 CARs in hematology	
-	Activity associated with high toxicity	
-	Challenging manufacturing and regulatory processes	

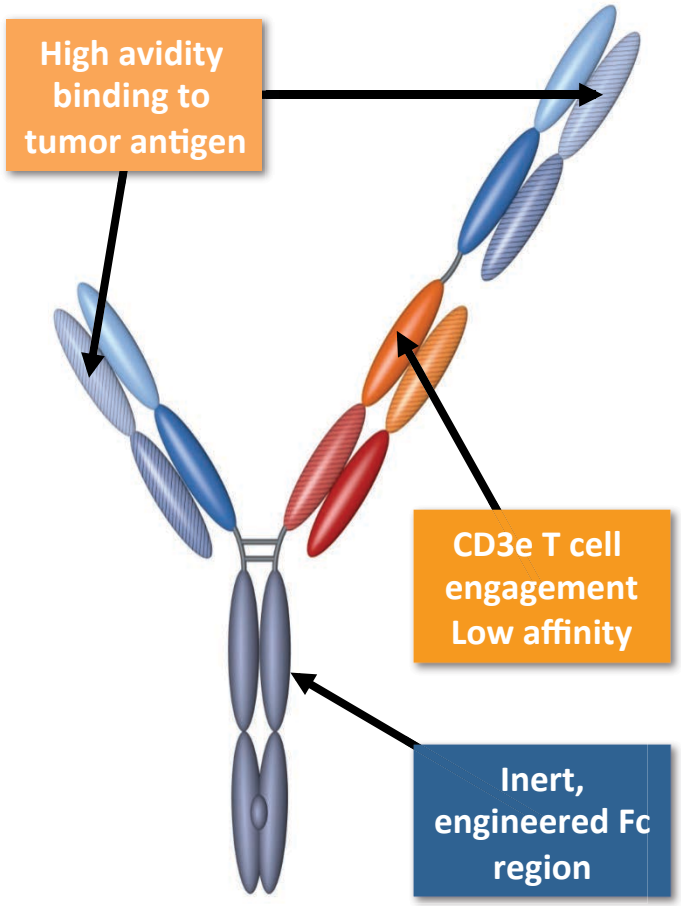
T-CELL ENGAGING ANTIBODIES



	BITE	"1:1" FORMAT	"2:1" FORMAT
Potency	+++	+	+++
Long half-life	-	+++	+++
Differentiation between high and low antigen expressing cells	+	+	+++

CEA T-Cell Bispecific Antibody (CEA-TCB) (RG7802)

First anti-tumor T-cell engager from Roche Group to enter clinical trials



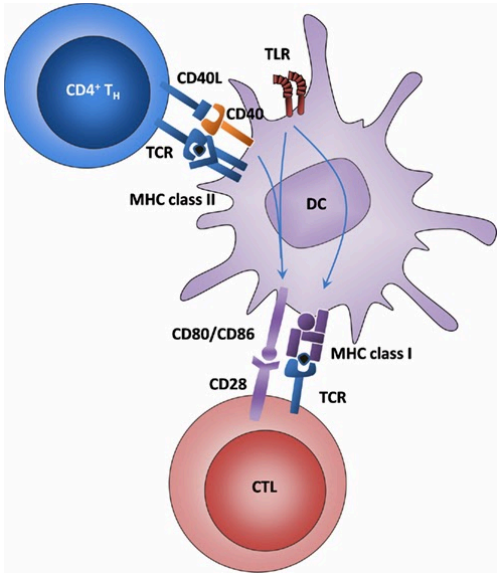
Mechanism of action:

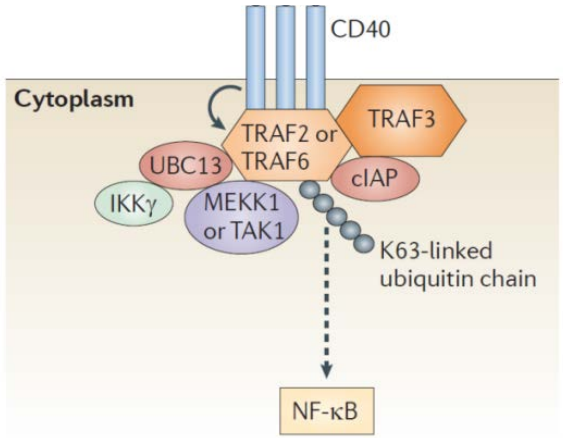
- Binds T cells and tumor cells simultaneously
- Results in T cell activation/proliferation and killing of tumor cells
- Does not require MHC:peptide complex presentation by tumor cells
- T cell engagement independent of specificity and activation status

Features

- Entry into human – study started in Dec 2014
- **Combination with IL2v & PD-L1 planned early in clinical development**

Role of CD40 in adaptive immunity





- CD40 is a receptor expressed on the surface of antigen-presenting cells (APCs), including B cells, macrophages, and dendritic cells, as well as on non-hematopoietic and tumor cells
- CD40 ligand (CD40L) is primarily expressed on the surface of activated T cells
- Engagement of CD40 on APC by CD40L promotes APC activation
  - Signaling through CD40 results in the TRAF-mediated activation of MAPK and NF-κB pathways, promoting upregulation of costimulatory and MHC molecules, and proinflammatory cytokine production
- APC activation via CD40 promotes activation and differentiation of cytotoxic T lymphocytes (CTL)

References: **1.** Bishop, *Nat Rev Immunol*, 2004;4(10):775-86. **2.** Elgueta, *Immunol Rev*, 2009; ;229(1):152-72. **3**. Hacker, *Nat Rev Immu*, 2011. **4.** Vonderheide et al. *Clin Canc Res*. 2013; 19(5):1035-4.

En conclusion

- Immunothérapies actuelles:
  - Risque d'infections pulmonaires faible.
  - A risque si pneumopathie médicamenteuses (5%) nécessitant traitement immunosuppresseurs
    - Corticothérapie
    - Anti-TNF
    - MMF/aza
  - Germes décrits ; Infections bacteriennes , virales, fungiques.
  - Risque plus important de pneumopathies ou de maladies auto-immunes justifiant un traitement à l'avenir.
  - Prophylaxies discutées.

MERCI POUR VOTRE ATTENTION ET BONNE JOURNEE

Questions?

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