Immunothérapie dans le cancer du sein

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IBDC 2016

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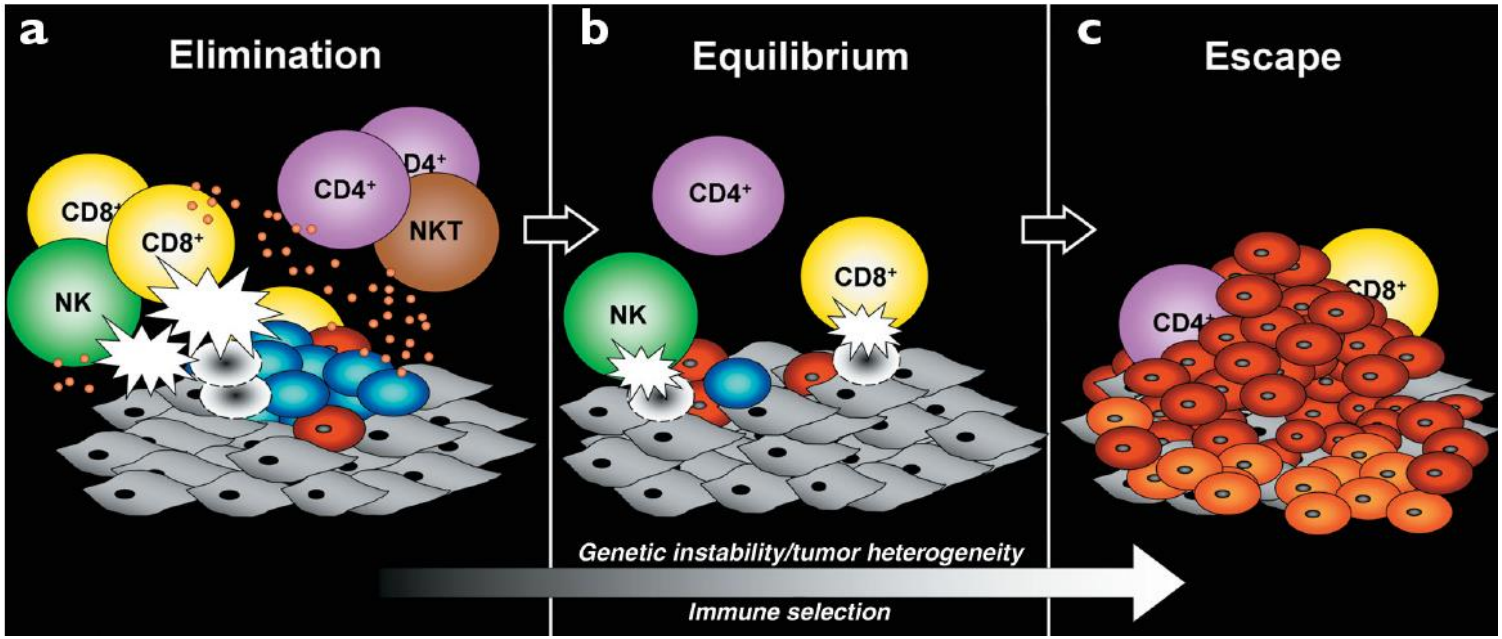
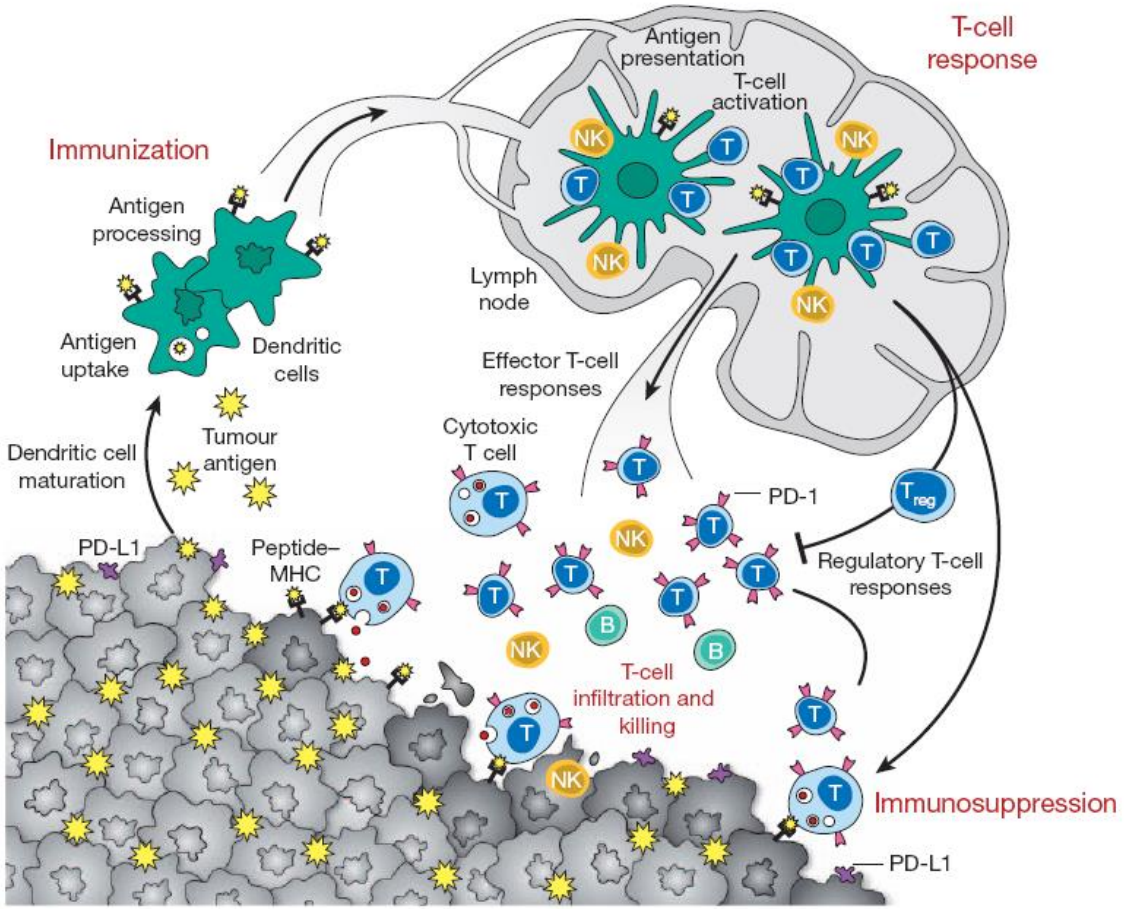
Plan

- Rationnel
- Différentes approches
- Arguments pour l'immunogénicité des cancers du sein
- Les « Check-points » inhibiteurs
- Résultats préliminaires disponibles
- Perspectives.

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

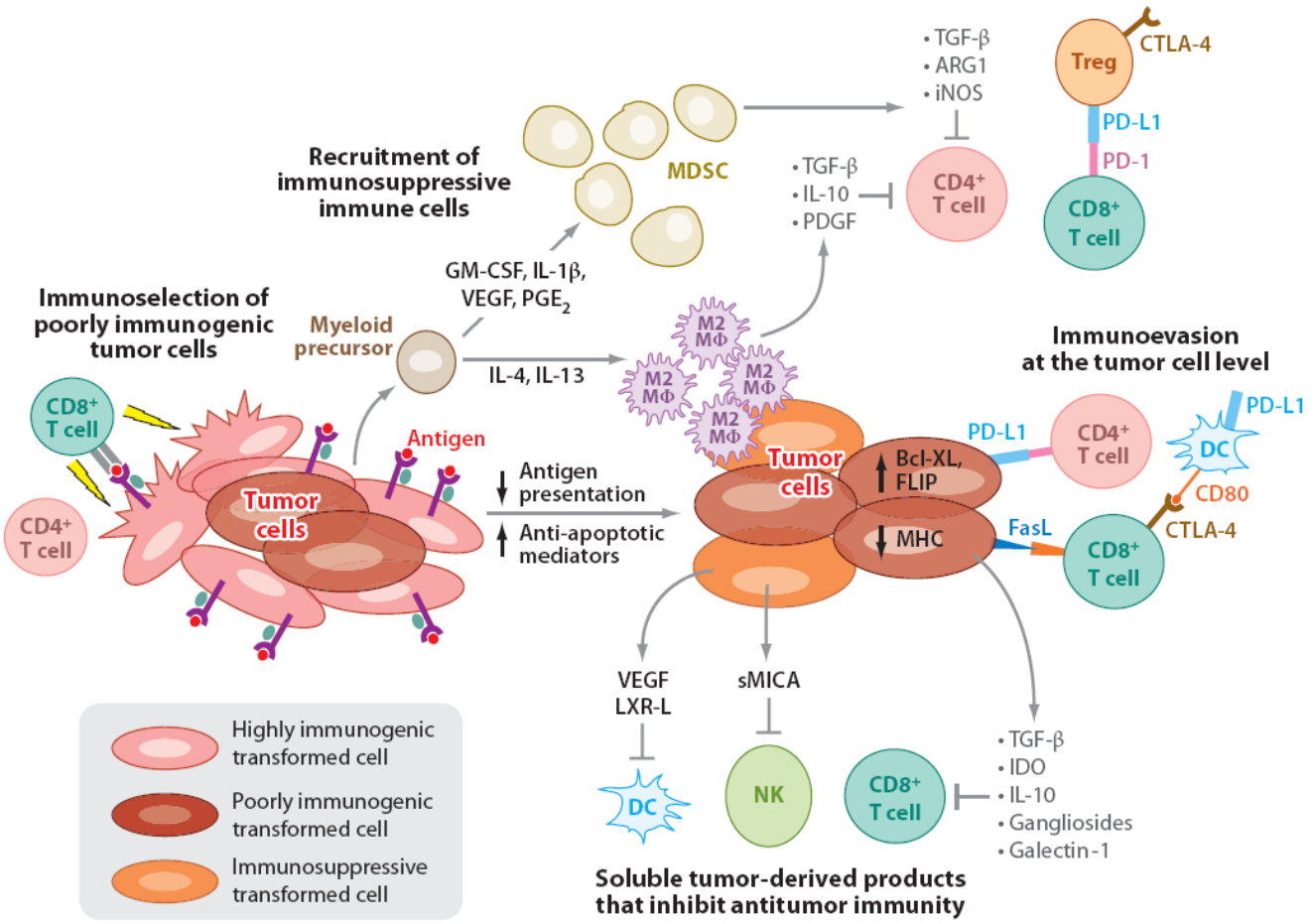


Intervention de l'immunité innée et acquise



Mellman, Nature 2011

Principaux mécanismes d'échappement



Vesely M.D. et al, Ann Rev Immunol 2011

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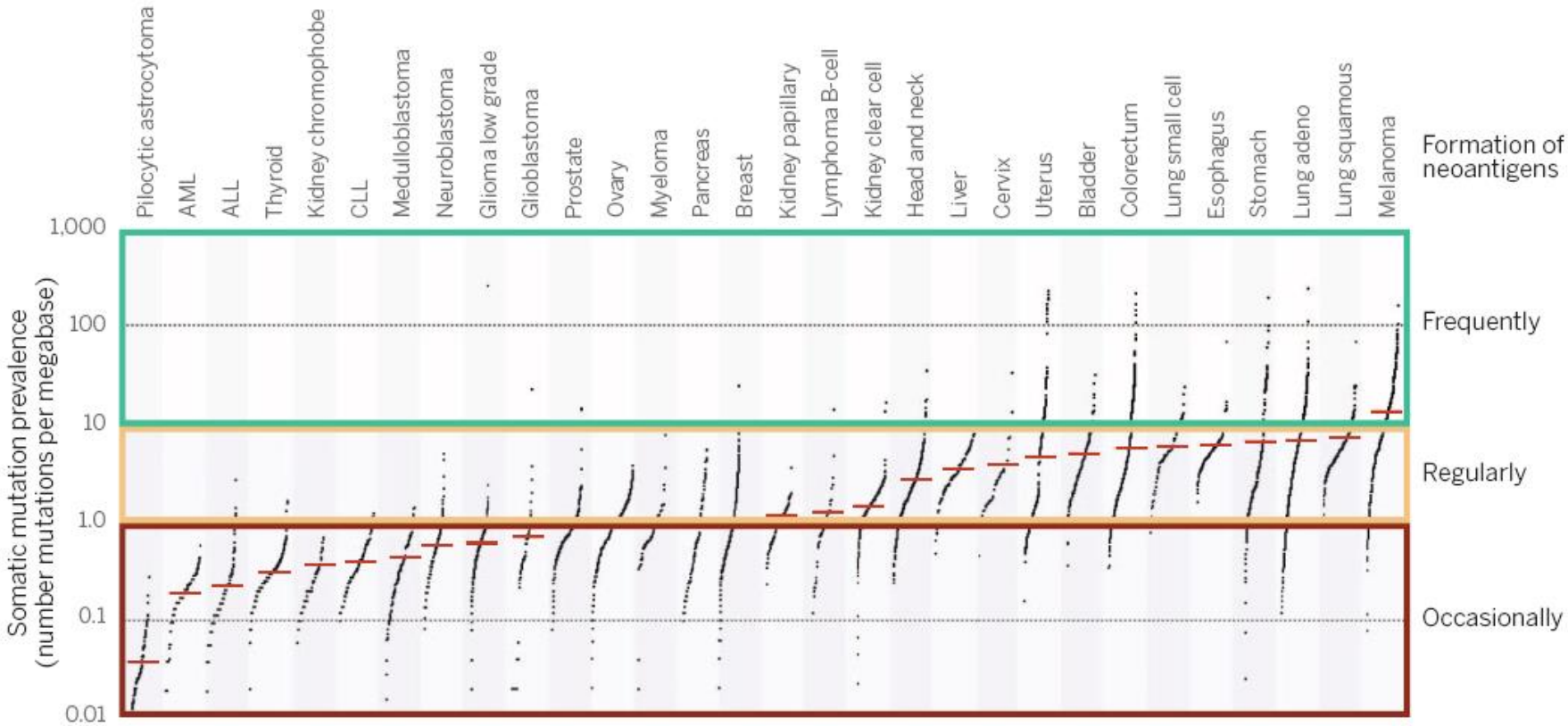
Immunogénicité des tumeurs: Théorie des Néoantigènes



Adapté de Lawrence et al, Nature 2013

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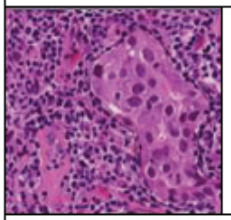
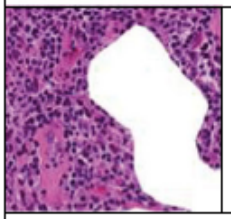
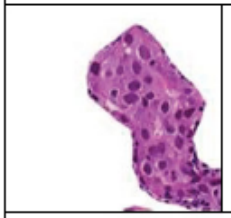
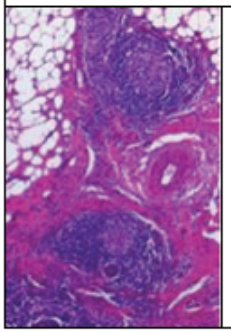
Implication du système immunitaire au cours du cancer du sein: arguments

- **Infiltrat lymphocytaire: TILS**
- **Signatures Immunes pronostiques**
- **PD1 et PDL1: facteurs pronostiques**

Différents types de TILs

Morphology	Definition and biological relevance	Diagnostic relevance
Lymphocyte-predominant breast cancer (LPBC)		
	Working category to describe tumors with "more lymphocytes than tumor cells".	Definitions vary across studies with stromal TILs of 50–60% used as a threshold. LPBC can be used for predefined subgroup analyses and for description of tumors with a particularly high immune infiltrate, however, keep in mind that TILs are a continuous parameter and the threshold for LPBC is still arbitrary.
Stromal TILs		
	Indicator of increased accumulation of immune-cells in tumor tissue	Stromal TILs have been shown to be predictive for increased response to neoadjuvant chemotherapy as well as improved outcome after adjuvant chemotherapy. Based on current data, this parameter is the best parameter for characterization of TILs.
Intratumoral TILs		
	TILs with direct cell-cell contact with carcinoma cells, might be an indicator of direct cell-based anti-tumor effects.	Several studies have shown that intratumoral TILs and more difficult to evaluate and do not provide additional predictive/prognostic information compared to stromal TILs.
TILs at the invasive margin		
The localization of TILs are the invasive edge is included in the evaluation approach presented in this guideline.		For breast cancer there are no studies with a separate evaluation of TILs at the invasive edge. For practical purposes, the reliable evaluation of the invasive edge might be difficult when using core biopsies in the neoadjuvant setting.
Tertiary lymphoid structures (TLS)		
	Typically localized in the surrounding area of the tumor, TLS might be localized in normal tissue directly adjacent to the tumor, consisting of a T cell zone next to a B cell follicle, often with germinal centers.	While these structures may be important for the biology of tumor-immune reactions, they are not yet optimized for non-research based assessments, The main problem is that TILS have a spatial heterogeneity and are principally localized in areas surrounding the tumor. They might not be in the plane of the tissue section that is being evaluated, in paricular when using core biopsies. Furthermore, it might be difficult to distinguish lymphoid aggregates from true TILS, in particular when the germinal center is not in the plane of the section.

Salgado R et al , Ann Oncol 2014

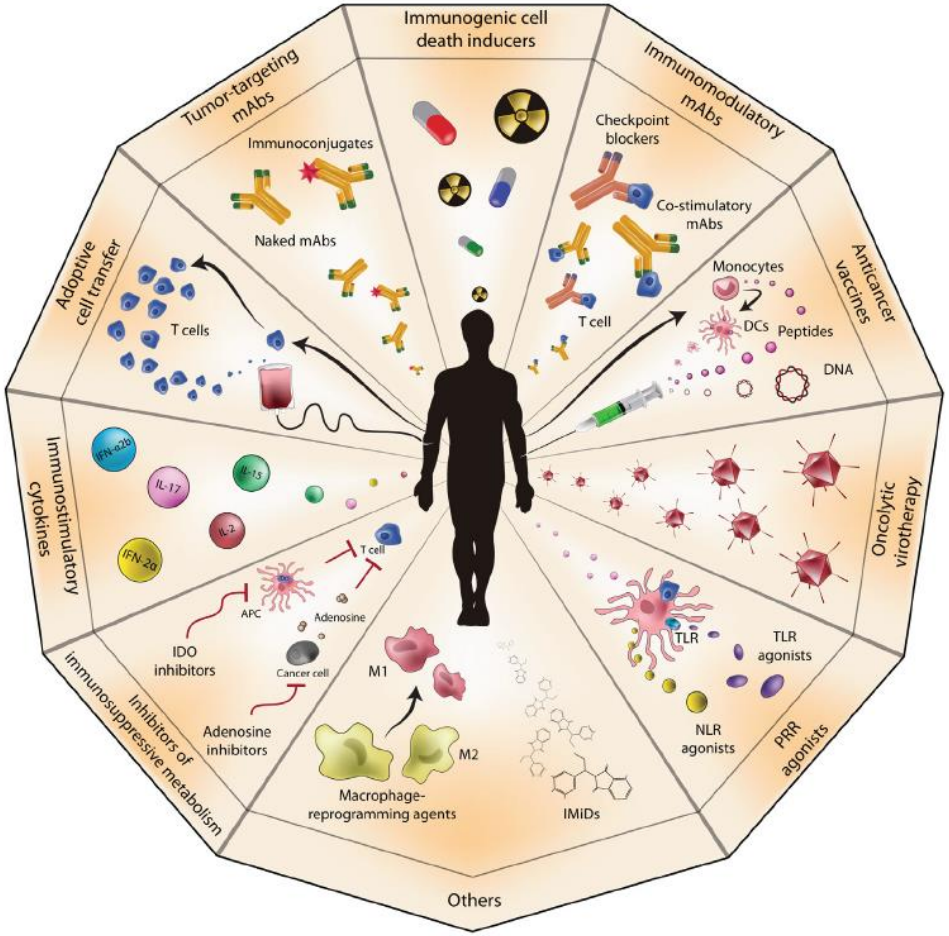
TILS corrélés à un meilleur pronostic

Reference	N	Trial	Endpoint	Subtype analyzed	Result
Denkert (JCO, 2010)	840	GBG G-3	pCR	all	pCR:41% in TIL+ BC Validated in G-5
Loi (JCO, 2013)	2009	BIG 2-98	DFS	Preplanned analysis of molecular subtypes	Prognostic impact in TNBC (n=256): HR:0.31 (0.11-0.84)
Loi (AnnOnc, 2014)	935	FinHer	DFS	Preplanned analysis of molecular subtypes	Prognostic impact in TNBC (n=134): HR:0.31 (0.12-0.8)
Adams (JCO, 2014)	506	ECOG 2197 ECOG 1199	DFS	TNBC	HR:0.84 (0.74-0.95)
Dieci (AnnOnc, 2014)	278		MFS OS	TNBC	HR:0.86 (0.77 -0.96) HR:0.86 (0.77 -0.97)

Plusieurs signatures « immunologiques » Pronostiques

Immune signature	Signature development
Immune response (IR) module [23]	A subclass of estrogen receptor-negative (ER^-) tumors that overexpress IR genes and that have a good prognosis compared with the rest of ER^- breast tumors independently of lymph node status or lymphocytic infiltration was identified. Subsequently, an associated module of complement and IR genes that define prognostic markers was identified and validated in over 240 ER^- samples.
STAT1 module [22]	On the basis of the literature, genes to act as 'prototypes' for different biological processes - ER for ER signaling, HER2 for HER2 signaling, AURKA for proliferation, CASP3 for apoptosis, VEGF for angiogenesis, PLAU for tumor invasion/metastasis, and, in this case, STAT1 for immune response - were selected. A comparison of linear models was then applied to generate modules of genes specifically associated with each of the prototype genes but not with the other prototypes.
B-cell metagene [7]	Gene expression patterns of 200 patients who did not receive systemic treatment and co-regulated genes related to proliferation, steroid hormone receptor expression, and B-cell and T-cell infiltration were identified after hierarchical cluster analysis was performed. Metagenes were calculated as a surrogate for all genes contained within a particular cluster and their expression was correlated to time to metastasis. The B-cell metagene showed independent prognostic information in carcinoma with high proliferative activity.
IgG, HCK, MHC-I, MHC-II, LCK, STAT1, and IFN metagenes [24]	Unsupervised hierarchical clustering of genes in 12 primary invasive breast cancer datasets as well as combined datasets revealed a large cluster of genes with functions in immune cells. Among this cluster, clusters that contained a minimum number of elements and a minimal average correlation were selected, and seven metagenes were derived. Each metagene then was associated with a cell type or immunological state or both.
HR^{neg}/T^{neg} signature [25]	A cohort of patients with node-negative, adjuvant treatment-naïve hormone receptor-negative (HR^{neg}), and triple-negative (T^{neg}) breast cancer has been used to define and validate genes predictive for distant metastatic relapse. A composite HR^{neg}/T^{neg} signature index was able to identify cases likely to remain free of metastatic relapse with high accuracy. Of note, significant positive correlation was observed between the HR^{neg}/T^{neg} index and three independent immune-related signatures (STAT1, IFN, and IR), and network analysis showed that the signature was linked to immune/inflammatory cytokine regulation.
Support Vector Machine (SVM) classifier [26]	Gene expression data of 2,145 invasive early breast adenocarcinomas were collected and used to test and validate the predictive performance of an SVM classifier based on a 368-gene expression signature associated with medullary breast carcinoma (MBC), which displays a basal profile but has good prognosis. The SVM model accurately classified all MBC samples in the learning and validation sets and was able to separate 466 cases of basal breast cancers into two subgroups (subgroup 1 and subgroup 2) containing, respectively, good- and poor-prognosis tumors. Ontology analysis revealed, among other features, effective IR in the good-prognosis subgroup.

Différents types d'immunothérapies dans le traitement du cancer



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Galuzzi et al Oncotarget 2014

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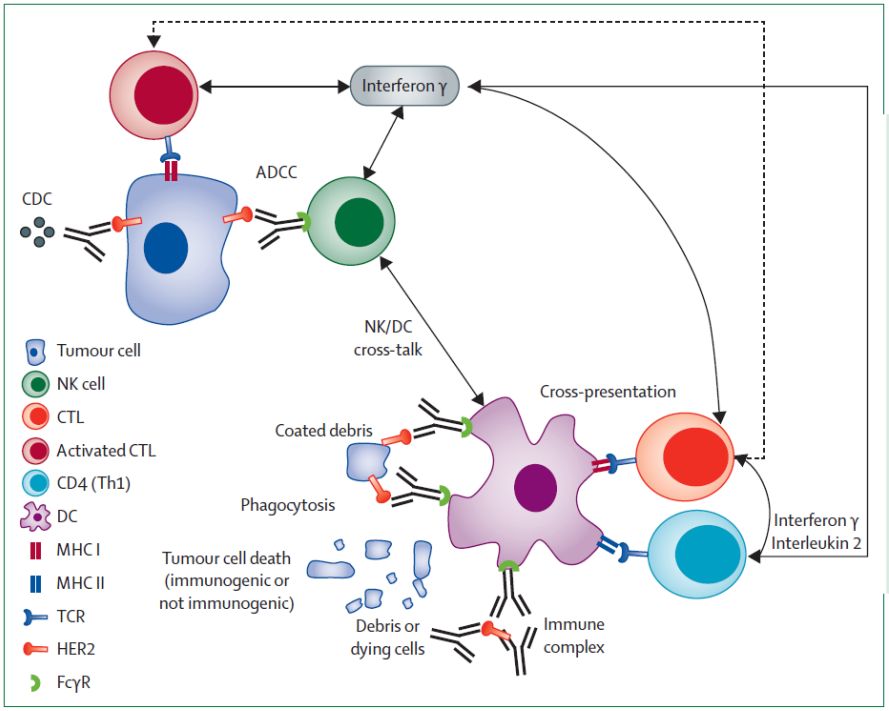
Action des cytotoxiques en partie par un mécanisme immunologique: Différences selon les molécules

DRUG	EFFECT ON IMMUNE SYSTEM
Doxorubicin	Induces immunogenic cell death Increases proliferation of CD8 T cells Stimulates antigen presentation by DCs Stimulates MCP1 and M6PR
Cyclophosphamide	Induces immunogenic cell death Suppressed Treg inhibitory functions and restoration of the proliferative capacity of effector T cells and NK cell cytotoxicity.
Taxanes	Enhance T cell and NK cell function Increase recruitment of TIL Increase efficacy of immuno-stimulatory agents
Gemcitabine	Reduce the number of myeloid suppressor cells Increase the antitumor activity of CD8(+) T cells and activated NK cells
Oxaliplatin	Induces immunogenic cell death Increases MHC I complex Inhibits PDL2

Zitvogel et al, Nat Immunology

Action du Trastuzumab en partie médiée par l'activation du système immunitaire

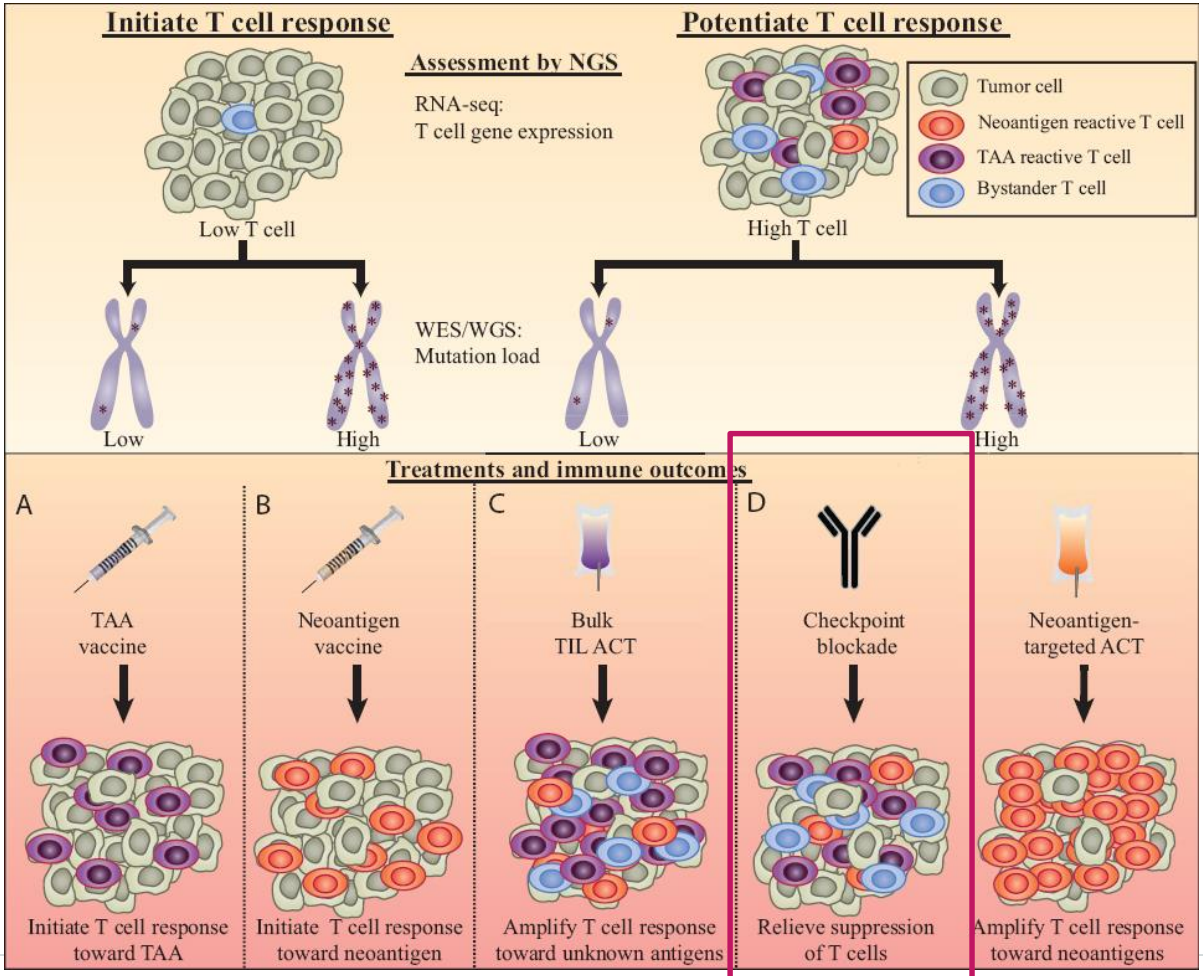


Immunological effects

- Antibody-dependent cell-mediated cytotoxicity
- Complement-dependent cytotoxicity
- Phagocytosis of monoclonal antibody-opsonised target cells through receptors for the Fc portion of IgG (antibody-dependent cellular phagocytosis)
- Immune complex (monoclonal antibody and tumour antigen) uptake by antigen-presenting cells
- Induction of cross-talk among immune cells, including natural killer cells and dendritic cells
- Induction of production of immunomodulatory cytokines (ie, type I and type II interferons)
- Induction of cross-presentation of tumour antigens, leading to priming of specific adaptive immune response (ie, tumour antigen-specific T lymphocyte response)

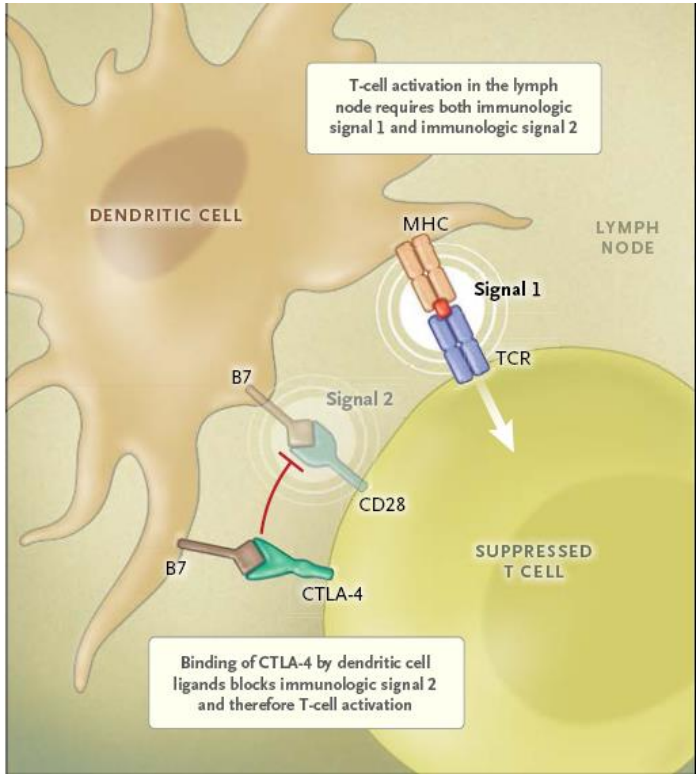
Bianchini and Giani, Lancet Oncol 2014

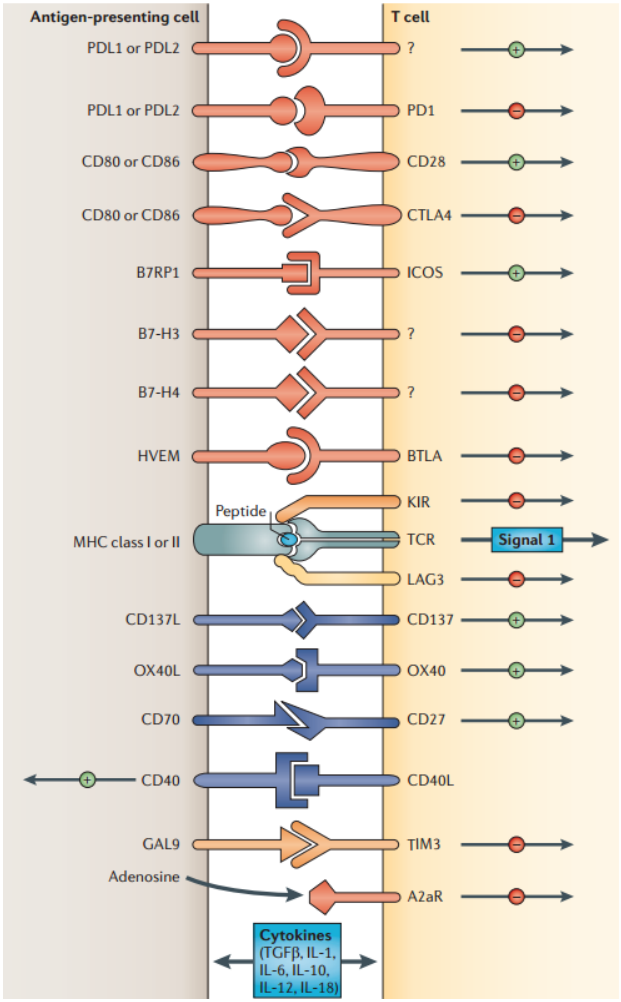
Différentes approches en immunothérapie ciblant les Ly T



Martin SD et al Ann Oncol sous presse

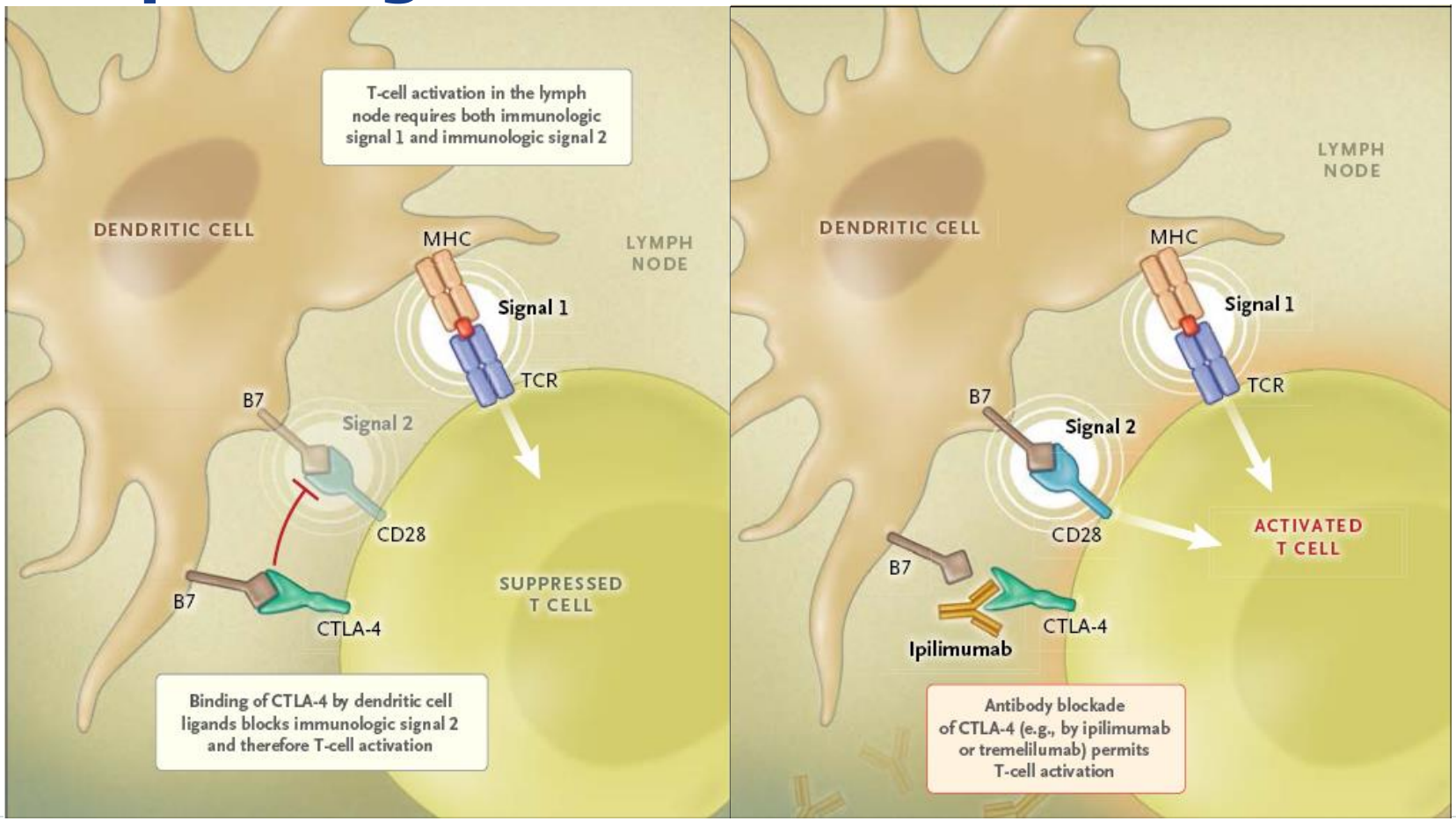
Activation des lymphocytes T: Synapse Immunologique





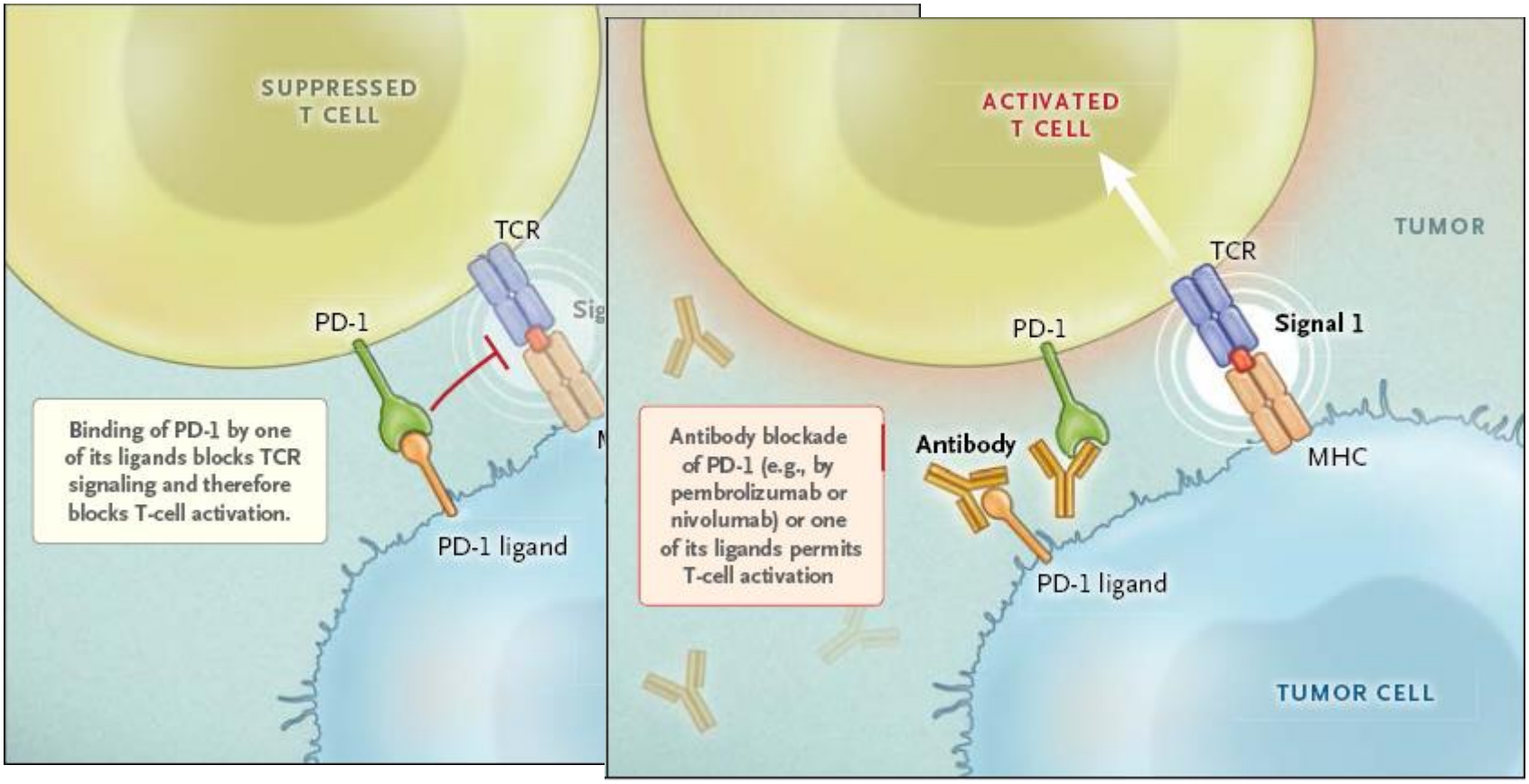
Pardoll et al Nat Rev Cancer 2012

Activation des lymphocytes T: « priming »



Ribas A NEJM 2015

Activation des Lymphocytes T: phase effectrice



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Ribas A NEJM 2015

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ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. D. Schadendorf, R. Dummer, M. Smylie, P. Ru J. Wagstaff, M.S. Carlino, J.B. Haanen, M. G.A. McArthur, P.A. Ascierto, G.V. Long, M K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, F.S. Hodi, and J.D. Wo

ORIGINAL ARTICLE

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

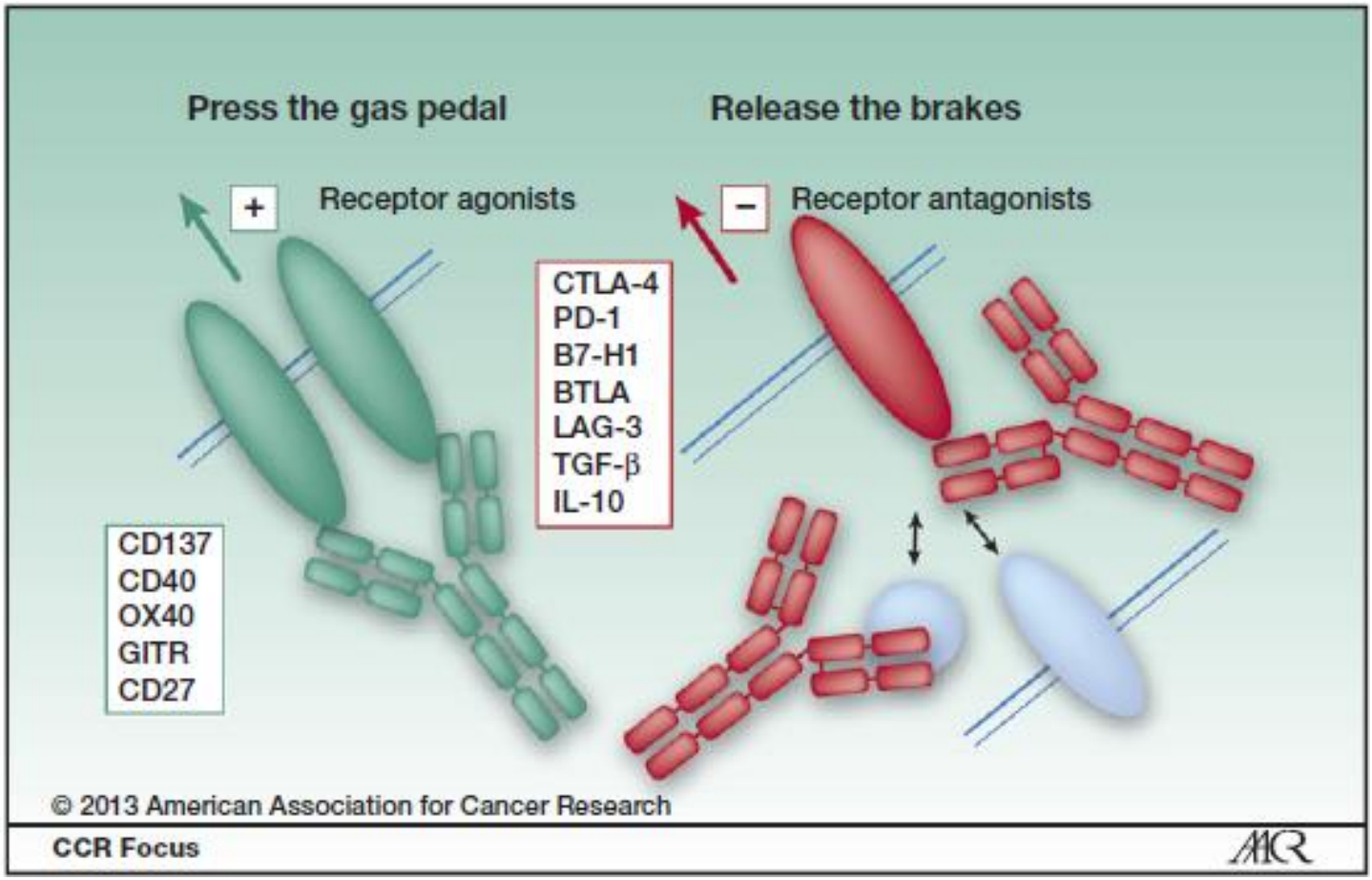
Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor,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



Ou la combinaison des 2

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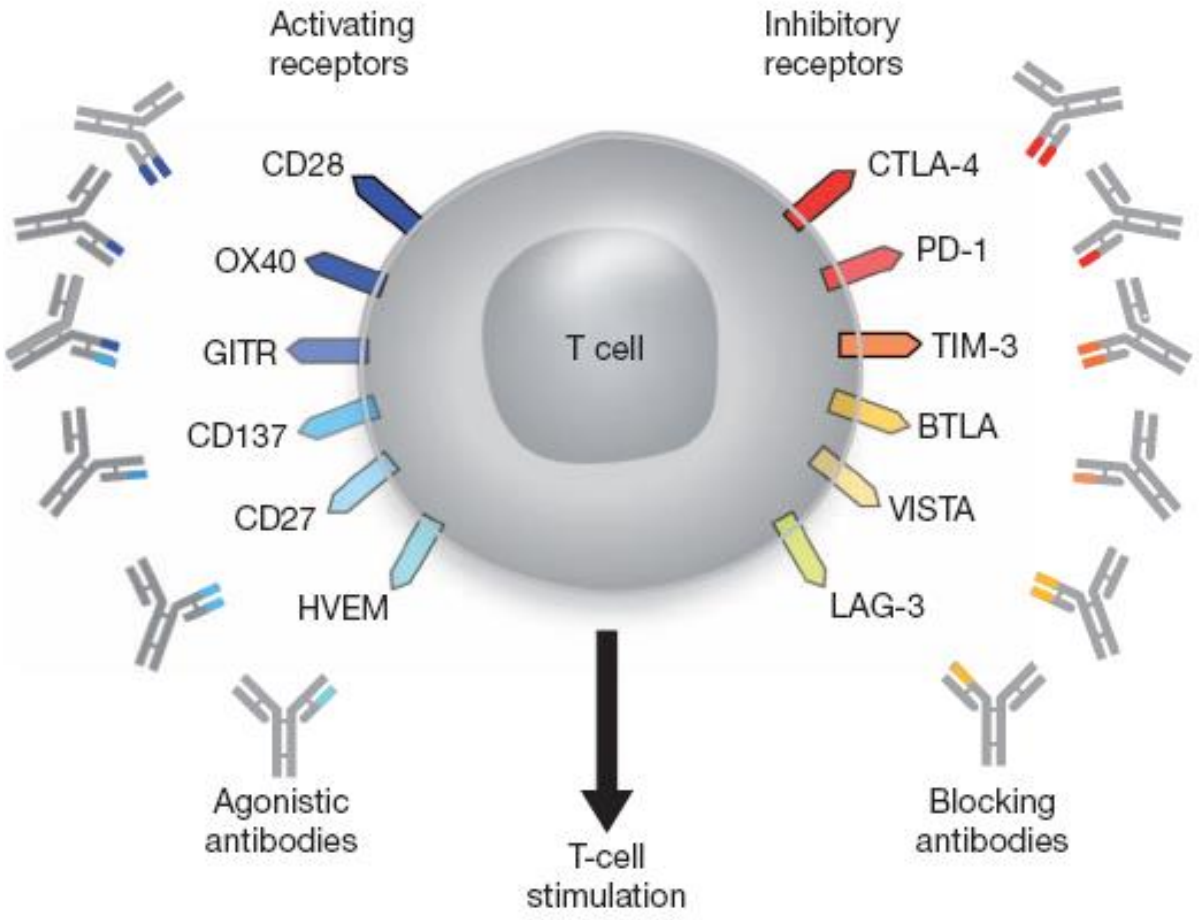
Agonistes sur les activateurs
Anticorps bloquants sur les inhibiteurs



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

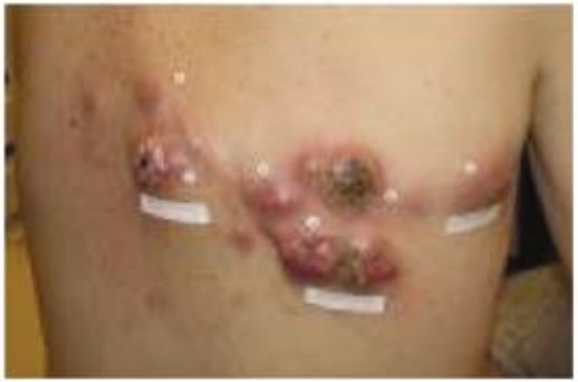
Particularités des évaluations sous immunothérapies

- **Les pseudo-progressions**

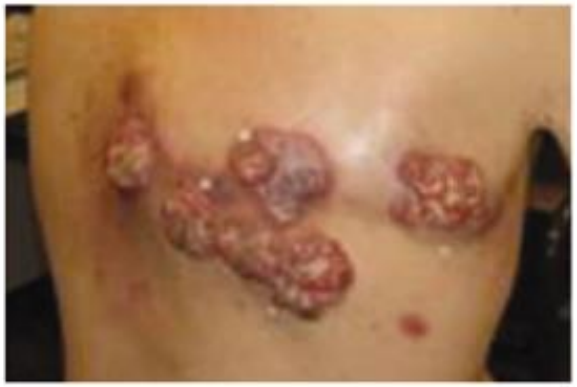
- **Le « spider plot »**

Historique: Observations cliniques sous Ipilimumab les « Pseudo-progressions »

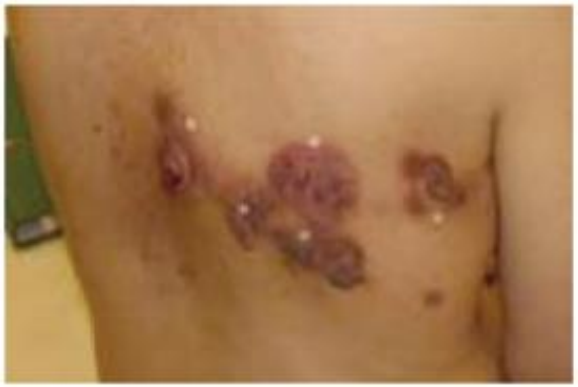
Baseline (Day 0)



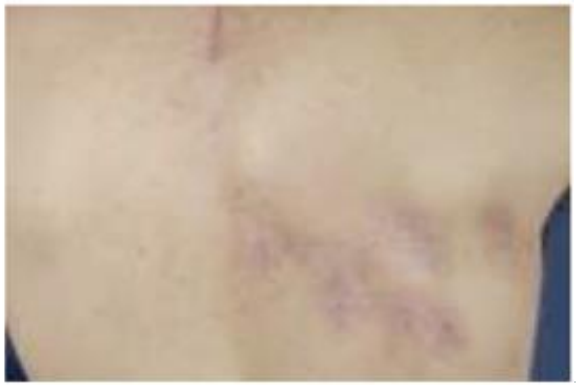
Week 12 (Day 84)



Week 16 (Day112)



Week 72 (Day 503)



Patient atteint de mélanome
Évolution sous Ipilimumab

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Wolchok et al JNCI 2010

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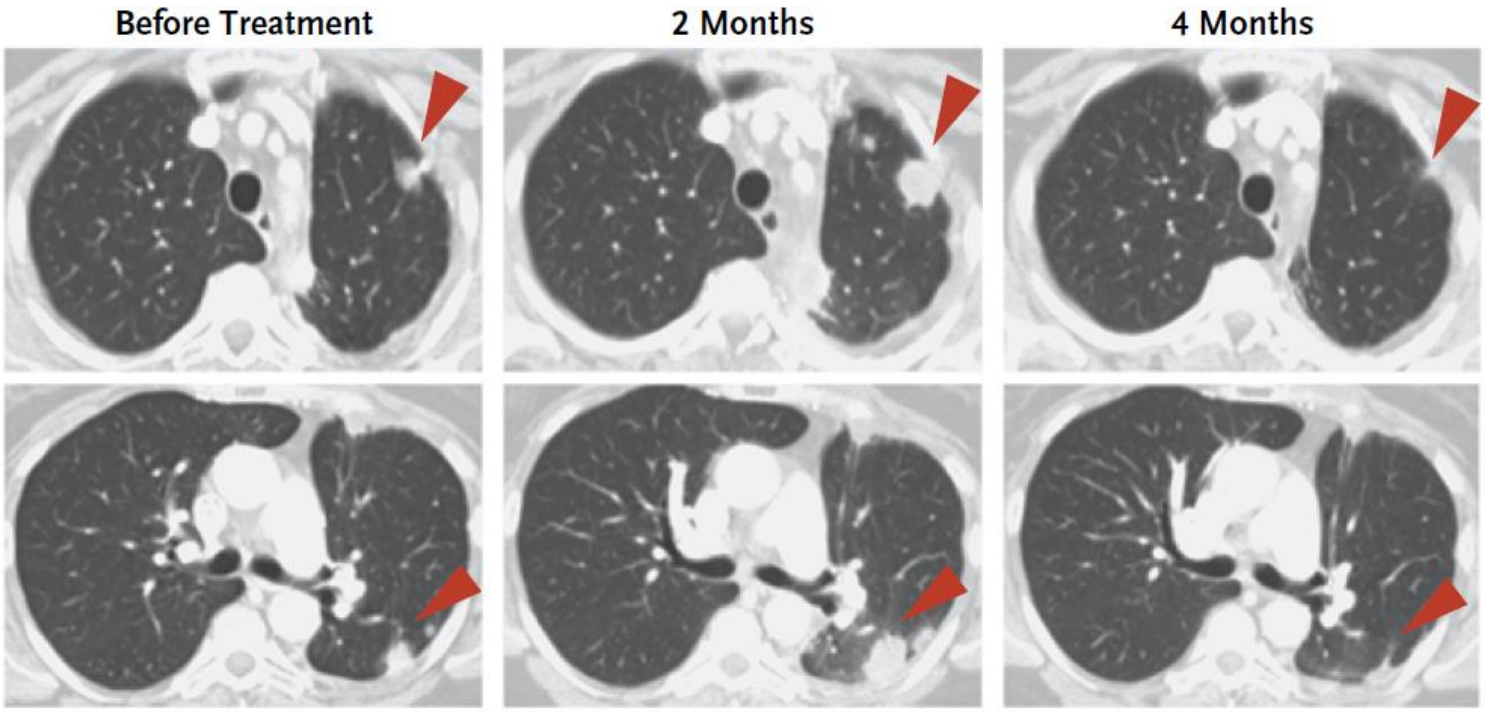
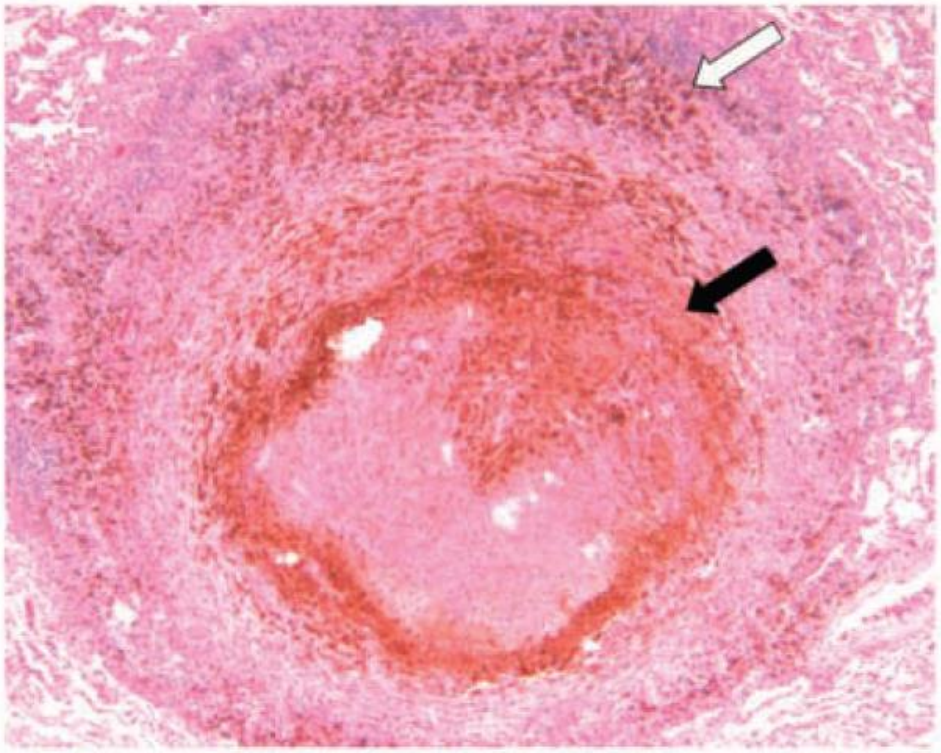
Effet « classe » des « check-point inhibiteurs »



Cancer bronchique non a petites cellules: Evolution sous anti-PD1

Topalian et al NEJM 2012

Données histologiques



- Métastase pulmonaire de mélanome sous Ipilimumab avec augmentation de taille
  - Flèche blanche infiltrat lymphocytaire
  - Flèche noire: zone de nécrose.
  - Plus de tissu tumoral

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Wolchok et al Clin Can Res 2009

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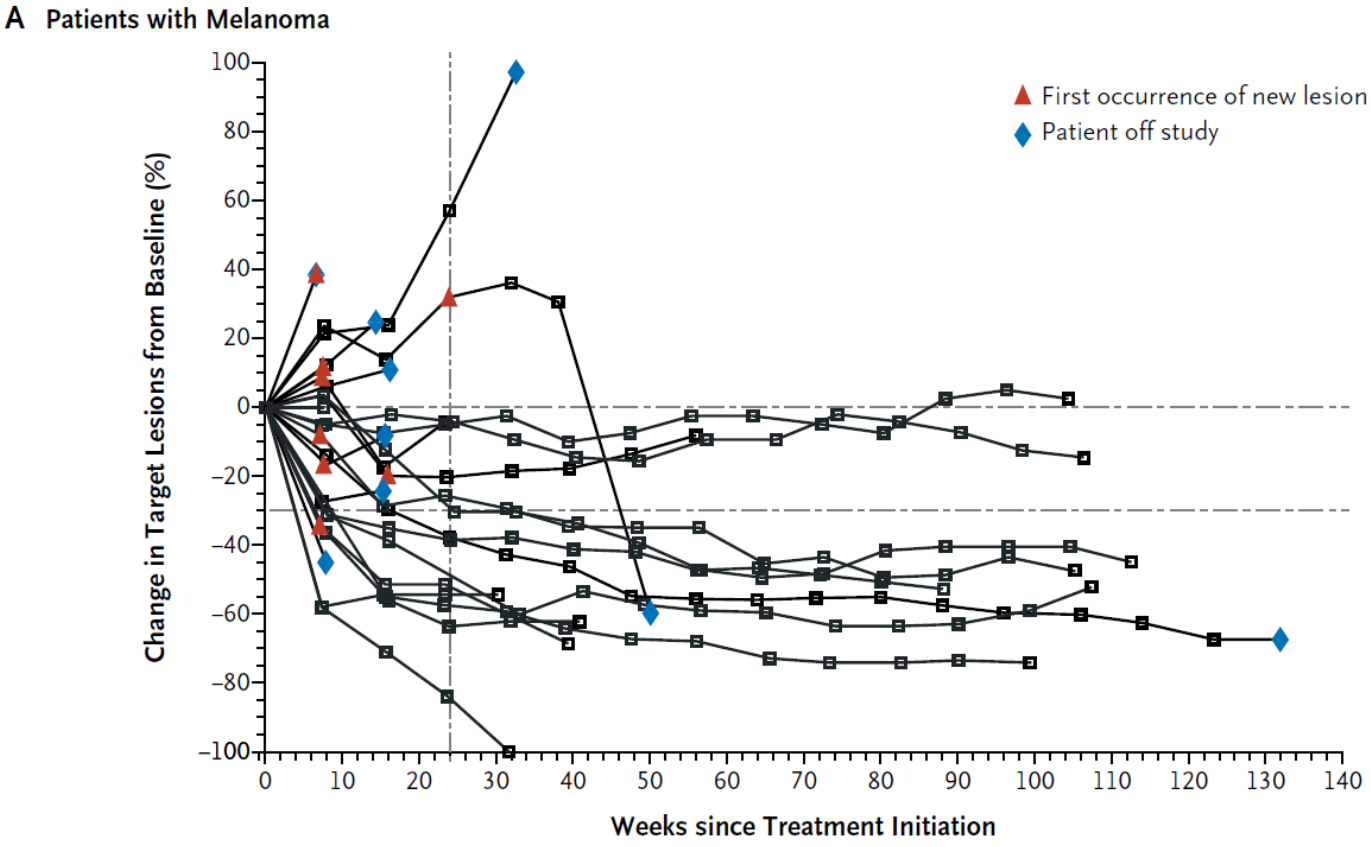
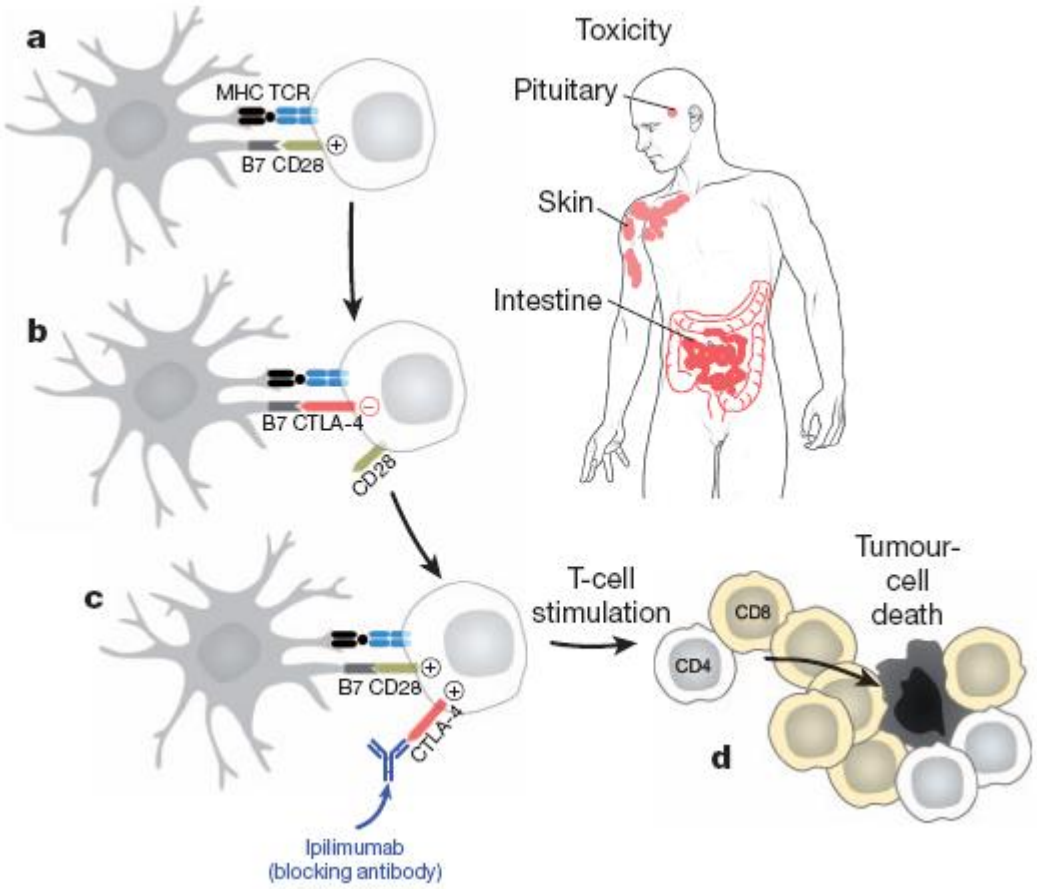
« Spider Plot » représentation dynamique pour chaque patient



Topalian et al NEJM 2012

Toxicités des « check-point » inhibiteurs



Mellman I et , Nature 2011

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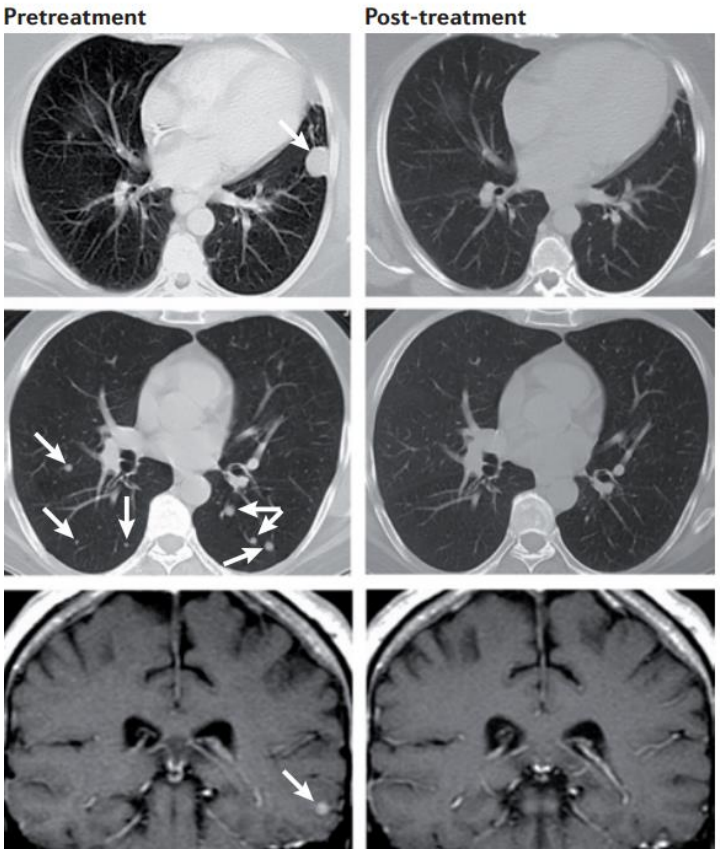
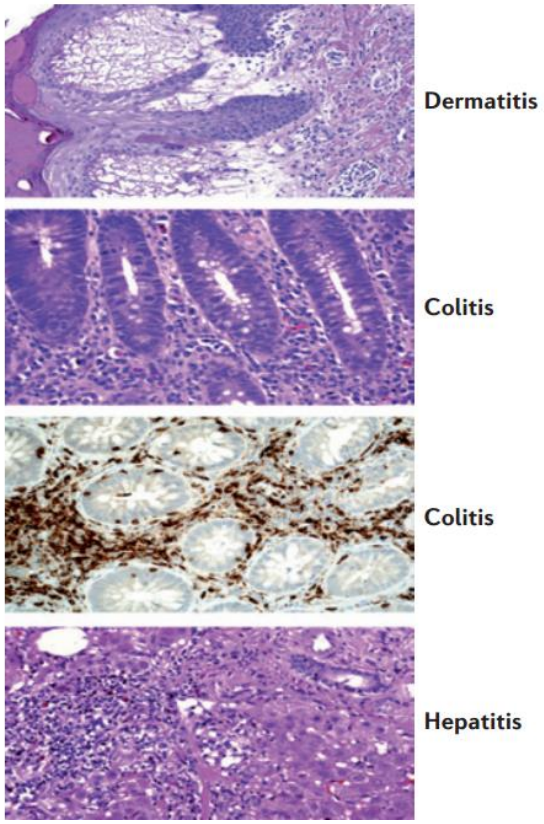
Toxicités des « check-point inhibiteurs »





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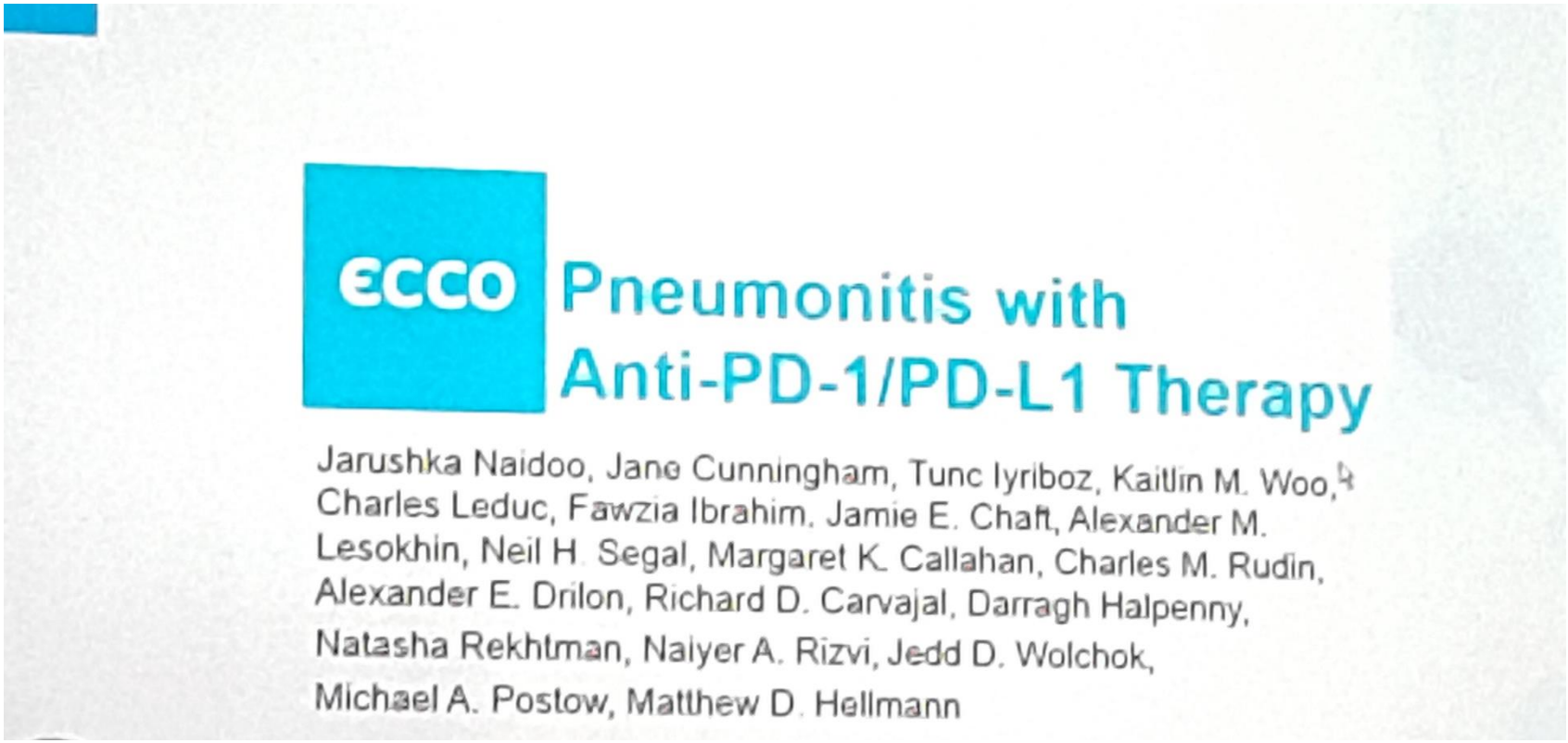
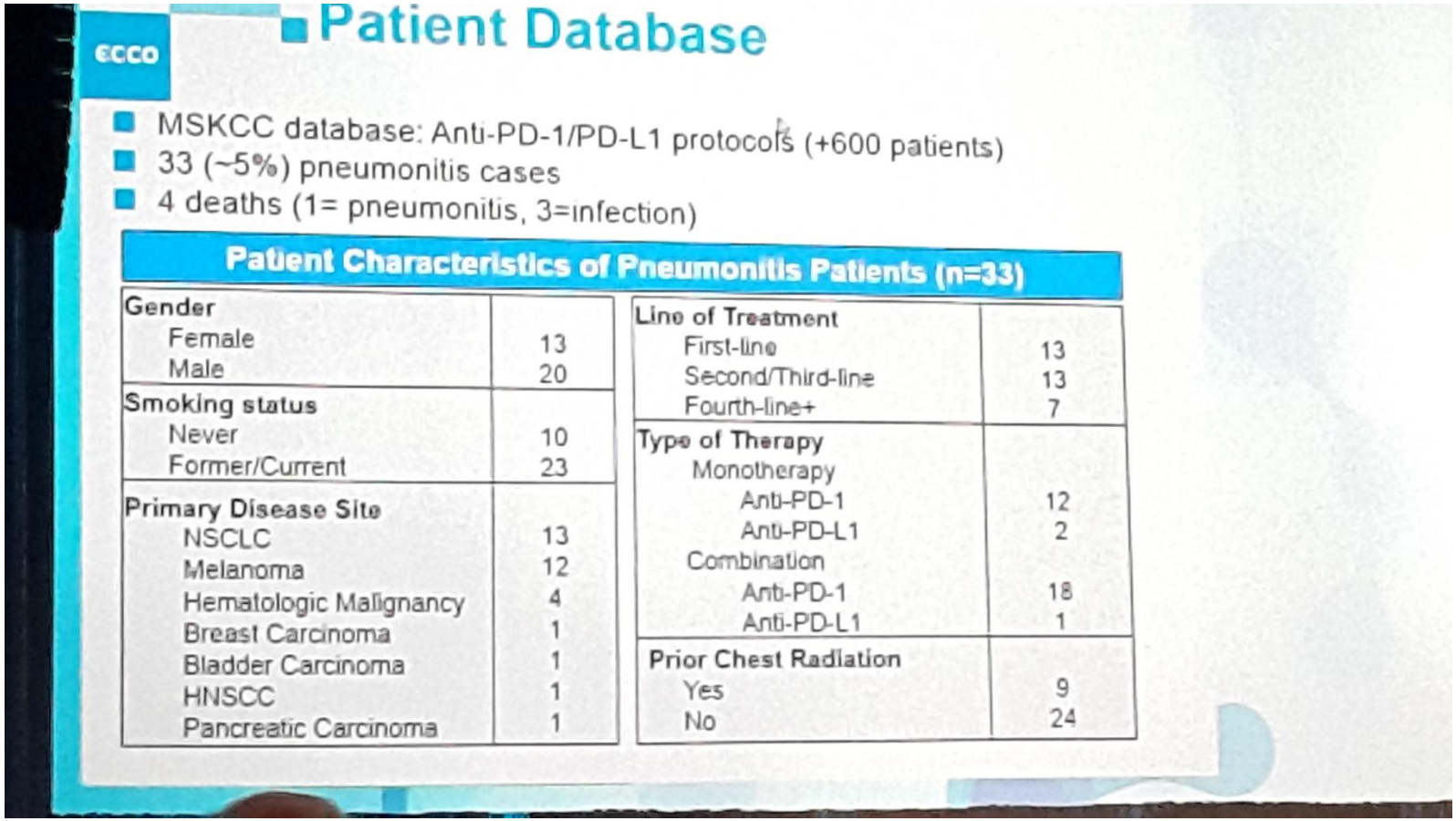
Pneumopathies interstitielles



Naidoo J et al abstract ESMO2015

Pneumopathies entre 2 et 5%



Naidoo J et al abstract ESMO/ECCO 2015

ecco

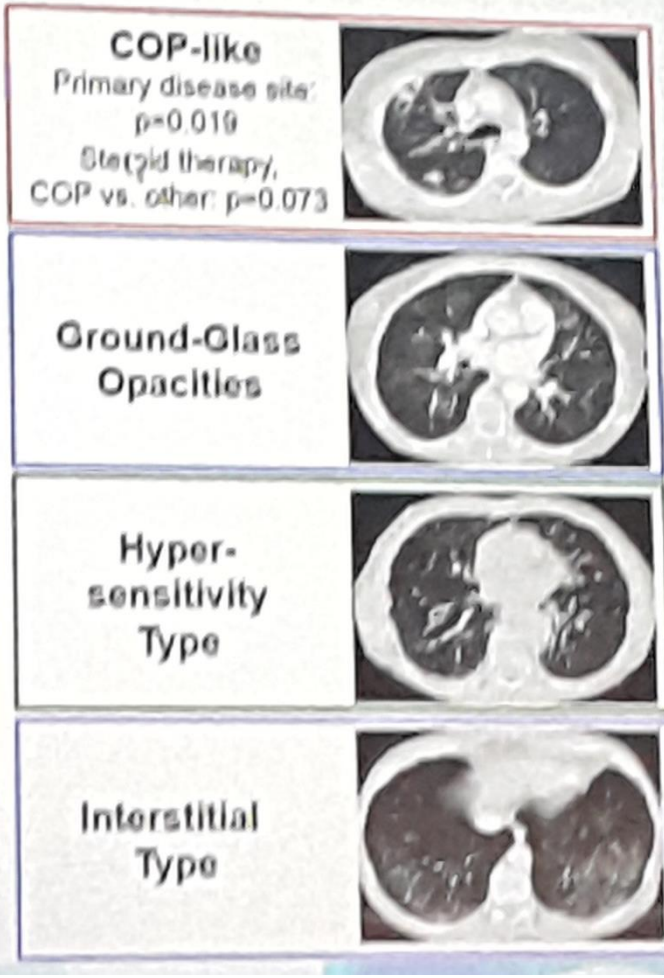
Radiologic Features

- 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 ESMO/ECCO 2015

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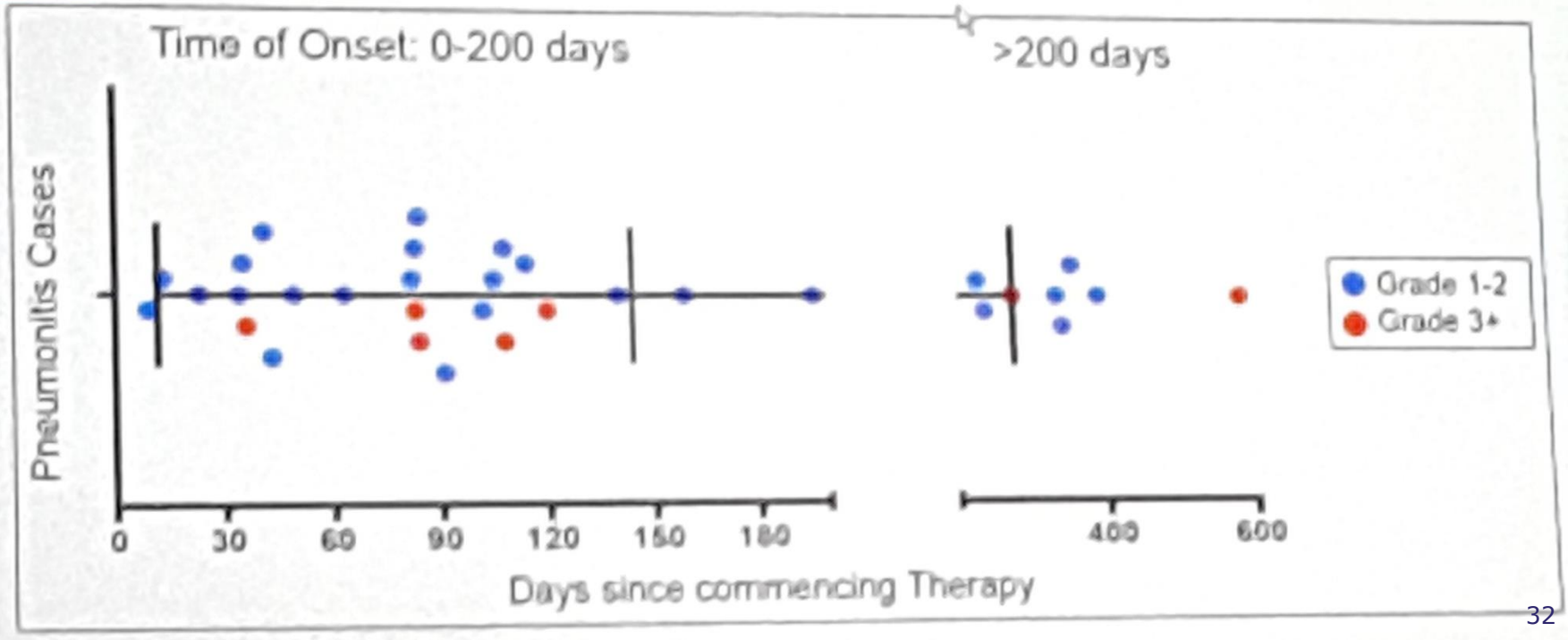
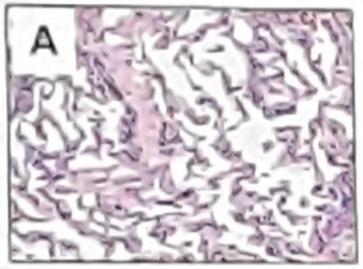
Timing of Pneumonitis



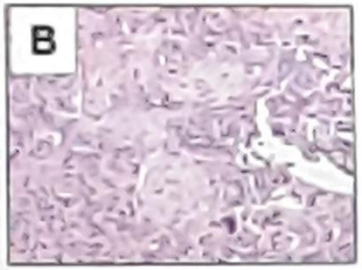
Naidoo J et al abstract ESMO2015

Pathologic Features

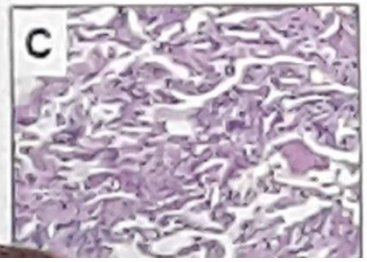
- 18/33 patients had bronchoscopy
- 7 patients had lung biopsy findings



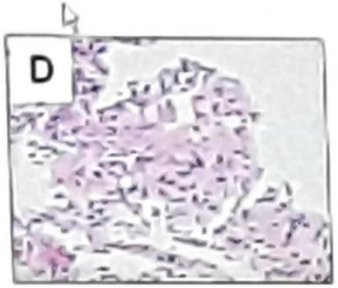
Cellular interstitial Pneumonitis (n=4)



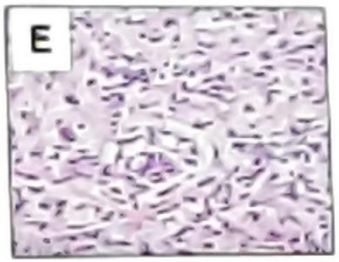
Organizing Pneumonia (n=2)



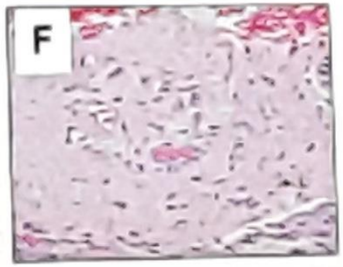
Diffuse Alveolar Damage (n=1)



Granulomas (n=2)



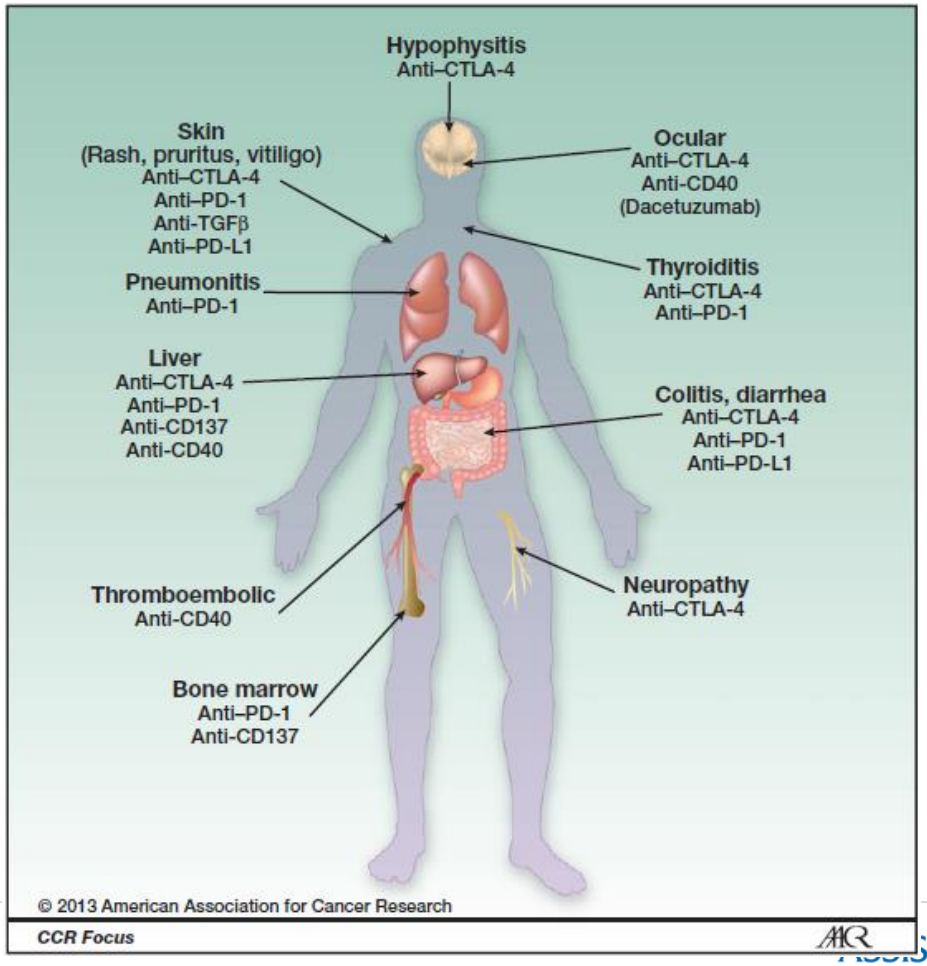
Eosinophils (n=3)



Vascular recanalization (n=1)

Naidoo J et al abstract ESMO/ECCO 2015

Toxicités de classe: Maladies auto-immunes



Essais en cours dans le cancer du sein

Reference	Status	Drug	Target	Patients	N	Results
Vonderheid,[108] 2010	Phase 1, completed	Tremelimumab + exemestane	CTLA-4	Metastatic ER+, HER2– BC	26	SD ≥12 weeks in 42%
Brahmer,[122] 2012	Phase 1, completed	BMS-936559	PD-1	Advanced carcinoma	207; 4 patients with BC	No efficacy data for patients with BC
Emens,[112] 2014	Phase 1, completed	MPDL3280A	PD-L1	Metastatic TNBC	9	ORR 33%; 1 CR
Nanda,[111] 2014	Phase 1, completed	MK-3475 (pembrolizumab)	PD-1	Metastatic TNBC	32	ORR 18.5%; 1 CR
NCT00083278	Phase 2, completed	MDX-10	CTLA-4	Metastatic BC	33	Not disclosed
NCT01502591	Phase 1, completed	Ipilimumab + cryoablation	CTLA-4	Early-stage BC before surgery	19	Not disclosed
NCT01792050	Phase 2, recruiting	Indoximod + taxane	IDO	Metastatic ER+, HER2– BC	≈154	
NCT01862900	Phase 1/2, recruiting	Anti-OX40 antibody + stereotactic radiation	OX40	Metastatic BC	≈40	
PANACEA NCT02129556	Phase 1b/2, not yet recruiting	MK-3475 (pembrolizumab)	PD-1	HER2+ BC resistant to trastuzumab	≈46	
BOSTON II NCT02303366	Phase 1, not yet recruiting	MK-3475 + stereotactic ablation	PD-1	Oligometastatic (1-5) BC	≈15	
NCT02309177	Phase 1, not yet recruiting	Nivolumab + nab-paclitaxel + gemcitabine + carboplatin	PD-1	Metastatic pancreatic cancer, NSCLC, and BC	≈138	

Gingras et al, Clinical Advances in Hematology & Oncology 2015

Quels sous types

- **Cancer du sein Triple négatif**
- **HER2+**
- **Luminales ?**

Quels sous-types?

Subtype[a]	Phenotype[a]	Treatment (non-metastatic)[b]	Treatment (metastatic)[b]	Tumor infiltration[c]
Luminal A	90% ER+ 89% PR+ 14% ERBB2+	Endocrine therapy with aromatase inhibitors and/or ER antagonists Chemotherapy with taxanes, anthracyclines or cyclophosphamide	First-line: endocrine therapy with aromatase inhibitors and/or ER antagonists, alone or combined with CDK4 inhibitors Second-line: MTOR inhibitors, generally in combination with endocrine therapy Others: chemotherapy with taxanes, anthracyclines or cyclophosphamide	2.9% LPBC phenotype Median stromal TILs = 10% Median intratumoral TILs = 1.5% TIL levels at diagnosis do not predict response to adjuvant chemotherapy in patients with non-metastatic disease
Luminal B	98% ER+ 82% PR+ 24% ERBB2+	Chemotherapy plus endocrine therapy with aromatase inhibitors and/or ER antagonists		
ERBB2-enriched	38% ER+ 20% PR+ 72% ERBB2+	Chemotherapy (with taxanes only, in patients with low tumor burden) plus trastuzumab Pertuzumab in patients with locally advanced disease, alone or combined with taxanes and trastuzumab	First-line: chemotherapy with taxanes plus trastuzumab and pertuzumab Second-line: trastuzumab emtansine (antibody-drug conjugate) Others: chemotherapy and/or targeted therapy with RTK inhibitors	11.1% LPBC phenotype Median stromal TILs = 15% Median intratumoral TILs = 3% TIL levels at diagnosis predict response to trastuzumab in patients with non-metastatic disease
Basal-like[d]	8% ER+ 7% PR+ 7% ERBB2+	Chemotherapy (including carboplatin in patients with *BRCA1* mutations)	Chemotherapy (including carboplatin in patients with *BRCA1* mutations)	10.6% LPBC phenotype Median stromal TILs = 20% Median intratumoral TILs = 5% TIL levels at diagnosis predict response to adjuvant chemotherapy in patients with non-metastatic disease

Kroemer et al , Nat Med 2015

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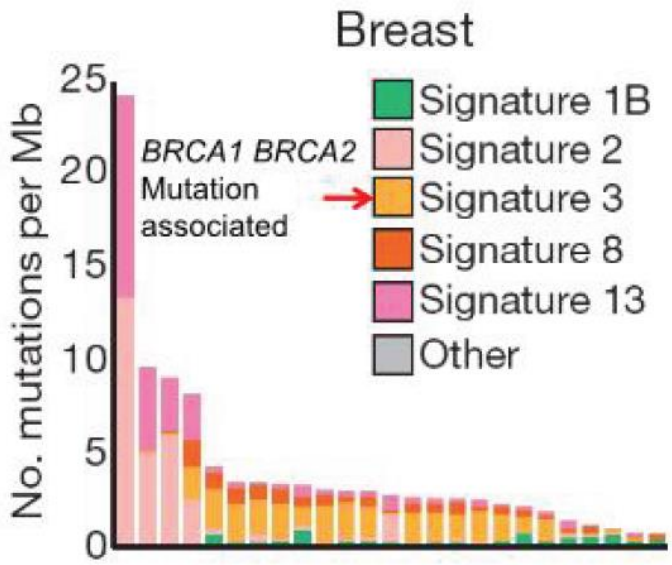
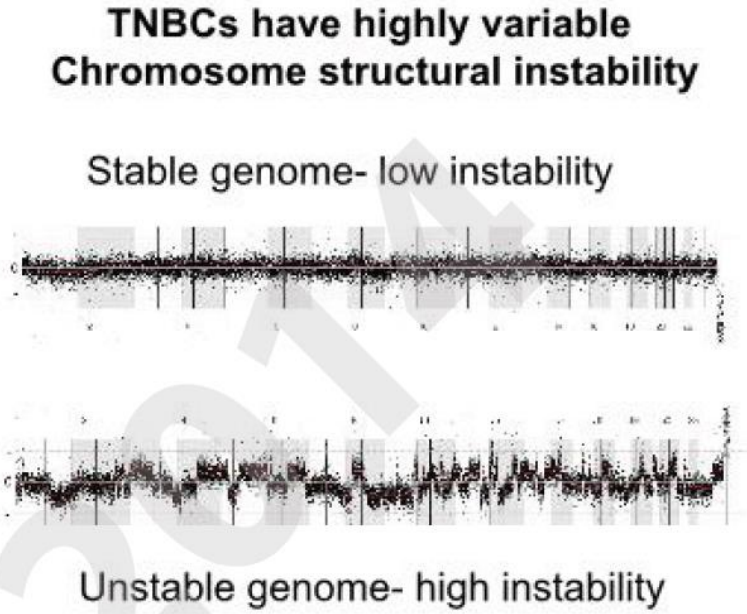
Cancers du sein Triple négatifs
En plus des TILS: taux de mutations élevés dans les cancer triples négatifs

Signatures of mutational processes in human cancer





Alexandrov et al Nature 2013

Pembrolizumab chez les patientes atteintes d'un cancer du sein triple-négatif *KEYNOTE-12*

- Cancer du sein en récidive ou métastatique RO–/RP–/HER2–
- ECOG PS 0-1
- Tumeur PD-L1+
- Pas de traitement corticoïde systémique
- Pas de maladie auto-immune (active ou antécédent)
- Pas de métastase cérébrale active

Pembrolizumab 10 mg/kg /2 sem.

- Réponse complète → Arrêt autorisé
- Réponse partielle ou maladie stabilisée → Traitement pendant 24 mois ou jusqu'à progression ou toxicité intolérable
- Progression confirmée → Arrêt

- Positivité de PD-L1 : 58 % des patientes testées avaient des tumeurs PD-L1+
- Traitement : 10 mg/kg i.v. Q2W
- Évaluation de la réponse : toutes les 8 semaines par RECIST v1.1

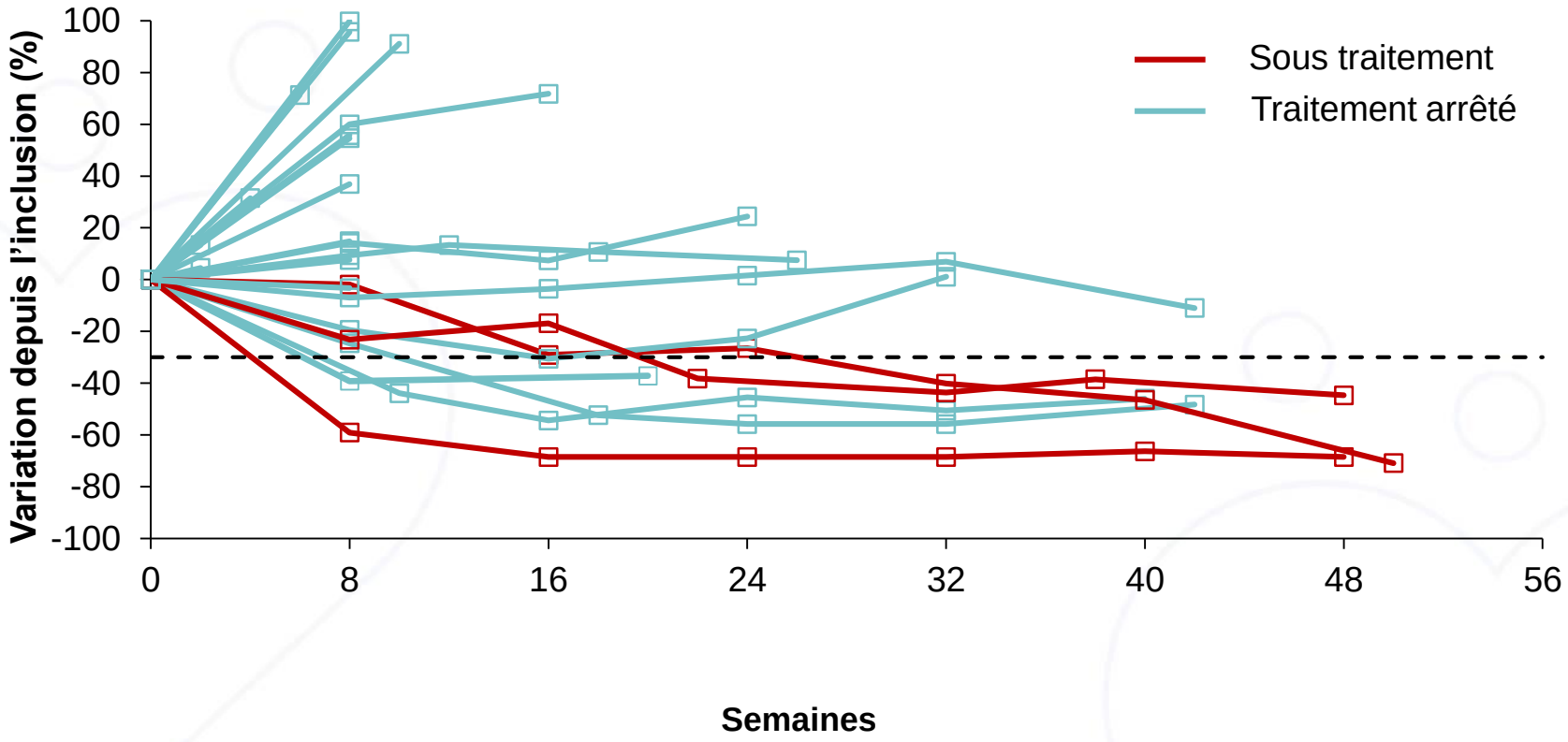
Pembrolizumab chez les patientes atteintes d'un cancer du sein triple-négatif

Meilleure réponse globale (RECIST v1.1, revue centralisée)

	Patientes évaluables (n = 27)
Réponse globale, n (%)	5 (18,5)
Meilleure réponse globale, n (%)	
Réponse complète	1 (3,7)
Réponse partielle	4 (14,8)
Maladie stabilisée	7 (25,9)
Maladie progressive	12 (44,4)
Patientes non évaluées	3 (11,1)

Pembrolizumab chez les patientes atteintes d'un cancer du sein triple-négatif

Variation depuis l'inclusion des lésions ciblées (revue centralisée)



Les Coups de cœur 2014 – D'après Nanda R et al., abstr. S1-09 actualisé

Pembrolizumab chez les patientes atteintes d'un cancer du sein triple-négatif

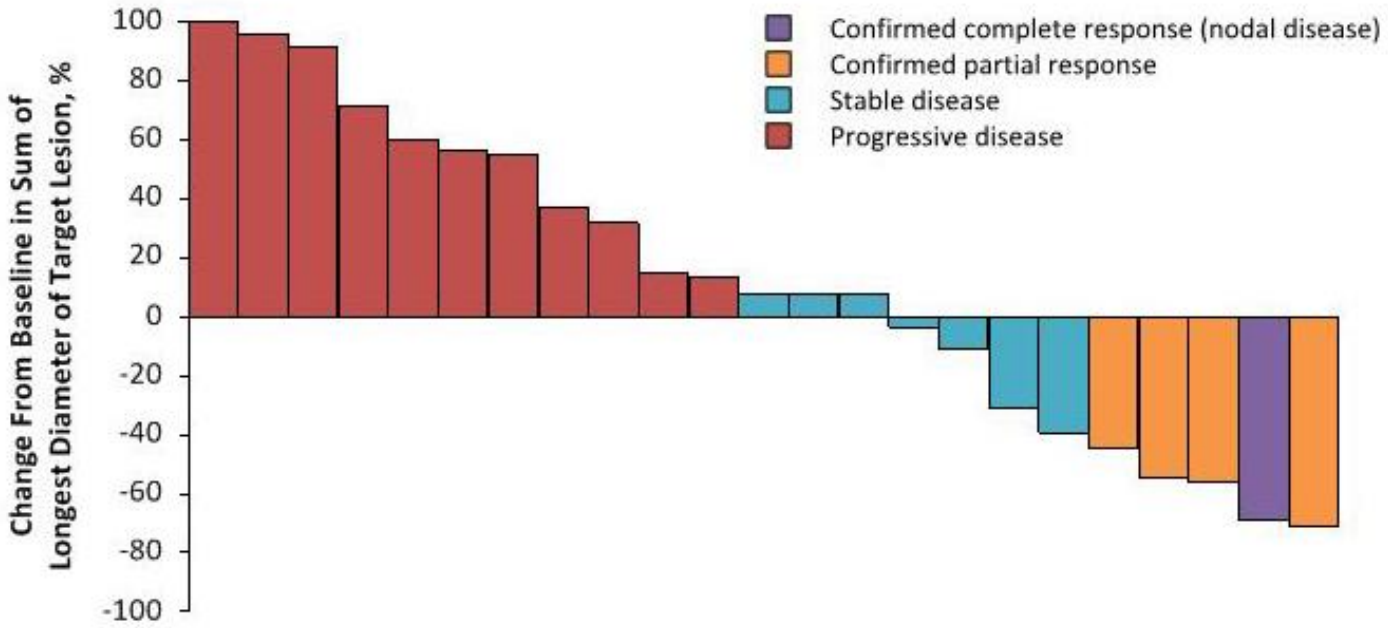
Effets indésirables

	Patientes évaluables (n = 32)
Tous grades, n (%)	18 (56,3)
Grade 3, n (%)	4 (12,5)
Grade 4, n (%)	1 (3,1)
Sérieux, n (%)	3 (9,4)
Décès dû au traitement, n (%)	1 (3,1)

- Temps médian de traitement par pembrolizumab : 59,5 jours (1-383)
- Événements indésirables de grade 3 liés au traitement : anémie (n = 1), maux de tête (n = 1), méningite aseptique (n = 1) et fièvre (n = 1)
- Événement indésirable de grade 4 lié au traitement : baisse du fibrinogène sanguin (n = 1)
- Événement indésirable lié au traitement ayant conduit au décès : coagulation intravasculaire disséminée

Keynote-12

Maximum Percentage Change From Baseline in Target Lesions (RECIST v1.1, Central Review)[a,b]



Les Rencontres Francophones
SABCS2014
Henry B. Gonzalez Convention Center
San Antonio, Texas, USA
9-13 DECEMBER 2014

Inhibition of PD-L1 by MPDL3280A leads to clinical activity in patients with metastatic triple-negative breast cancer

LA. Emens *et al.*, PD1-06

- **MPDL3280A**
  - Anticorps monoclonal anti-PD-L1
  - Humain, avec fragment Fc modifié
- **Phase I multicentrique avec une cohorte de cancers du sein métastatiques TPN avec expression de PD-L1 (TILs+ en IHC)**
- **Patients (N= 12)**
  - Atteinte viscérale (foie) pour 4 patientes (33%)
  - 92% pré-traitées par au moins 2 lignes de CT
    - *Anthracyclines (95%)*
    - *Taxanes (75%)*
    - *Platine (42%)*

Evénements indésirables reliés au traitement

- Grade 3-4 = 8% (1 insuffisance surrénale)
- Evénements indésirables immunologiques
  - *(1 épisode Fièvre grade 2)*
- Pas de décès toxique

9 patientes évaluables pour la réponse

- 3 réponses objectives (33% ; 1 RC et 2 RP)
- Obtenue dans les 6 semaines pour les 3 patientes
- 2 réponses supplémentaires mais avec apparition de nouvelles lésions (pseudoprogression ?)
- Durée médiane de réponse non atteinte

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

LA. Emens *et al.*, SABCS 2014, PD1-06

SABCS2015
Henry B. Gonzalez Convention Center
San Antonio, Texas, USA
8-12 DECEMBER 2015
Les Rencontres Francophones

AVELUMAB (MSB0010718C), AN ANTI-PD-L1 ANTIBODY, IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC BREAST CANCER: A PHASE IB JAVELIN SOLID TUMOR TRIAL

DIRIX L.Y. et al. – S1-04

Anti-PD-L1 et cancer du sein métastatique : design

SABCS 2015

Patients

- Cancer du sein métastatique ou localement avancé réfractaire ou progressant après traitement standard
  - ≤ 3 lignes cytotoxiques
  - Anthracyclines et taxanes préalables
  - Biopsie ou spécimen chirurgical disponible
- PS 0-1
- Pas de sélection sur l'expression PD-L1
- Pas de sélection sur le sous-type moléculaire (HER2/ER/PR)

Dosage

- Avelumab
- 10 mg/kg/IV
- Toutes les 2 semaines
- Jusqu'à progression

Objectifs

- Sécurité-tolérance
- Meilleure réponse objective (RECIST 1.1)
- PD-L1 expression (IHC)

Anti-PD-L1 et cancer du sein métastatique : patients

SABCS 2015

Caractéristiques	N=168
Âge médian, années (range)	53 (31-81)
ECOG PS, n (%)	
0	83 (49,4)
1	85 (50,6)
Sous-types moléculaires, n (%)	
TNBC	58 (34,5)
HER2-/ER ou PR+	72 (42,9)
HER2+	26 (15,5)
UK	12 (7,1)
Nombre de lignes préalables (hors adj/néo-adj)	
≥ 3	88 (52,4)
2	35 (20,8)
≤ 1	45 (26,8)
Nombre médian (range)	3 (0-10)
Intervalle médian diagnostic métastase – tumeur primitive Mois (range)	21,6 (0,7-176)

Population TNBC

Caractéristiques	N=58
Âge médian, années (range)	52,5 (31-80)
ECOG PS, n (%)	
0	33 (56,9)
1	25 (43,1)
Nombre de lignes préalables (hors adj/néo-adj)	
≥ 3	13 (22,4)
2	16 (27,6)
≤ 1	29 (50)
Intervalle médian diagnostic métastase – tumeur primitive Mois (range)	13,2 (0,7-176,8)

Dirix LY *et al.*, SABCS 2015, S1-04

Anti-PD-L1 et cancer du sein métastatique : toxicités

SABCS 2015

Nombre de patients avec EI	EI reliés au traitement, n (%)	EI reliés au traitement, grade 3-4 n (%)
Toute toxicité liée au traitement	115 (68,9)	23 (13,7)
Fatigue	32 (19,0)	3 (1,8)
Réaction à l'injection	24 (14,3)	0
Nausées	22 (13,1)	0
Diarrhées	15 (8,9)	0
Arthralgies	13 (7,7)	1 (0,6)
Anorexie	12 (7,1)	0
Syndrome pseudo-grippal	11 (6,5)	0
GGT increase	4 (2,4)	3 (1,8)
Hépatite auto-immune	3 (1,8)	3 (1,8)
Anémie	3 (1,8)	3 (1,8)

Dirix LY *et al.*, SABCS 2015, S1-04

Anti-PD-L1 et cancer du sein métastatique : efficacité

SABCS 2015

Meilleur réponse globale	Population globale n=168	Population TNBC n=58
CR, n(%)	1 (0,6)	0
PR, n(%)	7 (4,2)	5 (8,6)
SD[†], n(%)	39 (23,2)	13 (22,4)
PD, n(%)	106 (63,1)	38 (65,5)
Non-evaluable[‡], n (%)	15 (8,9)	2 (3,4)
ORR, % (95% CI)	4,8 (2,1 – 9,2)	8,6 (2,9 – 19,0)
DCR[§], %	28,0	31,0

CR = complete response, PR= partial response, SD = stable disease,
PD = progressive disease, ORR = overall response rate, DCR = disease control rate, CR+PR+ SD

Dirix LY *et al.*, SABCS 2015, S1-04

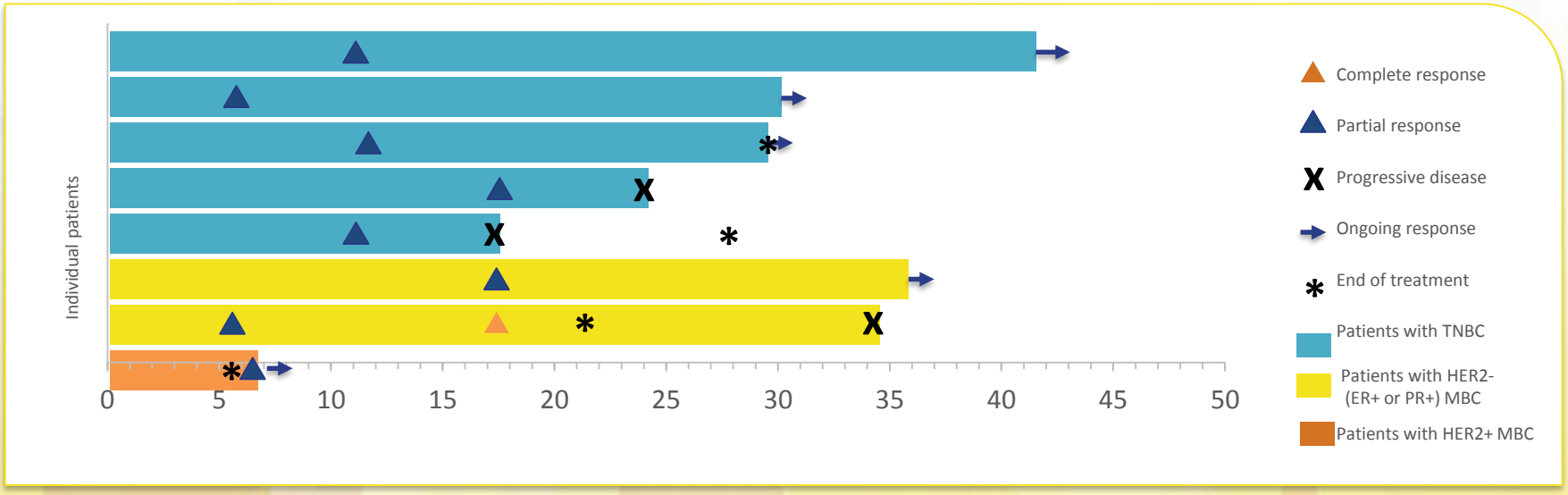
Anti-PD-L1 et cancer du sein métastatique : efficacité

SABCS 2015

Réponse selon le sous-type

PD-L1 expression (total évaluable = 48)	n/N1† (%)	95% CI
TNBC	5/58 (8,6)	2,9 - 19,0
HER2-/ER+ or PR+	2/72 (2,8)	0,3 - 9,7
HER 2+	1/26 (3,8)	0,1 - 19,6

- 5 des 8 répondeurs sont des TNBC
- Quelques réponses dans les autres sous-types…
- Durables (médiane = 28,7 semaines)



Dirix LY *et al.*, SABCS 2015, S1-04

Anti-PD-L1 et cancer du sein métastatique : efficacité

SABCS 2015

- **Réponse selon l'expression PD-L1**

Population globale

PD-L1 expression (total evaluable = 136)*	PD-L1+, n/N1† (%)	PD-L1-, n/N1† (%)	*p*-value‡
≥ 1 % tumor cells cut-off	3/85 (3,5)	4/51 (7,8)	*0,425*
≥ 5 % tumor cells cut-off	1/23 (4/3)	6/113 (5,3)	*1,000*
≥ 2,5 % tumor cells cut-off	0/3 (0)	7/133 (5,3)	*1,000*
≥ 10 % immune cell « hotspost » cut-off	**4/12 (33,3)**	3/124 (2,4)	*0,001*

Population TNBC

PD-L1 expression (total evaluable = 48)	PD-L1+, n/N1† (%)	PD-L1-, n/N1† (%)
≥ 1 % cut-off	2/33 (6,1)	3/15 (20,0)
≥ 5 % cut-off	1/13 (7,7)	4/35 (11,4)
≥ 2,5 % cut-off	0/2 (0)	5/46 (10,9)
≥ 10 % immune cell « hotspost » cut-off	**4/9 (44,4)**	1/39 (2,6)

Association significative entre le taux de réponse et l'expression de PD-L1 par les cellules immunes intra-tumorales ("hot-spot")

Dirix LY *et al.*, SABCS 2015, S1-04

SABCS2015
Henry B. Gonzalez Convention Center
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8-12 DECEMBER 2015
Les Rencontres Francophones

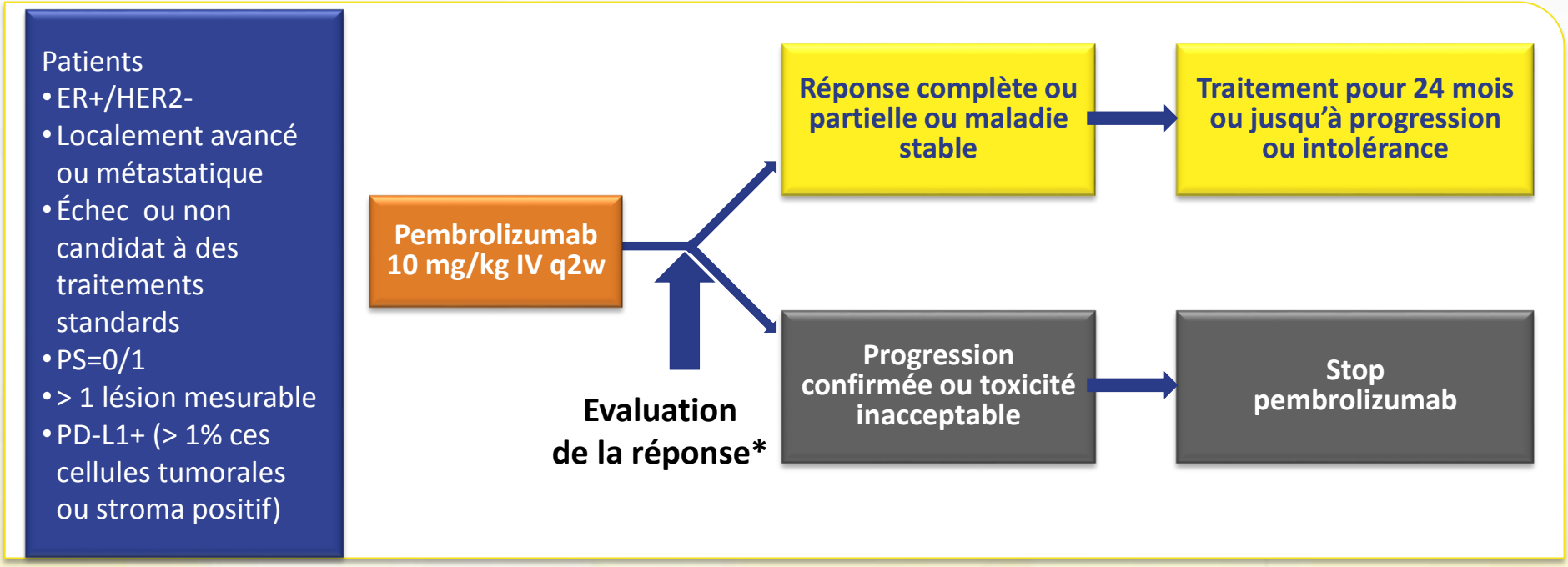
PRELIMINARY EFFICACY AND SAFETY OF PEMBROLIZUMAB (MK-3475) IN PATIENTS WITH PD-L1–POSITIVE, ESTROGEN RECEPTOR-POSITIVE (ER+)/HER2-NEGATIVE ADVANCED BREAST CANCER ENROLLED IN KEYNOTE-028

Rugo HS *et al.* – S5-07

KEYNOTE-028 : pembrolizumab et cancer du sein RE+/HER2-

SABCS 2015

Design



- **261 inclus - 248 analysés – 48 positifs pour PD-L1 - 25 traités**

*Evaluation de la réponse : toutes les 8 semaines pour les 6 premiers mois ; puis toutes les 12 semaines

Critère de jugement principal : taux de réponse globale (RECIST v1.1) et sécurité

Critères de jugement secondaires : PFS, OS, durée de réponse

Rugo HS *et al.*, SABCS 2013, S5-07

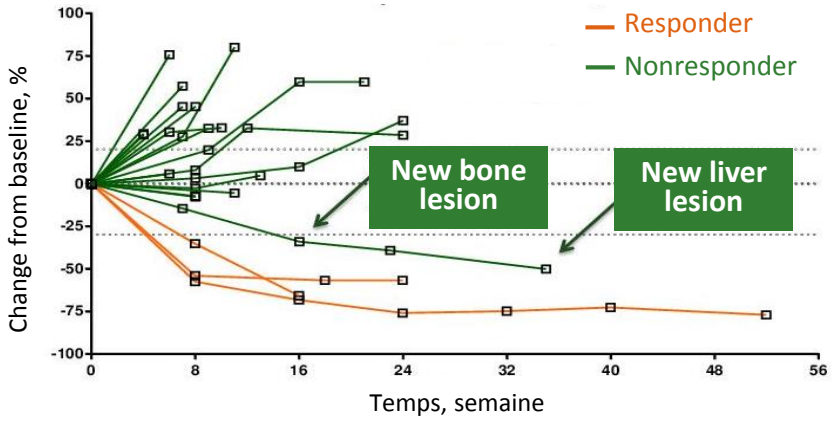
KEYNOTE-028 : pembrolizumab et cancer du sein RE+/HER2-

SABCS 2015

- **Activité anti-tumorale (RECIST 1.1)**

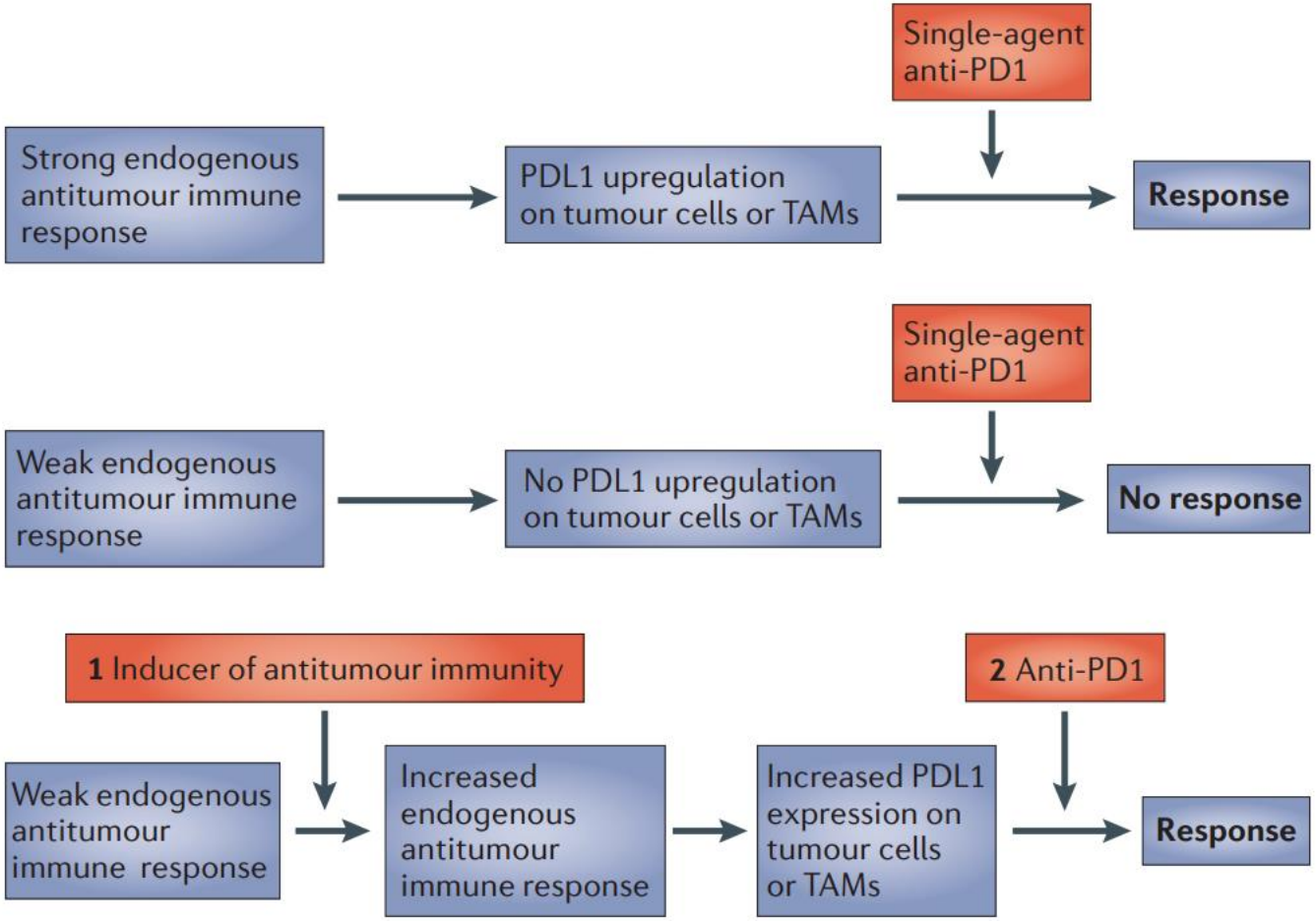
	n (%)	95% CI
Taux de réponse global	3 (12,0)	2,5 – 31,2
Réponse complète	0 (0,0)	0,0 – 13,7
Réponse partielle	3 (12,0)	2,5 – 31,2
Maladie stable	4 (16,0)	4,5 – 36,1
Bénéfice clinique	5 (20,0)	6,8 – 40,7
Maladie progressive	15 (60,0)	38,7 – 78,9
NE	3 (12,0)	2,5 – 31,2

Les réponses sont peu fréquentes mais semblent durables !



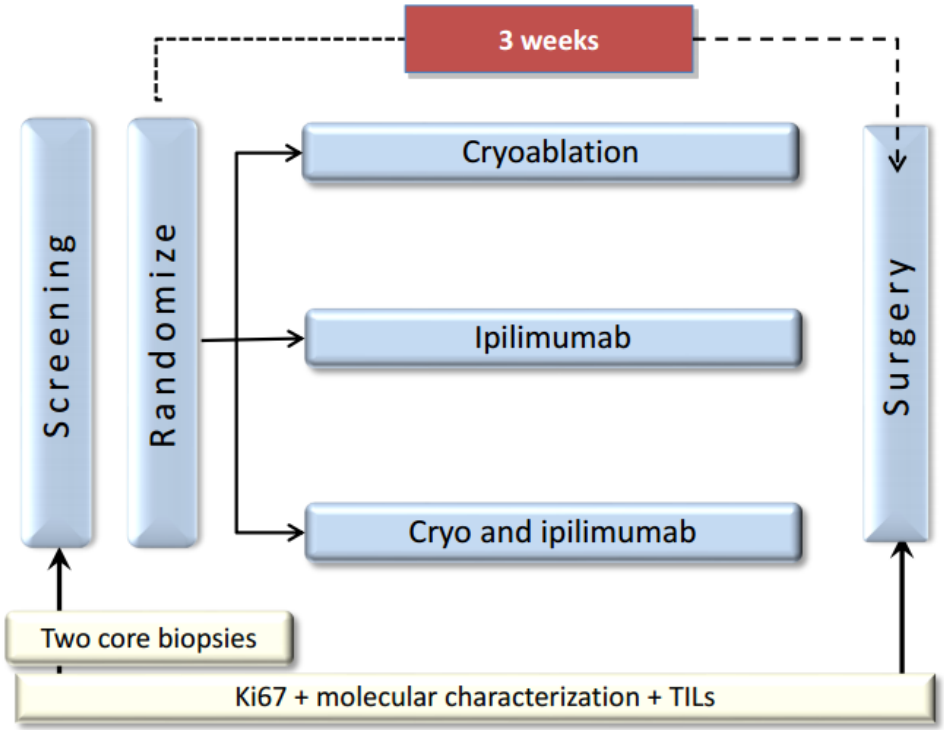
Rugo HS *et al.*, SABCS 2013, S5-07

Perpectives; les combinaisons afin d'augmenter l'immunogénicité et/ou l'activation du système immunitaire



Pardoll et al Nat Rev Cancer 2012

Perpectives; les combinaisons afin d'augmenter l'immunogénicité et/ou l'activation du système immunitaire



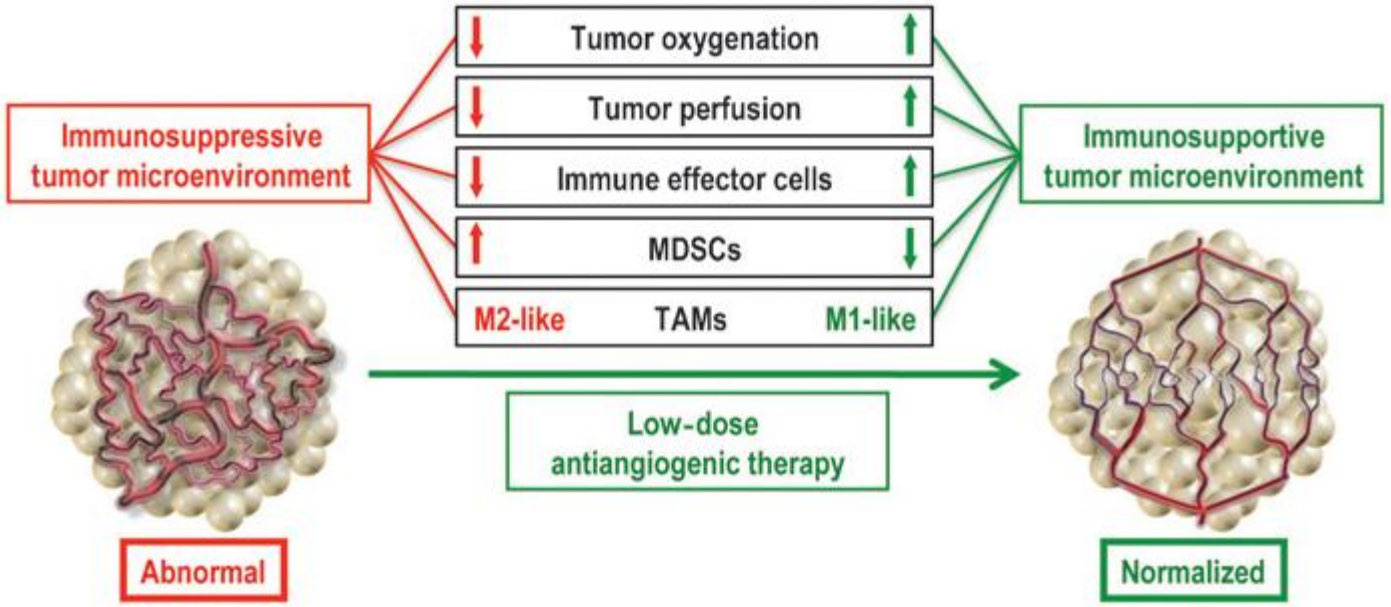
- Resectable tumor
- Diameter ≥1.5 cm by ultrasound
- Grade II-III

Primary Endpoint
- Proliferation: Ki67
- TILs following treatment

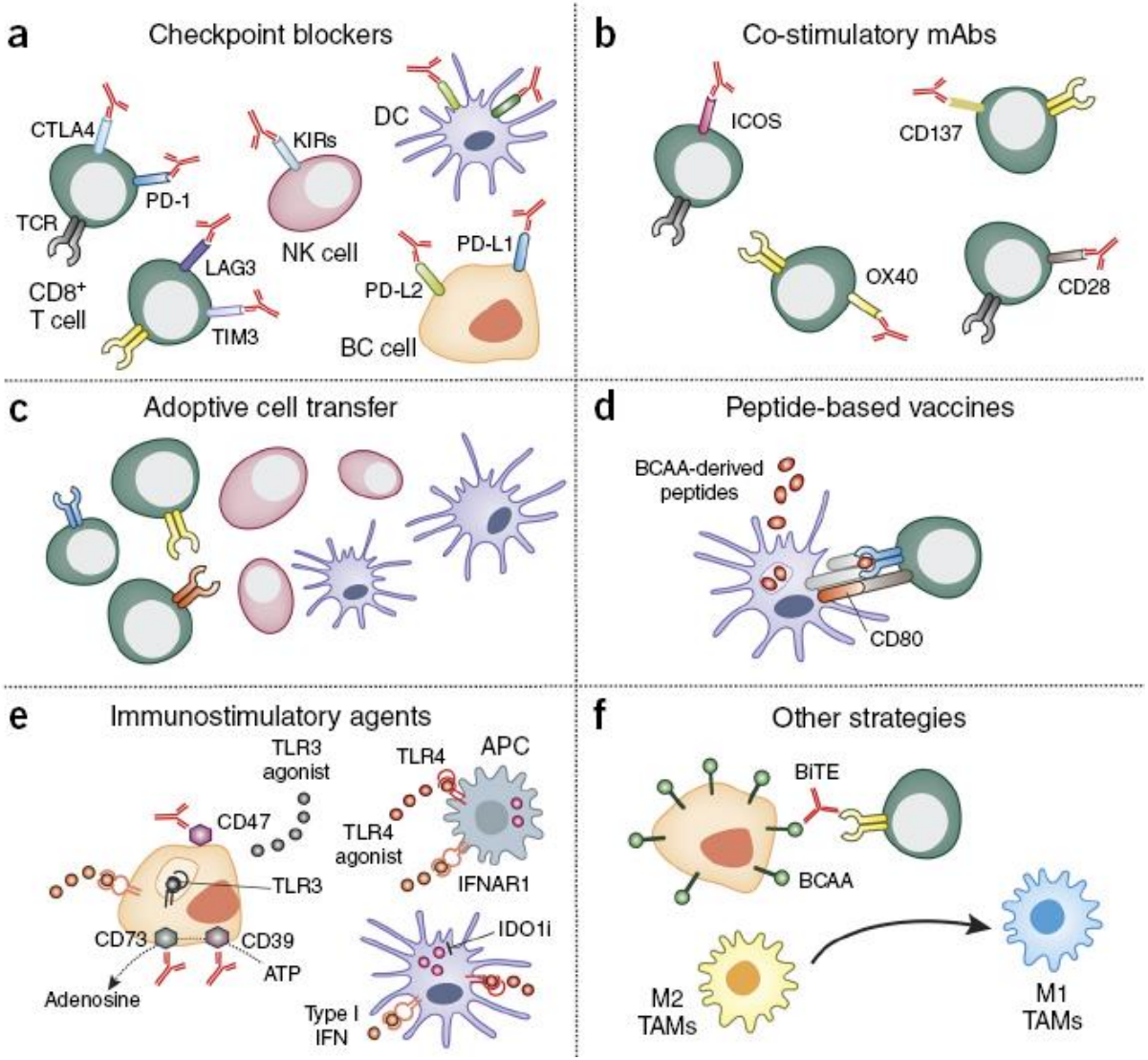
Secondary Endpoints
Systemic Inflammatory response

Diab A. et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 1098)

Combinaisons; retour du bevacizumab?



Hyang Y et al, Cancer Res 2013



Kroemer et al, Nat Med 2015

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