

Immunothérapie dans le cancer du sein

Luis Teixeira

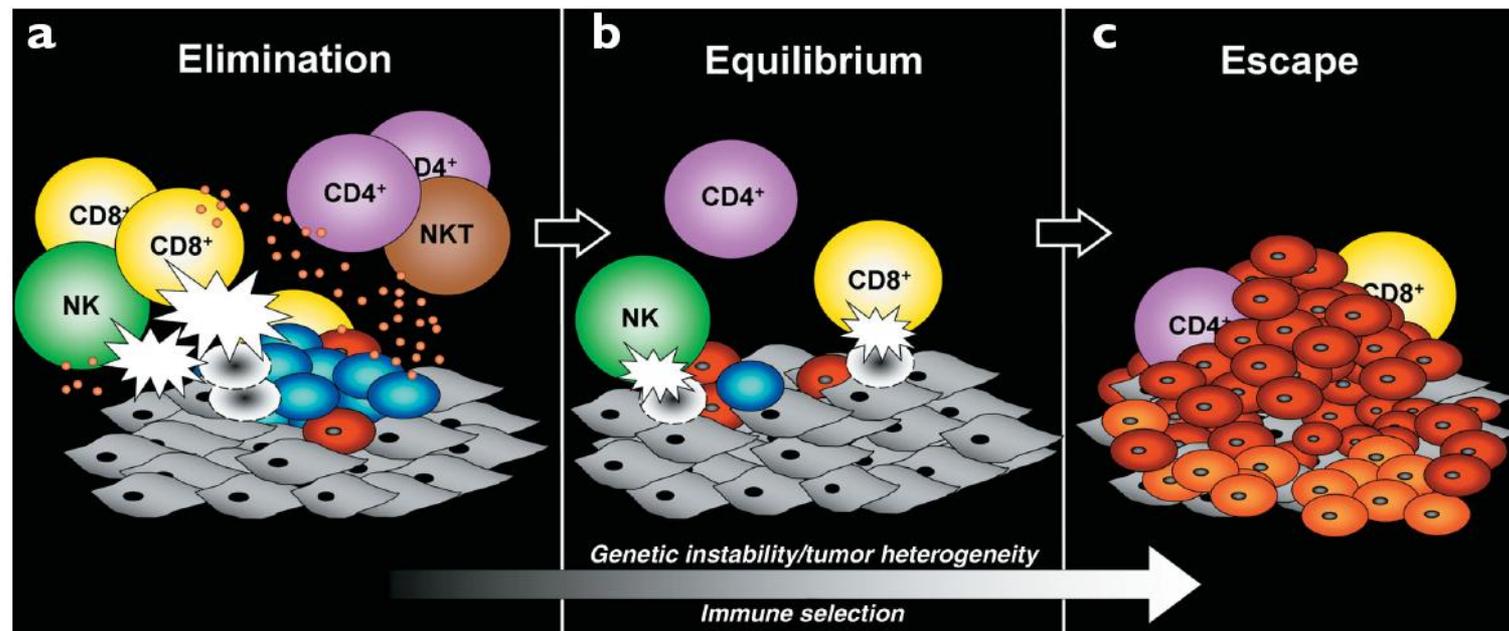
Journées de sénologie de Saint Louis

25 septembre 2015

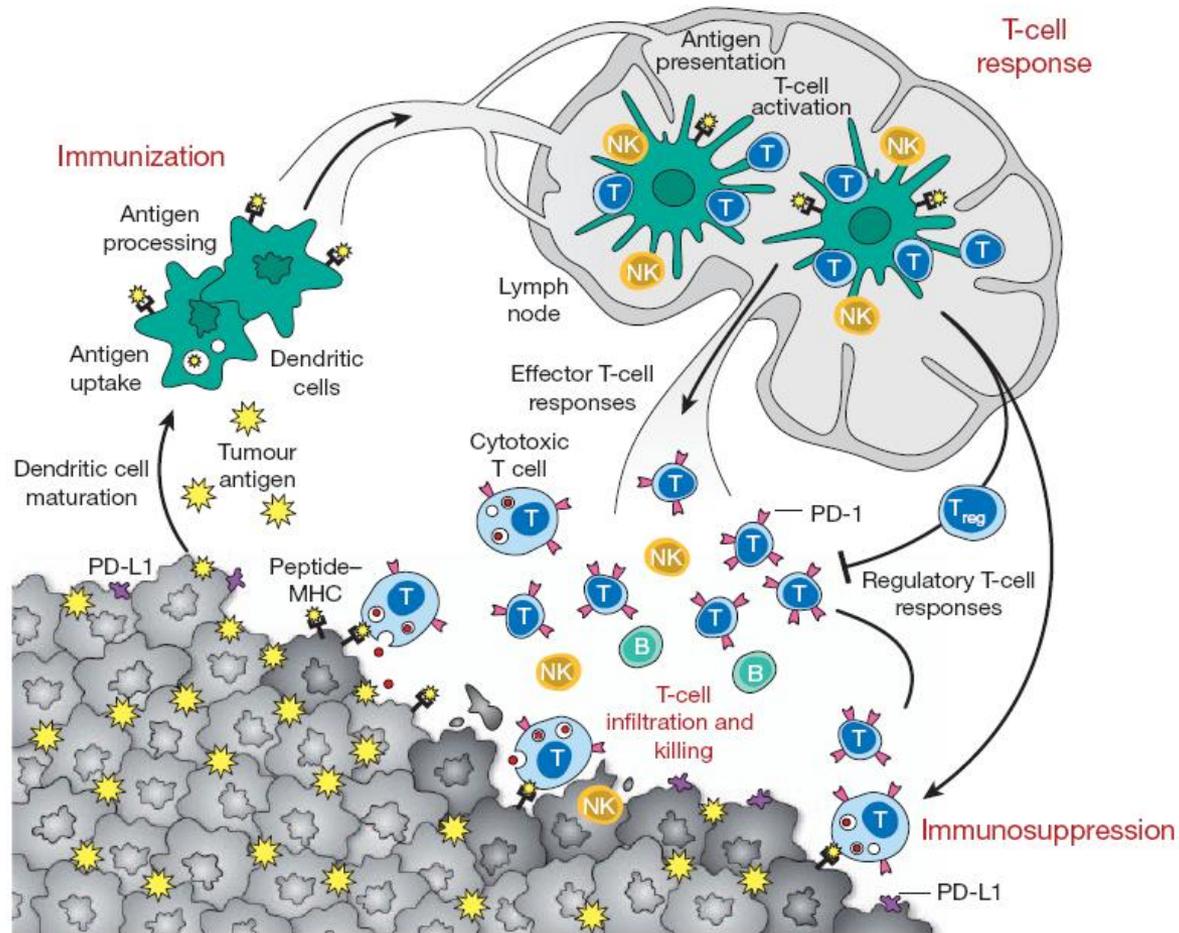
Plan

- **Rationnel**
- **Différentes approches**
- **Arguments pour immunogénicité des cancers du sein**
- **Les « Check-points » inhibiteurs**
- **Autres approches**
- **Perspectives.**

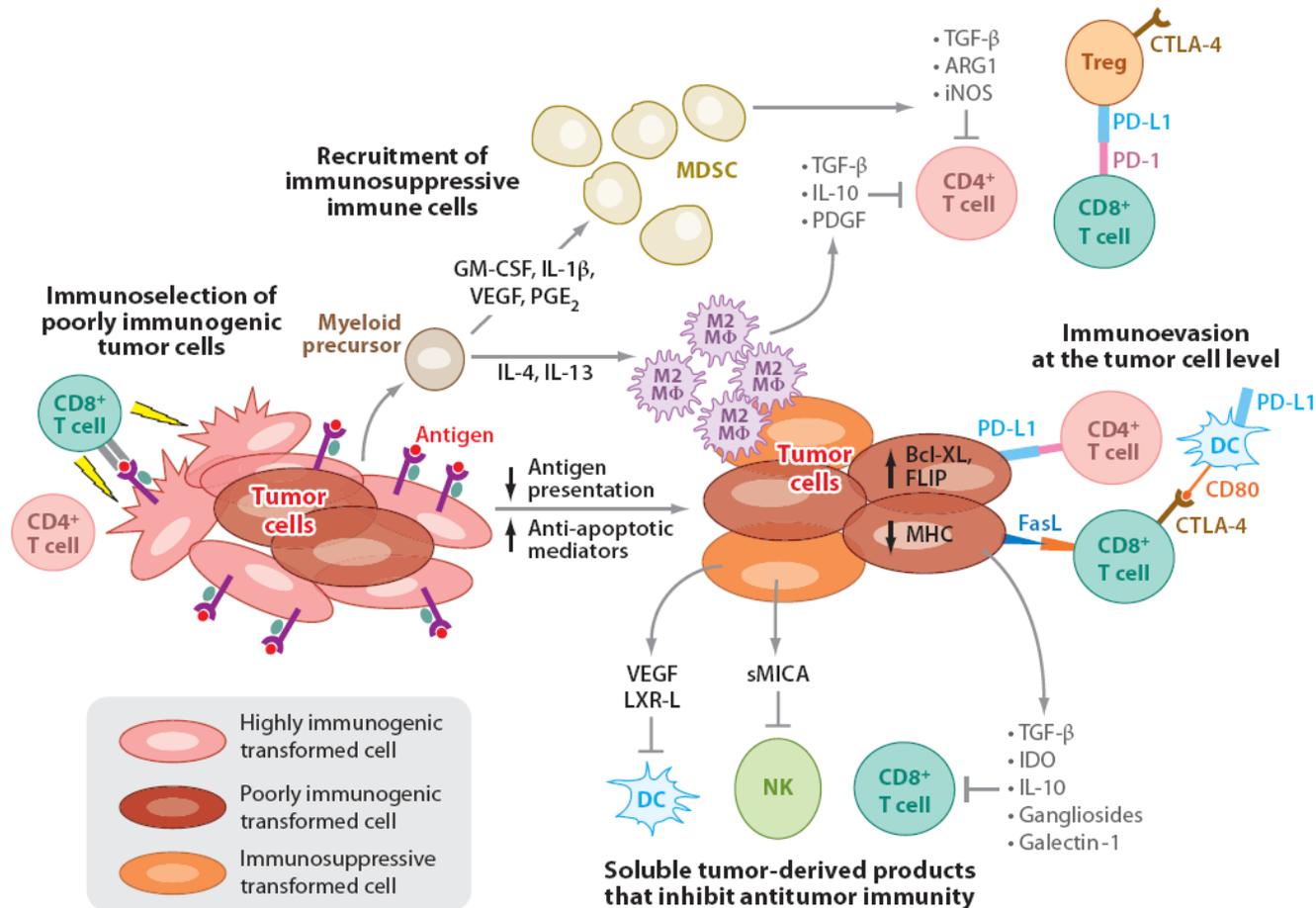
Concept d'immunosurveillance et d'immunoediting: les 3E



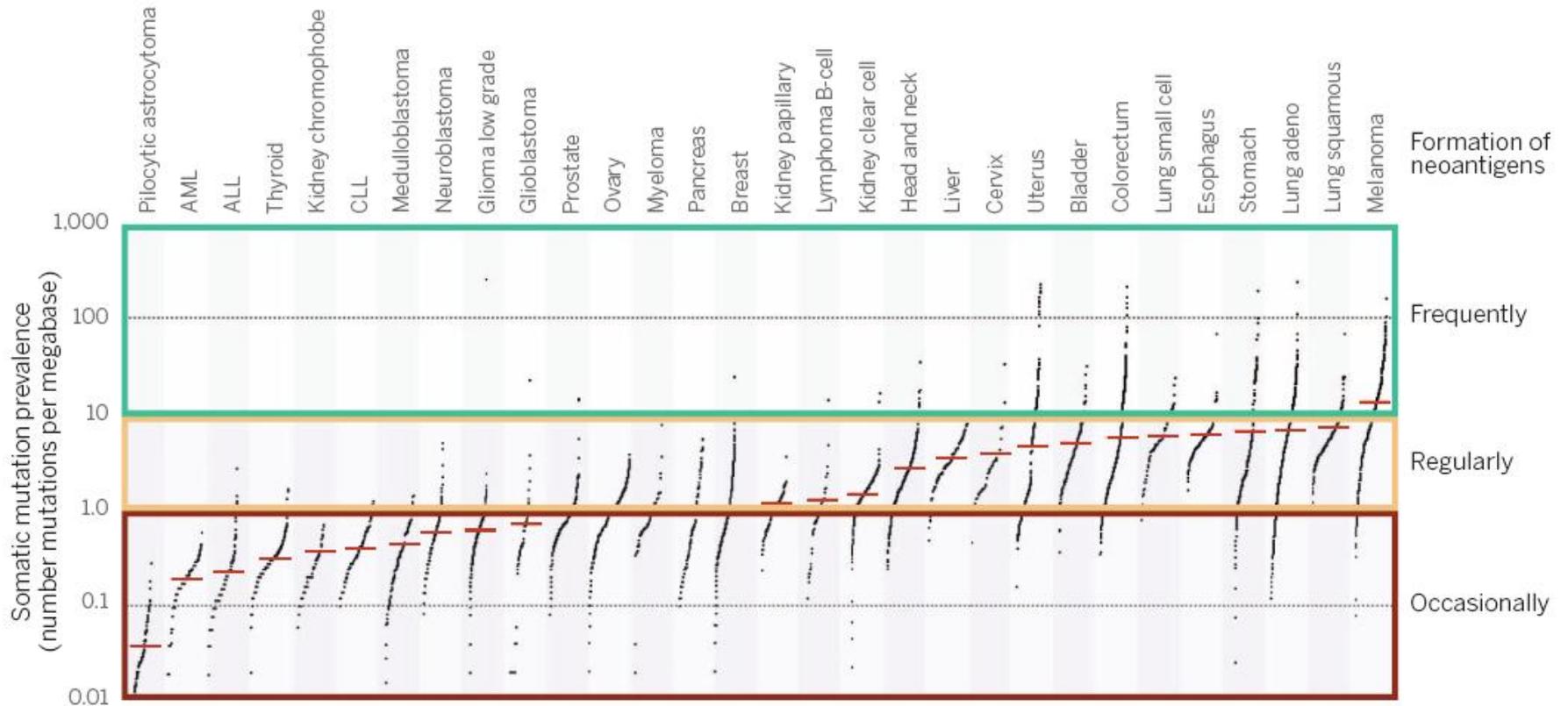
Intervention de l'immunité innée et acquise



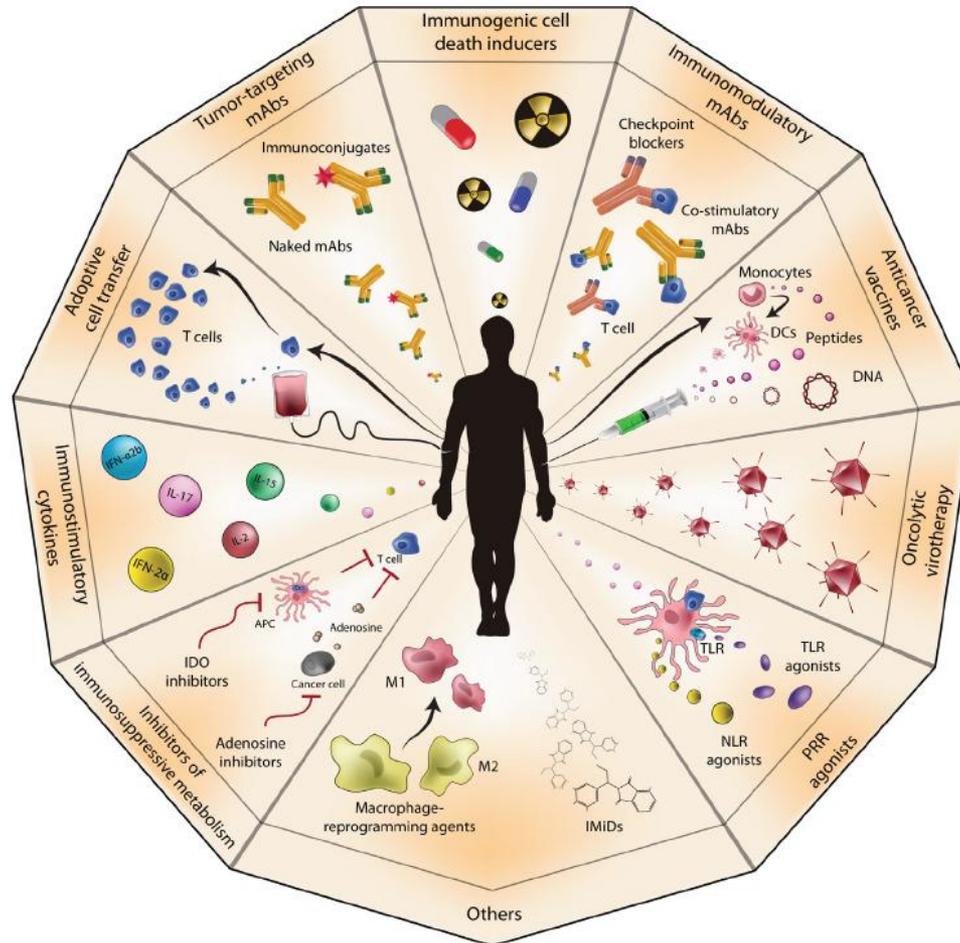
Principaux mécanismes d'échappement



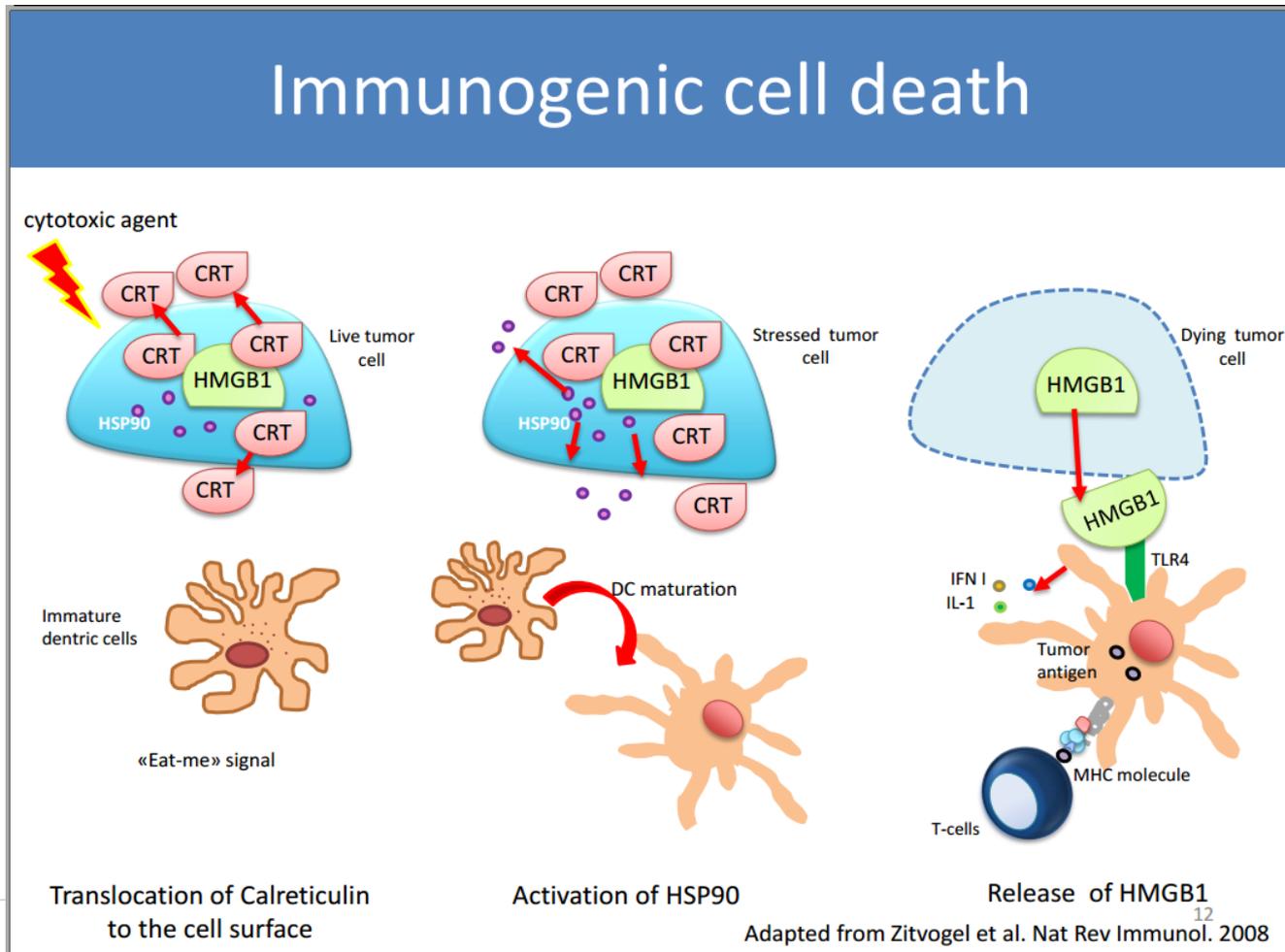
Théorie des Néoantigènes



Différents types d'immunothérapies dans le traitement du cancer



■ Action des cytotoxiques en partie par un mécanisme immunologique



Adapted from Zitvogel et al. Nat Rev Immunol. 2008

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

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

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

■ TILS corrélés à un meilleur pronostic

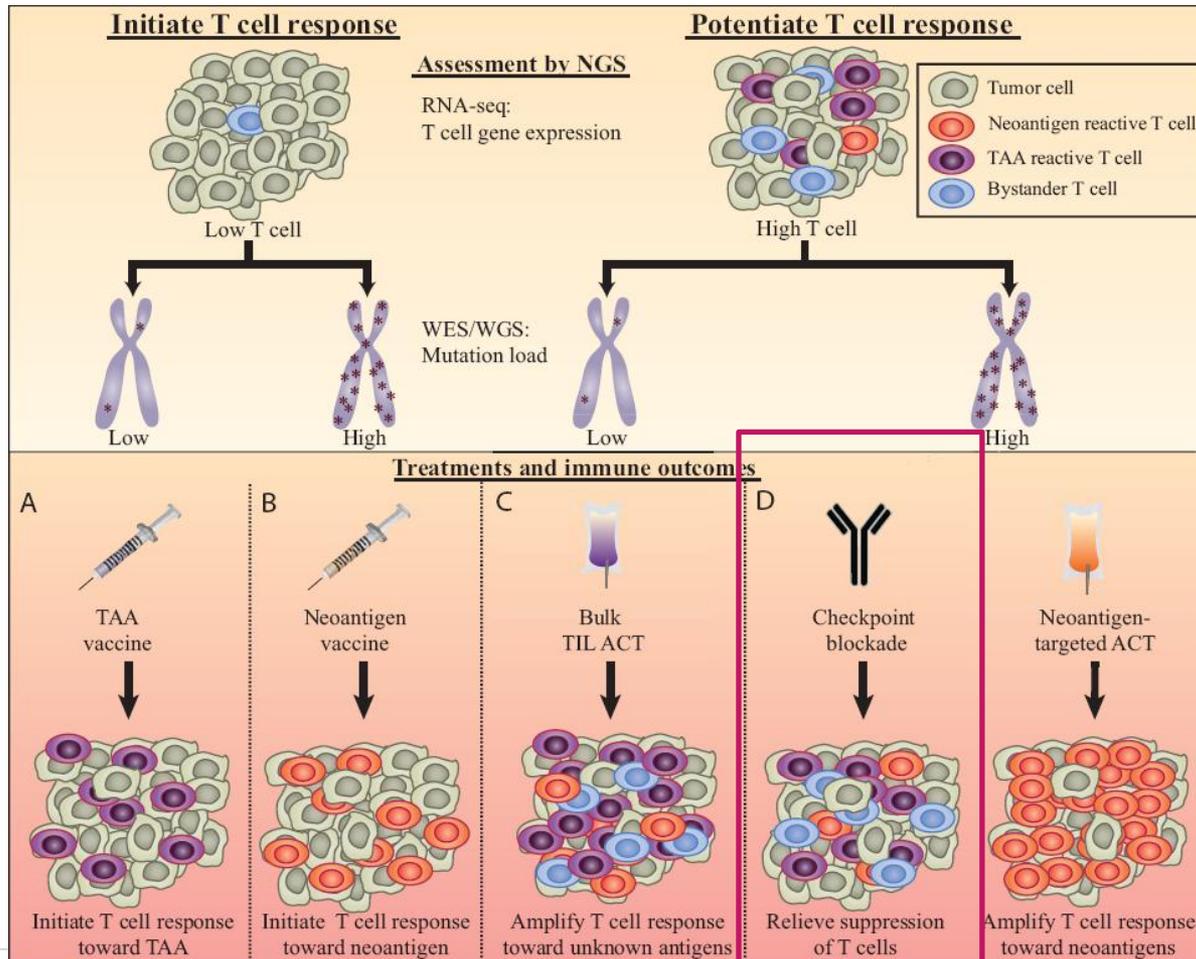
Reference	N	Trial	Endpoint	Subtype analyzed	Result
Denkert (JCO, 2010)	840	GBG G-3	pCR	all	pCR:41% in TIL+ BC Validated in G-5
Loi (JCO, 2013)	2009	BIG 2-98	DFS	Preplanned analysis of molecular subtypes	Prognostic impact in TNBC (n=256): HR:0.31 (0.11-0.84)
Loi (AnnOnc, 2014)	935	FinHer	DFS	Preplanned 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)

6

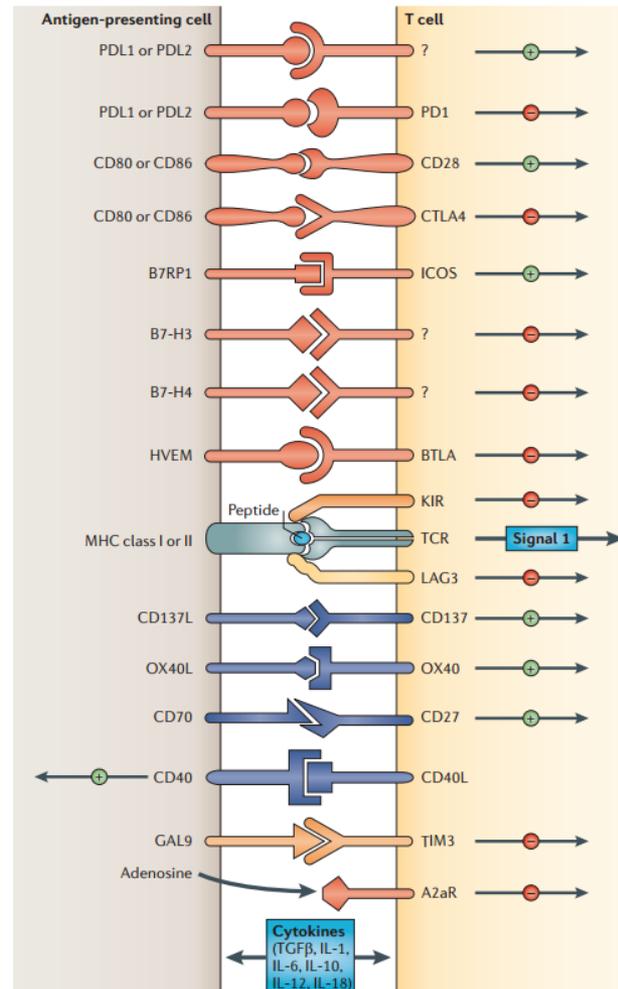
Plusieurs signatures « immunologiques » Pronostiques

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.

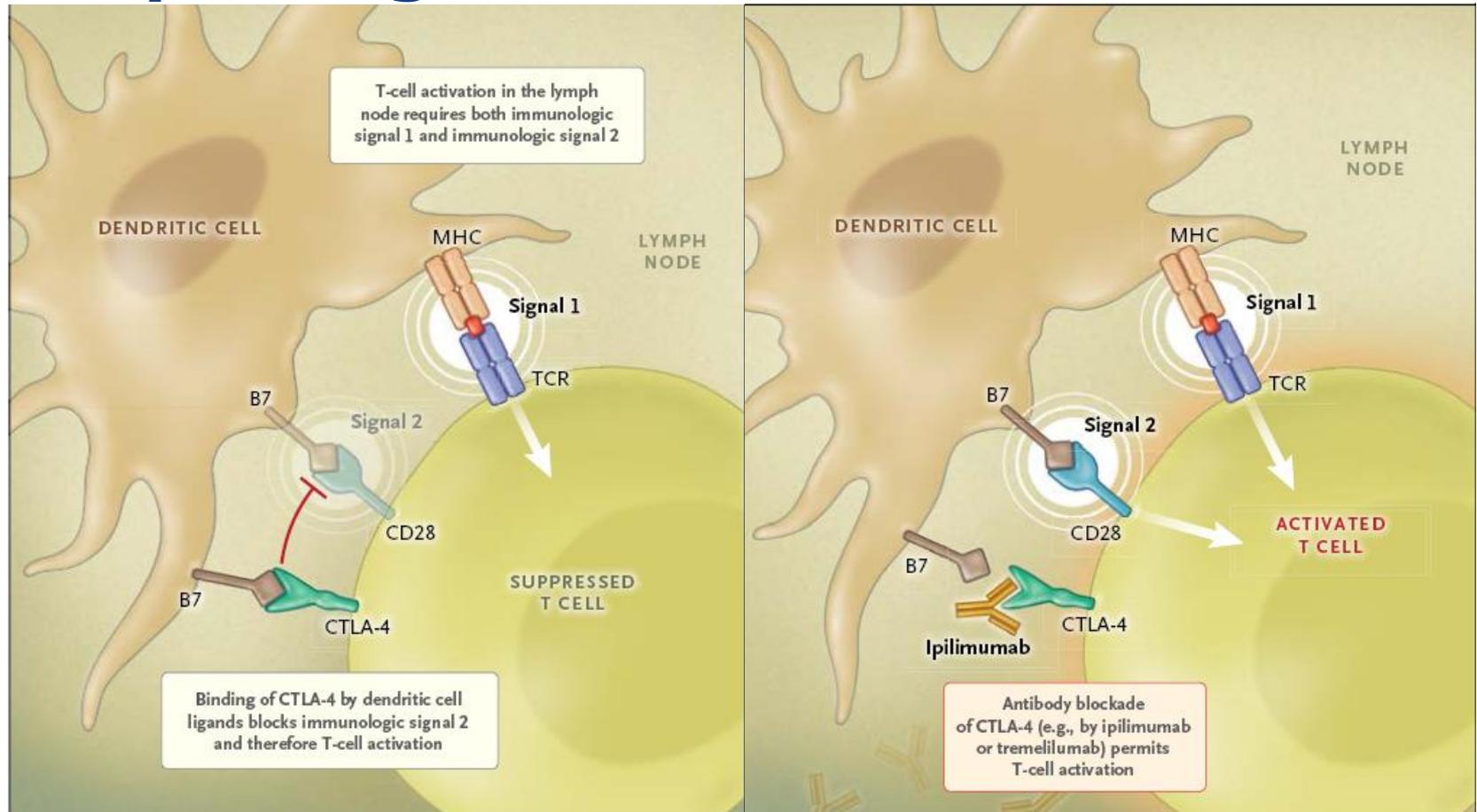
Différentes approches en immunothérapie ciblant les Ly T



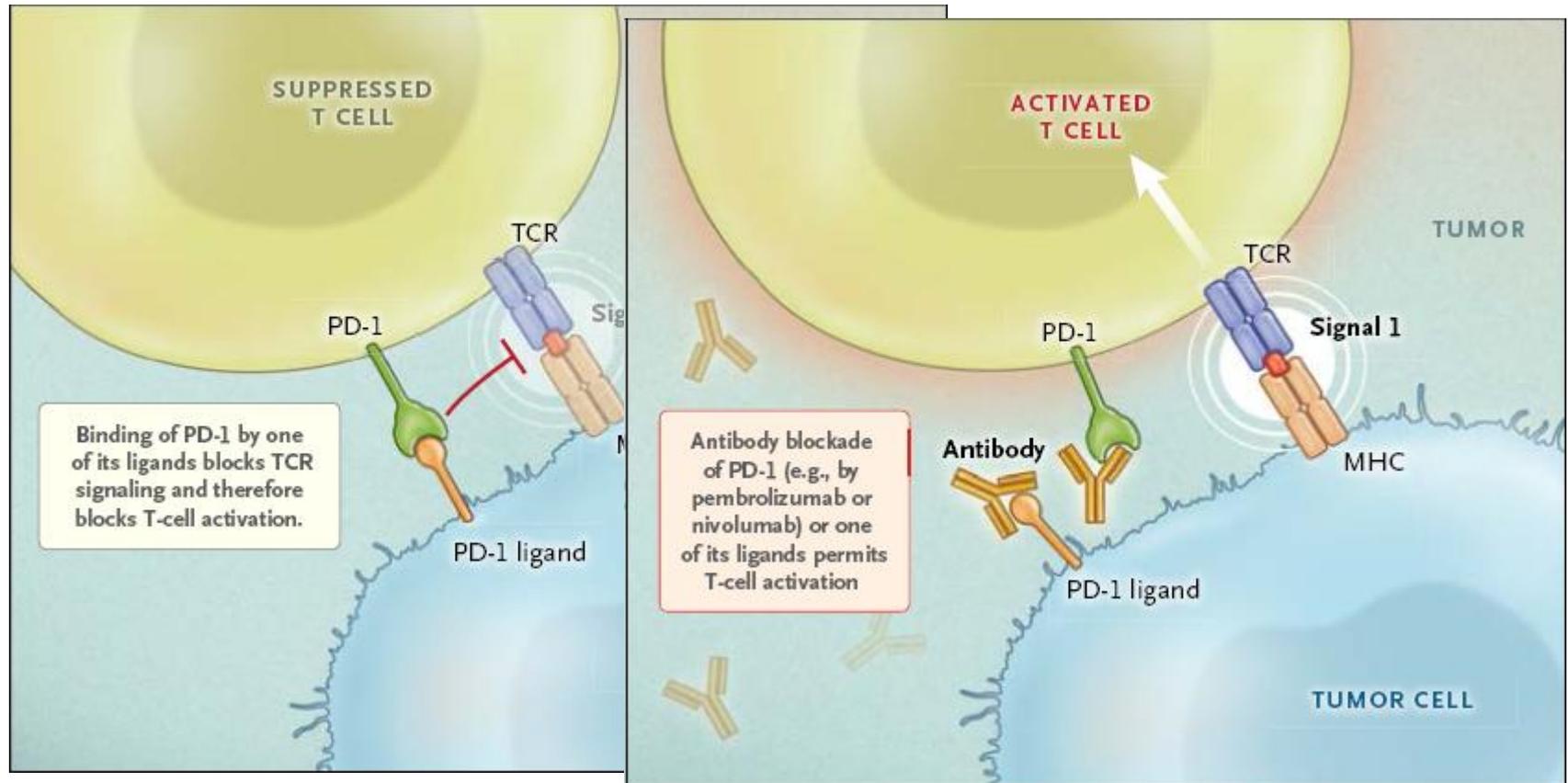
■ Activation des lymphocytes T: Synapse Immunologique



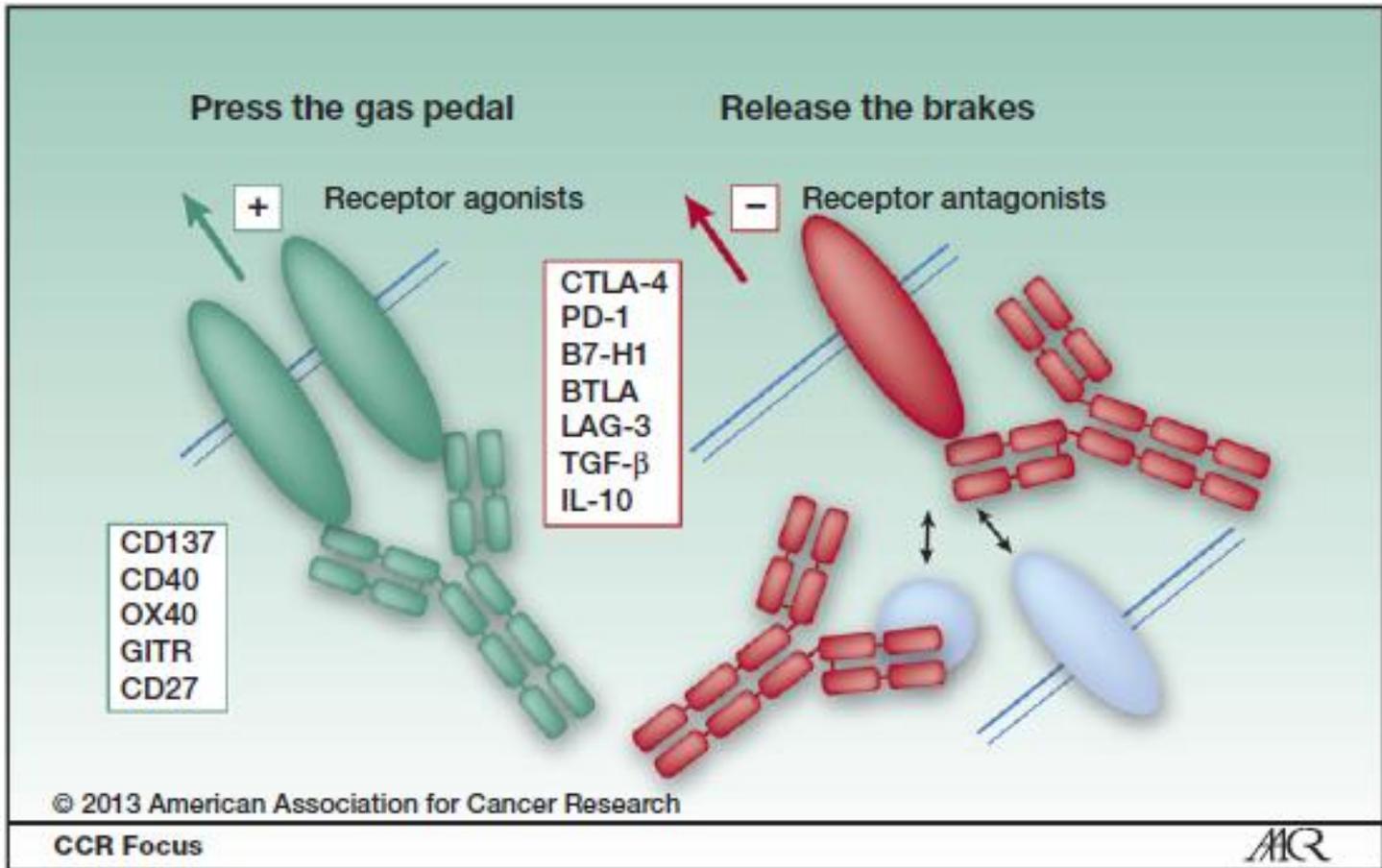
Activation des lymphocytes T: « priming »



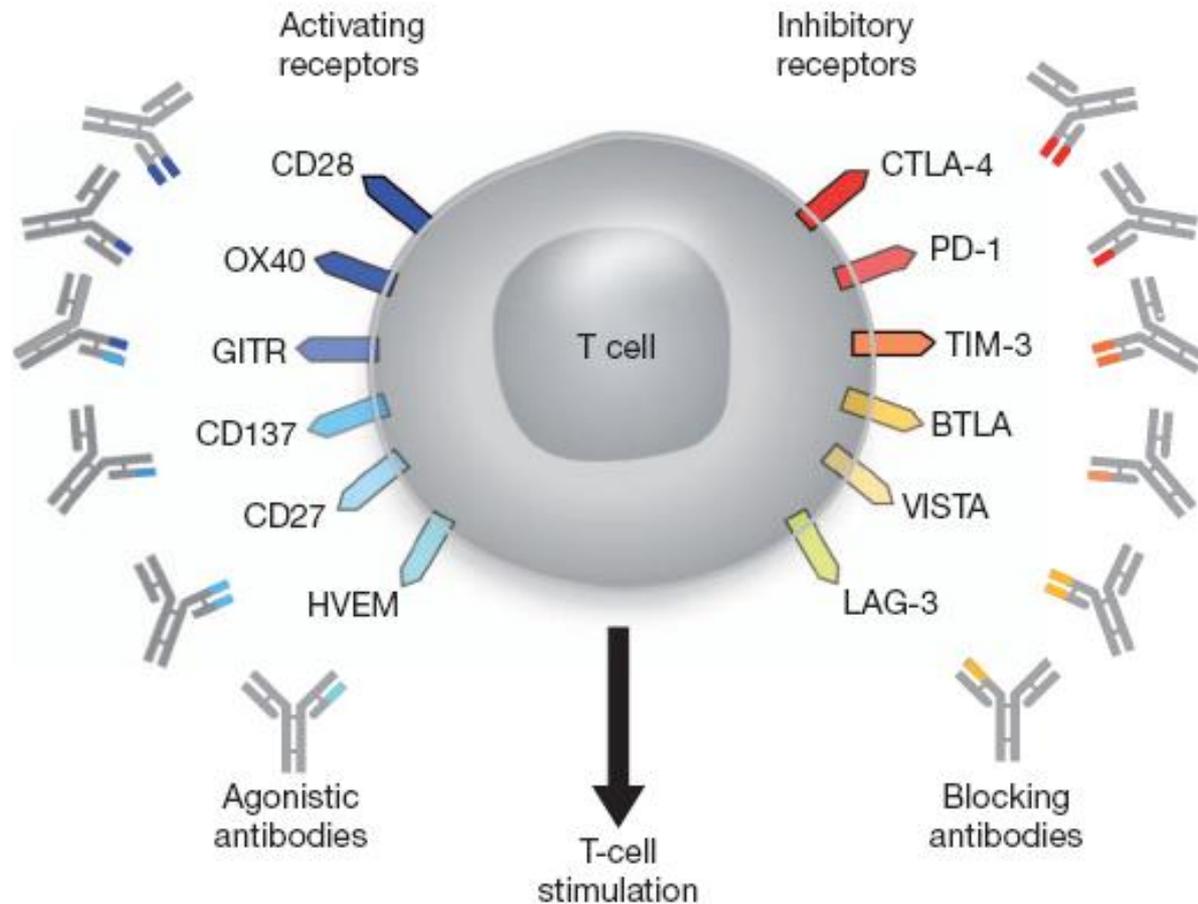
Activation des Lymphocytes T: phase effectrice



Stratégies d'activation des Ly T effecteurs



Agonistes sur les activateurs Anticorps bloquants sur les inhibiteurs



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

^aFully human mAbs were produced in genetically engineered mice.

^bFc-modified mAbs were engineered to abrogate ADCC and complement-dependent cytotoxicity (CDC).

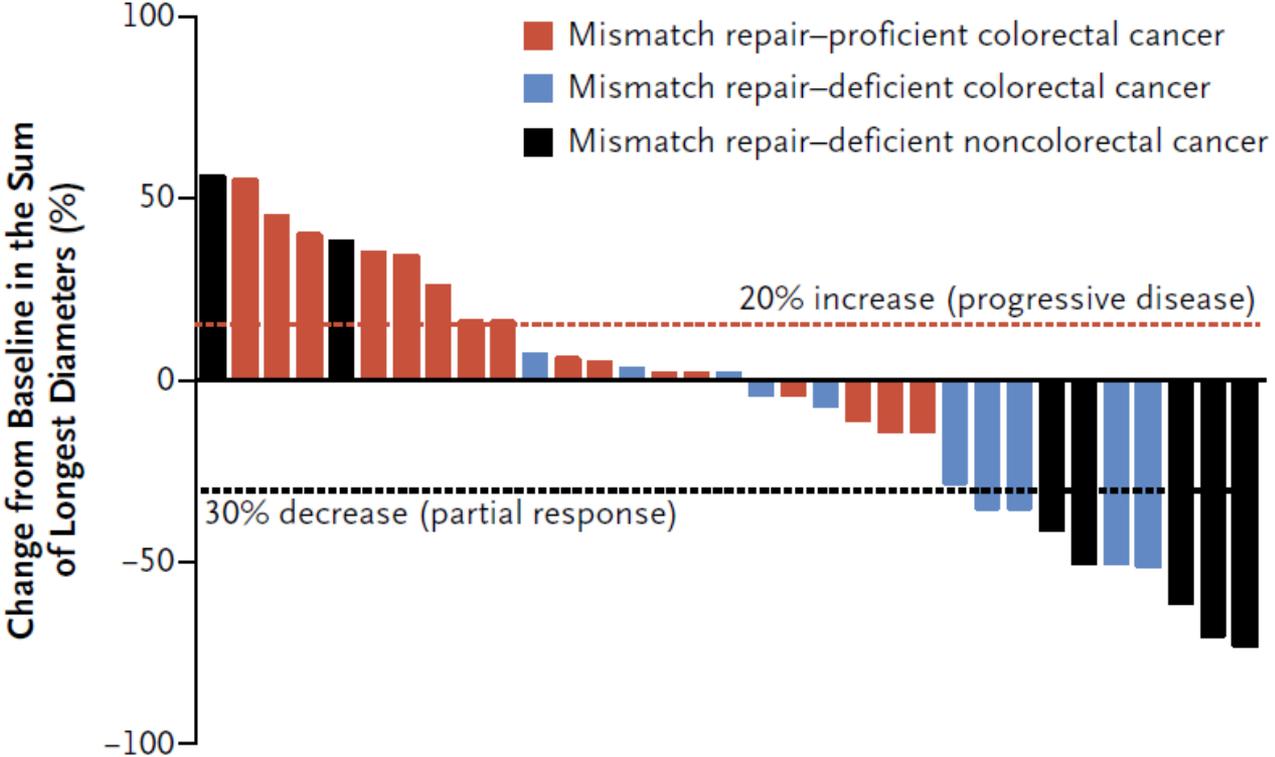
Particularités des évaluations sous immunothérapies

- Les critères d'évaluation

- Le « spider plot »

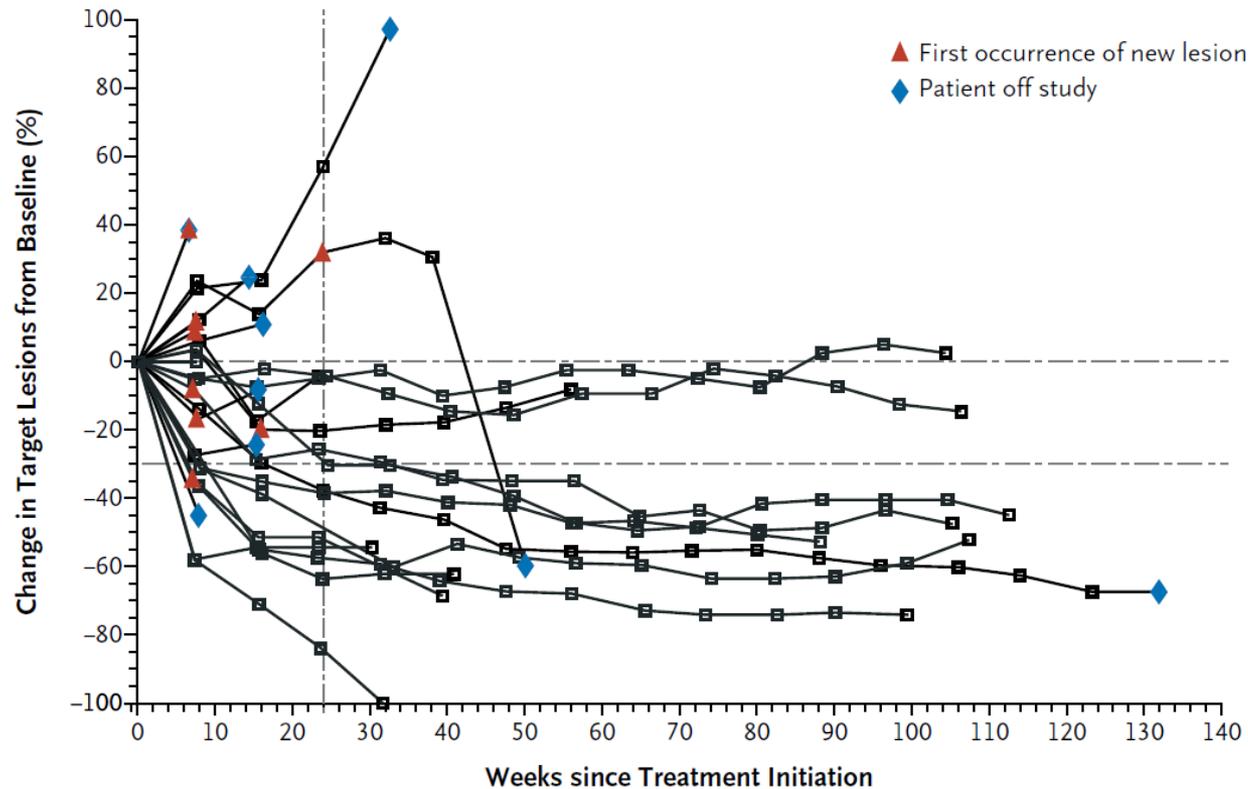
Les « indispensables »: Waterfall plot ou Représentation graphique « en chute d'eau »

B Radiographic Response



« Spider Plot » représentation dynamique pour chaque patient

A Patients with Melanoma



Historique: Observations cliniques sous Ipilimumab

Baseline (Day 0)



Week 12 (Day 84)



Patient atteint de
mélanome
Évolution sous
Ipilimumab

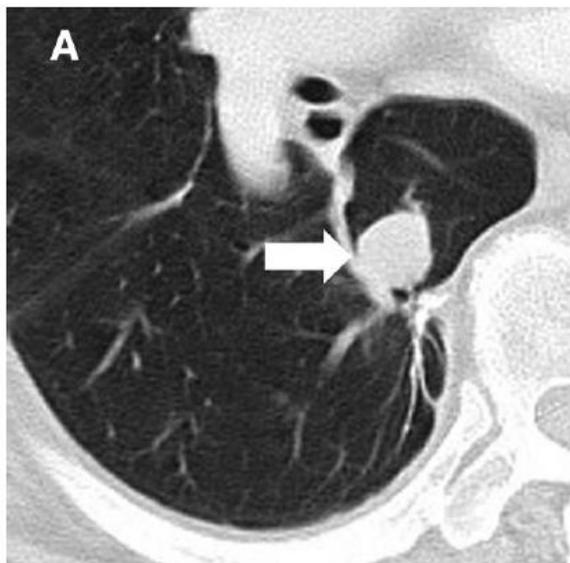
Week 16 (Day 112)



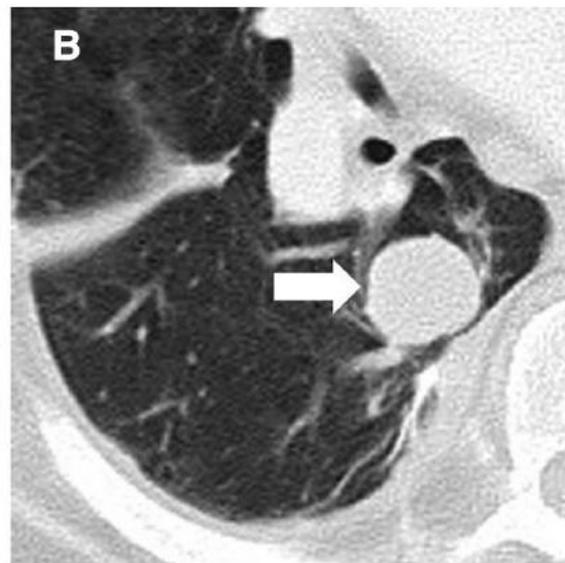
Week 72 (Day 503)



Evolution Radiologique sous IPI



Evaluation
initiale

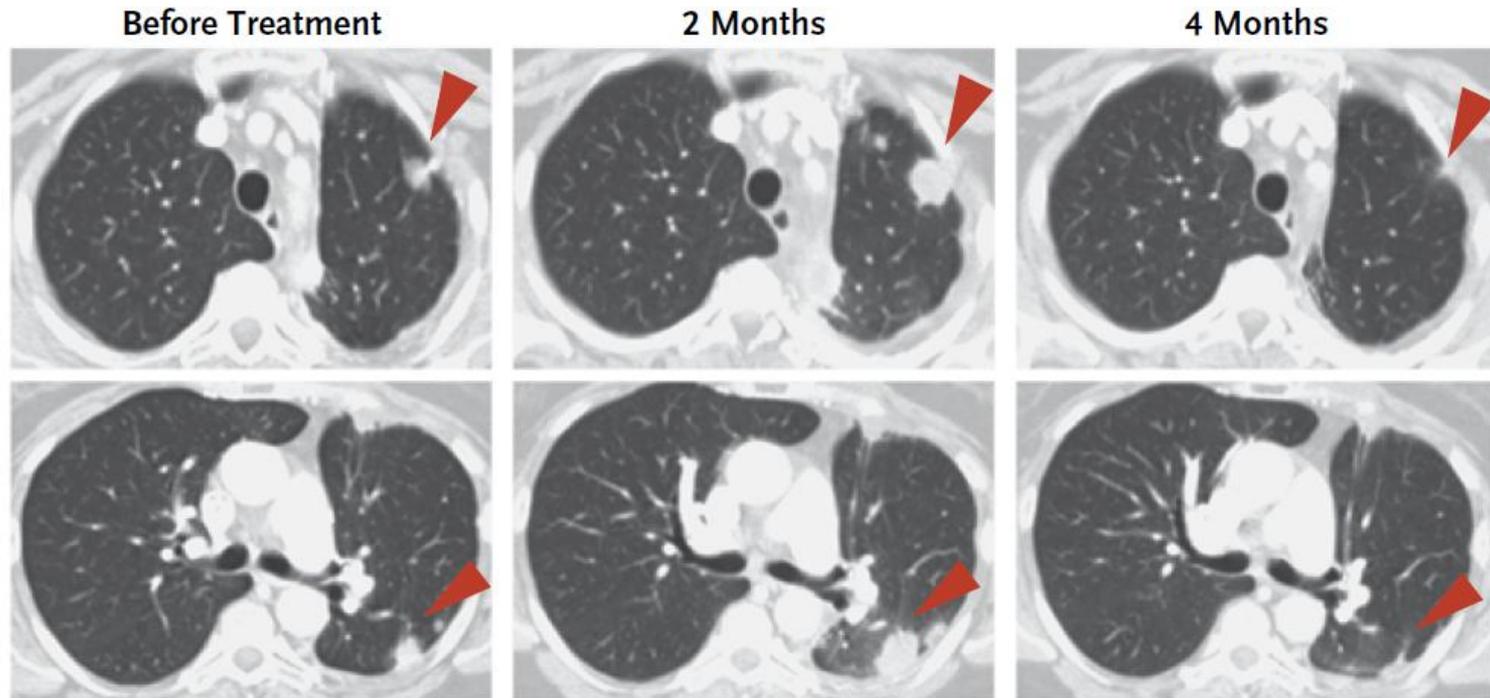


À 12
semaines



À 24
semaines

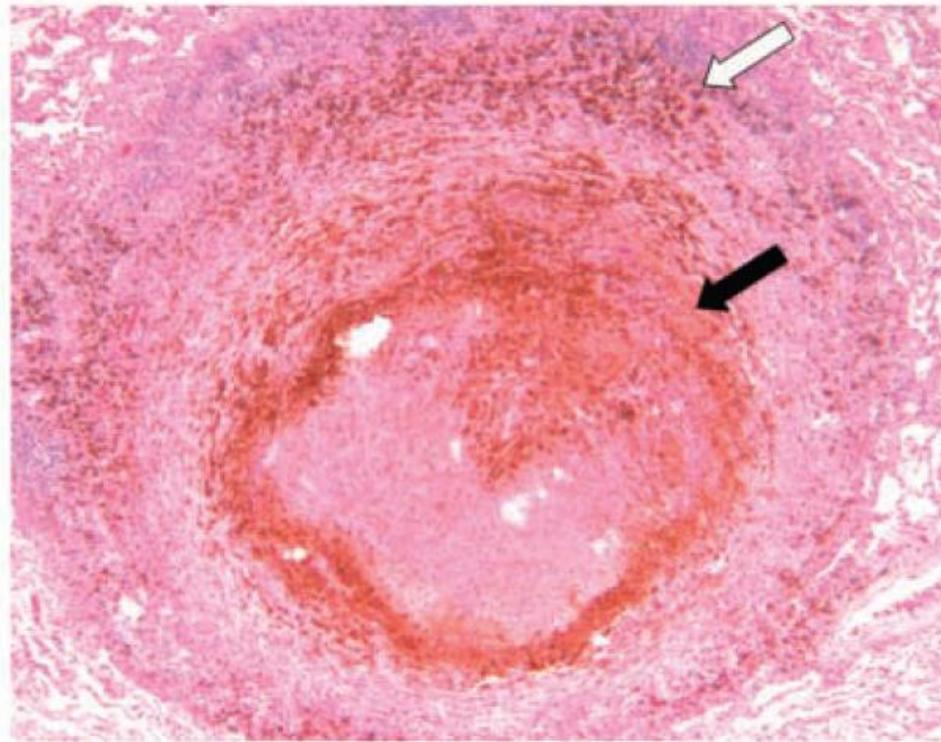
Effet « classe » des « check-point inhibiteurs »



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

26

Données histologiques

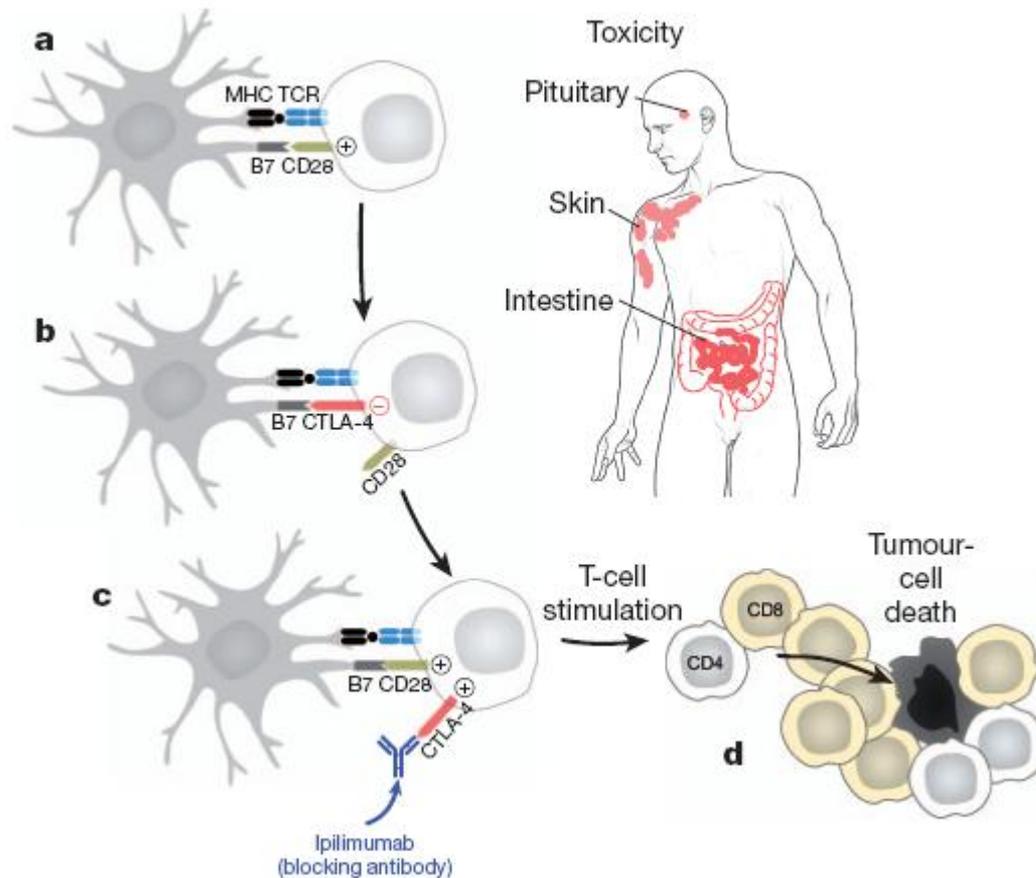


- Métastase pulmonaire de mélanome sous Ipilimumab avec augmentation de taille
- Flèche blanche infiltrat lymphocytaire
- Flèche noire: zone de nécrose.
- Plus de tissu tumoral

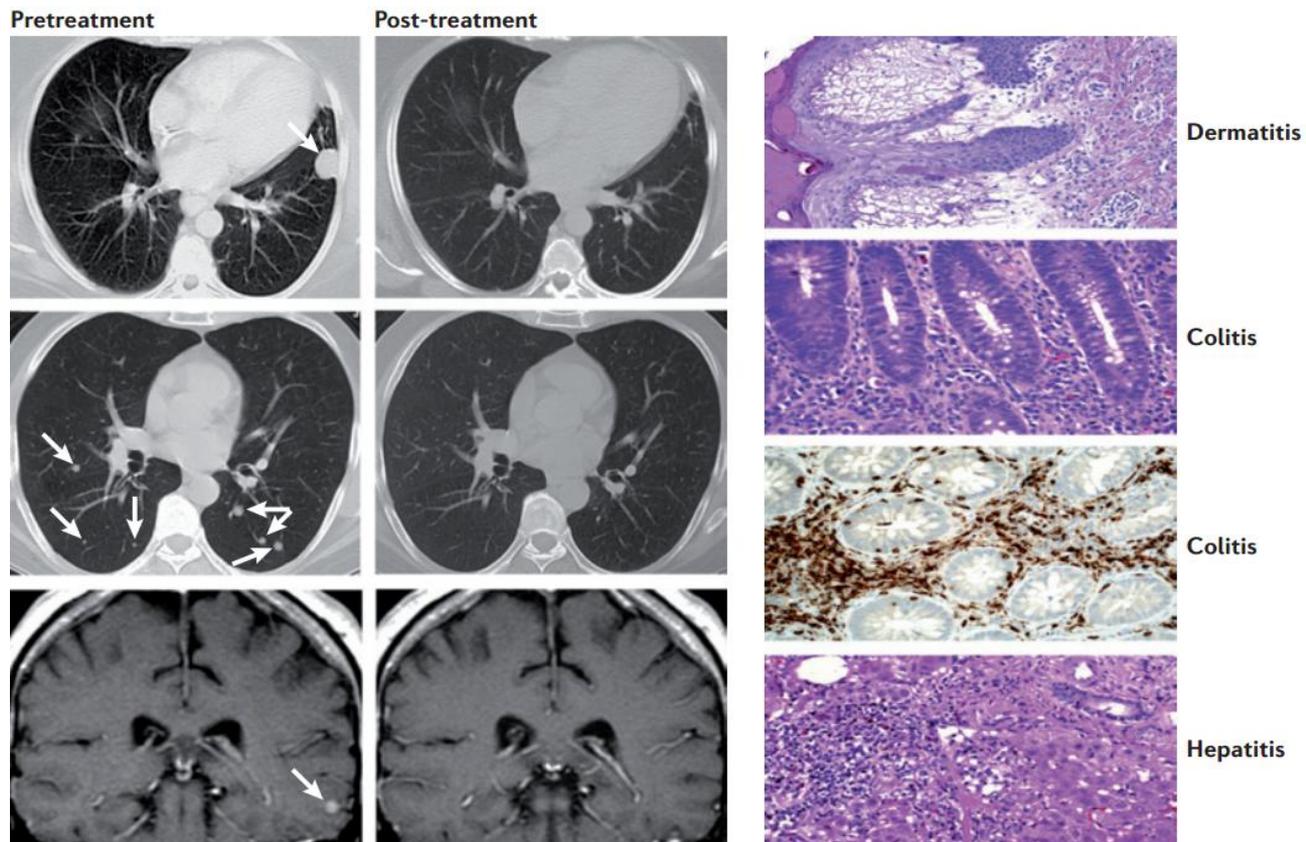
Définition des critères irRC

Factor	RECIST	irRC
Measurement of tumor burden	Unidimensional	Bidimensional
Complete response	Disappearance of all target and nontarget lesions; lymph nodes must regress to < 10-mm short axis; no new lesions; requires confirmation	Same as for RECIST
Partial response	≥ 30% decrease in tumor burden compared with baseline; requires confirmation	≥ 50% decrease in tumor burden compared with baseline; requires confirmation
Progressive disease	≥ 20% + 5-mm absolute increase in tumor burden compared with nadir; progression of nontarget lesions and/or appearance of new lesions (at any single time point)	≥ 25% increase in tumor burden compared with most recent prior evaluation; new lesions added to tumor burden; requires confirmation
Stable disease	Any response pattern that does not meet criteria for complete response, partial response, or progressive disease	Same as for RECIST

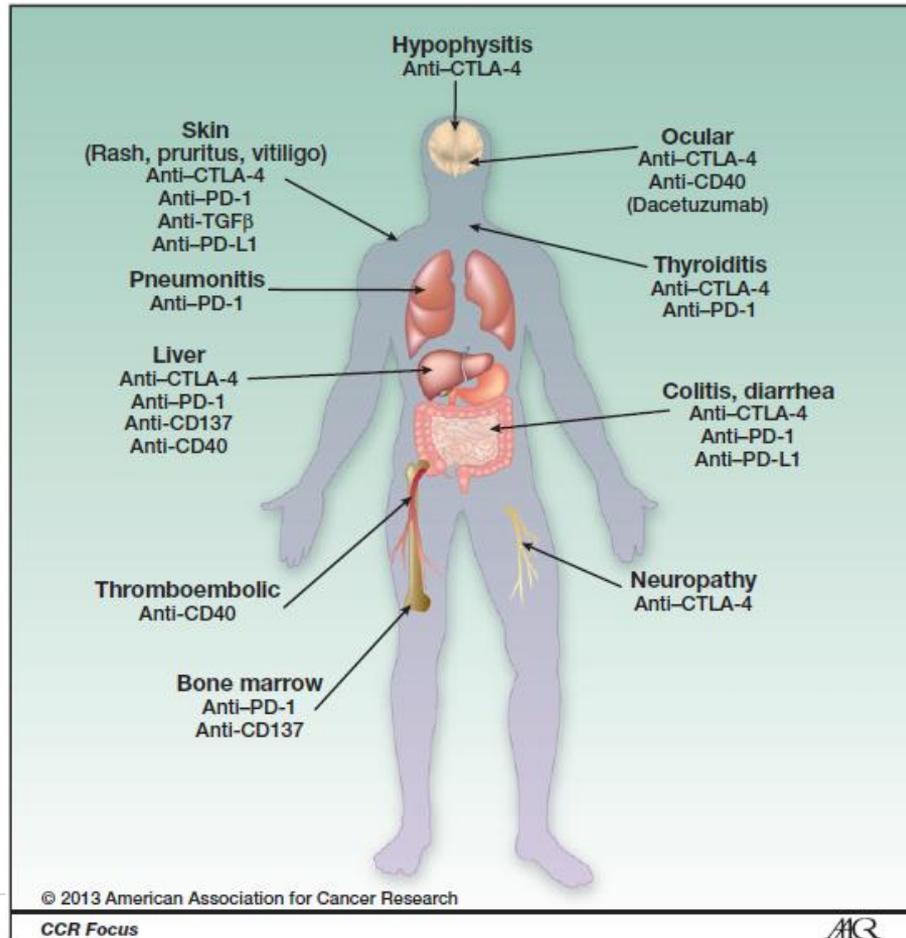
Toxicités des « check-point inhibiteurs »



■ Toxicités des « check-point inhibiteurs »



Toxicités de classe: Maladies auto-immunes



Essais en cours dans le cancer du sein

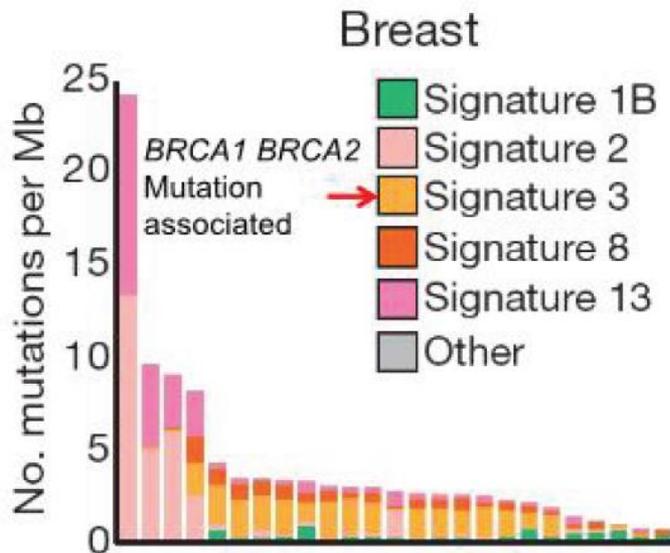
Reference	Status	Drug	Target	Patients	N	Results
Vonderheid, ¹⁰⁸ 2010	Phase 1, completed	Tremelimumab + exemestane	CTLA-4	Metastatic ER+, HER2- BC	26	SD ≥12 weeks in 42%
Brahmer, ¹²² 2012	Phase 1, completed	BMS-936559	PD-1	Advanced carcinoma	207; 4 patients with BC	No efficacy data for patients with BC
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	

Quels sous types

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

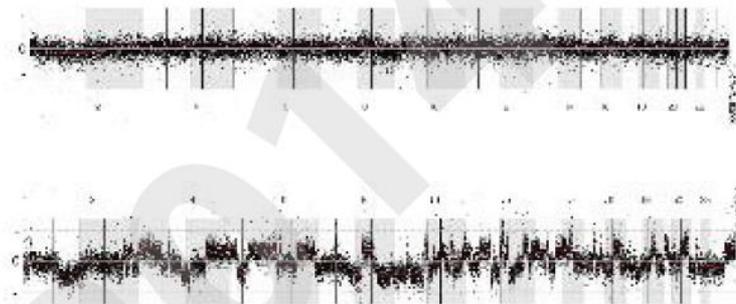
En plus des TILS: taux de mutations élevés dans les cancer triples négatifs

Signatures of mutational processes in human cancer



TNBCs have highly variable
Chromosome structural instability

Stable genome- low instability



Unstable genome- high instability

Alexandrov et al Nature 2013

34

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

- Cancer du sein en récurrence 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

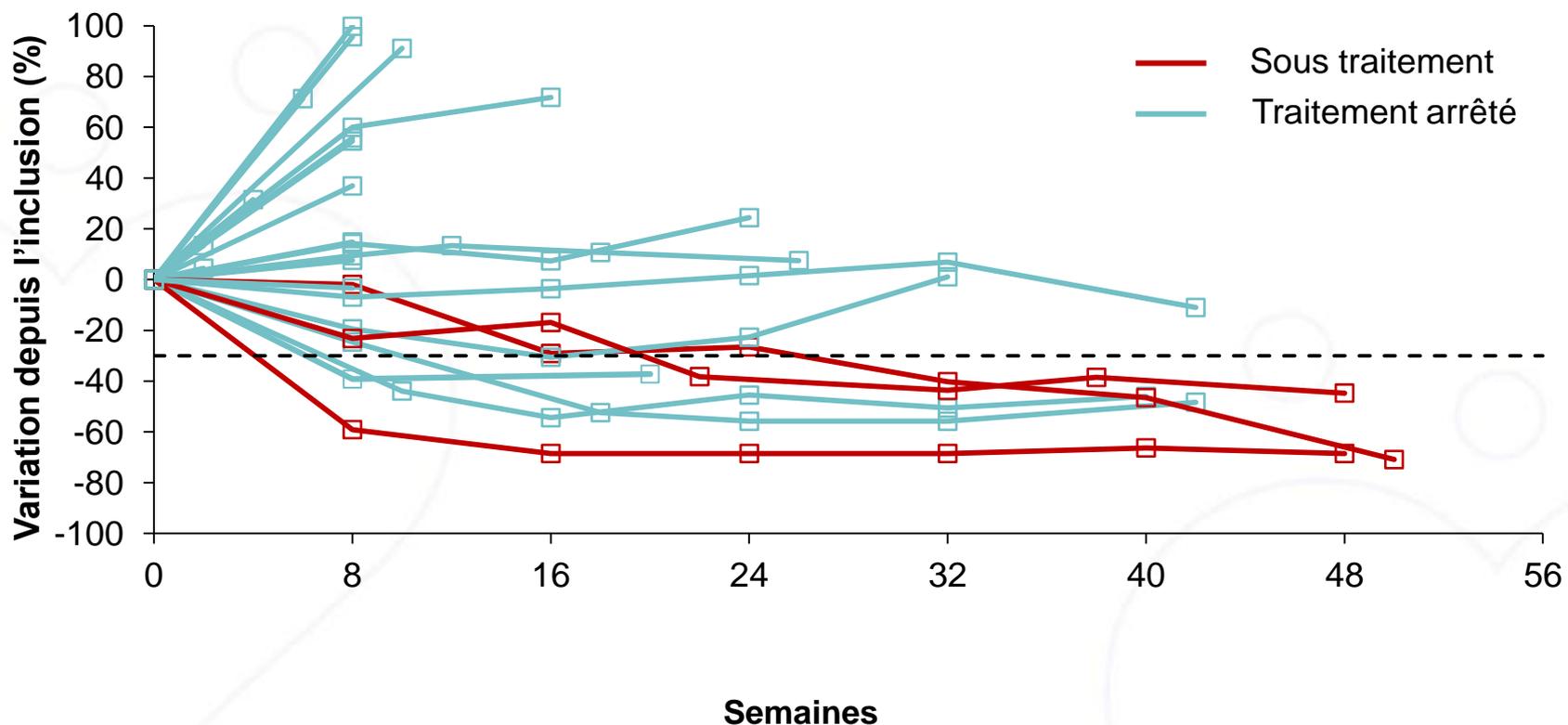
Pembrolizumab chez les patientes atteintes d'un cancer du sein triple-négatif

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)



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

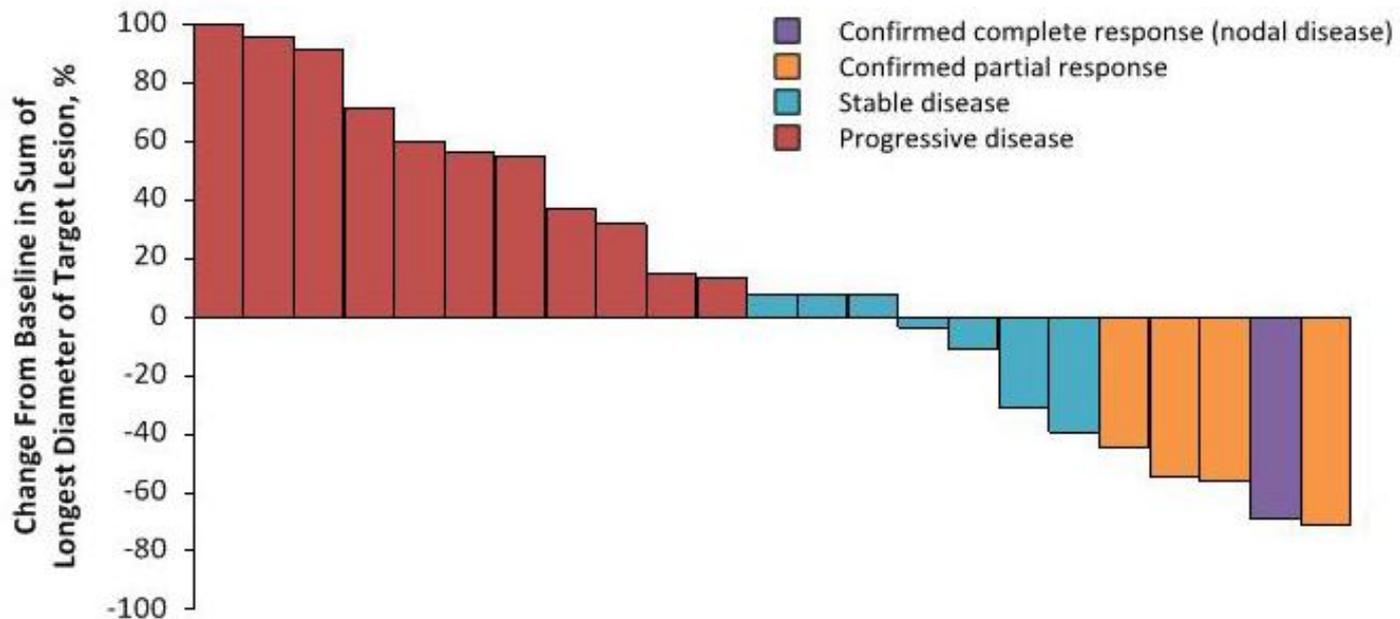
Effets indésirables

	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}





**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%)*

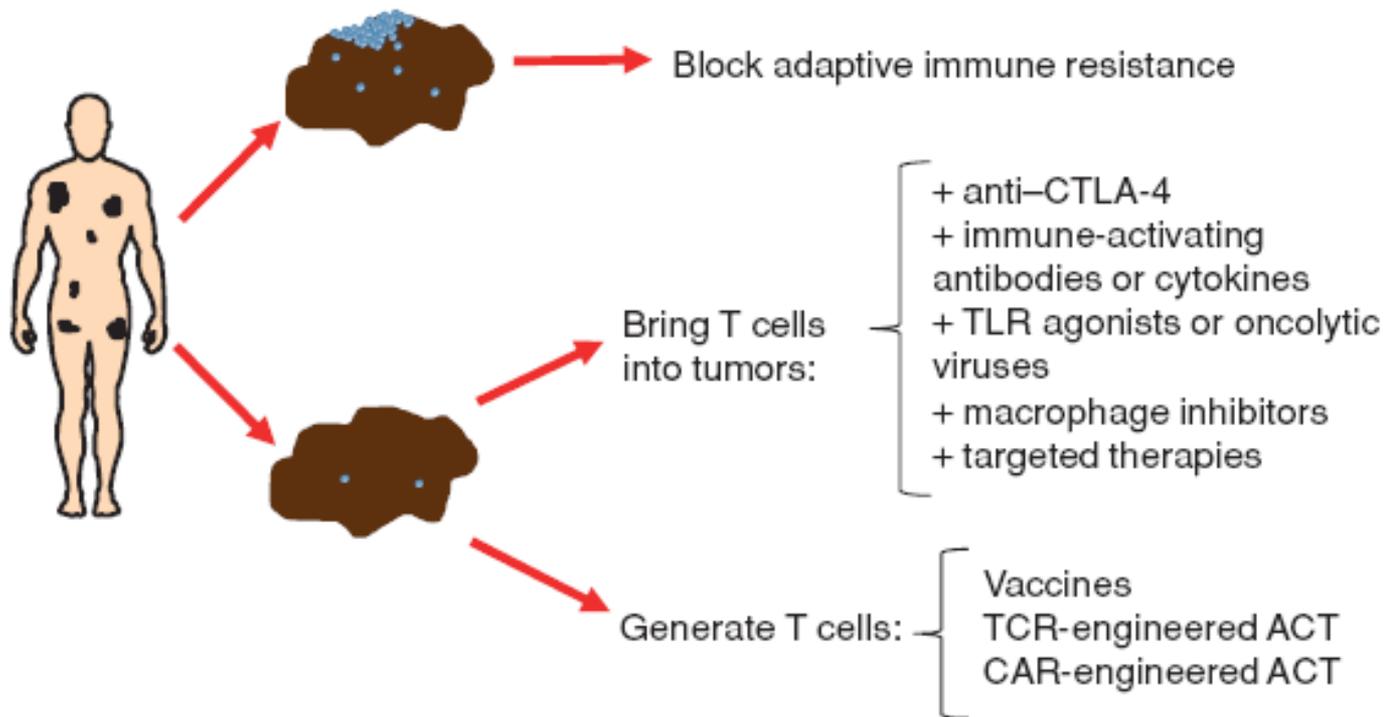
■ Événements indésirables reliés au traitement

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

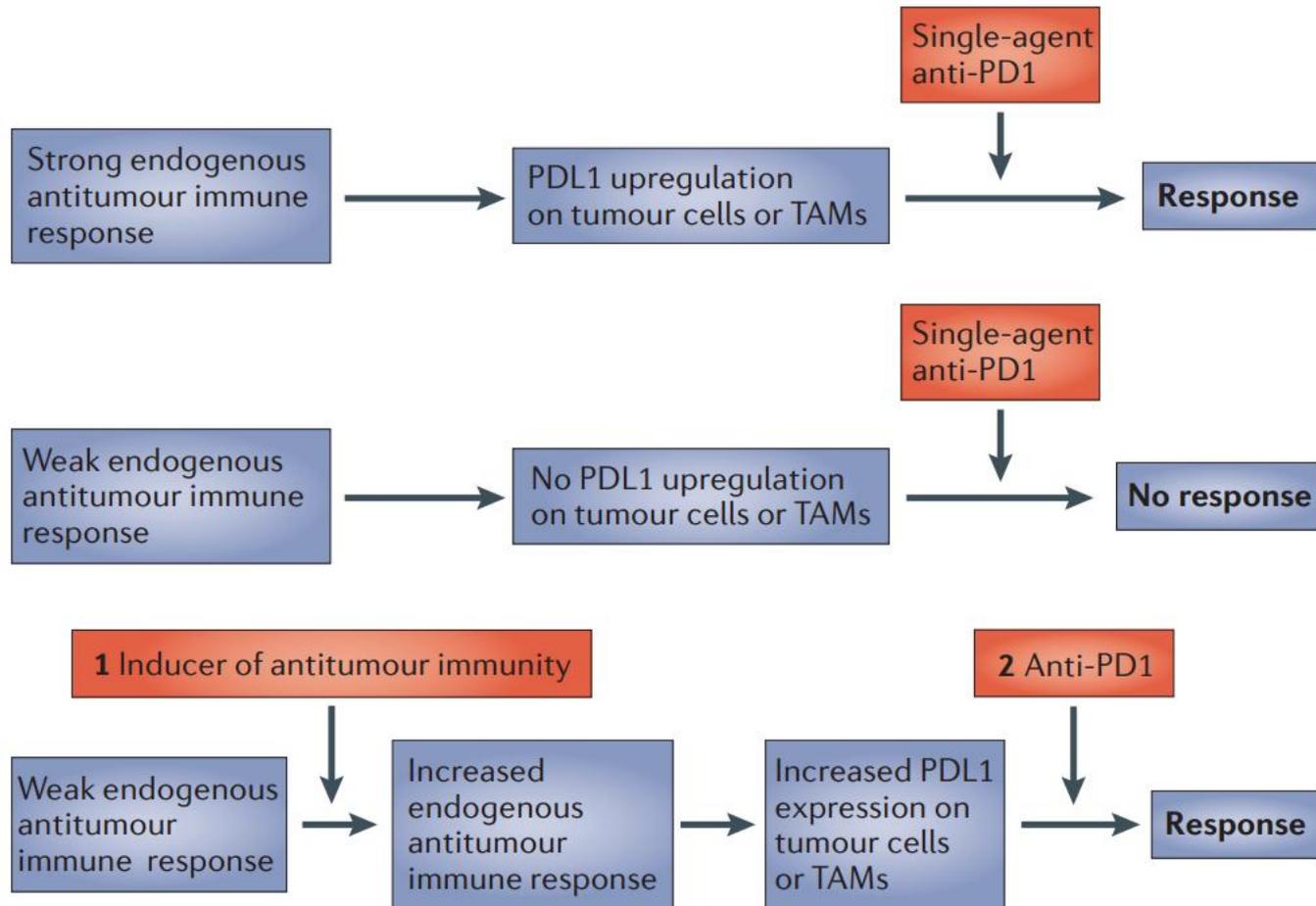
■ 9 patientes évaluables pour la réponse

- ▶ 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

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

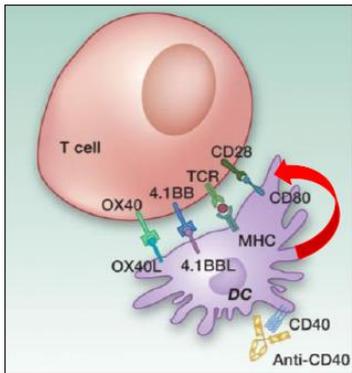


■ Perspectives; les combinaisons afin d'augmenter l'immunogénicité et/ou l'activation du système immunitaire

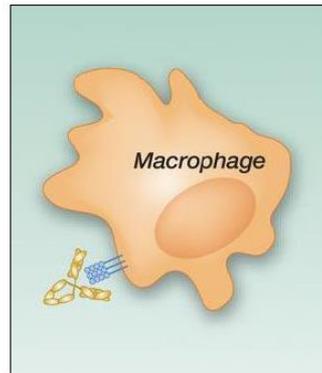


Combinaison anti-PDL1 + anti-CD40

Anti-CD40

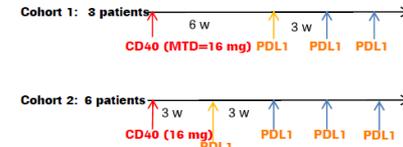


Induces T-cell priming via activation of APCs

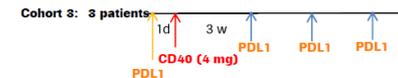


Augments macrophage tumoricidal activity

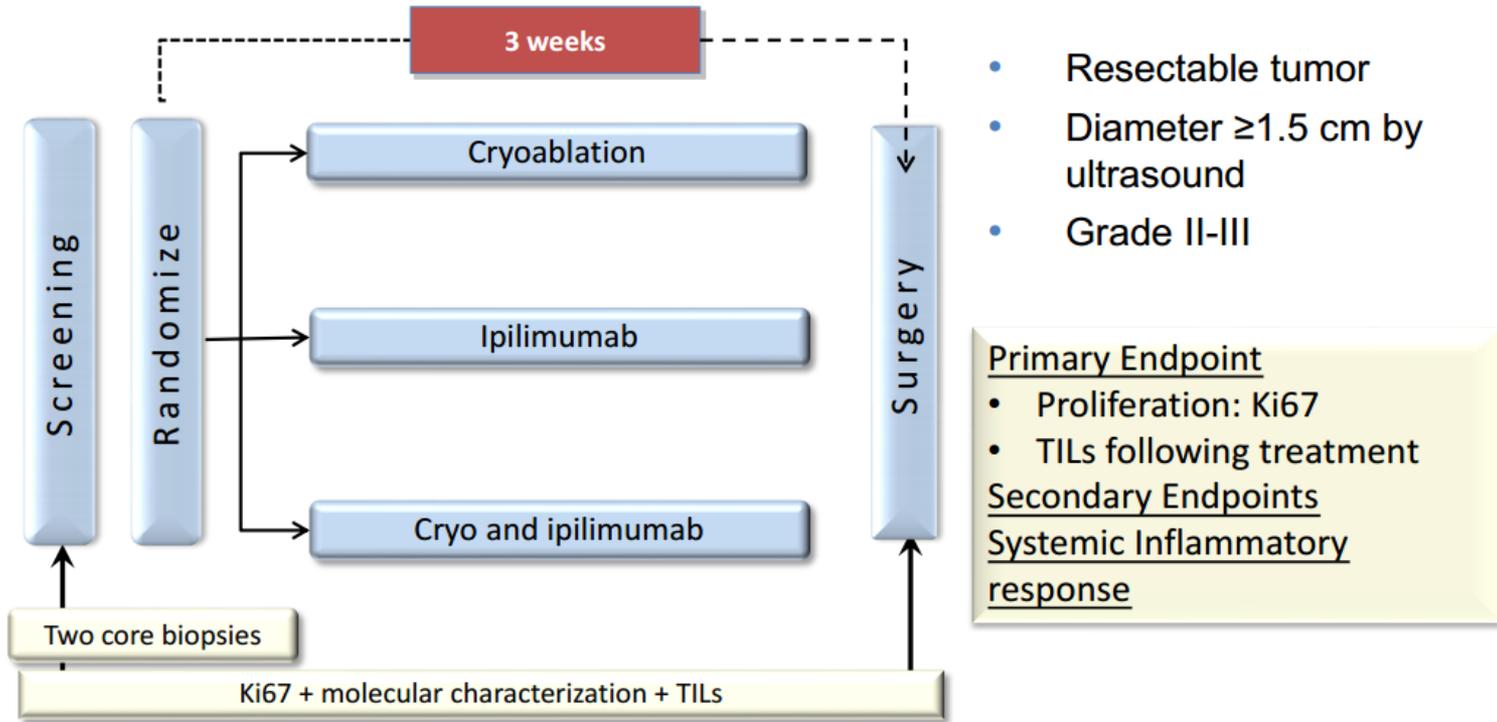
- CD40 sequential agent (PART IA IV):
 - Maximum Tolerated Dose defined by Pfizer studies: 0.2 mg/kg i.v.
 - In the SAD study (DLT = CRS, VTE, Gr3 headache and Gr3↑ transaminase)
 - In the MAD study (DLT = CRS (4), PE, urticaria)
 - The starting dose= MTD x 80 Kg= **16 mg** (flat dose)



- CD40 concomitant agent (PART IB IV):
 - The starting dose is 25% of the CD40 dose found safe in cohort 2 (PART IA IV)



■ Perspectives; 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

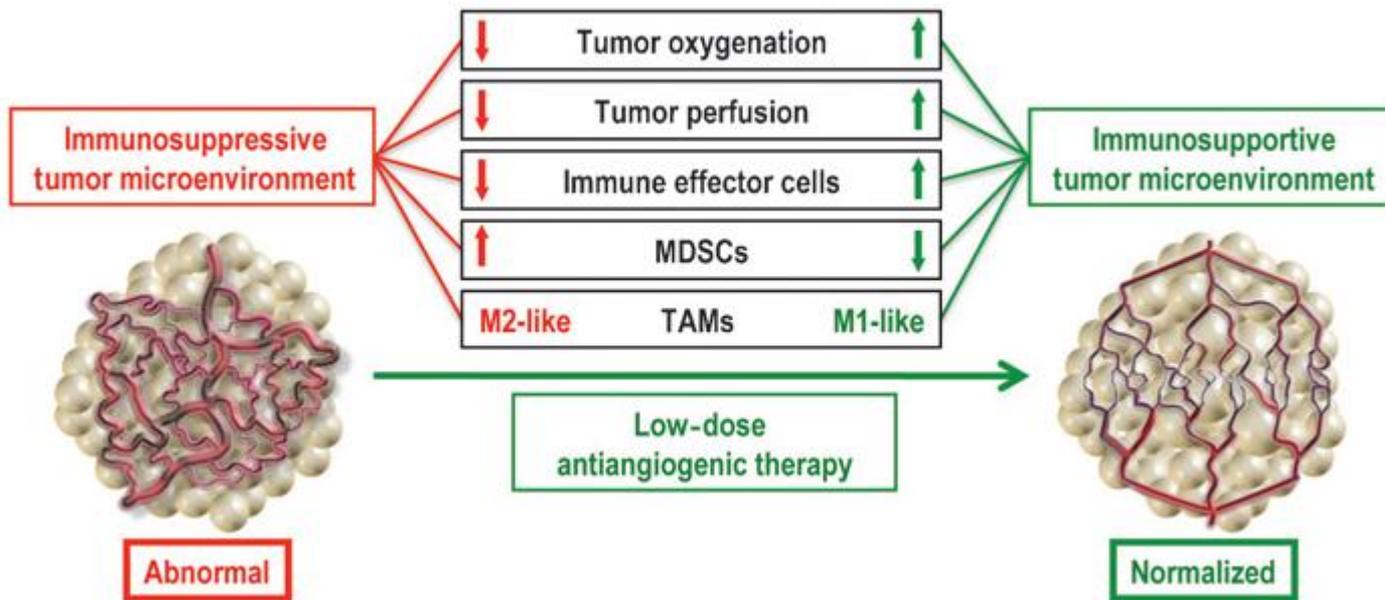
Primary Endpoint

- Proliferation: Ki67
 - TILs following treatment
- Secondary Endpoints
Systemic Inflammatory response

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

21

Combinaisons; retour du bevacizumab?



Les Vaccins

Les approches « classiques » des vaccins thérapeutiques

	Exemples	Expression tumorale
Ag de différenciation	Mart 1, gp100, Melan A PSA, PAP, PSMA	Mélanome Cancer de la prostate
Ag du groupe <i>cancer testis</i>	Mage 1-10 NY-ES01	Mélanome, sein, poumon, myélome Mélanome, poumon, vessie
Ag mutés	β -caténine CDK-4 Ras	Mélanome, tumeur du foie Mélanome Cancer côlon, pancréas, poumon
Ag surexprimés	Her2/neu ACE	Adénocarcinome sein, poumon, rein, vessie Adénocarcinome côlon, poumon
Ag glycosidiques modifiés	Muc 1	Adénocarcinome sein, poumon, rein
Ag viraux	HPV HCV, HBV EBV <i>Helicobacter pylori</i>	Col de l'utérus, ORL, anus Cancer du foie Lymphome Cancer de l'estomac



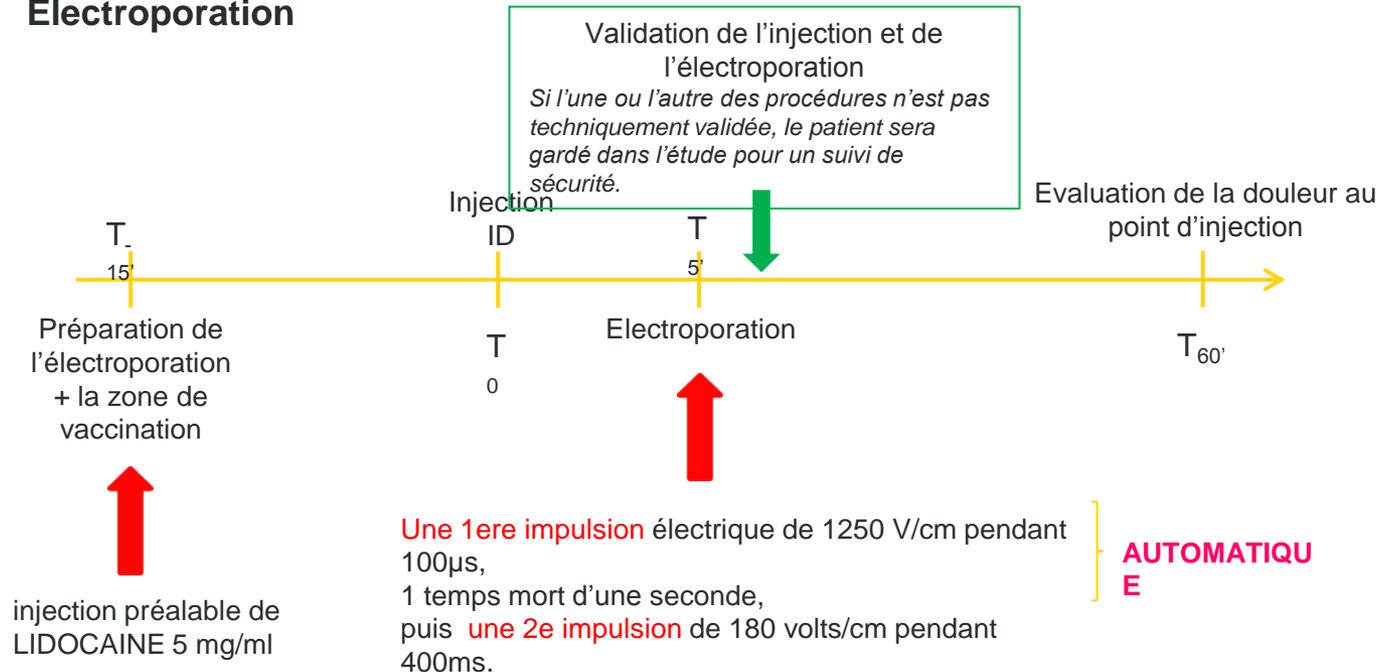
**A FIRST-IN-HUMAN PHASE I STUDY OF INVAC-1 AS A
SINGLE AGENT IN PATIENTS WITH ADVANCED CANCER**

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

Julie CRUZ
Tel: +33 1 41 34 28 44
Fax: +33 1 41 34 28 29
E-mail: julie.cruz@keyrus.com

DESIGN DE L'ETUDE – 4

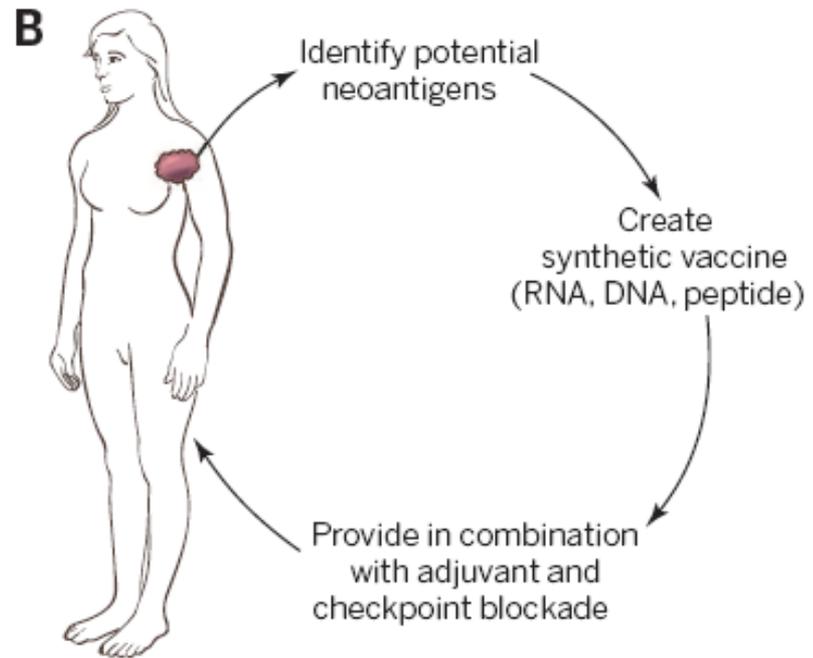
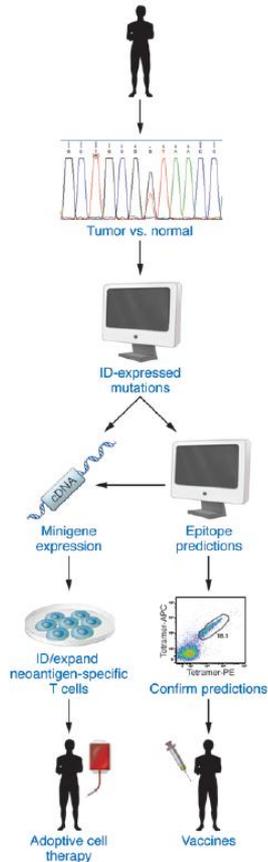
Electroporation



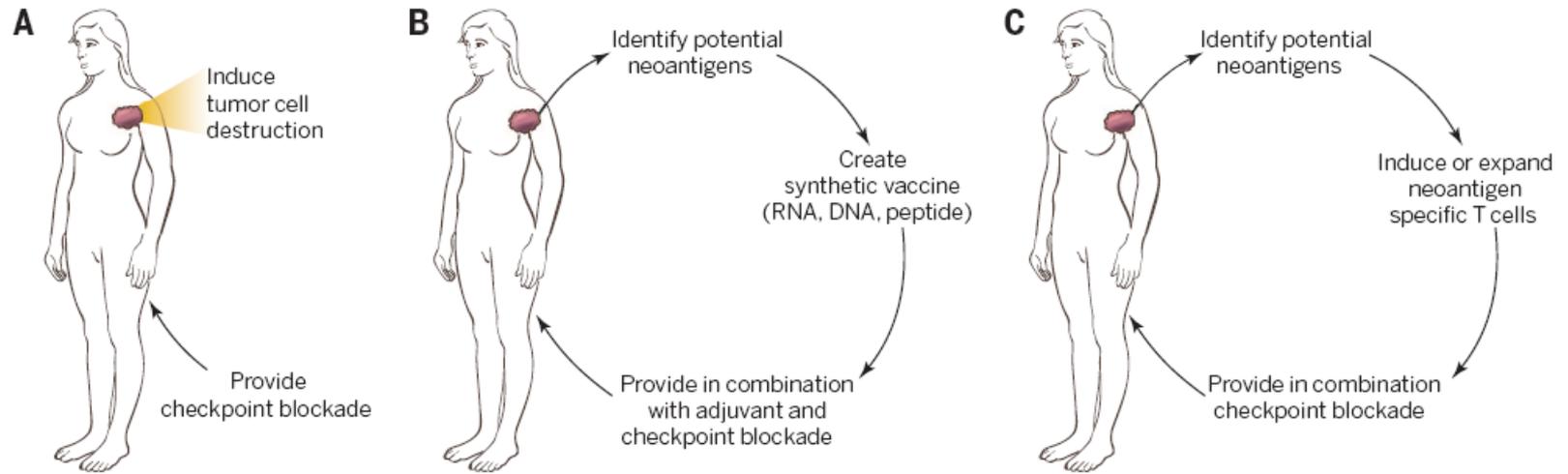
Les paramètres réels utilisés pour chaque électroporation seront enregistrés automatiquement par le Cliniporator®.

Ils doivent être enregistrés dans une clé USB et imprimés pour classement dans les dossiers médicaux des patients

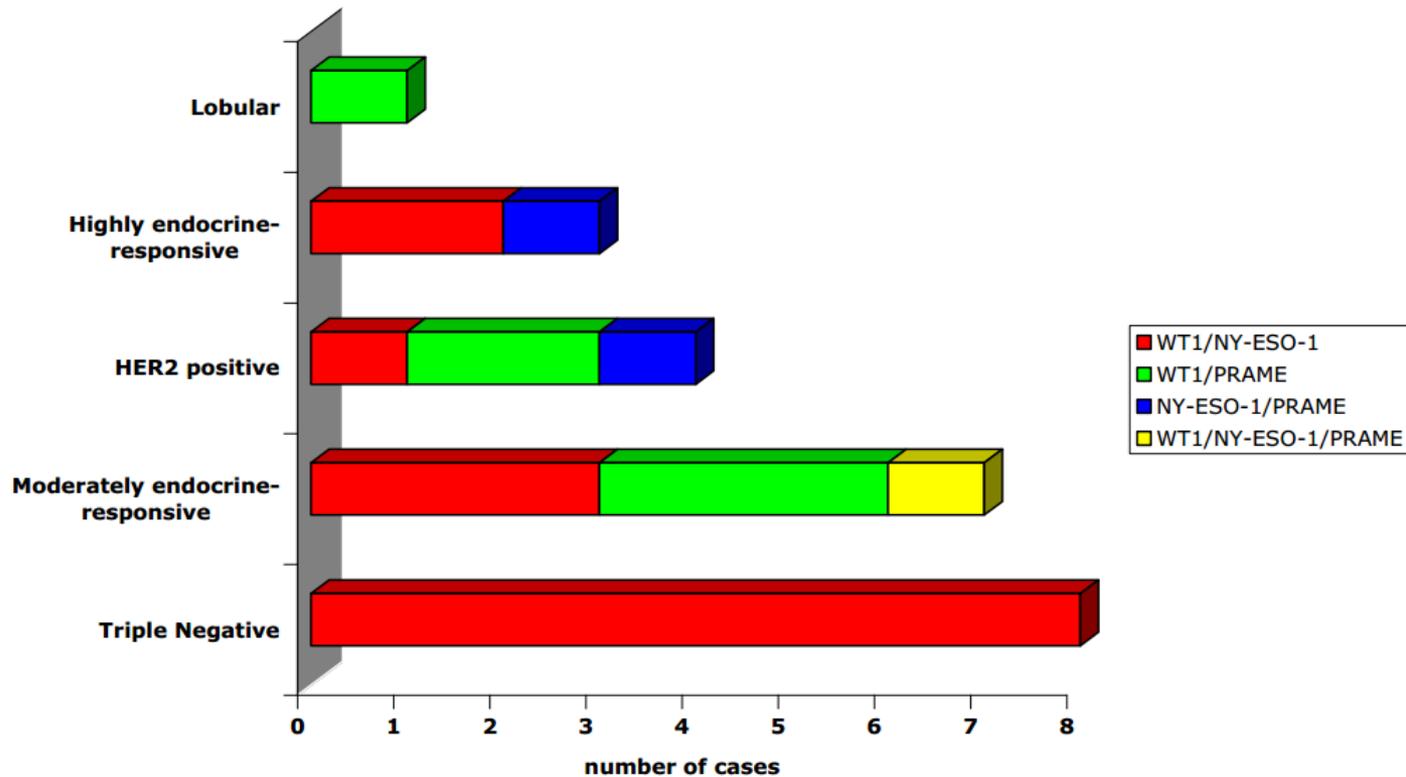
Stratégies pour les vaccins thérapeutiques



Différentes approches vaccination+ « check-point » inhibiteurs

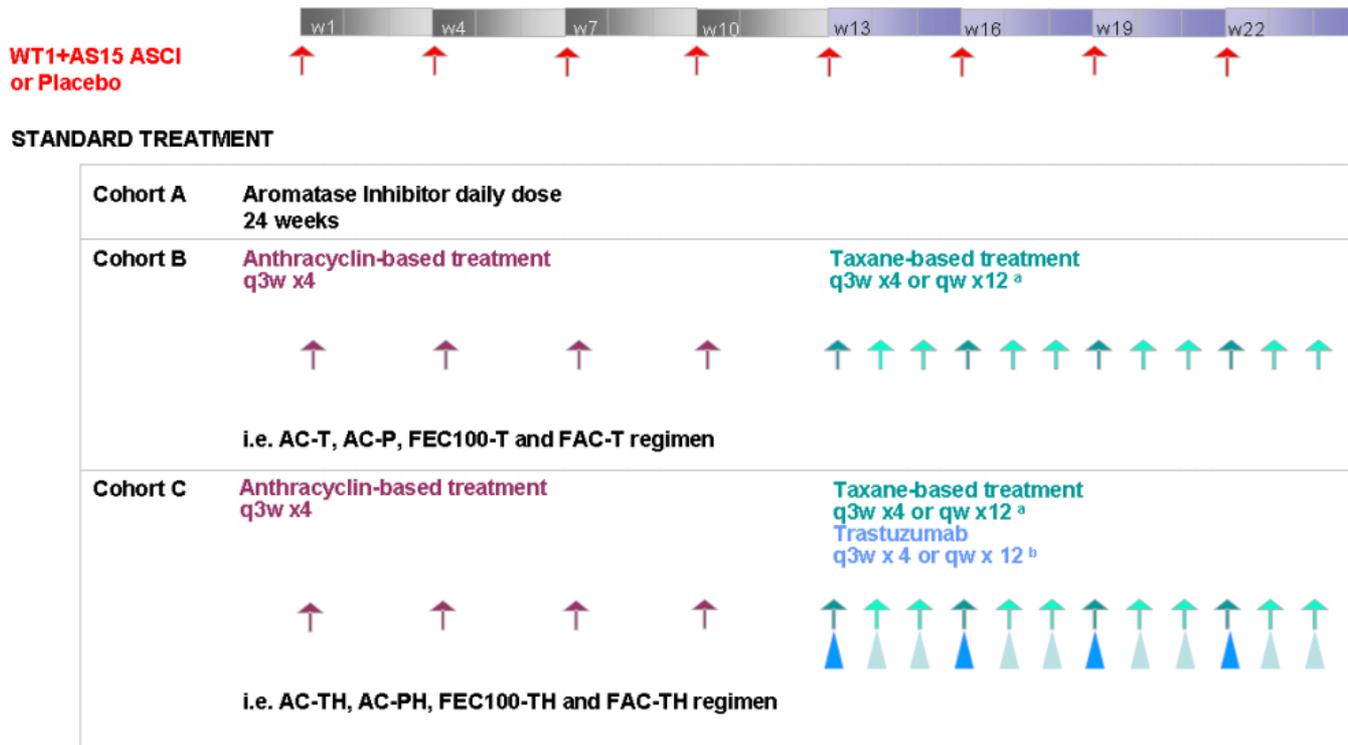


Immunogenic



Curigliano G et al Unpublished

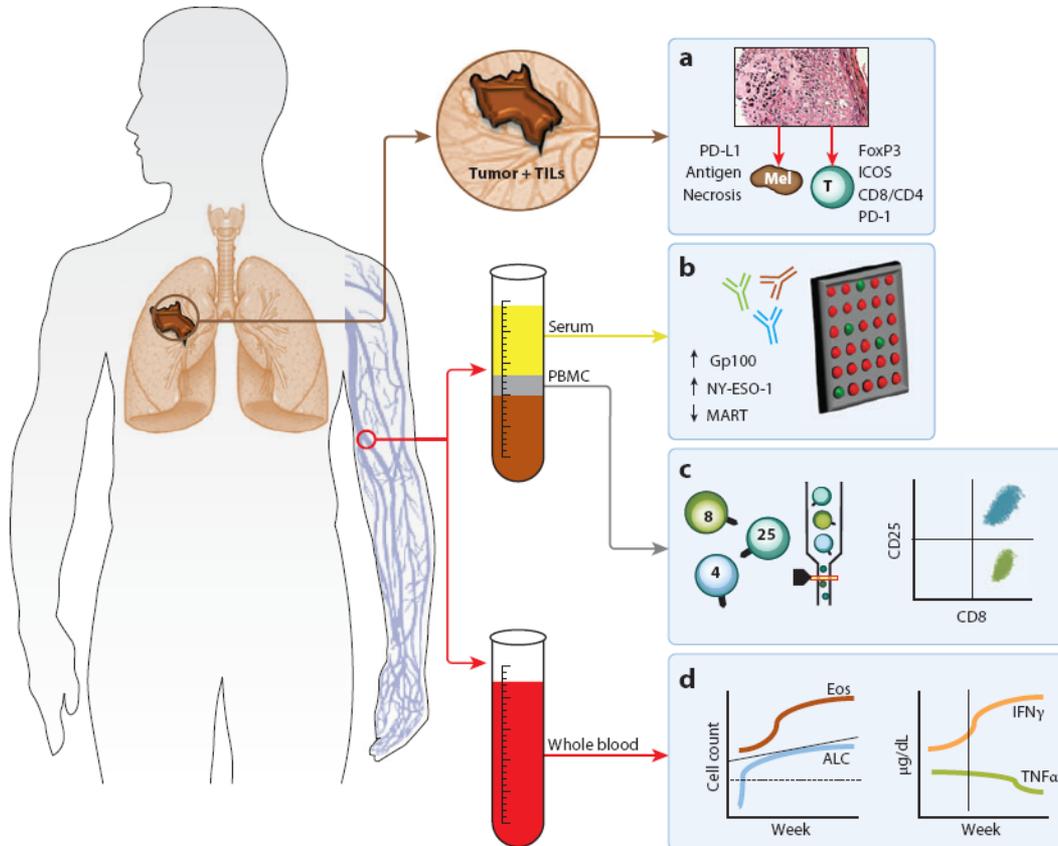
WT-1 vaccine Combined With Standard Neoadjuvant Treatment in WT1-positive EBC (INDUCT)



ClinicalTrials.gov Identifier: NCT01220128

25

« Monitoring » des réponses



Différents niveaux d'analyse et de suivi sous traitement.