

le rôle du microenvironnement tumoral sur la thérapie

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du 9 au 11 oct 2019
Palais des Papes - Avignon



Liens d'intérêt

Scientific collaboration

- BMS, Servier, Roche/Genentech, Enterome

Clinical trials

- AstraZeneca

Scientific & Medical Consulting

- Amgen, Merck Serono, Roche, Servier, Sanofi

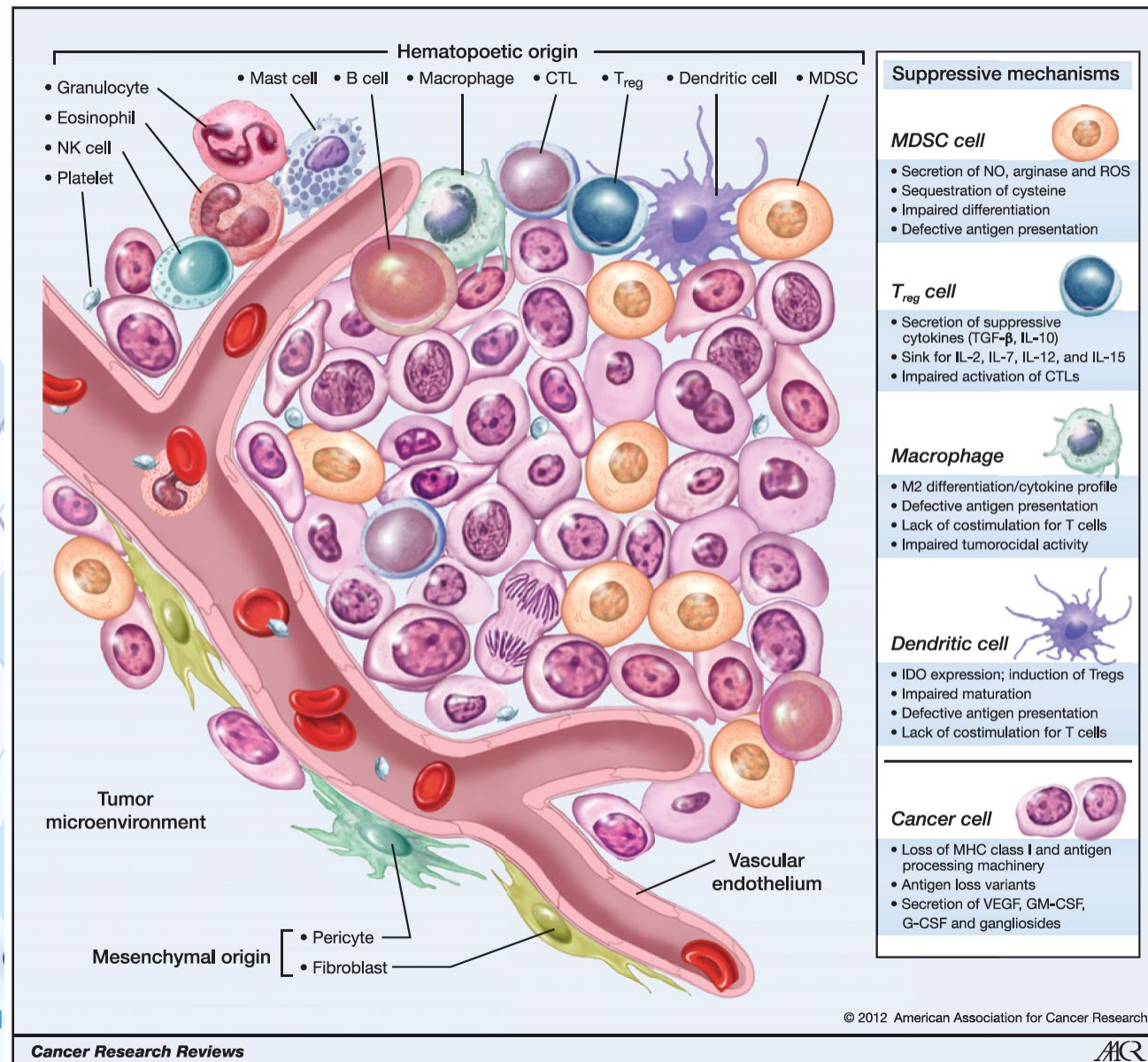


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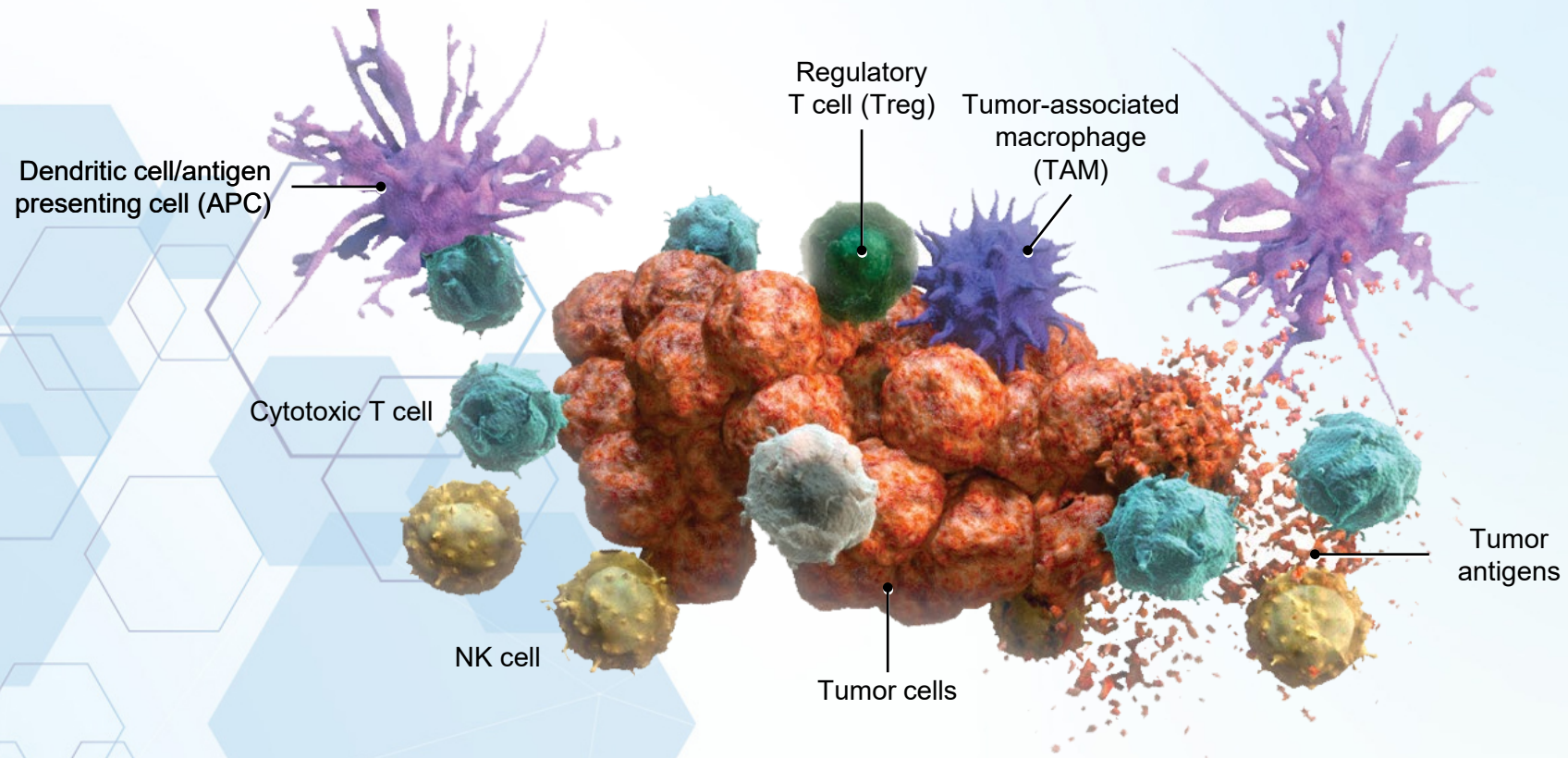
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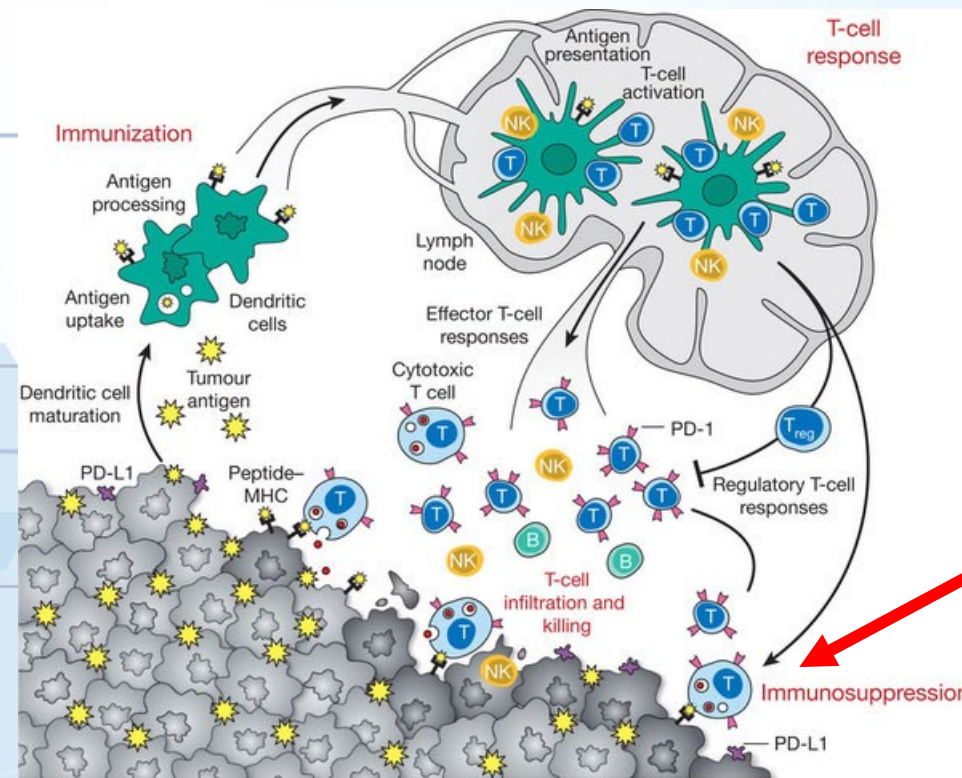
Le microenvironnement tumoral n'est pas seulement constitué de cellules tumorales



Le microenvironnement immunitaire : un système complexe

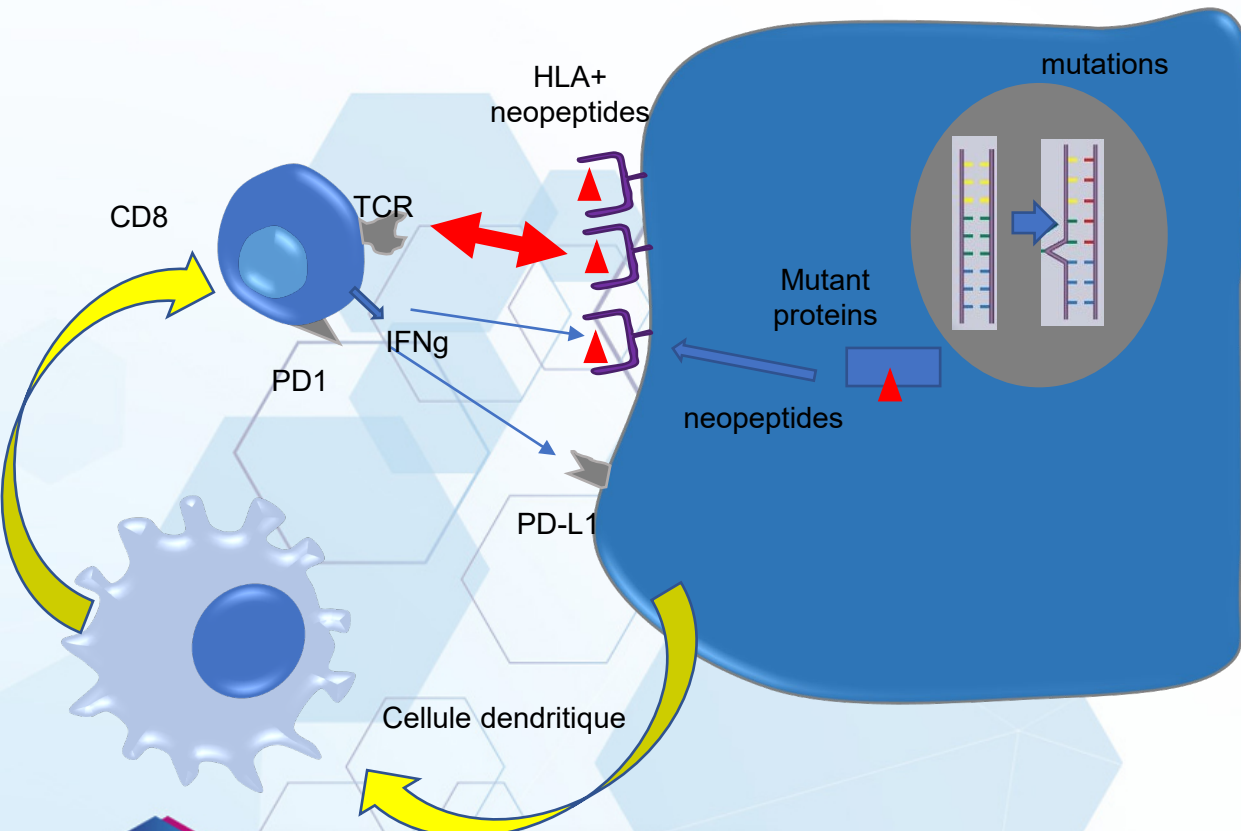


Contexte : la réponse immunitaire adaptative anti-tumorale

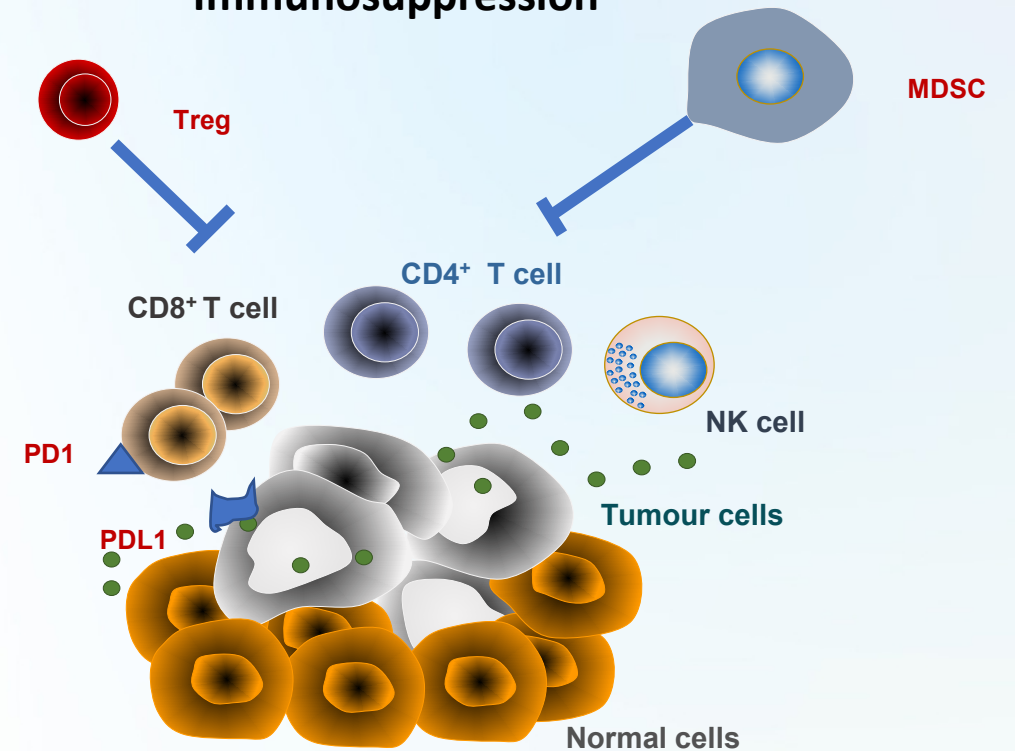


Les 2 pans de la réponse immunitaire

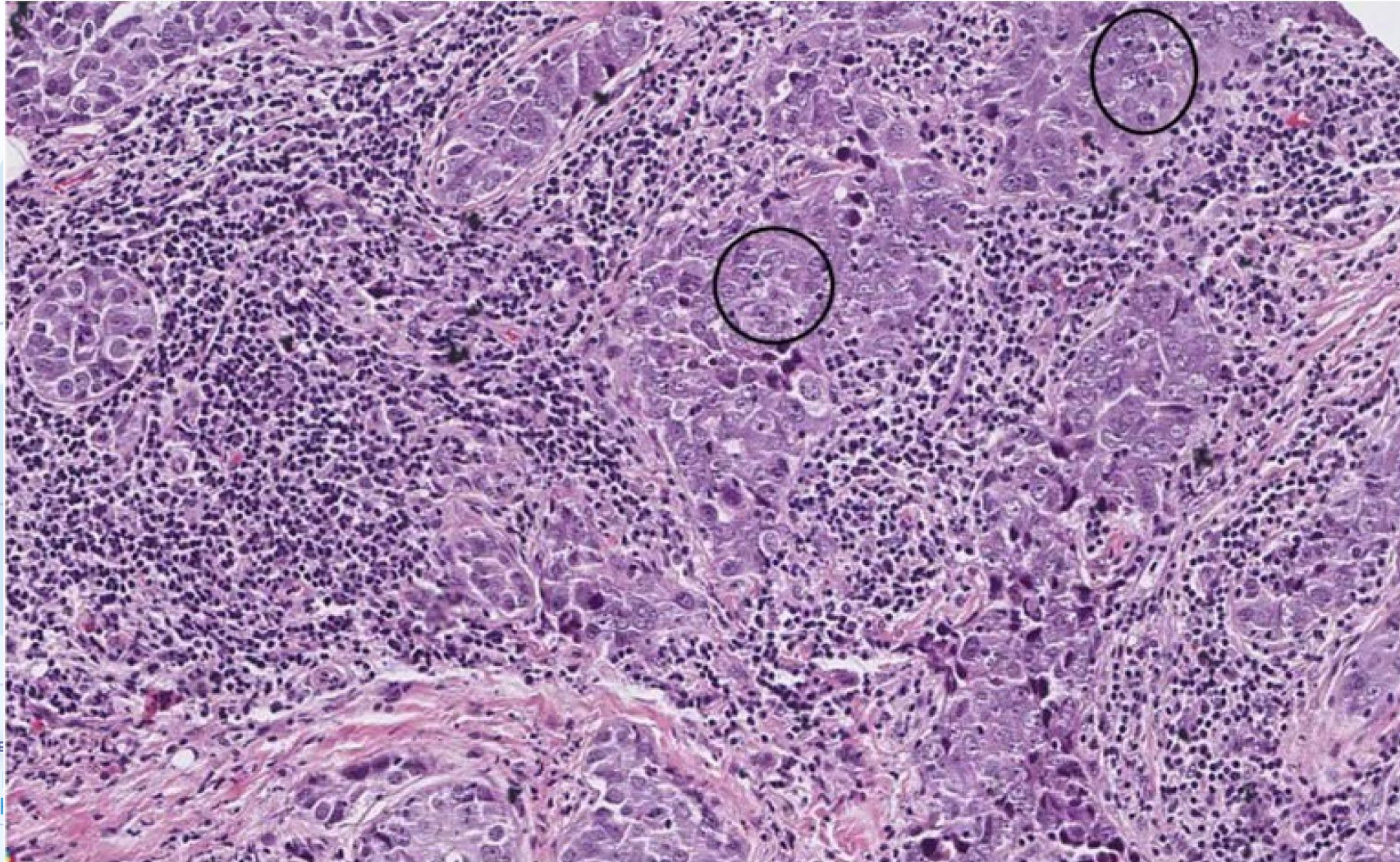
Réponse effectrice



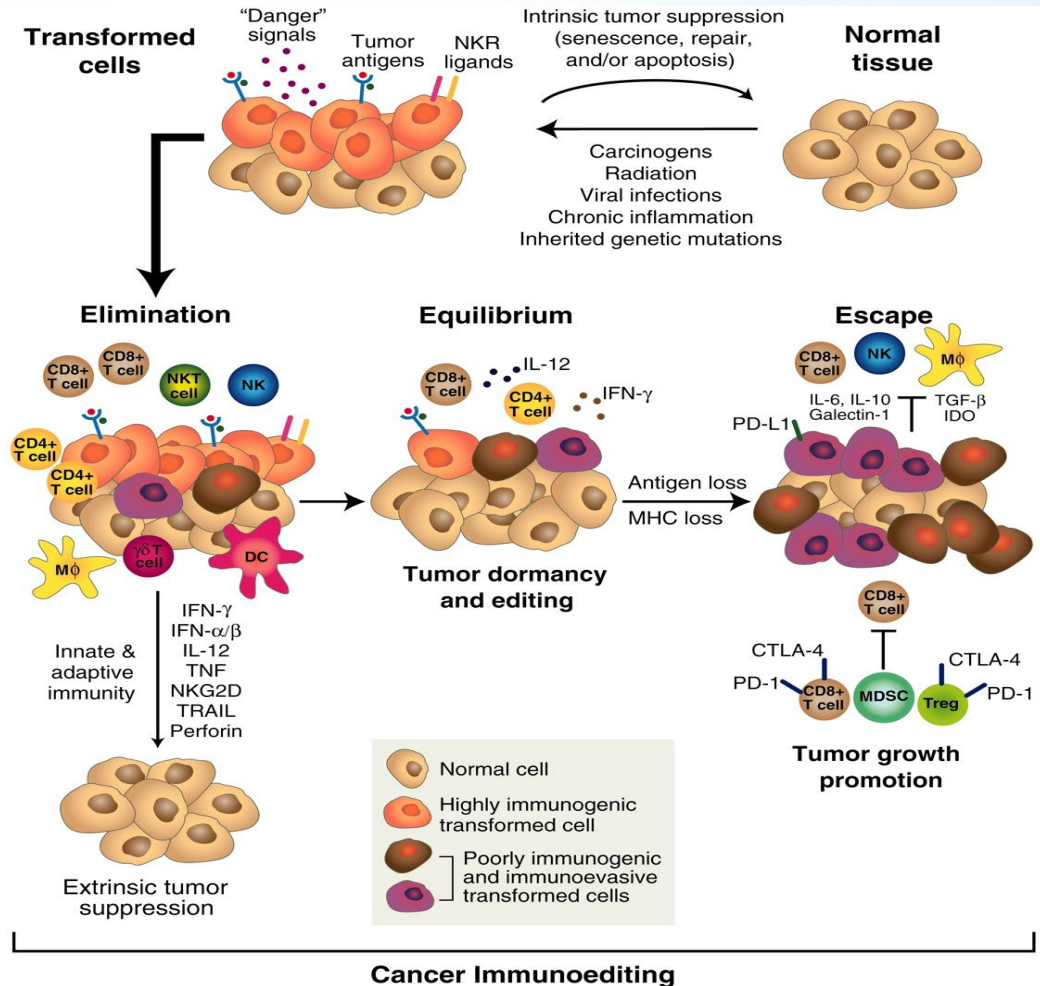
Immunosuppression



Role pronostic de la réponse immunitaire in situ

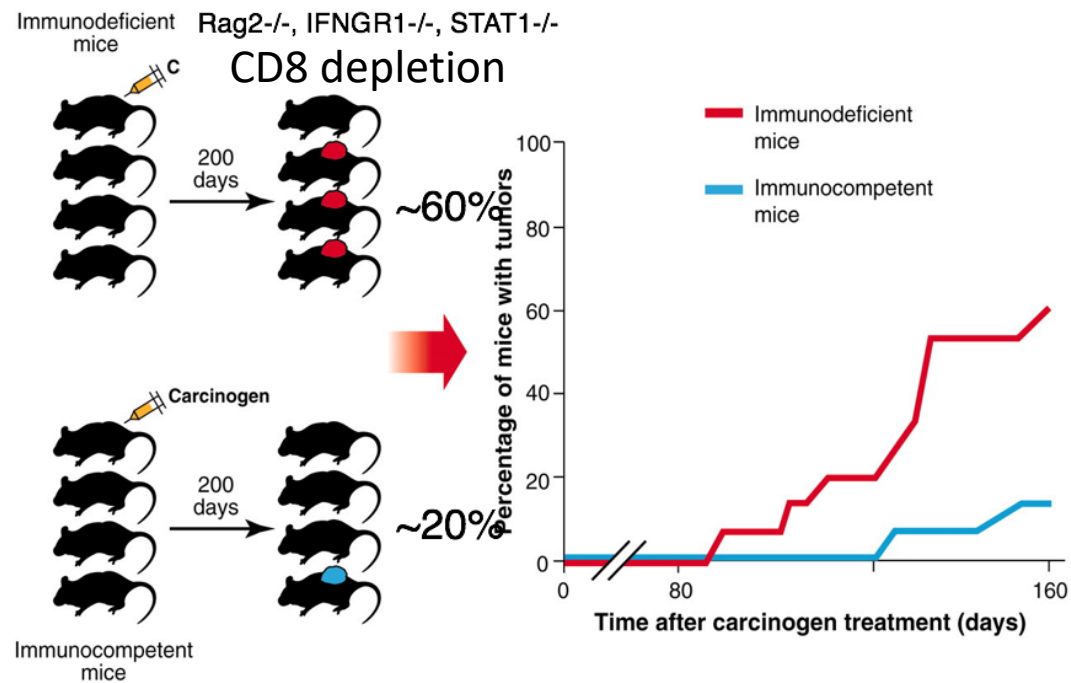


Un rôle majeur des cellules T dans l'immunosurveillance et la protection contre le cancer



Un rôle majeur des cellules T dans l'immunosurveillance et la protection contre le cancer

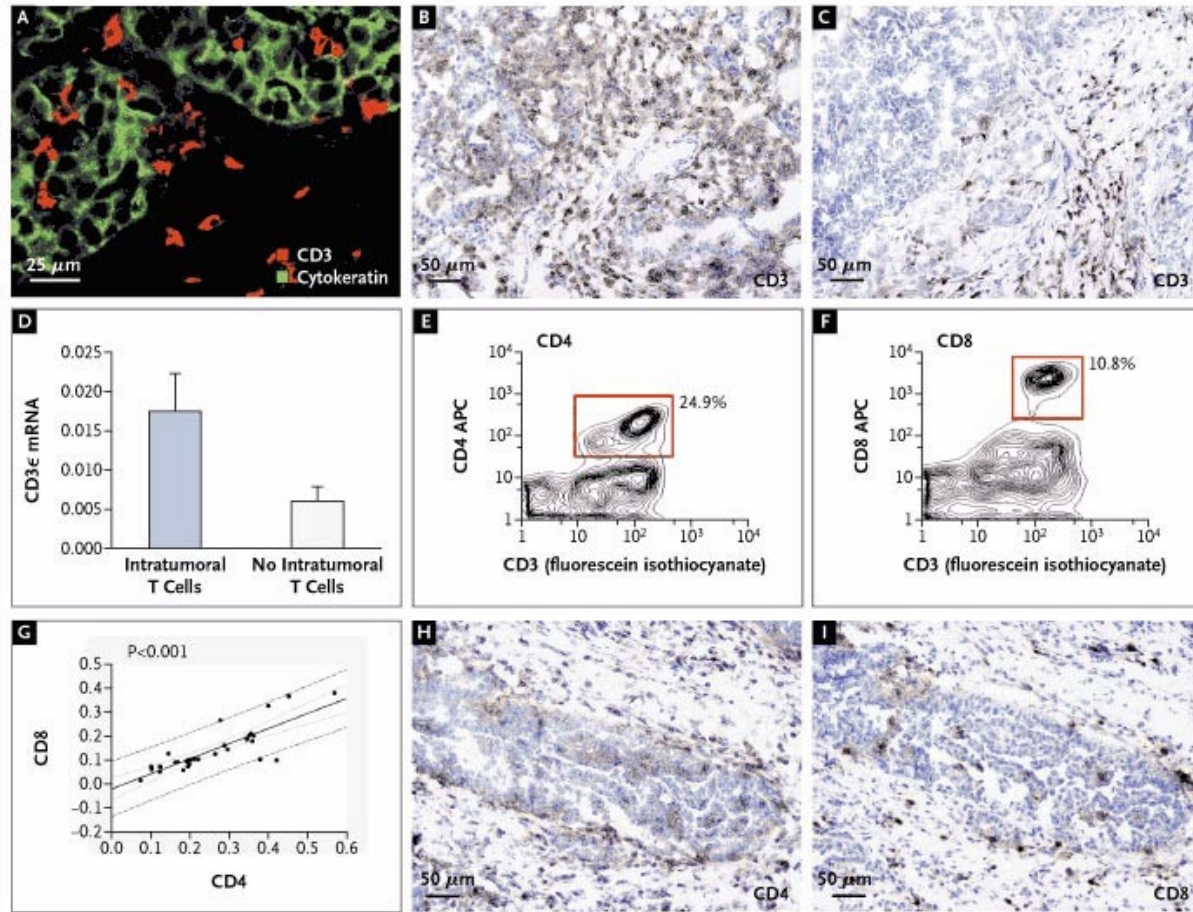
The immune system has a role in suppressing endogenous tumor growth



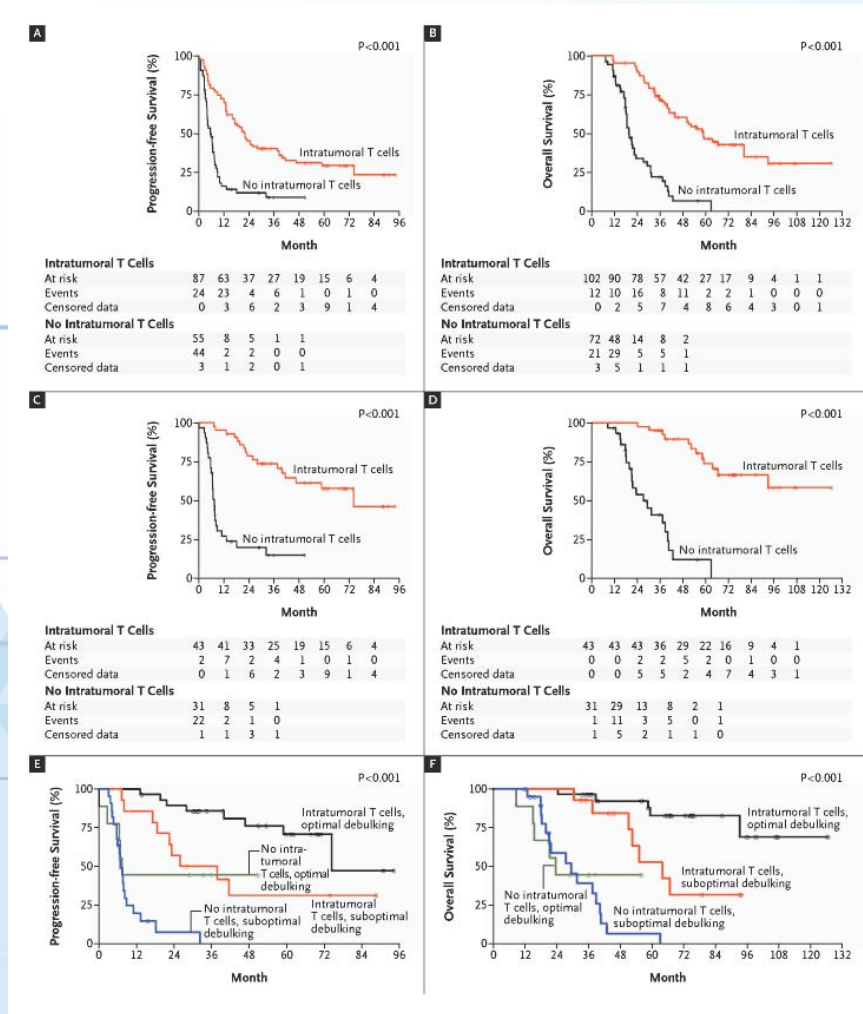
R D Schreiber et al. Science 2011;331:1565-1570

*similar observations for spontaneous tumor development

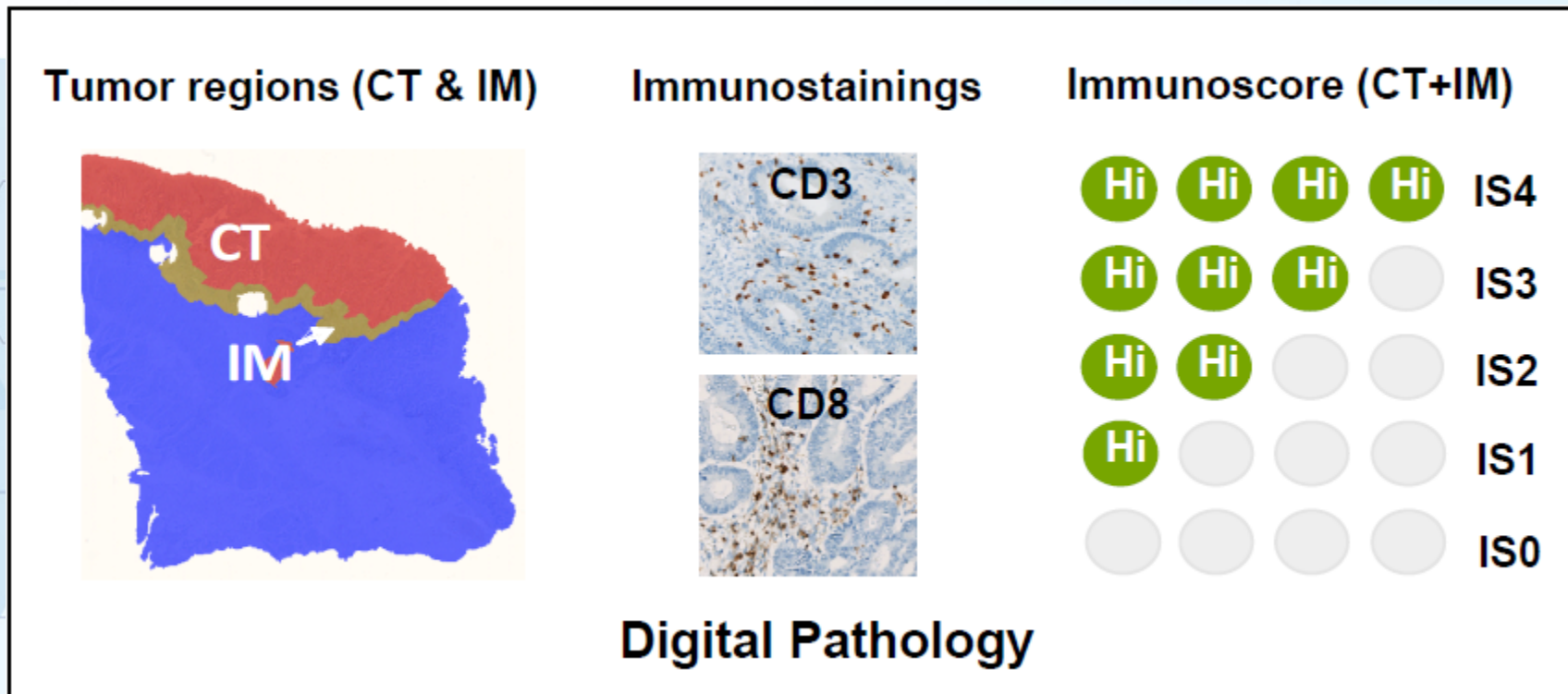
1° démonstration dans le cancer de l'ovaire: Patterns of T-Cell Infiltration in Ovarian Carcinoma.



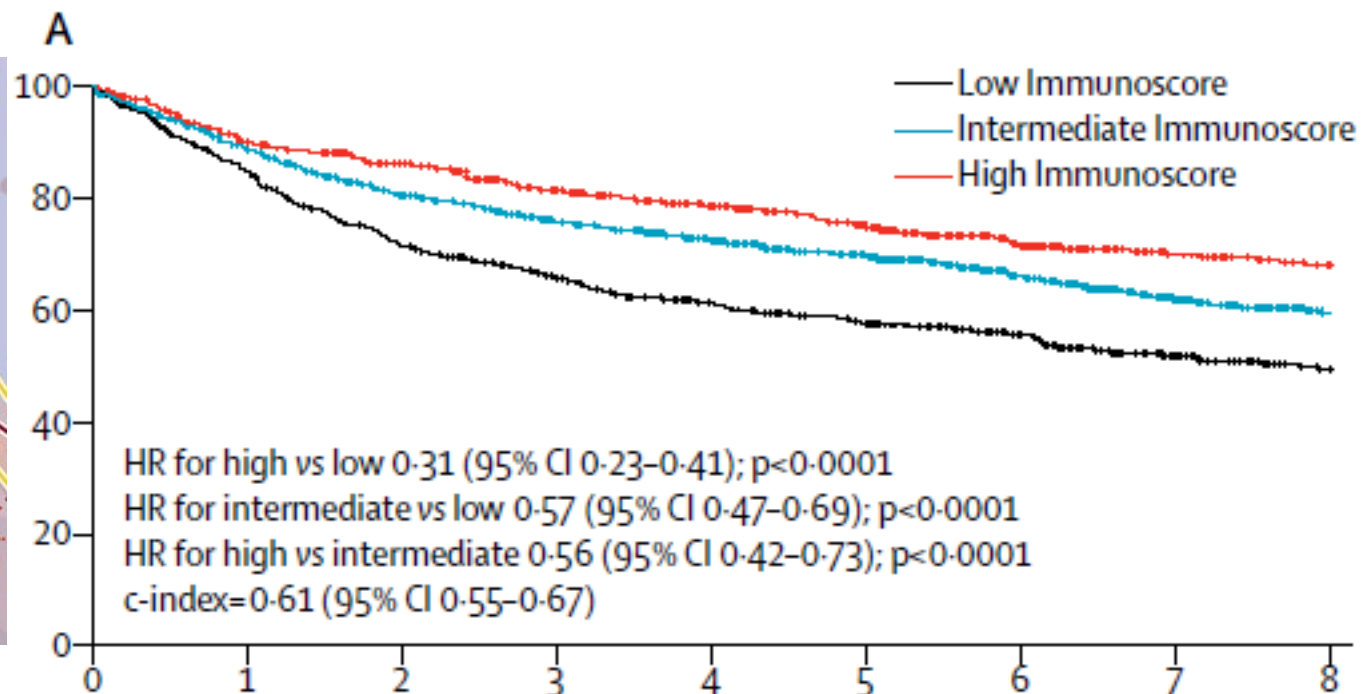
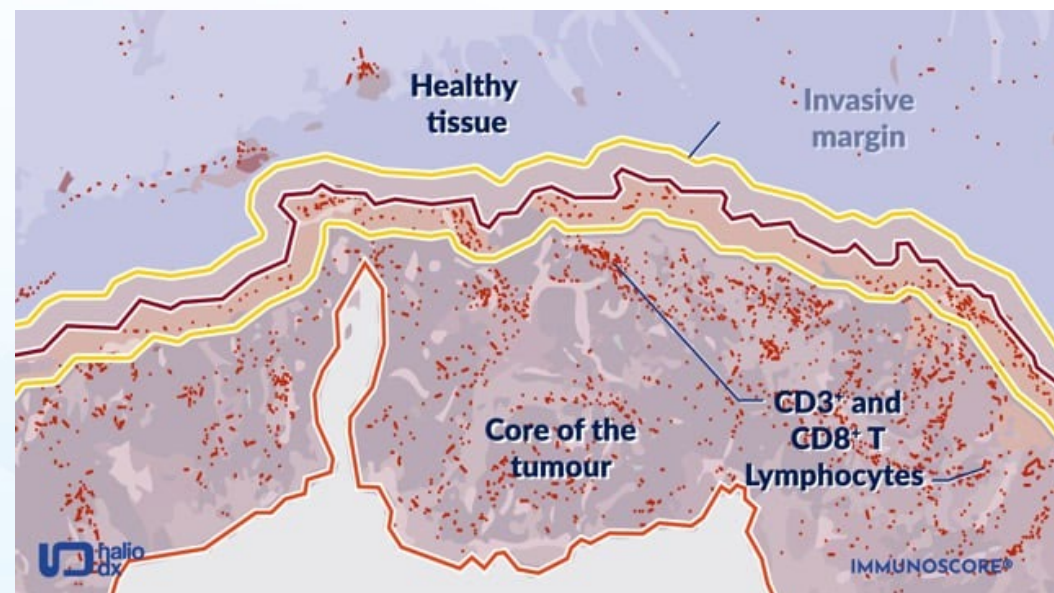
Survival Analyses of Patients with Ovarian Carcinoma, According to the Presence or Absence of Intratumoral T Cells.



L'exemple du cancer colorectal: l'immunoscore

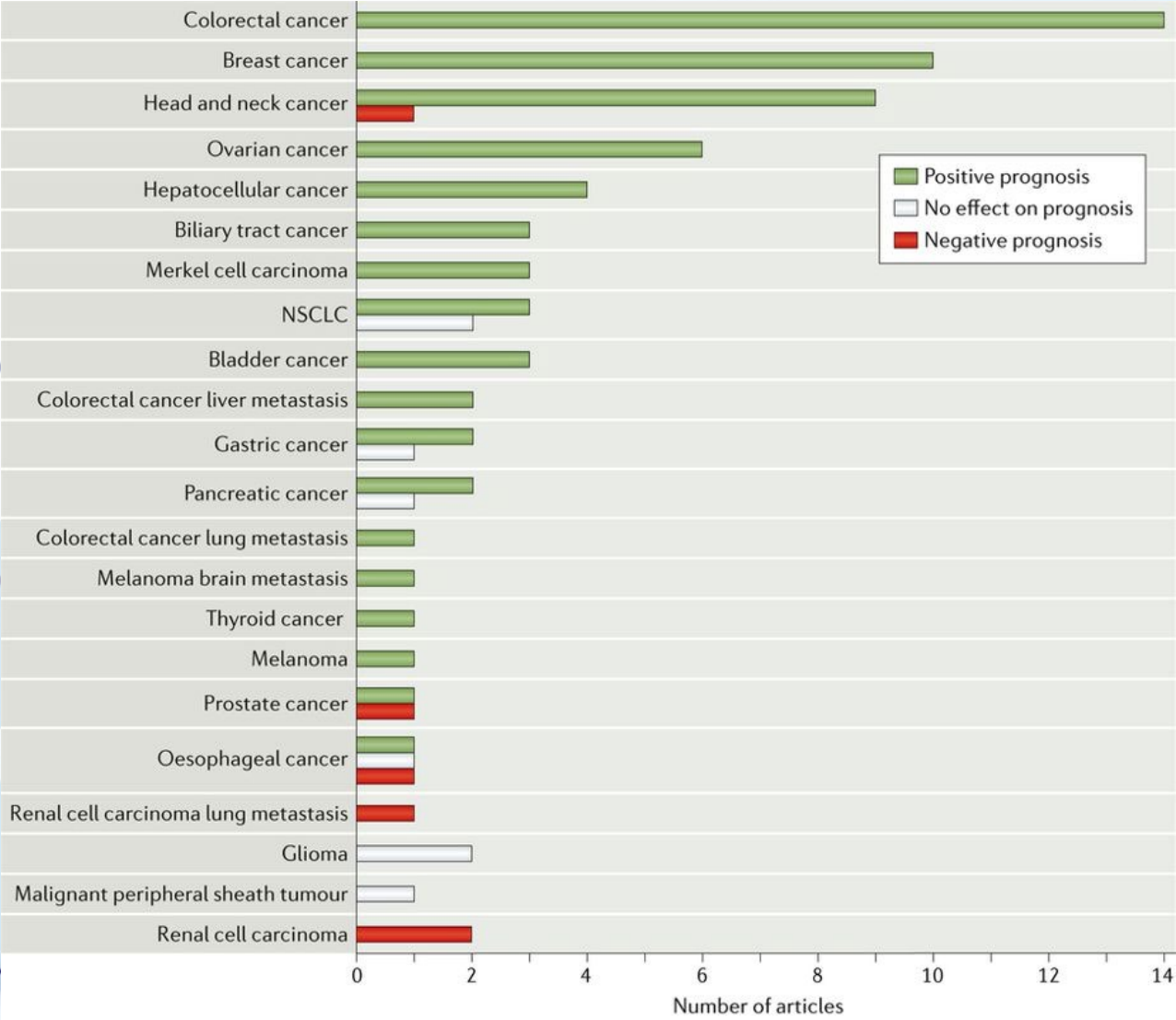


L'exemple du cancer colorectal: l'immunoscore



	Number at risk								
	0	1	2	3	4	5	6	7	8
Low Immunoscore	702	566	468	411	358	321	259	194	150
Intermediate Immunoscore	1271	1069	930	839	763	675	526	406	324
High Immunoscore	708	594	535	469	417	359	273	208	172

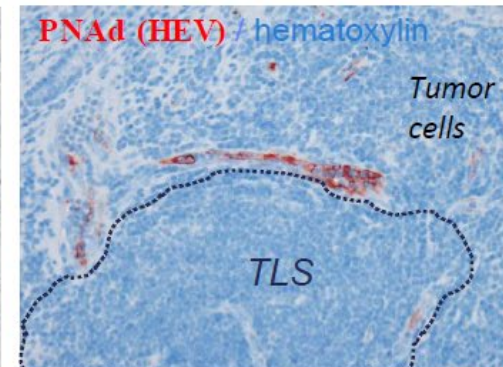
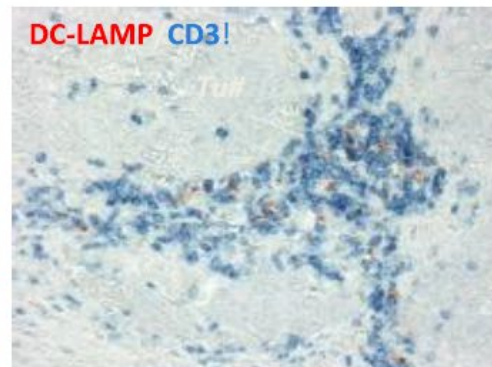
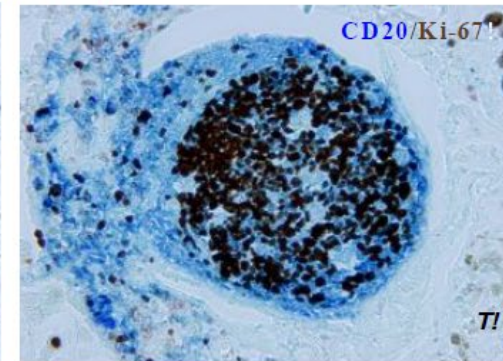
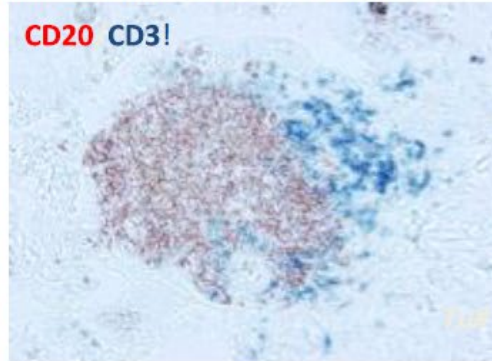
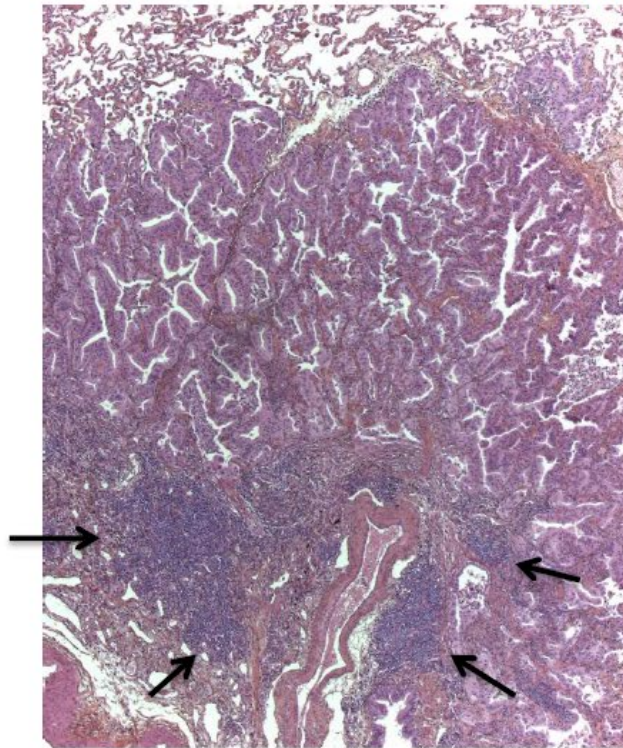
Une généralité dans presque tous les cancers



La presence de TLS est aussi une marque essentielle

Identification of Tertiary Lymphoid Structures (TLS) in most human cancers

NSCLC-associated TLS
(= lymph node-like structures in tumor stroma)

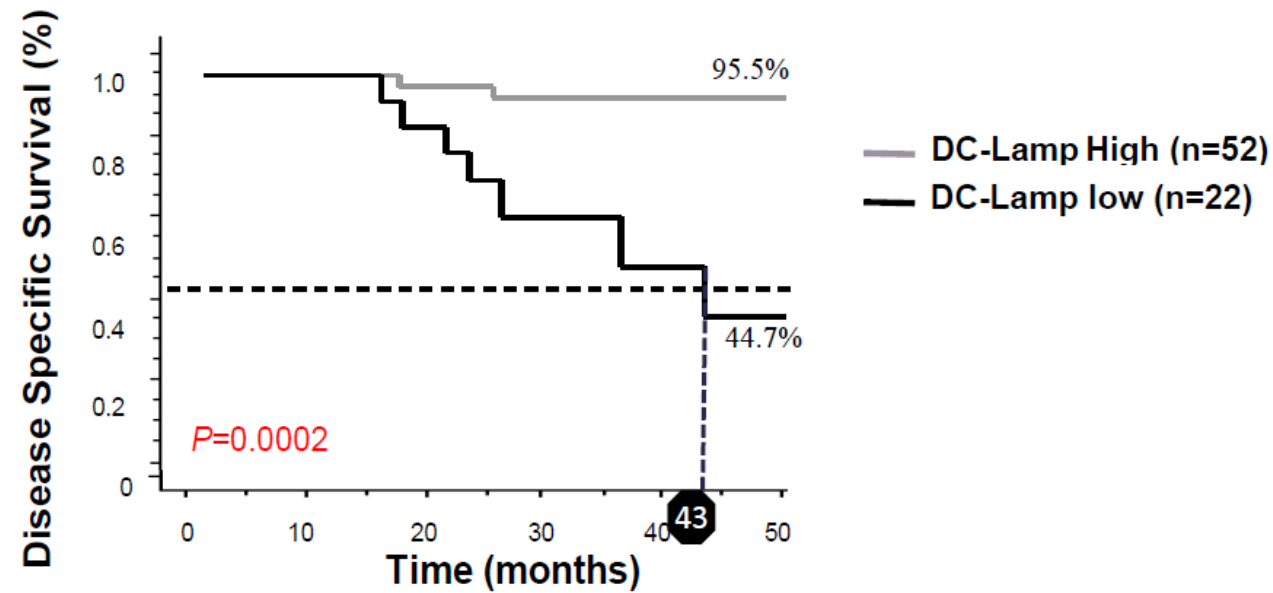
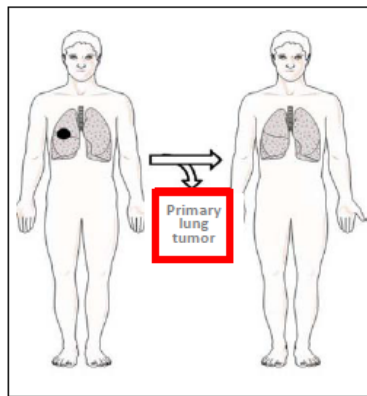


Dieu-Nosjean *et al.*, J Clin Oncol, 2008

Un role majeur dans le cancer bronchique

High density of mature DC is associated with a favorable clinical outcome in patients at early stage lung cancer

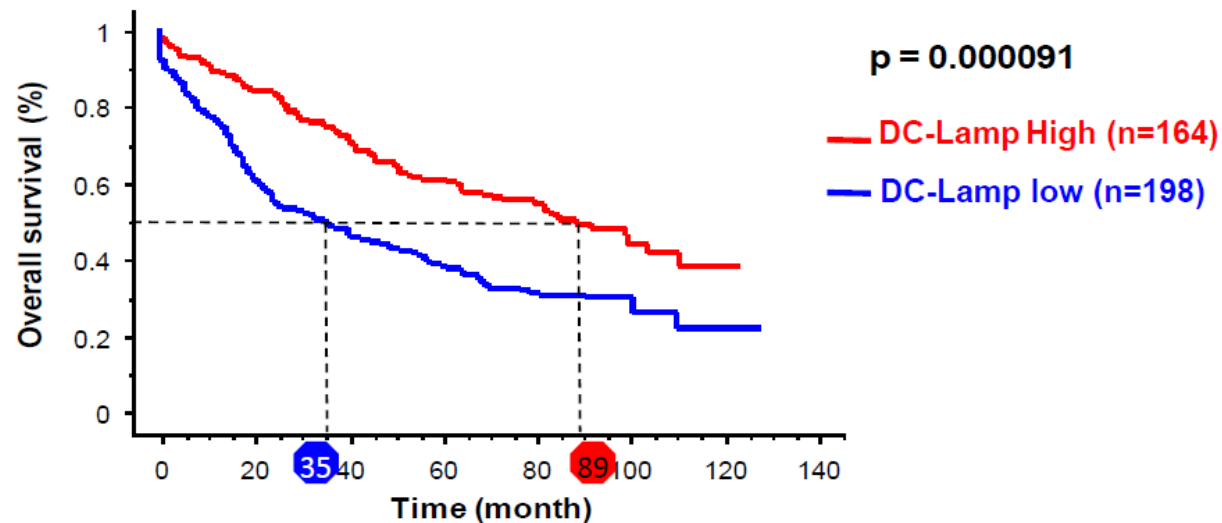
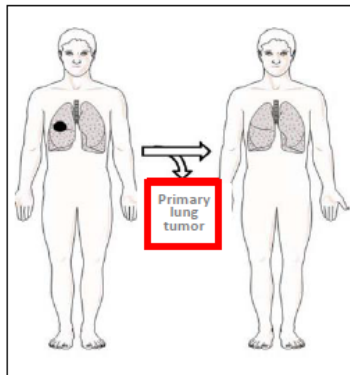
N=74 patients with primary early NSCLC



Un role majeur dans le cancer bronchique

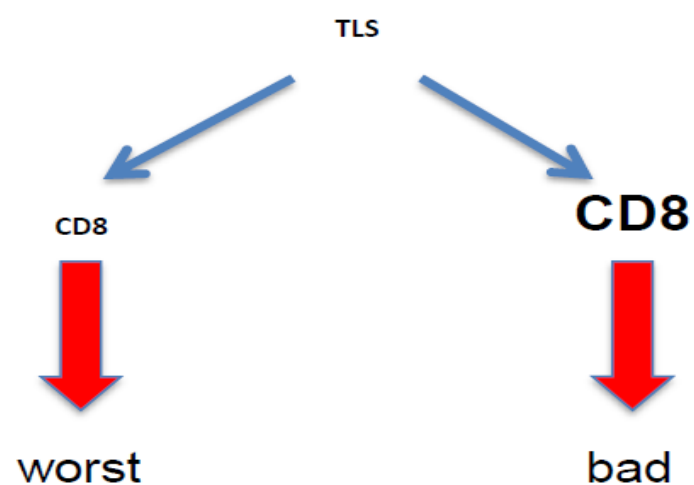
High density of mature DC is associated with a favorable clinical outcome in patients at any stage lung cancer

N=372 patients with primary NSCLC (stages I to IIIa, wo neo-adj chemotherapy)

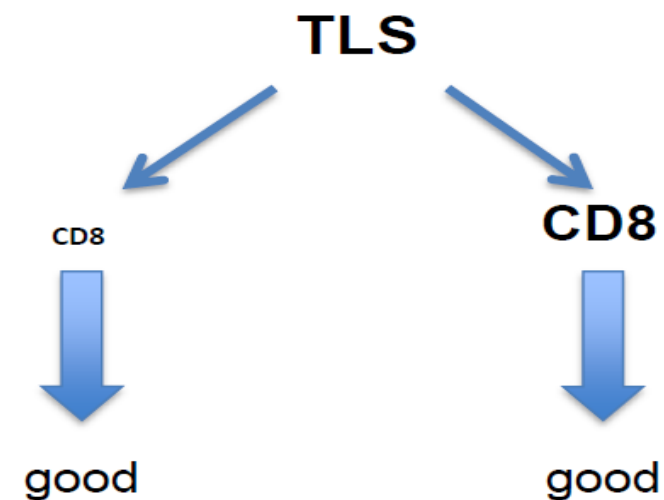


Intérêt d'une analyse combinée TLS CD8

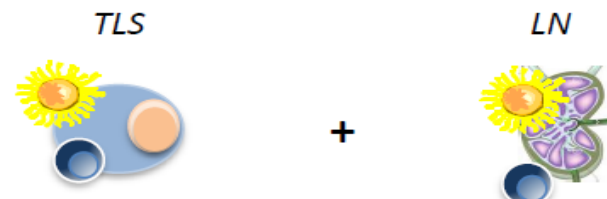
TLS can shape the immune microenvironment in NSCLC



No local education of specific T cells
Priming in lymph node only



Local education of specific T cells (TLS)
± priming in lymph node



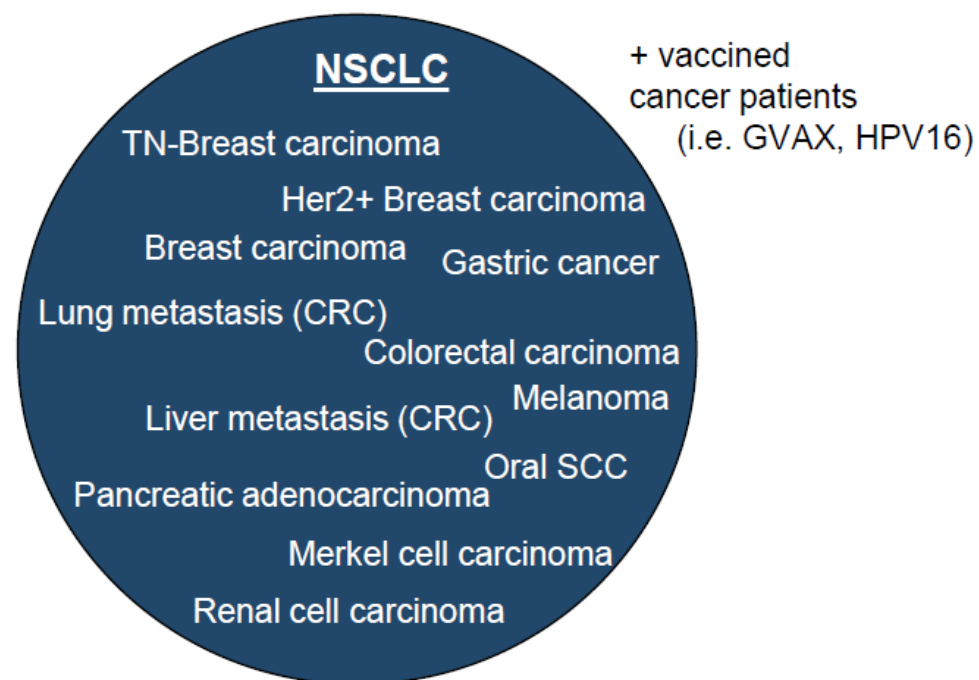
Une généralisation du concept

TLS is a powerful biomarker in almost all human cancers

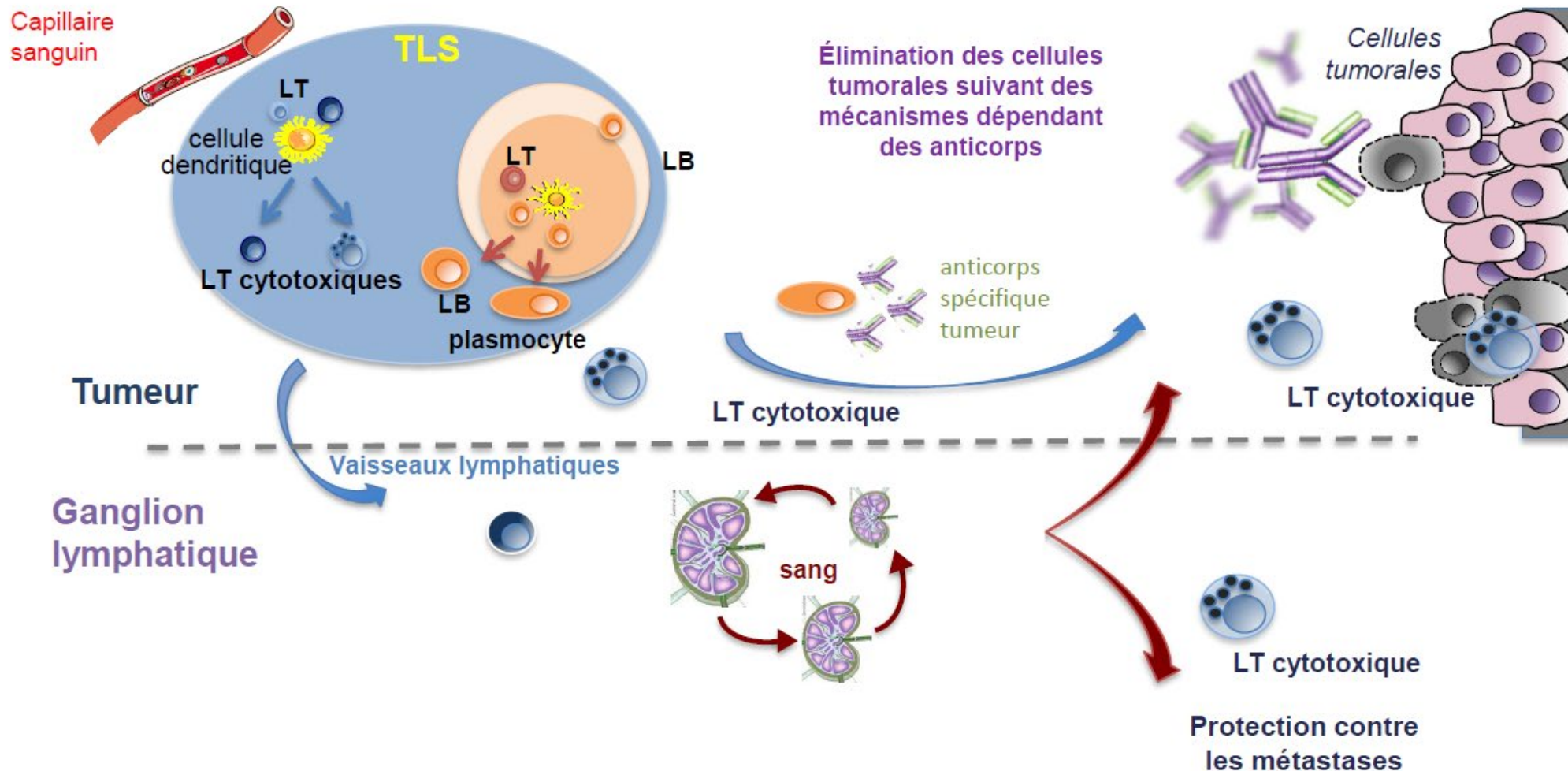
Poor prognosis

HCC (HCV+ alcohol-)

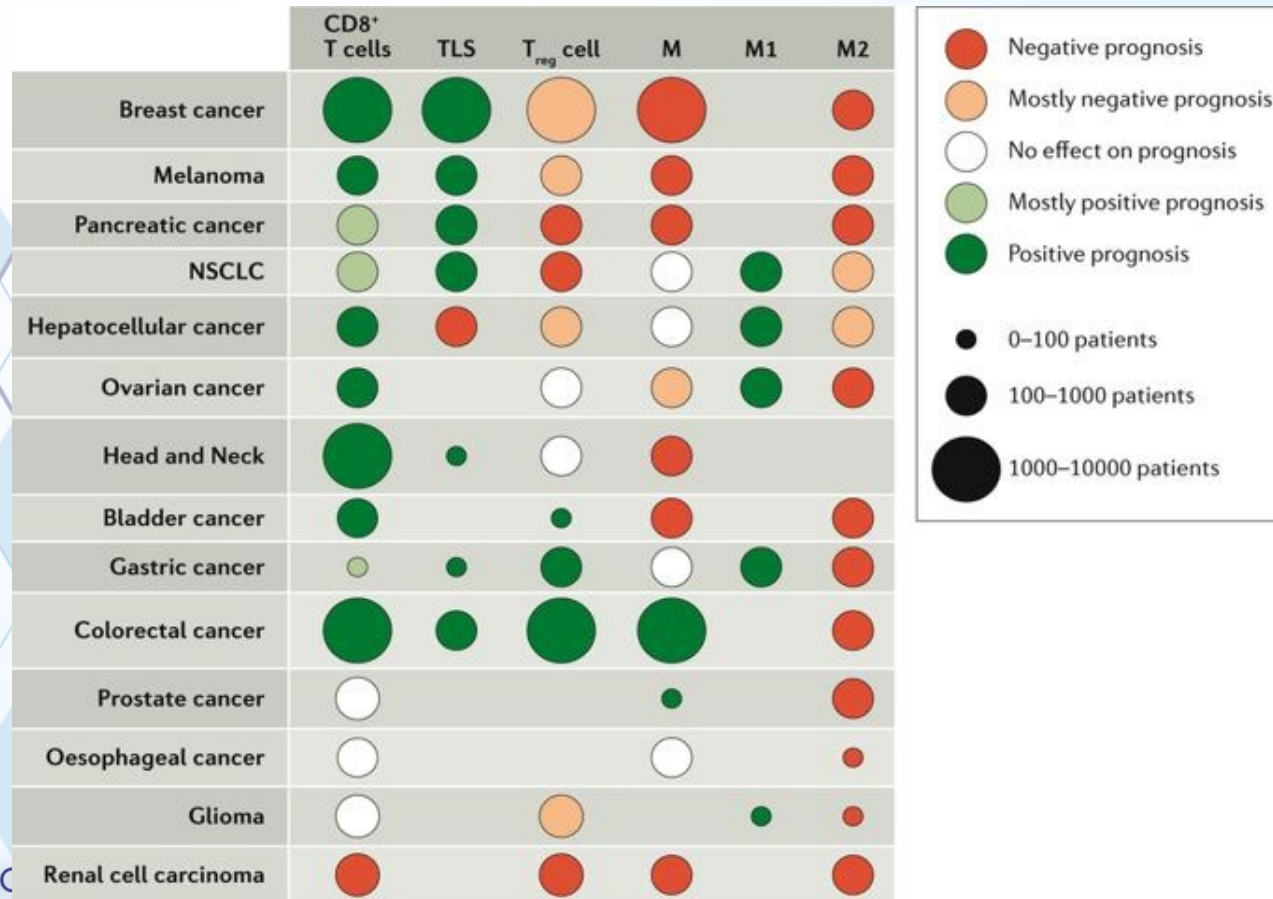
Favorable prognosis



La présence de TLS est très importante pour développer une immunité dirigée contre le tumeur



Un rôle pronostic majeur dans la plupart des cancers



Role prédictif de la réponse à la chimiothérapie

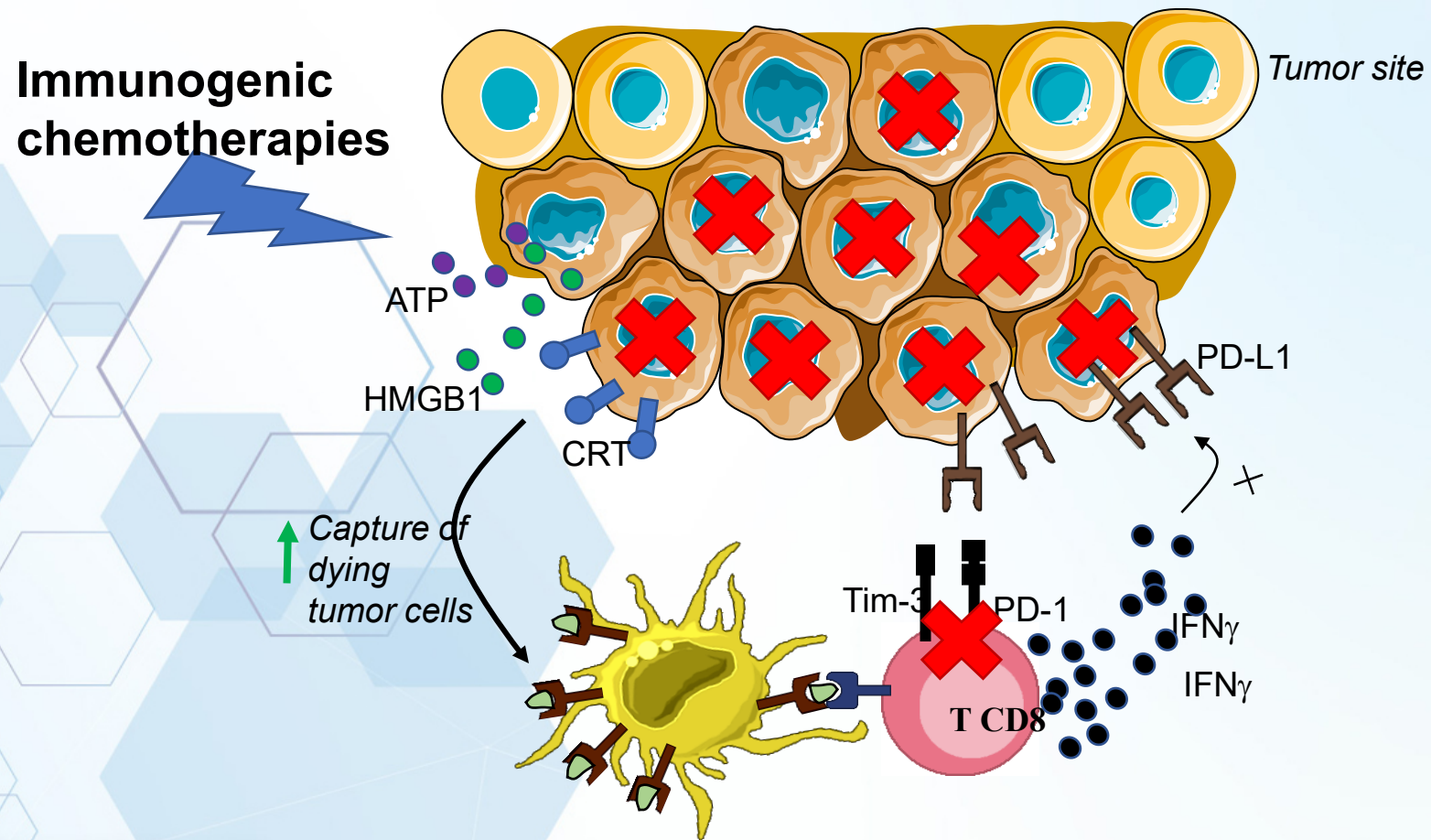


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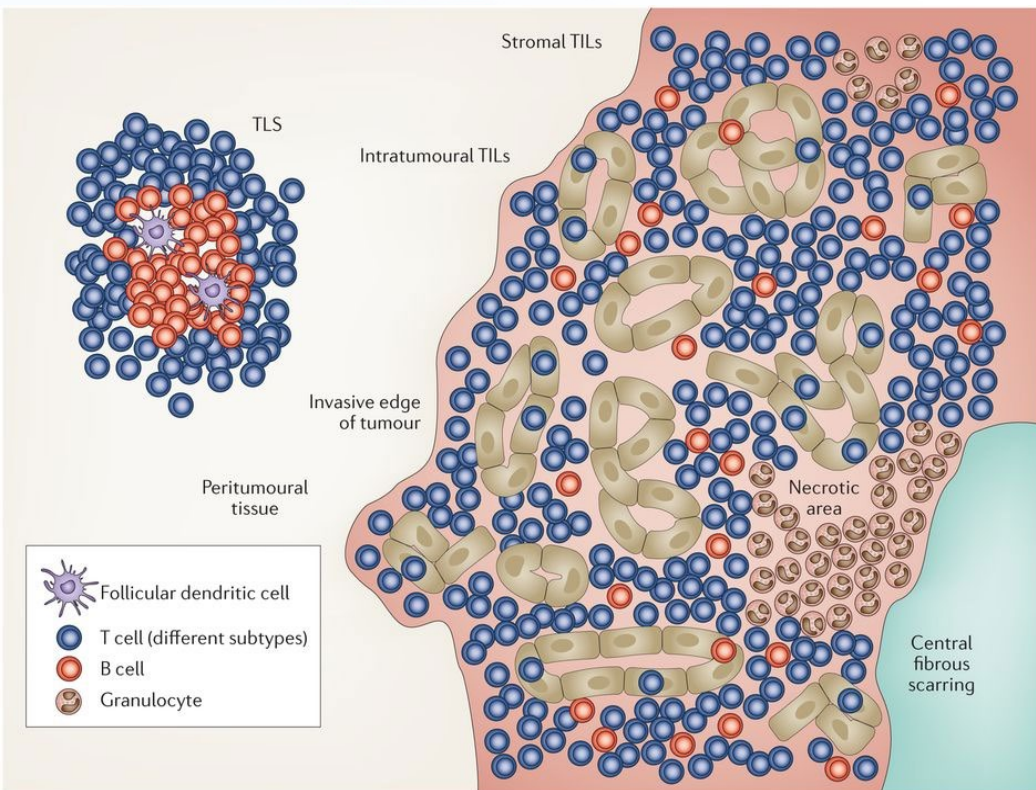
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Le concept de la mort immunogène

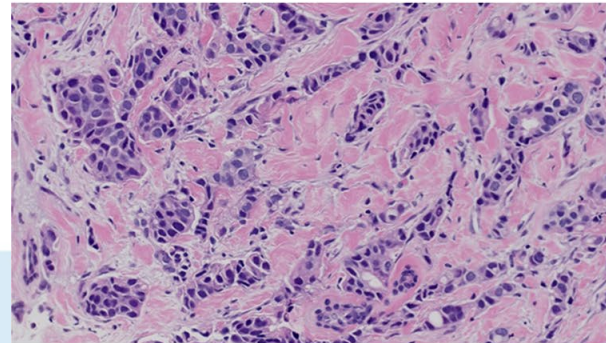


Une façon simple de mesurer la réponse immunitaire

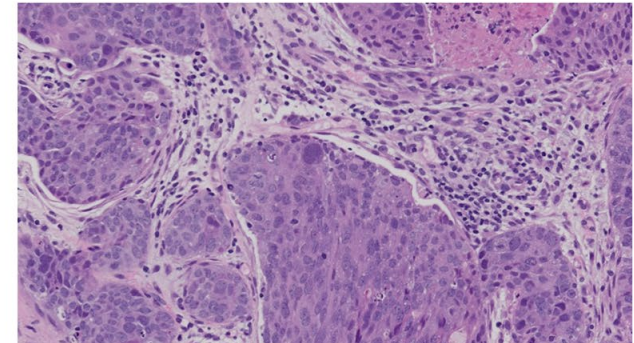


Nature Reviews | Clinical Oncology

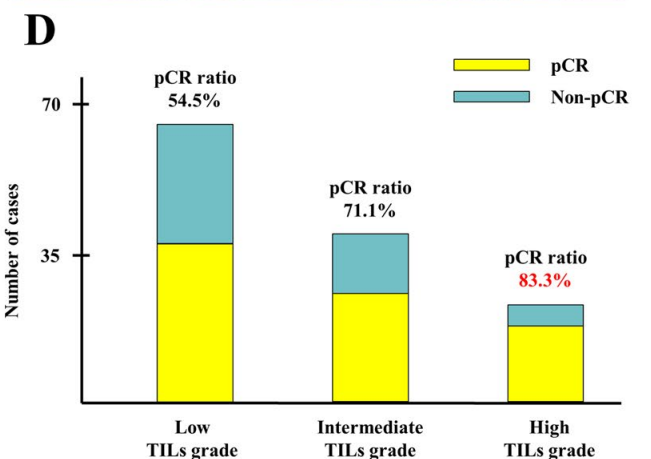
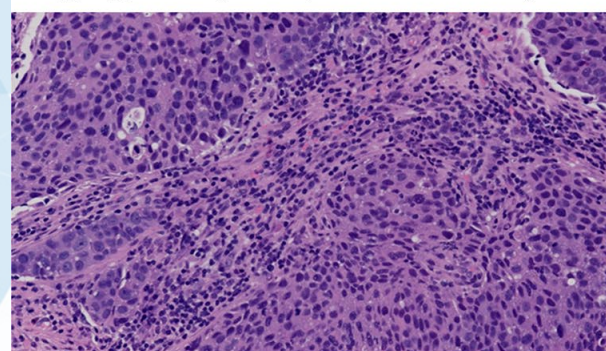
A
Low grade (TILs, 0% to 10%)



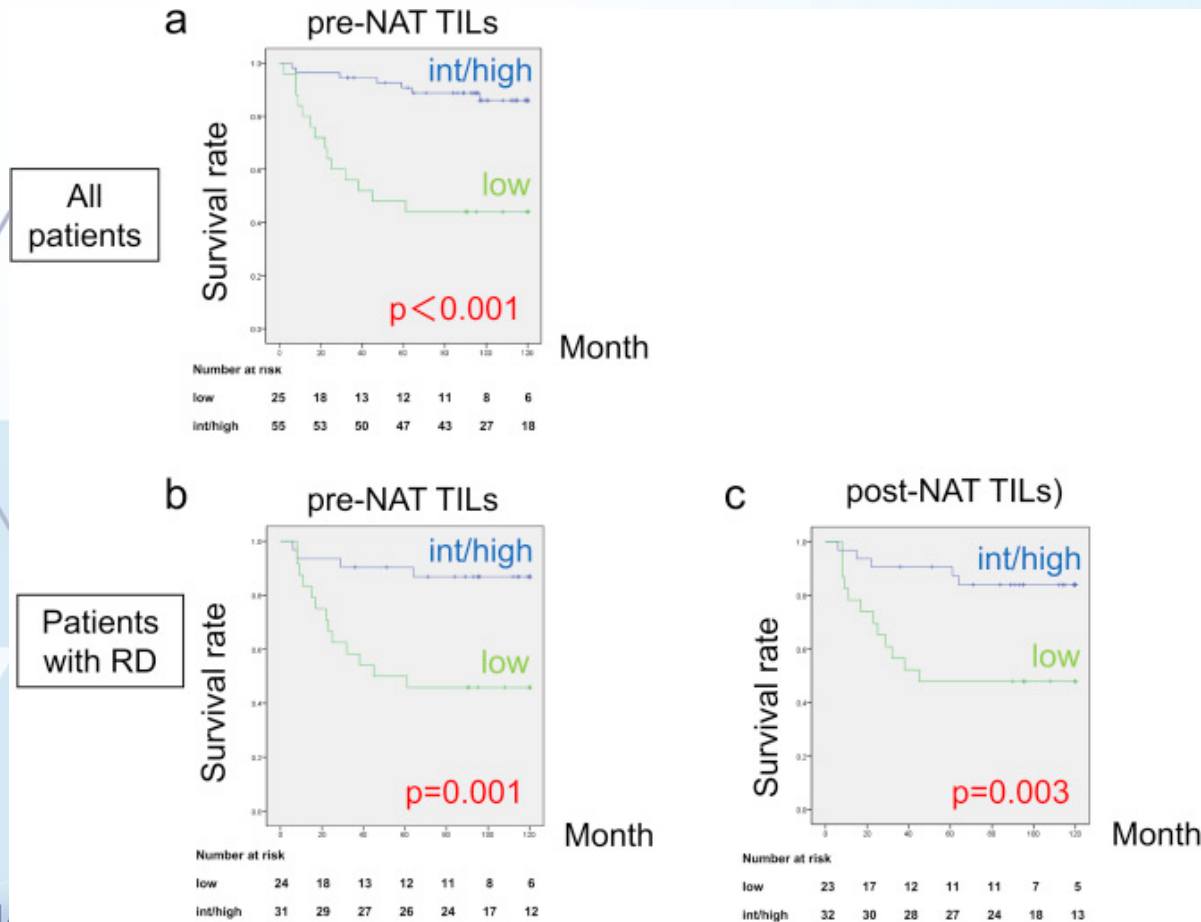
B
Intermediate grade (TILs, 10% to 40%)



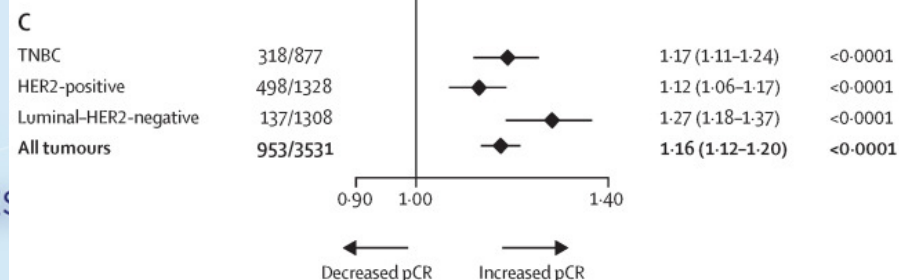
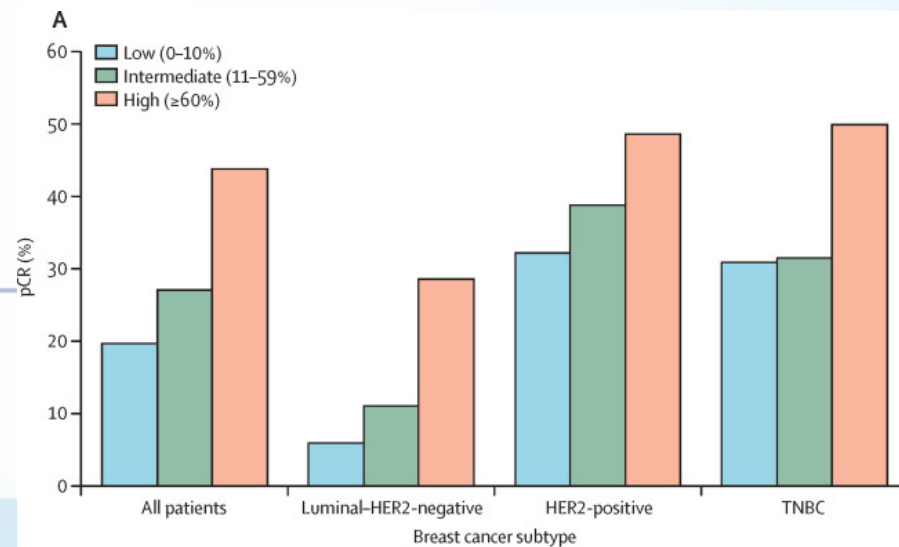
C
High grade (TILs, 40% to 90%)



Un fort infiltrat est associé à une meilleure réponse à la chimiothérapie néoadjuvante dans le cancer du sein TN.



Une generalisation dans une métaanalyse

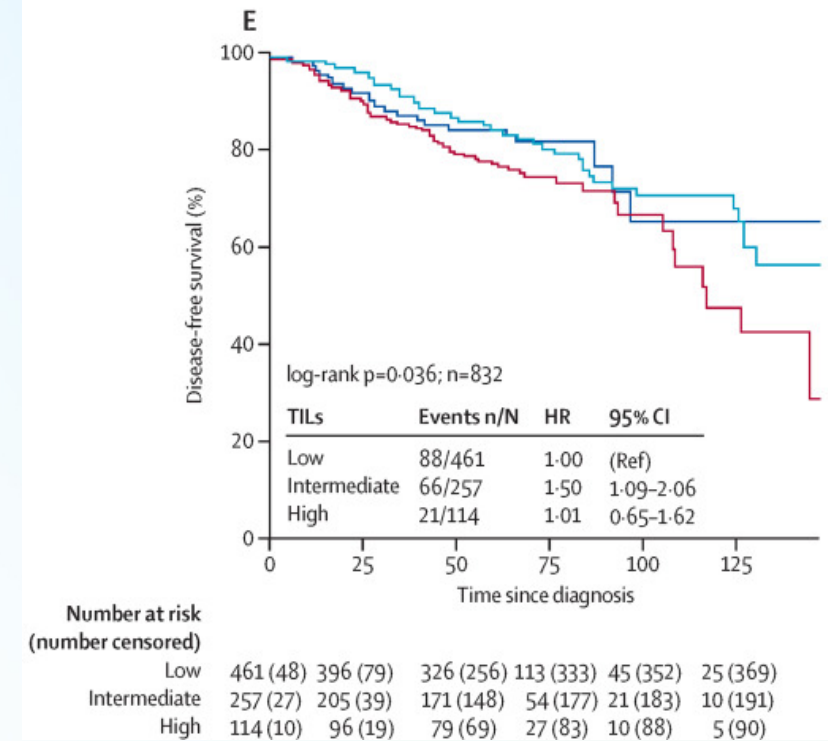
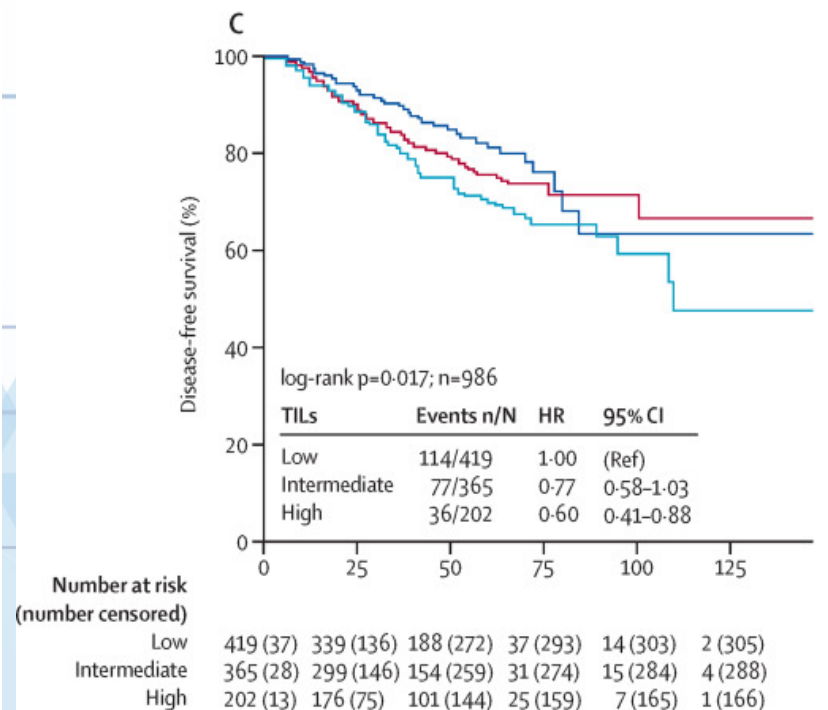
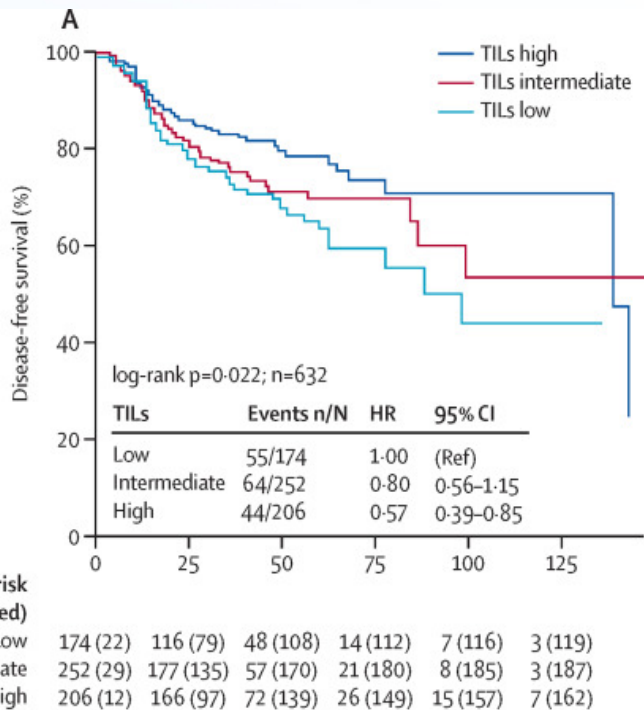


Une generalisation dans une métaanalyse

TN

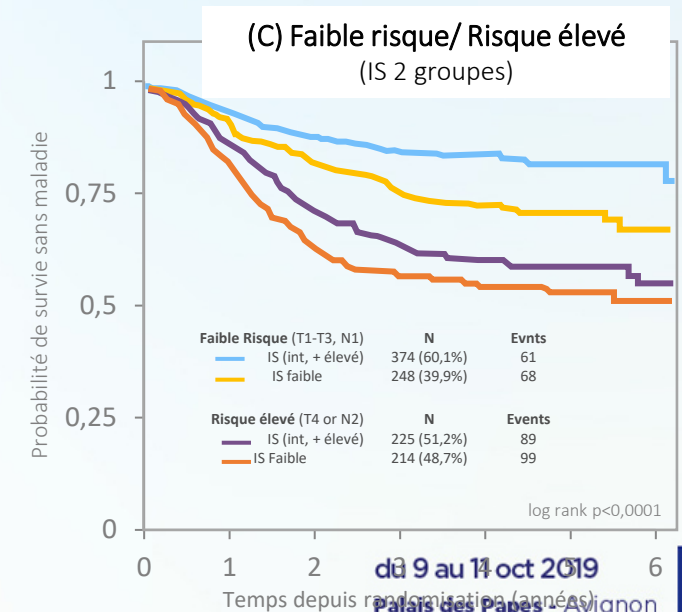
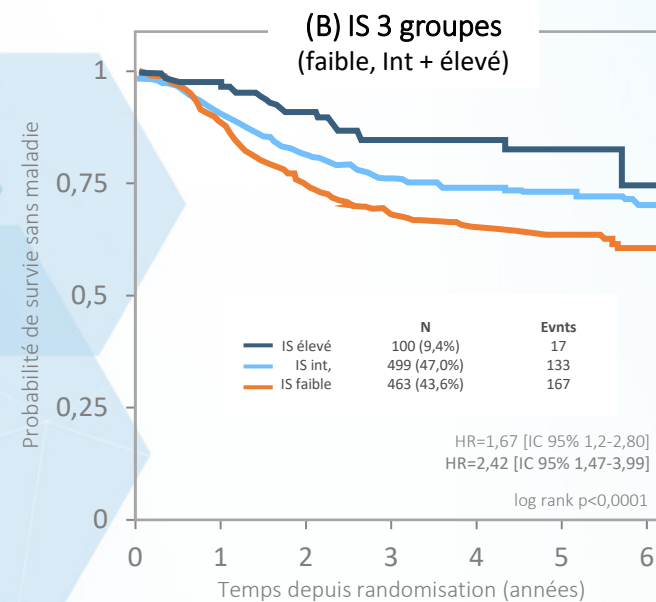
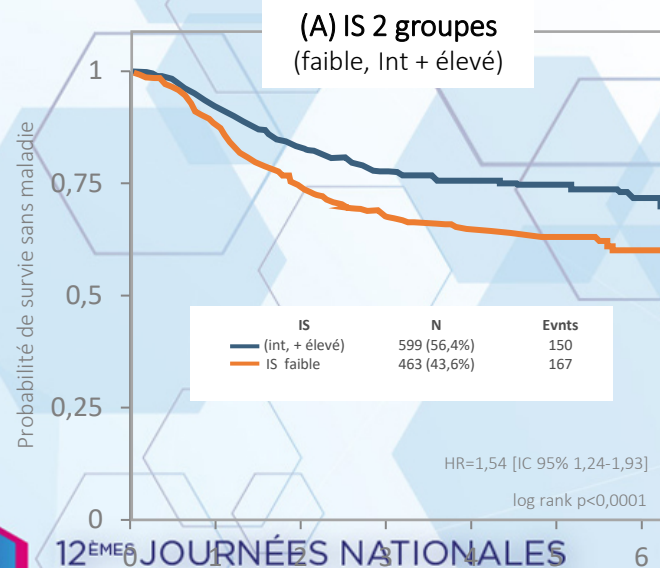
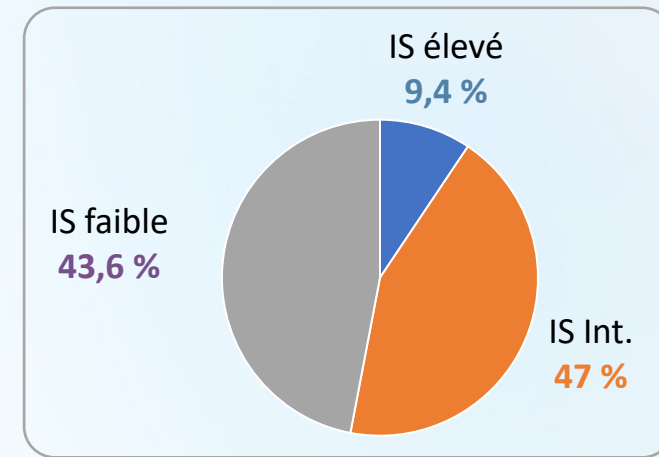
HER2

RH+



Immunoscore et réponse à la chimiothérapie

- Immunoscore® chez pts de l'étude IDEA France
- Objectifs :
 - confirmer le rôle pronostique de l'IS sur une grande étude prospective randomisée,
 - explorer sa valeur prédictive.



Immunoscore et réponse à la chimiothérapie

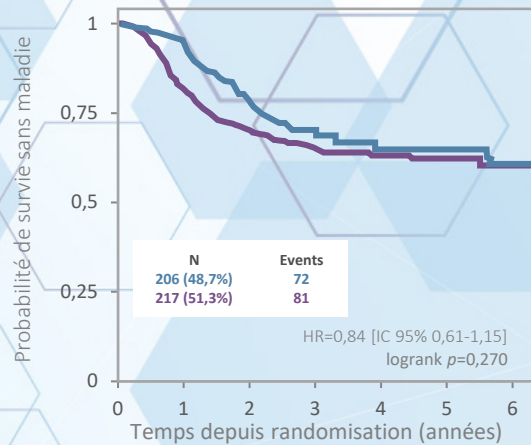
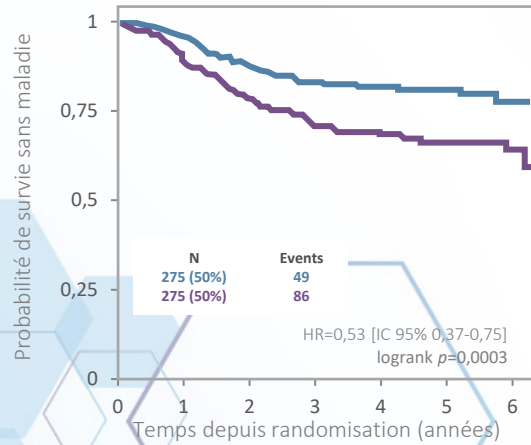
IS haut/int

6 mois

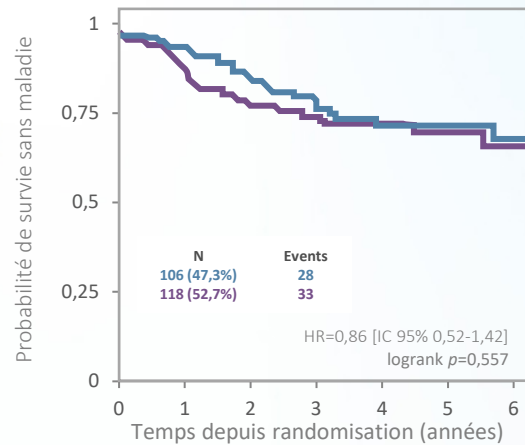
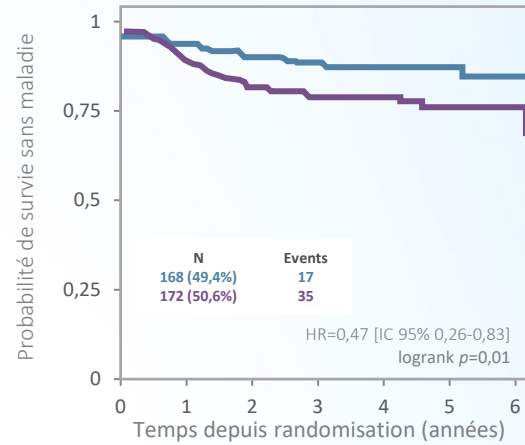
3 mois

IS faible

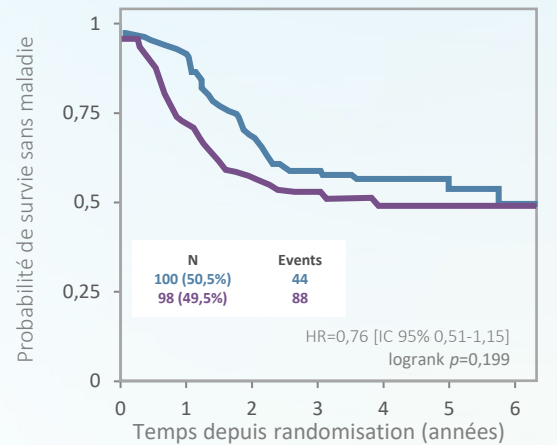
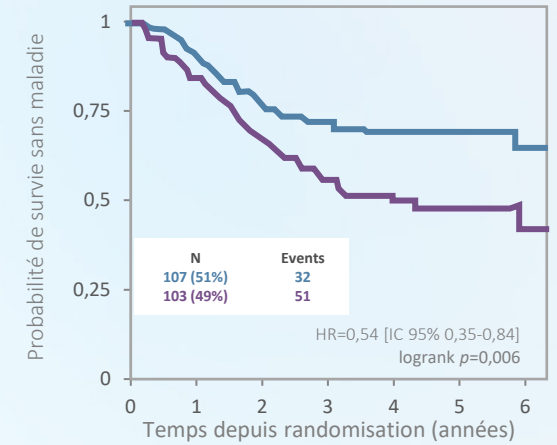
(A) Tous les patients



(B) Faible risque
(T1-T3, N1)



(C) Haut risque
(T4 et/ou N2)



Immunoscore et réponse à la chimiothérapie

- Un effet bénéfique de 6 mois de FOLFOX chez les patients avec un IS élevé ou intermédiaire
- 6 mois de traitement ne semblent pas, en revanche, améliorer significativement la survie sans récurrence des patients avec un IS faible
- Ces résultats sont les mêmes quel que soit le groupe de stade III étudié (T4/N2 ou T1-3/N1)

Role prédictif de la réponse à l'immunothérapie

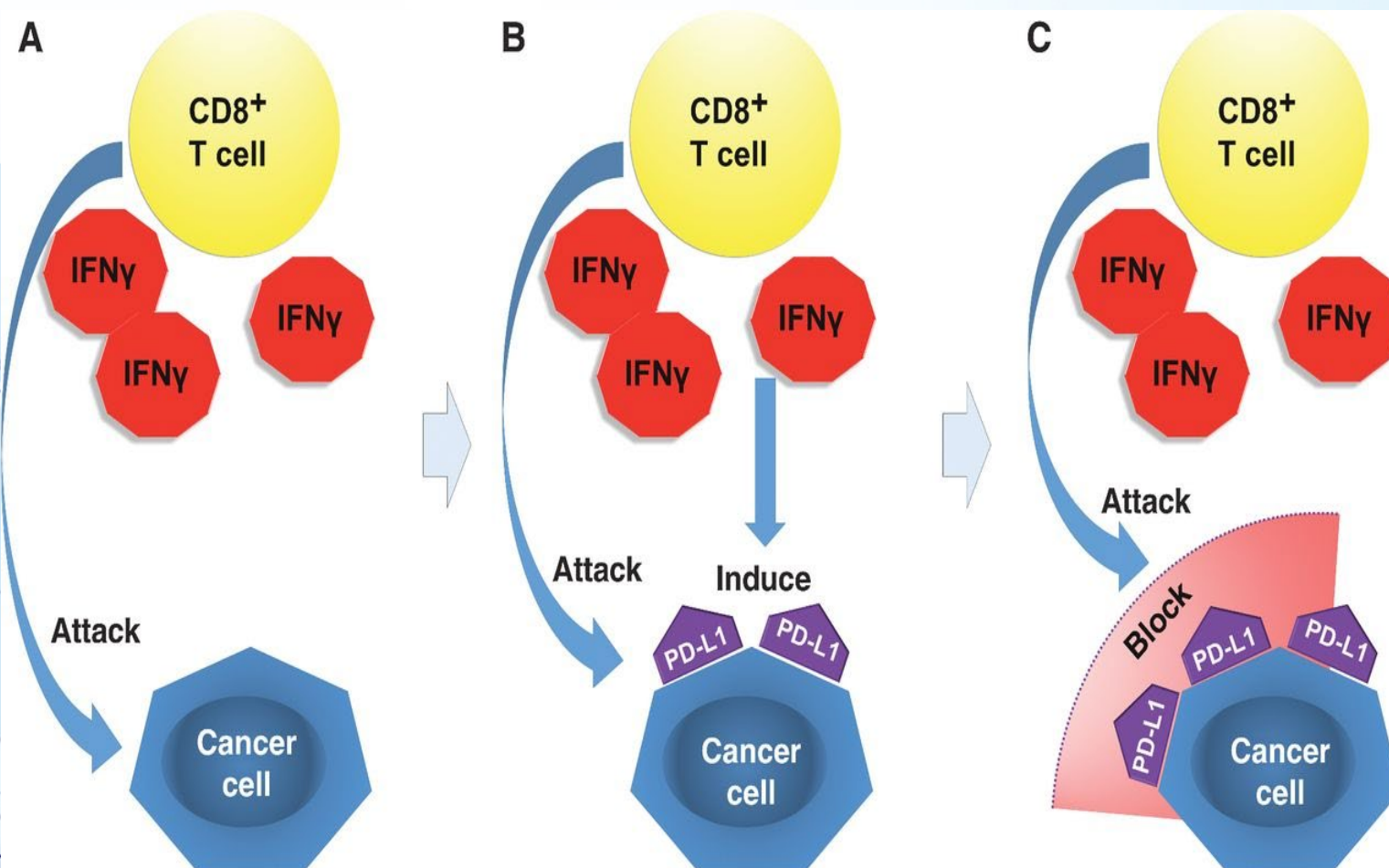


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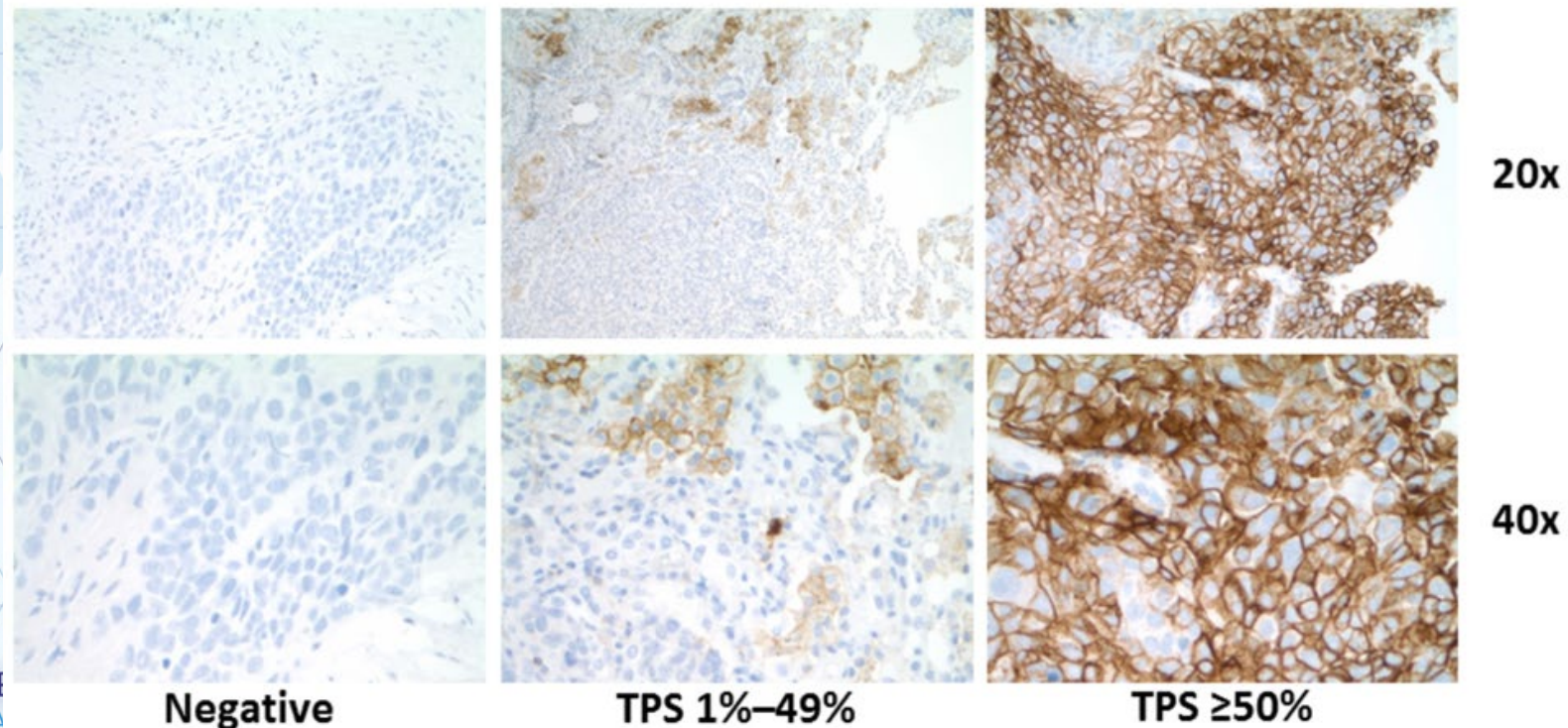


Induction de PDL1 un élément clé

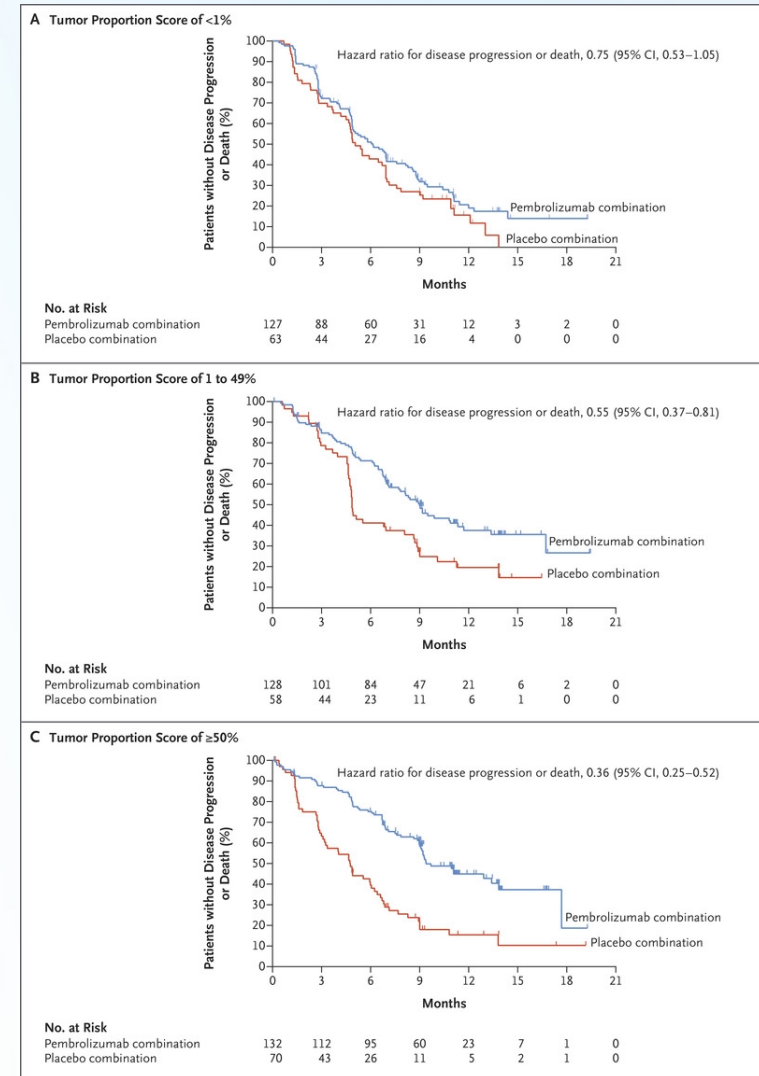
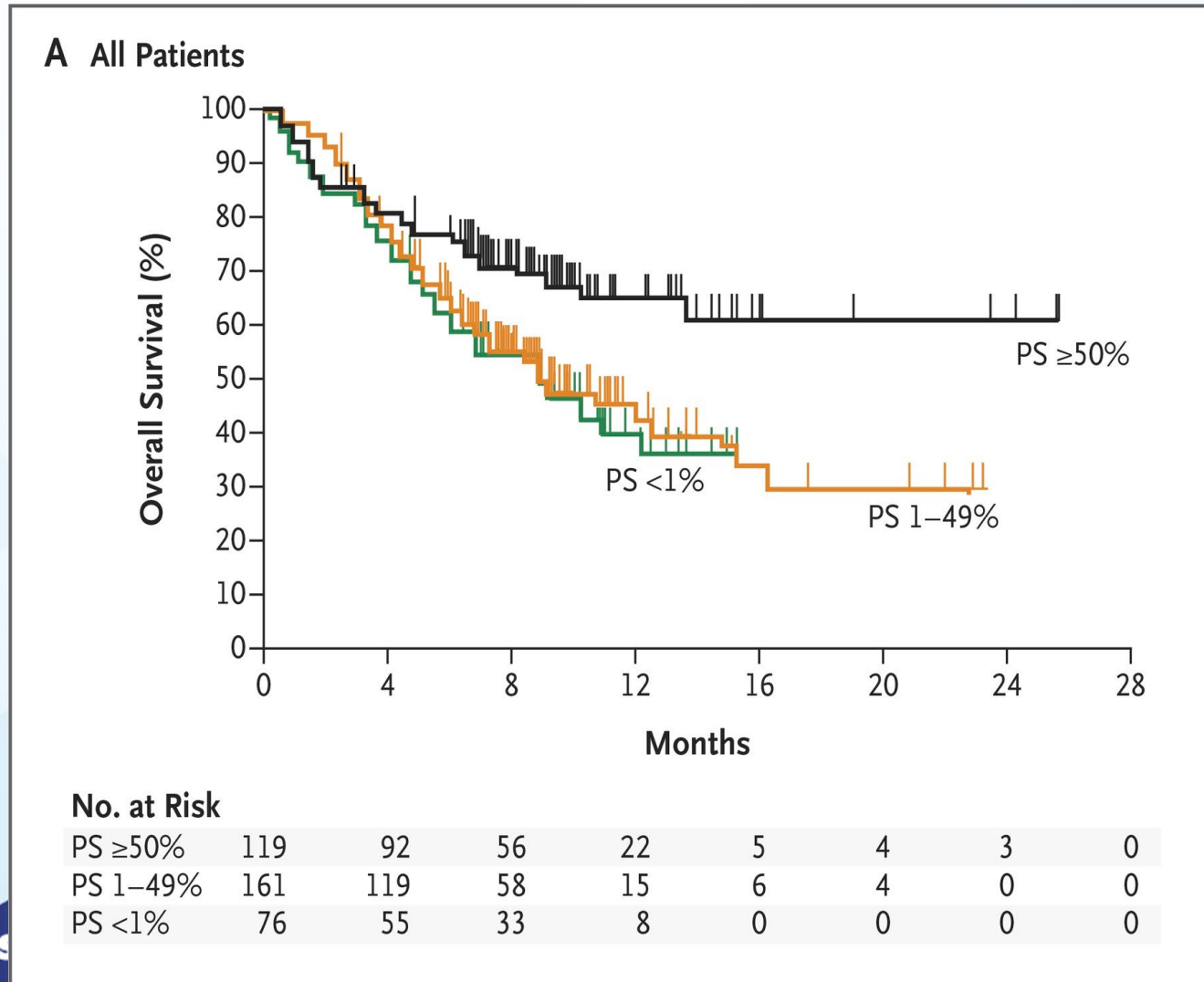


L'expression de PDL1 est associée à l'efficacité de l'immunothérapie

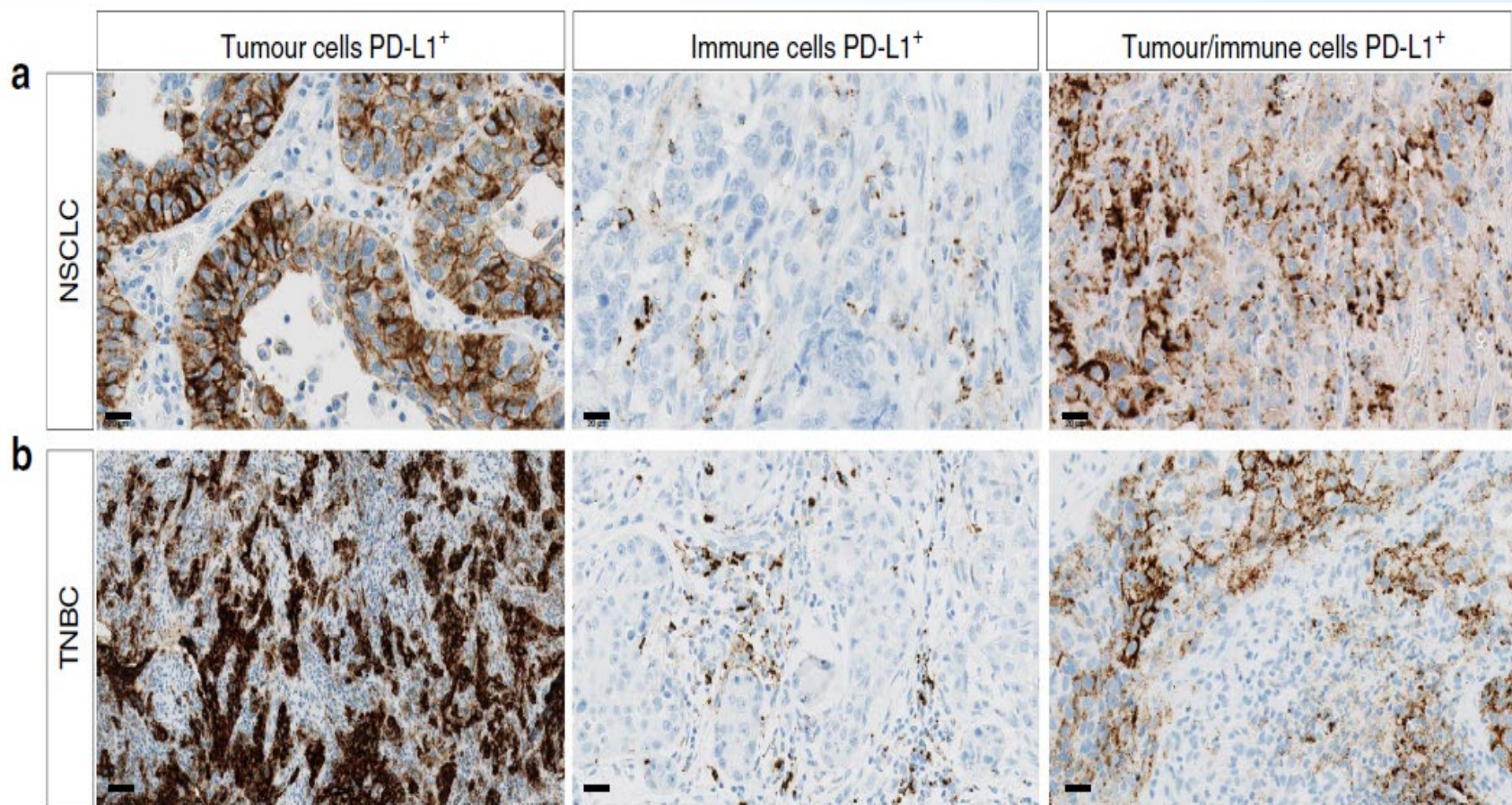
- TPS $\geq 50\%$ cutpoint rigorously determined using independent training and validation sets derived from KEYNOTE-001
- PD-L1 IHC 22C3 pharmDx approved in the US as a companion diagnostic for pembrolizumab



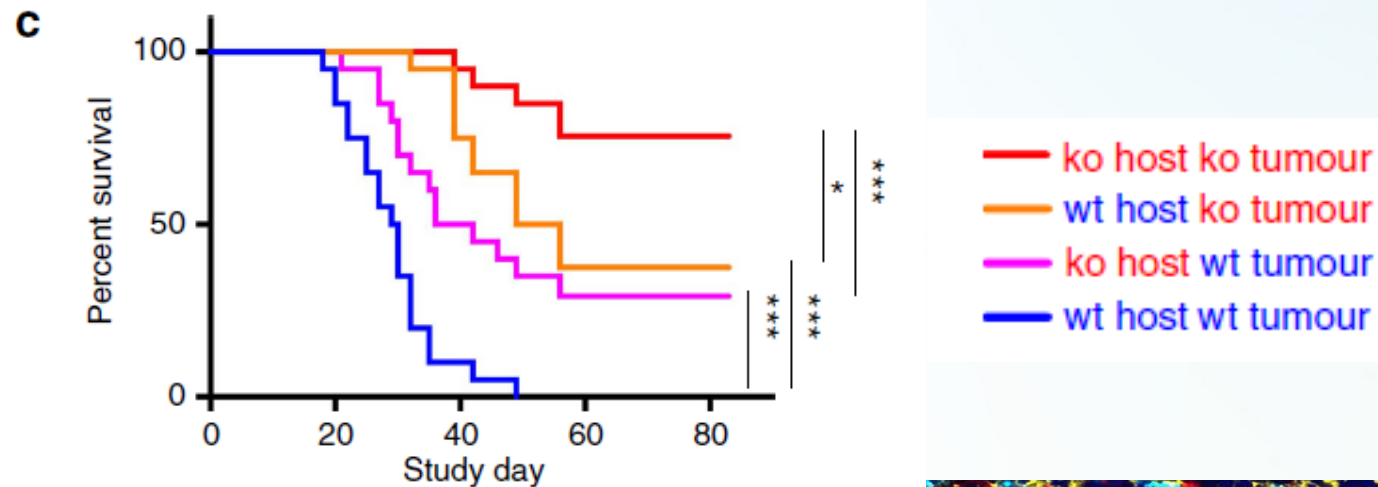
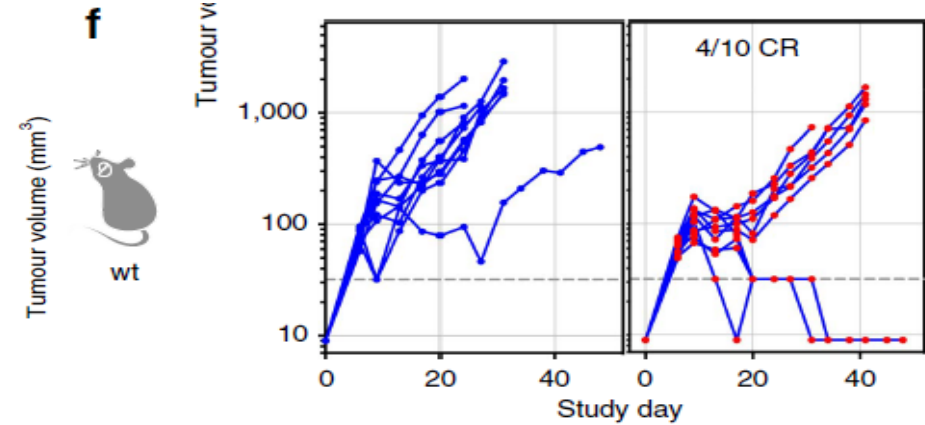
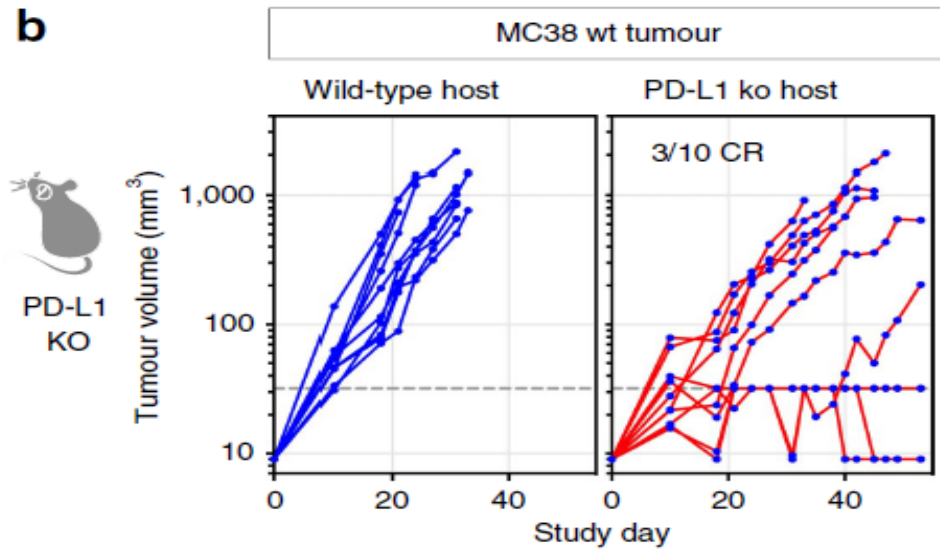
Augmentation de l'efficacité en fonction du statut PDL1



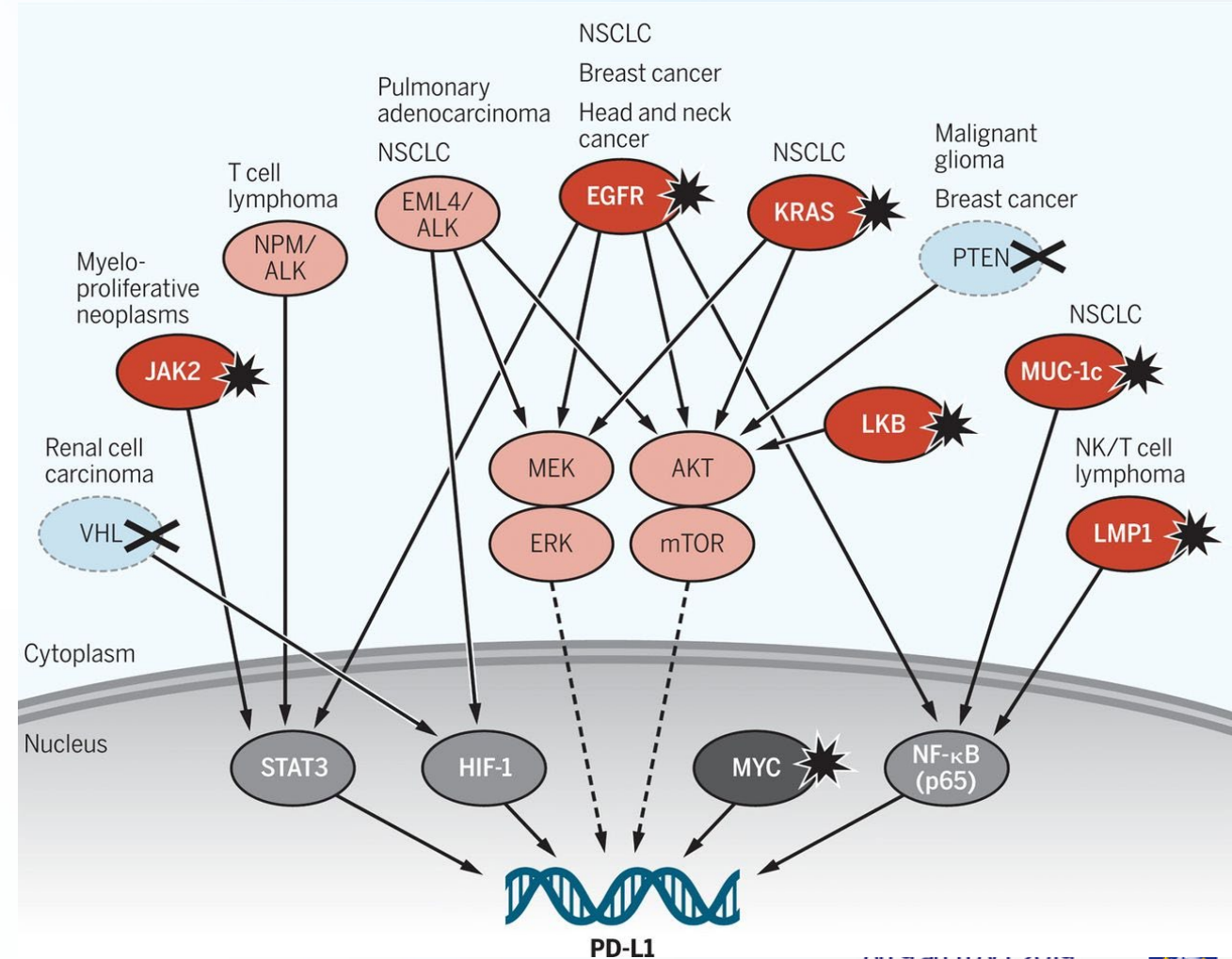
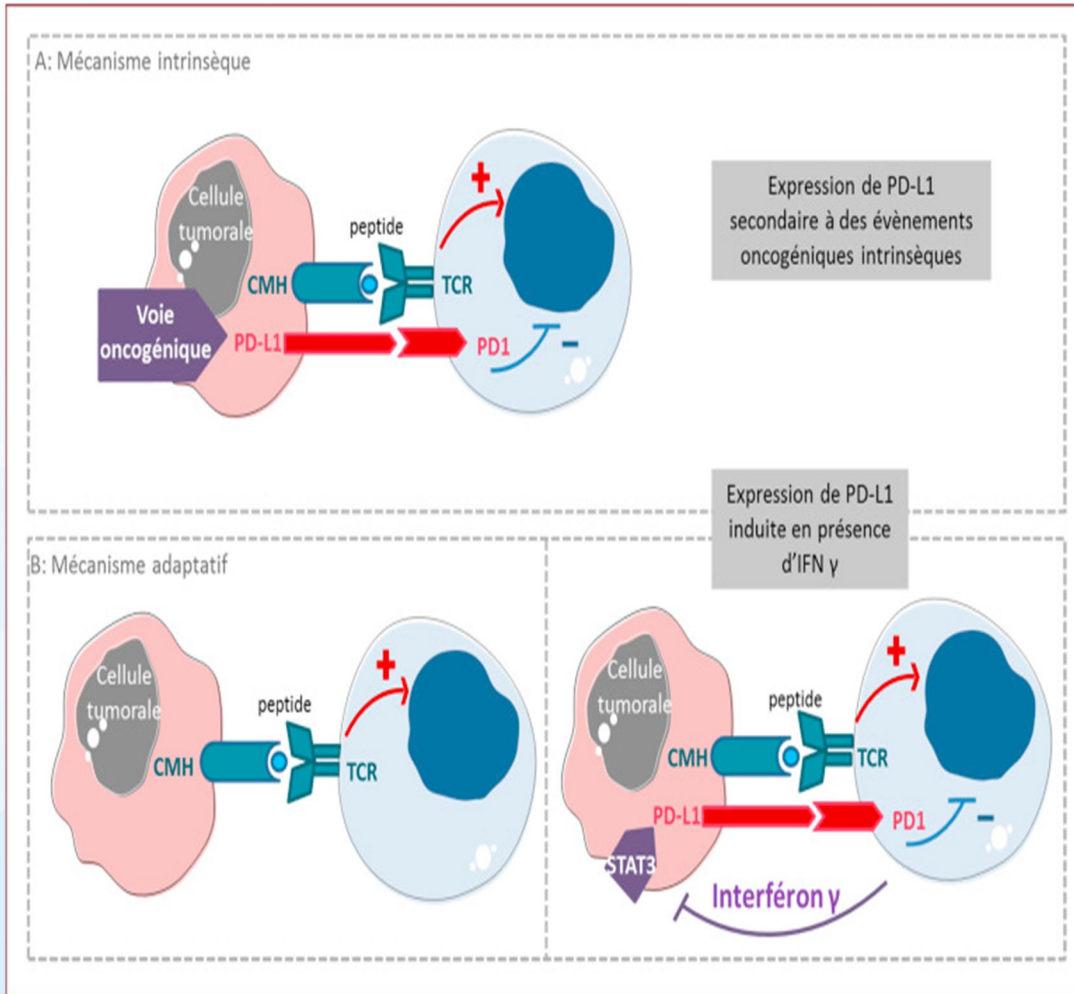
PDL1 est exprimé sur les cellules tumorales et immunitaires



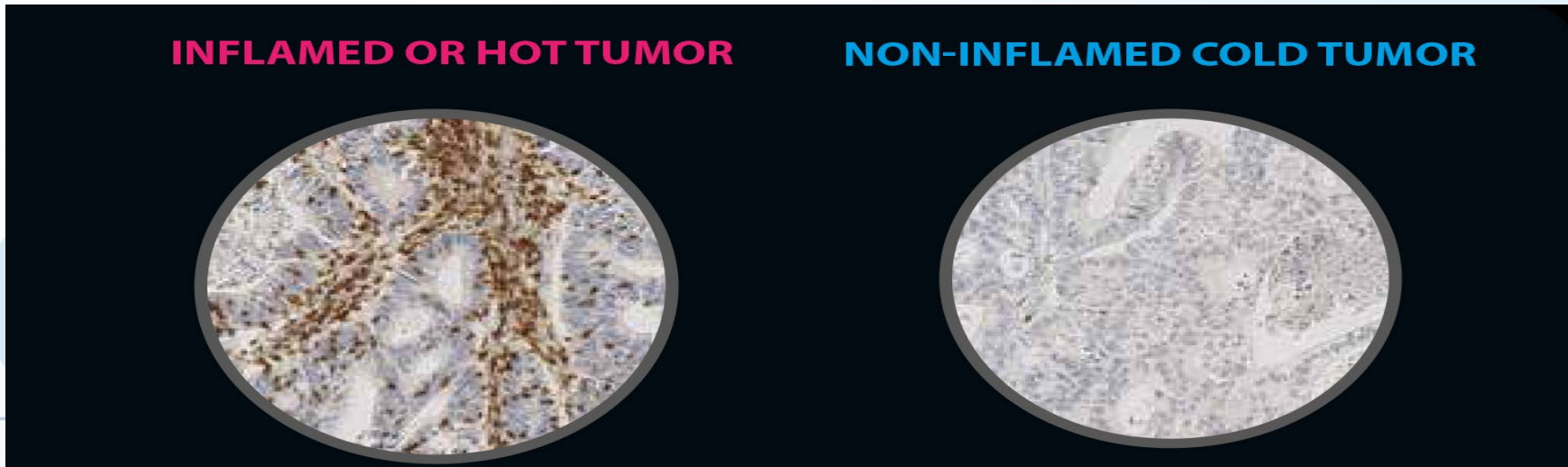
PDL1 est exprimé sur les cellules tumorales et immunitaires



Mais PDL1 ne signifie pas qu'une activation immunitaire



Quelles types de tumeurs sont sensibles aux checkpoints inhibiteurs: un role des lymphocytes ?



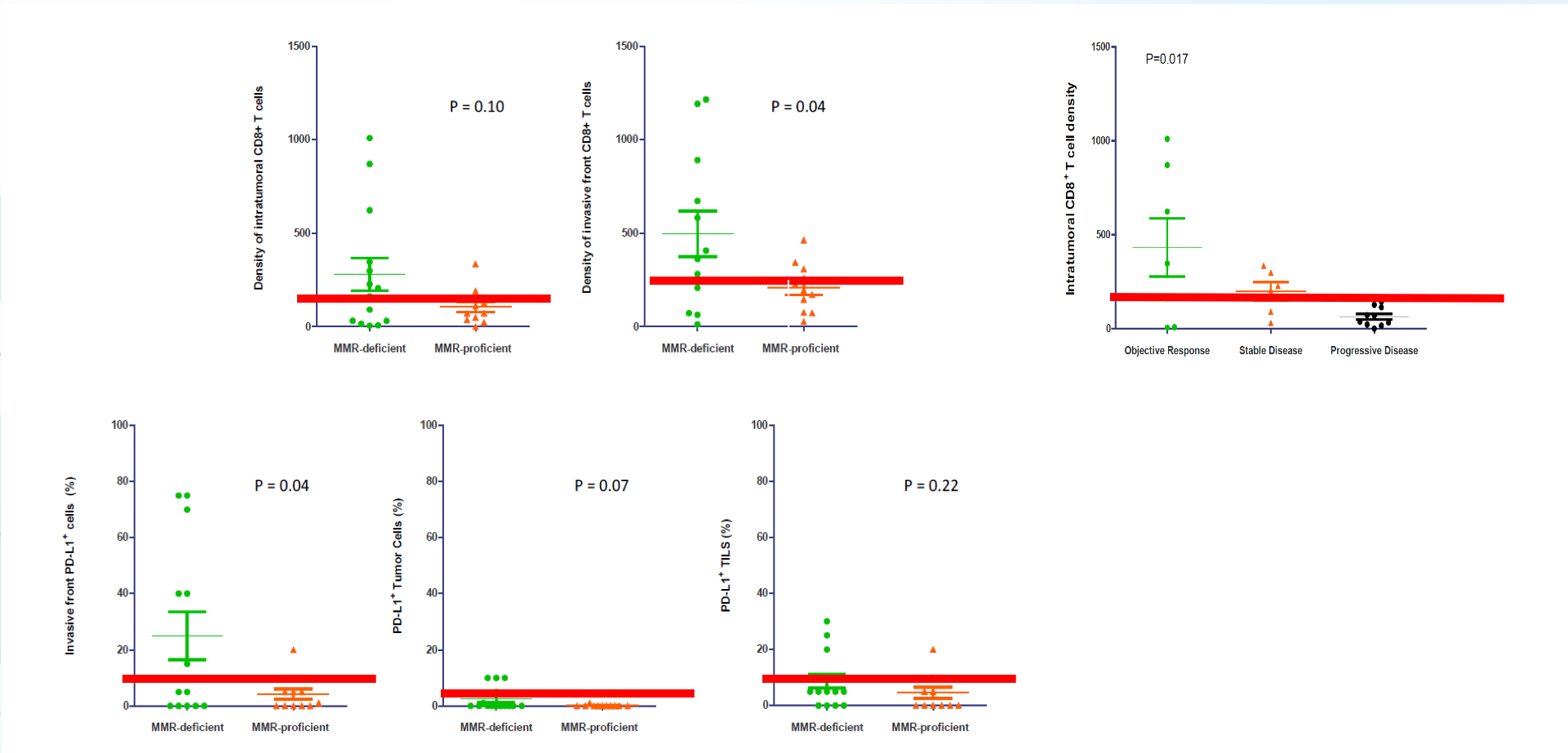
- Forte infiltration en Ic T
- Expression PDL1
- Forte charge mutationnelle
- Nombreux néopeptides

= MSI CRC

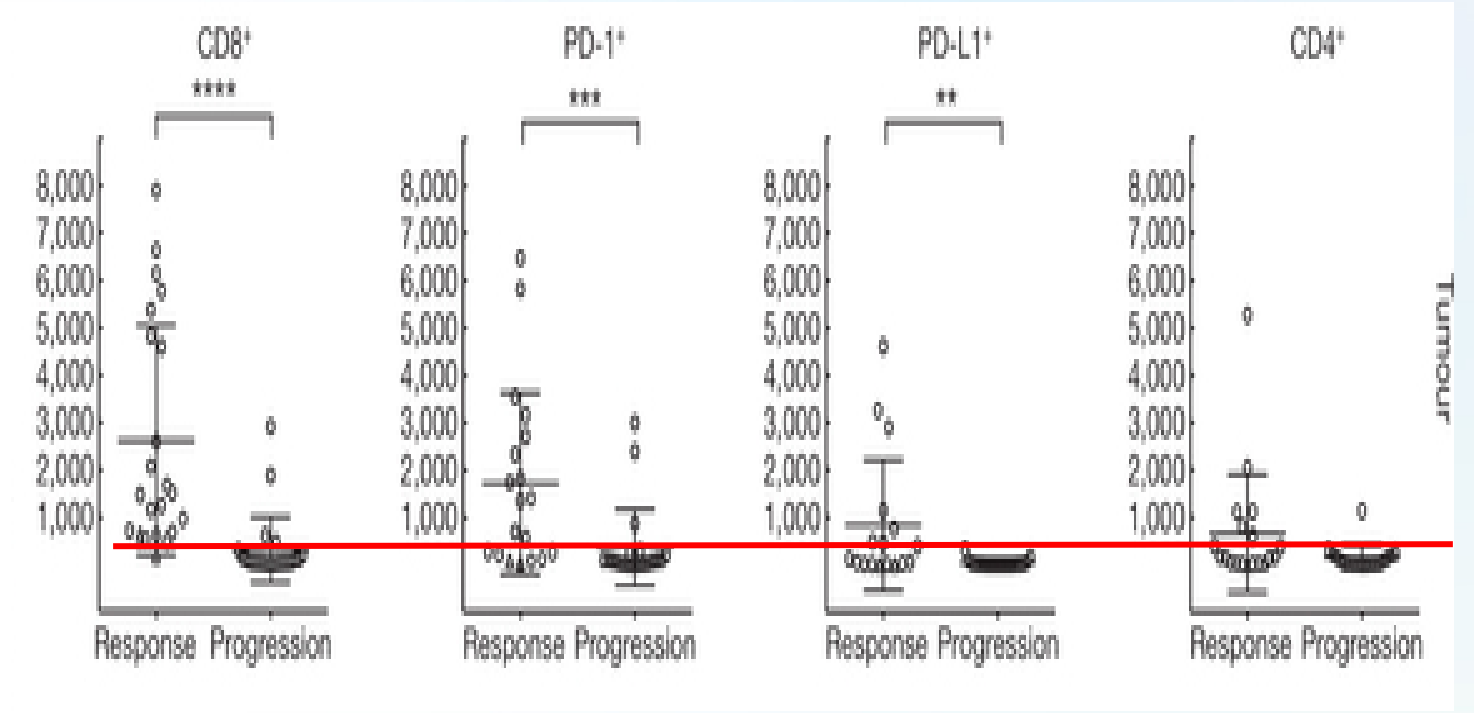
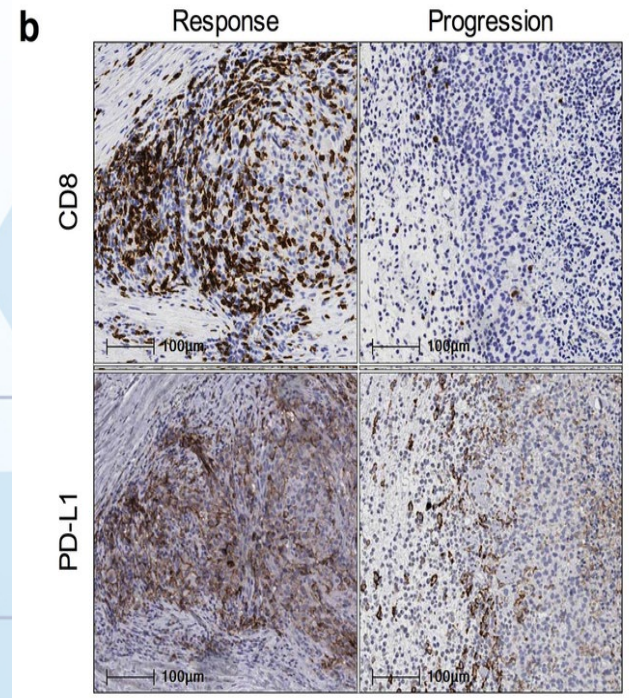
- Faible infiltration en Ic T
- Absence de PDL1
- Faible charge mutationnelle
- Peu de néopeptides

= MSS CRC

A Role de l'infiltration T dans le cancer du colon



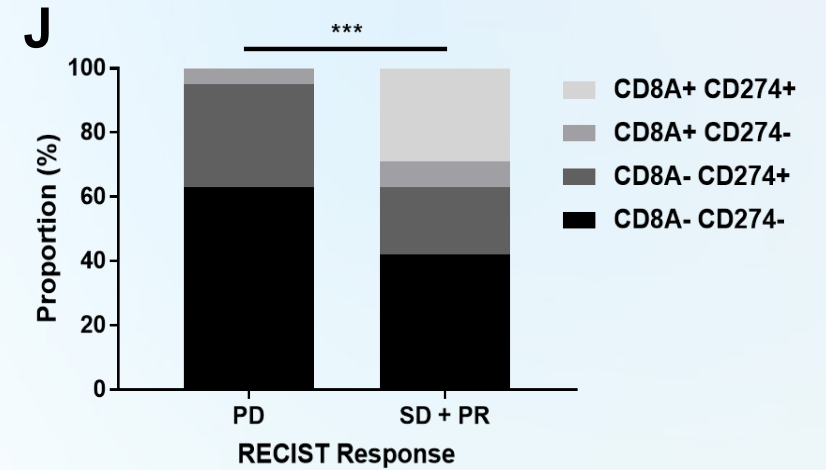
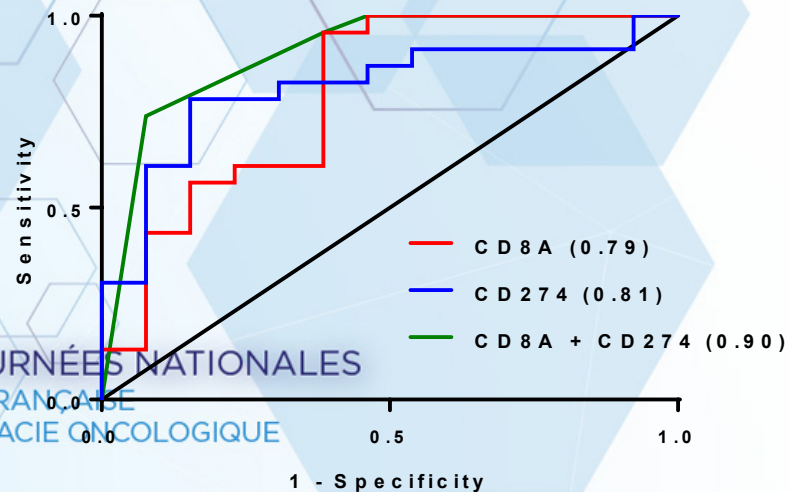
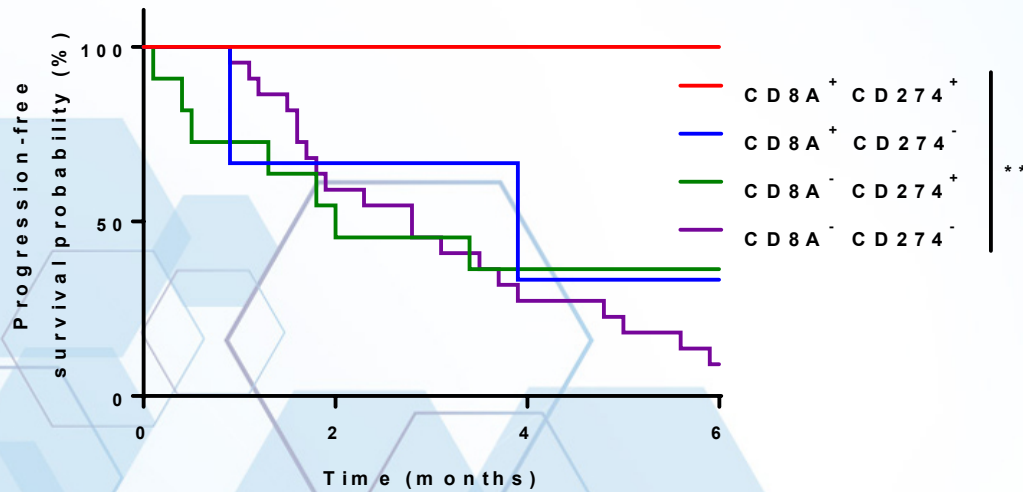
A Role de l'infiltration T dans le mélanome



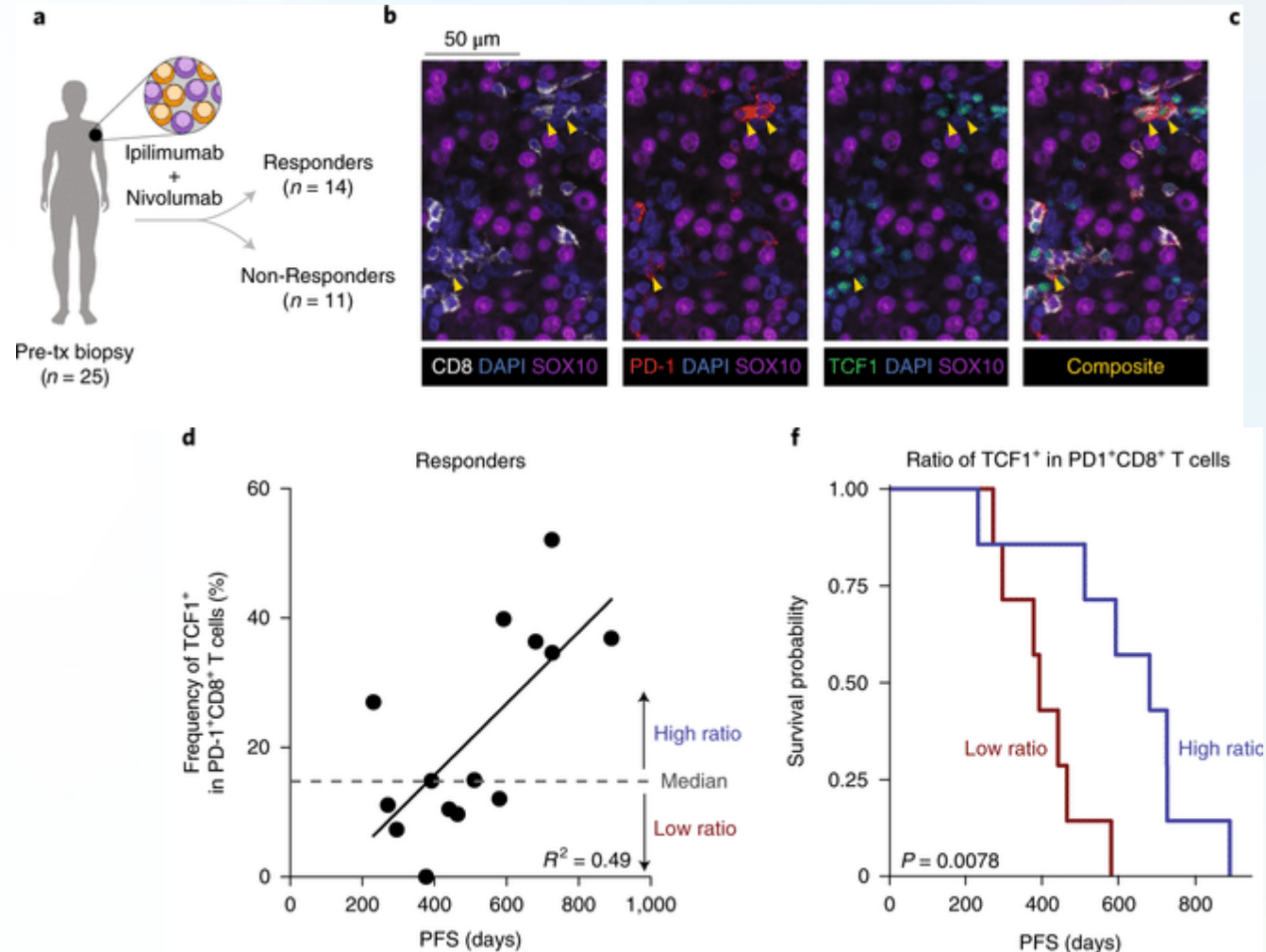
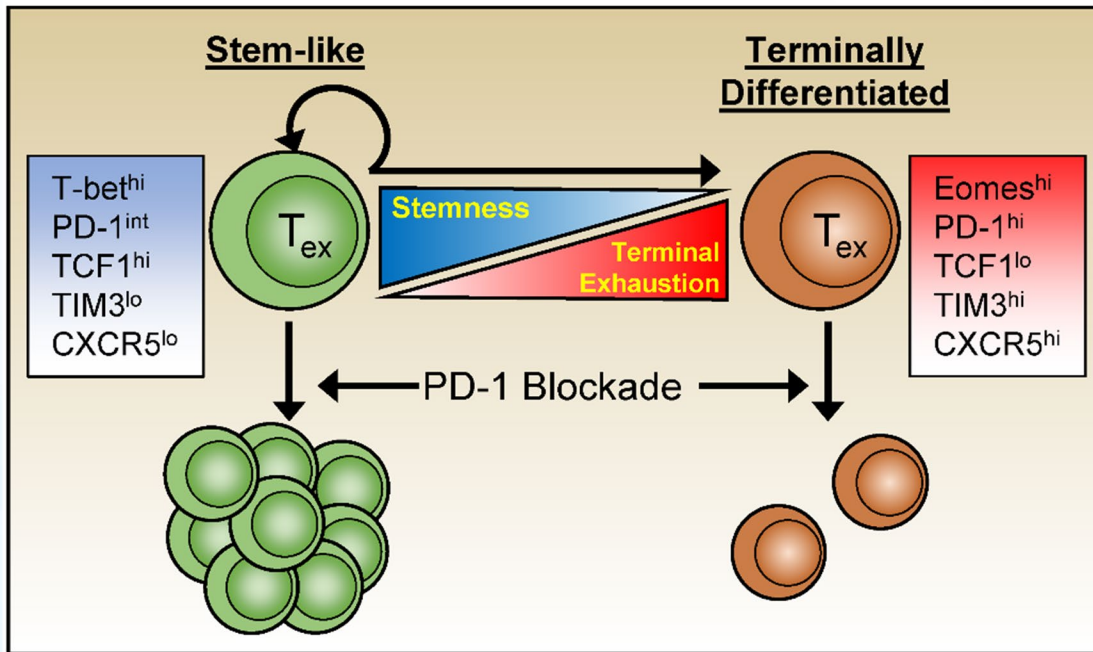
LETTER
PD-1 blockade induces responses by inhibiting adaptive immune resistance
(Tumeh PC et al. *Nature* 2014)

Response to anti-PD1 is associated with baseline immune infiltration in metastatic melanoma

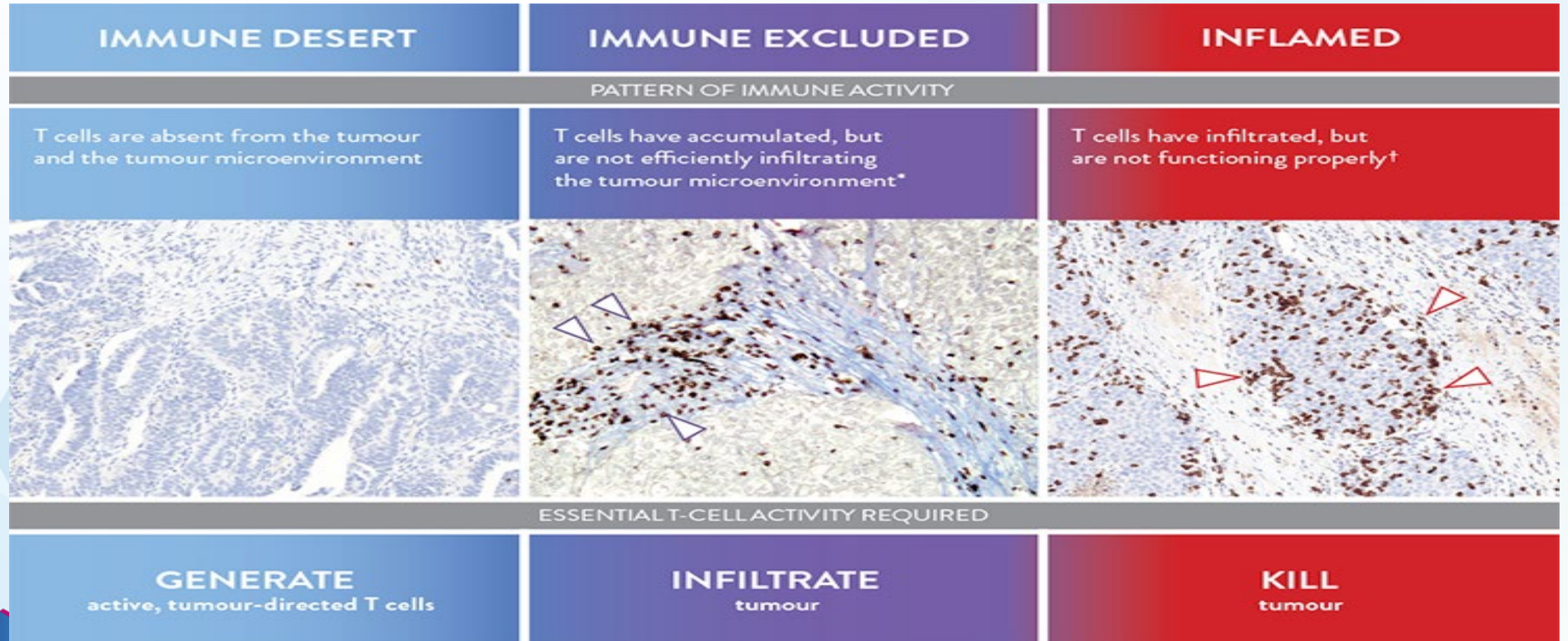
Un intérêt de combiner l'étude de PDL1 et des lymphocytes



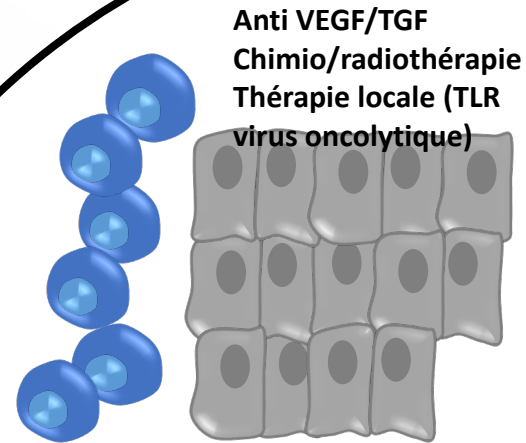
Mais pour aller plus loin: Different types of exhausted T cells



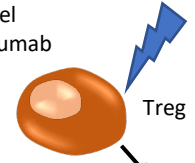
Mais pour aller plus loin: Different types de recrutement immunitaire



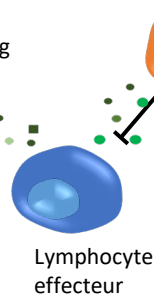
Immuno
exclusion



Cyclophosphamide
paclitaxel
bevacizumab



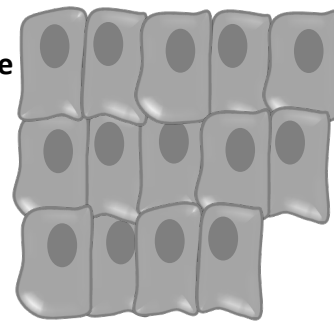
5-fluorouracil
gemcitabine
bevacizumab



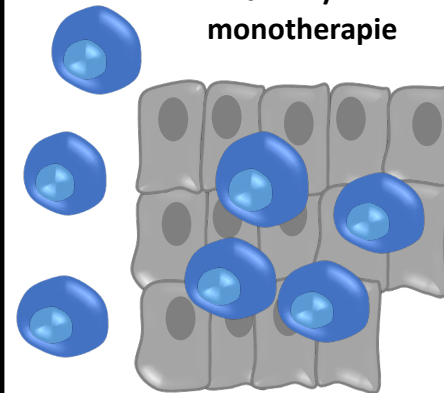
Immunosuppression
dans une tumeur
inflammatoire

Vaccination
neopeptidique

Chimio/radiothérapie
virus oncolytique)



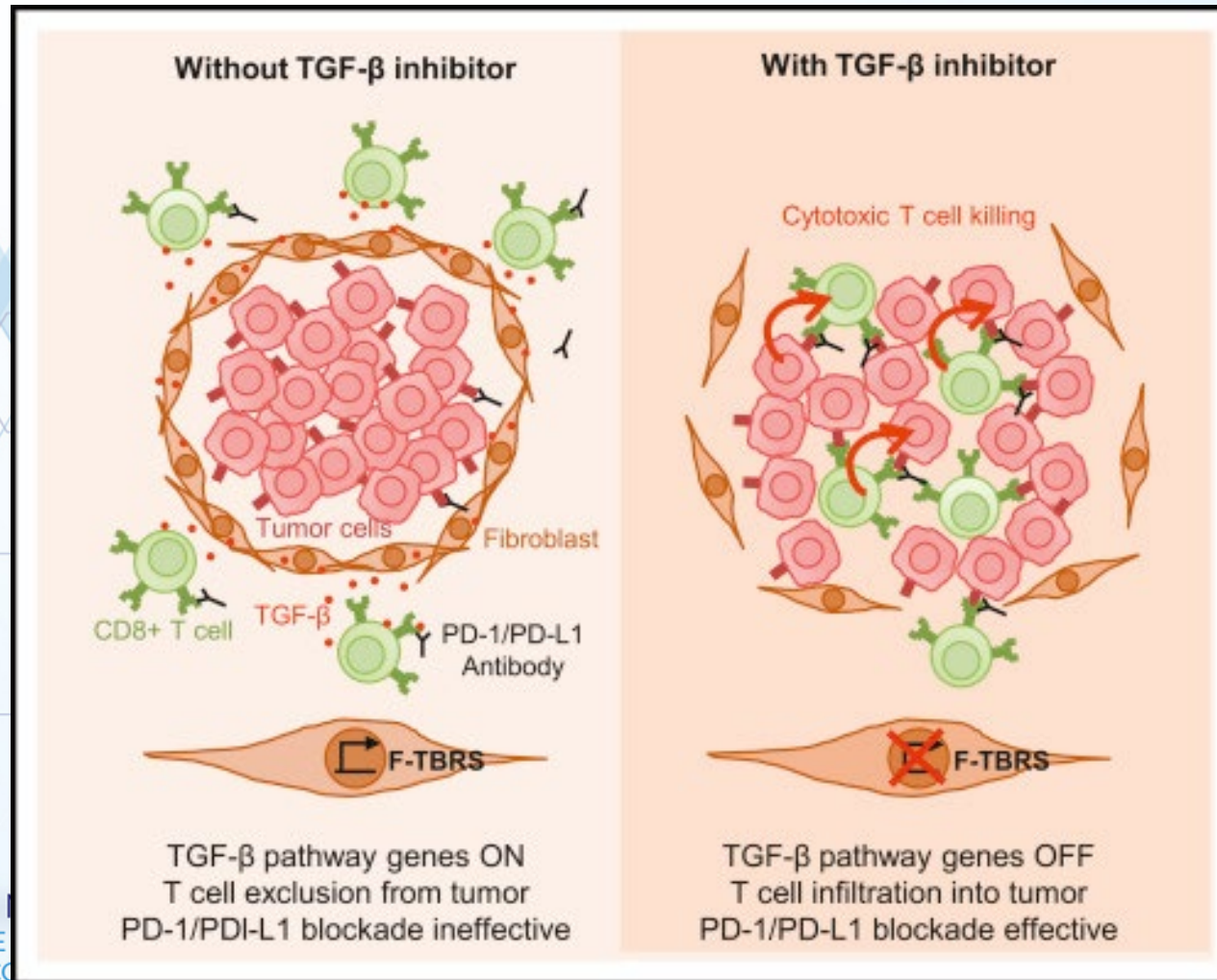
Anti PD1/PDL1
monothérapie



Tumeur inflammatoire

Désert
immunitaire

Immune exclusion et role du TGF-beta



Merci

