Immunité et réponse au traitements systémiques

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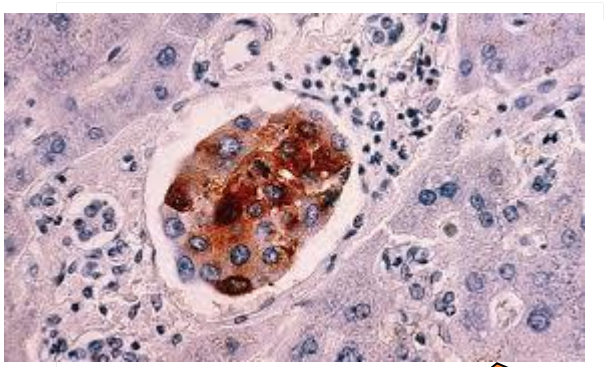
Centre Georges Francois Leclerc
INSERM UMR866 Dijon, France

- Aucun lien d’intérêt vis-à-vis de cette présentation

« Le concept de la chimiothérapie immunogène

Radiothérapie

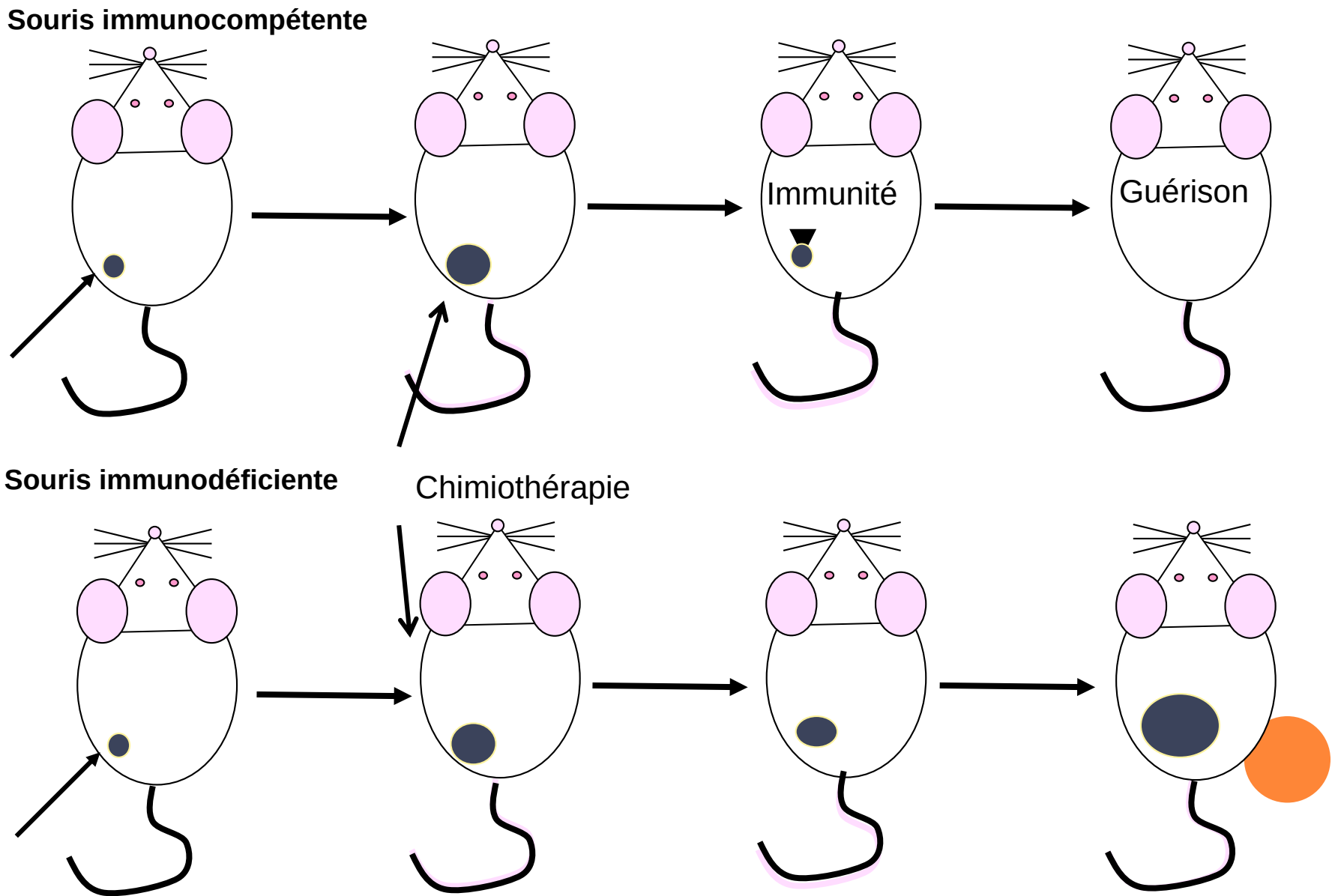
Chimiothérapie



Cancer

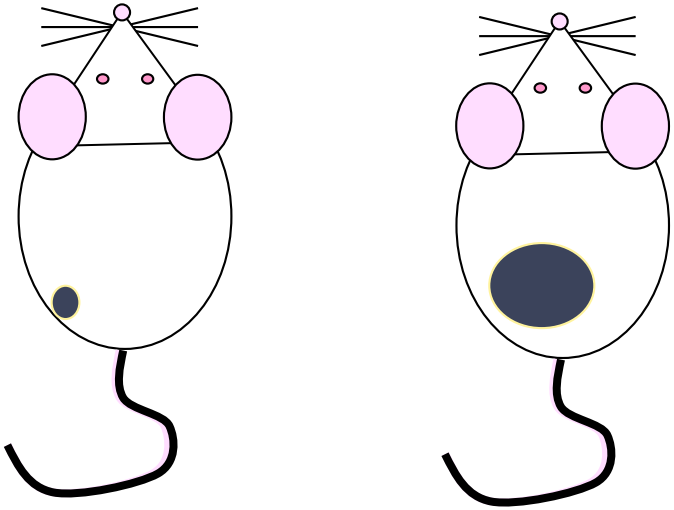
Réponse immunitaire

Comment tester les effets immunologiques d'une chimiothérapie



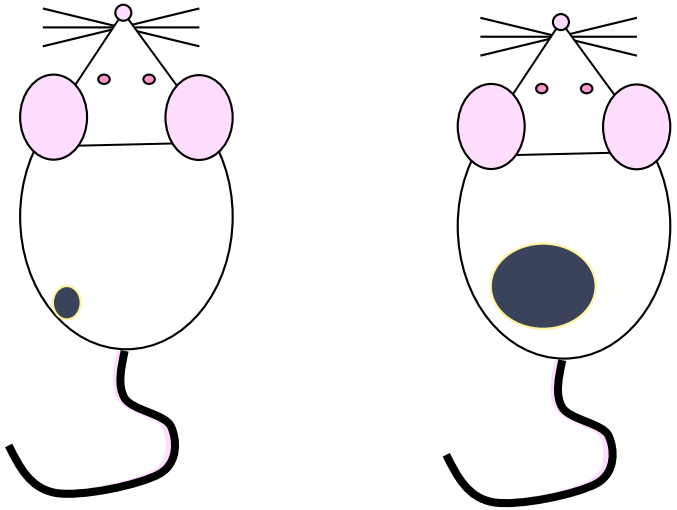
Premier screening des agents immunogènes

Immunocompétante vs immunodeficiente



Anthracyclines,
cyclophosphamide
Ionizing radiation,
Taxanes

Immunocompétante vs immunodeficiente

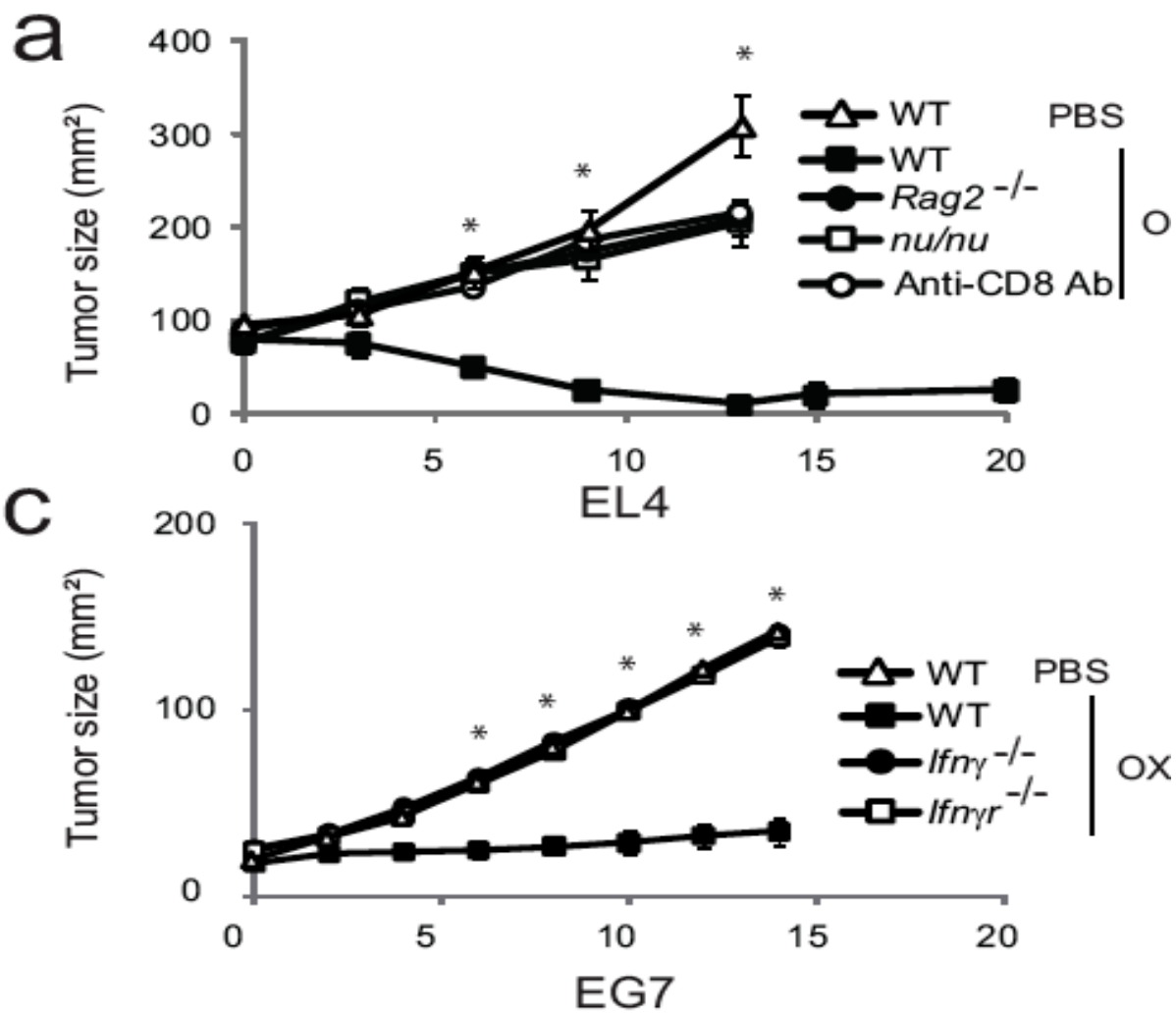


Cis platine,
Etoposide,
Mitomycin C,
5 FU

Comment ca marche?

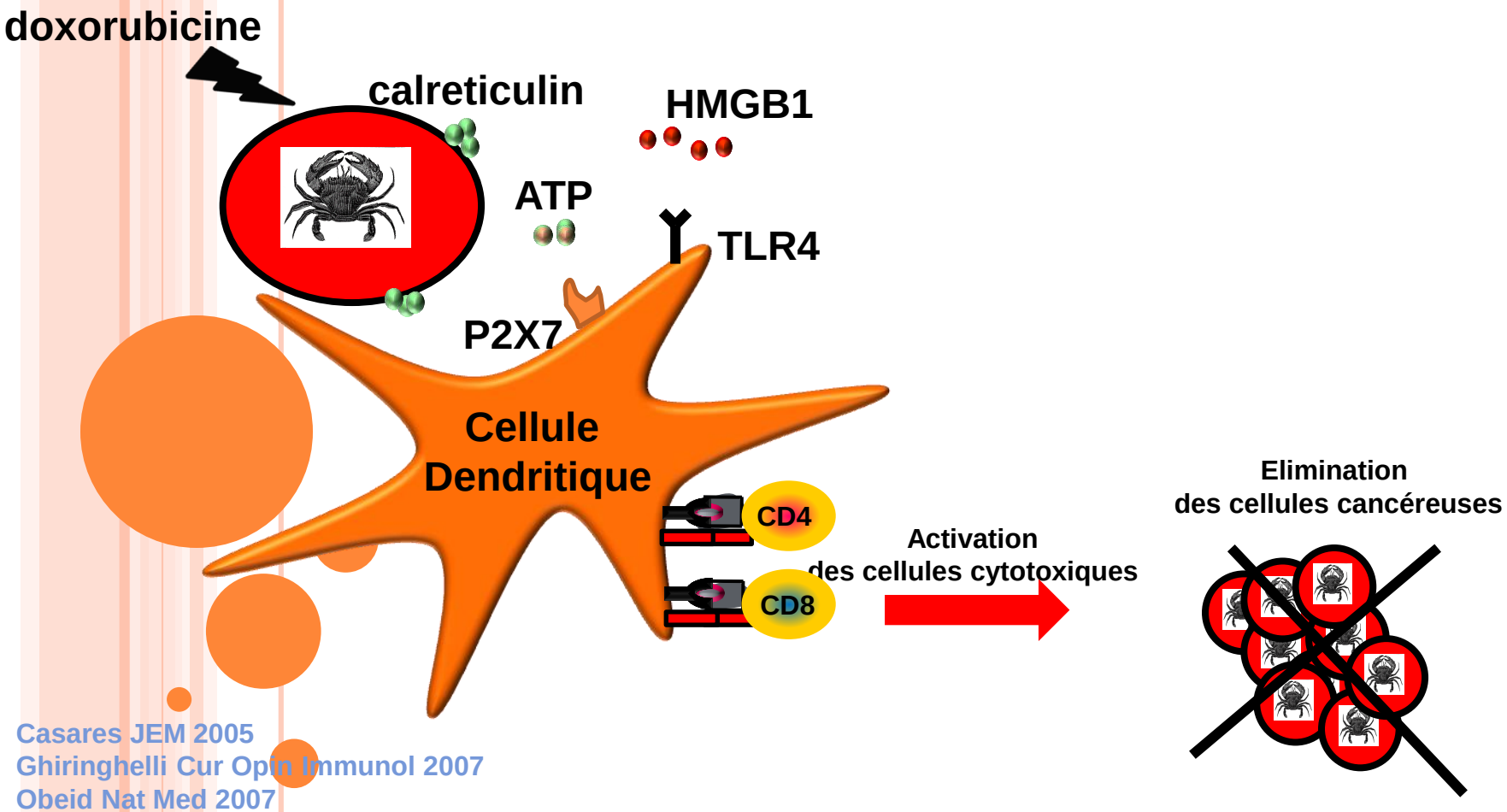
Un peu de mécanistique….

L'effet est dépendant des lymphocytes T CD8 et de l'Interferon gamma



Ghiringhelli et al. Nat. Med. 2009

Le concept de la chimiothérapie immunogène

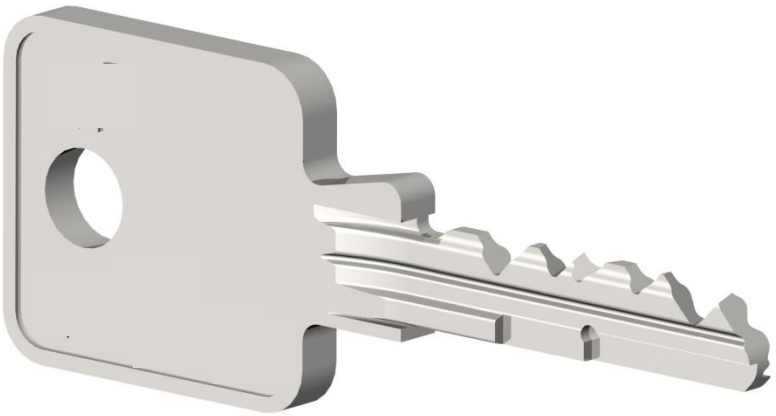


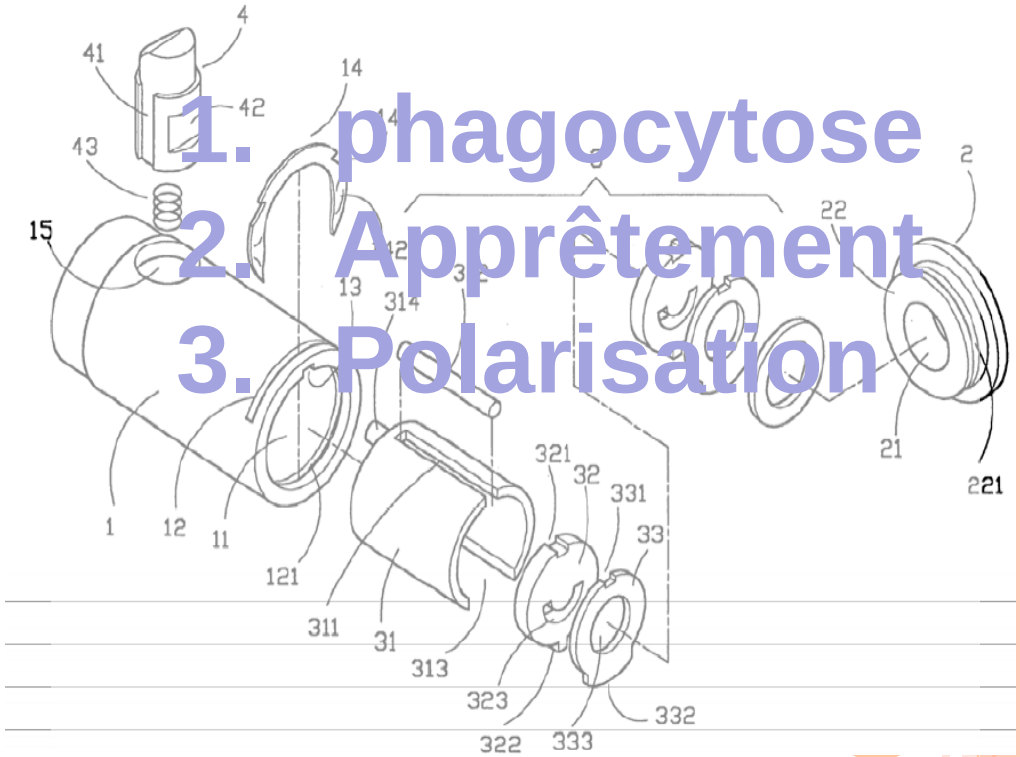
Casares JEM 2005
Ghiringhelli Cur Opin Immunol 2007
Obeid Nat Med 2007
Apetoh and Ghiringhelli et al. Nat Med 2007
Ghiringhelli et al. Nat Med 2009
Zitvogel, Ghiringhelli and Kroemer. Nat Rev Immunol 2008

Le concept de chimiothérapie immunogène: Ou le problème de la clé et de la serrure

Molécules secrétées
Ou exprimées par les cellules tumorales

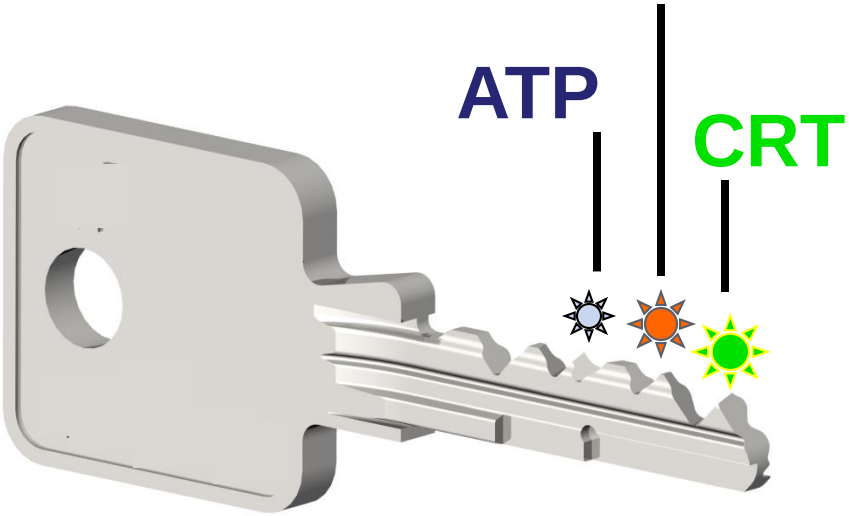
Détecteur de l'immunité





Tesniere et al. Curr Op Immunol 2008

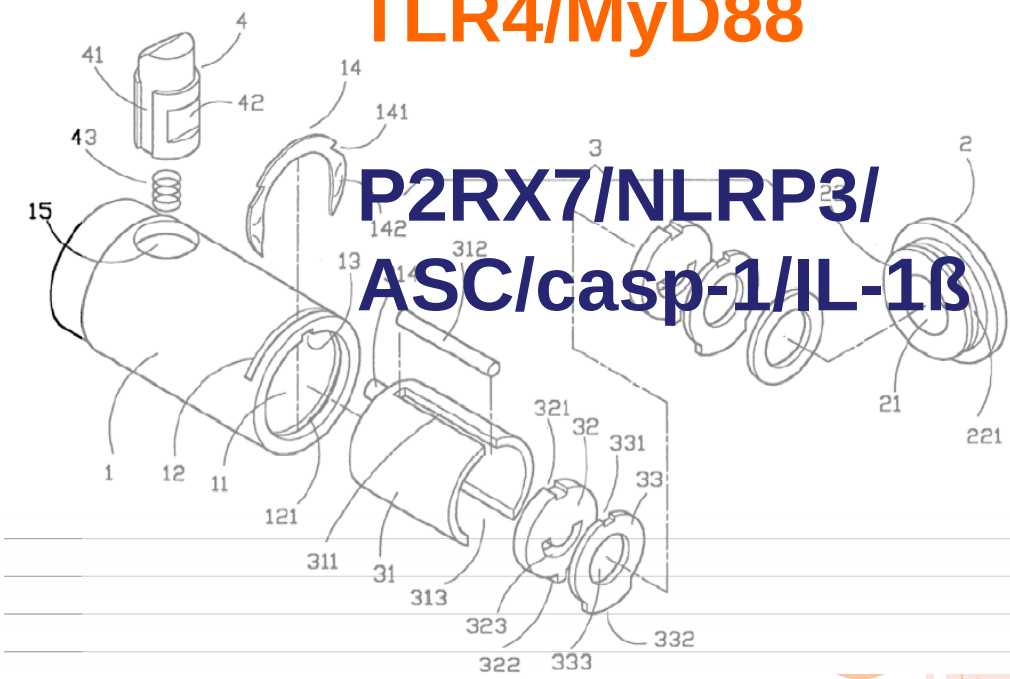
Le concept de chimiothérapie immunogène: Ou le problème de la clé et de la serrure



CRT receptor

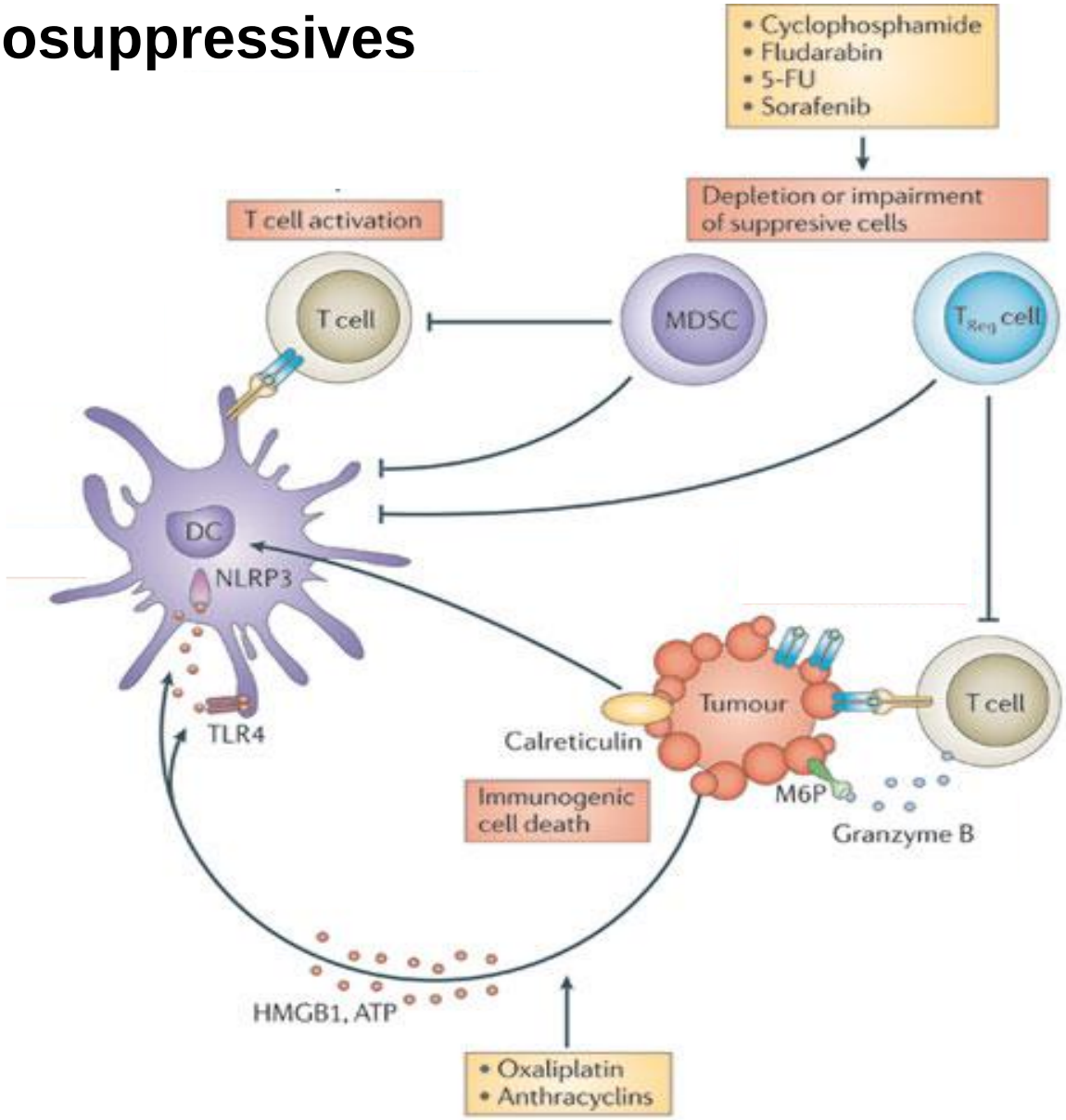
TLR4/MyD88

P2RX7/NLRP3/
ASC/casp-1/IL-1ß



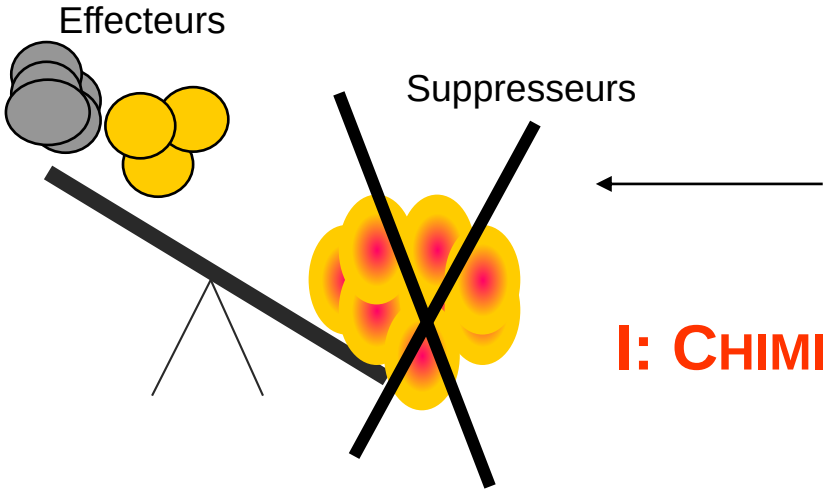
Obeid et al Nat Med 2006, Apetoh et al Nat Med 2007, Ghiringhelli et al. Nat. Med. 2009

Un autre effet possible : L'action sur les cellules immunosuppressives

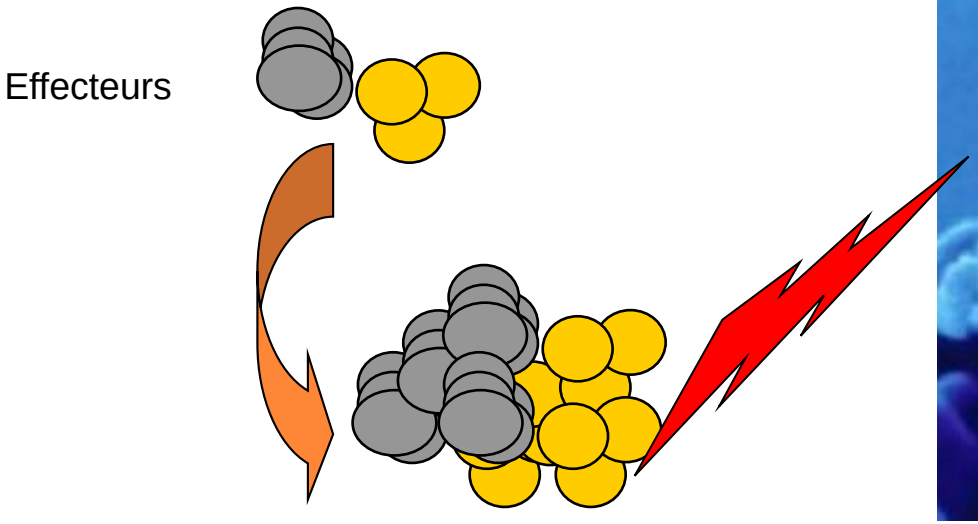


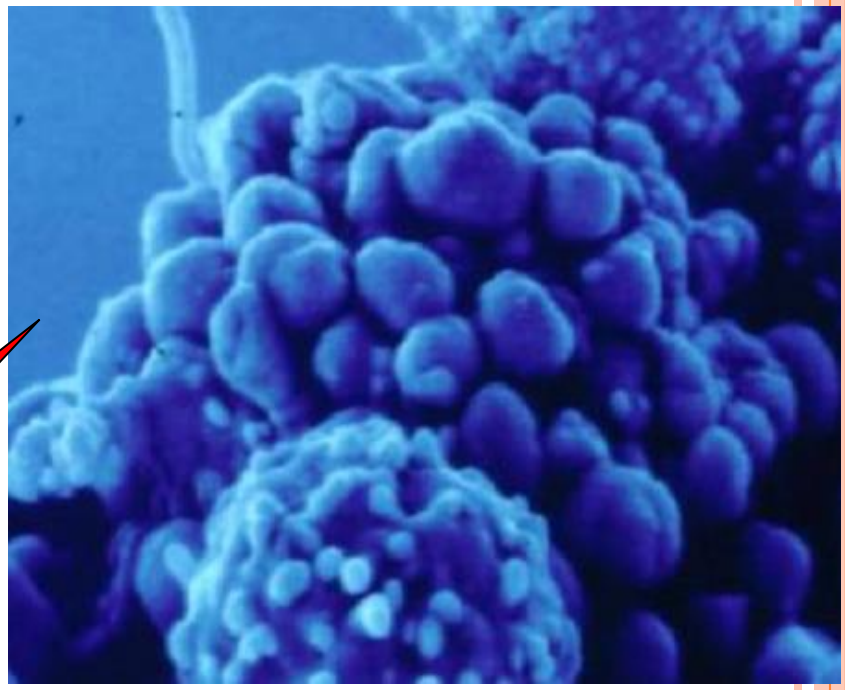
Nature Reviews | Drug Discovery

La chimiothérapie : une réveil pour le système immunitaire?



I: CHIMIOTHÉRAPIE

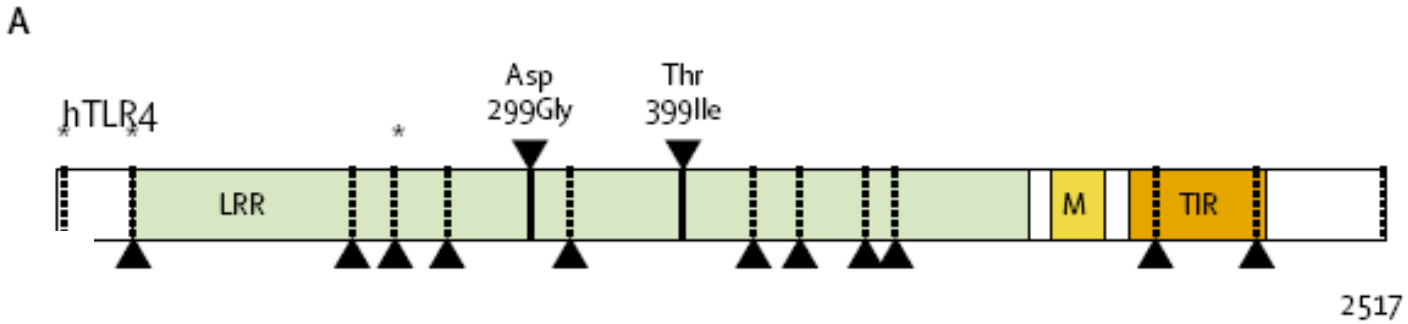




Comment utiliser cela en clinique:

Création d'algo-rythme de prédiction de la réponse à la chimio

Relevance of the TLR4 SNPs Asp299Gly in the response to chemotherapy: cohort of 280 breast cancers

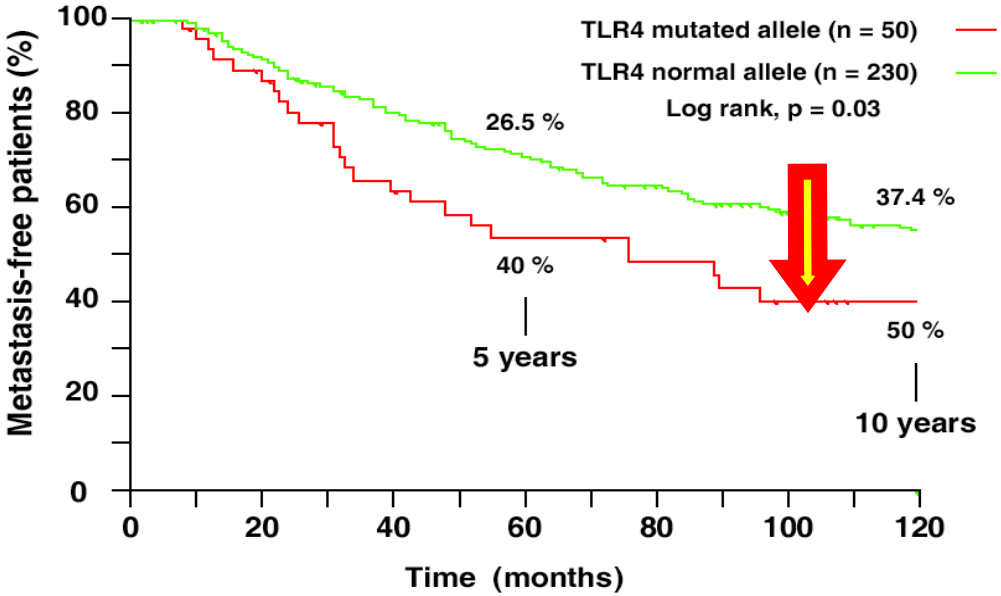


(Arbour et al. Nat. Genet. 25, 2000: 187-191)

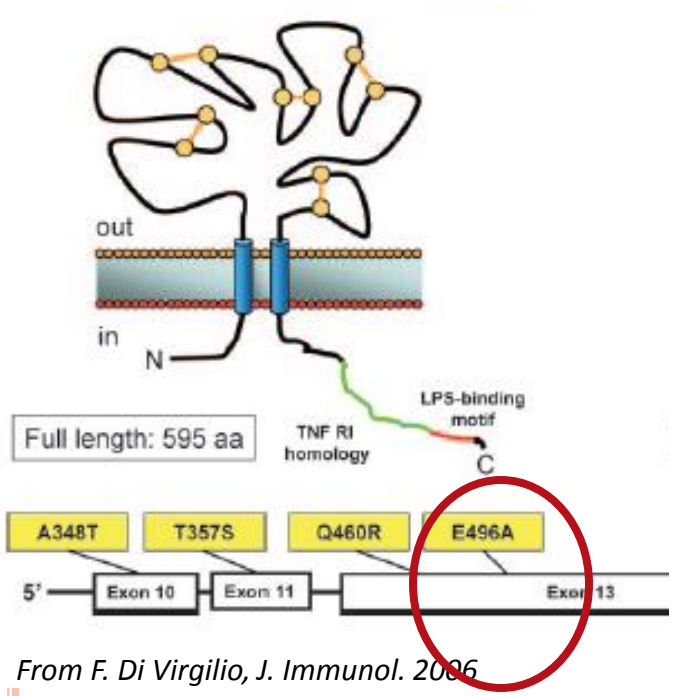
Supplemental Table 1.Characteristics of the breast cancer patients according to TLR4 status.

	Normal TLR4 (n=230)	Asp299Gly TLR4 (n=50)	P Value
Age (years)	50 ± 11	49 ± 11	NS
pT (mm)	29 ± 17	28 ± 10	NS
Tumor grade I (%) II (%) III (%)	9.7 49.3 41.0	8.5 55.3 36.2	NS NS NS
Number of metastatic lymph nodes	5.2 ± 5	4.5 ± 7	NS
HR positive (%)	80	82	NS
Followup (months)	94 ± 64	108 ± 63	NS

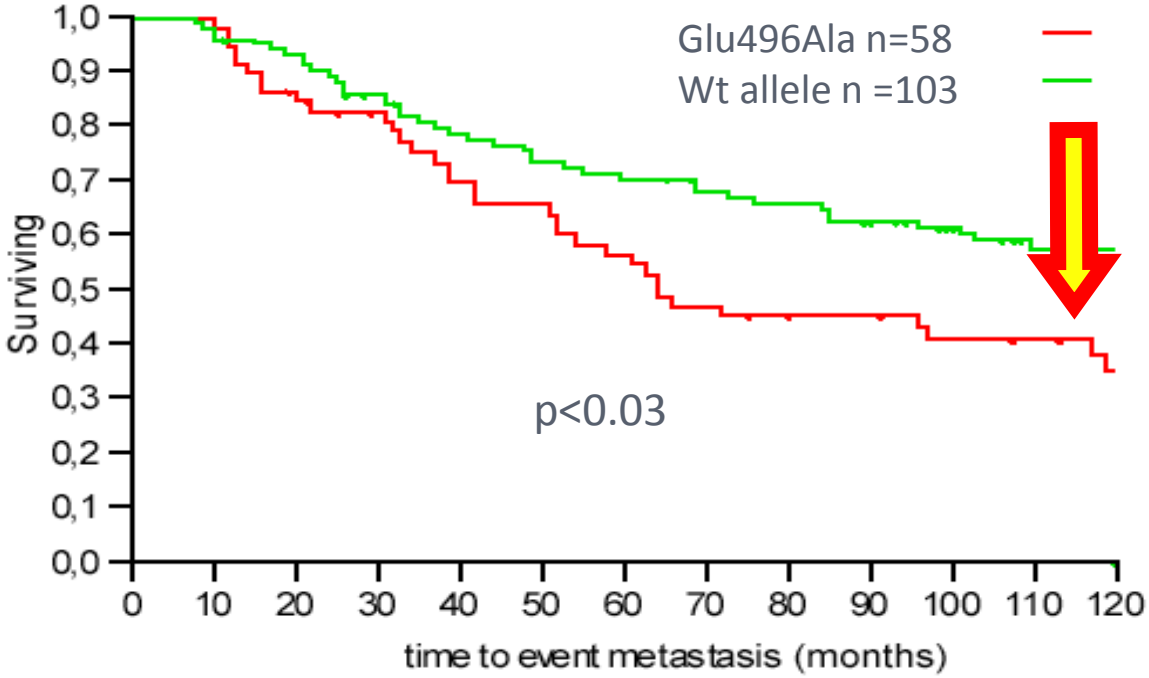
pT: pathological tumor size. HR: hormonal receptors. All data are presented as means ± standard deviation, or percentages.



P2RX$_7$ Glu496Ala)



From F. Di Virgilio, J. Immunol. 2006



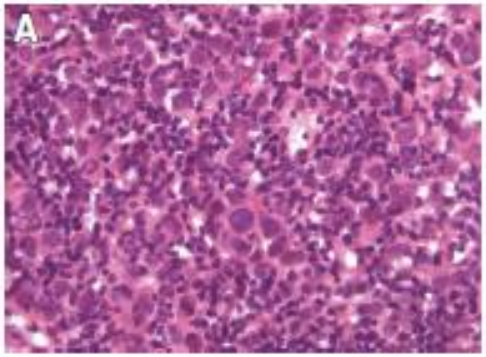
Reduced therapeutic response in breast cancer patients with a loss-of-function allele of P2X$_7$(E496A, 1513A>C): Prevalence: 20-35% caucasiens

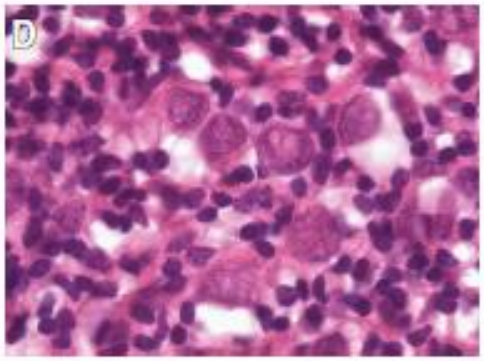
K+ influx is markedly reduced in association with the 1513C allele.

JS Wiley, J Biol Chem, 2001, Di Virgilio, J Immunol 2005

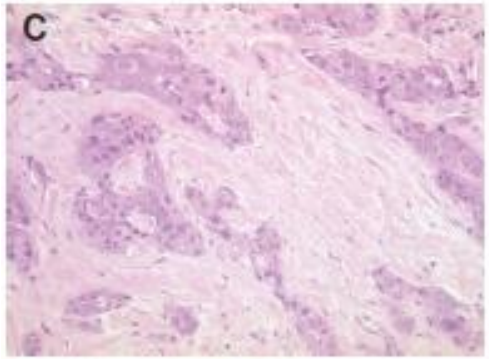
La présence de lymphocytes : un biomarqueur prédictif de l'efficacité de la chimiothérapie

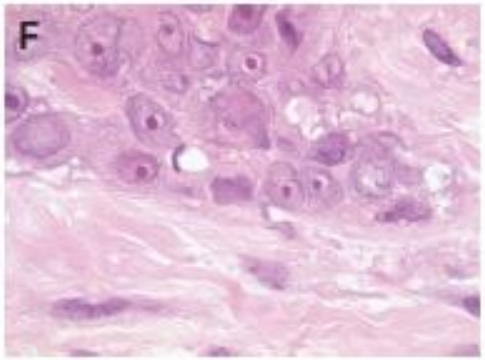
Nombreux lymphocytes





Pas de lymphocytes





La présence de lymphocytes : un biomarqueur prédictif de l'efficacité de la chimiothérapie

VOLUME 28 · NUMBER 1 · JANUARY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Tumor-Associated Lymphocytes As an Independent Predictor of Response to Neoadjuvant Chemotherapy in Breast Cancer

Carsten Denkert, Sibylle Loibl, Aurelia Noske, Marc Roller, Berit Maria Muller, Marina Komor, Jan Budczies, Silvia Darb-Esfahani, Ralf Kronenwett, Claus Hanusch, Christian von Torne, Wilko Weichert, Knut Engels, Christine Solbach, Iris Schrader, Manfred Dietel, and Gunter von Minckwitz

original articles

Annals of Oncology

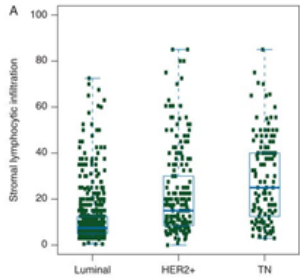
Annals of Oncology 25: 1544–1550, 2014
doi:10.1093/annonc/mdu112
Published online 7 March 2014

Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial

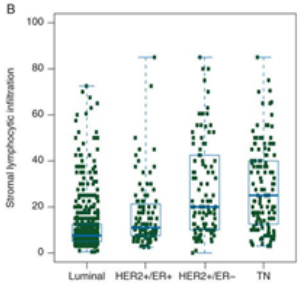
S. Loi[1,2*], S. Michiels[1,3], R. Salgado[4], N. Sirtaine[4], V. Jose[1], D. Fumagalli[1], P.-L. Kellokumpu-Lehtinen[5], P. Bono[6], V. Kataja[7], C. Desmedt[1], M. J. Piccart[8], S. Loibl[9], C. Denkert[10], M. J. Smyth[11], H. Joensuu[6] & C. Sotiriou[1]

Association entre les infiltrats et le type triple négatif

FinHER dataset: distribution of tumor-infiltrating lymphocytes in breast cancer according to the (A) three breast cancer subtypes and (B) HER2 divided into ER-positive and -negative groups.



	Luminal	HER2+	TN
n	591	209	134
Min	0.5	0	3
Q1	5	8.5	12.5
Q2	7.5	15	25
Q3	12.5	30	40
Max	72.5	85	85

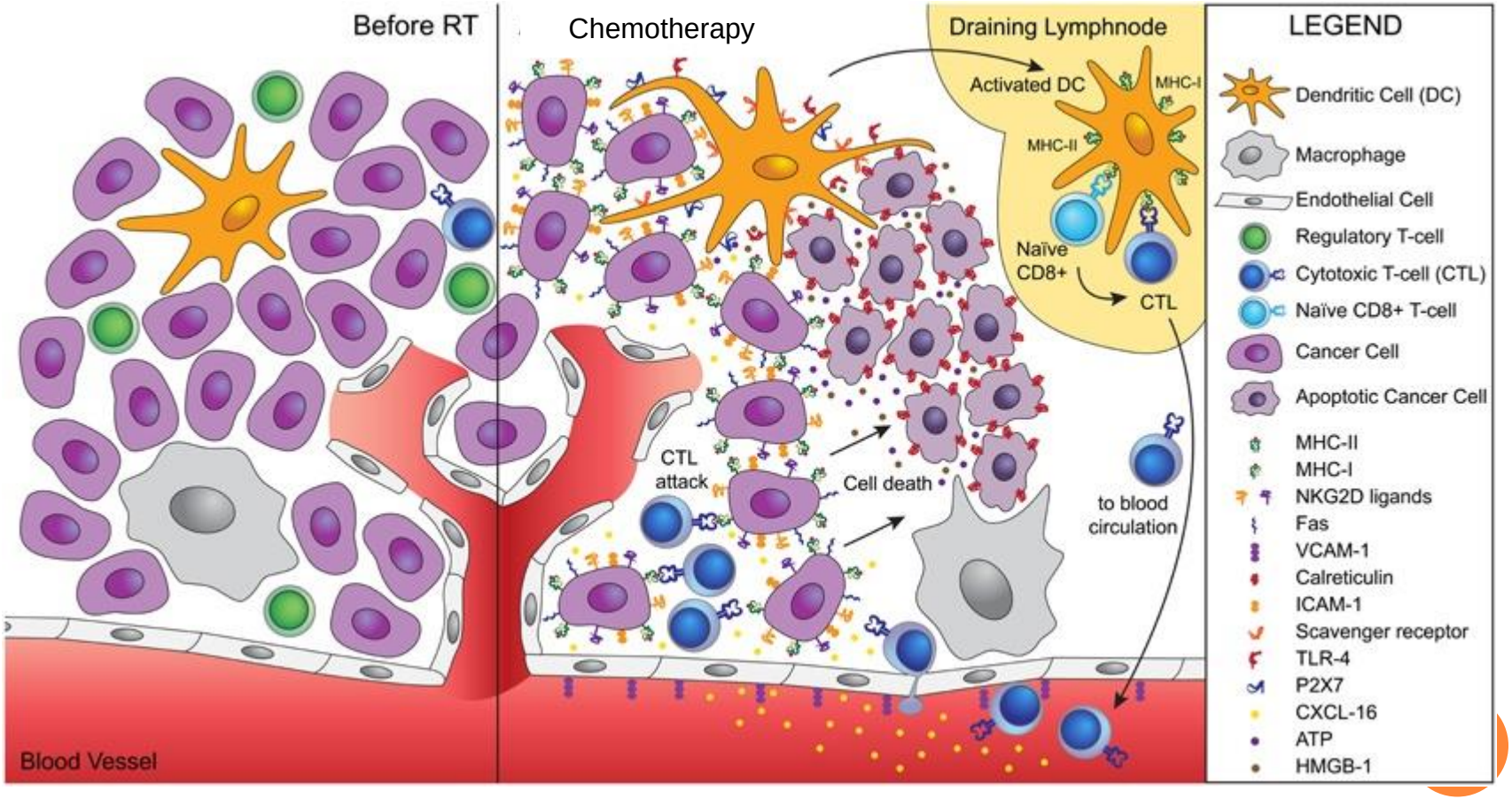


	Luminal	HER2+/ER+	HER2+/ER–	TN
n	591	103	106	134
Min	0.5	2.5	0	3
Q1	5	7.5	10	12.5
Q2	7.5	11	20	25
Q3	12.5	21.2	42.5	40
Max	72.5	85	85	85

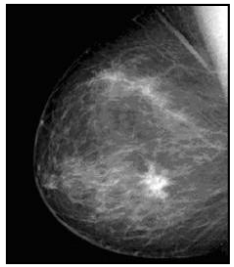
Loi S et al. Ann Oncol 2014;25:1544-1550

Annals of Oncology

La présence de lymphocytes apres chimiotherapie : un biomarqueur de l'efficacité de la chimiothérapie



La chimiothérapie néoadjuvante



Diagnosis → Neoadjuvant CT → Surgery → evolution

Pre-treatment sample

Per-treatment sample

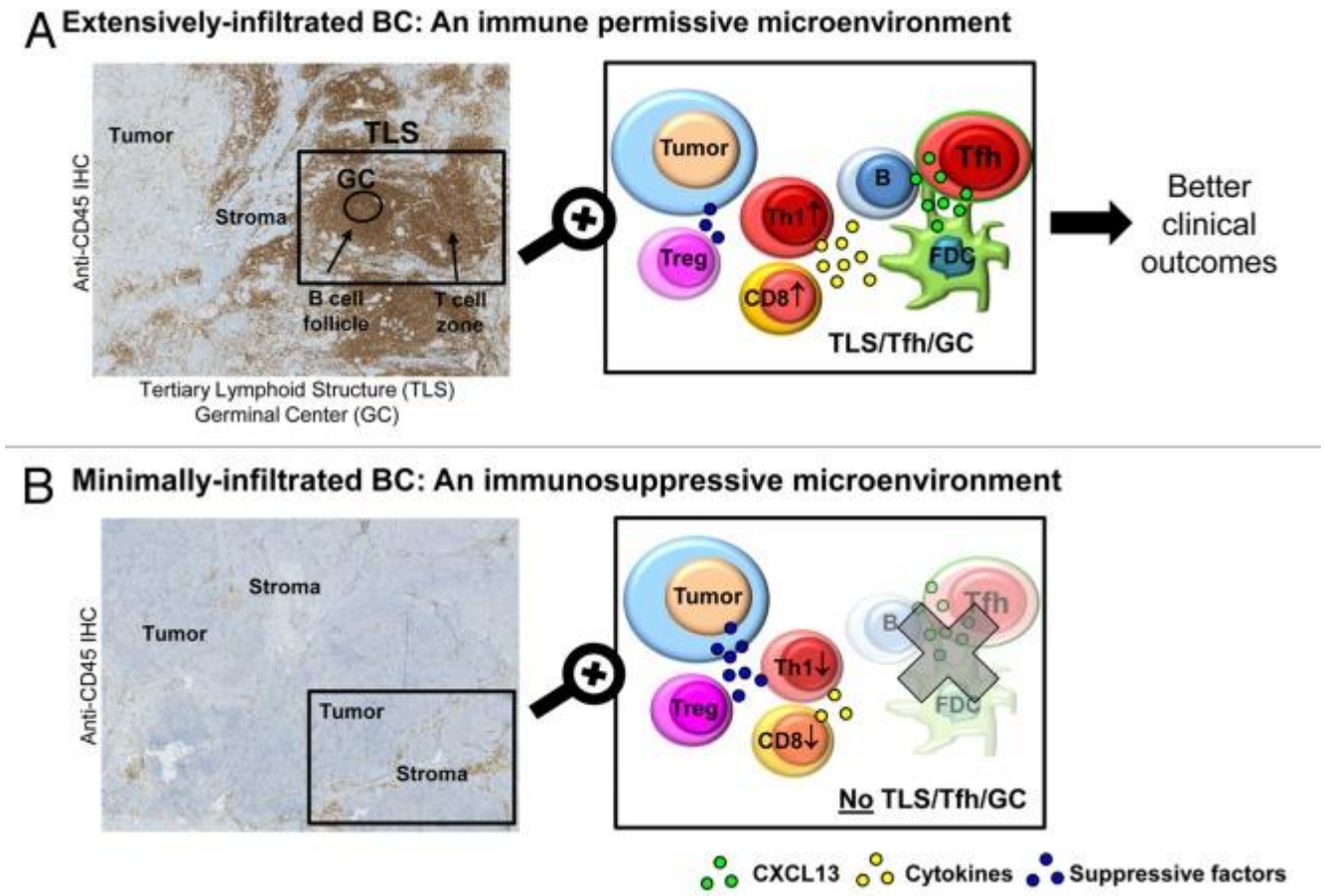
Post-treatment sample

Histological response

Tumor evolution under treatment

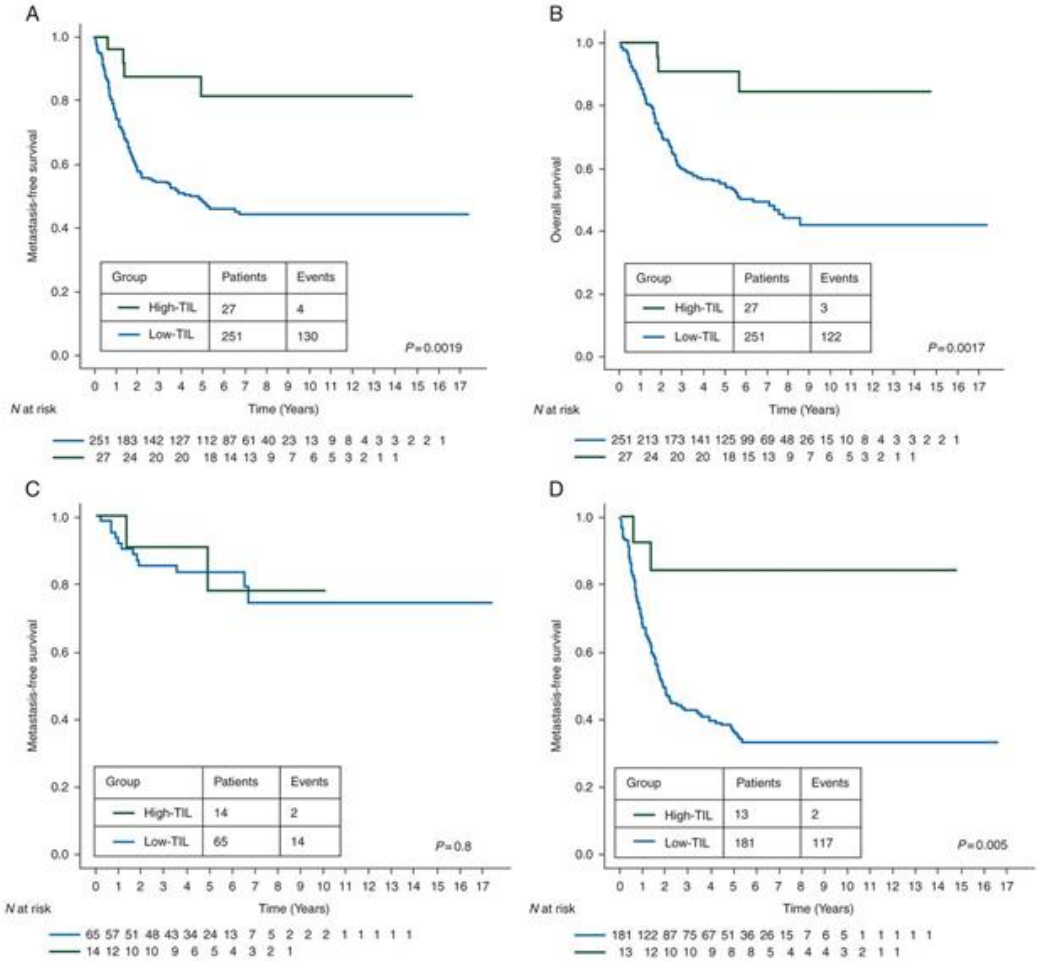
Surrogate markers of response/resistance to chemotherapy

Une autre facon d'appréhender la réponse immunitaire induite par la chimiothérapie et son rôle pronostic



Prognostic value of high lymphocytic infiltration on residual disease after neoadjuvant chemotherapy.

N- ou <2cm

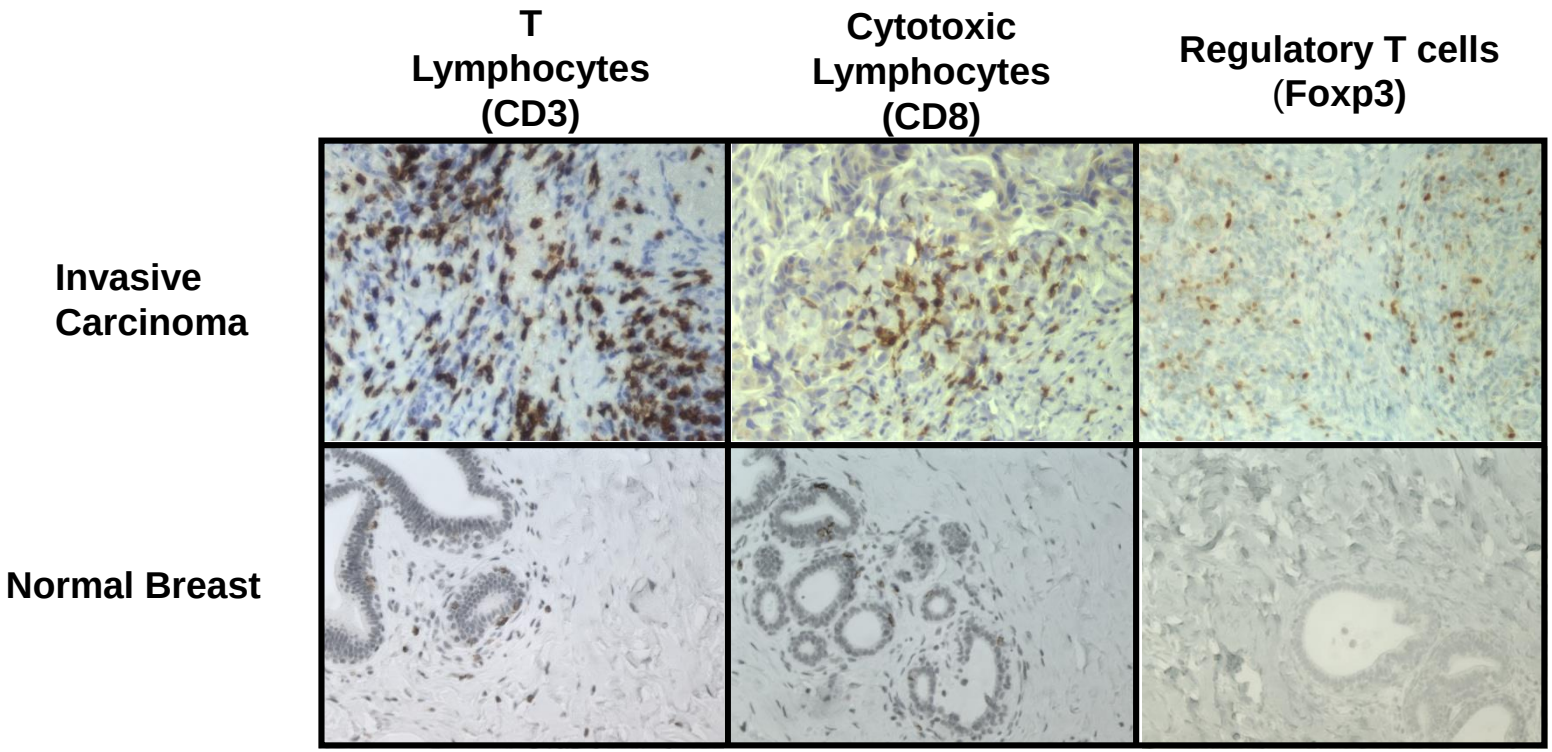


N+ ou >2cm

Dieci M V et al. Ann Oncol 2014;25:611-618

Annals of Oncology

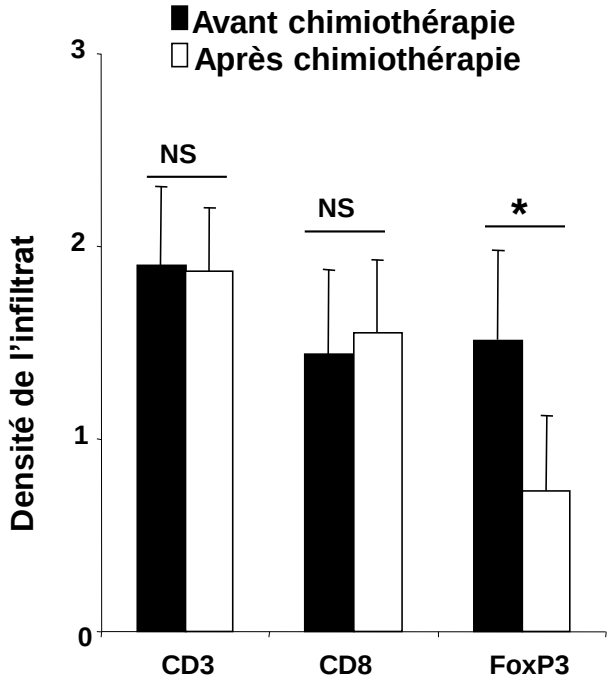
Les cancers du seins sont infiltrés par des cellules effectrices et régulatrices



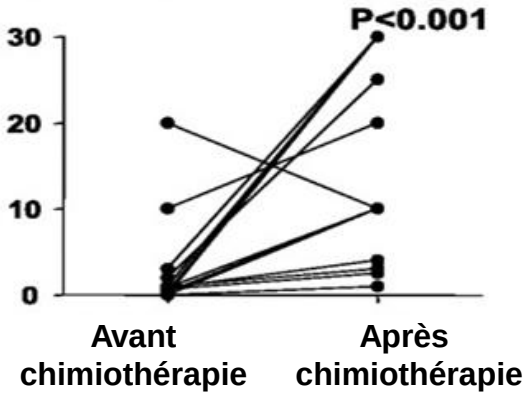
Ladoire et al Clin Cancer Res 2008

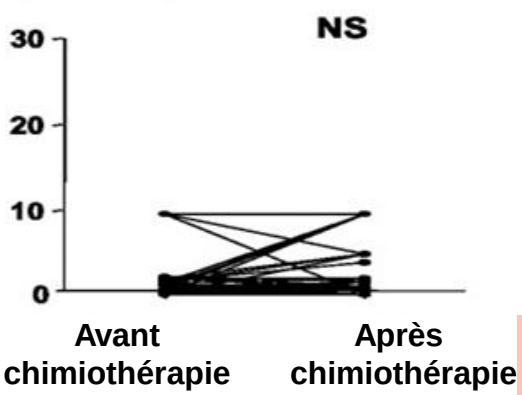
La chimiothérapie diminue le nombre de lymphocytes T immunosuppresseurs

Cohorte 60 patientes
40 traitées par anthracycline
20 traitées par taxane



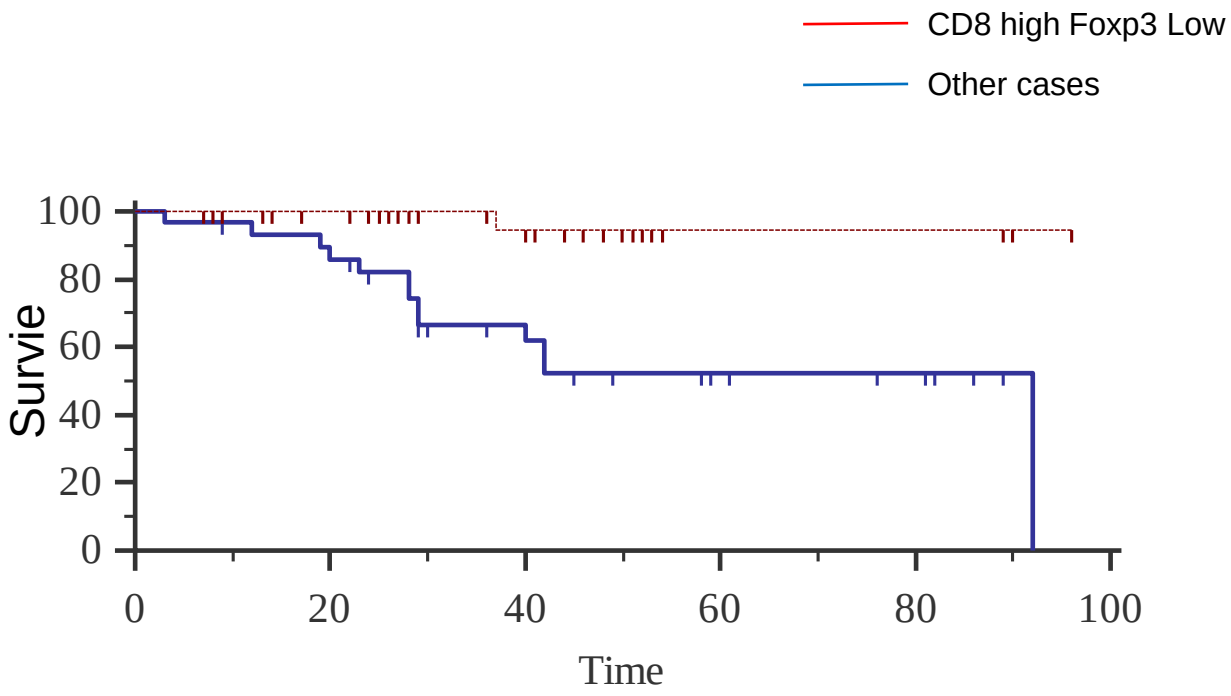
Ratio effecteur CD8 / suppresseur Foxp3





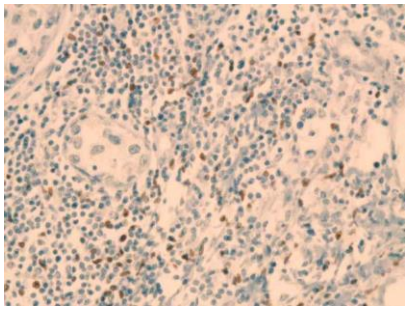
La réponse immunitaire induite par la chimiothérapie permet de prédire la survie

111 patientes traitées entre 1976 et 2007 pour un cancer mammaire N+ et HER2 + par chimiothérapie néoadjuvante



Pathologique –Immunologique Score (*PathIm*)

Tumor and nodal categories	Stage
T0N0 (including residual ductal carcinoma in situ)	0
T1N0	I
T0-1N1; T2N0	IIA
T2N1; T3N0	IIB
T0-3N2; T3N1	IIIA
Any T4	IIIB
Any N3	IIIC



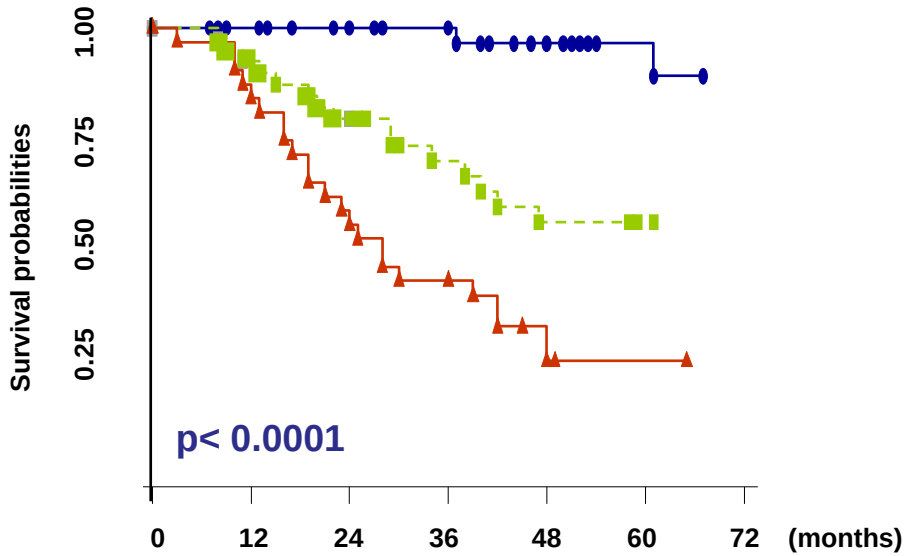
AJCC pathologic stage (0: favourable; 1: unfavourable)	**CD8/Foxp3 infiltrates** (0: favourable; 1: unfavourable)	**PathIm score**
0 (≤ IIA)	**0** (CD8 high + Foxp3 low)	**0**
1 (>IIA)	**0** (CD8 high + Foxp3 low)	**1**
0 (≤ IIA)	**1** (CD8 low and/or Foxp3 high)	**1**
1 (>IIA)	**1** (CD8 low and/or Foxp3 high)	**2**

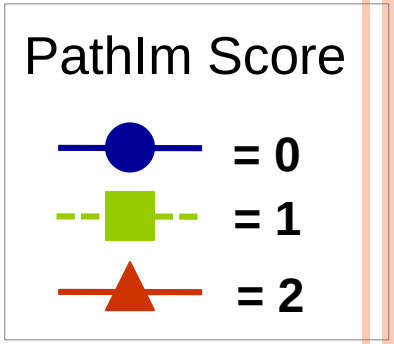
Pathologic-Immunologic score (PathIm score)

Ladoire et al. J Pathol 2011

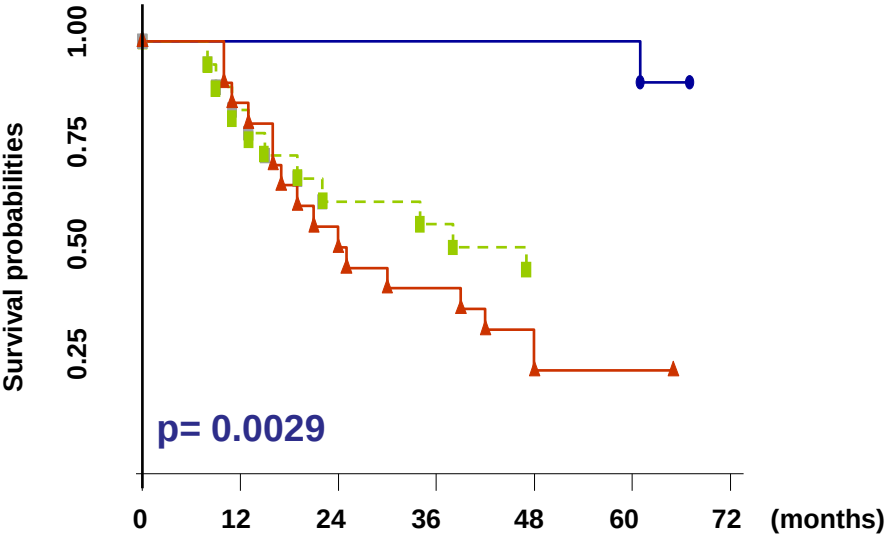
SSR

Whole population

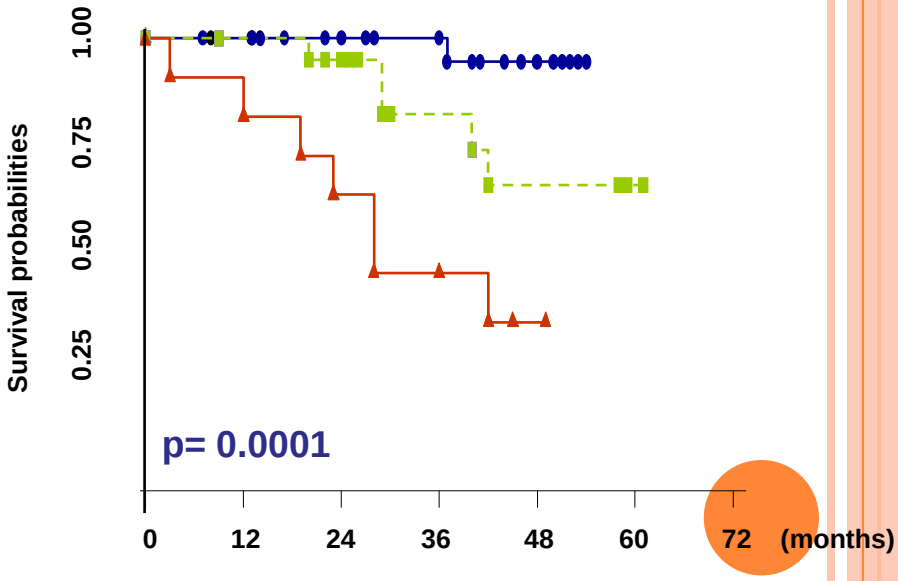




Anthracyclines



Trastuzumab-Taxanes



Ladoire et al. J Pathol 2011

Etude prospective du rôle des infiltrats tumoraux lymphocytaires T CD8 et Foxp3 comme nouveau biomarqueur pronostic des cancers du sein traités par chimiothérapie néoadjuvante (PRIMUNEO PHRC 2011)

Prospective study of the **R**elevance of T lymphocytes tumor **I**nfiltrates CD8 and Foxp3 as a new im**MU**ne prognostic biomarker in breast cancer treated by **NEO**adjuvant chemotherapy.

Elimine les lymphocytes suppresseurs

Action anti angiogénique

Cytotoxicité directe

Actives les lymphocytes effecteurs

Remerciement
Docteur Sylvain Ladoire

Instituts thématiques

Inserm

Institut national de la santé et de la recherche médicale

INSERM UMR866

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