

Réponse immunitaire et chimiothérapie: Perspectives thérapeutiques dans les cancers du sein

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Centre Georges François Leclerc

Plateforme UB de Transfert en Biologie Cancérologique

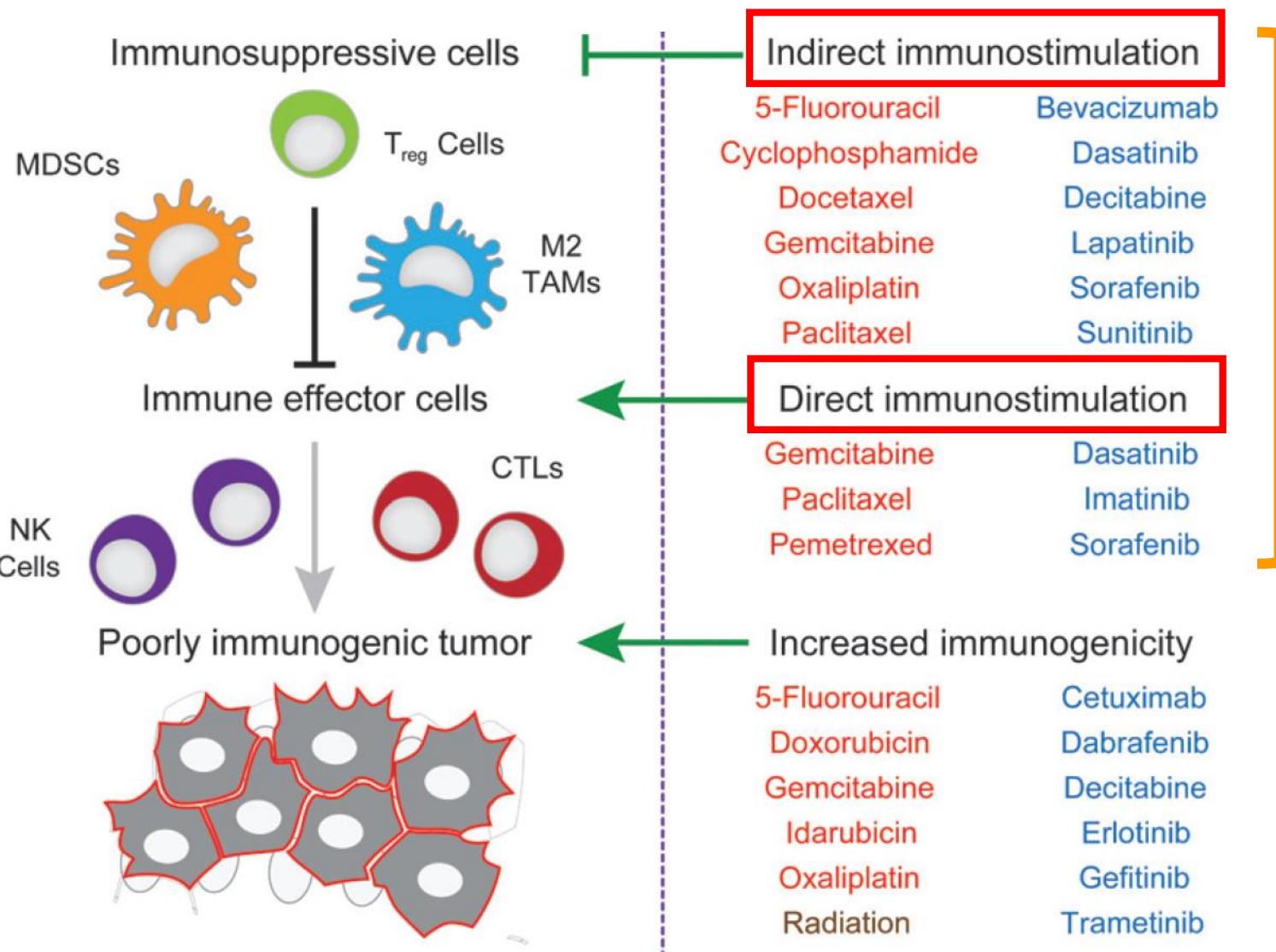


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INSERM U1231
Equipe « Chimiothérapie & réponse immunitaire »
Faculté de Médecine-Université de Bourgogne





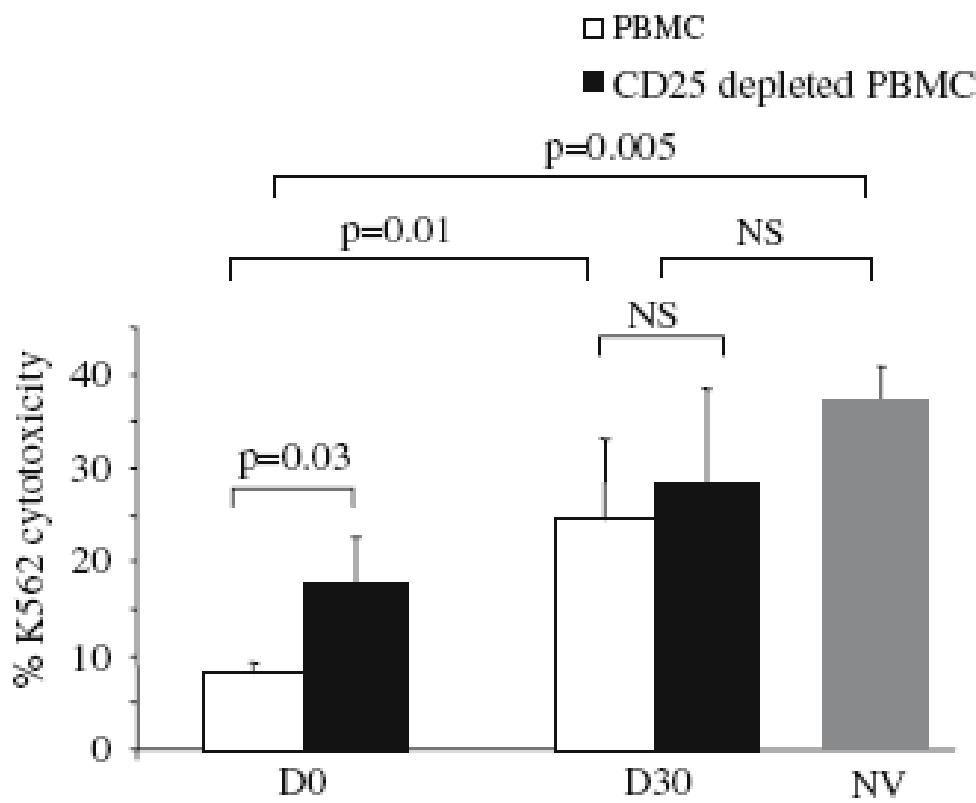
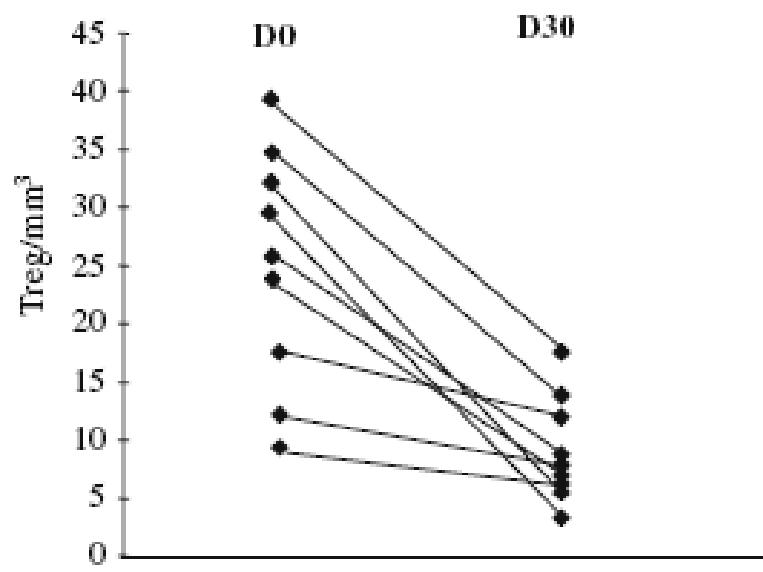
« off -target »

Elimination / Différenciation des cellules immuno-suppressives

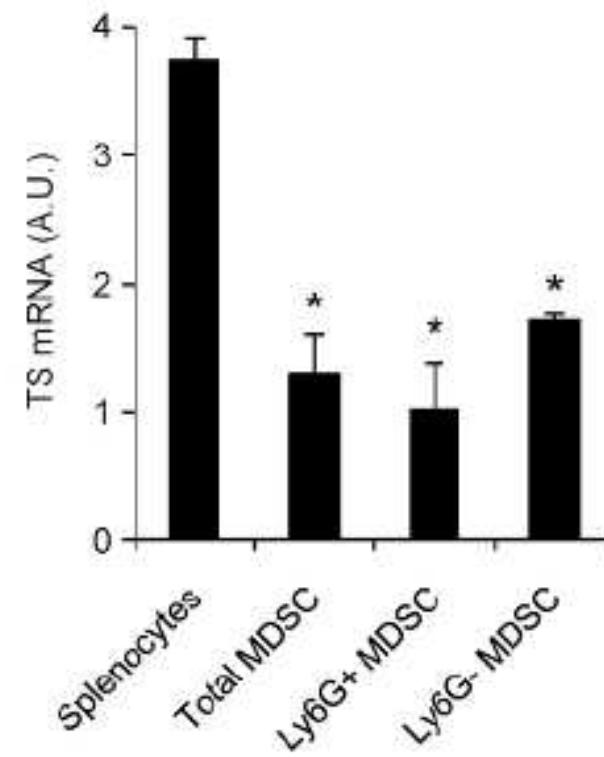
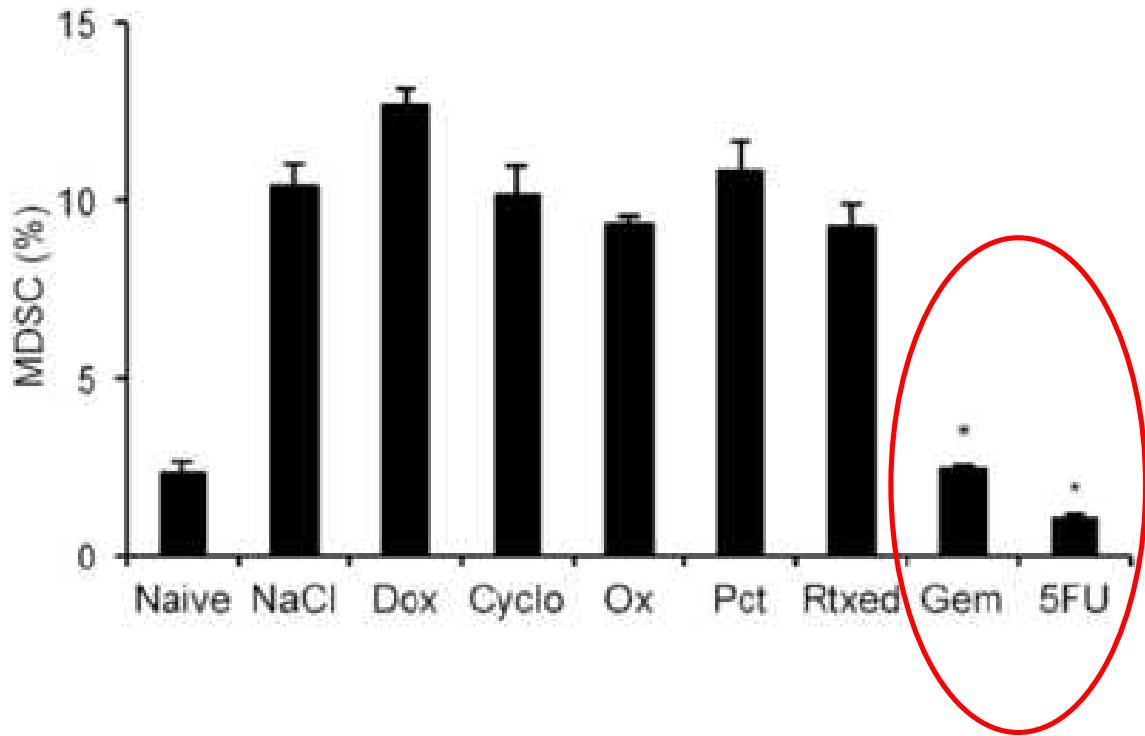
Stimulation directe des effecteurs myéloïdes ou lymphoïdes

Metronomic cyclophosphamide regimen selectively depletes CD4⁺CD25⁺ regulatory T cells and restores T and NK effector functions in end stage cancer patients

François Ghiringhelli · Cédric Menard · Pierre Emmanuel Puig · Sylvain Ladoire ·



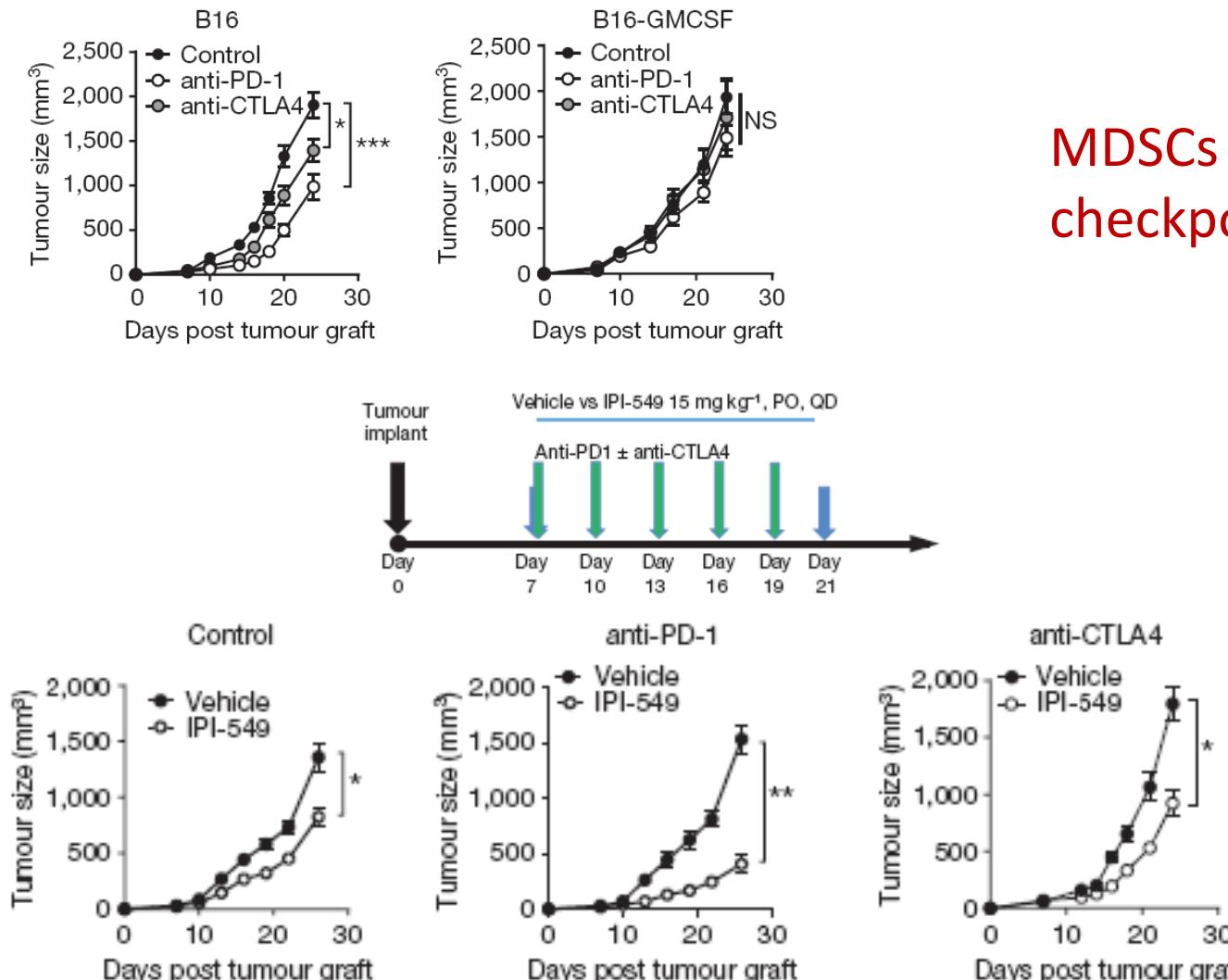
MDSCs are selectively depleted by pyrimidines analogs



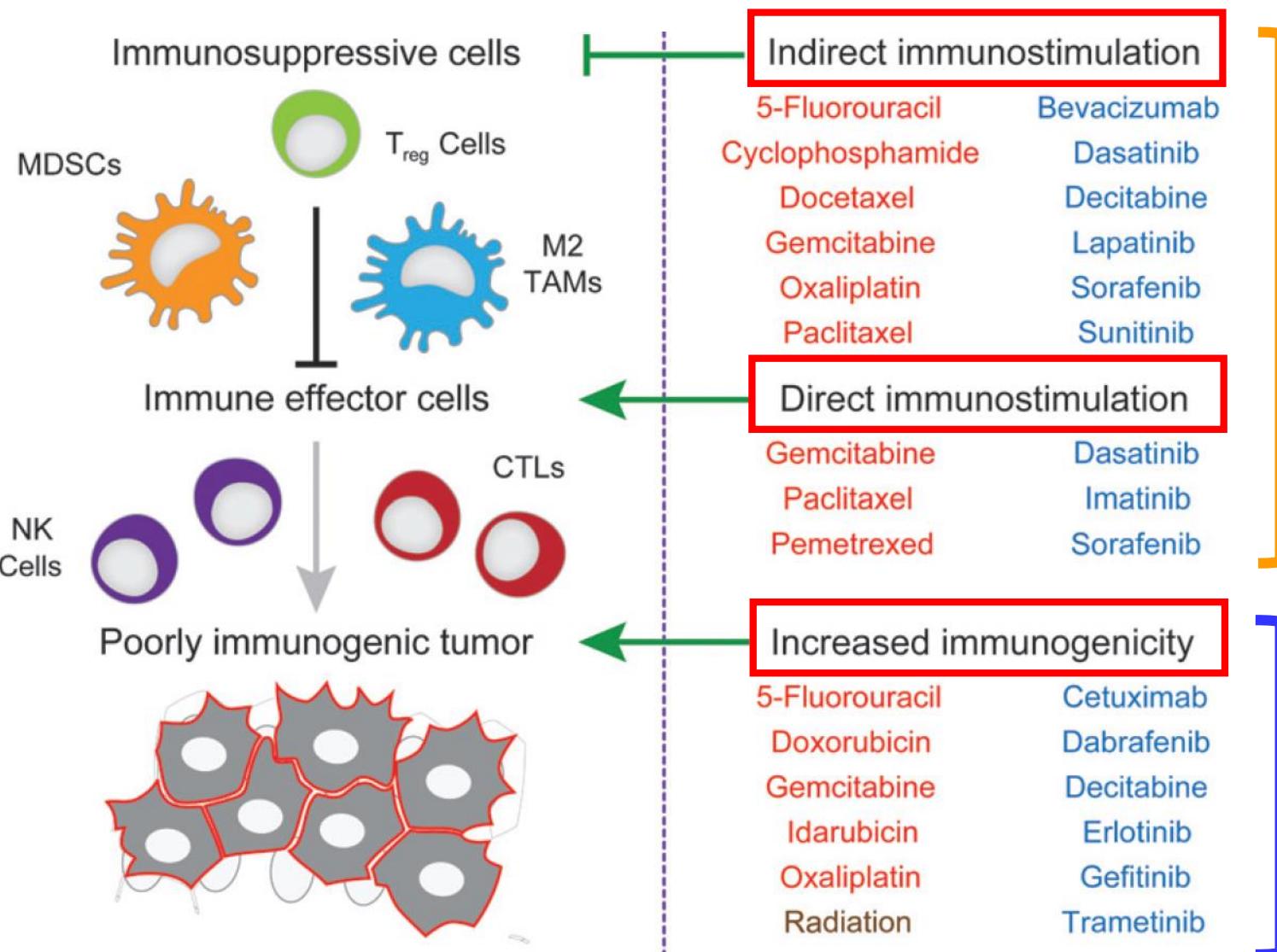
Overcoming resistance to checkpoint blockade therapy by targeting PI3K γ in myeloid cells

LETTER

Olivier De Henau¹, Matthew Rausch², David Winkler², Luis Felipe Campesato¹, Cailian Liu¹, Daniel Hirschhorn-Cymerman¹, Sadna Budhu¹, Arnab Ghosh¹, Melissa Pink², Jeremy Tchaicha², Mark Douglas², Thomas Tibbitts², Sujata Sharma², Jennifer Proctor², Nicole Kosmider², Kerry White², Howard Stern², John Soglia², Julian Adams², Vito J. Palombella², Karen McGovern², Jeffery L. Kutok², Jedd D. Wolchok^{1,3}§ & Taha Merghoub¹§



MDSCs = Resistance to immune checkpoint inhibitors



« off –target »

Elimination / Différenciation des cellules immuno-suppressives

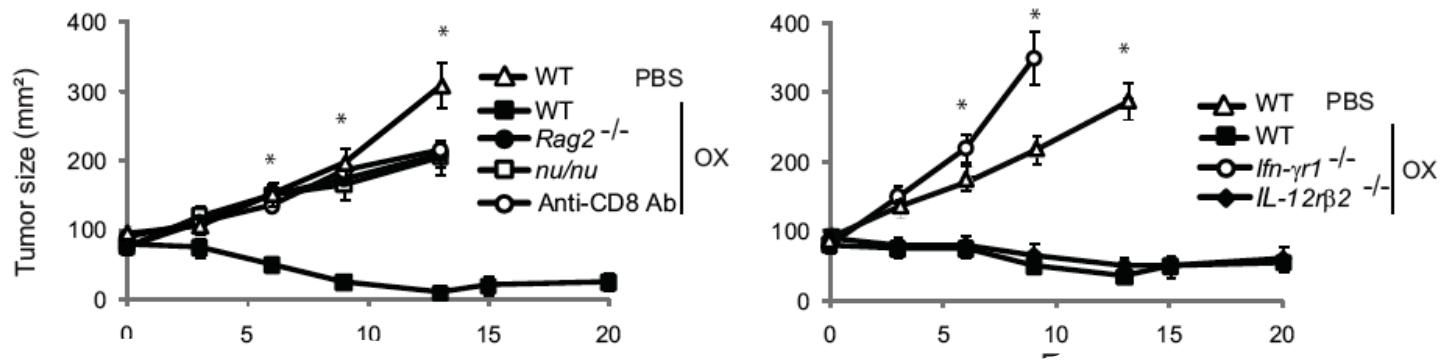
Stimulation directe des effecteurs myéloïdes ou lymphoïdes

« on –target »

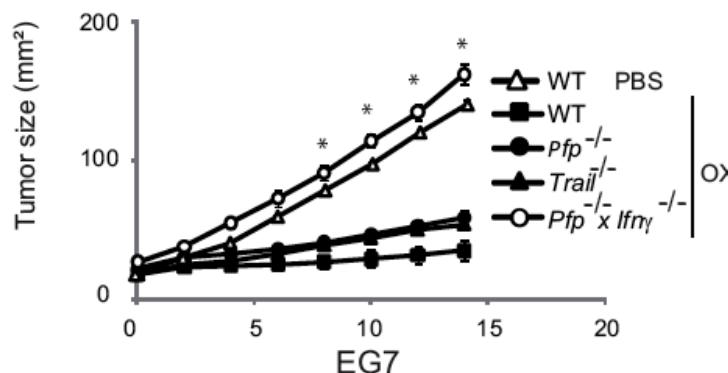
↑ Antigénicité: ↑ CMH classe I, ↑ charge mutationnelle

↑ Adjuvantivité : MORT IMMUNOGENE

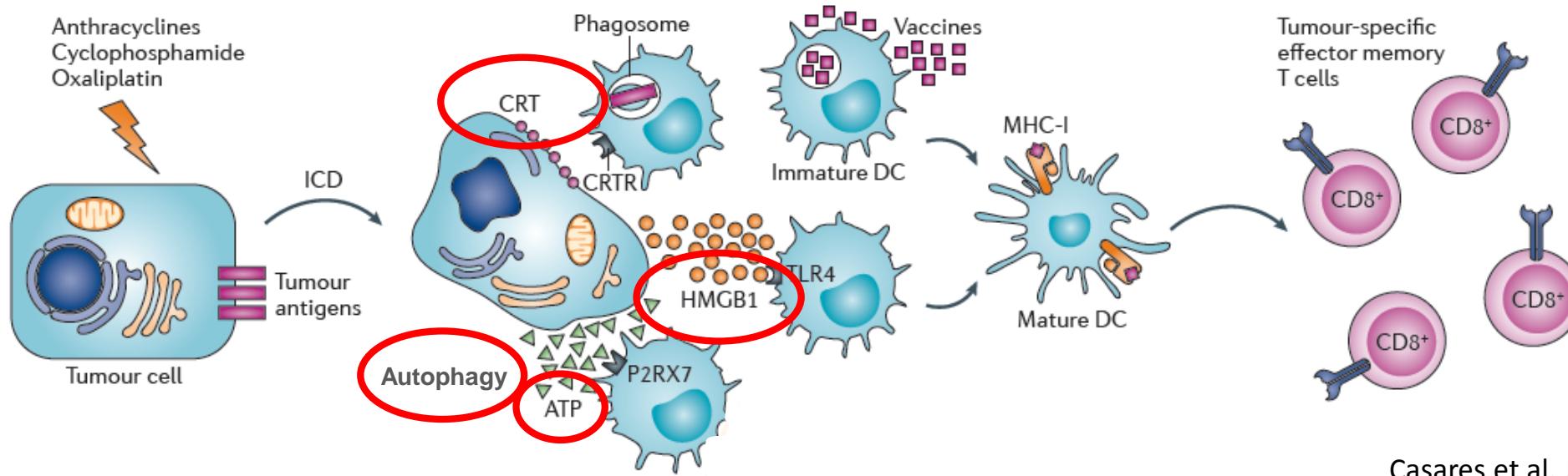
Naissance du concept en cancérologie



Vrai avec les anthracyclines, l'oxaliplatine,
la radiothérapie
Pas observé avec le cisplatine, l'étoposide



Mécanismes moléculaires impliqués dans la mort immunogène induite par les chimiothérapies:

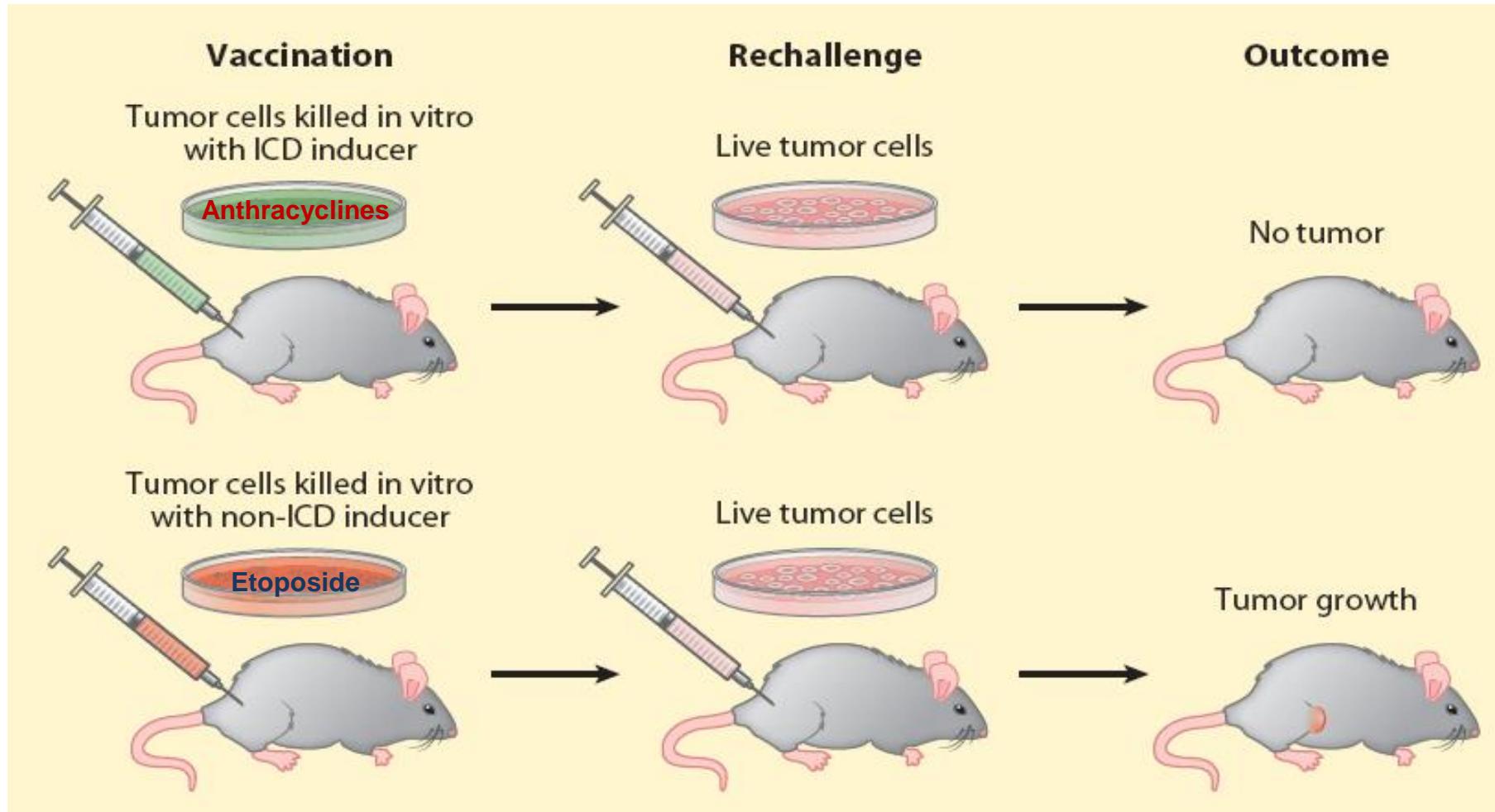


Modèles pré-cliniques \longleftrightarrow Tumeurs humaines ?

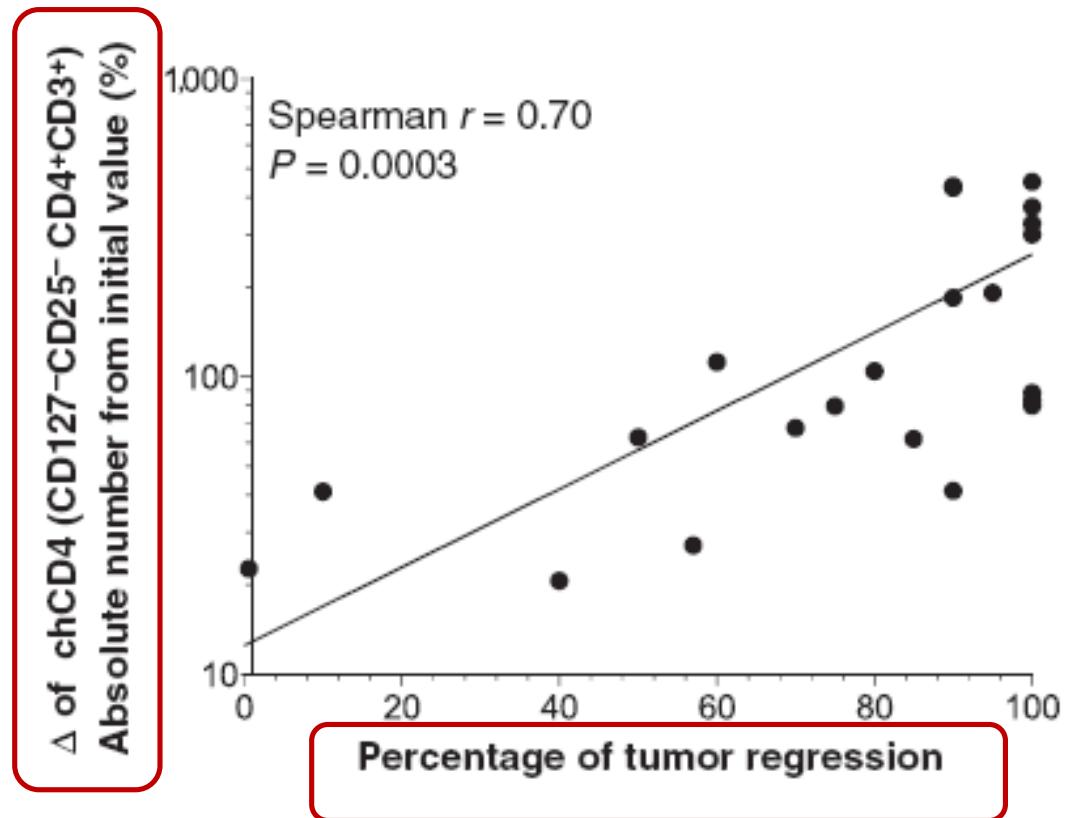
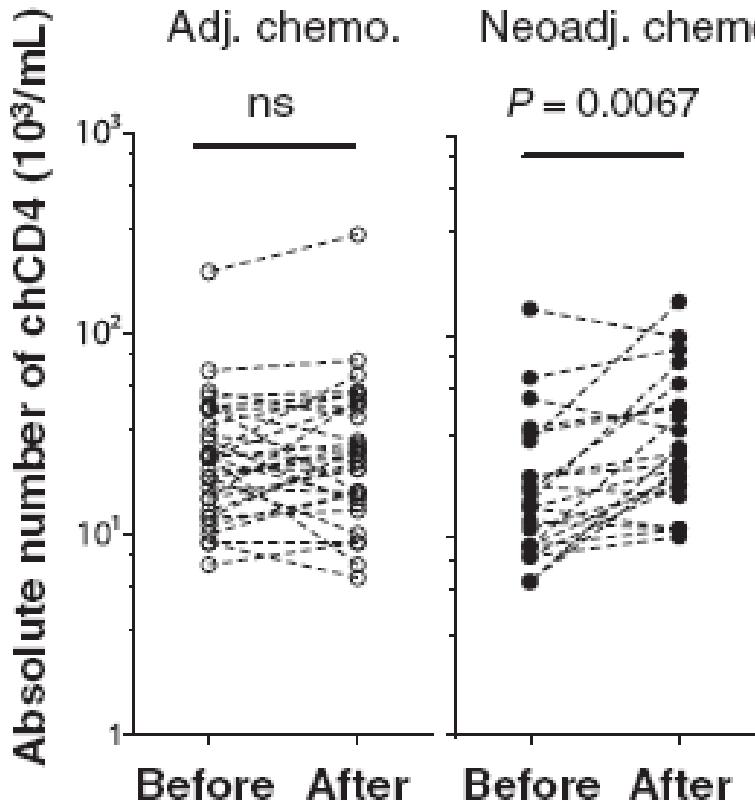
- Casares et al. J. Exp. Med. 2005
Zitvogel et al. Nat. Rev. Immunol. 2006, 2008
Obeid et al. Nat. Med. 2007
Apetoh et al. Nat. Med. 2007
Zitvogel et al. J Clin Invest. 2008
Panaretakis et al. EMBO J. 2009
Green et al. Nat. Rev. Immunol. 2009
Ghiringhelli et al. Nat. Med. 2009
Michaud et al. Science 2011
Sistigu et al. Nat Med 2014
Vacchelli et al. Science 2015

Naissance du concept en cancérologie

Mise en évidence **fonctionnelle** (pas biochimique ou morphologique)



Chimiothérapie néoadjuvante par anthracyclines et réponse T circulante :



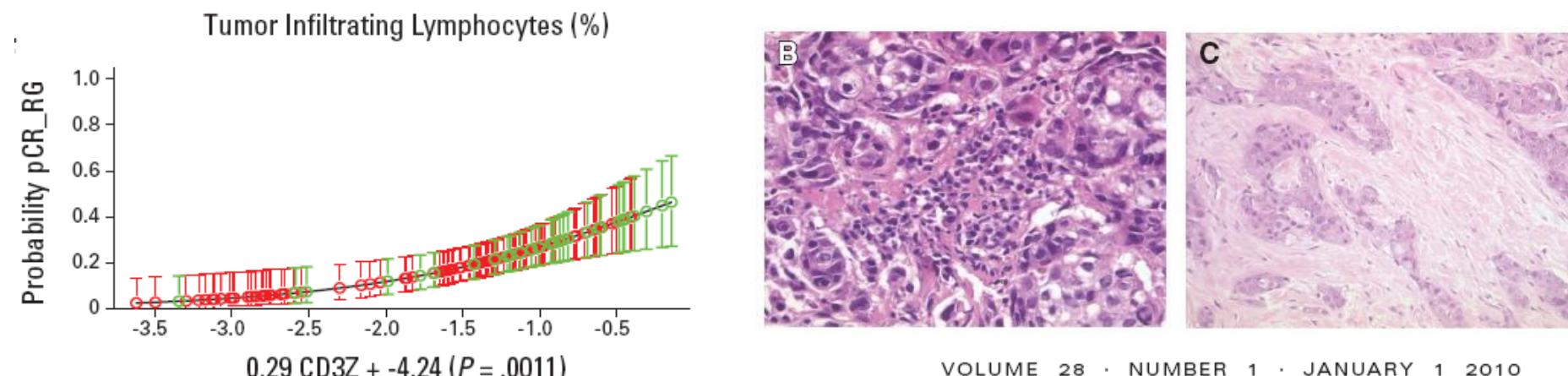
Tumor-Associated Lymphocytes As an Independent Predictor of Response to Neoadjuvant Chemotherapy in Breast Cancer

JOURNAL OF CLINICAL ONCOLOGY

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

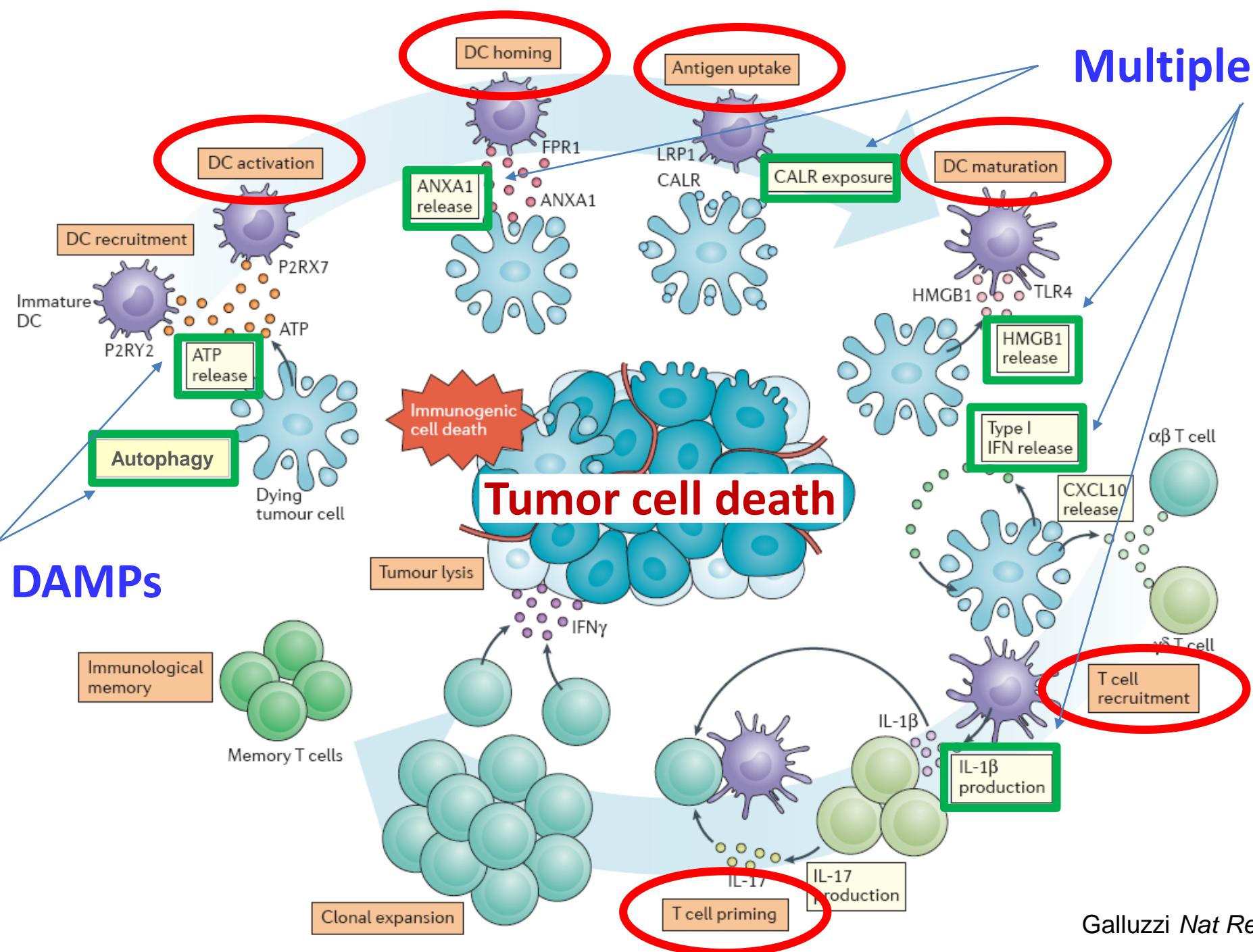
Table 2. Validation Cohort (GeparTrio): Factors Associated With a Pathologic Complete Response in the GeparTrio Cohort in Univariate and Multivariate Analysis

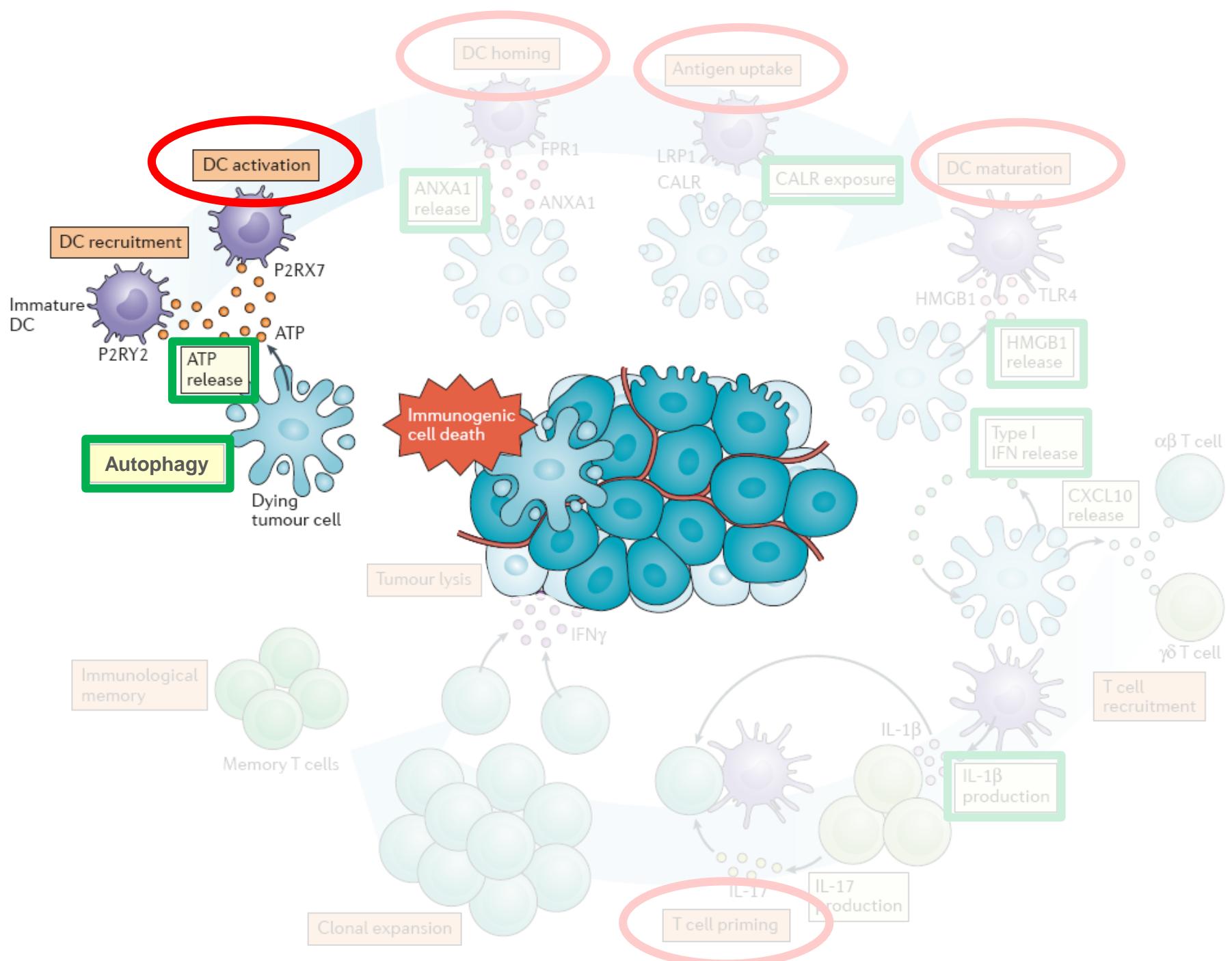
Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
iTu-Ly (per 10%)	1.36	1.26 to 1.47	< .0005	1.21	1.08 to 1.35	.001
str-Ly (per 10%)	1.27	1.19 to 1.35	< .0005			
Age: < 50 v ≥ 50 years	1.50	1.04 to 2.15	.028	1.81	1.10 to 2.99	.02
Tumor type: ductal/other v lobular	2.40	1.22 to 4.71	.01	1.38	0.54 to 3.52	.51
Tumor grade: 3 v 1/2	2.91	1.94 to 4.35	< .0005	1.61	0.95 to 2.71	.076
ER/PR status: ER negative/PR negative v ER positive and/or PR positive	6.00	3.97 to 9.08	< .0005	4.13	2.42 to 7.04	< .0005
Tumor size: < 4 v ≥ 4 cm	1.09	0.75 to 1.57	.66	0.78	0.47 to 1.30	.34
Nodal status: cN0 v cN+	0.82	0.56 to 1.18	.28	0.84	0.50 to 1.40	.50
HER-2 status: negative v positive	0.86	0.57 to 1.27	.44	0.83	0.50 to 1.39	.47



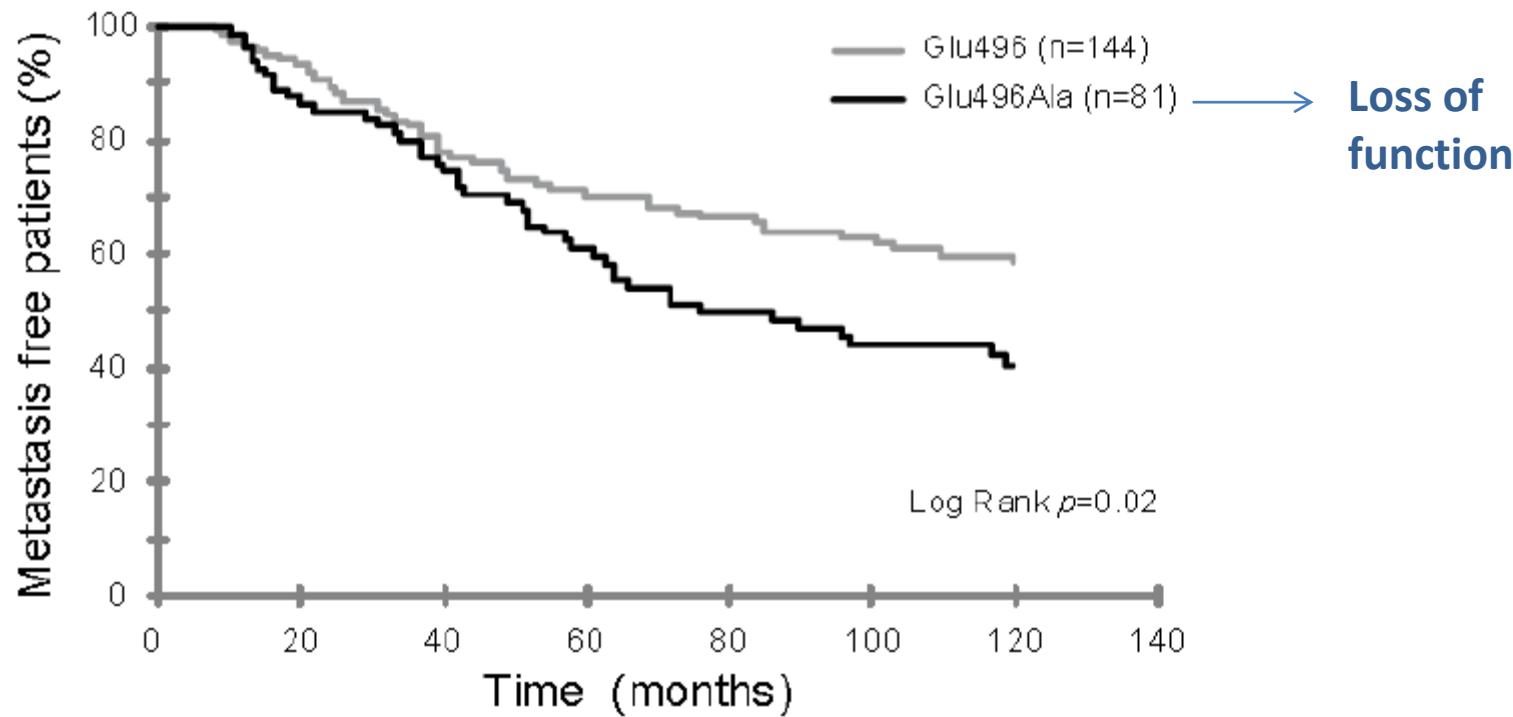
Multiple DAMPs

Multiple DAMPs

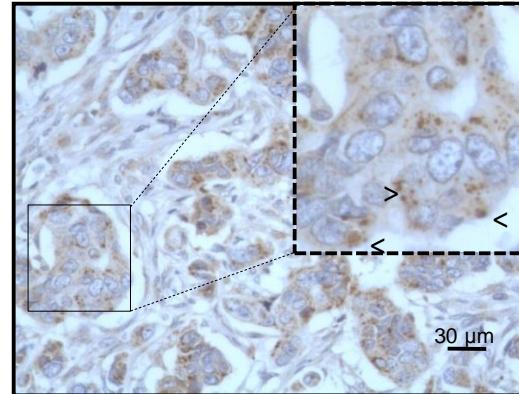
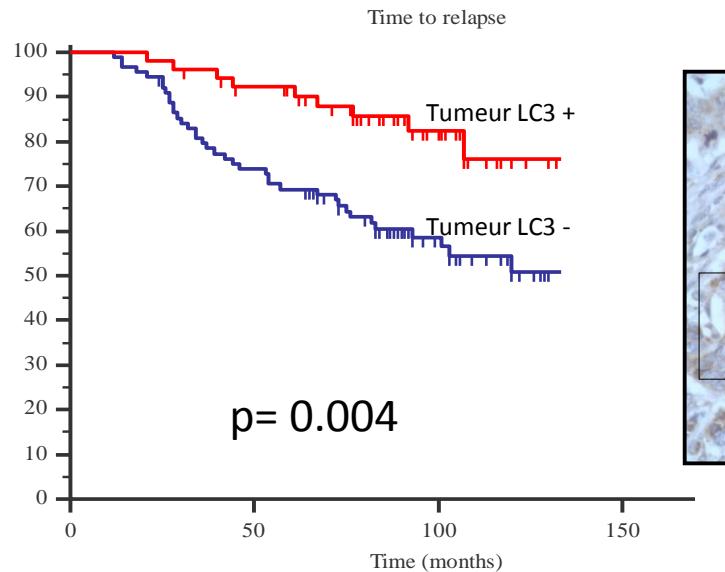




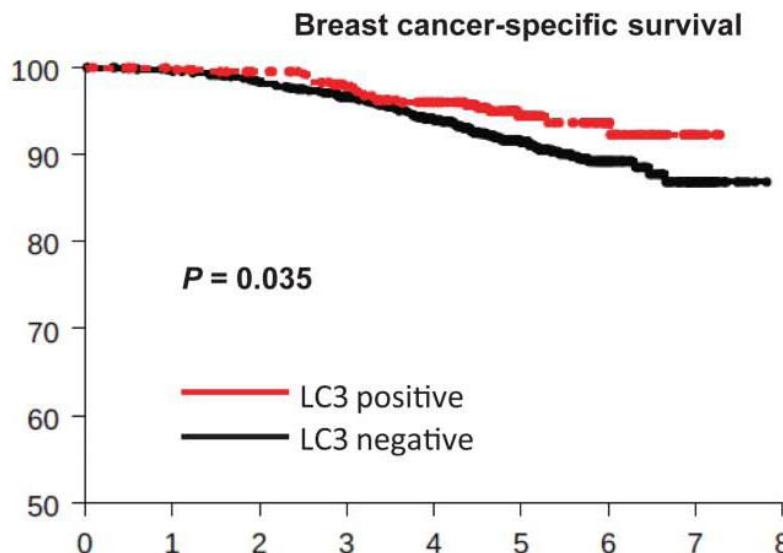
Time to relapse after adjuvant anthracyclins according to *P2RX7* polymorphisms



Autophagy tumor level in primary breast tumors before anthracyclin-based adjuvant chemotherapy



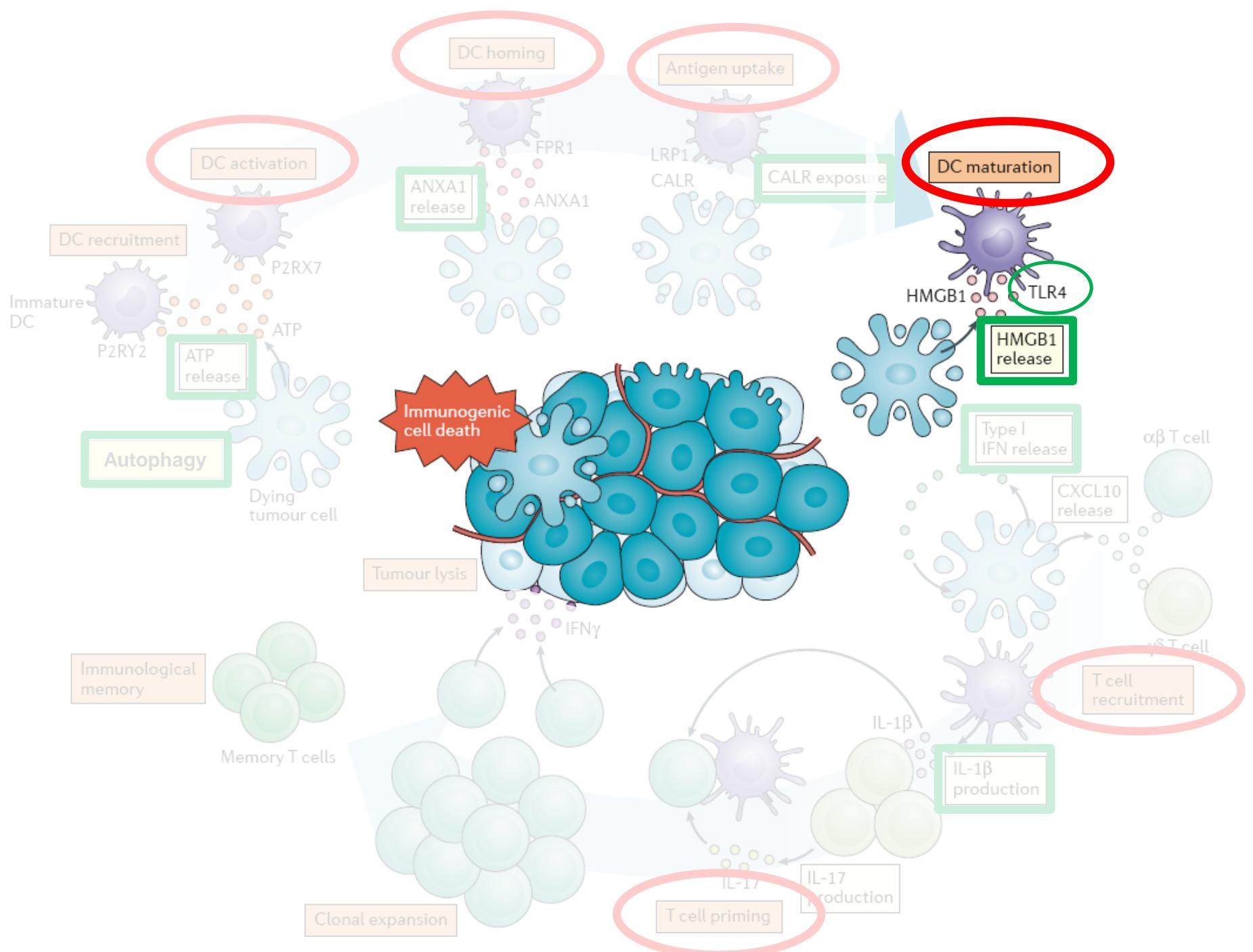
Les tumeurs avec un haut niveau basal d'autophagie (LC3) et traitées par anthracyclines sont de meilleur pronostic



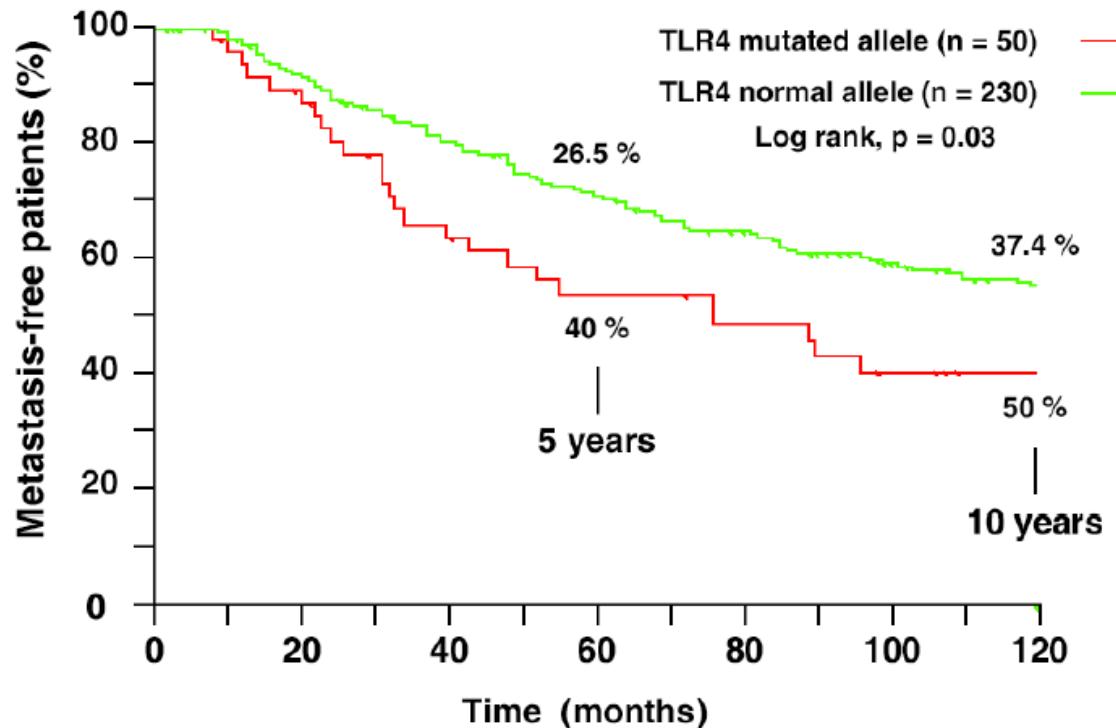
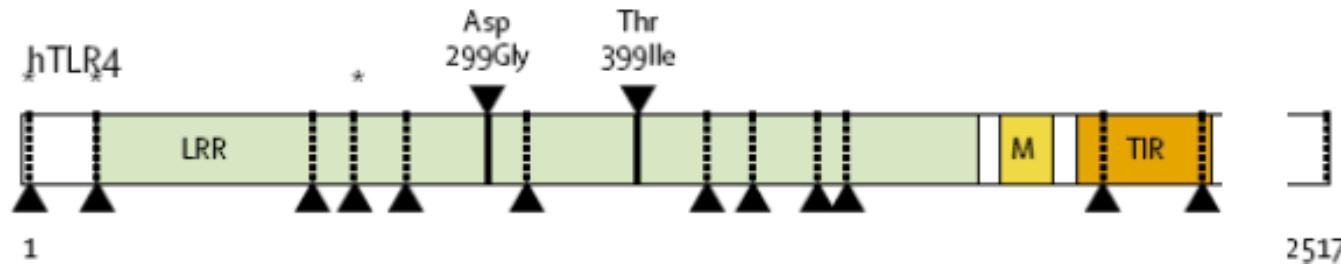
N= 1581 BC patients treated with anthracycline-adjuvant chemotherapy

Ladoire et al, *Autophagy* 2012

Ladoire et al, *Autophagy* 2015



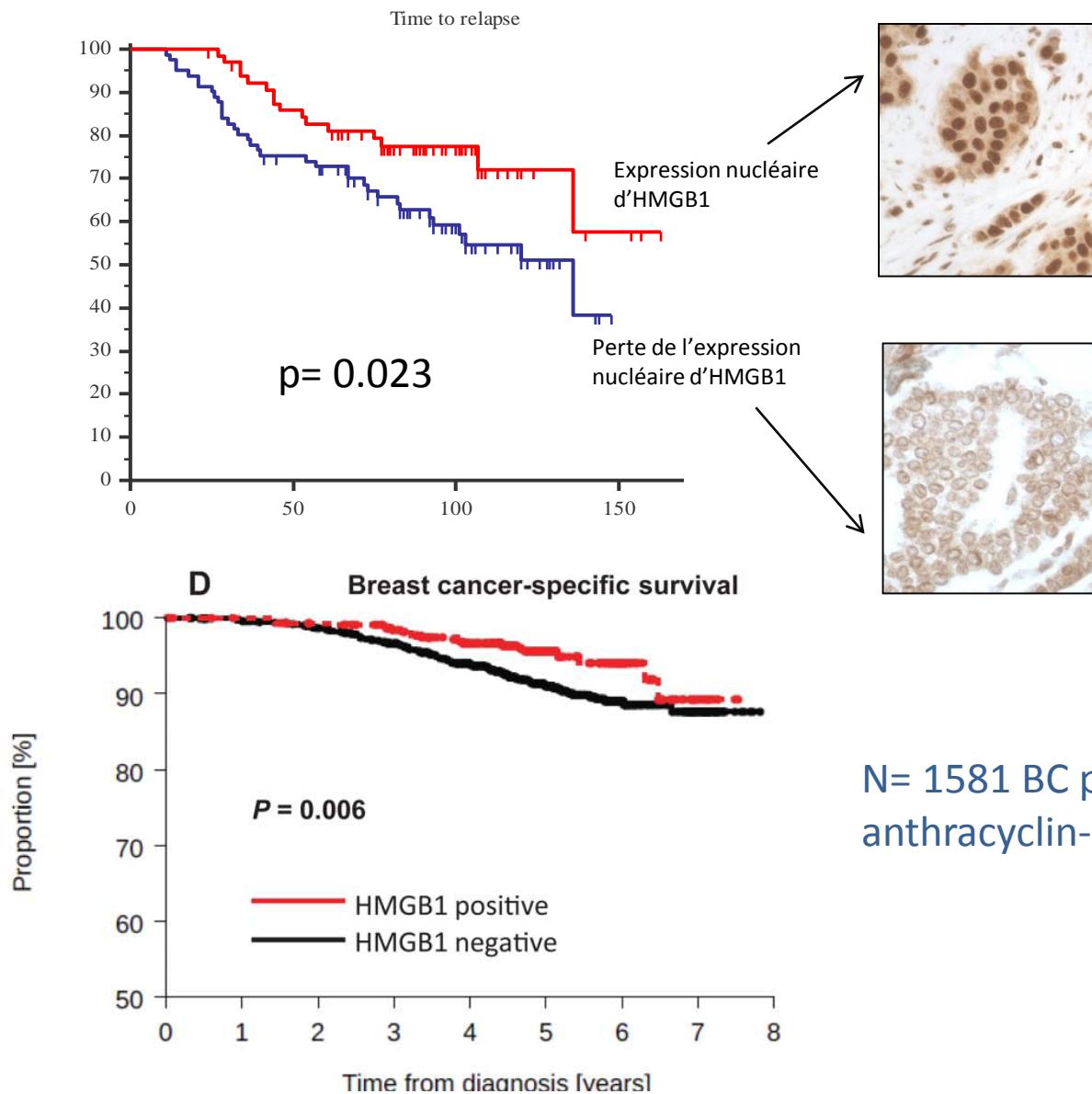
Human *TLR4* polymorphisms and anthracycline-based chemotherapy in breast cancer patients



Arbour et al, *Nat Genet* 2000

Apetoh et al, *Nat Med* 2007

HMGB1 expression level in primary BC tumors before anthracyclin-based adjuvant chemotherapy

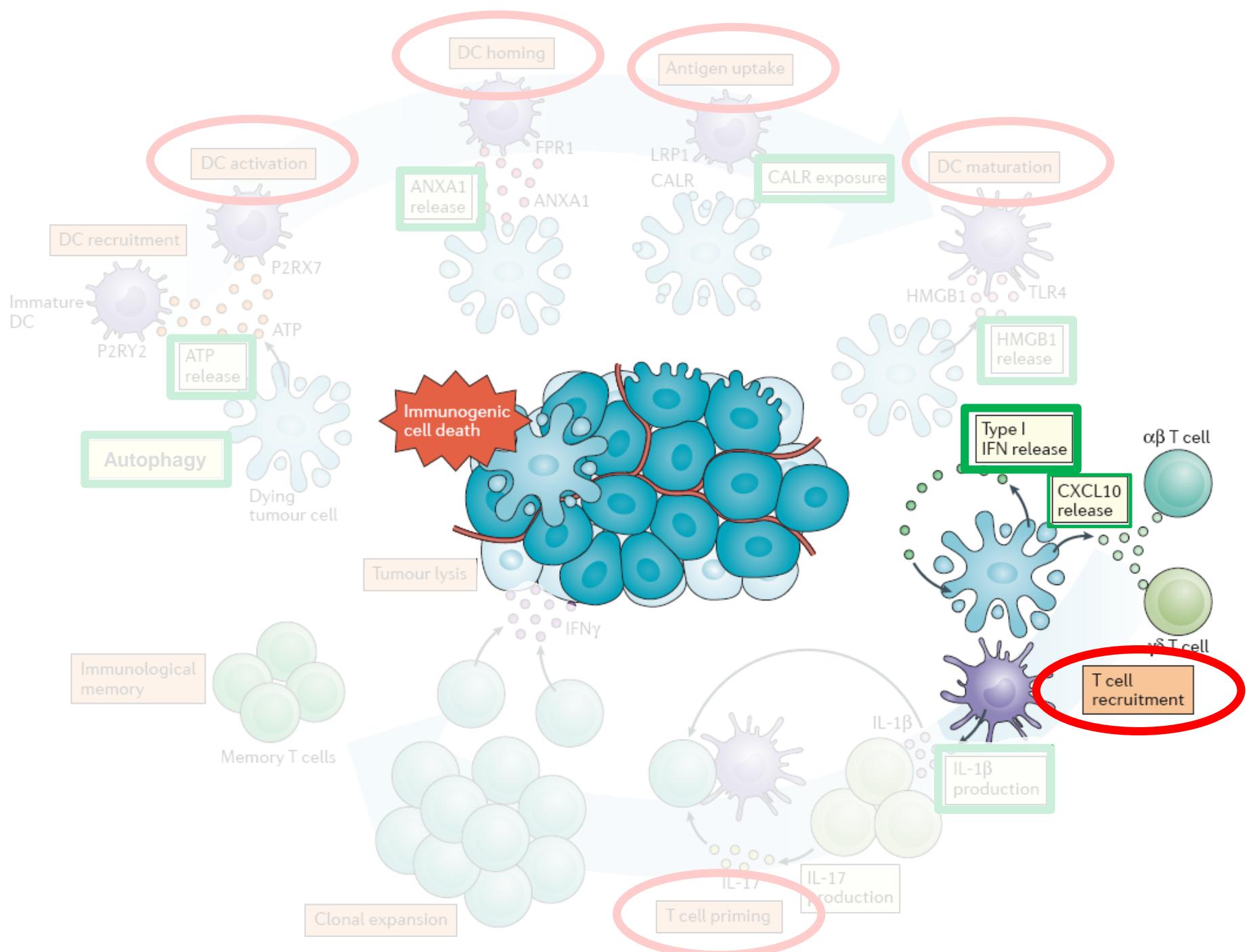


L'absence d'expression d'HMGB1 par la tumeur est associée à un mauvais pronostic

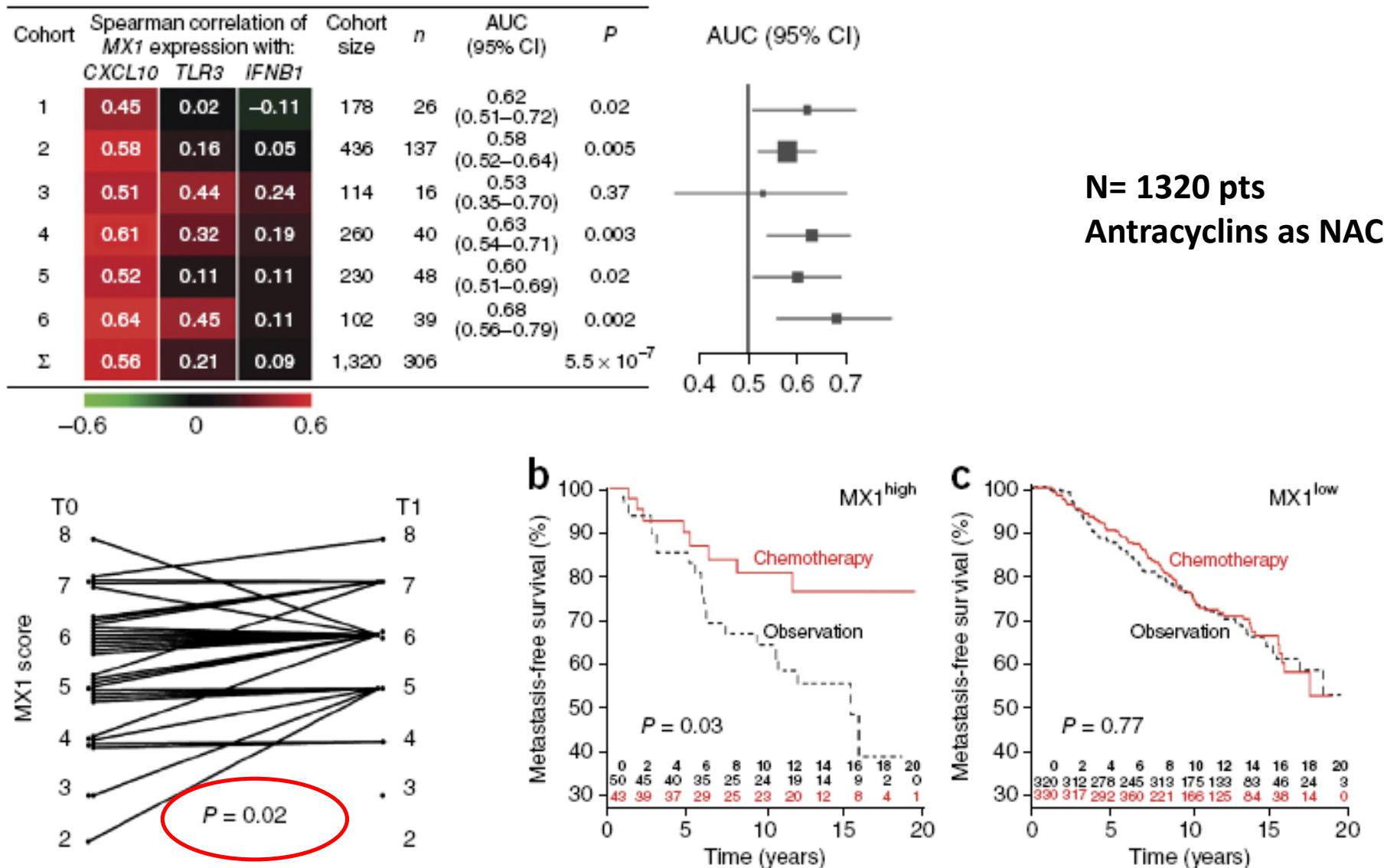
N= 1581 BC patients treated with anthracyclin-adjuvant chemotherapy

Ladoire et al, *Autophagy* 2012

Ladoire et al, *Autophagy* 2015



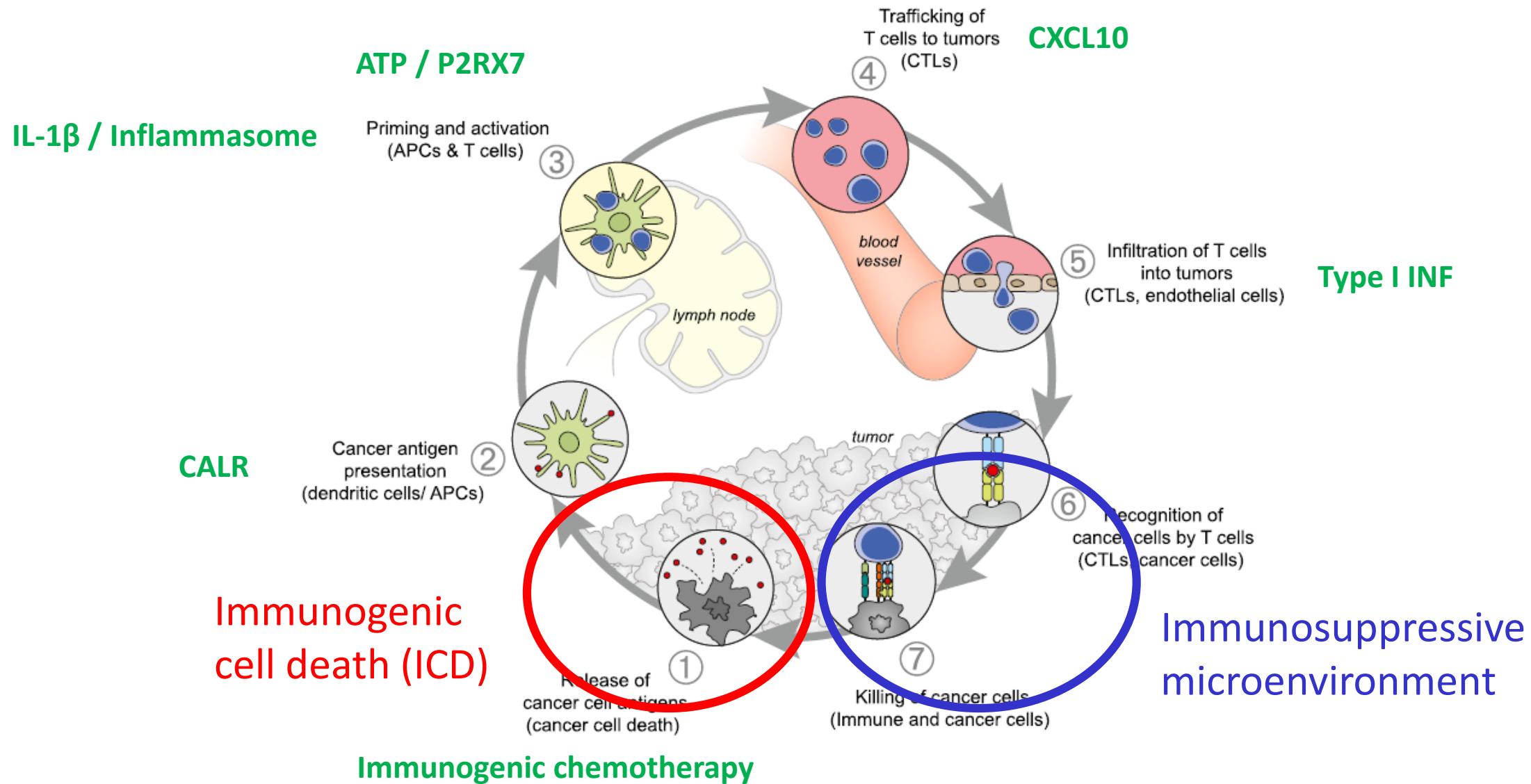
Type I interferon signature and benefit from anthracyclins



Immunogenic Cell Death : pour quoi faire ?

- . Concept clé en immuno-oncologie des 10 dernières années
- . Arguments indirects multiples pour penser que existe également en clinique
- . Processus multi-étapes: difficulté à choisir le(s) biomarqueur(s) à utiliser
- . Rationnel de combinaisons thérapeutiques
 - Vaccination
 - Chimiothérapies modulant la réponse immunitaire
 - Inhibiteurs de points de contrôle de la réponse immunitaire

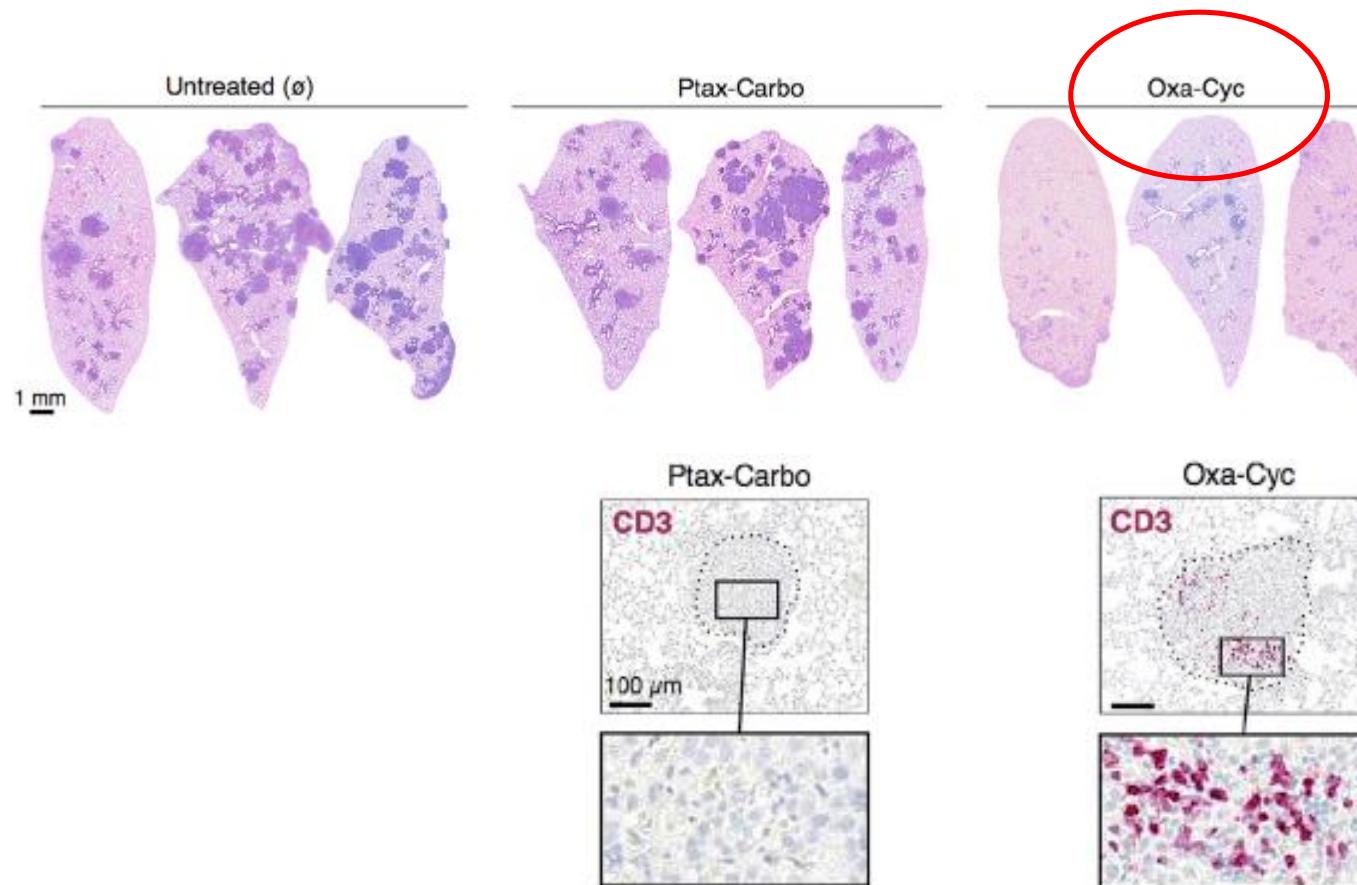
Conventional chemotherapies could have immunological effects



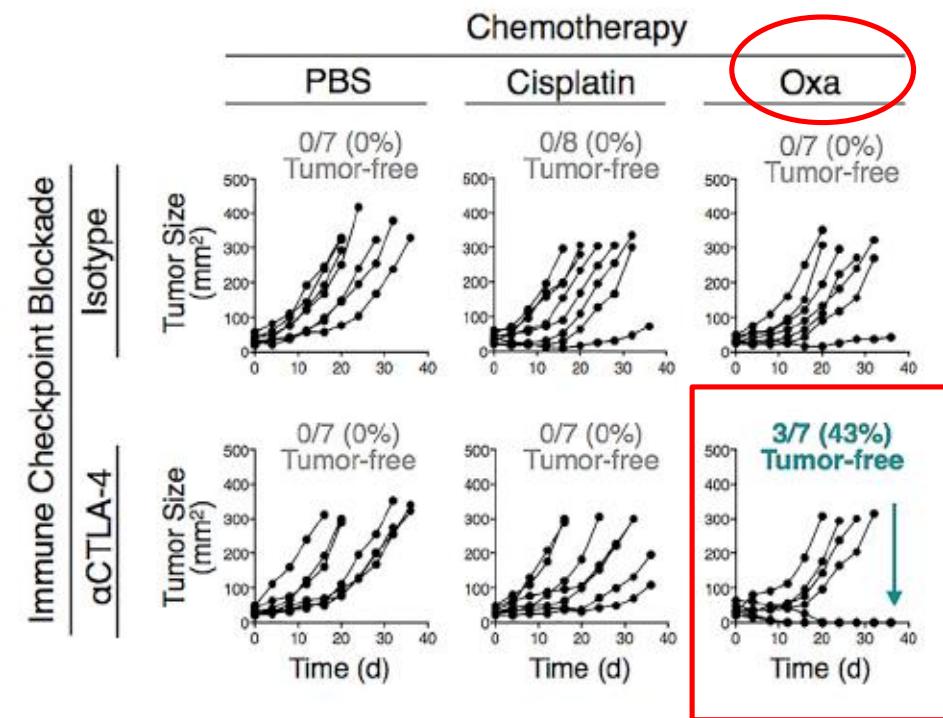
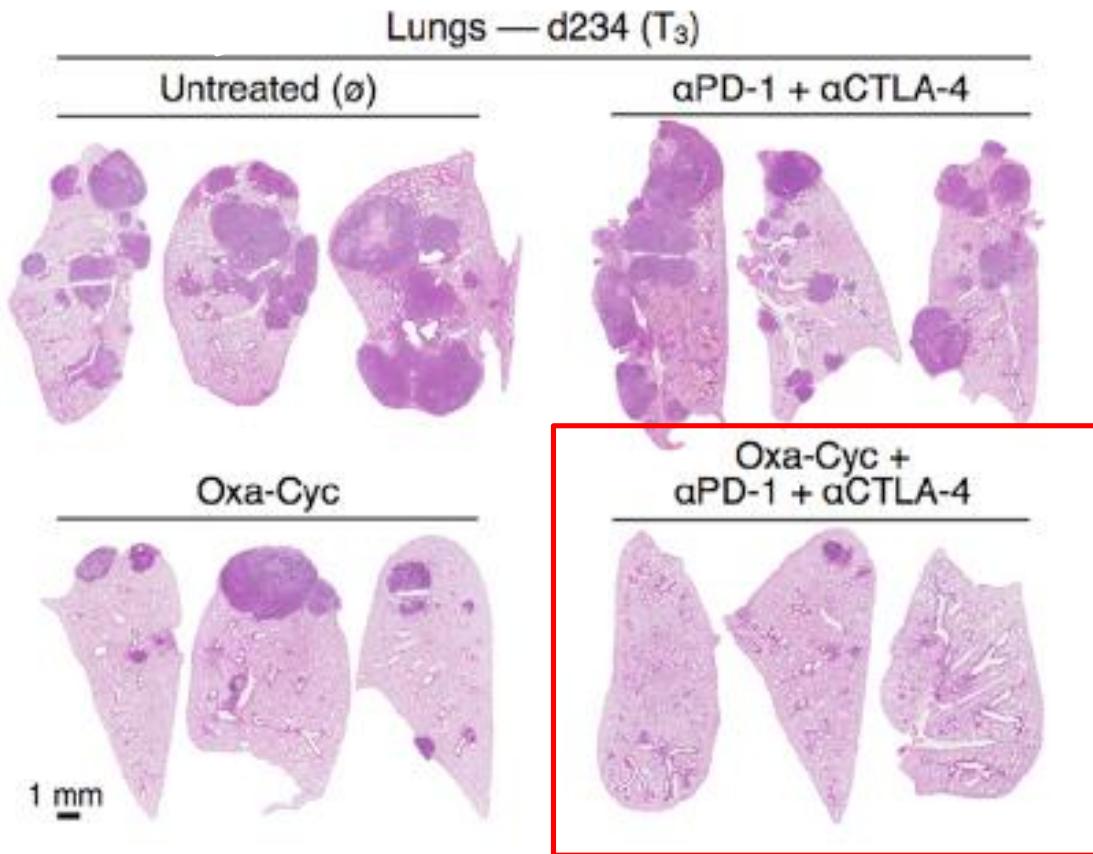
Immunogenic Chemotherapy Sensitizes Tumors to Checkpoint Blockade Therapy

Immunity
Article

Christina Pfirschke,^{1,7} Camilla Engblom,^{1,2,7} Steffen Riekele,³ Virna Cortez-Retamozo,¹ Christopher Garris,^{1,2} Ferdinando Pucci,¹ Takahiro Yamazaki,⁴ Vichnou Poirier-Colame,⁴ Andita Newton,¹ Younes Redouane,¹ Yi-Jang Lin,¹ Gregory Wojtkiewicz,¹ Yoshiko Iwamoto,¹ Mari Mino-Kenudson,⁵ Tiffany G. Huynh,⁵ Richard O. Hynes,³ Gordon J. Freeman,⁶ Guido Kroemer,⁴ Laurence Zitvogel,⁴ Ralph Weissleder,¹ and Mikael J. Pittet^{1,*}



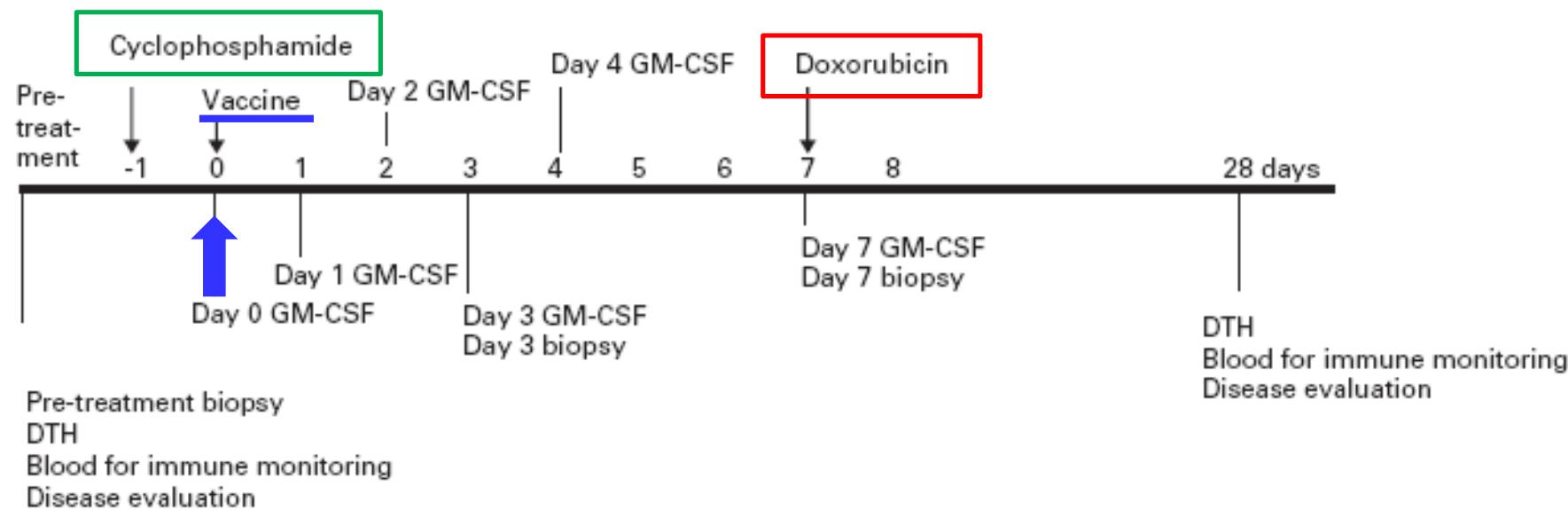
Synergistic activity of Immunogenic chemotherapies and immune checkpoint blocking:



Timed Sequential Treatment With Cyclophosphamide, Doxorubicin, and an Allogeneic Granulocyte-Macrophage Colony-Stimulating Factor–Secreting Breast Tumor Vaccine: A Chemotherapy Dose-Ranging Factorial Study of Safety and Immune Activation

Leisha A. Emens, Justin M. Asquith, James M. Leatherman, Barry J. Kobrin, Silvia Petrik, Marina Laiko, Joy Levi, Maithili M. Daphtary, Barbara Biedrzycki, Antonio C. Wolff, Vered Stearns, Mary L. Disis, Xiaobu Ye, Steven Piantadosi, John H. Fetting, Nancy E. Davidson, and Elizabeth M. Jaffee

Concept de chimio-immunothérapie



VOLUME 27 • NUMBER 35 • DECEMBER 10 2009

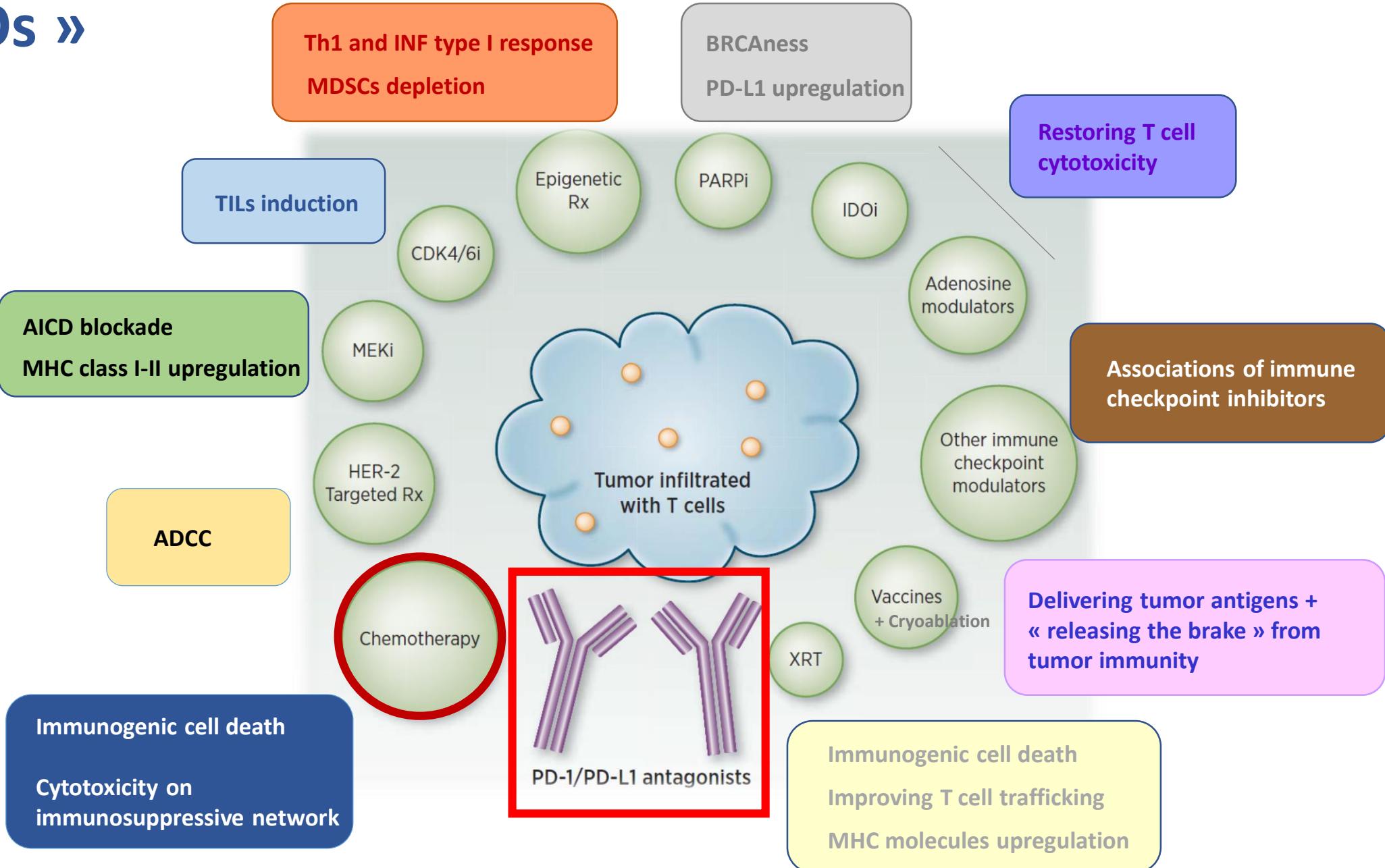
JOURNAL OF CLINICAL ONCOLOGY

« COMBOs »

Types

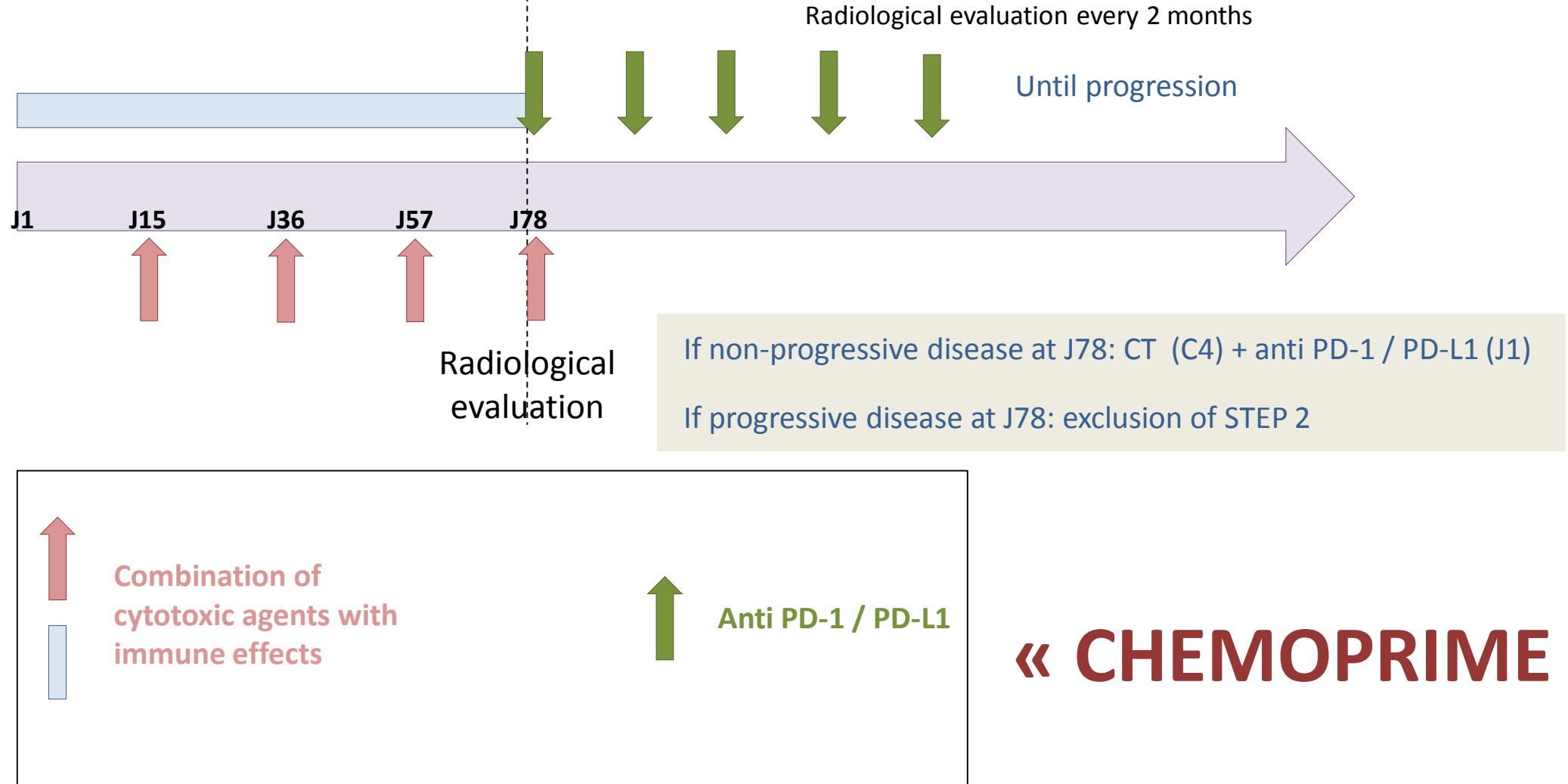
Séquence +++

Biomarqueurs

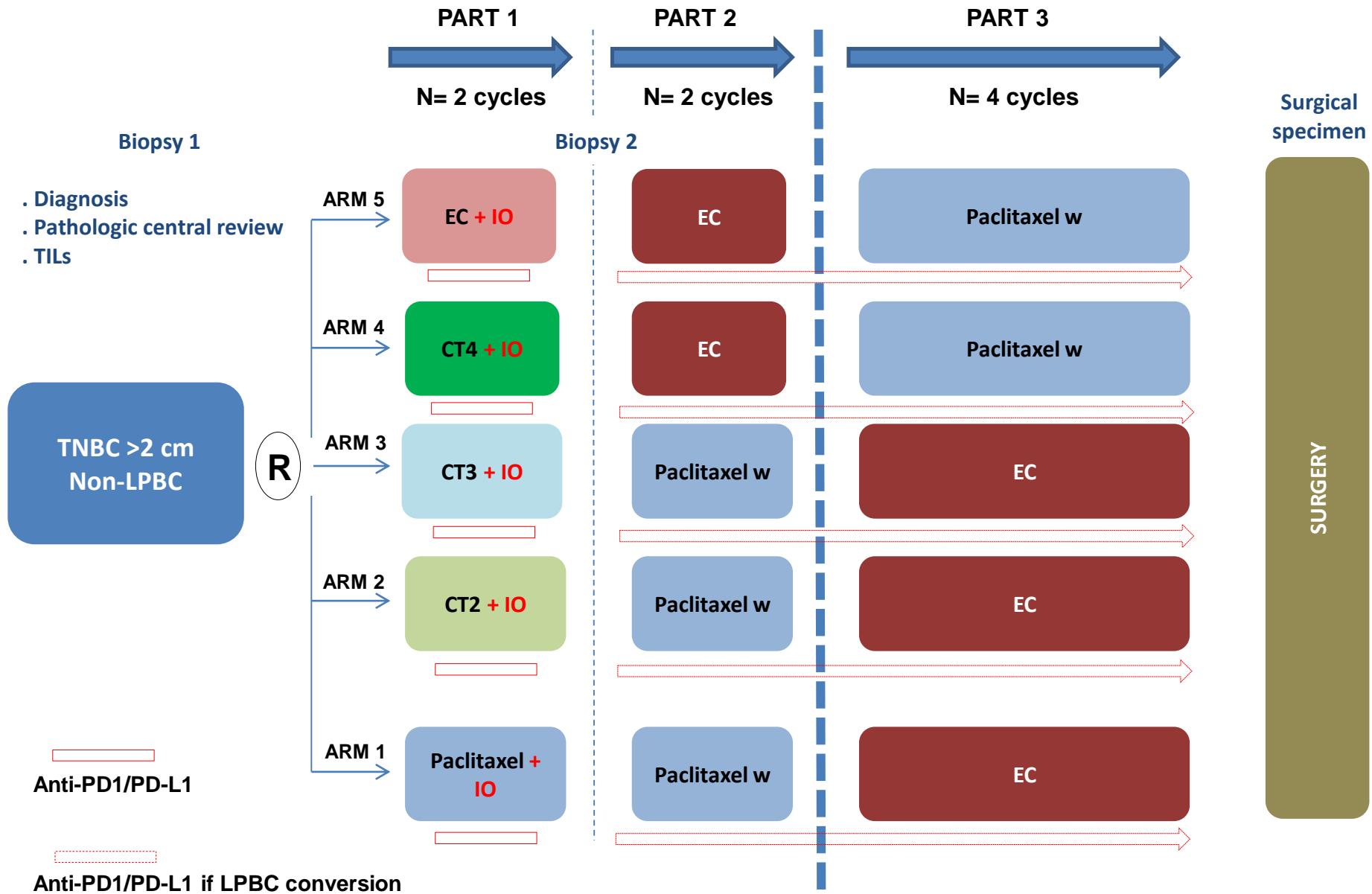


STEP 1: « fertilizing the immune soil » with chemotherapy for anti-PD-L1 efficacy

STEP 2: « reinvigorate host immune response » with *anti PD-L1* after immunosuppressive removal and T cell priming



« PIWI- combo »



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