ESMO 2012 – MONDAY OCTOBER 1st
Special symposium. Melanoma therapy: from frustration to enthusiasm

Chemotherapy and immunity : Friends or Foes?

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Immunostimulatory effects of conventional anti-cancer therapies

- **Dacarbazine Promotes Stromal Remodeling and Lymphocyte Infiltration in Cutaneous Melanoma Lesions**

  Alessandra Nardin[1], Wing-Cheong Wong[2], Charlene Tow[1], Thierry Jo Molina[3,8], Frédérique Tissier[4,5,6,8], Anne Audebourg[4], Marylene Garcette[5,6], Anne Caignard[5,6], Marie-Francoise Avril[5,6,7], Jean-Pierre Abastado[1,9] and Armelle Prévost-Blondel[5,6,9]

- **Dacarbazine Treatment before Peptide Vaccination Enlarges T-Cell Repertoire Diversity of Melan-A –Specific, Tumor-Reactive CTL in Melanoma Patients**

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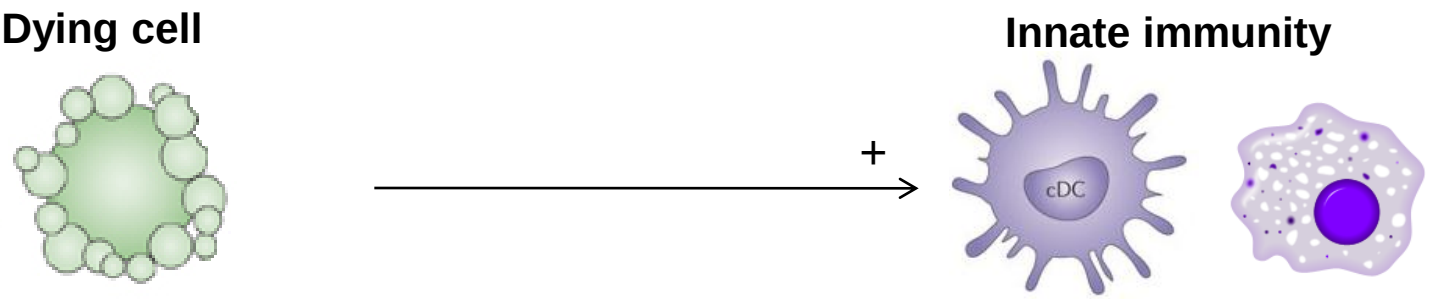
- **Chemotherapy Induces Intratumoral Expression of Chemokines in Cutaneous Melanoma, Favoring T-cell Infiltration and Tumor Control**

  Michelle Hong, Anne-Laure Puaux, Caleb Huang, et al.

  Cancer Res 2011;71:6997-7009. Published OnlineFirst September 26, 2011.

Endogenous danger signals that can lead to activation of innate immunity

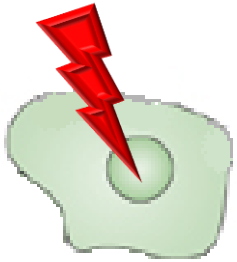


Endogenous danger signals *Damage associated molecular pattern*		PRR
HMGB1, HSP	↔	TLR-2, -4
DNA	↔	TLR-9
RNA	↔	TLR-3
ATP, uric acid	↔	**NLRP3**
SAP130	↔	CLEC4A

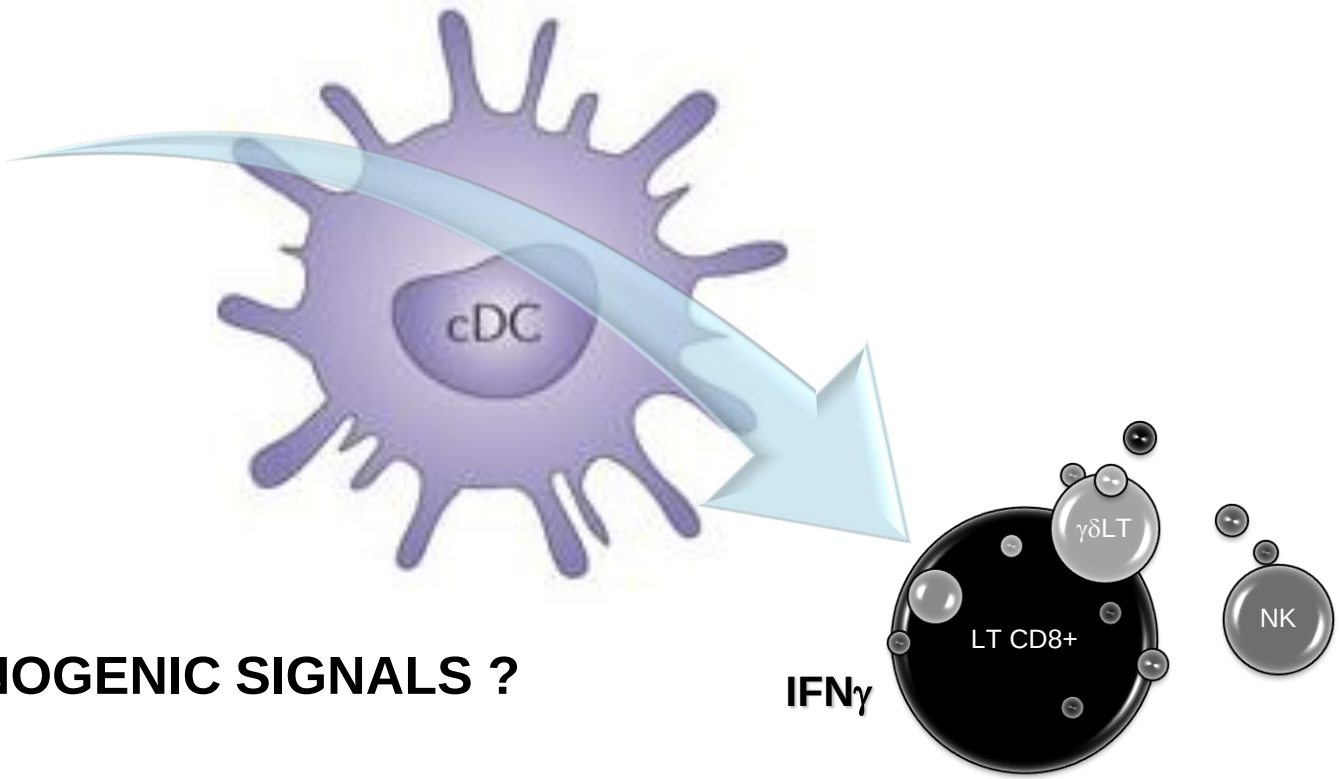
From Chen GY, Nat Rev Immunol, 2010

Can conventional anticancer treatments lead to immunogenic cell death?

Oxaliplatin, anthracyclins, Radiotherapy



Living tumor cell

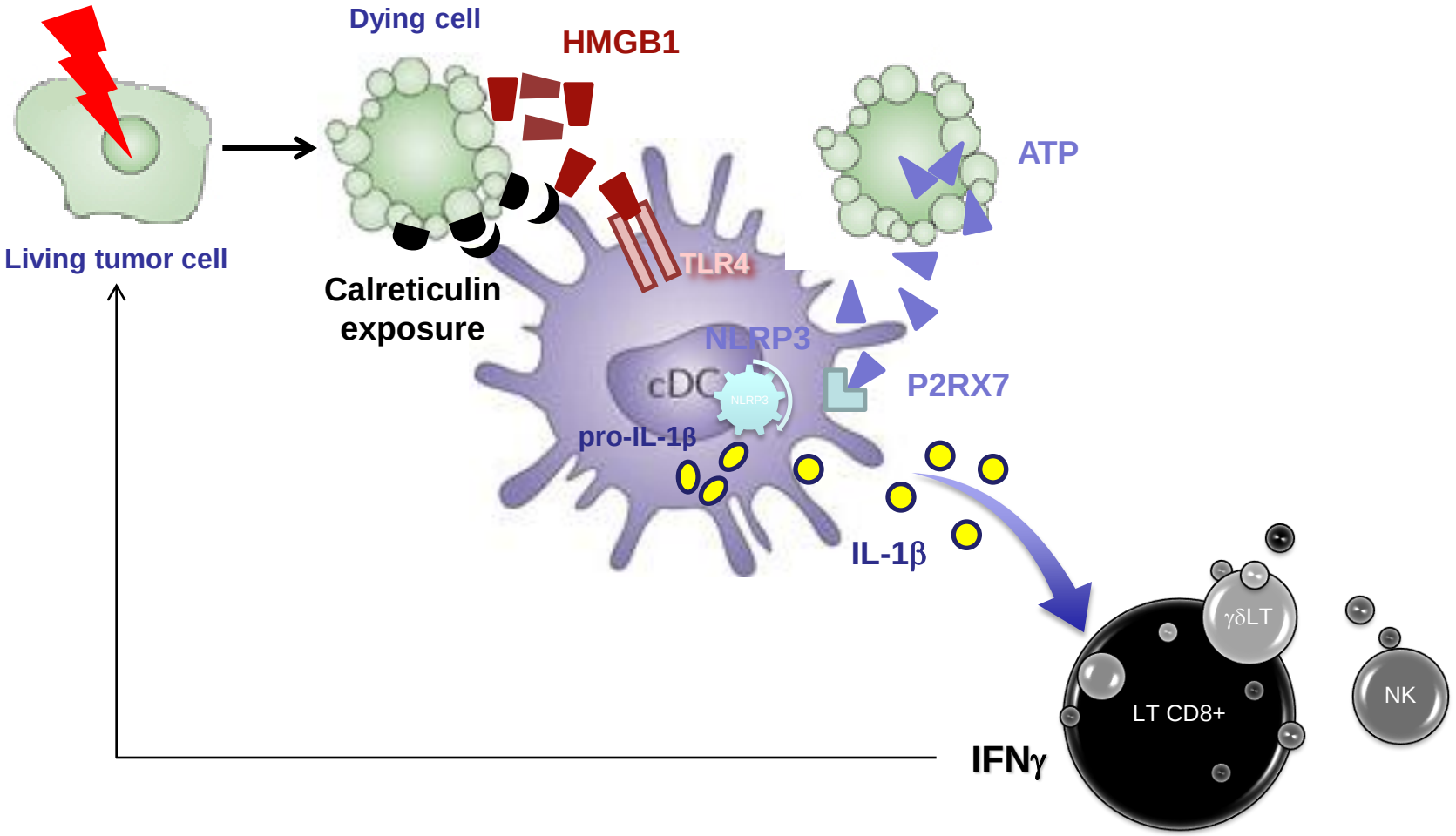


IMMUNOGENIC SIGNALS ?

IFNγ

Molecular events leading to immunogenic cell death

Oxaliplatin, anthracyclins, Radiotherapy



Calreticulin exposure dictates the immunogenicity of cancer cell death

VOLUME 13 | NUMBER 1 | JANUARY 2007 NATURE MEDICINE

Toll-like receptor 4–dependent contribution of the immune system to anticancer chemotherapy and radiotherapy

NATURE MEDICINE VOLUME 13 | NUMBER 9 | SEPTEMBER 2007

Activation of the NLRP3 inflammasome in dendritic cells induces IL-1β–dependent adaptive immunity against tumors

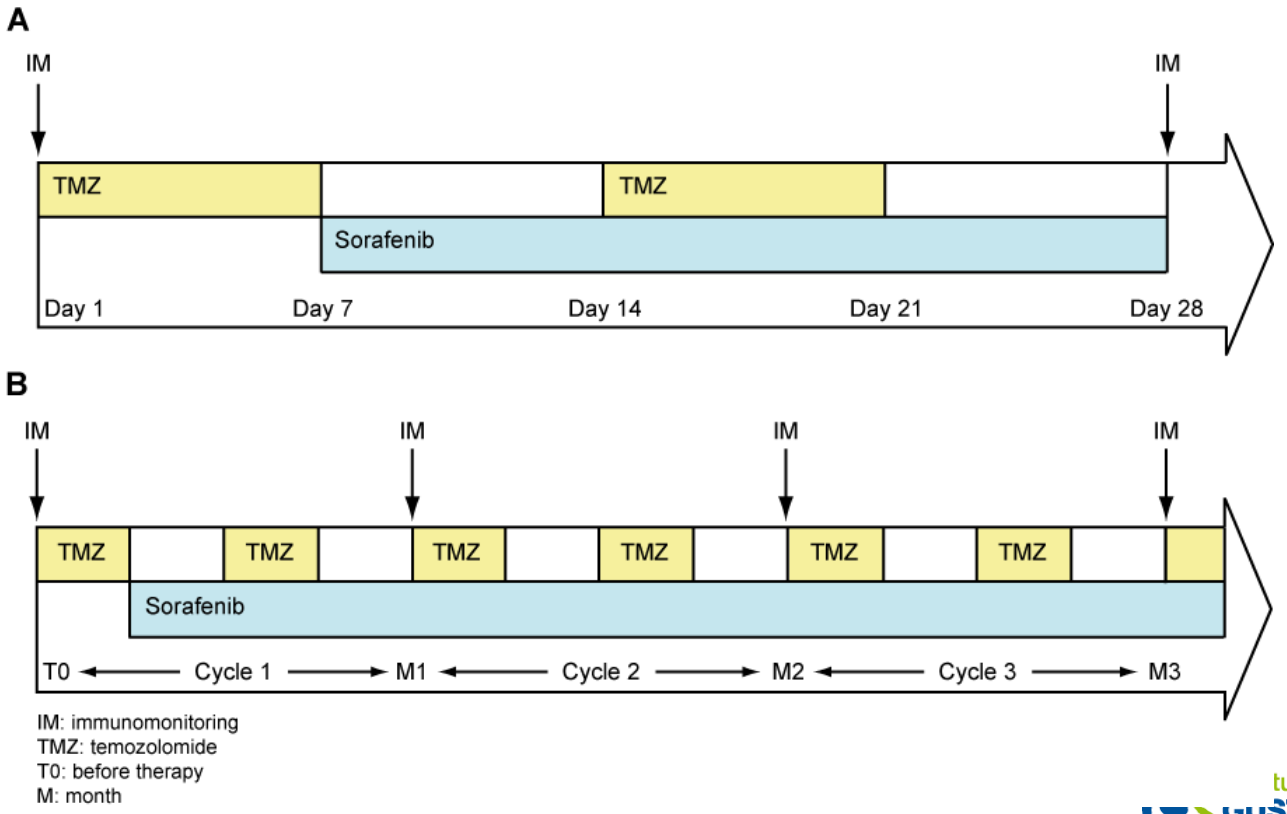
VOLUME 15 | NUMBER 10 | OCTOBER 2009 NATURE MEDICINE

Apetoh, Nat Med 2007

Temozolomide and sorafenib combination in advanced melanoma patients

Schema of IGR Phase II Trial: Dr Caroline ROBERT, 2006-2009

European Union Drug Regulating Authorities clinical trial EudraCT 2007-000527-18

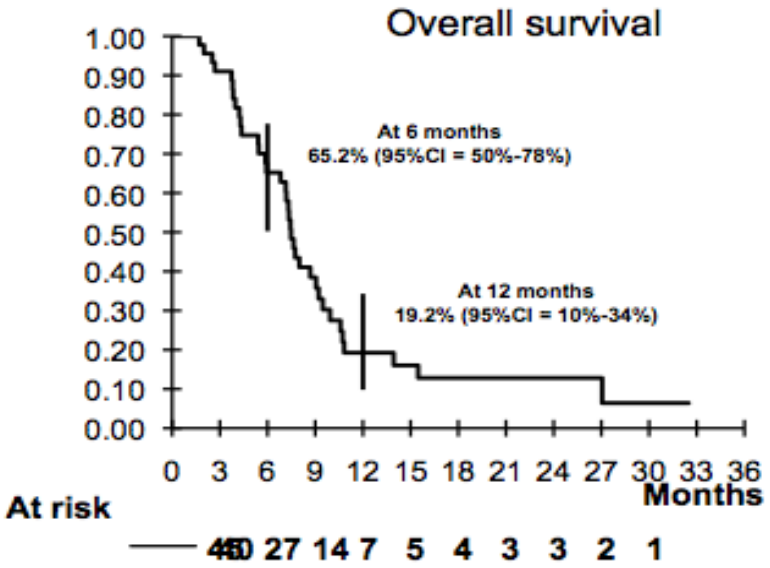


Patients characteristics

Table 1. Characteristics of Patients (n=45)

Gender (male/female)	24/21
Age (mean ± SD)	48.6 ± 13.8 [22-75]
Type	
SSM [1]	12
Nodular	8
Lentigo maligna	1
Acral lentiginuous	2
Mucous	6
Ophtalmologique	4
Other	12
Metastasis (n=43)	
Number of metastases lesions per patient (mean ± SD)	5.1 ± 2.0 [1-10]
Metastatic sites	
Nodes	40
Liver	11
Lung	22
Peritoneum	8
Skin	19
Bone	7
Muscle	4
LDH level U/l (mean)	288.3 U/l
LDH < 250 U/L	25
LDH > 250 U/L	15
ND	5
Treatment schedule	
sorafenib 400 mg/j, temozolomide 100 mg/m^2	3
sorafenib 400 mg/j, temozolomide 150 mg/m^2	5
sorafenib 800 mg/j, temozolomide 150 mg/m^2	37
Previous chemotherapy	
No	7
One line	15
Two lines	15
Three lines	7
Four lines	1
3-month evaluation	
Objective response or stabilization	18
Progressive disease or death	27

(1) SSM: Spreading Superficial Melanoma; ND : Not determined



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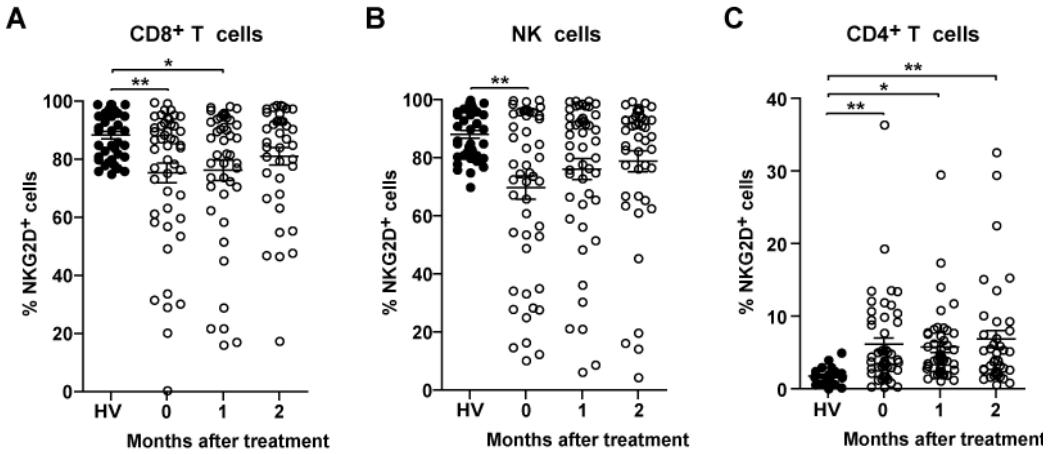
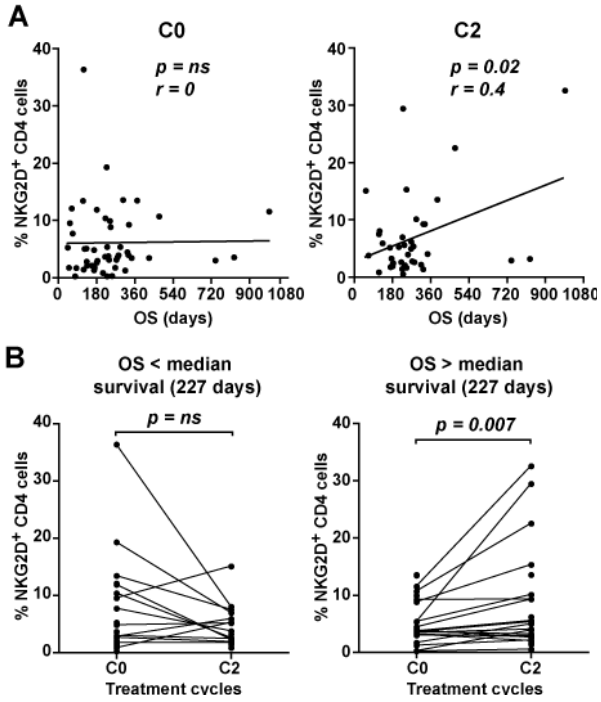
Accumulation of a CD4+ NKG2D+T cell subset in MM patients…





These cells are correlated with OS after two cycle of treatment

Only patients with OS > median survival had an augmentation in the proportion of CD4+NKG2D+ T after treatment.

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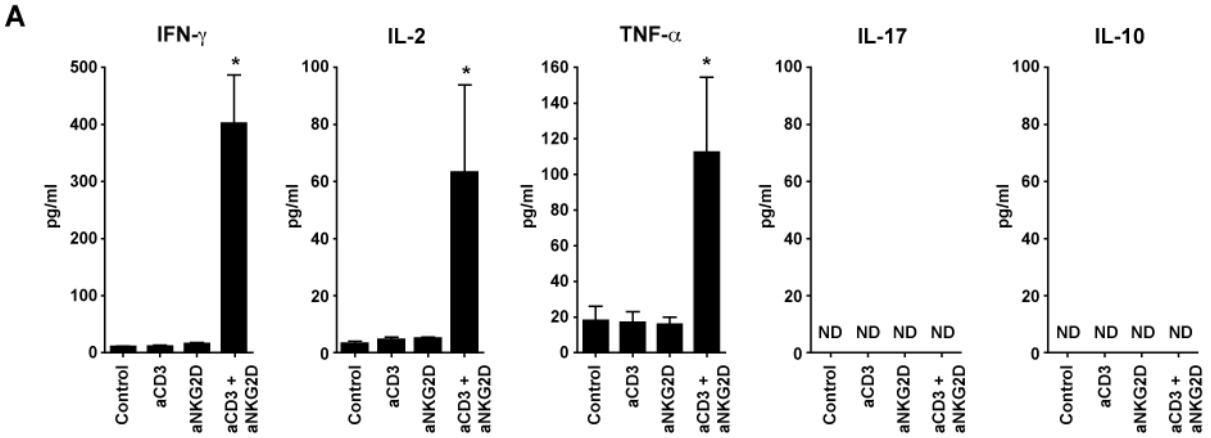
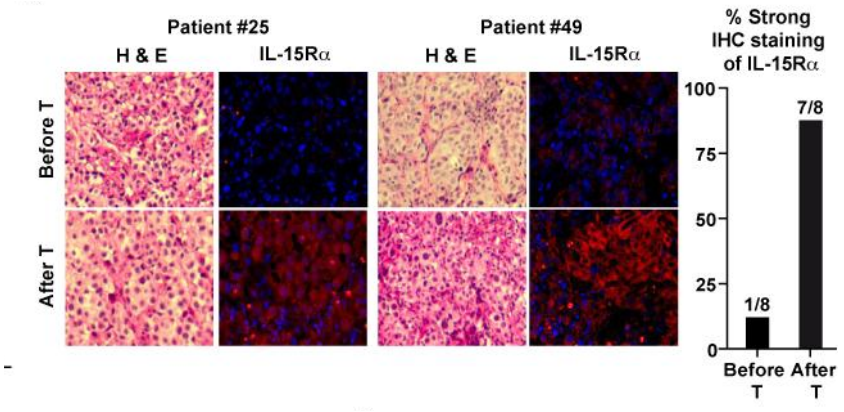
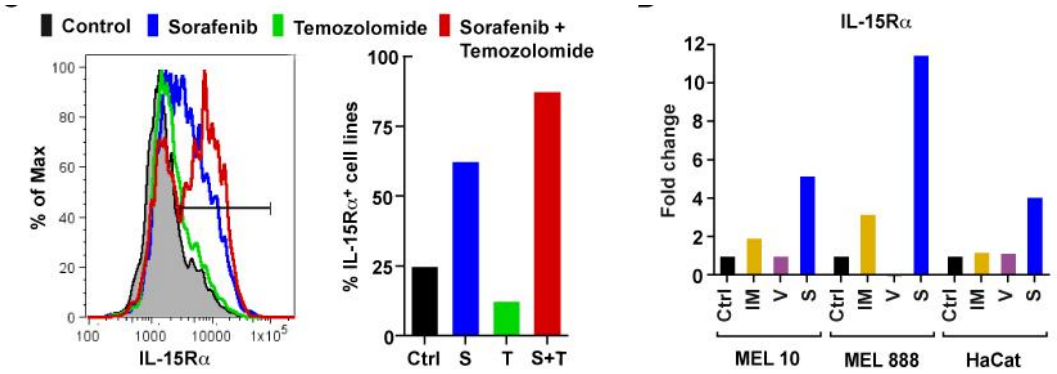
$CD4^+$ $NKG2D^+$ T cells produce Th1 cytokines after stimulation through TCR or CD122 in synergy with NKG2D triggering.



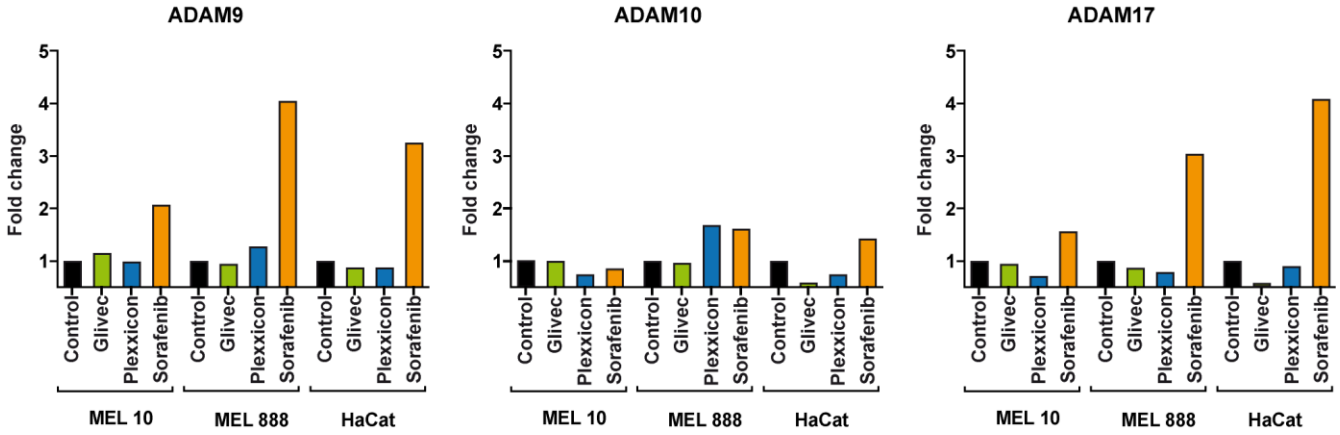
CD4+ NKG2D+ T cells constituted a Th1 polarized T-cell subset with a potential to react in a TCR independent fashion when stimulated by IL-15 along with sMIC.

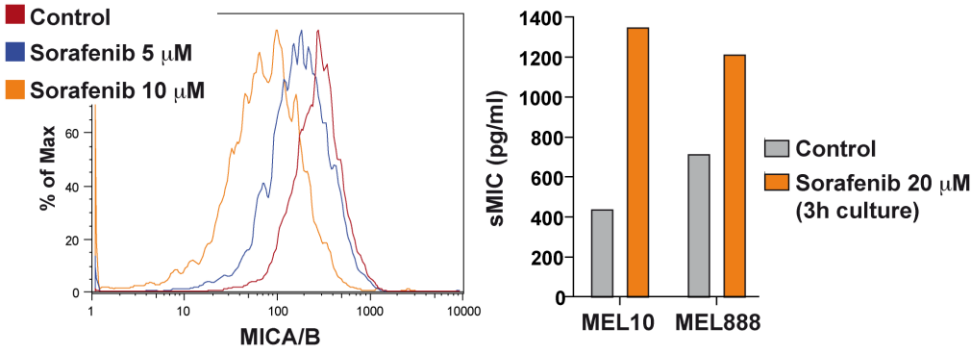
Sorafenib-induced IL-15Ra expression in the tumor

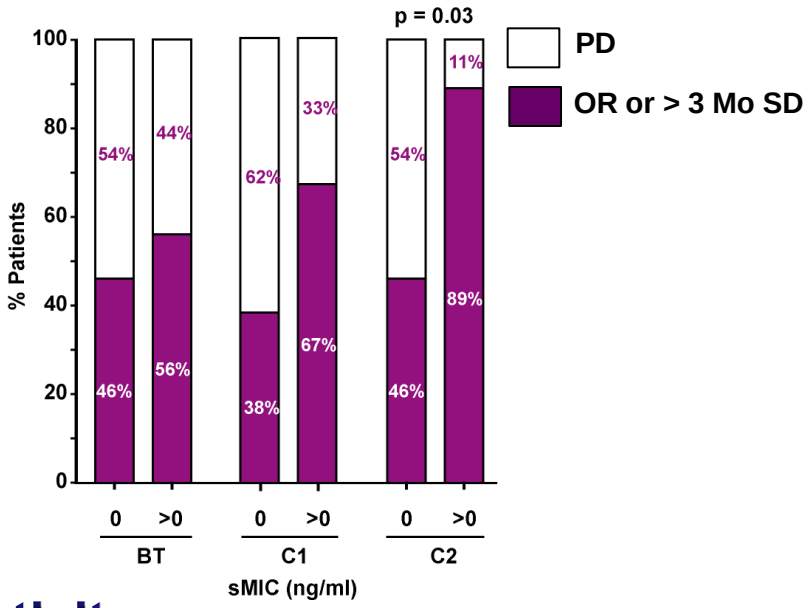




Sorafenib–induced shedding of MICA/B leading to accumulation of sMIC in these MM

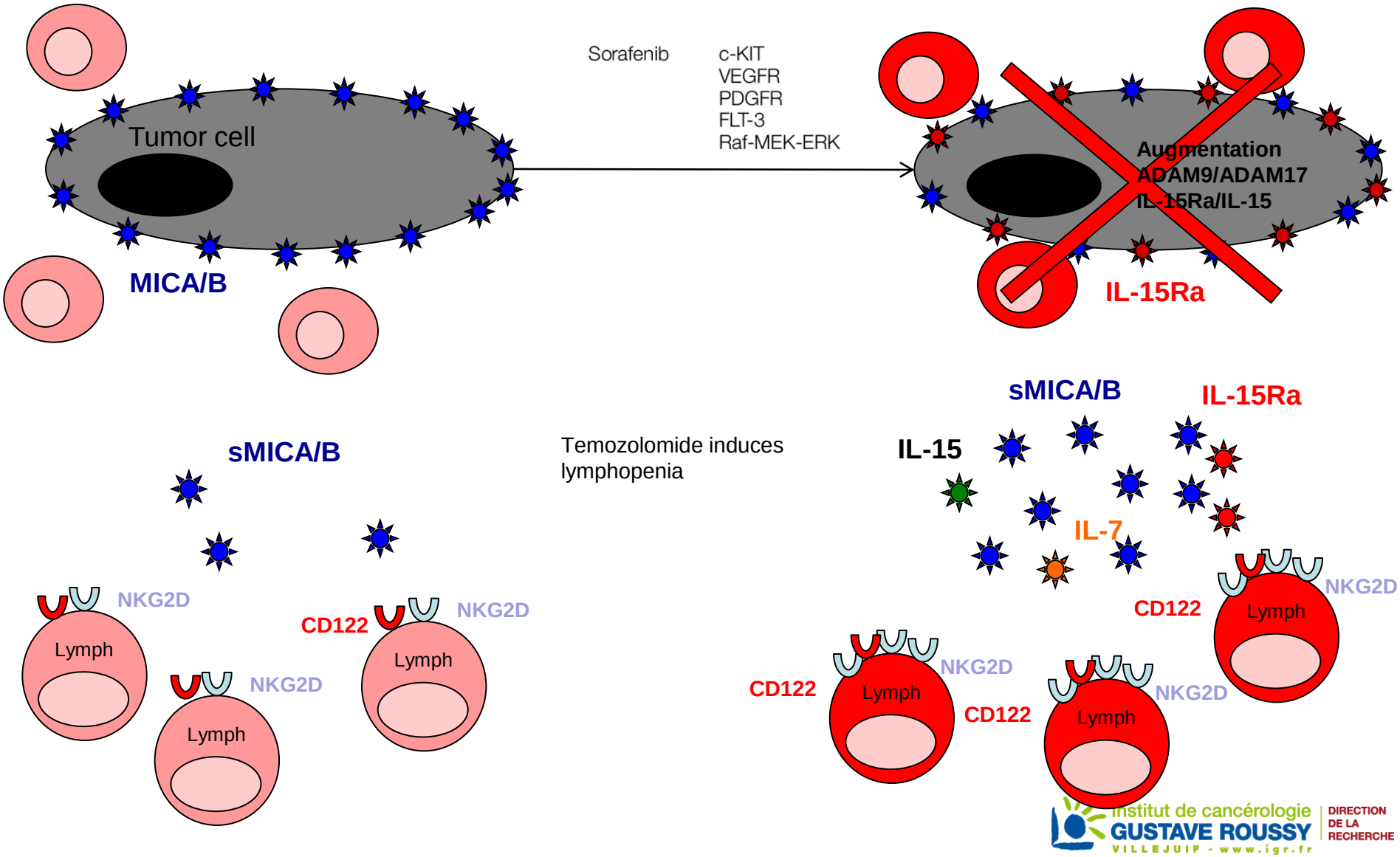




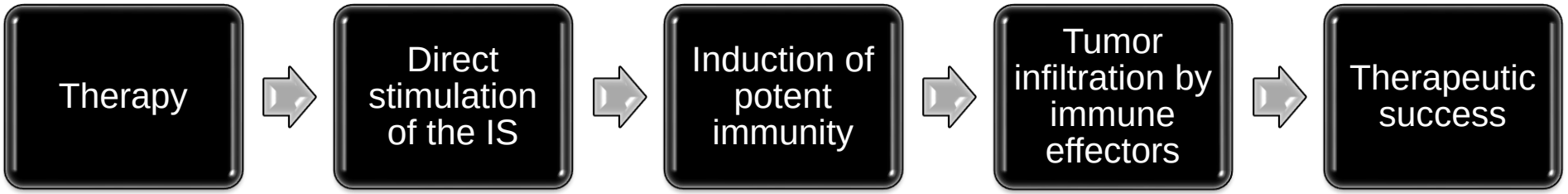


sMIC being associated with clinical activity

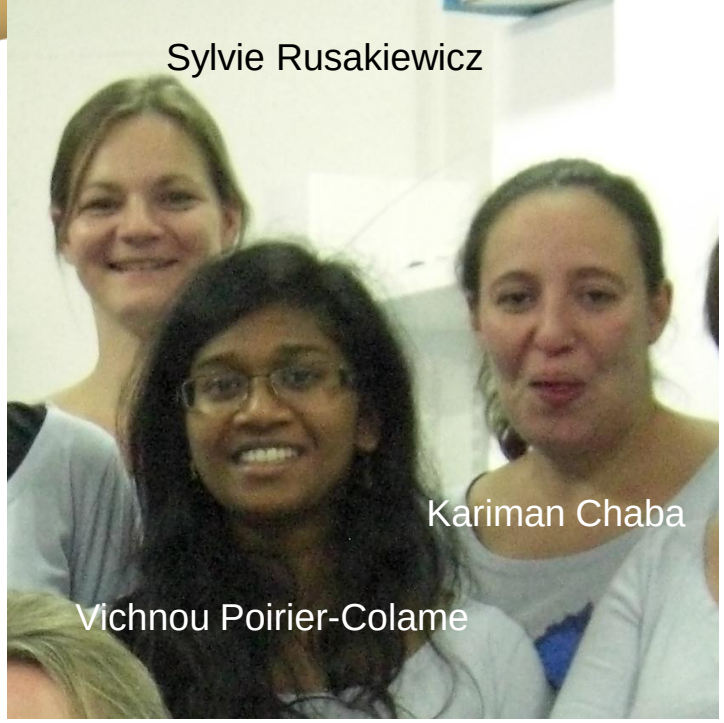
Putative scenario during MM treatment by Sorafenib & Temozolomide



Anti-cancer treatments : A new point of view



A better comprehension of these mechanisms should help to determine which treatment should be combine with immunoregulators and to select groups of patients that could benefit from this chemo/immuno-approaches.



Sophie Caillat Zücman

St Vincent de Paul

Antoine Toubert

Saint Louis

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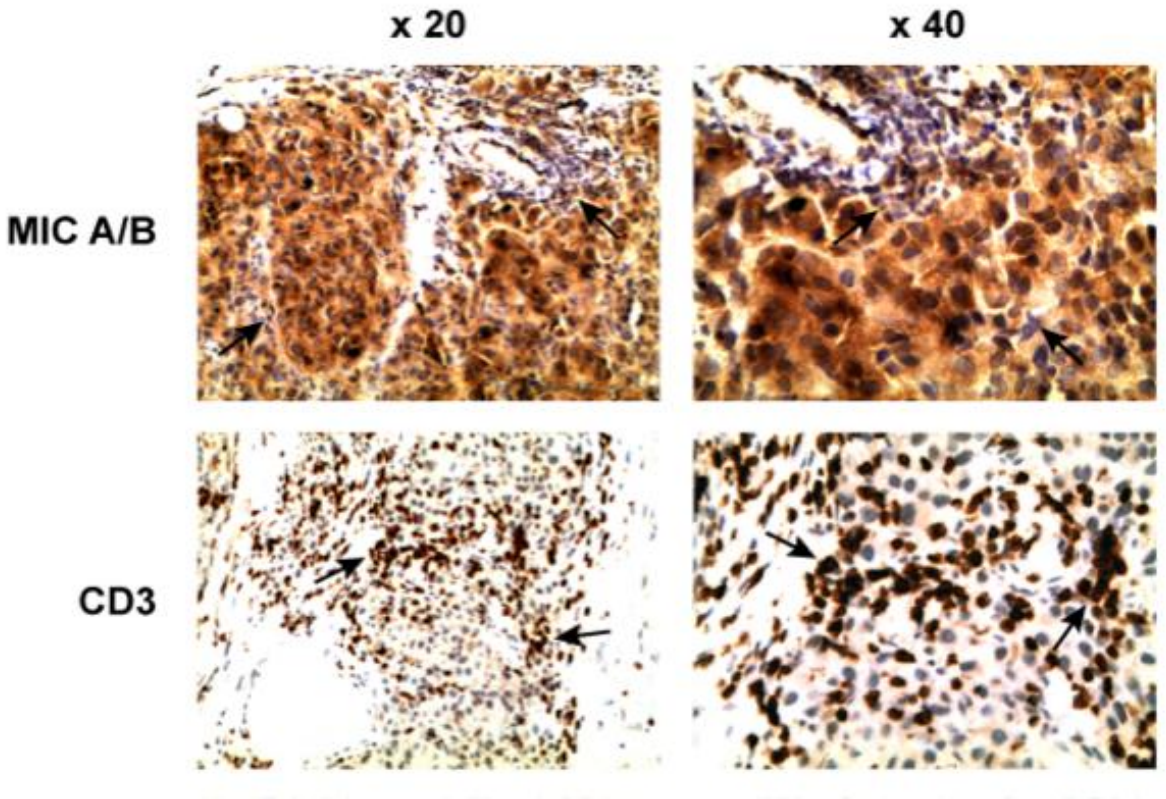
LA LIGUE
101 comités

Immunohistochemistry stainings of melanoma: No significant modulation of T cell infiltrates nor NKG2DL expression with the combo therapy.



	Clinical response	Before therapy				After therapy			
		CD3	CD4	CD8	MICA/B	CD3	CD4	CD8	MICA/B
Nr. 1	SD	++	+/-	++	++	++	+	++	+
Nr. 2	SD	-	-	-	++	-	-	-	+
Nr. 3	SD	++	+	+	+	++	+	+	+
Nr. 4	NR	+	-	+	+	+	-	-	+
Nr. 5	NR	+	-	-	+	+	-	-	+
Nr. 6	NR	+	-	-	++	+	-	-	++
Nr. 7	NR	+	-	++	+	++	-	++	+
Nr. 8	NR	+	-	++	++	+	-	+	++

Can drugs in melanoma treatment lead to immunity?

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