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IFODS 2021 4e Edition

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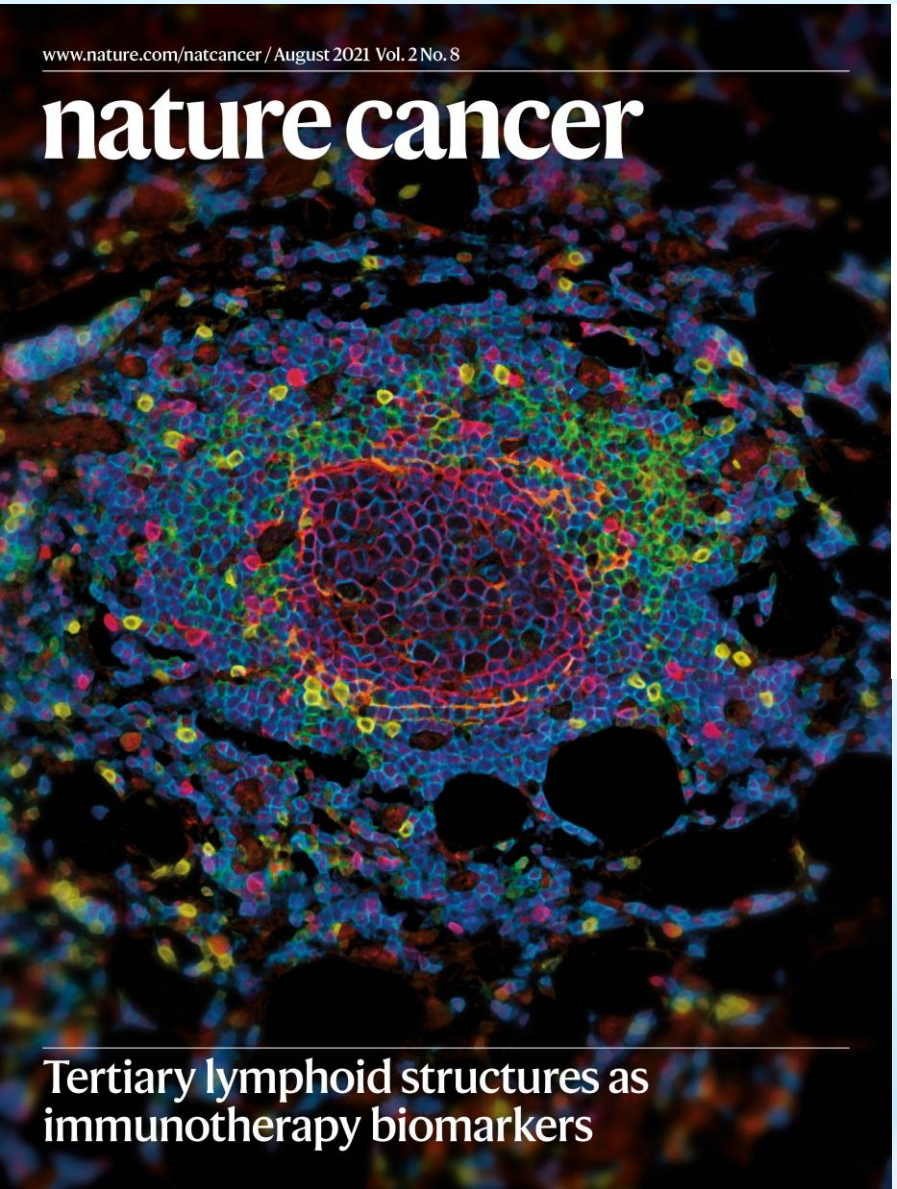


Mature tertiary lymphoid structures predict immune checkpoint inhibitor efficacy in solid tumors independently of PD-L1 expression

Lucile Vanhersecke[1,2,11], Maxime Brunet[2,3,11], Jean-Philippe Guégan[4], Christophe Rey[4], Antoine Bougouin[5], Sophie Cousin[3], Sylvestre Le Moulec[6], Benjamin Besse[7], Yohann Loriot[7], Mathieu Larroquette[2,3], Isabelle Soubeyran[1], Maud Toulmonde[3], Guilhem Roubaud[3], Simon Pernot[3], Mathilde Cabart[3], François Chomy[3], Corentin Lefevre[3], Kevin Bourcier[3], Michèle Kind[8], Ilenia Giglioli[5], Catherine Sautès-Fridman[5], Valérie Velasco[1], Félicie Courgeon[4], Ezoglin Oflazoglu[9], Ariel Savina[9], Aurélien Marabelle[7], Jean-Charles Soria[7], Carine Bellera[10], Casimir Sofeu[10], Alban Bessede[4,11], Wolf H. Fridman[5,11], François Le Loarer[1,2,11] and Antoine Italiano[2,3,7,11] ✉

Lucile VANHERSECKE

Sous la direction du Pr François LE LOARER et du Pr Antoine ITALIANO

Introduction

Biomarqueurs et Inhibiteurs de Checkpoint Immunitaire (ICI) : PD-L1, TILs, LT, …

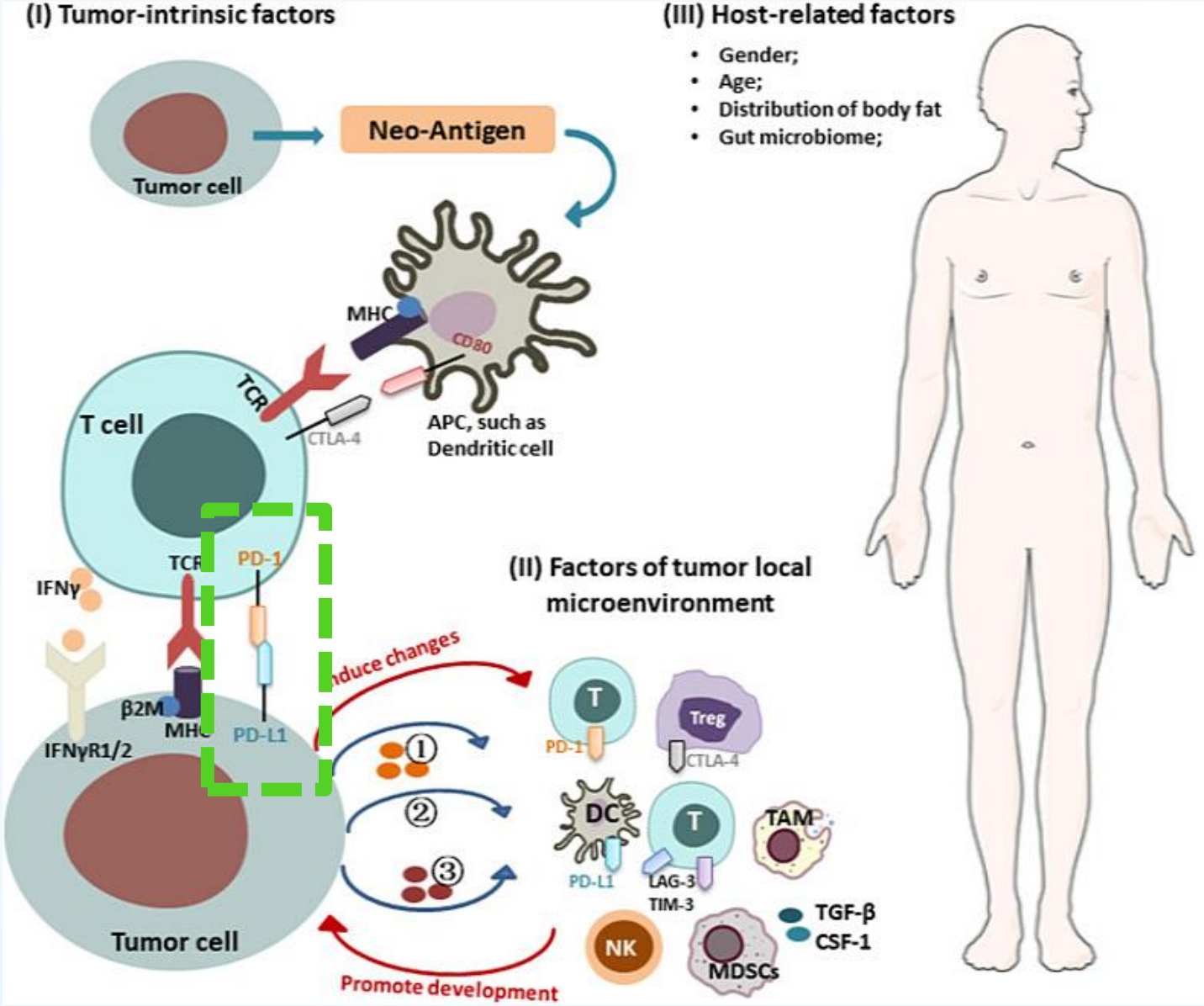
PD-L1

Evalué par **immunohistochimie (IHC)**

Résultats **divergents**

Hétérogénéité : seuils, clones, type de cancer

Disparité d'expression de PD-L1
→ entre différents sites anatomiques d'un patient
→ entre tumeur primitive et métastase / récidive
→ suite à un traitement antitumoral



Bai R, Chen N, Li L, Du N, Bai L, Lv Z, et al. Mechanisms of Cancer Resistance to Immunotherapy. Front Oncol, 6 août 2020;10.

Introduction

Biomarqueurs et Inhibiteurs de Checkpoint Immunitaire (ICI) : PD-L1, TILs, LT, … et LB ?

Article

B cells are associated with survival and immunotherapy response in sarcoma

https://doi.org/10.1038/s41586-019-1906-8
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Florent Petitprez[1,2,3,4], Aurélien de Reyniès[4,24], Emily Z. Keung[5,24], Tom Wei-Wu Chen[6,7,8,9], Cheng-Ming Sun[1,2,3], Julien Calderaro[1,10,11], Yung-Ming Jeng[9,12], Li-Ping Hsiao[7], Laetitia Lacroix[1,2,3], Antoine Bougoüin[1,2,3], Marco Moreira[1,2,3], Guillaume Lacroix[1,2,3], Ivo Natario[1,2,3], Julien Adam[13], Carlo Lucchesi[14,15], Yec'han Laizet[14,15], Maud Toulmonde[14,16], Melissa A. Burgess[17], Vanessa Bolejack[18], Denise Reinke[19], Khalid M. Wani[20], Wei-Lien Wang[20], Alexander J. Lazar[20,21], Christina L. Roland[5], Jennifer A. Wargo[5,21], Antoine Italiano[14,16,22], Catherine Sautès-Fridman[1,2,3], Hussein A. Tawbi[23]* & Wolf H. Fridman[1,2,3]*

Article

Tertiary lymphoid structures improve immunotherapy and survival in melanoma

https://doi.org/10.1038/s41586-019-1914-8
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Published online: 15 January 2020

Rita Cabrita[1,12], Martin Lauss[1,12], Adriana Sanna[1], Marco Donia[2], Mathilde Skaarup Larsen[3], Shamik Mitra[1], Iva Johansson[1], Bengt Phung[1], Katja Harbst[1], Johan Vallon-Christersson[1], Alison van Schoiack[4], Kristina Lövgren[1], Sarah Warren[4], Karin Jirström[1], Håkan Olsson[1], Kristian Pietras[5], Christian Ingvar[6], Karolin Isaksson[6], Dirk Schadendorf[7], Henrik Schmidt[8], Lars Bastholt[9], Ana Carneiro[1,10], Jennifer A. Wargo[11], Inge Marie Svane[2] & Göran Jönsson[1]*

Article

B cells and tertiary lymphoid structures promote immunotherapy response

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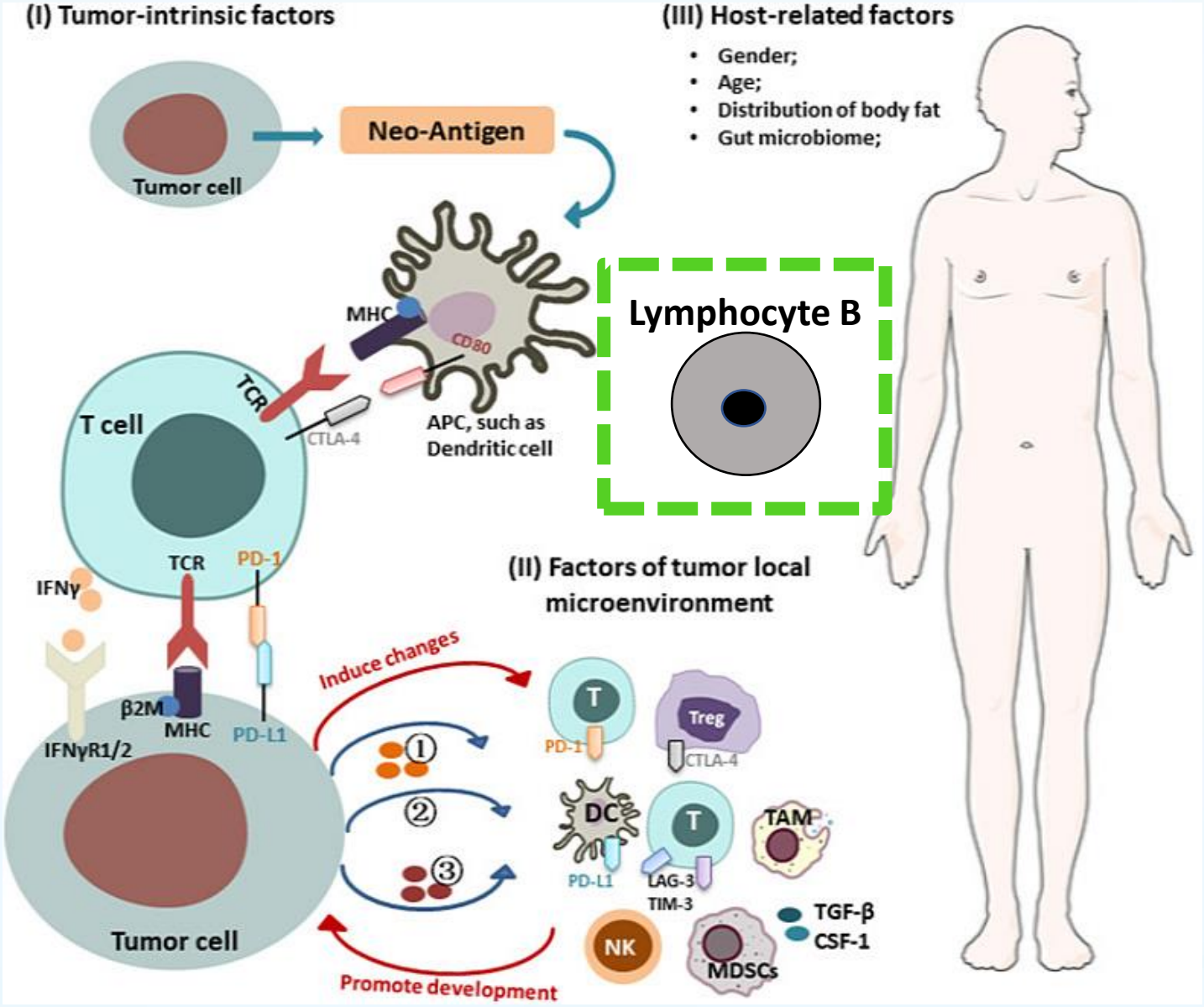
Published online: 15 January 2020

Beth A. Helmink[1,24]*, Sangeetha M. Reddy[2,24], Jianjun Gao[3,24], Shaojun Zhang[4,24], Rafet Basar[5,24], Rohit Thakur[1], Keren Yizhak[6], Moshe Sade-Feldman[6,7], Jorge Blando[8], Guangchun Han[4], Vancheswaran Gopalakrishnan[1], Yuanxin Xi[9], Hao Zhao[8], Rodabe N. Amaria[10], Hussein A. Tawbi[10], Alex P. Cogdill[1], Wenbin Liu[8], Valerie S. LeBleu[11], Fernanda G. Kugeratski[11], Sapna Patel[10], Michael A. Davies[10], Patrick Hwu[10], Jeffrey E. Lee[1], Jeffrey E. Gershenwald[1], Anthony Lucci[1], Reetakshi Arora[4], Scott Woodman[10], Emily Z. Keung[1], Pierre-Olivier Gaudreau[1], Alexandre Reuben[12], Christine N. Spencer[13], Elizabeth M. Burton[1], Lauren E. Haydu[1], Alexander J. Lazar[4,14,15], Roberta Zapassodi[16], Courtney W. Hudgens[14], Deborah A. Ledesma[14], SuFey Ong[17], Michael Bailey[17], Sarah Warren[17], Disha Rao[18], Oscar Krijgsman[18], Elisa A. Rozeman[18], Daniel Peeper[18], Christian U. Blank[18], Ton N. Schumacher[18], Lisa H. Butterfield[19], Monika A. Zelazowska[20], Kevin M. McBride[20], Raghu Kalluri[11], James Allison[8], Florent Petitprez[21,22,23], Wolf Herman Fridman[21,22], Catherine Sautès-Fridman[21,22], Nir Hacohen[6,7], Katayoun Rezvani[5,25], Padmanee Sharma[3,8,25], Michael T. Tetzlaff[14,15,25], Linghua Wang[4,25] & Jennifer A. Wargo[1,4,25]*



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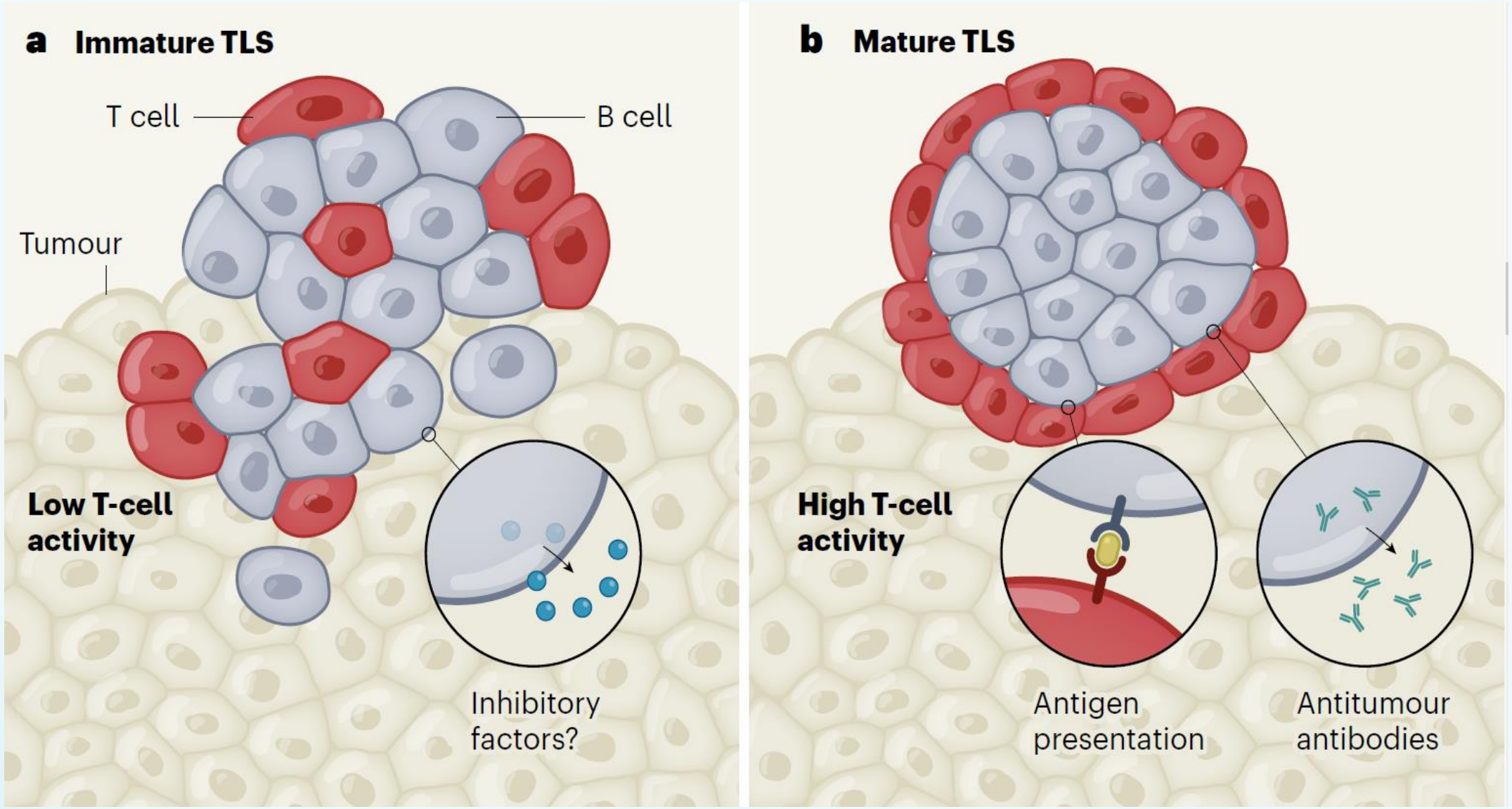
Introduction



Bruno TC. New predictors for immunotherapy responses sharpen our view of the tumour microenvironment. Nature. 23 janv 2020;577(7791):474-6.

Objectif principal

Comparer le **pouvoir prédictif du statut TLS sur la réponse aux inhibiteurs de checkpoint immunitaire**

versus autres marqueurs prédictifs couramment utilisés

(PDL1, infiltrat lymphocytaire T CD8+, TMB)

Matériel et méthodes

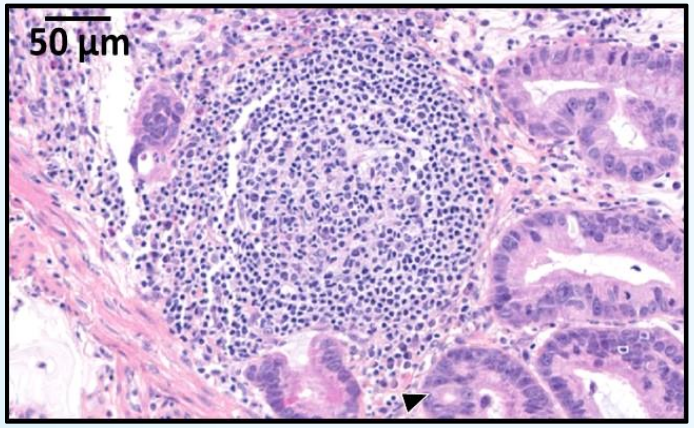
PATIENTS

3 cohortes rétrospectives indépendantes de patients traités par anti-PDL1/anti-PD1

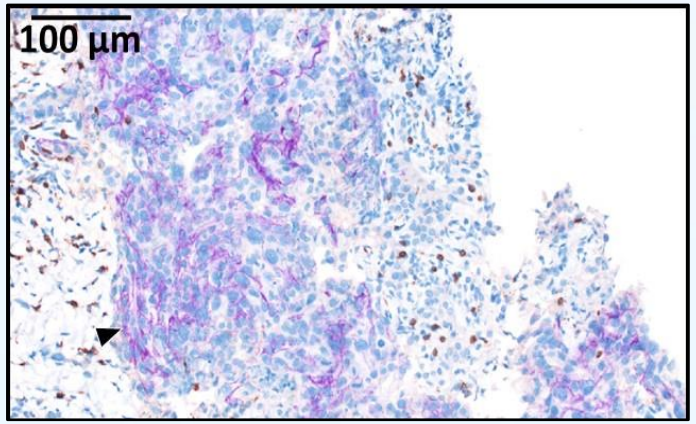
Institut Bergonié (Bordeaux), Clinique Marzet (Pau), Institut Gustave Roussy (Villejuif)

Structures Lymphoïdes Tertiaires (TLS)

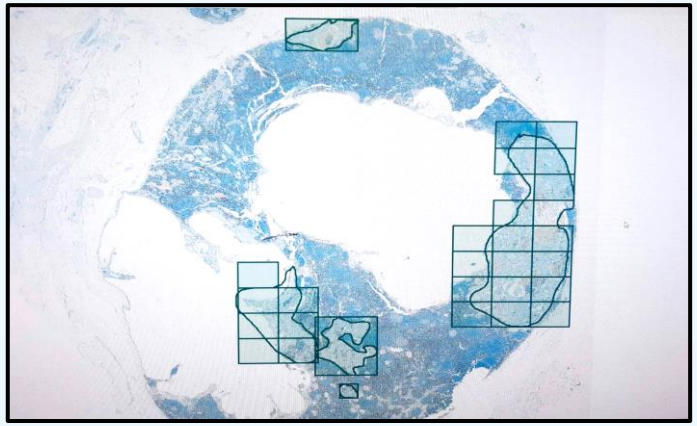
Matures / Immatures



PDL1



Lymphocytes T CD8



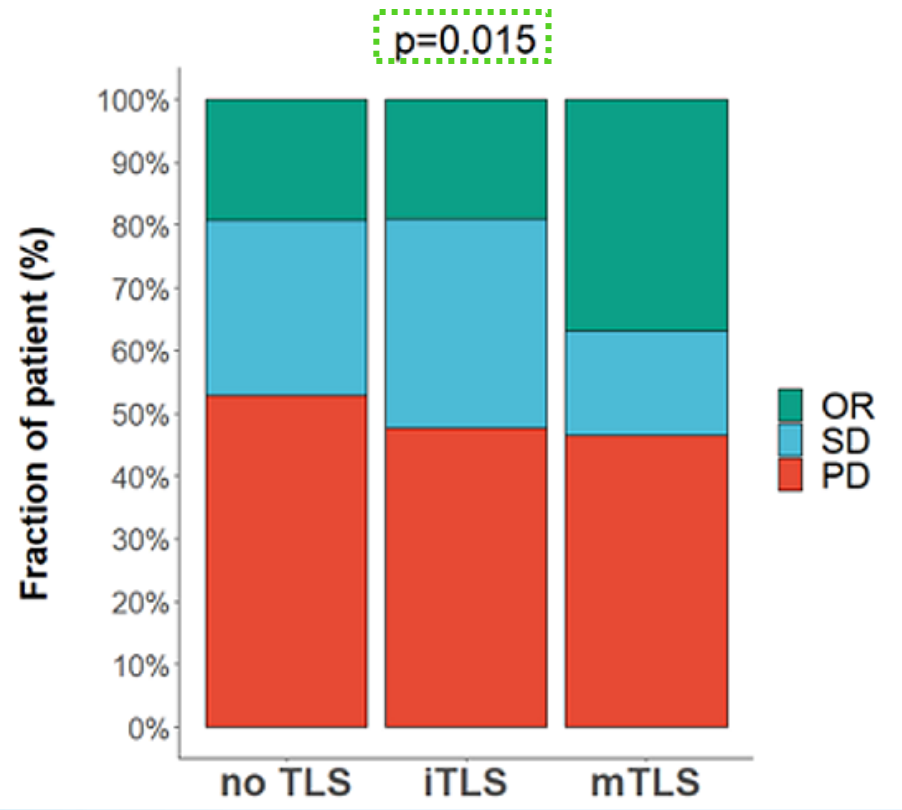
Résultats

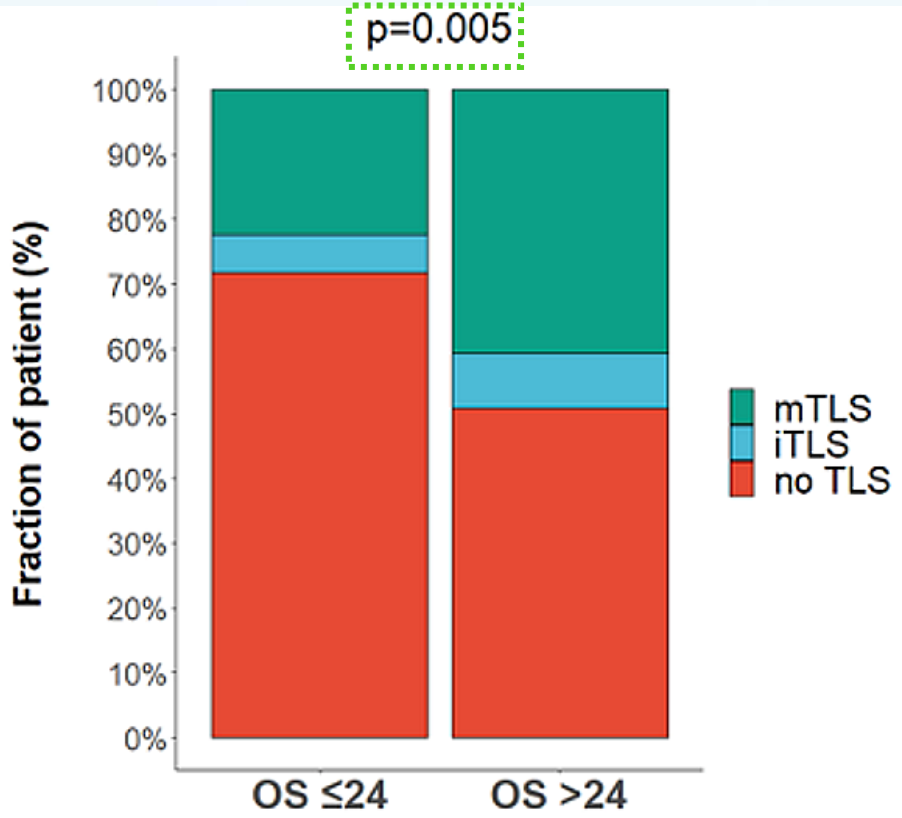
OR :

- **mTLS : 36,9%** (n=31/84)
- iTLS: 19.3% (n=4/21)
- No TLS : 19% (n=43/221)

Survival :

- **Long terme > 24 mois : mTLS 40%**
- Court terme < 24 mois : mTLS 22,4%

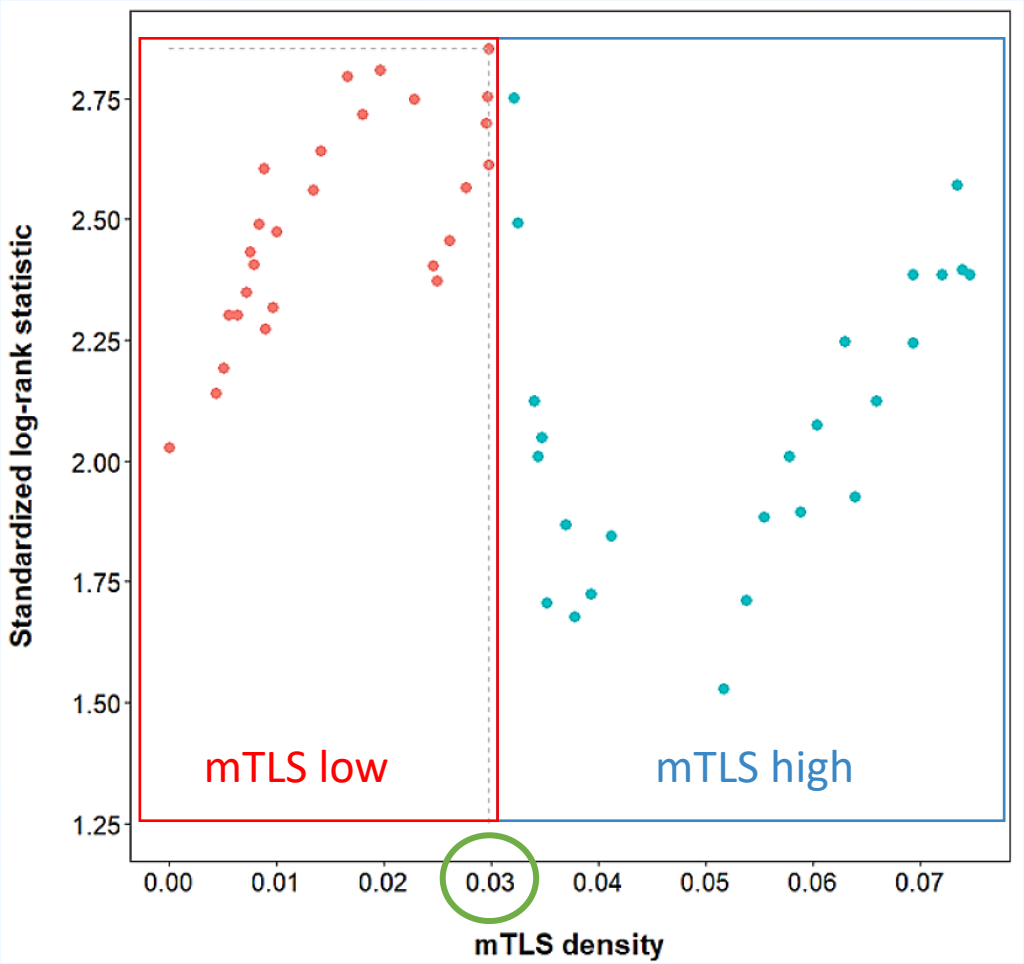




Résultats

mTLS low :

réponse objective = 19,6%



Seuil de stratification

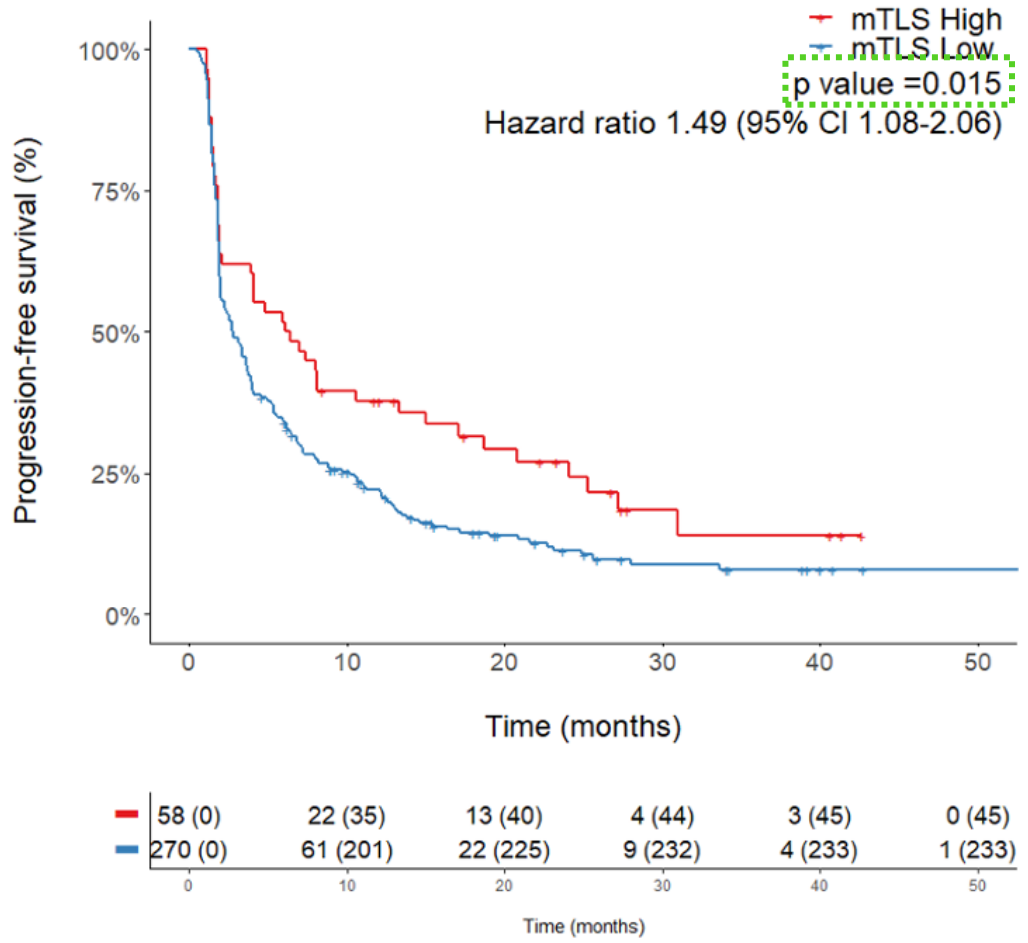
mTLS high :

réponse objective = 43,1%

Résultats

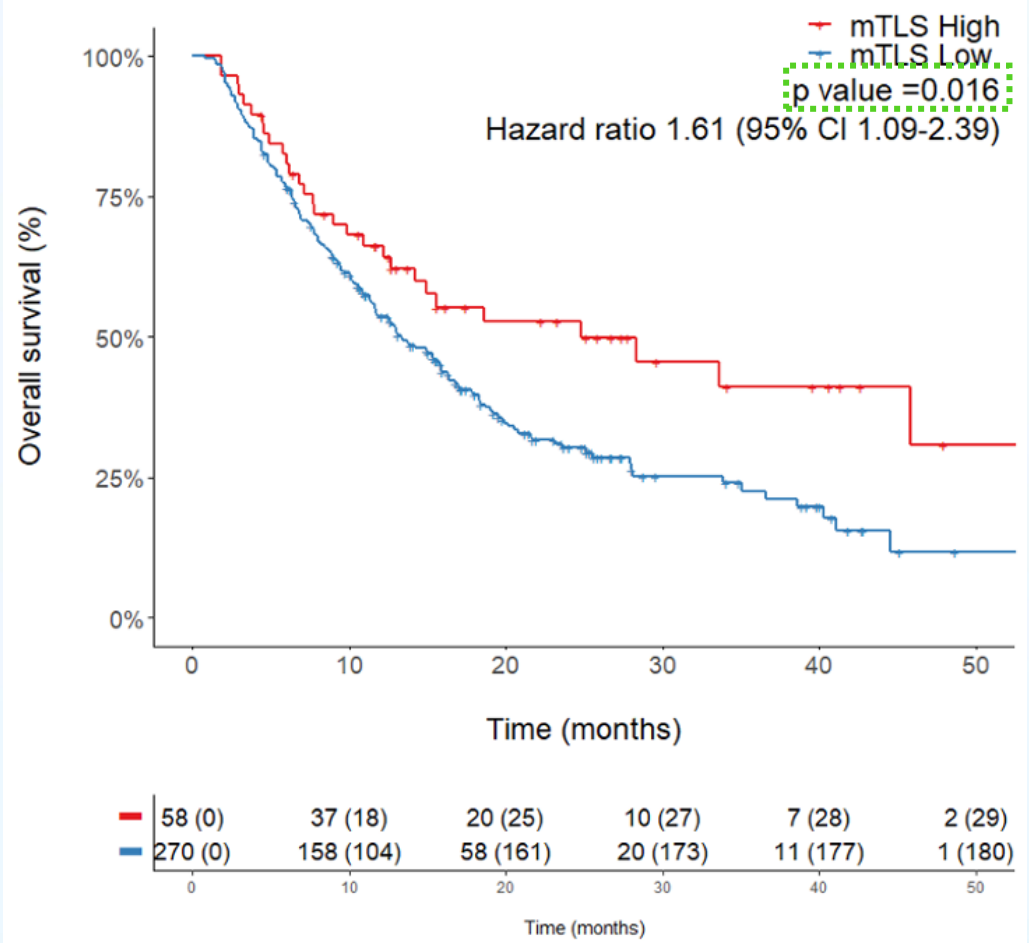
PFS (médiane) :

- **mTLS high : 6,1 mois**
- mTLS low / no mTLS : 2,7 mois



OS (médiane) :

- **mTLS high : 24,8 mois**
- mTLS low / no mTLS : 13,3 mois



Résultats

Analyse multivariée

mTLS = facteur le plus prédictif OR

Variable	Odds ratio (95 % C.I.)	p-value
Performance status		
≤ 1	5.9 (1.2 to 28.2)	0.024
> 1	1 (referent)	
Tumor type		
NSCLC	1 (referent)	0.021
Other	0.49 (0.26 to 0.89)	
TPS code		
< 1	0.41 (0.21 to 0.81)	0.01
≥ 1	1 (referent)	
CD8 density		
Low density	0.39 (0.21 to 0.73)	0.003
High density	1 (referent)	
Presence of mature TLS		
Low density	0.34 (0.17 to 0.67)	<0.0001
High density	1 (referent)	

Résultats

Analyse multivariée

mTLS = valeur prédictive indépendante PFS et OS

Table 3. Univariate and multivariate Cox analyses for progression-free and overall survival

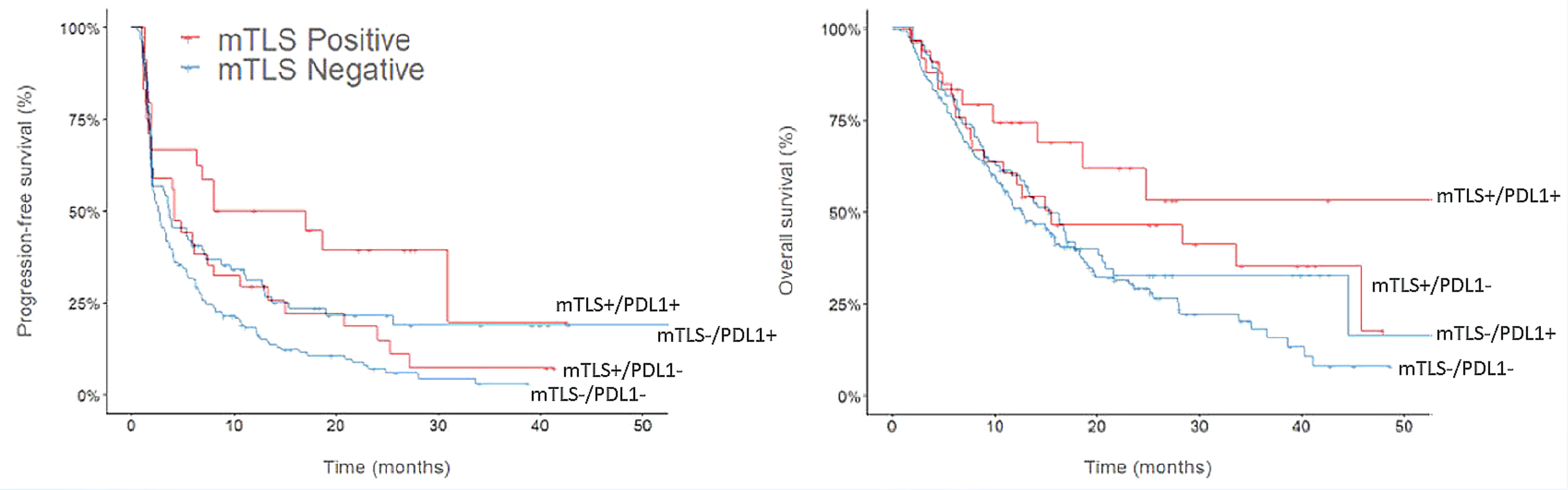
		Univariate analysis for PFS (n=328)			Multivariate analysis for PFS (n=328)		
Variable		Median (Months)	95% CI	*p* value	HR	95% CI	*p* value
Whole population		**3.3**	**[2.5-4.1]**	**-**	-		
Performance status (ECOG)	≤ 1	3.6	[2.9-4.3]	<0.0001	0.4	[0.3-0.6]	<0.0001
	> 1	1.6	[1.1-2.1]		1		
Cancer Type	NSCLC	4	[2.3-5.7]	0.003	-		
	Other	2.6	[1.9-3.3]				
Previous lines of treatment	≤ 1	3.9	[2.9-4.8]	0.003	-		
	> 1	2.5	[1.9-3.1]				
TPS score (%)	< 1	2.7	[1.9-3.5]	<0.0001	1.7	[1.3-2.5]	0.001
	≥ 1	7.0	[1.4-12.6]		1		
CD8 density	Low density	2.7	[1.7-3.6]	0.005	-		
	High density	3.7	[1.9-5.4]				
Presence of mature TLS	Low density	2.7	[1.9-3.5]	0.015	1.4	[1.1-2.0]	0.04
	High density	6.1	[1.9-10.2]		1		

Table 3. Univariate and multivariate Cox analyses for progression-free and overall survival

		Univariate analysis for OS (n=328)			Multivariate analysis for OS (n=328)		
Variable		Median (Months)	95% CI	*p* value	HR	95% CI	*p* value
Whole population		14.9	[12.9-16.9]	-	-		
Performance status	≤ 1	15.6	[12.9-18.3]	<0.0001	0.32	[0.20-0.51]	<0.0001
	> 1	5	[2.1-7.9]		1		
Cancer Type	NSCLC	16.8	[13-20.6]	0.06	-		
	Other	12.9	[10.7-15.1]				
TPS score (%)	< 1	13.1	[10.8-15.4]	0.07	-		
	≥ 1	16.9	[12.8-20.9]				
CD8 density	Low	13.1	[10.2-15.9]	0.18	-		
	High	14.9	[11.9-17.9]				
Presence of mature TLS	Low density	13.3	[11.1-15.5]	0.016	1.5	[1.1-2.3]	0.03
	High density	24.8	[6.8-42.8]		1		

Perspectives

Combinaison mTLS et PD-L1 ?

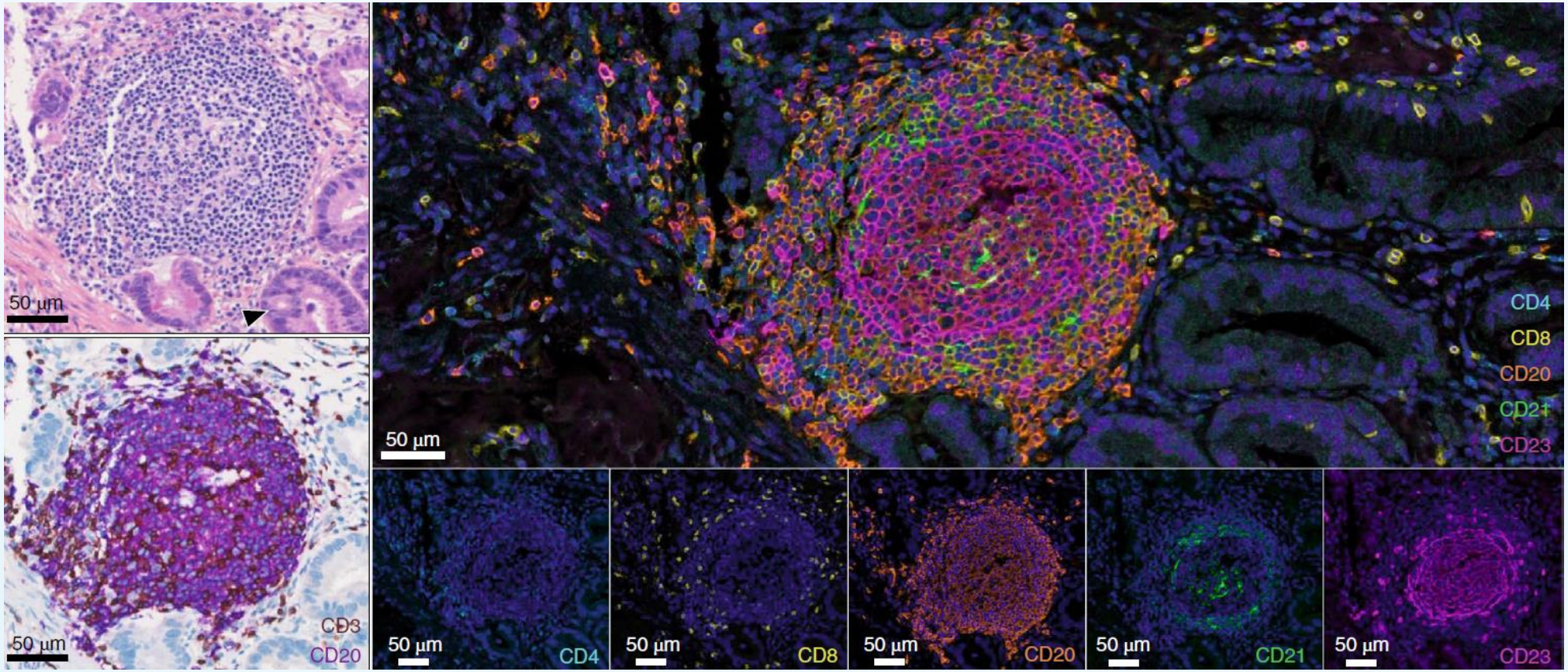


Cyril ADDI, AstraZeneca

Perspectives

Collaboration avec l'**équipe française de l'Institut de Recherche des Cordeliers**

Méthode standardisée de screening des TLS dans les échantillons tumoraux



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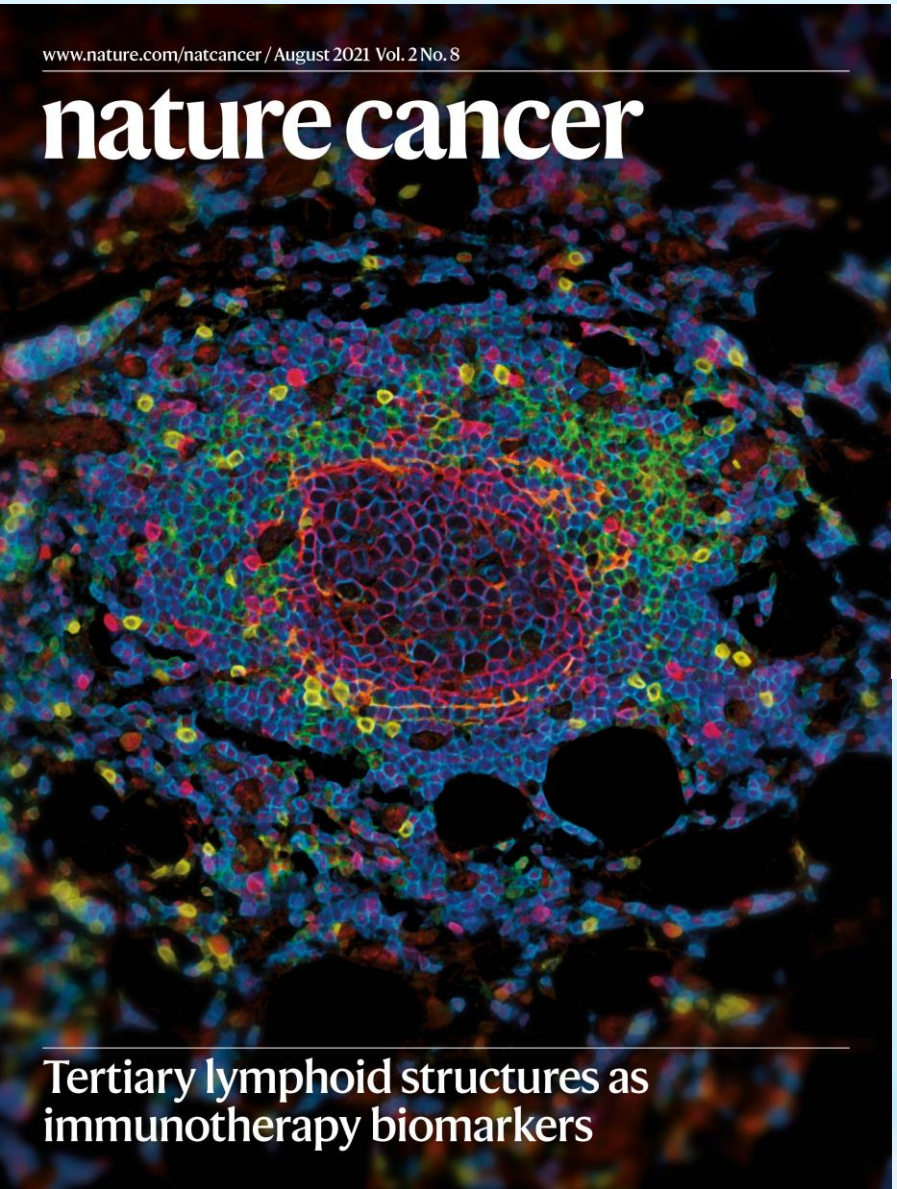

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