

L'IMMUNOTHÉRAPIE POUR LES NULS

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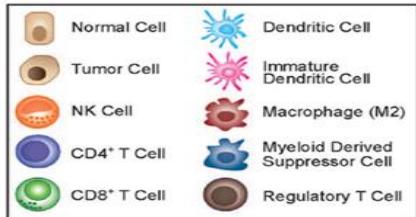
Disclosure of Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments since October 1, 2016, and anything else which could potentially be viewed as a conflict of interest:

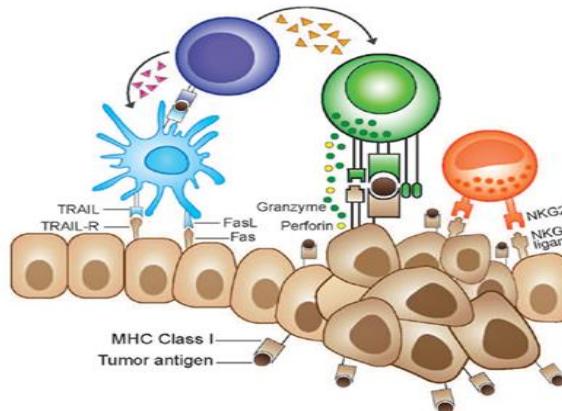
Name of the enterprise // Nature of the interest

Astra-Zeneca	Consulting, Advisory Board
ArQule	Research
Bayer	Advisory Board & Teaching
BMS	Consulting, Advisory Board & Teaching
BTG	Teaching
GenoScience	Research
Ipsen	Consulting, Advisory Board & Teaching
Roche	Research
Sirtex	Consulting, Advisory Board

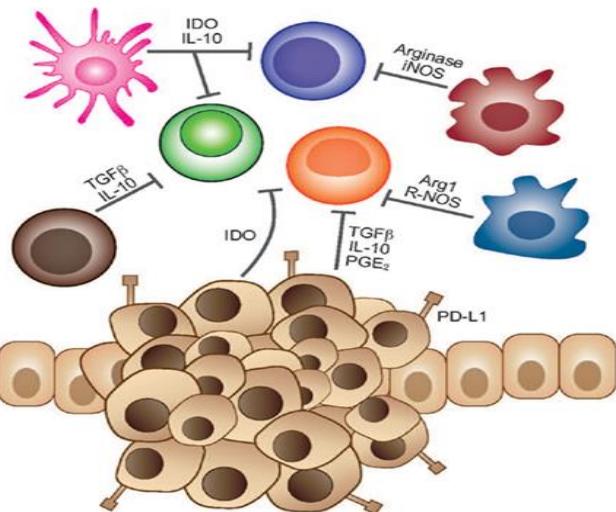
Pourquoi immunothérapie dans le cancer ?



Microenvironnement tumoral



Elimination

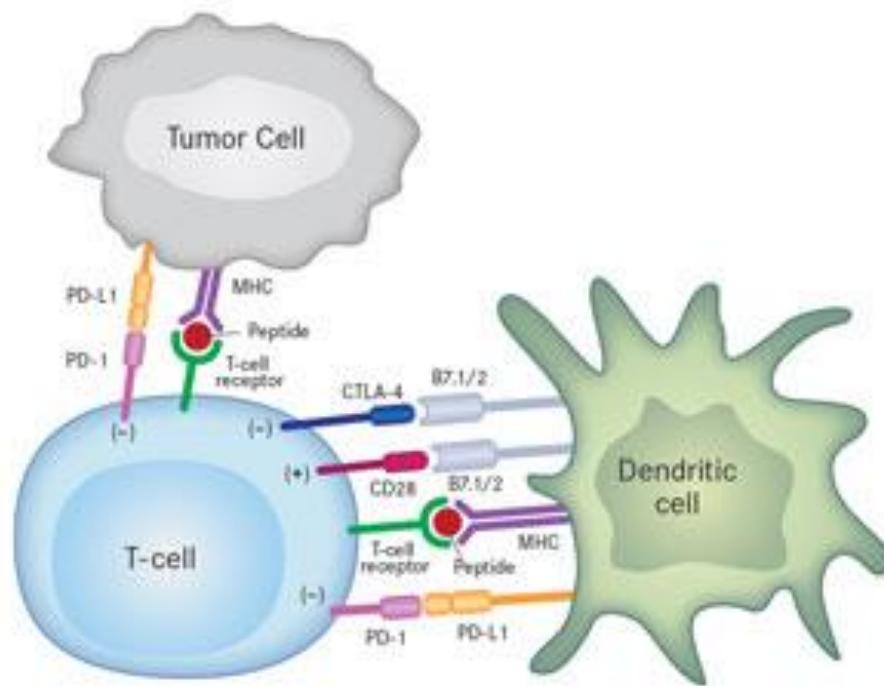


Echappement

Mécanismes d'action de l'immunothérapie

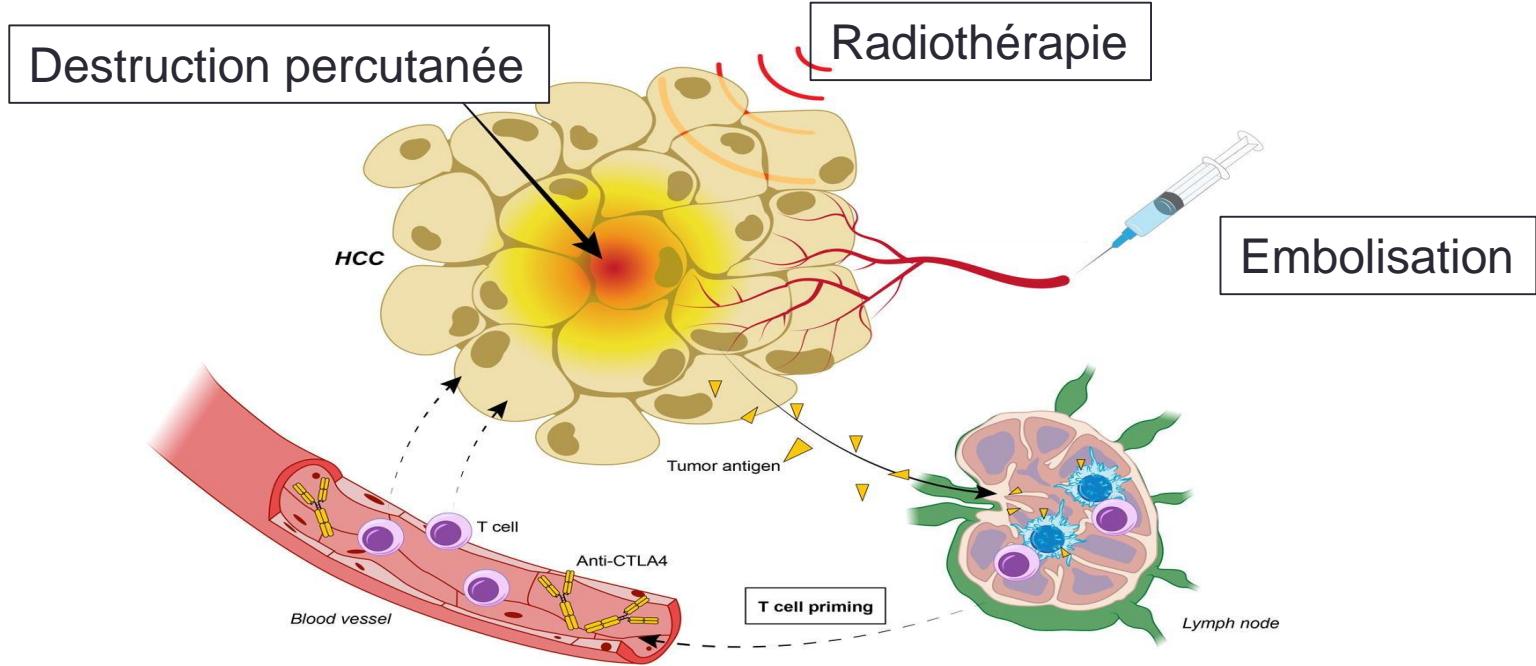
- Restaurer la reconnaissance immunitaire
- Modalités thérapeutiques
 - Vaccins : basés sur les antigènes associés aux tumeurs
 - Cytokines : IFN α , IL-12 intra-tumoral, inhibiteur de TGF- β 1, IL-2
 - Transfert adoptif cellulaire
 - Thérapie génique
 - Inhibition des régulateurs immunitaires (checkpoint = CPI)

Présentation des acteurs



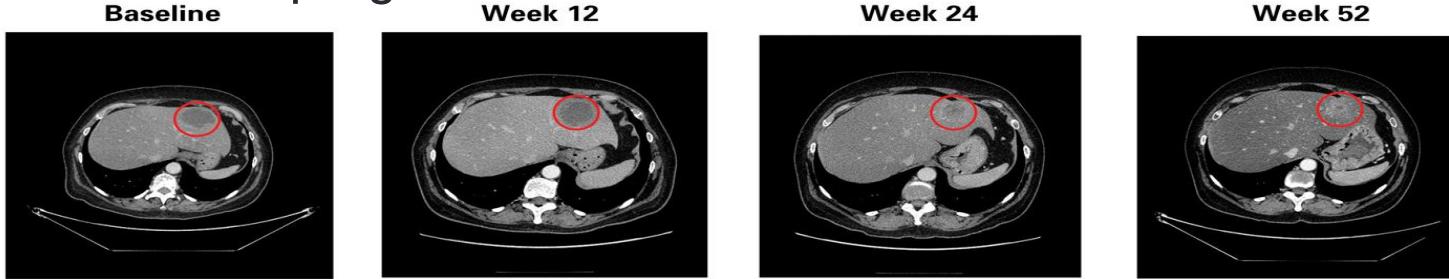
Effet abscopal

- Décrit en 1953 par RH Mole avec radiothérapie
- Destruction localisée d'une maladie étendue permettant une réponse généralisée



Immune-related Response Criteria: irRC

- Pseudo-progression tumorale



Hodi FS et al. J Clin Oncol 2016

- Nouveaux critères radiologiques +++

Variable	RECIST v1.1	irRC
Mesure des cibles	Unidimensionnel	Bidimensionnel
Nombre de cibles	Max 5	Max 15
Nouvelle lésion	Progression	Jusqu'à 10 lésions viscérales et 5 lésions cutanées ajouté aux lésions index
Réponse complète	Disparition de toute lésion	
Réponse partielle	≥30% de diminution / baseline (confirmation)	≥50% de diminution / baseline (confirmation)
Progression	≥20% d'augmentation / NADIR ou apparition de lésion ou progression de lésion non cible	≥25% d'augmentation / baseline ou NADIR, les nouvelles lésions sont associées
Maladie stable	Pas de réponse partielle ou de progression	

Phase 1/2 study with Nivolumab (anti-PD-1)

- Escalation cohort with 48 pts and expansion cohort with 214 pts (262 pts)

Variables	Patients (n = 262)
Age, median (range), years	63 (19–83)
Male, n (%)	207 (79)
Extra-hepatic metastasis, n (%)	198 (76)
Vascular invasion, n (%)	21 (8)
Child-Pugh score, n (%) ^a	
5	191 (73)
6	67 (26)
> 6	4 (2)
α -fetoprotein > 200 μ g/L, n (%) ^b	105 (40)
Previous treatment, n (%)	
Resection	161 (61)
Radiation	51 (19)
Loco-regional treatment	158 (60)
Systemic treatment	196 (75)
Sorafenib	176 (67)

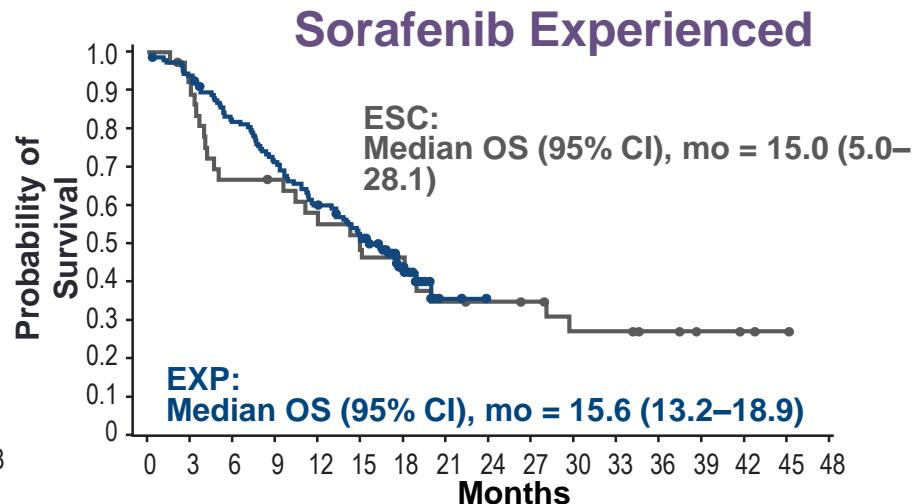
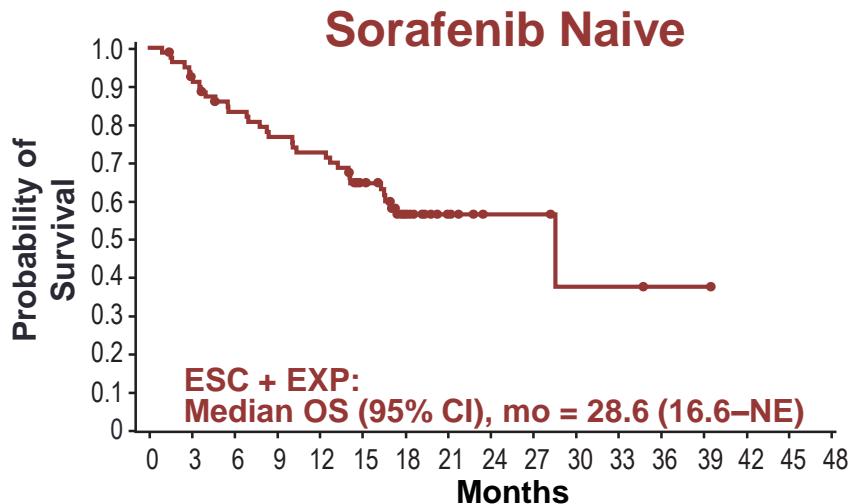
El-Khoueiry AB, et al. Lancet. 2017 Apr 20(17)31046-2

Parameters, n (%)	Tumor response	All Patients (n = 262)
Objective response ^a		42 (16)
Complete response		5 (2)
Partial response		37 (14)
Stable disease		135 (52)
Progression		78 (30)
Non assessable		7 (2)

^a RECIST v1.1.

- Very good tolerability with only 18% of SAE grade 3-4
- No degradation of the quality of life after 25 weeks of treatment

Overall survival



OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)

OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2–72.2)	60 (51.4–67.5)
18 months	46 (29.5–61.7)	44 (35.3–51.9)

Meilleure réponse tumorale en fonction de l'étiologie

**Sorafenib Naïve
ESC + EXP**

	Uninfected	HCV	HBV
ORR, n/N (%)	10/47 (21)	5/25 (20)	1/8 (13)

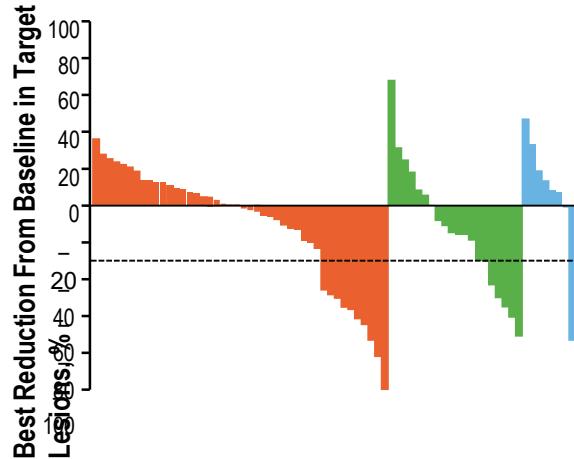
**Sorafenib Experienced
ESC**

	Uninfected	HCV	HBV
ORR, n/N (%)	3/17 (18)	2/5 (40)	2/15 (13)

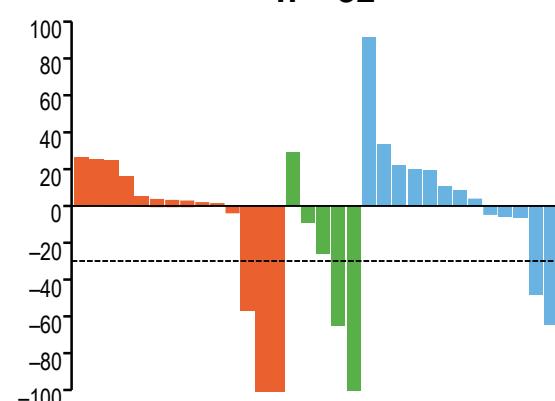
**Sorafenib Experienced
EXP**

	Uninfected	HCV	HBV
ORR, n/N (%)	9/72 (13)	6/30 (20)	6/43 (14)

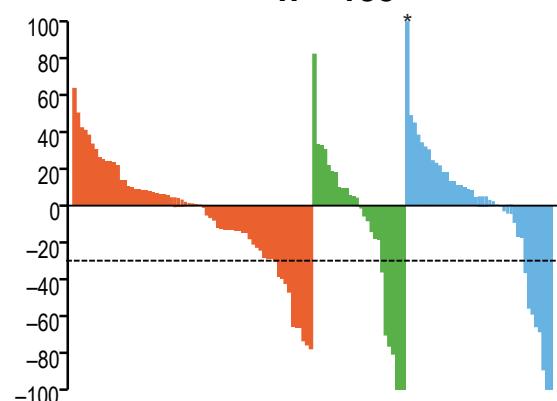
n = 72



n = 32



n = 135



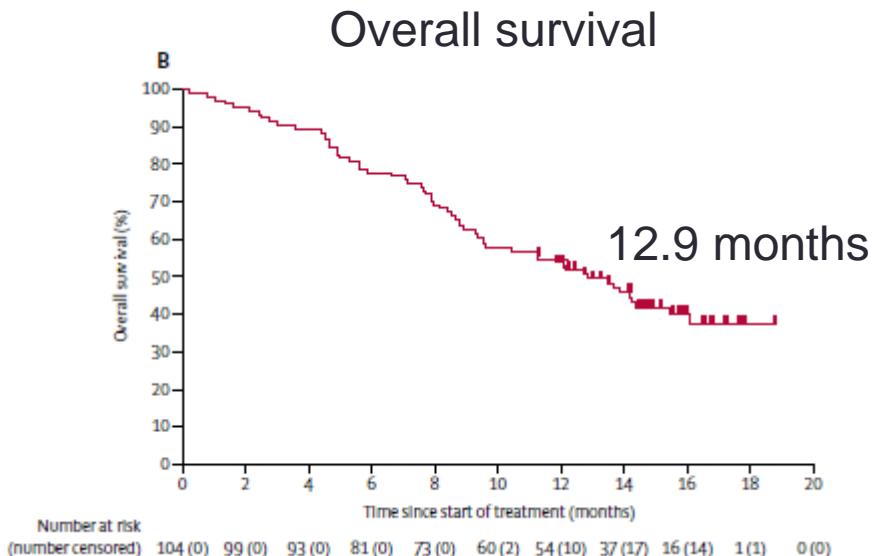
Tumor response assessed by BICR using RECIST v1.1.

* Percent change truncated to 100%.

Phase 2 study with Pembrolizumab (anti-PD-1)

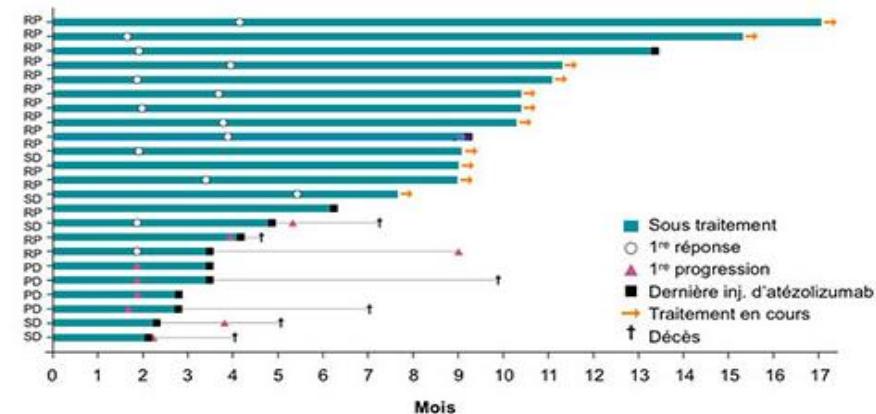
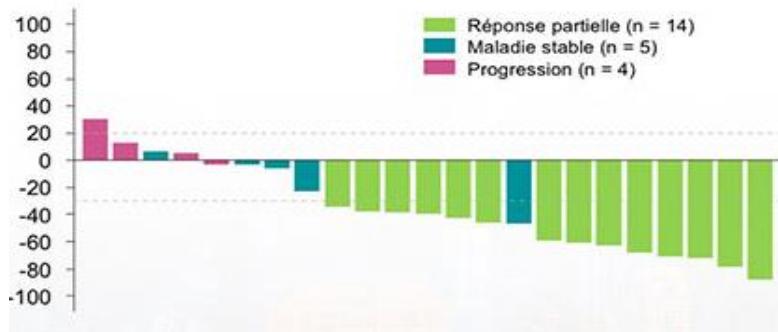
- In second line (intolerant or progression), 104 patients

	All treated participants (n=104)
Objective response*	18 (17%; 11-26)
Best overall response†	
Complete response	1 (1%)
Partial response	17 (16%)
Stable disease	46 (44%)
Progressive disease	34 (33%)
Not assessable‡	6 (6%)
Disease control§	64 (62%; 52-71)
Median time to response, months (IQR)¶	2.1 (2.1-4.1)
Median duration of response, months (range) ¶	Not reached (3.1-14.6+**)
Duration of response ≥9 months¶	12 (77%)



Atézolizumab (anti-PD-L1) + bevacizumab

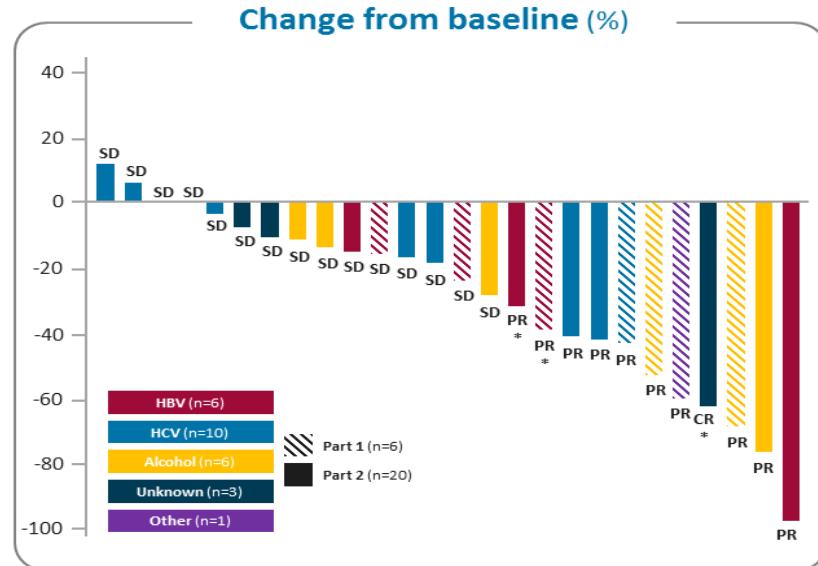
- Etude de phase 1b en première ligne
- 43 pts pour tox : AE grade 3-4 chez 35% (stt HTA), 2 décès toxiques (non reliés ??)
- 23 pts pour efficacité



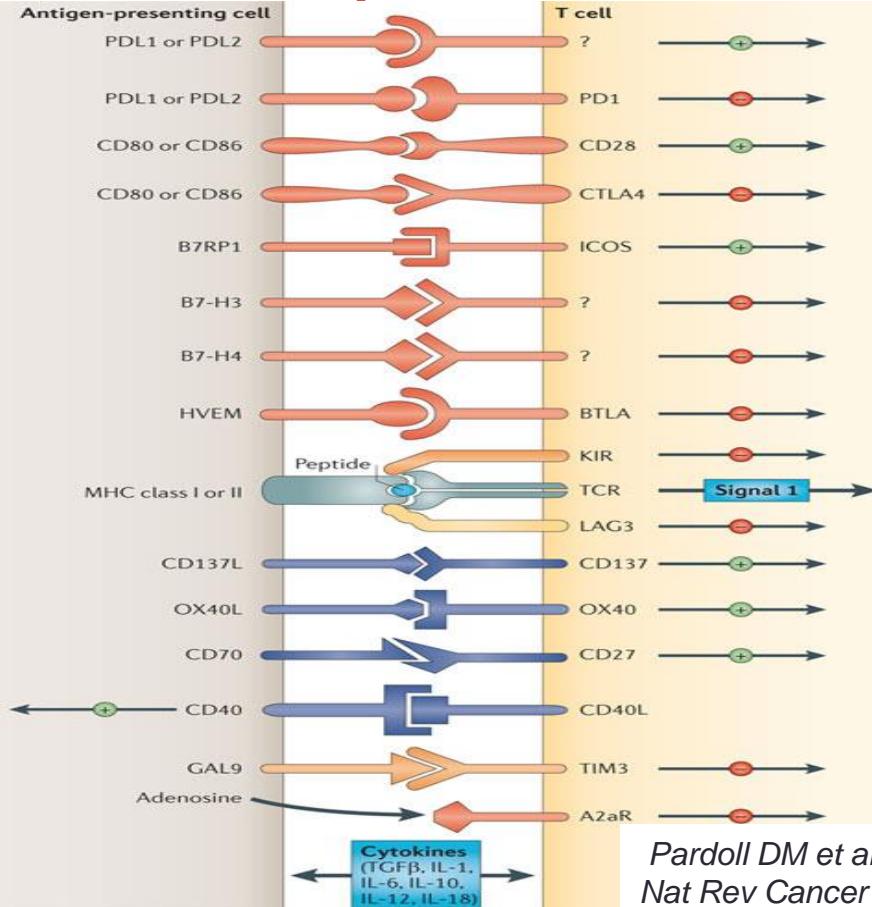
- Phase 3 en cours

Pembrolizumab + lenvatinib

- Etude de phase 1b
- 30 pts (6 puis 24)
- Données très préliminaires car 10 mois de suivi pour la partie 1, mais seulement 3 mois pour la partie 2
- 3 décès toxiques dans la partie 2

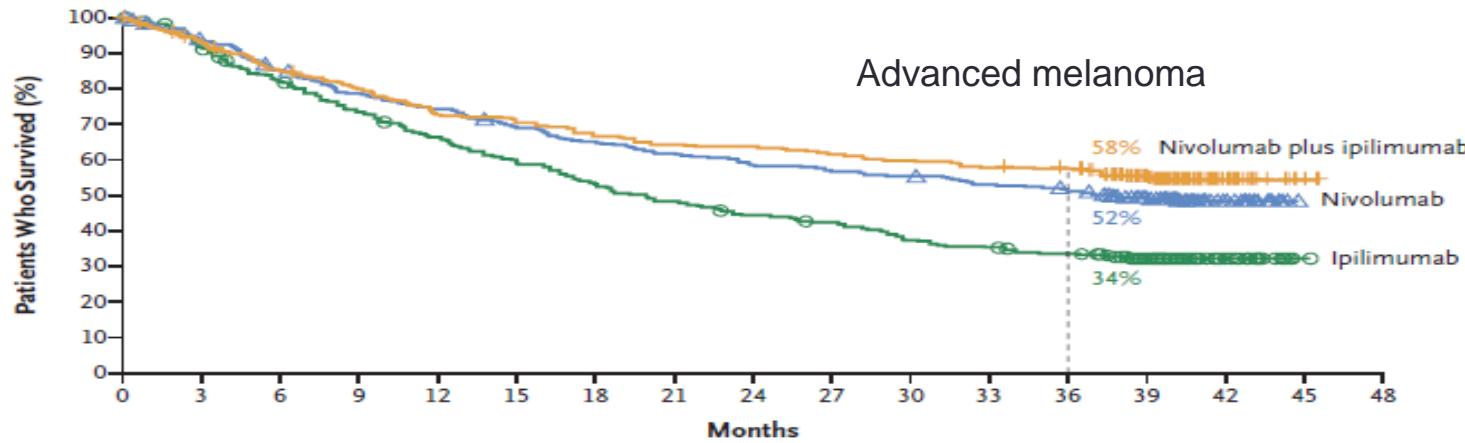


Check-point inhibitors



Targets	Products	Compagnie
CTLA-4	Ipilimumab	BMS
	Tremelimumab	MedImmune
PD-1	Nivolumab	BMS
	Pembrolizumab	MSD
	Pidilizumab	CureTech
	AMP-224	Amplimmune, GSK
	AMP-514	Amplimmune
PD-L1	MDX1105	BMS
	Atezolizumab	Genentech, Roche
	MEDI4736	MedImmune, Astra
	Avelumab	Merck, Pfizer
LAG-3	IMP321	Immutep
	BMS-986.016	BMS
B7-H3	MGA271	Macrogenics
CD200	ALXN6000	Alexion Pharma
KIR	Anti-KIR	Innate Pharma
	Lirilumab	Innate Pharma, BMS
IDO	IDO1 inhibitor	Incyte Corp.
	Indoximod	NewLink Genetics Corp.
	GDC-0919	Genentech, Roche
CD137	Urelumab	BMS
	PF-05082.566	Pfizer
CD40	CP-870.893	Pfizer
	Lucatumumab	Novartis
	Dacetuzumab	Seattle Genetics
OX40	Anti-OX40	AgonOx
	MEDI0562	MedImmune, Astra

Combination of IOs

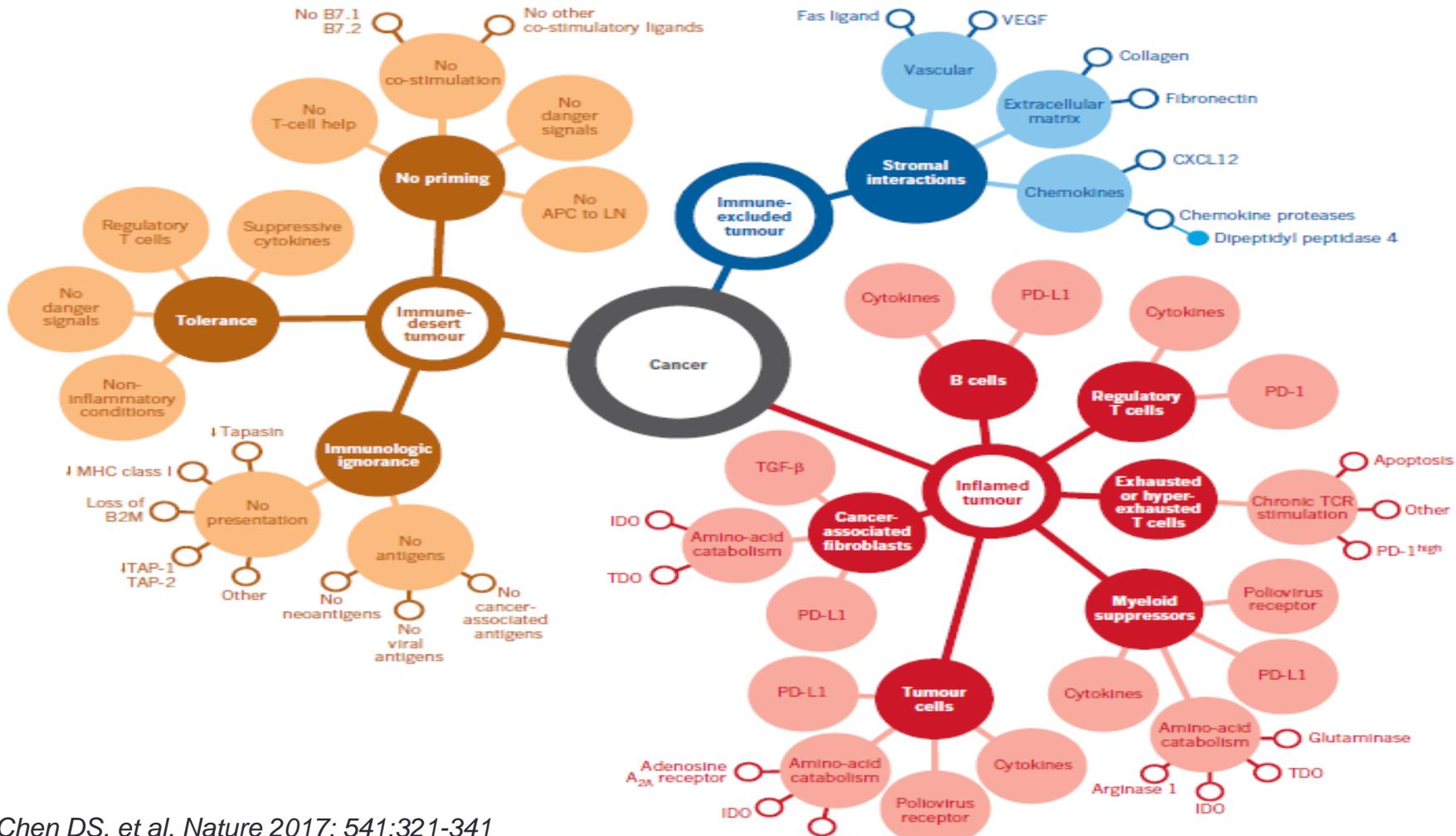


- Increase of immune-related AE

Wolchok JD et al., NEJM 2017

Characteristic	Nivolumab (N = 17,620)	Nivolumab plus Ipilimumab (N = 2974)
no. (%)		
Myocarditis		
Any*	10 (0.06)	8 (0.27)
Fatal events	1 (<0.01)	5 (0.17)
Myositis		
Any	27 (0.15)	7 (0.24)
Fatal events	2 (0.01)	1 (0.03)

Johnson DB et al., NEJM 2016



Predictive factors of tumor response to IOs

- Tissue inflammatory signature
 - Tumor
 - Non-tumor
- Mutational analysis
- Immuno-phenotyping

Tissue inflammatory signature

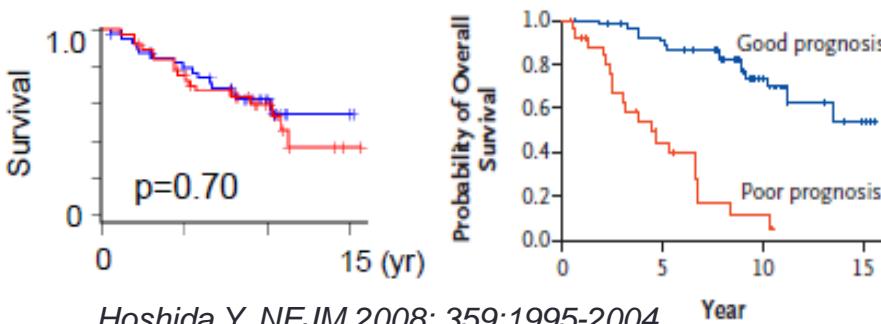
- PD-L1 immuno-staining in tumor

EI-Khoueiry AB, et al. Lancet. 2017; 389:2492-2502

Whole cohort (n = 169)	PD-L1 (+) (n = 34)	PD-L1 (-) (n = 135)
Objective response, n (%)	7 (21)	25 (19)

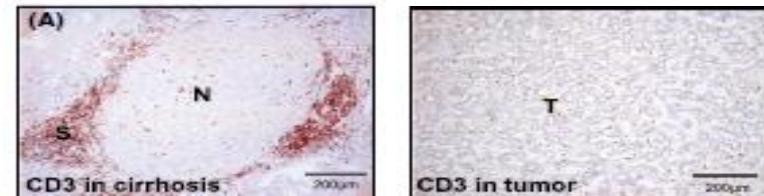
PD-L1, programmed death-ligand 1; PD-L1 (+), PD-L1 expression on $\geq 1\%$ of tumor cells; PD-L1 (-), PD-L1 expression on < 1% of tumor cells.

- Non-tumor signatures



Hoshida Y, NEJM 2008; 359:1995-2004

Liver Infiltrating Lymphocytes (LIL) Tumor Infiltrating Lymphocytes (TIL)

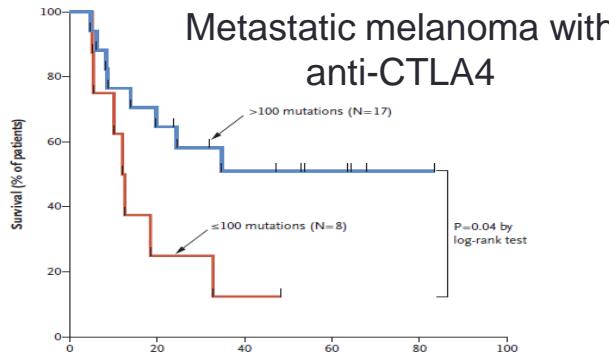


→ 6 to 13 times more LIL than TIL
Ramzan M et al., Liver International 2016

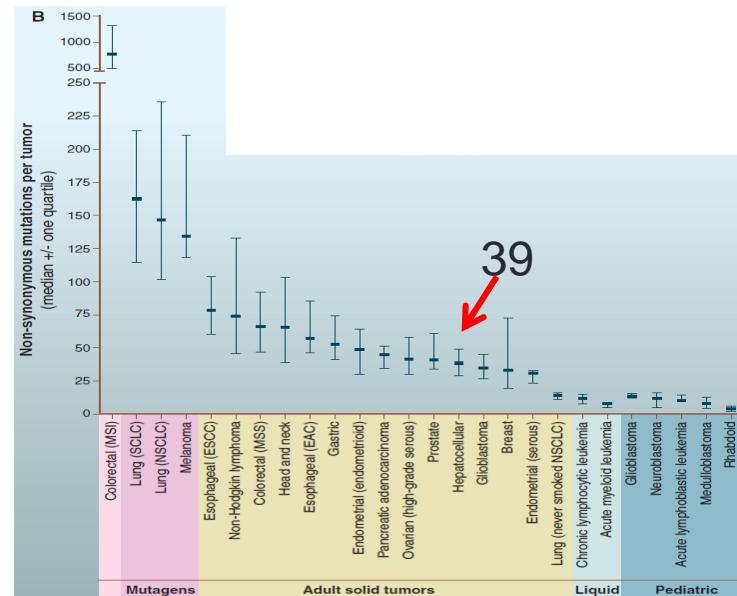
- Test different panels of tumor and non-tumor signatures!

Mutational analysis

- Mutational load

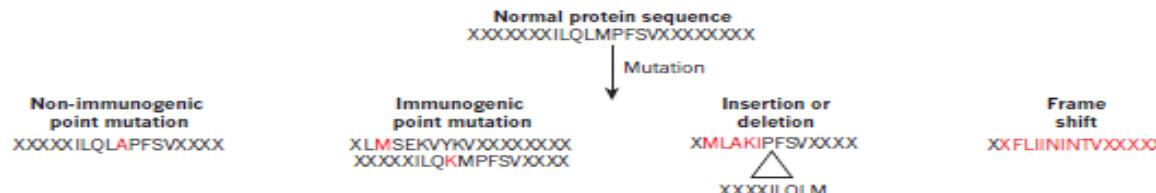


Snyder A et al., NEJM 2014



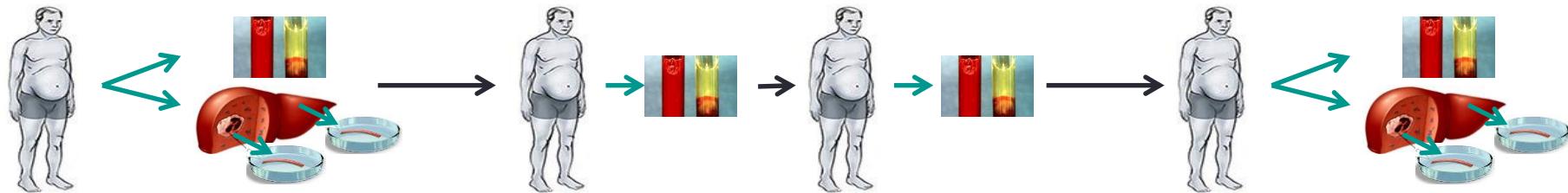
Vogelstein B et al., Science 2013;339

- Immunogenicity analysis of mutations

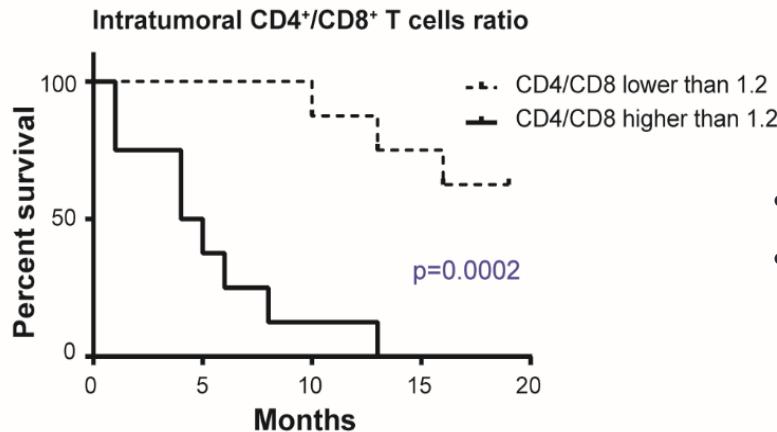


XS Liu and ER Mardis. Cell;2017(168):600-612

Immunophenotyping

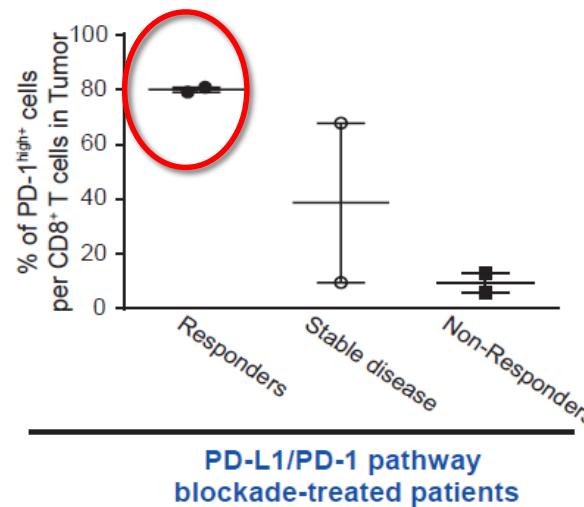
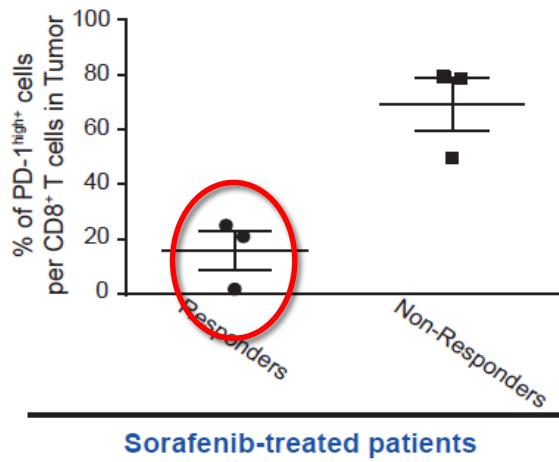


- Multiparameter FACS analysis, on fresh samples (tumor, non tumor surrounding tissue, and blood)

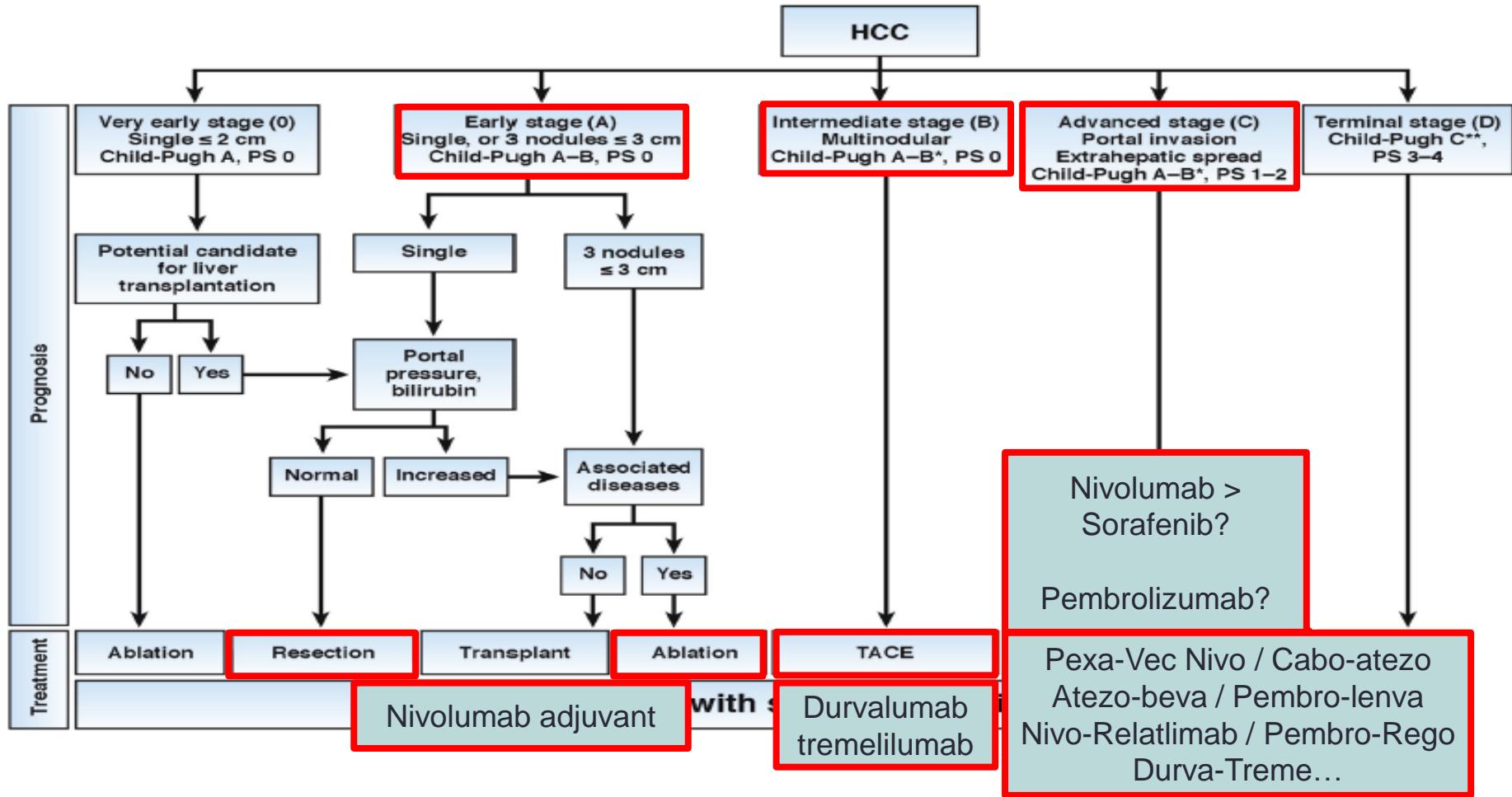


- Based on 21 patients
- Intratumoral CD4⁺/CD8⁺ T cells ratio correlates with overall survival

Baseline intra-tumoral PD-1^{high+}CD8⁺ T cells



Frequency of intratumoral PD-1^{high+}CD8⁺ T cells may serve as marker to identify which individuals will benefit from which treatment



Merci pour votre attention



Le cancer du foie en questions

Aide et Recherche en Cancérologie Digestive

- Sous l'égide de :
 - AFEF
 - ACHBT
 - SIAD
- Disponible sur le site de l'ARCAD