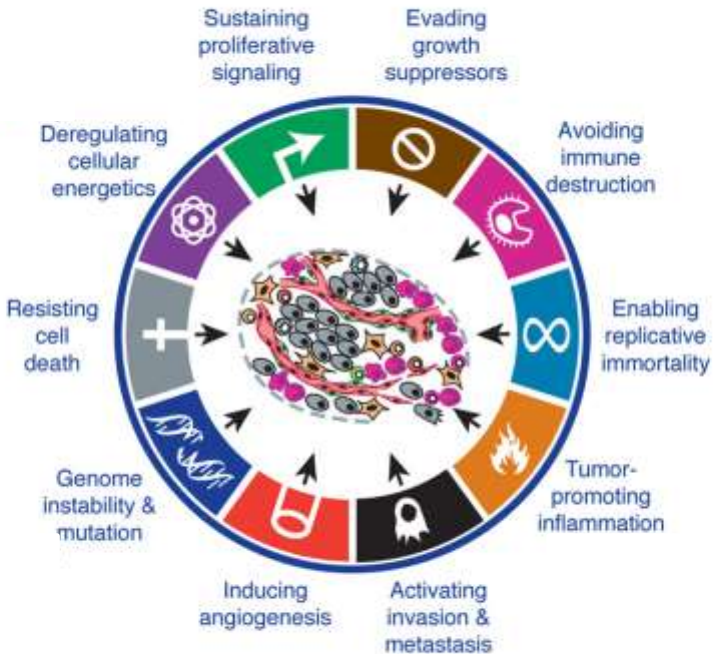
Immunothérapie et cancer digestifs

Dr David Sefrioui, Quoi de Neuf en Hépatogastroenterologie 2016

Carcinogénèse et ciblage thérapeutique



Hanahan et al. Cell 2011

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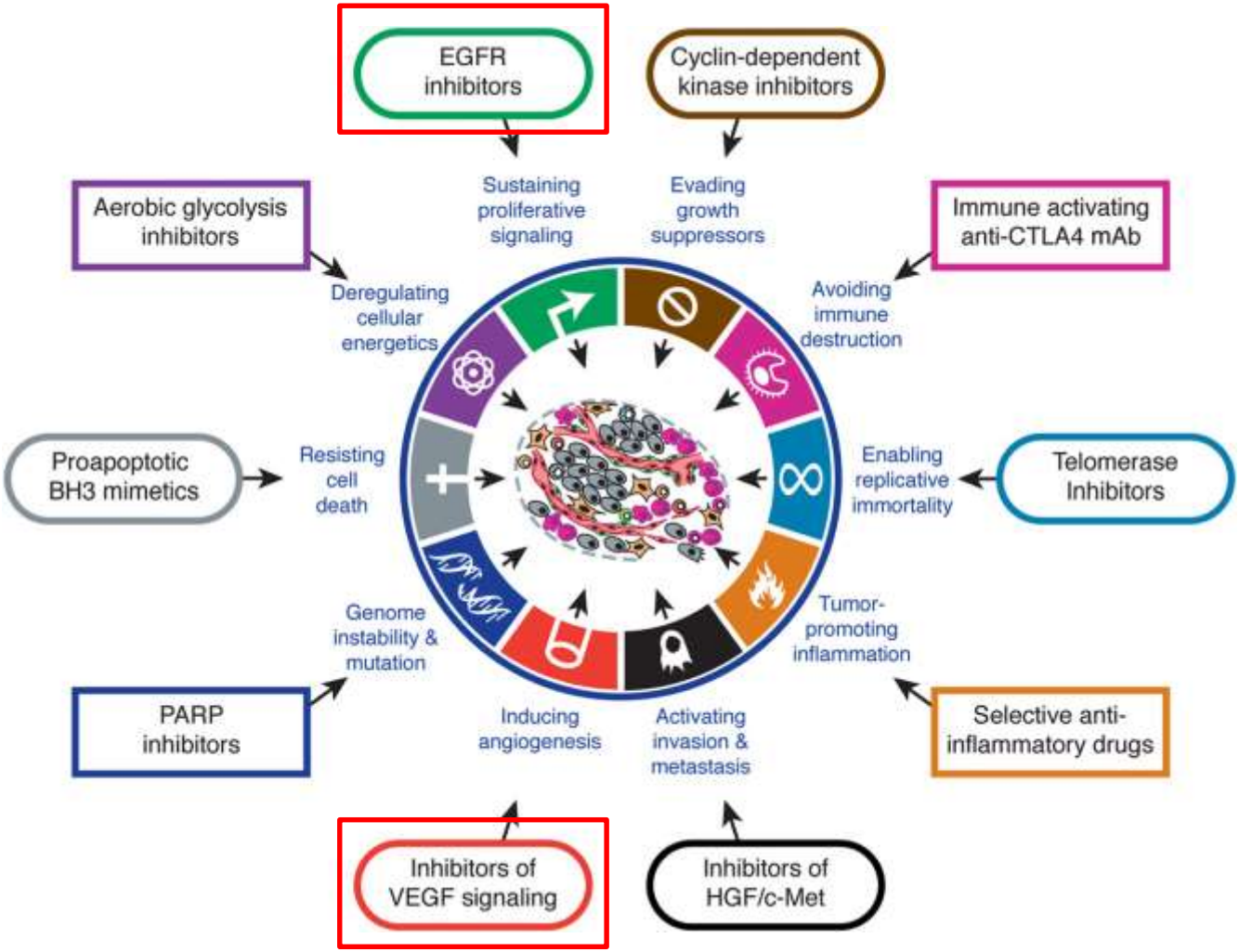

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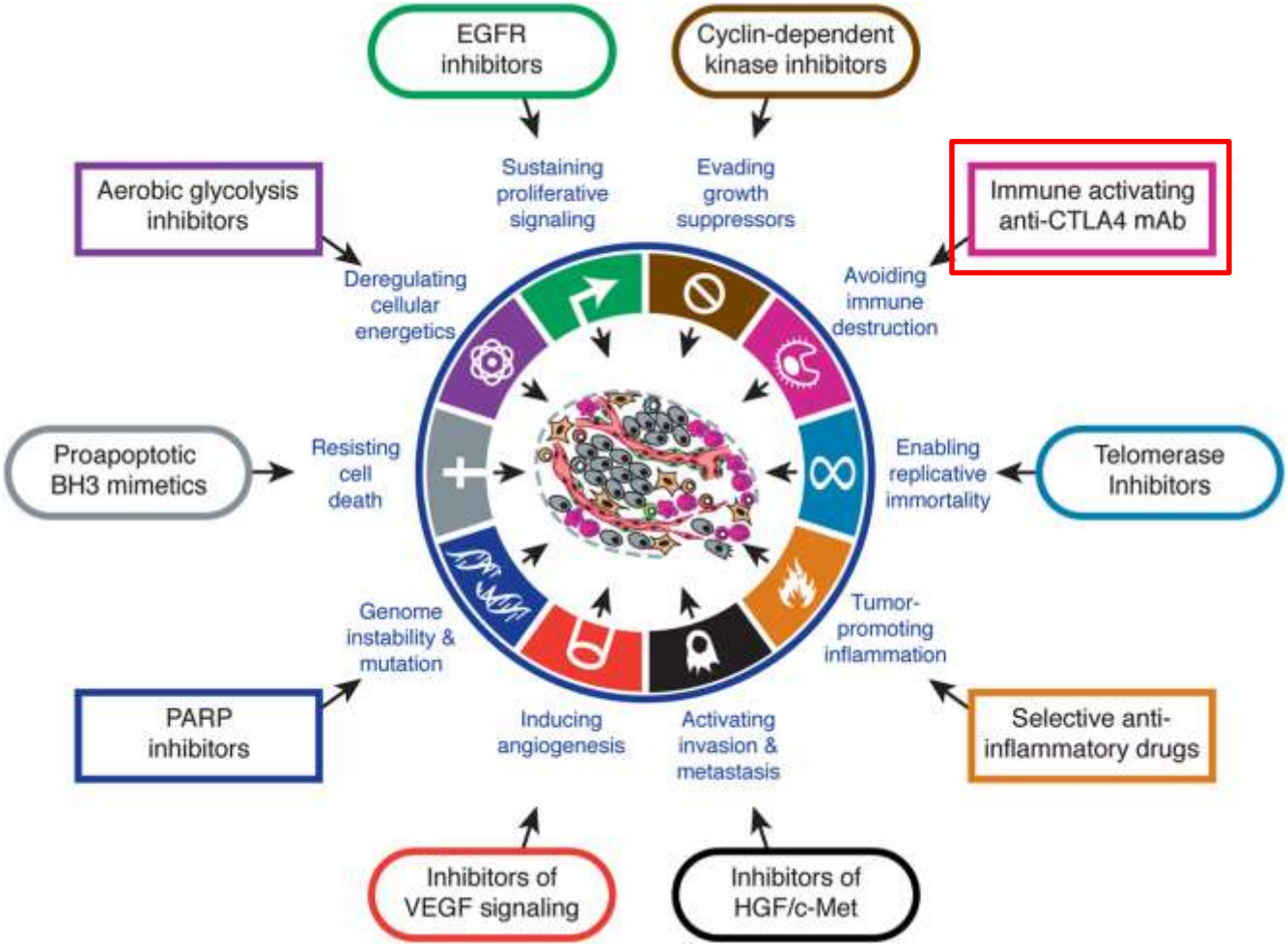
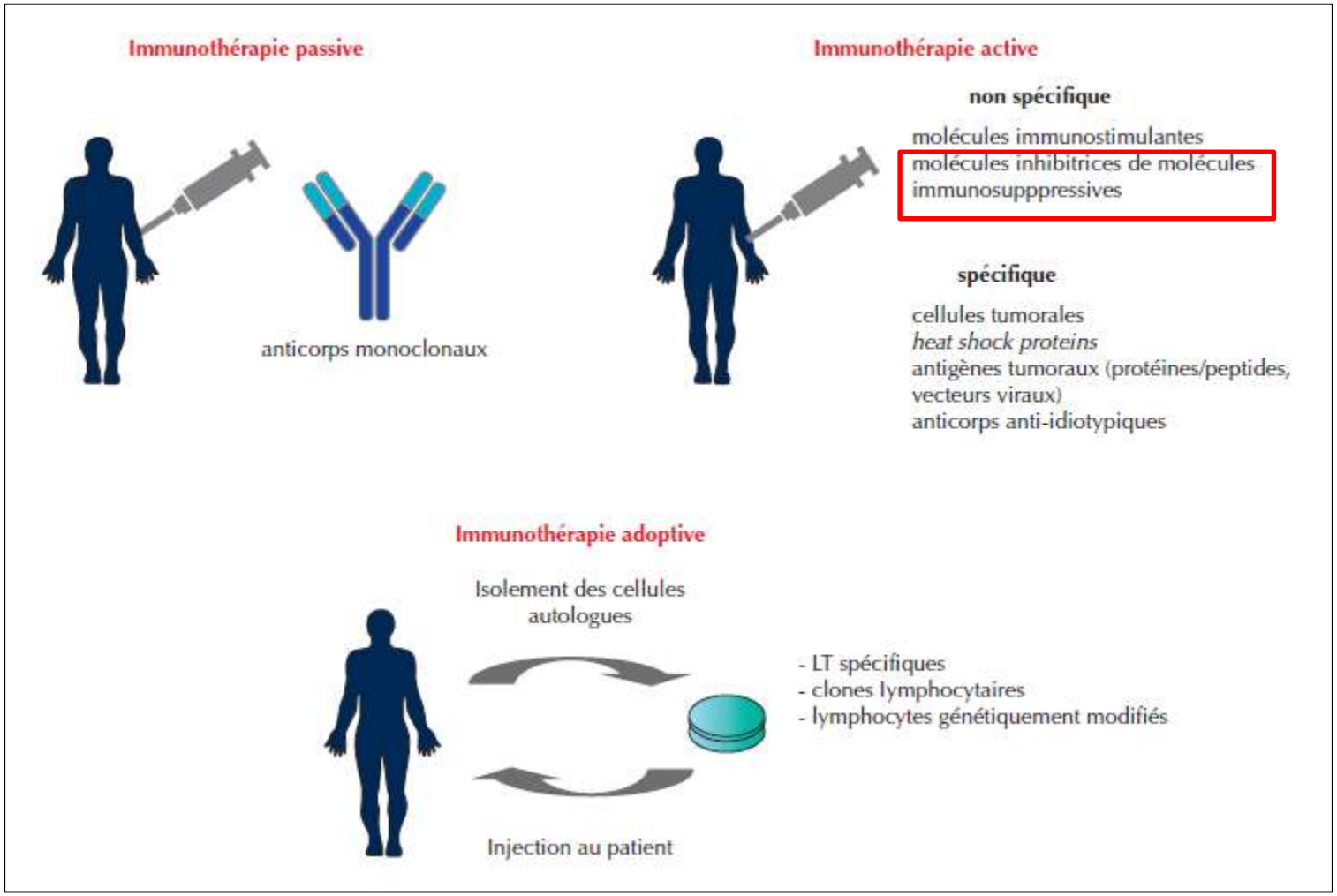


Hanahan et al. Cell 2011

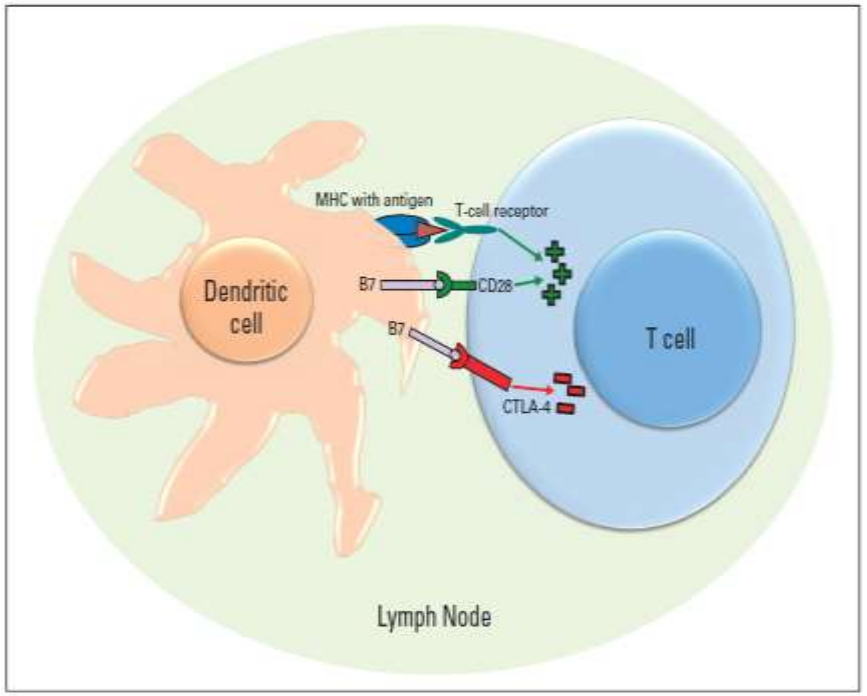
Types d'immunothérapie



Tougeron et al. Bulletin du Cancer 2013

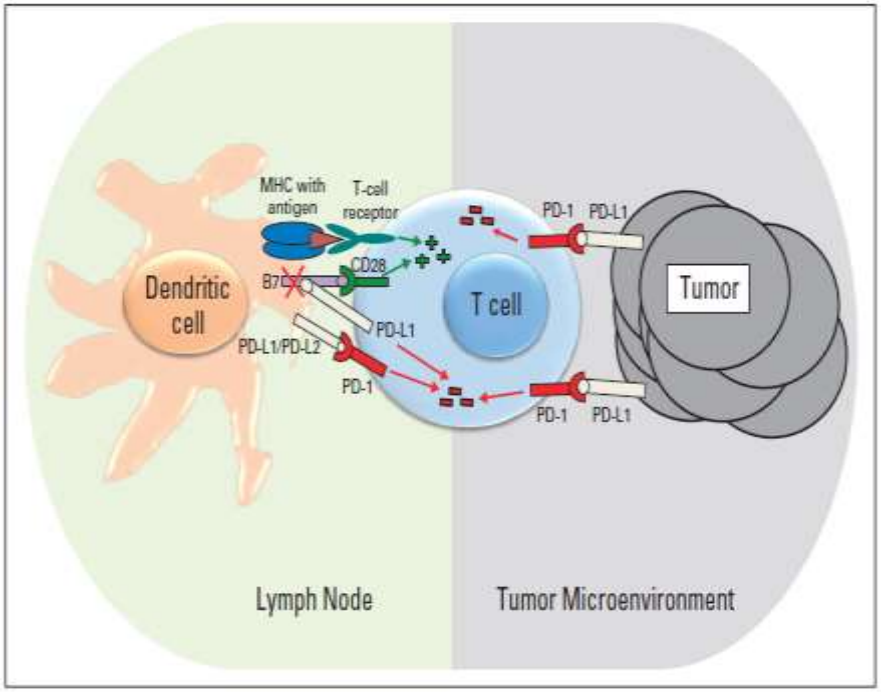
Mécanismes d'action

Checkpoint 1 : CTLA4



Ipililumab (Yervoy®, BMS),

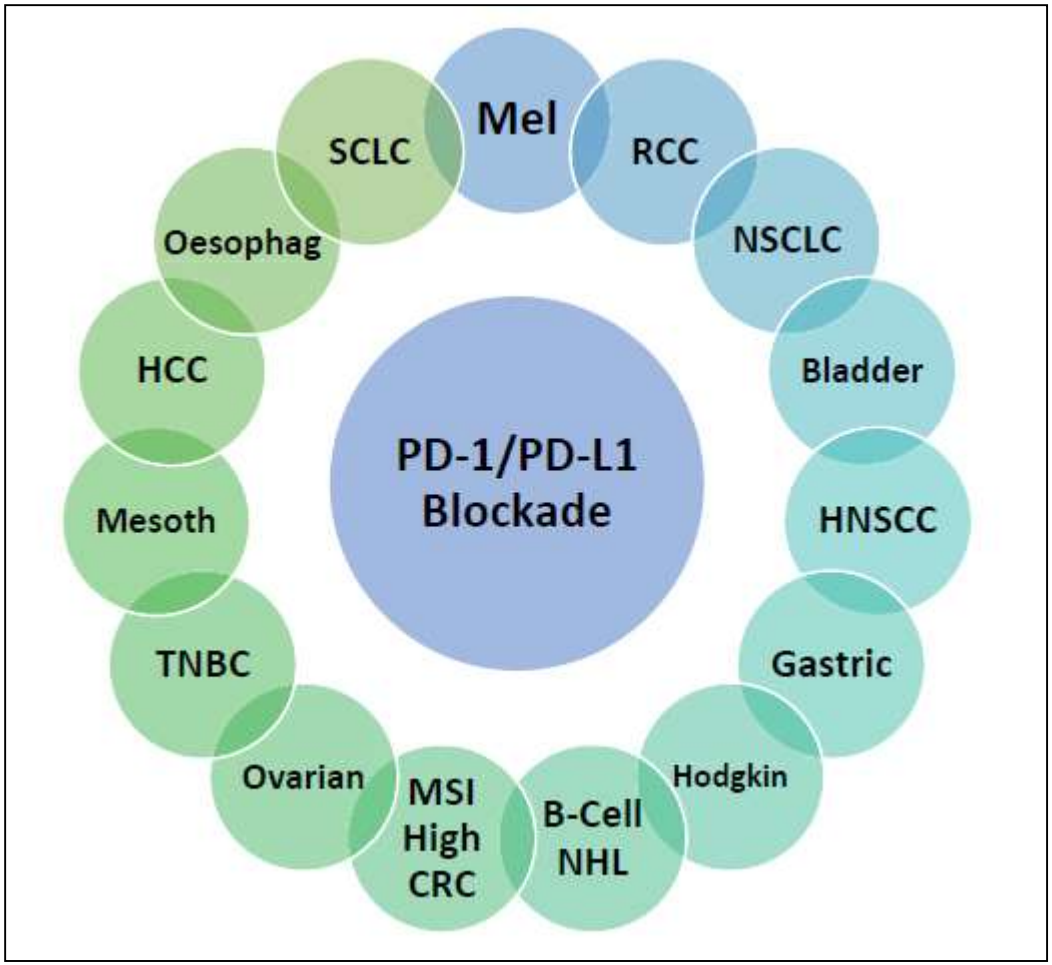
Checkpoint 2 : PD1/PDL1



Postow et al. Journal of Clinical Oncology 2015

Nivolumab (OPDIVO®, BMS)
Pembrolizumab (KEYTRUDA ®, MSD)

Données d'efficacité



Michot et al. European Journal of Cancer 2016

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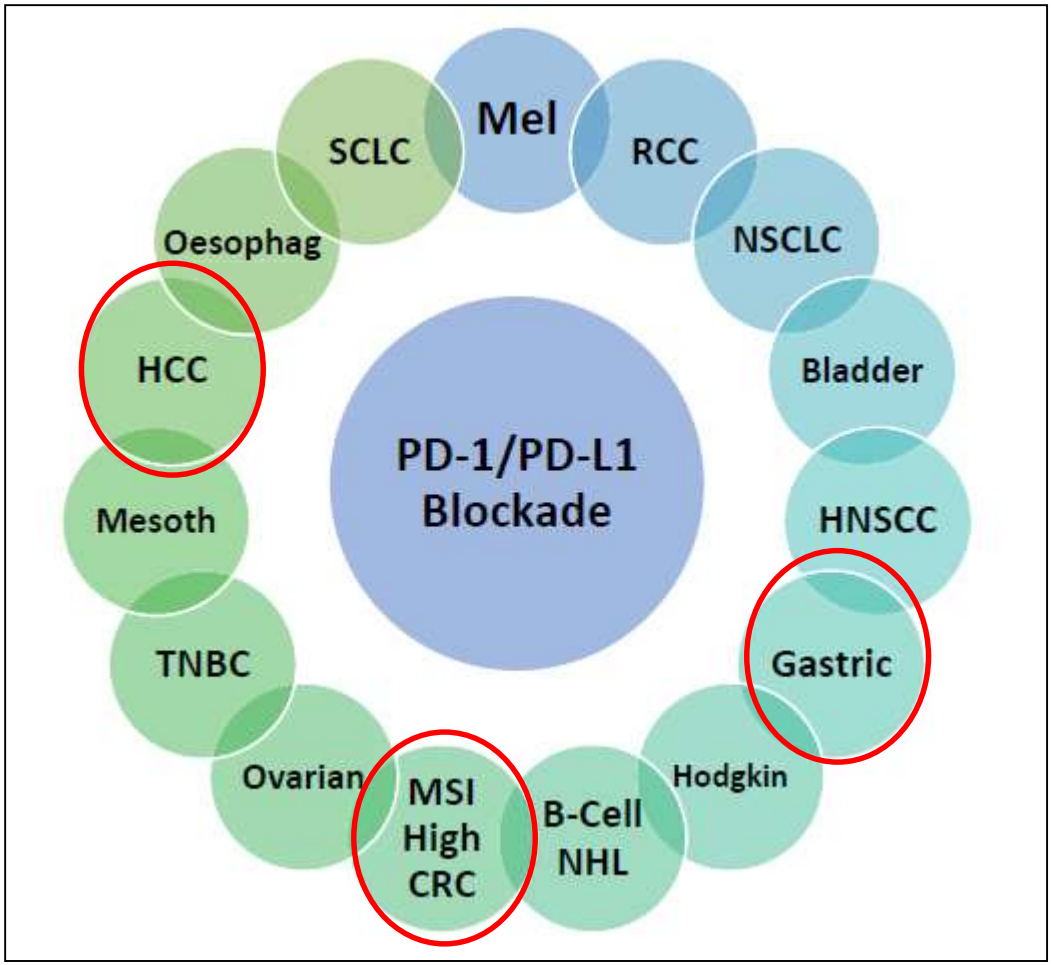


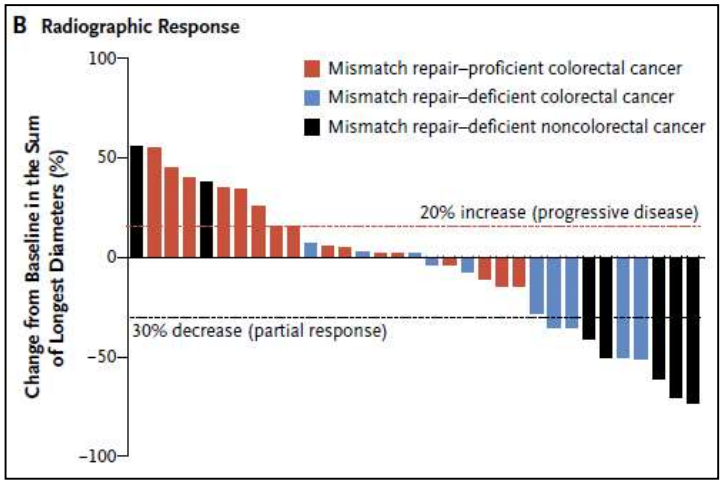
Michot et al. European Journal of Cancer 2016

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

New England Journal of Medicine, juin 2015

Etude de phase 2
41 patients
Pembrolizumab 10 mg/kg tous les 14 jours
CCR MSI = 11
CCR non MSI = 21
Cancer MSI non CR = 9
29/41 (71%) ≥ 3e ligne CT



Le et al. New England Journal of Medicine 2015

Type of Response	Mismatch Repair–Deficient Colorectal Cancer (N=10)	Mismatch Repair–Proficient Colorectal Cancer (N=18)	Mismatch Repair–Deficient Noncolorectal Cancer (N=7)
Complete response — no. (%)	0	0	1 (14)*
Partial response — no. (%)	4 (40)	0	4 (57)†
Stable disease at week 12 — no. (%)	5 (50)	2 (11)	0
Progressive disease — no. (%)	1 (10)	11 (61)	2 (29)
Could not be evaluated — no. (%)‡	0	5 (28)	0
Objective response rate (95% CI) — %	40 (12–74)	0 (0–19)	71 (29–96)
Disease control rate (95% CI) — %§	90 (55–100)	11 (1–35)	71 (29–96)

Le et al. New England Journal of Medicine 2015

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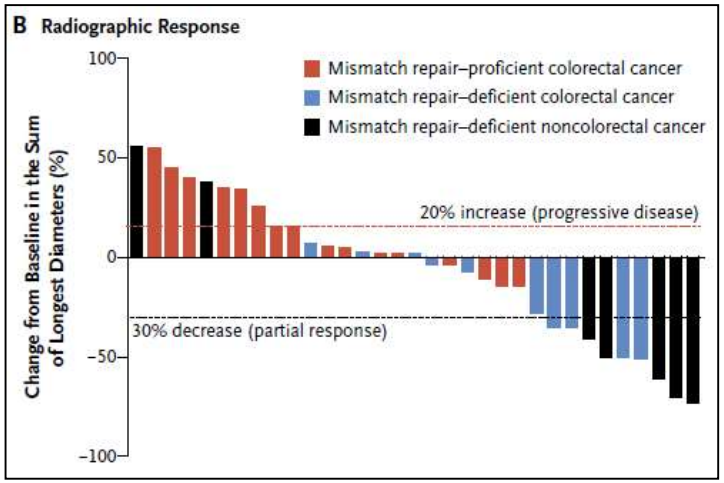

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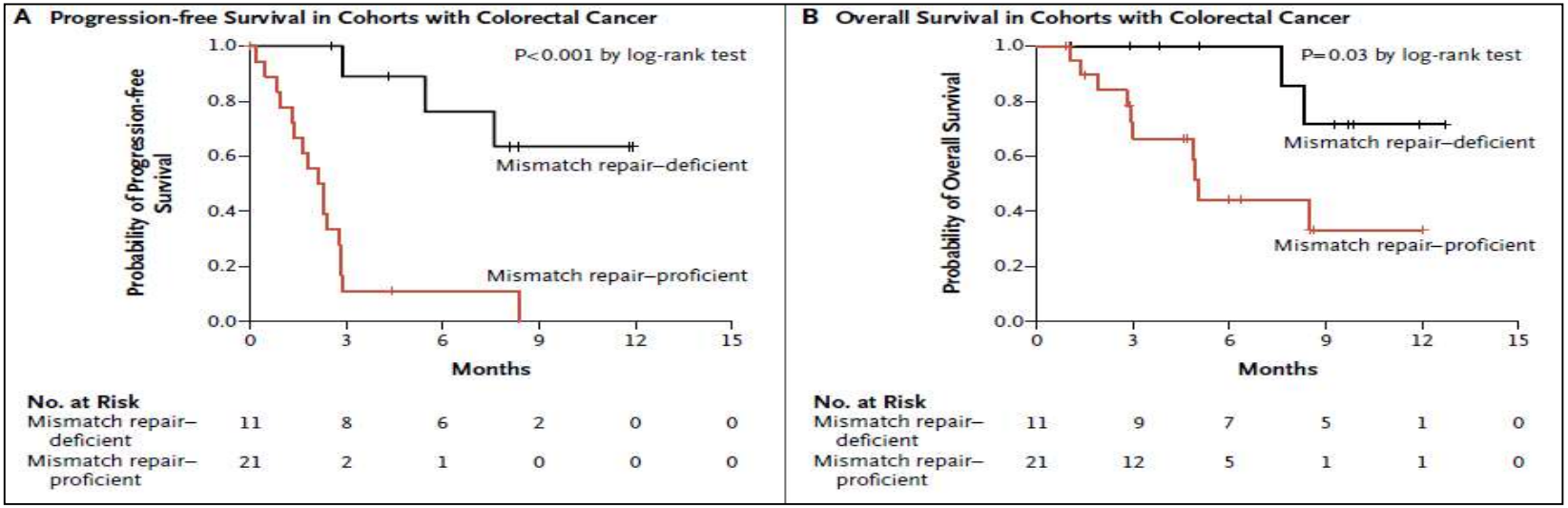
SSP = 2.2 mois (MSS) versus NA (MSI)
SG = 5.5 mois (MSS) versus NA (MSI)



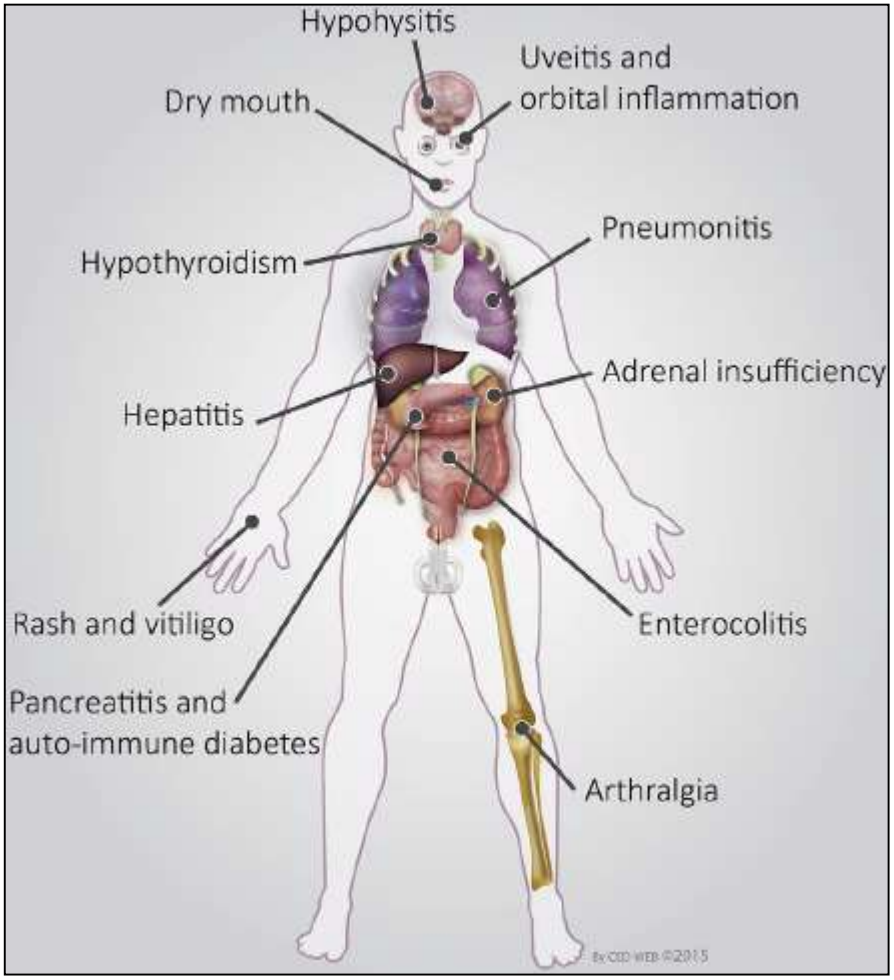
Le et al. New England Journal of Medicine 2015

Autres données d'efficacité

Etude	Type tumoral	Ligne CT	TTT	EI (gr 3-4)	résultats
Phase II [a]	CCRm (n=82)	≥3e L	Nivo (3mg/kg) Nivo + Ipil	10% 26%	SSP = 5.3m;SG=17.1 m SSP =NA; SG = NA
Phase II [b]	Canal anal M+ (n=37)	≥2e L	Nivo (3mg/kg)	15%	RO =24%; SSP = 3.9m
Phase I [c]	CHC avancé (n=51)	≥2e L	Nivo (3mg/kg)	20%	TC=65% (RO=15% S=50%);SG=14.1 m
Phase I-II [d]	Gastrique avancé (n=160)	≥3e L	N3 (4C) p. N3 N1+ I3 (4C) p. N3 N3 + I1 (4C) p. N3	17% 45% 27%	SG=5m SG = 6.9m SG=4.8m

[a] *Overman et al. OS 3501 ASCO 2016*
[b] *Morris et al. OS 3503 ASCO 2016*
[c] *El Khouery et al. PDS 4012 ASCO 2016*
[d] *Janjigian et al. PDS 4010 ASCO 2016*

Toxicité



Michot et al. European Journal of Cancer 2016

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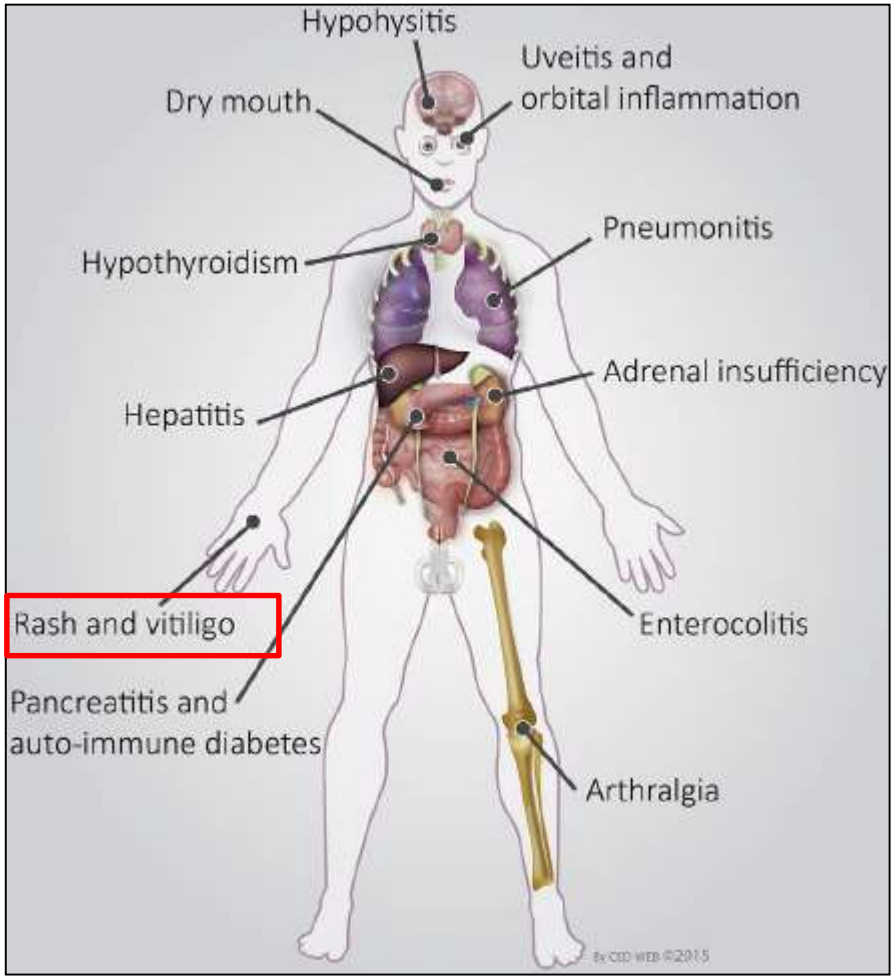

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Rash cutané, prurit :

- Fréquent : 40% (monothérapie) et 60 % (combinaison)
- Précoce : 2 à 4 semaines
- ≥ Grade 3 < 10%
- Autres = Syndrome Stevens-Johnson, Lyell ou vitiligo

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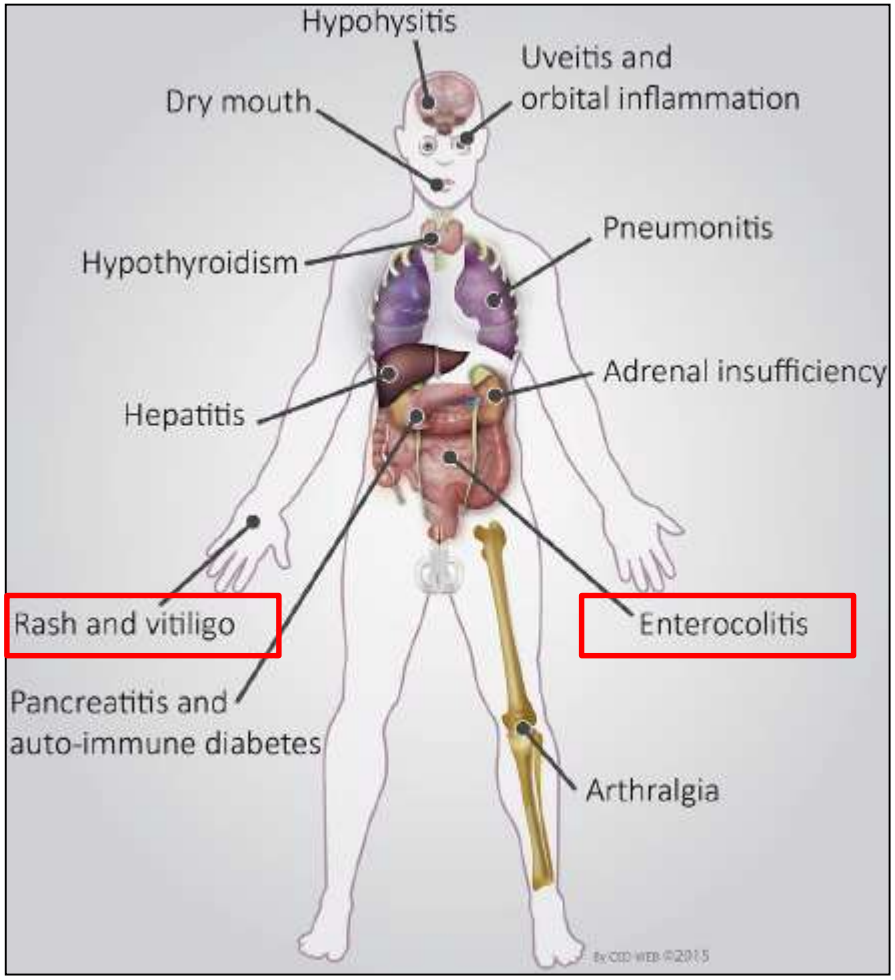

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<u>Diarrhée:</u>
- Fréquent :15-20% (P et N) et 20-30% (I) et 40 % (combinaison)
- ≥ Grade 3 = 2% (P, N); 6% (I) et 9% (combinaison)
- retardé: médiane = 6 à 8 semaines après le début du ttt

Hépatite (<5%); pneumopathie (2%), dysthyroidie (5-10%), asthénie (20à 30% (gr. 1-2)

Conclusion

1. Nouvelle arme dans l'arsenal thérapeutique
   - Inhibiteur check point immunitaire : PD1 et CTLA4

2. Signaux d'efficacité (CCRm MSI, CHC avancé, Oesogastrique avancé, Canal anal M+)

3. Ouverture prochaine du Protocole CA209-577 (BMS)

étude de phase III multicentrique, randomisée, en double aveugle, évaluant le nivolumab versus placebo en tant que traitement adjuvant chez des sujets ayant eu une résection complète d'un cancer de l'œsophage (CO) ou de la jonction œsogastrique (JOG) et ayant reçu une radio-chimiothérapie (CRT) préalablement à la résection chirurgicale, c'est à dire neo-adjuvante

Toxicité

AEOSI (Grade) (acc. NCI CTC v.4)	Examinations *For the detailed laboratory panel please refer to Table 4*	Management *Anti-PD-1 therapy / Methyl-prednisolone or equivalent* [a]	& Follow-up In case of: ↗ Improvement → No change ↘ Worsening	
Skin events				
°1		Topical steroid [b]		
°2		Topical steroid [b]		
°3-4	(⊙Skin biopsy)	△ or ■ **1.0-2.0** mg/kg/d	↗ : ●	
Diarrhea/Colitis				
°1	Stool test on pathogens	● --- [c]		
°2	(⊙ Colonoscopy)	△ **0.5-1.0** mg/kg/d	→ : ■	
°3-4	Colonoscopy	■ **1.0-2.0** mg/kg/d	→ / ↘ :	Infliximab *Cave!* [d]
Pneumonitis				
°1	Frequent controls [q2-3d]	● ---		
°2	Daily symptom contr.; (⊙ Bronchoscopy)	△ **1.0-2.0** mg/kg/d	↗ : ●	
°3-4	Bronchoscopy/biopsy	■ **2.0-4.0** mg/kg/d	→ / ↘ :	Immunosuppr. therapy [e]
Endocrine events	*Please refer primarily to full-text section for adequate guidance with regard to complex features of AEOSI*			
Asymptomatic °1	Regular controls; (⊙ Imaging)	● ---		
Symptomatic °2	Regular controls; (⊙ Imaging; ⊙ Further diagnostics)	△ (⊙HRT); **1.0-2.0** mg/kg/d	↗ : ●	→: Start/maintain HRT
°3-4		△ (⊙HRT); i.v. steroids [g]	↗ : ●	Regular controls
Renal events				
°1	Control for signs of renal dysfunction	● ---		
°2	(⊙Renal biopsy); Creatinine [q2-3d]	△ **0.5-1.0** mg/kg/d	↗ : ●	
°3-4	(⊙Renal biopsy)	■ **1.0-2.0** mg/kg/d		
Hepatic events				
°1	Control for signs of hepatitis	● ---		
°2	Frequent controls [transaminases]	△ **0.5-1.0** mg/kg/d	↗ : ●	
°3-4	Very frequent contr. [q1-2d]; (⊙Biopsy)	■ **1.0-2.0** mg/kg/d	→ / ↘ :	Immunosuppr. therapy [e]
Infusion reactions [h]				
°3-4	Vigilant controls/monitoring	■ **2.0-4.0** mg/kg/d or i.v. corticosteroids ≥ antihistamines		

Legend: ● continue therapy (Anti-PD-1); △ delay therapy (Anti-PD-1); ■ stop therapy (Anti-PD-1); (⊙): optional, i.e. !considerI

Eigentler et al. Cancer Treatment Reviews 2016