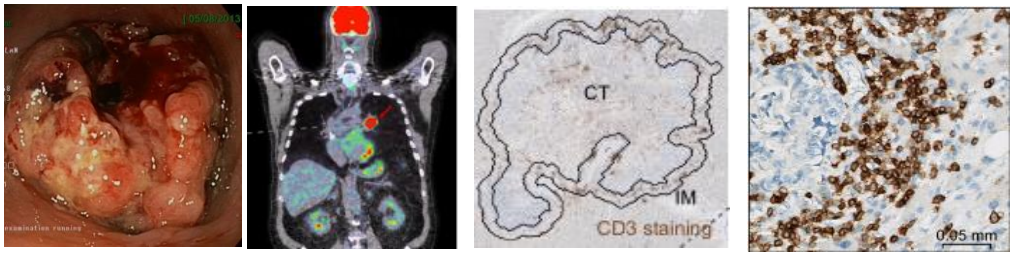
# L’immunothérapie dans le syndrome de Lynch: un traitement efficace et prometteur !

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Cliniques universitaires SAINT-LUC UCL BRUXELLES

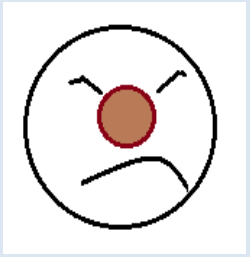
# Les deux grandes familles de cancers coliques

## Les CRC stables (MSS)

Cancérogenèse et expansion clonale démarrent avec la perte de la fonction APC

Evolution lente

Expriment toutes les protéines de la famille MMR (→ couleur marron en IHC)



## Les CRC instables (MSI-H)

## une toute autre maladie

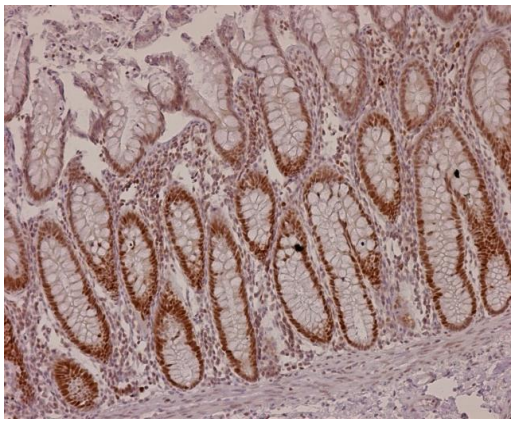
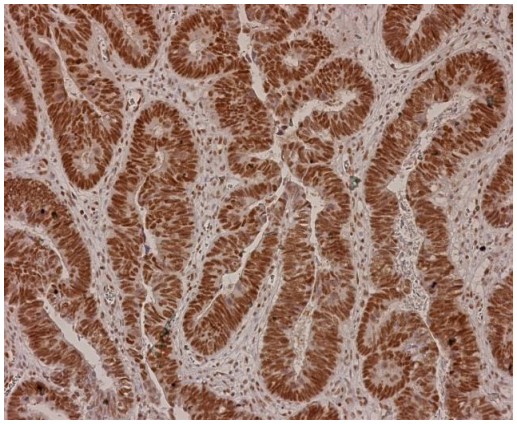
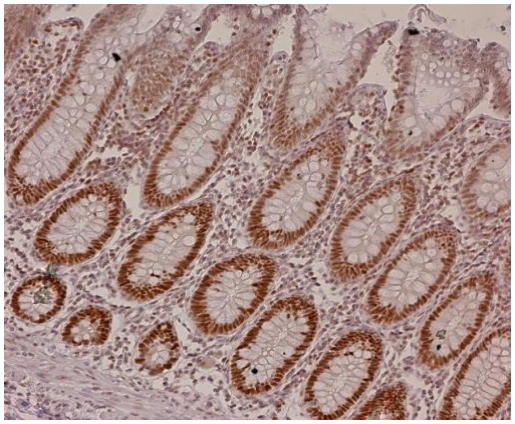
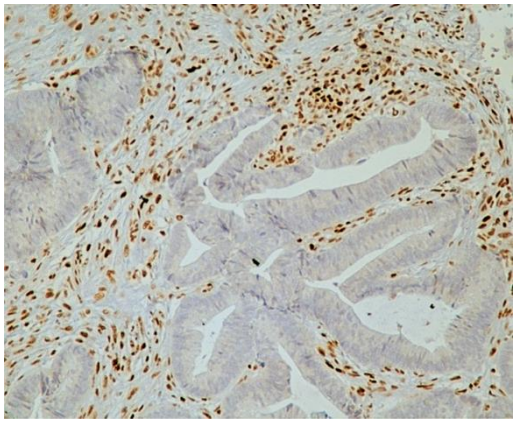
Début de l'histoire avec la perte de la fonction MMR

Evolution très rapide une fois démarrée la phase d'expansion

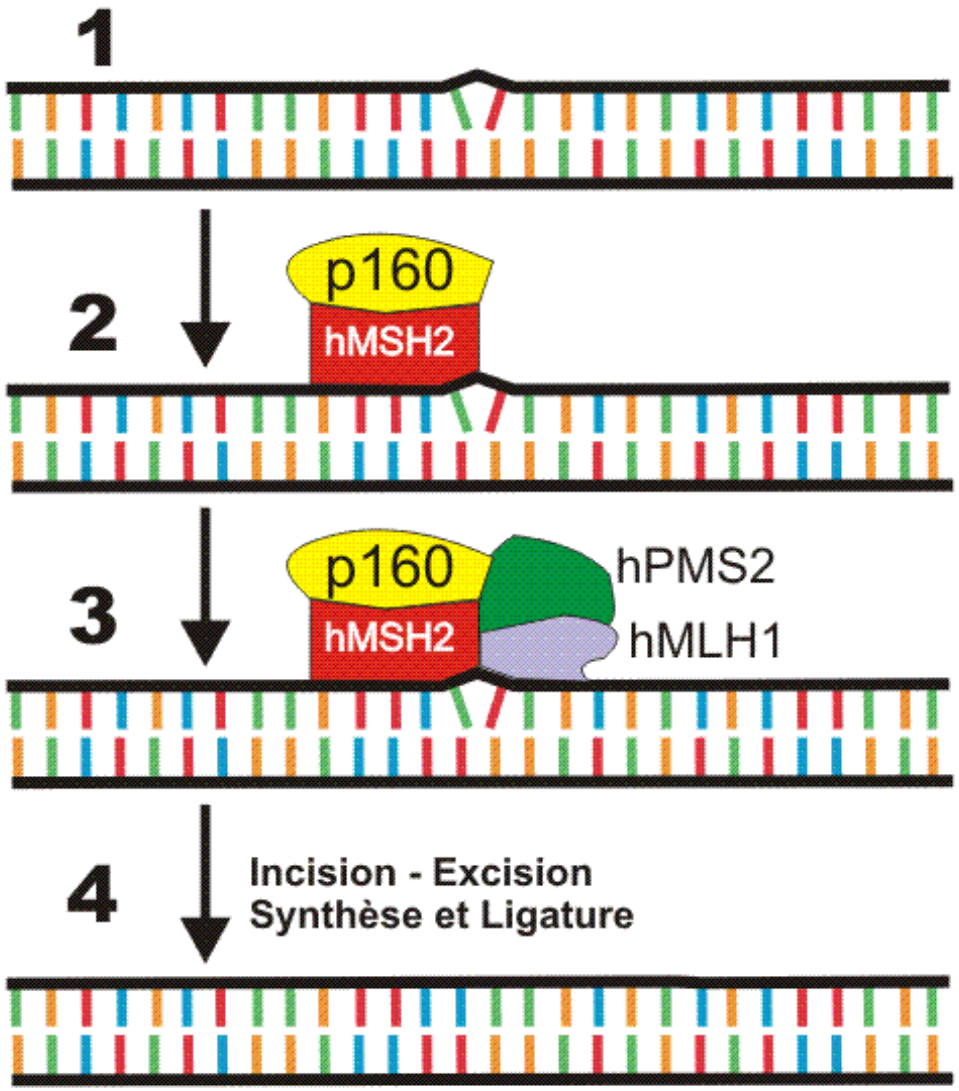
Ont perdu une ou plusieurs protéines MMR (→ jolie couleur bleu ciel en IHC)

# Immunohistochimie

## Protéines de réparation de l'AND (MMR): MLH1, PMS2, MSH2, MSH6 (1996)

| | *Muqueuse normale* | *Tumeur* |
|---|---|---|
| formalin fixation | | |
| MSI (-) |  |  |
| MSI (+) |  |  |

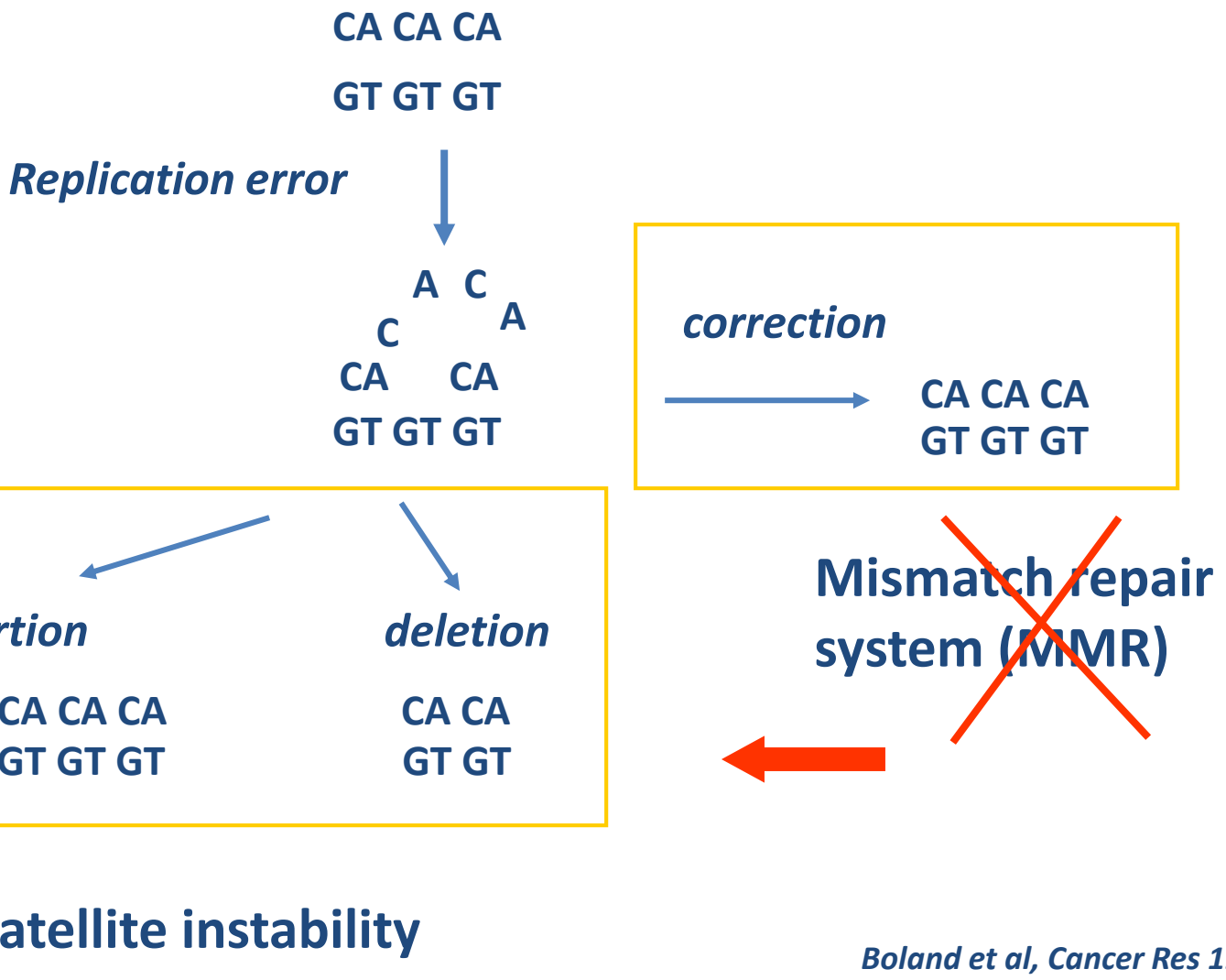
# Protéines de réparation de l'ADN: mécanisme



# Microsatellites

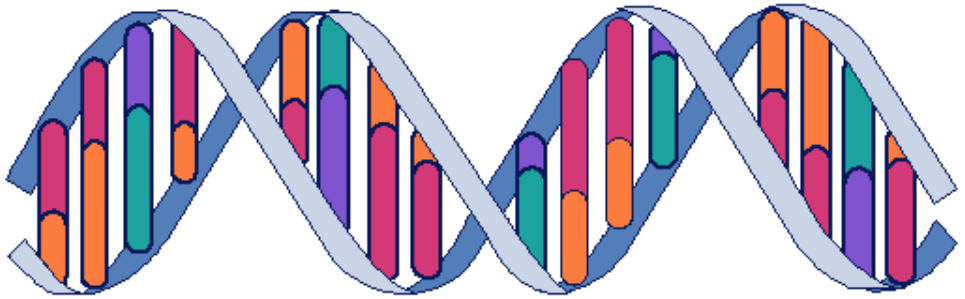
= short repetitive non coding DNA sequences

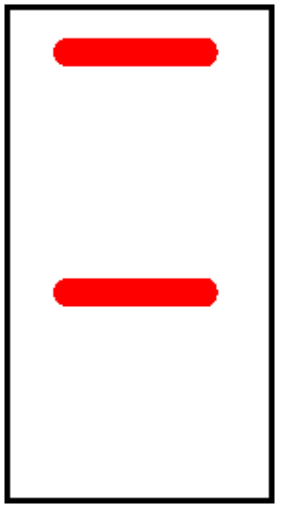
CA CA CA



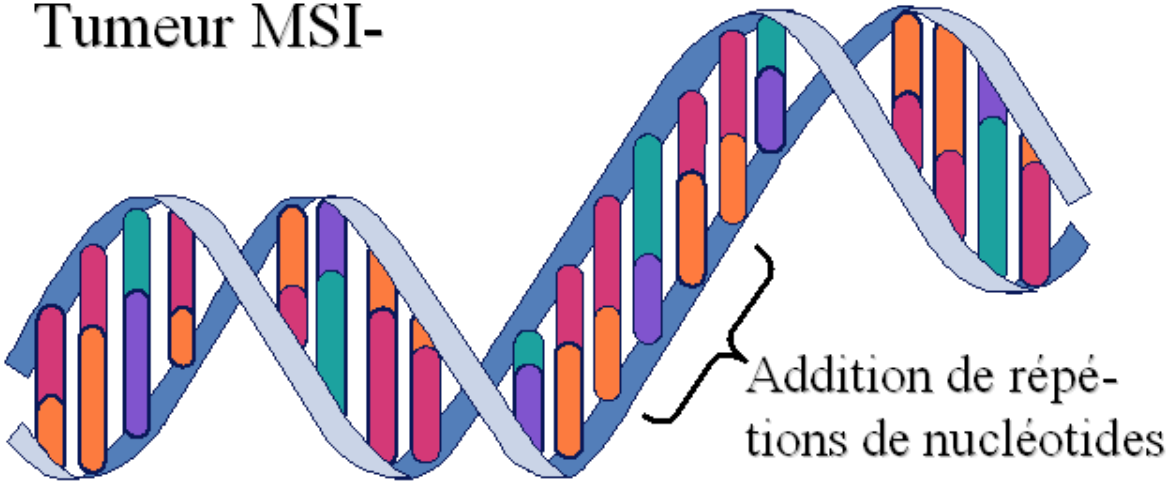

*Boland et al, Cancer Res 1998*

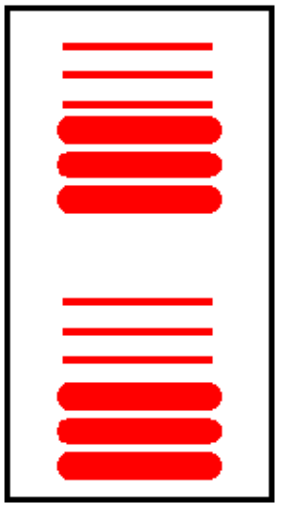
Tissus normal





Tumeur MSI-



Electrophorèse de l'AND (Southern blot)

# Colorectal cancer 100%

**CCR stables ~ 85% (MSS)**

**Voie de l'instabilité chromosomique**

**CCR instables ~ 15% (MSI)**

**Voie de l'instabilité des microsatellites**

**FAP** — **<0.5%**

**Sporadique** — **~ 85%**

**Lynch** — **~ 3-5%**

**Sporadique** — **~ 12-15%**

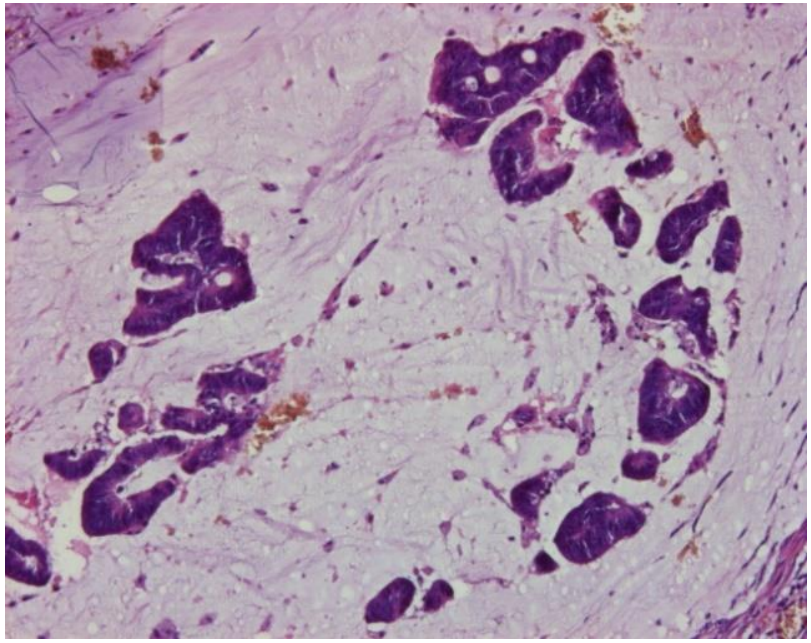
# Cancer colorectal instable

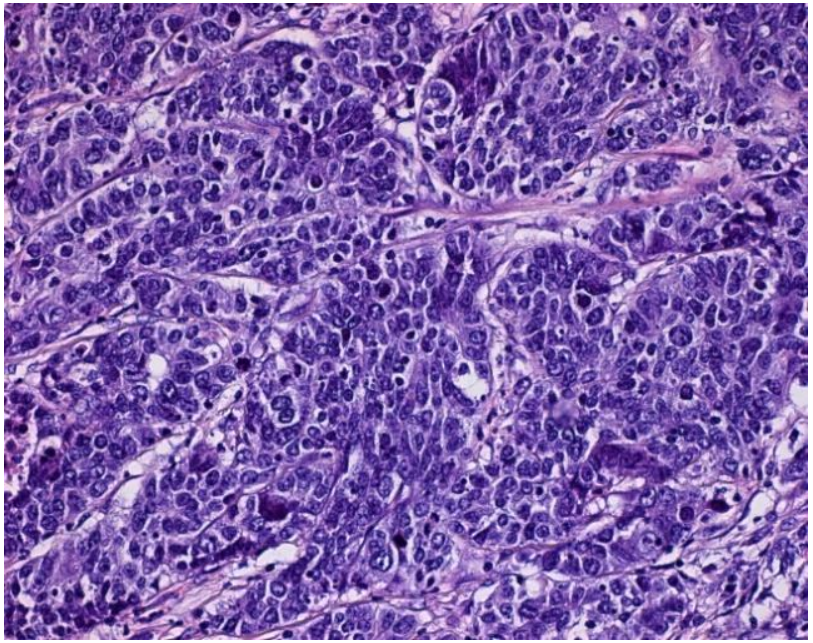

- **12- 15% des CRC**
  - **Lynch 3-5%: → 1994**

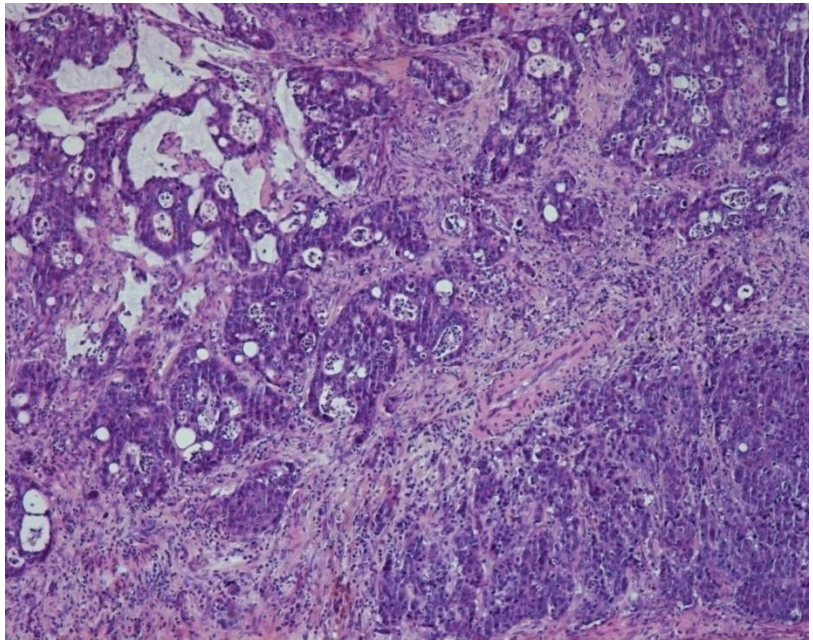
    **mutation gènes de réparation de l'ADN (MMR): MLH1, MSH2, pMS2 et MSH6**
  - **Sporadique 10-12% → 1997**

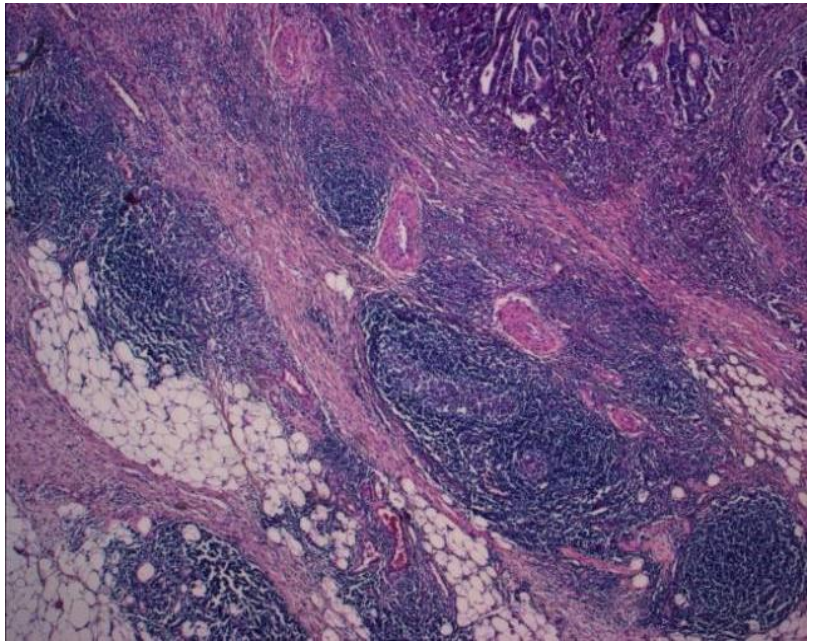
    **hyperméthylation du promoteur du gène MLH1**

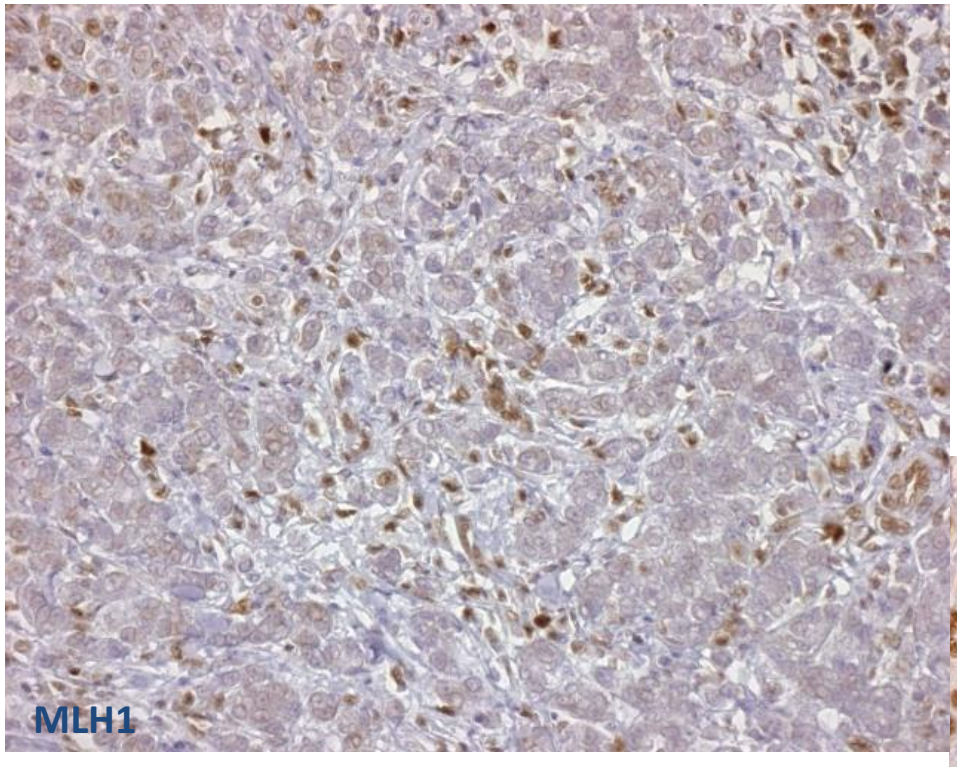
- **Colon droit, svt exophytiques et de grande taille**
- **Histologie spécifique**
- **Meilleur pronostic et réponse différente aux R/**

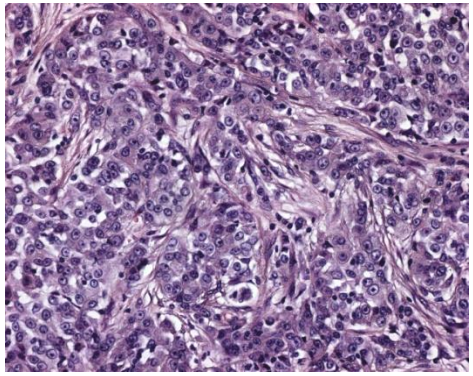


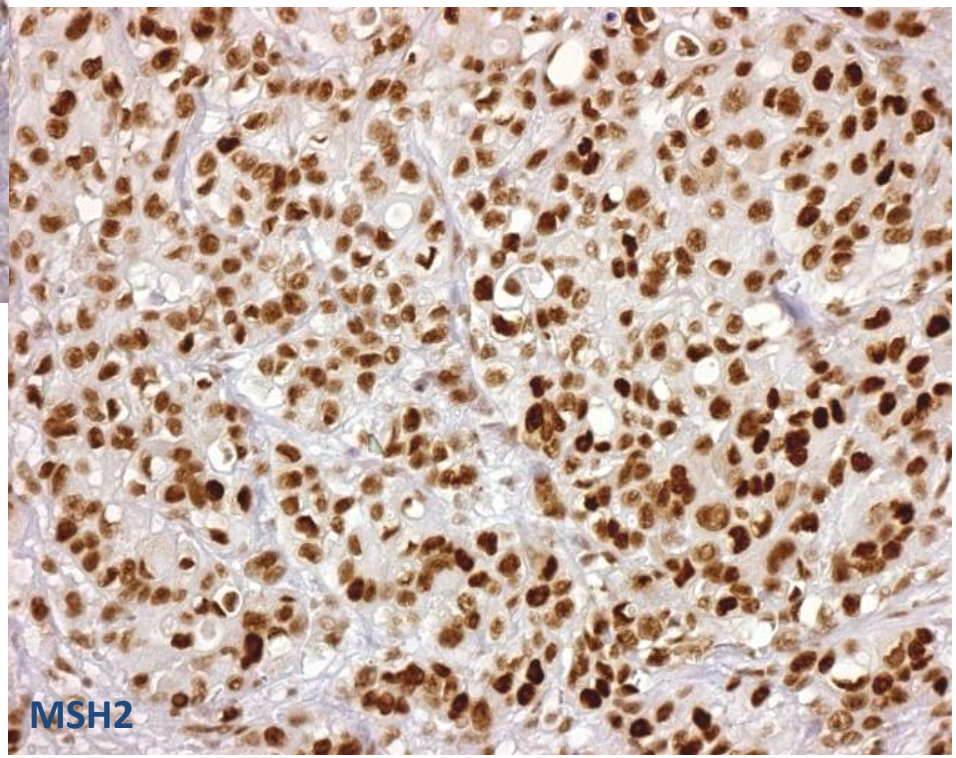


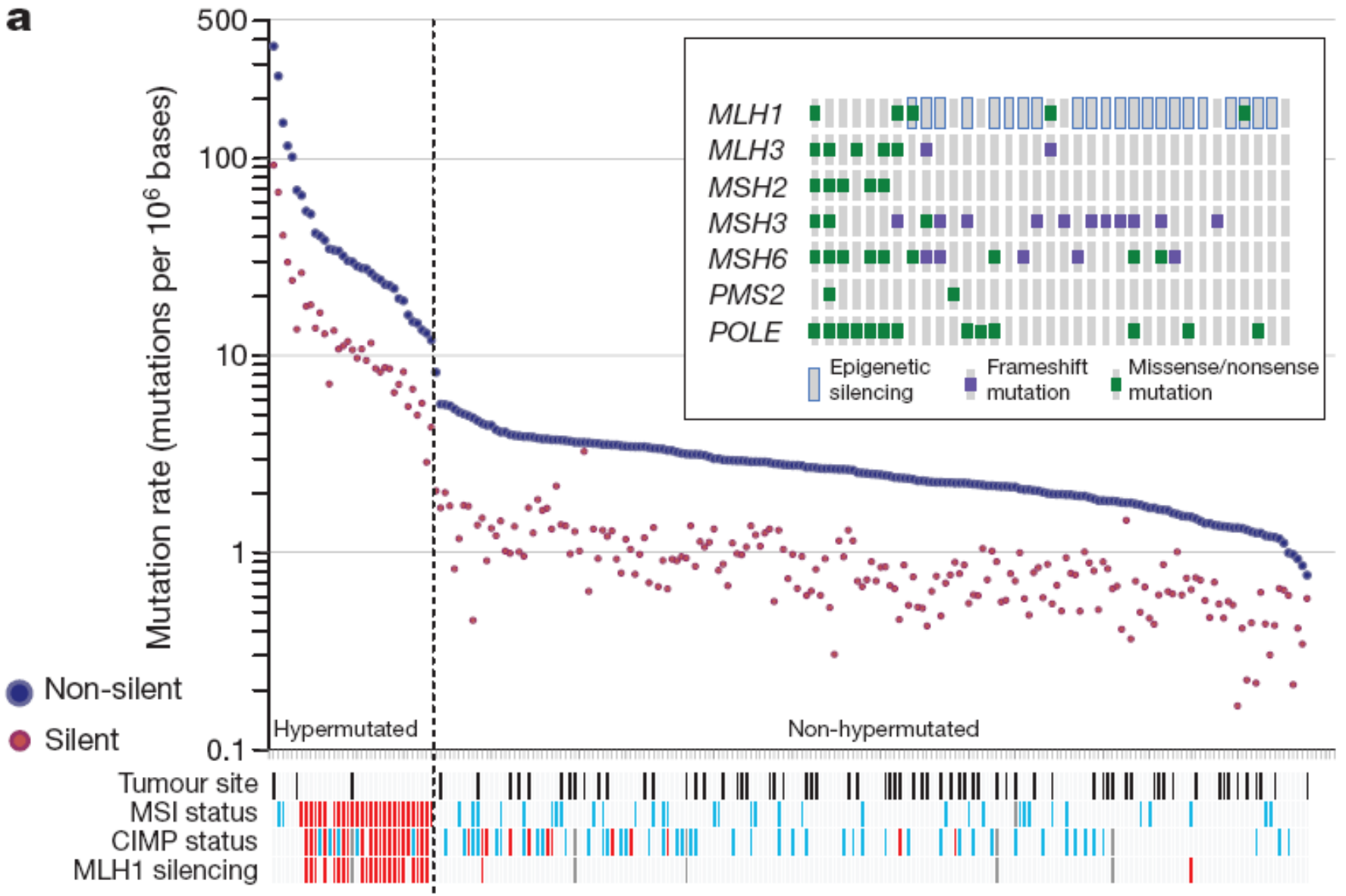




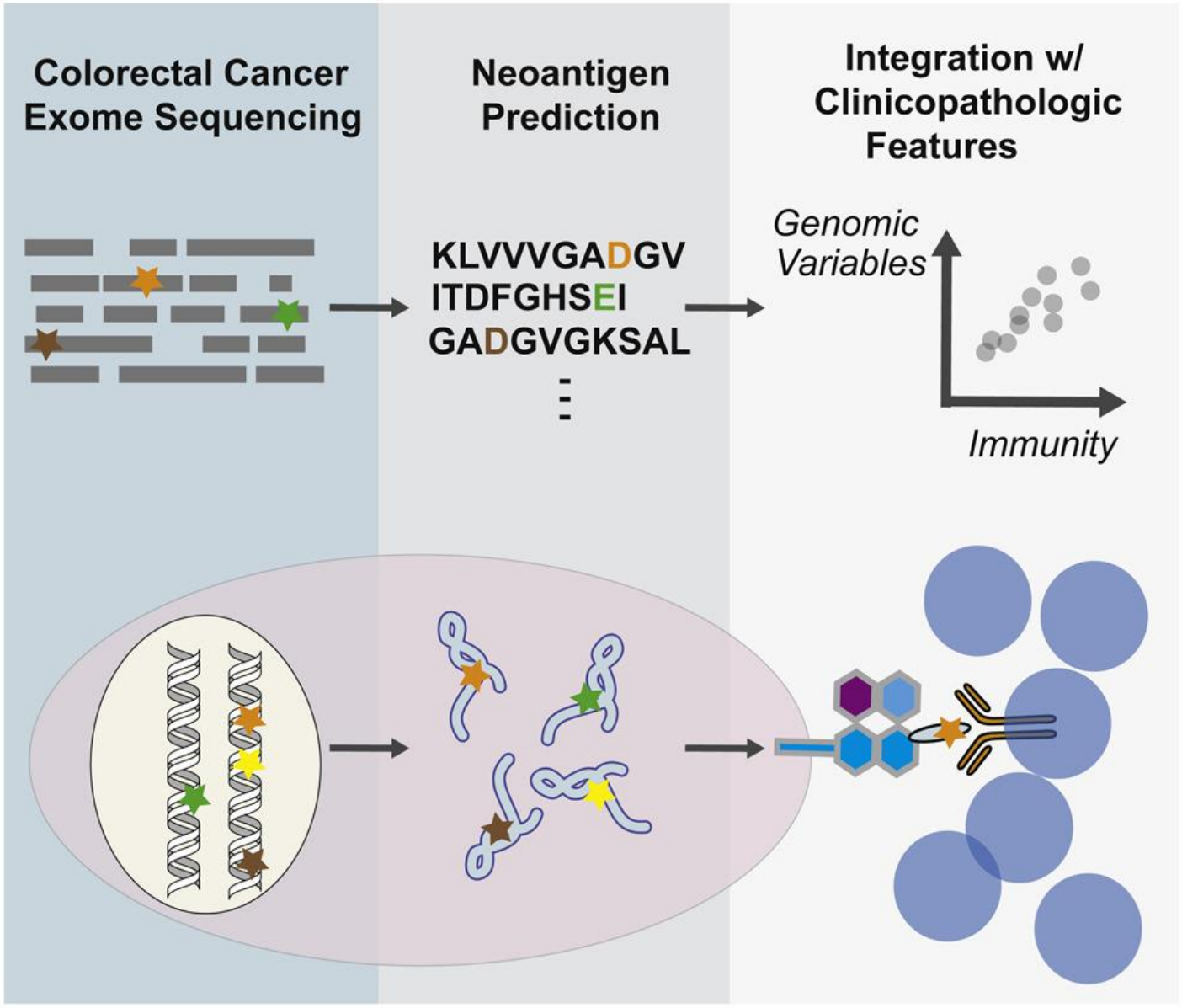

MLH1




MSH2



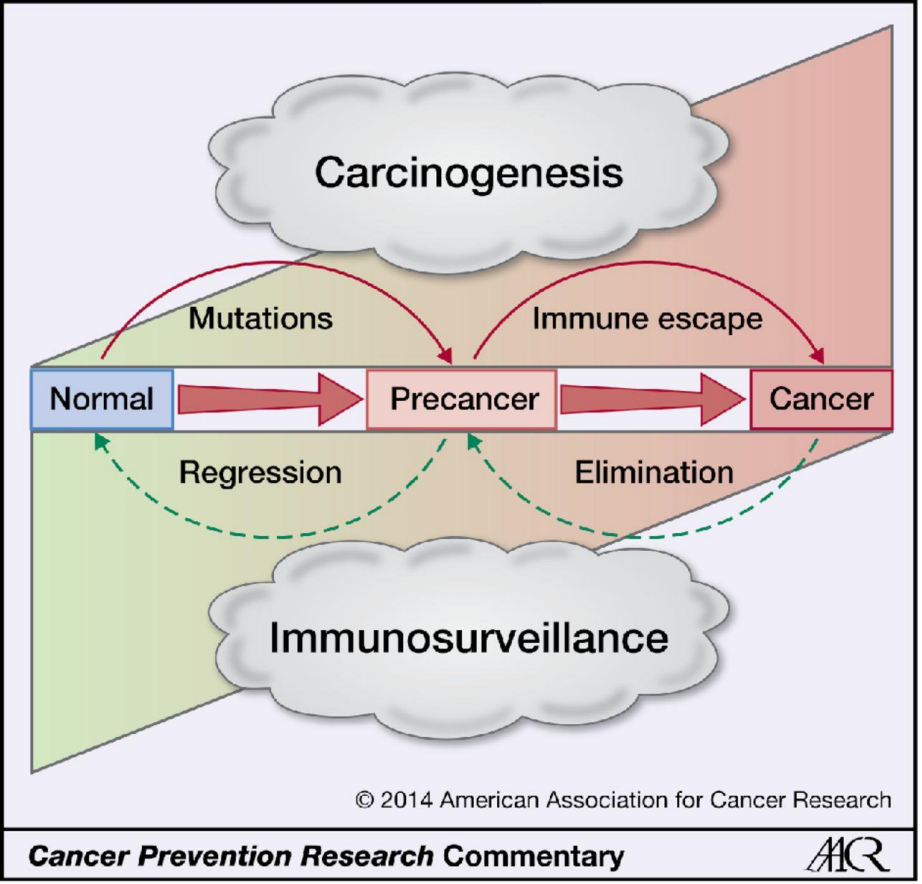

TCGA Nature 2012



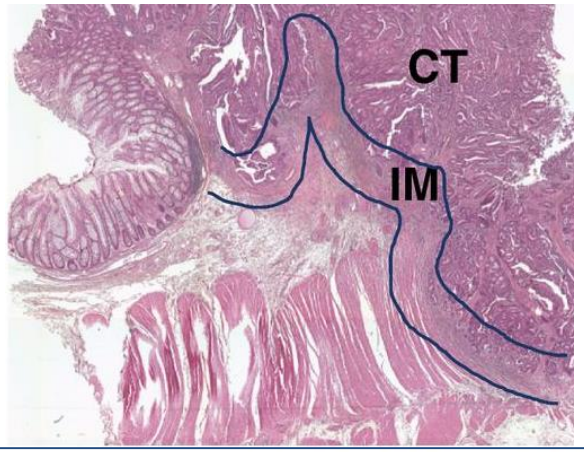

↑ Neoantigen Load

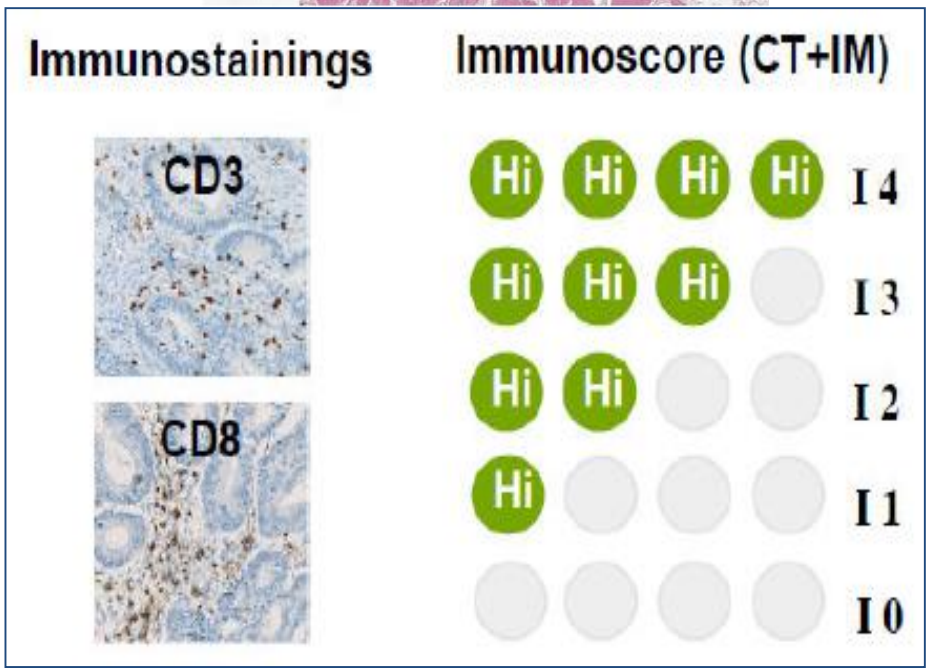
{ ↑ Tumor-Infiltrating Lymphocytes
Memory T cells
Survival

Giannakis, Cell reports 2016



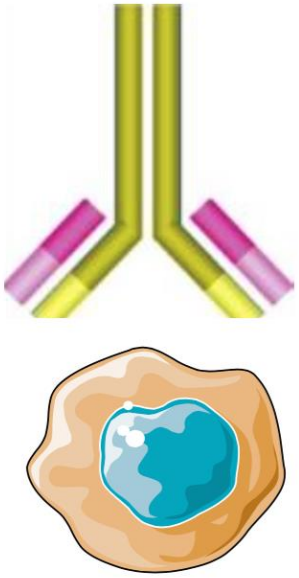

# Immunoscore: valeur pronostique ++



# Changement de paradigme dans le traitement du cancer

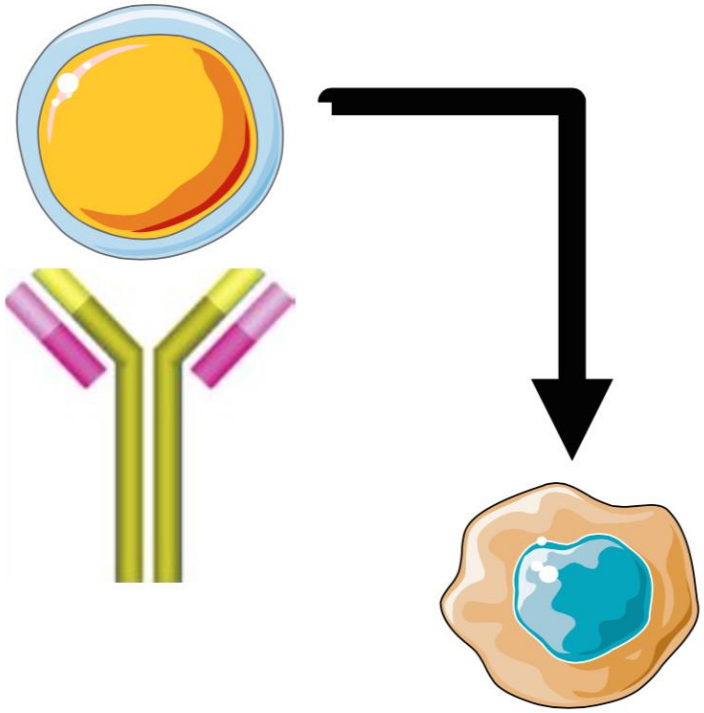
**Paradigme historique:**
**Cibler la cellule cancéreuse**



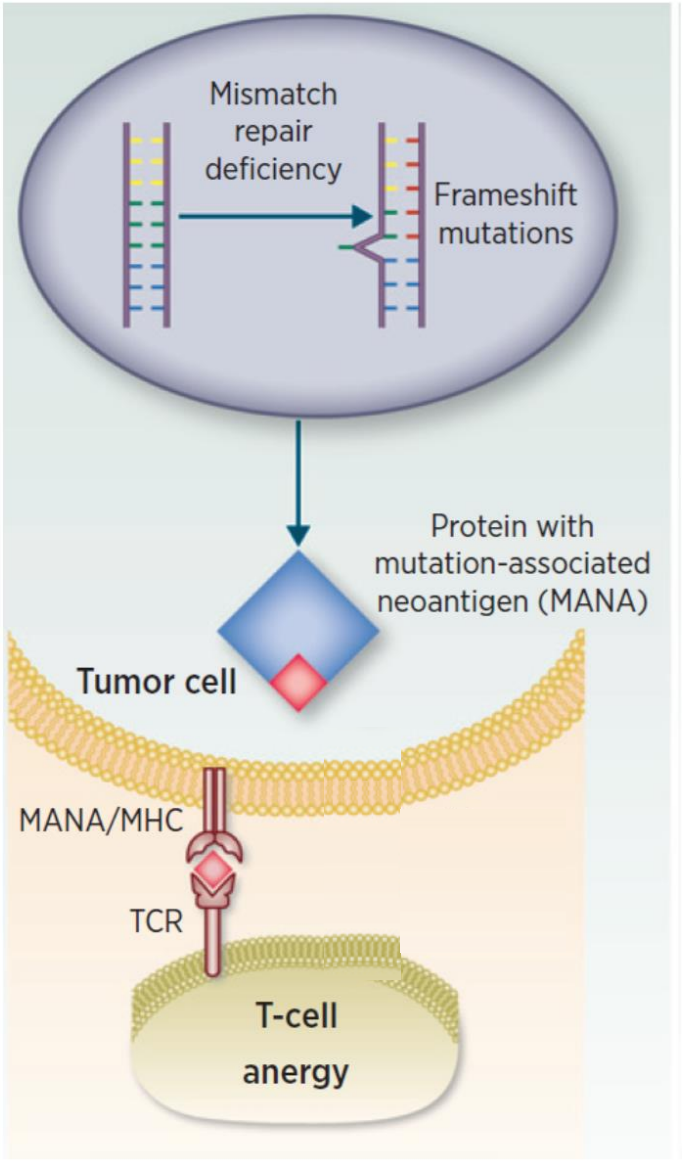
**Cellule cancéreuse**

**Nouveau paradigme:**
**Cibler les cellules immunitaires**

**Lymphocyte**

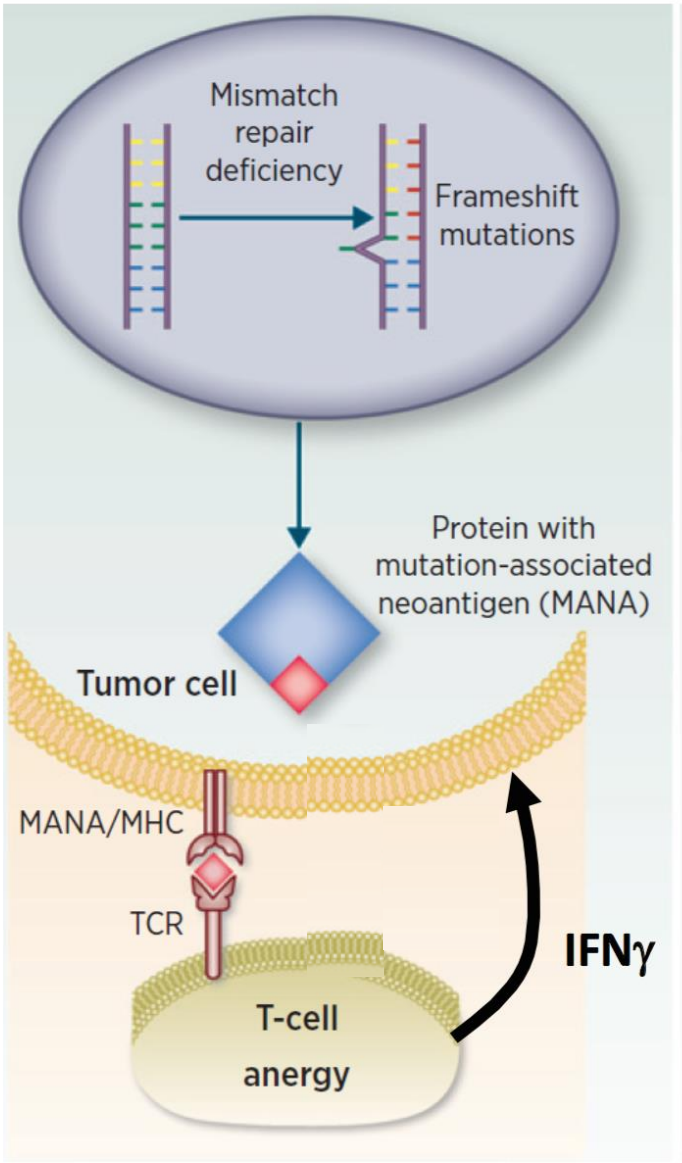


# Impact immun du statut MSI



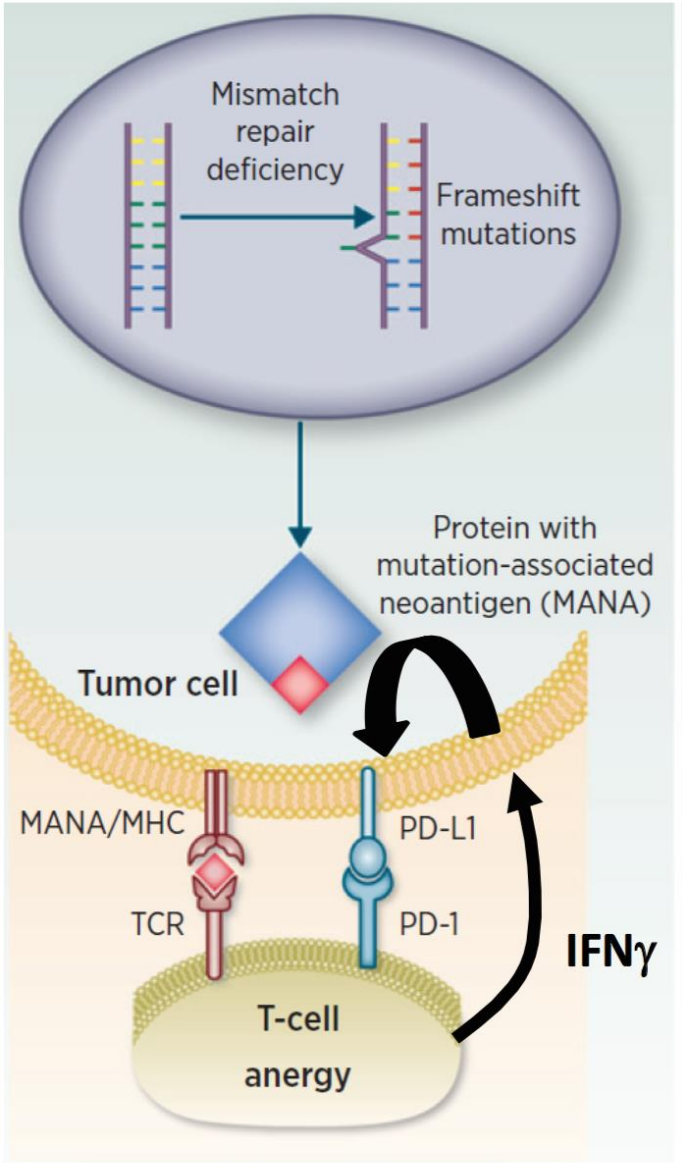

*Dudley JC, et al. Clin. Cancer Res. 2016.*

# Impact immun du statut MSI



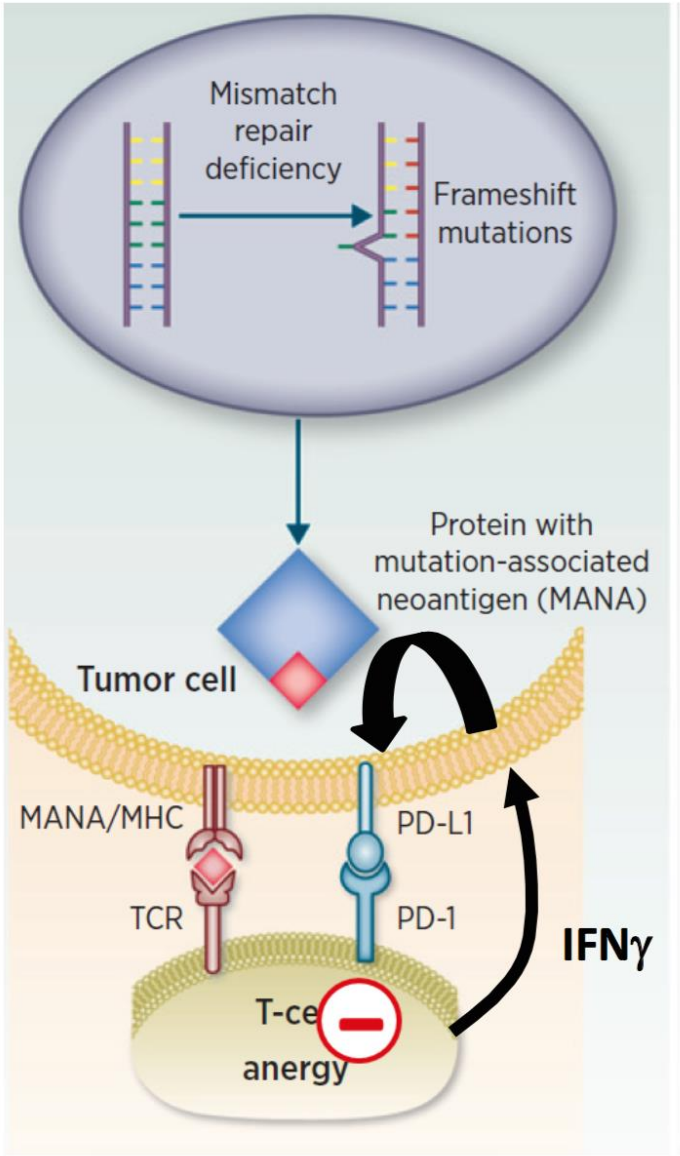

*Dudley JC, et al. Clin. Cancer Res. 2016.*

# Impact immun du statut MSI



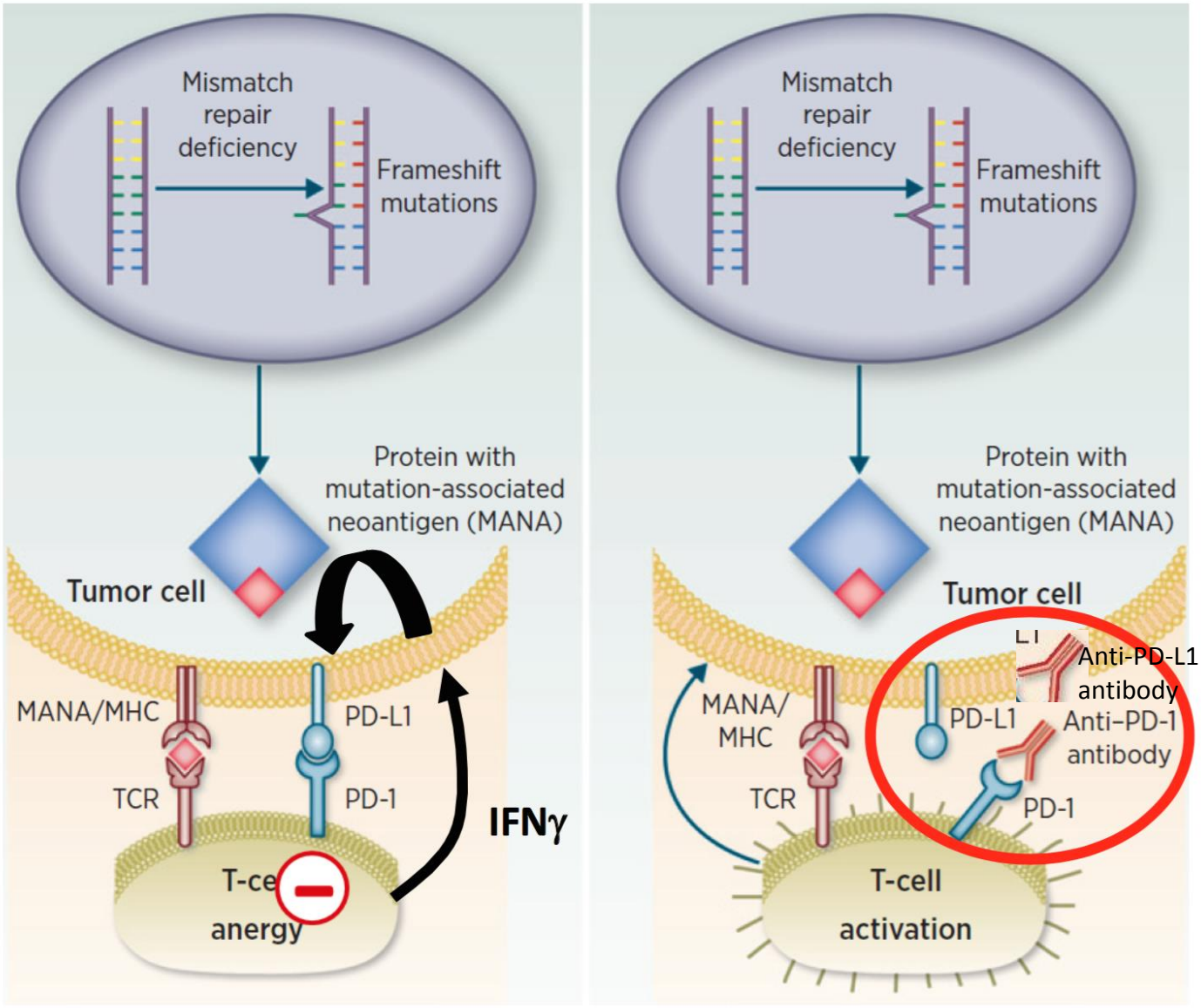

*Dudley JC, et al. Clin. Cancer Res. 2016.*

# Impact immun du statut MSI



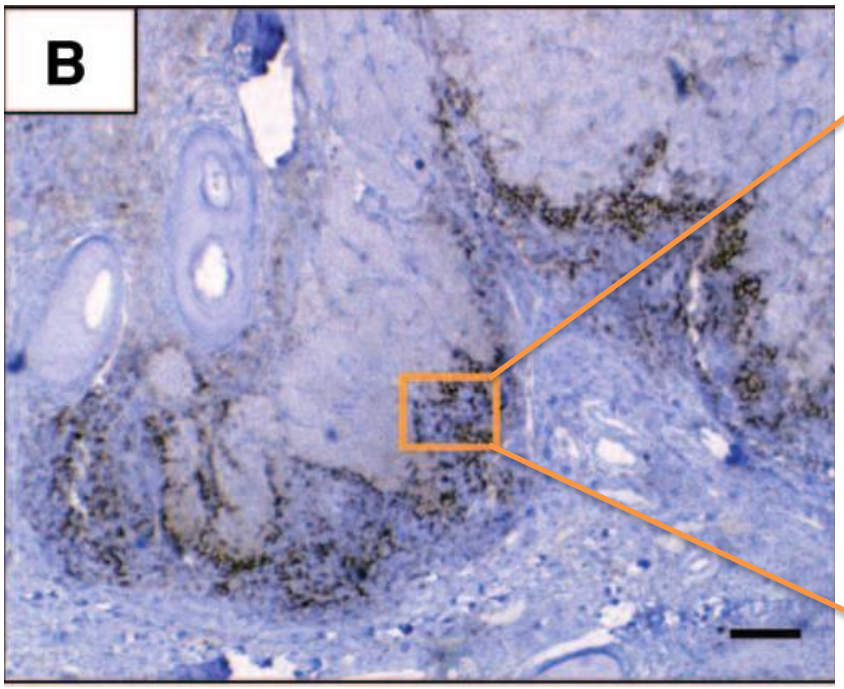

*Dudley JC, et al. Clin. Cancer Res. 2016.*

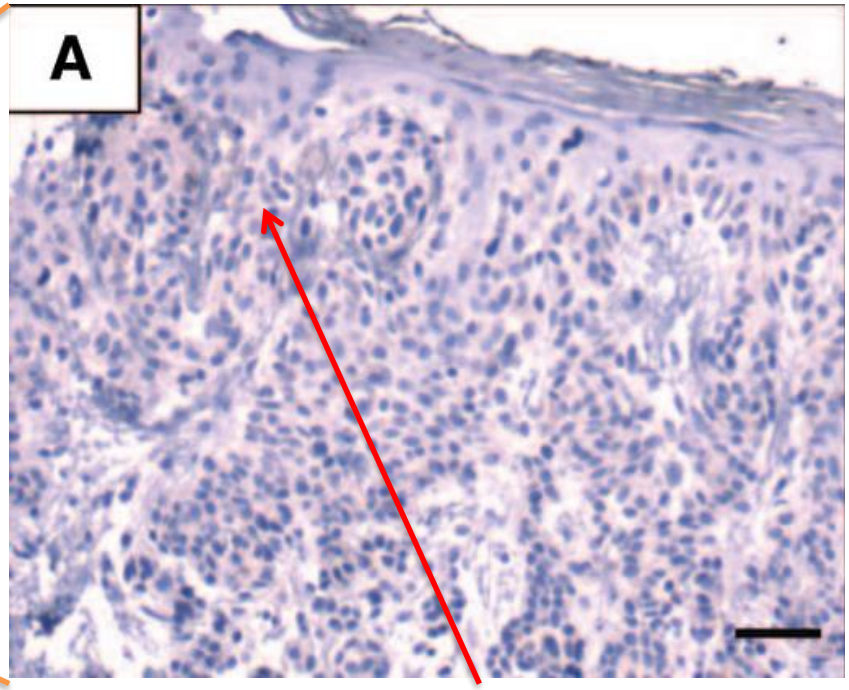
# Impact immun du statut MSI




*Dudley JC, et al. Clin. Cancer Res. 2016.*

# Infiltration des lymphocytes T conduit à un phénomène de défense de la tumeur qui exprime PD-L1




Cellules cancéreuse exprimant le PD-L1

Taube, science Transl Med 2012

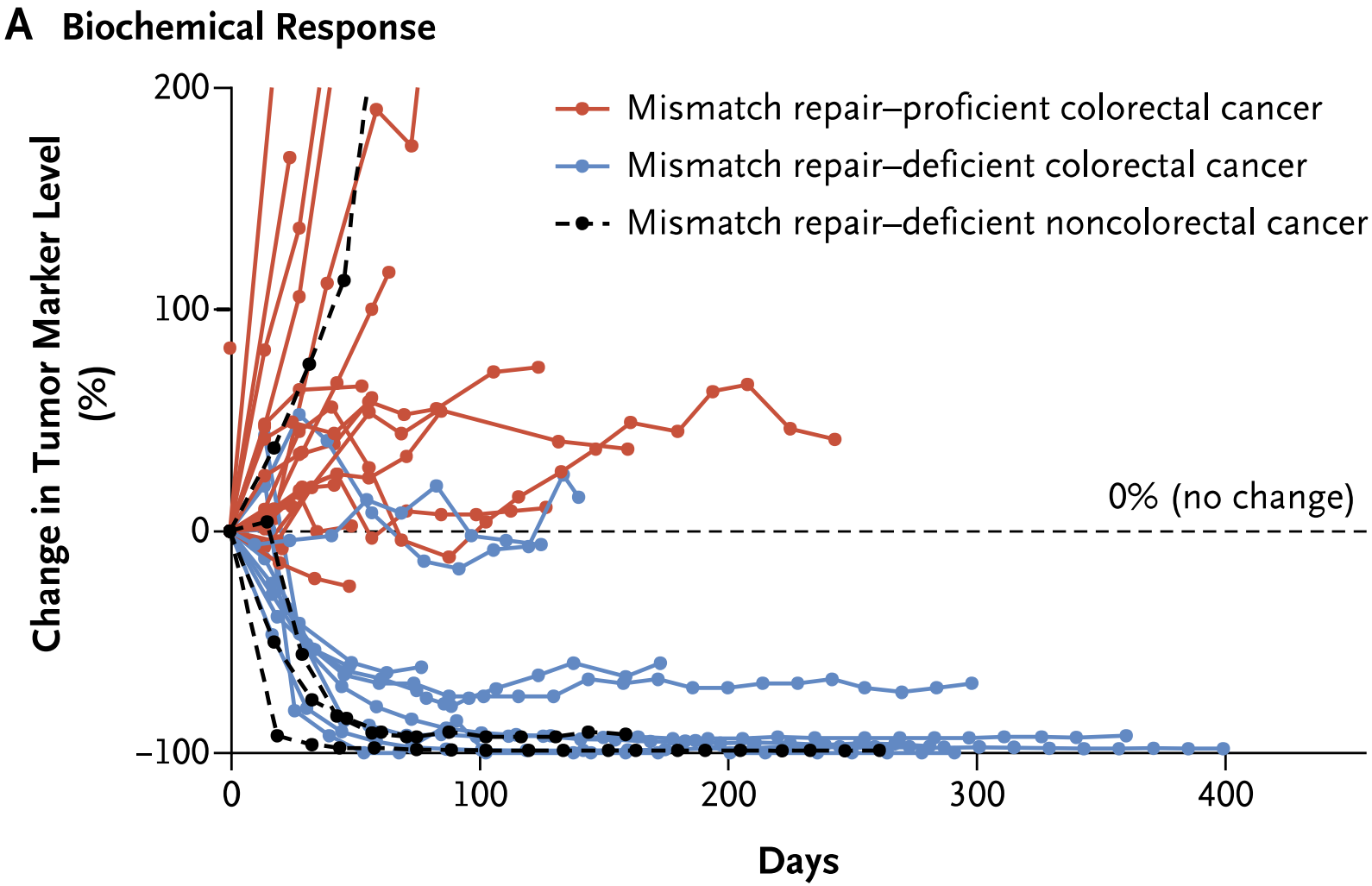
**Table 2.** Objective Responses According to RECIST Criteria.

| 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) |
| Median duration of response — wk | Not reached | NA¶ | Not reached |
| Median time to response (range) — wk | 28 (13–35) | NA¶ | 12 (10–13) |

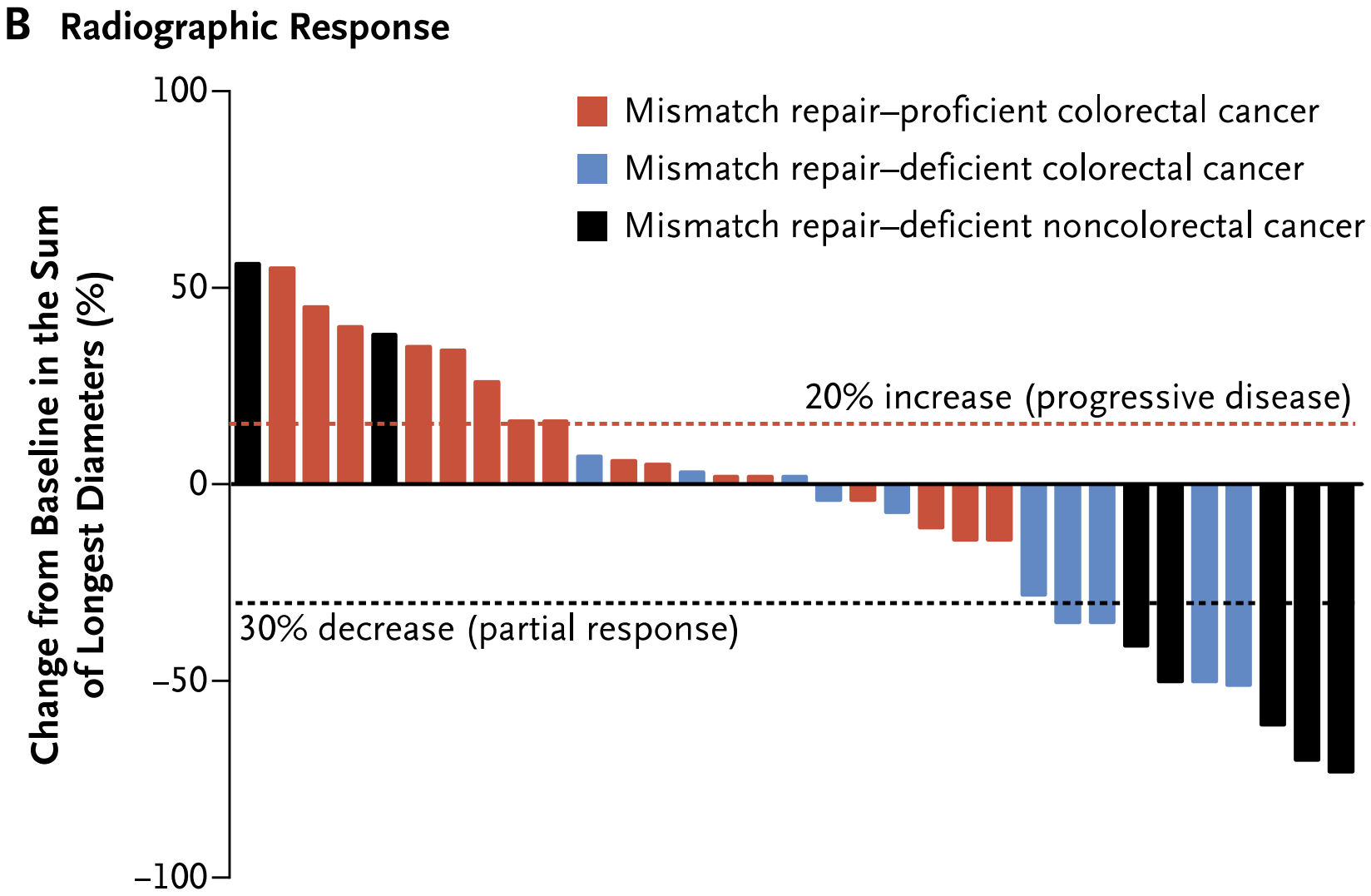
**Tumeurs MSI : mutations +++ ➔ Neoantigens**

**Pembrolizumab (anti PD1) 10 mg/kg /14 j**

Le, NEJM 2015


A Biochemical Response
Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer
Change in Tumor Marker Level (%)
200
100
0
−100
0% (no change)
0
100
200
300
400
Days

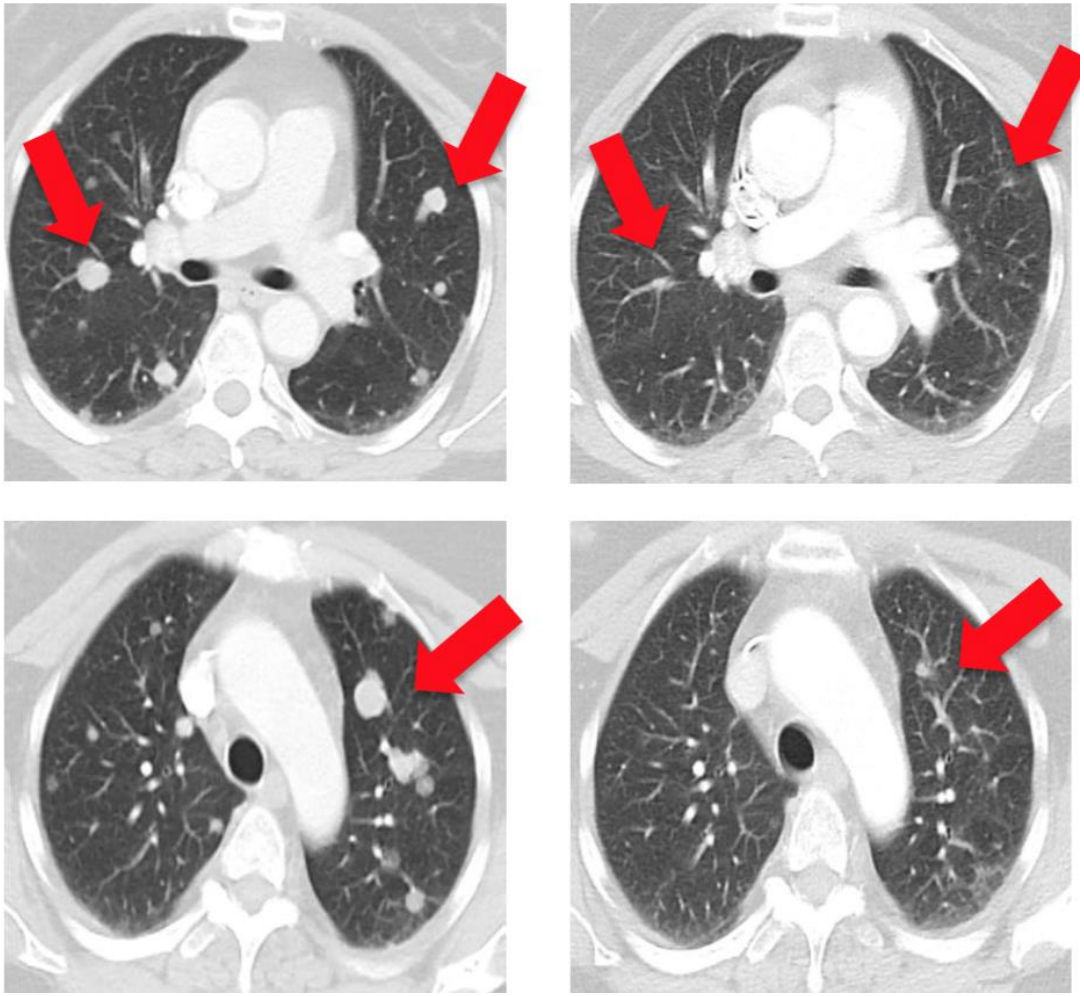
Le, NEJM 2015

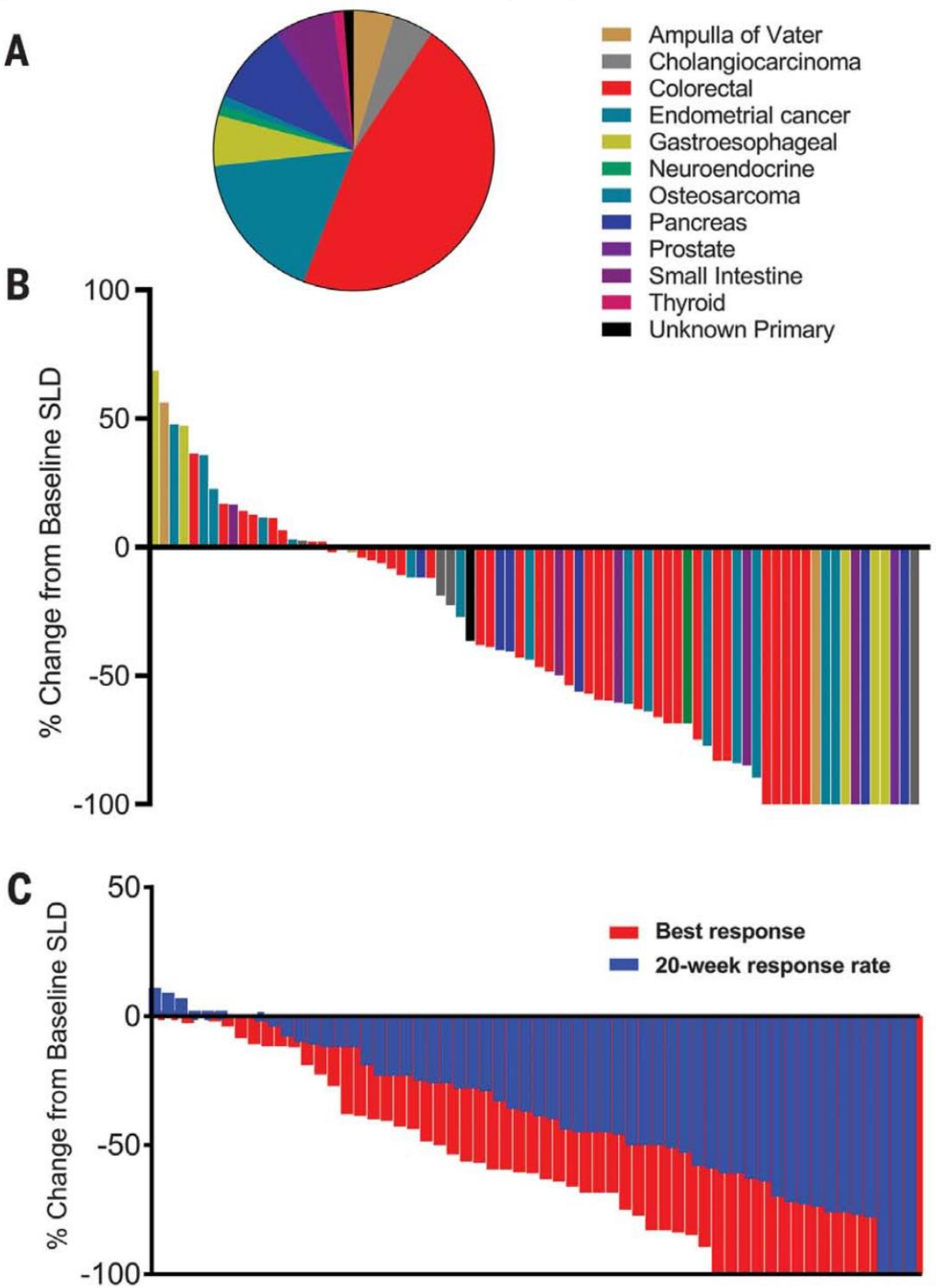

B Radiographic Response
Mismatch repair–proficient colorectal cancer
Mismatch repair–deficient colorectal cancer
Mismatch repair–deficient noncolorectal cancer
Change from Baseline in the Sum of Longest Diameters (%)
100
50
0
−50
−100
20% increase (progressive disease)
30% decrease (partial response)

Le, NEJM 2015

# Patient, 45 ans, Tumeur colon métastatique, MSI +, réfractaire à la chimiothérapie. Traitement Pembrolizumab (anti-PD1)

**Baseline** **Semaine 16**






## Toute tumeur MSI +

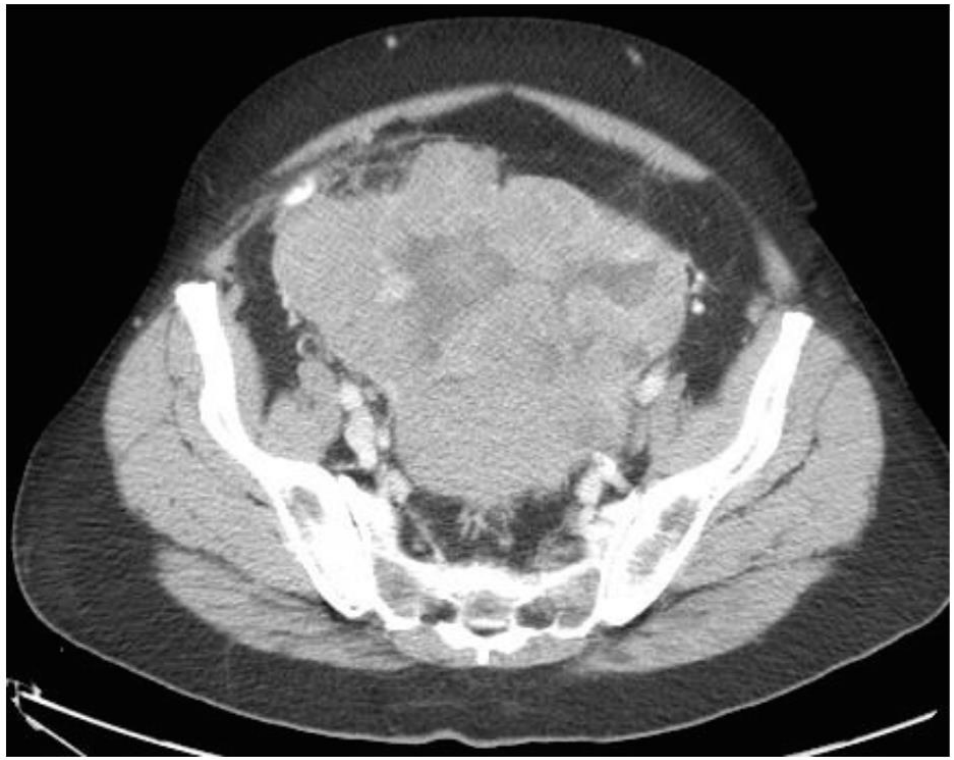
Le et al, Science 2017

# Réponse rapide au Nivolumab (anti-PD1)

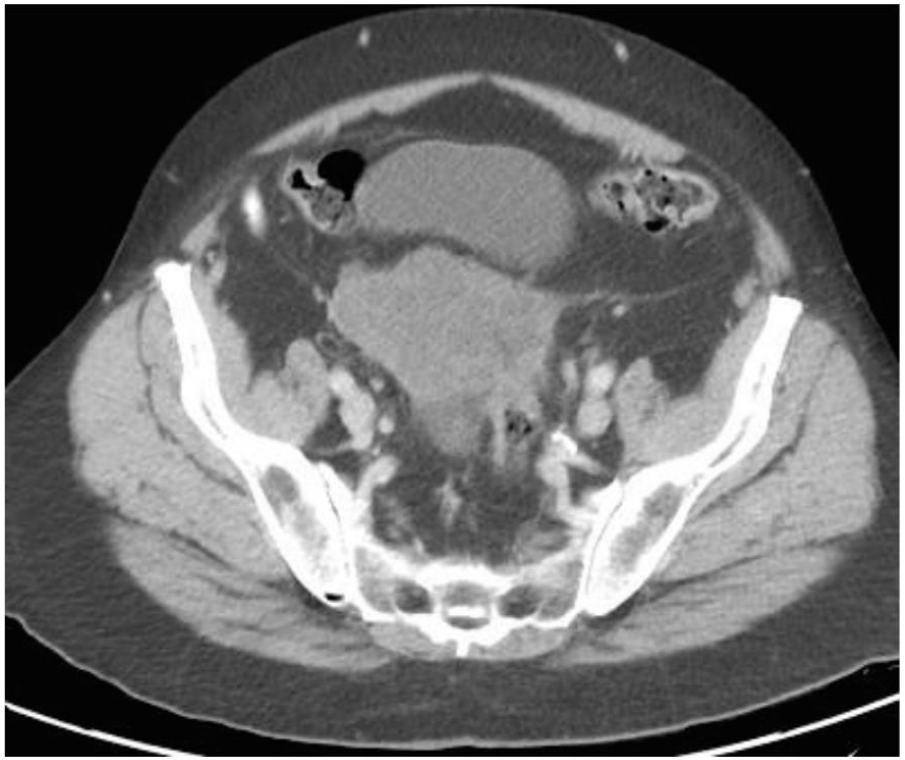
Patiente de 66 ans, tumeur de l'estomac (MSI +). Métastases foie-pelvis.

Réponse prolongée > 1 an

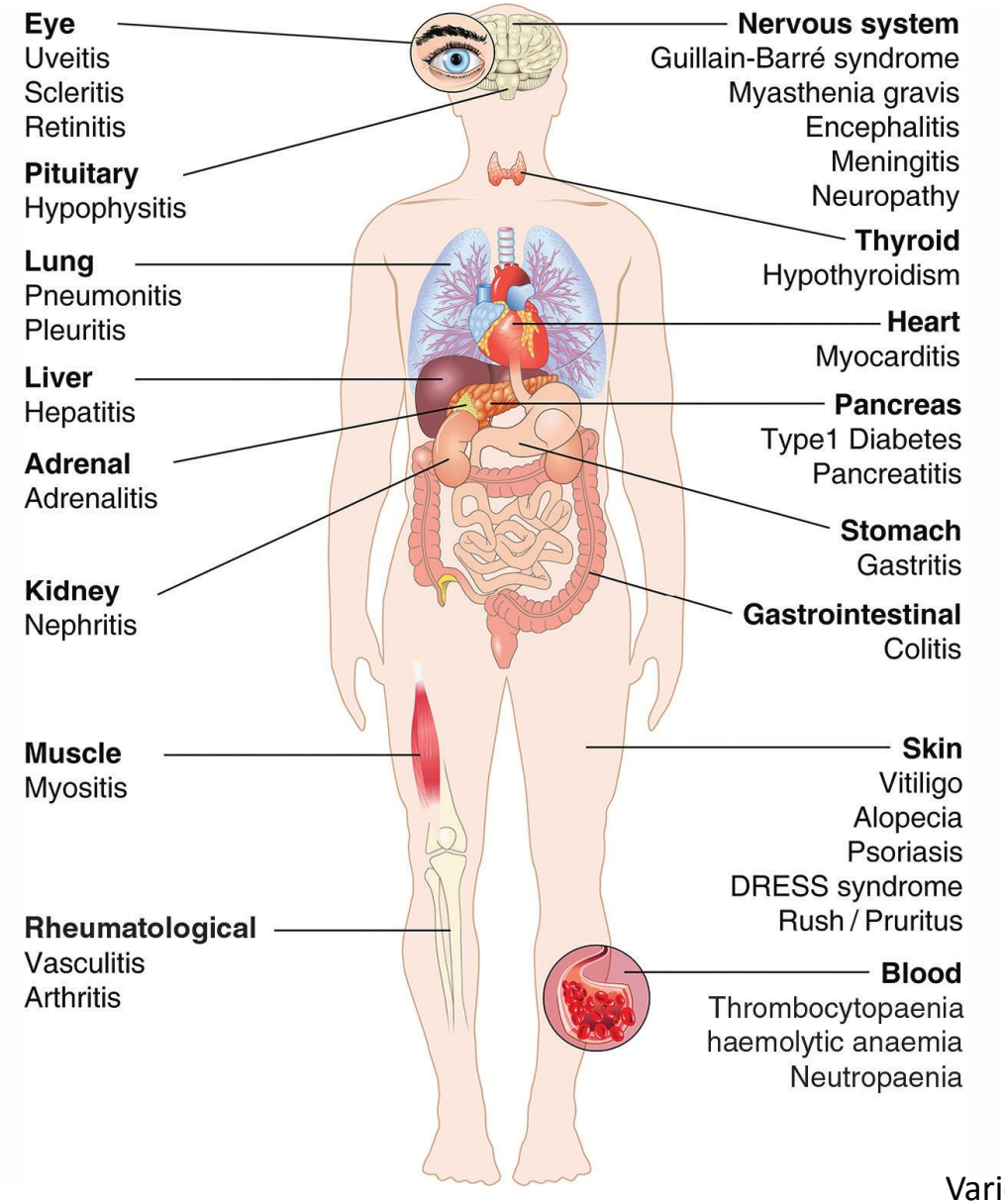
**Baseline**



**Semaine 8**



# Immunothérapies: effets secondaires ?




Varicchi, ESMO Open 2017


*« L'utilisation de l'immunothérapie a été l'avancée scientifique la plus significative en 2013 pour combattre le cancer »*

Science, décembre 2013

# Breaking News

August 1, 2017

## FDA Approves Nivolumab for MSI-H or dMMR Colorectal Cancer

The FDA has granted an accelerated approval to nivolumab (Opdivo) for the treatment of adult and pediatric patients with microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

## Major FDA Approvals of PD-1 / PD-L1 Inhibitors

| Drug | Commercial name | Owner | Target | First approval date |
|---|---|---|---|---|
| Pembrolizumab | Keytruda | MSD | PD-1 | September 2014 |
| Nivolumab | Opdivo | BMS | PD-1 | December 2014 |
| Atezolizumab | Tecentriq | Roche | PD-L1 | May 2016 |
| Avelumab | Bevancio | EMD and Pfizer | PD-L1 | March 2017 |
| Durmalumab | Imfinzi | AstraZeneca | PD-L1 | May 2017 |

# Merci de votre attention!