Actualités thérapeutiques

11/04/2024

Niort

Benjamin SUEUR

Liens d’intérêts

Invitation à des congrès: SANOFI
AMGEN

Orateur:
TILLOTS

Plan

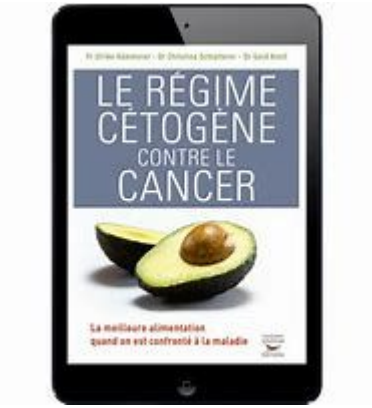
1) Généralités
2) Un point sur les régimes anti cancers
3) Cancer colorectal
4) Cancer oeso-gastrique
5) Carcinome hépato-cellulaire
6) Adénocarcinome du pancréas

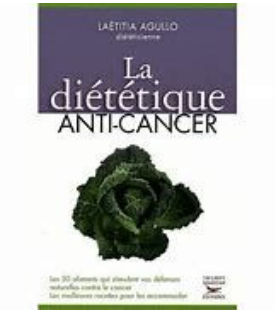
Généralités

- Age médian de diagnostic : 71 ans dans les cancers digestifs(1)
- Part des plus de 75 ans dans les principaux cancers digestifs entre 33 et 47% (43% colorectal)
- 25% de patients inclus dans les essais de phase 3 depuis 2010 ont plus de 75 ans(2)
- 7 études dans le cancer colorectal ont montré un gain de survie sans dégradation de la qualité de vie chez les plus de 80 ans(2)

Régimes “anti cancers”

- 10 % des patients réalisent un régime anti glucidiques
- ⅔ des patients attendent un bénéfice de leur régime spécifique sur l'évolution de leur maladie





Régime “anti cancers”

- 2 principaux régimes:
  régime cétogène (réduction à moins de 10% des glucides)

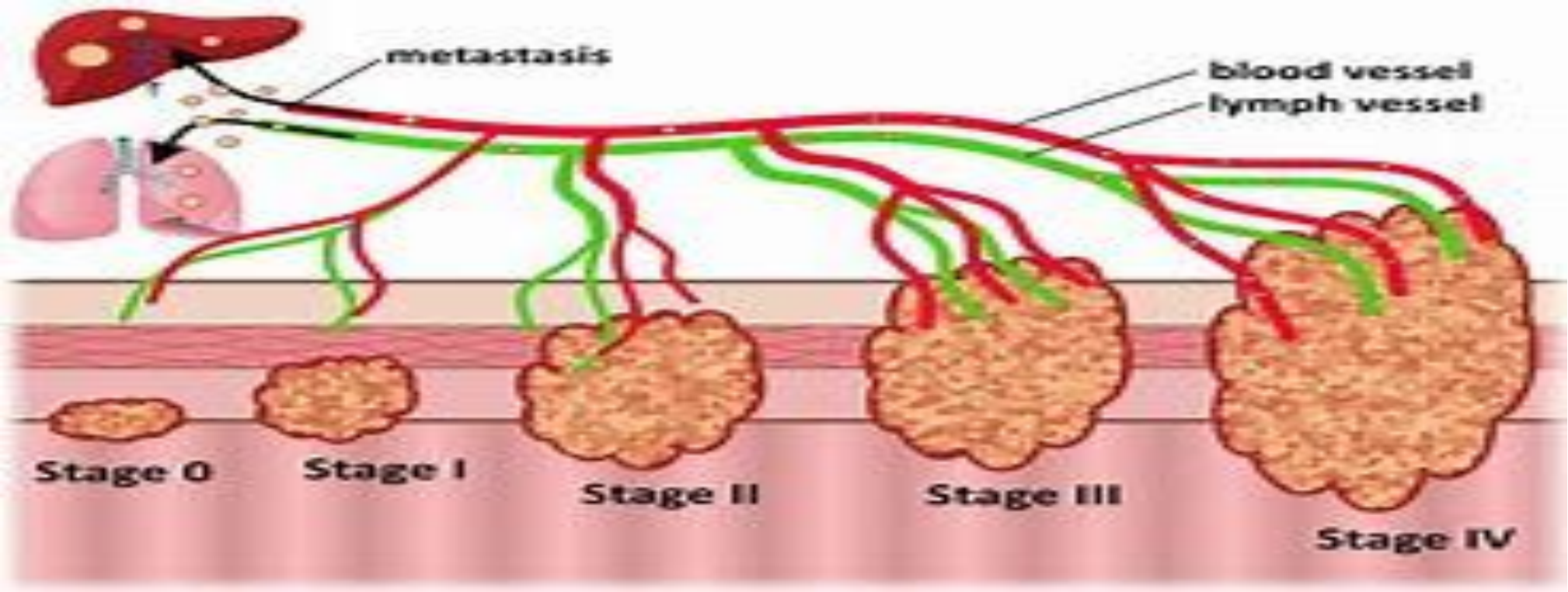
  jeune intermittent: arrêt complet entre 24 et 72 heures de macro nutriments

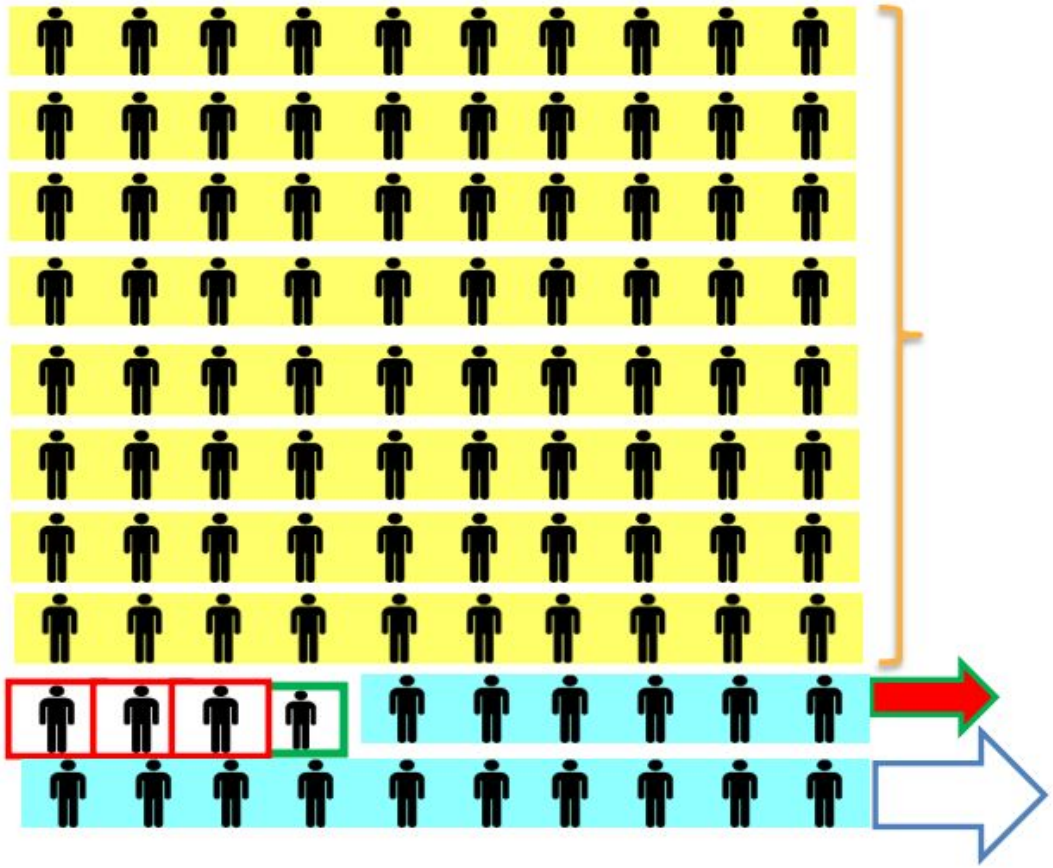
- Aucun bénéfice en survie et amélioration de la qualité de vie en études contrôlées/randomisées

- Effets délétères : sarcopénie, augmentation de la toxicité de certaines chimiothérapies (3)

Cancer colorectal

Rappel des différents stades



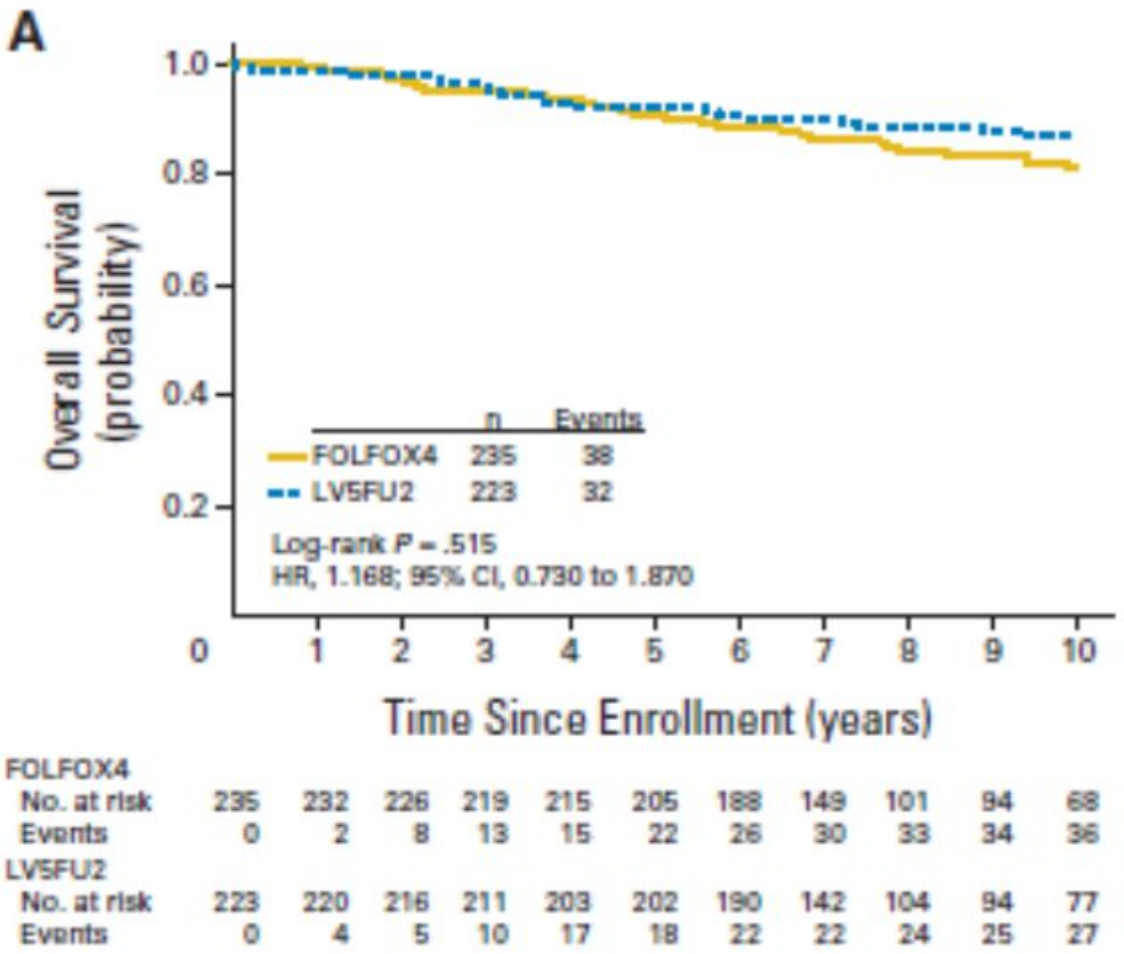


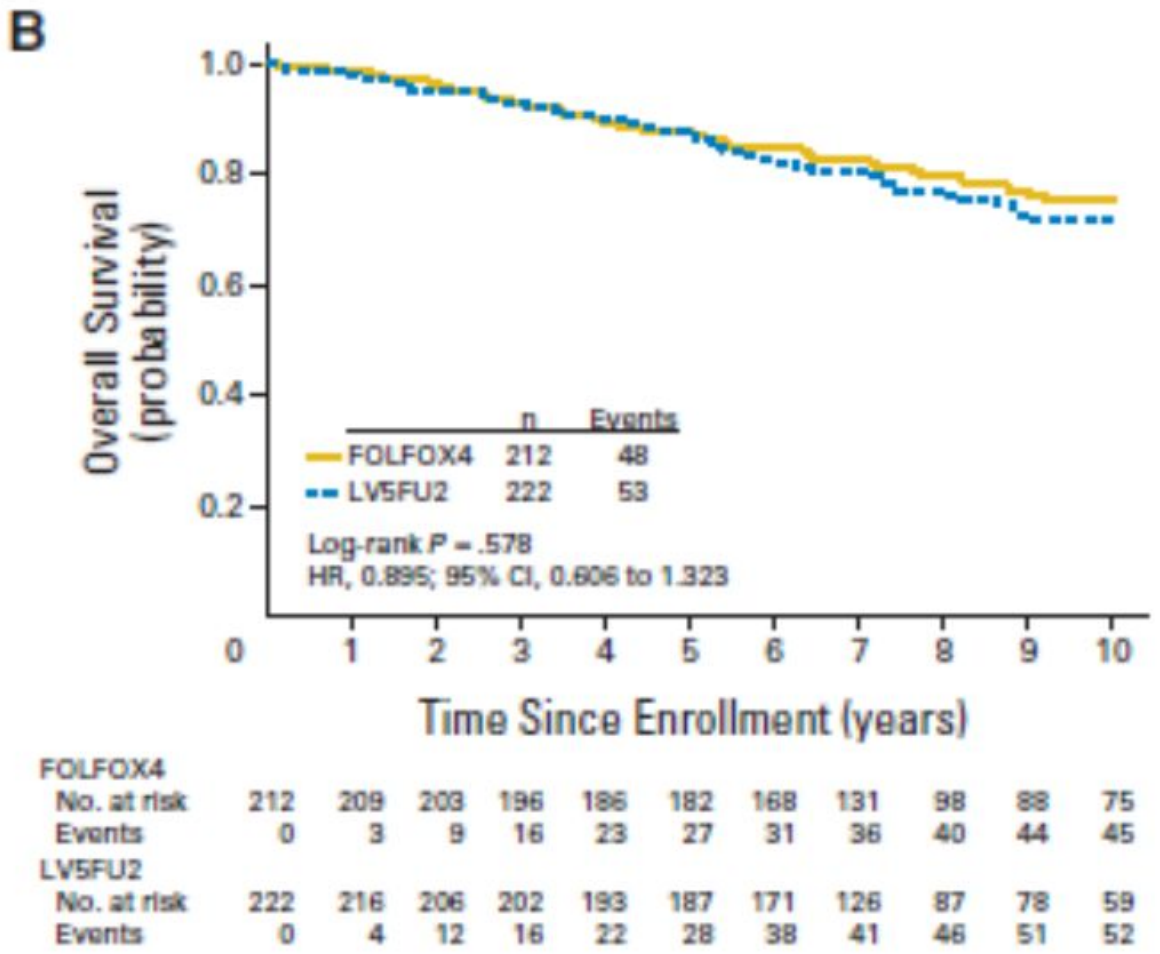
Patients guéris par chirurgie
(80%)

Patients guéris par chimio (3 à 4%)
Capecitabine ou LV5FU2 ou FOLFOX ou CAPOX

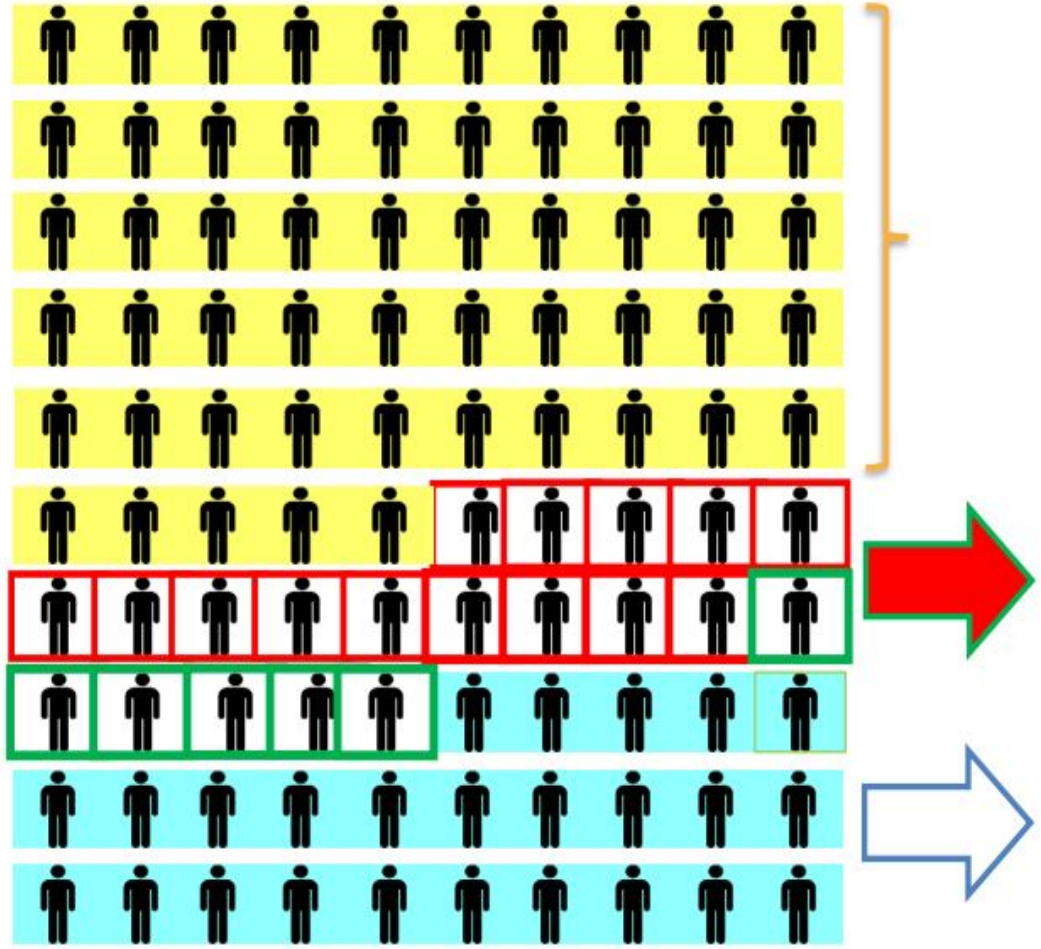
Patients qui vont rechuter (16 à 18%)

Stade II





Etude MOSAIC(4)



Patients guéris par chirurgie (55%)

Patients guéris par chimio (FOLFOX ou CAPOX): 20%
(12 à 15% par fluoropyrimidines et 5 à 8% par oxaliplatine)

Patients qui vont rechuter: 25 %

Stade III

		Regimen	
		CAPOX	FOLFOX
Groupe À Risque	Low-risk (T1-3 N1) ~60%	3 mois	(3-)6 mois
	High-risk (T4 et/ou N2) ~40%	3(-6) mois	6 mois

Etude IDEA(5)

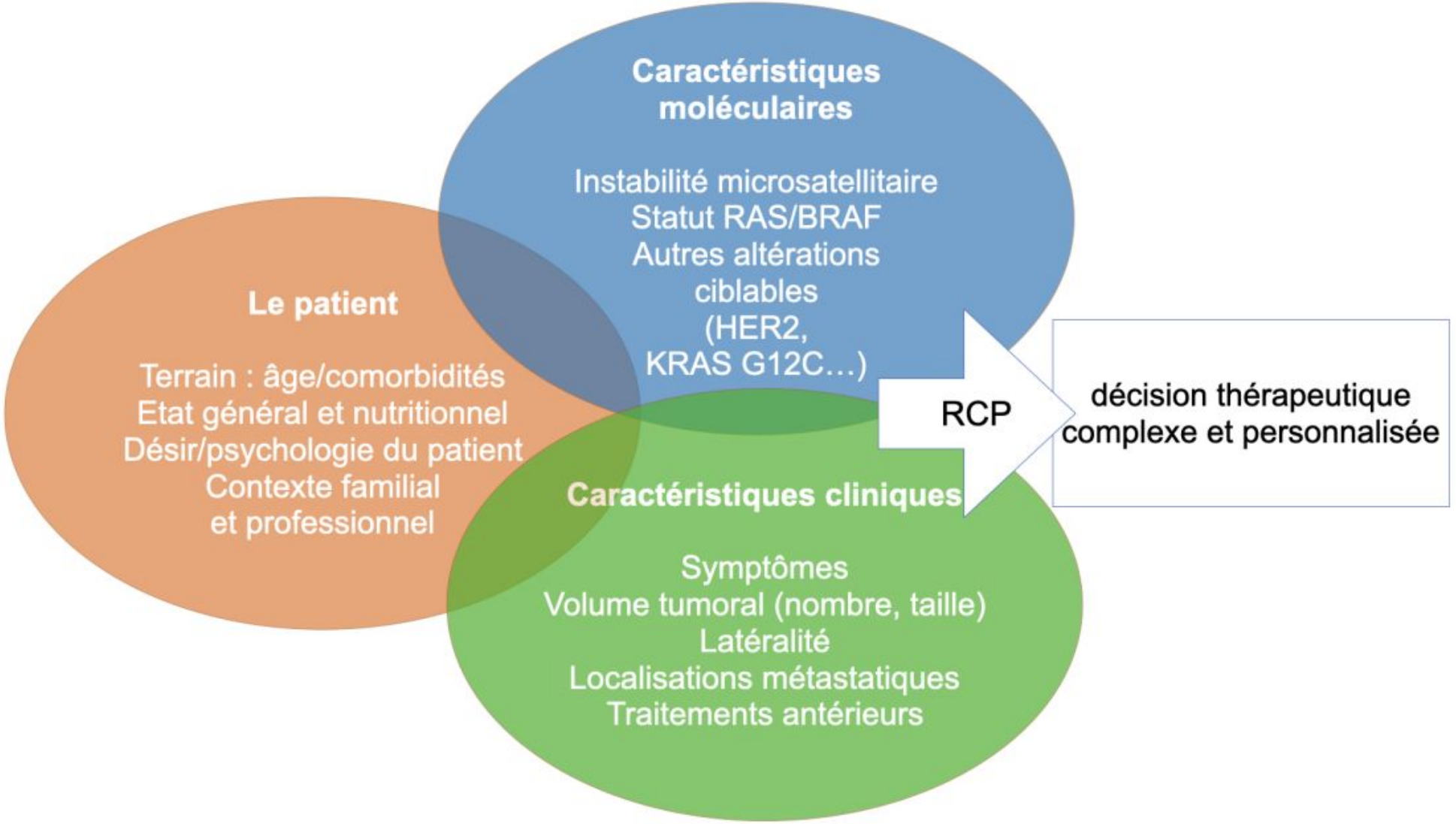
Cas particulier des plus de 70 ans

- Méta-analyse de 2001 chimio adjuvante par 5FU : augmentation survie par rapport chirurgie seule (6)

- Méta-analyse des essais MOSAIC, NSABPc07 et XELOXA sur Oxaliplatine après 70 ans: pas de bénéfice de l'ajout et risque plus élevé de neutropénie (7)

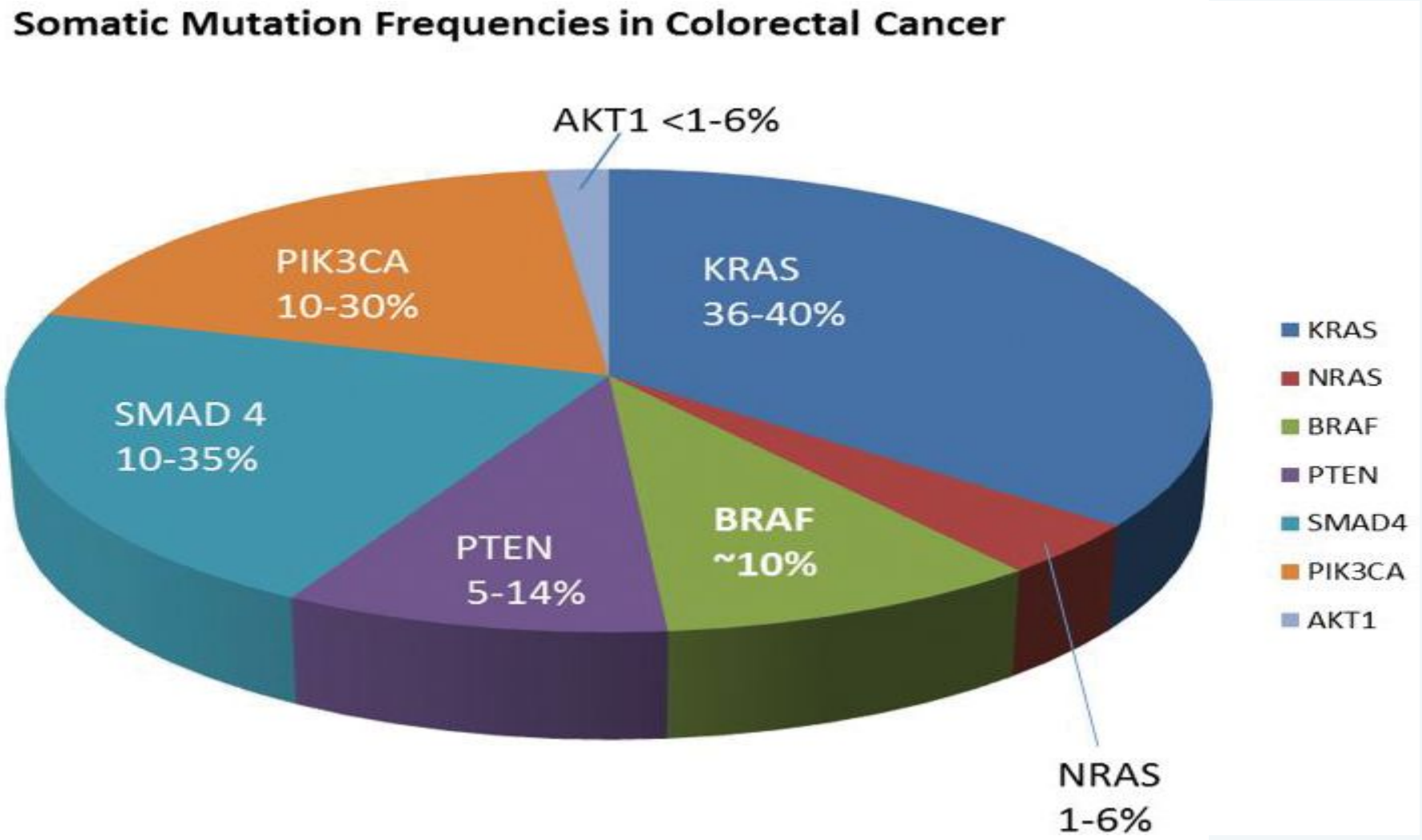
- Quid des hauts risques ? (T4, N2, N1c)

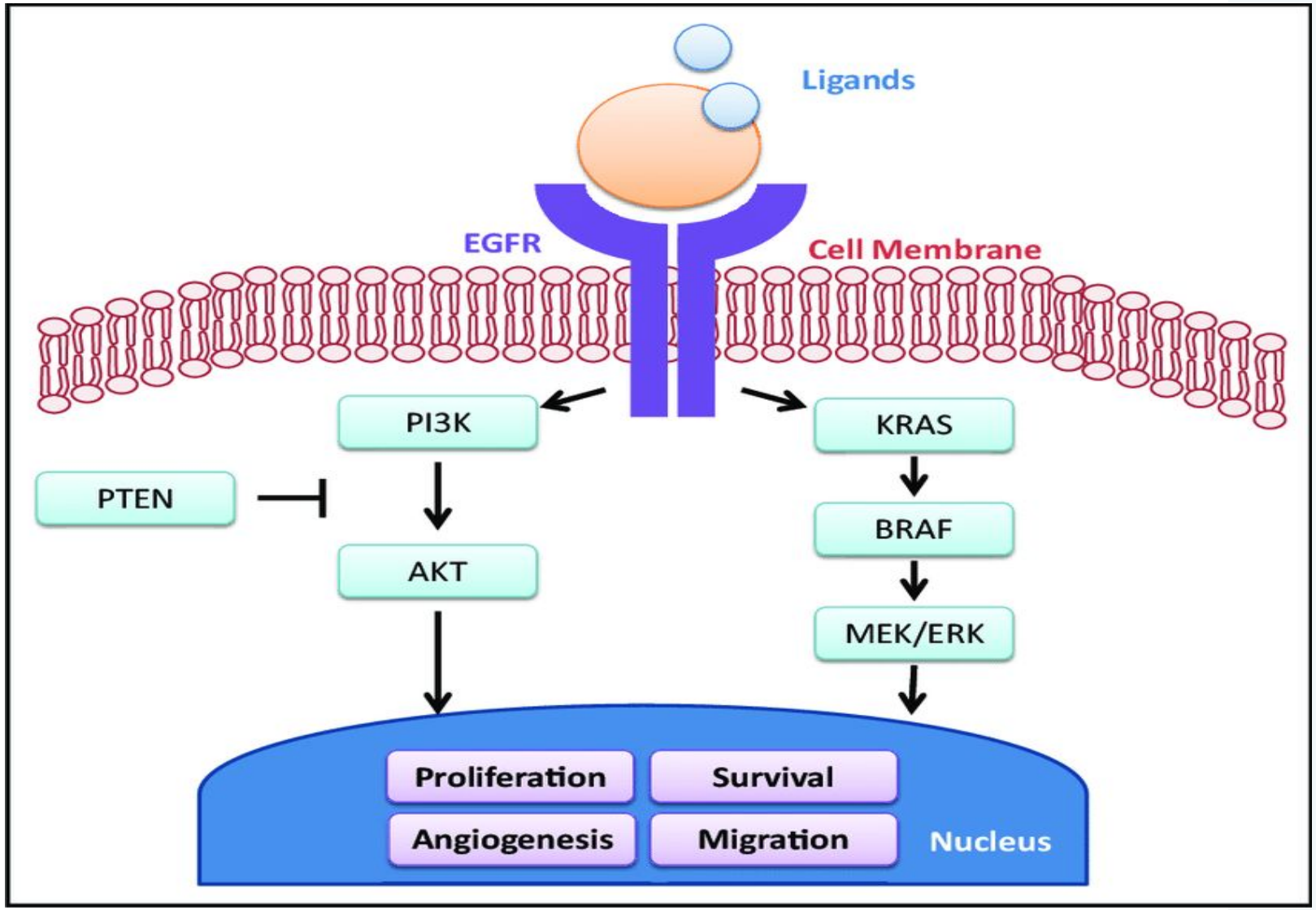
Etude PRODIGE 34+++



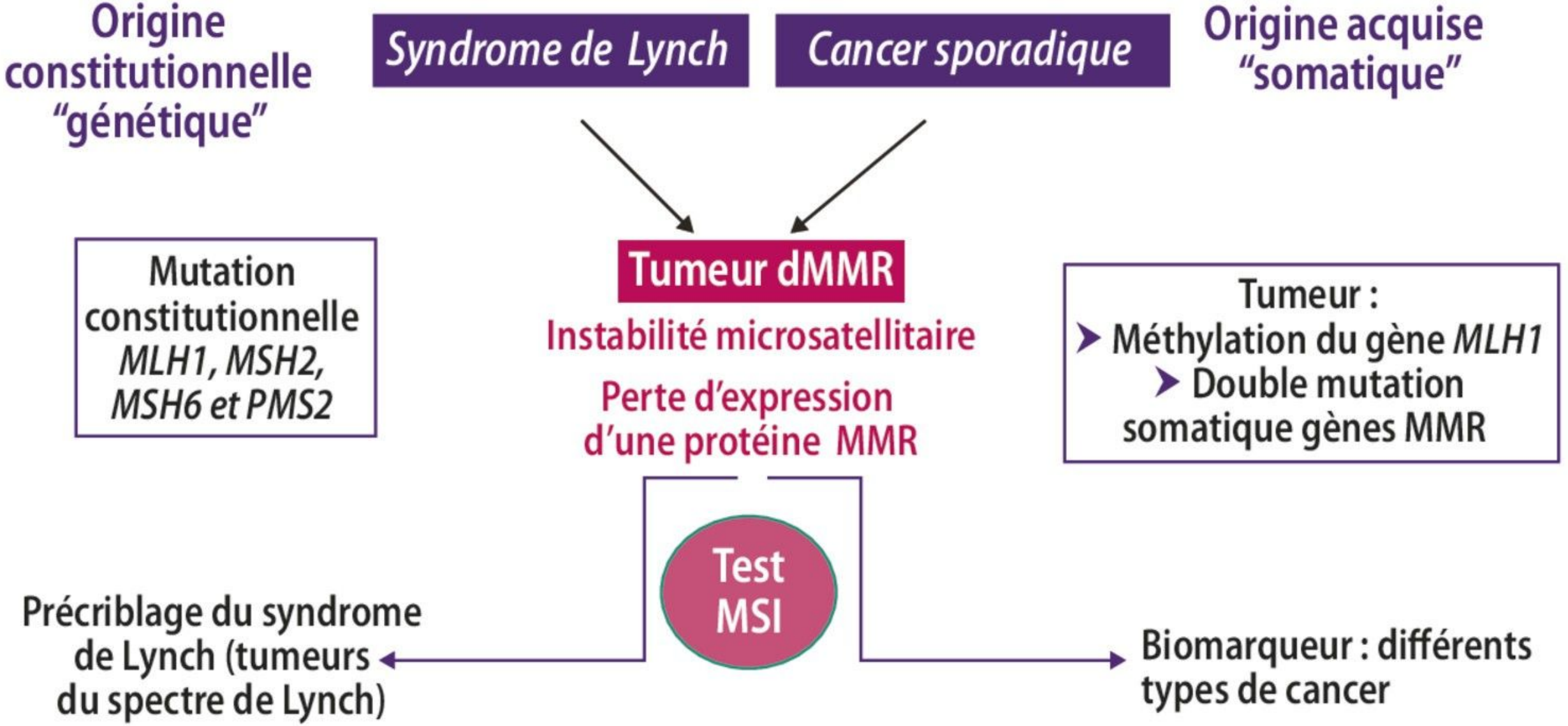
Prise en charge formes métastatiques

Somatic Mutation Frequencies in Colorectal Cancer




Ligands
EGFR
Cell Membrane
PI3K
PTEN
AKT
KRAS
BRAF
MEK/ERK
Proliferation
Survival
Angiogenesis
Migration
Nucleus

Voie de l'EGF


Origine constitutionnelle "génétique"
Syndrome de Lynch
Cancer sporadique
Origine acquise "somatique"
Mutation constitutionnelle MLH1, MSH2, MSH6 et PMS2
Tumeur dMMR
Instabilité microsatellitaire
Perte d'expression d'une protéine MMR
Tumeur :
➤ Méthylation du gène MLH1
➤ Double mutation somatique gènes MMR
Test MSI
Précriblage du syndrome de Lynch (tumeurs du spectre de Lynch)
Biomarqueur : différents types de cancer

Grandes lignes

- Tumeurs MSI métastatiques: immunothérapie seule en première ligne (PEMBROLIZUMAB); 5 à 8 % des tumeurs
- Mutations RAS: contre indications aux anti EGFR
- Mutations BRAF: très mauvais pronostic (SG = 9 mois)
- Nouveautés: retour de la latéralité, essai CAIRO 5
  colon gauche: préférer anti EGFR
- Recommandations SOFOG en cas d'absence de projet chirurgical: privilégier 5FU/Bevacizumab

Surveillance

Etude PRODIGE 13

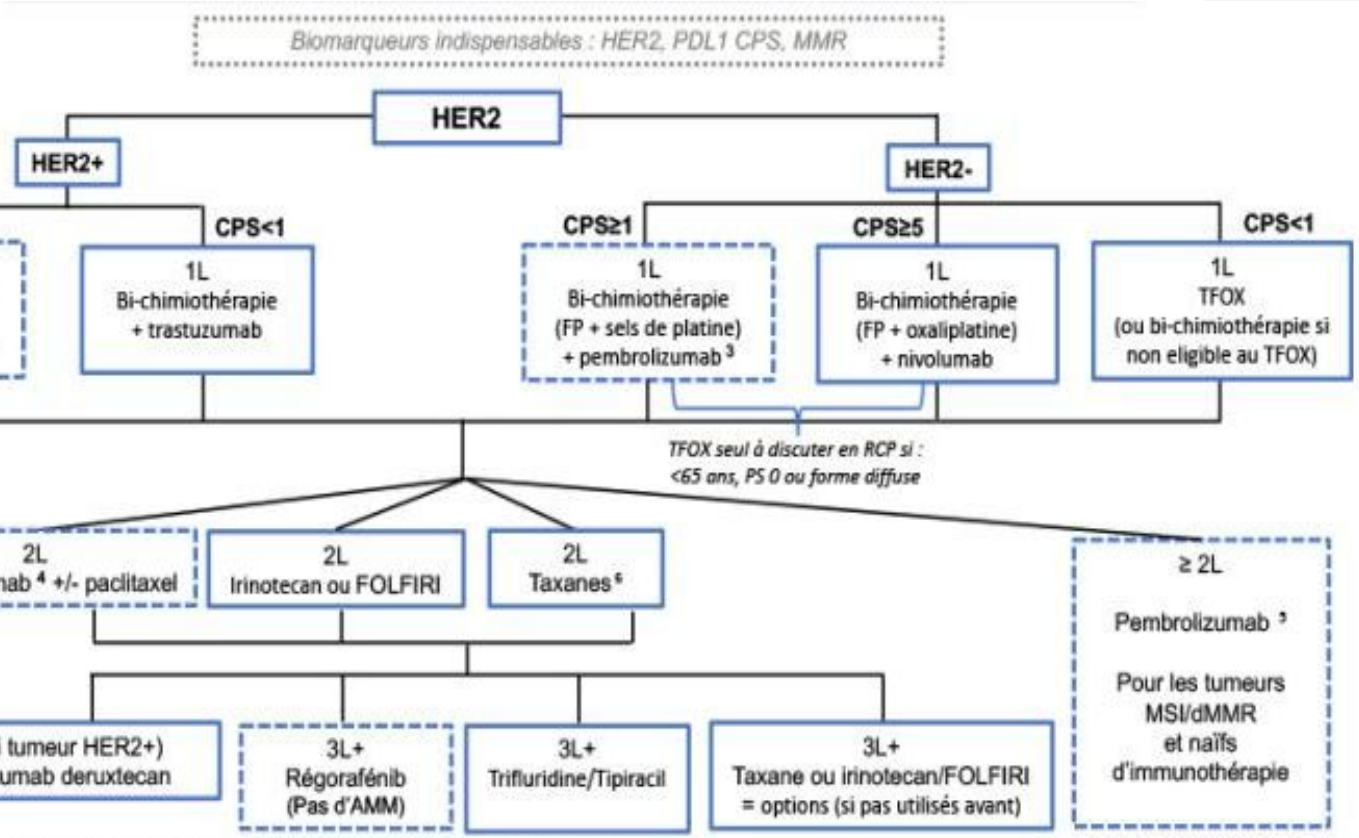
Dans les stades 1 , 2 et 3; pas d'intérêt dans le cadre du suivi (SG):

- au dosage de l'ACE
- à la réalisation de TDM systématiques par rapport au duo échographie abdominale/ radiographie de thorax

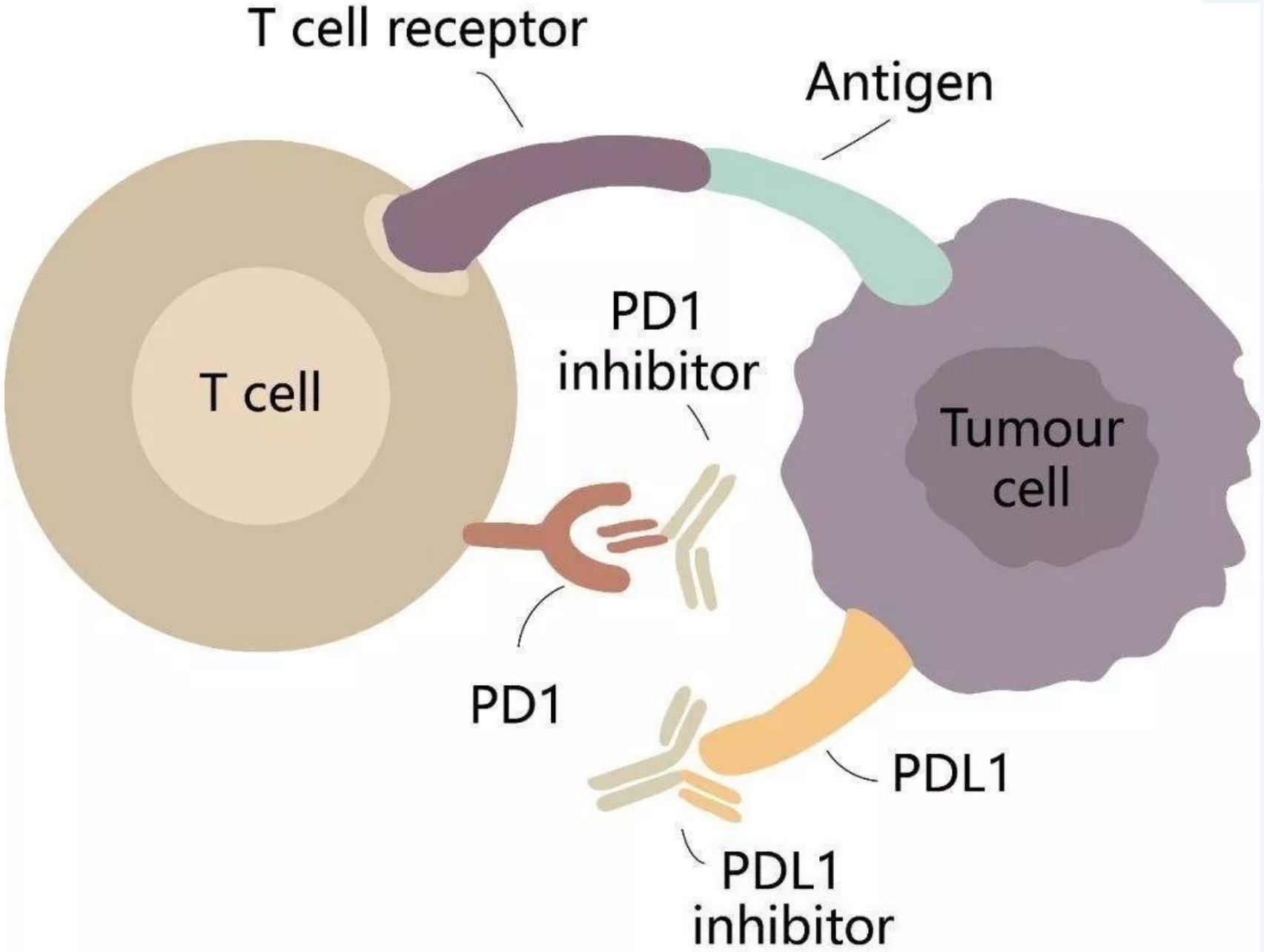
Cancers oeso-gastriques (hors tumeurs epidermoides)

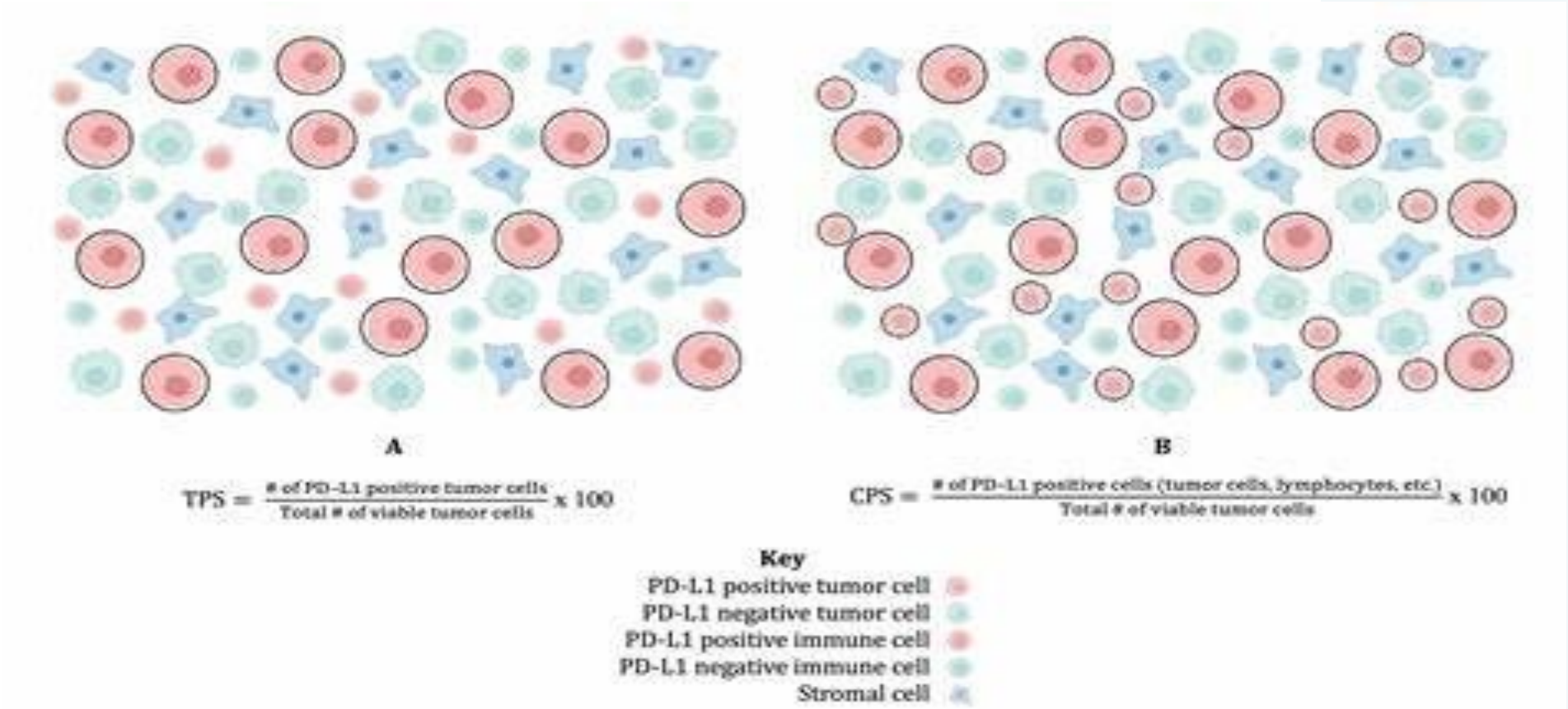
Adénocarcinomes oeso-gastriques

- Principales actualités concernent les formes métastatiques
- Arrivée en force des immunothérapies
- Complexification des RCP et du travail des anapaths
- Intérêt d'études de stratégies sur plusieurs lignes

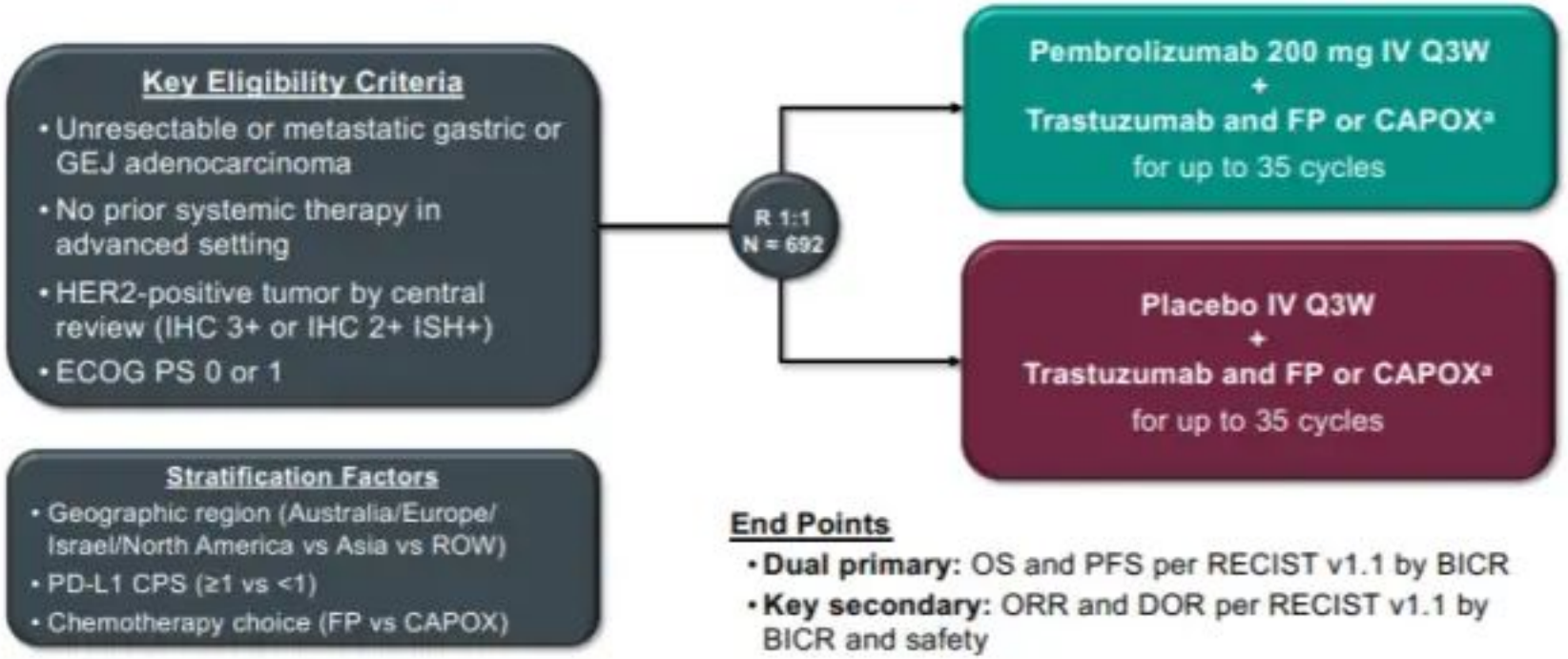


1. En cas de maladie oligo-métastatique résécable : discuter chirurgie si maladie bien contrôlée après chimiothérapie (inclusion étude SURGIGAST)
2. AMM (remboursement en attente)
3. AMM (remboursement en attente)
4. AMM du ramucirumab mais pas de remboursement en France
5. AMM du pembrolizumab mais pas de remboursement en France
6. Taxanes = paclitaxel ou docetaxel


T cell receptor
Antigen
T cell
PD1
inhibitor
Tumour
cell
PD1
PDL1
PDL1
inhibitor


A
B
TPS = # of PD-L1 positive tumor cells / Total # of viable tumor cells x 100
CPS = # of PD-L1 positive cells (tumor cells, lymphocytes, etc.) / Total # of viable tumor cells x 100
Key
PD-L1 positive tumor cell
PD-L1 negative tumor cell
PD-L1 positive immune cell
PD-L1 negative immune cell
Stromal cell

KEYNOTE-811 Global Cohort: Randomized, Double-Blind, Phase 3 Study



[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m² IV on D1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX: capecitabine 1000 mg/m² BID on D1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100). KEYNOTE-811 ClinicalTrials.gov identifier, NCT03615326.

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DOI 10.1186/s13045-017-0473-4

Journal of Hematology & Oncology

REVIEW Open Access

Anti-claudin 18.2 antibody as new targeted therapy for advanced gastric cancer

Prabhsimranjot Singh[1], Sudhamshi Toom[2] and Yiwu Huang[2*]

Abstract

Targeted therapy and immunotherapy have revolutionized treatment of various cancers in the past decade. Despite targeted therapy with trastuzumab in Her2-positive gastric cancer patients, survival has been dismal, mostly due to disease progression and toxicity related to the treatments. One area of active development is looking for ideal monoclonal antibodies (IMAB) specific to the proteins only on the tumor and hence avoiding unnecessary side effects. Claudin proteins with isoform 2 are one such protein, specific for several cancers, particularly gastric cancer and its metastases, leading to the development of anti-claudin 18.2 specific antibody, claudiximab. This review will highlight the latest development of claudiximab as first in class IMAB for the treatment of gastric cancer.

Keyword: Gastric cancer, Claudiximab, IMAB362, Targeted therapy, Anti-claudin antibody

Background

Gastric cancer is one of the most common cancers worldwide, the fourth (in males) and fifth (in females) most common causes of cancer-related deaths in the developed world. An estimated 951,600 new stomach cancer cases and 723,100 deaths occurred in 2012. The incidence of gastric cancer varies widely according to geographic region [1]. The majority of patients with gastric cancer are often diagnosed in the advanced stage of the disease. Early stages of gastric cancer are potentially curable with radical gastrectomy, although approximately 50% recur [2]. Adjuvant chemotherapy and chemo-radiation have led to improvement in overall survival (OS) [3]. Advanced gastric cancer is not curable and treatment currently is palliative chemotherapy conferring a median survival time of 8–10 months [4]. Multiple new chemotherapy regimens are studied with improved response rates and tolerability; however, the 5-year survival rates are dismal.

Immunotherapy and targeted agents like trastuzumab, ramucirumab, and tyrosine kinase inhibitors have revolutionized the treatments of various cancer including gastric cancer [5–16]. With the advent of targeted therapy, different molecules targeting different pathways were developed for the treatment of gastric cancer. In this review, we outline recently developed molecularly targeted therapy against claudin receptors—claudiximab (previously IMAB362). Claudiximab is first-in-class chimeric monoclonal antibody-IMAB (ideal monoclonal antibody), for the treatment of gastric cancer. IMABs bind to cancer-selective targets that are predominantly expressed in tumor cells and show little or no expression in healthy tissues. This unique cancer-cell selectivity of IMABs allows for maximal anticancer potency while diminishing toxicity. They have broader therapeutic window allowing optimal dosing.

Claudin proteins

Claudins are a family of proteins, first described by Shorichiro Tsukita et al. in 1998 which form the important components of the tight cell junctions [17]. They establish a paracellular barrier which controls the flow of molecules between the cells. The transmembrane domains of claudins include a N-terminus and a C-terminus in the cytoplasm (Fig. 1). Different claudins are expressed on different tissues, their altered function has linked to formation of cancers of respective tissues [18, 19]. Claudin-1 expression has been shown to have prognostic value in colon cancer [20], claudin-18 in gastric cancer [21], and claudin-10 in hepatocellular carcinoma [22]. Claudins, being surface proteins, represent a useful target for various therapeutic strategies.

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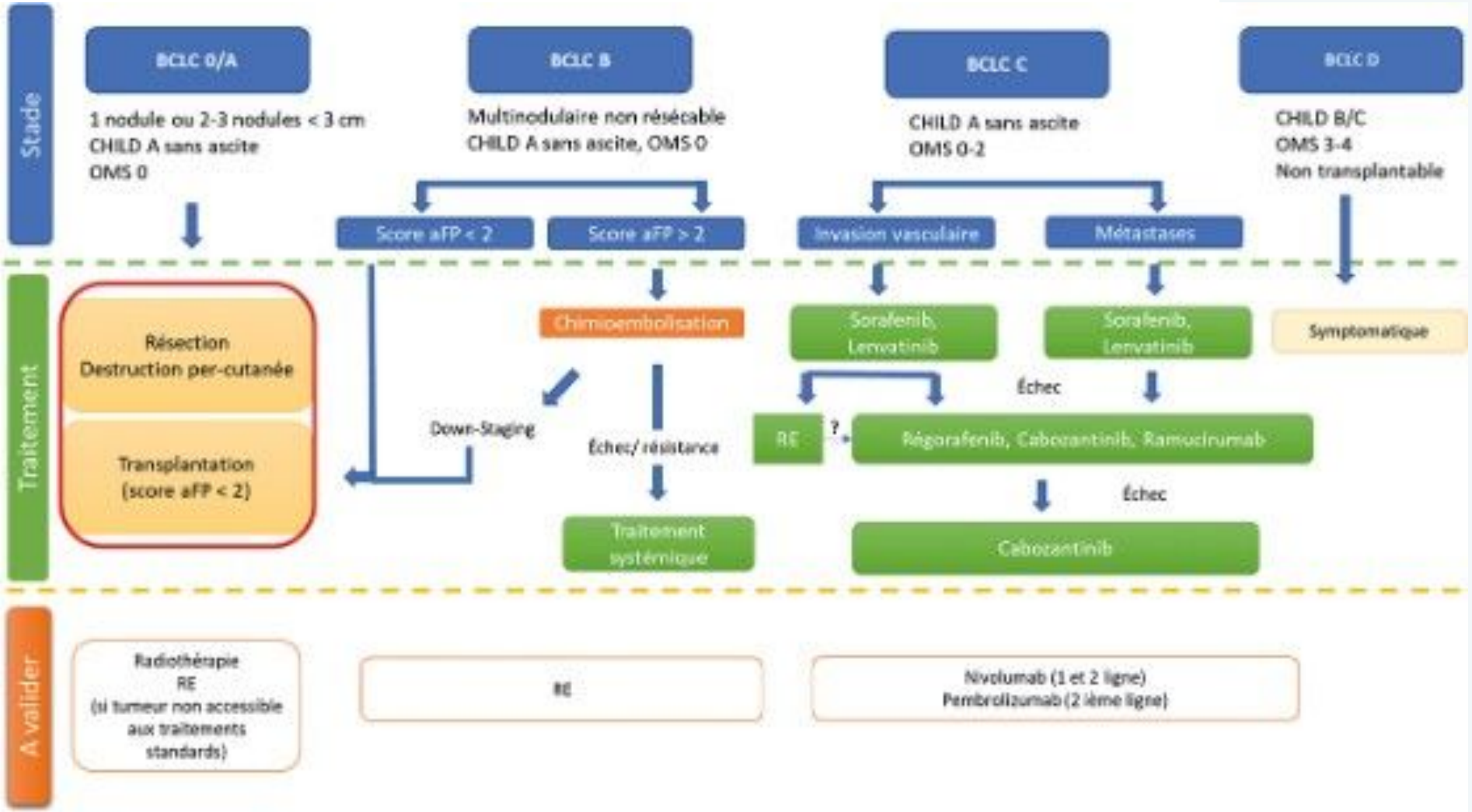
En pratique

- Bonne tolérance de l'immunothérapie chez les patients agés(8), interet du G8 et dosage albumine

- Intérêt chez les patients fragiles des anti HER2 ou de l'immunothérapie seule car toxicité majeure de l'association bi-chimiothérapie et immunothérapie

- Résultats très loin des "miracles" des mélanomes et/ou tumeurs pulmonaires

- **Enfin des avancées dans le CHC!!!**



classification de BARCELONE

L’essor de l’immunothérapie

- 2 protocoles comparés au SORAFENIB (essais IMbrave et HIMALAYA) :
  ATEZOLIZUMAB/bevacizumab
  et double immunothérapie (TREMELIMUMAB + DURVALUMAB)

- Amélioration SG et surtout de la qualité de vie

- La survenue d’effets immunomédiés est prédictif d’une bonne réponse thérapeutique (9)

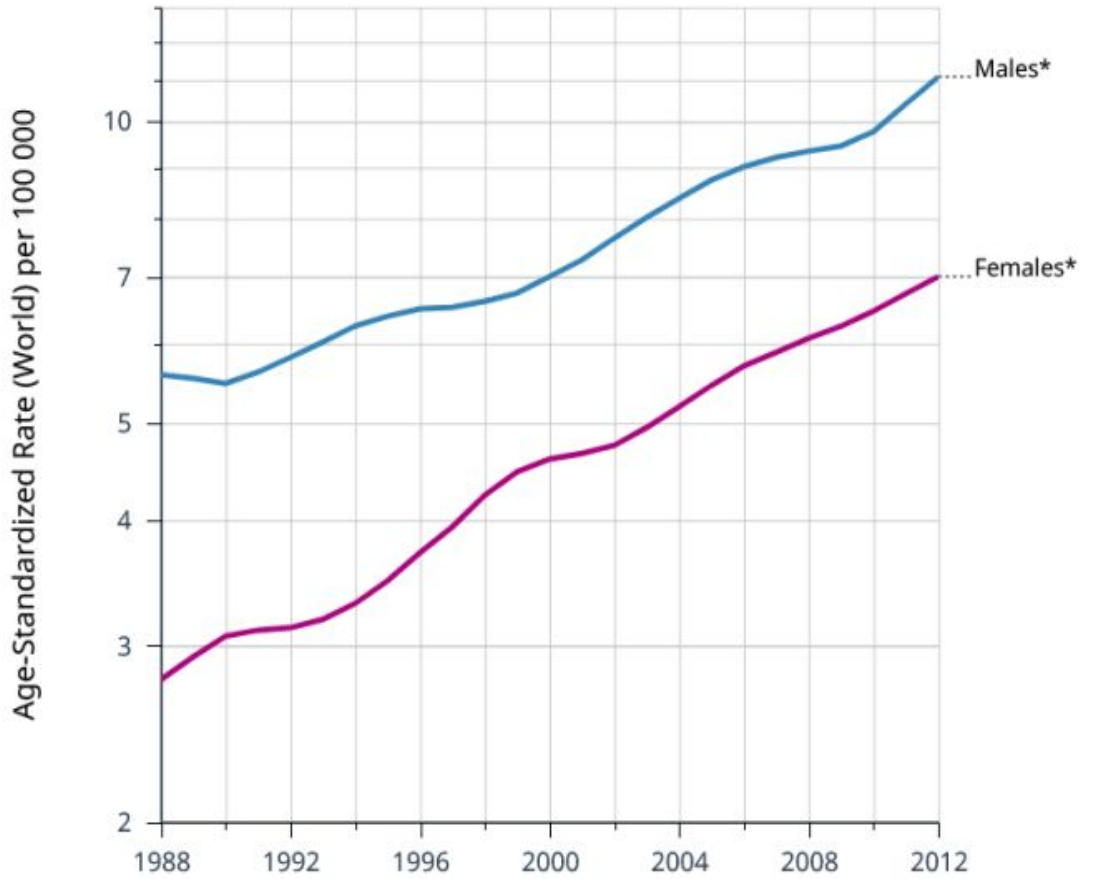
- Privilégier la double immuno si risque hémorragique/antécédents cardiovasculaires et rénaux

Le parent pauvre: l’adénocarcinome du pancréas

Adénocarcinome du pancréas

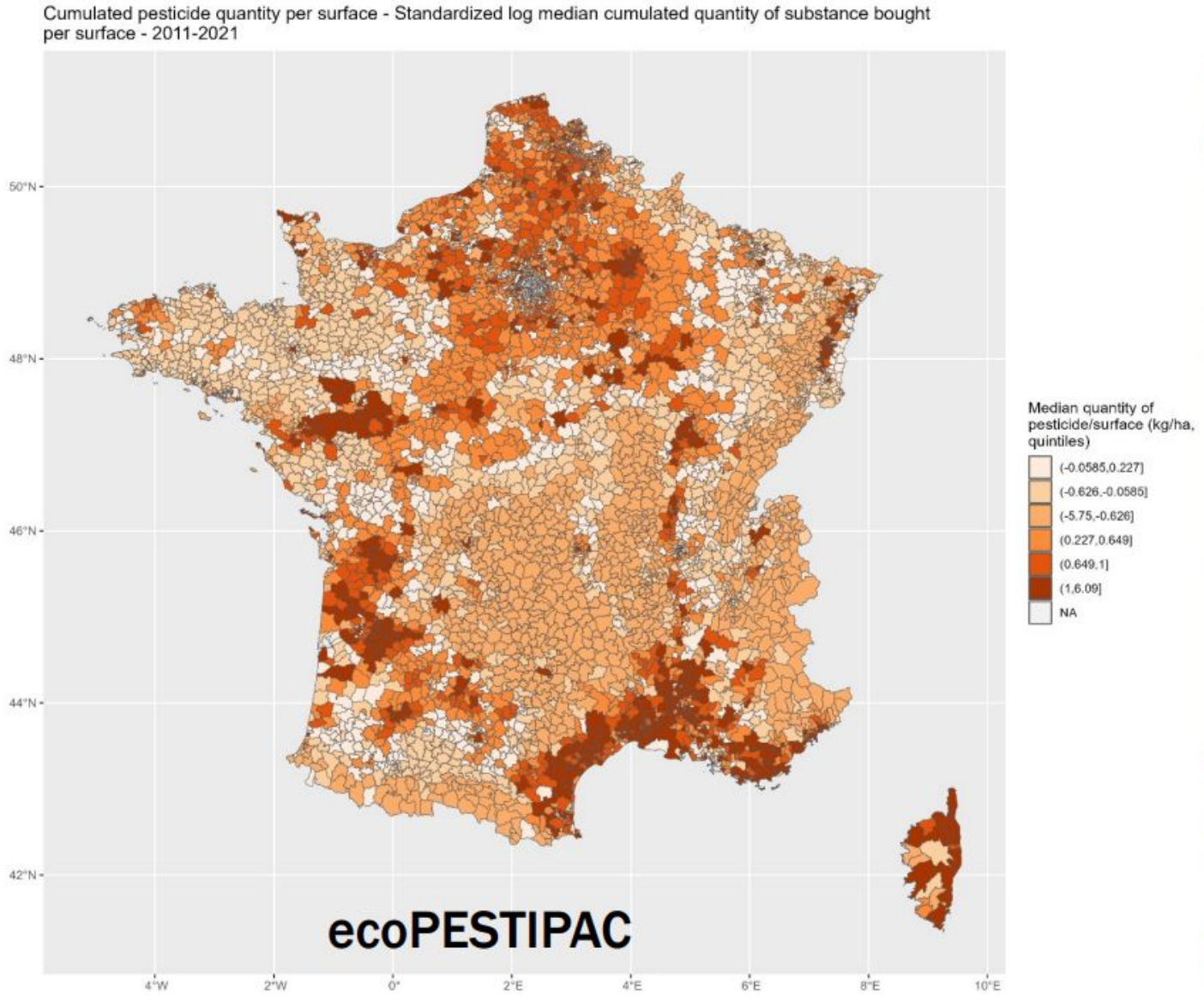
- Tumeur ayant l'augmentation d'incidence la plus importante ces 20 dernières années
- Quelques progrès thérapeutiques (FOLFIRINOX adjuvant)
- De nombreux echecs +++ (immunothérapie, anti EGFR, thérapies ciblées)
- Uniquement 20% de patients opérés
- 5 produits de chimiothérapies disponibles….

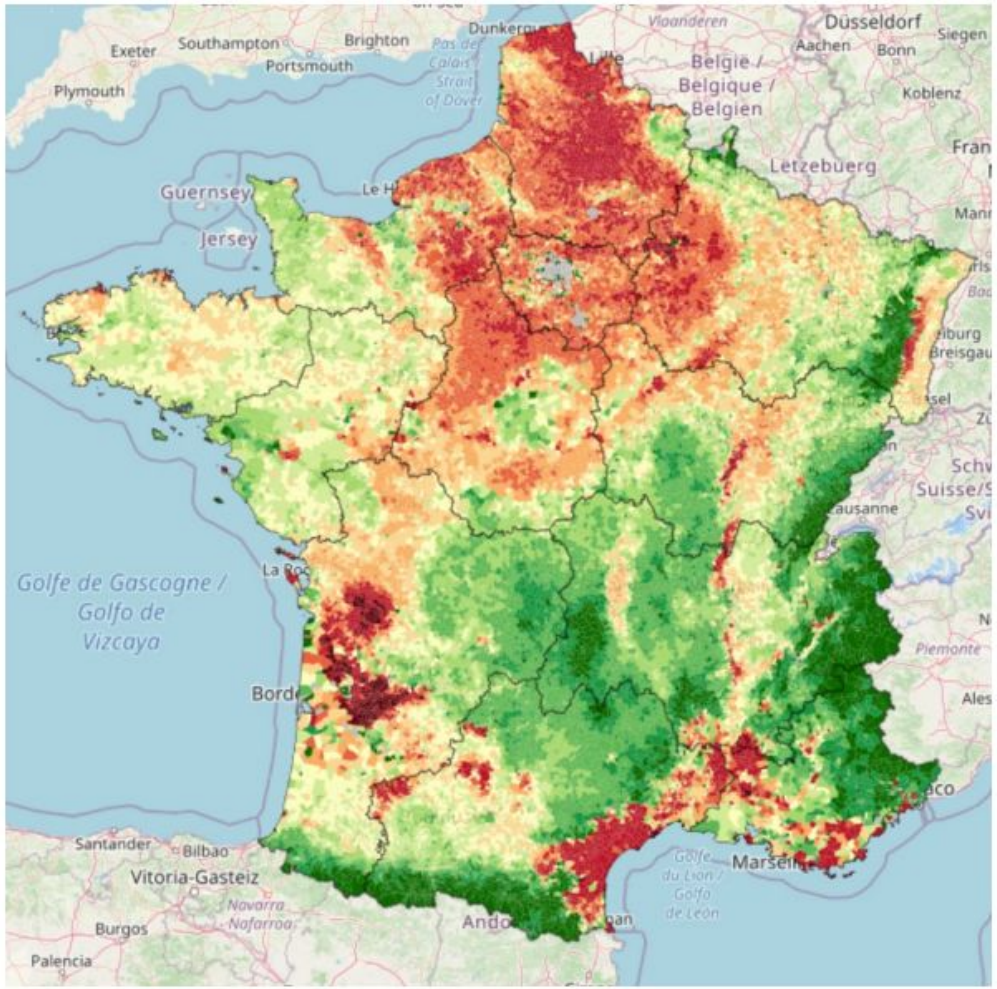
Contexte: l'adénocarcinome du pancréas



Global Cancer Observatory, WHO

Modelisation de l'exposition aux pesticides





Indicateur indépendant (SolAgro)

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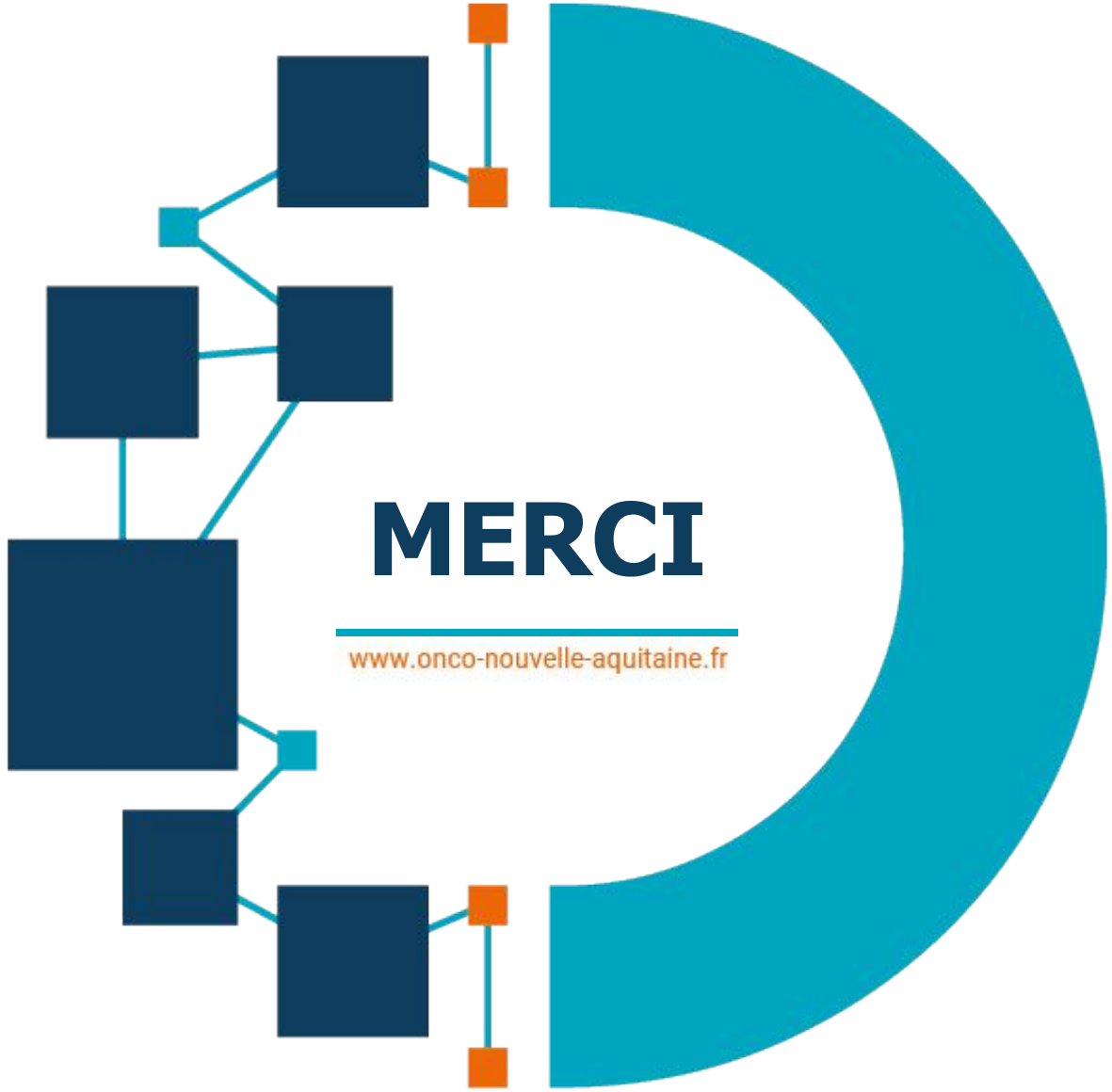
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