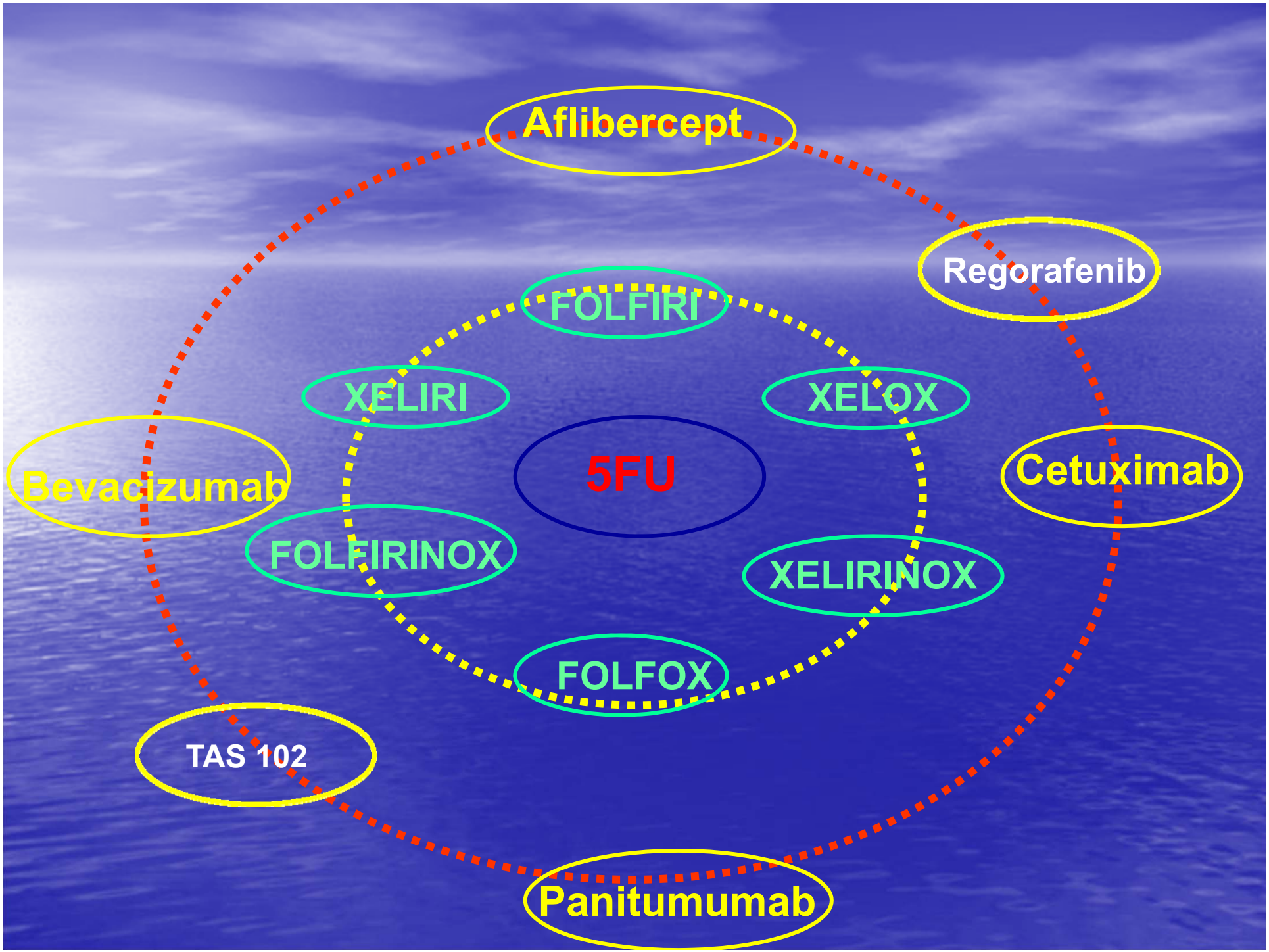
Métastases Hépatiques des Cancers colorectaux

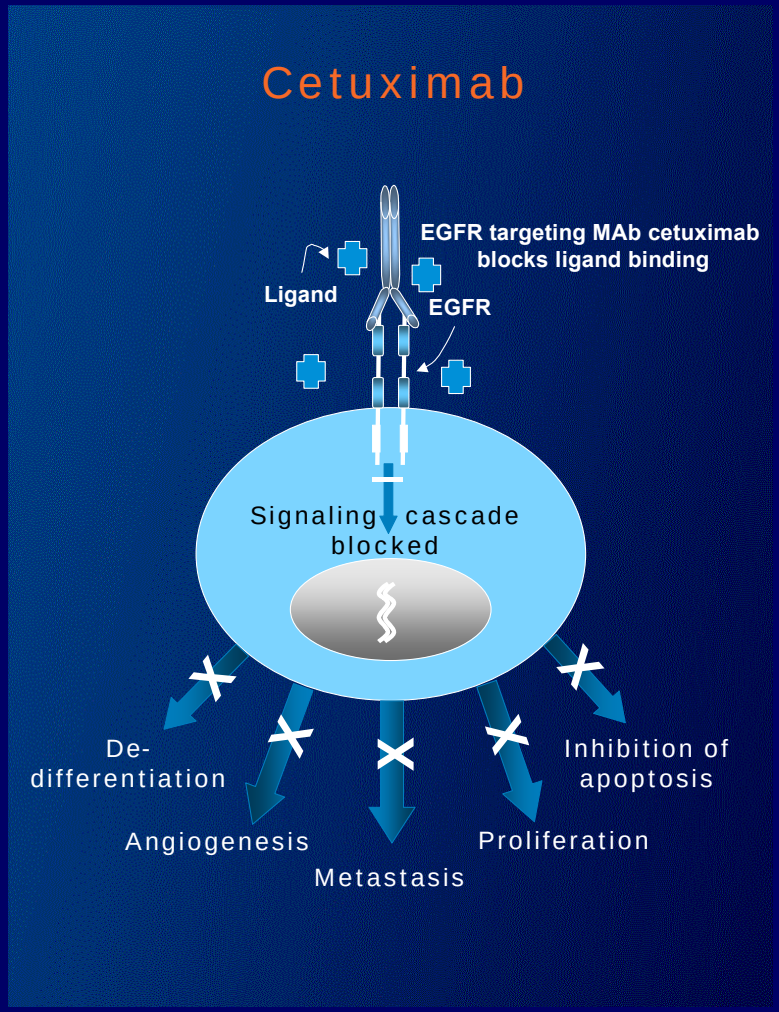
Une vue générale des thérapies actuelles

Pr Marc YCHOU

Montpellier


Aflibercept
Regorafenib
FOLFIRI
XELIRI
XELOX
5FU
Bevacizumab
Cetuximab
FOLFIRINOX
XELIRINOX
FOLFOX
TAS 102
Panitumumab

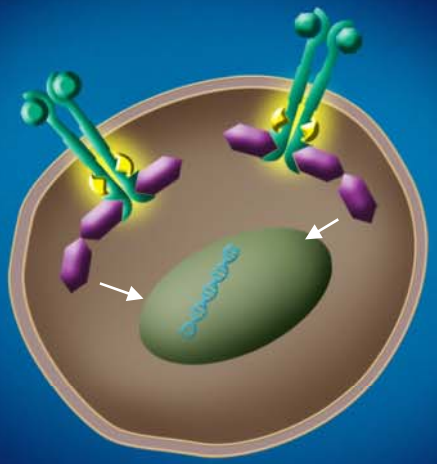
Cetuximab (Erbitux™) : background



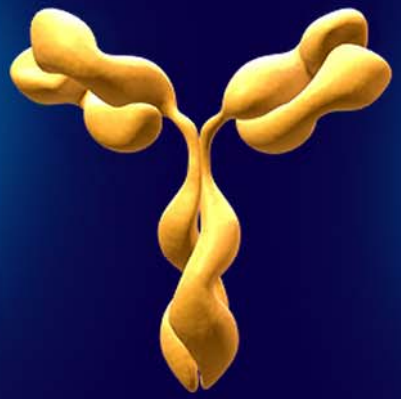
- IgG1 monoclonal antibody targeting the EGFR
- Binds specifically to the extra-cellular domain of human EGFR with high affinity (kd 0.5 nM)
- Prevents binding of EGF or TGF-α to EGFR and prevents activation of intracellular tyrosine kinase
- Stimulates receptor internalization
- Shows synergistic anti-tumor activity with anti-cancer drugs and radiation in in-vitro and in-vivo models

Le panitumumab inhibe la liaison d'un ligand à l'EGFR et sa dimérisation

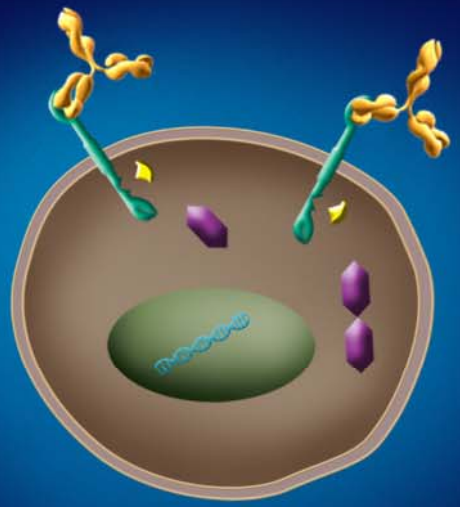
EGF, TGFα ou autres ligands se liant à l'EGFR



Panitumumab



Inhibition de la liaison de l'EGF à l'EGFR



Affinité

- K_D panitumumab (0,05 nM[1,2]) > cetuximab (0.4 nM[2]) > EGF (ligand naturel ; 3-7 nM[3])

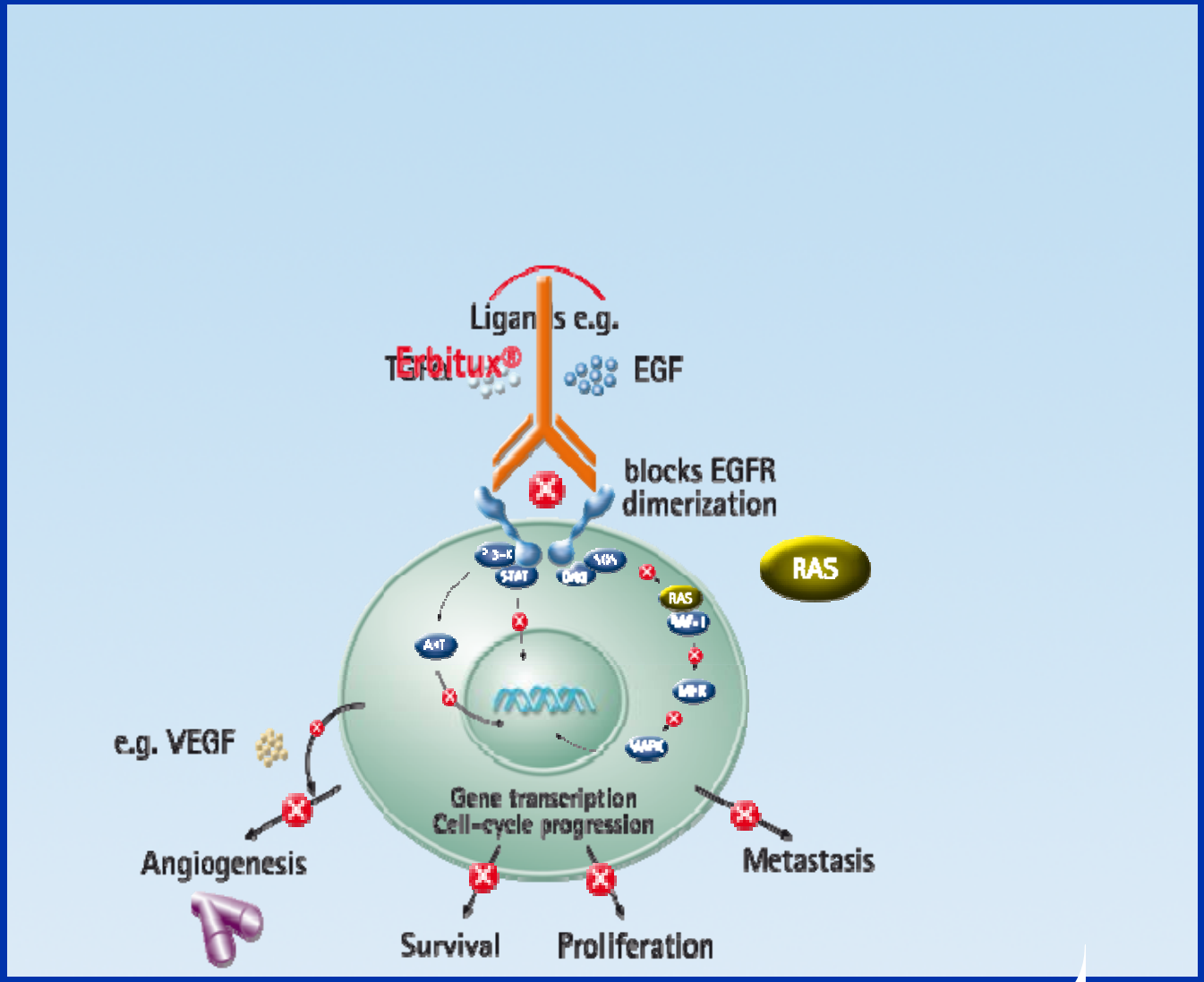
Panitumumab et cetuximab

- peut inhiber l'activation de l'EGFR par tous ses ligands connus
- se lie au niveau des mêmes acides aminés situés à la surface du domaine de liaison L2 de l'EGFR[2]

Ce qui peut aboutir à :
↓ prolifération cellulaire
↓ survie cellulaire
↓ angiogenèse
↓ dissémination métastatique

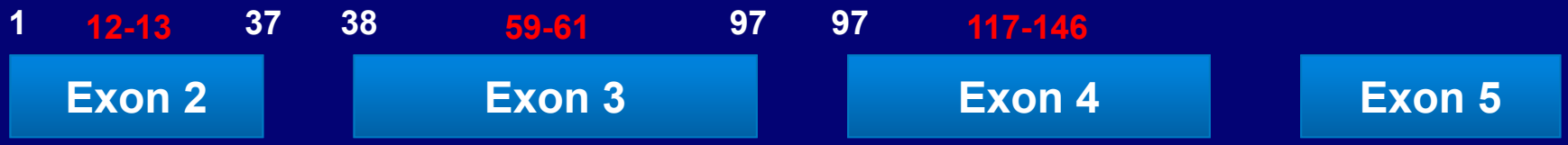
[1] Yang XD et coll. Cancer Res 1999;59:1236-43.
[2] Freeman D et coll. J Clin Oncol 2008 26:14536 and Poster. [3] Gill GN et coll. J Biol Chem 1984;259:7755-60.

Gène KRAS


Ligands e.g.
TGFα
Erbitux®
EGF
blocks EGFR
dimerization
RAS
RAS
AKT
STAT
e.g. VEGF
Gene transcription
Cell-cycle progression
Angiogenesis
Metastasis
Survival
Proliferation

Mutations distribution on different codons Kras and NRAS

KRAS: Around 42% of metastatic CRC KRAS mutated



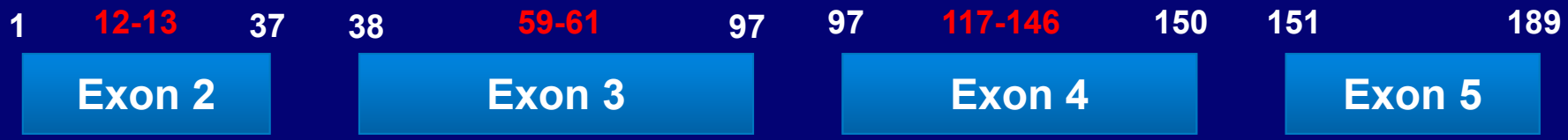
85% 2% 13%

Cosmic database

Peters Clin Cancer Res 2013

Andre Ann Oncol 2012

NRAS: 8% of mCRC are RAS mutated



42% 58%

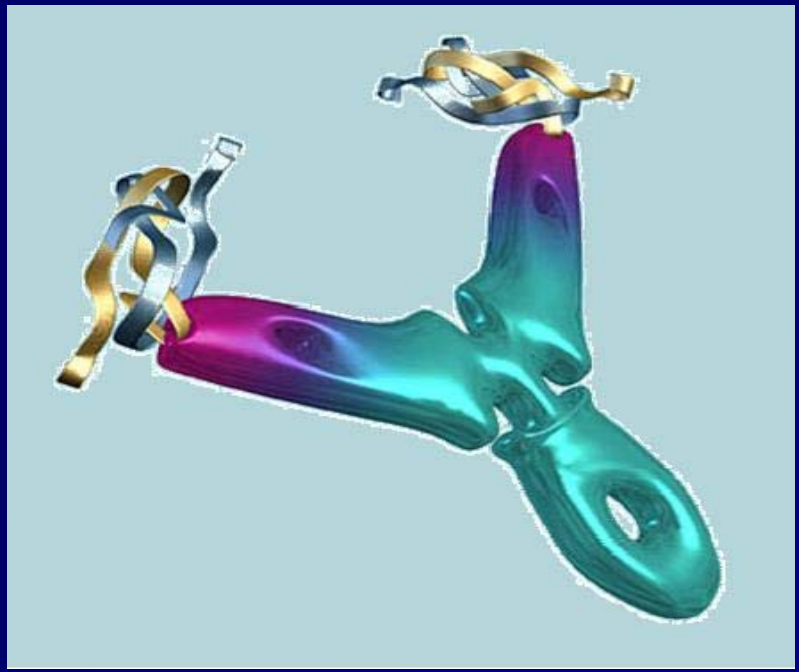
Cosmic database

André T, Ann Oncol 2013
Peeters M, Clin Cancer Res 2013
Oliner, et al. ASCO 2013

Bevacizumab (Avastin®, Roche)

Anticorps monoclonal recombinant anti-VEGF développé à partir de l'anti-VEGF murin mAb A4.6.1 (IgG1)

- 93 % humain, 7 % murin
- reconnaît tous les isoformes de VEGF ($VEGF_{121}$, $VEGF_{165}$*, $VEGF_{189}$)
- Kd = 8×10^{-10} M
- demi-vie terminale : 17–21 jours
- pas de DLT en monothérapie
- n'induit pas de réponse immunitaire chez l'homme

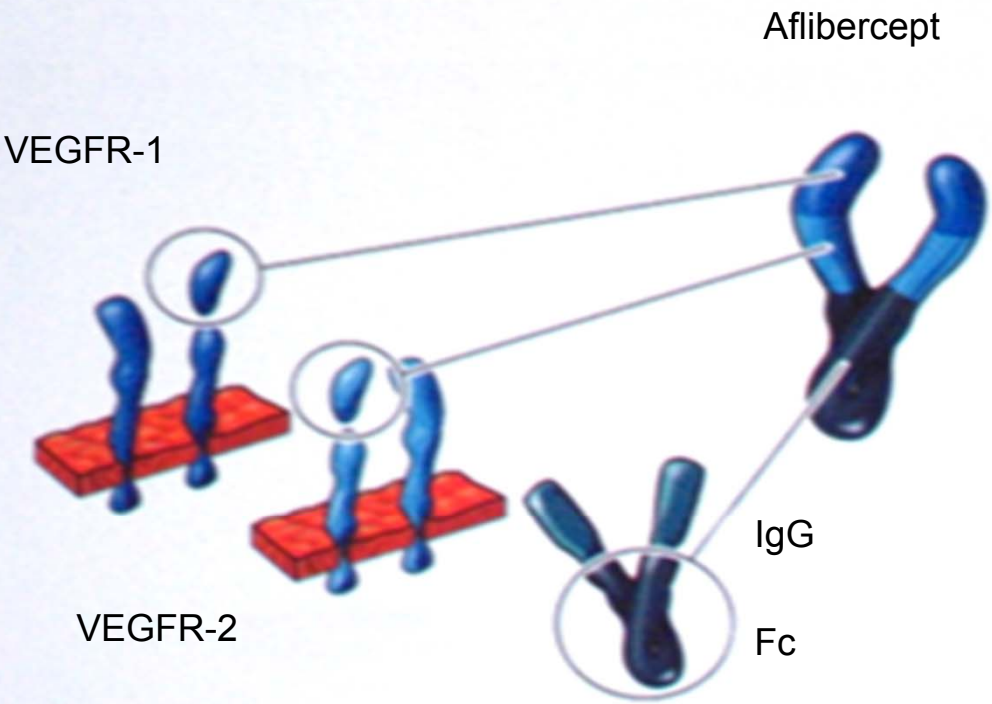


*Type moléculaire prédominant

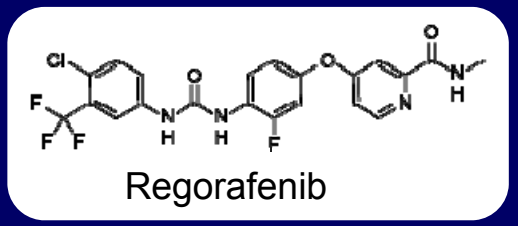
Presta LG, et al. Cancer Res 1997;57:4593–9

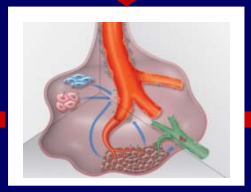
VEGF-Trap: AFLIBERCEPT

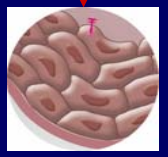
Un nouvel Anticorps anti-angiogénique

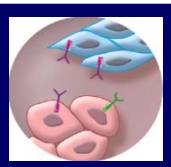


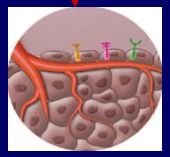
Regorafenib (BAY 73-4506), an oral multikinase inhibitor targeting multiple tumor pathways[1-3]











Inhibition of proliferation

KIT
PDGFR
RET

Inhibition of tumor microenvironment signaling

PDGFR-β
FGFR

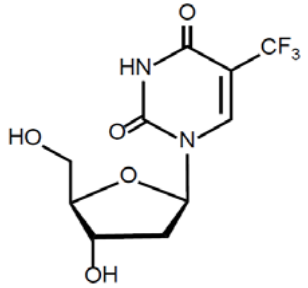
Inhibition of neoangiogenesis

VEGFR1-3
TIE2

1. Wilhelm SM *et al. Int J Cancer* 2011.
2. Mross K *et al. Clin Cancer Research* 2012.
3. Strumberg D *et al. Expert Opin Invest Drugs* 2012.

TAS-102- An Oral Combination of FTD and TPI

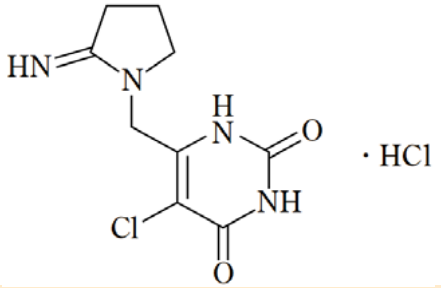
FTD (trifluridine)



Antitumor activity

+

TPI (tipiracil hydrochloride)

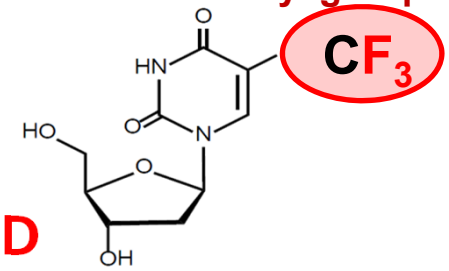


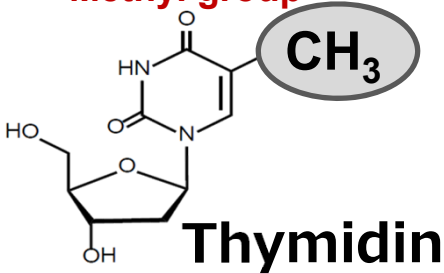
Suppression of FTD degradation

Molar ratio 1 : 0.5

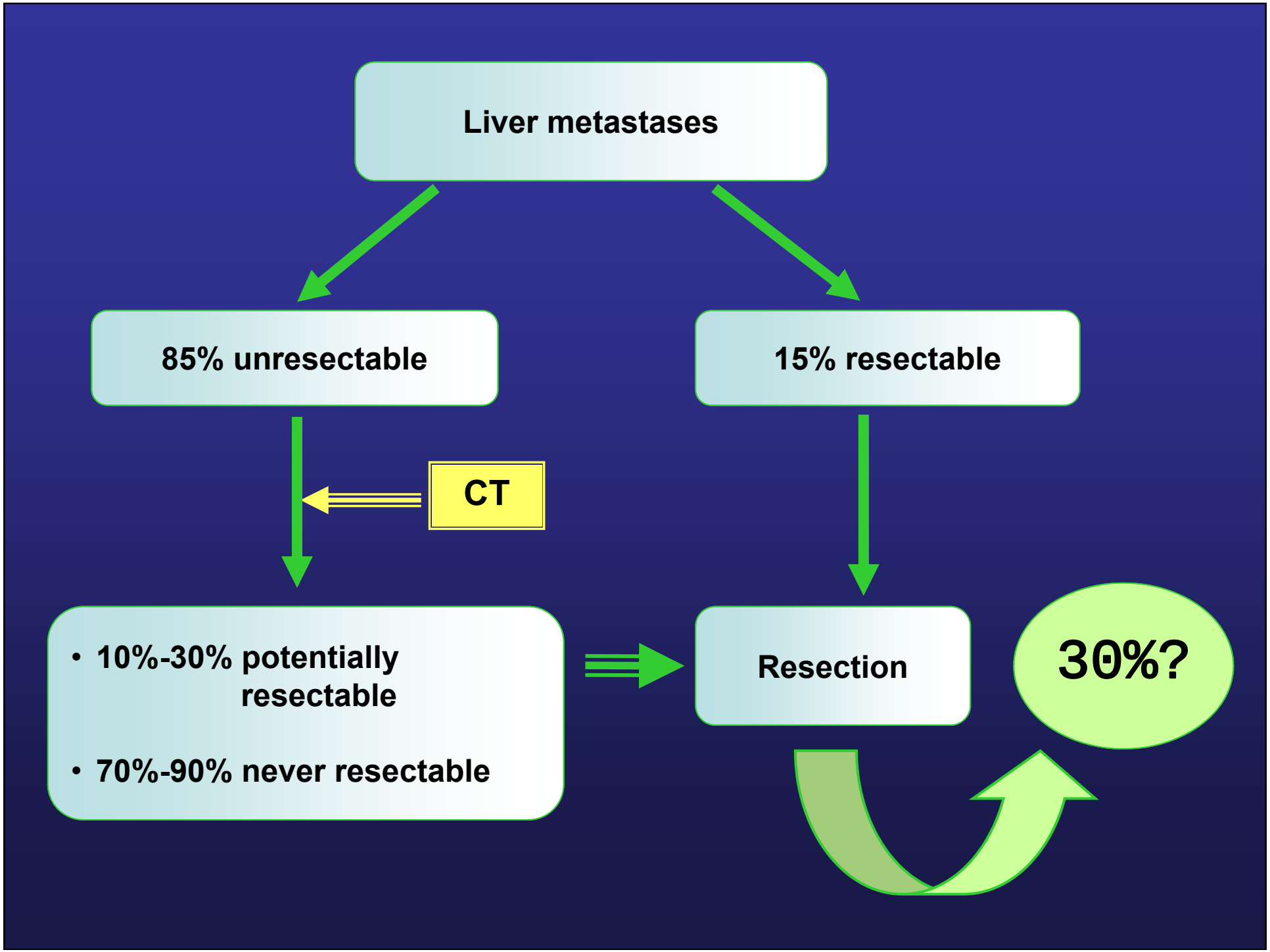
Thymidine analogue

FTD



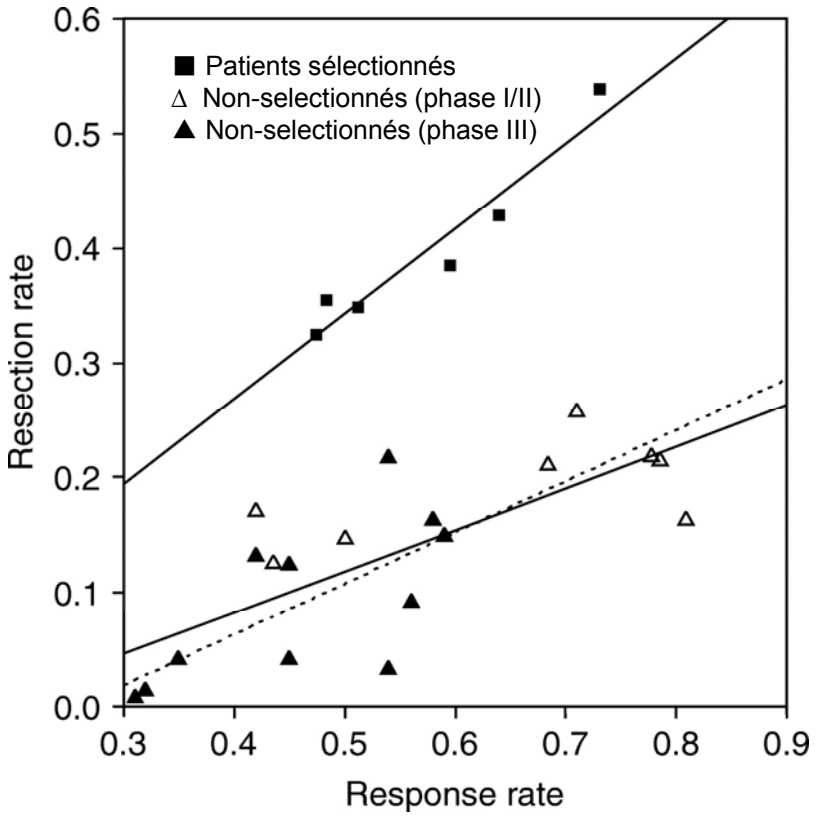


Thymidine


Liver metastases
85% unresectable
15% resectable
CT
• 10%-30% potentially resectable
• 70%-90% never resectable
Resection
30%?

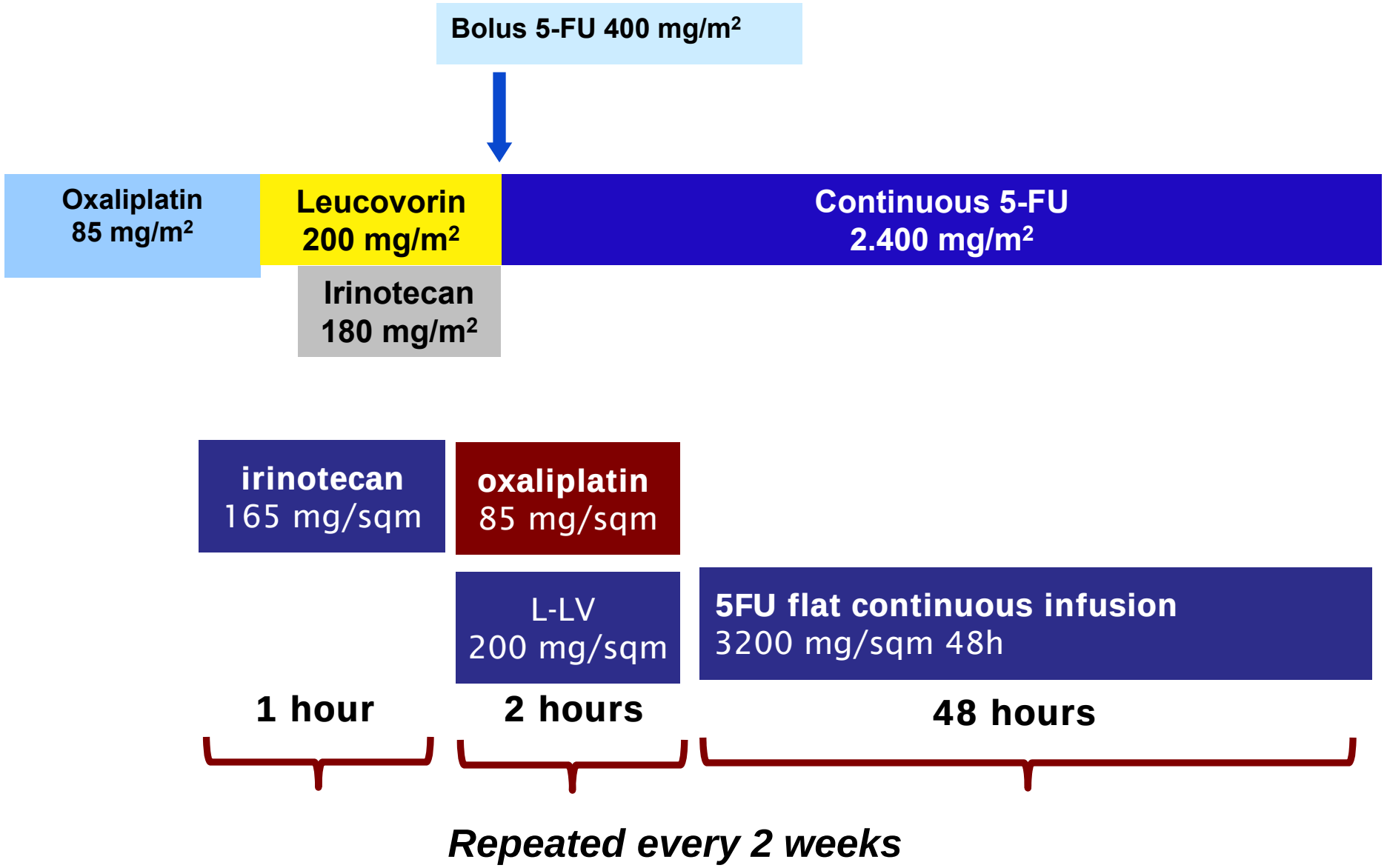
CORRELATION BETWEEN TUMOR RESPONSE AND RESECTION RATE ?

- Very high in studies included selected patients (Liver metastases only)
- Moderate in studies inluded non selected patients



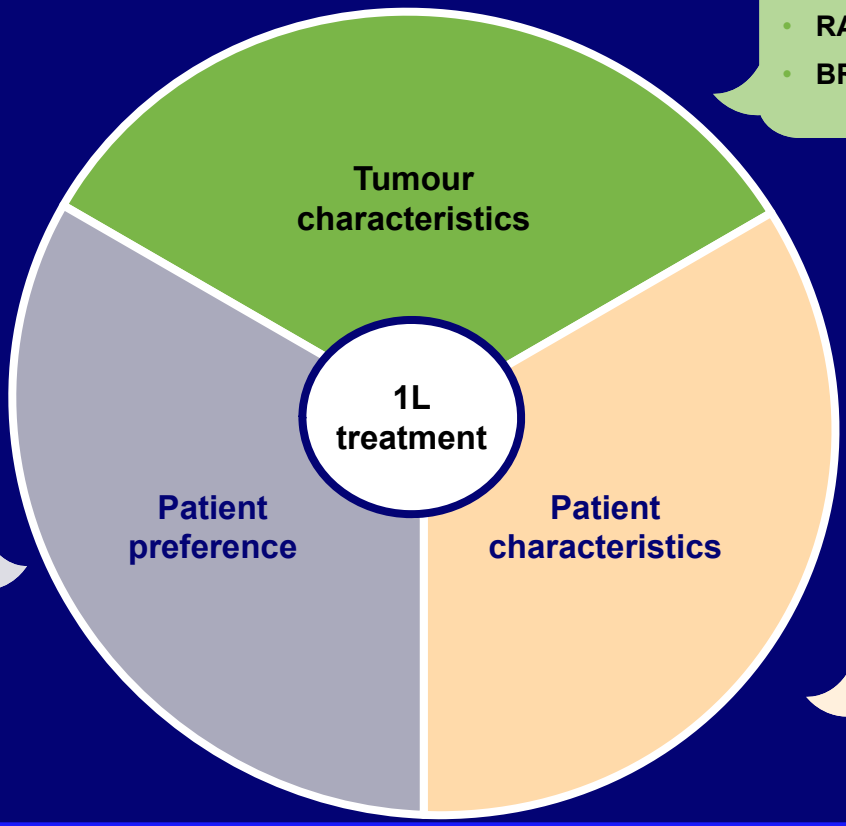
Folprecht et al. Ann Oncol, 2005

FOLFIRINOX et FOLFOXIRI



Repeated every 2 weeks

Treatment choice: more than efficacy



- Clinical presentation
- Tumour biology
- RAS mutation status
- BRAF mutation status

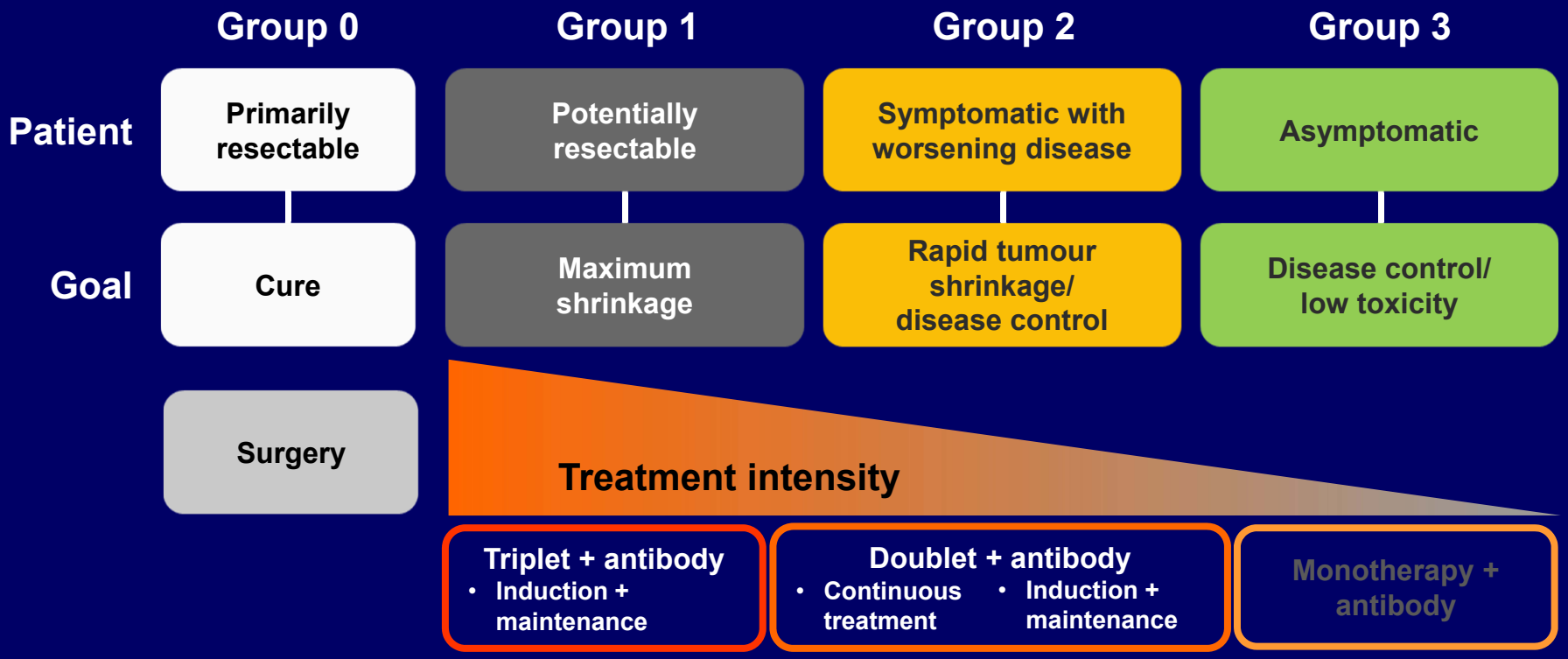
- Expectations
- Toxicity profile
- Flexibility
- Socio-economic factors
- Quality of life

- Age
- Performance status
- Prior adjuvant treatment
- Comorbidities

Treatment decisions should take into account patient preference

- 1L = first line

ESMO guidelines: treatment goal influences treatment intensity



Not all patients need high-intensity treatment

Van Cutsem E, et al. Ann Oncol 2014