Traitement personnalisé des cancers du sein

Impact sur la prise en charge systémique

Toulouse, 5-7 novembre 2014

Personnalisation des chimiothérapies et des traitements ciblés

Peut-on anticiper individuellement la toxicité ?

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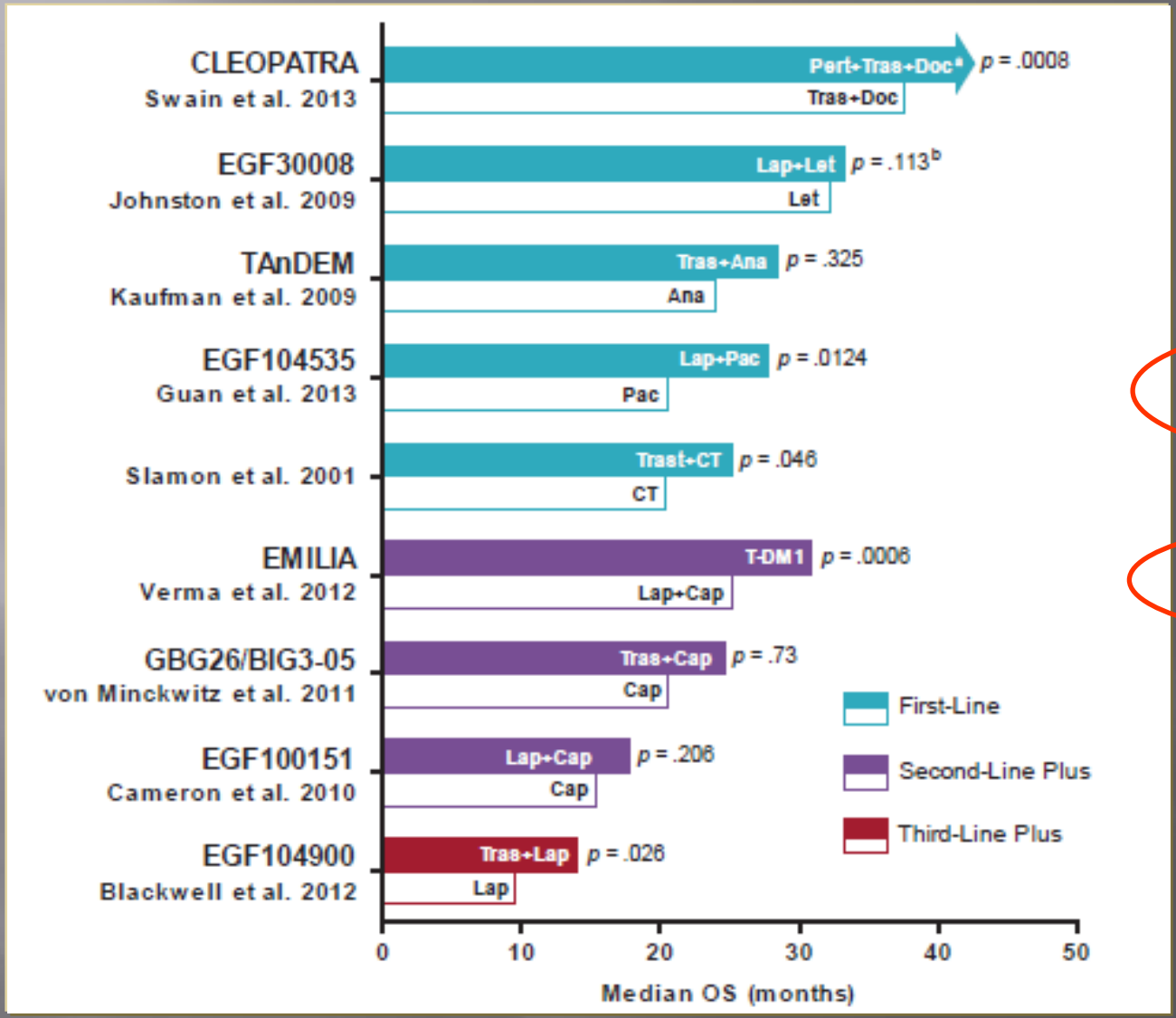
Avancées thérapeutiques majeures dans le ciblage du cancer du sein HER2+



Importance majeure du ciblage HER2

Place de la Capecitabine

(Verma S et al., The Oncologist 2013)

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC BREAST CANCER[1]

Preferred single agents:

Anthracyclines
- Doxorubicin
- Pegylated liposomal doxorubicin

Taxanes
- Paclitaxel

Anti-metabolites
- Capecitabine
- Gemcitabine

Other microtubule inhibitors
- Vinorelbine
- Eribulin

Other single agents:
- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

Chemotherapy combinations:
- CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
- FEC (fluorouracil/epirubicin/cyclophosphamide)
- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[2]

Preferred first-line agents for HER2-positive disease:
- Pertuzumab + trastuzumab + docetaxel (category 1)
- Pertuzumab + trastuzumab + paclitaxel

Other first-line agents for HER2-positive disease:

Trastuzumab alone or with:
- Paclitaxel ± carboplatin
- Docetaxel
- Vinorelbine
- Capecitabine

Preferred agents for trastuzumab-exposed HER2-positive disease:
- Ado-trastuzumab emtansine (T-DM1)

Other agents for trastuzumab-exposed HER2-positive disease:
- Lapatinib + capecitabine
- Trastuzumab + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents

[1]There is no compelling evidence that combination regimens are superior to sequential single agents.

[2]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

[3]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

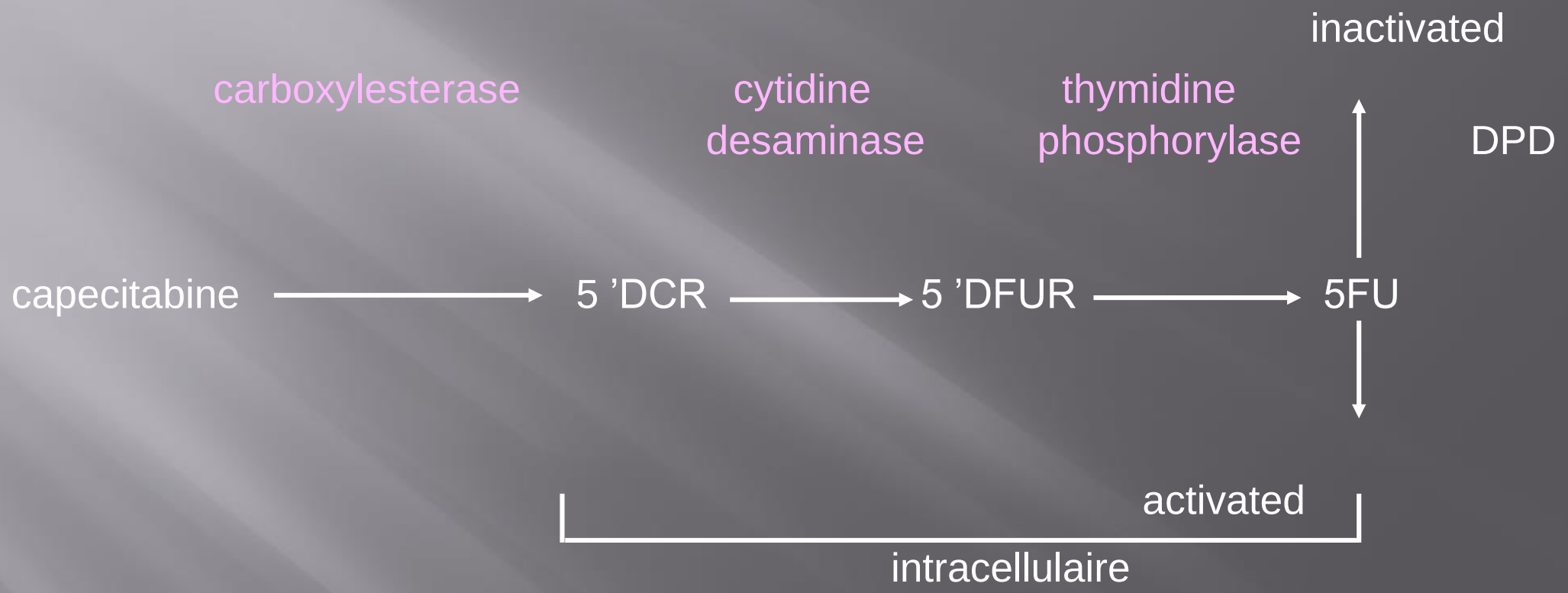
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Le revers de la médaille
- La toxicité -

Herceptin un peu (cardiotox)

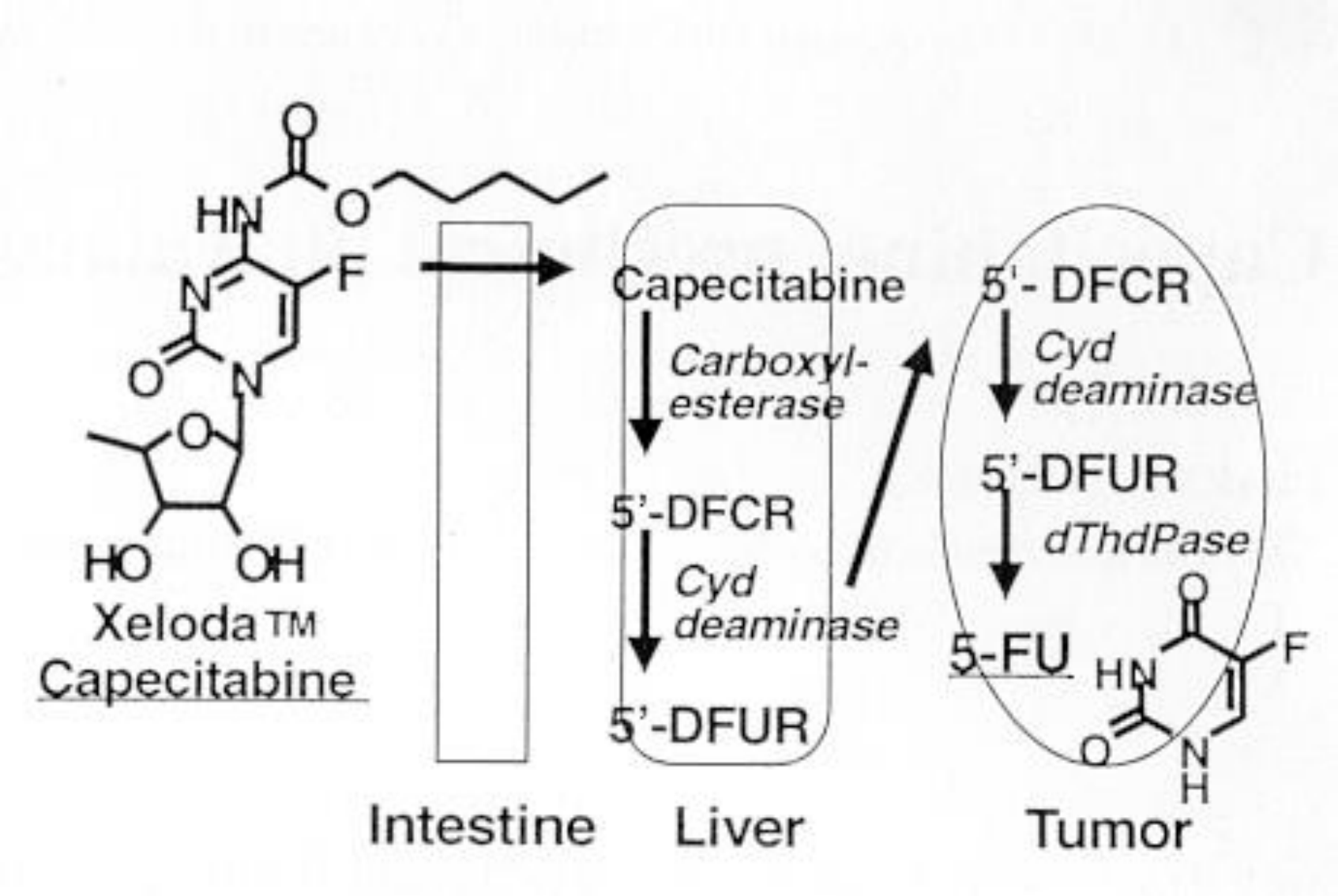
et Capecitabine beaucoup
(toxicité main-pied, hemato/digest)

Capecitabine = une (belle) poupée russe



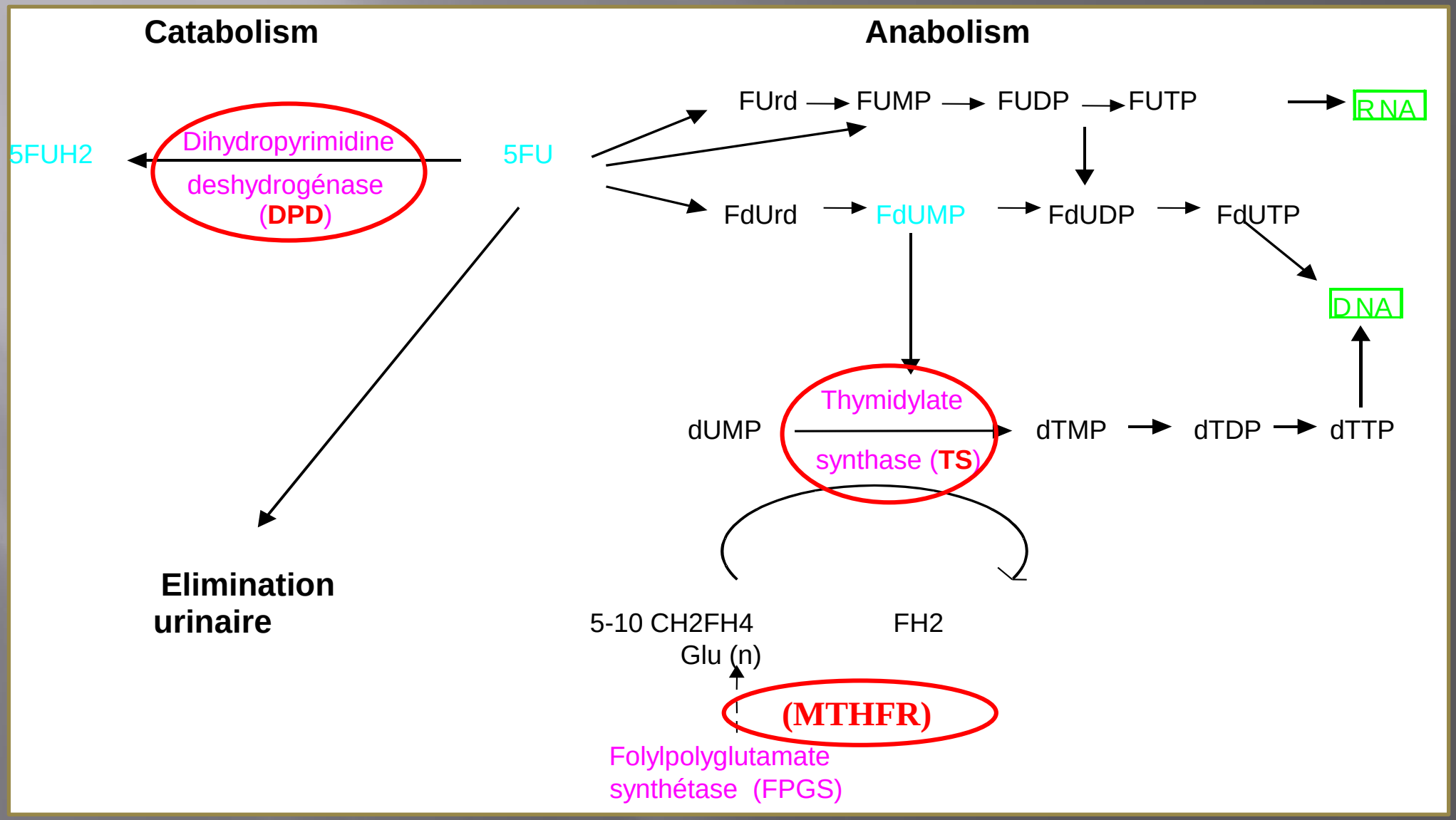
2500 mg/m^2/d x 14 d + stop 7 days

Capecitabine et anabolites – Activation en cascade

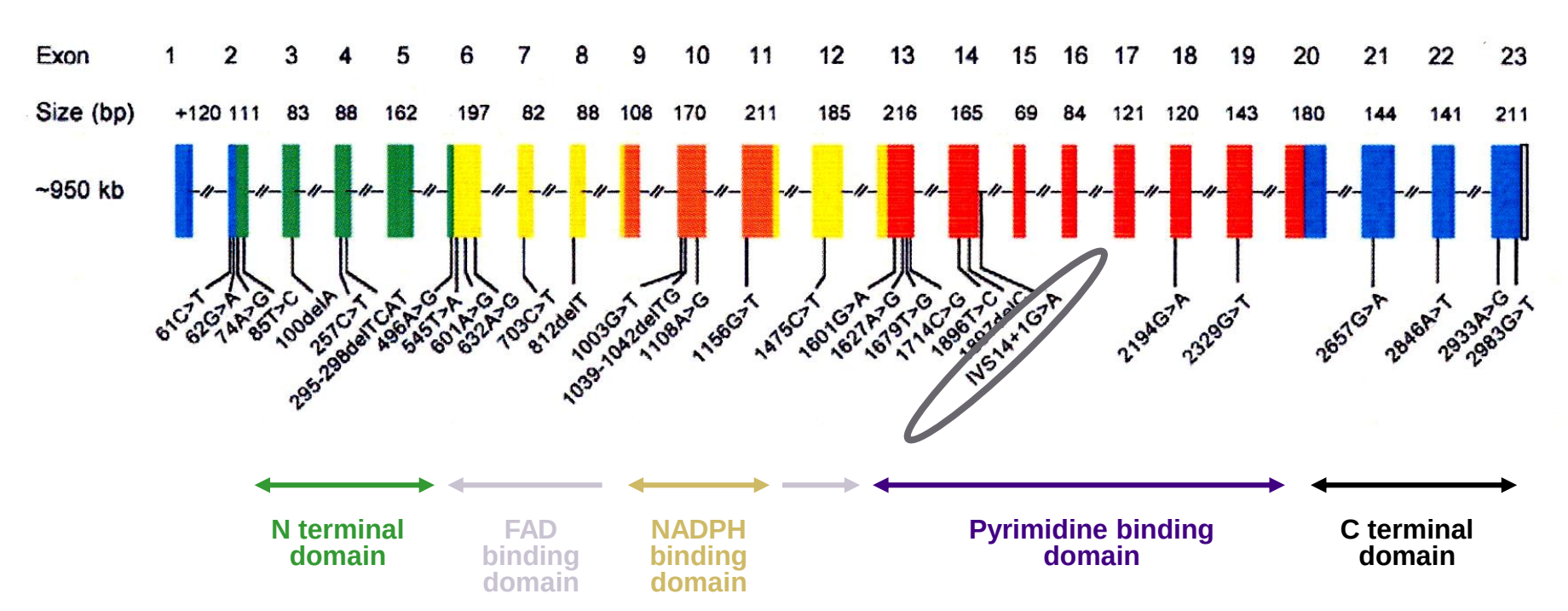


(Ishitsuka H, 2000)

Métabolisme du 5FU



Mutations du gène *DPYD*



(Van Kuilenburg A. Eur J Cancer 40 : 939, 2004)

Polymorphismes du gène *DPYD* (chromosome 1)

50 mutations décrites ...

La plus fréquente (IVS14+1, intron 14) est une mutation fonctionnelle associée à une forte diminution de l'activité DPD.

<u>Dans la population générale</u> :

- **prévalence des sujets hétérozygotes de l'ordre de 1 %**
- **prévalence des sujets homozygotes mutés estimée à 1/10 000**

(Van Kuilenburg A. Eur J Cancer 40 : 939, 2004)

Déficit en DPD – Capecitabine – Cancer du sein
Un risque non négligeable

Case report. The case is that of a 58-year-old breast cancer patient with hepatic metastasis, who had received no previous treatment by fluoropyrimidines. Capecitabine monotherapy was administered at a daily dose of 1,820 mg/m^2 (starting on day 0). She stopped capecitabine treatment on day 12. On day 14, she was hospitalized due to grade 4 hematologic toxicity (febrile neutropenia grade 4, thrombocytopenia grade 3), grade 3 digestive toxicity (diarrhea and mucositis), and grade 2 hand-foot syndrome. The patient was transferred to the intensive care unit and deceased on day 20. Two days before starting treatment, a blood sampling was done and lymphocytic DPD activity was measured. DPD activity was subnormal, at 142 pmol/min/mg protein, corresponding to the 18th percentile of a previous cancer patient population study (24). Interestingly, this patient carried the IVS14 + 1G>A mutation (heterozygous). In addition, the ratio of uracil to dihydrouracil in plasma was subsequently measured as a surrogate marker of DPD activity (the higher the ratio, the lower the activity; ref. 25). This uracil/dihydrouracil ratio was high, with a value of 4.9, strongly suggesting a DPD deficiency (25), when compared with the Gaussian distribution of previously measured ratios in a nonselected cancer population (n = 60, mean = 1.4). The 5′ TS genotype of this patient was 3RC3RG (class 3).

Patiente décédée sous Capecitabine

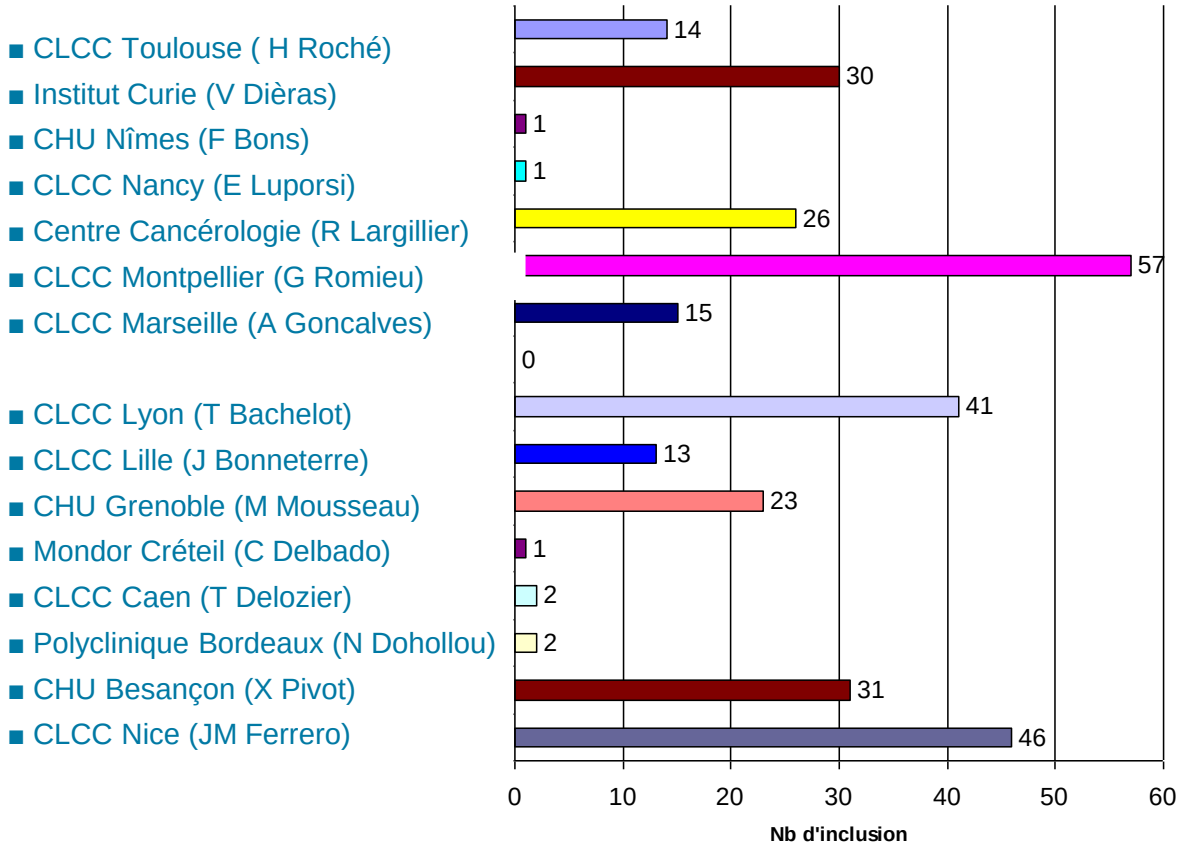
(Largillier R., Clin Cancer Res 2006) confirmé par Ciccolini J. et al., (Cancer Chemother Pharmacol 2007)

PHRC national CAL 2008 (JM Ferrero, G Milano)

Etude multicentrique

(303 patientes incluses en 2 ans sur 15 établissements)

Centres investigateurs



Laboratoires

- CLCC Toulouse (E Chatelut)
- CLCC Nantes (C Bobin-Dubigeon)
- CLCC Angers (M Boisdron-Celle)
- CHU Besançon (B Royer, C Ferrand)
- CLCC Nice (G Milano)
- CLCC Montpellier (F Pinguet)
- CHU Nîmes (JC Boyer)
- CLCC Nancy (JL Merlin)
- CLCC Caen (A Hardouin)
- Institut Curie (P de Crémoux)
- CHU Marseille (J Ciccolini)
- CLCC Lille (A Lansiaux)
- Htal G Pompidou (F Coudoré)
- Htal H Mondor (A Hulin)

Méthodes

- 303 cancers du sein métastatique traité par capécitabine.
- 286 patientes (94.4%) exploitables (age moyen 60) sur 303 incluses.
- Capécitabine en monothérapie (88%) ou + thérapie ciblée (12%)
- Dose moyenne au cycle 1 = 1957 mg/m^2/j.
- Uracile et dihydrouracile plasmatique pré-thérapeutique du matin dosés sur 3 sites (Toulouse, Nantes, Angers).
- Polymorphismes DPYD (IVS14+1G>A, 2846A>T, 1679T>G, 464 T>A) analysés sur 7 sites.
- Activité plasmatique de la CDA centralisée sur Nice.
- Etude PK optionnelle.

Analyse du lien Génotype / Toxicité

7 patientes mutées sur 281 génotypées (2.5%)

DPYD genotype	Capecitabine dose at cycle 1 (mg/m²/d)	Number of cycle	Toxicity grade 3-4-5	Pre-treatment Uracil (ng/ml)	Pre-treatment UH2/U	CDA activity (pmol/hlmg)
2846 AT	**1528**	**1**	**Grade 5 at cycle 1**	**17**	**6.5**	**320**
2846 AT	2484	2	Grade 3 at cycle 2	16	5.6	273
2846 AT	1645	3	No toxicity	16	6.4	195
IVS 14+1 GA	1961	3	Grade 3 at cycle 3	9.6	8.3	126
IVS 14+1 GA	1873	1	Grade 3 at cycle 1	14.5	7.6	250
IVS 14+1 GA	1923	3	Not documented	29	3.1	206
1679 TG	2409	3	Grade 3 at cycle 2	21	4.7	188

Risque Relatif de développer une hématotox ou diarrhée G3-4

	Sensibilité	Spécificité	VPP	VPN	RR (95% CI)	Fisher Exact Test
Genotype seul (IVS14+1, 1679TG, 2846AT)						
Patient with *DPYD* mutation *vs* no mutation	16.1%	99.6%	83.3%	89.6%	**8.04** (4.83-13.4)	p<0.001
Uracilémie seule						
Patient with U>cut-off *vs* U≤cut-off						
10.6 ng/ml (median)	65.6%	52.9%	16.5%	91.5%	**1.95** (0.98-3.93)	p=0.059
12 ng/ml (63th percentile)	59.4%	65.8%	19.8%	91.9%	**2.45** (1.27-4.73)	p=0.010
14 ng/ml (74th percentile)	46.9%	77.8%	23.1%	91.1%	**2.60** (1.38-4.91)	p=0.004
15 ng/ml (78th percentile)	43.8%	81.8%	25.5%	91.1%	**2.86** (1.52-5.37)	p=0.002
16 ng/ml (80th percentile)	43.8%	83.6%	27.5%	91.3%	**3.14** (1.68-5.88)	p=0.001
17 ng/ml (83th percentile)	34.4%	84.9%	24.4%	90.1%	**2.47** (1.28-4.75)	p=0.012
20 ng/ml (90th percentile)	21.9%	91.6%	26.9%	89.2%	**2.49** (1.19-5.18)	p=0.028
Approche combinée						
***DPYD* mutation and/or U>16 ng/ml**	50%	83.1%	29.6%	92.1%	**3.76** (2.01-7.02)	p<0.001

DPD : Comment identifier les sujets "à risque de toxicité" ?

Concordance insuffisante entre génotype et phénotype

Intérêt du Phénotypage

- → Dosage de l'activité DPD lymphocytaire
- → Dosage du rapport UH2/U plasmatique
- → Dosage de l'uracile plasmatique

- → Autres explorations biologiques ?

Polymorphisme génétique de HER2 et pharmacodynamie des traitements par herceptin dans le cancer du sein.

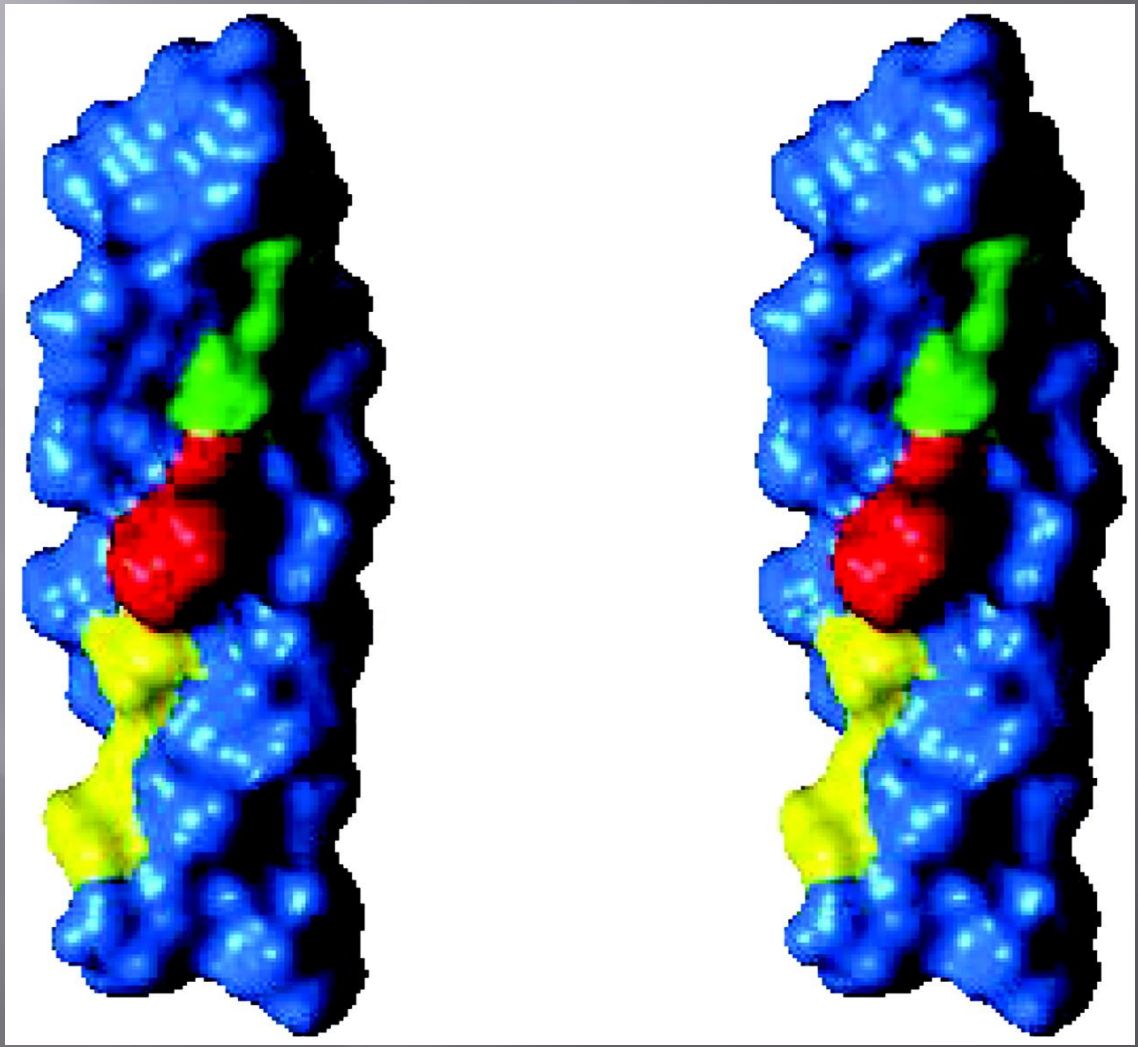
(Beauclair S et al., Ann Oncol 2007, 18:1335-1341)

Bases de l'étude

- **HER-2 : polymorphisme du codon 655 (domaine transmembranaire) : GTC/valine → ATC/isoleucine (Val 655 Ile) : *Papewalis et al., 1991*).**
- **Allele Val : peut predisposer au cancer du sein (*Xie et al., 2000*)**
- **Fréquence allélique Val significative : 45% (*Baxter and Campbell, 2001*).**
- **Val-655 → Ile pourrait destabiliser le dimère (*Fleishman et al., 2002*).**

(Beauclair S et al., Ann Oncol 2007, 18:1335-1341)

Domaine transmembrainaire de HER-2-
Motif N terminal de dimérisation



(Fleishman, Sarel J. et al. (2002) Proc. Natl. Acad. Sci. USA 99, 15937-15940)

Etude clinique

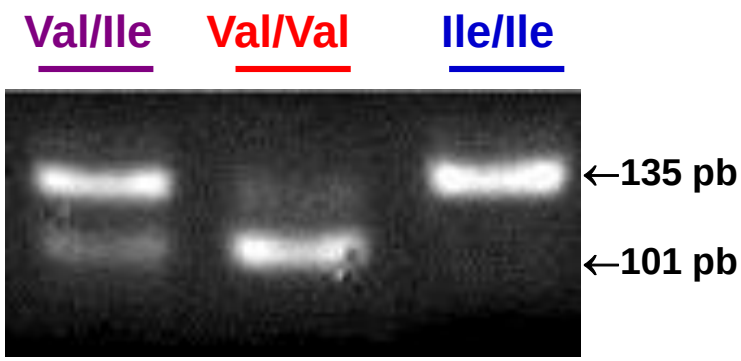
Génotypage HER2 au codon 655 et pharmacodynamie herceptin

- 61 cancers du sein avancés HER-2 (3+, IHC)
- âge médian 50.7 ans (30.5-83.1)
- PS : 0 = 13, 1 = 34, 2 = 14
- follow-up médiane : 22.4 mois (18.7-29.7)
- 87 % en première ligne : herceptin® + taxanes hebdomadaires
- anthracyclines (neoadjuvant/adjuvant) : oui : 36 (59 %)

  non : 25 (41 %)

(Beauclair S et al., Ann Oncol 2007, 18:1335-1341)

HER-2 genotyping



PCR-RFLP/ ADN germinal

Répartition du génotypage

	Ile/Ile	Ile/Val	Val /Val
61 Patients	36 (59%)	21 (34.4%)	4 (6.6%)

(Beauclair S et al., Ann Oncol 2007, 18:1335-1341)

Prédicteurs de cardiotoxicité - 2

Variable		toxicité cardiaque non	toxicité cardiaque oui	p. value*
anthracyclines				0.67
	no	23 (41.07 %)	2 (40 %)	
	yes	33 (58.93 %)	3 (60 %)	
genotype				0.0058
	Ile/Ile	36 (64.29 %)	0 (0 %)	-
	Val/Val	4 (7.14 %)	0 (0 %)	-
	Ile/Val	16 (28.57 %)	5 (100 %)	-

* Fisher exact test

(Beauclair S et al., Ann Oncol 2007, 18:1335-1341)

Confirmation récente Unicancer PACS 04 (Roca I. et al, Br Ca Res Treat 2013)

Toxicité cardiaque et polymorphisme HER2 codon 655

	I/I *N* (%)	I/V *N* (%)	V/V *N* (%)	I/I *N* (%)	I/V + V/V *N* (%)
No patients	79 (60)	48 (36)	5 (4)	79 (60)	53 (40)
Overall cardiac toxicity	$p = 0.854$			$p = 0.456$	
No	43 (54.4)	29 (60.4)	3 (60.0)	43 (54.4)	32 (60.4)
Yes	36 (45.6)	19 (39.6)	2 (40.0)	36 (45.6)	21 (39.6)
Trastuzumab discontinuation for cardiac toxicity	$p = 0.778$			$p = 0.563$	
No	64 (81.0)	40 (83.3)	5 (100.0)	64 (81.0)	45 (84.9)
Yes	15 (19.0)	8 (16.7)	0 (0.0)	15 (19.0)	8 (15.1)
Relative LVEF decrease >15 %*	$p = 0.753$			$p = 0.530$	
No	51 (64.6)	33 (68.7)	4 (80.0)	51 (64.6)	37 (69.8)
Yes	28 (35.4)	15 (31.3)	1 (20.0)	28 (35.4)	16 (30.2)
Left ventricular toxicity[a]	$p = 0.177$			$p = 0.091$	
No	59 (74.7)	42 (87.5)	4 (80.0)	59 (74.7)	46 (86.8)
Yes	20 (25.3)	6 (12.5)	1 (20.0)	20 (25.3)	7 (13.2)
LVEF value <50	$p = 0.049$			$p = 0.035$	
No	75 (94.9)	39 (81.2)	5 (100.0)	75 (94.9)	44 (83.0)
Yes	4 (5.1)	9 (18.8)	0 (0.0)	4 (5.1)	9 (17.0)

(Roca L et al, Breast Cancer Res Treat 2013)

Conclusions

- Herceptin et Capecitabine = progrès thérapeutiques incontestables dans le cancer du sein.

- Herceptin et Capecitabine = une toxicité reconnue et à risque identifié (DPD).

Peut-on anticiper individuellement la toxicité ?

- Herceptin et Capecitabine = OUI, nécessité de disposer de tests simples, peu coûteux, applicables à grande échelle (screening DPD).

Merci de votre attention ☺


Merci de votre attention !

M.A.C.C 9

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