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CENTRE RÉGIONAL DE LUTTE CONTRE LE CANCER DE BORDEAUX ET DU SUD-OUEST
UNICANCER
MEMBRE DU GROUPE

Paris,
Jeudi 15 novembre 2012
Société Française de Sénologie et de Pathologie mammaire

Acquis et limites en situation non métastatique…

L'hormonothérapie adjuvante

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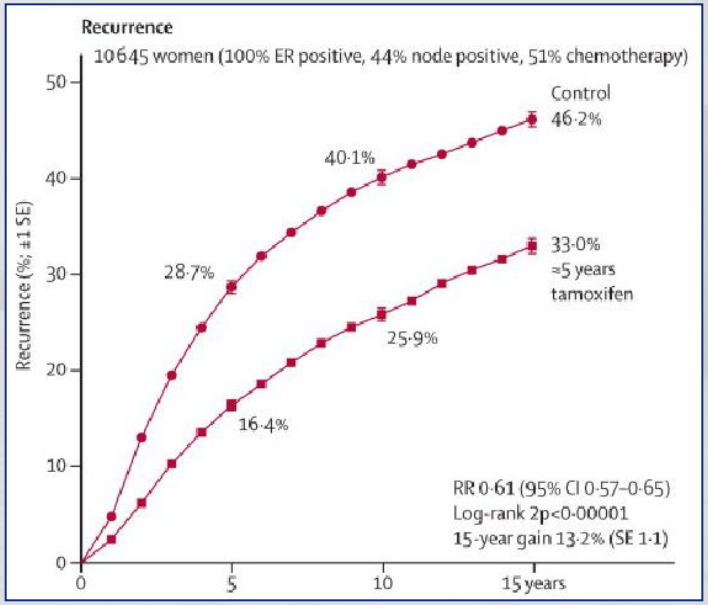
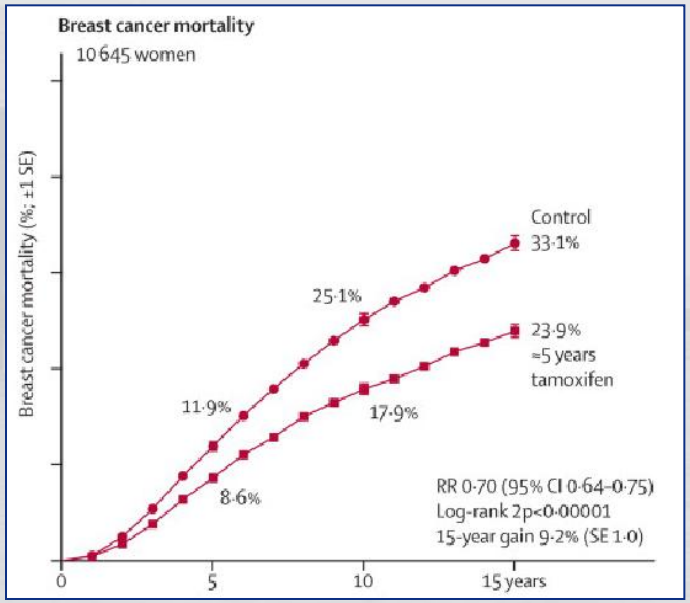
Impact du Tamoxifène en adjuvant…

- ✓ *Méta-analyse sur données individuelles ; 20 études, 21 000 ptes*
- ✓ *Impact de 5 ans de Tam vs placebo*





➔ **Une réduction relative du risque de rechute de 39% (± 3%) ($2p<10^{-5}$)**

➔ **Une réduction relative du risque de décès de 30% (± 5%) ($2p<10^{-5}$)**

EBCTCG, Lancet 2011

Impact (RR) du Tamoxifène en adjuvant… Réduction du risque de rechute

∇ dose

∇ administration d'une CT

∇ âge

∇ statut ggl

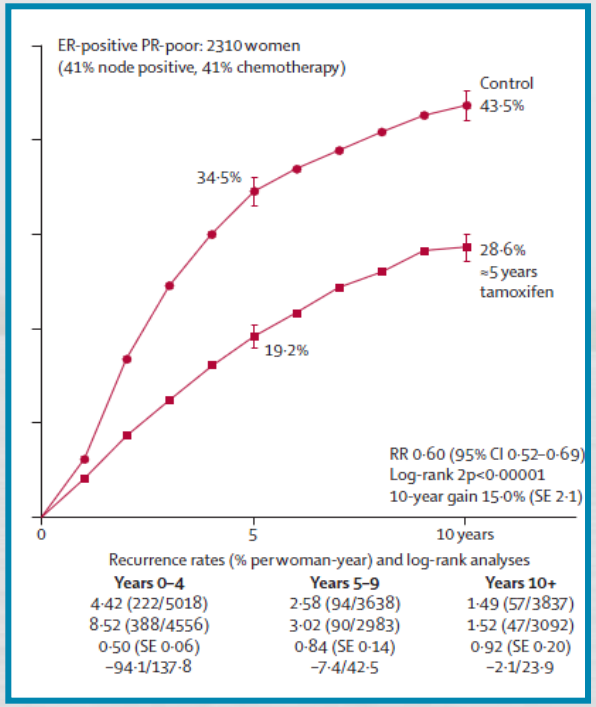
∇ différenciation

∇ taille tum.

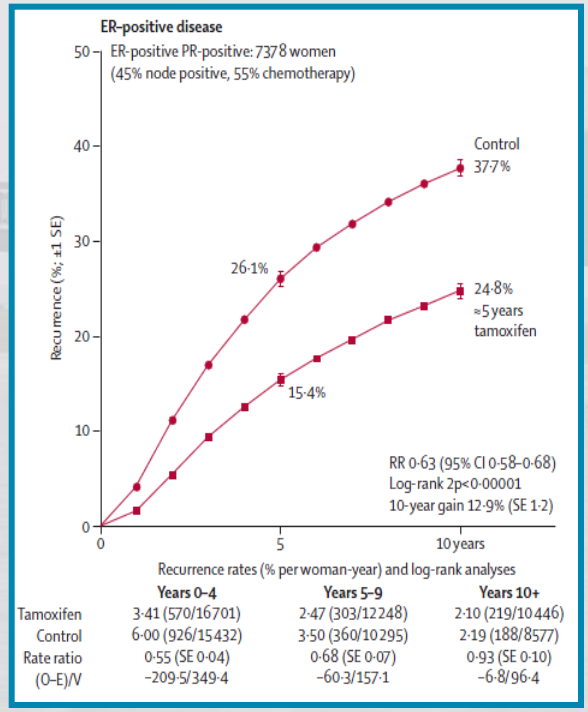
Category	Events/woman-years (rate [% per year])		Tamoxifen events		Ratio of annual event rates
	Allocated tamoxifen	Allocated control	Log-rank O–E	Variance of O–E	Tamoxifen : control
(a) Dose (trend χ^2_1=5·4; 2p=0·02)					
20 mg per day	1134/40 962 (2·8)	1547/36 557 (4·2)	−273·8	627·6	0·65 (SE 0·03)
30 mg per day	250/5710 (4·4)	313/4199 (7·5)	−76·6	118·4	0·52 (SE 0·07)
40 mg per day	269/10 075 (2·7)	358/8120 (4·4)	−83·1	135·4	0·54 (SE 0·06)
(b) Background chemotherapy (χ^2_1=7·7; 2p=0·006)					
Present	837/22 900 (3·7)	1057/20 528 (5·1)	−170·5	430·1	0·67 (SE 0·04)
Absent	816/33 847 (2·4)	1161/28 348 (4·1)	−263·1	451·3	0·56 (SE 0·04)
(c) Background chemotherapy (χ^2_1=2·1; 2p=0·1)					
Concurrent	352/7096 (5·0)	433/5817 (7·4)	−81·8	169·2	0·62 (SE 0·06)
Sequential	485/15 804 (3·1)	624/14 711 (4·2)	−88·7	260·9	0·71 (SE 0·05)
Absent	816/33 847 (2·4)	1161/28 348 (4·1)	−263·1	451·3	0·56 (SE 0·04)
(d) Entry age (years) (trend χ^2_1=5·5; 2p=0·02)					
<45	406/11 846 (3·4)	572/10 690 (5·4)	−105·1	226·9	0·63 (SE 0·05)
45–54	494/16 768 (2·9)	615/15 678 (3·9)	−83·8	256·8	0·72 (SE 0·05)
55–69	712/26 610 (2·7)	963/21 215 (4·5)	−228·8	374·9	0·54 (SE 0·04)
≥70	41/1512 (2·7)	68/1293 (5·3)	−15·8	22·8	0·50 (SE 0·15)
Age unknown	0/11 (0·0)	0/0			
(e) Nodal status (trend χ^2_1=0·2; 2p=0·7)					
N0/N–	753/37 672 (2·0)	1105/33 174 (3·3)	−227·6	443·3	0·60 (SE 0·04)
N1–3	348/10 126 (3·4)	445/8464 (5·3)	−79·8	180·1	0·64 (SE 0·06)
N4+	355/5097 (7·0)	432/3776 (11·4)	−93·2	161·3	0·56 (SE 0·06)
Other/unknown	197/3852 (5·1)	236/3462 (6·8)	−33·0	96·7	0·71 (SE 0·09)
(f) Tumour differentiation (χ^2_1=1·1; 2p=0·3)					
Poorly differentiated	101/2022 (5·0)	170/1730 (9·8)	−38·5	58·1	0·52 (SE 0·10)
Moderately/well	201/4285 (4·7)	251/3513 (7·1)	−48·8	99·3	0·61 (SE 0·08)
Grade unknown	1351/50 461 (2·7)	1797/43 645 (4·1)	−333·2	734·9	0·64 (SE 0·03)
(g) Tumour diameter (mm) (trend χ^2_1=1·2; 2p=0·3)					
1–20 (T1)	647/29 188 (2·2)	905/25 511 (3·5)	−188·2	365·8	0·60 (SE 0·04)
21–50 (T2)	771/20 603 (3·7)	1000/17 847 (5·6)	−169·0	403·5	0·66 (SE 0·04)
>50 (T3/T4)	78/1462 (5·3)	110/1337 (8·2)	−17·2	36·9	0·63 (SE 0·03)
Other/unknown	157/5495 (2·9)	203/4173 (4·9)	−40·5	78·8	0·60 (SE 0·09)

Impact du Tamoxifène en adjuvant… Réduction du risque de rechute

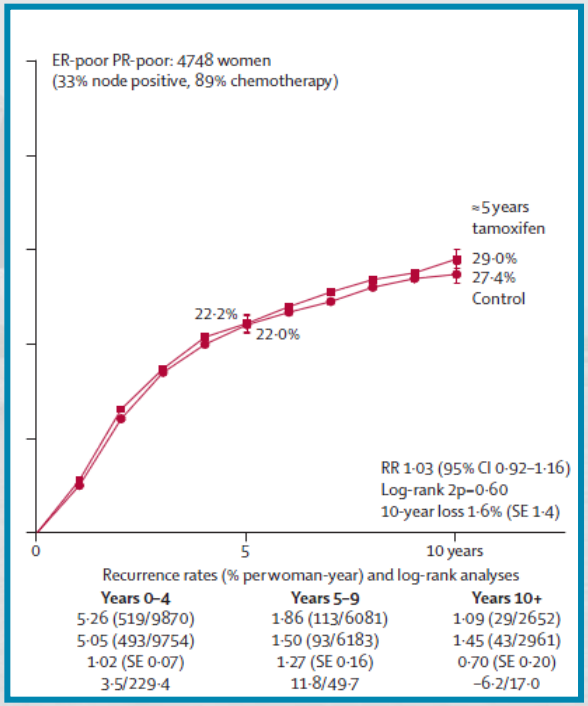
RE+ RP-



RE+ RP+



RE- RP-



➔ Un bénéfice dépendant de l'expression des RE,

➔ Les RP ne sont pas des facteurs prédictifs, mais pronostiques

Bénéfices de l'hormonothérapie adjuvante

Tamoxifène

R

	Réduction du risque (Tam/0)
Toute rechute	39 % +/- 5
Décès	30 % +/- 5

- 39%

- 30%

Rechute locale	46 % +/- 7
Rechute CL	38% % +/- 7
Rech à distance	37 % +/- 10

Inhib. Arom.

R

R

	Réduction du risque (AI/Tam)	Réduction du risque (AI/Tam)
Toute rechute	23 % +/- 5	29 % +/- 6
Décès	*11% +/- 7*	22 % +/- 9

Rechute locale	30 % +/- 10	40 % +/- 13
Rechute CL	41 %+/- 12	35 %+/- 17
Rech à distance	18 % +/- 6	23 % +/- 6

EBCTCG, Lancet 2011

Dowsett, J Clin Oncol 2010

Bénéfices de l'hormonothérapie adjuvante

Tamoxifène

R

	Réduction du risque (Tam/0)
Toute rechute	39 % +/- 5
Décès	30 % +/- 5

Rechute locale	46 % +/- 7
Rechute CL	38% % +/- 7
Rech à distance	37 % +/- 10

Activité ovarienne

Inhib. Arom.

R R

	Réduction du risque (AI/Tam)	Réduction du risque (AI/Tam)
Toute rechute	23 % +/- 5	29 % +/- 6
Décès	*11% +/- 7*	22 % +/- 9

Rechute locale	30 % +/- 10	40 % +/- 13
Rechute CL	41 %+/- 12	35 %+/- 17
Rech à distance	18 % +/- 6	23 % +/- 6

Ménopause

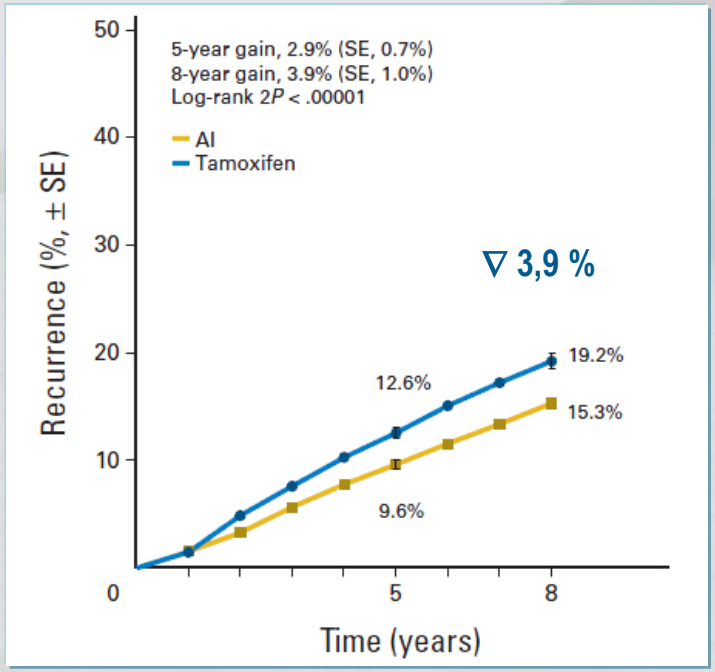
- 39% → - 57%

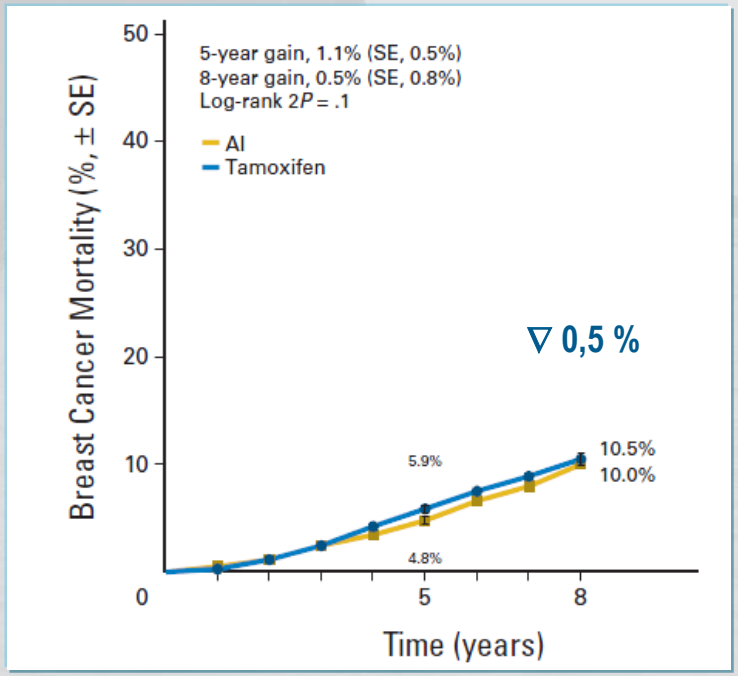
- 30% → - 45%

Remplacer le tamoxifène par un IA …. Un gain limité …

TRT par IA durant 5 ans vs Tam

Méta-analyse des études ATAC (anastrozole) et BIG 1-98 (letrozole)
N = 9,856 ; suivi médian de 5,8 ans





Une absence de bénéfice statistique en survie

Dowsett, J Clin Oncol 2010

IA 5 ans ou traitement séquentiel ?

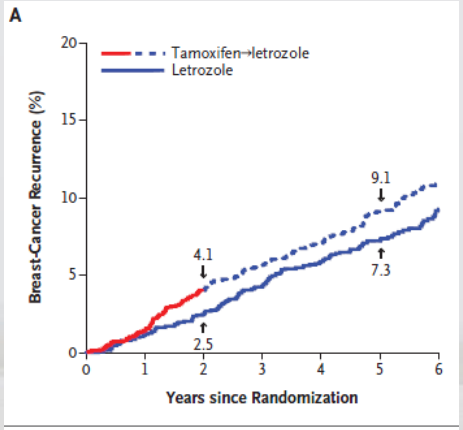
BIG 1-98, N Eng j Med 2009

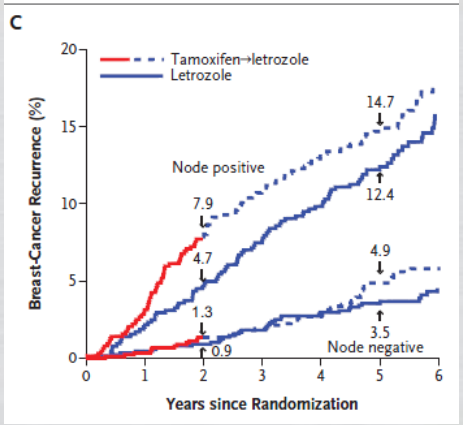
Letrozole	
Tam	Letrozole

} **3 094 patientes**

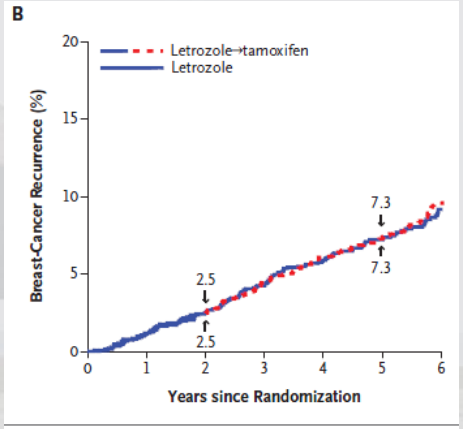
3 086 patientes {

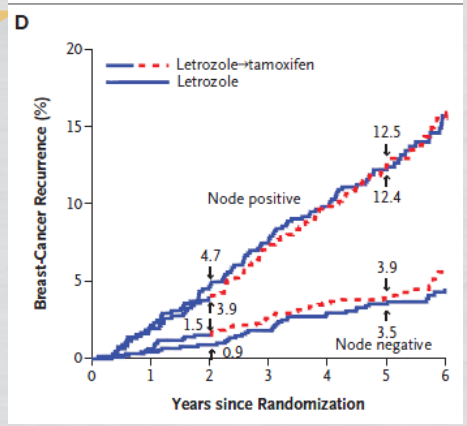
Letrozole	
Letrozole	Tam





Un suivi médian de 71 mois





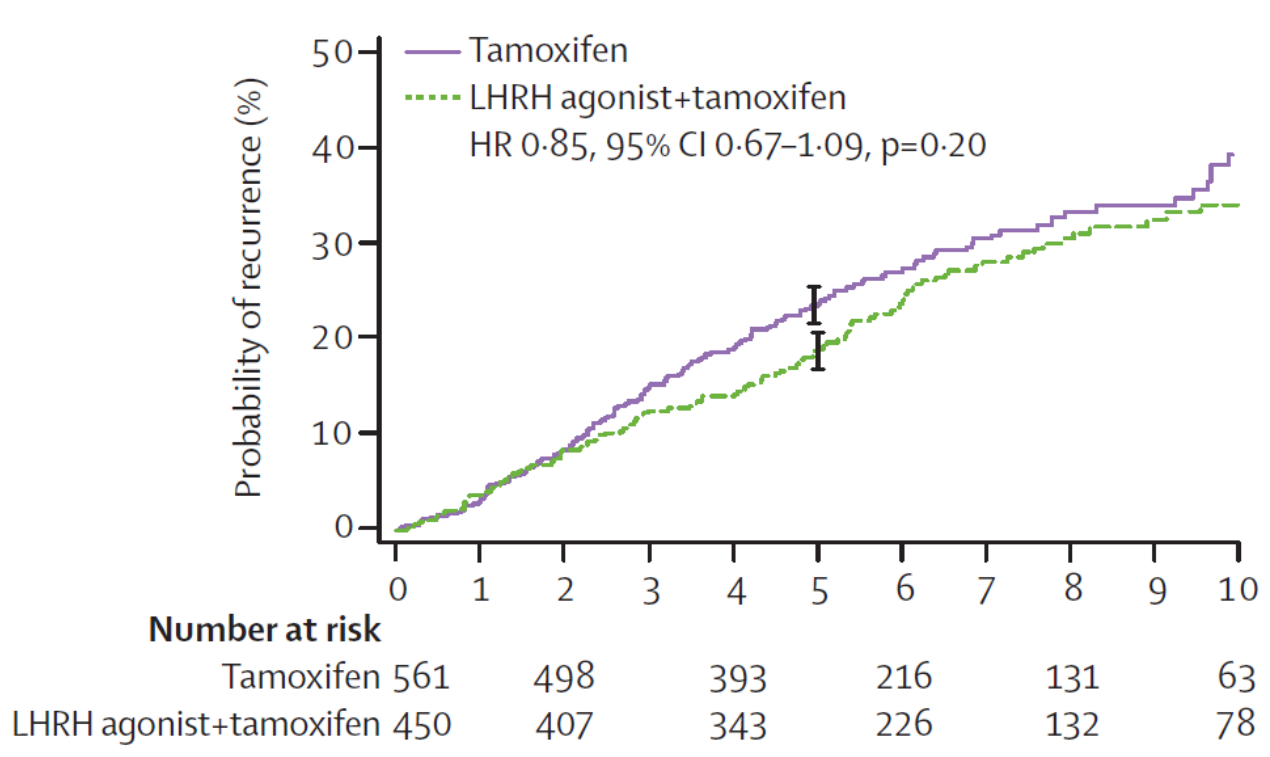
- TRT séquentiel IA ➔ Tam = IA
- initier le TRT par un IA si risque de rechute précoce (N+, haut grade…)

Effets secondaires et risques IA / Tam
Méta a-analyse sur données publiées (med FU : 28 à 100 mois)

Effets secondaires	Risque relatif IA / Tam	p	Taux sous Tam	Taux sous IA	Nombre de ptes à traiter
Plus fréquents sous IA					
Evènements cardio-vasculaires	1,26 [1,10 – 1,43]	<0,001	3,4%	4,2%	132
Fractures	1,47 [1,34 – 1,61]	<0,001	5,2 %	7,5 %	46
Dyslipidémie	2,36 [2,15 – 2,60]	<0,001	NP	NP	NP
Plus fréquents sous Tam					
Accidents veineux thrombo-emboliques	0,55 [0,46 – 0,64]	<0,001	2,8 %	1,6 %	69
Cancers de l'endomètre	0,34 [0,22 – 0,53]	<0,001	0,5 %	0,1 %	250
Pas de différence entre IA et Tam					
Evènements cérébro-vasculaires	1,01 [0,81 – 1,26]	0,93	1,4 %	1,5 %	-
Autres cancers	0,98 [0,85 – 1,14]	0,83	4,8 %	4,7 %	-
Décès sans rechute	1,04 [0,93 – 1,16]	0,51	4,1%	4,2 %	-

Amir, JNCI 2011

Situation adjuvante chez la pte non ménopausée :
Faut-il adjoindre une suppression ovarienne au Tam ?



N = 1 013	Réduction du risque de rechute	Réduction du risque de décès
	15% [IC 95% : 0,67 – 1,09] P = 0,20	16% [IC 95% : 0,59 – 1,19] P = 0,33

EBCTCG, Lancet 2007

Patientes en activité ovarienne : l'étude SOFT

- Activité ovarienne 8 mois après la CT
- RH+

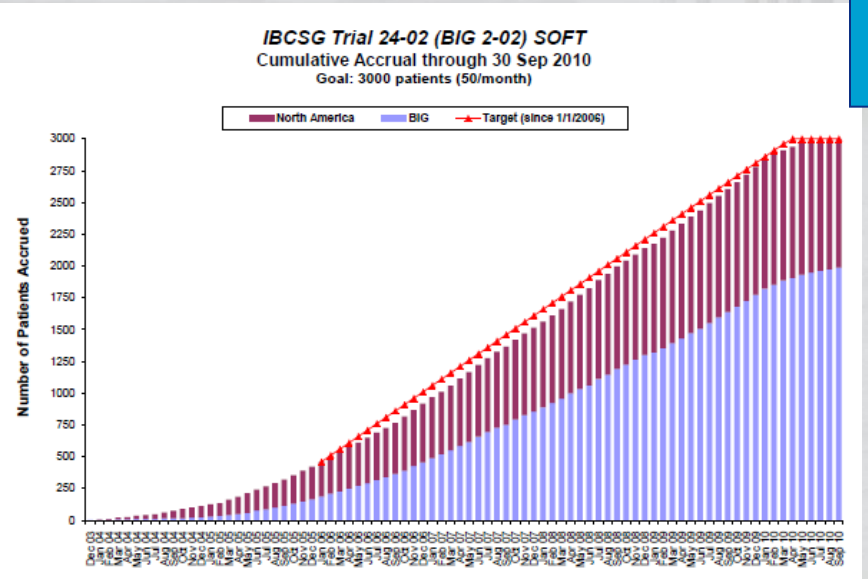
N = 3,000

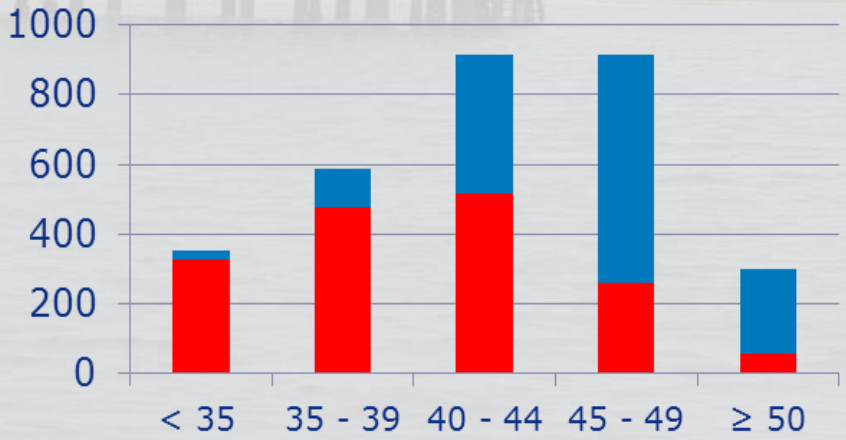
RANDOMISATION

→ T x 5y

→ Supp ovar. + Tam x 5 a

→ Supp ovar. + Exe x 5a





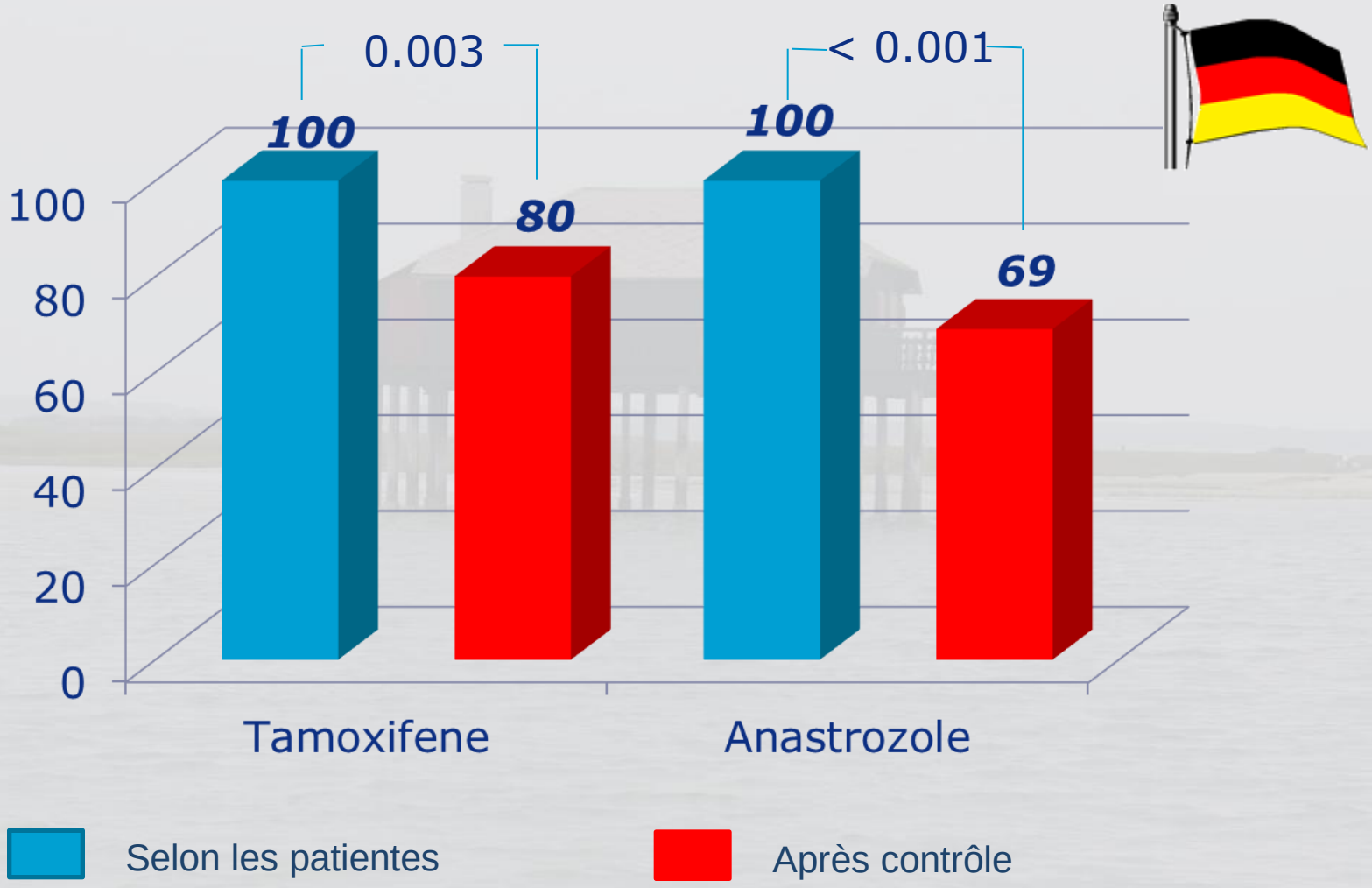
→ Les inclusions sont terminées

Les Limites :
1. l'adhérence … et donc la tolérance !

Etude	Pays	Critères	Nbre	% d'adhérence
Ziller	Allemand	Post-MP	50	80% à 1 an
Fink	Etats-Unis	≥ 65 ans	597	83% à 2 ans
Demissie	Etats-Unis	≥ 55 ans	303	85% à 2.75 ans
Barron	Irelande	≥ 35 ans	2,816	66% à 3.5 ans
Kahn	Etats-Unis	Tout âge	881	79% à 4 ans
Partridge	Etats-Unis	Tout âge	2,378	50% à 4 ans
McCowan	Ecosse	Tout âge	1,633	49% à 5 ans
Guth	Suisse	Tout âge	287	89% à 5 ans
Lash	Etats-Unis	≥ 65 ans	462	69% à 5 ans
Owusu	Etats-Unis	≥ 65 ans	961	51% à 5 ans

Hachshaw, J Clin Oncol 2011

… Quelle adhérence au traitement ?
Selon la patiente ou la délivrance …

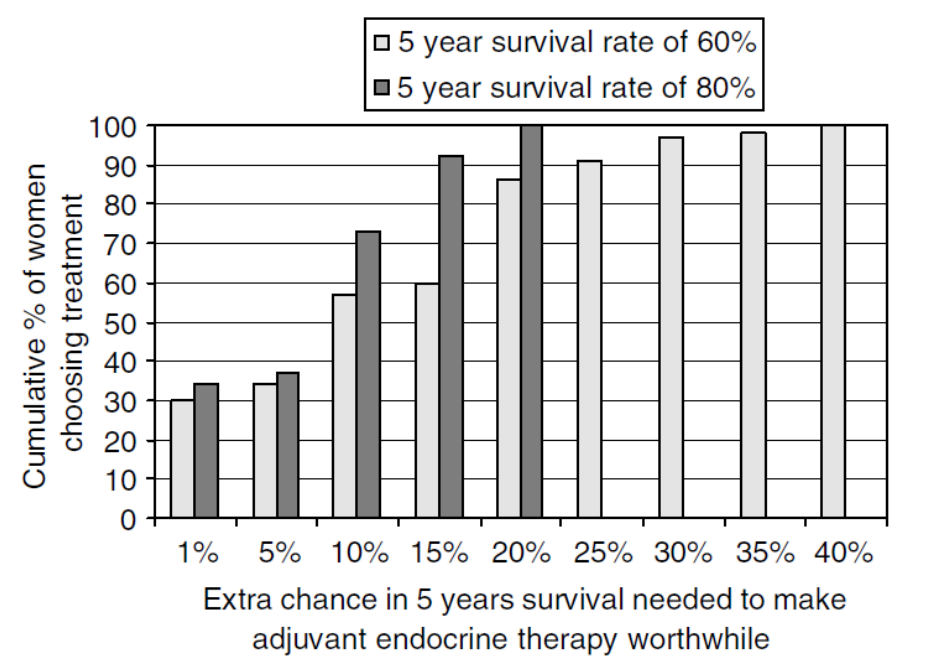


Ziller, Ann Oncol 2009

Les limites :

2. Mieux comprendre les souhaits et les attentes des patientes

85 ptes (age méd : 45 ans) ; Tam seul : 35% ; Tam + ag LHRH : 50%



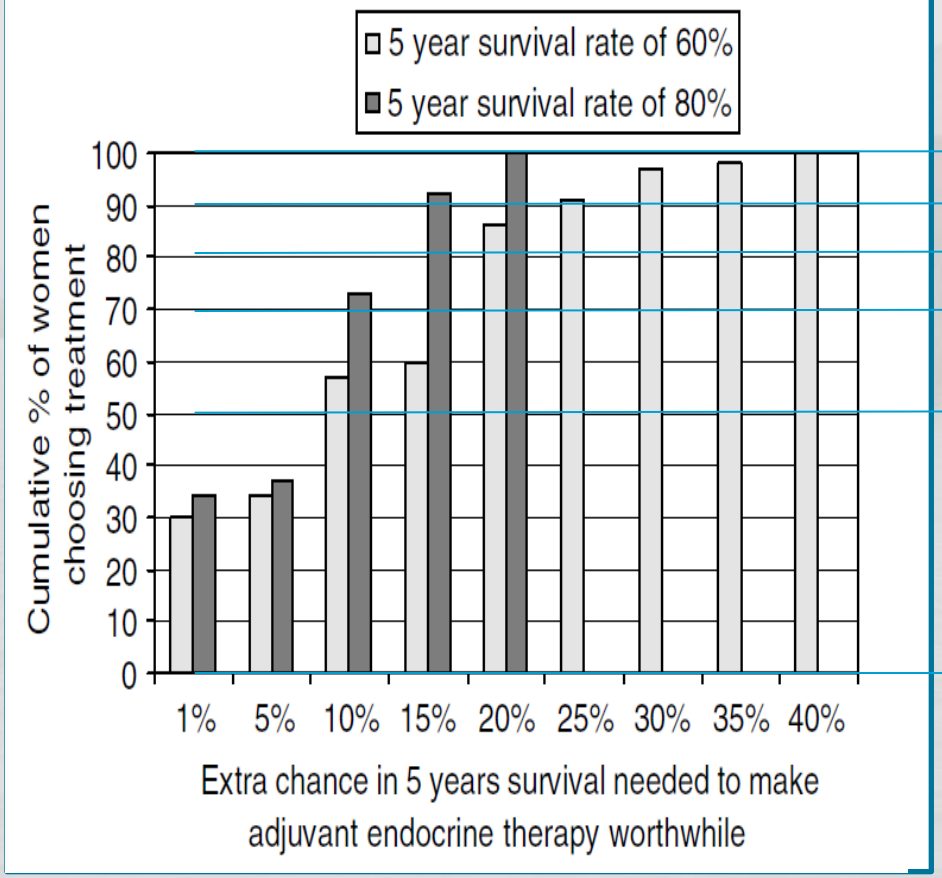
- 1/3 ptes jugent 1% de gain en survie suffisant pour justifier une HT
- 50% estiment qu'un bénéfice de 5% est nécessaire
- **… une grande variabilité**

Duric, Br J Cancer 2005

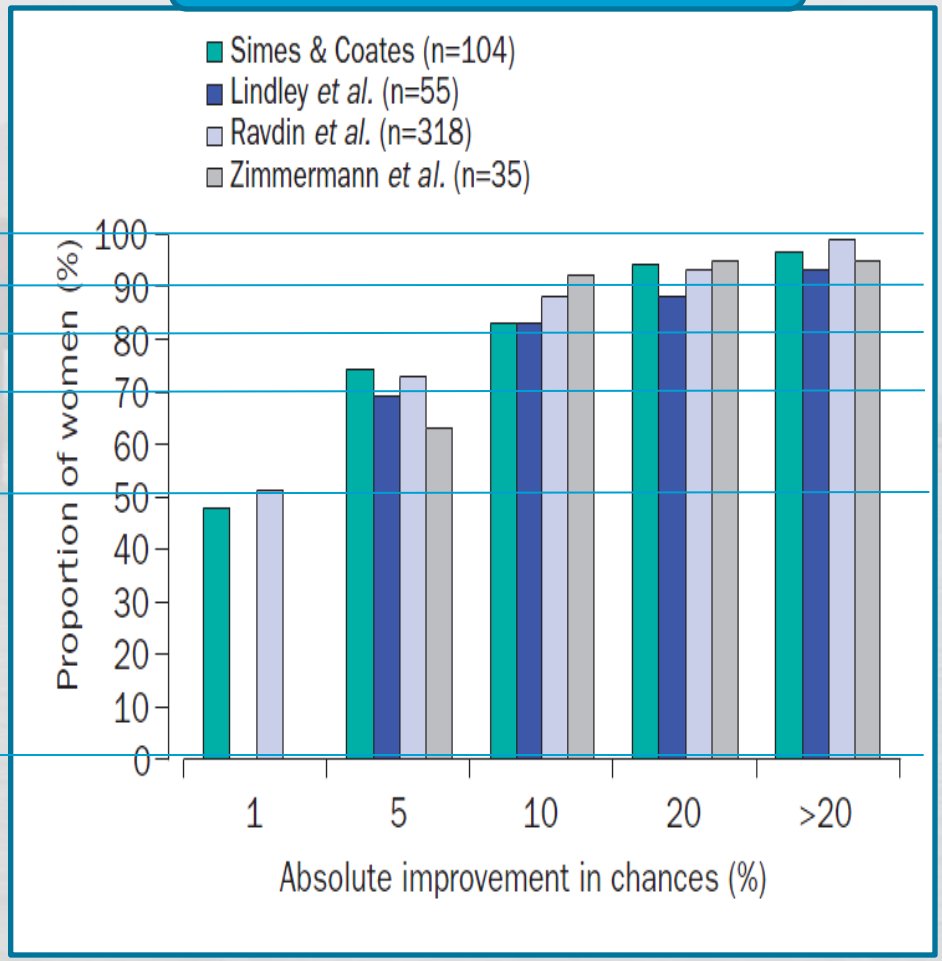
Les limites :

2. Mieux comprendre les souhaits et les attentes des patientes

Hormonothérapie



Chimiothérapie

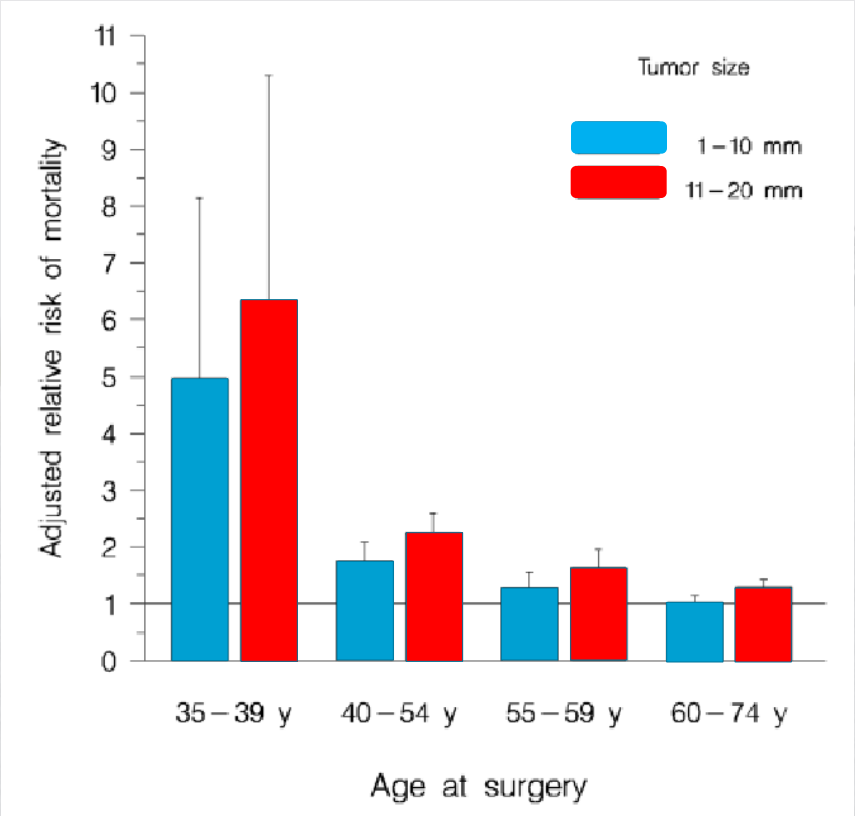


Thewes, Lancet Oncol 2005

Les limites :

3. des prescriptions trop systématisées ? …. ∇ le pronostic ?

3,197 ptes opérées d'emblée tumeur ≤ 20mm, pN0, CCI gr1 ou CLI gr1-2, RE+ et/ou RP+, sans TRT adjuvant



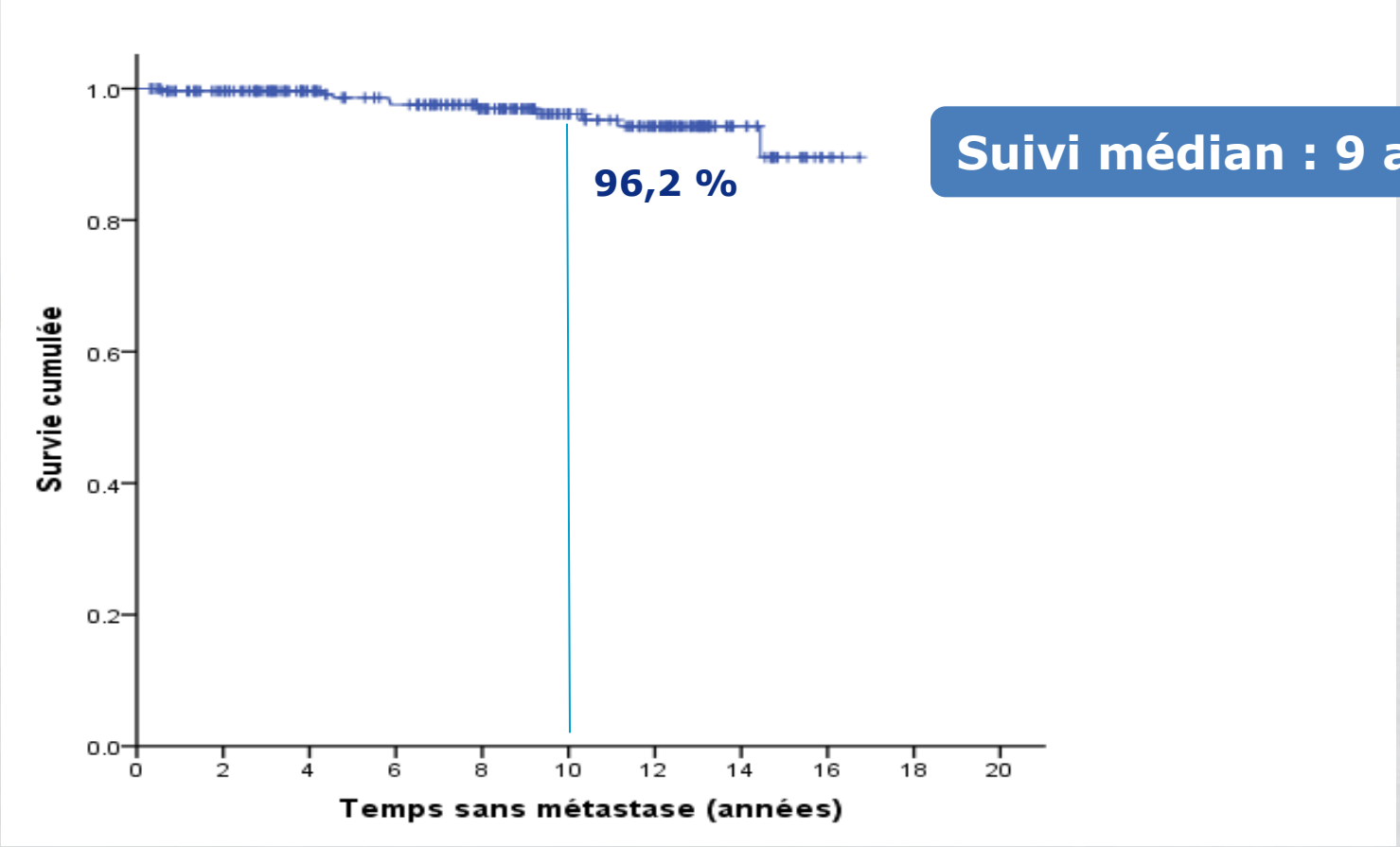
Ne pas proposer d'HT adjuvante aux CCI gr I, CLI gr I-II si pT1a,b N0 > 60 ans

Christiansen , JNCI 2011

Les limites :

3. des prescriptions trop systématisées ? …. ∇ le pronostic ?

Tumeurs opérées d'emblées pT1apT1b N0 LVI- RH+
sans traitement systémique adjuvant (1990 – 2008)
N = 275



Les limites :
4. Mieux définir l'hormonosensibilité …
Que sont les tumeurs RE 0-10 % ?

➔ Analyse de 465 tumeurs en IHC et sur puce Affymetrix : expression mRNA ESR1, d'une signature génétique ; classification moléculaire par PAM-50

ER IHC		ESR1 mRNA expression		SET Index		
IHC level	# patients.	Positive (%)	Negative (%)	High (%)	Intermediate (%)	Low (%)
0	183	16 (8.7)	167 (91.3)	2 (1.1)	2 (1.1)	179 (97.8)
1-9%	25	6 (24.0)	19 (76.0)	0	0	25 (100)
10%	6	4 (66.7)	2 (33.3)	0	1 (16.7)	5 (83.3)
>10%	251	232 (92.4)	19 (7.6)	12 (4.8)	27 (10.8)	212 (84.5)

* ER = Estrogen receptor, IHC = Immunohistochemistry, SET = Sensitivity to Endocrine Terapy gene index

IHC		Molecular subtypes by PAM50				
IHC level	No. of Pts.	Luminal A	Luminal B	HER2-amplified	Basal	Normal
0%	183	2	1	51	111	18
1 to 9%	25	0	2	8	12	3
10%	6	2	1	1	1	1
> 10%	251	120	61	38	16	16

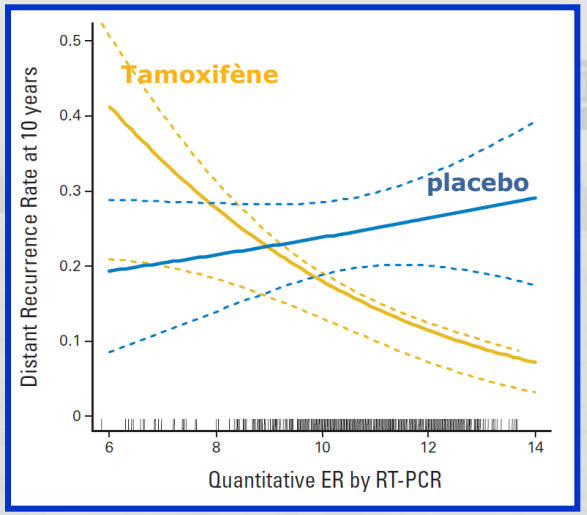
* ER = Estrogen receptor, IHC = Immunohistochemistry, Pts = Patients

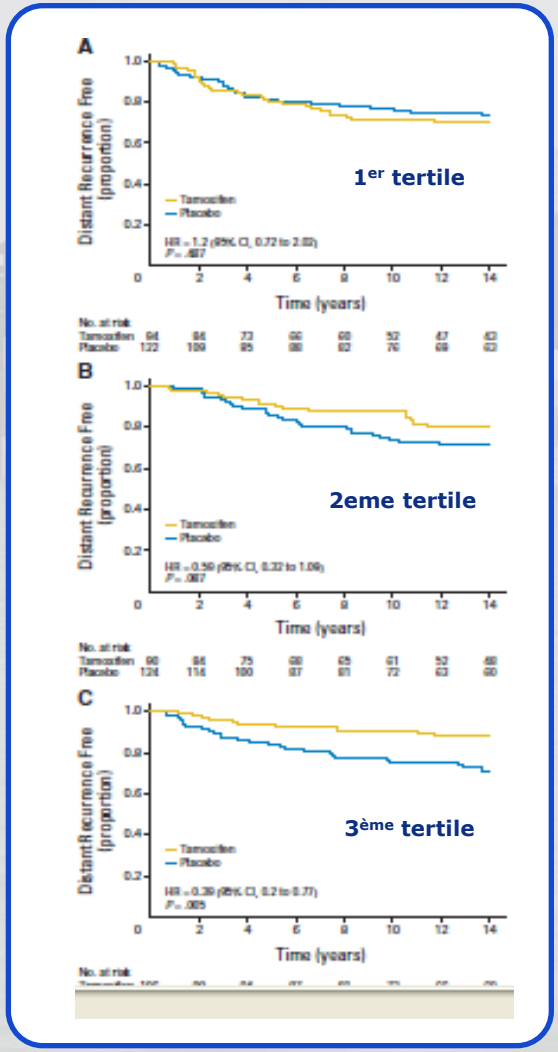
- La majorité doivent être considérées comme étant RH-
- Une absence d'hormonosensibilité …

Iwamoto, J Clin Oncol 2012

Impact du Tamoxifène en adjuvant… selon le niveau d'expression mRNA d'ESR1

Analyse de 645 patientes incluses dans le NSABP B-14 (Tam : 290 ; placebo : 355)





Faible niveau d'expression ARNm

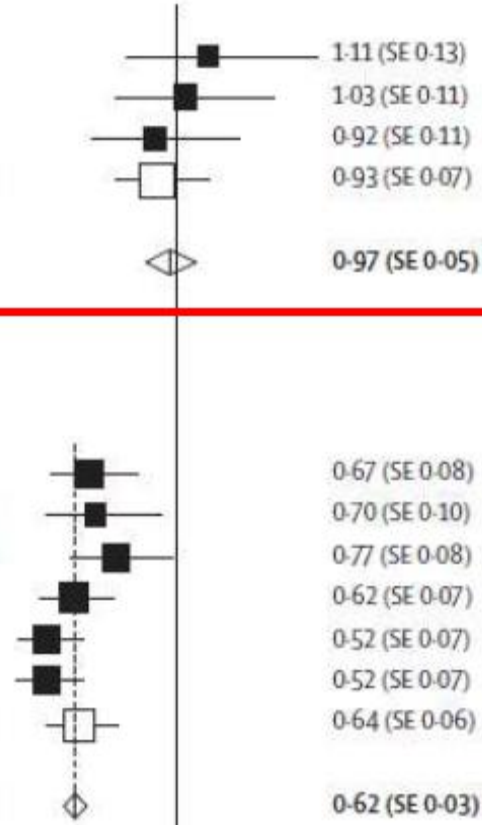
Niveau intermed. d'expression ARNm

Fort niveau d'expression ARNm

Kim, J Clin Oncol 2011

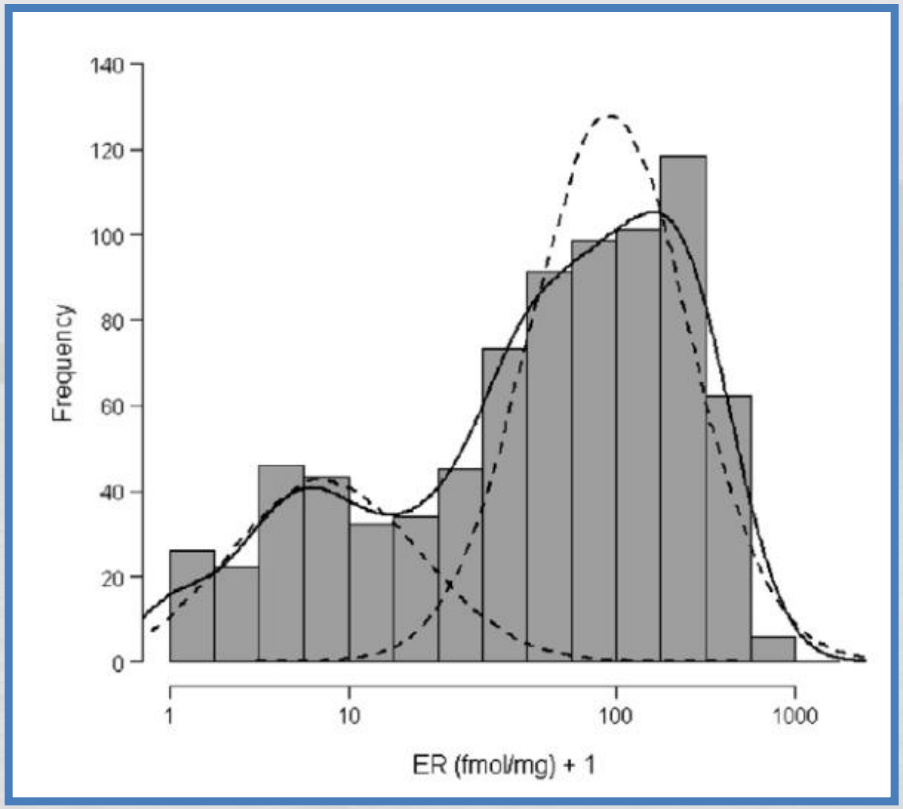
Bénéfice du tamoxifène selon le niveau d'expression des RE

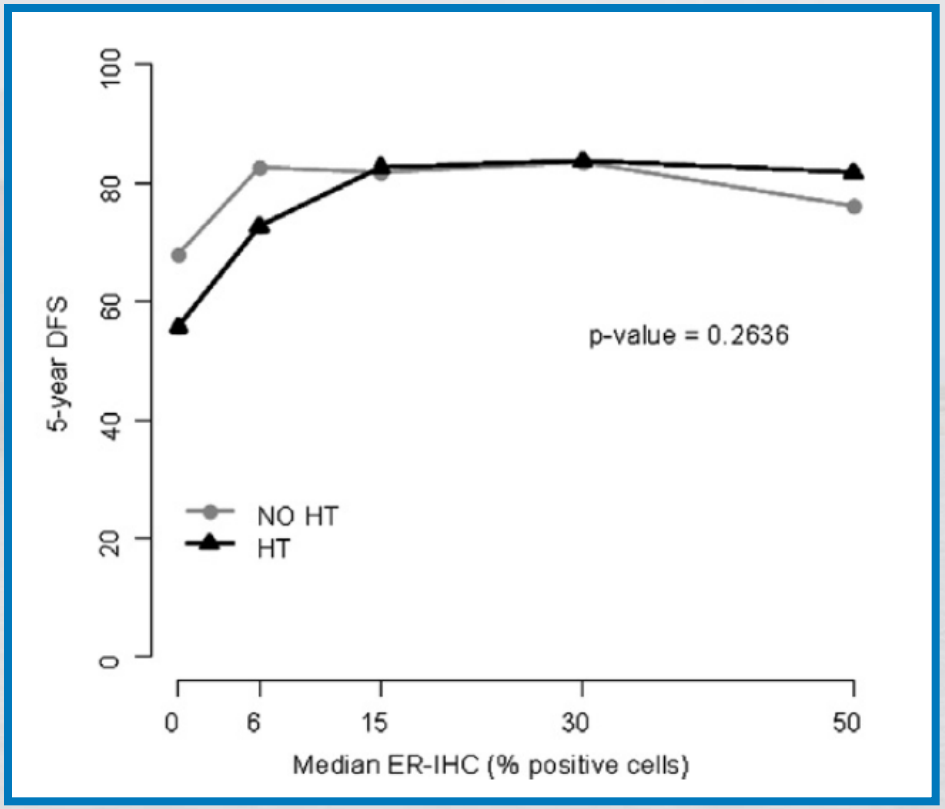
Category	Events/woman-years (rate [% per year])		Tamoxifen events		Ratio of annual event rates
	Allocated tamoxifen	Allocated control	Log-rank O-E	Variance of O-E	Tamoxifen : control
(a) ER-poor					
ER=0	162/5060 (3·2)	163/5941 (2·7)	7·4	69·5	1·11 (SE 0·13)
ER 1–3	202/6645 (3·0)	192/6357 (3·0)	2·2	85·5	1·03 (SE 0·11)
ER 4–9	185/5490 (3·4)	188/5588 (3·4)	−6·6	77·5	0·92 (SE 0·11)
Other ER-poor	449/9528 (4·7)	451/8995 (5·0)	−14·9	195·5	0·93 (SE 0·07)
(a) Subtotal	**998/26723 (3·7% per year)**	**994/26 881 (3·7% per year)**	**−12·0**	**428·0**	**0·97 (SE 0·05) 2p=0·6**
Test for trend χ^2_1=1·4; 2p=0·2					
(b) ER-positive by ER measurement					
ER 10–19	232/8173 (2·8)	316/7252 (4·4)	−47·4	120·6	0·67 (SE 0·08)
ER 20–29	158/5104 (3·1)	197/4630 (4·3)	−27·3	76·4	0·70 (SE 0·10)
ER 30–49	235/8107 (2·9)	260/6952 (3·7)	−29·0	112·1	0·77 (SE 0·08)
ER 50–99	293/10650 (2·8)	361/8973 (4·0)	−69·6	144·8	0·62 (SE 0·07)
ER 100–199	211/8429 (2·5)	344/7376 (4·7)	−80·4	122·8	0·52 (SE 0·07)
ER≥200	216/8279 (2·6)	325/6672 (4·9)	−78·2	119·0	0·52 (SE 0·07)
Other ER+	308/7868 (3·9)	415/6898 (6·0)	−72·9	161·3	0·64 (SE 0·06)
(b) Subtotal	**1653/56 610 (2·9% per year)**	**2218/48753 (4·5% per year)**	**−404·8**	**856·9**	**0·62 (SE 0·03) 2p<0·00001**
Test for trend χ^2_1=9·5; 2p=0·002					



EBCTCG, Lancet 2011

Impact du Tamoxifène en adjuvant… selon le niveau des RE … en IHC

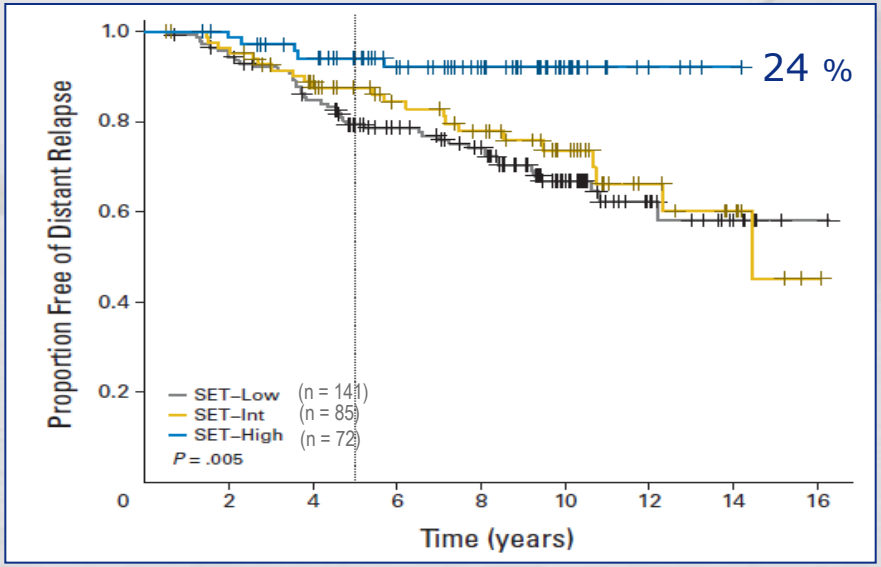




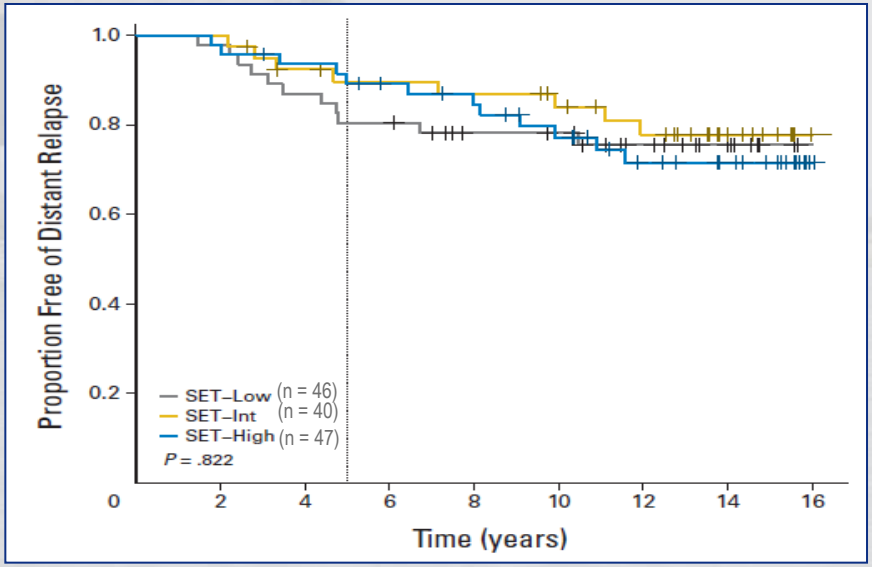
Mazouni, Eur J Cancer 2010

Impact du Tamoxifène en adjuvant…
Une signatures d'expression de gènes associés à l'activité RE…

Cohorte de ptes RE+ N0 Traitées par Tam



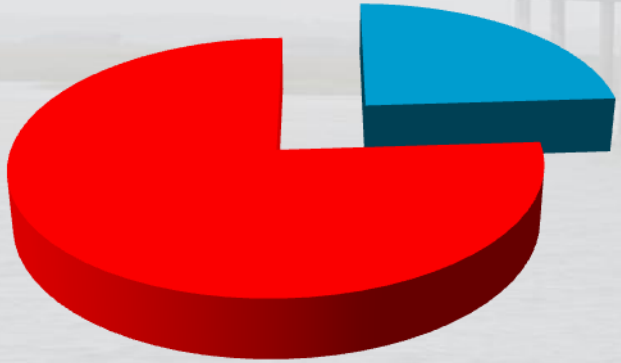
Cohorte de ptes RE+ N0 non traitées par HT

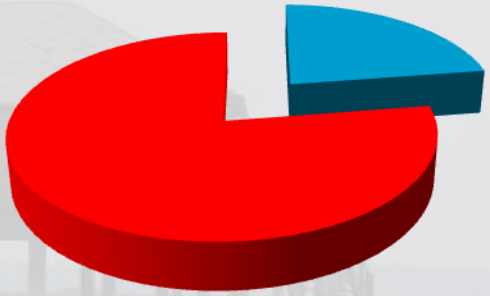


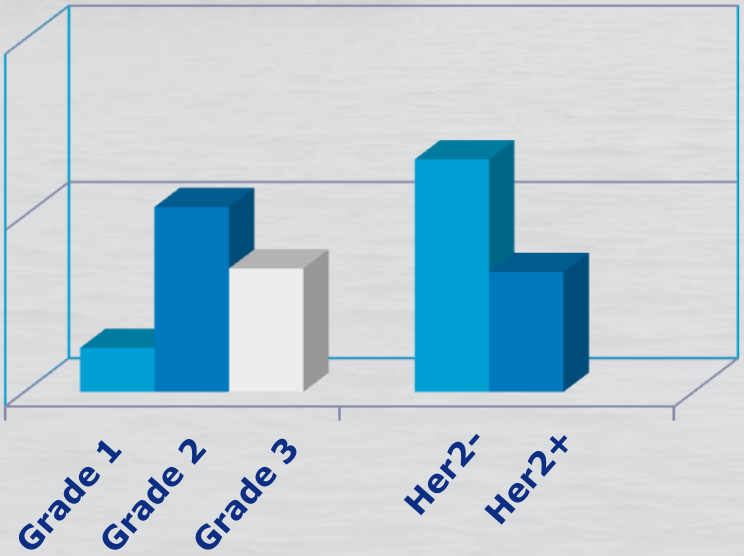
Symmans, JCO 2010

Les limites … Les échecs !!

Institut Bergonié : Patientes métastatiques (juin 2010-Mai 2012)
N = 303

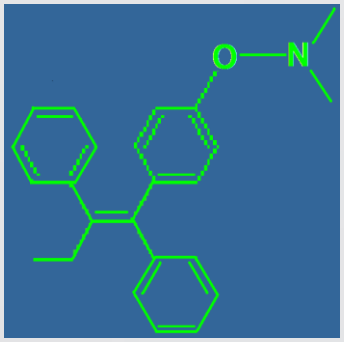






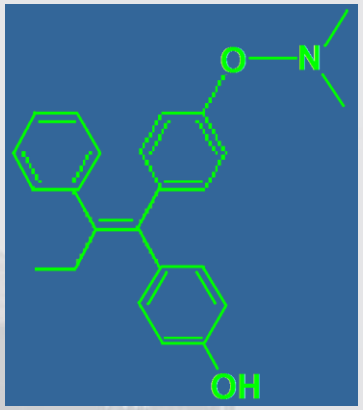
Les limites :

4. Comment choisir entre Tam et inhibiteur de l'aromatase ?



Tamoxifene (TAM)

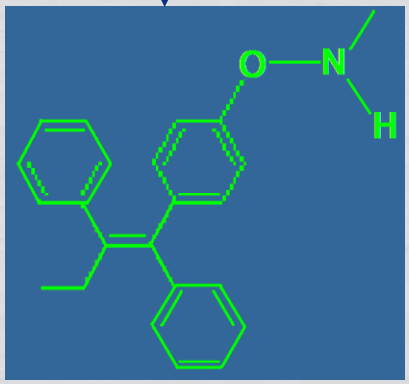
CYP 2D6



4-hydroxyTAM

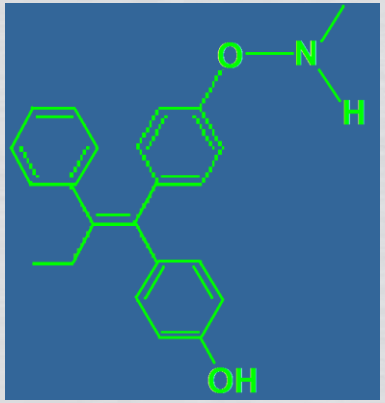
CYP 3A 4/5

CYP 3A 4/5



N-desmethylTAM

CYP 2D6



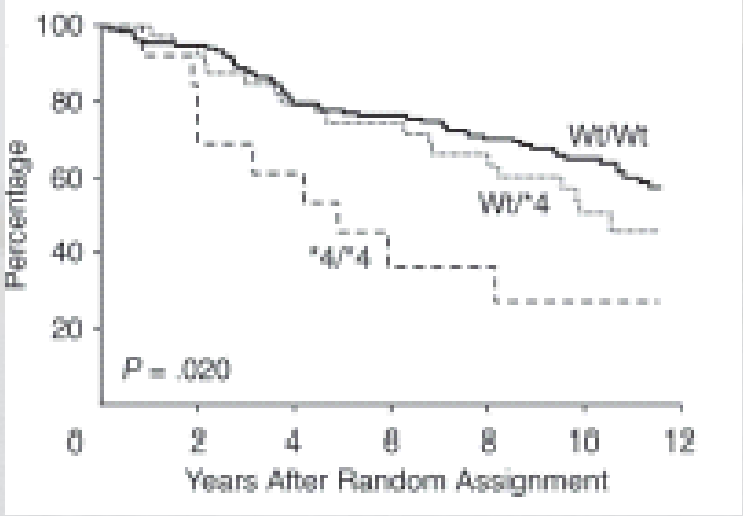
Endoxifene

Le métabolisme du tamoxifène

Variants allèliques CYP 2D6 *4

Fréquence du CYP 2D6 *4/*4 : environ 7 % de la population

Ce génotype pourrait expliquer 75 % des inactivations du CYP 2D6



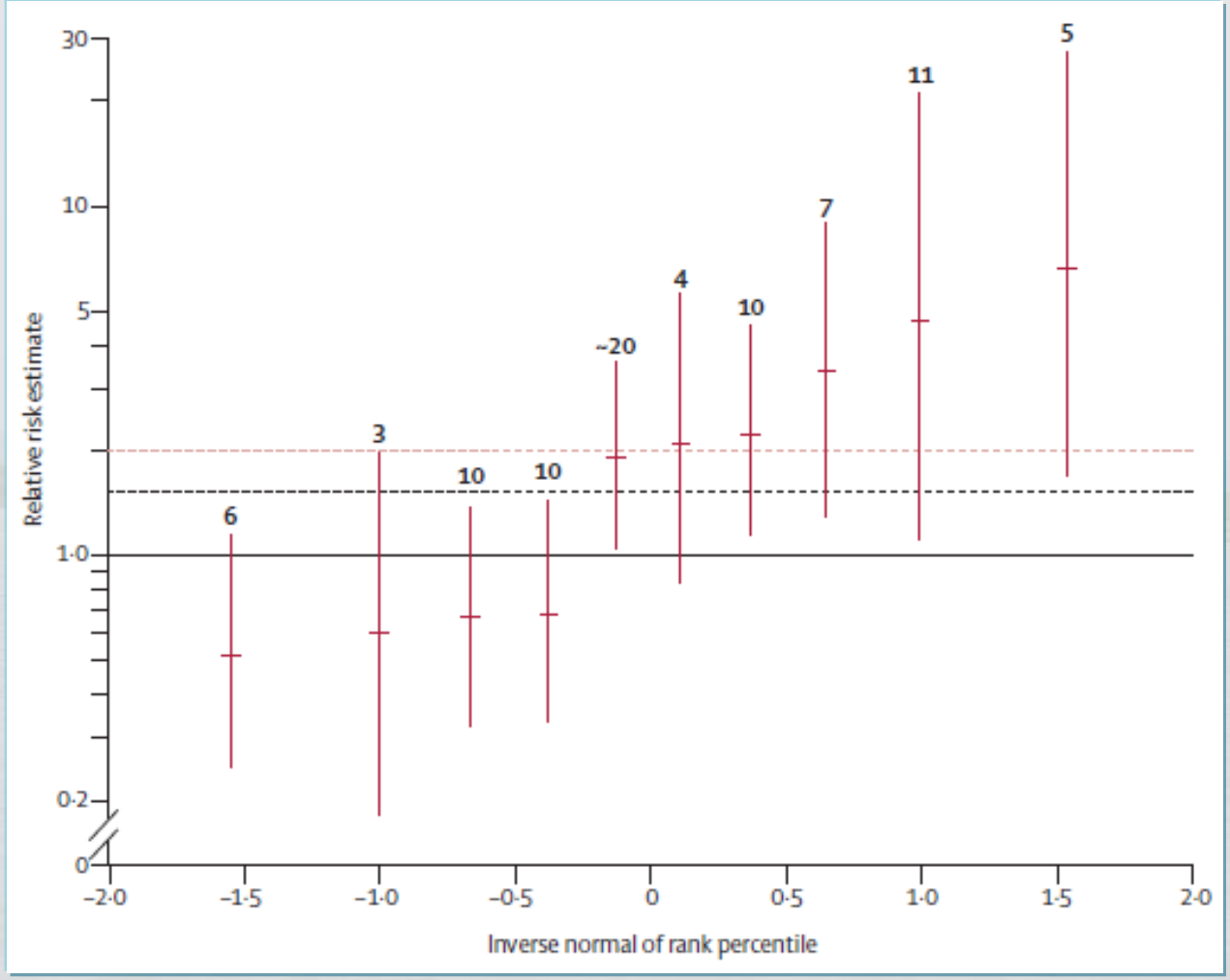
Bouffées de chaleur modérées à sévères

	Nombre	Bouffées de chaleur
wt/wt	137	20 %
*4/wt	40	23 %
*4/*4	13	0

Inhibiteurs du CYP 2D6:
- **puissants : Fluoxetine (Prozac), paroxetine (Deroxat)**
- **modérés : sertraline (Zoloft), cimetidine, amiodarone, doxepine (Quitaxon), ticlopidine, haloperidol)**

Goetz, JCO 2005, 23 : 9312-8.

Le métabolisme du tamoxifène
Des résultats discordants …



Lash, Lancet Oncol 2009

Le métabolisme du tamoxifène

La messe est dîte ?....

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ARTICLE

CYP2D6 Genotype and Tamoxifen Response in Postmenopausal Women with Endocrine-Responsive Breast Cancer: The Breast International Group 1-98 Trial

Meredith M. Regan*, Brian Leyland-Jones*, Mark Bouzyk, Olivia Pagani, Weining Tang, Roswitha Kammler, Patrizia Dell'Orto, Maria Olivia Biasi, Beat Thürlimann, Maria B. Lyng, Henrik J. Ditzel, Patrick Neven, Marc Debled, Rudolf Maibach, Karen N. Price, Richard D. Gelber, Alan S. Coates, Aron Goldhirsch, James M. Rae, Giuseppe Viale; on behalf of the Breast International Group (BIG) 1-98 Collaborative Group

*Authors contributed equally to this work.

Manuscript received June 30, 2011; revised January 17, 2012; accepted January 25, 2012.

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Background Adjuvant tamoxifen therapy is effective for postmenopausal women with endocrine-responsive breast cancer. Cytochrome P450 2D6 (CYP2D6) enzyme metabolizes tamoxifen to clinically active metabolites, and *CYP2D6* polymorphisms may adversely affect tamoxifen efficacy. In this study, we investigated the clinical relevance of *CYP2D6* polymorphisms.

Methods We obtained tumor tissues and isolated DNA from 4861 of 8010 postmenopausal women with hormone receptor–positive breast cancer who enrolled in the randomized, phase III double-blind Breast International Group (BIG) 1-98 trial between March 1998 and May 2003 and received tamoxifen and/or letrozole treatment. Extracted DNA was used for genotyping nine *CYP2D6* single-nucleotide polymorphisms using polymerase chain reaction–based methods. Genotype combinations were used to categorize CYP2D6 metabolism phenotypes as poor, intermediate, and extensive metabolizers (PM, IM, and EM, respectively; n = 4393 patients). Associations of CYP2D6 metabolism phenotypes with breast cancer-free interval (referred to as recurrence) and treatment-induced hot flushes according to randomized endocrine treatment and previous chemotherapy were assessed. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical tests were two-sided.

Results No association between CYP2D6 metabolism phenotypes and breast cancer-free interval was observed among patients who received tamoxifen monotherapy without previous chemotherapy ($P = .35$). PM or IM phenotype had a non-statistically significantly reduced risk of breast cancer recurrence compared with EM phenotype (PM or IM vs EM, HR of recurrence = 0.86, 95% CI = 0.60 to 1.24). CYP2D6 metabolism phenotype was associated with tamoxifen-induced hot flushes ($P = .020$). Both PM and IM phenotypes had an increased risk of tamoxifen-induced hot flushes compared with EM phenotype (PM vs EM, HR of hot flushes = 1.24, 95% CI = 0.96 to 1.59; IM vs EM, HR of hot flushes = 1.23, 95% CI = 1.05 to 1.43).

Conclusions CYP2D6 phenotypes of reduced enzyme activity were not associated with worse disease control but were associated with increased hot flushes, contrary to the hypothesis. The results of this study do not support using the presence or absence of hot flushes or the pharmacogenetic testing of *CYP2D6* to determine whether to treat postmenopausal breast cancer patients with tamoxifen.

J Natl Cancer Inst 2012;104:1–11

For decades, the standard adjuvant endocrine therapy for postmenopausal women with estrogen receptor (ER)– and/or progesterone receptor (PgR)–positive breast cancer was 5 years of the selective ER modulator tamoxifen, which improved disease-free survival and reduced the annual breast cancer death rate by 31% (1). Recent reports from the Breast International Group (BIG) 1-98 trial have shown that adjuvant therapy with the aromatase inhibitor letrozole given as a single agent for 5 years improves disease-free and overall survival compared with 5 years of tamoxifen in this population (2–5). However, there may be groups of patients, for example, those at lower risk for recurrence, for whom tamoxifen or a sequence of the two agents represents a reasonable choice

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ARTICLE

CYP2D6 and *UGT2B7* Genotype and Risk of Recurrence in Tamoxifen-Treated Breast Cancer Patients

James M. Rae, Suzy Drury, Daniel F. Hayes, Vered Stearns, Jacklyn N. Thibert, Ben P. Haynes, Janine Salter, Ivana Sestak, Jack Cuzick, Mitch Dowsett; on behalf of the ATAC trialists

Manuscript received July 6, 2011; revised January 24, 2012; accepted January 25, 2012.

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Background Adjuvant tamoxifen therapy substantially decreases the risk of recurrence and mortality in women with hormone (estrogen and/or progesterone) receptor–positive breast cancer. Previous studies have suggested that metabolic conversion of tamoxifen to endoxifen by cytochrome P450 2D6 (CYP2D6) is required for patient benefit from tamoxifen therapy.

Methods Tumor specimens from a subset of postmenopausal patients with hormone receptor–positive early-stage (stages I, II, and IIIA) breast cancer, who were enrolled in the randomized double-blind Arimidex, Tamoxifen, Alone or in Combination (ATAC) clinical trial, were genotyped for variants in *CYP2D6* (N = 1203 patients: anastrozole [trade name: Arimidex] group, n = 615 patients; tamoxifen group, n = 588 patients) and UDP-glucuronosyltransferase-2B7 (*UGT2B7*), whose gene product inactivates endoxifen (N = 1209 patients; anastrozole group, n = 606 patients; tamoxifen group, n = 603 patients). Genotyping was performed using polymerase chain reaction–based TaqMan assays. Based on the genotypes for CYP2D6, patients were classified as poor metabolizer (PM), intermediate metabolizer (IM), or extensive metabolizer (EM) phenotypes. We evaluated the association of *CYP2D6* and *UGT2B7* genotype with distant recurrence (primary endpoint) and any recurrence (secondary endpoint) by estimating the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) using Cox proportional hazards models. All statistical tests were two-sided.

Results After a median follow-up of 10 years, no statistically significant associations were observed between *CYP2D6* genotype and recurrence in tamoxifen-treated patients (PM vs EM: HR for distant recurrence = 1.25, 95% CI = 0.55 to 3.15, $P = .64$; HR for any recurrence = 0.99, 95% CI = 0.48 to 2.08, $P = .99$). A near-null association was observed between *UGT2B7* genotype and recurrence in tamoxifen-treated patients. No associations were observed between *CYP2D6* and *UGT2B7* genotypes and recurrence in anastrozole-treated patients.

Conclusion The results do not support the hypothesis that *CYP2D6* genotype predicts clinical benefit of adjuvant tamoxifen treatment among postmenopausal breast cancer patients.

J Natl Cancer Inst 2012;104:1–9

In hormone (estrogen and/or progesterone) receptor–positive breast cancer, 5 years of adjuvant tamoxifen therapy reduces disease recurrence by approximately half and breast cancer mortality by approximately a third (1). The parent compound tamoxifen is a relatively weak estrogen receptor (ER) antagonist but is converted in vivo into many metabolites with varying estrogenic and antiestrogenic properties. Of these, 4-hydroxy-N-desmethyl-tamoxifen (known as endoxifen) binds ER with 100-fold greater affinity than tamoxifen and metabolite N-desmethyl-tamoxifen, and its serum concentration is 6- to 10-fold higher than the high affinity metabolite 4-hydroxy-tamoxifen (2–7). Cytochrome P450 2D6 (CYP2D6) and UDP-glucuronosyltransferase-2B7 (UGT2B7) are the primary and rate-limiting enzymes responsible for the formation and inactivation of endoxifen, respectively (3,8).

CYP2D6 genotype is associated with plasma concentrations of endoxifen (2,4), a finding that raised the hypothesis that *CYP2D6* genotype may predict response to tamoxifen. We observed that the gene product of *UGT2B7**2, a common genetic variant of *UGT2B7* that exhibits decreased enzymatic activity (9), is associated with higher plasma endoxifen concentrations in patients receiving tamoxifen therapy (D. A. Flockhart, Indiana University, unpublished data). However, studies that tested associations between *CYP2D6* genotype and benefit from tamoxifen have provided conflicting results (10,11). Some studies found that tamoxifen-treated breast cancer patients who are carriers of *CYP2D6* alleles associated with reduced enzyme activity have worse outcomes compared with patients who carry the functional *CYP2D6* gene (12,13). In contrast, other investigators have failed to observe a difference or

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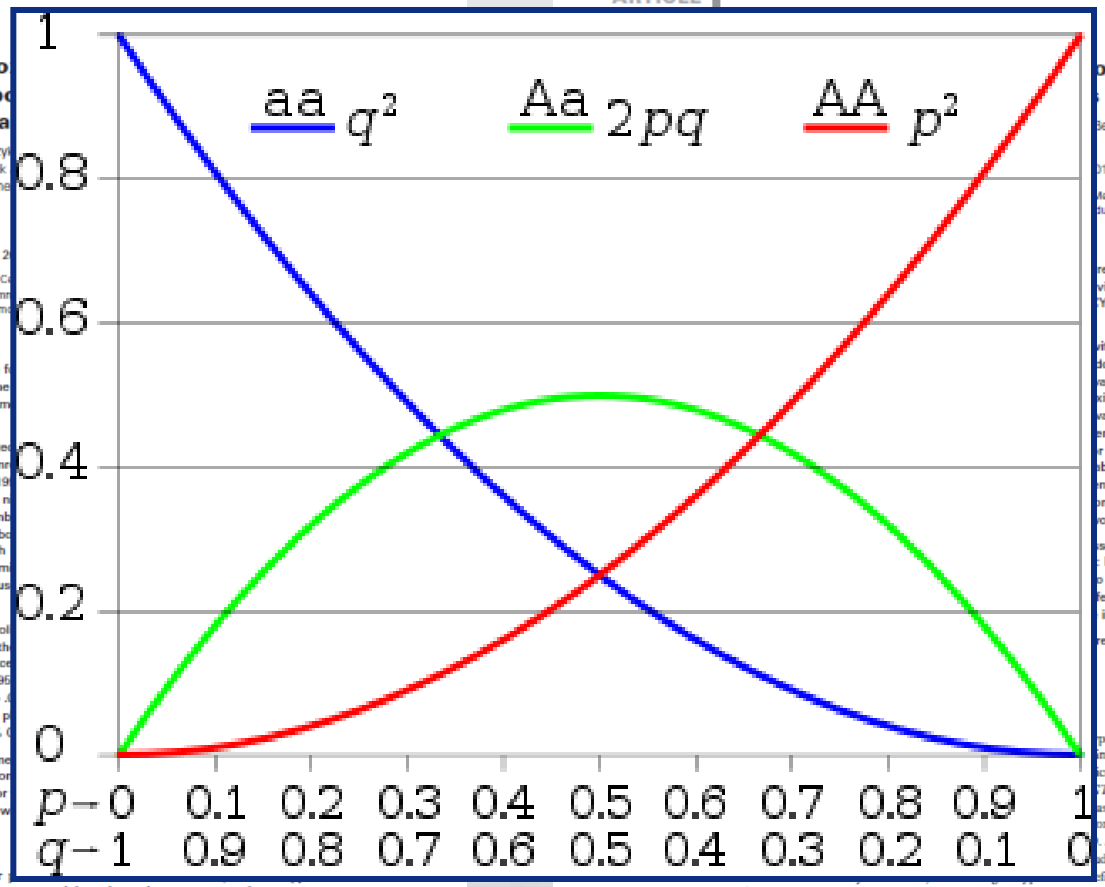
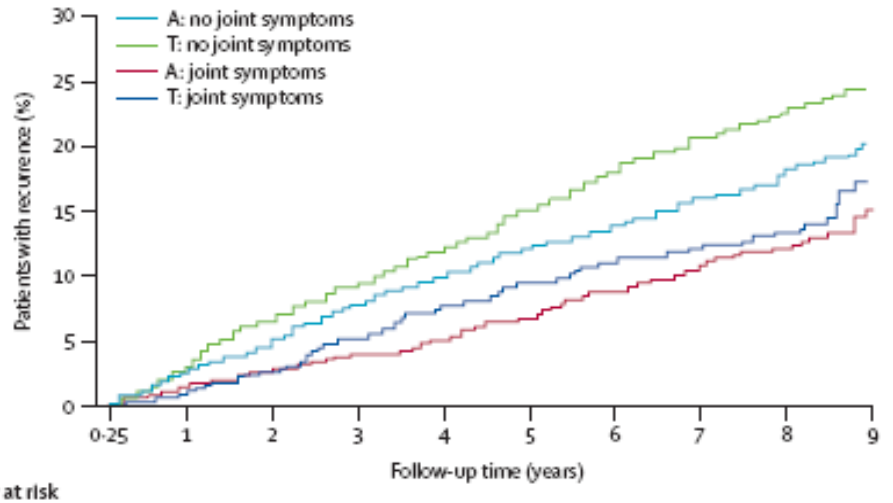
Le métabolisme du tamoxifène

La messe est dîte …. Les cierges ne fument pas encore !



Et l'équilibre de Hardy-Weinberg alors ?

Les inhibiteurs de l'aromatase : une question de métabolisme, aussi !



Number at risk						
A: no joint symptoms	1302	1190	1083	909	643	199
T: no joint symptoms	1417	1273	1154	966	624	181
A: joint symptoms	665	646	615	545	376	114
T: joint symptoms	580	563	523	460	333	96

T, pas de sympto articulaire (71%)

A, pas de sympto articulaire (66%)

T, symptômes articulaires (29%)

A, symptômes articulaires (34 %)

	Anastrozole (n = 1967)		Tamoxifène (n = 1997)		Ensemble (n = 3964)	
	RR de rech	P	RR de rech	P	RR de rech	P
Pas d'effet II	1		1		1	
S. vasomoteurs	0,85	0,3	0,81	0,06	0,84	0,04
S. articulaires	**0,65**	**0,0001**	**0,58**	**< 0,0001**	**0,60**	**<0,0001**
S. VM et articulaires	0,56	0,01	0,52	<0,0001	0,53	<0,0001

Cuzick, Lancet Oncol, déc 2008

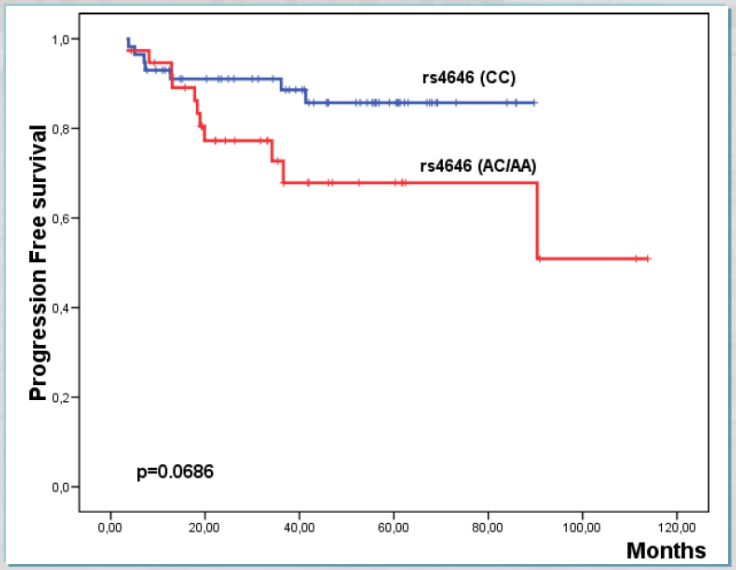
Polymorphisme de l'aromatase (rs4646, 40%) et inhibiteur de l'aromatase..

Table 3 Association of clinical, pathological and genotypic parameters with radiological response at 4th month of letrozole administration.

Parameters	Responders (%)	Non-responders (%)	p
Age (years)			
≤ 78.3	19 (54.3)	29 (48.3)	0.576
> 78.3	16 (45.7)	31 (51.7)	
Histological diagnosis			
IDC	25 (71.4)	42 (70.0)	0.843
ILC	5 (14.3)	11 (18.3)	
Others	5 (14.3)	7 (7.4)	
Histological grade			
I	13 (61.9)	16 (51.6)	0.606
II	6 (28.6)	13 (41.9)	
III	2 (9.5)	2 (6.5)	
Tumor size (T)			
T2	31 (88.6)	45 (75.0)	0.111
T3-T4	4 (11.4)	15 (25.0)	
Lymph node involvement (N)			
N0	28 (80.0)	48 (80.0)	1.000
N1-2	7 (20.0)	12 (20.0)	
Stage			0.546
IIa	26 (74.3)	39 (65.5)	
IIb	7 (20.0)	13 (21.7)	
IIIa-IIIb	2 (5.7)	8 (13.3)	
ER			
≤ 40%	3 (8.6)	10 (16.7)	0.268
> 40%	32 (91.4)	50 (83.3)	
PgR			
≤ 40%	15 (42.9)	31 (51.7)	0.407
> 40%	20 (57.1)	29 (48.3)	
HR			
≤ 40%	2 (5.7)	8 (13.3)	0.243
> 40%	33 (94.3)	52 (86.7)	
HER2			
0, +	21 (60.0)	42 (70.0)	0.320
++, +++	14 (40.0)	18 (30.0)	
Ki67			
Negative	15 (55.6)	25 (55.6)	1.000
Positive	12 (44.4)	20 (44.4)	
rs10046			
GG	6 (17.1)	9 (15.0)	0.782
AG/AA	29 (82.9)	15 (85.0)	
rs4646			
CC	26 (74.3)	31 (51.7)	**0.030**
AC/AA	9 (25.7)	29 (48.3)	

Table 3 Association of clinical, pathological and genotypic parameters with radiological response at 4th month of letrozole administration.

Parameters	Responders (%)	Non-responders (%)	p
rs4646			
CC	26 (74.3)	31 (51.7)	0.030
AC/AA	9 (25.7)	29 (48.3)	



PFS / polymorphisme rs4646

TAM ou IA : facteurs prédictifs d'un bénéfice > ?
➔L'index de masse corporelle … l'étude Trans-ATAC

4,939 / 5,172 ptes (95%) de l'étude ATAC ; Un suivi médian de 100 mois

B **Distant Recurrences**

BMI	Anastrozole No.	Anastrozole %	Tamoxifen No.	Tamoxifen %	HR*	95% CI
< 23	38	7.8	59	12.3	0.59	0.39 to 0.89
23-25	38	9.0	59	15.3	0.55	0.36 to 0.83
25-28	71	12.0	71	13.5	0.86	0.62 to 1.19
28-30	42	12.9	44	13.8	0.93	0.61 to 1.42
30-35	63	14.2	70	14.6	0.96	0.68 to 1.36
> 35	35	17.7	35	15.3	0.97	0.61 to 1.57
All	287	11.6	345	14.0	0.79	0.68 to 0.92

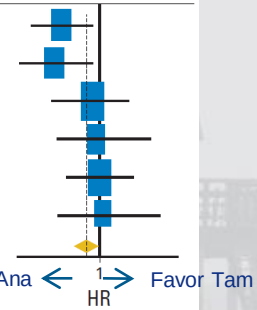


Table 4. HRs for Effect of Treatment Received on All Recurrences According to BMI Group

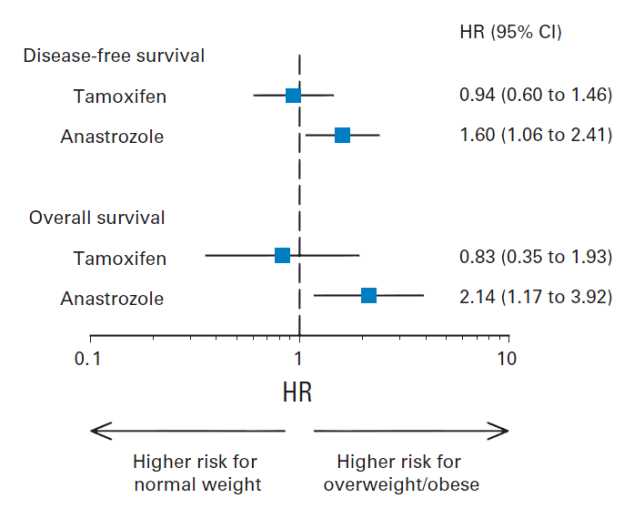
BMI (kg/m²)	No. of Patients	Tamoxifen HR*	Tamoxifen 95% CI	Anastrozole HR*	Anastrozole 95% CI
< 23	966	1	Reference	1	Reference
23-25	810	1.18	0.86 to 1.61	1.10	0.75 to 1.60
25-28	1,171	1.13	0.84 to 1.50	1.29	0.92 to 1.81
28-30	643	1.02	0.80 to 1.56	1.42	0.97 to 2.08
30-35	922	0.99	0.74 to 1.35	1.30	0.91 to 1.85
> 35	427	1.18	0.90 to 1.84	1.53	1.01 to 2.32
χ^2, *P* for trend		.23		.001	
1 *df*		1.42		10.1	
P for heterogeneity		.54		.01	
5 *df*		4.1		11.87	
P for interaction		.04			

Abbreviations: HR, hazard ratio; BMI, body mass index.
*HR adjusted for age, region (United States and Canada, United Kingdom, rest of the world), chemotherapy, radiotherapy, mastectomy, tumor size (continuous), tumor grade (well/moderate/poorly differentiated), nodal status (negative, positive, unknown).

Sestak, JCO 2010

TAM ou IA : facteurs prédictifs d'un bénéfice > ?
➔L'index de masse corporelle … l'étude ABCSG12

1,684 / 1,803 ptes (93%) de l'étude ABCSG12 ; Un suivi médian de 63 mois

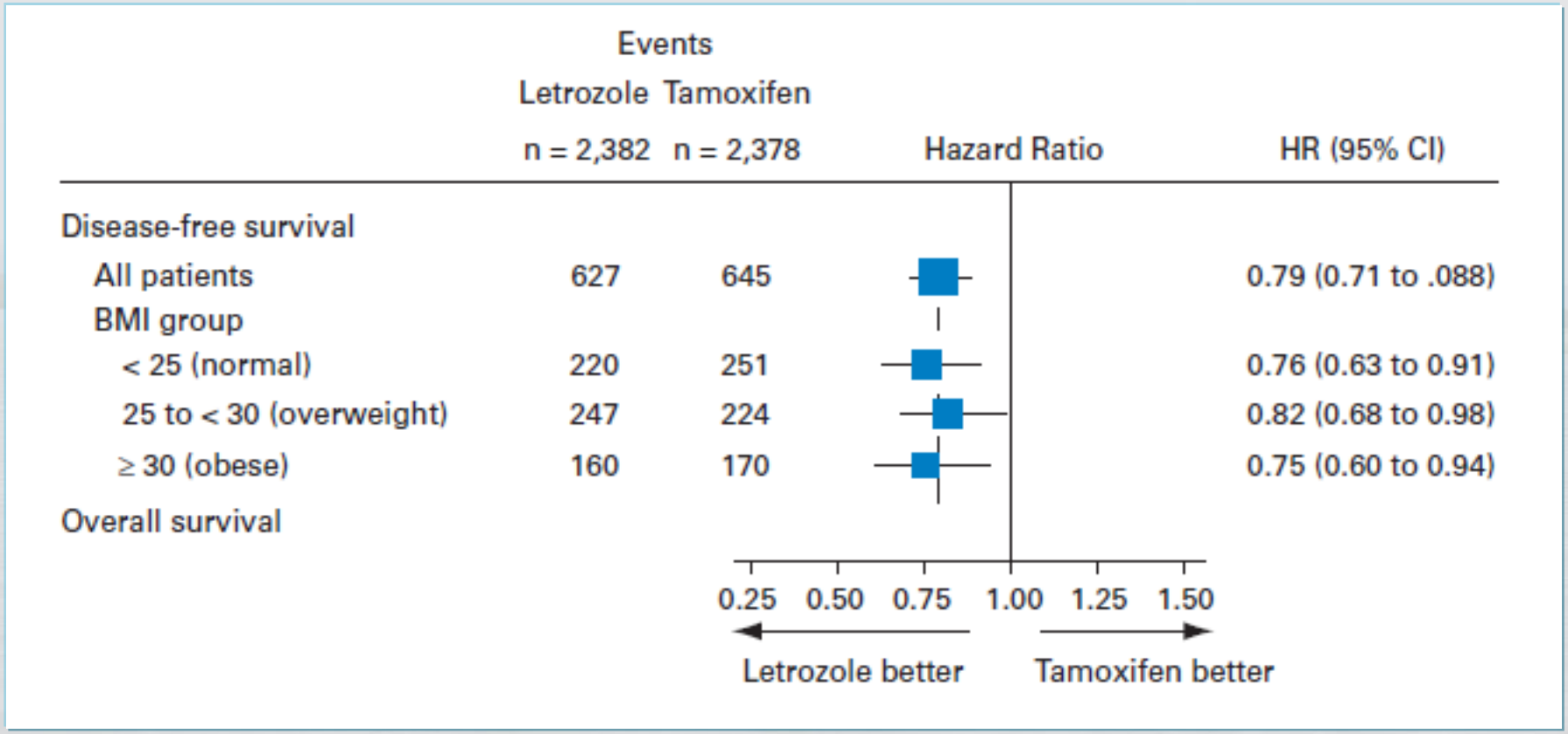


	Survie sans progression	Survie globale
Absence d'excès pondéral N= 1111 (66%)	A = T HR = 0.87 (0,59 – 1,27; p = 0,455)	A = T HR = 1,21 (0,63 – 2,33 ; p = 0,582)
Excès pondéral N=391 (34%)	T > A HR = 1,47* (0,90 – 2,40 ; p = 0,12)	T > A HR = 3,23* (1,39 – 7,53 ; p = 0,006)

** après ajustement sur la taille T, l'atteinte ggl, le grade, l'âge, RE, RP,*

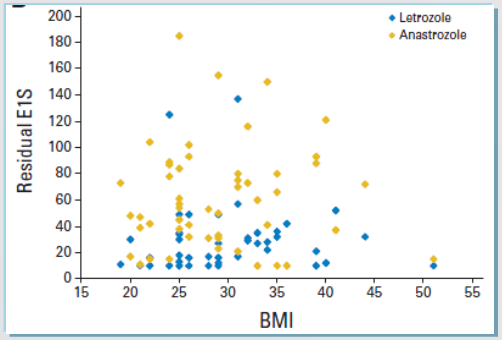
Pfeiler, JCO 2011

TAM ou IA : facteurs prédictifs d'un bénéfice > ?
➔L'index de masse corporelle … l'étude BIG 1-98



Ewertz, J Clin Oncol 2012

TAM ou IA : facteurs prédictifs d'un bénéfice > ?
➔L'index de masse corporelle … l'étude BIG 1-98



Taux d'E1S après 3 mois d'IA

Table 2. ALIQUOT Study[7]: Relationship Between BMI and Serum Estrone Sulphate Levels in Response to AI Treatment

	BMI			
	< 25 (n = 10)	25-29 (n = 16)	30-35 (n = 13)	> 35 (n = 5)
Estrone sulphate (pmol/L)				
Pretreatment				
Mean	668	1,307	1,801	1,763
SEM	77	246	264	584
Post anastrozole				
Mean	44	62	66	68
SEM	11	12	11	19
Post letrozole				
Mean	13	22	35	25
SEM	2.0	3.4	9.2	7.7
Mean A/L	4.0	3.0	2.7	3.8

Abbreviations: AI, aromatase inhibitor; A/L, mean of the within-patient ratios of plasma estradiol levels on anastrozole *v* letrozole; ALIQUOT, Anastrozole vs Letrozole, an Investigation of Quality Of Life and Tolerability; BMI, body mass index.

- Le taux d'estrone sulfate est corrélée au BMI.
- Une suppression plus marquée sous létrozole.

Folkerd, J Clin Oncol 2012

Les limites … les échecs .
5. Allonger la durée du traitement ?

Facteurs de risque de rechute après 5 ans de Tam

- **Cameron,** *San Antonio, abs 108*

631 ptes en RC après 5 ans de TAM

↓

Analyse multifactorielle
(âge, taille pathol, grade, RE, Nbre N+)

- **Kennecke**, *San Antonio, abs 1049*

1086 ptes en RC après 5 ans de TAM

↓

Analyse multifactorielle
(taille pathol, grade, atteinte vasculaire, Nbre N+, CT adjuvante)

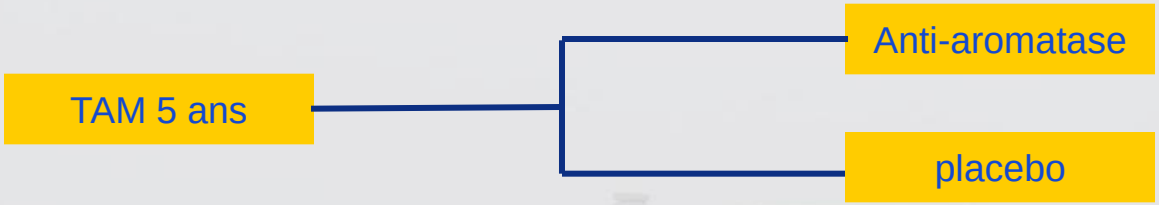
L'atteinte ganglionnaire est le seul facteur significatif en multifactoriel

Survie 5 ans	nbre
Env 90 %	507
Env 80 %	118
Env 65 %	11

N
0
1-3
> 3

Nbre	DFS 5 ans
460	90 %
413	85 %
125	70 %

Les limites … les échecs .
5. Allonger la durée du traitement ?



	Objectif	nbre	N+	HR	P
MA17	Survie sans M+ (4 ans)	5187	46%	0,80 [0,62 – 1,03]	0,08
ABCSG 6A	Survie sans M+ (5 ans)	856	34%	0,53 [0,29 – 0,96]	0,034
B33	Survie sans rech (4 ans)	1598	48%	0,68 [NP-NP]	0,07

M+ DFS 4 ans

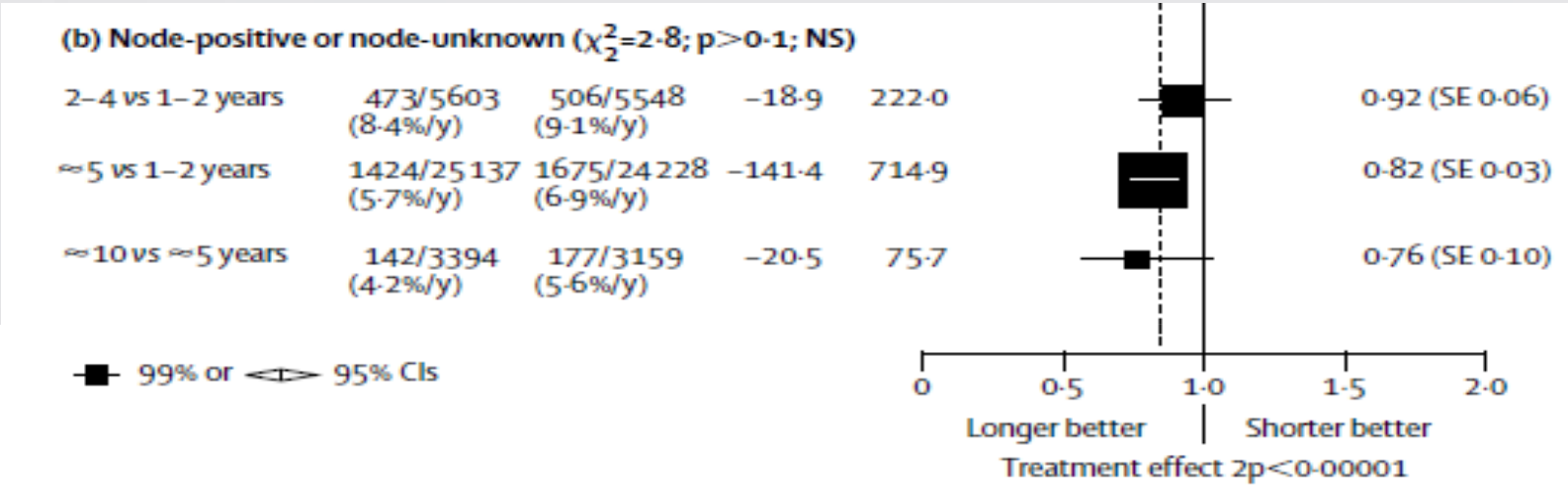
	Placebo	Letrozole	Différence (%)	Ptes à traiter
Global	**94,9%**	**96,3%**	**1,4%**	**71**
pN0	**98,1%**	**98,3%**	**0,2%**	**500**
pN+	**90,9%**	**94,3%**	**3,4%**	**29**

Goss, ASCO 2004

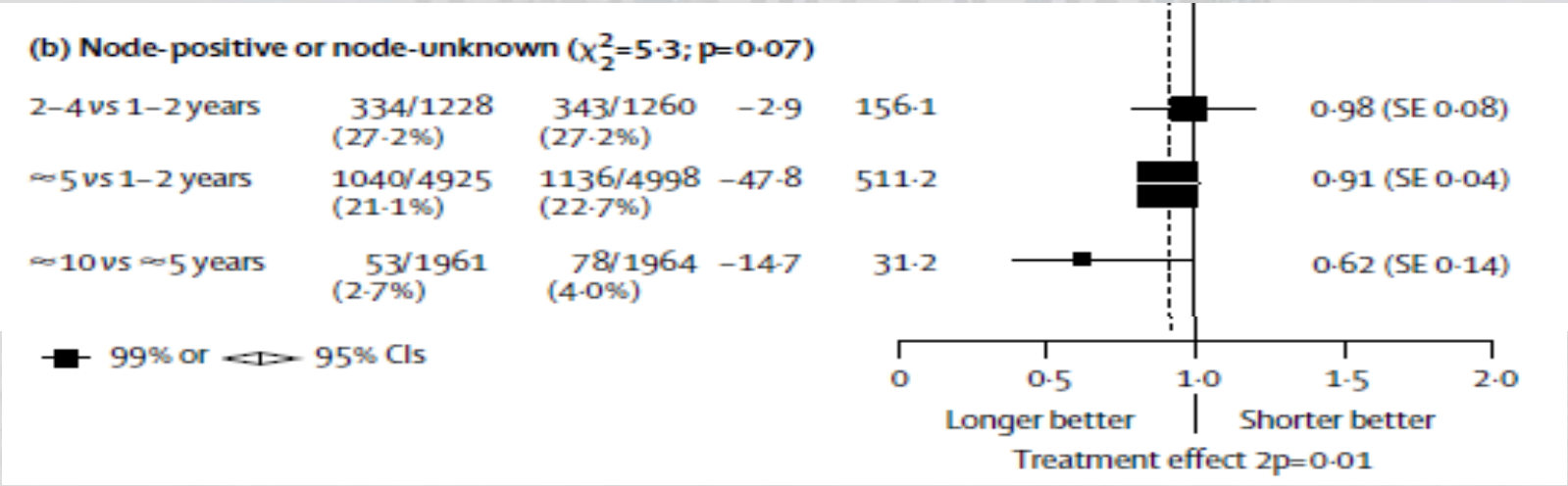
Jakesz, JNCI 2007 ; Ingle, Ann Oncol 2008 ; Mamounas, JCO 2008

… Des résultats non *(non totalement?)* liés au switch..

Taux de rechute



Taux de décès

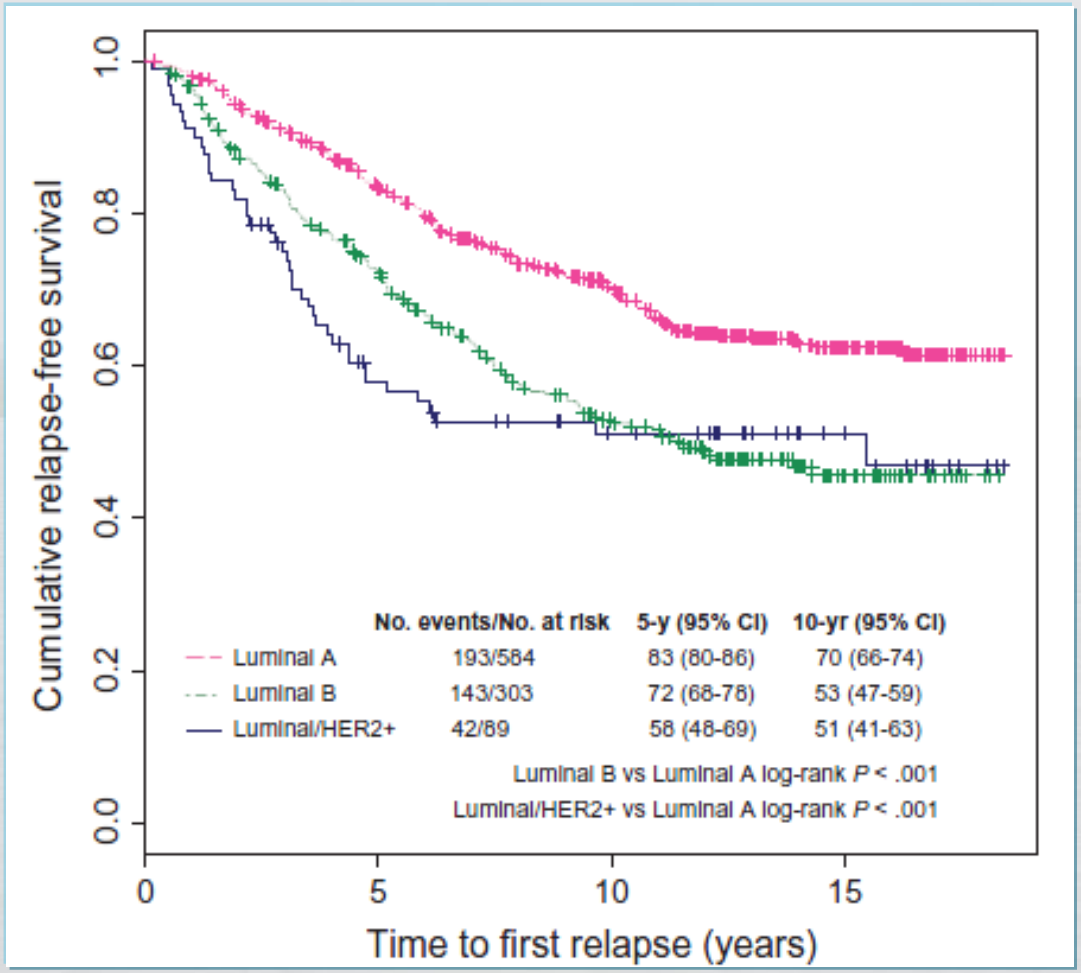


EBCTCG, Lancet 2005

Les limites … les échecs .

6. Hormonorésistance …. La classification luminale : prudence

976 patientes traitées par tamoxifène



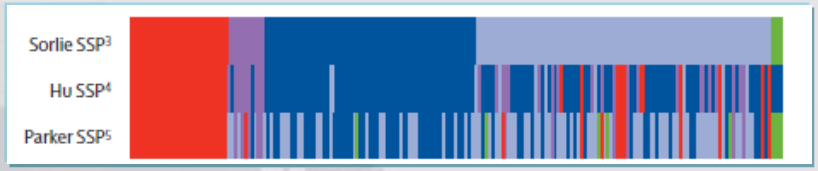
Cheang, JNCI 2009

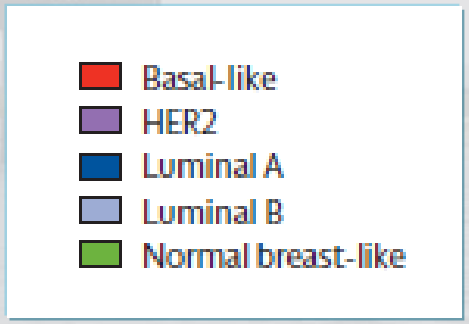
Hormonorésistance
La classification luminale : A ou B ?

	Sorlie vs Hu SSP	Sorlie vs Parker SSP	Hu vs Parker SSP
53 grade III invasive ductal carcinomas			
Basal-like	0·950 (0·854 to 1·047)	1·000 (1·000 to 1·000)	0·950 (0·854 to 1·047)
HER2	NA	NA	NA
Luminal A	0·195 (0·054 to 0·336)	0·296 (−0·086 to 0·678)	0·110 (0·002 to 0·217)
Luminal B	NA	0·710 (0·513 to 0·908)	NA
Normal breast-like	NA	NA	NA
NKI-295 dataset			
Basal-like	0·847 (0·767 to 0·928)	0·962 (0·920 to 1·005)	0·837 (0·754 to 0·920)
HER2	0·482 (0·340 to 0·625)	0·591 (0·468 to 0·715)	0·729 (0·621 to 0·837)
Luminal A	0·530 (0·434 to 0·625)	0·435 (0·325 to 0·545)	0·612 (0·524 to 0·700)
Luminal B	0·390 (0·268 to 0·512)	0·361 (0·242 to 0·480)	0·563 (0·451 to 0·674)
Normal breast-like	0·346 (0·165 to 0·527)	0·348 (0·172 to 0·524)	0·529 (0·347 to 0·710)
Wang dataset			
Basal-like	0·928 (0·872 to 0·985)	0·870 (0·795 to 0·945)	0·920 (0·861 to 0·978)
HER2	0·193 (0·046 to 0·341)	0·219 (−0·014 to 0·453)	0·487 (0·329 to 0·645)
Luminal A	0·542 (0·458 to 0·626)	0·384 (0·274 to 0·494)	0·318 (0·242 to 0·393)
Luminal B	0·154 (0·084 to 0·224)	0·305 (0·195 to 0·415)	0·140 (0·080 to 0·200)
Normal breast-like	NA	NA	0·137 (−0·104 to 0·379)
TransBig dataset			
Basal-like	0·827 (0·724 to 0·930)	0·812 (0·706 to 0·918)	0·922 (0·855 to 0·989)
HER2	0·389 (0·198 to 0·580)	0·422 (0·154 to 0·691)	0·496 (0·309 to 0·682)
Luminal A	0·463 (0·362 to 0·563)	0·478 (0·348 to 0·609)	0·473 (0·374 to 0·572)
Luminal B	0·086 (0·019 to 0·153)	0·308 (0·176 to 0·440)	0·145 (0·058 to 0·232)
Normal breast-like	NA	0·535 (0·179 to 0·891)	NA

Data are κ (95% CI). SSP=single sample predictor. NA=not applicable.

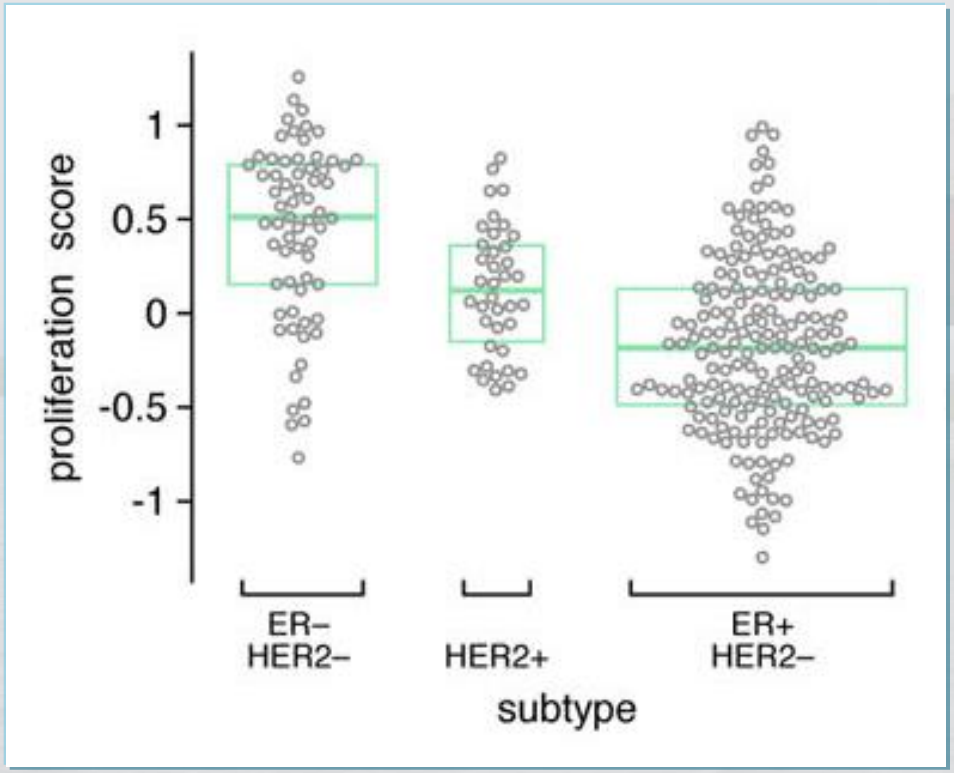
Table 3: **Agreement between single sample predictors for classification of each molecular subtype individually**

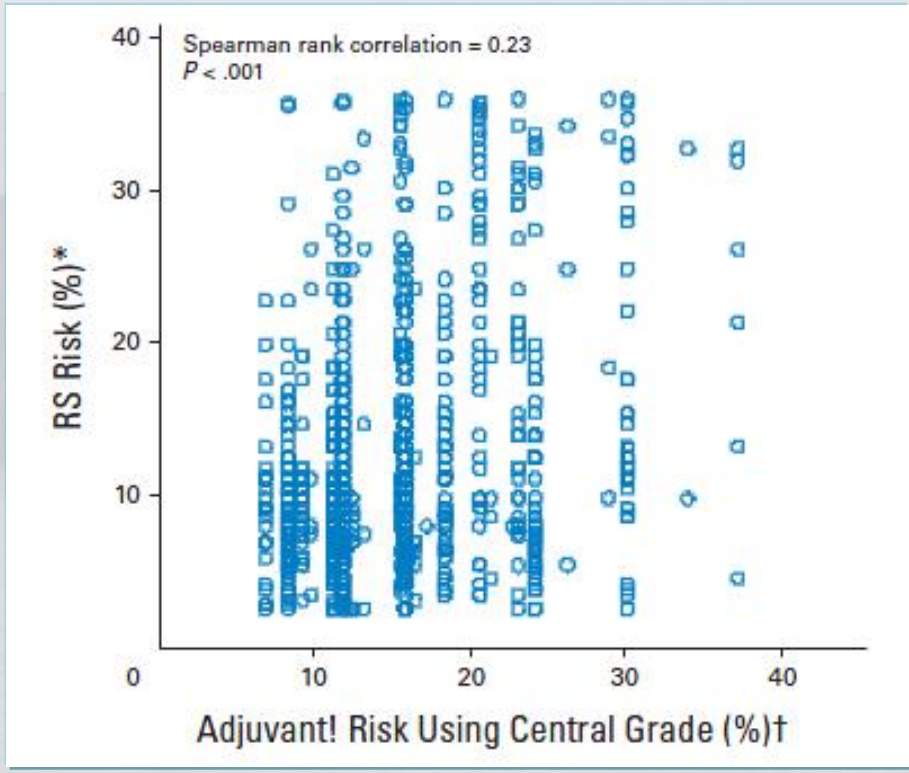




Weigelt, Lancet 2010

Hormonorésistance
La classification luminale : de A à Z ?

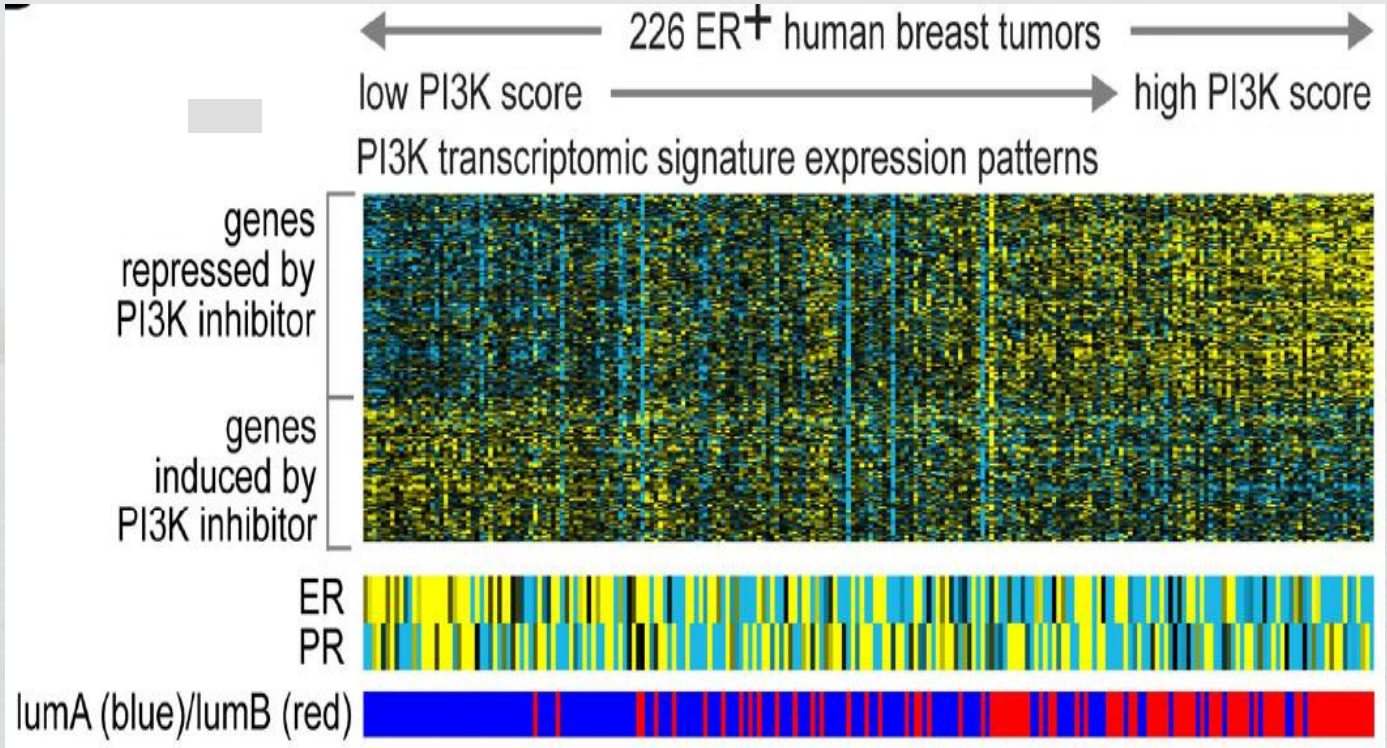




Wirapati, Breast Cancer Res 2008

Dowsett, J Clin Oncol 2010

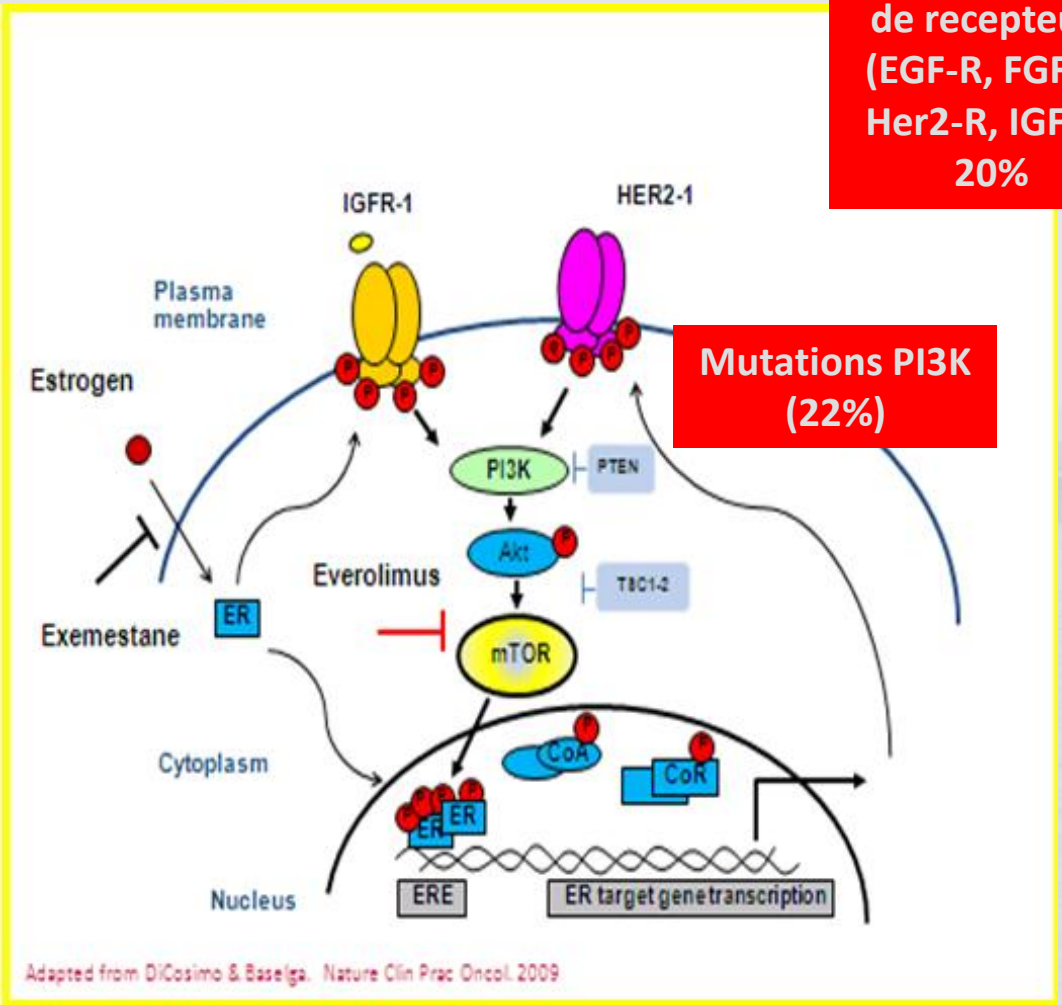
Hormonorésistance
La classification luminale : A/B ou A----Z ?



Creighton, Breast Cancer Research, 2010

Les limites … les échecs .
6. Vaincre l'hormonorésistance

Amplification de recepteurs (EGF-R, FGF-R, Her2-R, IGF-R) 20%



Adapted from DiCosimo & Baselga. Nature Clin Prac Oncol. 2009

Mutations PI3K (22%)

Les limites … les échecs .

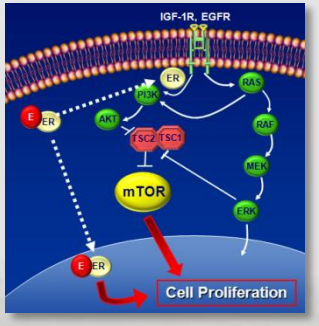
6. Vaincre l'hormonorésistance

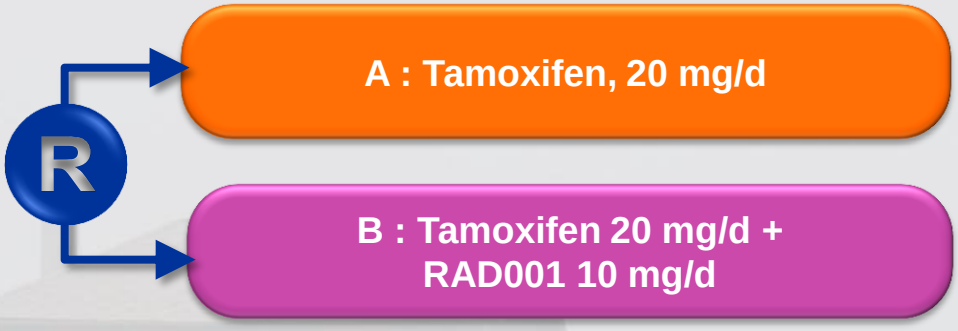
Auteur	médicament	Phase	Nombre	Objectif principal	Résultat
Inhibiteur de l'EGF-R					
Osborne, 2011	gefitinib	II random.	206	PFS	Négatif
Osborne, 2011	gefitinib	II random.	84	Bénéfice clinique	Négatif
Cristofanilli, 2010	gefitinib	II random.	94	TTP	Positif
Mauriac, 2008	gefitinib	II random.	71	TTP 1 an	Négatif
Inhibiteur de Her-2					
Johnston, 2009	lapatinib	III	1286	PFS	Négatif
Burstein, 2010	lapatinib	III	267	PFS	Négatif
Inhibiteur de l'IGF-R					
Kaufman, 2010	AMG 479	II random.	156	TTP	Négatif
Ryan, 2011	figitumumab	II random.	205	TTP	Négatif
Inhibiteur de mTOR					
Bachelot, 2012	Everolimus	II random.	101	Bénéfice clinique	Positif
Baselga, 2011	Everolimus	III	724	TTP	Positif
Inhibiteur de Farnesyl Transferase					
Johnston, 2008	tipifarnib	II random.	120	Réponse objective	Négatif
Inhibiteur de l'angiogénèse					
Hyams, 2009	cediranib	II random.	62	PFS	Négatif
Inhibiteur de Cox-2					
Dirix, 2008	celecoxib	II random.	111	Bénéfice clinique	Négatif
Falandry, 2009	celecoxib	III	157	TTP	Négatif
Inhibiteur de Src					
Chow, 2011	Bosutinib	II random.	16	PFS	Négatif
Moy, 2011	Bosutinib	II random.	42	PFS	Négatif
Wright, 2011	Dasatinib	II random.	99	PFS	Négatif
Llombart, 2011,	Dasatinib	II random.	157	PFS	Négatif
Inhibiteur d'histone déacétylase					
Yardley, 2011	Entinostat	II random.	130	PFS	Positif
Inhibiteur de CDK 4/6					
Finn, 2011	PD 0332991	II random.	66	PFS	NP

Les limites … les échecs .

6. Hormonorésistance …. L'étude TAM-RAD : phase II randomisée ouverte

- Tumeurs RE+ Her2-
- En Rechute ou progression après IANS





Objectif primaire :
le taux de bénéfice clinique à 6 mois

	TAM N = 57	TAM + RAD N = 54	HR	p
Bénéfice clinique - R primaire - R secondaire	42,1% 39,3% 44,8%	61,1% 46,2% 65,9%		
TTP - R primaire - R secondaire	4,5 m 3,9 m 5,0 m	8,6 m 5,4 m 17,4 m	0,53 0,74 0,38	0,0026 NS Signific.
OS	-	-	HR = 0,32	P = 0,0019

Bachelot, SABCS 2010

Les limites … les échecs .

6. Hormonorésistance …. L'étude BOLERO 2

N = 724

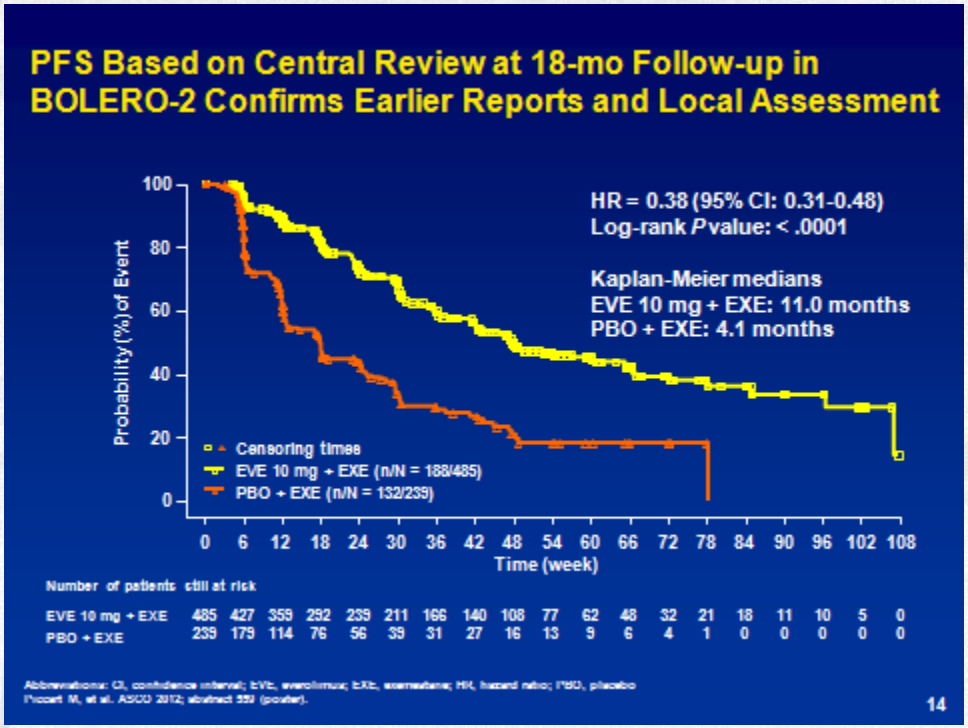
Postmenopausal
ER+ HER2- ABC
refractory to letrozole or anastrozole

Everolimus 10 mg/day +
Exemestane 25 mg/day
(N = 485)

Placebo +
Exemestane 25 mg/day
(N = 239)

PFS

OS
ORR
Bone Markers
Safety
PK



Piccart, ASCO 2012

Les limites … les échecs .

6. Hormonorésistance …. L'étude PACS 11

Etude randomisée de phase III évaluant la tolérance et la bénéfice de l'adjonction de l'évérolimus à l'hormonothérapie adjuvante chez des ptes traitées pour une tumeur RE+ Her2- de mauvais pronostic en rémission complète après 3 ans (Th Bachelot, F André)

Randomisation
N = 1984

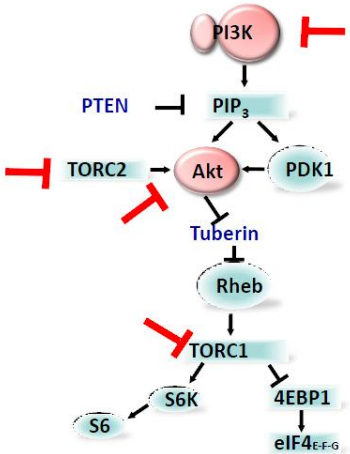
HT
+
Everolimus

HT
+
placebo

3 ans d'inclusion
+2 ans de suivi

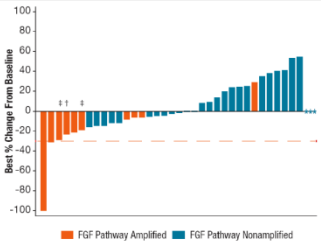
Les limites … les échecs .
6. Hormonorésistance …. De probables avancées rapides ….

PI3K pathway inhibitors in clinical trials



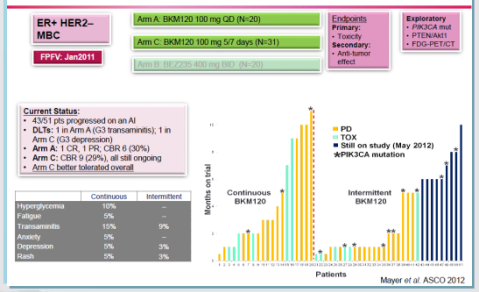
Agent	Target
BYL719	PI3Kα
INK-1117	PI3Kα
GDC-0032	PI3Kα,δ,Y
XL-147	Pan-PI3K
BKM120	Pan-PI3K
GDC-0941	Pan-PI3K
PKI-587	Pan-PI3K
XL-765	PI3K / mTOR
BEZ-235	PI3K / mTOR
PF-4691502	PI3K/mTOR
AZD8055	mTOR (catalytic)
INK 128	mTOR (catalytic)
MK-2206	AKT1,2,3
GDC-0068	AKT

Phase II Study of Dovitinib (TKI258) in patients with HER2 – breast cancer (Andre et al)



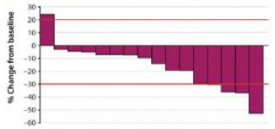
HR⁺ FGF-pathway–amplified (red bars; *FGFR1*, *FGFR2*, or *FGF3* amplification by qPCR) or FGF-pathway–nonamplified (blue bars) patients.

BKM120XUS13T (Mayer)
Summary of Phase Ib BKM120 + letrozole in ER+ MBC



Breast Cohort: XL184 Achieves Tumor Shrinkage in the Majority of Patients

Best Radiological Time Point Response in Patients with ≥ 1 Post-Baseline Tumor Assessment (N = 16)



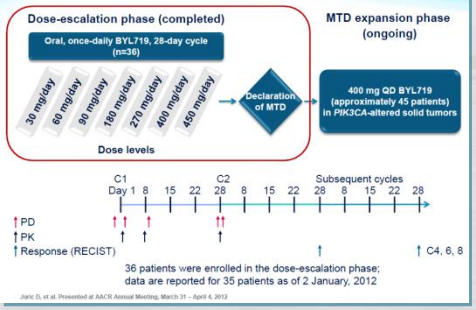
Overview of Breast Cancer Responders

Patient	Histology	Receptor Status	Site of Target Lesions	Number of Prior Treatments	Most Recent Prior Treatment (Best Response)	Time on XL184 (weeks)
1	Invasive lobular	ER+/PR–/ HER2+	lymph node	3	fulvestrant (UNK)	25+
2	Invasive ductal	ER+/PR+/ HER2 (ND)	liver	2	paclitaxel (UNK)	18+
3	Invasive ductal	ER+/PR–/ HER2–	lung and lymph nodes	3	exemestane/bosutinib (SD)	18+
4	Invasive ductal	ER+/PR+/ HER2 (ND)	chest wall	3	carboplatin/gemcitabine (UNK)	17

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; ND, not determined; SD, stable disease; UNK, unknown

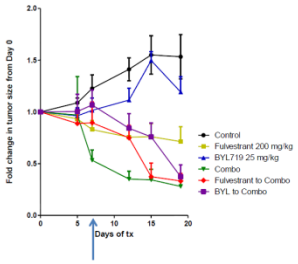
Exelixis R&D Day, December 2, 2010 15

BYL719 Phase I: Study design



Juric D, et al. Presented at AACR Annual Meeting, March 31 – April 4, 2012

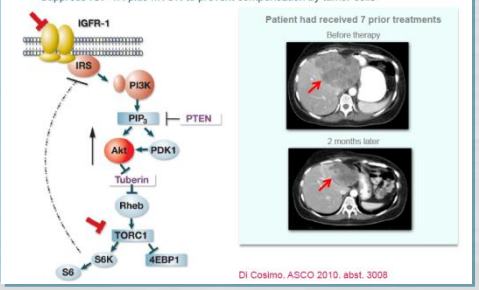
Combined Fulvestrant and BYL in MCF7 xenografts



Day 7: combo initiated on single agent fulvestrant and BYL arms

Phase I clinical trial of the combination of IGF-1R MAb (dalotuzumab) plus mTOR inh. (ridaforolimus)

Suppress IGF-1R plus mTOR to prevent compensation by tumor cells



En résumé …
…. Une désescalade possible ….nécessaire !

✓ Des standards solidement établis en hormonothérapie

- ✓ La compliance aux traitements doit nous interroger :
  - ✓ Mieux considérer les effets secondaires
  - ✓ Mieux expliquer l'impact des traitements
  - ✓ Maintenir mieux la surveillance
- ✓ Des prescriptions excessives …
  - ✓ Un traitement trop systématique … facteurs pronostiques
  - ✓ Mieux définir une tumeur hormonosensible : seuil des RH
- ✓ **La principale limite : les rechutes**
  - ✓ Trouver des paramètres prédictifs / types d'hormonosensibilité
    (body mass index pour l'anastrozole ; pharmacongénétique ?)
  - ✓ Allonger la durée de traitement pour les tumeurs pN+
  - ✓ Evaluer vite et bien les thérapies ciblées en adjuvant !