Institut de Recherche en Cancérologie
I R C Montpellier

Prolonger l'hormonothérapie rend service à toutes les femmes

Moduler la durée ou potentialiser ?

Dr Séverine Guiu, MD PhD
SFSPM Lille
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ICM
Institut régional du Cancer
Montpellier | *Val d'Aurelle*

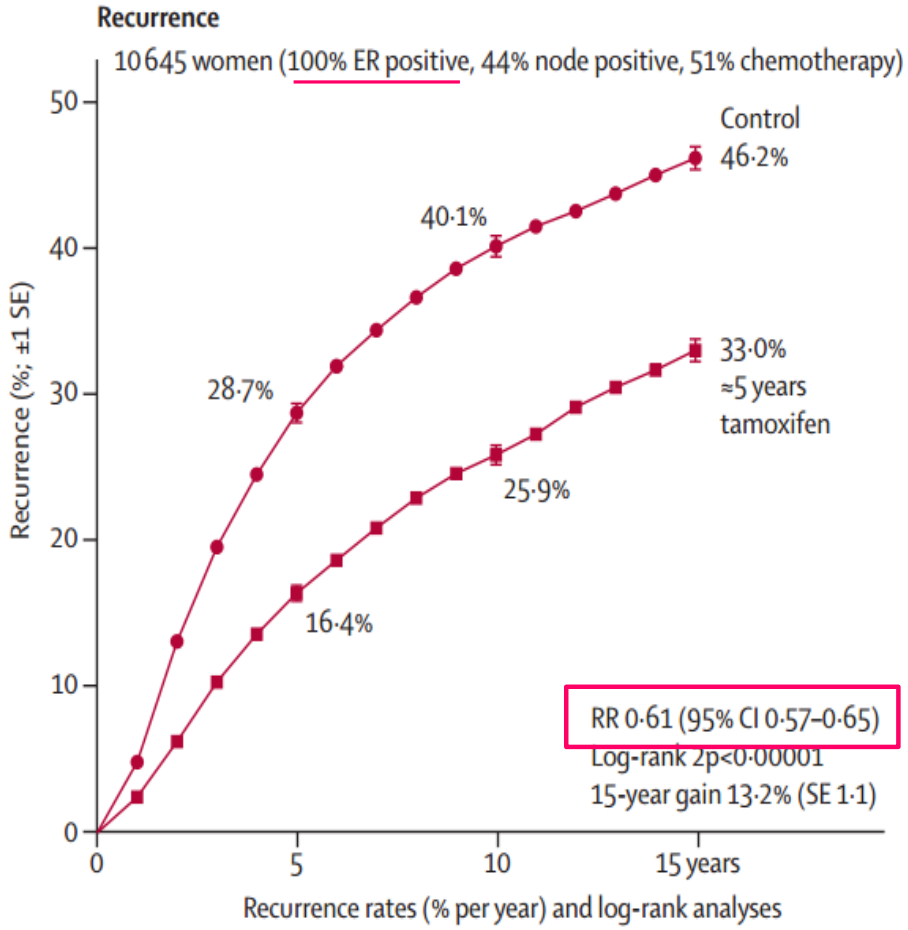
Conflits d’intérêt

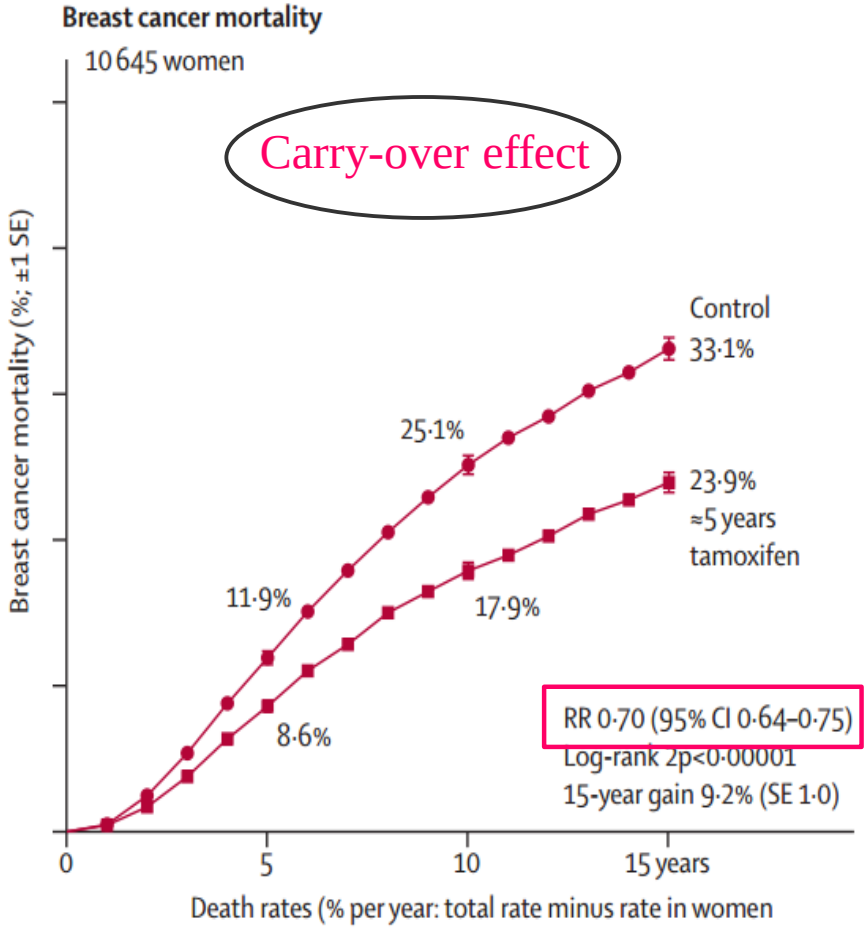
- Aucun

Bénéfices du tamoxifène 5 ans

- **Méta-analyse de l'EBCTCG** (Early Breast Cancer Trialists' Collaborative Group) sur données individuelles, 2011
- 20 essais randomisés, 21 457 femmes, **10 645 RE+**
- 5 ans Tam *versus* observation ou placebo
- ~ 80% compliance

Davies et al, Lancet 2011





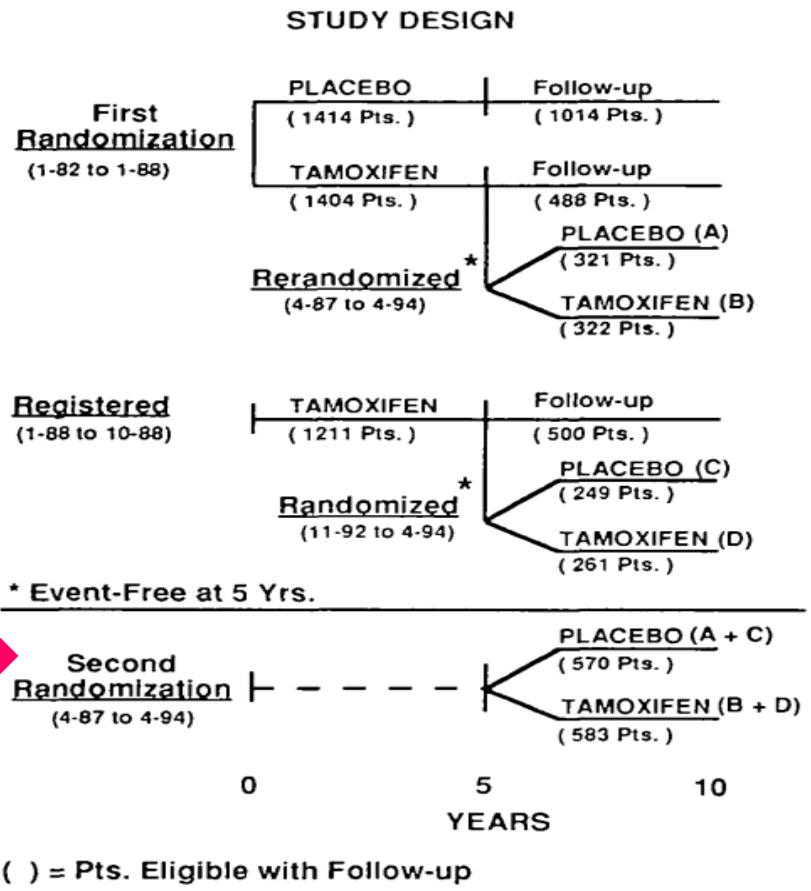
	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3	−4·4/35·5

Years 0–4	Years 5–9	Years 10–14	Year 15+
1·79 (SE 0·08)	2·25 (SE 0·11)	1·54 (SE 0·11)	1·48 (SE 0·16)
2·46 (SE 0·10)	3·23 (SE 0·13)	2·28 (SE 0·14)	1·89 (SE 0·19)
0·71 (SE 0·05)	0·66 (SE 0·05)	0·68 (SE 0·08)	0·88 (SE 0·14)
−84·4/244·8	−95·8/233·2	−38·6/99·4	−5·7/42·6

Davies et al, Lancet 2011

Tam 5 ans versus 10 ans

NSABP B-14 (RE+, N0 uniquement)

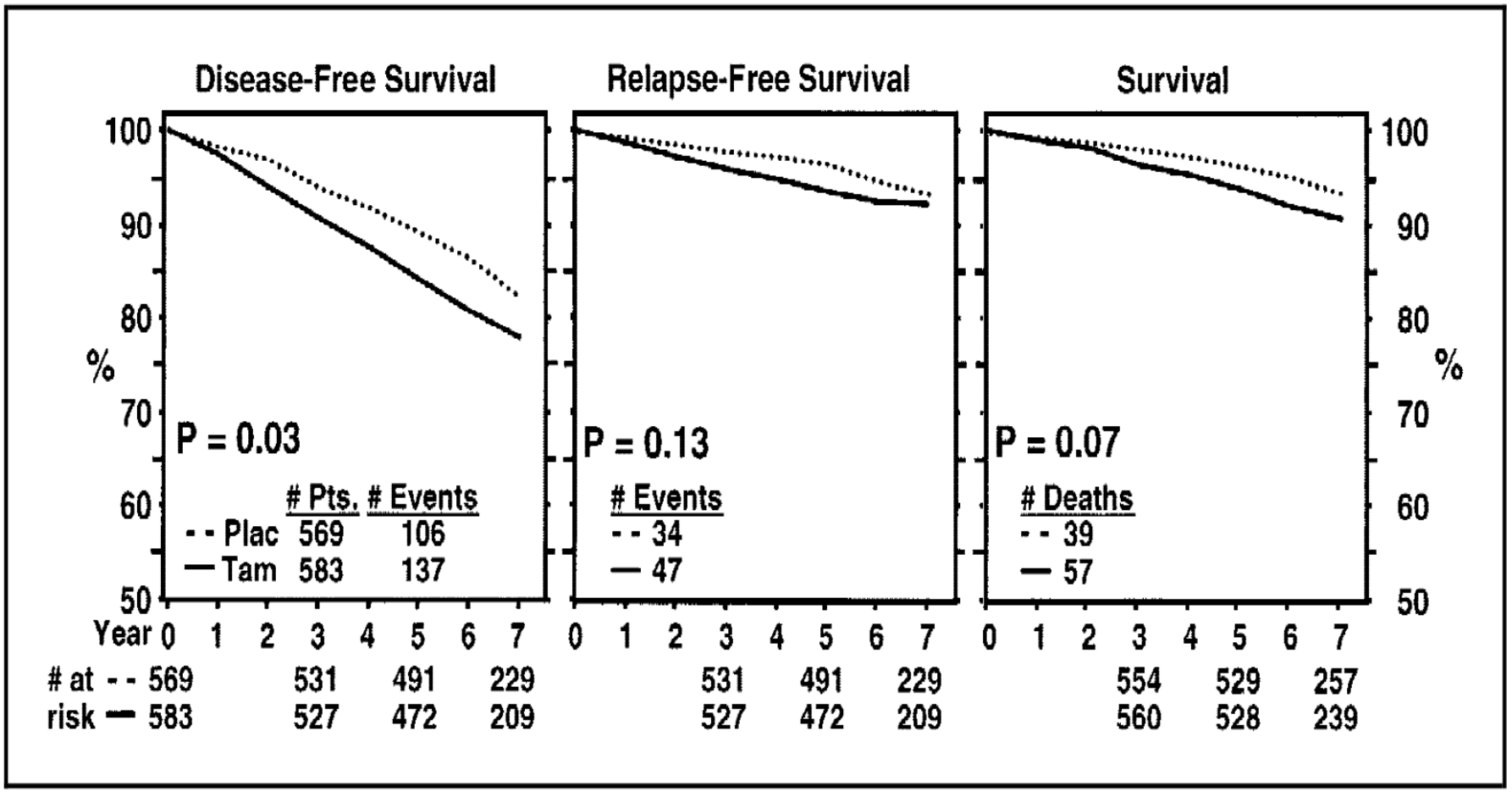


Characteristic*	Placebo, % (n = 569)	Tamoxifen, % (n = 583)
Age, y		
≤49	26	26
50–59	30	30
≥60	44	44
Mean ± standard deviation	56 ± 9	56 ± 10
Menopausal status		
Premenopausal/perimenopausal	25	27
Postmenopausal	74	73
Unknown	1	<1
Type of surgery		
Total mastectomy	56	56
Lumpectomy + XRT†	44	44
Clinical tumor size, cm		
≤2.0	65	68
2.1–4.0	33	28
≥4.1	2	4
Mean ± standard deviation	2.1 ± 1.1	2.0 ± 1.2
Estrogen receptor level, fmol/mg of cytosol protein		
10–49	40	44
50–99	25	21
≥100	35	35
Progesterone receptor level, fmol/mg of cytosol protein		
0–9	20	22
10–49	22	24
50–99	14	15
≥100	44	40
Unknown	0	0
Race		
White	92	92
Black	4	3
Other	3	4
Unknown	2	1

*At time of initial randomization or registration.
†XRT = radiation therapy.

Fisher et al, JNCI 1996 & 2001

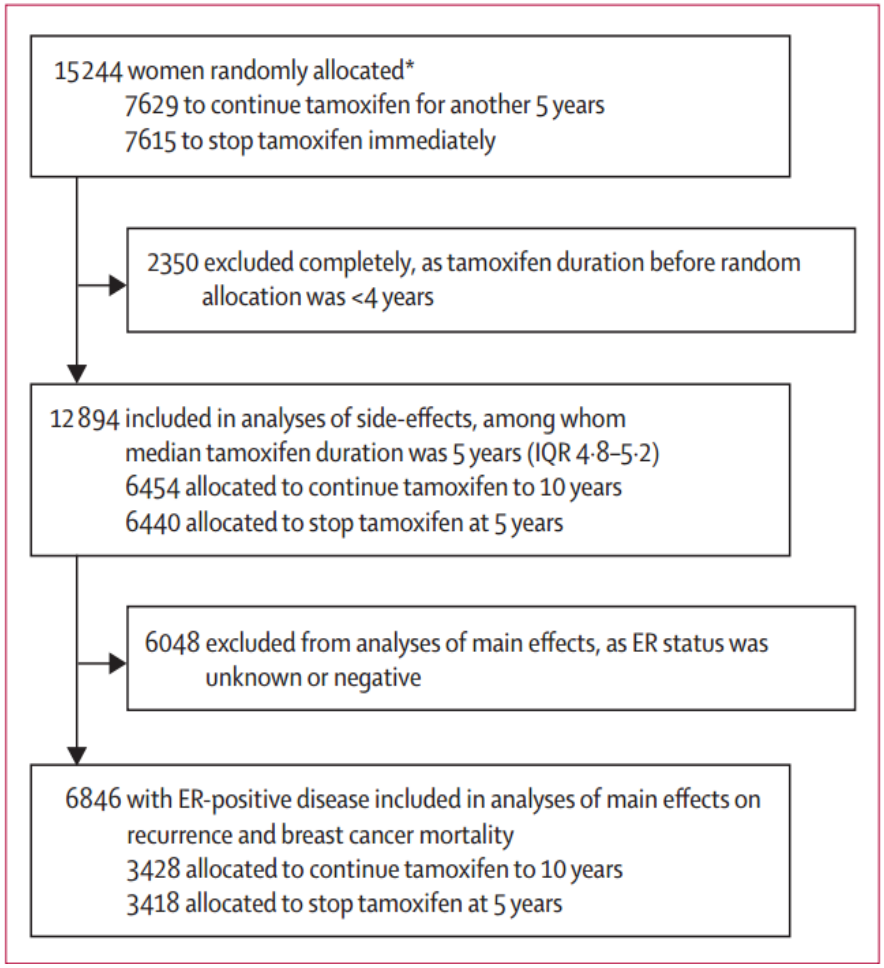
NSABP B-14 (ER+, N0 uniquement)



Fisher et al, JNCI 2001

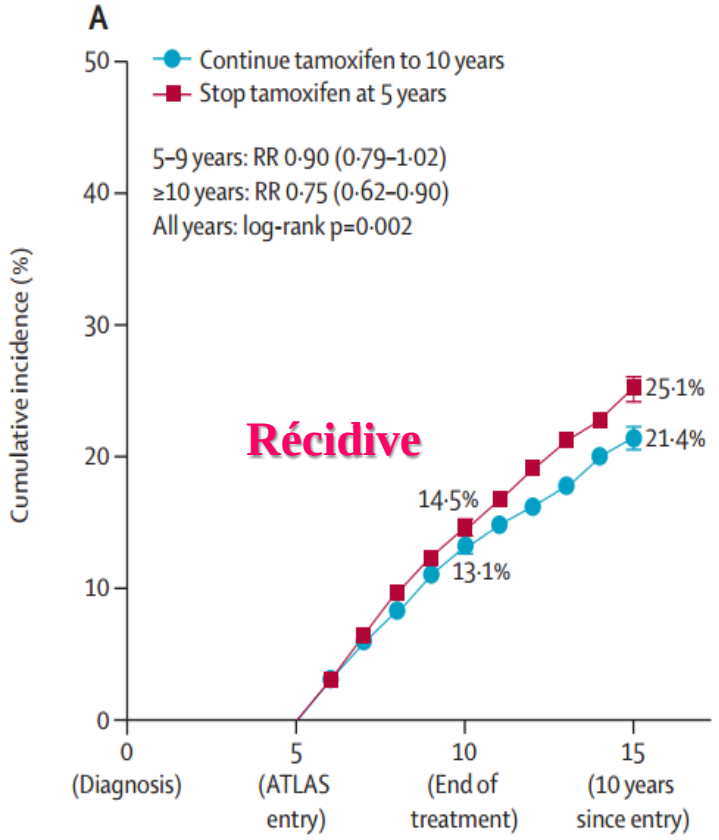
Tam 5 ans versus 10 ans

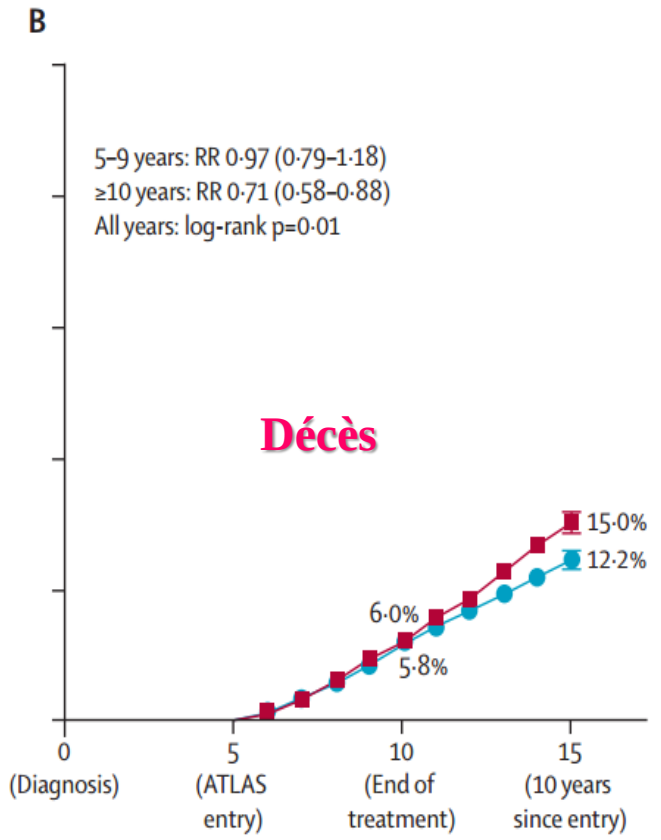
ATLAS (Adjuvant Tamoxifen: Longer Against Shorter)



- ✓ **53% N0**
- ✓ **47% T≤2cm**
- ✓ **89% ménopausées**

Davies et al, Lancet 2013



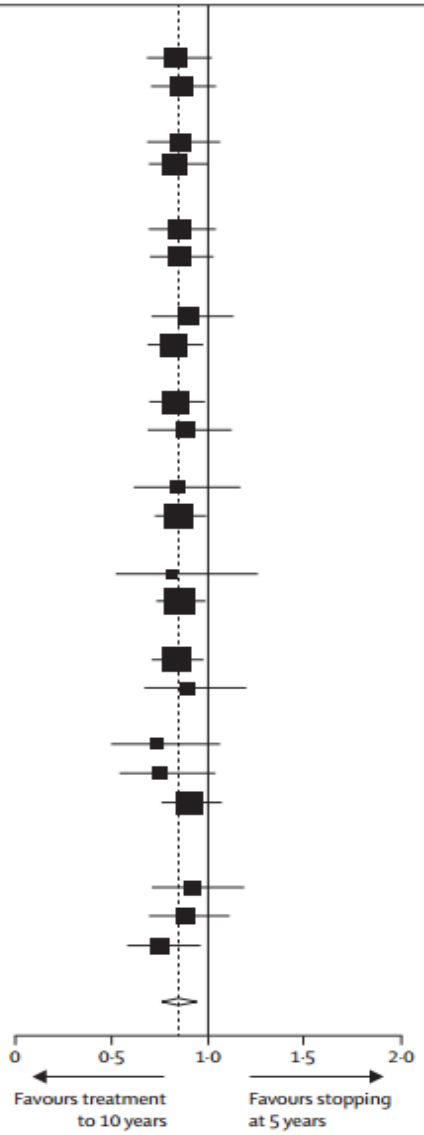


	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	–24·8/224·7	–29·1/94·7	–2·1/12·5	–3·2/94·0	–27·2/77·5	–2·5/10·6

Davies et al, Lancet 2013

	Events/women		10 years events		Ratio of annual event rates (SE)
	Continue tamoxifen to 10 years	Stop tamoxifen at 5 years	Log-rank O–E	Variance of O–E	
Age at diagnosis (p=0·82)					
<55 years	303/1730 (18%)	354/1729 (20%)	−29·6	164·2	0·83 (0·07)
≥55 years	314/1698 (18%)	357/1689 (21%)	−26·2	167·6	0·86 (0·07)
Nodal status at diagnosis (p=0·82)					
Node-negative	252/1832 (14%)	295/1845 (16%)	−22·0	136·7	0·85 (0·08)
Node-positive/unknown	365/1596 (23%)	416/1573 (26%)	−36·2	195·0	0·83 (0·07)
Tumour diameter (p=0·99)					
1–20 mm/unknown	298/1868 (16%)	338/1838 (18%)	−26·3	158·9	0·85 (0·07)
>20 mm	319/1560 (20%)	373/1580 (24%)	−29·0	172·9	0·85 (0·07)
Previous duration of tamoxifen (p=0·43)					
4–4·9 years	223/1095 (20%)	242/1081 (22%)	−12·7	116·2	0·90 (0·09)
≥5 years	394/2333 (17%)	469/2337 (20%)	−43·3	215·6	0·82 (0·06)
Entire breast ever removed (p=0·61)					
Yes	414/2230 (19%)	472/2162 (22%)	−42·2	221·2	0·83 (0·06)
No/unknown	203/1198 (17%)	239/1256 (19%)	−14·4	110·4	0·88 (0·09)
Ever hysterectomised (p=0·99)					
Yes	115/620 (19%)	143/679 (21%)	−10·8	64·4	0·85 (0·11)
No/unknown	502/2808 (18%)	568/2739 (21%)	−45·2	267·3	0·84 (0·06)
Menopausal status at ATLAS entry (p=0·79)					
Premenopausal	64/326 (20%)	73/304 (24%)	−7·2	34·2	0·81 (0·15)
Postmenopausal or unknown	553/3102 (18%)	638/3114 (20%)	−48·8	297·6	0·85 (0·05)
Geographic distribution (p=0·58)					
European origin*	470/2577 (18%)	552/2570 (21%)	−47·3	255·4	0·83 (0·06)
Asian/Middle Eastern origin	147/851 (17%)	159/848 (19%)	−8·7	76·4	0·89 (0·11)
Site of first recurrence (p=0·24)					
Isolated local	79/3428 (2%)	106/3418 (3%)	−14·7	46·2	0·73 (0·13)
Isolated contralateral	109/3428 (3%)	141/3418 (4%)	−18·0	62·5	0·75 (0·11)
Distant†	429/3428 (13%)	464/3418 (14%)	−23·2	223·2	0·90 (0·06)
Period of endpoint (years since diagnosis) (p=0·30)					
0–4 (not applicable before ATLAS entry)			..	..	
5–6	196/3428 (6%)	213/3418 (6%)	−9·0	102·2	0·92 (0·09)
7–9	232/3110 (7%)	258/3073 (8%)	−15·7	122·5	0·88 (0·08)
≥10	189/2605 (7%)	240/2526 (10%)	−31·1	107·1	0·75 (0·08)
Total	**617/3428 (18%)**	**711/3418 (21%)**	**−55·9**	**331·9**	**0·845 (0·051)**
					p=0·002

99% CI or 95% CI
Global heterogeneity p=0·8



Davies et al, Lancet 2013

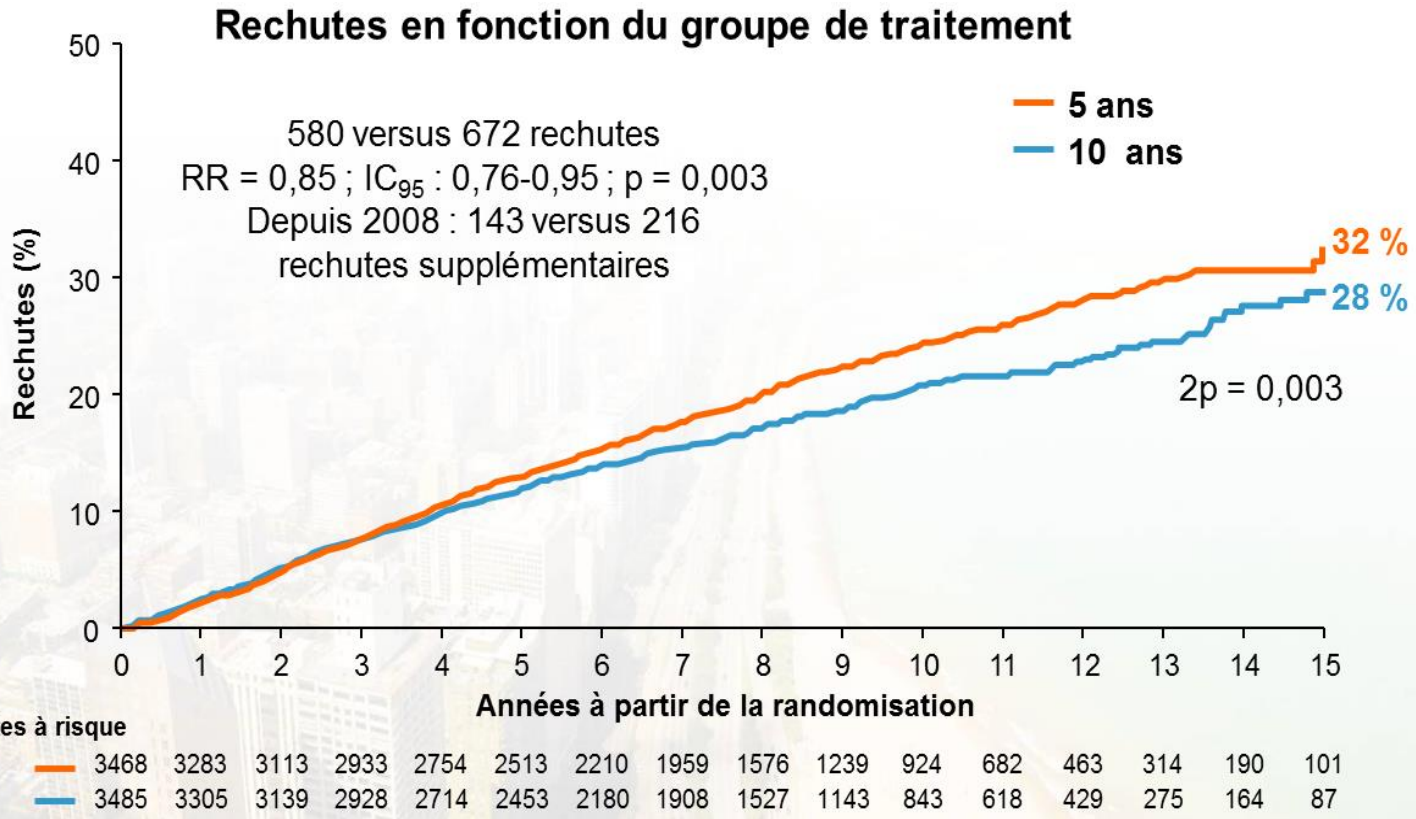
	Number of events		Log-rank O–E	Variance of O–E	Event rate ratio (95% CI)	p value*
	Continue tamoxifen to 10 years	Stop tamoxifen at 5 years				
Analyses of events without prior recurrence‡, any ER status						
Death without recurrence						
Vascular death						
Stroke	62	59	0·8	30·2	1·03 (0·72–1·46)	0·89
Pulmonary embolus	10	8	0·8	4·5	1·21 (0·48–3·04)	0·69
Heart disease§	178	205	−16·1	95·7	0·85 (0·69–1·03)	0·10
Neoplastic death						
Endometrial cancer¶	17	11	2·8	7·0	1·49 (0·71–3·13)	0·29
Other neoplastic disease	78	75	0·4	38·2	1·01 (0·74–1·39)	0·94
Other death						
Specified cause	171	161	2·3	82·9	1·03 (0·83–1·28)	0·80
Unspecified cause	175	160	5·1	83·7	1·06 (0·86–1·32)	0·58
Second cancer incidence						
Contralateral breast cancer	419	467	−28·9	221·5	0·88 (0·77–1·00)	0·05
Endometrial cancer¶	116	63	24·8	44·8	1·74 (1·30–2·34)	0·0002
Primary liver cancer	3	3	−0·0	1·5	0·99 (0·20–4·90)	0·99
Colorectal cancer	46	52	−3·8	24·5	0·86 (0·58–1·27)	0·44
Unspecified site	254	251	−1·3	126·2	0·99 (0·83–1·18)	0·91
Non-neoplastic disease (ever hospitalised or died)						
Stroke	130	119	3·8	62·2	1·06 (0·83–1·36)	0·63
Pulmonary embolus	41	21	9·7	15·5	1·87 (1·13–3·07)	0·01
Ischaemic heart disease	127	163	−20·2	72·5	0·76 (0·60–0·95)	0·02
Gallstones	75	66	3·7	35·2	1·11 (0·80–1·54)	0·54
Cataract	72	63	3·5	33·7	1·11 (0·79–1·56)	0·54
Bone fracture	62	70	−4·9	33·0	0·86 (0·61–1·21)	0·39

Davies et al, Lancet 2013

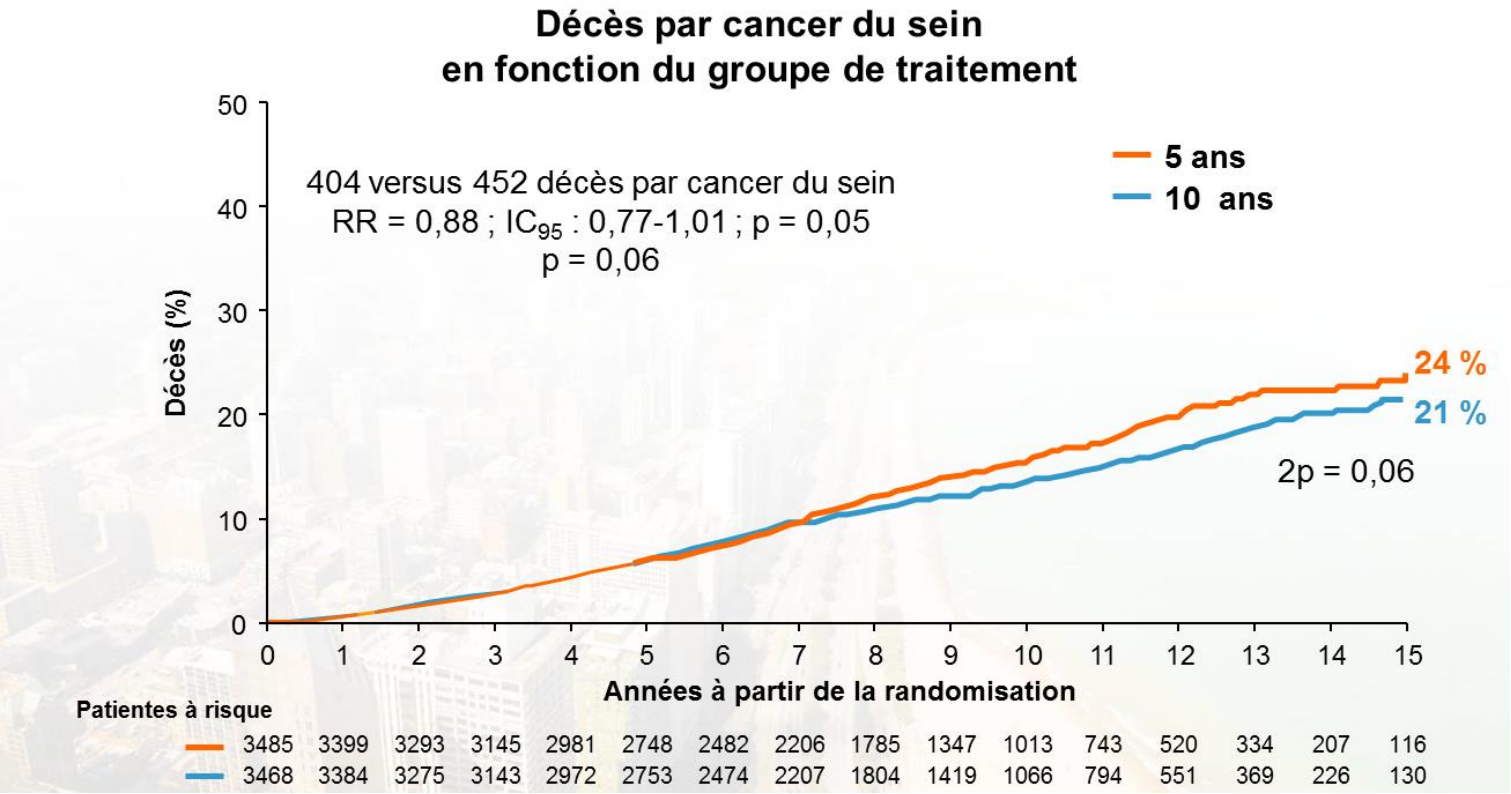
Tam 5 ans versus 10 ans

aTTom (Adjuvant Tamoxifen- To offer more? Trial)

N = 6 953, 61% statut RE inconnu



Gray et al, ASCO 2013



	10 ans n (%)	5 ans n (%)	RR (IC_{95})	p
Cancers de l'endomètre	102 (2,9)	45 (1,3)	2,20 (1,31-2,84)	< 0,0001
Décès par cancer de l'endomètre	37 (1,1)	20 (0,6)	1,83 (1,09-3,09)	0,02

Gray et al, ASCO 2013

Tam 5 ans versus 10 ans

Méta-analyse *(Al-Mubarak et al, PLoS One 2014)*

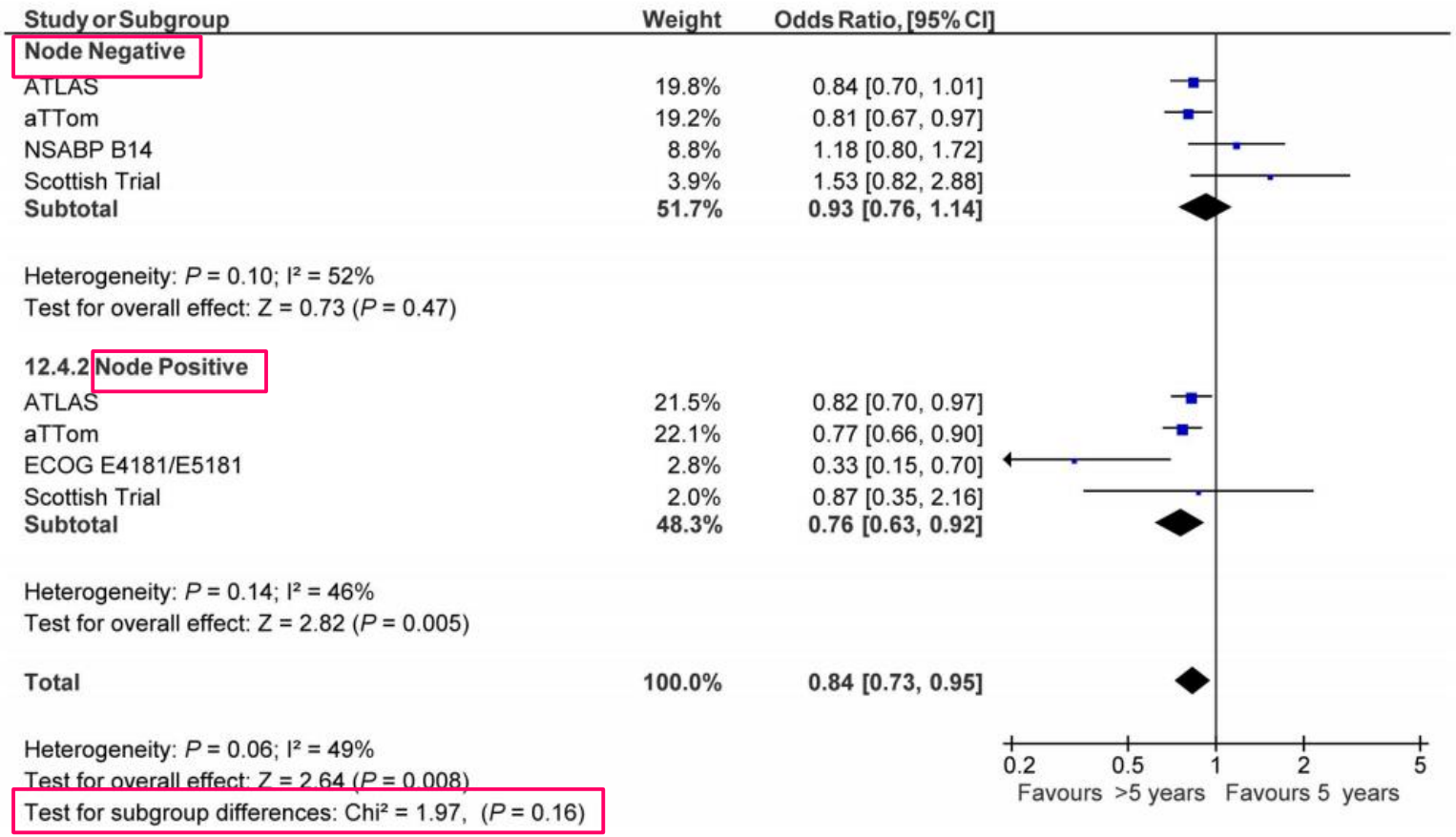
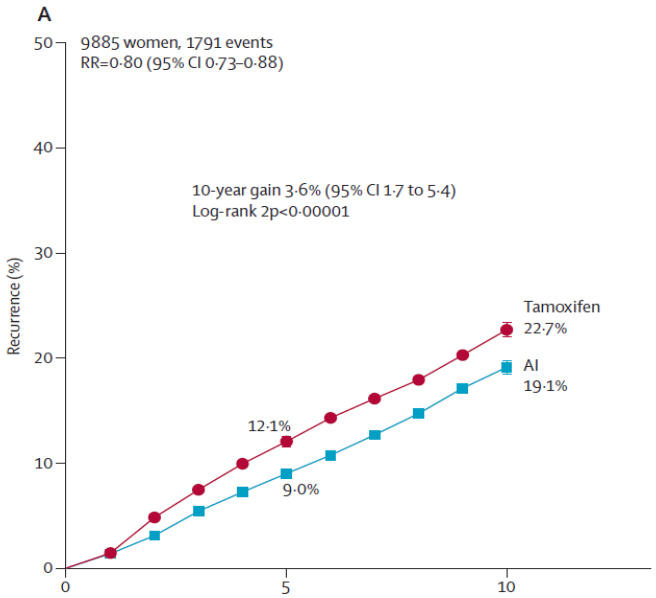


Figure 4. Forest plots of odds ratios for breast cancer recurrence in node negative and in node positive patients with extended adjuvant tamoxifen (>5 years) versus adjuvant tamoxifen (5 years) based on primary analysis of individual trials. Odds ratios for each trial are represented by the **squares**, the **size of the square** represents the weight of the trial in the meta-analysis, and the **horizontal line** crossing the square represents the 95% confidence interval. The diamonds represent the estimated pooled effect based for each cohort individually (labeled subtotal) and for all cohorts together (labeled total).

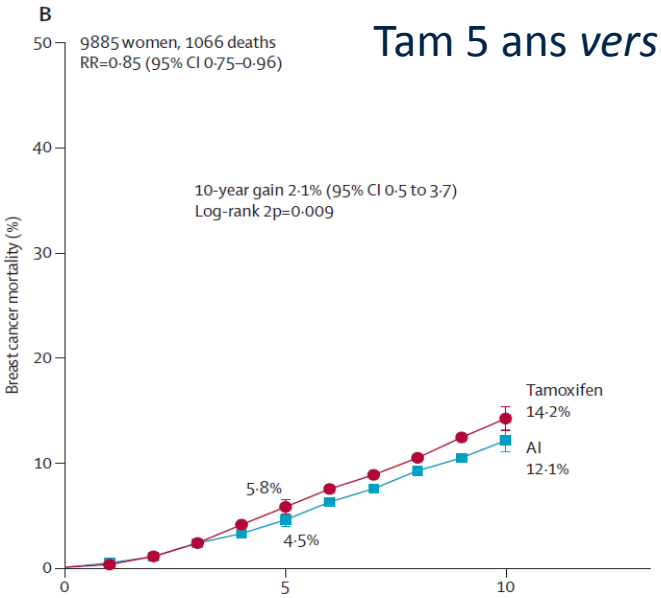
Bénéfices des inhibiteurs aromatase

- **Méta-analyse de l'EBCTCG** sur données individuelles
- 31 920 femmes ménopausées, RE+



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13336)	2·33 (365/15648)	3·23 (20/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12906)	2·48 (372/14985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O-E)/V	−41·1/92·8	−34·1/149·0	−15·5/177·2	−3·6/10·7

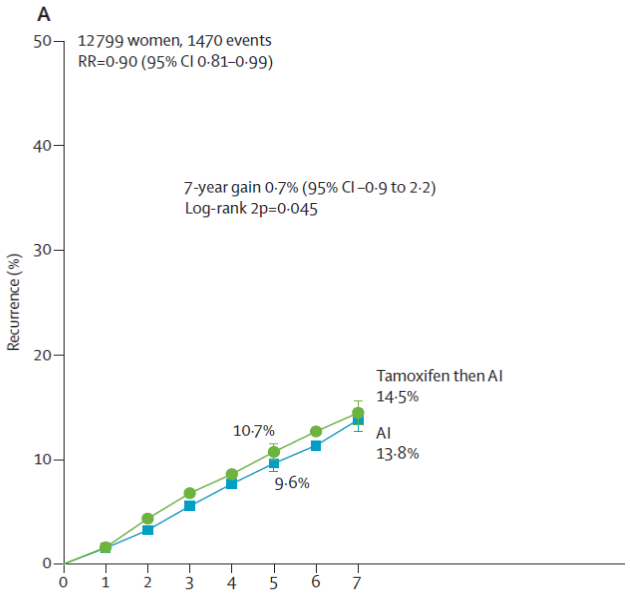


Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	0·52 (0·39–0·66)	1·23 (1·05–1·41)	1·66 (1·46–1·86)	1·93 (0·88–2·99)
Tamoxifen	0·51 (0·39–0·67)	1·60 (1·38–1·83)	1·81 (1·60–2·02)	1·88 (0·77–2·99)
Rate ratio (95% CI)	0·98 (0·66–1·46)	0·74 (0·60–0·91)	0·90 (0·76–1·07)	1·01 (0·45–2·33)
from (O-E)/V	−0·4/24·3	−27·2/90·7	−13·6/129·4	0·1/5·6

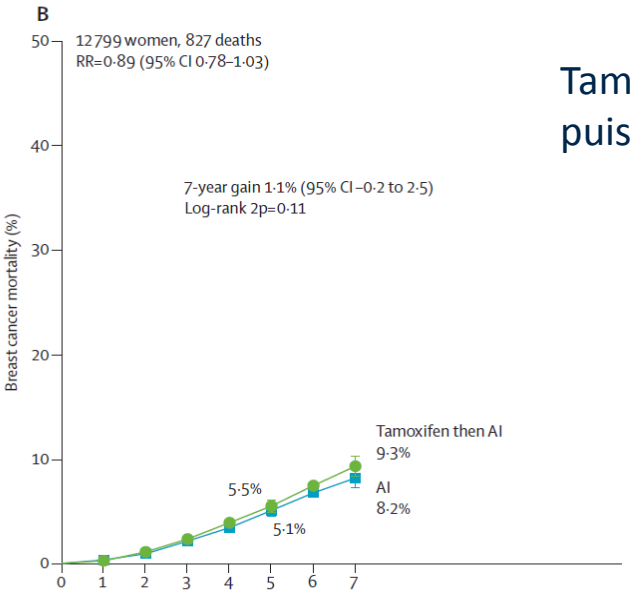
Tam 5 ans *versus* IA 5 ans

EBCTCG, Lancet 2015



Recurrence rate/year (%), events/woman-years and log-rank statistics

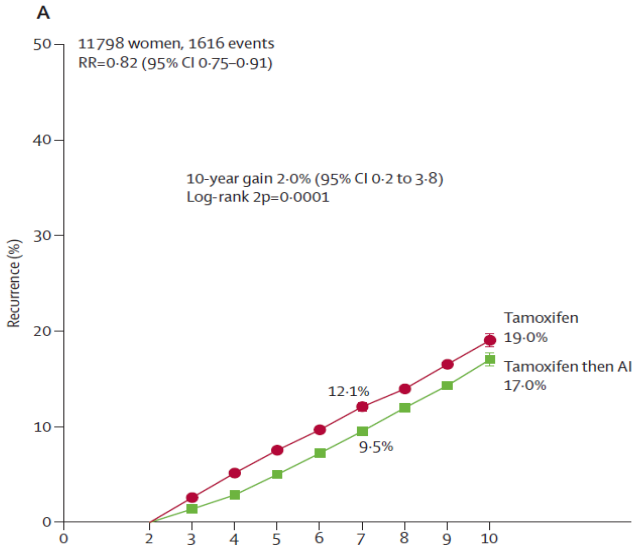
Allocation	Years 0–1	Years 2–4	Year 5+
AI	1·64 (204/12435)	2·31 (360/15589)	2·43 (141/5811)
Tamoxifen then AI	2·22 (273/12290)	2·29 (348/15183)	2·52 (144/5715)
Rate ratio (95% CI)	0·74 (0·62–0·89)	0·99 (0·86–1·15)	0·96 (0·76–1·22)
from (O-E)/V	–34·0/115·0	–1·2/170·6	–2·6/69·2



Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

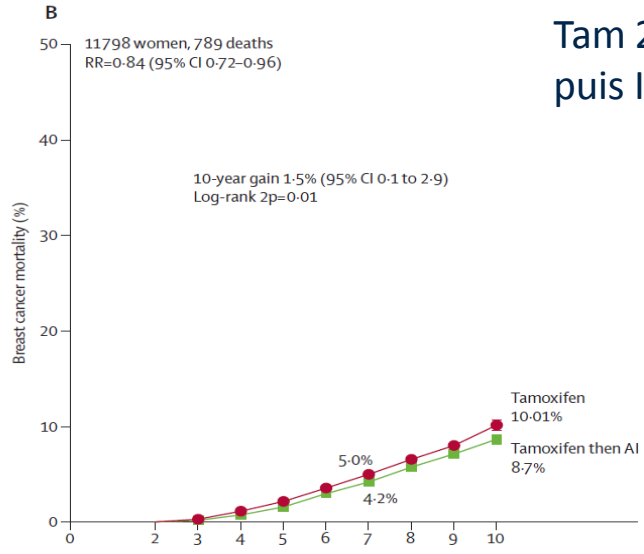
Allocation	Years 0–1	Years 2–4	Year 5+
AI	0·46 (0·35–0·58)	1·41 (1·23–1·57)	1·77 (1·44–2·10)
Tamoxifen then AI	0·55 (0·42–0·68)	1·49 (1·30–1·69)	2·08 (1·72–2·44)
Rate ratio (95% CI)	0·84 (0·59–1·20)	0·93 (0·78–1·13)	0·84 (0·65–1·09)
from (O-E)/V	–5·3/30·7	–7·5/110·9	–9·6/55·5

Tam 2-3 ans
puis IA *versus* IA 5 ans



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	1·48 (170/11515)	2·48 (495/19920)	3·26 (88/2696)
Tamoxifen	2·64 (300/11360)	2·51 (479/19101)	3·35 (84/2505)
Rate ratio (95% CI)	0·56 (0·46–0·67)	0·97 (0·86–1·11)	0·92 (0·68–1·25)
from (O-E)/V	–65·3/111·5	–5·9/234·0	–3·3/40·8



Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	0·37 (0·25–0·48)	1·28 (1·12–1·44)	1·68 (1·63–1·72)
Tamoxifen	0·56 (0·43–0·70)	1·40 (1·26–1·56)	2·54 (2·45–2·59)
Rate ratio (95% CI)	0·65 (0·44–0·96)	0·91 (0·77–1·08)	0·69 (0·48–1·00)
from (O-E)/V	–11·0/25·8	–11·9/132·0	–10·6/28·9

Tam 2-3 ans
puis IA *versus* Tam 5 ans

Bénéfices IA > 5 ans Tam : MA-17

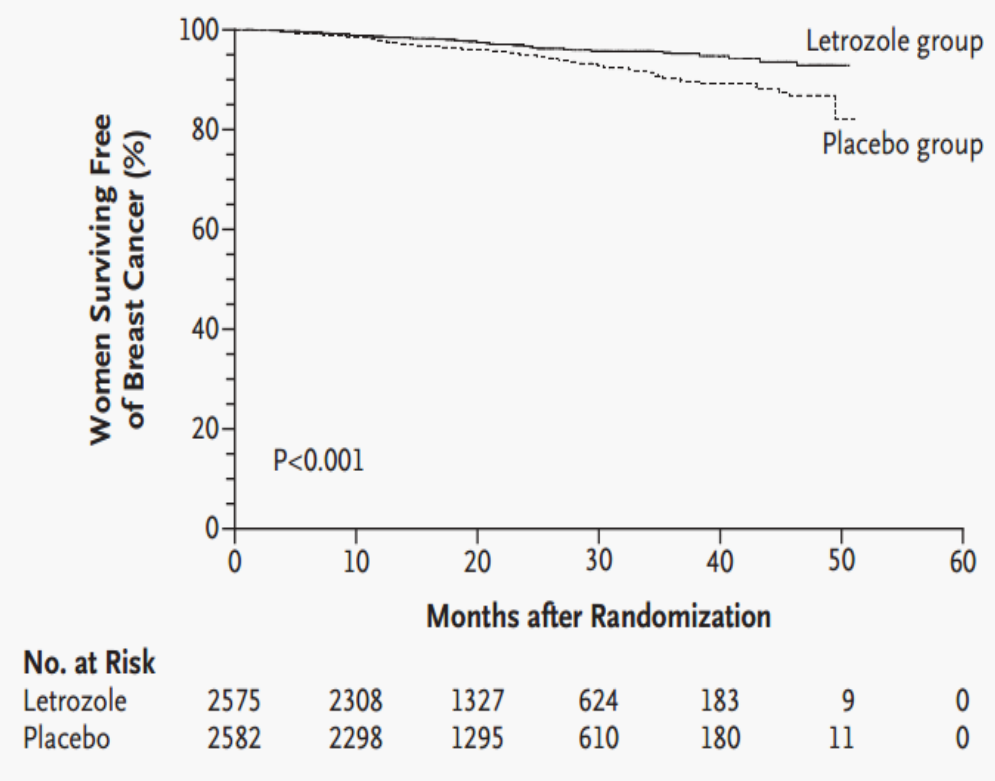
- Phase 3 randomisée, double aveugle, **letrozole 5 ans**
- **N = 5187**
- Suivi médian = **2,4 ans**

- *Objectif principal* : survie sans maladie (récidives locales, à distance et cancer controlatéral)

- *Facteurs stratification* : RH, N, chimio adjuvante

- Age médian=62 ans, 98% RH+, 46% N+, 46% CT adjuvante

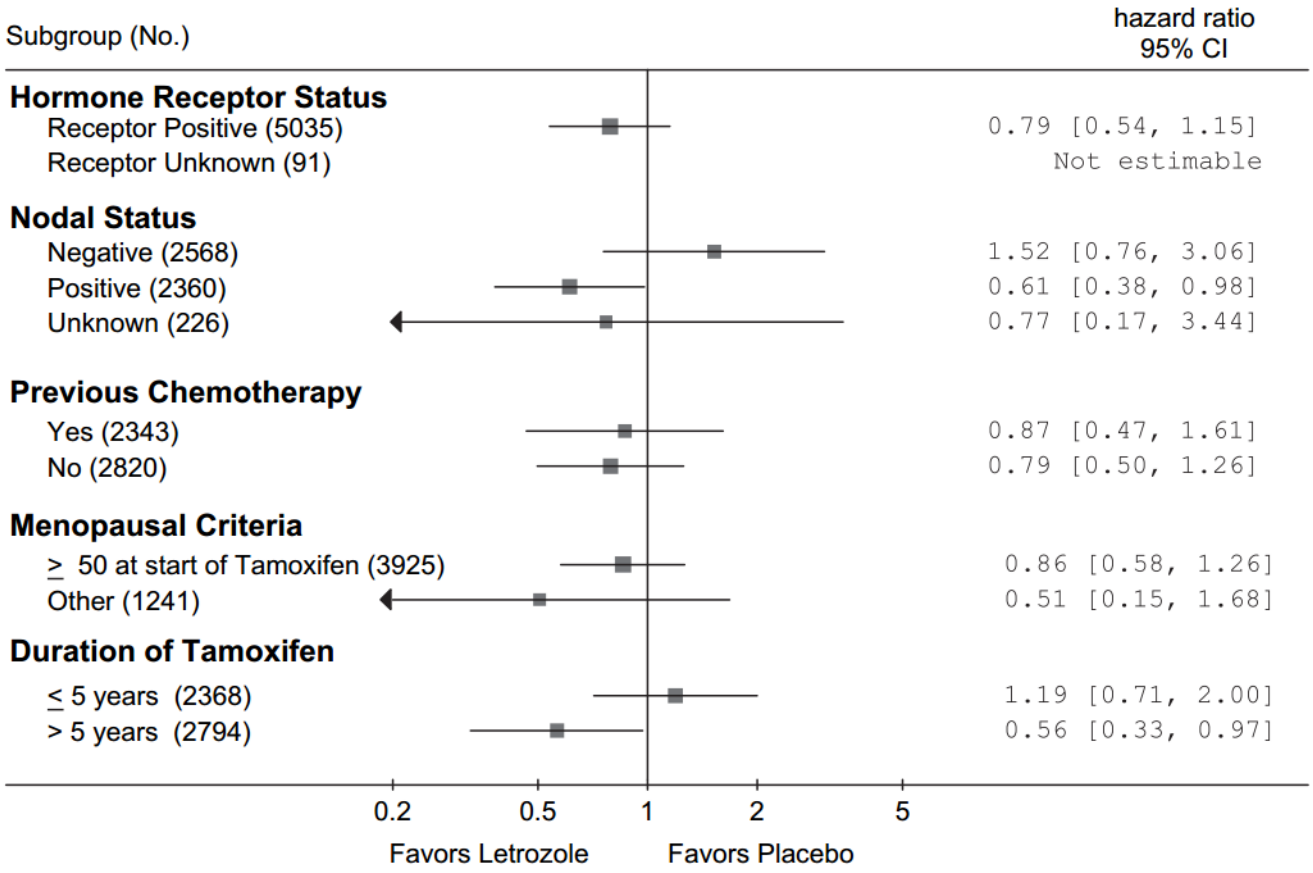
1ère analyse intermédiaire → STOP étude



- ✓ **Taux SSM 4 ans** : **93% *vs* 87%**
  HR=0.57 (IC95% 0.43-0.75)
- ✓ Chez N0 et N+
- ✓ Pas de différence en survie globale

Goss et al, NEJM 2003

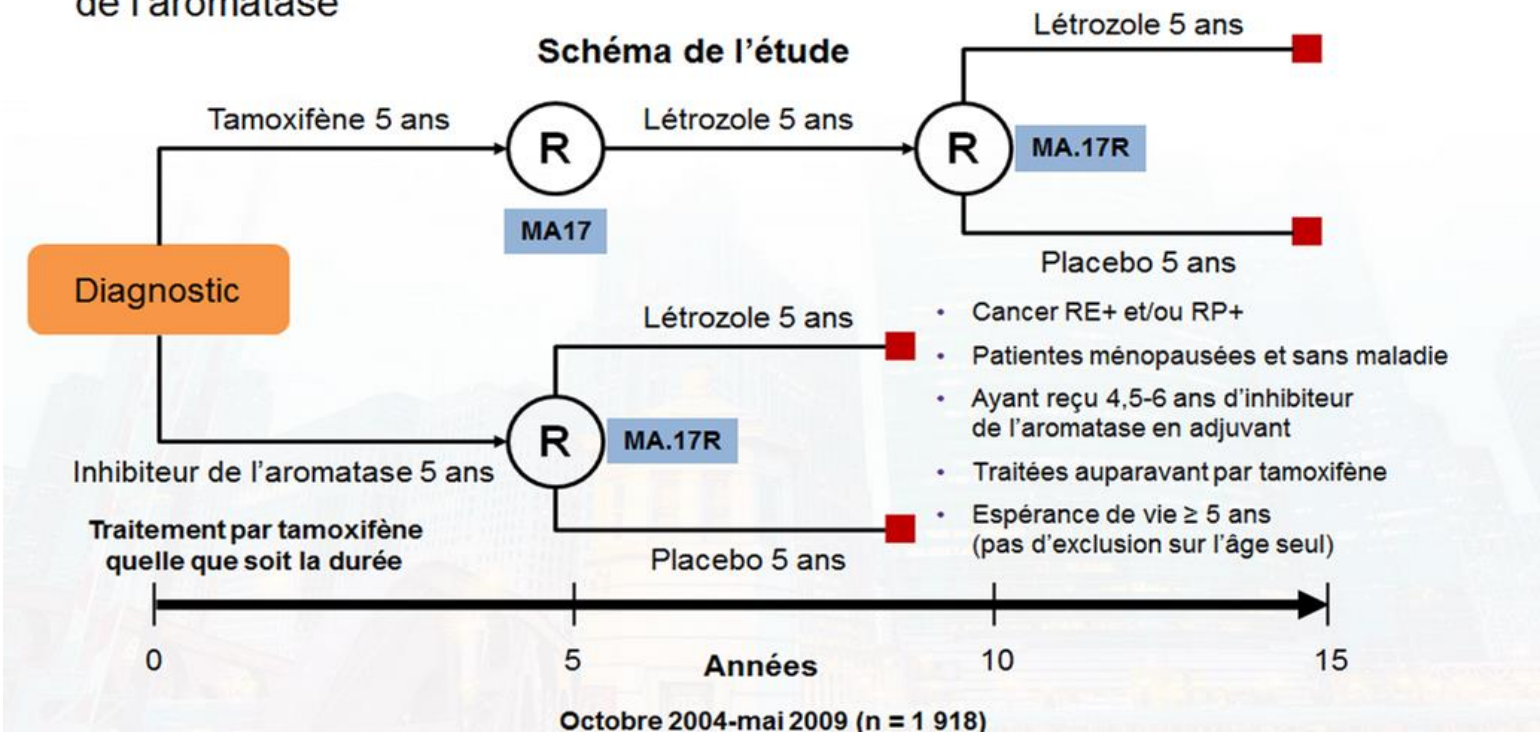
Survie globale : Analyse en sous groupe



Goss et al, JNCI 2005

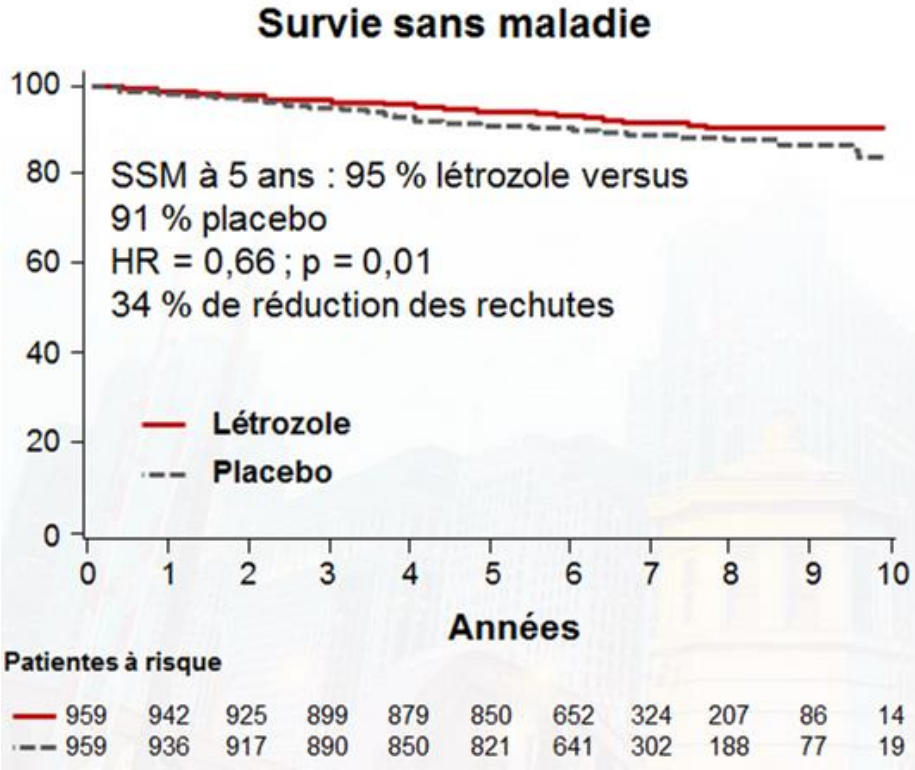
IA 5 ans versus 10 ans : MA-17R

- Essai randomisé d'extension de 5 ans du létrozole après 5 ans d'inhibiteurs de l'aromatase



D'après Goss et al, ASCO 2016

- **N = 1918**
- Age médian=65 ans, 90% T1-T2, 46% N0, 80% Tam adjuvant (4,5-6 ans++)
- Suivi médian = **6,3 ans**
- *Objectif principal* : **survie sans maladie** (récidives locales, à distance et cancer controlatéral)

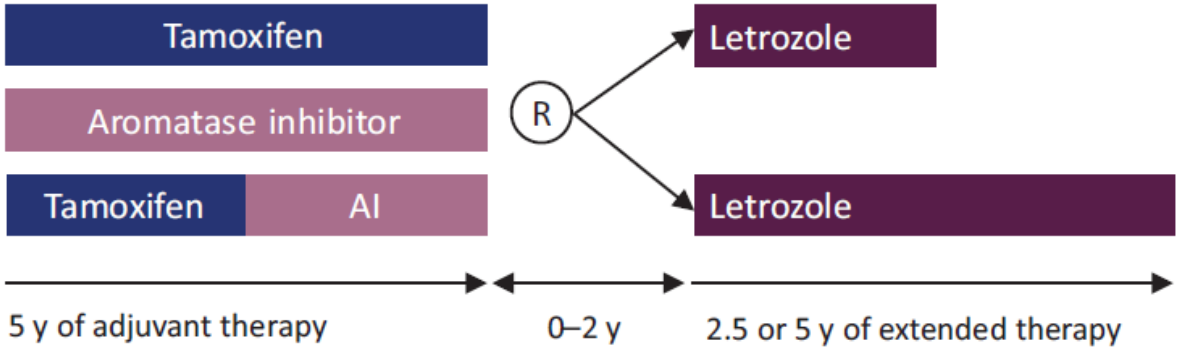


	Létrozole	Placebo
Événements SSM (%)	67 (7,0)	98 (10,2)
Rechutes à distance (%)	42 (4,4)	53 (5,5)
Récidives locorégionales	19	30
Récidives osseuses	28	37
Nouveau cancer controlatéral (%)	13 (1,4)	31 (3,2)

- **Pas de différence en survie globale et qualité de vie**
- **Fractures (14% *vs* 9%; p=0,001) et ostéoporose (11% *vs* 6%; p<0,0001)**

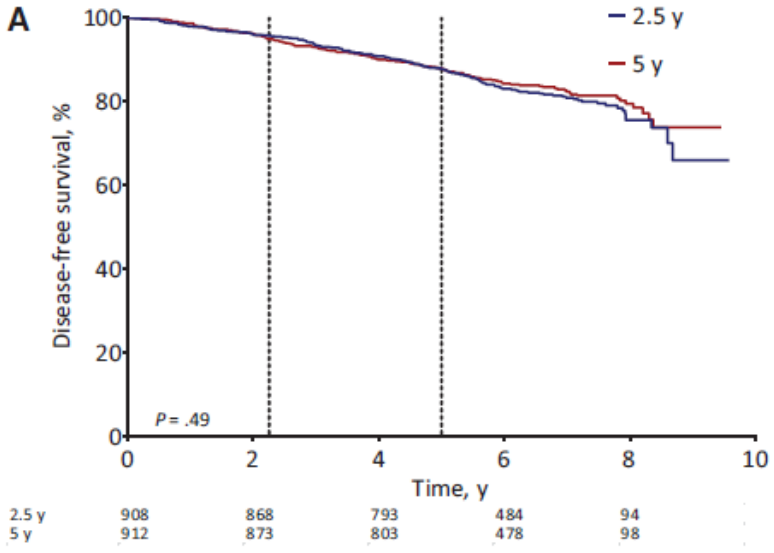
Goss et al, NEJM 2016

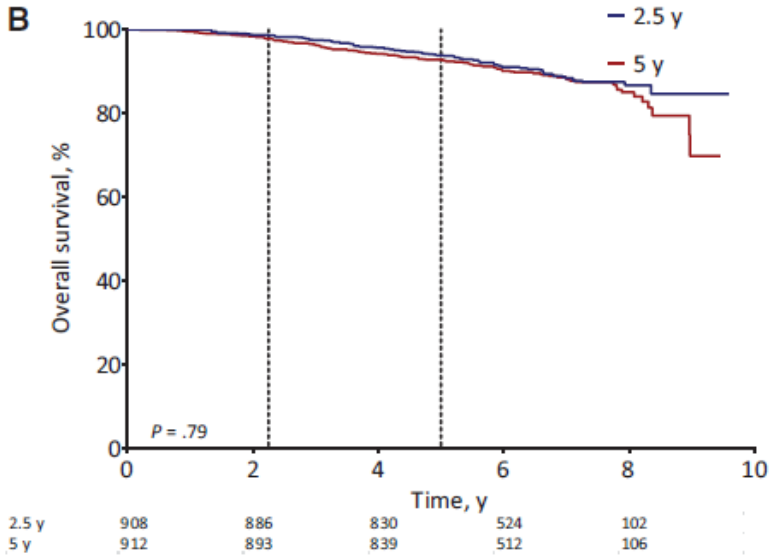
IA 2,5 ans versus 5 ans > 5 ans HT : IDEAL trial

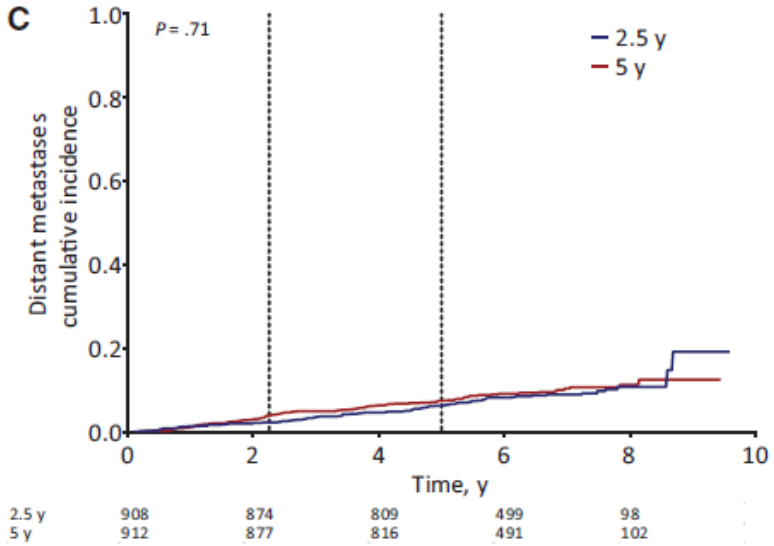


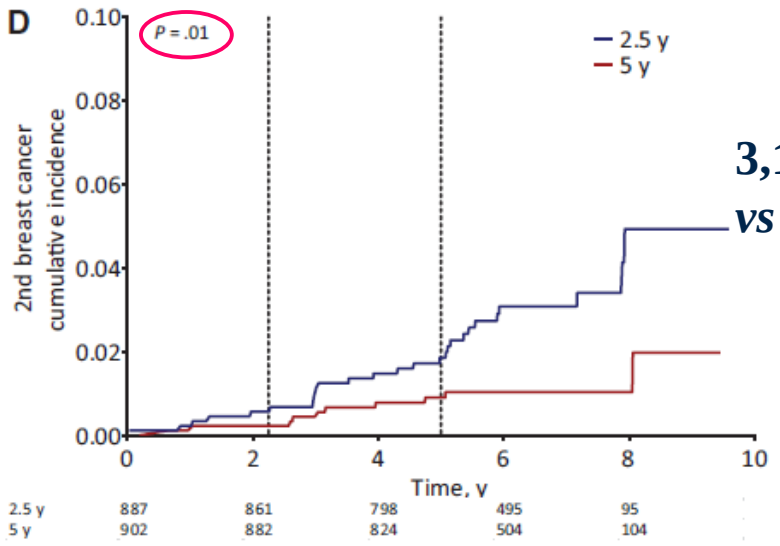
- **N = 1824**
- 25% pN0, grade 2++ (42%), 19% HER2+, 68% ont reçu CT adjuvante, 59% ont reçu une HT séquentielle (tam ➔ IA), 28% IA 5 ans, 88% arrêt HT adjuvante < 6 mois
- Suivi médian = **6,6 ans**
- *Objectif principal* : **survie sans maladie** (récidives locales, à distance, décès quelle que soit la cause)
- Compliance générale = 60%

Block et al, JNCI 2017



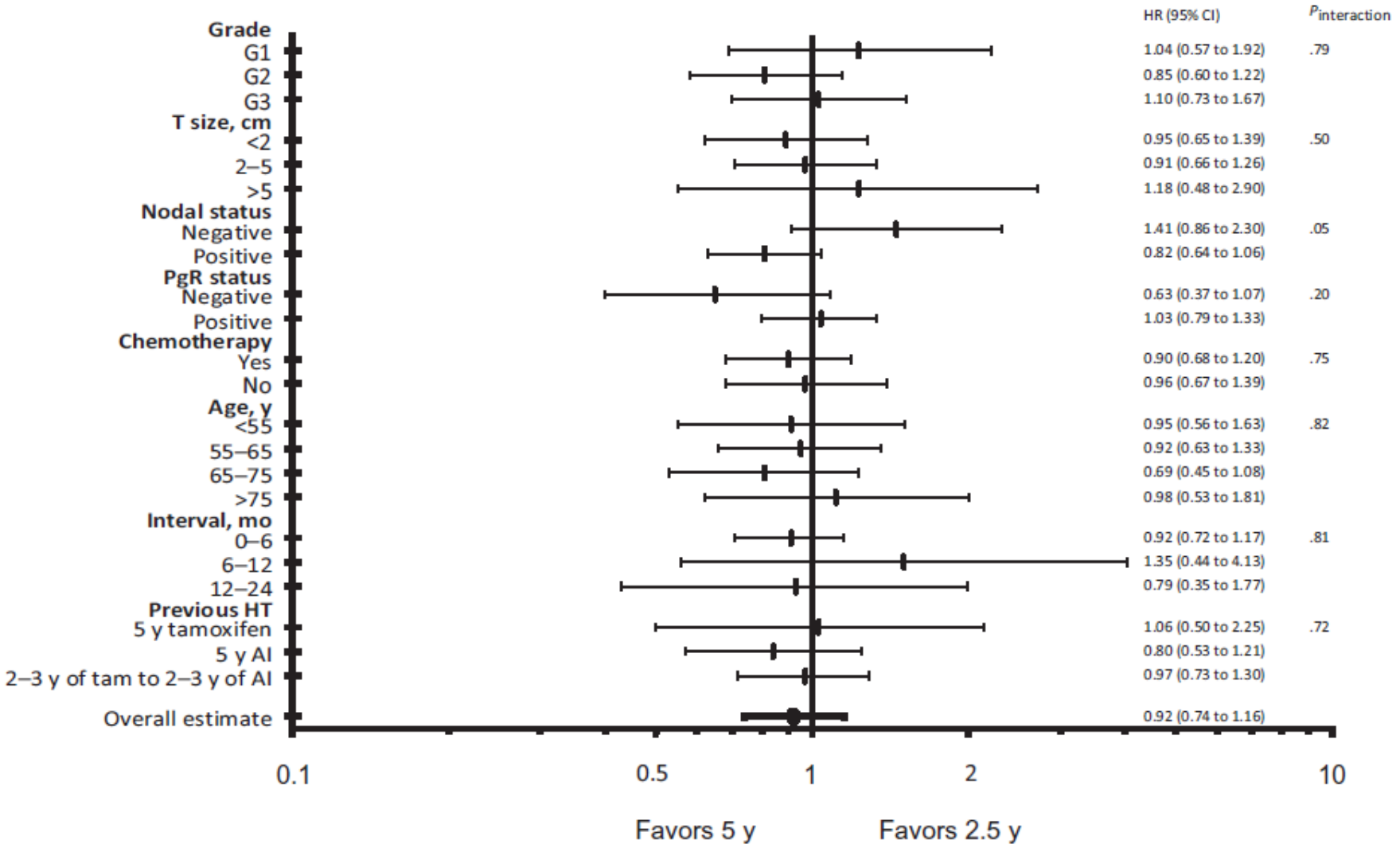






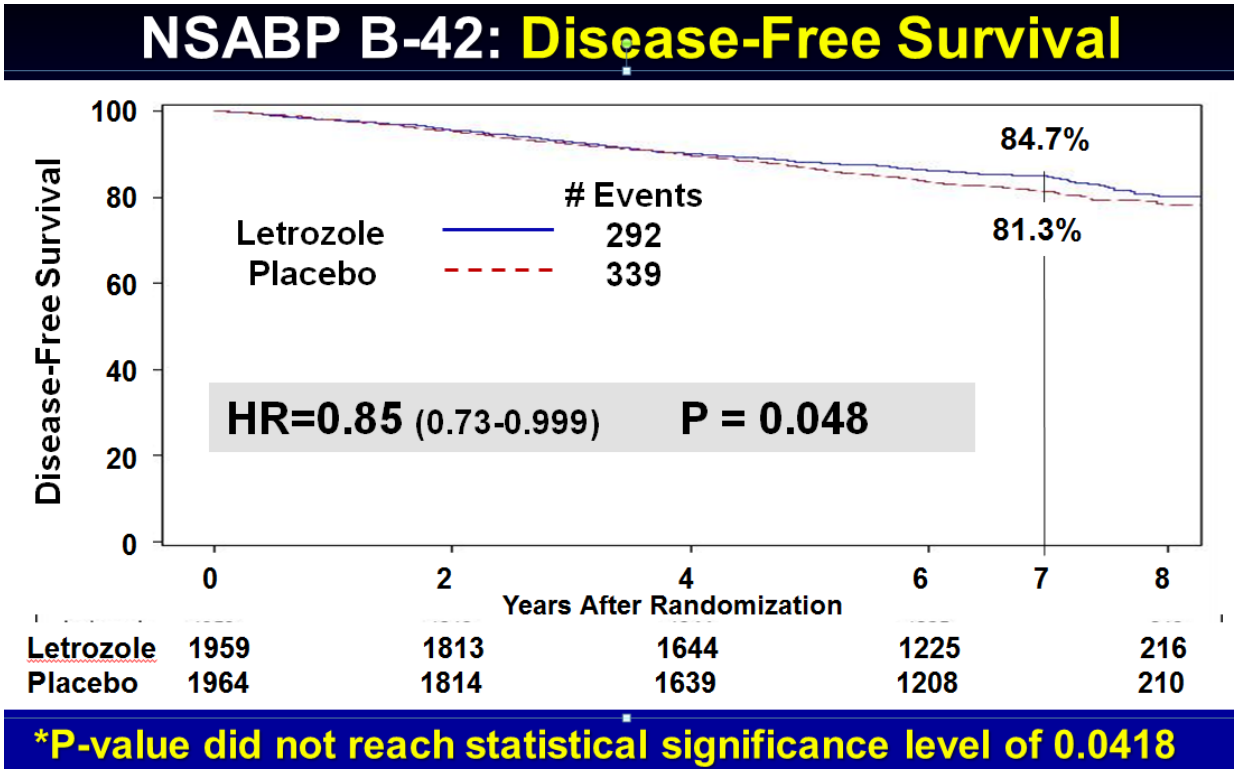
3,1%
***vs* 1,1%**

Block et al, JNCI 2017



Block et al, JNCI 2017

IA 5 ans > 5 ans HT incluant un IA : NSABP-B42



- ✓ N=3966
- ✓ *Suivi médian* **= 6,9 ans**
- ✓ Plus d'accidents thrombo-emboliques artériels après 2,5 ans IA

Mamounas et al, abstract S1-05, SABCS 2016

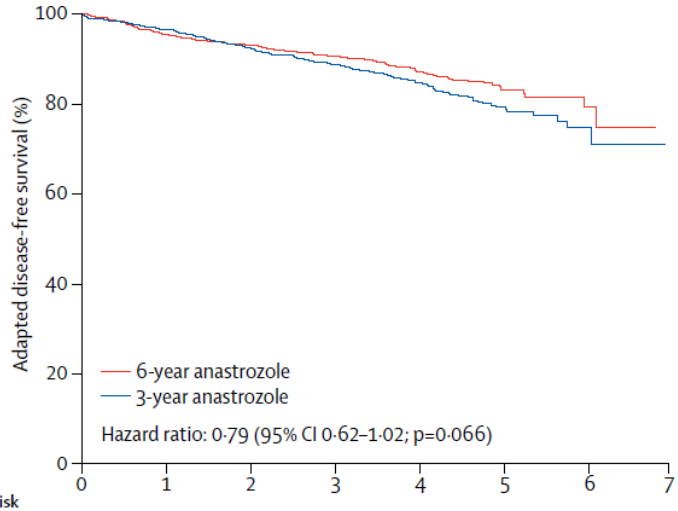
IA 3 ans versus 6 ans > 2-3 ans tam : DATA trial

- Phase 3 randomisée, **anastrozole**
- **N = 1860**
- Suivi médian = **4,2 ans**

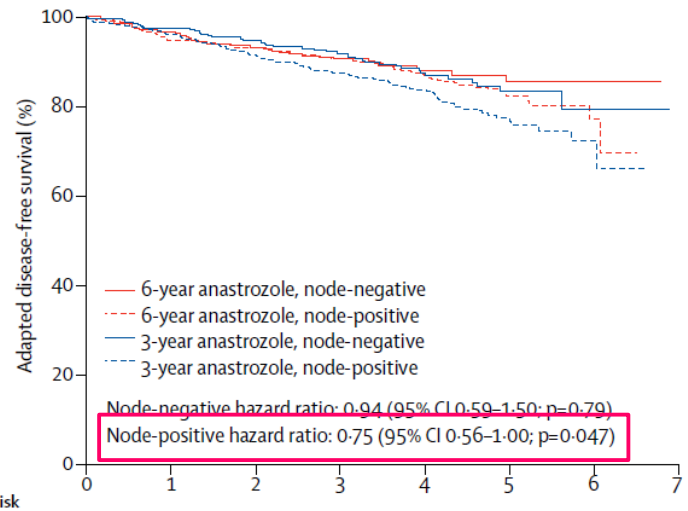
- *Objectif principal* : survie sans maladie (locale, à distance, 2nd cancer, décès quelle que soit la cause)

- *Facteurs stratification* : RH, N, HER2, durée tam

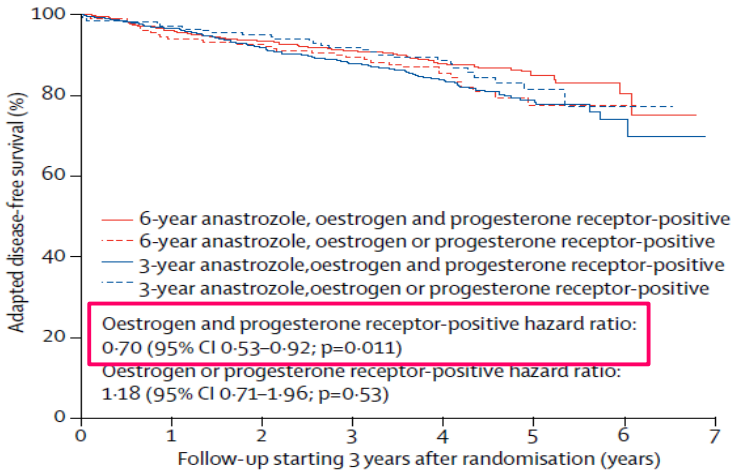
- Age médian=57 ans, 2/3 N+, 75% RE+ et RP+



Number at risk (number censored)								
6-year anastrozole	827 (0)	789 (0)	769 (2)	698 (52)	445 (283)	182 (533)	24 (688)	0 (711)
3-year anastrozole	833 (0)	801 (4)	762 (8)	692 (49)	453 (262)	169 (525)	28 (661)	0 (688)



Number at risk (number censored)								
6-year anastrozole, node-negative	266 (0)	257 (0)	247 (1)	224 (17)	128 (108)	50 (184)	9 (225)	0 (234)
6-year anastrozole, node-positive	561 (0)	532 (0)	522 (1)	474 (35)	317 (175)	132 (349)	15 (463)	0 (477)
r anastrozole, ıode-negative	282 (0)	275 (0)	264 (3)	243 (16)	156 (93)	64 (180)	12 (231)	0 (243)
r anastrozole, node-positive	551 (0)	526 (4)	498 (5)	449 (33)	297 (169)	105 (345)	16 (430)	0 (445)



Number at risk (number censored)								
6-year anastrozole, oestrogen and progesterone receptor-positive	627 (0)	601 (0)	585 (1)	533 (38)	345 (210)	149 (399)	21 (524)	0 (544)
6-year anastrozole, oestrogen or progesterone receptor-positive	200 (0)	188 (0)	184 (1)	165 (14)	100 (73)	33 (134)	3 (164)	0 (167)
3-year anastrozole, oestrogen and progesterone receptor-positive	633 (0)	611 (0)	577 (3)	529 (28)	343 (193)	132 (389)	22 (495)	0 (516)
3-year anastrozole,	200 (0)	190 (4)	185 (5)	163 (21)	110 (69)	37 (136)	6 (166)	0 (172)

Intérêt traitement intermittent ? : SOLE

- *Pré-clinique* : sur des cellules privées d'estrogènes, la restauration de faibles doses d'estrogènes pourrait avoir un effet cytotoxique

- **Letrozole intermittent (9 mois / 12) *versus* continu**
- Phase 3, **N = 4851**
- Suivi médian = 60 mois
- *Objectif principal* : survie sans récidive

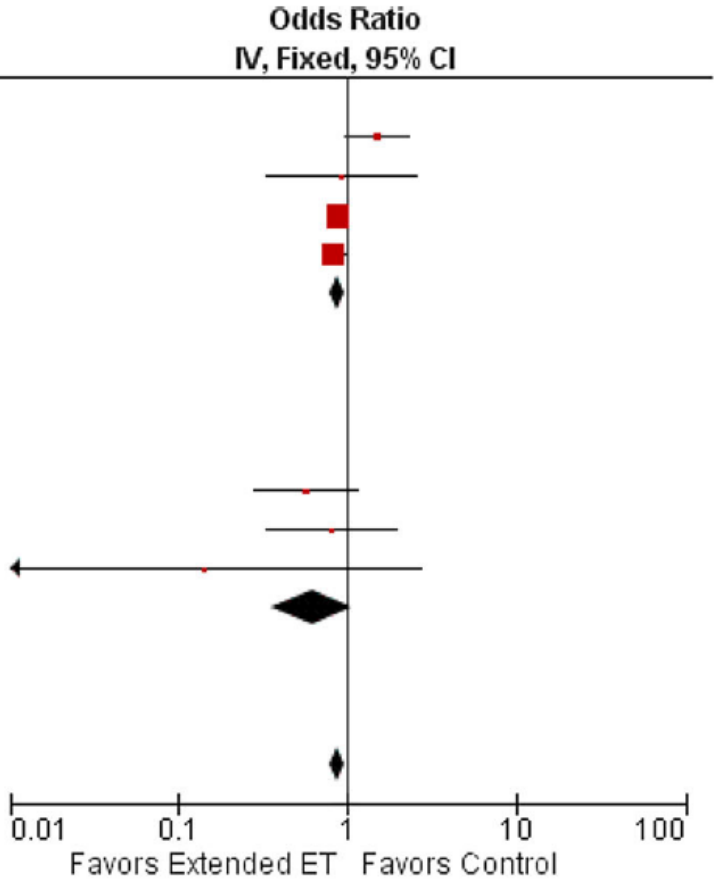
- **Pas de différence : 85,8% *vs* 87,5% (HR=1,08; p=0,31)**
- **Pas de différence en qualité de vie globale et EI**

Colleoni et al, abstract 503, ASCO 2017

Méta-analyse prolongation HT

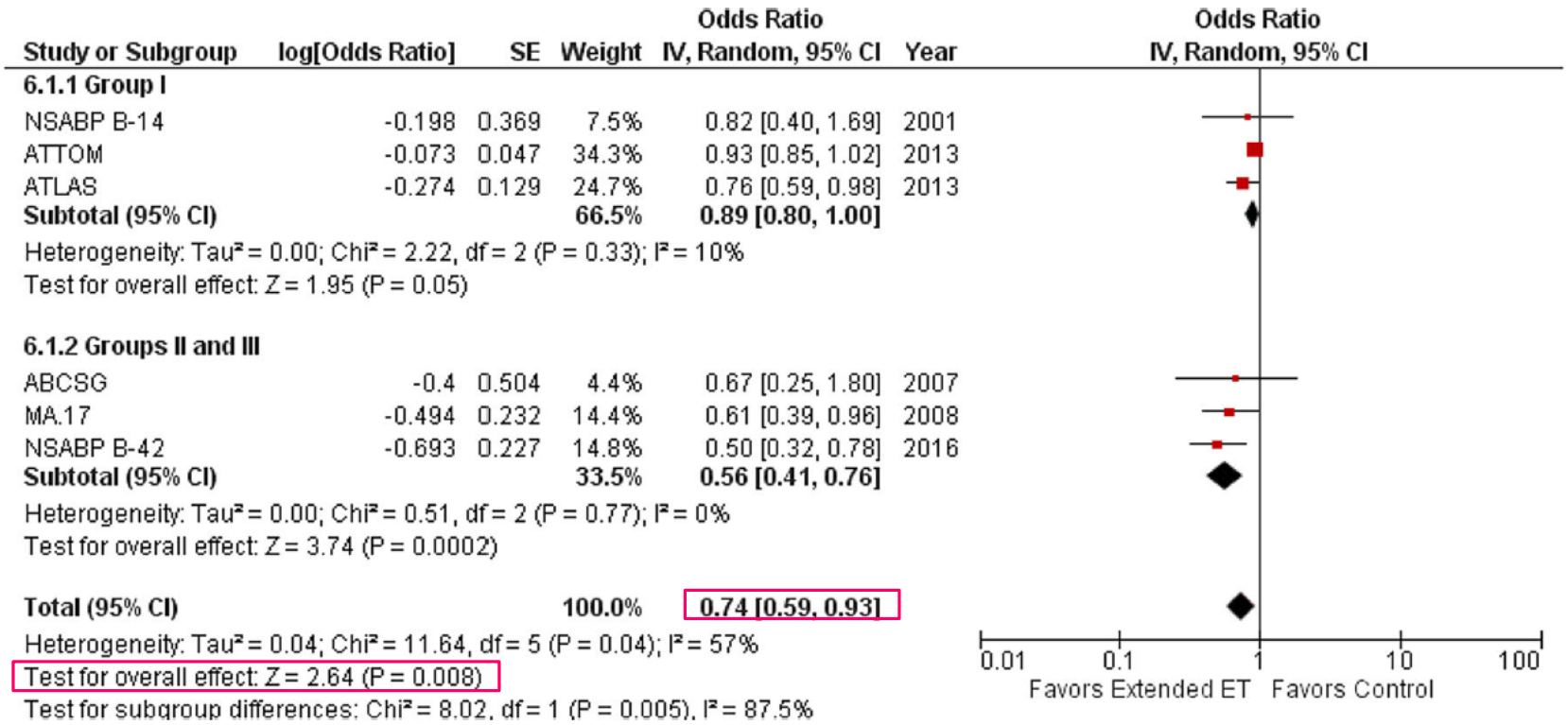
Breast cancer-specific survival

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI	Year
3.1.1 Group I					
SCOTTISH	0.405	0.228	4.4%	1.50 [0.96, 2.34]	1996
ECOG	-0.083	0.524	0.8%	0.92 [0.33, 2.57]	1996
ATTOM	-0.128	0.069	48.4%	0.88 [0.77, 1.01]	2013
ATLAS	-0.186	0.073	43.3%	0.83 [0.72, 0.96]	2013
Subtotal (95% CI)			**97.0%**	**0.88 [0.80, 0.97]**	
Heterogeneity: Chi² = 6.10, df = 3 (P = 0.11); I² = 51%					
Test for overall effect: Z = 2.65 (P = 0.008)					
3.1.2 Groups II and III					
ABCSG	-0.562	0.36	1.8%	0.57 [0.28, 1.15]	2007
NSABP B-33	-0.211	0.456	1.1%	0.81 [0.33, 1.98]	2008
LATER	-1.966	1.52	0.1%	0.14 [0.01, 2.75]	2016
Subtotal (95% CI)			**3.0%**	**0.62 [0.36, 1.07]**	
Heterogeneity: Chi² = 1.36, df = 2 (P = 0.51); I² = 0%					
Test for overall effect: Z = 1.72 (P = 0.08)					
Total (95% CI)			**100.0%**	**0.87 [0.79, 0.96]**	
Heterogeneity: Chi² = 8.99, df = 6 (P = 0.17); I² = 33%					
Test for overall effect: Z = 2.91 (P = 0.004)					
Test for subgroup differences: Chi² = 1.54, df = 1 (P = 0.22), I² = 34.9%					



Ibrahim et al, Med Oncol, 2017

Controlateral breast cancer



Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Year
6.1.1 Group I					
NSABP B-14	-0.198	0.369	7.5%	0.82 [0.40, 1.69]	2001
ATTOM	-0.073	0.047	34.3%	0.93 [0.85, 1.02]	2013
ATLAS	-0.274	0.129	24.7%	0.76 [0.59, 0.98]	2013
Subtotal (95% CI)			**66.5%**	**0.89 [0.80, 1.00]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.22, df = 2 (P = 0.33); I² = 10%					
Test for overall effect: Z = 1.95 (P = 0.05)					
6.1.2 Groups II and III					
ABCSG	-0.4	0.504	4.4%	0.67 [0.25, 1.80]	2007
MA.17	-0.494	0.232	14.4%	0.61 [0.39, 0.96]	2008
NSABP B-42	-0.693	0.227	14.8%	0.50 [0.32, 0.78]	2016
Subtotal (95% CI)			**33.5%**	**0.56 [0.41, 0.76]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.77); I² = 0%					
Test for overall effect: Z = 3.74 (P = 0.0002)					
Total (95% CI)			**100.0%**	**0.74 [0.59, 0.93]**	
Heterogeneity: Tau² = 0.04; Chi² = 11.64, df = 5 (P = 0.04); I² = 57%					
Test for overall effect: Z = 2.64 (P = 0.008)					
Test for subgroup differences: Chi² = 8.02, df = 1 (P = 0.005), I² = 87.5%					

- Exclusion études MA-17R et IDEAL (bras standard avec prolongation HT)
- Pas de différence en OS
- Bénéfice en terme de dim récidive si N+ et RE+/RP+ surtout
- MA sur données publiées

Ibrahim et al, Med Oncol, 2017

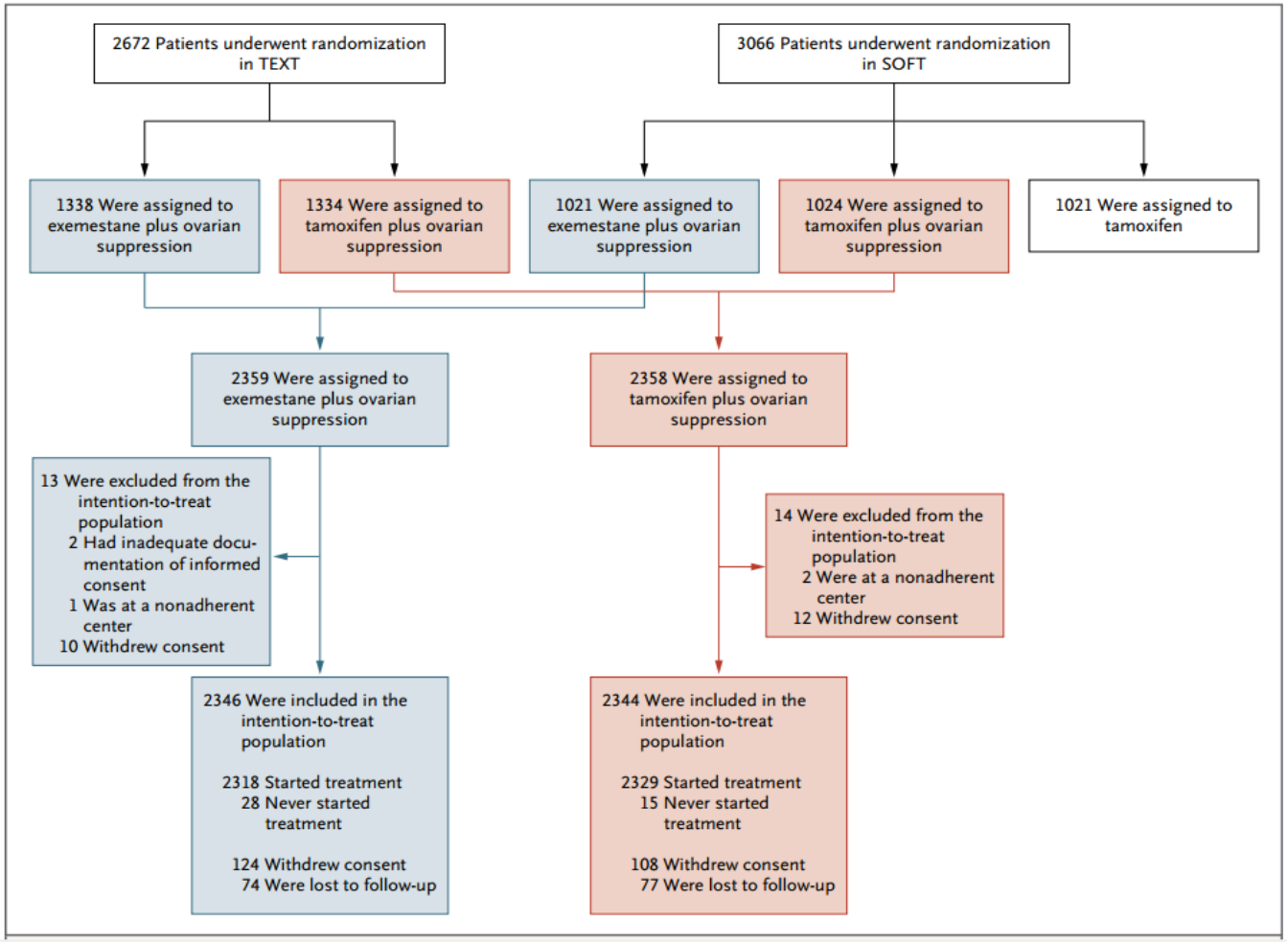
Conclusions

- ✓ ***Après 5 ans de Tam*** : **stop / Tam 5 ans** (**N+?**) / **IA 2,5 à 5 ans** (**N+**)
- ✓ ***Après 5 ans IA*** : **stop / IA au moins 2,5 ans / Tam ?** (**avis d'experts**)
- ✓ ***Après HT séquentielle*** : **3 ans IA** (**N+; RE+ et RP+ ?**)

- ✓ ***Prendre en compte***
  - **Risque de récidive** (taille, grade, prolifération, **N**)
  - **Statut RE et RP**
  - **Statut ménopausique**
  - **Tolérance**
  - **Rapport bénéfice / risque**

- ✓ **Discussion RCP++**
- ✓ **Décision partagée+++**

Intérêt blocage ovarien : SOFT et TEXT



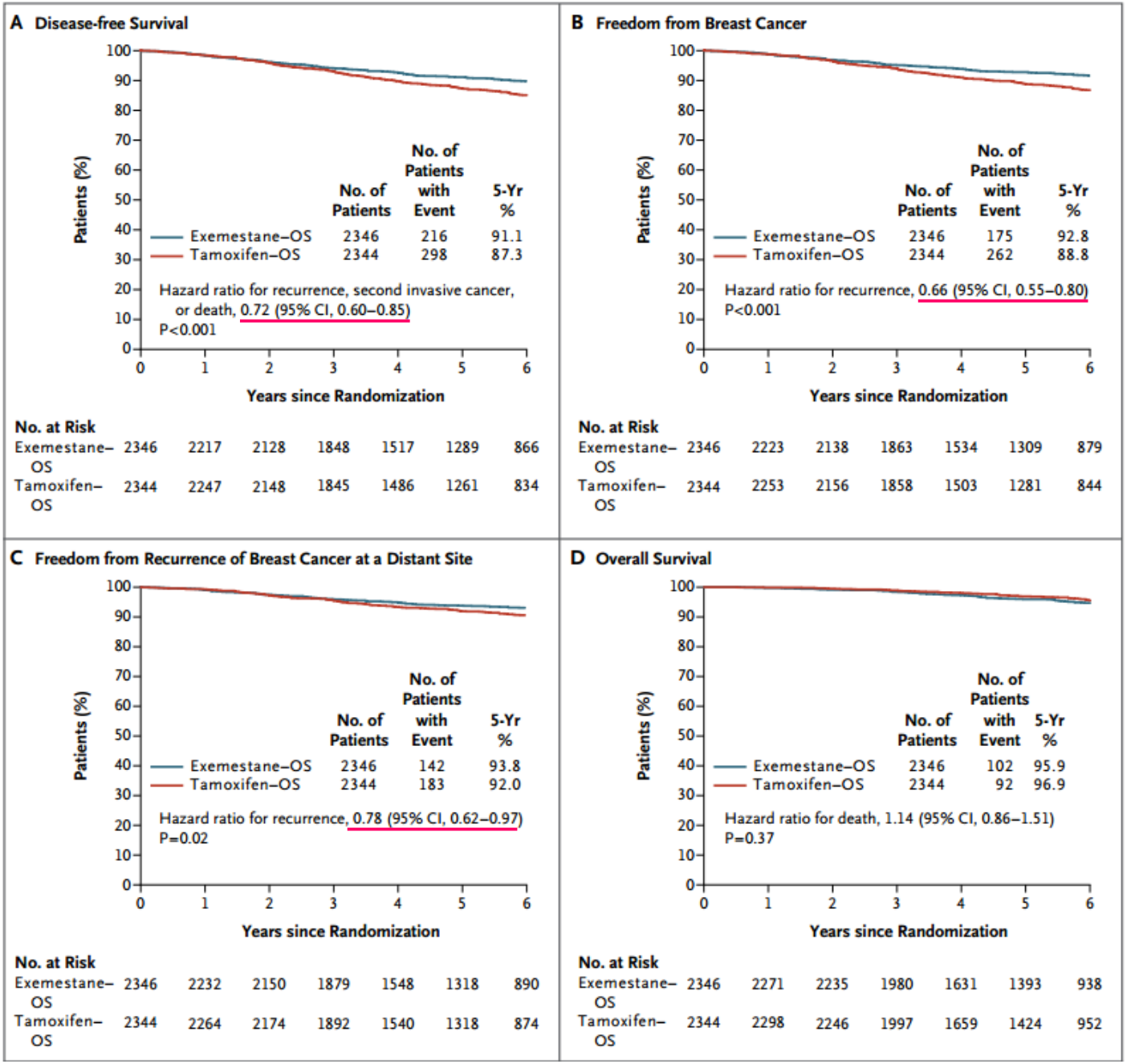
Pagani et al, NEJM, 2014

Table 1. Characteristics of Patients in TEXT and SOFT, Overall and According to Trial and Chemotherapy Stratum.*

Characteristic	No-Chemotherapy Cohorts		Chemotherapy Cohorts†		Overall (N=4690)
	TEXT (N=1053)	SOFT (N=943)	TEXT (N=1607)	SOFT (N=1087)	
Age at randomization — no. (%)					
<35 yr	41 (3.9)	14 (1.5)	191 (11.9)	224 (20.6)	470 (10.0)
35–39 yr	123 (11.7)	68 (7.2)	289 (18.0)	312 (28.7)	792 (16.9)
40–49 yr	768 (72.9)	690 (73.2)	1048 (65.2)	515 (47.4)	3021 (64.4)
≥50 yr	121 (11.5)	171 (18.1)	79 (4.9)	36 (3.3)	407 (8.7)
Lymph-node status — no. (%)					
Negative	835 (79.3)	865 (91.7)	542 (33.7)	470 (43.2)	2712 (57.8)
Positive	218 (20.7)	78 (8.3)	1065 (66.3)	617 (56.8)	1978 (42.2)
Tumor size — no. (%)‡					
≤2 cm	847 (80.4)	800 (84.8)	738 (45.9)	537 (49.4)	2922 (62.3)
>2 cm	203 (19.3)	139 (14.7)	844 (52.5)	508 (46.7)	1694 (36.1)
HER2 positive — no. (%)	54 (5.1)	30 (3.2)	272 (16.9)	211 (19.4)	567 (12.1)
Interval from surgery to randomization — mo					
Median	1.5	1.8	1.2	8.0	1.6
Interquartile range	1.1–1.9	1.3–2.4	0.9–1.6	5.7–10.1	1.1–2.7
Endocrine therapy before randomization — no. (%)§	—	44 (4.7)	—	453 (41.7)	—

Pagani et al, NEJM, 2014

Suivi =
68 mois



Pagani et al, NEJM, 2014

Subgroup	No. of Patients		No. of Patients with Event		Hazard Ratio (95% CI)	5-Yr Disease-free Survival (%)	
	Exemestane–OS	Tamoxifen–OS	Exemestane–OS	Tamoxifen–OS		Exemestane–OS	Tamoxifen–OS
All patients	2346	2344	216	298	0.72 (0.60–0.85)	91.1	87.3
Cohort							
No chemotherapy							
TEXT	526	527	22	40	0.54 (0.32–0.92)	96.1	93.0
SOFT	470	473	20	30	0.68 (0.38–1.19)	95.8	93.1
Chemotherapy							
TEXT	806	801	93	130	0.69 (0.53–0.90)	89.8	84.6
SOFT	544	543	81	98	0.84 (0.62–1.13)	84.3	80.6
Lymph-node status							
Negative	1362	1350	70	115	0.60 (0.45–0.81)	95.1	91.6
Positive	984	994	146	183	0.79 (0.64–0.98)	85.6	81.4

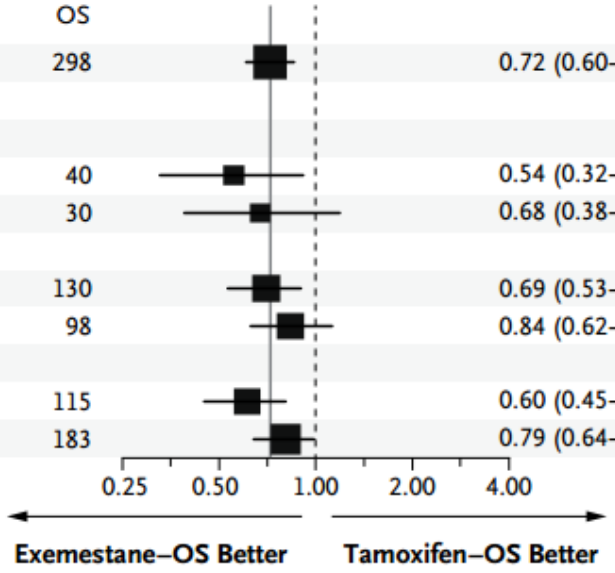


Figure 3. Results of the Cox Proportional-Hazards Model for the Comparison of Disease-free Survival, According to Treatment Group, among All Patients and According to Patient Cohort.

The solid vertical line at 0.72 indicates the overall hazard-ratio estimate. The x axis is scaled according to the natural logarithm of the hazard ratio. The size of the squares is inversely proportional to the standard error of the hazard ratio. Among patients who received chemotherapy, the patients in TEXT began receiving chemotherapy concurrently with adjuvant ovarian suppression with triptorelin, whereas those in SOFT had completed all chemotherapy before enrollment.

Pagani et al, NEJM, 2014

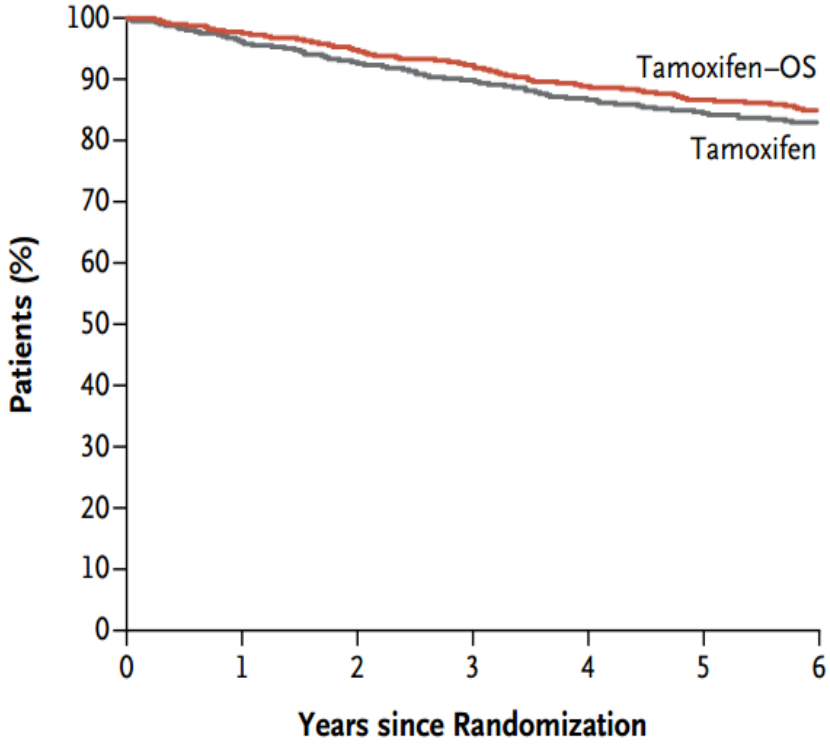
SOFT : intérêt du BO en association au tam ?

Table 1. Characteristics of Patients in the Primary Analysis, Overall and According to Chemotherapy Cohort.*

Characteristic	No Chemotherapy (N=949)	Prior Chemotherapy (N=1084)	Overall (N=2033)
Age at randomization			
Median — yr	46	40	43
Distribution — no. (%)			
<35 yr	14 (1.5)	219 (20.2)	233 (11.5)
35–39 yr	78 (8.2)	309 (28.5)	387 (19.0)
40–49 yr	702 (74.0)	522 (48.2)	1224 (60.2)
≥50 yr	155 (16.3)	34 (3.1)	189 (9.3)
Lymph-node status — no. (%)			
Negative	861 (90.7)	463 (42.7)	1324 (65.1)
Positive	88 (9.3)	621 (57.3)	709 (34.9)
Tumor size — no. (%)†			
≤2 cm	806 (84.9)	526 (48.5)	1332 (65.5)
>2 cm	136 (14.3)	513 (47.3)	649 (31.9)
Tumor grade — no. (%)‡			
1	389 (41.0)	151 (13.9)	540 (26.6)
2	483 (50.9)	523 (48.2)	1006 (49.5)
3	65 (6.8)	374 (34.5)	439 (21.6)
HER2-positive — no. (%)	40 (4.2)	196 (18.1)	236 (11.6)
Interval from surgery to randomization — mo			
Median	1.8	8.0	3.2
Interquartile range	1.2–2.4	5.8–10.3	1.7–8.33
Endocrine therapy before randomization — no. (%)§	47 (5.0)	475 (43.8)	522 (25.7)

Francis et al, NEJM, 2015

Disease-free Survival



No. at Risk							
Tamoxifen	1018	951	895	847	719	525	309
Tamoxifen–OS	1015	966	927	878	742	556	349

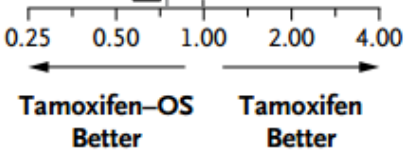
	No. of Patients	No. of Patients with Event	5-Yr Rate %
Tamoxifen	1018	160	84.7
Tamoxifen–OS	1015	139	86.6

Hazard ratio for recurrence, second invasive cancer, or death, 0.83 (95% CI, 0.66–1.04)
P=0.10

Francis et al, NEJM, 2015

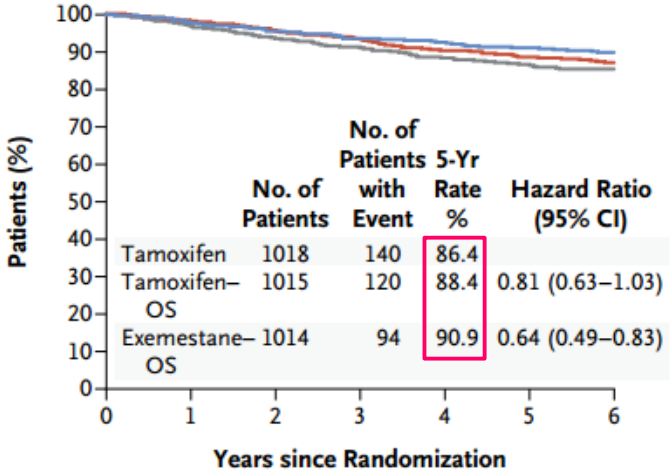
B **End Points, Overall and According to Chemotherapy Cohort**

End Point	No. of Patients		No. of Patients with Event		5-Yr Rate (%)		Hazard Ratio (95% CI)	P Value
	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen		
Disease-free survival								
All patients	1015	1018	139	160	86.6	84.7	0.83 (0.66–1.04)	0.10
Prior chemotherapy								
No	473	476	32	38	93.4	93.3	0.83 (0.52–1.34)	0.96
Yes	542	542	107	122	80.7	77.1	0.82 (0.64–1.07)	
Freedom from breast cancer								
All patients	1015	1018	120	140	88.4	86.4	0.81 (0.63–1.03)	0.09
Prior chemotherapy								
No	473	476	23	24	95.1	95.8	0.95 (0.54–1.69)	0.54
Yes	542	542	97	116	82.5	78.0	0.78 (0.60–1.02)	
Freedom from distant recurrence								
All patients	1015	1018	89	96	91.3	90.7	0.88 (0.66–1.18)	0.40
Prior chemotherapy								
No	473	476	7	6	98.7	98.6	1.16 (0.39–3.44)	0.62
Yes	542	542	82	90	84.8	83.6	0.87 (0.64–1.17)	
Overall survival								
All patients	1015	1018	47	59	96.7	95.1	0.74 (0.51–1.09)	0.13
Prior chemotherapy								
No	473	476	8	2	99.2	99.8	3.84 (0.81–18.08)	0.03
Yes	542	542	39	57	94.5	90.9	0.64 (0.42–0.96)	



Francis et al, NEJM, 2015

A Freedom from Breast Cancer

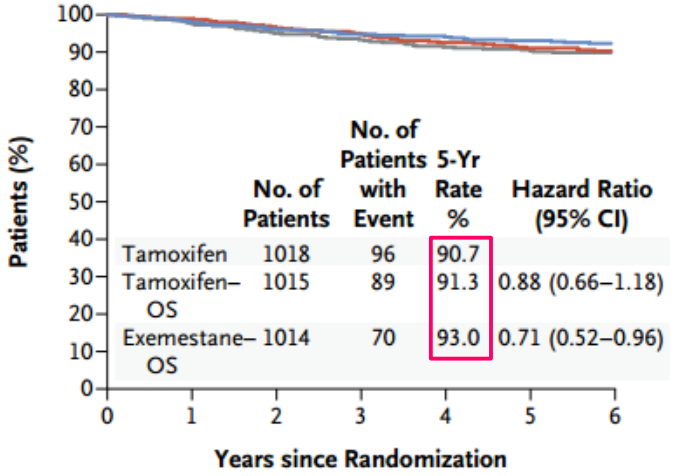


	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	1018	140	86.4	
Tamoxifen–OS	1015	120	88.4	0.81 (0.63–1.03)
Exemestane–OS	1014	94	90.9	0.64 (0.49–0.83)

No. at Risk

Tamoxifen	1018	956	900	855	728	533	314
Tamoxifen–OS	1015	970	932	886	752	568	356
Exemestane–OS	1014	957	912	869	766	550	342

B Freedom from Distant Recurrence

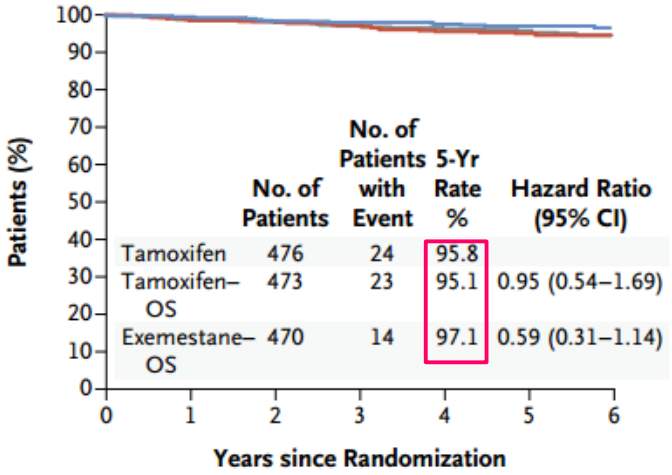


	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	1018	96	90.7	
Tamoxifen–OS	1015	89	91.3	0.88 (0.66–1.18)
Exemestane–OS	1014	70	93.0	0.71 (0.52–0.96)

No. at Risk

Tamoxifen	1018	966	915	875	755	559	333
Tamoxifen–OS	1015	977	943	901	772	582	363
Exemestane–OS	1014	962	920	882	783	562	352

C No Chemotherapy, Freedom from Breast Cancer

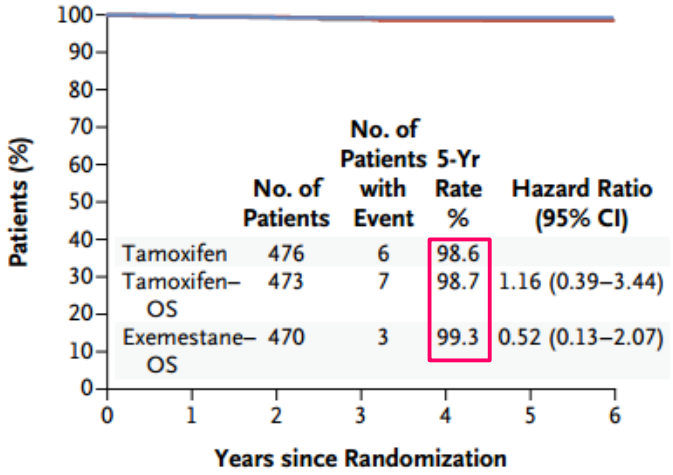


	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	476	24	95.8	
Tamoxifen–OS	473	23	95.1	0.95 (0.54–1.69)
Exemestane–OS	470	14	97.1	0.59 (0.31–1.14)

No. at Risk

Tamoxifen	476	461	445	429	377	277	169
Tamoxifen–OS	473	454	447	429	373	285	179
Exemestane–OS	470	443	425	414	374	278	176

D No Chemotherapy, Freedom from Distant Recurrence

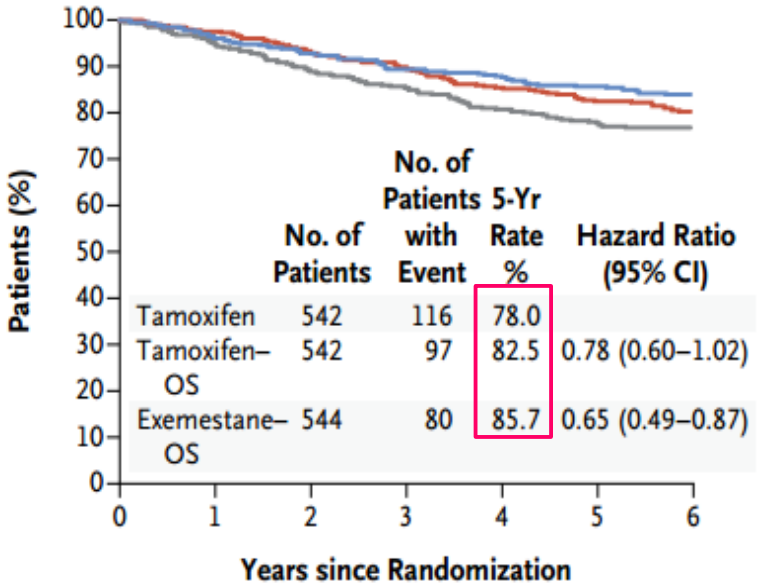


	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	476	6	98.6	
Tamoxifen–OS	473	7	98.7	1.16 (0.39–3.44)
Exemestane–OS	470	3	99.3	0.52 (0.13–2.07)

No. at Risk

Tamoxifen	476	465	449	436	386	284	176
Tamoxifen–OS	473	458	453	437	385	293	184
Exemestane–OS	470	444	429	419	381	283	180

E Prior Chemotherapy, Freedom from Breast Cancer

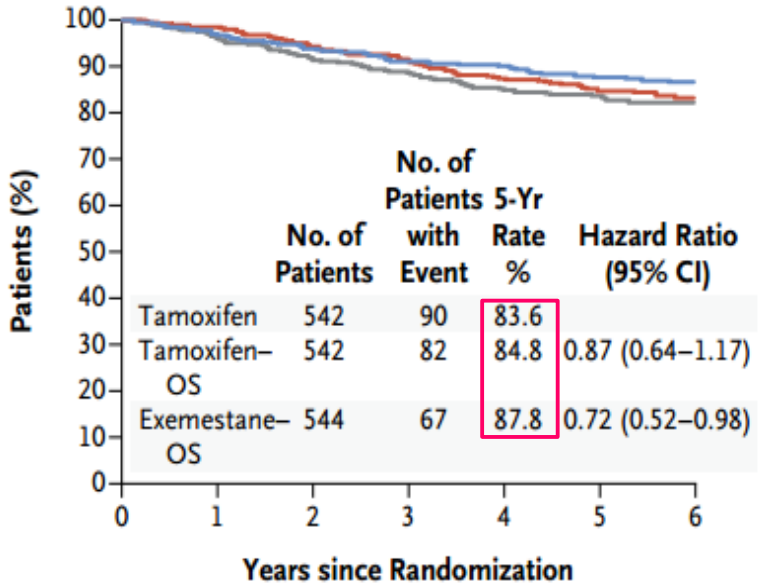


	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	542	116	78.0	
Tamoxifen–OS	542	97	82.5	0.78 (0.60–1.02)
Exemestane–OS	544	80	85.7	0.65 (0.49–0.87)

No. at Risk

Tamoxifen	542	494	455	426	352	255	144
Tamoxifen–OS	542	516	485	456	378	283	176
Exemestane–OS	544	514	487	455	391	273	166

F Prior Chemotherapy, Freedom from Distant Recurrence



	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	542	90	83.6	
Tamoxifen–OS	542	82	84.8	0.87 (0.64–1.17)
Exemestane–OS	544	67	87.8	0.72 (0.52–0.98)

No. at Risk

Tamoxifen	542	501	466	439	369	274	156
Tamoxifen–OS	542	519	490	463	386	289	178
Exemestane–OS	544	518	491	463	401	280	172

Francis et al, NEJM, 2015

SOFT

- **N=240** patients, RH+, HER2-, **<35 ans**
- **Survie sans cancer du sein à 5 ans** :
  - 67,1% (IC 95%, 54,6-76,9%) Tam
  - 75,9% (IC95%, 64,0-84,4%) tam + BO
  - **83,2%** (IC95%, 72,7-90,0%) exemestane + BO

TEXT

- **N=145** patients, RH+, HER2-, **< 35 ans**
- **Survie sans cancer du sein à 5 ans** :
  - 79,2% (IC 95%, 66,2-87,7%) tam + BO
  - **81,6%** (IC95%, 69,8-89,2%) exemestane + BO

Saha et al, JCO, 2017

Conclusions blocage ovarien

- ✓ ***Exemestane + BO :*** **Alternative recevable si CI Tamoxifène**
- ✓ ***HT + BO : à discuter si***
  - **Patiente très jeune**
  - **Risque élevé de rechute**
  - **Reprise cycles après chimiothérapie ?**
  - **Tolérance+++**
  - **Rapport bénéfice / risque**

- ✓ **Discussion Réunion Concertation Pluridisciplinaire ++**
- ✓ **Décision partagée+++**

- ***Prolonger la durée de l'hormonothérapie ne rend pas service à toutes les femmes***
  - ***A privilégier si N+ surtout***
  - ***Essais futurs : SSR objectif principal++, biomarqueurs, associations avec autres thérapies (inhibiteurs CDK4/6)***
- ***Ajouter un blocage de la fonction ovarienne ne rend pas service à toutes les femmes***
  - ***A privilégier si femmes très jeunes, reprise cycles, risque élevé de rechute***
- ***Rapport bénéfice / risque***