Les indications d'hormonothérapie prolongée

Séverine Guiu, Véronique D'Hondt, Gilles Romieu, William Jacot

Institut du Cancer de Montpellier – Val d'Aurelle

SFSPM Toulouse – Novembre 2014

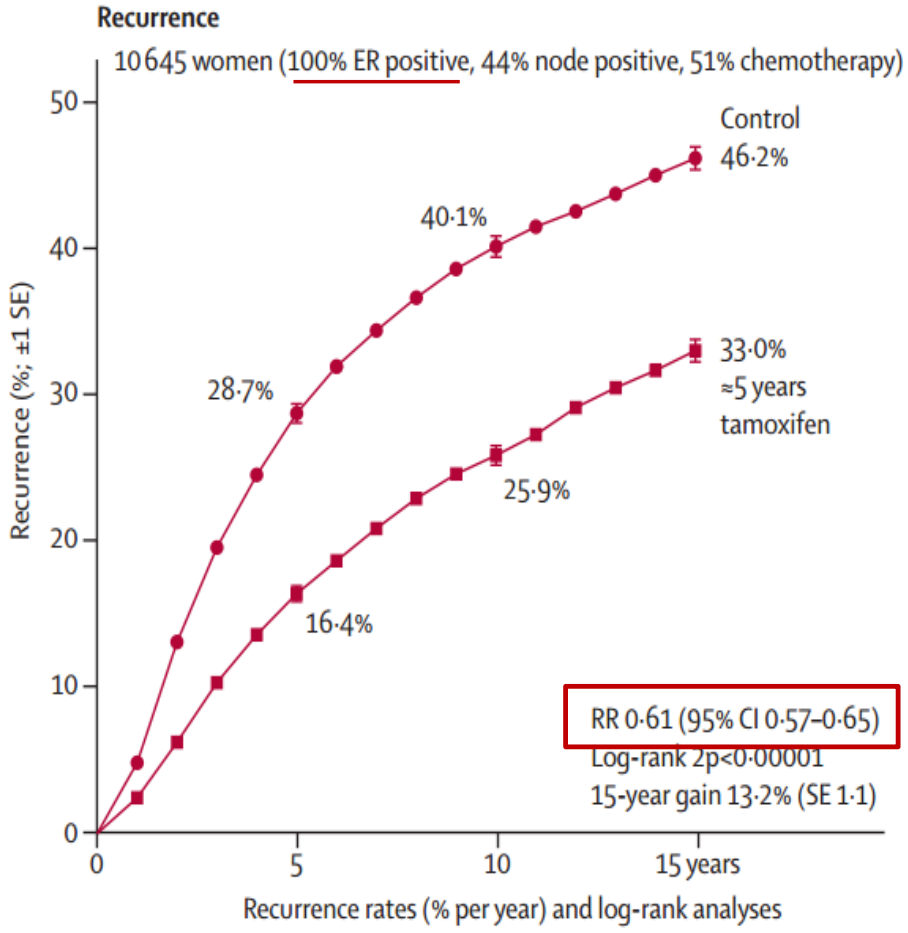
Conflits d’intérêt

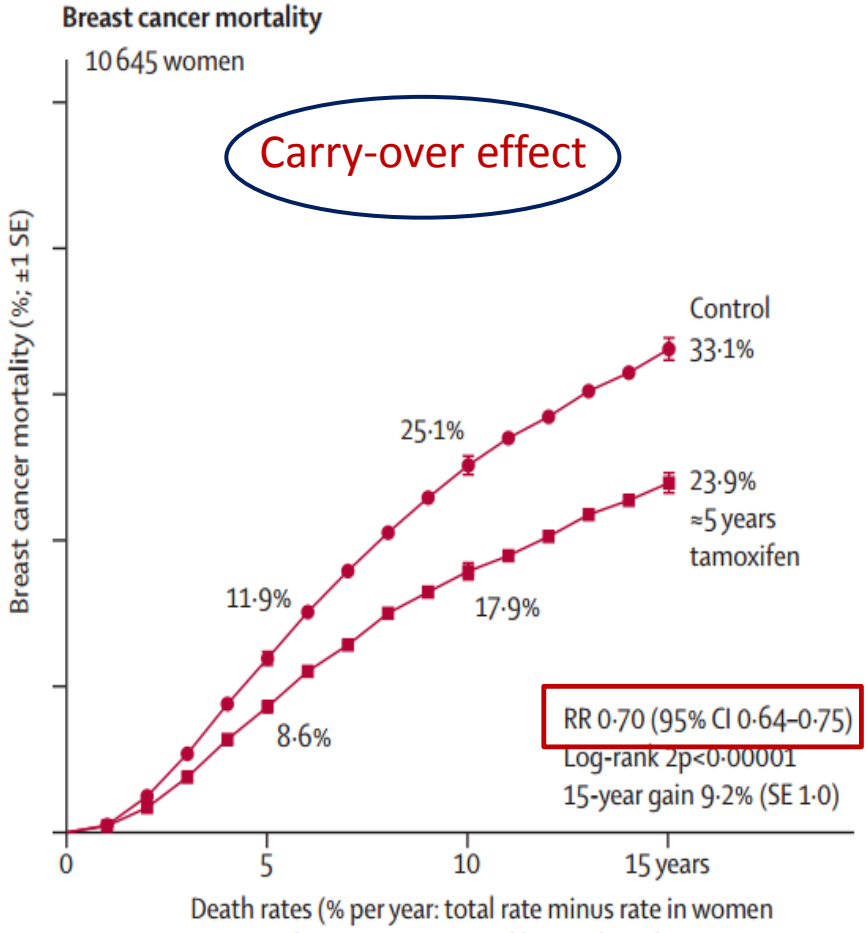
- Aucun

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

Bénéfices Tam au-delà de 5 ans

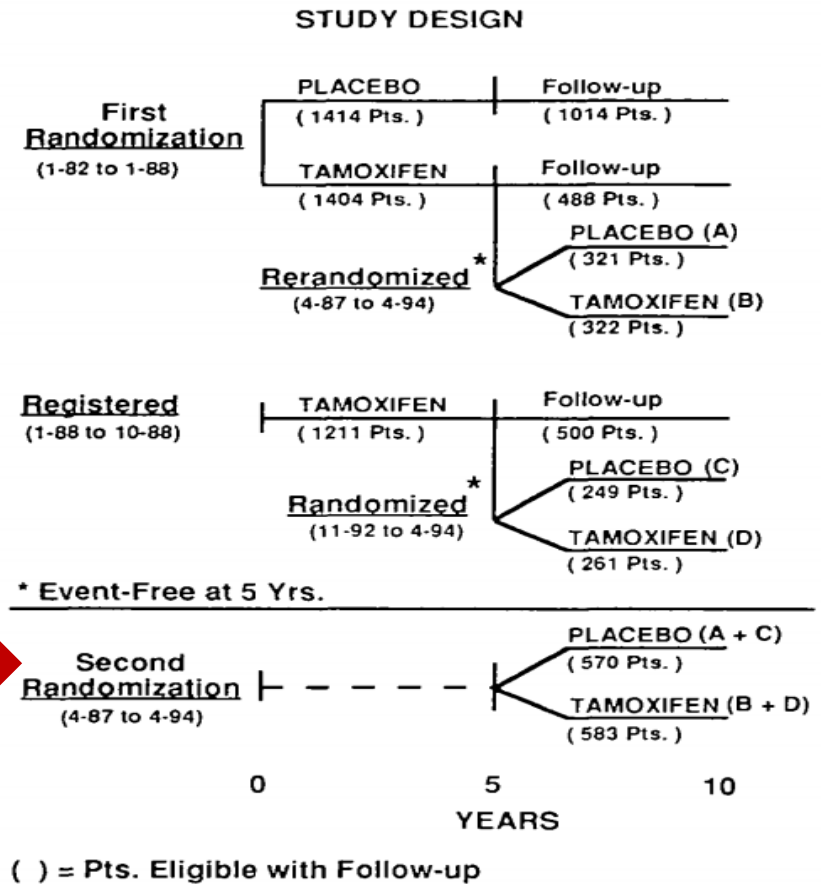
2 études Tam 5 ans vs jusqu'à progression ou décès

- **Torney et al, JNCI 1996**
  - N = 193, 72% ER+, **100% N+**, 100% CT adjuvante
  - Suivi médian = 5,6 ans ; durée médiane Tam = 9,3 ans
  - ↗ TTP chez ER+, pas différence de survie

- **Stewart et al, Scottish Adjuvant Tamoxifen Trial, BJC 1996 & JNCI 2001**
  - N = 342
  - Suivi médian = 10 ans, durée médiane Tam = 13,5 ans
  - Etude négative

Tam 5 ans versus 10 ans

NSABP B-14 (ER+, N0 uniquement)

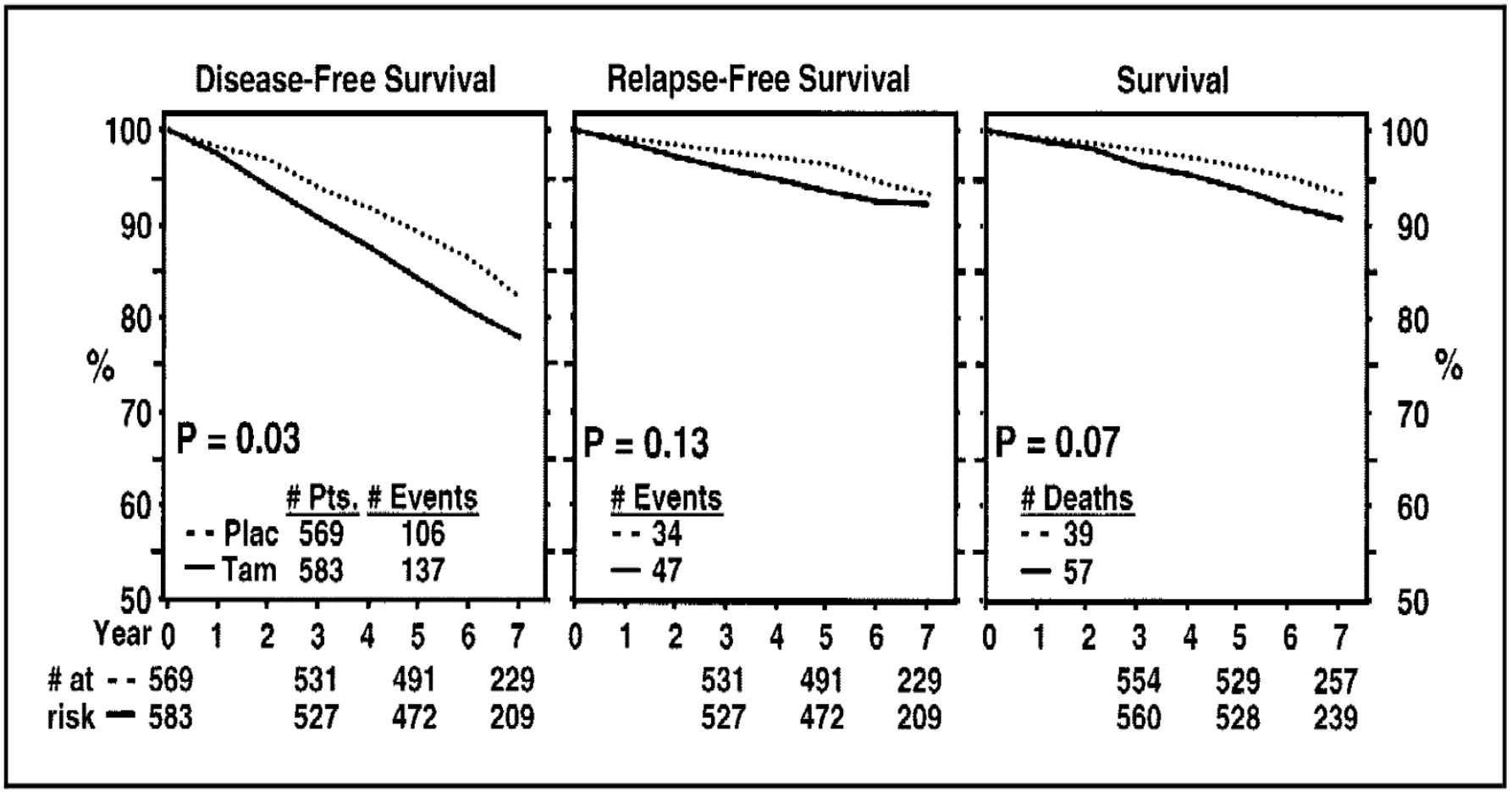


Characteristic*	Placebo, % (n = 569)	Tamoxifen, % (n = 583)
Age, y		
≤49	26	26
50–59	30	30
≥60	44	44
Mean ± standard deviation	56 ± 9	56 ± 10
Menopausal status		
Premenopausal/perimenopausal	25	27
Postmenopausal	74	73
Unknown	1	<1
Type of surgery		
Total mastectomy	56	56
Lumpectomy + XRT†	44	44
Clinical 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

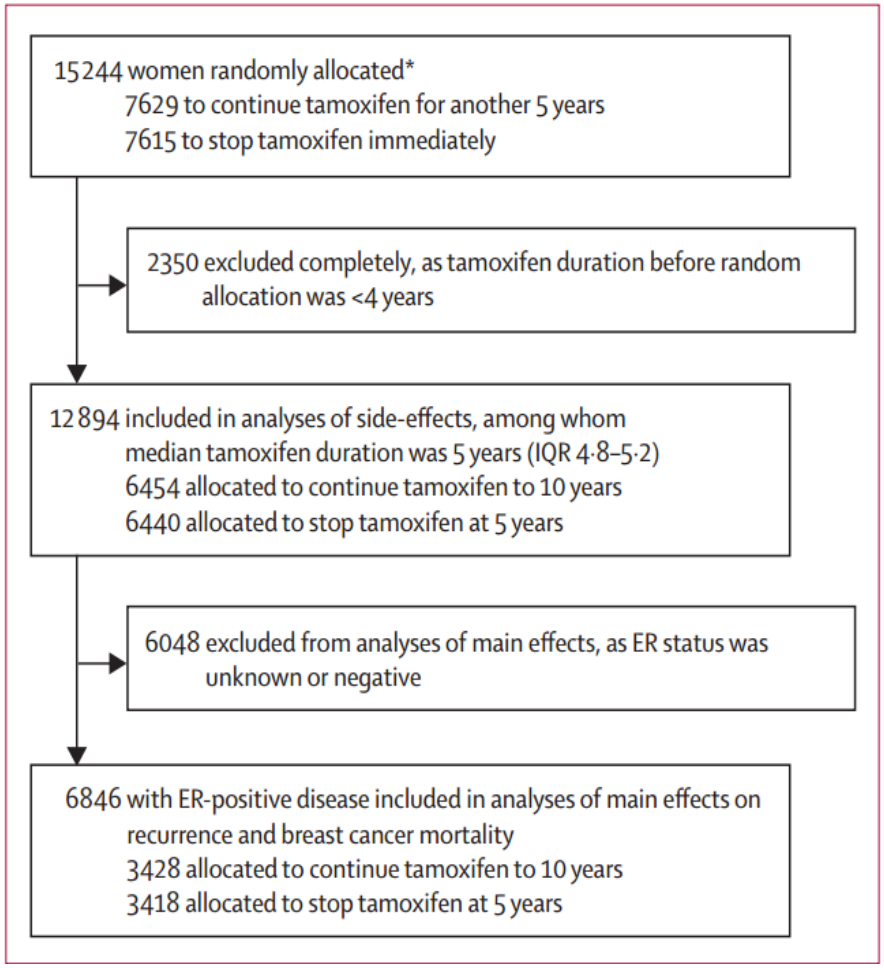
NSABP B-14 (ER+, N0 uniquement)



Fisher et al, JNCI 2001

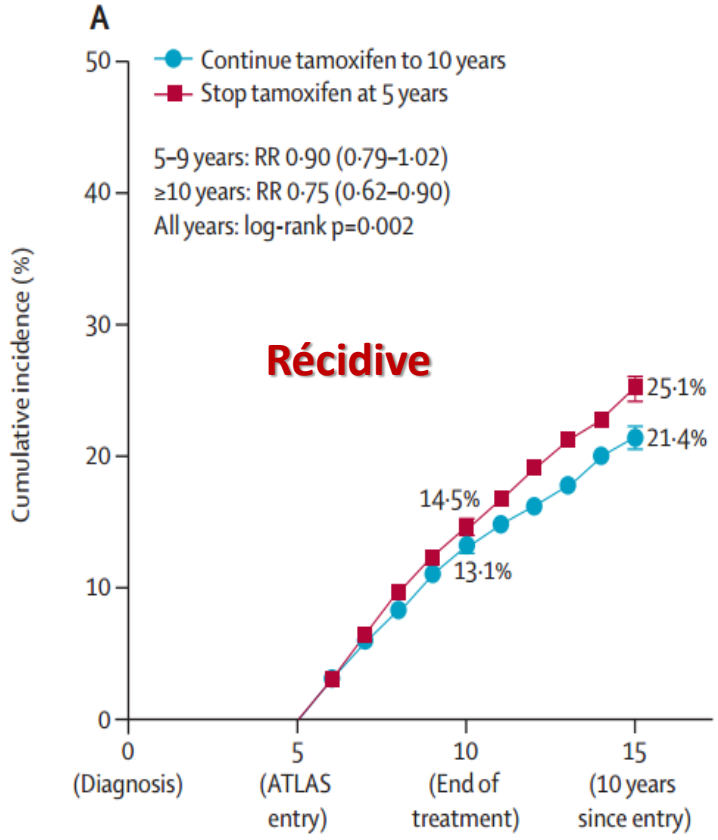
Tam 5 ans versus 10 ans

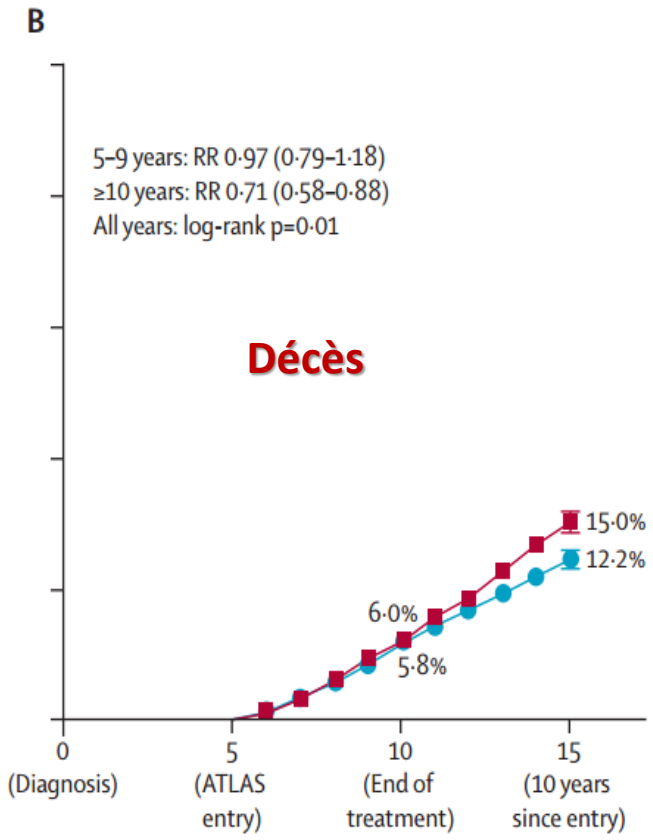
ATLAS (Adjuvant Tamoxifen: Longer Against Shorter)



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

Davies et al, Lancet 2013





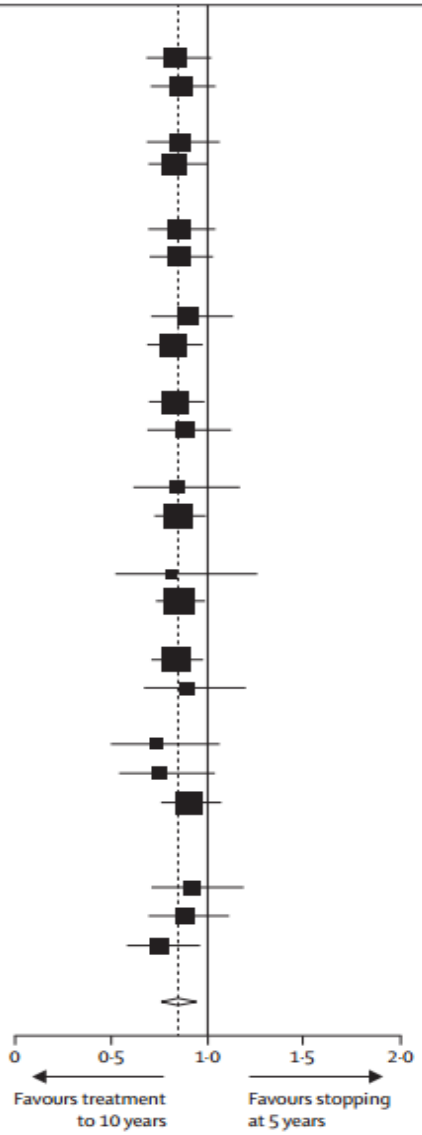
	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15115)	1·96% (165/8439)	2·54% (24/945)
Stop tamoxifen at 5 years	3·16% (471/14889)	2·66% (214/8038)	3·03% (26/859)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)
Log-rank O–E and variance V	–24·8/224·7	–29·1/94·7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

	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	–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

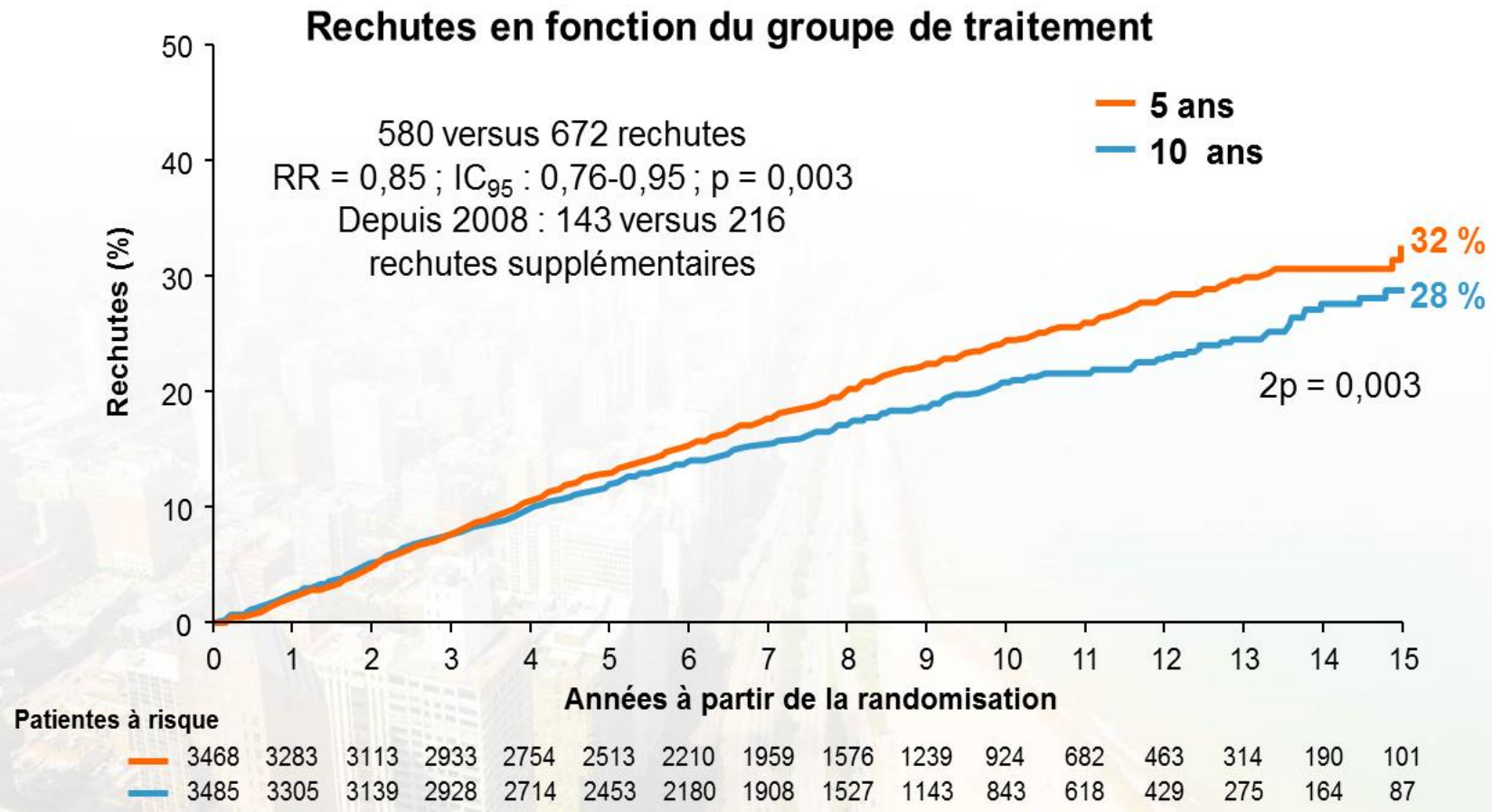
	Number of events		Log-rank O–E	Variance of O–E	Event rate ratio (95% CI)	p value*
	Continue tamoxifen to 10 years	Stop tamoxifen at 5 years				
Analyses of events without prior recurrence‡, any ER status						
Death without recurrence						
Vascular death						
Stroke	62	59	0·8	30·2	1·03 (0·72–1·46)	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

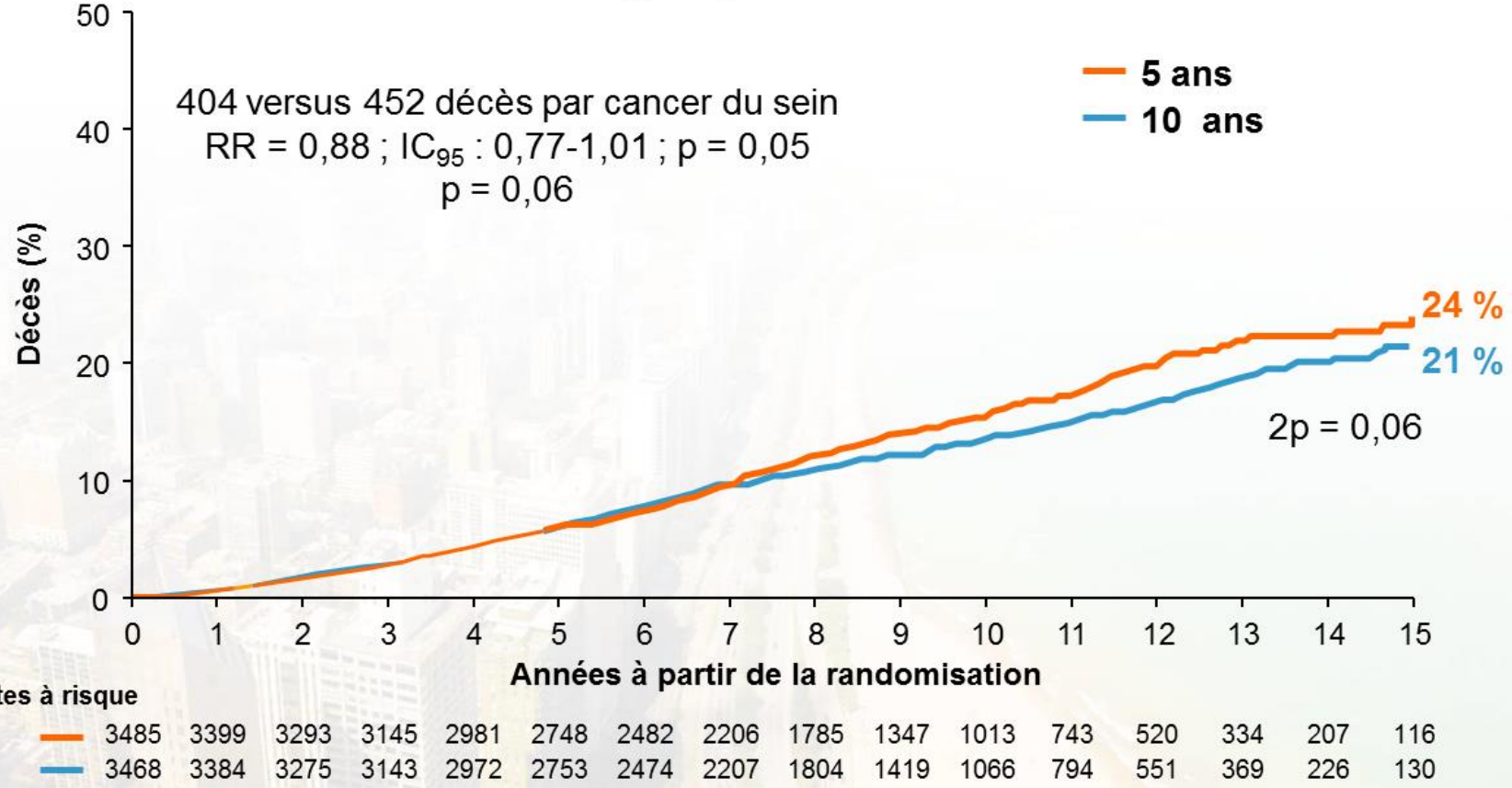
aTTom (Adjuvant Tamoxifen- To offer more? Trial)

N = 6 953, 61% statut RE inconnu



Gray et al, ASCO 2013

Décès par cancer du sein en fonction du groupe de traitement



Gray et al, ASCO 2013

aTTom (Adjuvant Tamoxifen- To offer more? Trial)

	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

Méta-analyse : Tam 5 ans versus >5 ans

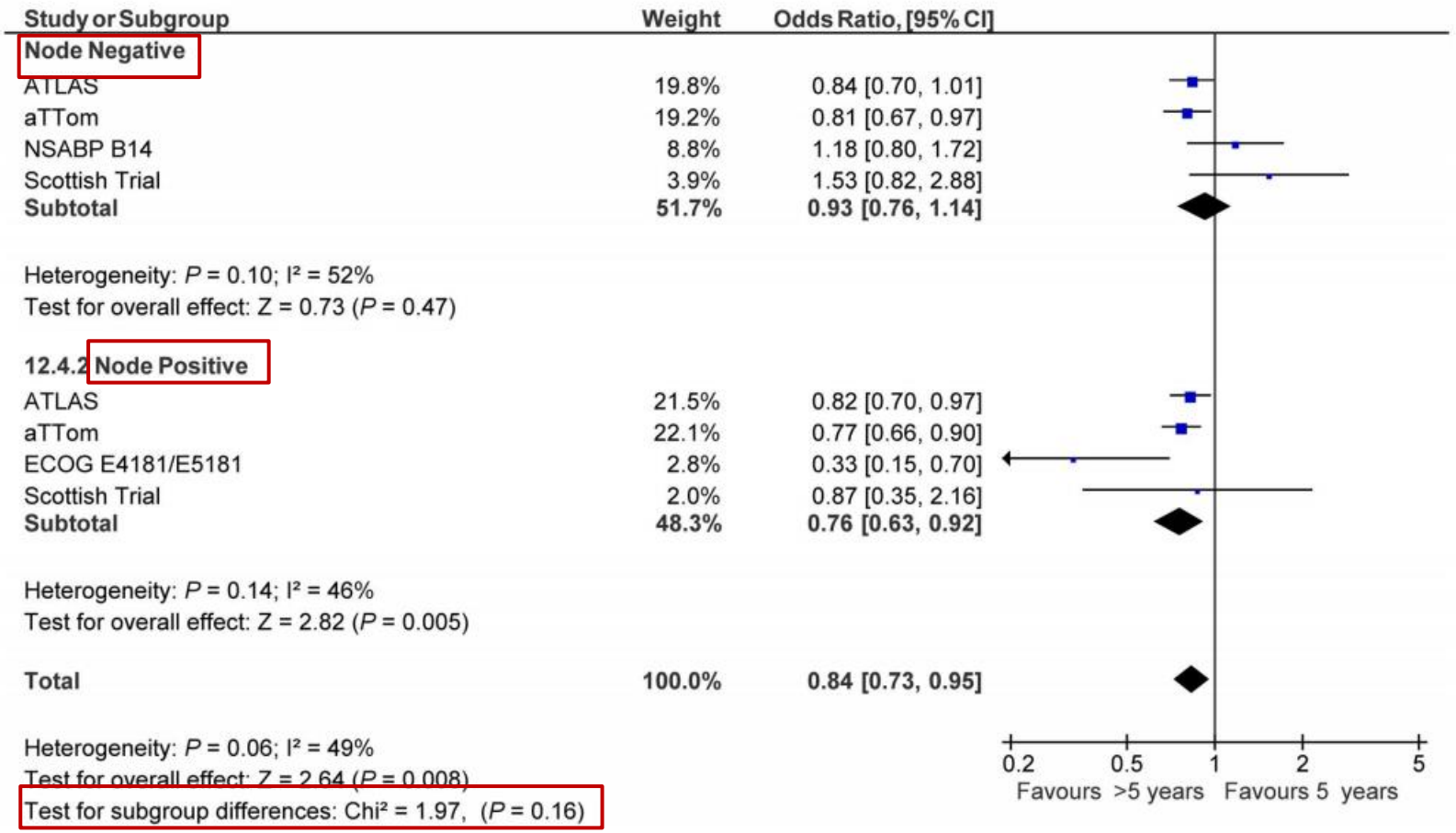


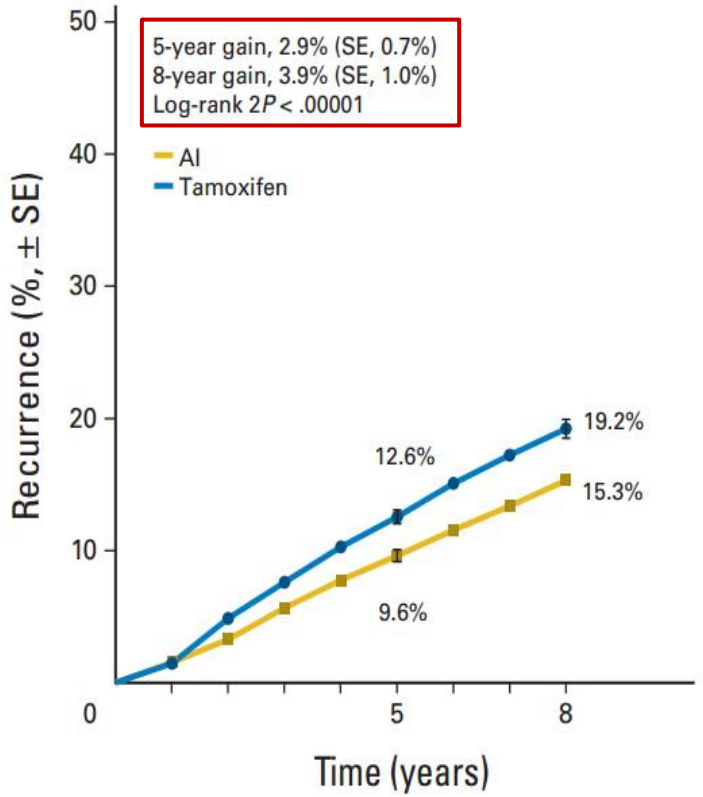
Figure 4. Forest plots of odds ratios for breast cancer recurrence in node negative and in node positive patients with extended adjuvant tamoxifen (>5 years) versus adjuvant tamoxifen (5 years) based on primary analysis of individual trials. Odds ratios for each trial are represented by the **squares**, 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).

Al-Mubarak et al, PLOS One 2014

Bénéfices des Inhibiteurs Aromatase

Cohorte 1 Tam 5 ans *vs* IA 5 ans, n=9856, suivi moyen=5,8 ans

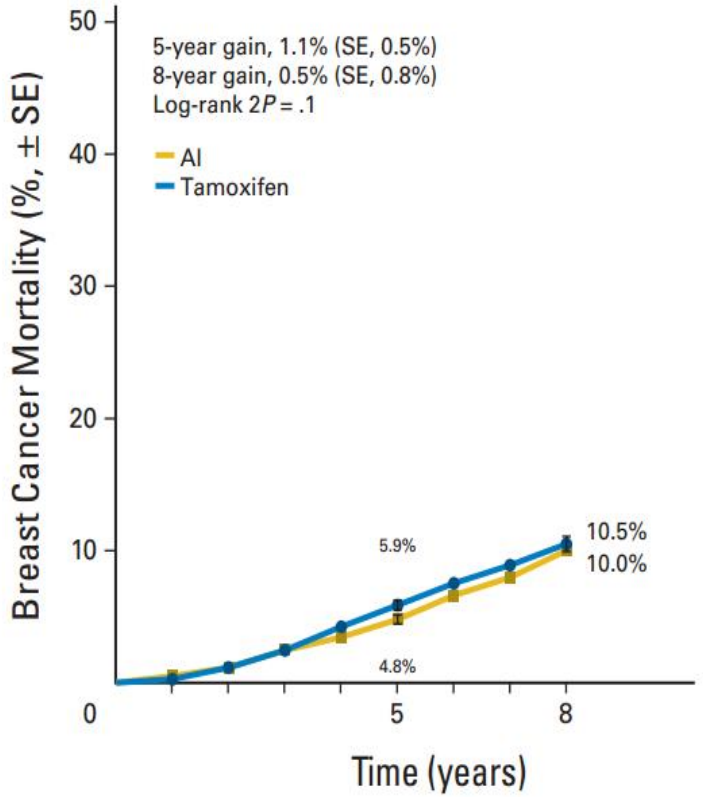
A



Recurrence rates (% / year) and log-rank analyses

	Years 0–1	Years 2–4	Years 5+
AI	1.69 (163 / 9,647)	2.31 (261 / 11,297)	2.33 (160 / 6,879)
Tamoxifen	2.46 (234 / 9,510)	2.81 (307 / 10,938)	2.78 (180 / 6,478)
Rate ratio, from	0.67 (SE, 0.08)	0.81 (SE, 0.08)	0.83 (SE, 0.10)
(O–E) / V	-38.4 / 96.6	-29.5 / 137.9	-15.7 / 83.0

B



Death rates (%/year: total rate—rate in women without recurrence) & log-rank analyses

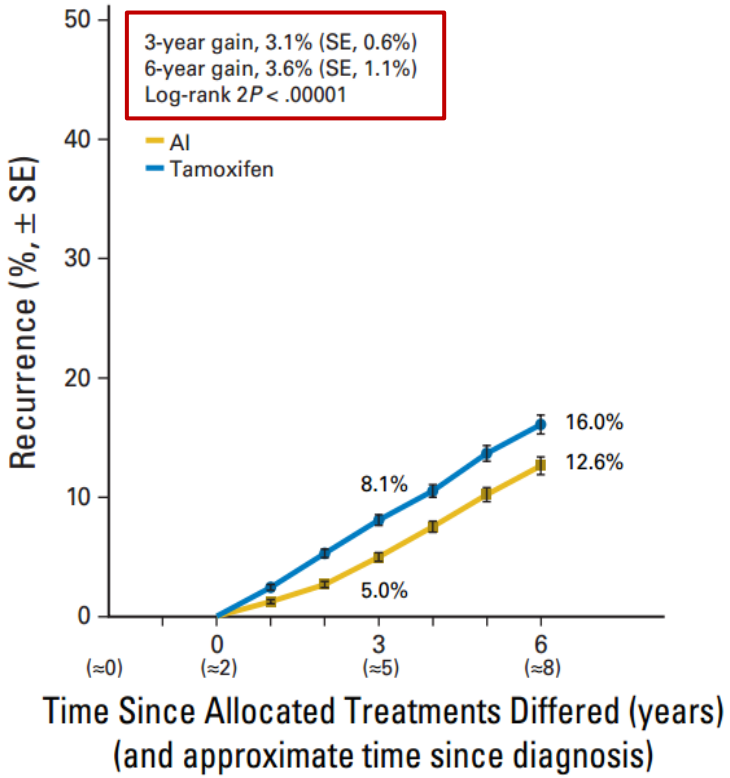
	Years 0–1	Years 2–4	Years 5+
AI	0.59 (SE, 0.08)	1.26 (SE, 0.10)	1.78 (SE, 0.16)
Tamoxifen	0.57 (SE, 0.08)	1.60 (SE, 0.12)	1.79 (SE, 0.16)
Rate ratio, from	1.01 (SE, 0.19)	0.77 (SE, 0.10)	1.01 (SE, 0.13)
(O–E) / V	0.2 / 27.5	-20.5 / 80.2	0.4 / 61.5

Dowsett et al, JCO 2010

Bénéfices des Inhibiteurs Aromatase

Cohorte 2 Tam 5 ans *vs* Tam 2-3 ans et IA 2-3 ans
n=9015, suivi moyen=3,9 ans

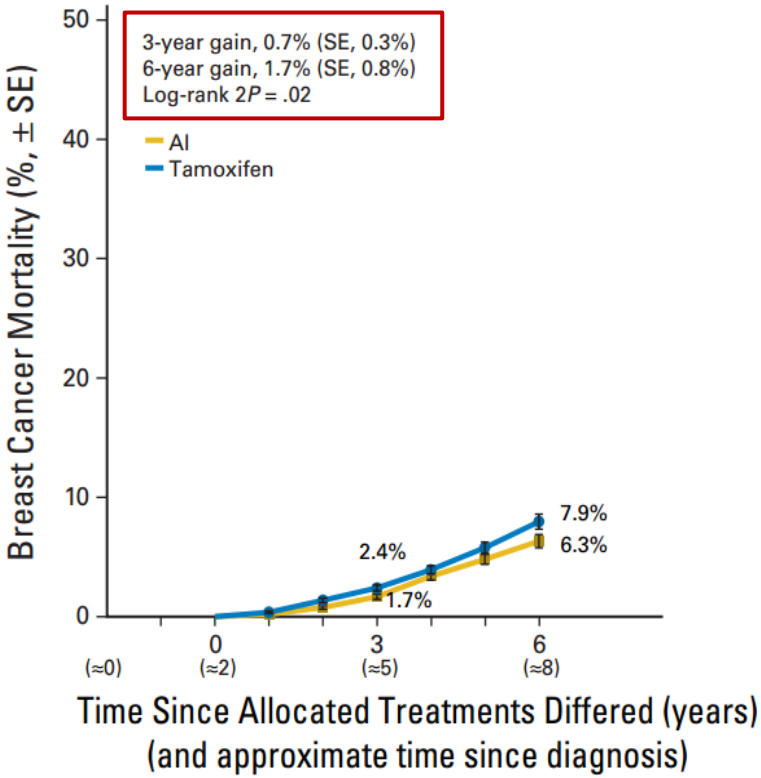
A



Recurrence rates (% / year) and log-rank analyses

	Years 0–2 (≈2–4)	Years 2–4 (≈5–7)	Years 5+ (≈8+)
AI	1.68 (187 / 11,134)	2.78 (147 / 5,298)	3.21 (23 / 716)
Tamoxifen	2.76 (303 / 10,962)	2.99 (149 / 5,007)	3.87 (27 / 697)
Rate ratio, from	0.60 (SE, 0.07)	0.92 (SE, 0.11)	0.85 (SE, 0.27)
(O–E) / V	-61.0 / 118.4	-6.0 / 71.9	-2.0 / 12.1

B



Death rates (%/year: total rate—rate in women without recurrence) & log-rank analyses

	Years 0–2 (≈2–4)	Years 2–4 (≈5–7)	Years 5+ (≈8+)
AI	0.54 (SE, 0.07)	1.60 (SE, 0.17)	1.17 (SE, 0.39)
Tamoxifen	0.79 (SE, 0.08)	1.83 (SE, 0.18)	1.80 (SE, 0.48)
Rate ratio, from	0.68 (SE, 0.14)	0.88 (SE, 0.14)	0.65 (SE, 0.34)
(O–E) / V	-13.9 / 36.5	-5.8 / 45.5	-2.5 / 5.7

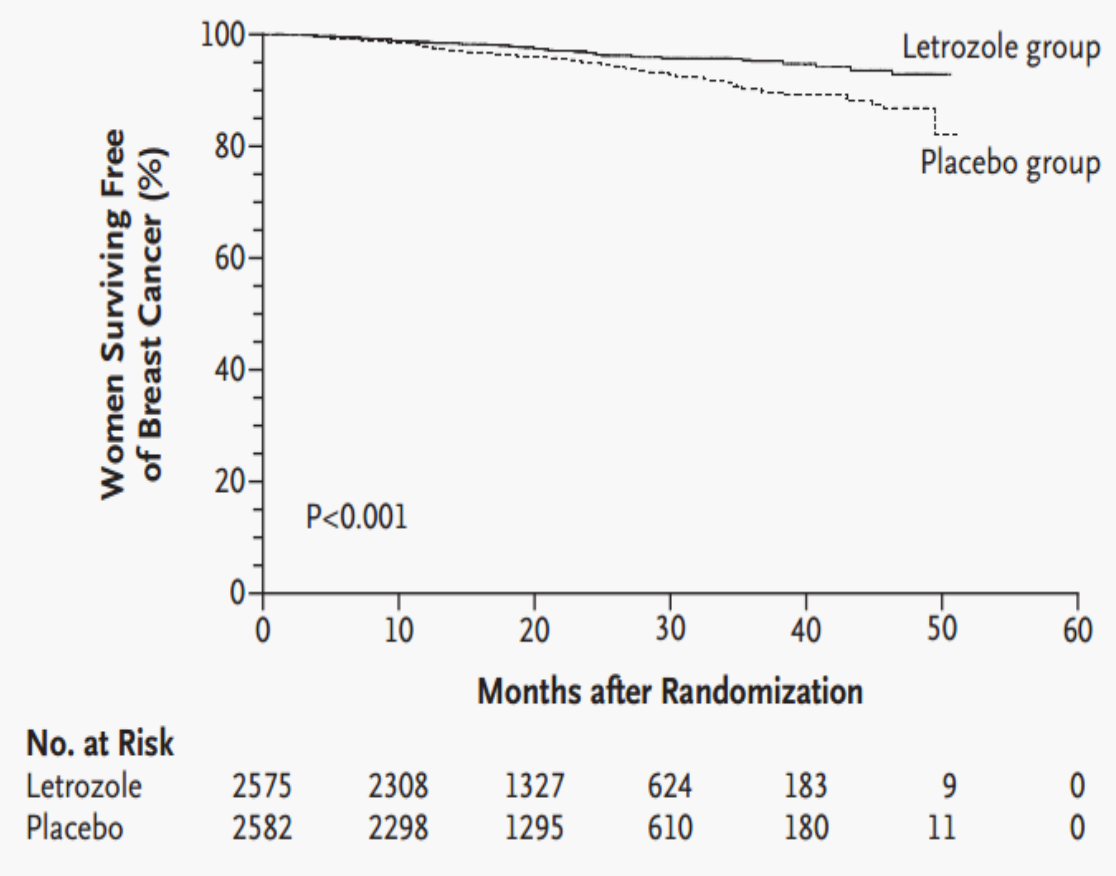
Dowsett et al, JCO 2010

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

Bénéfices IA > 5 ans TAM : MA-17

1ère analyse intermédiaire → STOP étude

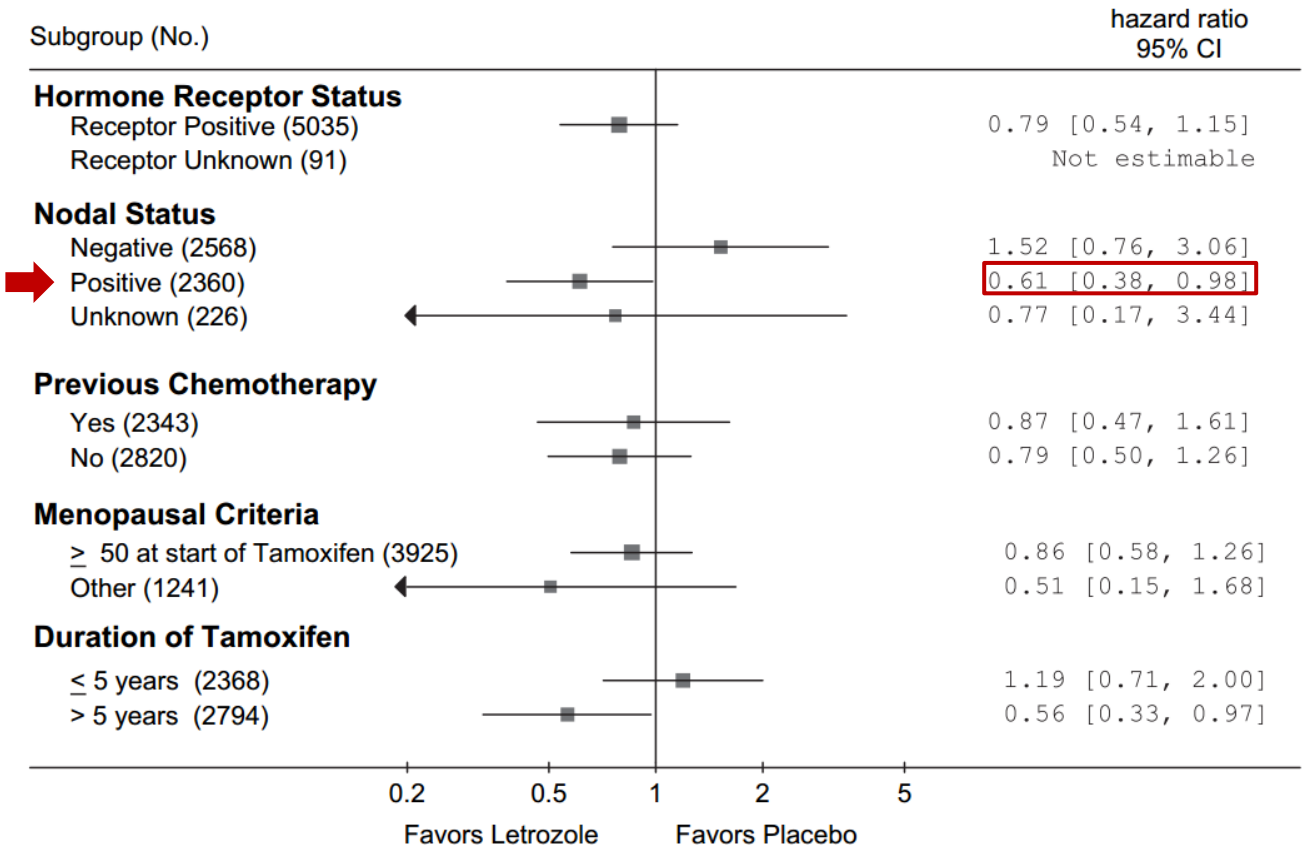


- ✓ **Taux SSM 4 ans** : **93% *vs* 87%**
  HR=0.57 (IC95% 0.43-0.75)
- ✓ Chez N0 et N+
- ✓ Pas de différence en survie globale

Goss et al, NEJM 2003

Bénéfices IA > 5 ans TAM : MA-17

Survie globale : Analyse en sous groupe



Goss et al, JNCI 2005

Bénéfices IA > 5 ans TAM : MA-17

***Cross-over :* 61%**

Ingle et al, Ann Oncol 2008 : analyse en ITT > suivi médian de 64 mois

→ Amélioration significative de la SSM mais pas de la SSM à distance ni de la SG

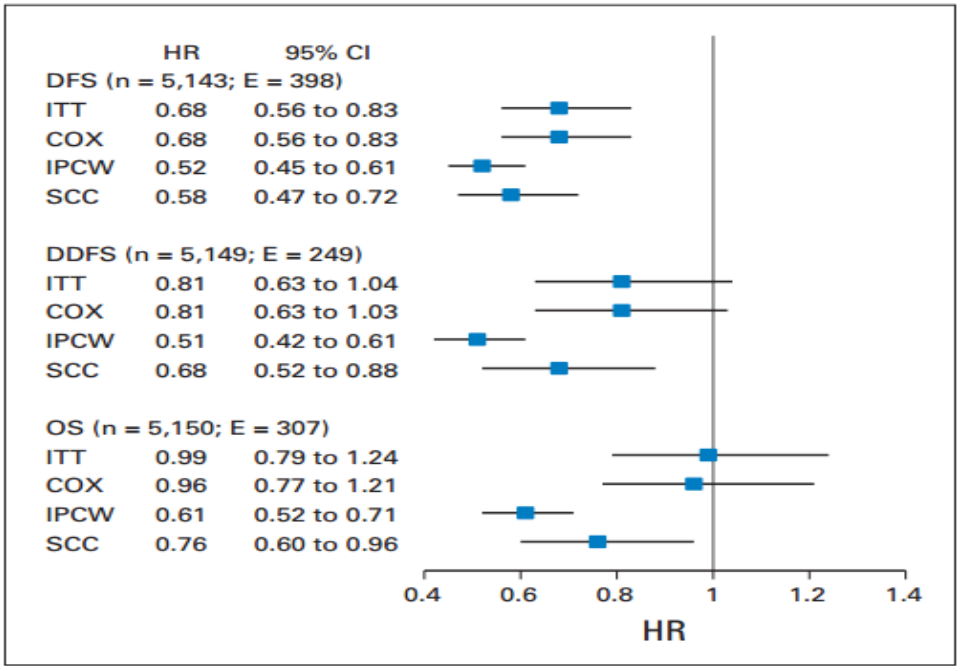


Fig 1. Hazard ratios (HRs) and 95% CIs for letrozole versus placebo for all women randomly assigned in the National Cancer Institute of Canada Clinical Trials Group MA.17 study. Inverse probability of censoring weighted (IPCW) analyses excluded 34 disease-free survival (DFS), 19 distant disease-free survival (DDFS), and 21 overall survival (OS) events observed after the crossover. COX, Cox proportional hazard model; E, number of events; ITT, intent to treat; SCC, approach proposed by Shao, Chang, and Chow.[12].

Jin et al, JCO 2012

Bénéfices IA > 5 ans TAM

- ***Exemestane*** *(NSABP B-33, Mamounas et al, JCO 2008)*
  - 5 ans, N = 1598 (/3000 prévus), 50% N0
  - Suivi médian = 30 mois, ↕ résultats MA-17, cross over 44%
  - Pas d'↗ significative SSM (obj principal) ni SG
  - Amélioration taux SSR à 4 ans : 96% *vs* 94%, HR=0.44 (IC95%?), p=0.004
  - Analyse exploratoire : <60 ans, T>2cm, N+

- ***Anastrozole*** *(ABCSG 6a, Jakesz et al, JNCI 2007)*
  - 3 ans, N = 856 (/1700), 67% N0
  - Suivi médian = 62,3 mois
  - ↘ risque de récidive [HR=0.62 (IC95% 0.40-0.96, p=0.031)]
  - Pas de différence en SG

Recommandations actuelles

- ***ASCO*** *(Burstein et al, JCO 2014)*
  - *Pré-ménopause* : poursuite Tam 10 ans ou switch IA (10 ans) si ménopause
  - *Ménopause* : Tam 10 ans / IA 5 ans / Tam 5 ans puis IA 5 ans / Tam 2-3 ans puis IA 5 ans

- ***ESMO*** *(Senkus et al, Ann Oncol 2013)*
  - *Pré-ménopause* : Tam 5 à 10 ans, switch IA si ménopause
  - *Ménopause* : Tam et/ou IA; discuter prolongation HT excepté chez les patientes à très faible risque

- ***St Gallen*** *(Untch et al, Breast Care 2013)*
  - *Pré-ménopause* : Tam 10 ans à discuter si bonne tolérance et risque de récidive augmenté (ex N+)
  - *Ménopause* : à discuter ; Tam 5 ans puis IA si N+, Tam 2-3 ans puis IA 5 ans, Tam 10 ans si CI IA et risque élevé de récidive

Avenir????

- ***Distinguer les patientes à haut risque de récidive tardive***
  - Signatures génomiques
    - Oncotype, Grade génomique, PAM50 *(Bianchini et al, BCR 2013)*
    - Endopredict *(Dubsky et al, BJC 2013)*
    - Breast Cancer Index *(Sgroi et al, Lancet Oncol 2013)*
    - PAM50 (ROR score) *(Sestak et al, JCO 2014)*
  - BMI & IA *(Gnant et al, BJC 2013)*

- ***Etudes en cours***

  MA-17R extension trial : letrozole *vs* placebo > IA 5 ans

Conclusions

- ***Après 5 ans de Tam*** : **stop** / **Tam** / **IA**
- ***Après 5 ans IA*** : **stop** / IA ? (pas de données) / **Tam** ? (**avis d'experts**)

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

- **Discussion RCP++**

- **Décision partagée+++**