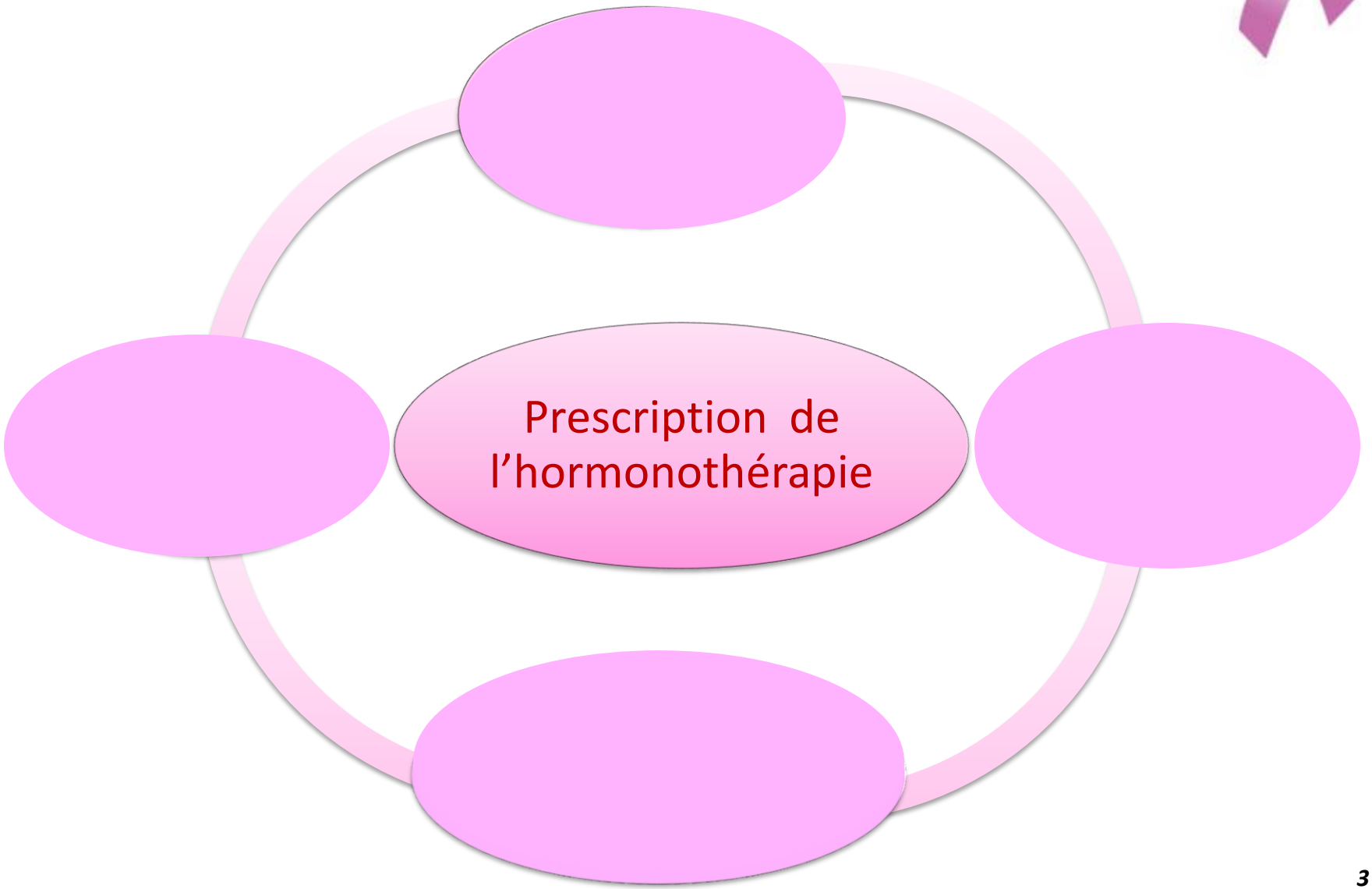
Hormonothérapie adjuvante dans les cancers du sein de la femme préménopausée

Pr Nabil TOUMI,
Service carcinologie médicale
CHU Habib Bourguiba Sfax

Introduction

- 1er cancer de la femme
- Maladie complexe:
  - * clinique,
  - * histologique,
  - * moléculaire.
- K luminaux: 60-70% des cas
- K femme préménopausée de plus en plus fréquent

K sein de la femme préménopausée: Critères décisionnels



K sein de la femme préménopausée: Hormonosensibilité

Annals of Oncology 30: 1194–1220, 2019
doi:10.1093/annonc/mdz173
Published online 4 June 2019

SPECIAL ARTICLE

Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Table 4. Summary of biomarkers used in treatment decision making

Biomarker	Method	Use	LoE	GoR
ER	IHC Positive if ≥1%	Essential to the characterisation of the IHC luminal-like group Poor prognostic marker if negative Predictive marker for ET Mandatory for ET prescription	I	A
PgR	IHC Positive if ≥1%	If negative tumour classified as IHC luminal B-like Strong poor prognostic marker if negative Predictive marker for ET	I	A

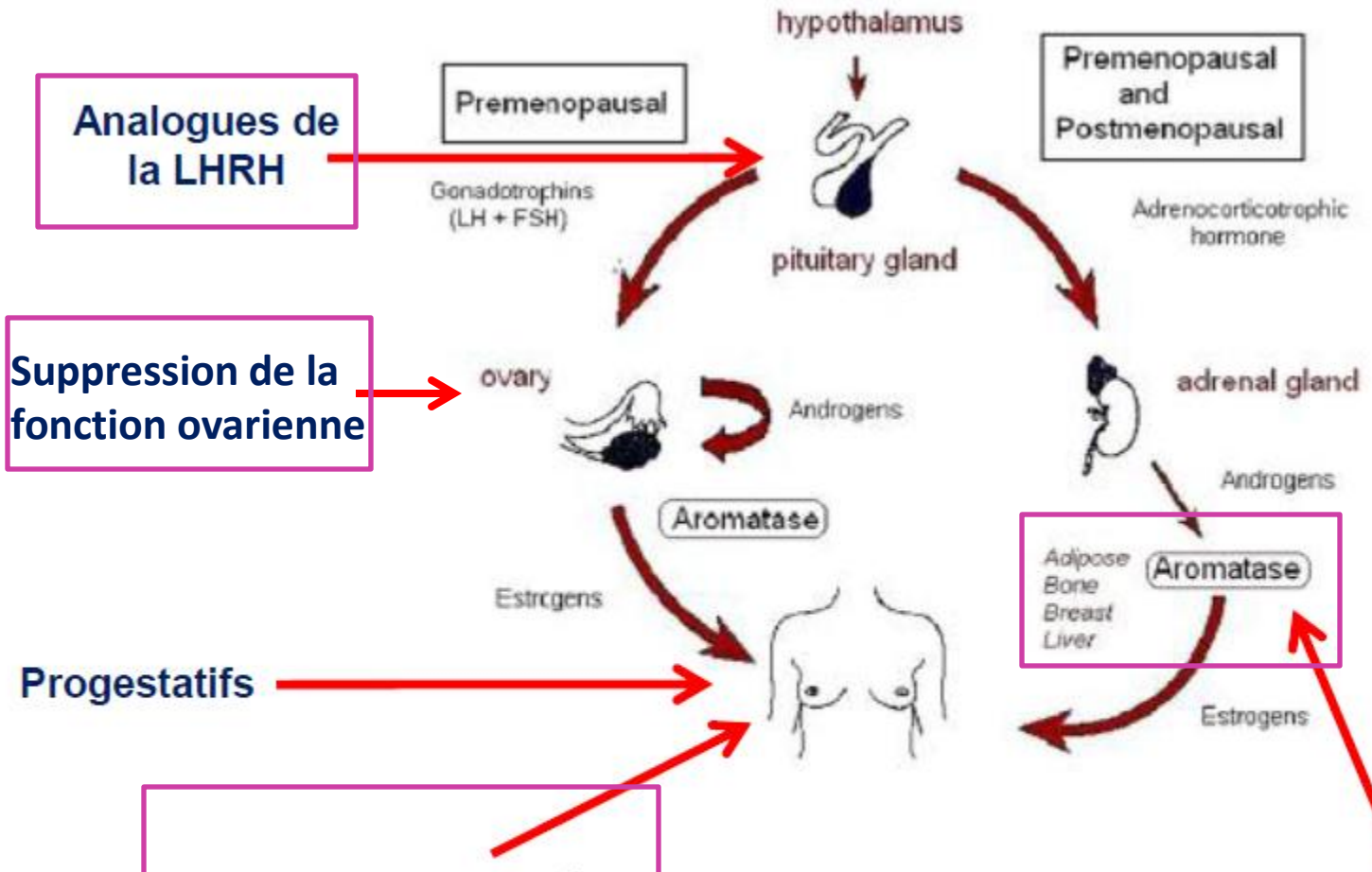
K sein de la femme préménopausée: Hormonosensibilité

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Recommendations

The Panel recommends that ER and PgR status be determined on all invasive breast cancers and breast cancer recurrences. A testing algorithm that relies on accurate, reproducible assay performance is proposed. Elements to reliably reduce assay variation are specified. It is recommended that ER and PgR assays be considered positive if there are at least 1% positive tumor nuclei in the sample on testing in the presence of expected reactivity of internal (normal epithelial elements) and external controls. The absence of benefit from endocrine therapy for women with ER-negative invasive breast cancers has been confirmed in large overviews of randomized clinical trials. This guideline was developed through a collaboration between American Society of Clinical Oncology and College of American Pathologists and has been published jointly by invitation and consent in both the Journal of Clinical Oncology and the Archives of Pathology & Laboratory Medicine.

Hormonothérapie dans le K du sein



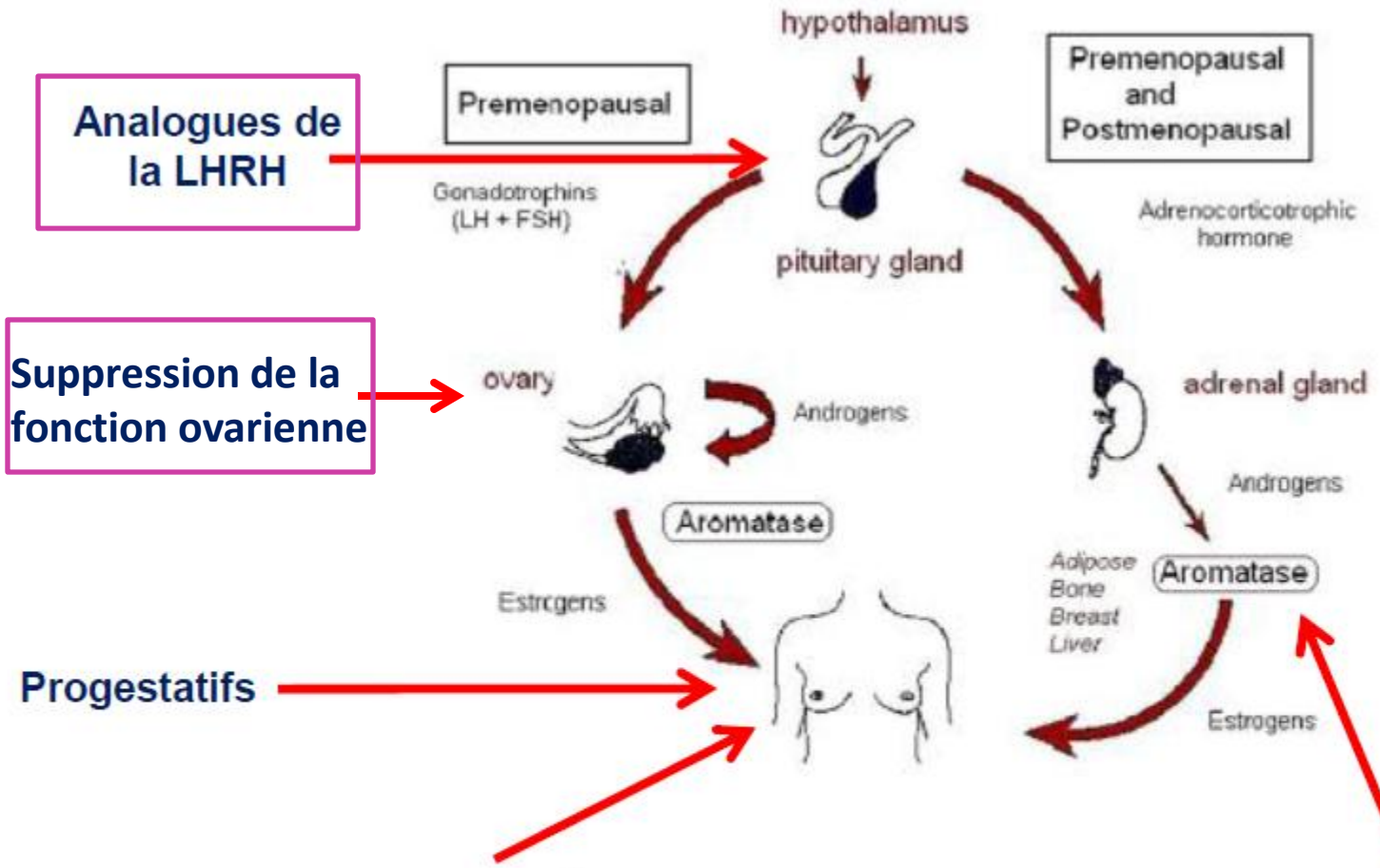
SERM = **Anti-oestrogènes**

Selective Estrogen Receptor Modulators

- 35 ans d'utilisation
- Standard

Déplétion en oestrogènes au mieux réalisée par une **inhibition spécifique de l'aromatase** qui convertit les précurseurs des oestrogènes en oestradiol et oestrone

Hormonothérapie dans le K du sein



SERM = **Anti-oestrogènes**

Selective Estrogen Receptor Modulators

- 35 ans d'utilisation
- Standard

Déplétion en oestrogènes au mieux réalisée par une **inhibition spécifique de l'aromatase** qui convertit les précurseurs des oestrogènes en oestradiol et oestrone

Hormonothérapie par ablation ou suppression ovarienne

- Traitement ciblé “pionnier”
  - 20 mai 1896 Edinburgh
    - Sir George Thomas Beatson (1848-1933) ouvre la voie de l’hormonothérapie en démontrant l’efficacité de l’ovariectomie bilatérale sur les cancers du sein métastatiques

Classics in Oncology

On The Treatment of Inoperable Cases of Carcinoma of the Mamma: Suggestions for a New Method of Treatment, with Illustrative Cases

George Thomas Beatson, M.D.

Apsley-place, May 6th, 1895
Dear Dr. Beatson, The bearer is, and has been, suffering, I fear, from a malignant breast. She has been in the Royal Infirmary before she came to me. My own opinion is that nothing can be done for her, but as she is a woman of great courage you might have a look at it for my sake, and perhaps you can order her something in the way of dressing. Even this little will be accepted by her as a great deal. With kindest regards,
yours very truly,
James W. Wallace

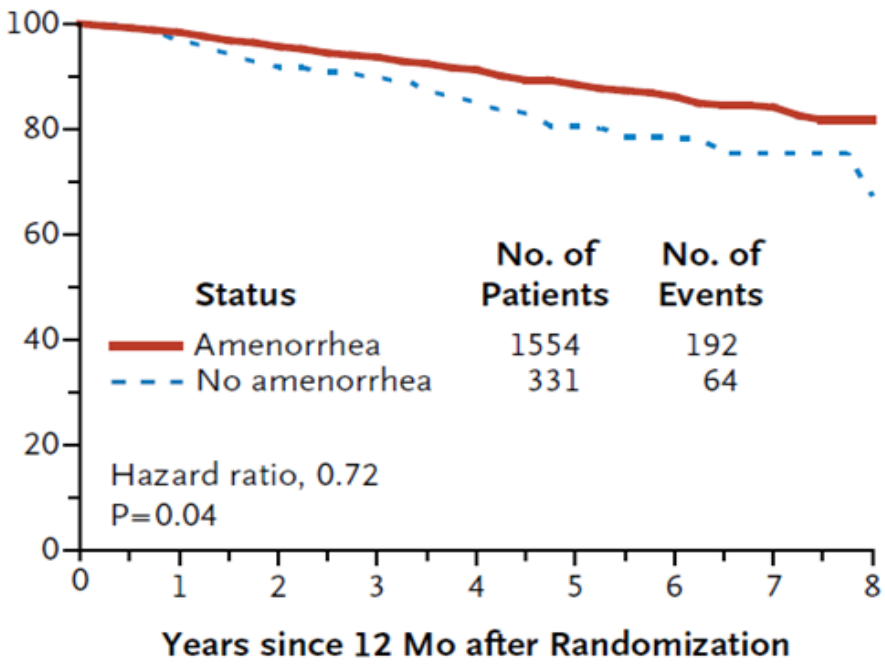
Beatson. Lancet 1896

Hormonothérapie par ablation ou suppression ovarienne

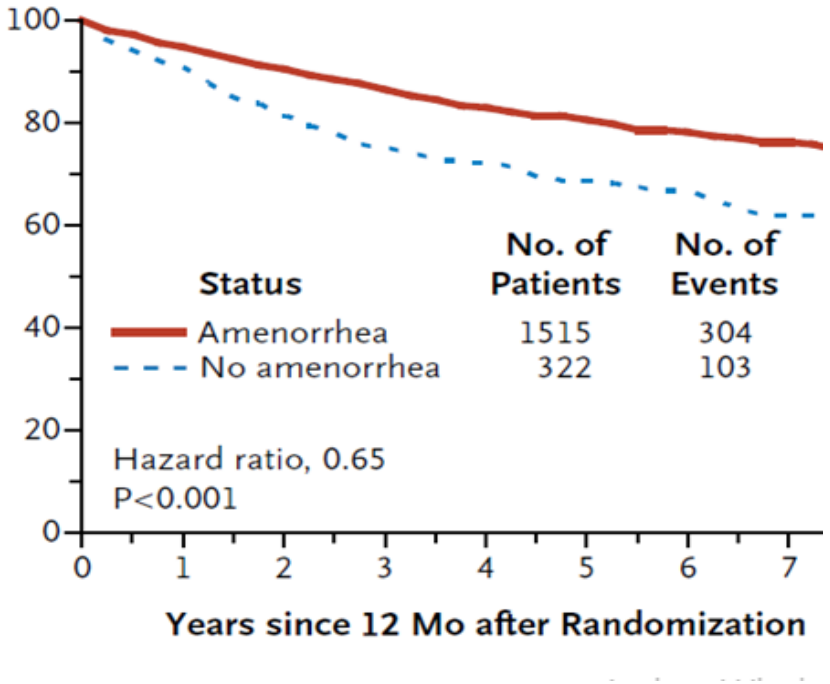
ETUDE NSABP B-30:

L'obtention d'une aménorhée persistante > 6 mois est un facteur pronostique pour les tumeurs RH+

Survie globale



Survie sans maladie



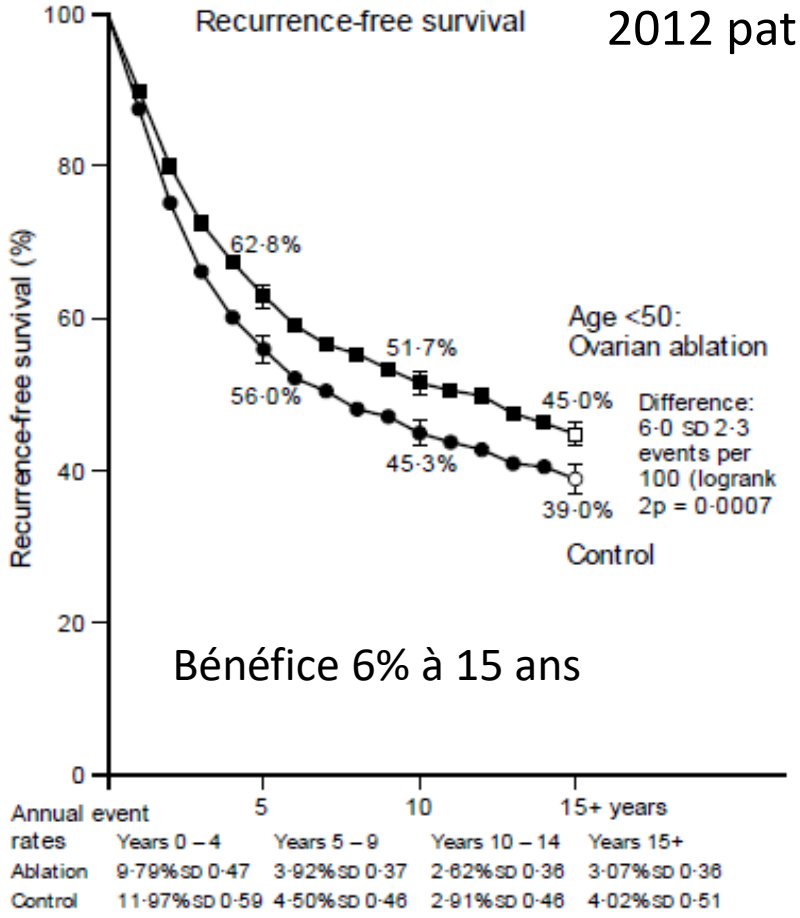
Hormonothérapie par ablation ou suppression ovarienne

Ovarian ablation in early breast cancer: overview of the randomised trials

Vol 348 • November 2, 1996

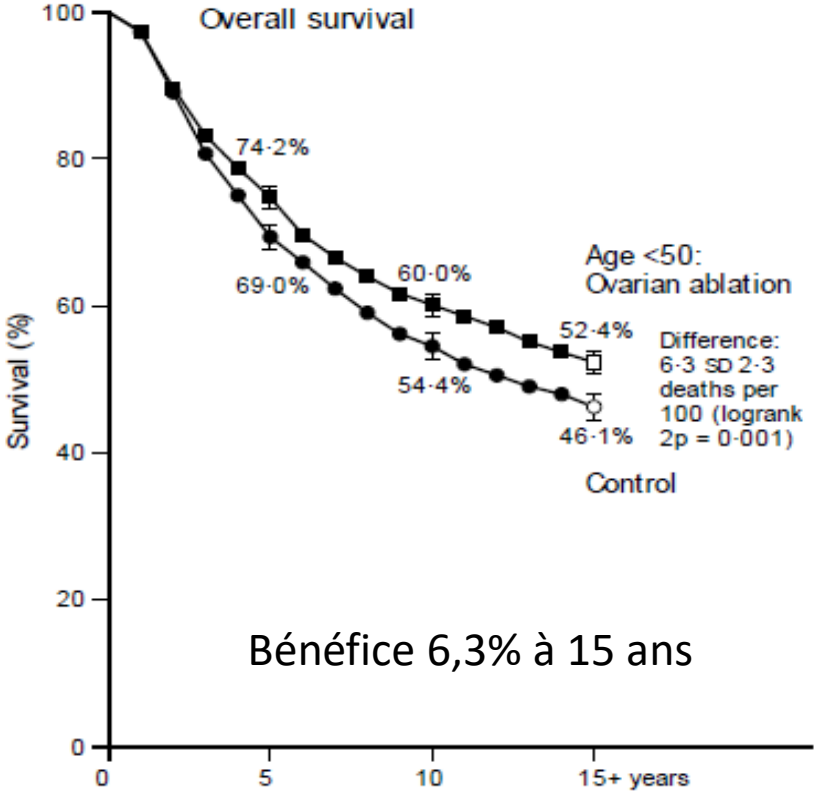
*Early Breast Cancer Trialists' Collaborative Group**

2012 patientes



Bénéfice 6% à 15 ans

Annual event rates	Years 0 – 4	Years 5 – 9	Years 10 – 14	Years 15+
Ablation	9·79% SD 0·47	3·92% SD 0·37	2·62% SD 0·36	3·07% SD 0·36
Control	11·97% SD 0·59	4·50% SD 0·46	2·91% SD 0·46	4·02% SD 0·51



Bénéfice 6,3% à 15 ans

Annual death rates	Years 0 – 4	Years 5 – 9	Years 10 – 14	Years 15+
Ablation	6·15% SD 0·35	4·39% SD 0·36	2·90% SD 0·36	2·63% SD 0·31
Control	7·18% SD 0·42	4·91% SD 0·43	3·17% SD 0·44	3·90% SD 0·46

Hormonothérapie par ablation ou suppression ovarienne

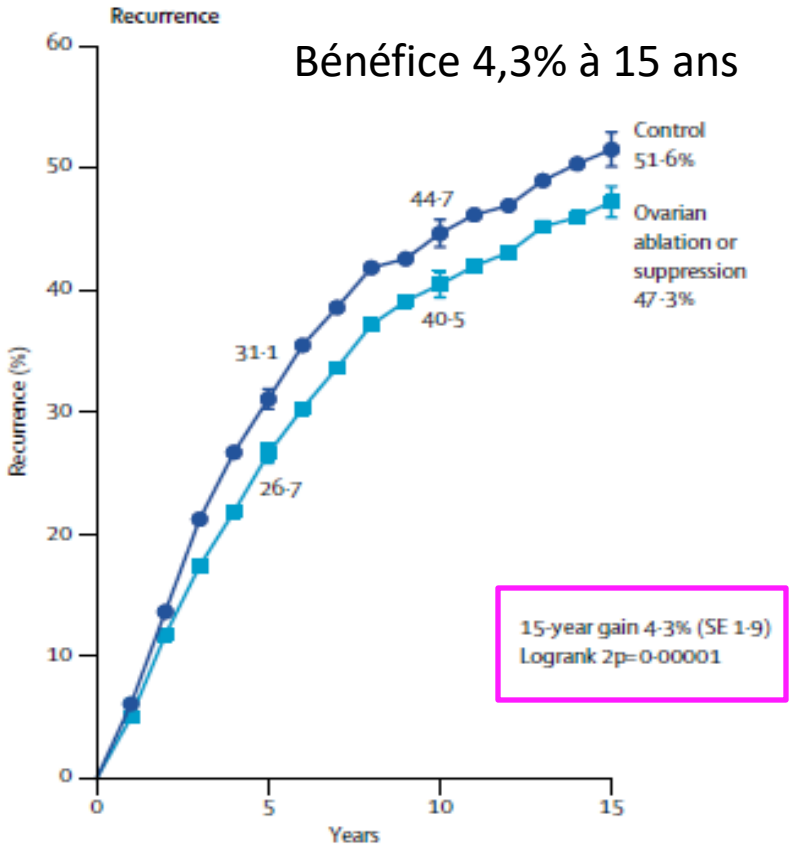
Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

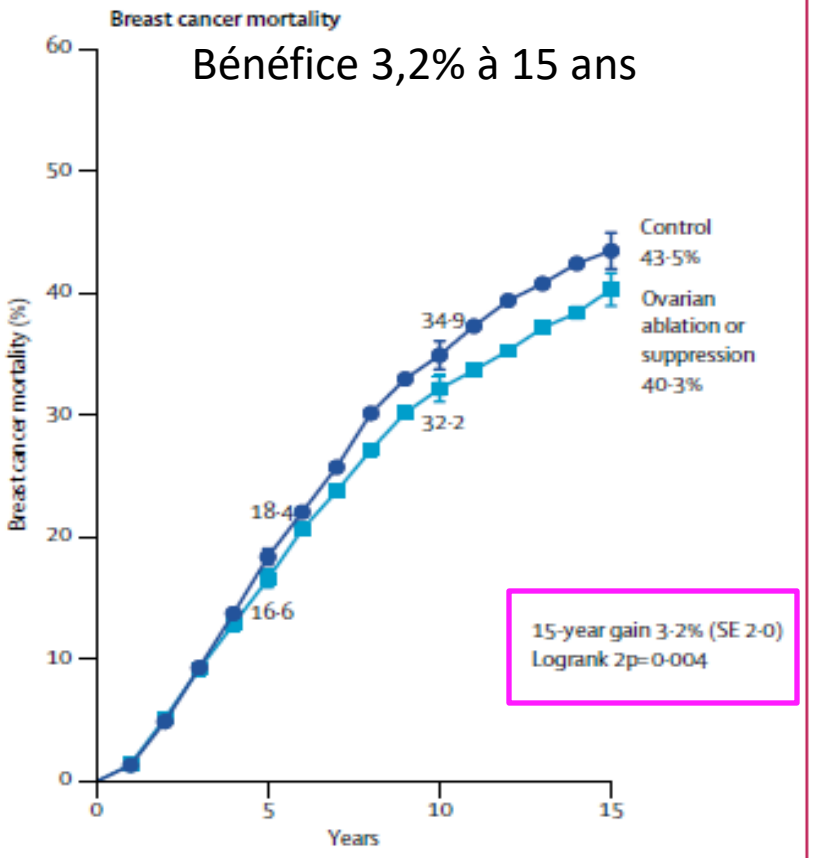
7601 patientes, 47% RE inconnus

Lancet 2005; 365: 1687–1717

Bénéfice 4,3% à 15 ans



Bénéfice 3,2% à 15 ans



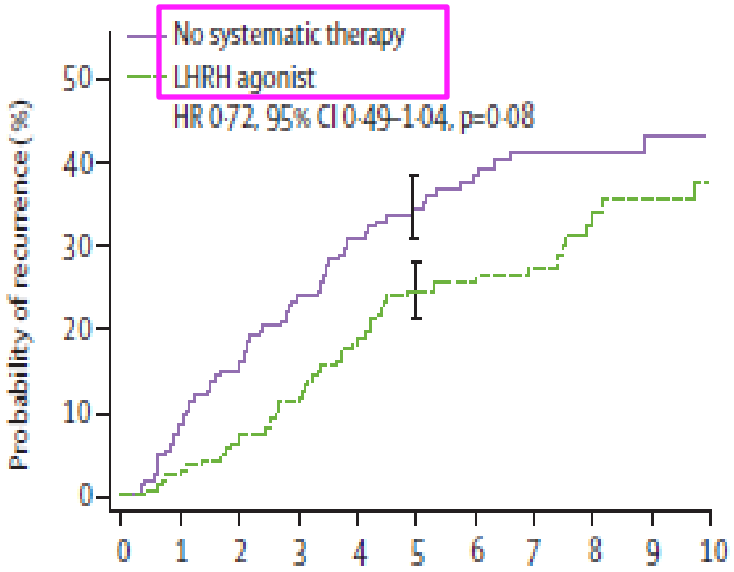
Hormonothérapie par ablation ou suppression ovarienne

Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials

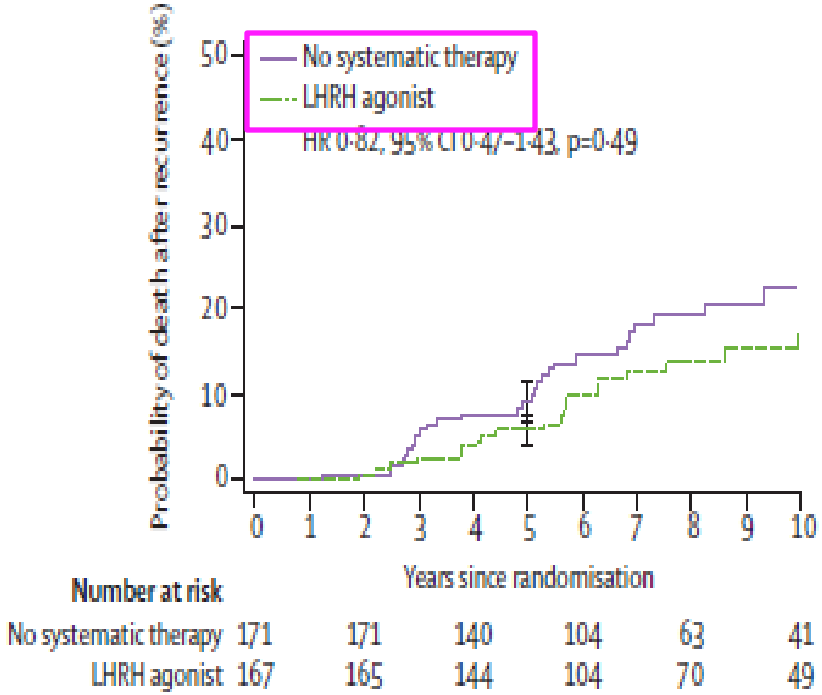
Lancet 2007; 369: 1711–23

*LHRH-agonists in Early Breast Cancer Overview group**

16 essais , 11887 patients



Rechutes



Décès

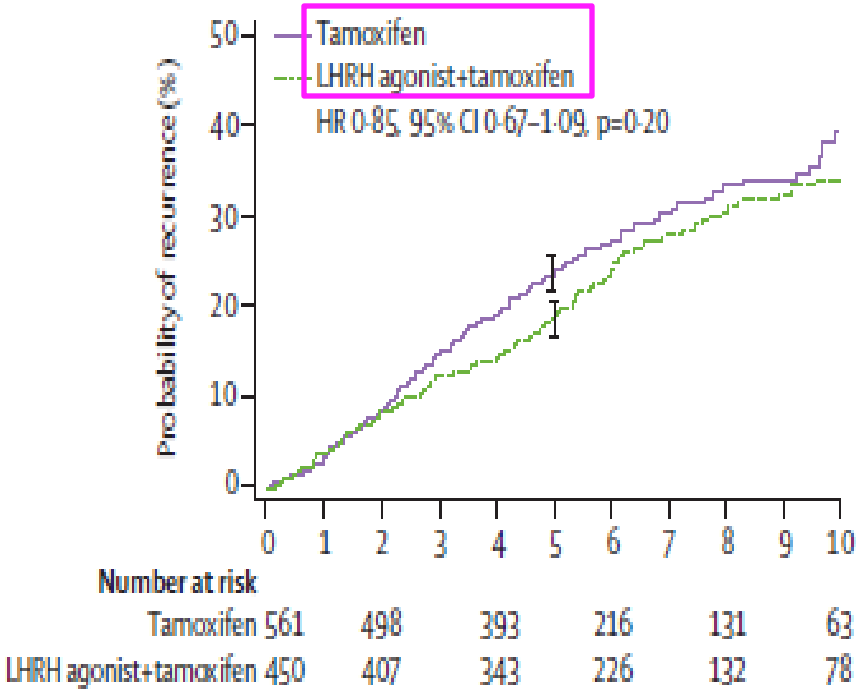
Hormonothérapie par ablation ou suppression ovarienne

Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials

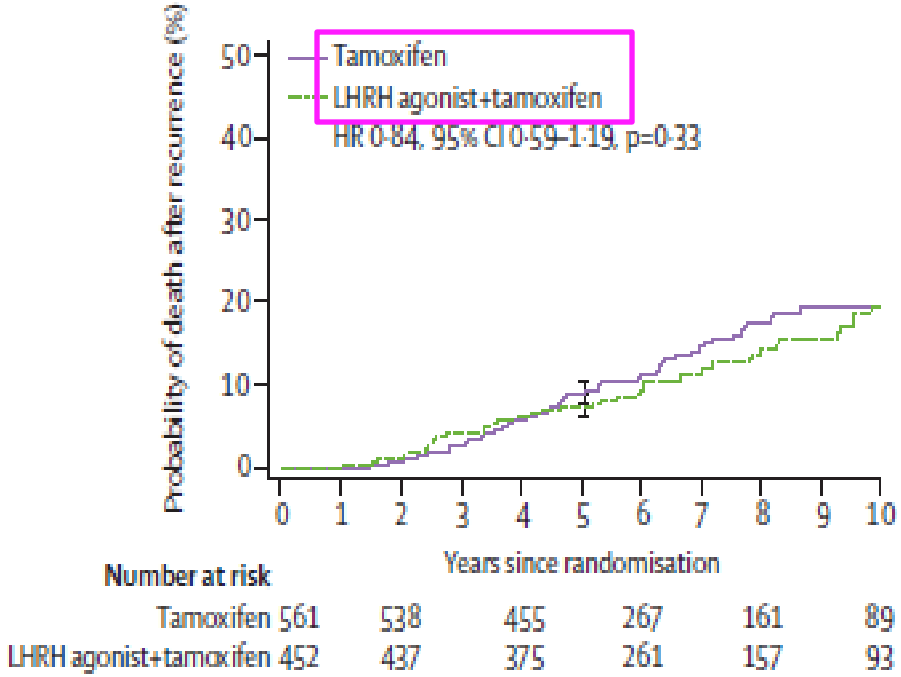
Lancet 2007; 369: 1711–23

*LHRH-agonists in Early Breast Cancer Overview group**

16 essais , 11887 patients



Rechutes



Décès

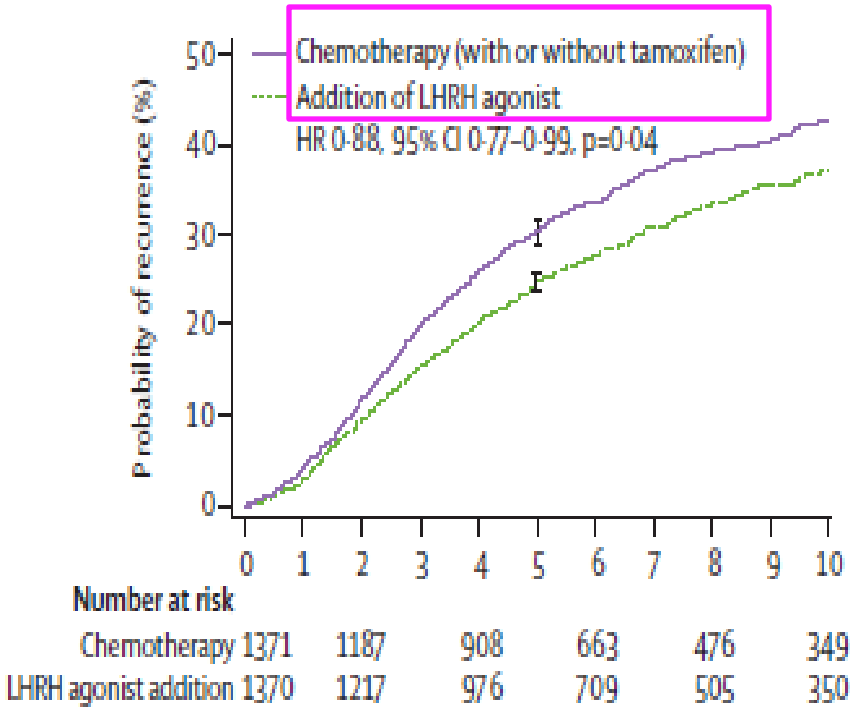
Hormonothérapie par ablation ou suppression ovarienne

Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials

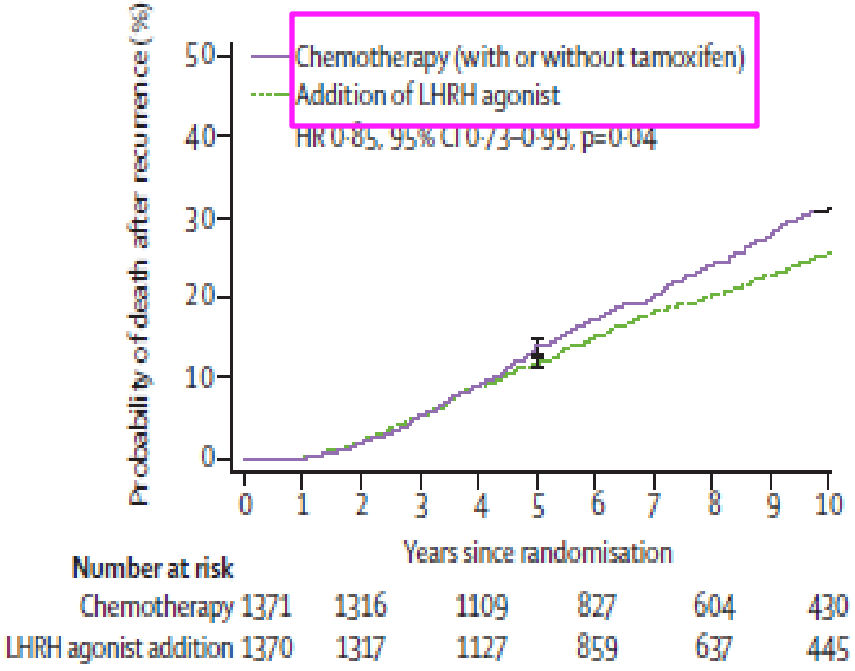
Lancet 2007; 369: 1711–23

*LHRH-agonists in Early Breast Cancer Overview group**

16 essais , 11887 patients



Rechutes

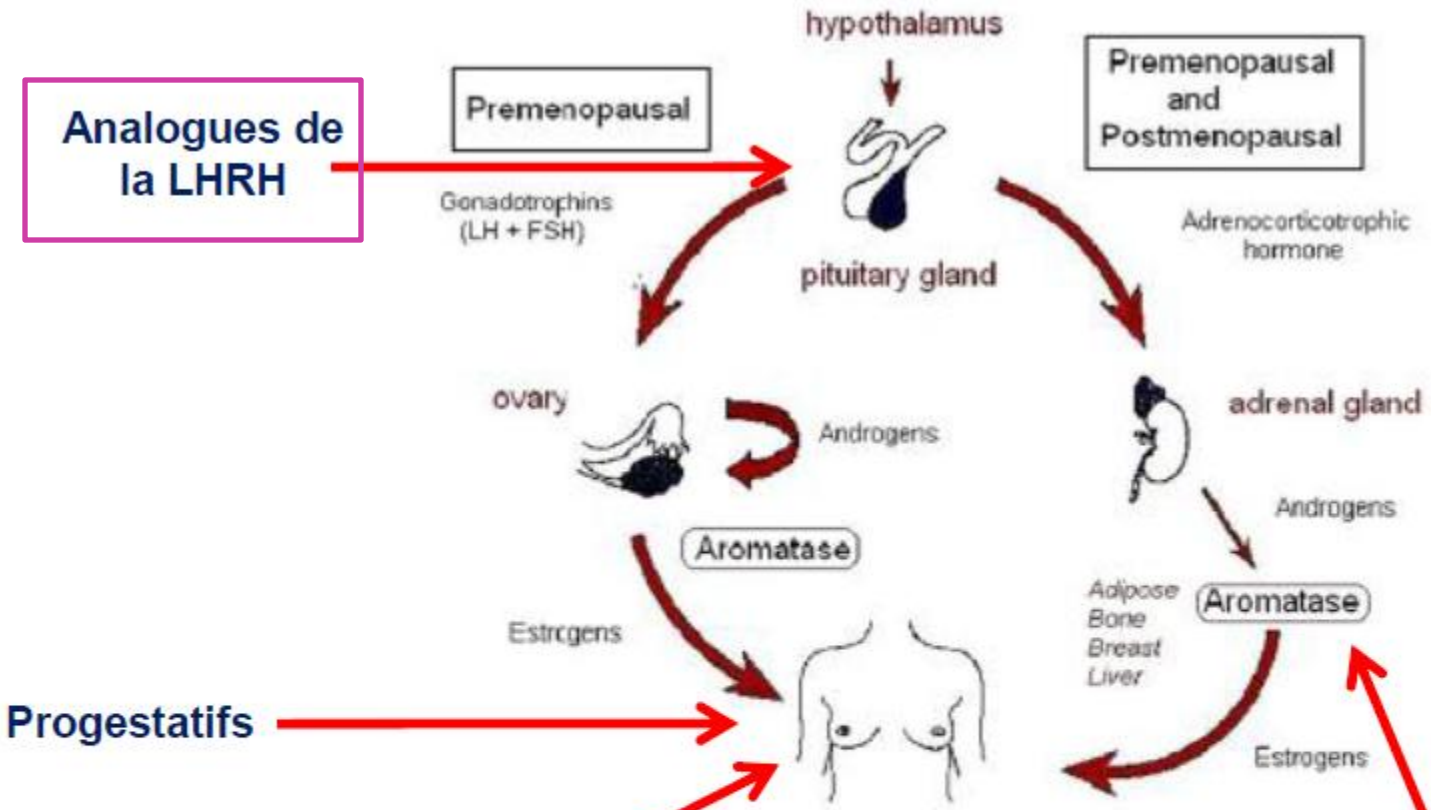


Décès

Hormonothérapie par ablation ou suppression ovarienne

	n	Recurrence	Recurrence or death	Death after recurrence	All deaths
No sys±LHRH					
Age ≤40 years	62	..	..	..	..
Age >40 years	276	..	..	..	..
No sys±(LHRH+tam)					
Age ≤40 years	71	−7·9 (−65·4 to 145·2), p=0·87	−20·6 (−68·6 to 100·9), p=0·63	−30·5 (−81·5 to 161·5), p=0·59	−46·7 (−84·6 to 84·5), p=0·32
Age >40 years	336	−64·7 (−77·8 to −43·8), p<0·0001	−66·2 (−78·4 to −46·9), p<0·0001	−51·2 (−74·3 to −7·4), p=0·03	−52·4 (−73·9 to −13·2), p=0·02
Tam±LHRH					
Age ≤40 years	203	−32·0 (−58·1 to 10·2), p=0·12	−31·3 (−57·3 to 10·5), p=0·12	−35·6 (−67·2 to 26·2), p=0·20	−33·5 (−65·3 to 27·6), p=0·22
Age >40 years	810	−1·5 (−25·6 to 30·2), p=0·91	−2·0 (−25·3 to 28·5), p=0·88	−0·1 (−34·3 to 52·0), p=0·99	0·3 (−32·3 to 48·7), p=0·99
Chemo±LHRH					
Age ≤40 years	714	−24·7 (−39·5 to −6·2), p=0·01	−25·0 (−39·6 to −6·9), p=0·01	−27·3 (−44·4 to −4·9), p=0·02	−27·5 (−44·2 to −5·7), p=0·02
Age >40 years	1662	−5·1 (−20·1 to 12·7), p=0·55	−2·4 (−14·8 to 11·8), p=0·73	−5·3 (−24·2 to 18·3), p=0·63	−2·2 (−20·9 to 20·8), p=0·83
Chemo+tam±LHRH					
Age ≤40 years	81	−31·2 (−67·5 to 46·0), p=0·33	−31·1 (−66·4 to 41·1), p=0·31	−21·1 (−72·1 to 123·7), p=0·66	−26·3 (−71·4 to 89·6), p=0·53
Age >40 years	284	5·3 (−33·3 to 66·3), p=0·82	7·1 (−31·4 to 67·2), p=0·76	−23·4 (−59·2 to 43·9), p=0·41	−24·3 (−58·2 to 37·2), p=0·36
(Chemo±tam)±LHRH*					
Age ≤40 years	795	−25·2 (−39·4 to −7·7), p=0·01	−25·5 (−39·5 to −8·4), p=0·01	−28·3 (−44·9 to −6·8), p=0·01	−27·4 (−43·6 to −6·5), p=0·01
Age >40 years	1946	−3·9 (−18·1 to 12·9), p=0·63	−3·8 (−18·6 to 13·8), p=0·65	−7·5 (−25·0 to 14·1), p=0·47	−5·0 (−22·1 to 15·9), p=0·61
Any sys±LHRH†					
Age ≤40 years	998	−26·3 (−39·3 to −10·7), p=0·002	−26·5 (−39·2 to −11·1), p=0·001	−27·4 (−43·9 to −5·9), p=0·02	−28·2 (−43·3 to −9·2), p=0·01
Age >40 years	2756	−3·3 (−15·9 to 11·1), p=0·64	−2·5 (−16·6 to 14·1), p=0·75	−6·1 (−22·1 to 13·3), p=0·51	−3·9 (−19·6 to 14·7), p=0·66
Chemo±(LHRH+tam)					
Age ≤40 years	372	−32·3 (−50·1 to −8·2), p=0·01	−32·8 (−50·1 to −9·3), p=0·01	−34·8 (−53·9 to −7·6), p=0·02	−34·8 (−53·5 to −8·5), p=0·01
Age >40 years	838	−24·2 (−39·2 to −5·4), p=0·01	−19·3 (−34·7 to −0·2), p=0·04	−19·2 (−38·5 to 6·1), p=0·13	−11·3 (−31·3 to 14·5), p=0·36

Hormonothérapie dans le K du sein



SERM = **Anti-oestrogènes**

Selective Estrogen Receptor Modulators

- 35 ans d'utilisation
- Standard

Déplétion en oestrogènes au mieux réalisée par une **inhibition spécifique de l'aromatase** qui convertit les précurseurs des oestrogènes en oestradiol et oestrone

Hormonothérapie par Tamoxifene

Effects of Adjuvant Tamoxifen and of Cytotoxic Therapy on Mortality in Early Breast Cancer

Early Breast Cancer Trialists' Collaborative Group

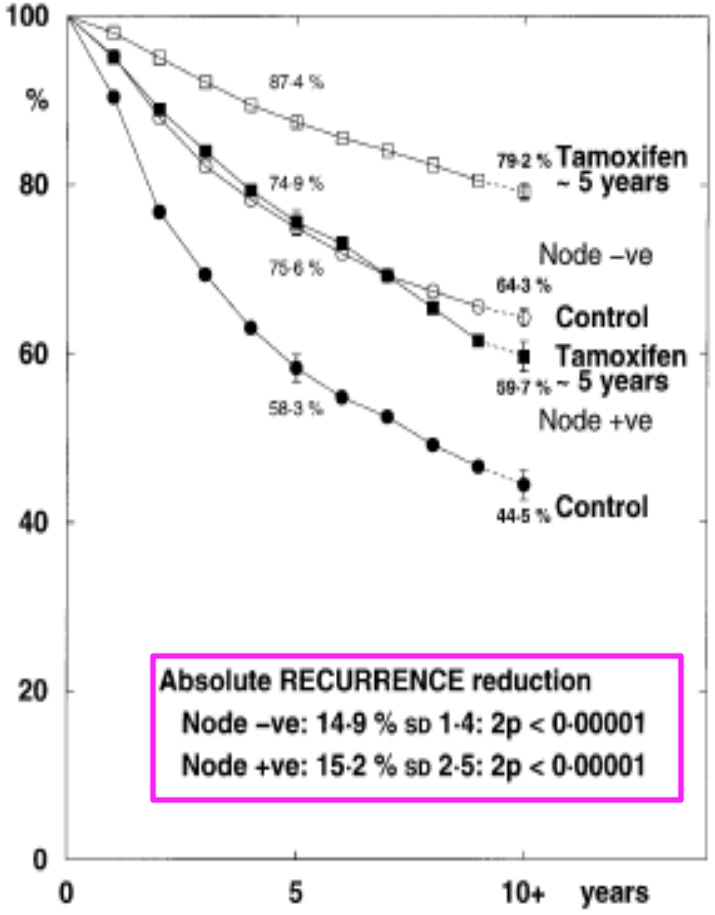
December 29, 1988
N Engl J Med 1988; 319:1681-1692

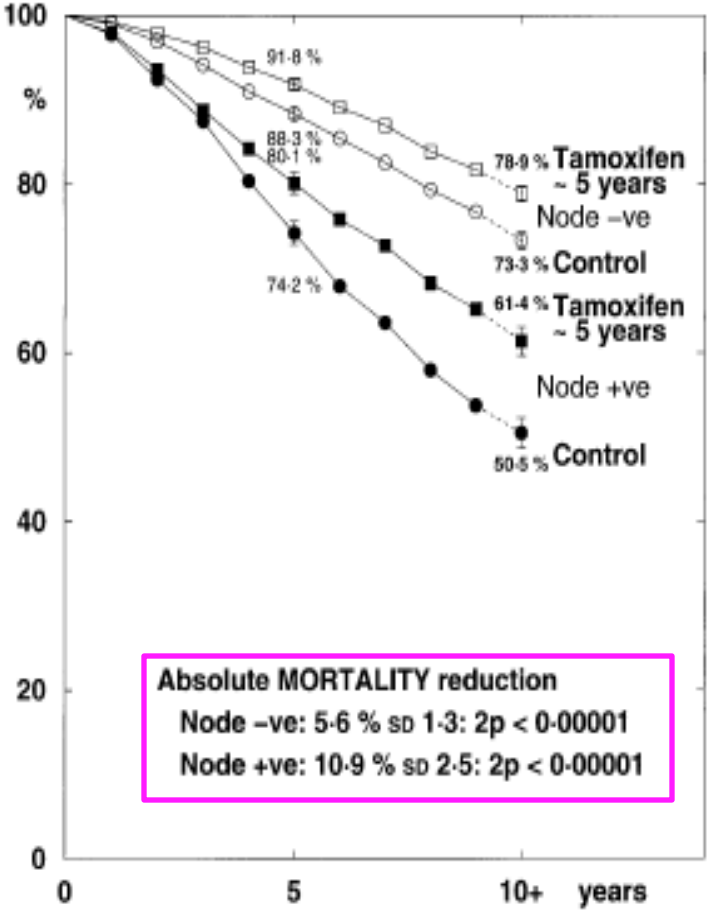
28 essais
16513 patientes
Réduction significative de la mortalité ($p<0,0001$)
pour les femmes de plus de 50 ans

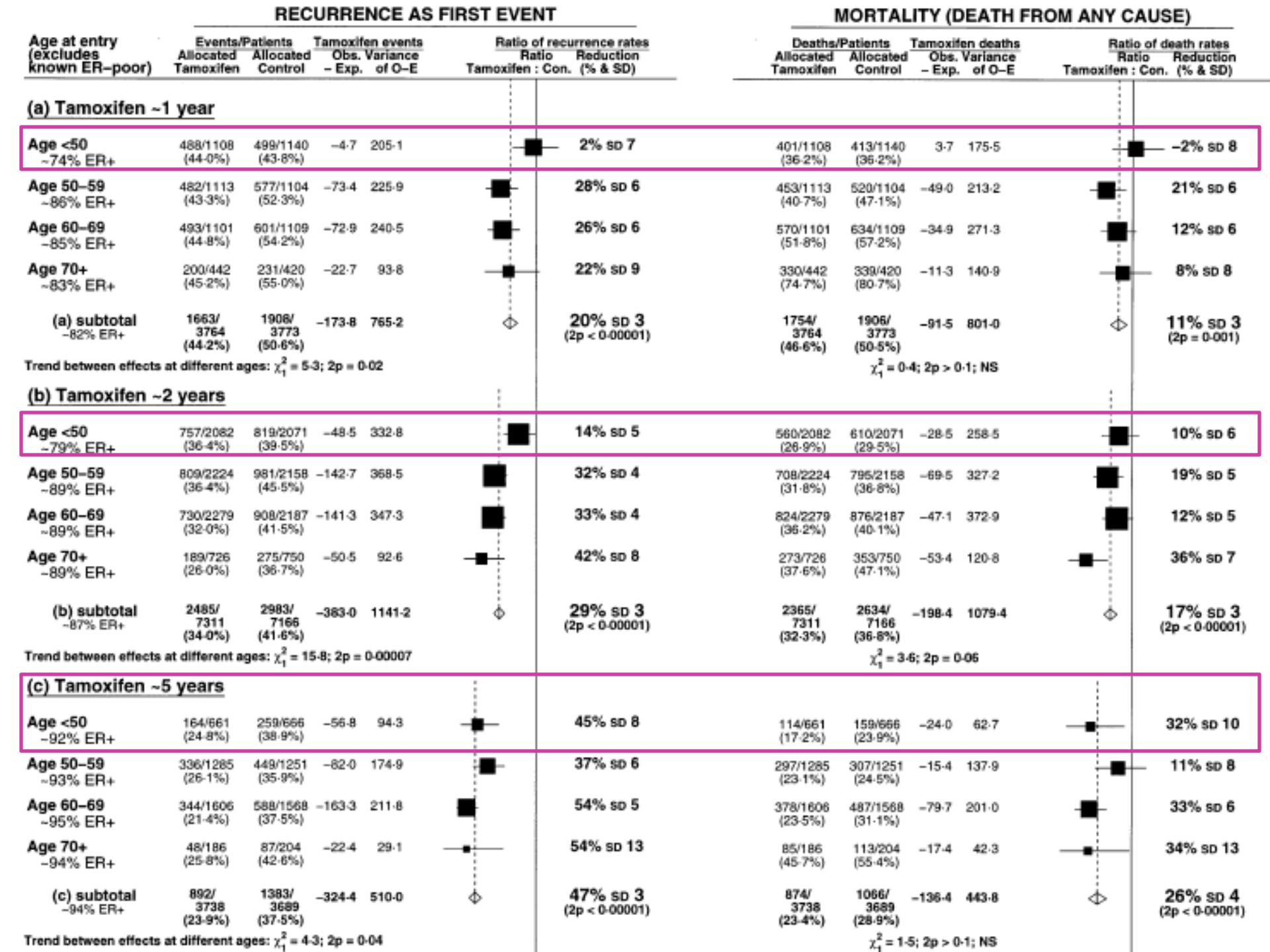
Hormonothérapie par Tamoxifene

Tamoxifen for early breast cancer: an overview of the randomised trials *Early Breast Cancer Trialists' Collaborative Group*

THE LANCET • Vol 351 • May 16, 1998



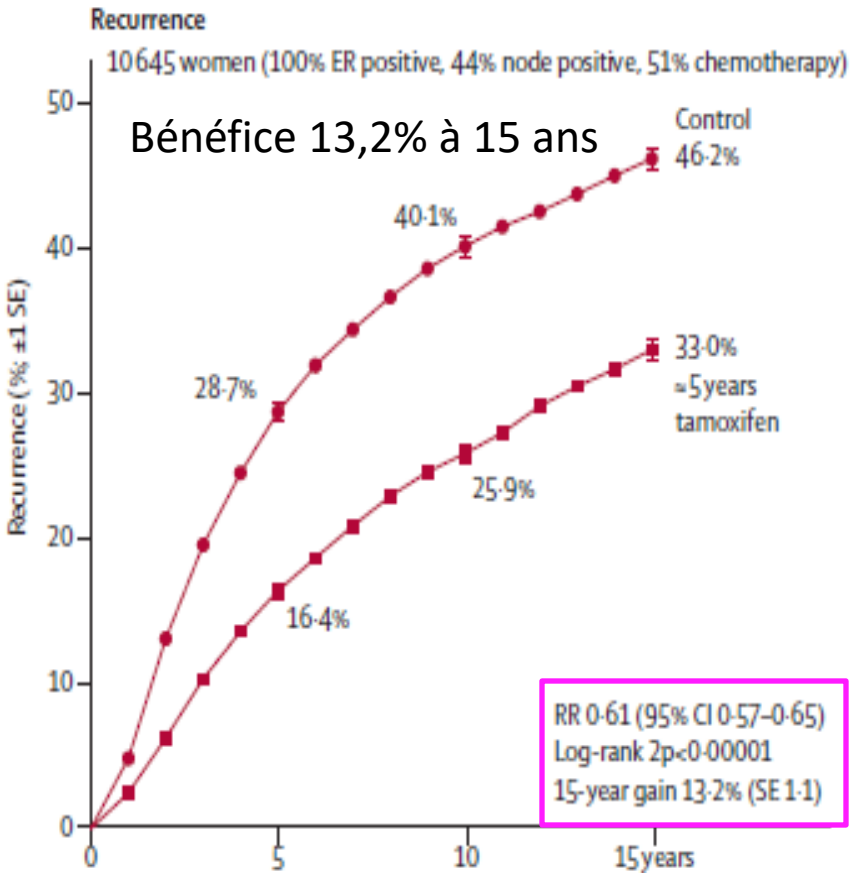


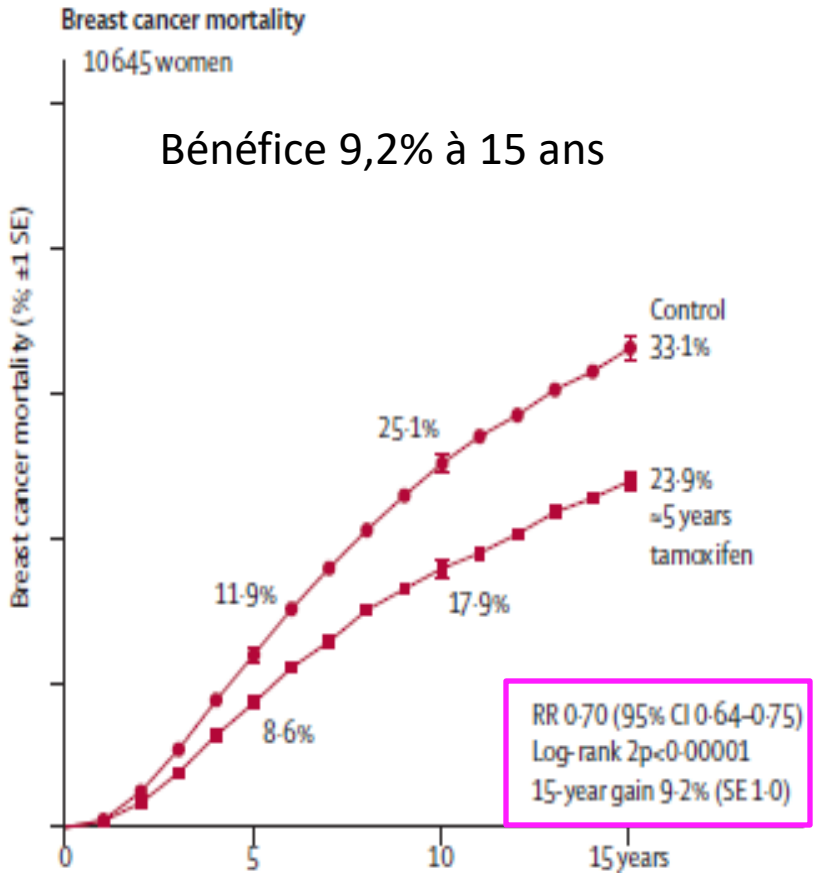

RECURRENCE AS FIRST EVENT
MORTALITY (DEATH FROM ANY CAUSE)
Age at entry (excludes known ER–poor)
Events/Patients Allocated Tamoxifen
Allocated Control
Tamoxifen events Obs. – Exp.
Variance of O–E
Ratio of recurrence rates Ratio Tamoxifen : Con.
Reduction (% & SD)
Deaths/Patients Allocated Tamoxifen
Allocated Control
Tamoxifen deaths Obs. – Exp.
Variance of O–E
Ratio of death rates Ratio Tamoxifen : Con.
Reduction (% & SD)
(a) Tamoxifen ~1 year
Age <50 ~74% ER+ 488/1108 (44·0%) 499/1140 (43·8%) −4·7 205·1 2% SD 7 401/1108 (36·2%) 413/1140 (36·2%) 3·7 175·5 −2% SD 8
Age 50–59 ~86% ER+ 482/1113 (43·3%) 577/1104 (52·3%) −73·4 225·9 28% SD 6 453/1113 (40·7%) 520/1104 (47·1%) −49·0 213·2 21% SD 6
Age 60–69 ~85% ER+ 493/1101 (44·8%) 601/1109 (54·2%) −72·9 240·5 26% SD 6 570/1101 (51·8%) 634/1109 (57·2%) −34·9 271·3 12% SD 6
Age 70+ ~83% ER+ 200/442 (45·2%) 231/420 (55·0%) −22·7 93·8 22% SD 9 330/442 (74·7%) 339/420 (80·7%) −11·3 140·9 8% SD 8
(a) subtotal ~82% ER+ 1663/3764 (44·2%) 1906/3773 (50·6%) −173·8 765·2 20% SD 3 (2p < 0·00001) 1754/3764 (46·6%) 1906/3773 (50·5%) −91·5 801·0 11% SD 3 (2p = 0·001)
Trend between effects at different ages: χ^2_1 = 5·3; 2p = 0·02
χ^2_1 = 0·4; 2p > 0·1; NS
(b) Tamoxifen ~2 years
Age <50 ~79% ER+ 757/2082 (36·4%) 819/2071 (39·5%) −48·5 332·8 14% SD 5 560/2082 (26·9%) 610/2071 (29·5%) −28·5 258·5 10% SD 6
Age 50–59 ~89% ER+ 809/2224 (36·4%) 981/2158 (45·5%) −142·7 368·5 32% SD 4 708/2224 (31·8%) 795/2158 (36·8%) −69·5 327·2 19% SD 5
Age 60–69 ~89% ER+ 730/2279 (32·0%) 908/2187 (41·5%) −141·3 347·3 33% SD 4 824/2279 (36·2%) 876/2187 (40·1%) −47·1 372·9 12% SD 5
Age 70+ ~89% ER+ 189/726 (26·0%) 275/750 (36·7%) −50·5 92·6 42% SD 8 273/726 (37·6%) 353/750 (47·1%) −53·4 120·8 36% SD 7
(b) subtotal ~87% ER+ 2485/7311 (34·0%) 2983/7166 (41·6%) −383·0 1141·2 29% SD 3 (2p < 0·00001) 2365/7311 (32·3%) 2634/7166 (36·8%) −198·4 1079·4 17% SD 3 (2p < 0·00001)
Trend between effects at different ages: χ^2_1 = 15·8; 2p = 0·00007
χ^2_1 = 3·6; 2p = 0·06
(c) Tamoxifen ~5 years
Age <50 ~92% ER+ 164/661 (24·8%) 259/666 (38·9%) −56·8 94·3 45% SD 8 114/661 (17·2%) 159/666 (23·9%) −24·0 62·7 32% SD 10
Age 50–59 ~93% ER+ 336/1285 (26·1%) 449/1251 (35·9%) −62·0 174·9 37% SD 6 297/1285 (23·1%) 307/1251 (24·5%) −15·4 137·9 11% SD 8
Age 60–69 ~95% ER+ 344/1606 (21·4%) 588/1568 (37·5%) −163·3 211·8 54% SD 5 378/1606 (23·5%) 487/1568 (31·1%) −79·7 201·0 33% SD 6
Age 70+ ~94% ER+ 48/186 (25·8%) 87/204 (42·6%) −22·4 29·1 54% SD 13 85/186 (45·7%) 113/204 (55·4%) −17·4 42·3 34% SD 13
(c) subtotal ~94% ER+ 892/3738 (23·9%) 1383/3689 (37·5%) −324·4 510·0 47% SD 3 (2p < 0·00001) 874/3738 (23·4%) 1066/3689 (28·9%) −136·4 443·8 26% SD 4 (2p < 0·00001)
Trend between effects at different ages: χ^2_1 = 4·3; 2p = 0·04
χ^2_1 = 1·5; 2p > 0·1; NS

Hormonothérapie par Tamoxifene

Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials *Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2011; 378: 771–84





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)
(h) Site of first recurrence (χ^2_1=2·1; p=0·4)					
Isolated local	205/34 320 (0·6)	317/29 618 (1·1)	−74·6	121·7	0·54 (SE 0·07)
Contralateral	237/54 952 (0·4)	327/47 539 (0·7)	−65·1	136·8	0·62 (SE 0·07)
Distant/multiple	1098/54 960 (2·0)	1417/47 560 (3·0)	−262·4	558·8	0·63 (SE 0·03)
Unknown	113/56 714 (0·2)	157/48 827 (0·3)	−31·4	64·1	0·61 (SE 0·10)
(i) Time since randomisation (years) (trend χ^2_1=43·7; 2p<0·00001)					
0–1	343/10 229 (3·4)	676/9825 (6·9)	−175·3	230·2	0·47 (SE 0·05)
2–4	548/13 434 (4·1)	790/11 894 (6·6)	−168·0	304·9	0·58 (SE 0·04)
5–9	454/17 258 (2·6)	499/14 372 (3·5)	−82·5	217·6	0·68 (SE 0·06)
≥10	308/15 631 (2·0)	253/12 610 (2·0)	−7·7	128·8	0·94 (SE 0·09)
Total	**1653/56 747 (2·9% per year)**	**2218/48 876 (4·5% per year)**	**−433·5**	**881·4**	**0·611 (SE 0·027; 95% CI 0·57–0·65)**

99% or 95% CIs

0·25 0·5 1·0 2·0

Tamoxifen better Tamoxifen worse

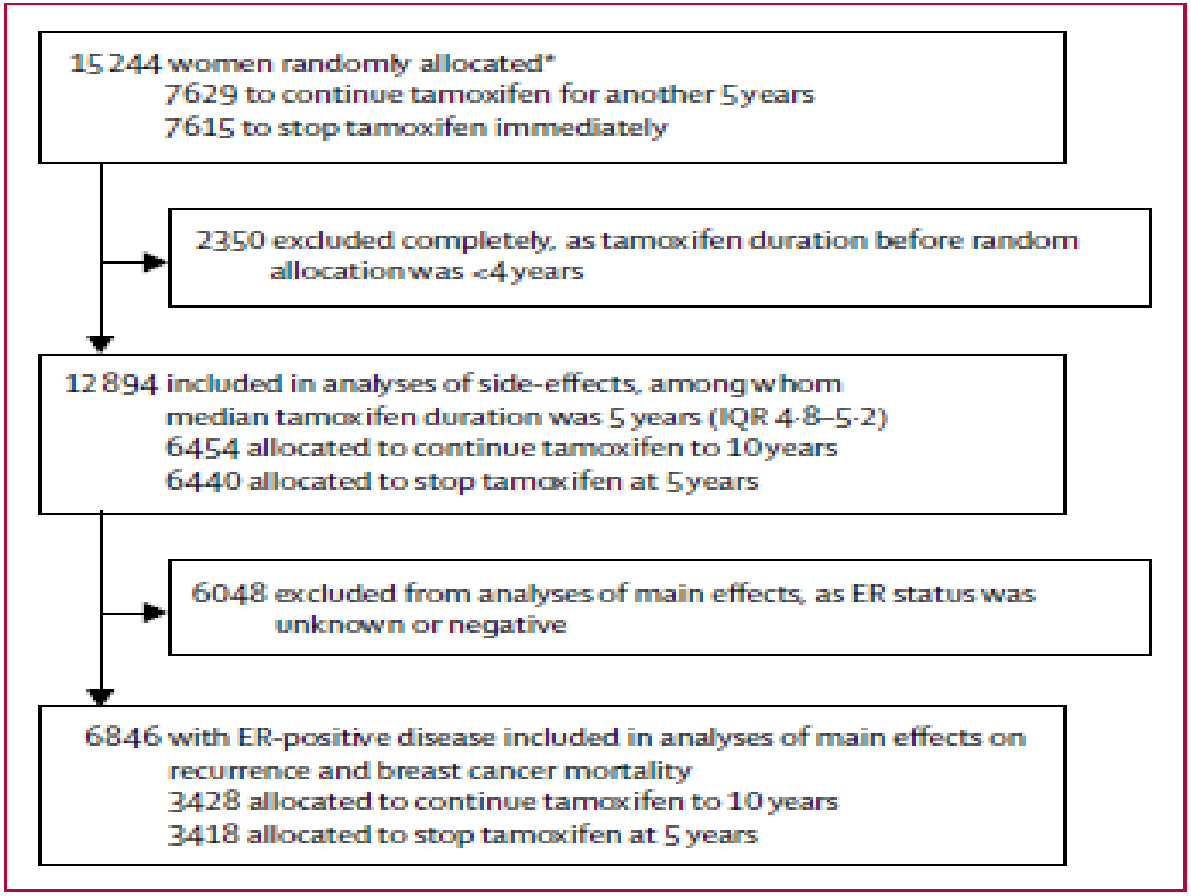
Treatment effect 2p<0·00001

Tamoxifene: durée du traitement

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

Lancet 2013; 381: 805–16

1996-2005



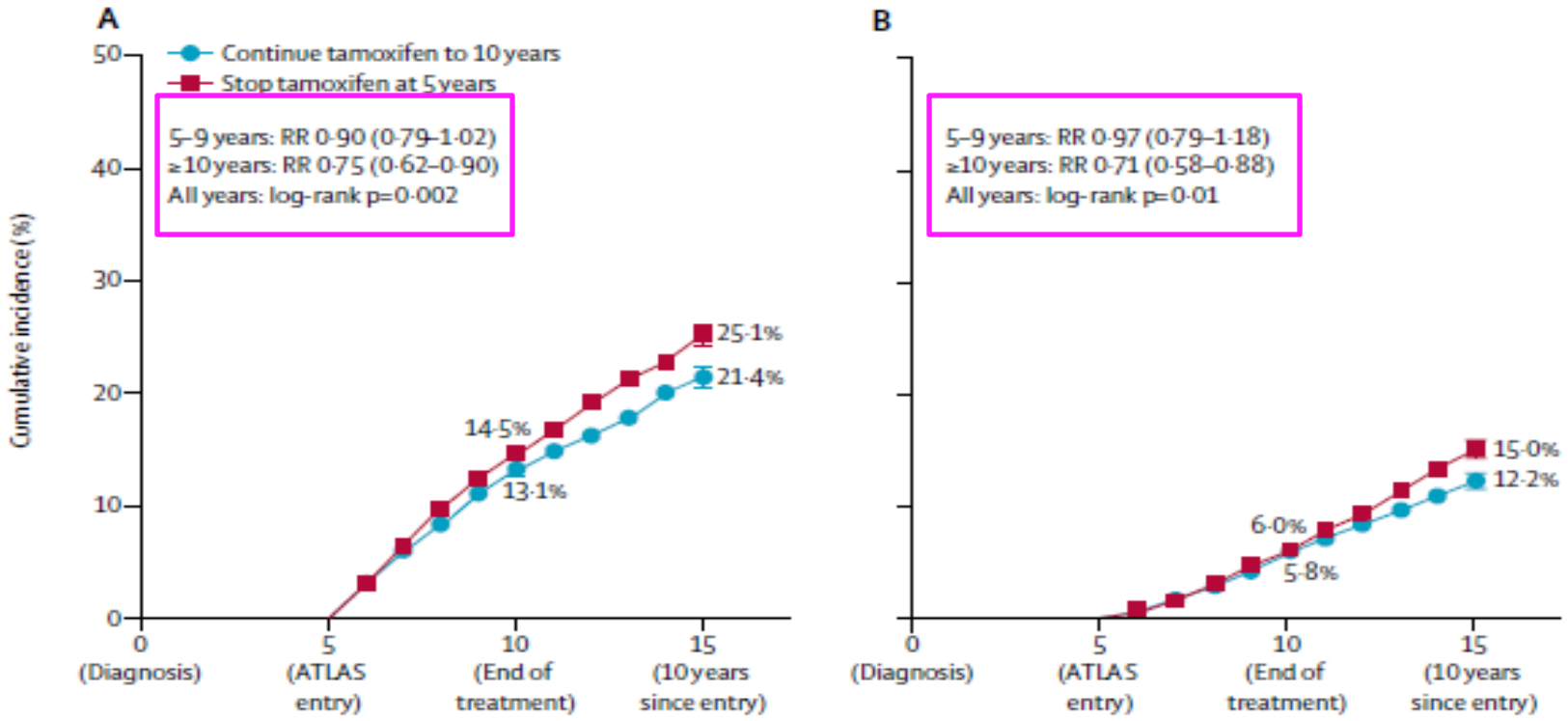
Tamoxifene: durée du traitement

	Any ER status	
	Continue tamoxifen to 10 years (n=6454)	Stop tamoxifen at 5 years (n=6440)
Status at diagnosis		
ER status		
ER-positive	3428 (53%)	3418 (53%)
ER-negative	625 (10%)	623 (10%)
ER-unknown	2401 (37%)	2399 (37%)
Age, years		
<45 (median 40)	1246 (19%)	1236 (19%)
45–54 (median 49)	2070 (32%)	2076 (32%)
55–69 (median 61)	2557 (40%)	2567 (40%)
≥70 (median 73)	581 (9%)	561 (9%)
Nodal status		
Node-negative	3360 (52%)	3354 (52%)
N1–3	1667 (26%)	1621 (25%)
N4 or more	968 (15%)	965 (15%)
Unknown	459 (7%)	500 (8%)
Tumour diameter		
1–20 mm	2462 (38%)	2463 (38%)
21–50 mm	2749 (43%)	2727 (42%)
>50 mm	620 (10%)	628 (10%)
Unknown	623 (10%)	622 (10%)
Menopausal status		
Premenopausal	537 (8%)	521 (8%)
Postmenopausal*	5778 (90%)	5784 (90%)
Perimenopausal or unknown	139 (2%)	135 (2%)

Tamoxifene: durée du traitement

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

Lancet 2013; 381: 805–16



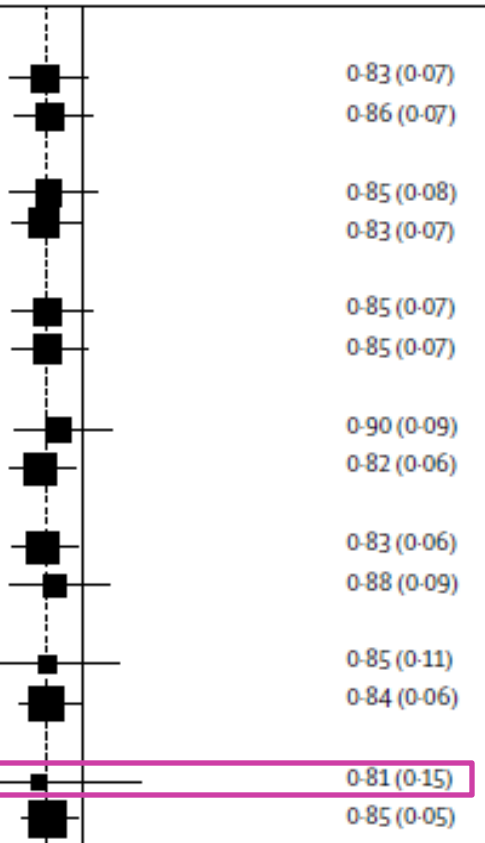
La différence apparait après la 10ème année du traitement soit 5 ans après la randomisation

Tamoxifene: durée du traitement

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

Lancet 2013; 381: 805–16

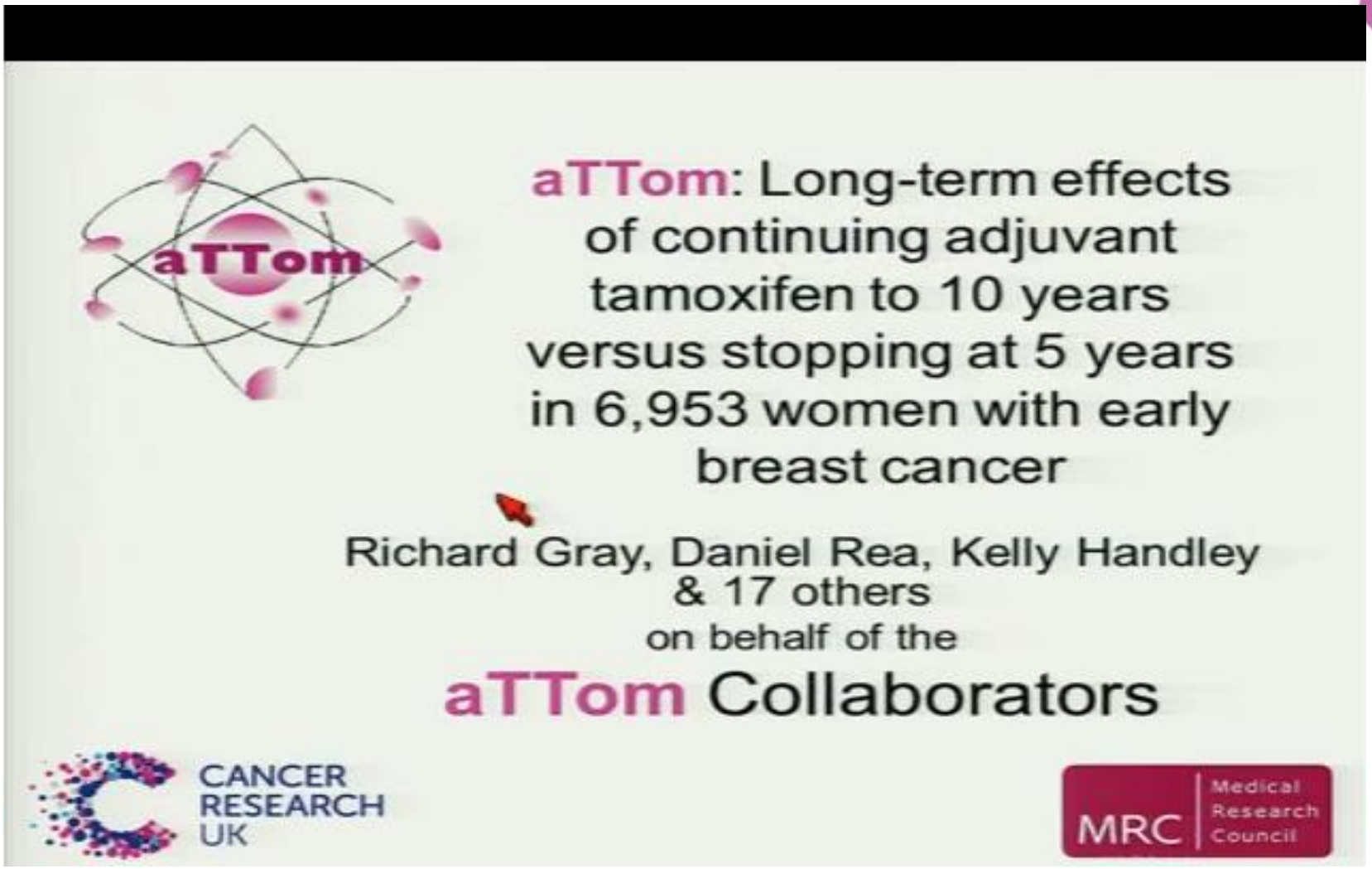
	Events/women		10 years events		Ratio of annual event rates (SE)
	Continue tamoxifen to 10 years	Stop tamoxifen at 5 years	Log-rank O–E	Variance of O–E	
Age at diagnosis (p=0·82)					
<55 years	303/1730 (18%)	354/1729 (20%)	−29·6	164·2	0·83 (0·07)
≥55 years	314/1698 (18%)	357/1689 (21%)	−26·2	167·6	0·86 (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)



Tamoxifene: durée du traitement

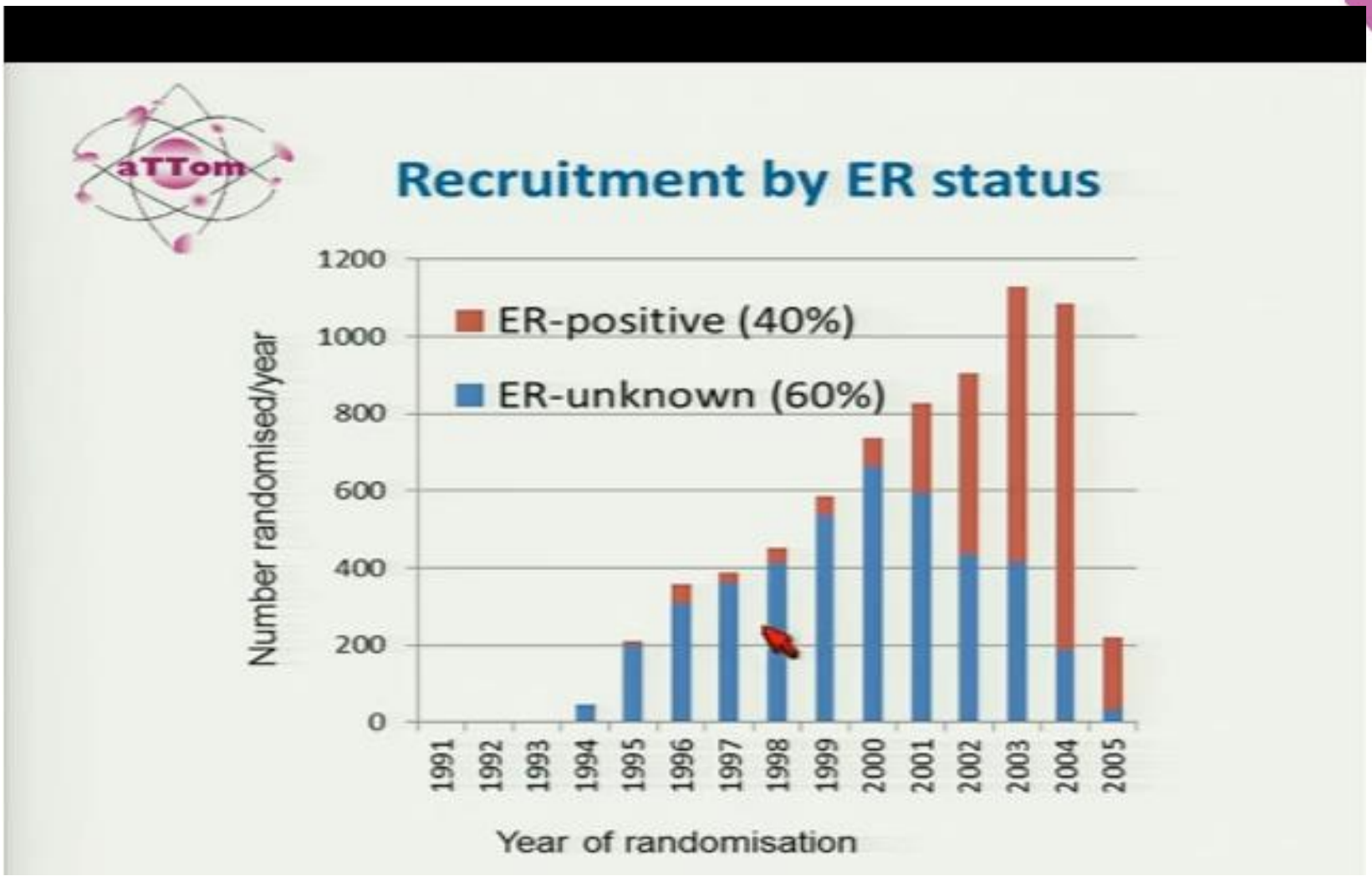
	Number of events		Log-rank O–E	Variance of O–E	Event rate ratio (95% CI)	p value*
	Continue tamoxifen to 10 years	Stop tamoxifen at 5 years				
Analyses of events without prior recurrence‡, any ER status						
Death without recurrence						
Vascular death						
Stroke	62	59	0·8	30·2	1·03 (0·72–1·47)	0·89
Pulmonary embolus	10	8	0·9	4·5	1·21 (0·48–3·04)	0·69
Heart disease§	175	205	−17·5	95·0	0·83 (0·68–1·02)	0·07
Neoplastic death						
Endometrial cancer¶	17	11	2·8	7·0	1·49 (0·71–3·13)	0·29
Other neoplastic disease	78	75	0·5	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	415	460	−27·2	218·7	0·88 (0·77–1·01)	0·07
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	−1·2	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	126	163	−20·7	72·2	0·75 (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	4·0	32·0	0·86 (0·61–1·21)	0·39

Tamoxifene: durée du traitement

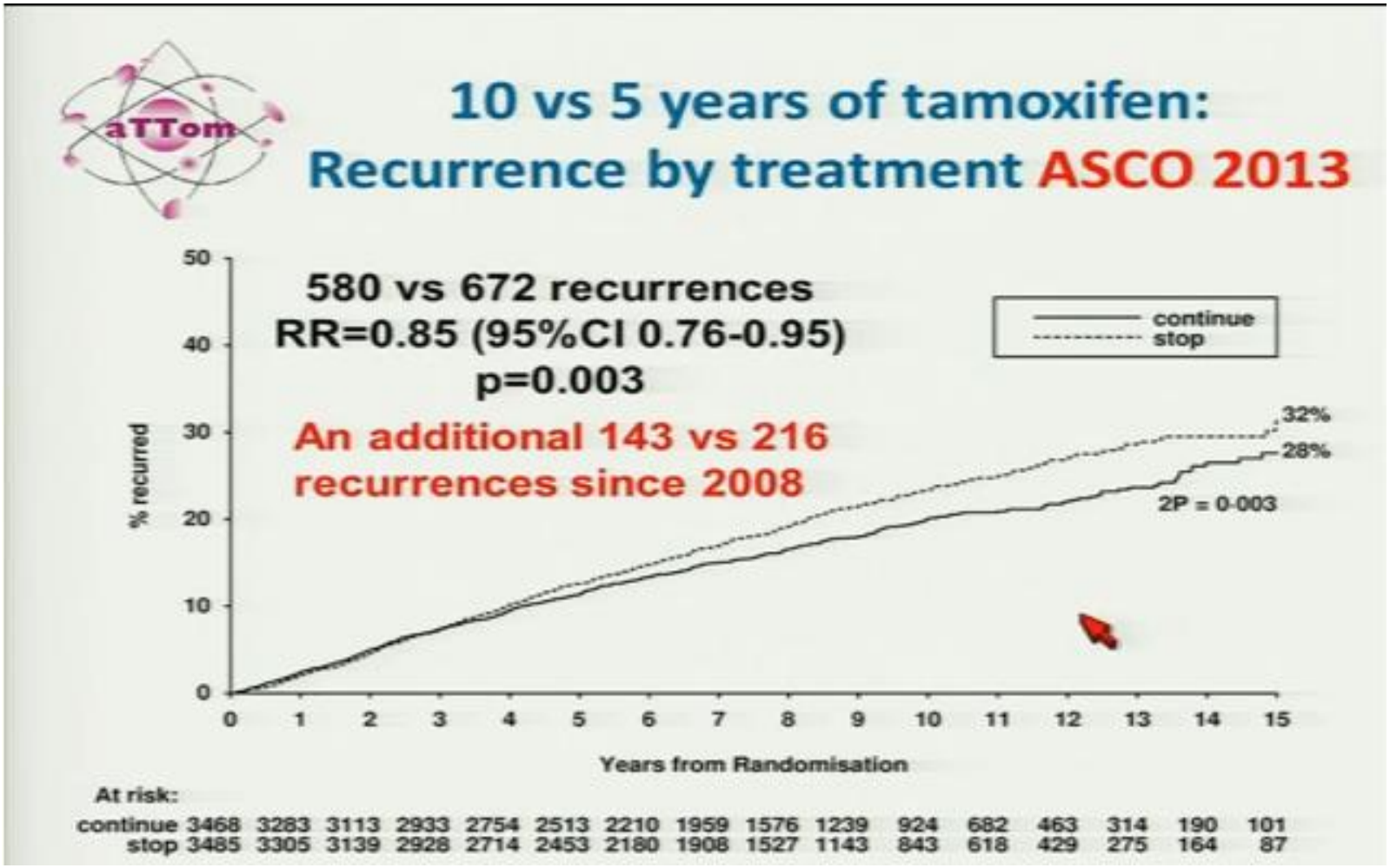


ASCO 2013

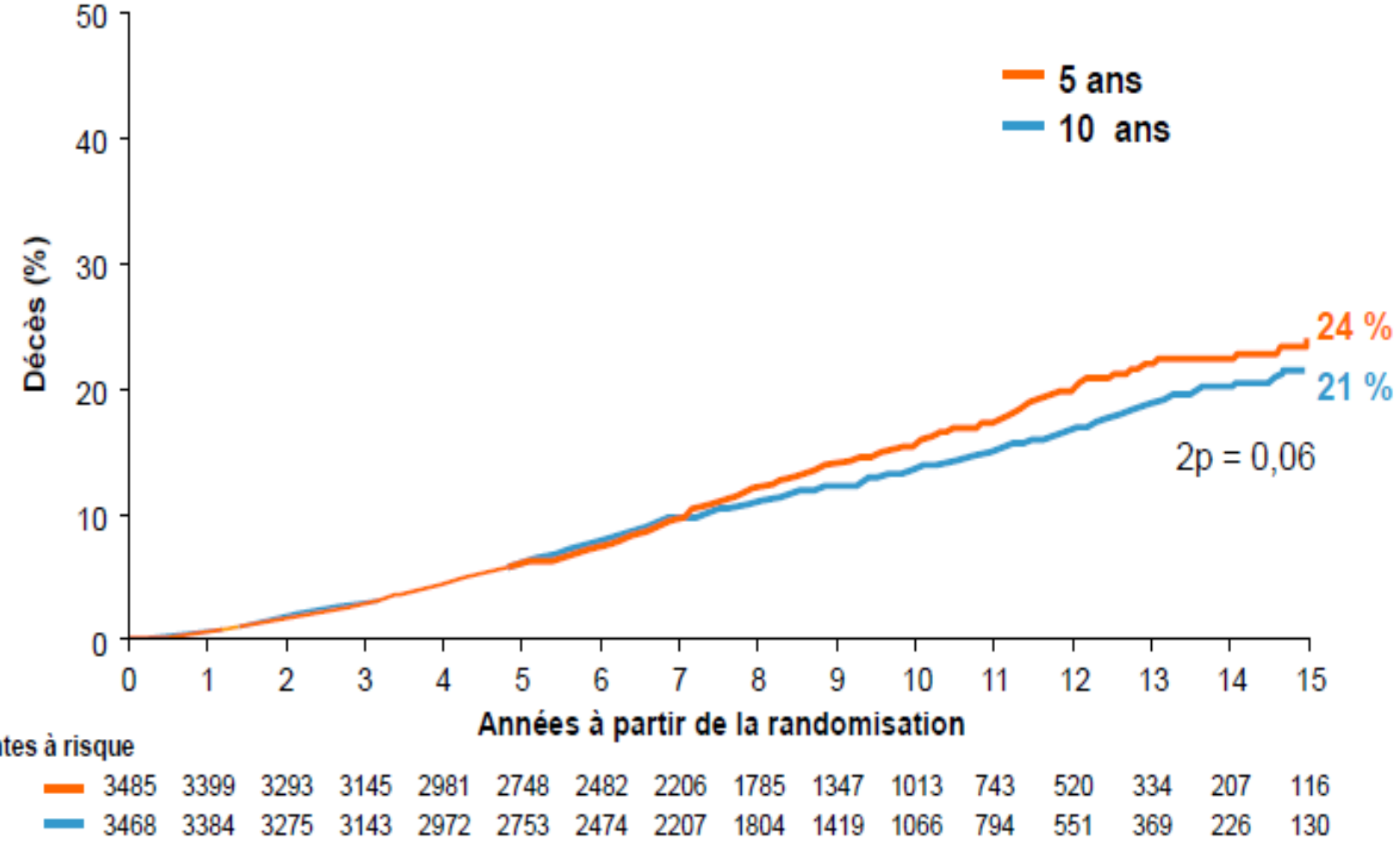
Tamoxifene: durée du traitement



Tamoxifene: durée du traitement



Tamoxifene: durée du traitement



Tamoxifene: durée du traitement

10 yrs vs 5 yrs BREAST CANCER MORTALITY IN ER+
rate ratio* by period in aTTom and ATLAS

	10 yrs tam. vs 5: aTTom trial (n=6934 ER+/UK)	10 yrs tam. vs 5: ATLAS trial* (n=10,543 ER+/UK)	10 yrs tam. vs 5: aTTom & ATLAS combined (n=17,477 ER+/UK)
years 5-9	**1.08** (0.85-1.38)	**0.92** (0.77-1.09)	**0.97** (0.84-1.15)
years 10+	**0.75**† (0.63-0.90)	**0.75**§ (0.63-0.90)	**0.75**† (0.65-0.86)
All years	**0.88**‡ (0.74-1.03)	**0.83**‡ (0.73-0.94)	**0.85**‡ (0.77-0.94)
	†p=0.007 ‡p=0.1	§p=0.002 ‡p=0.004	†p=0.00004 ‡p=0.001

*Inverse-variance-weighted estimate of the effect in ER+.(ATLAS, *Lancet* 2013)

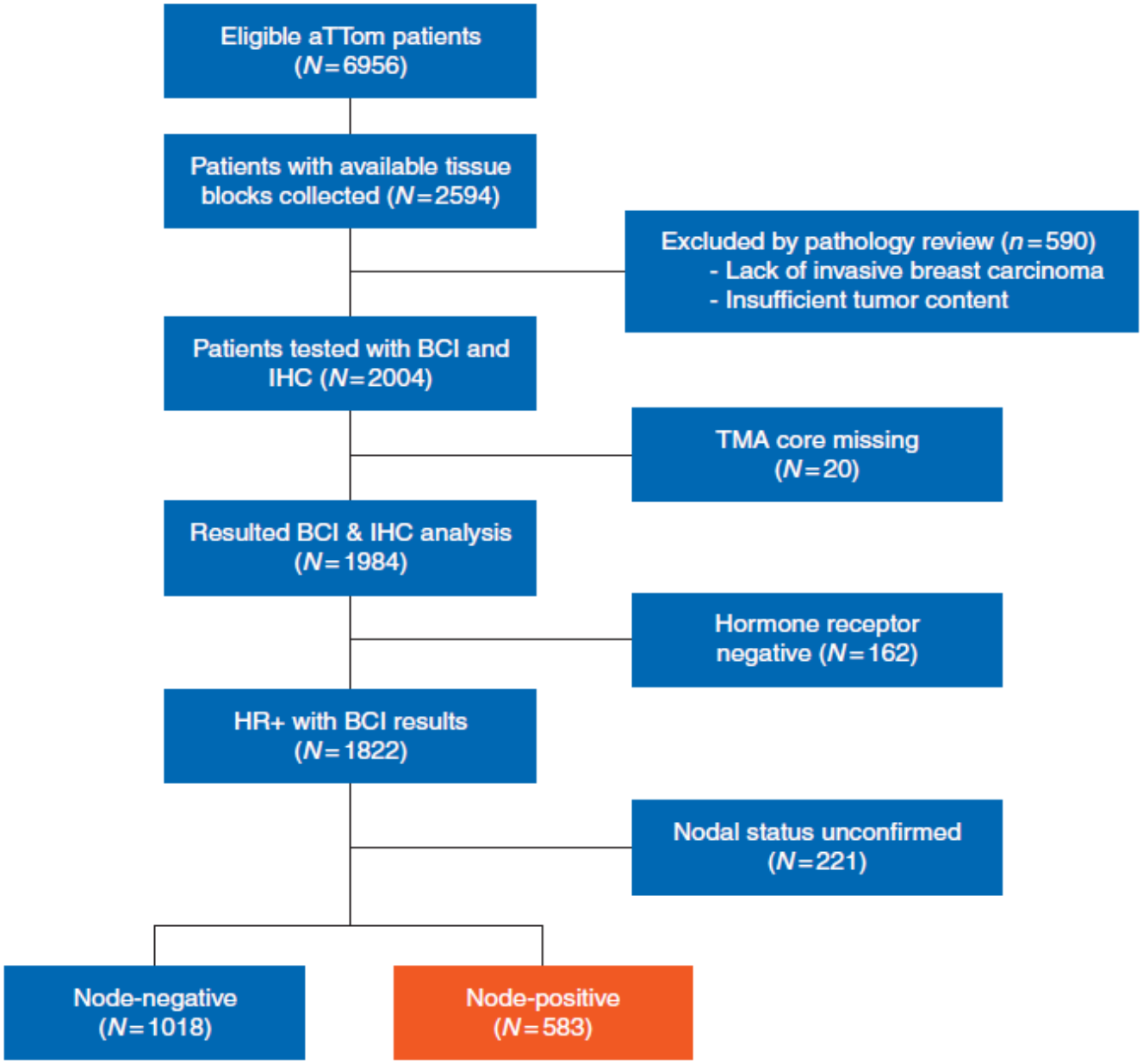
Tamoxifene: durée du traitement

ESM

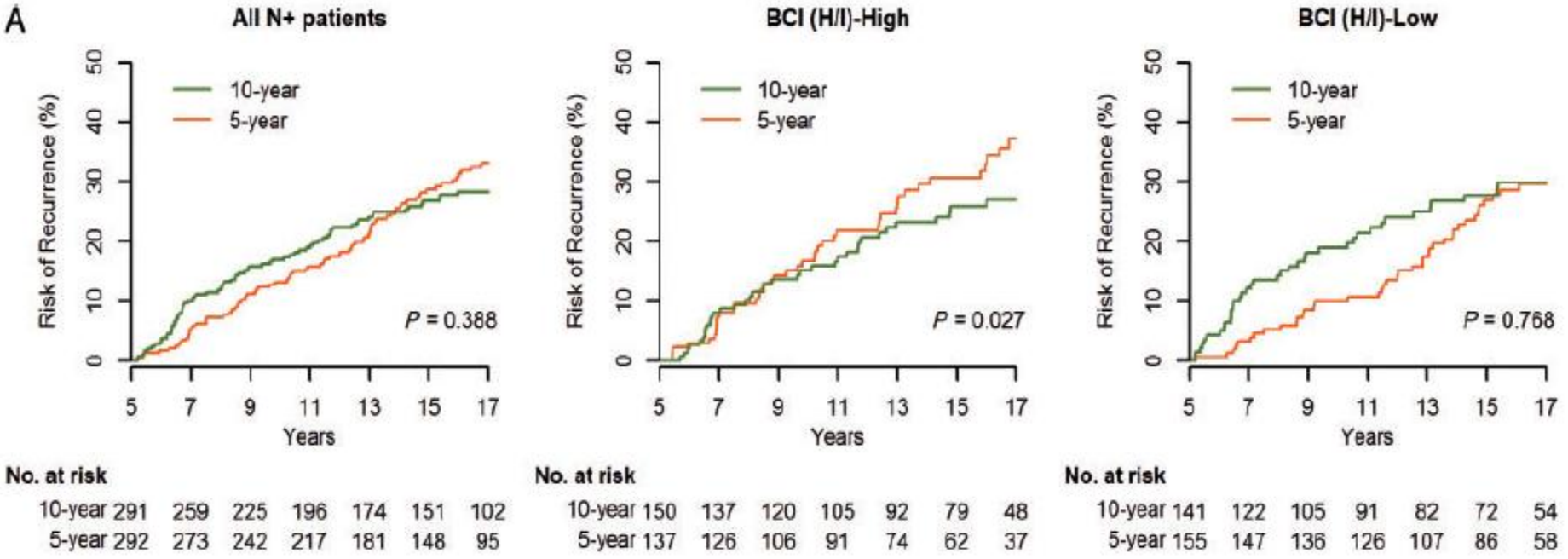
ORIGIN

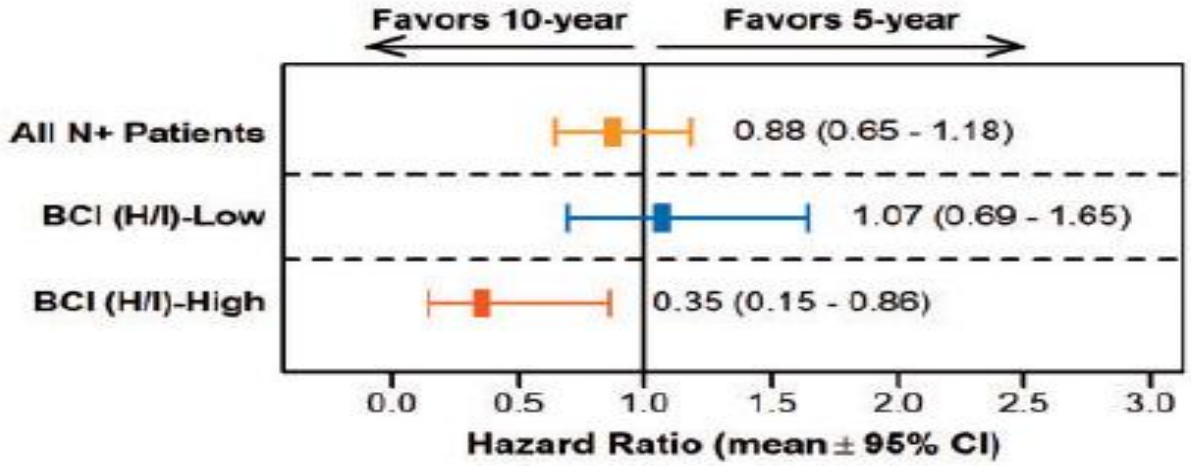
Brea
exte
treat
(aTT

J. M. S. B



Tamoxifene: durée du traitement





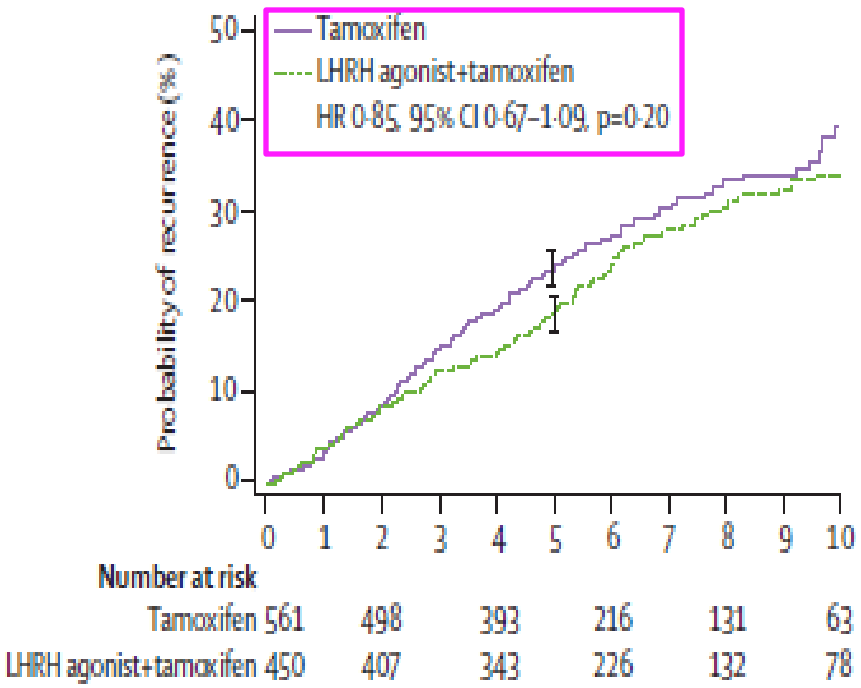
Tamoxifene et suppression ovarienne

Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials

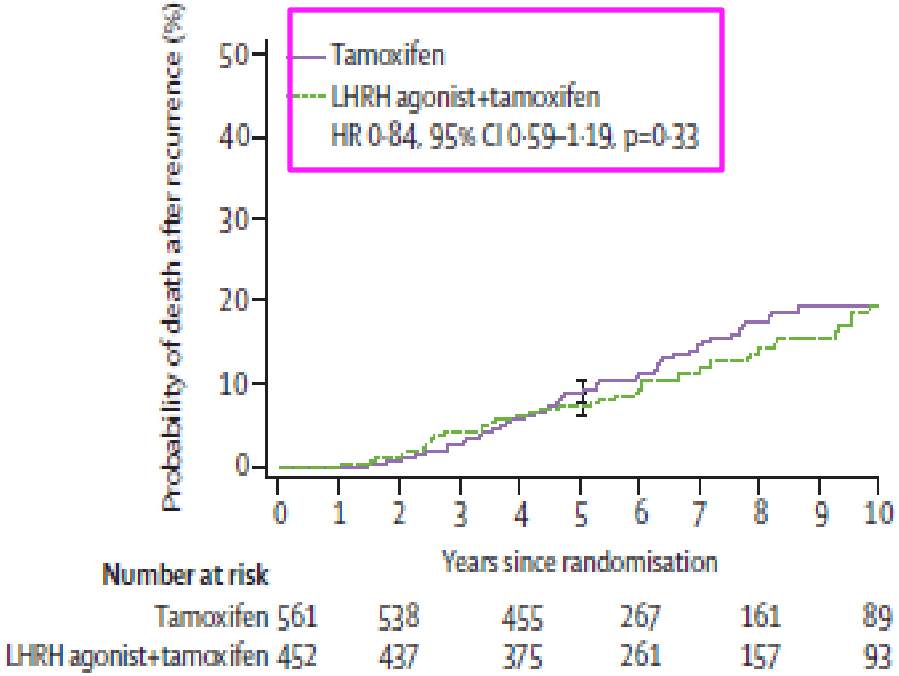
Lancet 2007; 369: 1711–23

*LHRH-agonists in Early Breast Cancer Overview group**

1061 patients



Rechutes



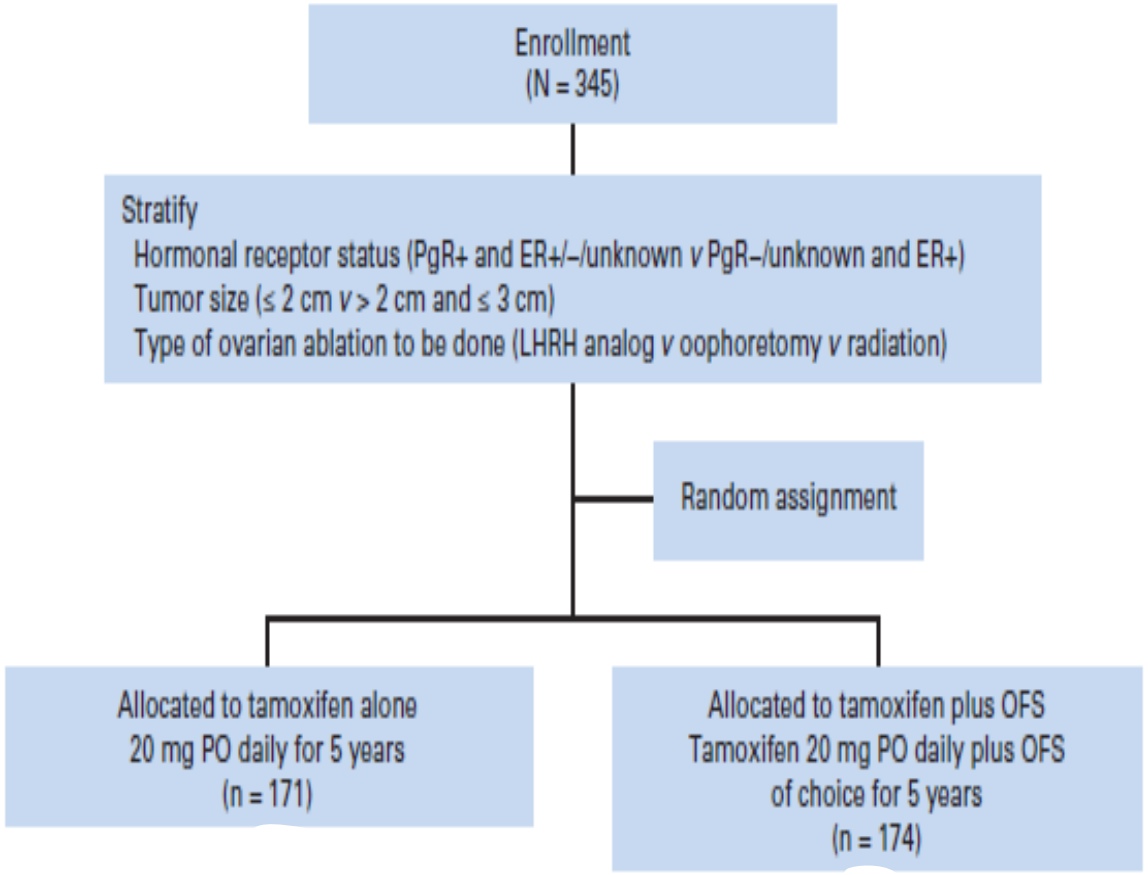
Décès

Tamoxifene et suppression ovarienne

Phase III Comparison of Tamoxifen Versus Tamoxifen Plus Ovarian Function Suppression in Premenopausal Women With Node-Negative, Hormone Receptor–Positive Breast Cancer (E-3193, INT-0142): A Trial of the Eastern Cooperative Oncology Group

Amye J. Tevaarwerk, Molin Wang, Fengmin Zhao, John H. Fetting, David Cella, Lynne

J Clin Oncol 32:3948-3958. © 2014



***RH +**

***Taille < 3 cm**

***N –**

***Pas de chimiothérapie**

***Castration chimique, radique ou chirurgicale**

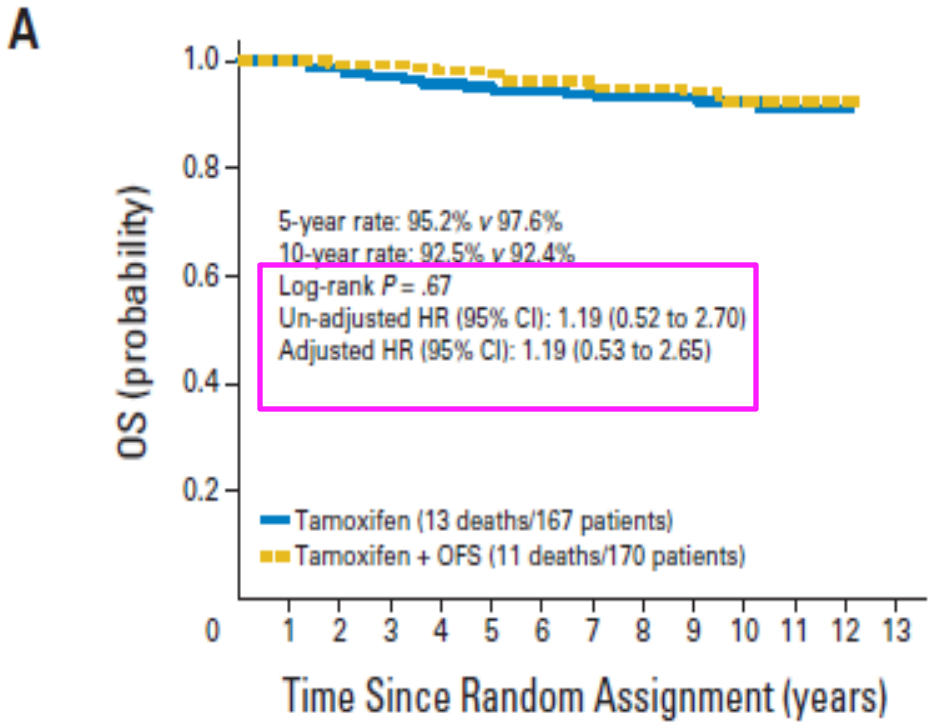
***Durée du traitement: 5 ans**

***Objectif primaire: SG et SSM**

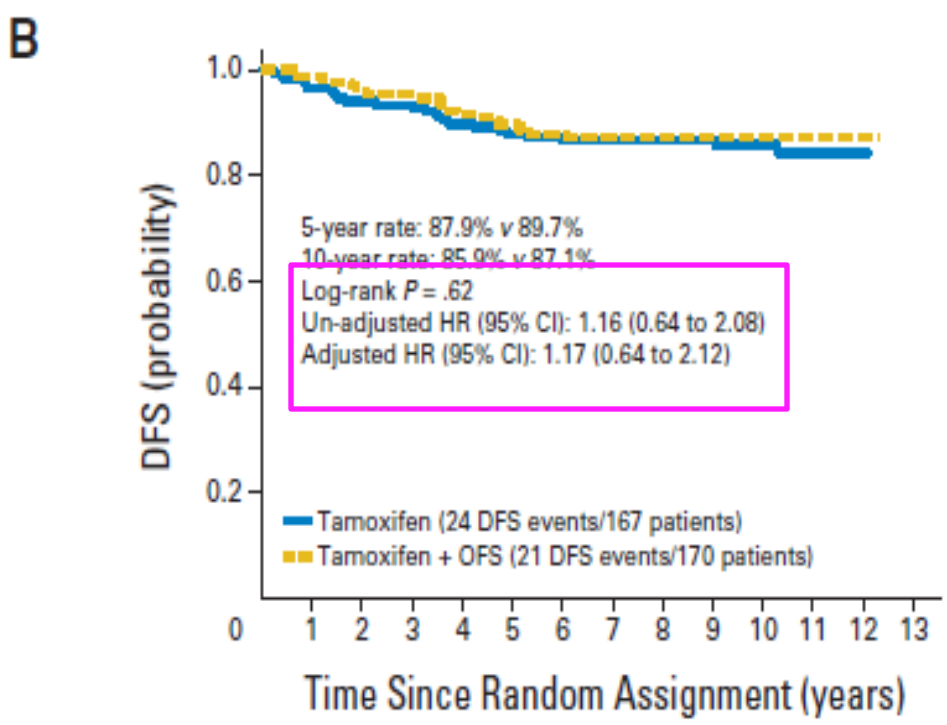
Tamoxifene et suppression ovarienne

Phase III Comparison of Tamoxifen Versus Tamoxifen Plus Ovarian Function Suppression in Premenopausal Women With Node-Negative, Hormone Receptor–Positive Breast Cancer (E-3193, INT-0142): A Trial of the Eastern Cooperative Oncology Group

Amye J. Tevaarwerk, Molin Wang, Fengmin Zhao, John H. Fetting, David Cella, Lynne I. Wagner,



No. at risk														
Tamoxifen	167	167	163	160	157	153	149	143	140	128	76	27	2	0
Tamoxifen + OFS	170	169	167	165	160	155	152	147	136	115	69	23	6	0



No. at risk														
Tamoxifen	167	161	155	154	147	141	136	131	130	118	68	24	2	0
Tamoxifen + OFS	170	166	160	156	148	141	137	133	124	105	65	21	5	0

Tamoxifene et suppression ovarienne

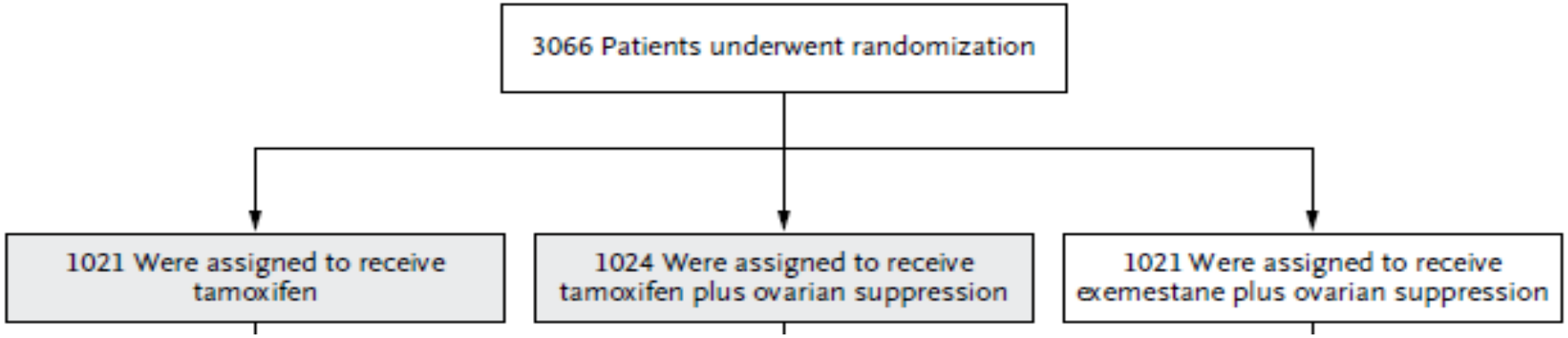
ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

N Engl J Med 2015;372:436-46.

Prudence A. Francis, M.D., Meredith M. Regan, Sc.D., Gini F. Fleming, M.D.,

SOFT



***K sein opérable**

***RH + (≥ 10%)**

***femme préménopausée ou statut non ménopausique dans les 8 mois suivant la CT**

***Castration chimique (Triptorelin 3,75 mg mensuel), radique ou chirurgicale**

***Suivie de 67 mois**

***Durée du traitement: 5 ans**

***Objectif primaire : survie sans maladie**

Tamoxifene et suppression ovarienne

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)

Tamoxifene et suppression ovarienne

ORIGINAL ARTICLE

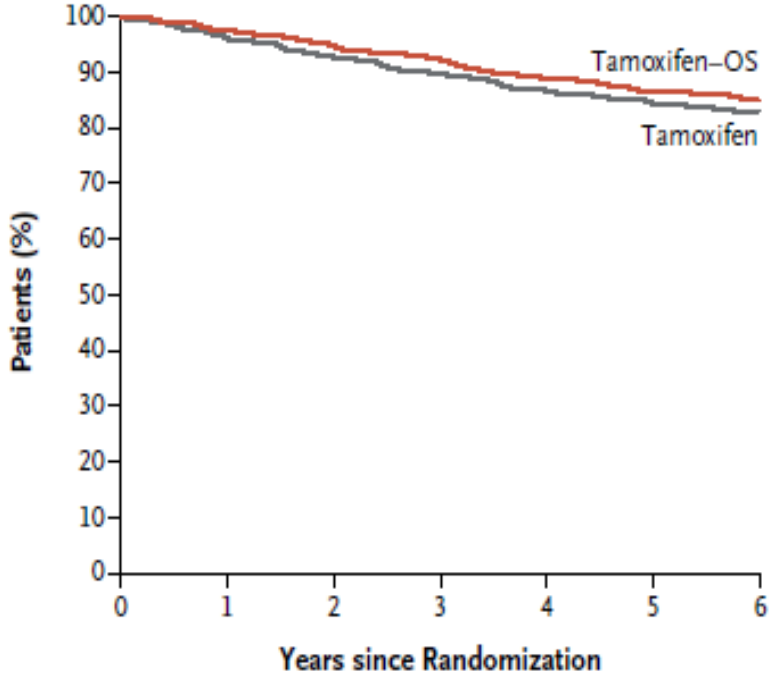
Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

N Engl J Med 2015;372:436-46.

Prudence A. Francis, M.D., Meredith M. Regan, Sc.D., Gini F. Fleming, M.D.,

SOFT

A Disease-free Survival



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

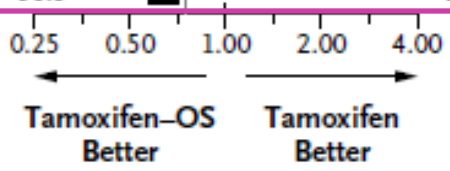
	No. of Patients	No. of Patients with Event	5-Yr Rate %
Tamoxifen	1018	160	84.7
Tamoxifen–OS	1015	139	86.6

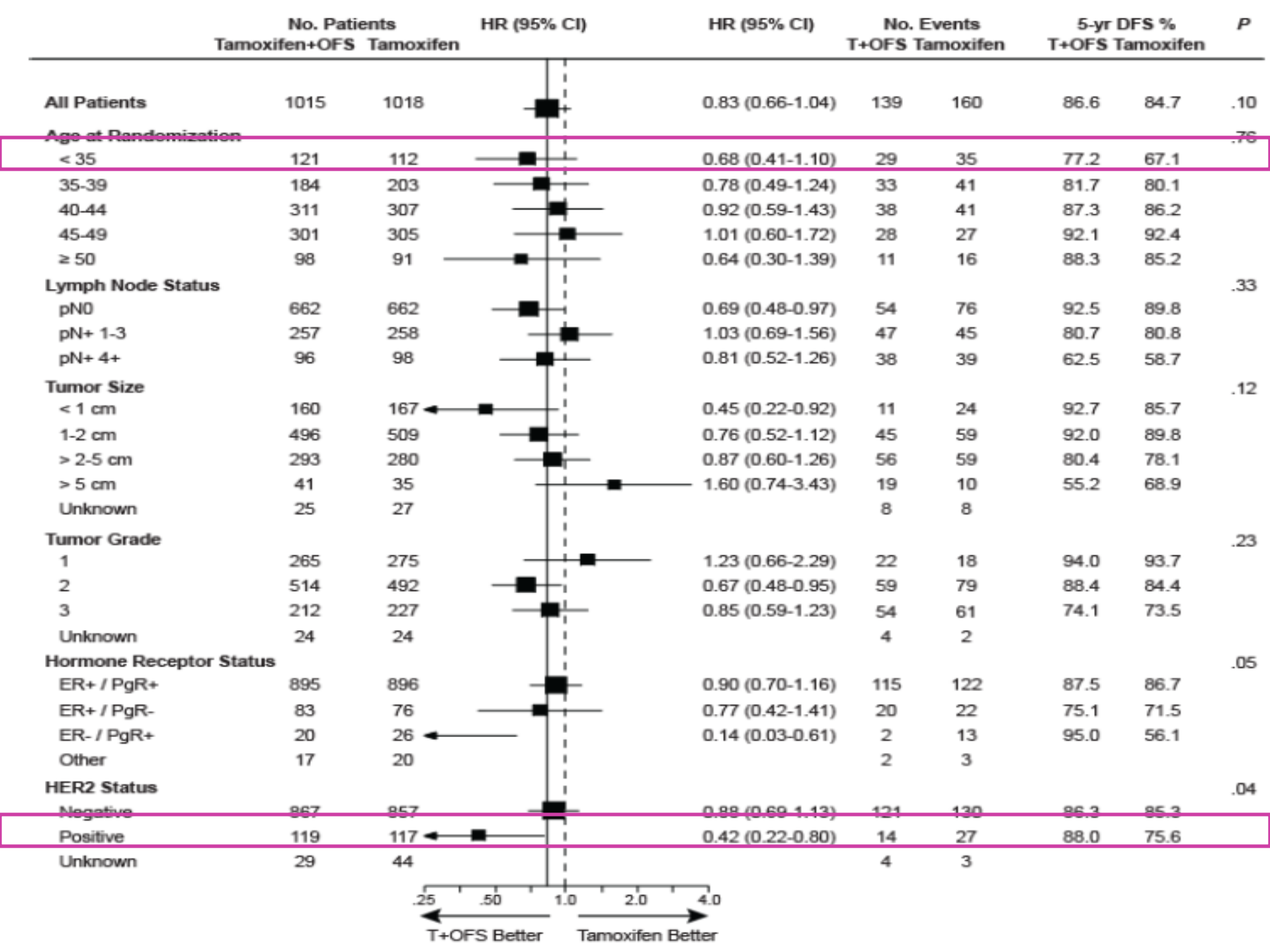
Hazard ratio for recurrence, second invasive cancer, or death, 0.83 (95% CI, 0.66–1.04)
P=0.10

Tamoxifene et suppression ovarienne

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)	




No. Patients
Tamoxifen+OFS
Tamoxifen
HR (95% CI)
HR (95% CI)
No. Events
T+OFS
Tamoxifen
5-yr DFS %
T+OFS
Tamoxifen
P
All Patients 1015 1018 0.83 (0.66-1.04) 139 160 86.6 84.7 .10
Age at Randomization .76
< 35 121 112 0.68 (0.41-1.10) 29 35 77.2 67.1
35-39 184 203 0.78 (0.49-1.24) 33 41 81.7 80.1
40-44 311 307 0.92 (0.59-1.43) 38 41 87.3 86.2
45-49 301 305 1.01 (0.60-1.72) 28 27 92.1 92.4
≥ 50 98 91 0.64 (0.30-1.39) 11 16 88.3 85.2
Lymph Node Status .33
pN0 662 662 0.69 (0.48-0.97) 54 76 92.5 89.8
pN+ 1-3 257 258 1.03 (0.69-1.56) 47 45 80.7 80.8
pN+ 4+ 96 98 0.81 (0.52-1.26) 38 39 62.5 58.7
Tumor Size .12
< 1 cm 160 167 0.45 (0.22-0.92) 11 24 92.7 85.7
1-2 cm 496 509 0.76 (0.52-1.12) 45 59 92.0 89.8
> 2-5 cm 293 280 0.87 (0.60-1.26) 56 59 80.4 78.1
> 5 cm 41 35 1.60 (0.74-3.43) 19 10 55.2 68.9
Unknown 25 27 8 8
Tumor Grade .23
1 265 275 1.23 (0.66-2.29) 22 18 94.0 93.7
2 514 492 0.67 (0.48-0.95) 59 79 88.4 84.4
3 212 227 0.85 (0.59-1.23) 54 61 74.1 73.5
Unknown 24 24 4 2
Hormone Receptor Status .05
ER+ / PgR+ 895 896 0.90 (0.70-1.16) 115 122 87.5 86.7
ER+ / PgR- 83 76 0.77 (0.42-1.41) 20 22 75.1 71.5
ER- / PgR+ 20 26 0.14 (0.03-0.61) 2 13 95.0 56.1
Other 17 20 2 3
HER2 Status .04
Negative 867 857 0.88 (0.69-1.13) 121 130 86.3 85.3
Positive 119 117 0.42 (0.22-0.80) 14 27 88.0 75.6
Unknown 29 44 4 3
.25
.50
1.0
2.0
4.0
T+OFS Better
Tamoxifen Better

Tamoxifene et suppression ovarienne

Tamoxifen with ovarian function suppression versus tamoxifen alone as an adjuvant treatment for premenopausal breast cancer: a meta-analysis of published randomized controlled trials

Shunchao Yan[1] OncoTargets and Therapy 2015:8

Table 1 Characteristics of the studies included in this meta-analysis

Study name	Recruitment period	Entry criteria (stage)	HR status	Determination of menopausal status	Median age	Treatment arms (patients number)	TAM treatment	Chemotherapy	Median follow-up
ZIPP[8]	1987–1999	Stage I or II	Regardless of ER status	LMP of <6 months	44	Observation (451) Goserelin (469) TAM (880) TAM + goserelin (885)	2 years	Permitted	5.5 years
ABC (OSA)[9]	1993–2000	T1-3a, N0-1, M0	Regardless of ER status	LMP of <12 months	43	TAM (1,081) TAM + OSA (1,063)	5 years	Permitted	5.9 years
E-3193[14]	1994–1997	T ≤3 cm, N0	ER positive and/or PR positive	LMP ≤6 months, or premenopausal estradiol level in women of ≤55 years	45	TAM (167) TAM + OFS (170)	5 years	Not permitted	9.9 years
SOFT[15]	2003–2011	T1-3, N0-2	ER or PR in at least 10% of the cells	LMP of ≤6 months and/or premenopausal estradiol level	43	TAM (1,018) TAM + OFS (1,015) Exemestane + OFS (1,021)	5 years	Permitted	5.6 years

Tamoxifene et suppression ovarienne

Tamoxifen with ovarian function suppression versus tamoxifen alone as an adjuvant treatment for premenopausal breast cancer: a meta-analysis of published randomized controlled trials

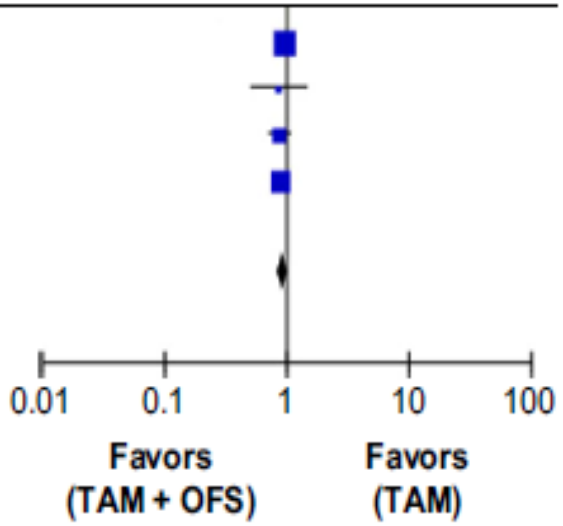
Shunchao Yan[1] OncoTargets and Therapy 2015:8

DFS

A

Study or subgroup	TAM + OFS Events	Total	TAM Events	Total	Weight	Risk ratio M–H, fixed, 95% CI
ABC (OAS)[9]	290	1,063	306	1,081	41.3%	0.96 (0.84, 1.10)
E-3193[14]	21	170	24	167	3.3%	0.86 (0.50, 1.48)
SOFT[15]	139	1,015	160	1,018	21.7%	0.87 (0.71, 1.07)
ZIPP[8]	221	885	247	880	33.7%	0.89 (0.76, 1.04)
Total (95% CI)		**3,133**		**3,146**	**100%**	**0.92 (0.84, 1.00)**
Total events	671		737			

Heterogeneity: χ^2=0.94, *df*=3 (*P*=0.82); I^2=0%
Test for overall effect: *Z*=1.90 (*P*=0.06)



Tamoxifene et suppression ovarienne

Tamoxifen with ovarian function suppression versus tamoxifen alone as an adjuvant treatment for premenopausal breast cancer: a meta-analysis of published randomized controlled trials

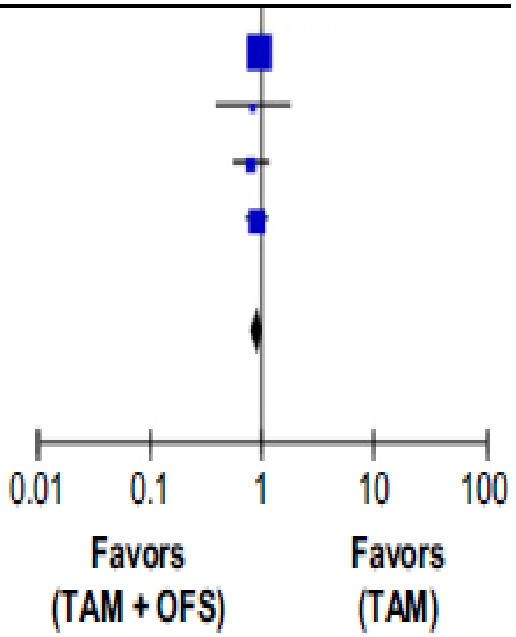
Shunchao Yan[1] OncoTargets and Therapy 2015:8

OS

B

Study or subgroup	TAM + OFS Events	TAM + OFS Total	TAM Events	TAM Total	Weight	Risk ratio M–H, fixed, 95% CI
ABC (OAS)[9]	215	1,063	230	1,081	53.2%	0.95 (0.81, 1.12)
E-3193[14]	11	170	13	167	3.1%	0.83 (0.38, 1.80)
SOFT[15]	47	1,015	59	1,018	13.7%	0.80 (0.55, 1.16)
ZIPP[8]	116	885	128	880	30.0%	0.90 (0.71, 1.14)
Total (95% CI)		**3,133**		**3,146**	**100%**	**0.91 (0.80, 1.03)**
Total events	389		430			

Heterogeneity: χ^2=0.79, *df*=3 (*P*=0.85); I^2=0%
Test for overall effect: *Z*=1.45 (*P*=0.15)



Tamoxifene et suppression ovarienne

Tamoxifen with ovarian function suppression versus tamoxifen alone as an adjuvant treatment for premenopausal breast cancer: a meta-analysis of published randomized controlled trials

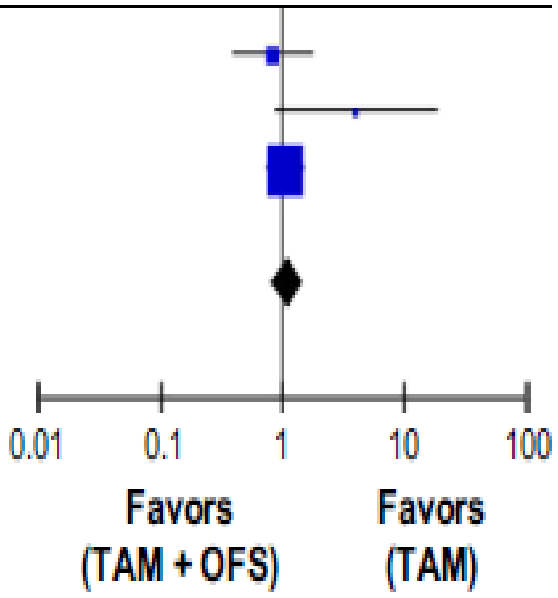
Shunchao Yan[1] OncoTargets and Therapy 2015:8

OS CT-

A

Study or subgroup	TAM + OFS Events	Total	TAM Events	Total	Weight	Risk ratio M–H, fixed, 95% CI
E-3193[14]	11	170	13	167	19.7%	0.83 (0.38, 1.80)
SOFT[15]	8	473	2	476	3.0%	4.03 (0.86, 18.86)
ZIPT[8]	55	527	51	517	77.3%	1.06 (0.74, 1.52)
Total (95% CI)		**1,170**		**1,160**	**100%**	**1.10 (0.80, 1.51)**
Total events	74		66			

Heterogeneity: χ^2=3.26, df=2 (P=0.20); I^2=39%
Test for overall effect: Z=0.60 (P=0.55)



Tamoxifene et suppression ovarienne

Tamoxifen with ovarian function suppression versus tamoxifen alone as an adjuvant treatment for premenopausal breast cancer: a meta-analysis of published randomized controlled trials

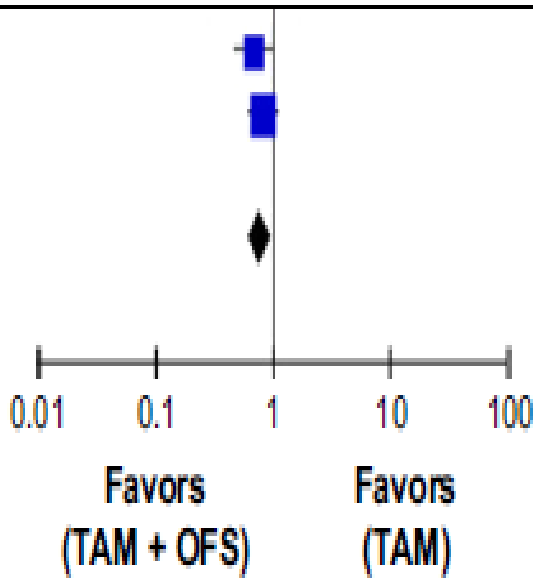
Shunchao Yan[1] OncoTargets and Therapy 2015:8

OS CT+

B

Study or subgroup	TAM + OFS Events	TAM + OFS Total	TAM Events	TAM Total	Weight	Risk ratio M–H, fixed, 95% CI
SOFT[15]	39	542	57	542	43.6%	0.68 (0.46, 1.01)
ZIPP[8]	60	355	74	358	56.4%	0.82 (0.60, 1.11)
Total (95% CI)		**897**		**900**	**100%**	**0.76 (0.60, 0.97)**
Total events	99		131			

Heterogeneity: χ^2=0.50, *df*=1 (*P*=0.48); I^2=0%
Test for overall effect: *Z*=2.23 (*P*=0.03)



Tamoxifene et suppression ovarienne

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

SOFT: SUPPRESSION OF OVARIAN FUNCTION TRIAL

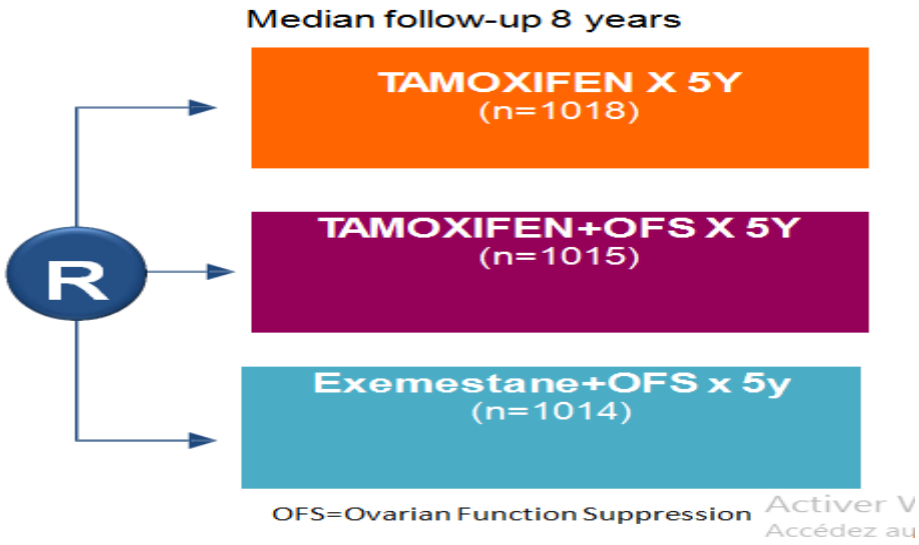
Durée: Dec 2003-Jan 2011

Stratification

CT:
- 47% des femmes : Pas de CT
-53% en pré ménopause après une CT

Statut ganglionnaire:
-Positive (34.5%)

Castration:
-Triptorelin (91%)



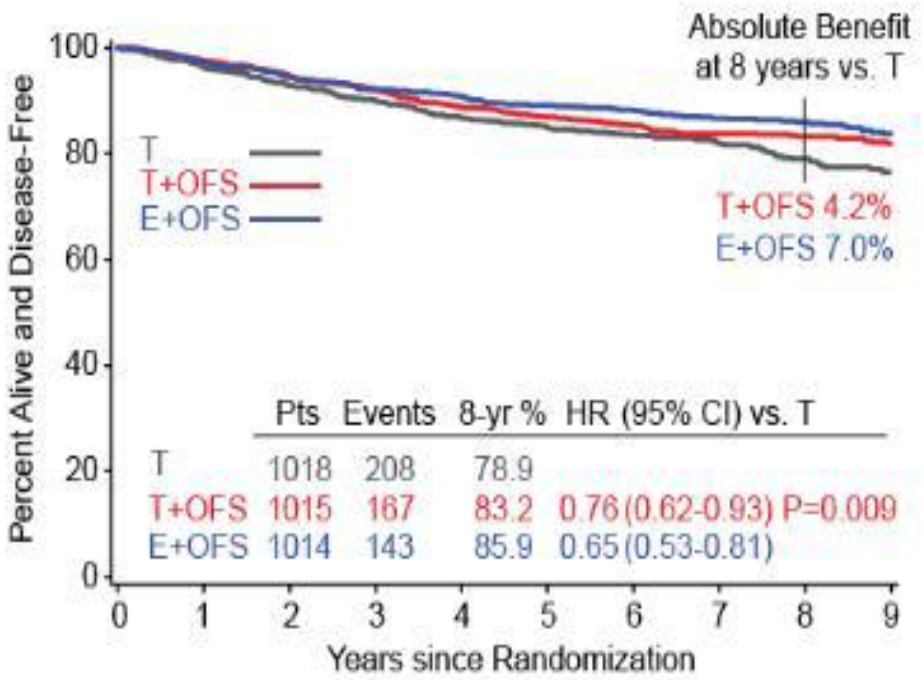
Francis P et al; NEJM 2018

Tamoxifene et suppression ovarienne

2017 SAN ANTONIO BREAST CANCER SYMPOSIUM December 5-9, 2017

SOFT DFS

8 years median follow-up



T+OFS significantly improves DFS vs T-alone in the overall population

Tamoxifene et suppression ovarienne

2017 SAN ANTONIO BREAST CANCER SYMPOSIUM — December 5-9, 2017

SOFT DFS

8 years median follow-up

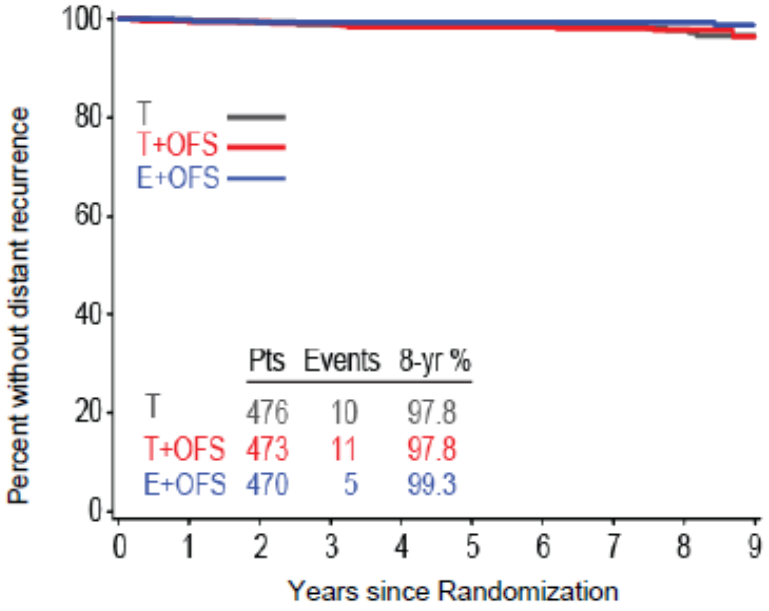
	8-yr DFS T	8-yr DFS T + OFS	HR: T + OFS vs T	8-yr DFS E + OFS	HR: E + OFS vs T
All	**78.9%**	**83.2%**	0.76 (0.62-0.93)	**85.9%**	0.65 (0.53-0.81)
No chemo	**87.4%**	**90.6%**	0.76 (0.52-1.12)	**92.5%**	0.58 (0.38-0.88)
Prior chemo	**71.4%**	**76.7%**	0.76 (0.60-0.97)	**80.4%**	0.68 (0.53-0.88)
<35 years (n=350)	**64.3%**	**73.0%**	0.66 (0.41-1.07)	**77.4%**	0.52 (0.31-0.87)

Fleming G. et al., SABCS 2017, GS4-03

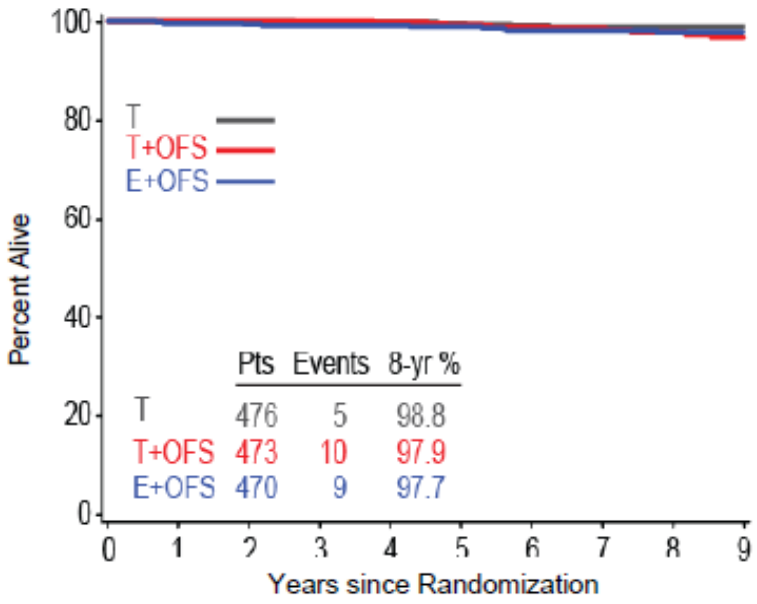
Tamoxifene et suppression ovarienne

Etude SOFT: Patientes sans CT adjuvante

Distant Recurrence-Free Interval



Overall Survival



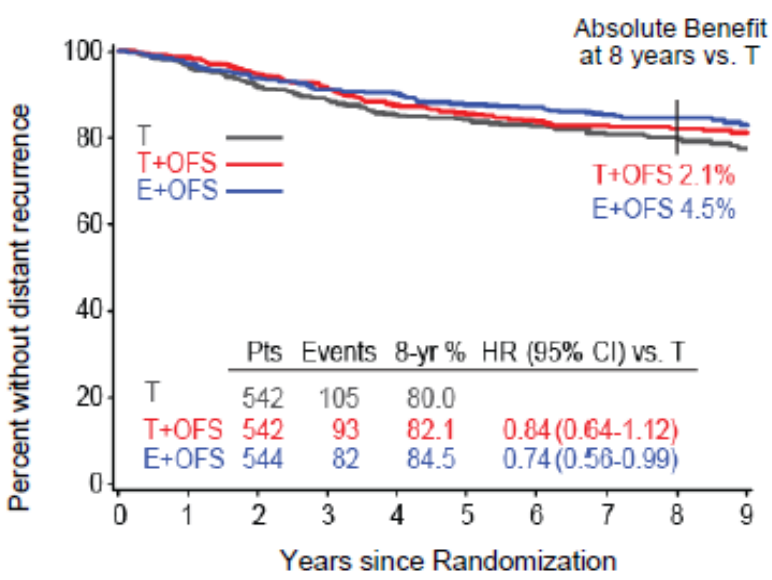
→ Population à très faible risque de rechute.

Fleming G. et al., SABCS 2017, GS4-03

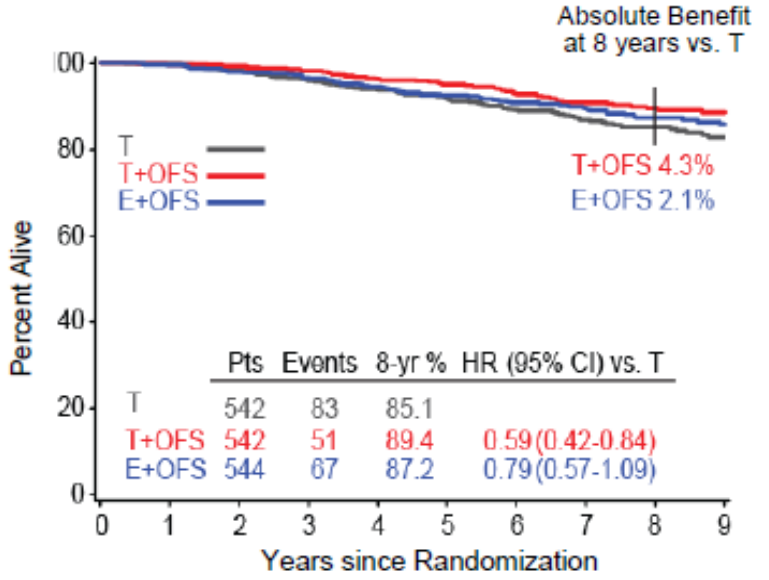
Tamoxifene et suppression ovarienne

Etude SOFT: Patientes avec CT adjuvante

Distant Recurrence-Free Interval



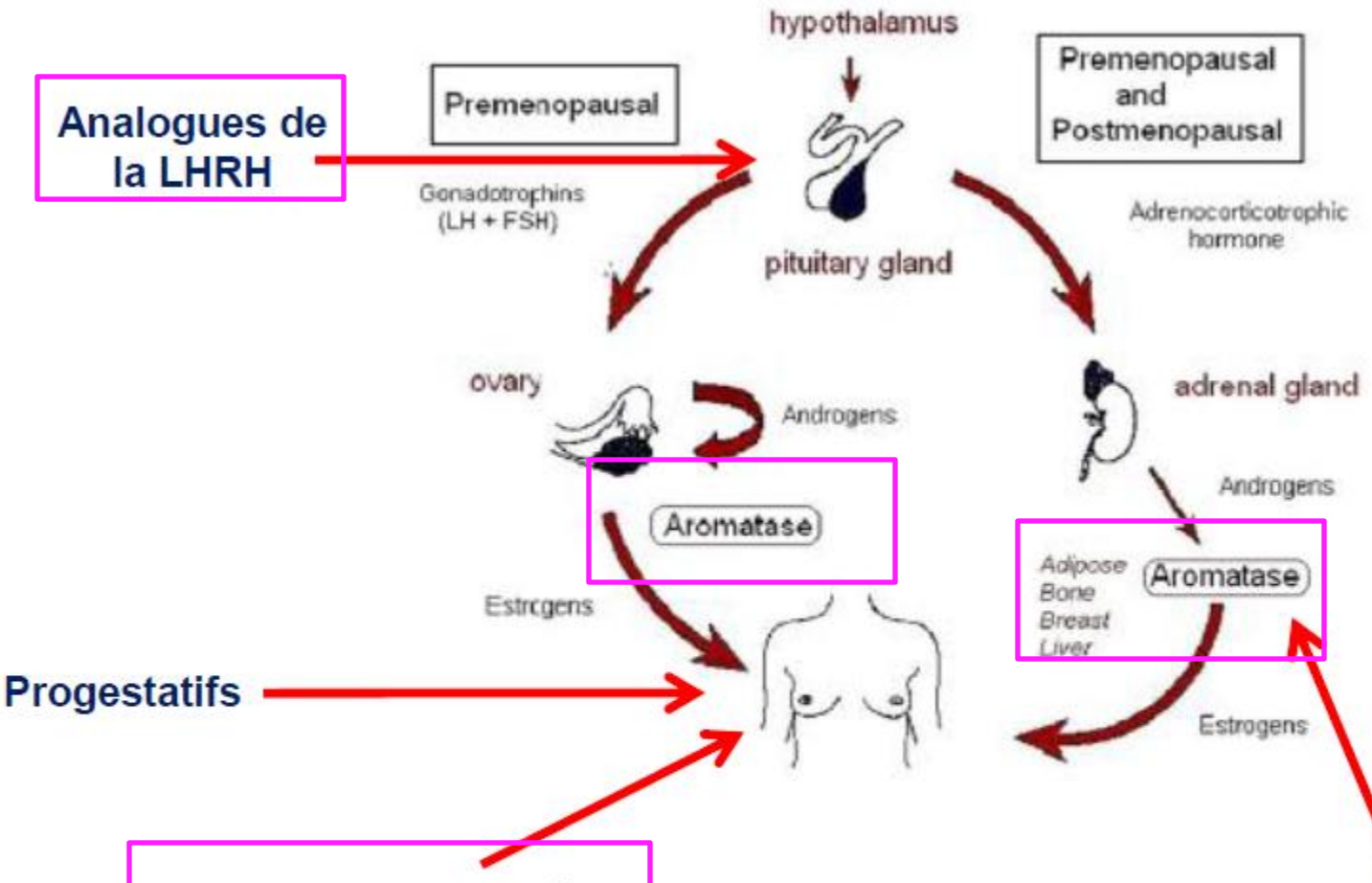
Overall Survival



→ Amélioration significative de la survie globale (HR = 0,59) dans le bras TAM + SO.

Fleming G. et al., SABCS 2017, GS4-03

Hormonothérapie dans le K du sein



SERM = **Anti-oestrogènes**

Selective Estrogen Receptor Modulators

- 35 ans d'utilisation
- Standard

Déplétion en oestrogènes au mieux réalisée par une **inhibition spécifique de l'aromatase** qui convertit les précurseurs des oestrogènes en oestradiol et oestrone

Hormonothérapie par anti aromatases

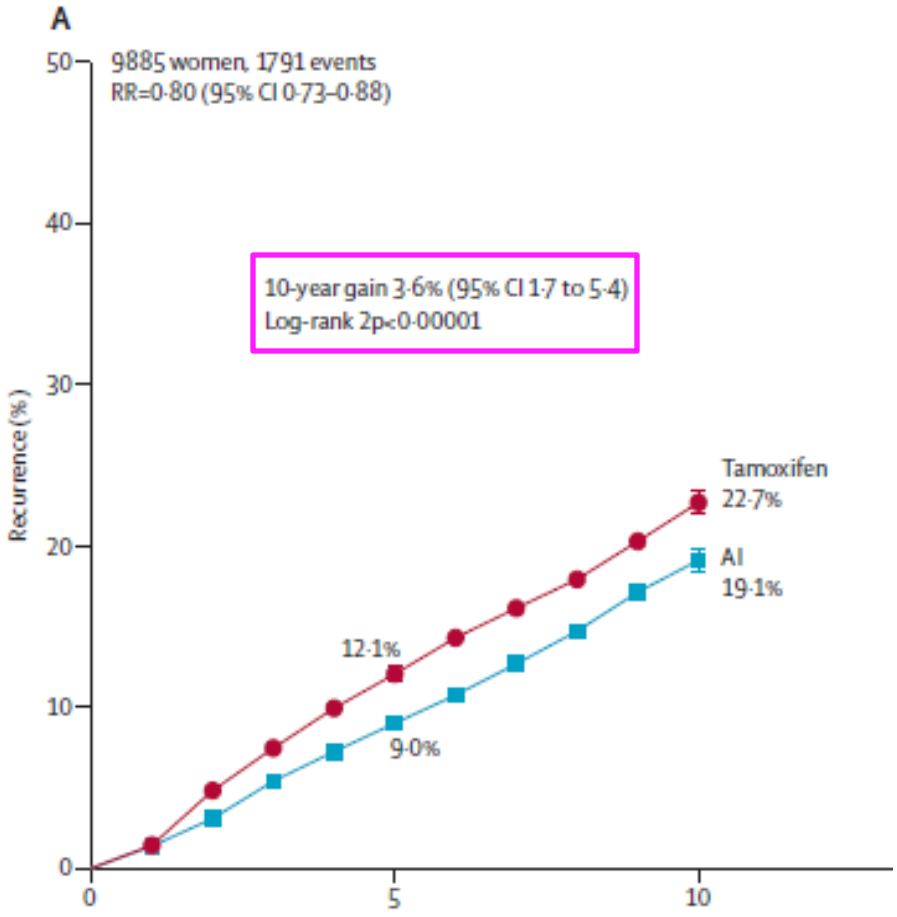
Study	Arms	DFS hazard ratio (95% CI)	TTR or RFS hazard ratio (95% CI)	TTDR or DRFI or DRFS or DDFS hazard ratio (95% CI)	BCFI or BCFS hazard ratio (95% CI)	OS hazard ratio (95% CI)
			Monotherapy analysis (versus tamoxifen)			
ATAC [53] 120-month follow-up	A versus T versus T + A (5 years)	0.91 (0.83-0.99) $P = 0.04$	TTR 0.84 (0.75-0.93) $P = 0.001$	TTDR 0.87 (0.77-0.99) $P = 0.03$	NA	0.97 (0.88-1.08) $P = 0.6$
		HR^+ patients 0.86 (0.78-0.95) $P = 0.003$	HR^+ patients 0.79 (0.70-0.89) $P = 0.0002$	HR^+ patients 0.85 (0.73-0.98) $P = 0.02$		HR^+ patients 0.95 (0.84-1.06) $P = 0.4$
BIG 1-98 [54] 8.1-year follow-up	L versus T	0.53 (0.78-0.96) $P = 0.007$	NA	DRFI 0.86 (0.74-0.998) $P = 0.047$	BCFI 0.86 (0.76-0.98) $P = 0.03$	0.87 (0.77-0.999) $P = 0.048$
		IPCW 0.82 (0.74-0.92) $P < 0.0002$		IPCW 0.79 (0.68-0.92) $P = 0.003$	IPCW 0.80 (0.70-0.92) $P = 0.002$	IPCW 0.79 (0.69-0.90) $P < 0.0006$
TEAM [45] 2.75-year follow-up (before the switch)	Upfront E (2.75 years) versus T	0.89 (0.77-1.03) $P = 0.12$	NA	NA	NA	NA
			Sequential therapy analysis			
IES [46] 91-month follow-up	T→ E versus T→ T (5 years)	0.81 (0.72-0.91) $P < 0.001$	NA	TTDR 0.84 (0.73-0.97) $P = 0.01$	BCFS 0.81 (0.71-0.92) $P < 0.001$	0.53 (0.75-0.99) $P < 0.04$
ARNO 95 [47] 30.1-month follow-up	T (2 years)→A (3 years) versus T (2 years)→T (3 years)	0.66 (0.44-1.00) $P = 0.049$	NA	NA	NA	0.53 (0.28-0.99) $P = 0.045$
ABCSG Trial 8 [48] 60-month follow-up	T (2 years)→A (3 years) versus T (5 years)	0.91 (0.75-1.103) $P = 0.33$	RFS 0.80 (0.631-1.013) $P = 0.06$	DRFS 0.78 (0.60-0.99) $P = 0.046$	NA	0.87 (0.64-1.16) $P = 0.33$
ITA [49] 128-month follow-up	T (2-3 years)→A (5 years) versus T (5 years)	NA	RFS 0.64 (0.44-0.94) $P = 0.02$	NA	BCFS 0.72 (0.44-1.17) $P = 0.2$	0.79 (0.52-1.21) $P = 0.3$
BIG 1-98 [54] 8.1-year follow-up	L→T versus T→L (5 years)	L→T 1.06 (0.91-1.23) $P = 0.48$	NA	L→T DRFI 1.14 (0.92-1.42) $P = 0.24$	L→T BCFI 1.10 (0.91-1.32) $P = 0.34$	L→T 0.97 (0.80-1.19) $P = 0.79$
		T→L 1.07 (0.92-1.25) $P = 0.36$		T→L 1.23 (0.99-1.53) $P = 0.06$	T→L 1.16 (0.96-1.40) $P = 0.12$	T→L 1.10 (0.90-1.33) $P = 0.36$
TEAM [55] 5-year follow-up (after the switch)	E (5 years) versus sequential T→E	1.06 (0.91-1.24) $P = 0.42$	RFS 1.06 (0.88-1.28) $P = 0.53$	NA	NA	1.00 (0.89-1.14) $P > 0.99$

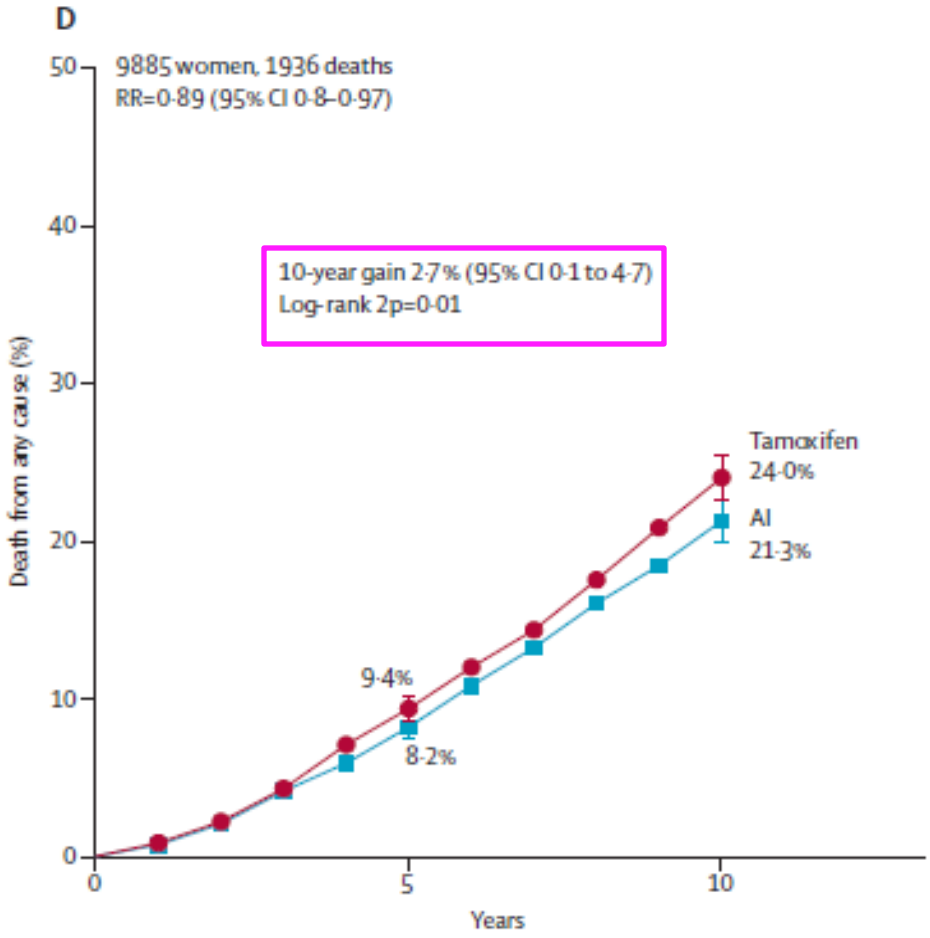
Hormonothérapie par anti aromatases

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2015; 386: 1341–52





Hormonothérapie par anti aromatases

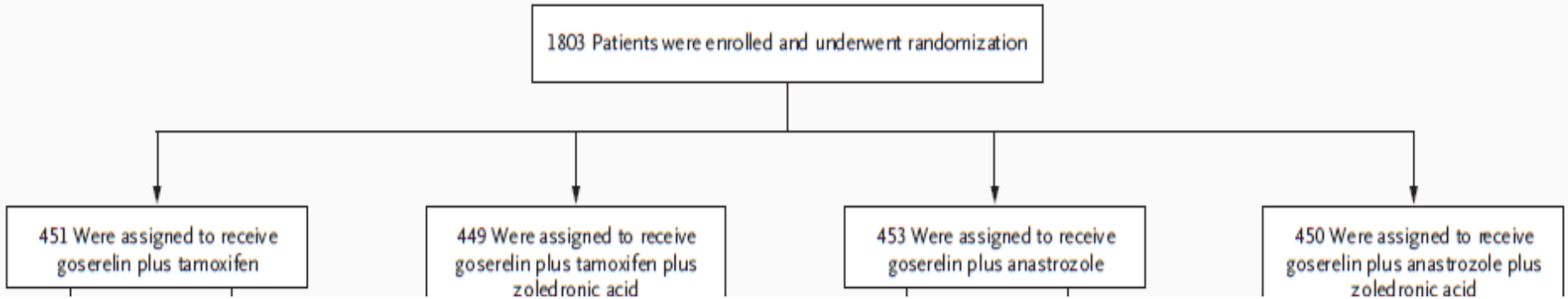
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

ABCSG 12

Michael Gnant, M.D., Brigitte Mlineritsch, M.D., Walter Schippinger, M.D.,



***1803 patientes avec K sein stade I-II**
***RH + (> 10%)**
***< 10 N+**
***Pas de tumeurs pT4**
***Pas de chimiothérapie adjuvante (CT néoadjuvante possible)**
***Castration chimique par Goserelin 3,6 mg mensuel**
***Durée du traitement: 3 ans**
***Objectif primaire : survie sans maladie**

Gnant M et al, N Engl J Med 2009.

Table 1. Demographic and Baseline Disease Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Tamoxifen (N=451)	Tamoxifen plus Zoledronic Acid (N=449)	Anastrozole (N=453)	Anastrozole plus Zoledronic Acid (N=450)
Age at study entry				
Median — yr	45.5	45.3	45.0	44.5
Range — yr	27.6–56.5	27.5–56.3	25.9–56.3	28.8–56.4
≤40 yr — no. (%)	80 (17.7)	67 (14.9)	88 (19.4)	91 (20.2)
>40 yr — no. (%)	370 (82.0)	382 (85.1)	364 (80.4)	358 (79.6)
Cancer stage — no. (%)				
T1	338 (74.9)	335 (74.6)	348 (76.8)	339 (75.3)
≥T2	99 (22.0)	98 (21.8)	93 (20.5)	97 (21.6)
Unknown	13 (2.9)	16 (3.6)	11 (2.4)	13 (2.9)
Nodal status — no. (%)				
Negative	301 (66.7)	295 (65.7)	303 (66.9)	302 (67.1)
Positive	136 (30.2)	138 (30.7)	139 (30.7)	135 (30.0)
Unknown	13 (2.9)	16 (3.6)	10 (2.2)	12 (2.7)
Histologic grade — no. (%)				
1 or 2	344 (76.3)	344 (76.6)	344 (75.9)	339 (75.3)
3	93 (20.6)	89 (19.8)	97 (21.4)	98 (21.8)
Unknown	13 (2.9)	16 (3.6)	11 (2.4)	12 (2.7)
Estrogen-receptor status — no. (%)†				
Negative	16 (3.5)	19 (4.2)	15 (3.3)	17 (3.8)
Low expression	51 (11.3)	61 (13.6)	54 (11.9)	58 (12.9)
Medium expression	166 (36.8)	149 (33.2)	167 (36.9)	153 (34.0)
High expression	204 (45.2)	204 (45.4)	206 (45.5)	210 (46.7)
Unknown‡	14 (3.1)	16 (3.6)	11 (2.4)	12 (2.7)
Progesterone-receptor status — no. (%)†				
Negative	40 (8.9)	32 (7.1)	34 (7.5)	36 (8.0)
Low expression	52 (11.5)	64 (14.3)	58 (12.8)	59 (13.1)
Medium expression	160 (35.5)	142 (31.6)	149 (32.9)	131 (29.1)
High expression	185 (41.0)	195 (43.4)	200 (44.2)	212 (47.1)
Unknown‡	14 (3.1)	16 (3.6)	12 (2.6)	12 (2.7)
Preoperative chemotherapy — no. (%)				
No	406 (90.0)	404 (90.0)	408 (90.1)	405 (90.0)
Yes	24 (5.3)	23 (5.1)	24 (5.3)	26 (5.8)
Unknown	21 (4.7)	22 (4.9)	21 (4.6)	19 (4.2)

Hormonothérapie par anti aromatases

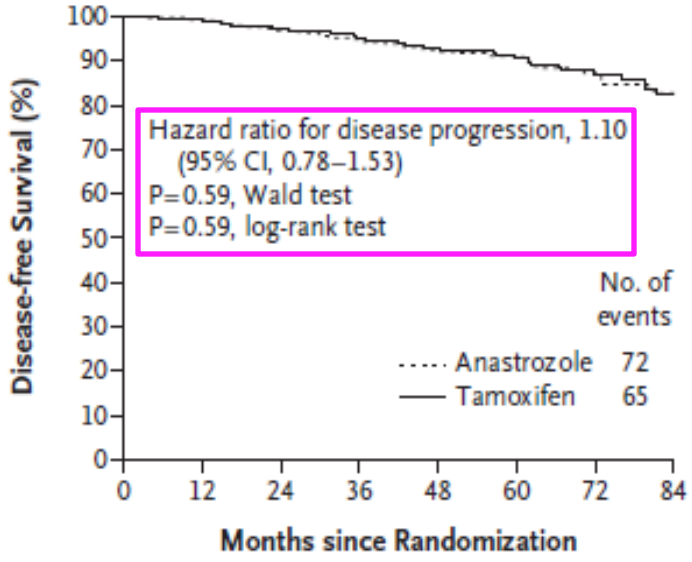
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Endocrine Therapy plus Zoledronic Acid in Premenopausal Breast Cancer

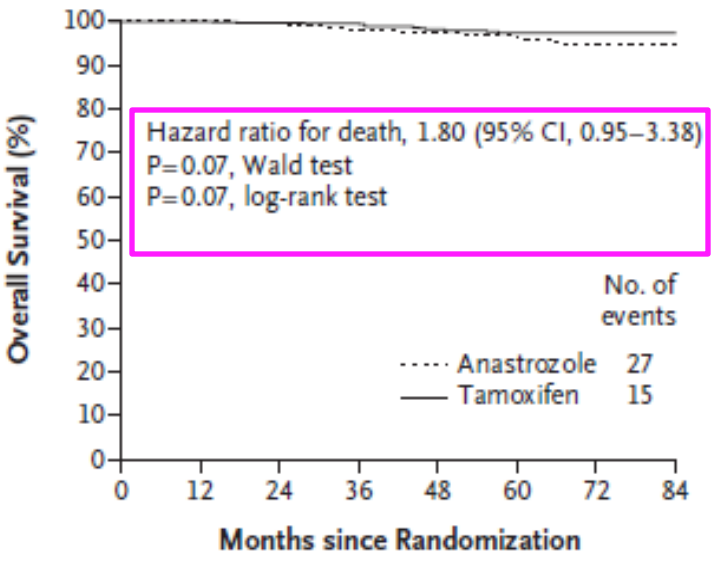
Michael Gnant, M.D., Brigitte Mlineritsch, M.D., Walter Schippinger, M.D.,

A



No. at Risk								
Anastrozole	903	844	725	540	411	255	139	51
Tamoxifen	900	834	718	552	411	243	129	50

E



No. at Risk								
Anastrozole	903	849	743	558	436	271	151	59
Tamoxifen	900	840	736	580	439	264	141	60

Hormonothérapie par anti aromatases

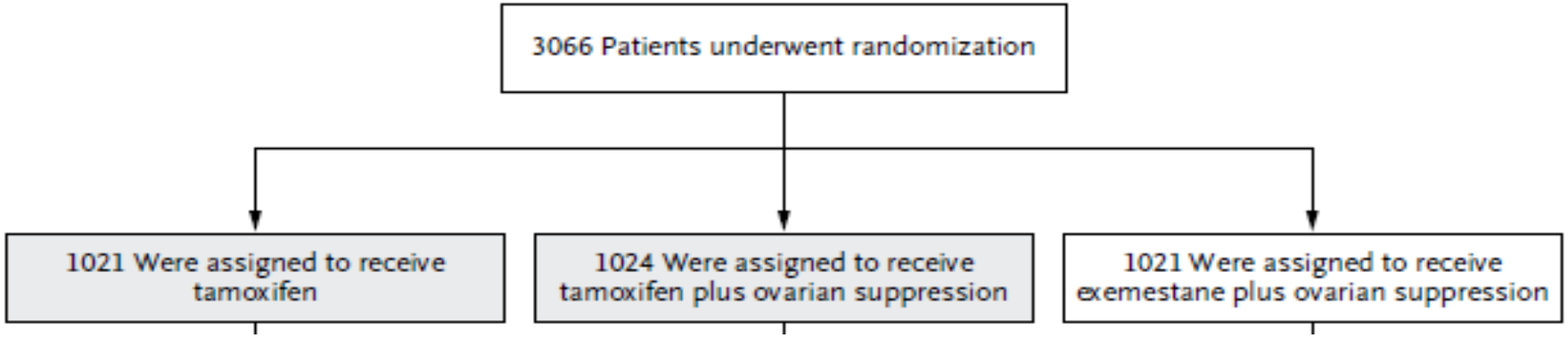
ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

N Engl J Med 2015;372:436-46.

Prudence A. Francis, M.D., Meredith M. Regan, Sc.D., Gini F. Fleming, M.D.,

SOFT



***3066 patientes avec K sein opérable (2003-2011)**
***RH + (> 10%)**
***femme préménopausée ou statut non ménopausique dans les 8 mois suivant la CT**
***Castration chimique (Triptorelin 3,75 mg mensuel), radique ou chirurgicale**
***Suivie de 67 mois**
***Durée du traitement: 5 ans**
***Objectif primaire : survie sans maladie**

Hormonothérapie par anti aromatases

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

TEXT

TEXT

Population: Premenopausal women with endocrine-responsive early breast cancer who should receive OFS from the start of adjuvant therapy.

Enrollment November 2003 through April 2011
Final accrual: 2672 (revised target: 2639)

Stratify:

- Chemo planned
- Nodal Status

RANDOMIZE

Tamoxifen + OFS (Triptorelin)

Exemestane + OFS (Triptorelin)

Hormonothérapie par anti aromatases

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

TEXT

***2672 patientes avec K sein opérable (2003-2011)**

***RH + (> 10%)**

***femme préménopausée ou statut non ménopausique dans les 8 mois suivant la CT**

***Castration chimique (Triptorelin 3,75 mg mensuel en concomitant avec la CT si indiquée), radique ou chirurgicale**

*** TAM ou EXE débutés après CT ou 6 à 8 semaines après Triptorelin**

***Suivie de 67 mois**

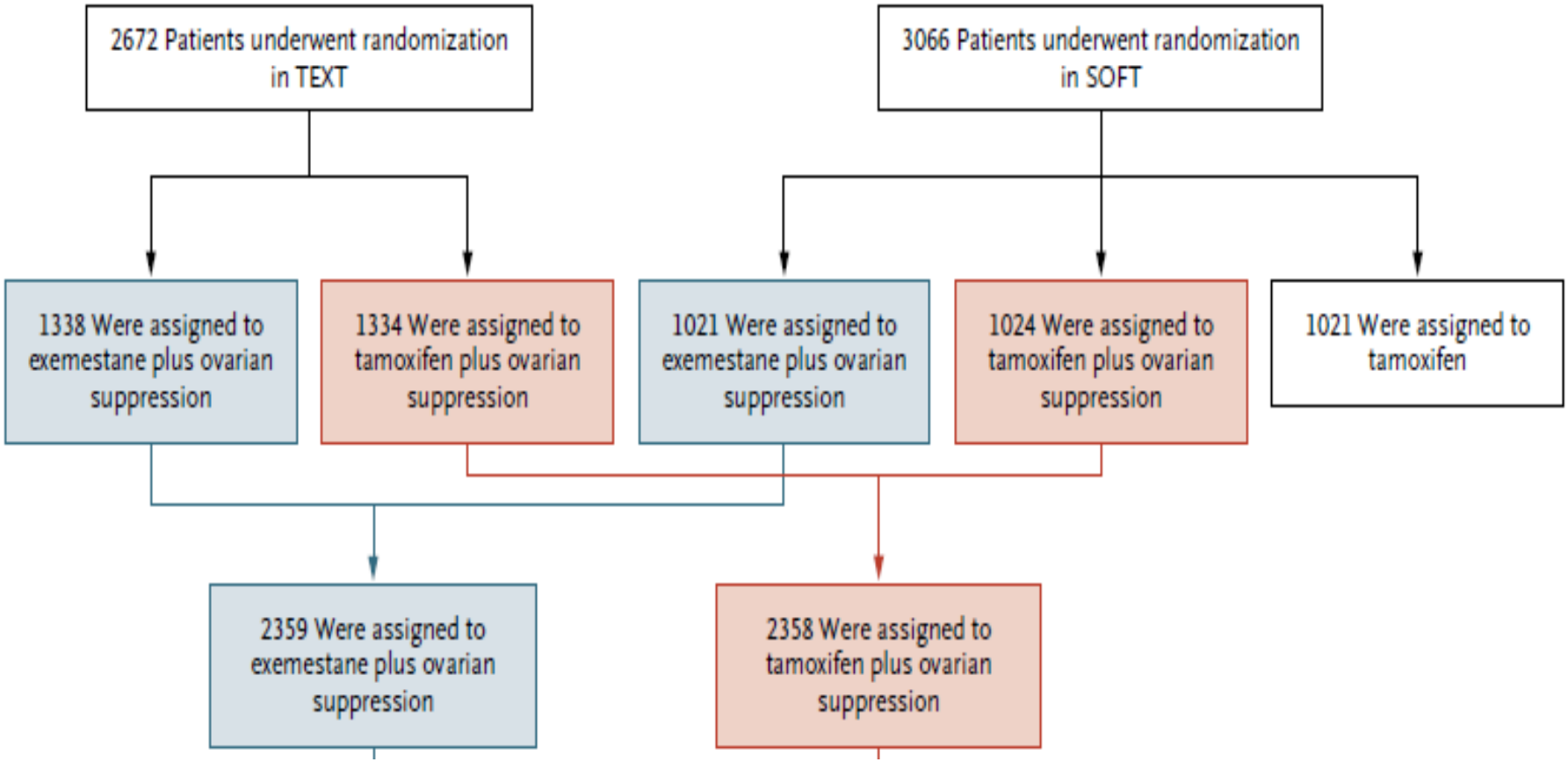
***Durée du traitement: 5 ans**

***Objectif primaire : survie sans maladie**

Hormonothérapie par anti aromatases

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

Olivia Pagani, N ENGL J MED 371;2 NEJM.ORG JULY 10, 2014



Hormonothérapie par anti aromatases

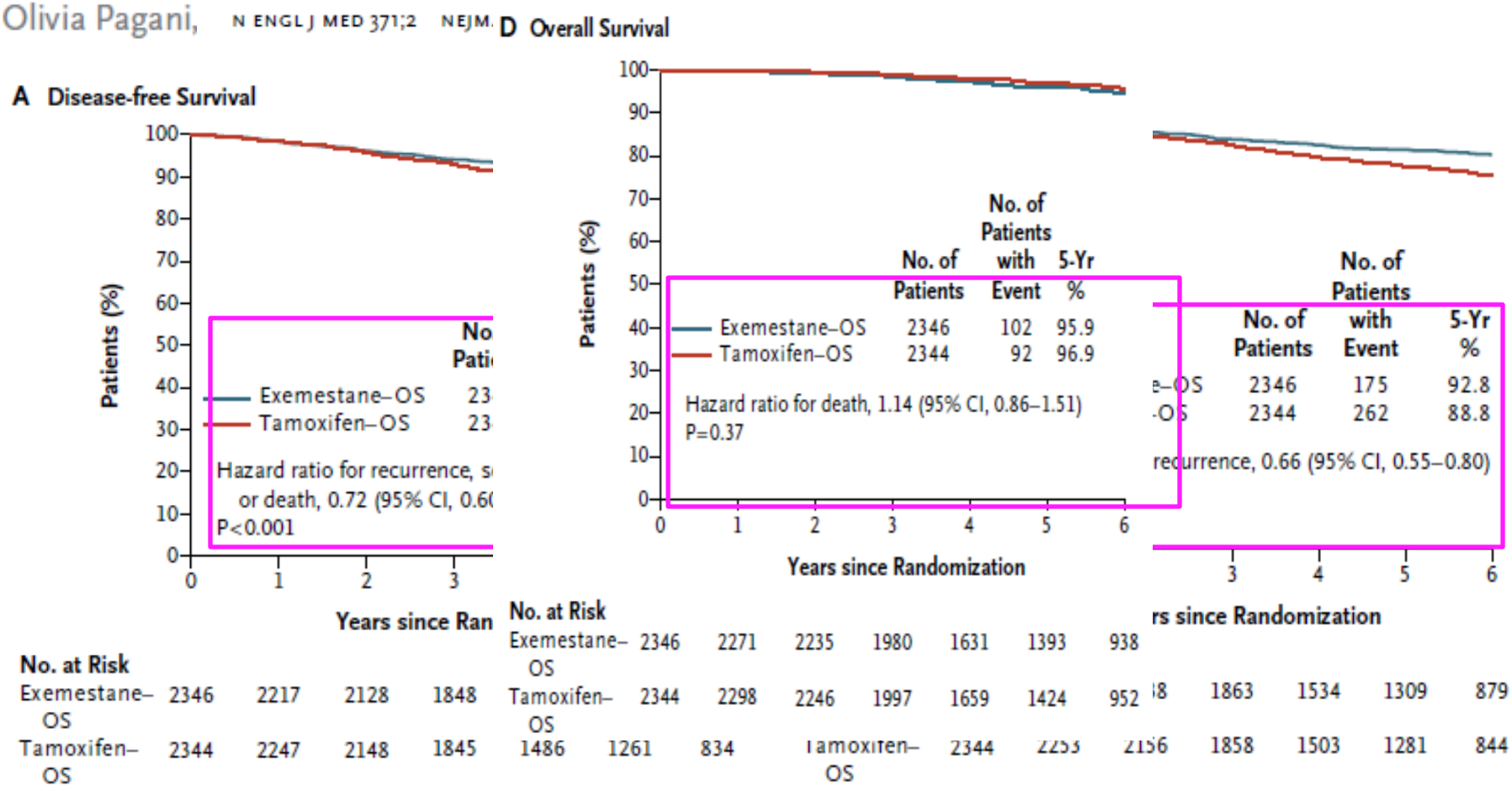
Table 1. Characteristics of Patients in TEXT and SOFT, Overall and According to Trial and Chemotherapy Stratum.*

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)	—

Hormonothérapie par anti aromatases

Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer

Olivia Pagani, N ENGL J MED 371;2 NEJM.



Hormonothérapie par anti aromatases

2017 SAN ANTONIO BREAST CANCER SYMPOSIUM — December 5-9, 2017

Randomized Comparison of Adjuvant Aromatase Inhibitor Exemestane plus Ovarian Function Suppression vs Tamoxifen plus Ovarian Function Suppression in Premenopausal Women with HR+ Early Breast Cancer: Update Of The Combined TEXT and SOFT Trials

Prudence Francis
on behalf of Olivia Pagani, MD
TEXT and SOFT Investigators and
International Breast Cancer Study Group (IBCSG)

Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

P.A. Francis, O. Pagani, G.F. Fleming, B.A. Walley, M. Colleoni, I. Láng, H.L. Gómez,

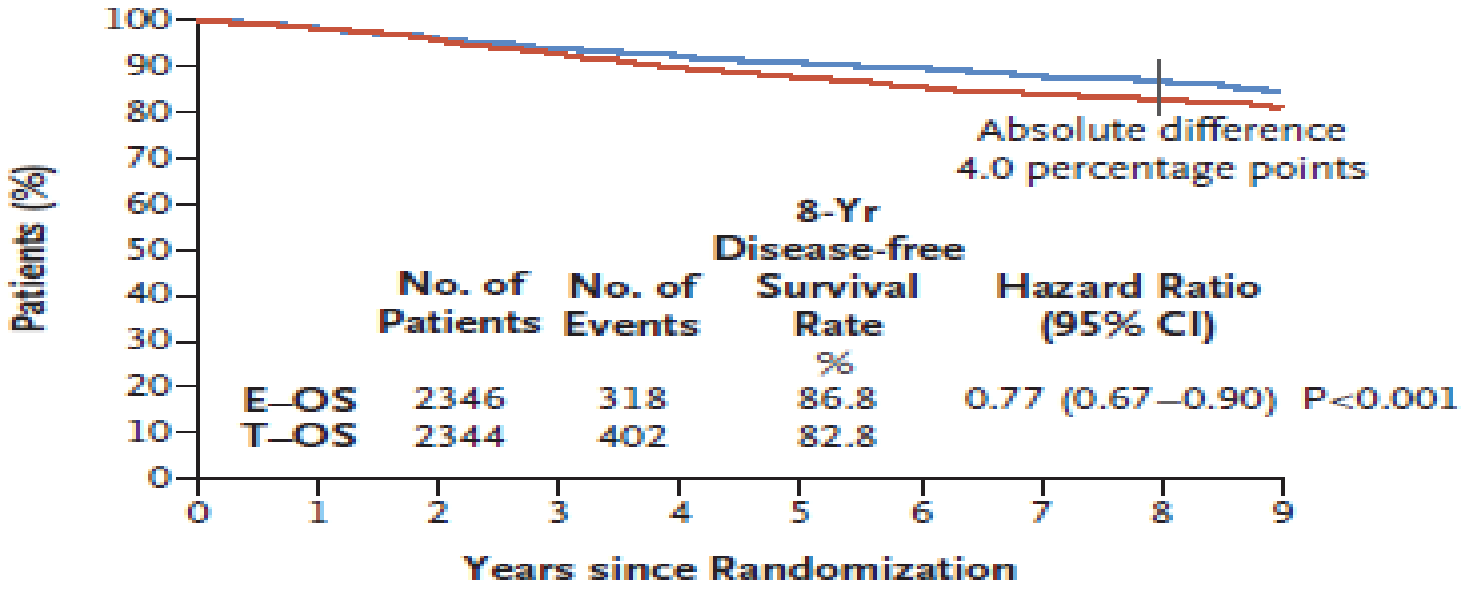
N ENGL J MED 379;2 NEJM.ORG JULY 12, 2018

Hormonothérapie par anti aromatases

2017 SAN ANTONIO BREAST CANCER SYMPOSIUM December 5-9, 2017

Sustained Improvement in DFS

A Disease-free Survival



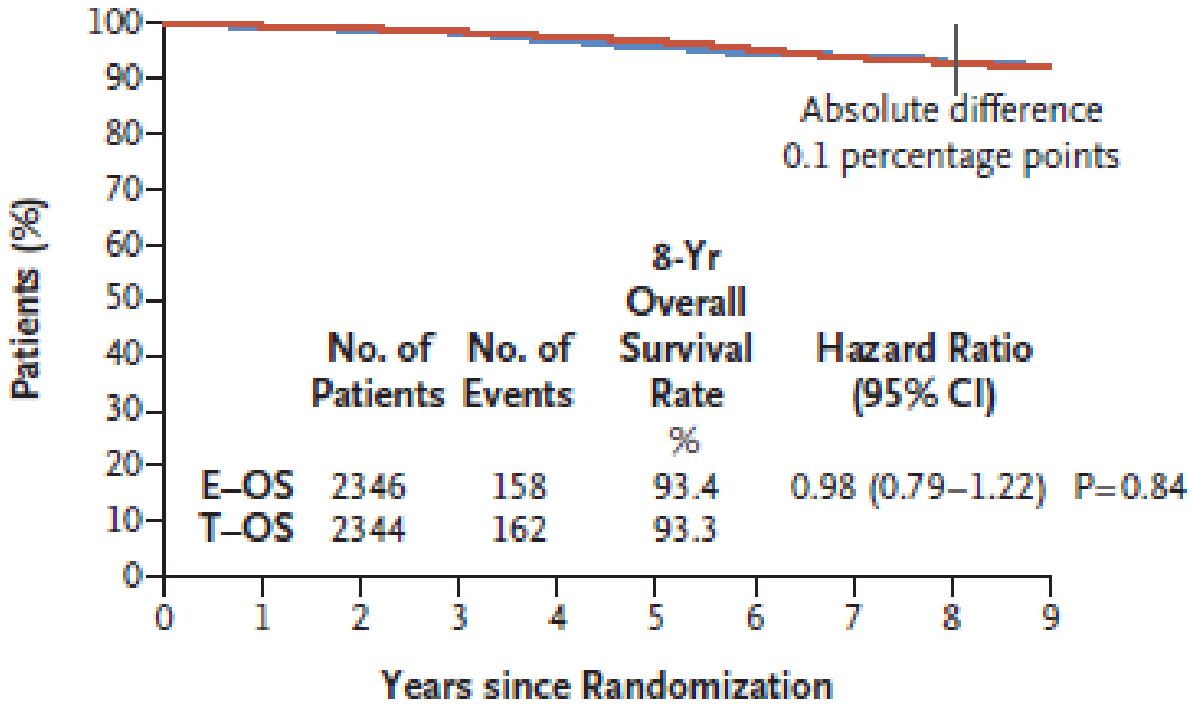
No. at Risk					
E–OS	2232	2073	1931	1391	861
T–OS	2257	2066	1866	1337	834

4.0% absolute improvement in 8-yr DFS for E+OFS after 9 years median follow-up

Hormonothérapie par anti aromatases

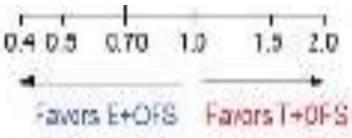
HER2-negative Patients (N=4035)

C Overall Survival



No. at Risk

E–OS	2289	2224	2101	1551	988
T–OS	2308	2238	2123	1547	988



Disease-free surv
All HER2-negative
Cohort
No chemotherap
No chemotherap
Chemotherapy i
Previous chemo

DFS

+ 5,4%
+ 4,1%
+ 1,4%
+ 6,9%
+ 9,2%

Hormonothérapie par anti aromatases

	Tamoxifène + SFO versus tamoxifène seul[1]		Exémestane + SFO versus tamoxifène + SFO[2]	
	Taux à 8 ans (%)	*Hazard ratio* (IC95 %) ; *p*	Taux à 8 ans (%)	*Hazard ratio* (IC95 %) ; *p*
Survie sans maladie	83,2 % vs 78,9 %	0,76 (0,62-0,93) ; *p* 0,009	86,8 % vs 82,8 %	0,77 (0,67-0,90) ; *p* < 0,001
Survie globale	93,3 % vs 91,5 %	0,67 (0,48-0,92) ; *p* 0,01	93,4 % vs 93,3 %	0,98 (0,79-1,22) ; *p* 0,84
Survie sans récidive à distance	89,4 % vs 88,4 %	0,86 (0,66-1,13) ; *p* 0,28	91,8 % vs 89,7 %	0,80 (0,66-0,96) ; *p* 0,02

Daguenet E et al; Bull cancer 2019

Hormonothérapie par anti aromatases

2017 SAN ANTONIO BREAST CANCER SYMPOSIUM — December 5-9, 2017

Selected Adverse Events (all patients)

	E + OFS (N=2317)	T + OFS (N=2326)
Endometrial cancer	n=4	n=9
Musculoskeletal symptoms (G3-4)	11%	6%
Osteoporosis (G2		7%
Fractures (G3-4)		1.0%
Hot Flashes (G3)		12%
Libido decrease (G2)	15%	12%
Vaginal dryness (G2)	27%	22%
Depression (G3-4)	4.1%	4.6%
Thrombosis/embolism (G2-4)	1.2%	2.3%

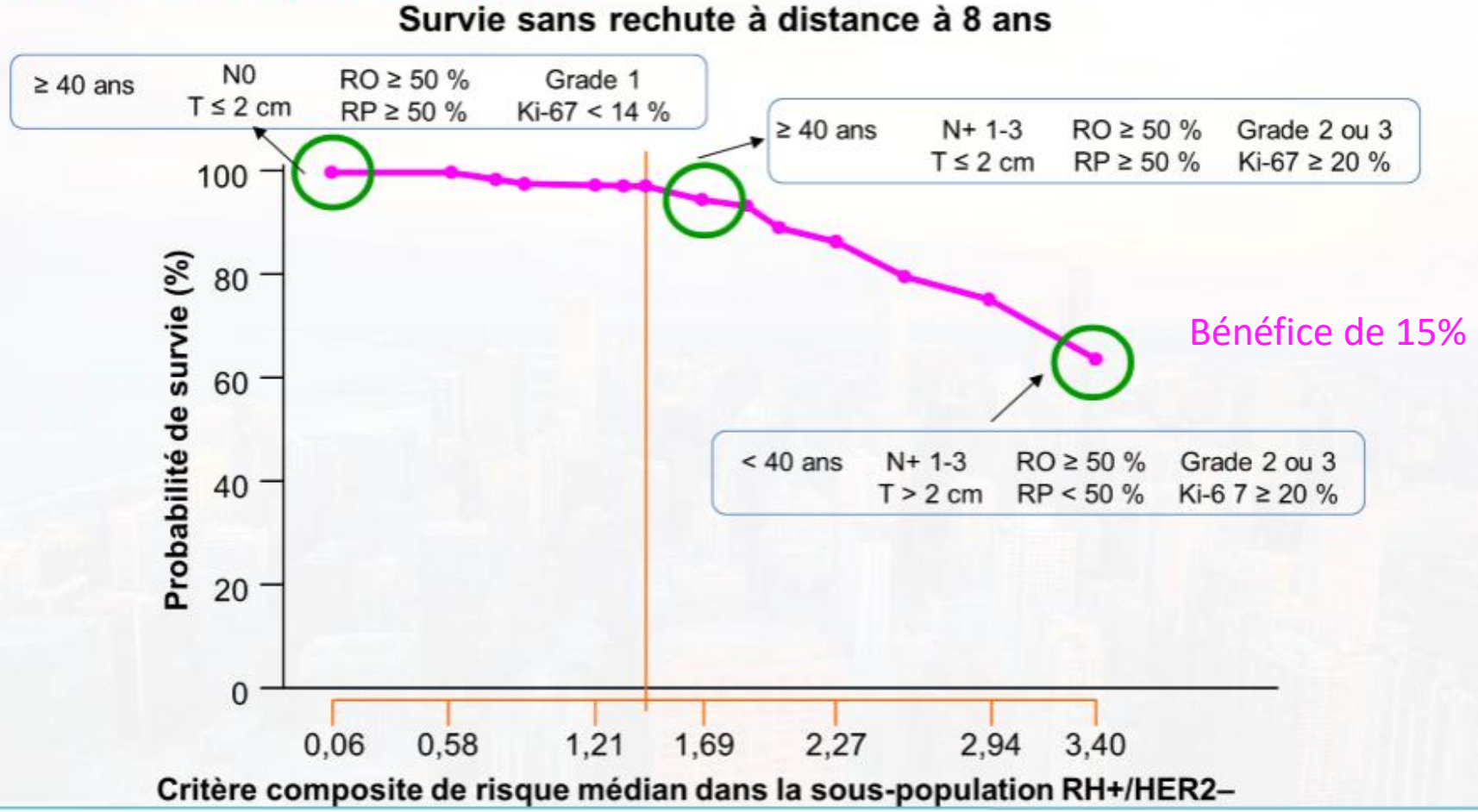
Arrêt du traitement adjuvant:

* 14% vs 6% à 1 an
* 25% vs 19% à 4 ans

Hormonothérapie par anti aromatases

SOFT et TEXT : actualisation *(2)*

Critère de risque composite



Congrès américain d'oncologie clinique 2018 - D'après Francis PA et al., abstr. 503, actualisé

Hormonothérapie par anti aromatases

Author Manuscript

HHS Public Access

Author manuscript

Breast Cancer Res Treat. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Breast Cancer Res Treat. 2015 November ; 154(2): 275–286. doi:10.1007/s10549-015-3612-z.

Predictive value and clinical utility of centrally-assessed ER, PgR and Ki-67 to select adjuvant endocrine therapy for premenopausal women with hormone receptor-positive, HER2-negative early breast cancer: TEXT and SOFT trials

Hormonothérapie par anti aromatases

Marker and Category		Trial and Treatment Comparison					
		SOFT				TEXT	
		T+OFS vs Tam		E+OFS vs Tam		E+OFS vs T+OFS	
		HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
All HR+/HER2-	--	*0.90*	*(0.67, 1.21)*	*0.70*	*(0.51, 0.96)*	*0.52*	*(0.37, 0.72)*
PgR	<20%	1.44	(0.75, 2.78)	0.60	(0.29, 1.25)	0.41	(0.20, 0.84)
	20-49%	0.90	(0.37, 2.15)	0.54	(0.20, 1.50)	0.52	(0.24, 1.13)
	≥50%	0.88	(0.61, 1.26)	0.75	(0.51, 1.11)	0.52	(0.34, 0.80)
P(Interaction)		*P= 0.42*		*P= 0.76*		*P= 0.85*	
Ki-67	<14%	0.58	(0.28, 1.20)	0.35	(0.15, 0.79)	0.73	(0.24, 2.23)
	14-19%	1.16	(0.63, 2.12)	0.95	(0.50, 1.82)	0.73	(0.36, 1.49)
	20-25%	1.01	(0.53, 1.93)	0.99	(0.51, 1.95)	0.33	(0.16, 0.67)
	≥26%	0.99	(0.58, 1.70)	0.72	(0.39, 1.34)	0.47	(0.29, 0.76)
P(Interaction)		*P= 0.53*		*P= 0.21*		*P= 0.40*	
luminal A/B-like	A-like	0.91	(0.55, 1.50)	0.59	(0.33, 1.05)	0.68	(0.36, 1.29)
	B-like	1.01	(0.69, 1.49)	0.76	(0.49, 1.16)	0.45	(0.30, 0.65)
P(Interaction)		*P= 0.74*		*P= 0.50*		*P= 0.27*	

Recommandations

Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Annals of Oncology 30: 1194–1220, 2019

Recommendations:

- For premenopausal women, tamoxifen for 5–10 years is a standard of care [I, A].
- In patients becoming postmenopausal during the first 5 years of tamoxifen, a switch to letrozole should be considered, depending on predicted risk of late recurrence [II, A].
- In patients requiring ChT and who recover menses (in particular in the first year but acceptable within the first 2 years), addition of OFS to ET should be strongly considered [I, A].
- The role of replacing tamoxifen with an AI can be considered in high-risk patients; if used, it mandates effective OFS, with regular biochemical control of oestrogen levels [I, A].

Recommandations

Table 5. Systemic therapy for ER+ HER2− breast cancer

Stage		Ovarian Suppression	Type and duration of endocrine therapy	Chemotherapy
Stage 1	T1ab	No OFS	AI or tam (5 years)	No
	T1c	No OFS	AI or tam (5 years)	Individualized decision based on: T size, N status, histological subtype, LVI, grade, proliferation, quantitative hormone receptor expression, genomic signatures, and patient preferences
Stage 2	Node-negative	OFS and AI/tam for higher risk historically warranting chemo (e.g large T, age < 35, high grade, adverse gene signature	• AI preferred as initial therapy. • Extended therapy favored (especially after initial 5 years of tamoxifen)	
	Node-positive	OFS and AI/tam	• AI based. • Extended therapy.	
Stage 3		OFS and AI/tam	• AI based. • Extended therapy.	Yes

[a]Some consider OFS along same criteria as stage 2, node-negative.

AI, aromatase inhibitor; Tam, tamoxifen; LVI, lymphovascular invasion; OFS, ovarian function suppression.

Conclusions

Indications de l'hormonothérapie:

* Expression des RH
* Statut ovarien pré
* Carac logique de la tumeur
* Balance isques

Discuter avec la patiente:
* les bénéfices attendus
* les risques encourus

Le Futur

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1514–1520, 2019
doi:10.1093/annonc/mdz198
Published online 28 June 2019

ORIGINAL ARTICLE

A phase II feasibility study of palbociclib in combination with adjuvant endocrine therapy for hormone receptor-positive invasive breast carcinoma

E. L. Mayer[1*], A. DeMichele[2], H. S. Rugo[3], K. Miller[4], A. G. Waks[1], S. E. Come[5], T. Mulvey[6], R. Jeselsohn[1], B. Overmoyer[1], H. Guo[7], W. T. Barry[7], C. Huang Bartlett[8], M. Koehler[8], E. P. Winer[1] & H. J. Burstein[1]


Merci pour votre
attention