Terapia ormonale adiuvante: quali novità?

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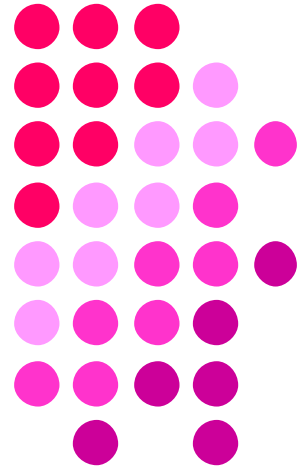
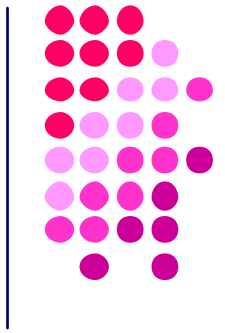


Azienda Ospedaliera
Città della Salute e
della Scienza di Torino

Ormonoterapia adiuvante



- Durata del trattamento ormonale adiuvante
- Ormonoterapia adiuvante in premenopausa

Ricaduta dopo 5 anni di Tam

Table 1
Long-term recurrence rates of estrogen receptor positive breast cancer treated with 5 years of adjuvant tamoxifen according to PR expression and nodal status [2].

	ER-positive without knowledge of PR	ER-positive and PR-positive	ER-positive and PR-poor	ER-poor and PR-positive	ER-positive and node negative no chemotherapy	ER-positive and node positive no chemotherapy
Recurrence						
5 years	16.4%	15.4%	19.2%	20.8%	11.8%	25.3%
10 years	25.9%	24.8%	28.6%	30.9%	19.1%	41.5%
15 years	33.0%	–	–	–	–	–

ER, estrogen receptor; PR, progesterone receptor. Positive ≥10 fmol/mg.

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)*

Lancet 2005; 365: 1687–1717

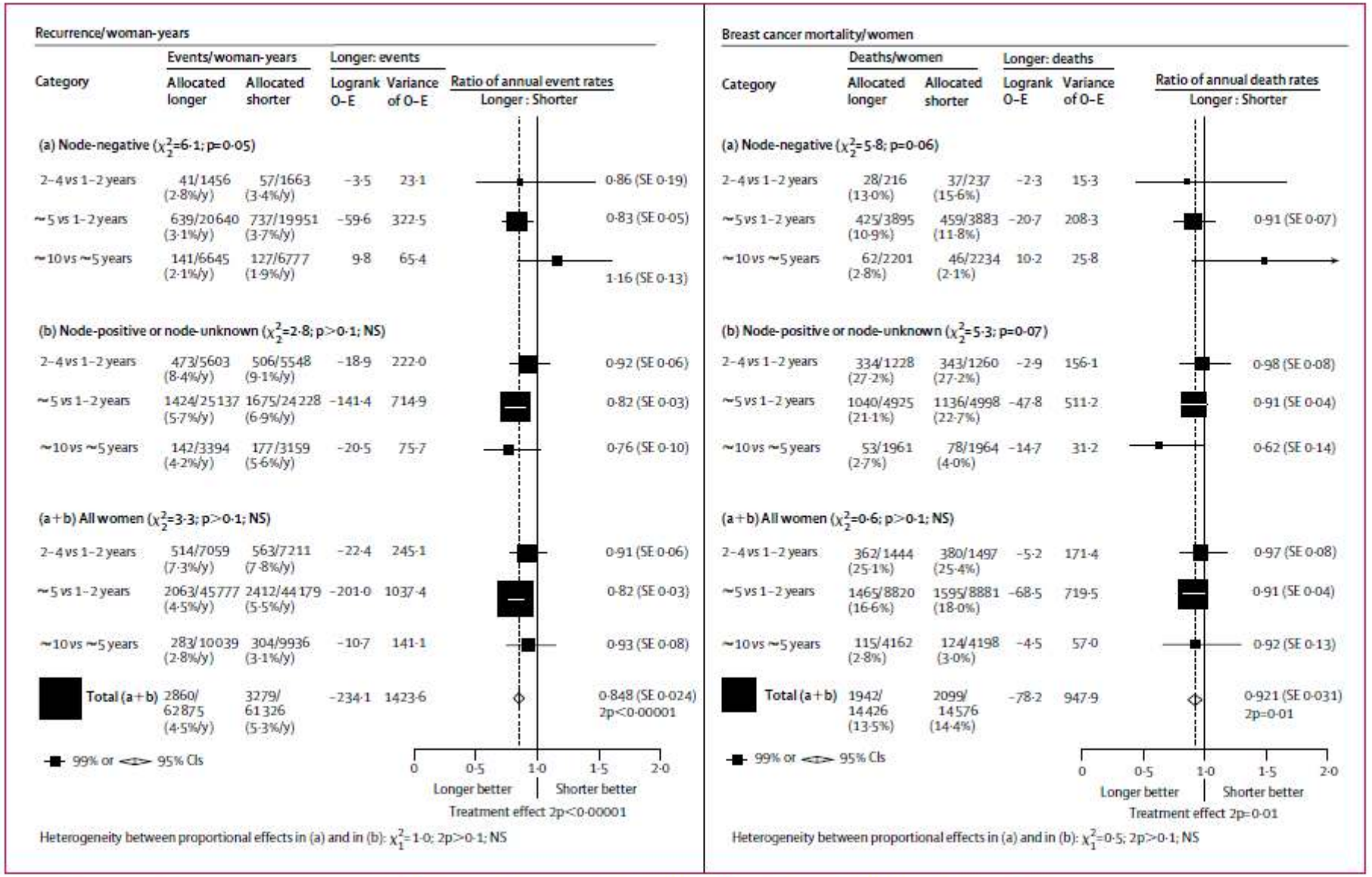


Figure 11: Longer versus shorter tamoxifen duration in ER-positive (or ER-unknown) disease, by treatment type and nodal status: event rate ratios

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

Christina Davies, Hongchao Pan, Jon Godwin, Richard Gray, Rodrigo Arriagada, Vinod Raina, Mirta Abraham, Victor Hugo Medeiros Alencar, Atef Badr, Xavier Bonfill, Joan Bradburry, Michael Clarke, Rory Collins, Susan R Davies, Antonella Delmestri, John F Forbes, Peiman Haddad, Ming-Feng Hou, Moshe Inbar, Hussein Khaled, Joanna Kilzanowska, Wing-Hong Kwan, Beela S Mathew, Indraneel Mittra, Bettina Müller, Antonio Nicolucci, Octavio Peralta, Fary Pienos, Lubos Petruzelka, Tadeusz Pienkowski, Ramachandran Radhika, Balakrishnan Rajan, Maryna T Rubach, Sera Tort, Gerard Urrútia, Miriam Valentini, Yaochen Wang, Richard Peto, for the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group*

- Accrual dal 1995 al 2005 da 36 Paesi

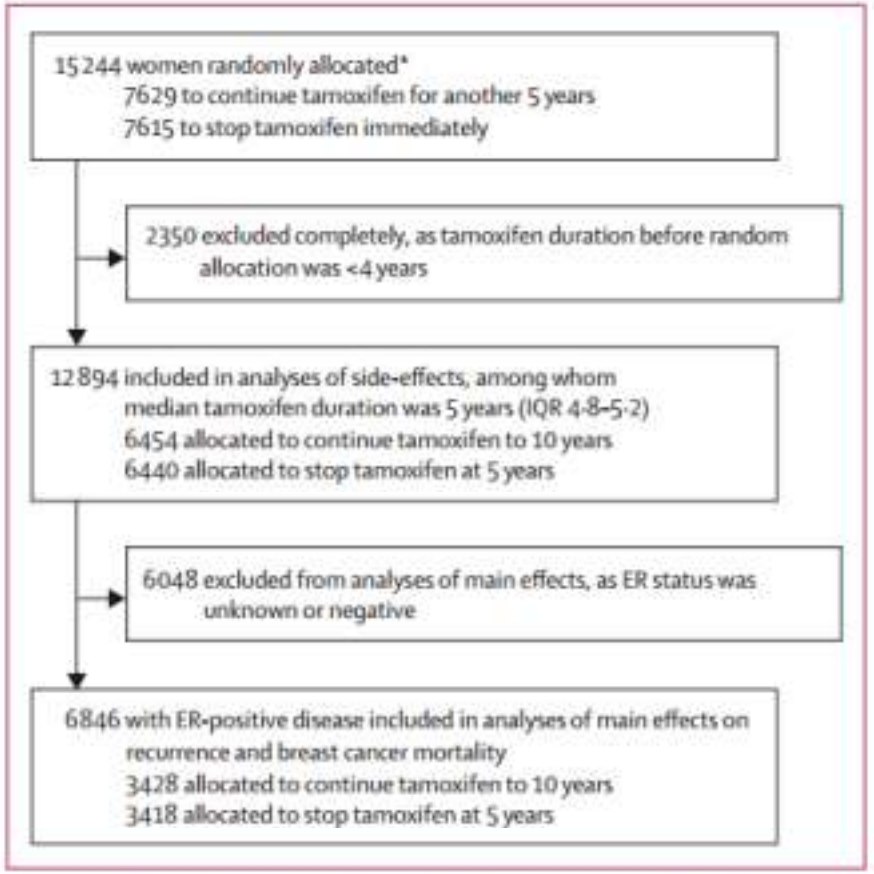
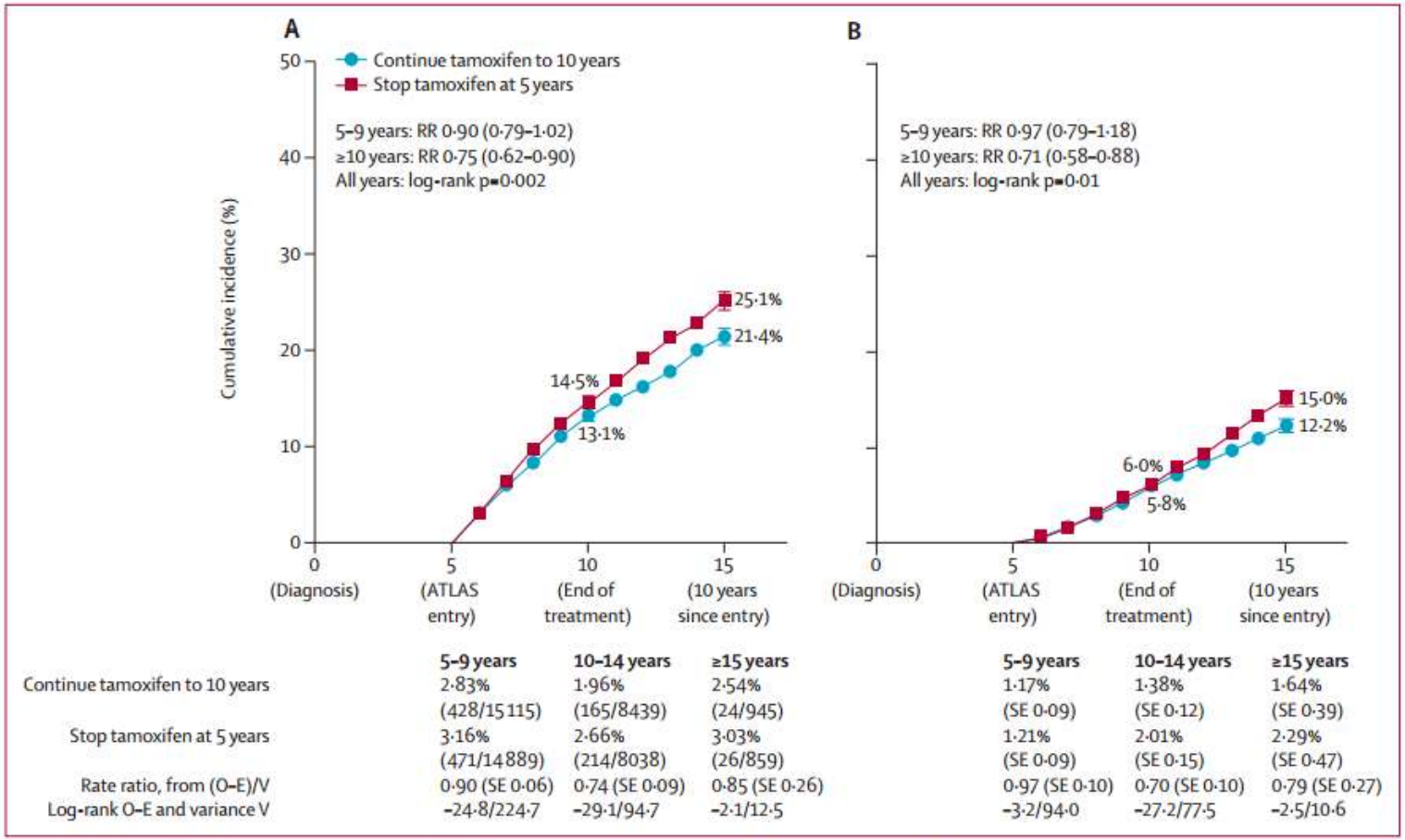


Figure 1: **Trial profile, showing the different populations analysed to assess the side-effects and the main effects of continuing tamoxifen to 10 years versus stopping tamoxifen at 5 years**

ER=oestrogen receptor. *39 patients were allocated twice in error, but stayed on their original allocation. Excludes 18 patients entered in error (17 with distant recurrence and one without ethics approval).

Lancet, 2012

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



	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15 115)	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% (471/14 889)	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

***Figure 3*: Recurrence (A) and breast cancer mortality (B) by treatment allocation for 6846 women with ER-positive disease**
Bars show SE. Recurrence rates are percentage per year (events/patient-years of follow-up). Death rates (overall rate – rate in women without recurrence) are percentage per year (SE). ATLAS=Adjuvant Tamoxifen: Longer Against Shorter.

Lancet, 2012

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

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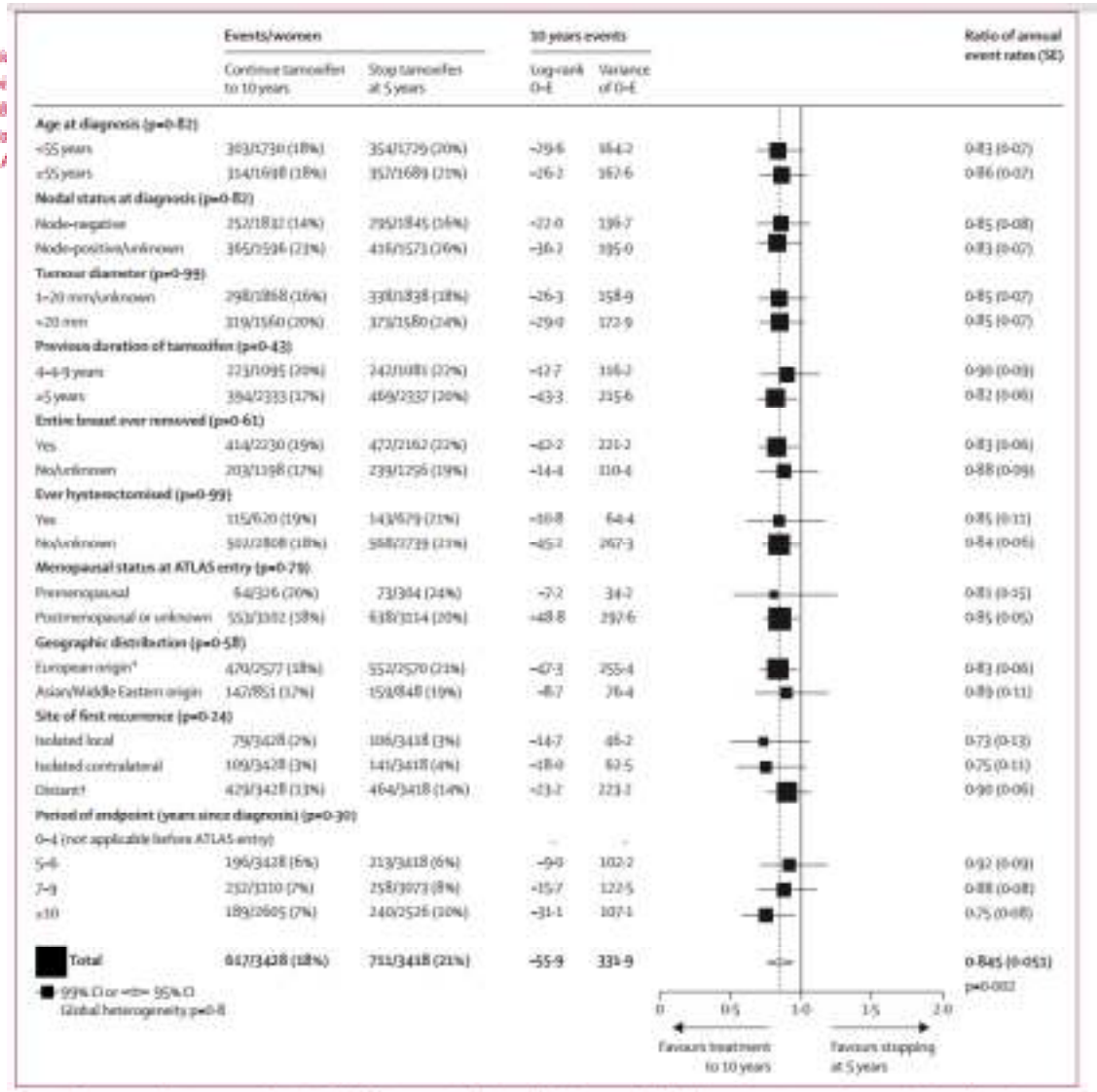

Figure 4: Recurrence by treatment allocation for 6846 women with ER-positive disease, subdivided by patient or tumour characteristics and location or time of first recurrence

Lancet, 2012

aTTom: 10 vs. 5 years Tamoxifen N=6953

- Recurrence RR = 0.85 (95% CI 0.76-0.95; p=0.003)
  - Absolute reduction 4%

- Breast Cancer Mortality RR = 0.88 (95%CI 0.77-1.01; p=0.06)
  - Absolute reduction 2%

Gray *et al.*, Abstract 5, ASCO 2013

Assessing the Risks for the Individual Patient

- Serious Adverse Events
  - Endometrial cancer- 3.1% (mortality 0.4%) vs. 1.6%
  - Cardiovascular events- ↑ PE, ↓ Ischemic heart disease

    (Davies *et al*. Lancet 2012)
- Symptoms/Quality of Life
  - Vasomotor symptoms, alterations in mood, sexual functioning, musculoskeletal problems

- Patient Preferences and Values
  - Minor side effects can become deeply troubling over time

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JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update

Harold J. Burstein, Sarah Temin, Holly Anderson, Thomas A. Buchholz, Nancy E. Davidson, Karen E. Gelmon, Sharon H. Giordano, Clifford A. Hudis, Dania Rowden, Alexander J. Solky, Vered Stearns, Eric P. Winer, and Jennifer J. Griggy

Conclusioni practice-changing

RECOMMENDATIONS

Clinical Question I

Which adjuvant endocrine treatments should be offered to women with hormone receptor–positive breast cancer who are pre- or perimenopausal? What is the appropriate duration?

Recommendation 1. Women diagnosed with hormone receptor–positive breast cancer who are pre- or perimenopausal should be offered adjuvant endocrine therapy with:

Recommendation IA. Tamoxifen for an initial duration of 5 years (supported by 2010 evidence).

Recommendation IB. After 5 years, women should receive additional therapy based on menopausal status.

- *Recommendation IB1.* If women are pre- or perimenopausal, or if menopausal status is unknown or cannot be determined, they should be offered continued tamoxifen for a total duration of 10 years. (*Type:* Evidence-Based, *Evidence Quality:* High, *Strength of Recommendation:* Strong; supported by 2013 evidence, see Literature Review section).
- *Recommendation IB2.* If women have become definitively postmenopausal, they should be offered the choice of continuing tamoxifen for a total duration of 10 years or switching to up to 5 years of an AI, for a total duration of up to 10 years of adjuvant endocrine therapy. (*Type:* Evidence-Based, *Evidence Quality for tamoxifen:* High, *Evidence Quality* for AI: High; *Strength of Recommendation:* Strong; supported by 2010 and 2013 evidence).

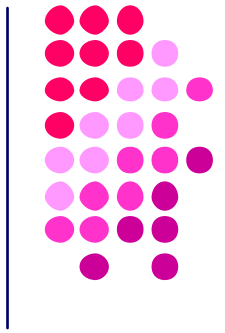
Linee guida

NEOPLASIE DELLA MAMMELLA

Conclusioni practice-changing

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	Nelle pazienti in premenopausa o perimenopausa con diagnosi di carcinoma mammario infiltrante operato ER-positivo e/o PgR positivo indipendentemente dalle altre caratteristiche della neoplasia deve essere somministrato Tamoxifene per 5 anni [128].	**Positiva forte**
B	Nelle pazienti con diagnosi di carcinoma mammario infiltrante operato ER-positivo e/o PgR positivo ancora in premenopausa o perimenopausa dopo 5 anni di terapia ormonale adiuvante con Tamoxifene, può essere valutata la prosecuzione di Tamoxifene per ulteriori 5 anni [141].	**Positiva debole**
A	Le pazienti in postmenopausa con carcinoma mammario operato ER-positivo e/o PgR-positivo candidate ad ormonoterapia adiuvante devono essere trattate con terapia che comprenda antiaromatasici[155].	**Positiva forte**

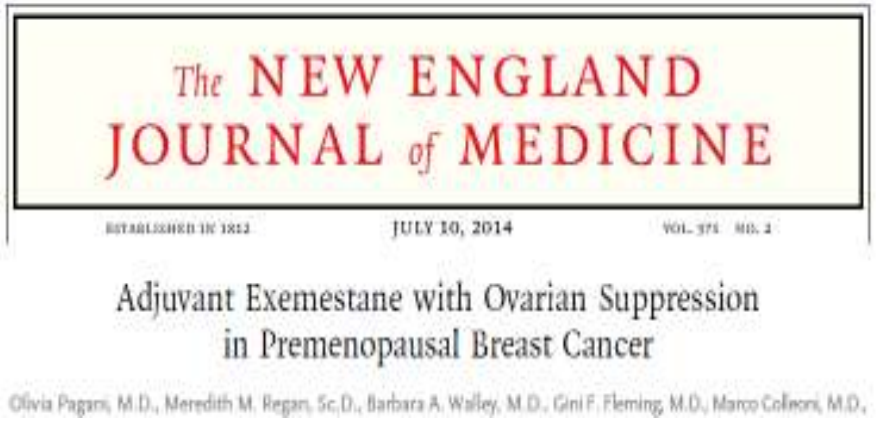
Ormonoterapia adiuvante



- Durata del trattamento ormonale adiuvante
- Ormonoterapia adiuvante in premenopausa

Studi SOFT e TEXT

Ruolo di Exemestane (EXE) e Soppressione Ovarica (OS) in adiuvante in premenopausa



TEXT + SOFT
(EXE vs TAM) + OS

SOFT
TAM vs TAM + OS

Disegno degli studi

Trial multicentrici US, arruolamento 11/2003-04/2011
completo disegno statistico

TEXT (N=2672)

- Premenopausa
- =12 sett da chirurgia
- Indicazione a OFS
- CT oppure no CT programmata

SOFT (N=3066))

- Premenopausa
- =12 sett da chirurgia
- No CT

Oppure
Premenopausali a = 8 mesi dal termine CT

RANDOM

RANDOM

Tamoxifene+OFS x 5 anni

Exemestane +OFS x 5 anni

Strata → N e CT

Tamoxifene x 5 anni

Tamoxifene+OFS x 5 anni

Exemestane +OFS x 5 anni

Strata → N, CT e modo OFS

Pubblicazione n. 1
TEXT + SOFT,
analisi congiunta
(N=4690)
EXE vs TAM

Pubblicazione n. 2
SOFT, ruolo
LHRH-a

Premenopausal status definition

Characteristic	Treatment Assignment				Overall	
	Exemestane +OFS		Tamoxifen +OFS			
	N	%	N	%	N	%
N Patients	*2346*	*100*	*2344*	*100*	*4690*	*100*
Age at randomization						
< 35	231	9.8	239	10.2	470	10.0
35-39	419	17.9	373	15.9	792	16.9
40-44	748	31.9	775	33.1	1523	32.5
45-49	731	31.2	767	32.7	1498	31.9
≥ 50	217	9.2	190	8.1	407	8.7
Median [IQR]	43	[39-47]	43	[39-47]	43	[39-47]

SOFT: 618/2030 pts < 40 yrs: 30%

TEXT: 607/2660 pts < 40 yrs: 23%

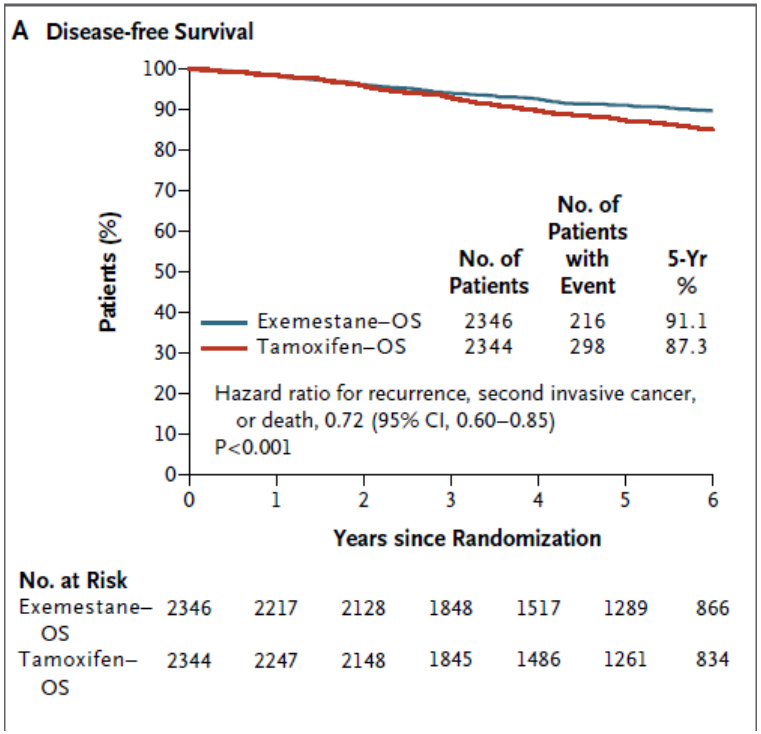
TEXT + SOFT

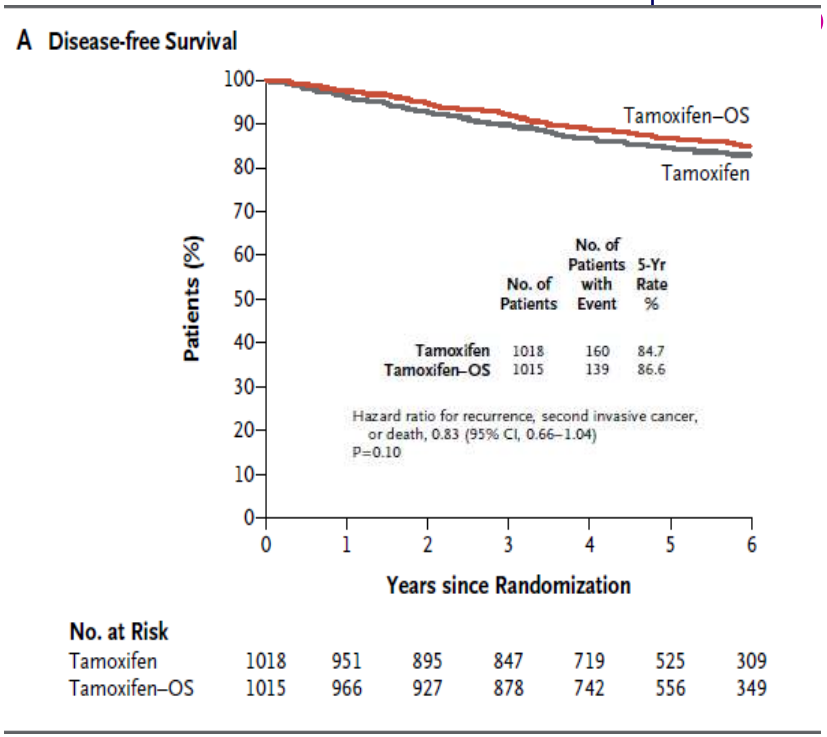
(EXE vs TAM) + OS

EP1
DFS

SOFT

TAM vs TAM + OS





Follow-up 5,7 anni
Vantaggio in DFS (differenza del 3,8% a 5 anni) per EXE+OS
Non beneficio in OS
Non sottogruppi differenti

Follow-up 5,7 anni
Possibile beneficio a analisi multivariata
Trend di beneficio in DFS per pz non menopausali dopo CT

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

This article was published on December 12, 2014, at NEJM.org.

CONCLUSIONS

Adding ovarian suppression to tamoxifen did not provide a significant benefit in the overall study population. However, for women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of ovarian suppression improved disease outcomes. Further improvement was seen with the use of exemestane plus ovarian suppression. (Funded by Pfizer and others; SOFT ClinicalTrials.gov number, NCT00066690.)

TEXT + SOFT

(EXE vs TAM) + OS

Safety

SOFT

TAM vs TAM + OS

Table 2. Targeted Adverse Events Reported during Follow-up, According to Treatment Assignment.*

Adverse Event	Exemestane plus Ovarian Suppression (N=2318)				Tamoxifen plus Ovarian Suppression (N=2325)			
	Any Event		Grade 3 or 4 Event		Any Event		Grade 3 or 4 Event	
	no. of patients with event	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*
Hot flushes	2125	91.7 (90.5–92.8)	232	10.0 (8.8–11.3)	2169	93.3 (92.2–94.3)	279	12.0 (10.7–13.4)
Depression	1165	50.3 (48.2–52.3)	87	3.8 (3.0–4.6)	1164	50.1 (48.0–52.1)	102	4.4 (3.6–5.3)
Sweating	1264	54.5 (52.5–56.6)	—	—	1371	59.0 (56.9–61.0)	—	—
Insomnia	1348	58.2 (56.1–60.2)	89	3.8 (3.1–4.7)	1361	58.5 (56.5–60.5)	100	4.3 (3.5–5.2)
Fatigue	1420	61.3 (59.2–63.2)	73	3.1 (2.5–3.9)	1463	62.9 (60.9–64.9)	67	2.9 (2.2–3.6)
Musculoskeletal symptoms	2057	88.7 (87.4–90.0)	254	11.0 (9.7–12.3)	1766	76.0 (74.2–77.7)	122	5.2 (4.4–6.2)
Osteoporosis	894	38.6 (36.6–40.6)	10	0.4 (0.2–0.8)	586	25.2 (23.5–27.0)	6	0.3 (0.1–0.6)
Fractures	158	6.8 (5.8–7.9)	29	1.3 (0.8–1.8)	120	5.2 (4.3–6.1)	18	0.8 (0.5–1.2)
Vaginal dryness	1214	52.4 (50.3–54.4)	—	—	1101	47.4 (45.3–49.4)	—	—
Decreased libido	1042	45.0 (42.9–47.0)	—	—	950	40.9 (38.9–42.9)	—	—
Dyspareunia	707	30.5 (28.6–32.4)	53	2.3 (1.7–3.0)	601	25.8 (24.1–27.7)	32	1.4 (0.9–1.9)

Table 2. Key Targeted Adverse Events Reported during Follow-up, According to Treatment Assignment.*

Adverse Event	Tamoxifen (N=1006)				Tamoxifen plus Ovarian Suppression (N=1005)			
	Any Event		Grade 3 or 4 Event		Any Event		Grade 3 or 4 Event	
	no. of patients with event	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*
Hot flushes	803	79.8 (77.2–82.3)	76	7.6 (6.0–9.4)	939	93.4 (91.7–94.9)	133	13.2 (11.2–15.5)
Depression	469	46.6 (43.5–49.8)	38	3.8 (2.7–5.1)	522	51.9 (48.8–55.1)	44	4.4 (3.2–5.8)
Sweating	486	48.3 (45.2–51.4)	—	—	621	61.8 (58.7–64.8)	—	—
Insomnia	466	46.3 (43.2–49.5)	29	2.9 (1.9–4.1)	575	57.2 (54.1–60.3)	46	4.6 (3.4–6.1)
Hypertension	173	17.2 (14.9–19.7)	54	5.4 (4.1–6.9)	233	23.2 (20.6–25.9)	75	7.5 (5.9–9.3)
Musculoskeletal symptoms	694	69.0 (66.0–71.8)	63	6.3 (4.8–7.9)	755	75.1 (72.3–77.8)	55	5.5 (4.1–7.1)
Osteoporosis	124	12.3 (10.4–14.5)	1	0.1 (0.0–0.6)	201	20.0 (17.6–22.6)	3	0.3 (0.1–0.9)
Vaginal dryness	421	41.8 (38.8–45.0)	—	—	500	49.8 (46.6–52.9)	—	—
Decreased libido	427	42.4 (39.4–45.6)	—	—	477	47.5 (44.3–50.6)	—	—
Glucose intolerance†	18	1.8 (1.1–2.8)	3	0.3 (0.1–0.9)	35	3.5 (2.4–4.8)	14	1.4 (0.8–2.3)
Any targeted adverse event‡	959	95.3 (93.8–96.5)	238	23.7 (21.1–26.4)	989	98.4 (97.4–99.1)	315	31.3 (28.5–34.3)

Status of Protocol-assigned Treatment	Cohort										
	No chemotherapy TEXT		No chemotherapy SOFT		Chemotherapy TEXT		Prior Chemotherapy SOFT		Treatment Assignment		
	E+OFS %	T+OFS %	E+OFS %	T+OFS %	E+OFS %	T+OFS %	E+OFS %	T+OFS %	E+OFS %	T+OFS %	Overall %
N Patients	*N=526*	*N=527*	*N=470*	*N=473*	*N=806*	*N=801*	*N=544*	*N=543*	*N=2346*	*N=2344*	*N=4690*
Status overall											
Continuing	27.0	28.8	34.9	39.3	21.0	24.2	39.3	36.3	29.4	31.1	30.2
Completed	58.4	60.5	41.9	48.0	64.1	64.9	47.4	52.7	54.5	57.7	56.1
Stopped early	13.5	10.4	21.3	11.4	13.8	10.1	12.5	10.7	14.9	10.6	12.8
Never started	1.1	0.2	1.9	1.3	1.1	0.7	0.7	0.4	1.2	0.6	0.9

Conclusioni practice-changing (1)

TAM vs TAM + OS

SOFT

- Tamoxifene + OFS = Tamoxifene come DFS

→→→ rimane opzione terapeutica per le donne in premenopausa, in particolare se non amenorrea dopo CT.

Linee guida

NEOPLASIE DELLA MAMMELLA

Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
BASSA	Nelle donne in pre-menopausa affette da carcinoma mammario ormono-responsivo gli LH-RH analoghi in associazione a Tamoxifen somministrato x 5 anni possono essere utilizzati. * La valutazione del rapporto tra i benefici ed i rischi correlati e la formulazione della raccomandazione relativa al quesito posto, sono state analizzate secondo metodologia GRADE (vedere capitolo 11)	Positiva debole

Stessa posizione da parte LG ESMO-13, NCCN-14 e ASCO-14

Conclusioni practice-changing (2)

TEXT + SOFT

(EXE vs TAM) + OS

- Exemestane + OFS > Tamoxifene + OFS come DFS

→→→ nuova opzione terapeutica per le donne in premenopausa con indicazione a OT adiuvante

Nessuna differenza significativa in OS → follow-up relativamente «breve» rispetto al limitato n° di eventi e al tempo intercorso: beneficio OT adiuvante con TAM fino a 10 anni [EBCTCG, Lancet 2011]

Effetti collaterali di Exemestane + OFS sono sovrapponibili a quelli riscontrati utilizzando gli AIs in postmenopausa, ma indispensabile un follow-up più lungo per valutare la tossicità a lungo termine in queste giovani donne

Qualità dell'evidenza SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	Nelle pazienti in premenopausa o perimenopausa con diagnosi di carcinoma mammario infiltrante operato ER-positivo e/o PgR positivo indipendentemente dalle altre caratteristiche della neoplasia deve essere somministrato Tamoxifene per 5 anni [126].	**Positiva forte**

Non ancora recepito da linee guida

Ruolo in pazienti N+?