Gino Severini
Maternità (1916).

Museo
dell'Accademia
Etrusca- Cortona

CARCINOMA MAMMARIO: quando la donna è GIOVANE

Ospedale Sacro Cuore - Don Calabria, Negrar (VR)

24 giugno 2015

CARCINOMA MAMMARIO: quando la donna è GIOVANE

Convegno GOIRC
Ospedale Sacro Cuore - Don Calabria, Negrar (VR)
24 giugno 2015

Il ruolo degli analoghi LHRH nella terapia sistemica adiuvante in premenopausa

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Presidio Ospedaliero Regione Veneto

Carcinoma mammario in premenopausa

I DATI EPIDEMIOLOGICI

Carcinoma mammario in Italia
Età: 0-49 anni

Età	STIMA NUOVI CASI anno 2015			DECESSI ISS – anno 2012	
	No.	%		No.	%
0-34	850	2%		50	0,4%
35-39	1.650	3%		146	1,2%
40-44	3.600	8%		322	2,7%
45-49	5.400	11%		583	4,9%
Tutte le età	47.900	100%		11.962	100%

5%

~ 24%
sul totale di carcinomi mammari

Carcinoma mammario in premenopausa

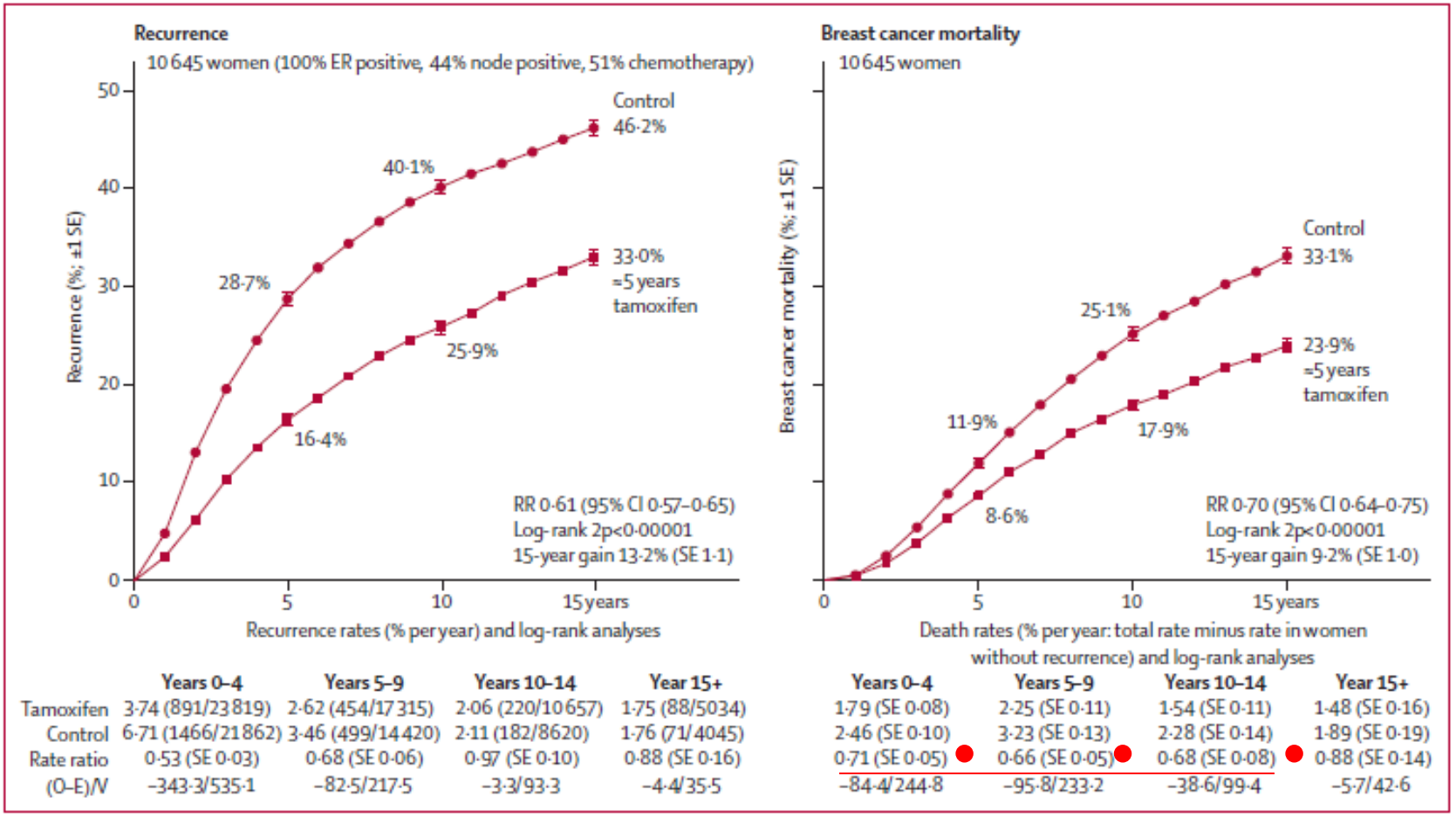
TERAPIA ORMONALE STANDARD

DEFINIZIONE DI MENOPAUSA

- **Lo stato di menopausa dovrebbe essere definito da uno dei seguenti criteri** (NCCN Guidelines 2005 v.1):
- - annessiectomia bilaterale
- - età > 60 anni
- - età < 60 anni e amenorrea da almeno 12 mesi in assenza di chemioterapia, tamoxifene, toremifene e valori di FSH e estradiolo nei range di menopausa.
- - in caso di assunzione di tamoxifene o toremifene e età < 60 anni, amenorrea da almeno 12 mesi, e valori di FSH e estradiolo nei range di menopausa.

Non è possibile stabilire lo stato menopausale delle pazienti in trattamento con LHRHa.

TAMOXIFEN impact



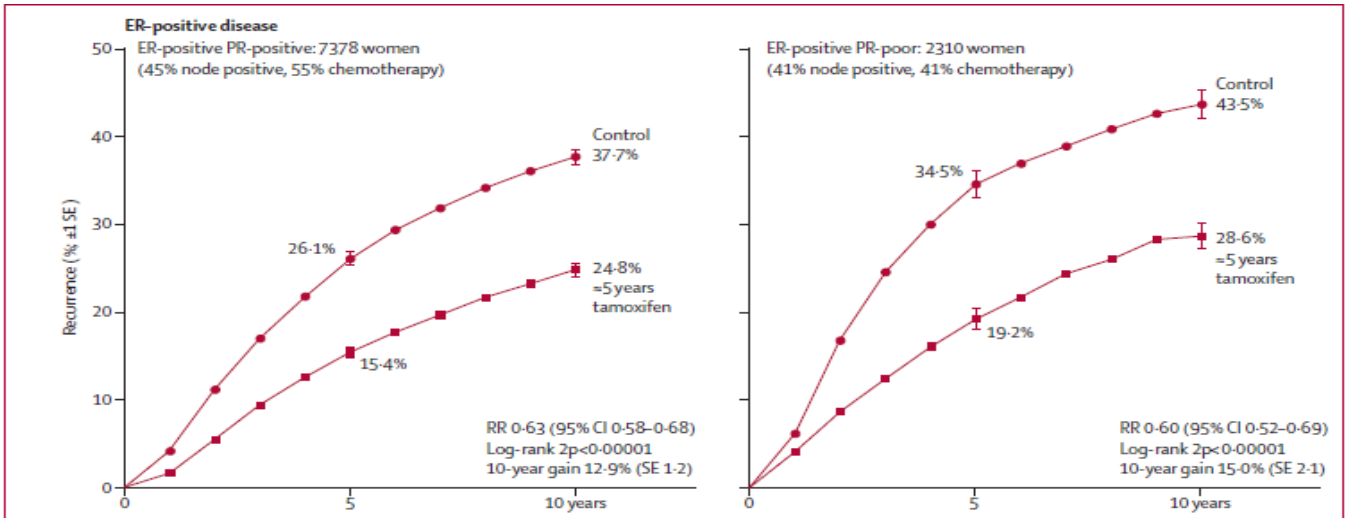
	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	3·74 (891/23 819)	2·62 (454/17 315)	2·06 (220/10 657)	1·75 (88/5034)
Control	6·71 (1466/21 862)	3·46 (499/14 420)	2·11 (182/8620)	1·76 (71/4045)
Rate ratio	0·53 (SE 0·03)	0·68 (SE 0·06)	0·97 (SE 0·10)	0·88 (SE 0·16)
(O–E)/V	−343·3/535·1	−82·5/217·5	−3·3/93·3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

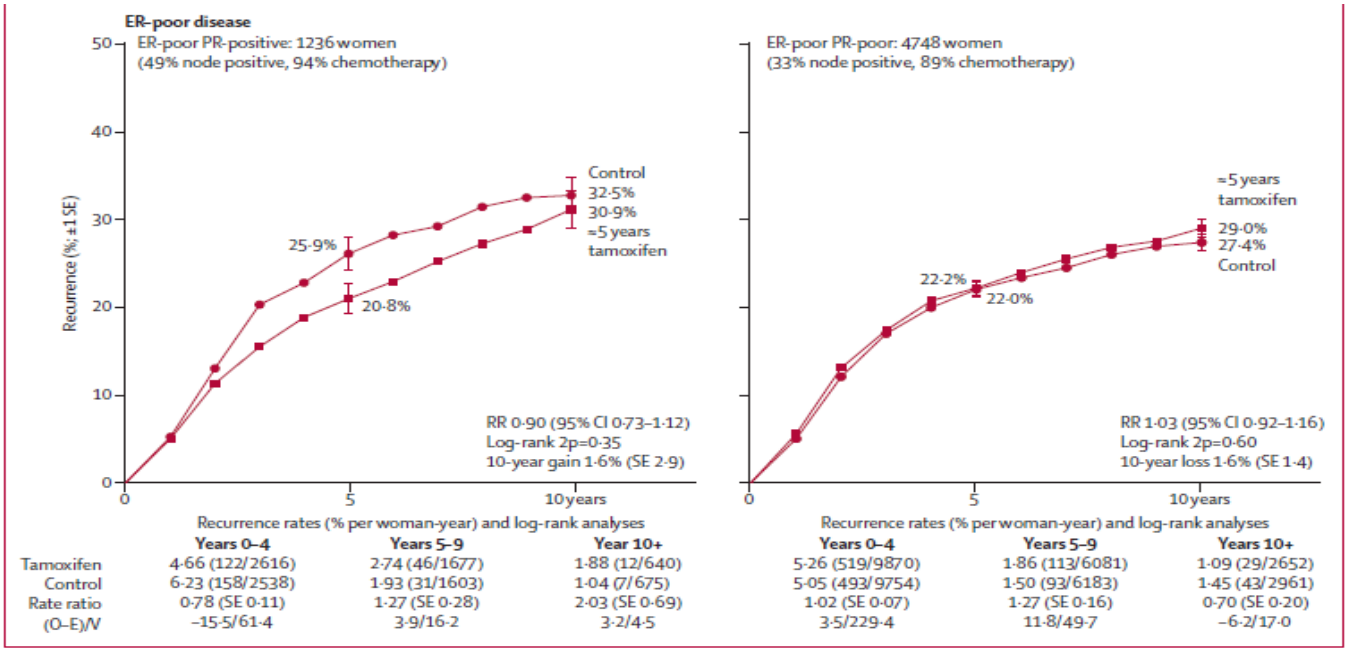
Figure 5: **Effects of about 5 years of tamoxifen on the 15-year probabilities of recurrence and of breast cancer mortality, for ER-positive disease**
Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen. Event rate ratio (RR) is from summed log-rank statistics for all time periods. Gain (and its SE) is absolute difference between ends of graphs. ER=oestrogen receptor. O–E=observed minus expected, with variance V.

● (each p<0.00001)

ECBTCG- Lancet 2011; 378:771-84



ER status was the only recorded factor importantly predictive of the proportional reductions.
In ER+ disease, the PR measurements were not predictive of who would respond to TAM



Recurrence rates (% per woman-year) and log-rank analyses

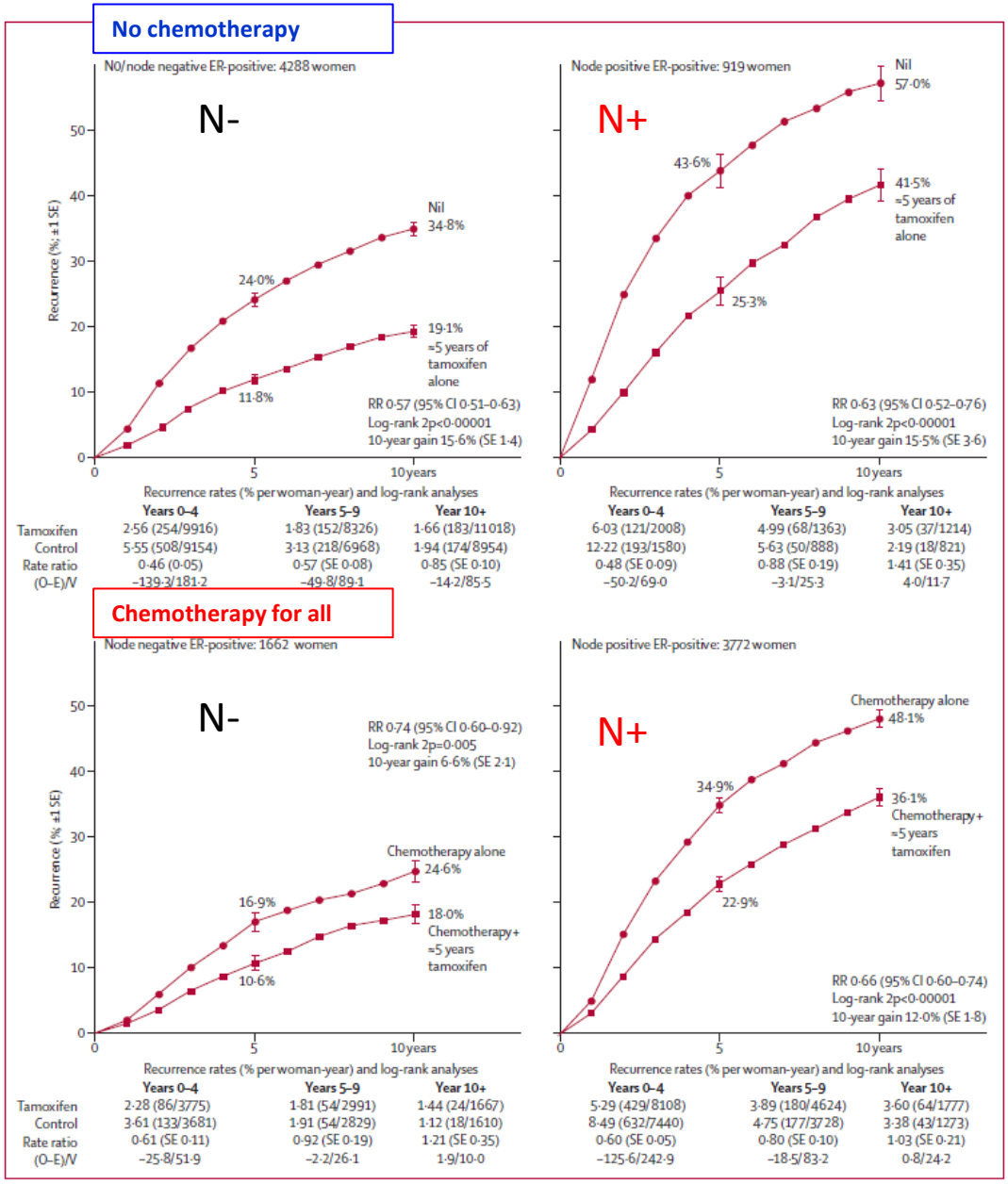
	Years 0–4	Years 5–9	Year 10+
Tamoxifen	4·66 (122/2616)	2·74 (46/1677)	1·88 (12/640)
Control	6·23 (158/2538)	1·93 (31/1603)	1·04 (7/675)
Rate ratio	0·78 (SE 0·11)	1·27 (SE 0·28)	2·03 (SE 0·69)
(O–E)/V	−15·5/61·4	3·9/16·2	3·2/4·5

Recurrence rates (% per woman-year) and log-rank analyses

	Years 0–4	Years 5–9	Years 10+
Tamoxifen	5·26 (519/9870)	1·86 (113/6081)	1·09 (29/2652)
Control	5·05 (493/9754)	1·50 (93/6183)	1·45 (43/2961)
Rate ratio	1·02 (SE 0·07)	1·27 (SE 0·16)	0·70 (SE 0·20)
(O–E)/V	3·5/229·4	11·8/49·7	−6·2/17·0

Figure 1: **Relevance of measured ER and PR status to the effects of about 5 years of tamoxifen on the 10-year probability of recurrence**
Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen. Event rate ratio (RR) is from summed log-rank statistics for all time periods. Gain (and its SE) is absolute difference between ends of graphs. ER=oestrogen receptor. PR=progesterone receptor. O–E=observed minus expected, with variance V.

ECBTCG- Lancet 2011; 378:771-84



	Years 0–4	Years 5–9	Year 10+
Tamoxifen	2·56 (254/9916)	1·83 (152/8326)	1·66 (183/11018)
Control	5·55 (508/9154)	3·13 (218/6968)	1·94 (174/8954)
Rate ratio	0·46 (0·05)	0·57 (SE 0·08)	0·85 (SE 0·10)
(O–E)/V	−139·3/181·2	−49·8/89·1	−14·2/85·5

	Years 0–4	Years 5–9	Year 10+
Tamoxifen	6·03 (121/2008)	4·99 (68/1363)	3·05 (37/1214)
Control	12·22 (193/1580)	5·63 (50/888)	2·19 (18/821)
Rate ratio	0·48 (SE 0·09)	0·88 (SE 0·19)	1·41 (SE 0·35)
(O–E)/V	−50·2/69·0	−3·1/25·3	4·0/11·7

	Years 0–4	Years 5–9	Year 10+
Tamoxifen	2·28 (86/3775)	1·81 (54/2991)	1·44 (24/1667)
Control	3·61 (133/3681)	1·91 (54/2829)	1·12 (18/1610)
Rate ratio	0·61 (SE 0·11)	0·92 (SE 0·19)	1·21 (SE 0·35)
(O–E)/V	−25·8/51·9	−2·2/26·1	1·9/10·0

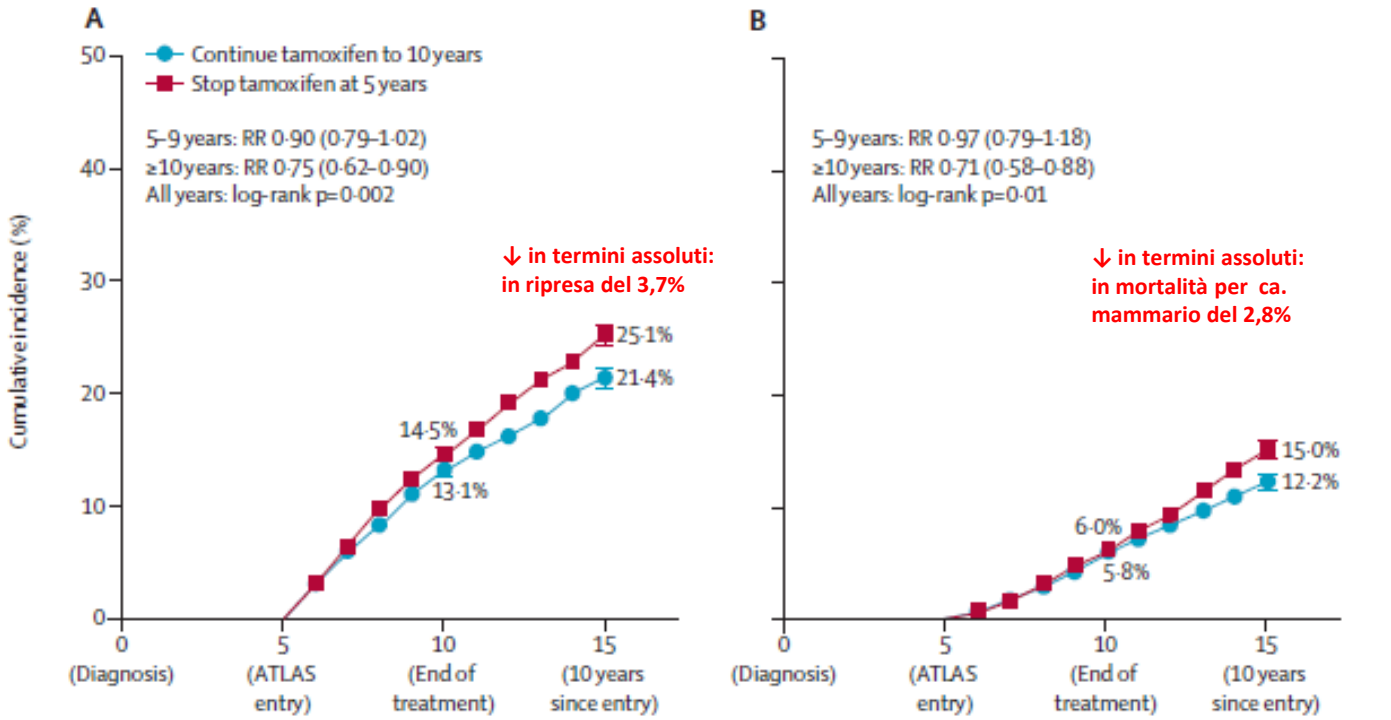
	Years 0–4	Years 5–9	Year 10+
Tamoxifen	5·29 (429/8108)	3·89 (180/4624)	3·60 (64/1777)
Control	8·49 (632/7440)	4·75 (177/3728)	3·38 (43/1273)
Rate ratio	0·60 (SE 0·05)	0·80 (SE 0·10)	1·03 (SE 0·21)
(O–E)/V	−125·6/242·9	−18·5/83·2	0·8/24·2

Figure 3: **Relevance of nodal status and of background chemotherapy to the effects of tamoxifen on the 10-year probability of recurrence, for ER-positive disease**
Outcome by allocated treatment in trials of about 5 years of adjuvant tamoxifen. Event rate ratio (RR) is from summed log-rank statistics for all time periods. Gain (and its SE) is absolute difference between ends of graphs. ER=oestrogen receptor. PR=progesterone receptor. O–E=observed minus expected, with variance V.

TAMOXIFEN impact by N status and CT

ECBTCG- Lancet 2011; 378:771-84

10-yr Tamoxifen (ATLAS)

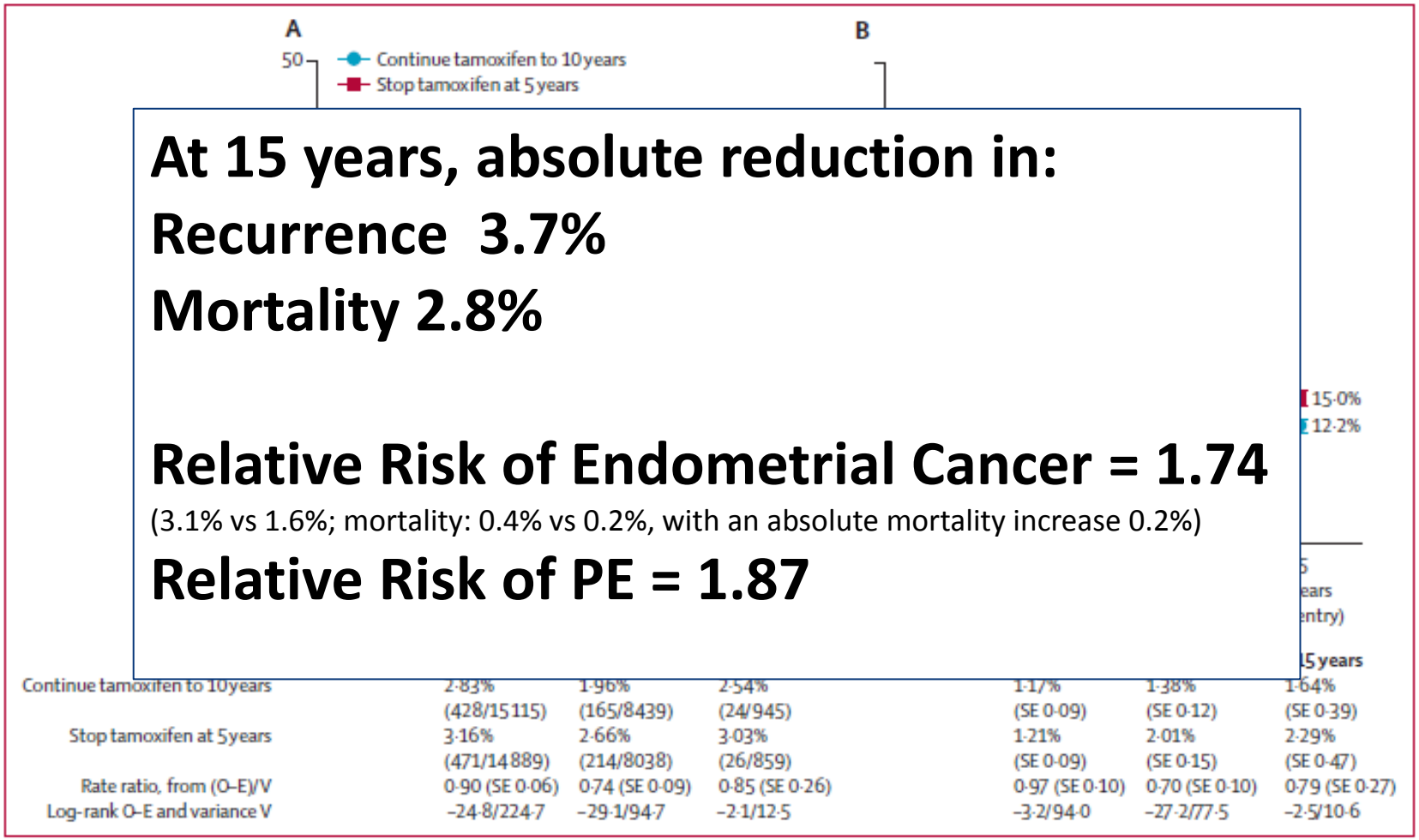


	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15 115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14 889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	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.

C Davies, Lancet 2013

10-yr Tamoxifen (ATLAS)



At 15 years, absolute reduction in:

Recurrence 3.7%

Mortality 2.8%

Relative Risk of Endometrial Cancer = 1.74

(3.1% vs 1.6%; mortality: 0.4% vs 0.2%, with an absolute mortality increase 0.2%)

Relative Risk of PE = 1.87

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.

C Davies, Lancet 2013

Breast Cancer Mortality, Overall Survival in ER+ rate ratio* by period in aTTom and ATLAS

	Breast Cancer Mortality			OS
	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)	10 yrs tam. vs 5: aTTom & ATLAS combined (n=17477 ER+/UK)
years 5-9	1.08 (0.85-1.38)	0.92 (0.77-1.09)	0.97 (0.84-1.15)	0.99 (0.89-1.10)
years 10+	0.75† (0.63-0.90)	0.75§ (0.63-0.90)	0.75† (0.65-0.86)	0.84† (0.77-0.93)
All years	0.88‡ (0.74-1.03)	0.83‡ (0.73-0.94)	0.85‡ (0.77-0.94)	0.91‡ (0.84-0.97)
	†p=0.007 ‡p=0.1	§p=0.002 ‡p=0.004	†p=0.00004 ‡p=0.001	†p=0.0007 ‡p=0.008

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

Adjuvant endocrine therapy in early breast cancer

	No of pts	CT+ ET	only CT
HR+/N+	368	81%	17%
HR+/N-	173	74%	23%
HR- unknown/ N+ or N-	45	49%	49%

Endocrine therapy was not prescribed

Modified from Roila F et al, Ann Oncol 2003;14:843-8

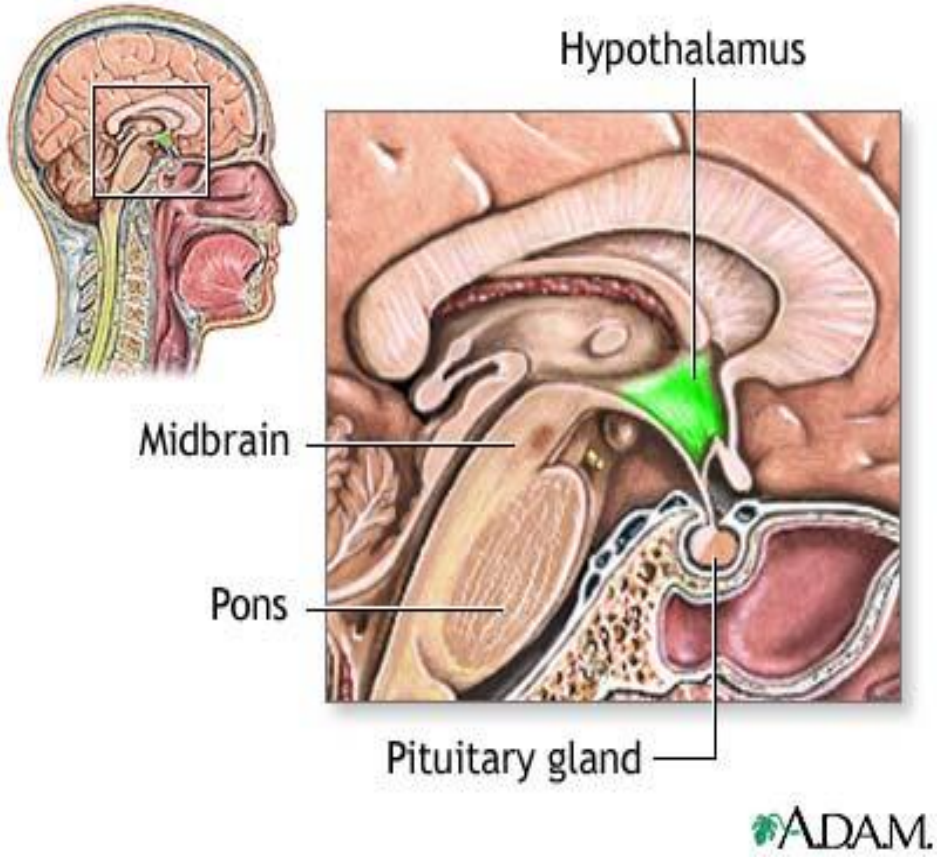
Carcinoma mammario in premenopausa

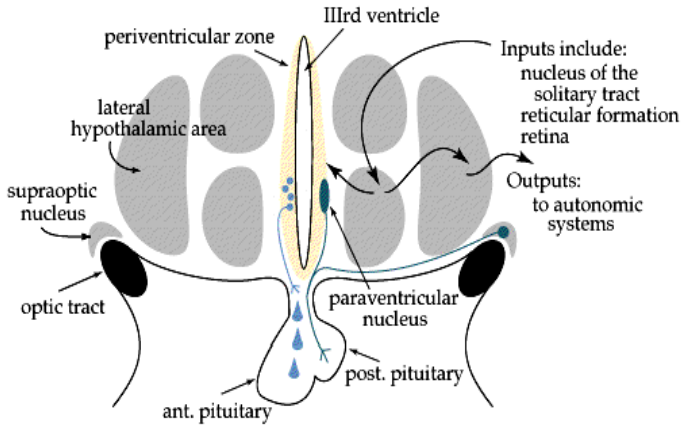
Gli analoghi LH-RH
(LH-Rha o GnRHa)

Ipotalamo

E’ la parte ventrale anteriore del diencefalo

Neurosecrezione: Capacità di produzione, trasporto e secrezione in circolo di ormoni da parte delle cellule nervose. Controlla la funzione ipofisaria.

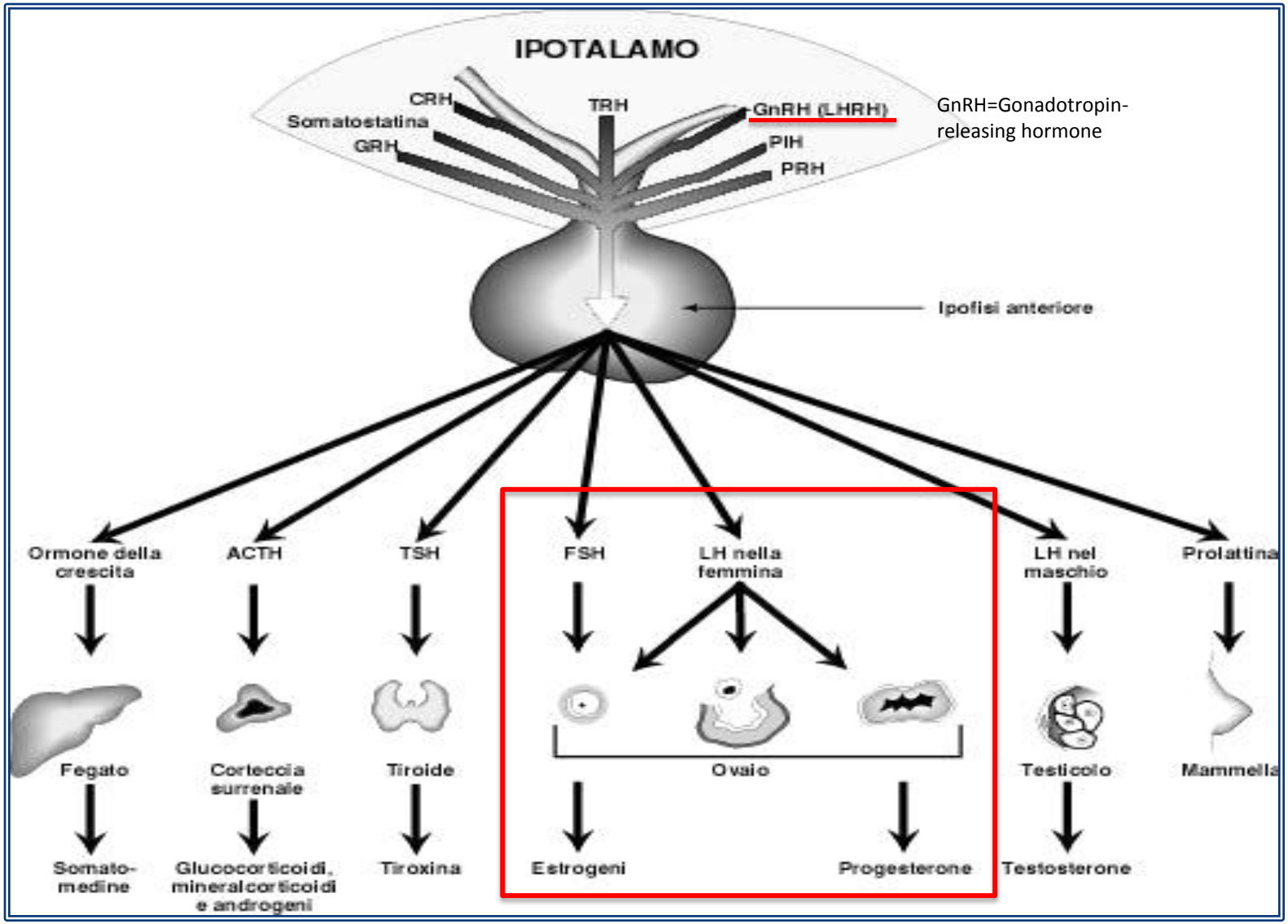




Controlla anche altre funzioni come l’appetito, la sete, la temperatura corporea, il sonno e l’emotività

STIMOLI ESOGENI ED ENDOGENI

SISTEMA NERVOSO CENTRALE



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

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

Summary

Background Several trials have been done to assess treatment of premenopausal breast cancer with luteinising-hormone-releasing hormone (LHRH) agonists, but results have been inconclusive, especially for patients with hormone-receptor-positive cancer.

Methods We collected individual patients' data from published trials and did analyses focused on women with tumours positive for oestrogen receptor, progesterone receptor, or both. The main endpoints were recurrence and death after recurrence.

Findings We obtained data for 11906 premenopausal women with early breast cancer randomised in 16 trials. When used as the only systemic adjuvant treatment, LHRH agonists did not significantly reduce recurrence (28·4% relative reduction, 95% CI consistent with 50·5% reduction to 3·5% increase, p=0·08) or death after recurrence (17·8%, 52·8% reduction to 42·9% increase, p=0·49) in hormone-receptor-positive cancers. Addition of LHRH agonists to tamoxifen, chemotherapy, or both reduced recurrence by 12·7% (2·4–21·9, p=0·02); and death after recurrence by 15·1% (1·8–26·7, p=0·03). LHRH agonists showed similar efficacy to chemotherapy (recurrence 3·9% increase, 7·7% reduction to 17·0% increase; death after recurrence 6·7% reduction, 20·7% reduction to 9·6% increase; both not significant). No trials had assessed an LHRH agonist versus chemotherapy with tamoxifen in both arms. LHRH agonists were ineffective in hormone-receptor-negative tumours.

Interpretation LHRH agonists provide an additional class of agents for treatment of premenopausal women with hormone-receptor-positive breast cancer. Optimum duration of use is unknown.

Lancet 2007; 369: 1711–23

See **Comment** page 1668

See **Perspectives** page 1685

*Collaborators listed at end of report

Correspondence to:
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jack.cuzick@cancer.org.uk

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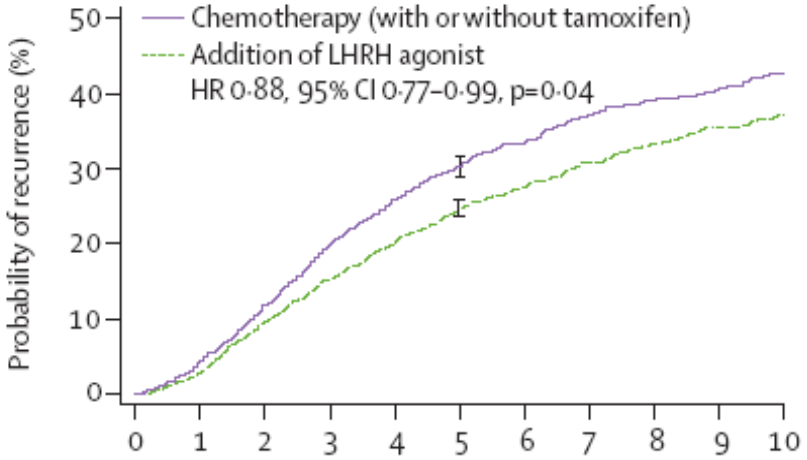
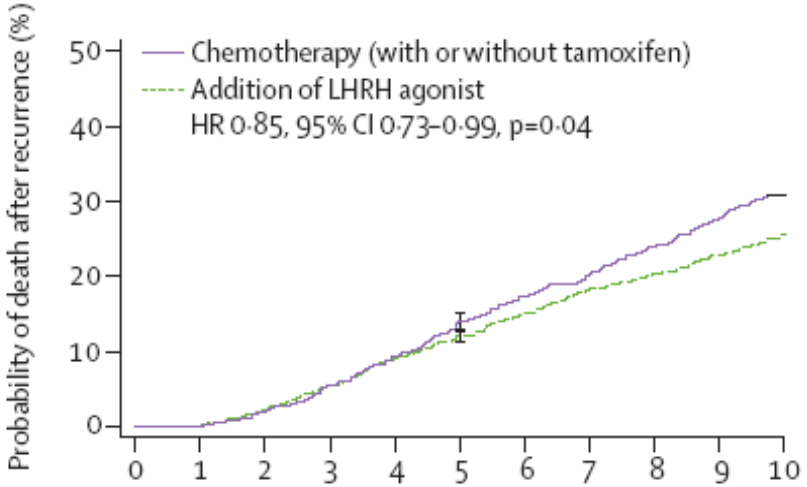


Number at risk						
Chemotherapy	1371	1187	908	663	476	349
LHRH agonist addition	1370	1217	976	709	505	350



Number at risk						
Chemotherapy	1371	1316	1109	827	604	430
LHRH agonist addition	1370	1317	1127	859	637	445

Cuzick J, Lancet 2007

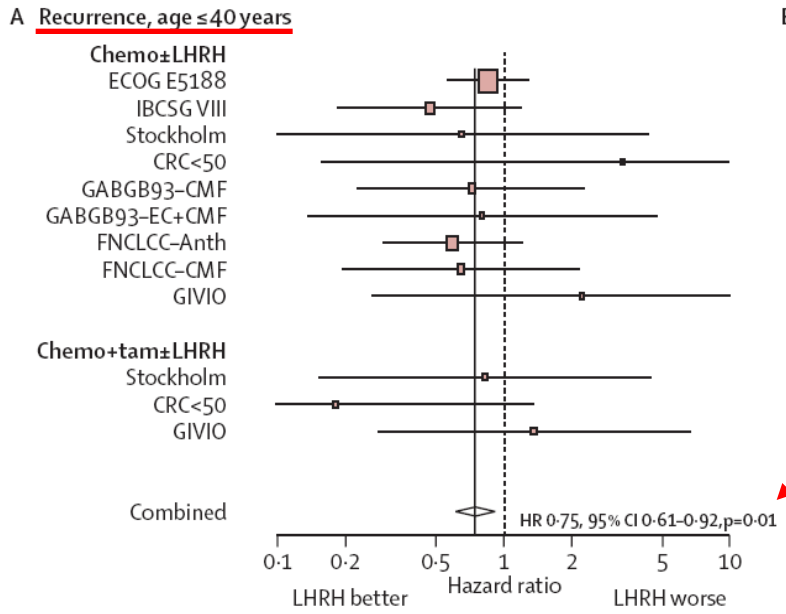
..↓ significantly:

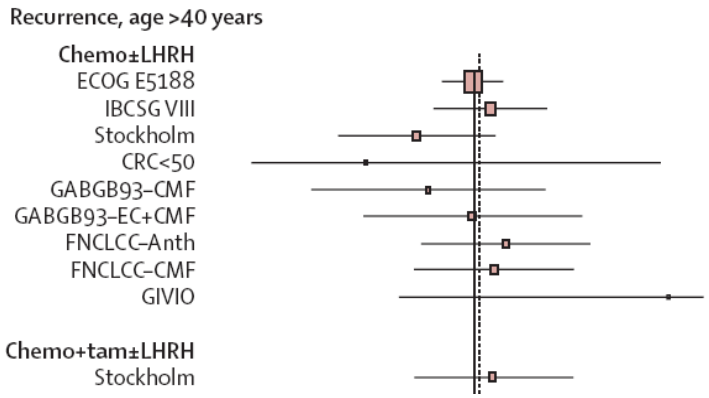
HR (12%) for recurrence

HR (15%) for death after recurrence

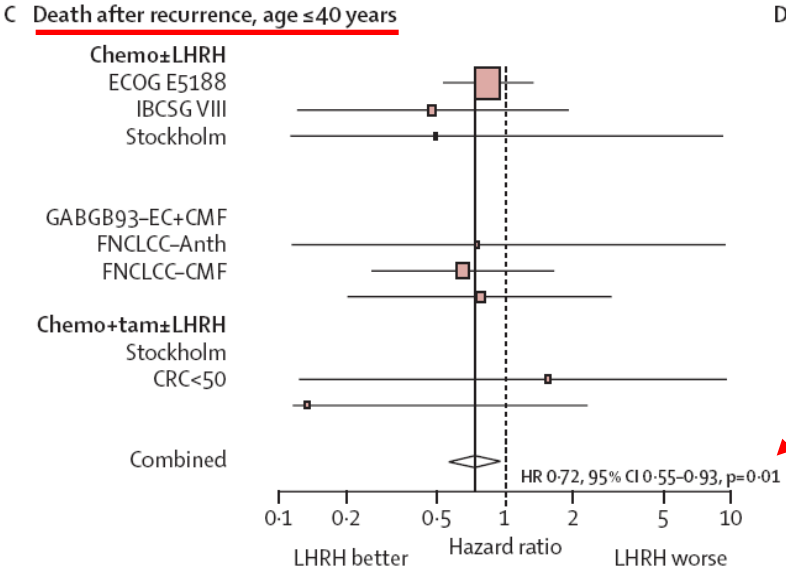
Addition of LHRH agonist to chemotherapy± TAM

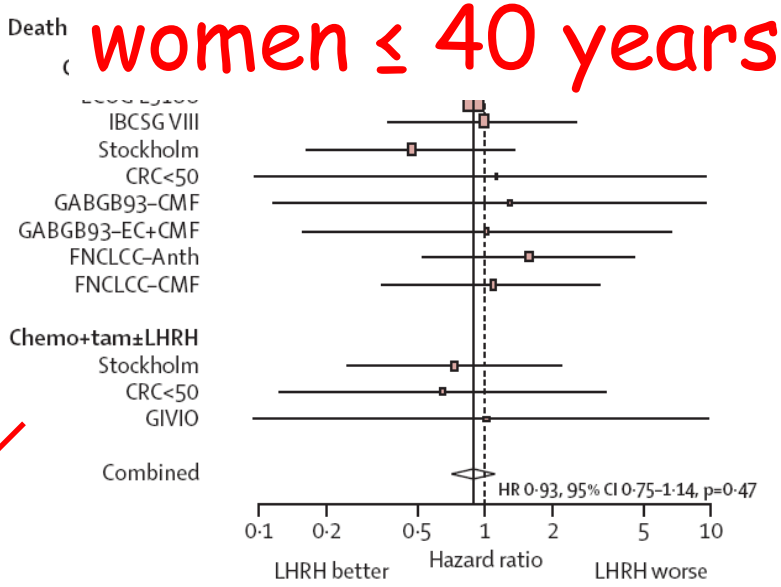
Cuzick J, Lancet 2007





..and is more effective in women ≤ 40 years





Addition of LHRH agonist to CT with or without TAM by age

American Society of Clinical Oncology Endorsement of the Cancer Care Ontario Practice Guideline on Adjuvant Ovarian Ablation in the Treatment of Premenopausal Women With Early-Stage Invasive Breast Cancer

Jennifer J. Griggs, Mark R. Somerfield, Holly Anderson, N. Lynn Henry, Clifford A. Hudis, James L. Khatcheressian, Ann H. Partridge, Ann Alexis Prestrud, and Nancy E. Davidson

A B S T R A C T

Purpose
The American Society of Clinical Oncology (ASCO) has policies and procedures for endorsing practice guidelines that have been developed by other professional organizations.

Methods
The Cancer Care Ontario (CCO) Guideline on Adjuvant Ovarian Ablation (OA) in the Treatment of Premenopausal Women With Early-Stage Invasive Breast Cancer was reviewed for developmental rigor by methodologists. An ad hoc review panel of experts reviewed the content.

Results
The ASCO ad hoc OA guideline review panel concurred that the recommendations are clear, thorough, based on the most relevant scientific evidence in this content area, and present options that will be acceptable to patients. According to the CCO guideline: one, OA should not be routinely added to systemic therapy with chemotherapy, tamoxifen, or the combination of tamoxifen and chemotherapy; two, OA alone is not recommended as an alternative to any other form of systemic therapy, except in the specific case of patients who are candidates for other forms of systemic therapy but who, for some reason, will not receive any other systemic therapy (eg, patients who cannot tolerate other forms of systemic therapy or patients who choose no other form of systemic therapy); and three, when chemical suppression using luteinizing hormone–releasing hormone agonists is the chosen method of OA, in the opinion of the Breast Cancer Disease Site Group, monthly injection is the recommended mode of administration. The mode of administration in nearly all of the available trials has been monthly administration.

Conclusion
The ASCO review panel agrees with the recommendations as stated in the CCO guideline, with the qualification that ongoing research studies may alter the recommendations of the panel.

J Clin Oncol 29:3939-3942.

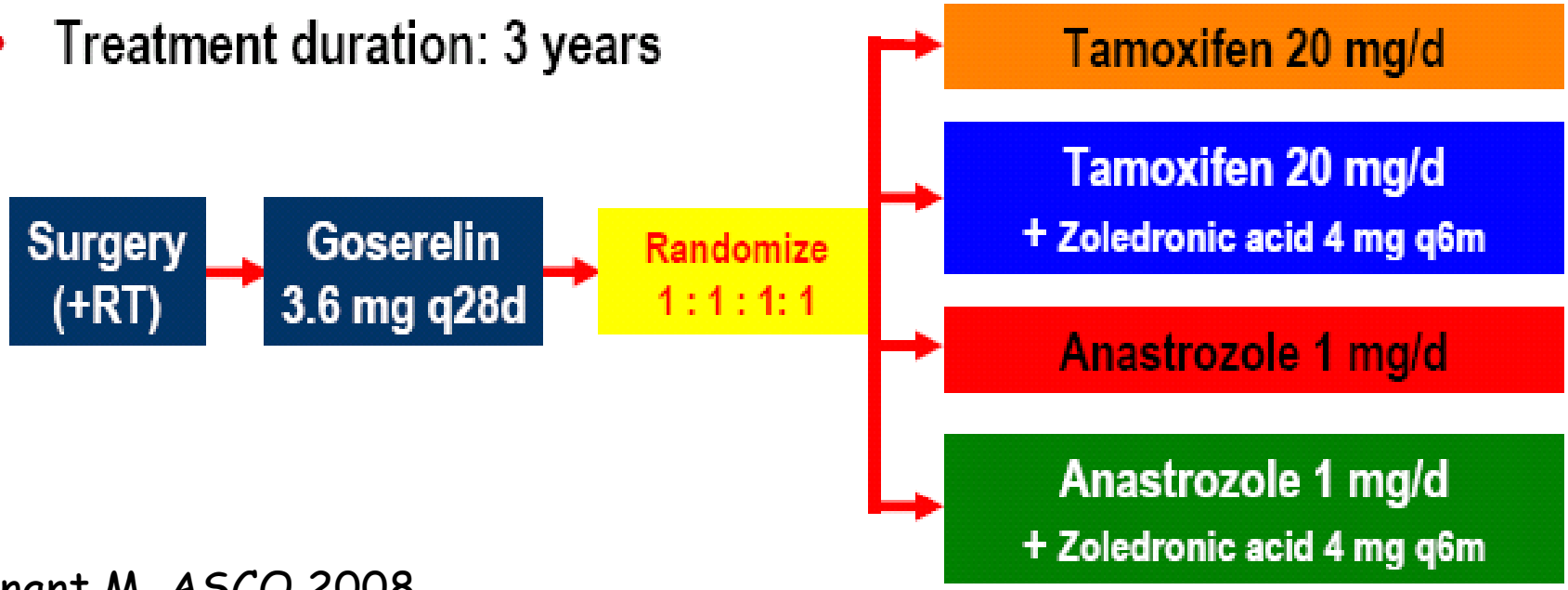
Table 1. Ongoing Studies of Ovarian Ablation/Suppression in Premenopausal Women With Breast Cancer

Clinical Trial	Study Arm	Method of OA
Tamoxifen citrate alone or ovarian function suppression and tamoxifen citrate or exemestane in treating premenopausal women who have undergone surgery for breast cancer (SOFT Trial) Clinical trials identifier: NCT00917969	1: Tamoxifen 2: OA + tamoxifen 3: OA + exemestane	Triptorelin Triptorelin pamoate Goserelin Bilateral oophorectomy Bilateral ovarian irradiation
Evaluating the role of the addition of ovarian function suppression to tamoxifen in young women (ASTRRA Trial) Clinical trials identifier: NCT00912548	1: Zoladex + tamoxifen 2: Tamoxifen	
Suppression of ovarian function plus either tamoxifen or exemestane compared with tamoxifen alone in treating premenopausal women with hormone-responsive breast cancer Clinical trials identifier: NCT00066690	1: Tamoxifen 2: Tamoxifen + OA 3: OA	Triptorelin Surgical oophorectomy Ovarian irradiation
Suppression of ovarian function and either tamoxifen or exemestane with or without chemotherapy in treating premenopausal women with resected breast cancer (PERCHE Trial) Clinical trials identifier: NCT00066807	1: OA + tamoxifen or exemestane 2: OA + concurrent chemotherapy + tamoxifen/exemestane	Triptorelin Oophorectomy Ovarian irradiation
Tamoxifen, OA, and/or chemotherapy in treating women with stage I, stage II, or stage IIIA breast cancer (Adjuvant Breast Cancer Trial) Clinical trials identifier: NCT00002582, NCT00002580	1: Tamoxifen 2: Tamoxifen + CMF or AC chemotherapy 3: Tamoxifen + OA 4: Tamoxifen + OA + CMF or AC chemotherapy	Oophorectomy Radiation castration Leuprolide Goserelin
Adjuvant hormone therapy in treating women with operable breast cancer Clinical trials identifier: NCT00002460	1: No treatment 2: Tamoxifen 3: OA (goserelin) 4: OA (goserelin) + tamoxifen	Goserelin
Suppression of ovarian function plus either tamoxifen or exemestane compared with tamoxifen alone in treating premenopausal women with hormone-responsive breast cancer Clinical trials identifier: NCT00066690	1: Tamoxifen 2: Tamoxifen + OA 3: Exemestane + OA	Triptorelin Surgical oophorectomy Ovarian irradiation
Triptorelin with either exemestane or tamoxifen in treating premenopausal women with hormone-responsive breast cancer (TEXT Trial) Clinical trials identifier: NCT00066703	1: OA (triptorelin) + tamoxifen 2: OA (triptorelin) + exemestane	Triptorelin

Abbreviations: AC, doxorubicin/cyclophosphamide; CMF, cyclophosphamide, methotrexate, fluorouracil; OA, ovarian ablation.

ABCSG-12 Trial Design

- Accrual 1999-2006
- 1,803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PR positive)
- Stage I&II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



Gnant M, ASCO 2008

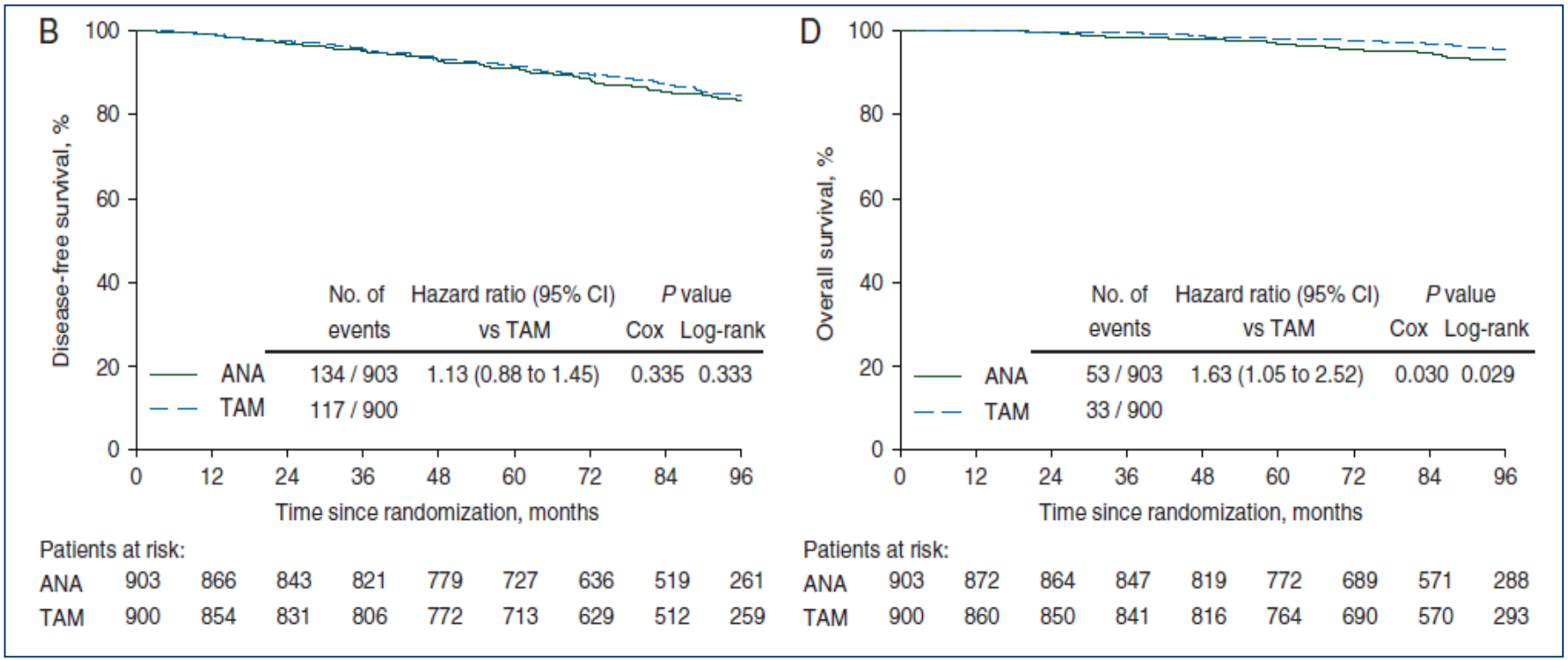
Patients

n (%)	TAM (n = 452)	TAM + ZOL (n = 449)	ANA (n = 450)	ANA + ZOL (n = 449)
Median age, years	45.5	45.3	45.0	44.5
T1	338 (75.1)	335 (74.6)	348 (77.0)	339 (75.5)
≥ T2	99 (22.0)	98 (21.8)	93 (20.6)	97 (21.6)
Node negative	301 (66.9)	295 (65.7)	303 (67.0)	302 (67.3)
Node positive	136 (30.2)	138 (30.7)	139 (30.8)	135 (30.1)
ER + / ++	216 (48)	212 (47.3)	218 (48.3)	213 (47.4)
ER +++	205 (45.6)	202 (45.0)	208 (46.0)	207 (46.1)
PgR + / ++	211 (46.9)	200 (44.6)	206 (45.6)	182 (40.6)
PgR +++	186 (41.3)	201 (44.8)	201 (44.5)	219 (48.8)
Grading III	93 (20.7)	89 (19.8)	97 (21.5)	98 (21.8)
Breast conservation	359 (79.6)	357 (79.5)	364 (80.4)	358 (79.6)
Neoadjuvant chemo	24 (5.3)	23 (5.1)	24 (5.3)	26 (5.8)
Per-protocol treatment	413 (91.6)	406 (90.4)	419 (92.5)	415 (92.2)

Gnant M, ASCO 2008

ABCSG-12: RESULTS at median follow up of 94.4 months

ANA+Goserelin *vs*
TAM+Goserelin



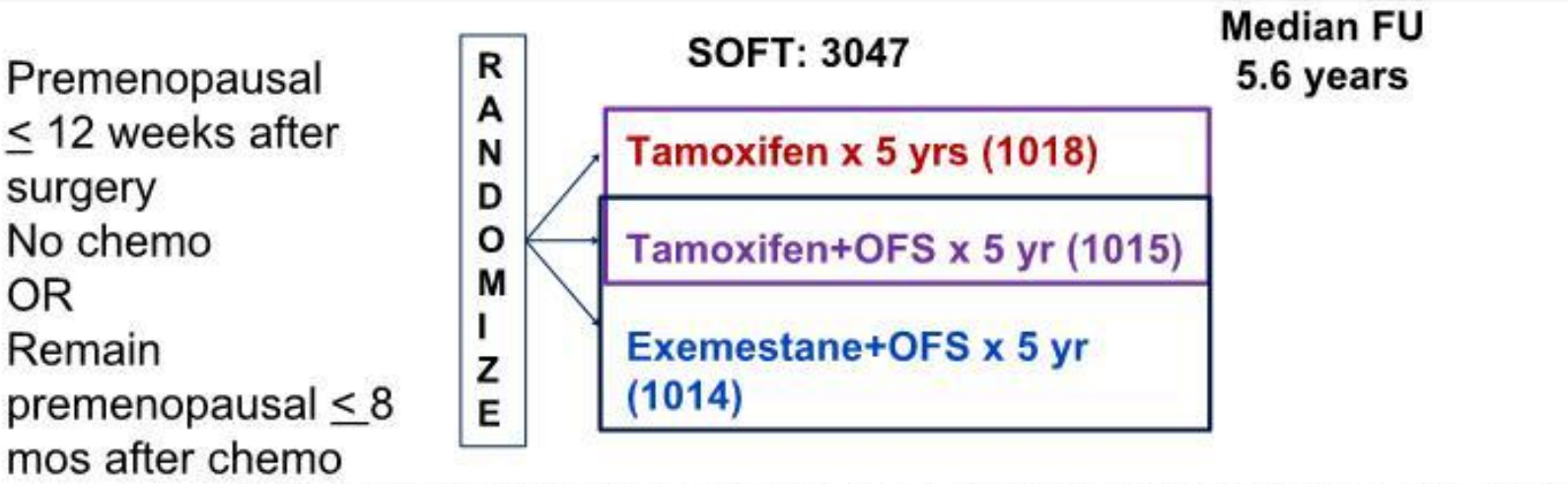
Gnant M, Ann Oncol 2015;26:313-320

SOFT TRIAL

Primary analisys

N=2.033 pts

2011: Emendamento dello studio disegnando il test di superiorità del TAM+OFS vs TAM come analisi primaria del SOFT



Francis et al, NEJM 2015

SOFT TRIAL

Primary analisys

N=2.033 pts

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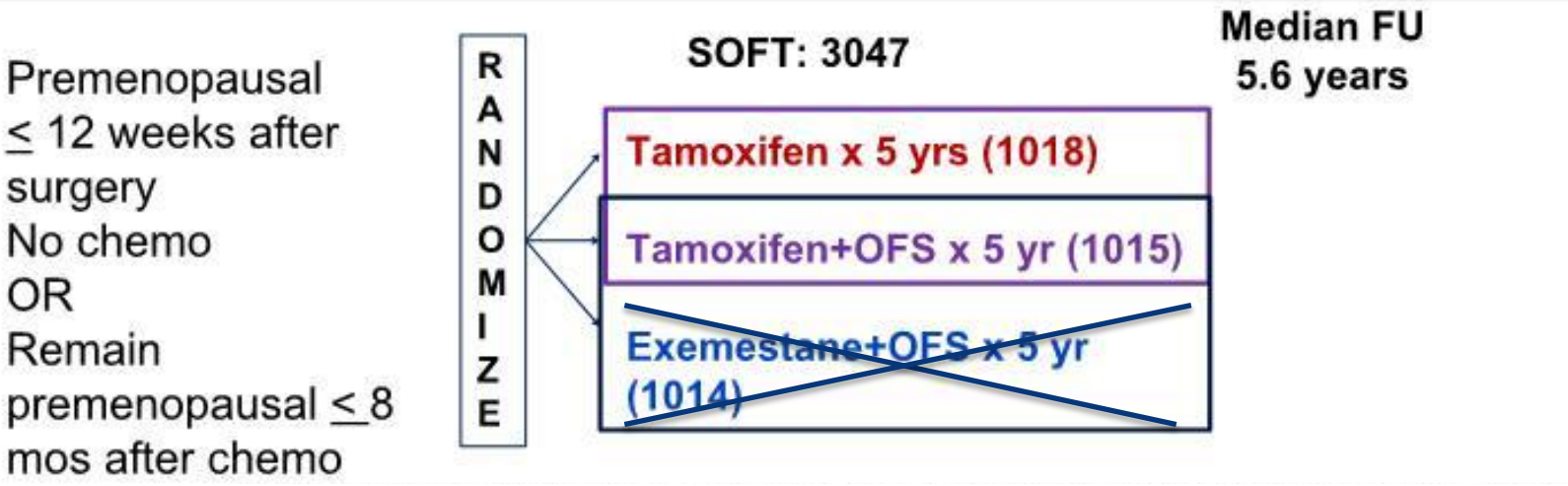


Francis et al, NEJM 2015

Endpoints

Primary

- Disease – Free Survival
  - Invasive recurrence (local, regional, distant)
  - Invasive contralateral breast cancer
  - Second non-breast invasive malignancy
  - Death without prior cancer event

Secondary

- Breast cancer-free interval
- Distant recurrence-free interval
- Overall Survival

SOFT Study

- Mayor inclusion criteria: premenopausal status, operable breast cancer, positivity for ER e/o PgR (**>10%**).

- **Ovarian suppression** was achieved by choice of
  - **triptorelin** [triptorelin acetate] at a dose of 3.75 mg administered by means of im injection every 28 days,
  - **bilateral oophorectomy**,
  - **bilateral ovarian irradiation.**

- The patients choice was farmacological in **80.7%**.

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

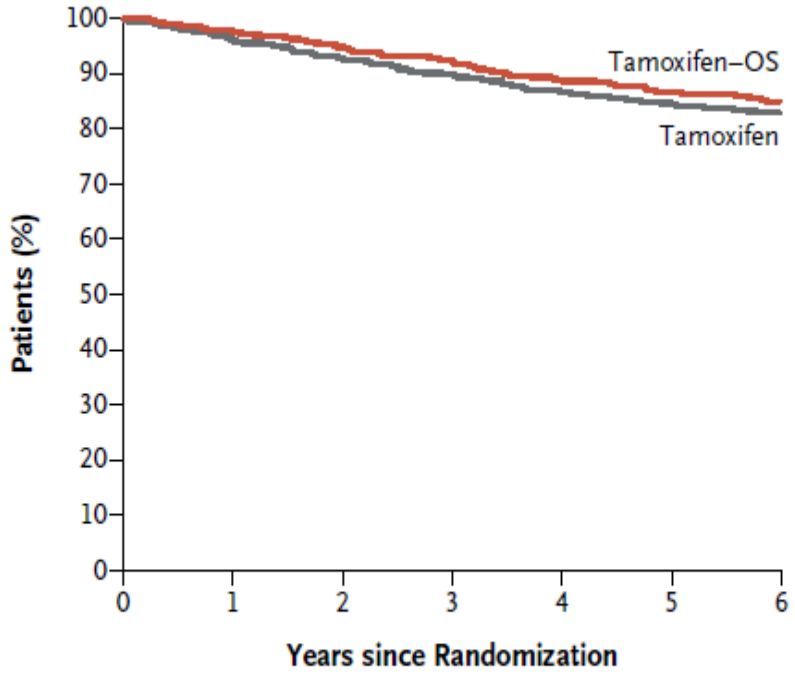
Table 1. Characteristics of Patients in the Primary Analysis, Overall and According to Chemotherapy Cohort.*

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)

Characteristic	Chemotherapy Stratum				Overall	
	No Chemotherapy		Prior Chemotherapy			
	All		All			
	N	%	N	%	N	%
Other[2]	10	1.1	12	1.1	22	1.1
Prior endocrine therapy[3]						
No	902	95.0	609	56.2	1511	74.3
Yes	47	5.0	475	43.8	522	25.7
HER2-targeted therapy						
Not HER2+	909	95.8	883	81.5	1792	88.1
HER2+, no therapy	39	4.1	61	5.6	100	4.9
HER2-targeted therapy	1	0.1	140	12.9	141	6.9

DFS: Primary Endpoint
median FU 5.6 yrs

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

SOFT trial

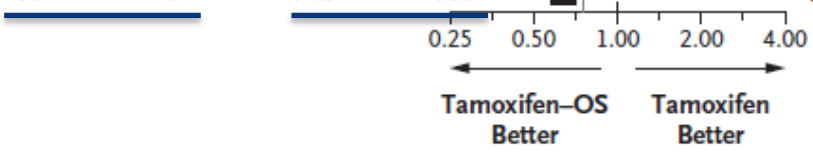
Statistical Considerations Post-Amendment

- Primary analysis: T+OFS vs T
- After median follow-up of at least 5 years
- Anticipated 186 DFS events, power 80% for HR=0.665 comparing T+OFS vs T (two sided α=0.05)
- Analysis according to use of prior chemotherapy (no/yes) was prospectively planned
- E+OFS vs T became secondary objective

End points, overall and according to CT cohort

Median follow up 5.6 yrs

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)	

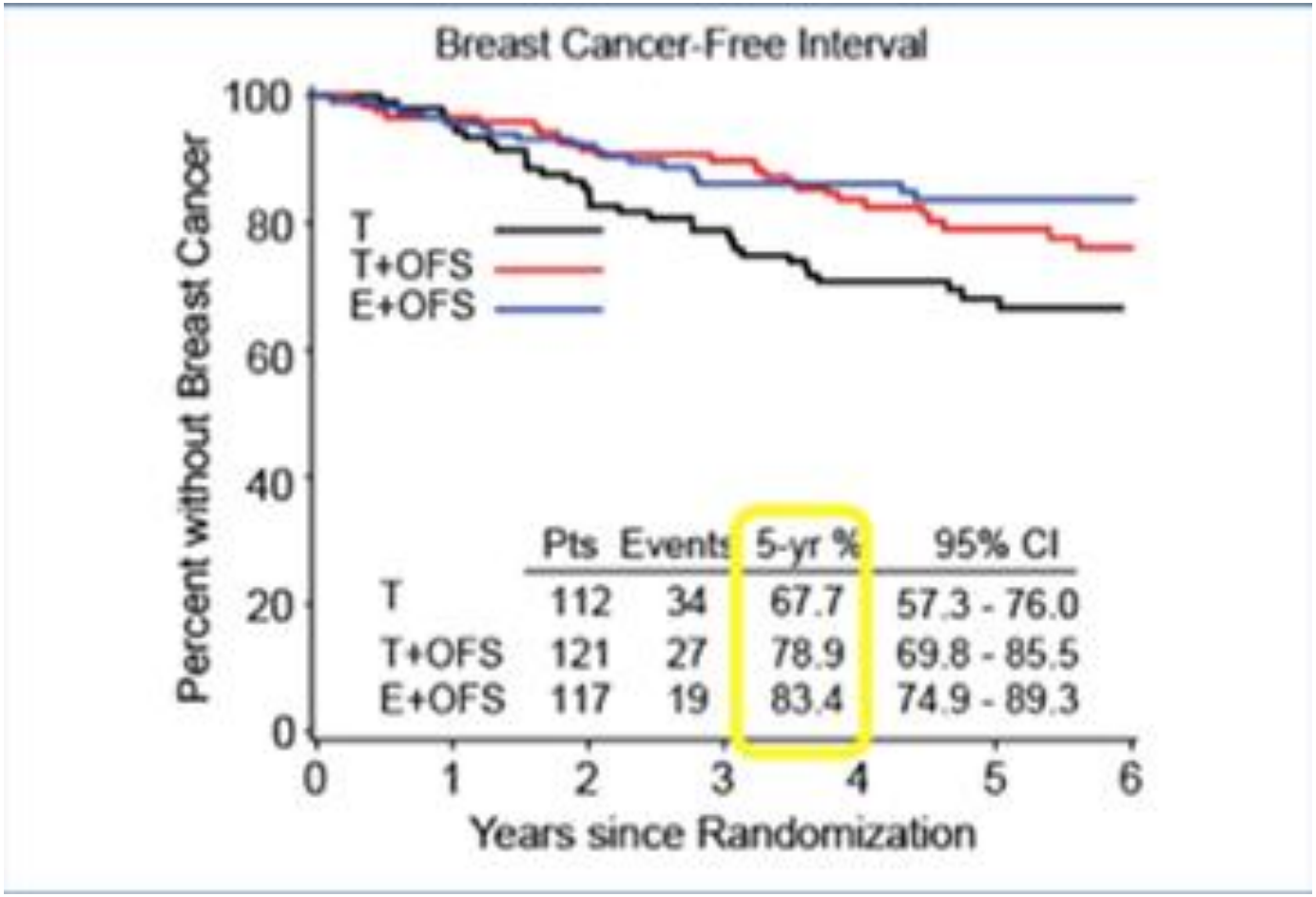


.. Oltre il 95% delle morti si è verificato in pts che hanno ricevuto PRIOR CT.

All Women < 35yr

350 patients (11.5% of total pts)

94% received chemotherapy



SOFT - Safety

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)

* Data are for the 2011 patients in the safety population who received a protocol-assigned treatment (except for 3 patients who withdrew consent within 1 month after randomization and had no adverse-event data submitted). Targeted adverse events (22 events; see Table S6 in the Supplementary Appendix) and other adverse events of grade 3 or higher were categorized according to the *Common Terminology Criteria for Adverse Events*, version 3.0.[11] A dash indicates that grade 3 or 4 was not a possible grade for the specified adverse event. There was one targeted adverse event of grade 5 (cardiac ischemia or infarction in a patient randomly assigned to tamoxifen).

† Glucose intolerance (diabetes) was added as a targeted adverse event in 2011 and therefore may be underreported.

‡ The category of any targeted adverse event includes the 22 targeted adverse events summarized in Table S6 in the Supplementary Appendix.

Francis PA et al. N Engl J Med 2014

Conclusioni

- Nella popolazione dello studio, l'aggiunta di soppressione ovarica al TAM non aumenta significativamente la DFS.

- In donne a rischio di ripresa tale da richiedere chemioterapia adiuvante e che rimangono in premenopausa, l'aggiunta della soppressione ovarica al TAM:
↑ la DFS, la Freedom from BC, la Freedom from distant recurrence;
↑ significativamente la sopravvivenza globale.

- In donne giovani in premenopausa (< 35 anni; 94% delle quali aveva ricevuto CT) l'aggiunta di soppresssione ovarica al TAM aumenta la sopravvivenza libera da eventi BC.

- E' richiesto un f-up più lungo perché il SOFT è "currently underpowered" e l'analisi della OS è prematura (solo 5% di decessi).

Randomized Comparison of Adjuvant Aromatase Inhibitor Exemestane plus Ovarian Function Suppression vs Tamoxifen plus Ovarian Function Suppression in Premenopausal Women with Hormone Receptor Positive Early Breast Cancer: Joint Analysis of IBCSG TEXT and SOFT

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

TEXT and SOFT Designs

Enrolled: Nov03-Apr11

- Premenopausal
- ≤12 wk after surgery
- Planned OFS

RANDOMIZE

TAMOXIFEN AND EXEMESTANE TRIAL (N=2672)

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

(± chemo)

- Premenopausal
- ≤12 wk after surgery
- No chemo

OR

- Remain premenopausal ≤ 8 mo after chemo

RANDOMIZE

SUPPRESSION OF OVARIAN FUNCTION TRIAL (N=3066)

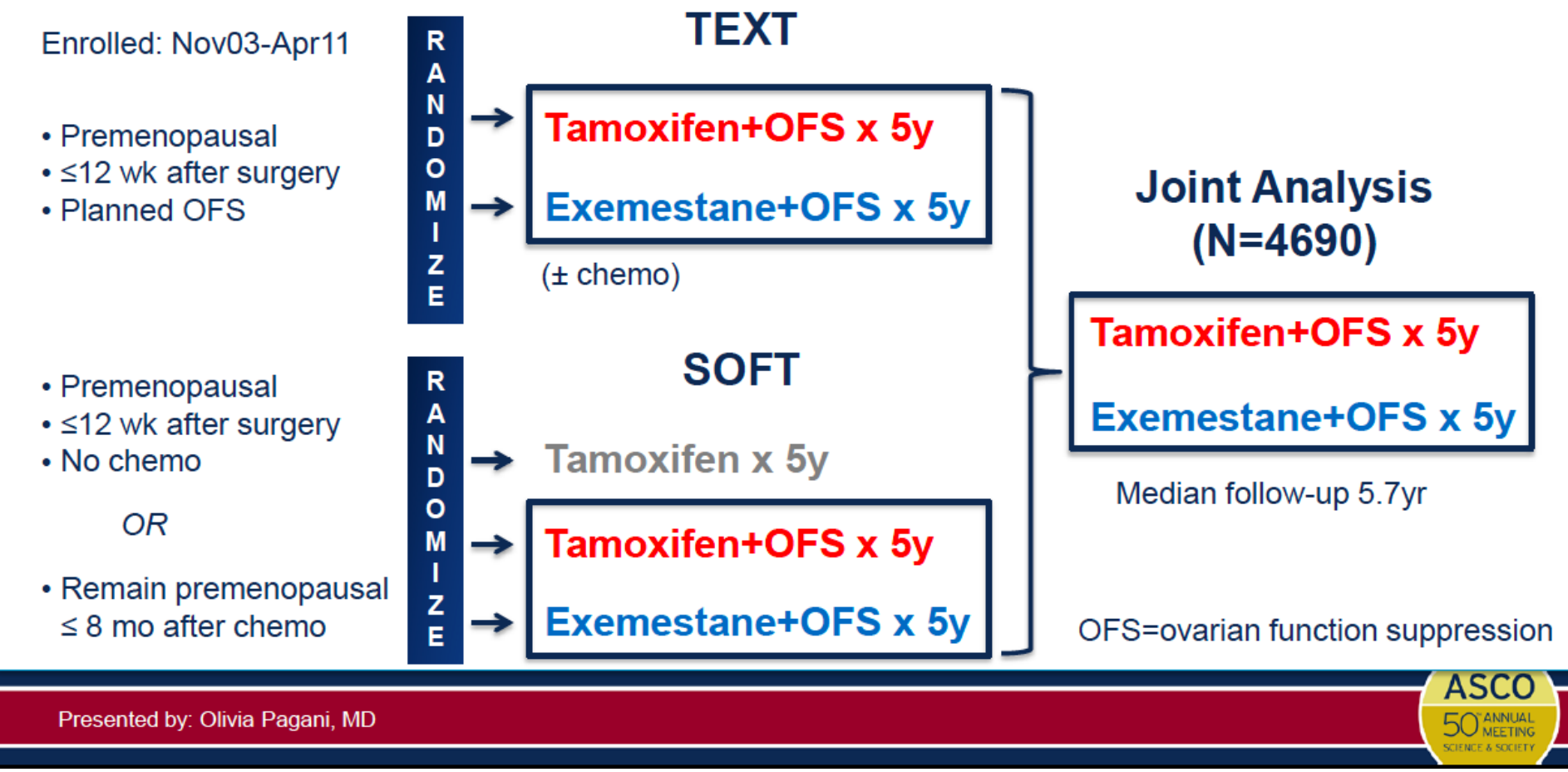
→ **Tamoxifen x 5y**

→ **Tamoxifen+OFS x 5y**

→ **Exemestane+OFS x 5y**

OFS=ovarian function suppression

TEXT and SOFT Designs



Presented by: Olivia Pagani, MD

ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

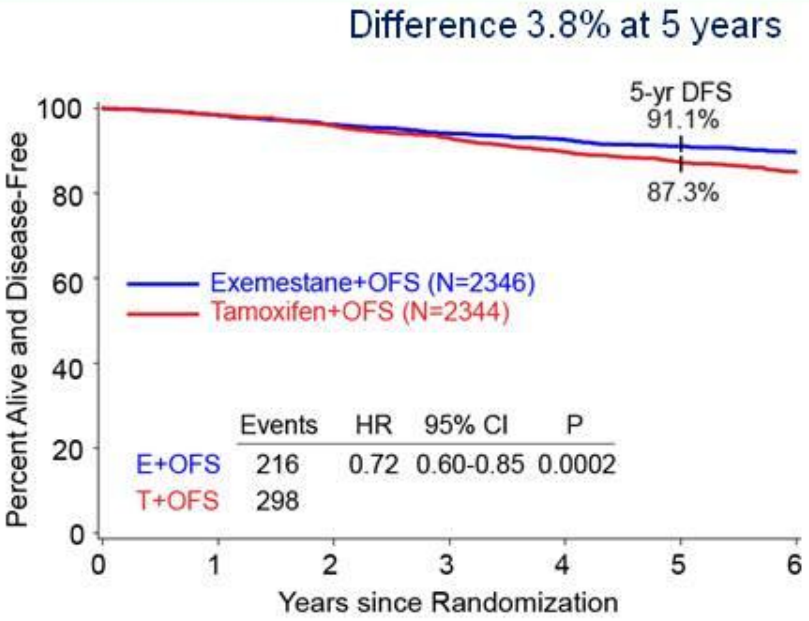
End point primario: DFS

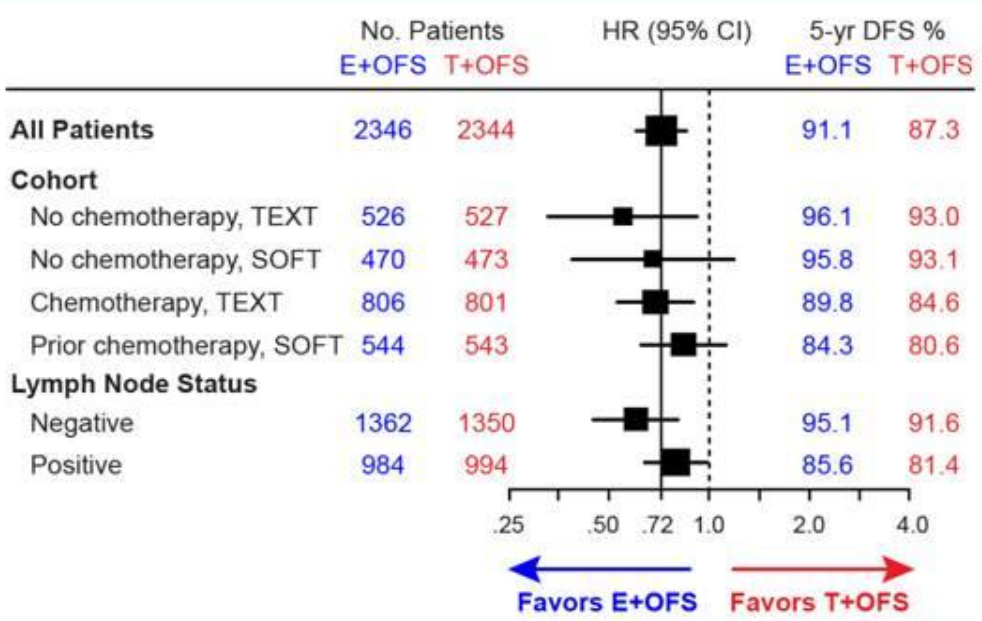
OFS in the TEXT trial: triptorelin 3.75 mg im every 28 days;
in the SOFT: triptorelin, RT or surgery

Characteristics

	No chemo TEXT (N=1053)	No chemo SOFT (N=943)	Chemo TEXT (N=1607)	Prior chemo SOFT (N=1087)	Overall (N=4690)
Age <40 yr	16%	9%	30%	49%	27%
LN +	21%	8%	66%	57%	42%
T-size >2cm	19%	15%	53%	47%	36%
HER2 +	5%	3%	17%	19%	12%
Surgery to random. (median)	1.5 mo	1.8 mo	1.2 mo	8.0 mo	1.6 mo

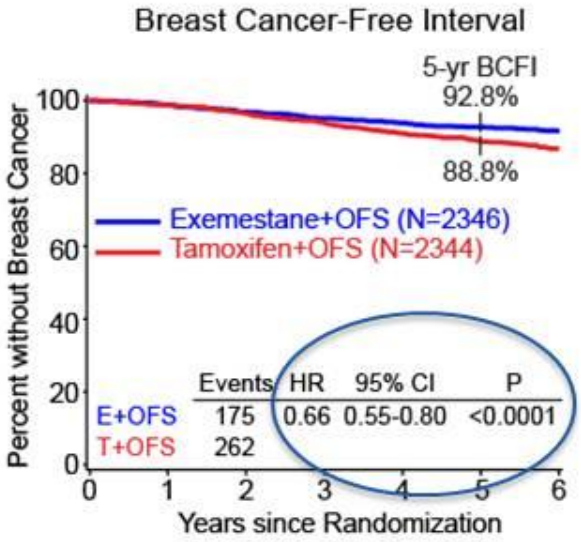
Exemestane+OFS Improved DFS

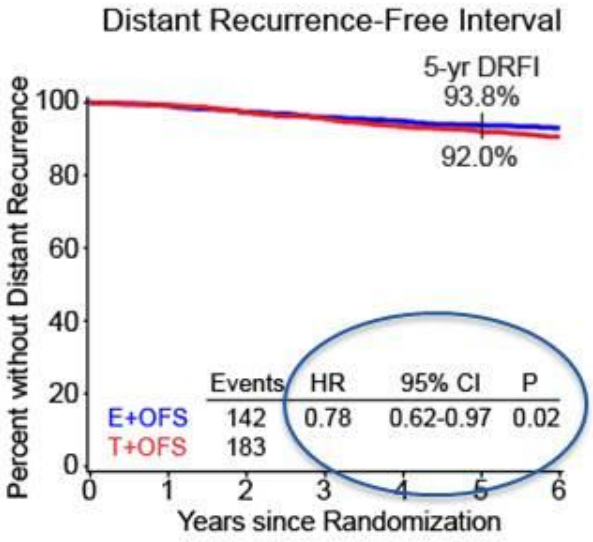


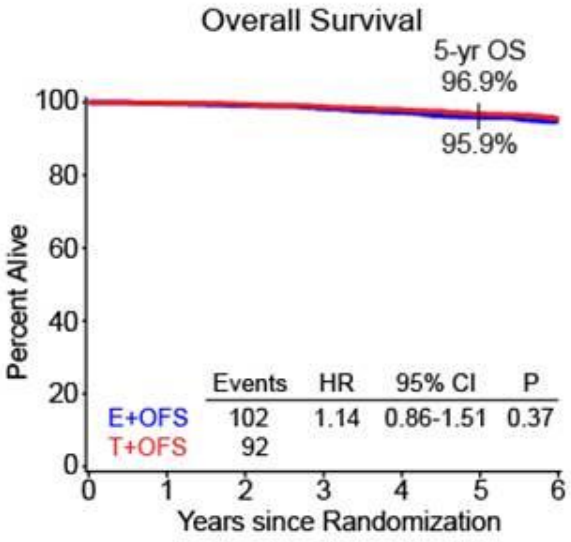


5.7 years median follow-up

Exemestane+OFS Reduced Recurrence

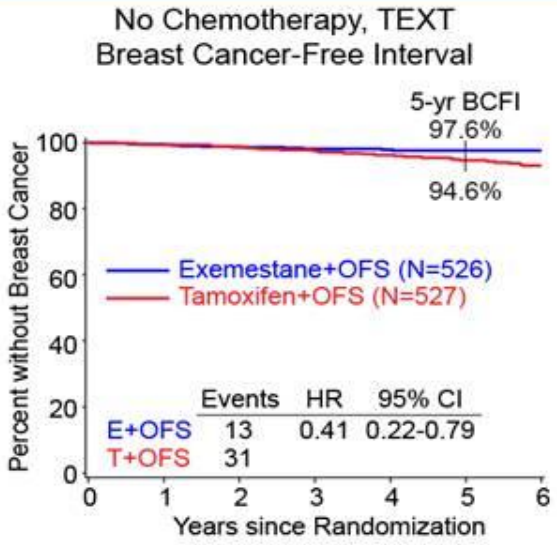






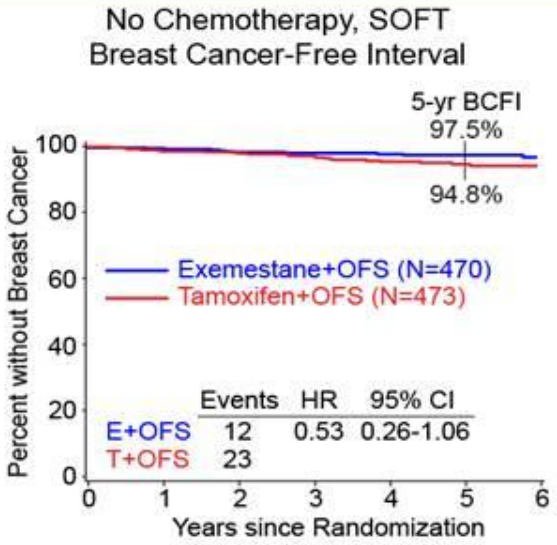
- 4% absolute improvement in 5-yr freedom from breast cancer for exemestane+OFS
- No significant difference in overall survival

Women Who Did Not Receive Chemotherapy



16% <40 years; 19% T-size >2cm; 21% N+

N=1996



9% <40 years; 15% T-size >2cm; 8% N+

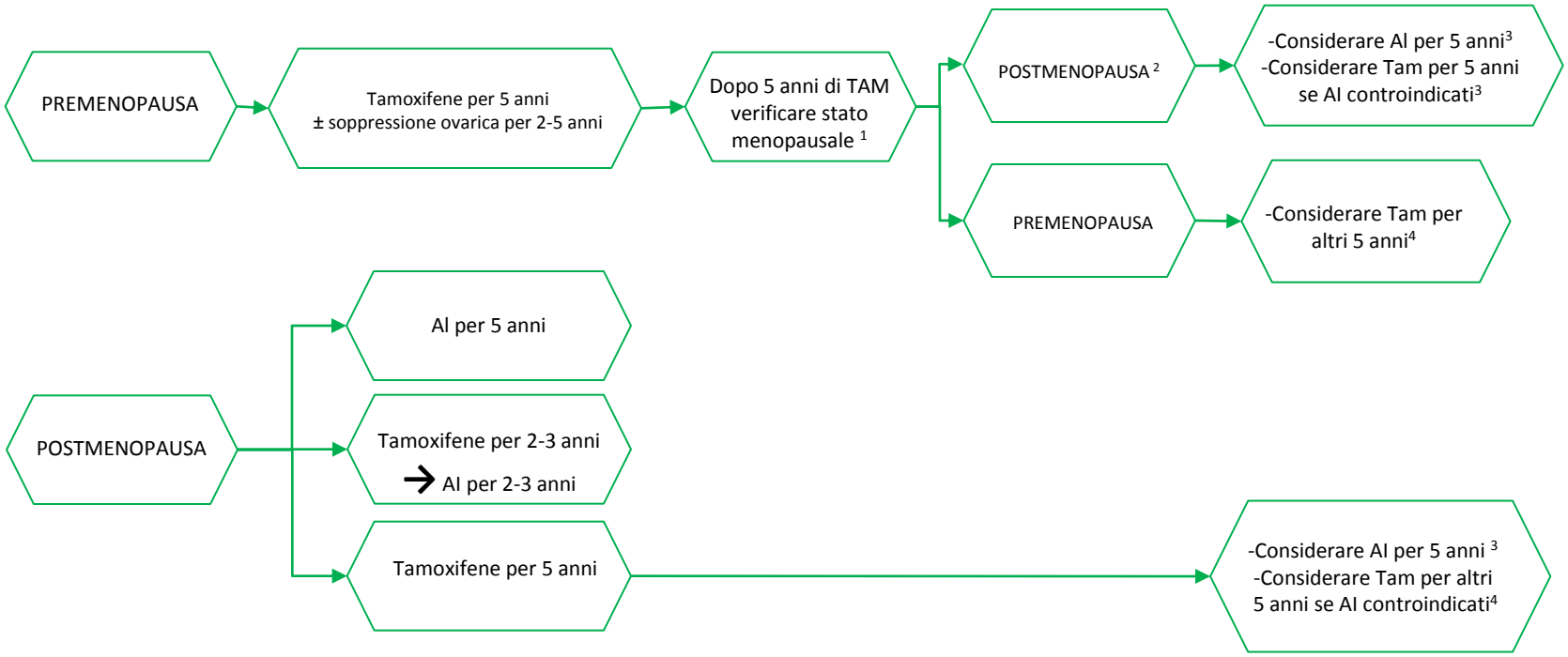
Some women have excellent prognosis with highly-effective endocrine therapy alone
>97% breast cancer-free at 5 years when treated with exemestane+OFS

Predictable Adverse Events Profile

CTCAE V3.0 Grade 3-4	E + OFS	T + OFS
Musculoskeletal	11%	5.2%
Fracture	1.3%	0.8%
Cardiac	0.3%	0.1%
Thrombosis/embolism	0.8%	1.9%
Dyspareunia	2.3%	1.4%
Premature discontinuation	16%	11%

Figura 9 – CARCINOMA MAMMARIO INFILTRANTE

Terapia sistemica ormonale adiuvante in base allo stato menopausale



NOTA 1 - Vedere definizione di menopausa paragrafo 4.2.2.b

NOTA 2 - E' necessaria una valutazione completa dello stato menopausale con dosaggi ripetuti di FSH, LH, estradiolo e progesterone per accertarsi nel modo più accurato possibile dello stato di postmenopausa in questo setting di pazienti.

NOTA 3 – Soprattutto in alcuni sottogruppi, come N+.

NOTA 4 - La decisione clinica deve essere presa previa valutazione del rapporto rischio/beneficio.

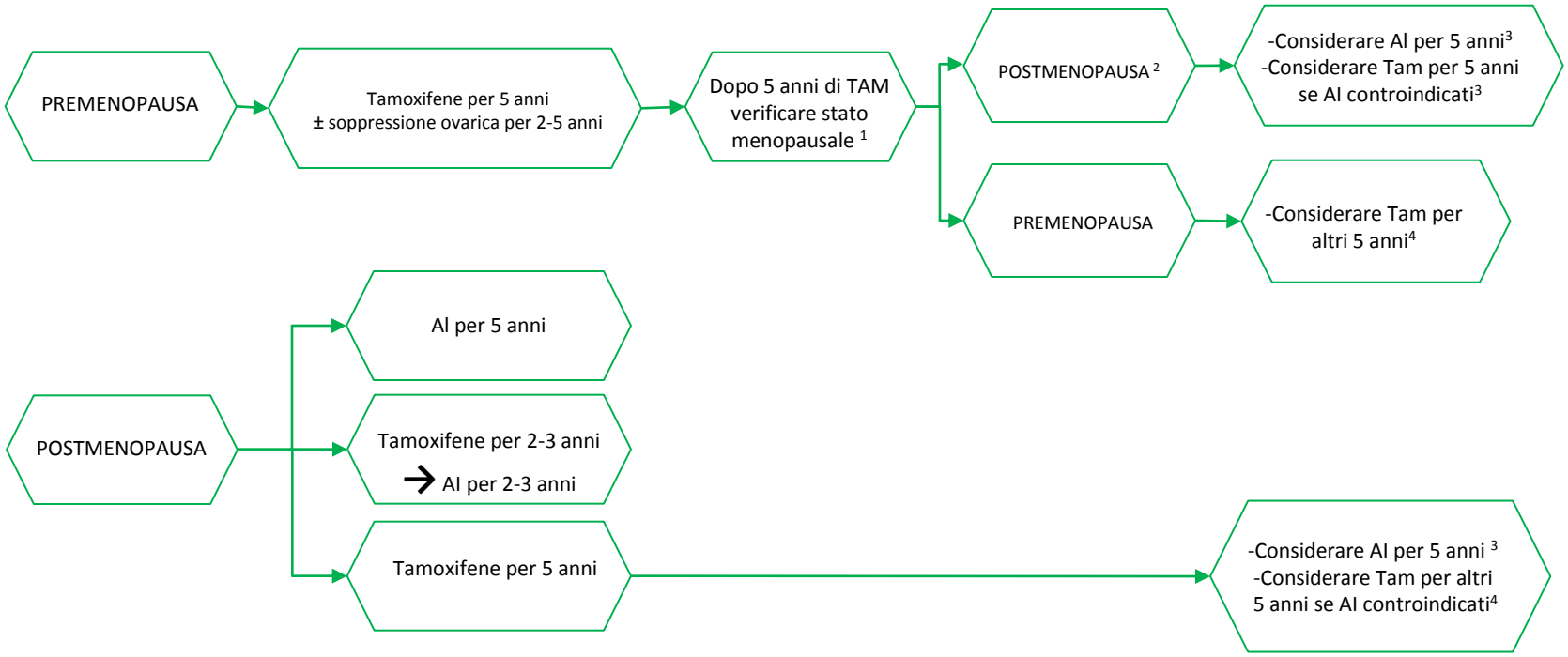
Advising Patients on Ovarian Suppression: risk stratification

Risk	Higher typically stage II or III, intermediate-high grade		Intermediate Higher anatomic stage, lower risk biology; lower stage, higher risk biology	Lower typically stage I, lower-grade
Age	< 35	40+	Variable	40+
Chemo?	Yes	Yes*	±	No
OFS	Yes	Discuss	?	No
Tablet	Tamoxifen or AI		Tamoxifen	Tamoxifen

*more likely to experience chemotherapy-induced amenorrhea

Figura 9 – CARCINOMA MAMMARIO INFILTRANTE

Terapia sistemica ormonale adiuvante in base allo stato menopausale



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JOURNAL OF CLINICAL ONCOLOGY

ART OF ONCOLOGY

You Have Nothing to Lose

Lee N. Newcomer

I hope my oncologist colleague reads this and adjusts his behavior in the same way. The sentence, "You have nothing to lose," is too cavalier for any of us to use. Our desperate and sincere desire to do something for our patients does not grant us the authority to overestimate the benefits, underplay the toxicities, or ignore the evidence.

Associazione Italiana Oncologia Medica

THANK YOU !

Ospedale **“SACRO CUORE -DON CALABRIA “ Negrar-VR**

Presidio Ospedaliero Accreditato- Regione Veneto

ADJUVANT ENDOCRINE THERAPY

Premenopausal[1] at diagnosis → **Tamoxifen[2,3] for 5 y (category 1) ± ovarian suppression or ablation (category 2B)**

- **Postmenopausal[1]** → **Aromatase inhibitor for 5 y[4] (category 1) or Consider tamoxifen[2] for an additional 5 y to complete 10 y**
- **Premenopausal[1]** → **Consider tamoxifen[2] for an additional 5 y to complete 10 y or No further endocrine therapy**

Postmenopausal[1] at diagnosis

- **Aromatase inhibitor[4] for 5 y (category 1) or Tamoxifen[2] for 2–3 y or Aromatase inhibitor[4] for 2–3 y (category 1)** → **Aromatase inhibitor to complete 5 y[4] of endocrine therapy (category 1) or Up to 5 y of an aromatase inhibitor[4] (category 2B)**
- **Aromatase inhibitor[4] for 2–3 y (category 1)** → **Tamoxifen[2] to complete 5 y of endocrine therapy (category 1)**
- **Tamoxifen[2] for 4.5–6 y** → **Aromatase inhibitor for 5 y[4] (category 1) or Consider tamoxifen[2] for an additional 5 y to complete 10 y**
- **Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors** → **Tamoxifen[2] for 5 y (category 1) or Consider tamoxifen[2] for up to 10 y**

[1] See Definition of Menopause (BINV-L).

[2] Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

[3] Aromatase inhibitor for 5 y + ovarian suppression may be considered as an alternative option based on SOFT and TEXT clinical trial outcomes. Pagani O, Regan M, Walley B, et al. Adjuvant Exemestane with Ovarian Suppression in Premenopausal Breast Cancer. N Engl J Med 2014; 371:107-118.

[4] The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and neoadjuvant settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.