Adjuvant endocrine therapy in premenopausal women – The state of the art

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No significant COI to disclose apart from being a medical oncologist

De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017

Annals of Oncology 28: 1700–1712, 2017

High receptor, low tumor burden (pT1a, pT1b), no nodal involvement (pN0), low proliferation, low grade or low "genomic risk"	**Tamoxifen for 5 years** No role for extended adjuvant tamoxifen beyond 5 years No OFS
High/Intermediate degree of ER and PgR expression, intermediate tumor burden pT1c, pT2, pN0 or pN1 (1-3), intermediate or high proliferation or grade, and/or intermediate "genomic risk"	**OFS + Tam or OFS + Exemestane** Extended Tam in some cases

The Breast 35 (2017) 203–217

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journal homepage: www.elsevier.com/brst

Original article

ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3)

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Tamoxifen alone for 5 years is indicated for low risk patients.

Switching to an AI, after 5 years of tamoxifen, should be considered for women who have become definitively post-menopausal.

Tamoxifen for 10 years should be considered in high-risk patients, if tolerated.

The addition of a GnRH agonist to tamoxifen is indicated in patients at higher risk who remain premenopausal after chemotherapy.

AIs alone are contra-indicated in pre-menopausal women.

The combination of an aromatase inhibitor and a GnRH agonist (or ovarian ablation) should be considered in high risk patients if tolerated.

JOURNAL OF CLINICAL ONCOLOGY J Clin Oncol 34. © 2016

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

Harold J. Burstein, Christina Lacchetti, Holly Anderson, Thomas A. Buchholz, Nancy E. Davidson, Karen E. Gelmon, Sharon H. Giordano, Clifford A. Hudis, Alexander J. Solky, Vered Stearns, Eric P. Winer, and Jennifer J. Griggs

Recommendation 1.1

The Panel recommends that higher-risk patients should receive ovarian suppression in addition to adjuvant endocrine therapy, whereas lower-risk patients should not.

Recommendation 1.2

Women with stage II or stage III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression in addition to endocrine therapy.

Recommendation 1.3

Women with stage I or II breast cancers at higher risk of recurrence, who might consider chemotherapy, may also be offered ovarian suppression in addition to endocrine therapy.

Recommendation 1.4

Women with stage I breast cancers not warranting chemotherapy should receive endocrine therapy but not receive ovarian suppression.

Recommendation 1.5

Women with node-negative cancers 1 cm or less (T1a, T1b) should receive endocrine therapy but not receive ovarian suppression.

TEXT e SOFT

- Investigated
  - The role of aromatase inhibitor **[TEXT+SOFT]**
  - The role of ovarian function suppression (OFS) **[SOFT]**

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)

Joint Analysis (N=4690)
Median follow-up 5.7 years

Stratify:
- Chemo planned
- Nodal Status

RANDOMIZE

- Tamoxifen + OFS (Triptorelin)
- Exemestane + OFS (Triptorelin)

SOFT

Population: Premenopausal women with endocrine-responsive early breast cancer who remain premenopausal after chemotherapy or after surgery alone.

Enrollment December 2003 through January 2011

Final accrual: 3066 (target: 3000)

Primary Analysis (n= 2033)
Median follow-up 5.6 years

Stratify:
- Prior chemo
- Intended OFS
- Nodal Status

RANDOMIZE

- Tamoxifen
- Tamoxifen + OFS
- Exemestane + OFS

OFS=Ovarian function suppression

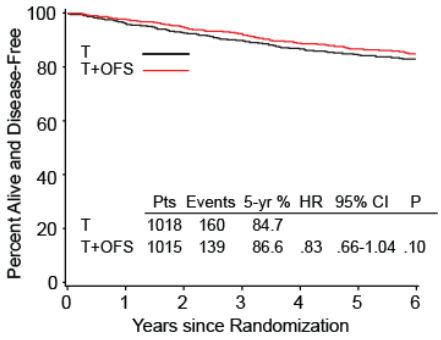
Characteristics by Trial and Chemotherapy Use

		No Chemotherapy		Chemotherapy	
TEXT	TEXT No Chemo N=1053	Median Age	45 yr		
		LN+	21%		
		T-size>2cm	19%		
		Grade 3	12%		
		Surgery to random.	Median 1.5 mo		
	TEXT Chemo N=1607			Median Age	43 yr
				LN+	66%
				T-size>2cm	53%
				Grade 3	37%
				Surgery to random.	Median 1.2 mo
SOFT	SOFT No Chemo N=1419	Median Age	46 yr		
		LN+	9%		
		T-size>2cm	14%		
		Grade 3	7%		
		Surgery to random.	Median 1.8 mo		
	SOFT Prior Chemo N=1628			Median Age	40 yr
				LN+	57%
				T-size>2cm	47%
				Grade 3	35%
				Surgery to random.	Median 8.0 mo

SOFT

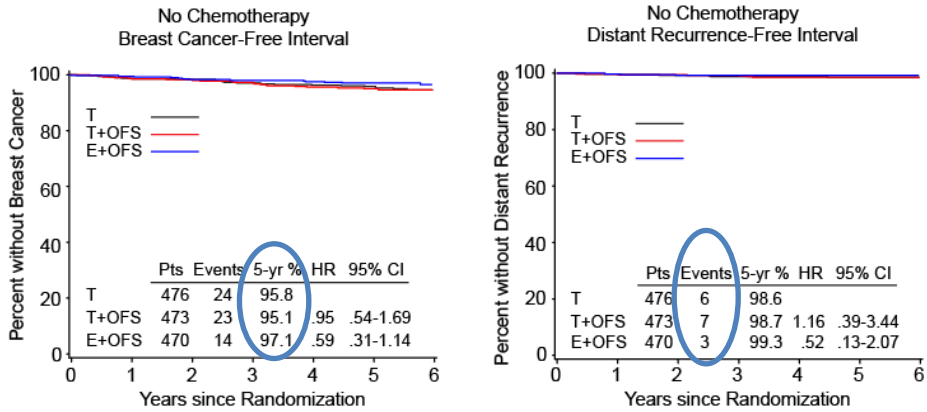
Primary Analysis: Disease-free Survival

5.6 years median follow-up



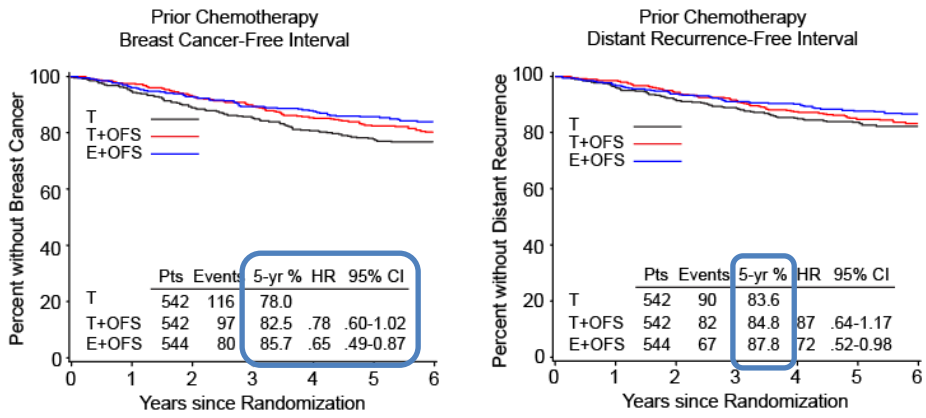
Primary analysis in overall population not significant (p=0.10)
Multivariable Cox model HR=0.78 (95% CI 0.62-0.98) p=0.03

Premenopausal No Chemotherapy



Cohort selected for low risk clinicopathologic features
90% ≥ age 40yr, 91% node negative, 85% tumor ≤ 2cm, 41% grade 1

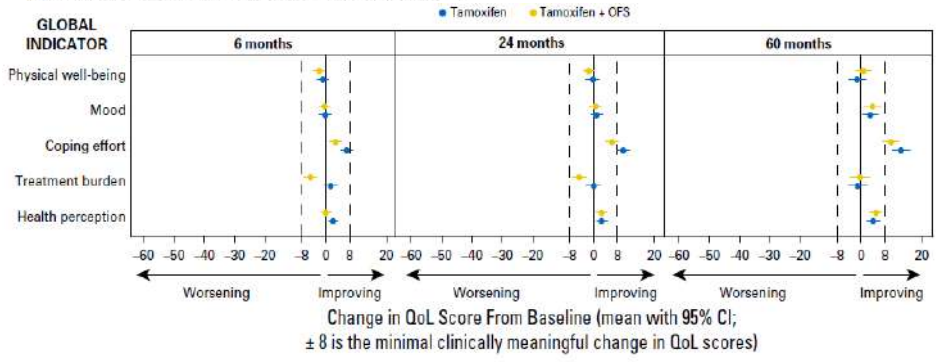
Premenopausal after Prior Chemotherapy



T+OFS v T: Absolute improvement in 5-yr BCFI of 4.5%
E+OFS v T: Absolute improvement in 5-yr BCFI of 7.7% and 5-yr DRFI of 4.2%

Adjuvant Tamoxifen Plus Ovarian Function Suppression Versus Tamoxifen Alone in Premenopausal Women With Early Breast Cancer: Patient-Reported Outcomes in the Suppression of Ovarian Function Trial

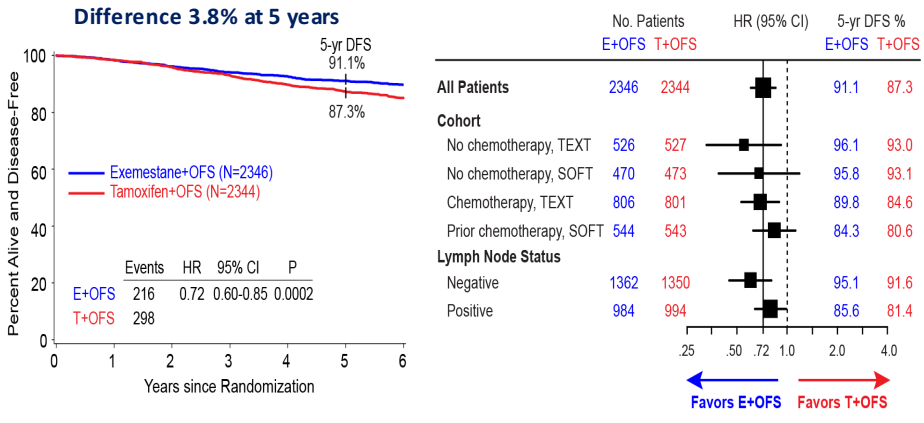
J Clin Oncol 2016; 34:1601-1610.



OFS added to tam: worse endocrine symptoms and sexual functioning during the first 2 years of treatment. Effects were less pronounced for patients with prior chemotherapy, the cohort that benefited most from OFS in terms of disease control

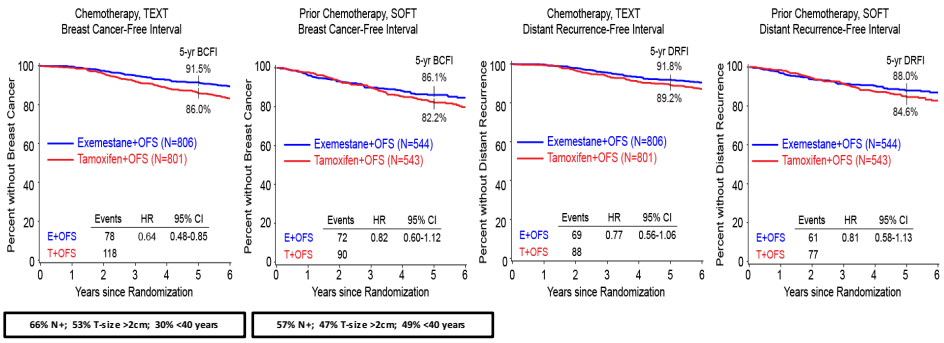
TEXT

Exemestane+OFS Improved DFS



5.7 years median follow-up

Women Who Received Chemotherapy

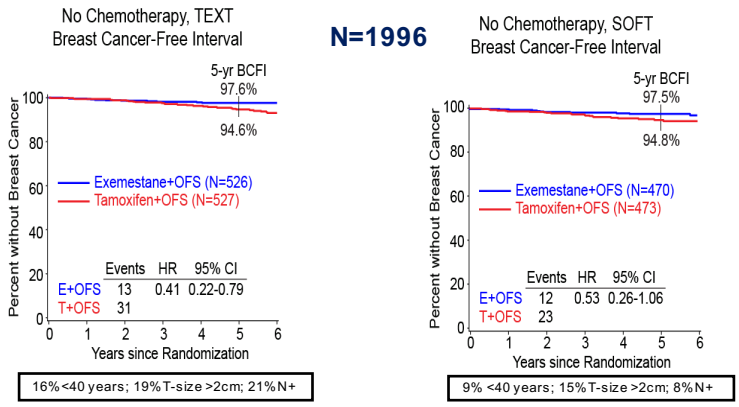


Absolute improvement with exemestane+OFS

5-yr freedom from breast cancer: 5.5% in TEXT and 3.9% in SOFT

5-yr freedom from distant recurrence: 2.6% in TEXT and 3.4% in SOFT

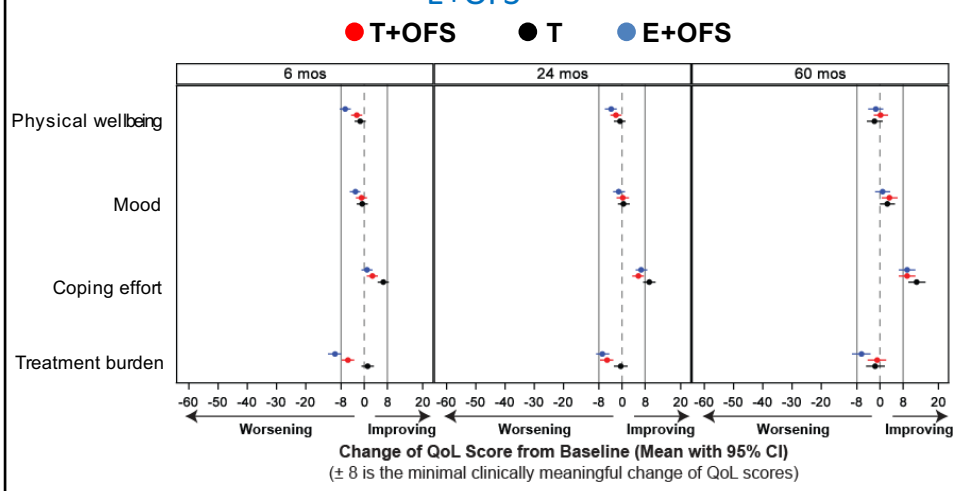
Women Who Did Not Receive Chemotherapy



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

Global QoL

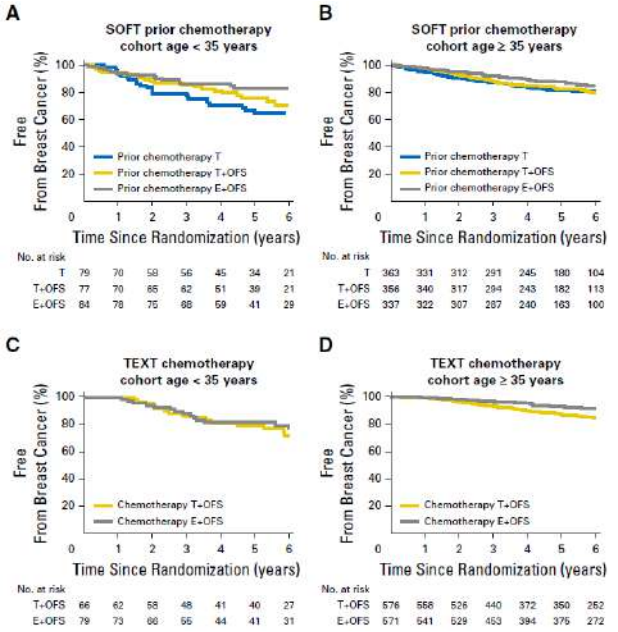
E+OFS



Bernhard J Lancet Oncol. 2015 Jul;16(7):848-58

Very young women

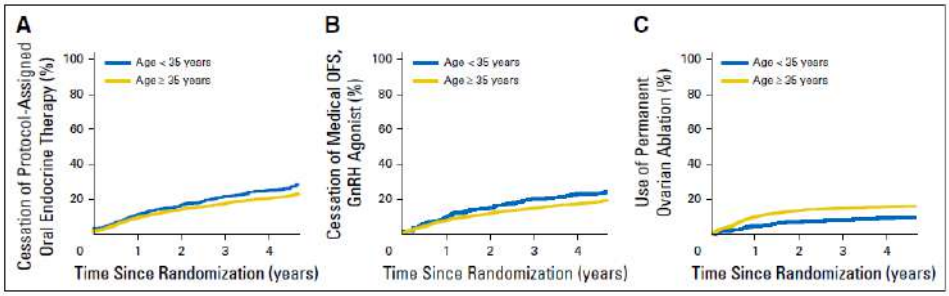
All women < 35 years of age in SOFT and TEXT



385 HER2- pts < 35
93% received CT

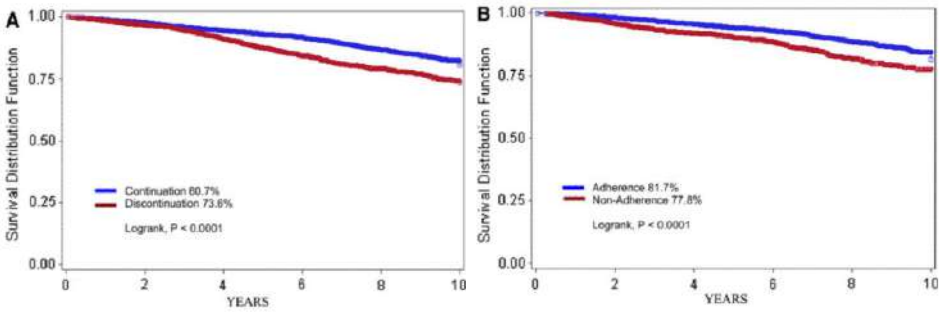
Saha P e al JCO 35, June 27, 2017

Treatment adherence



Saha P e al JCO 35, June 27, 2017

Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer Dawn L. Hershman, *Breast Cancer Res Treat.* 2011 April ; 126(2): 529–537.



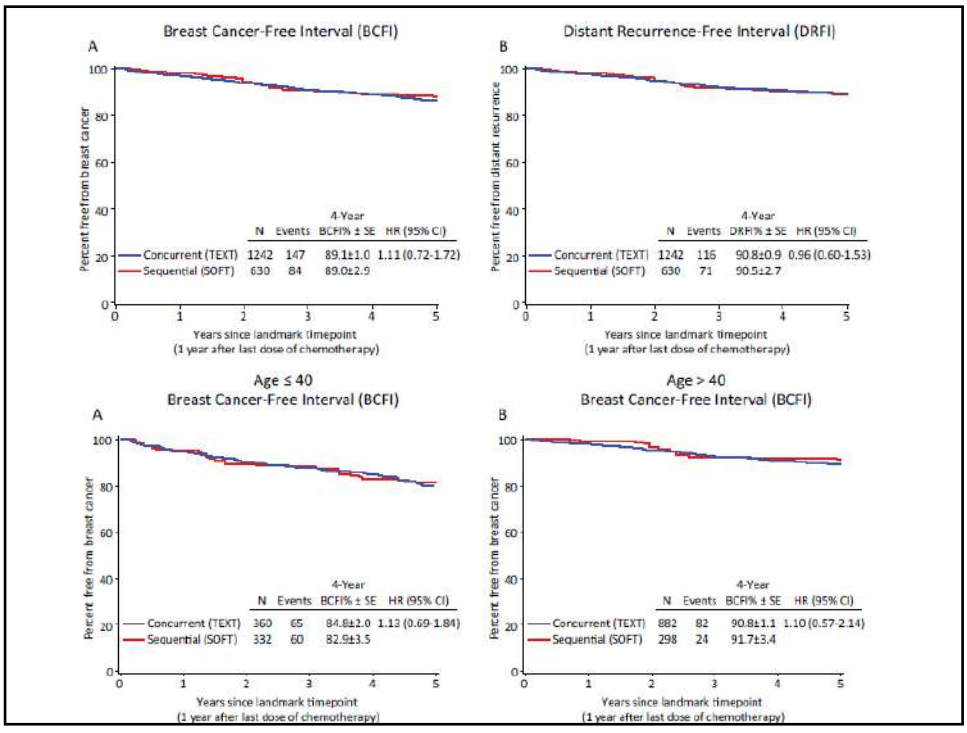
Both early discontinuation and non-adherence to HT were common and associated with increased mortality. Interventions to improve continuation of and adherence to HT may be critical to improve BC survival.

Timing of OFS

Timing of OFS with Chemotherapy

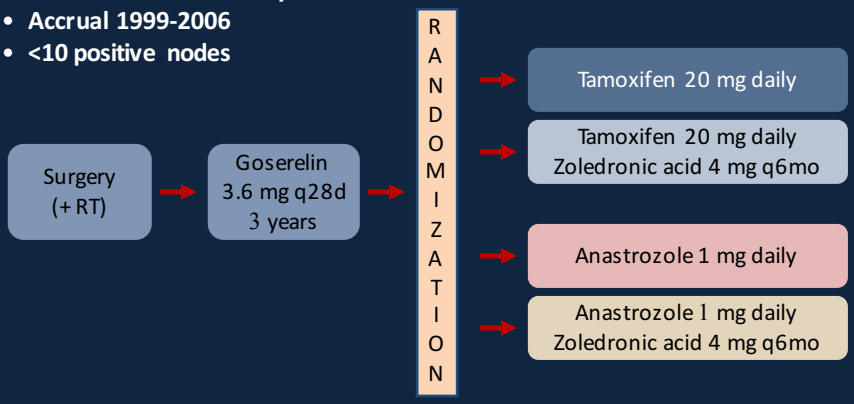
- Is beneficial to start OFS as quickly as possible, concurrently with chemotherapy?
- Or might concurrent administration be detrimental?
- Is it equally beneficial to wait and see if chemotherapy induces menopause thereby avoiding costly OFS?
- Should age be taken into consideration when deciding when to start OFS?

1872 HER2-negative patients in TEXT / SOFT
Received adjuvant CT and LH-RH
BCFI defined from 1 year after final dose of CT
About 5-years median follow-up



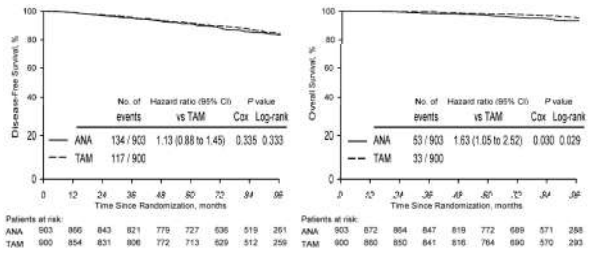
Trial Design ABCSG-12

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



Similar Outcomes with OFS+Anastrozole or OFS+Tamoxifen

Median age	45 yrs
T1 tumor	75%
N0	66%
Grade 1/2	75%
Preop CT	5%



Gnant et al Ann Oncol 2014 Nov 17

ATLAS Trial Design

Eligibility (n = 12,894)*

Early breast cancer (BC)
Completed 5 y of TAM

R

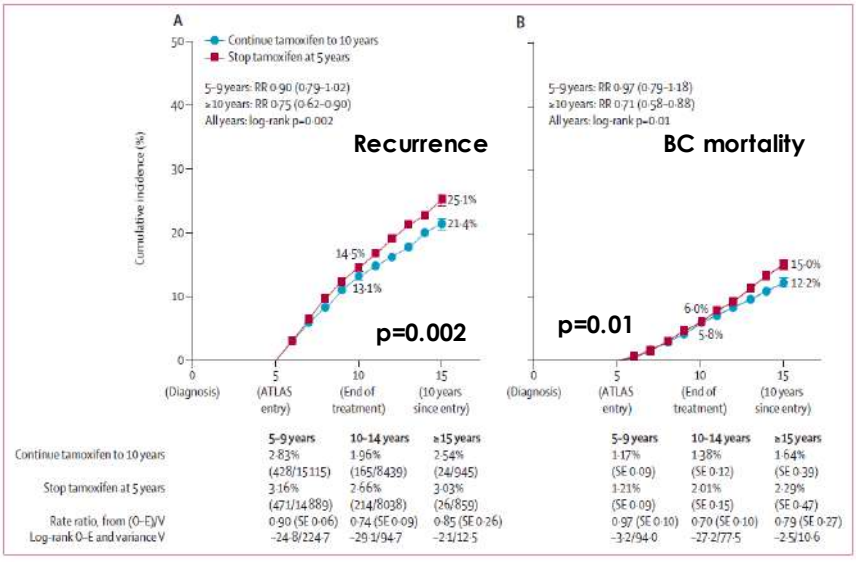
Continue TAM therapy to 10 years (n = 6,454)

Stop TAM therapy at 5 years (n = 6,440)

*Of the study's entire population
ER+ 53%; ER- 10%; unknown ER status 37%

•Recurrence was defined as first recurrence of any form of BC after ATLAS entry.

Davies C et al. *Lancet* 2012



10% premenopausal **25% N+**

Conclusions

- **In premenopausal women several options now available, according to risk (individualized treatment !!!)**
- **Combined ET is very effective and manageable also in very young women**
- **Quality of life should be taken into consideration when proposing ET**

Open questions

- **Define the additive impact of chemotherapy, if any, in very young women**
- **Endocrine resistance**
  Drugs addressing endocrine resistance under evaluation in early disease
- **Pharmaco-genetic** (CYP2-D6/CYP19)
- **BMI**
- **What is the optimal ET in HER2+ patients**

Thank you