

Optimal adjuvant hormonal therapy in premenopausal women

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Disclosure slide

No relevant financial relationships to disclose

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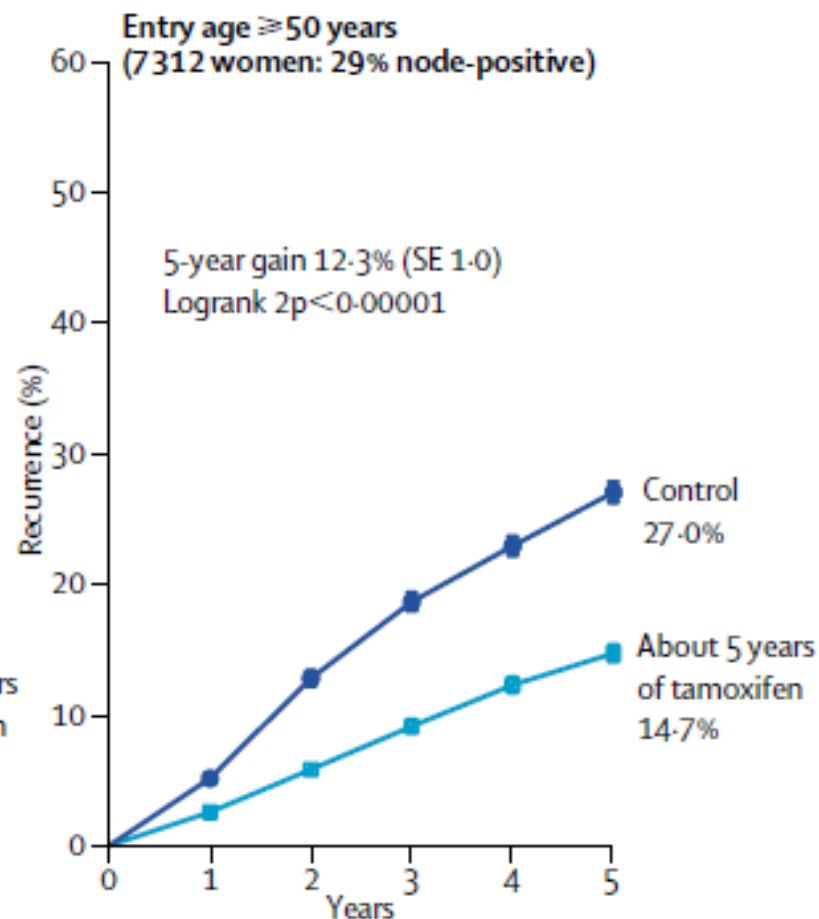
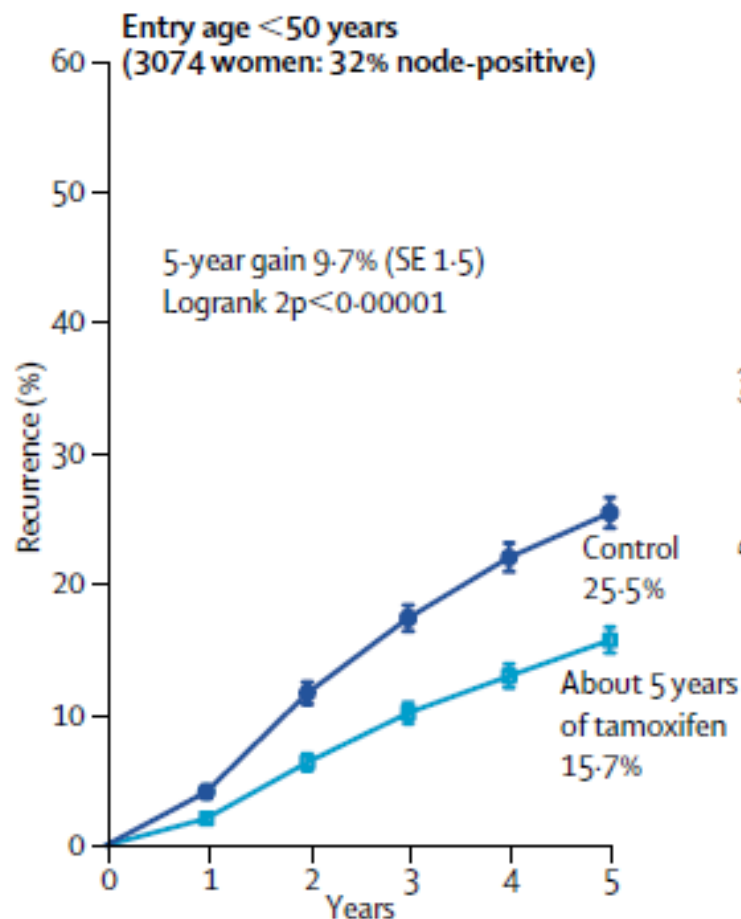
- Healthy, married woman, 40 years old
- Mastectomy +SNB + axillary dissection
- Histology: Ductal invasive carcinoma G2
- pT2 (2.5 cm) pN1a (1/26) ER 90% PgR 90%
HER-2 absent KI-67 16%
- No peritumoral vascular invasion

Premenopausal Patients

- Treatment selection
 - Tamoxifen
 - OFS
 - Tamoxifen plus OFS
 - Ais plus OFS
- Treatment duration

Tamoxifen

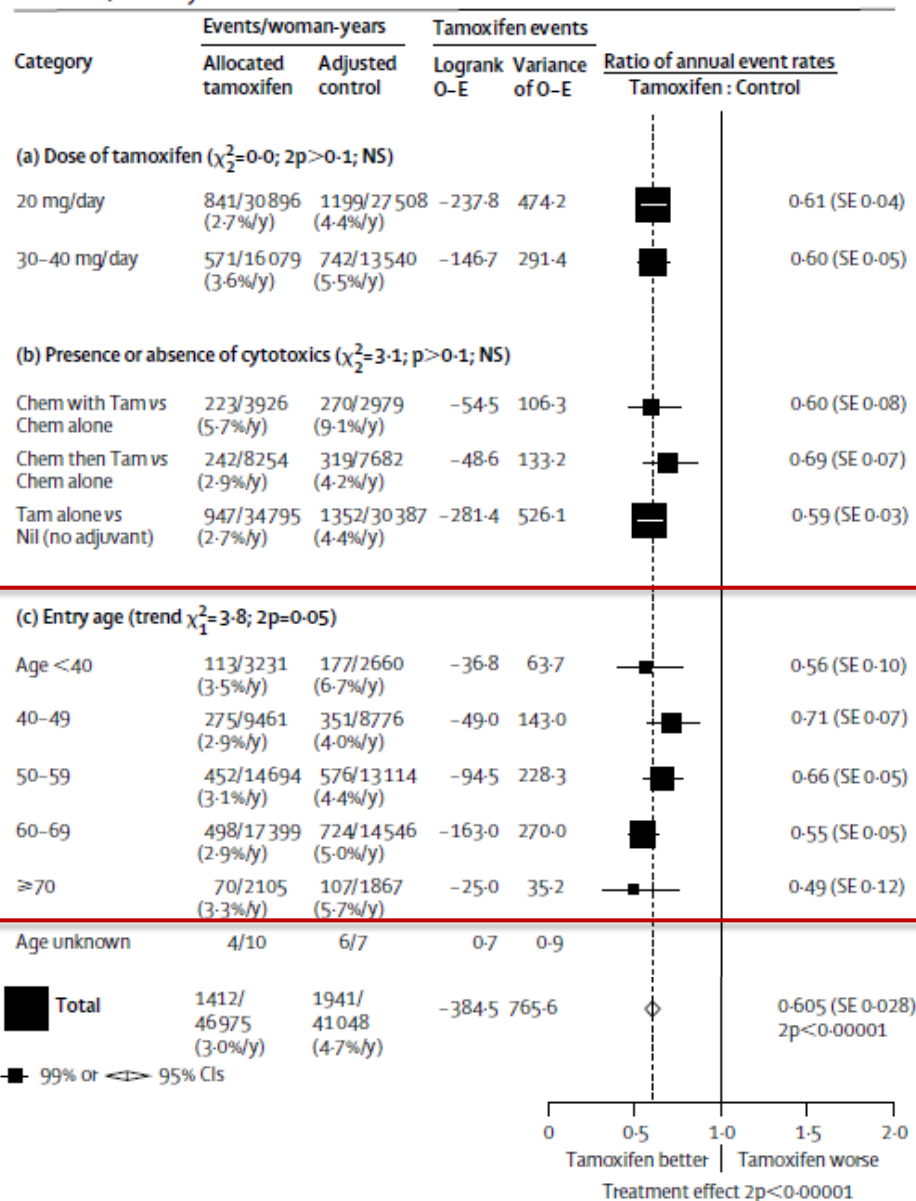
About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease, by entry age



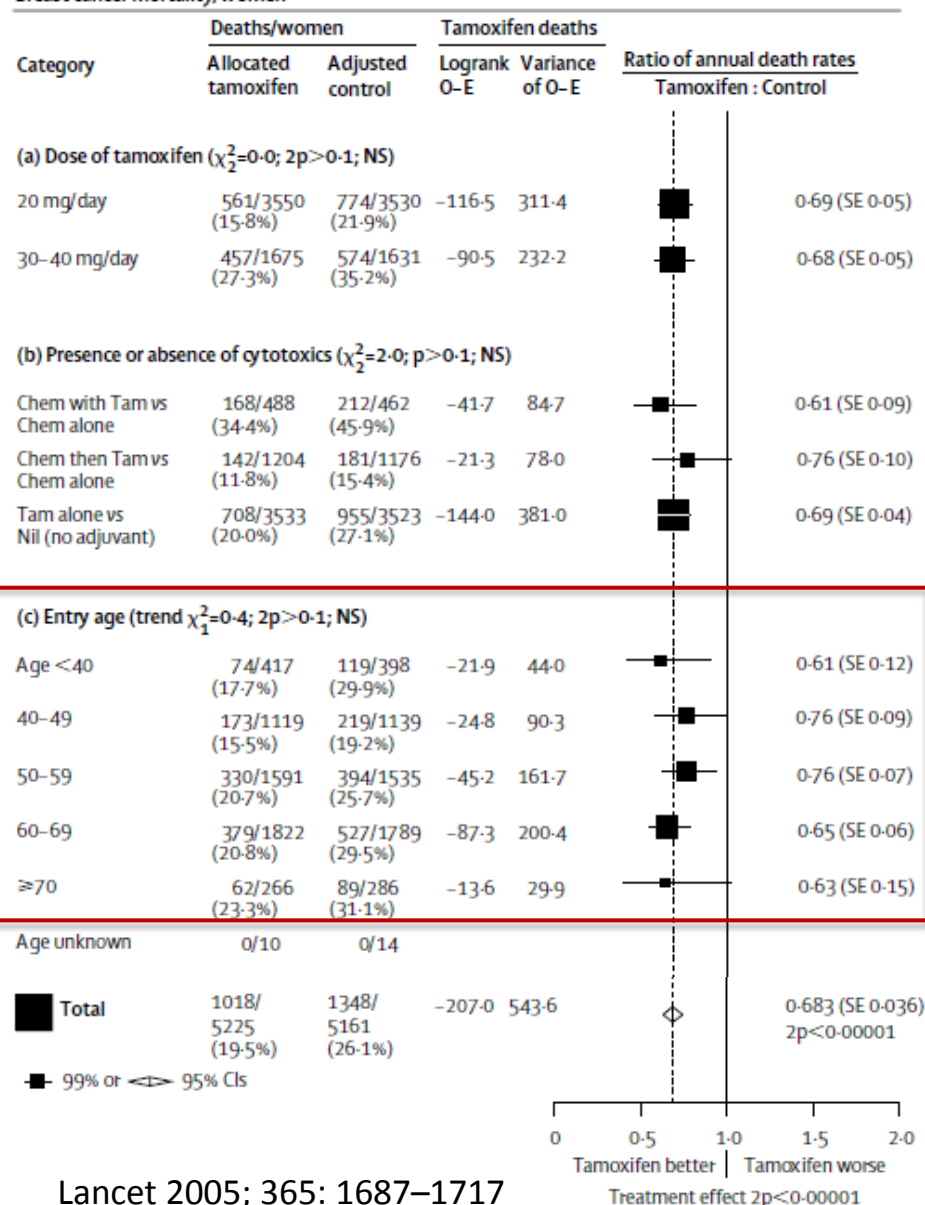
Tamoxifen

About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease, by entry age

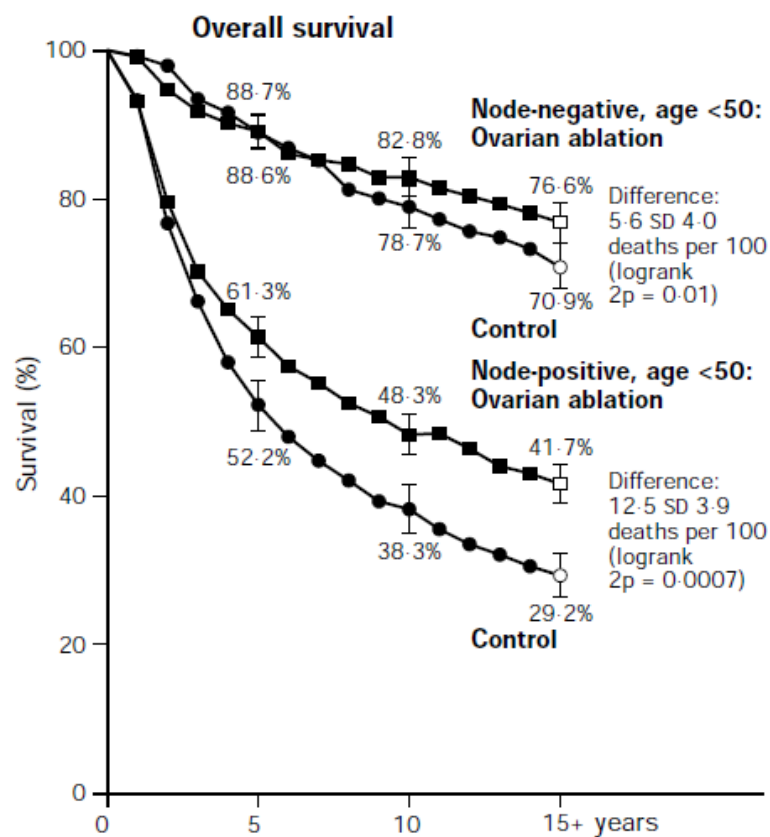
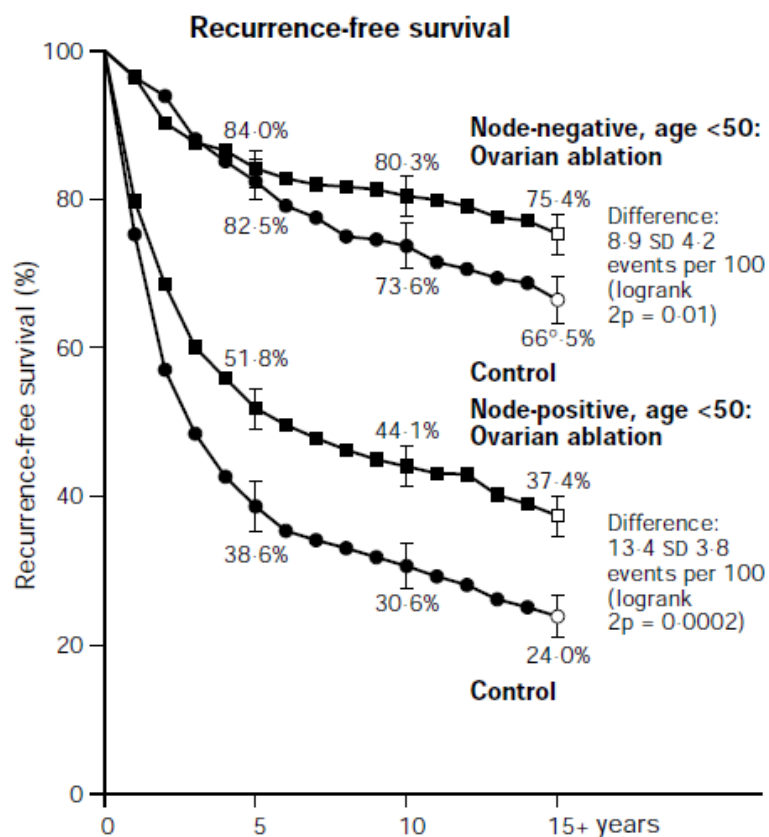
Recurrence/woman-years



Breast cancer mortality/women

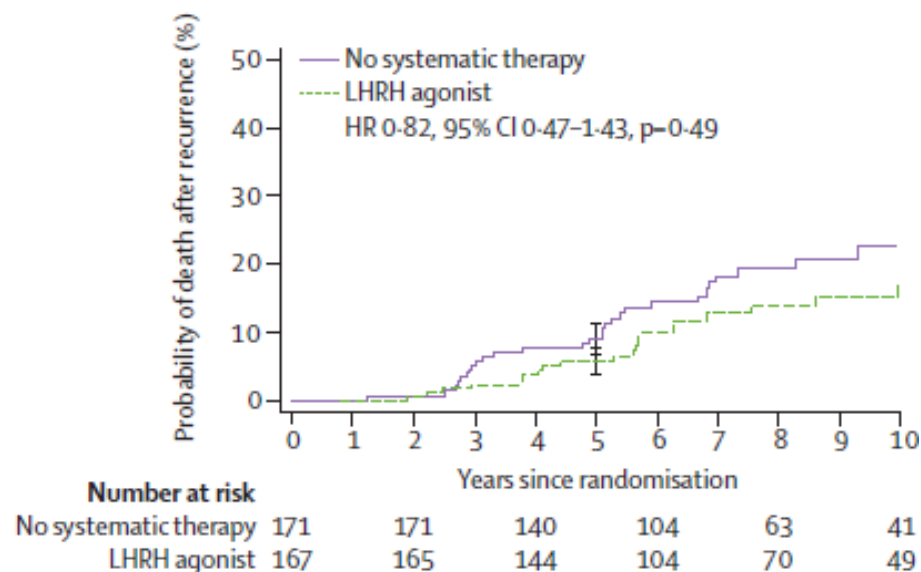
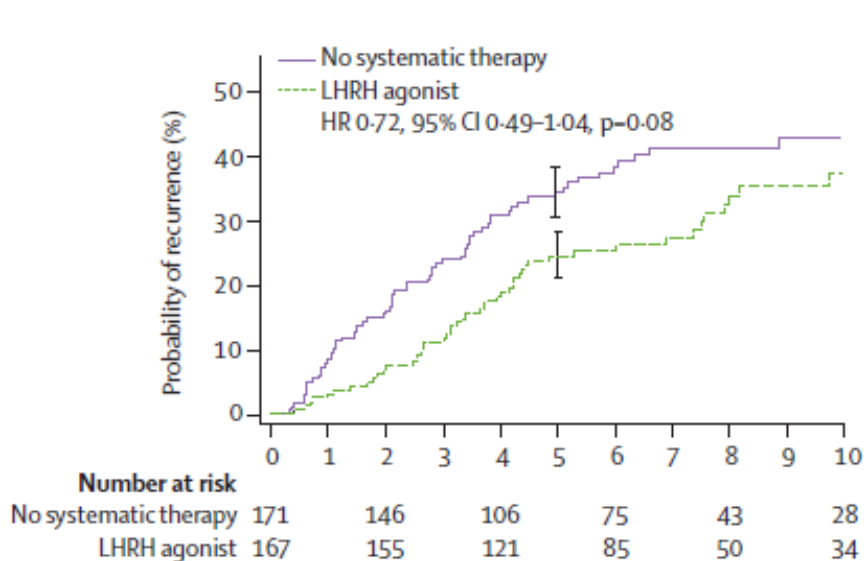


Overview: effects of ovarian ablation in the absence of chemotherapy



OFS

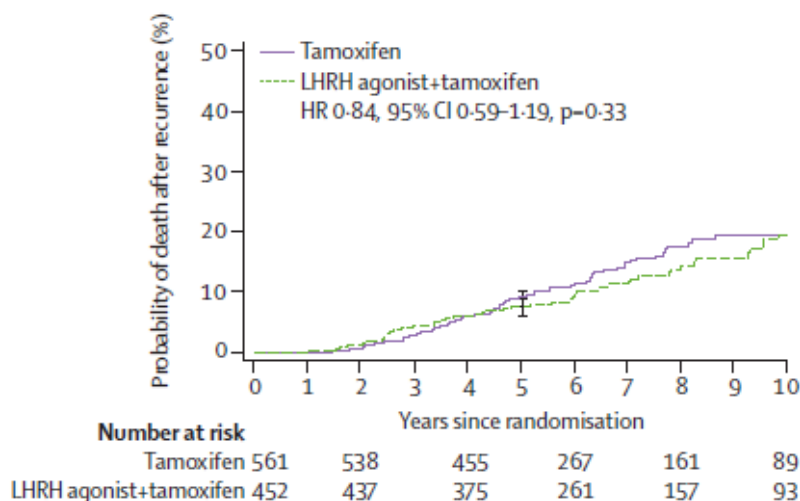
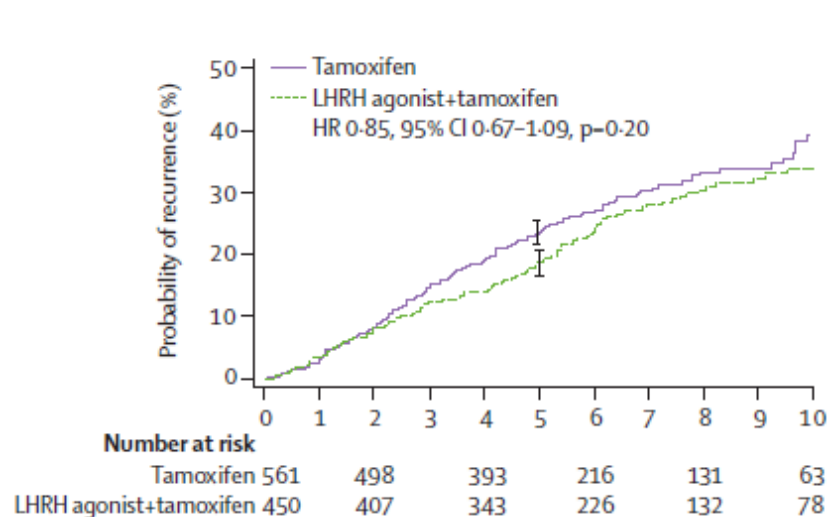
Overview: effects of LHRH agonist in the absence of chemotherapy



Lancet 369: 1711-23, 2007

OFS

Overview: addition of LHRH agonist to tamoxifen



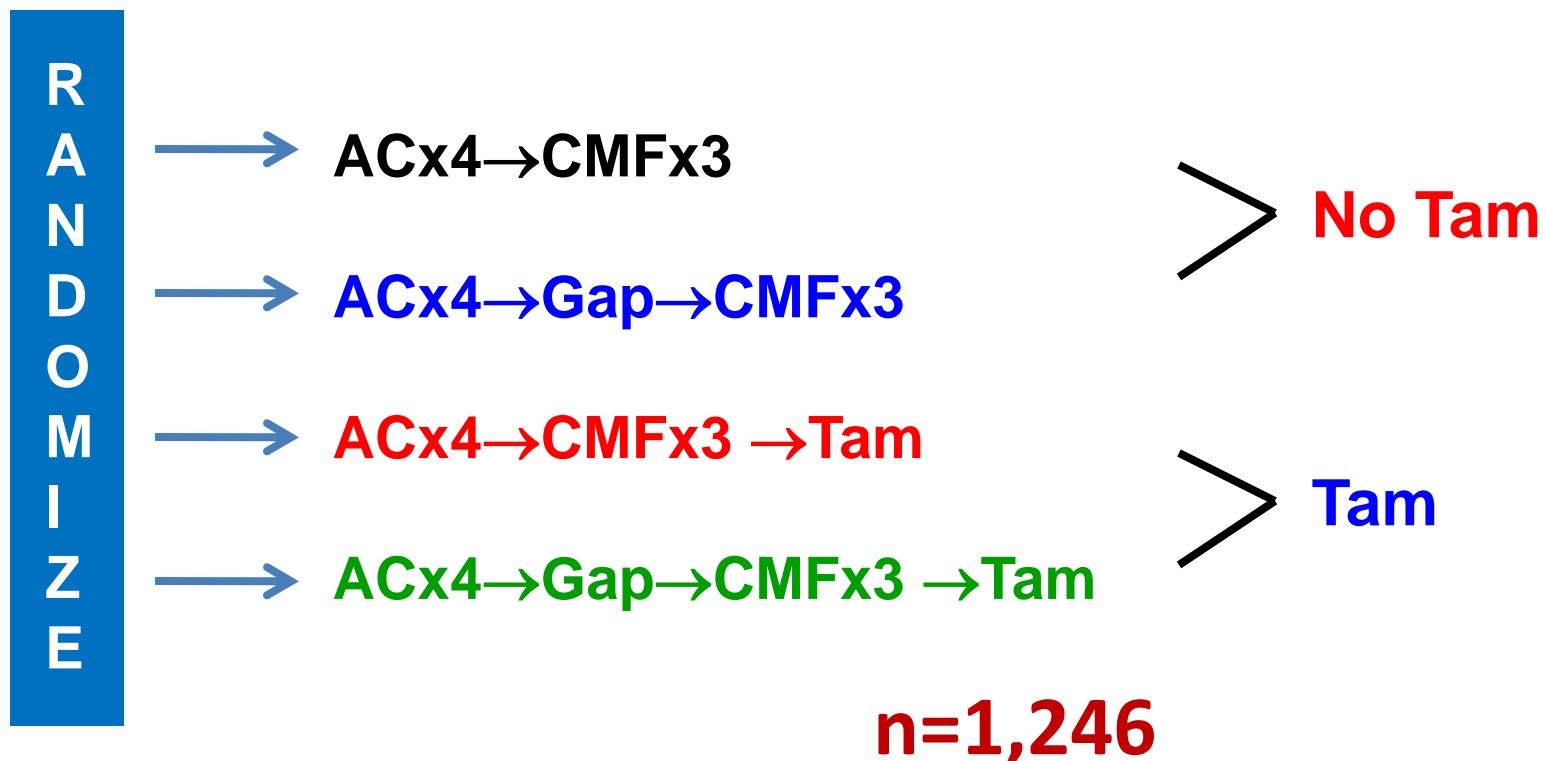
Lancet 369: 1711-23, 2007

OFS

IBCSG 13-93

Accrual: 1993-1999

Premenopausal, node-positive breast cancer

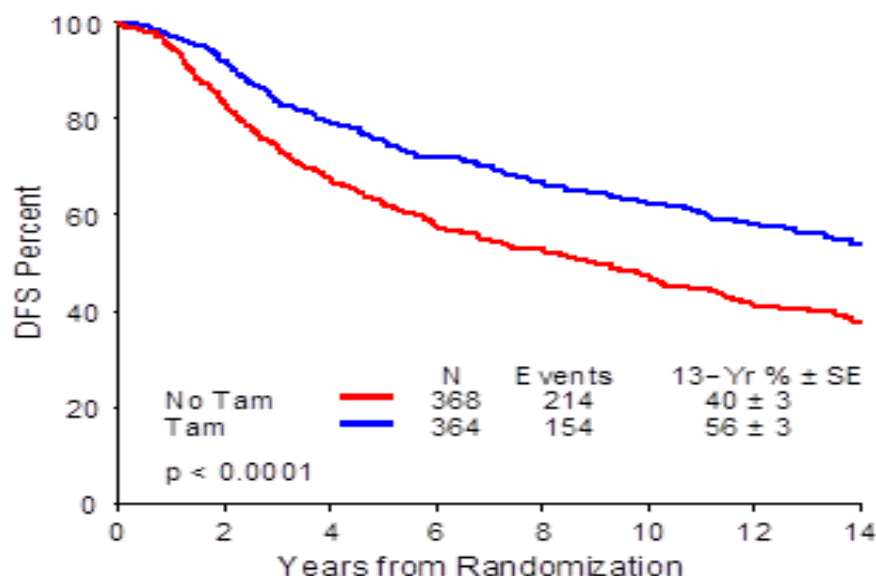


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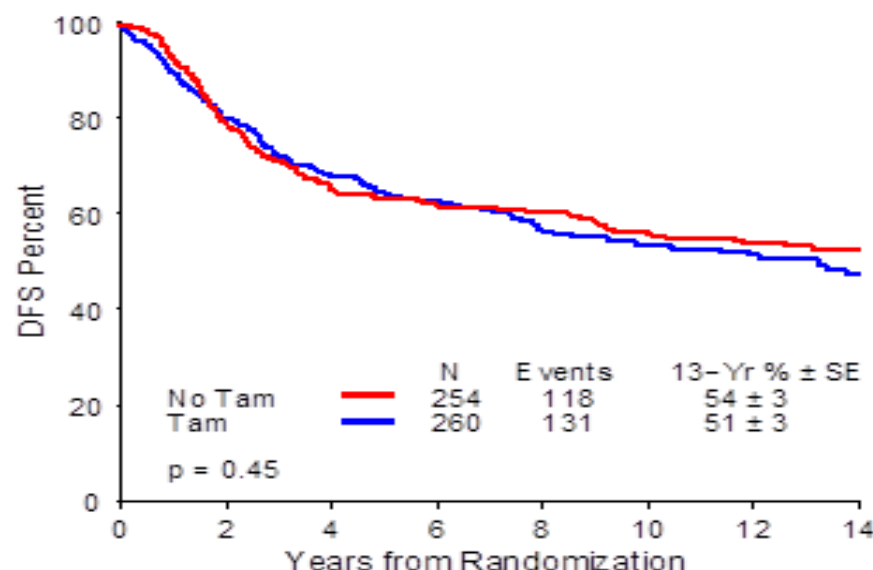
Trial 13-93: Tamoxifen Question

ER+ and ER-, Disease-Free Survival

ER+

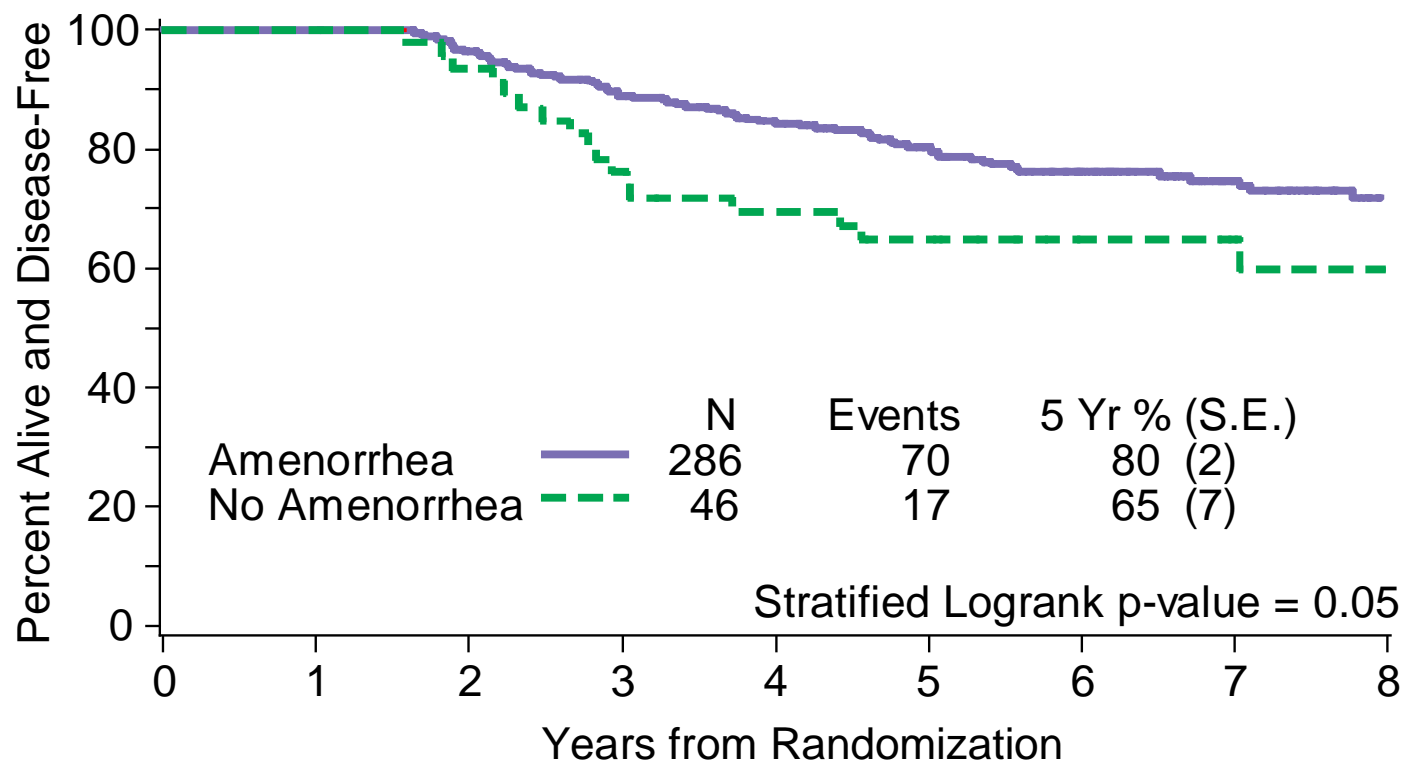


ER-



OFS

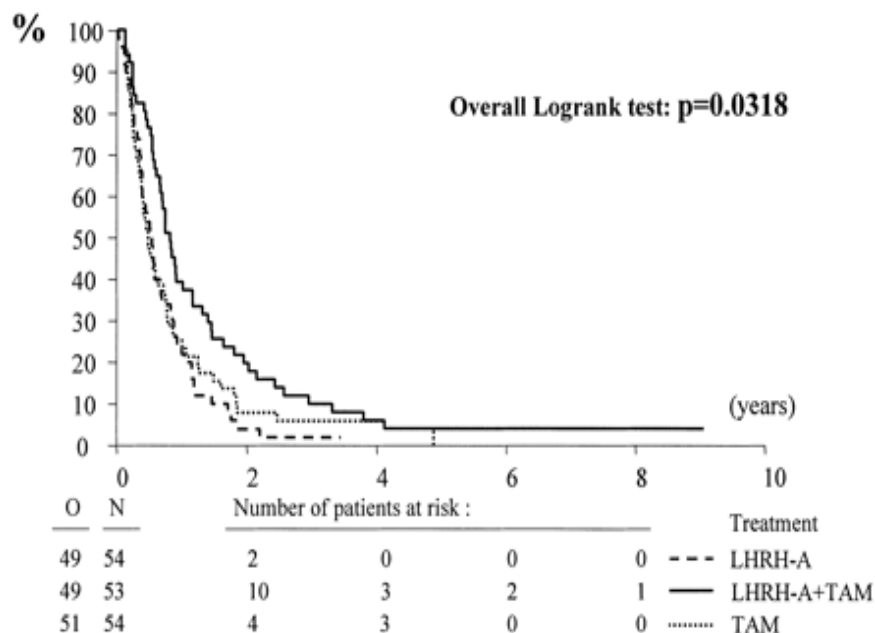
IBCSG Trial 13-93: Amenorrhea and Tamoxifen for ER+



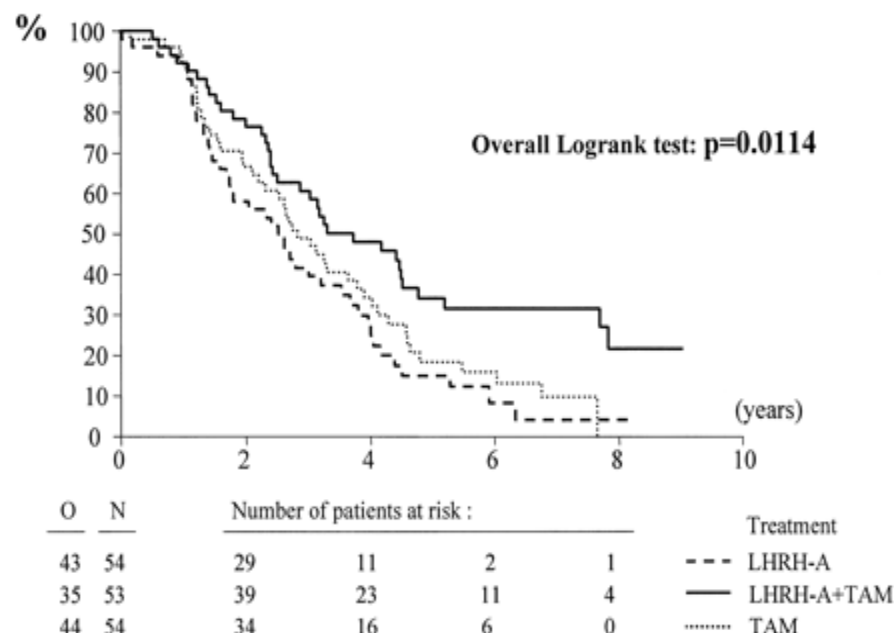
OFS

LHRH analogue + Tamoxifen advanced disease

PFS



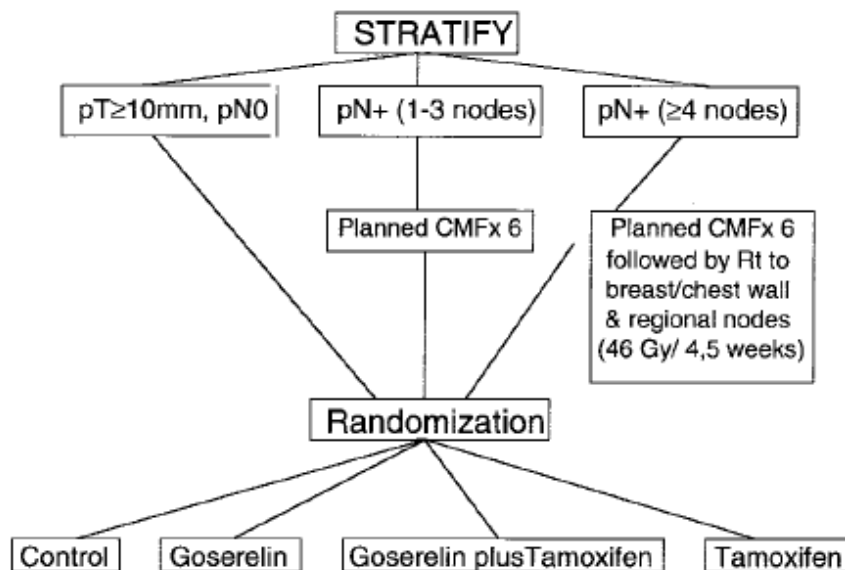
OS



Klijn. J et. Al. JNCI J Natl Cancer Inst . 92,: 903-911; 2000

ZIPPP Trial

Side effects of ovarian function suppression



J Clin Oncol 21: 1836-1844, 2003

ZIPPP Trial

Side effects of ovarian function suppression

In the Goserelin group significantly higher problem levels in terms of:

- Vasomotor symptoms
- Vaginal dryness
- Changes in body Image
- Sleep Disturbances
- Sexual function

J Clin Oncol 19: 2788-2796, 2001

J Clin Oncol 21: 1836-1844, 2003

Panel Voting St Gallen 2013

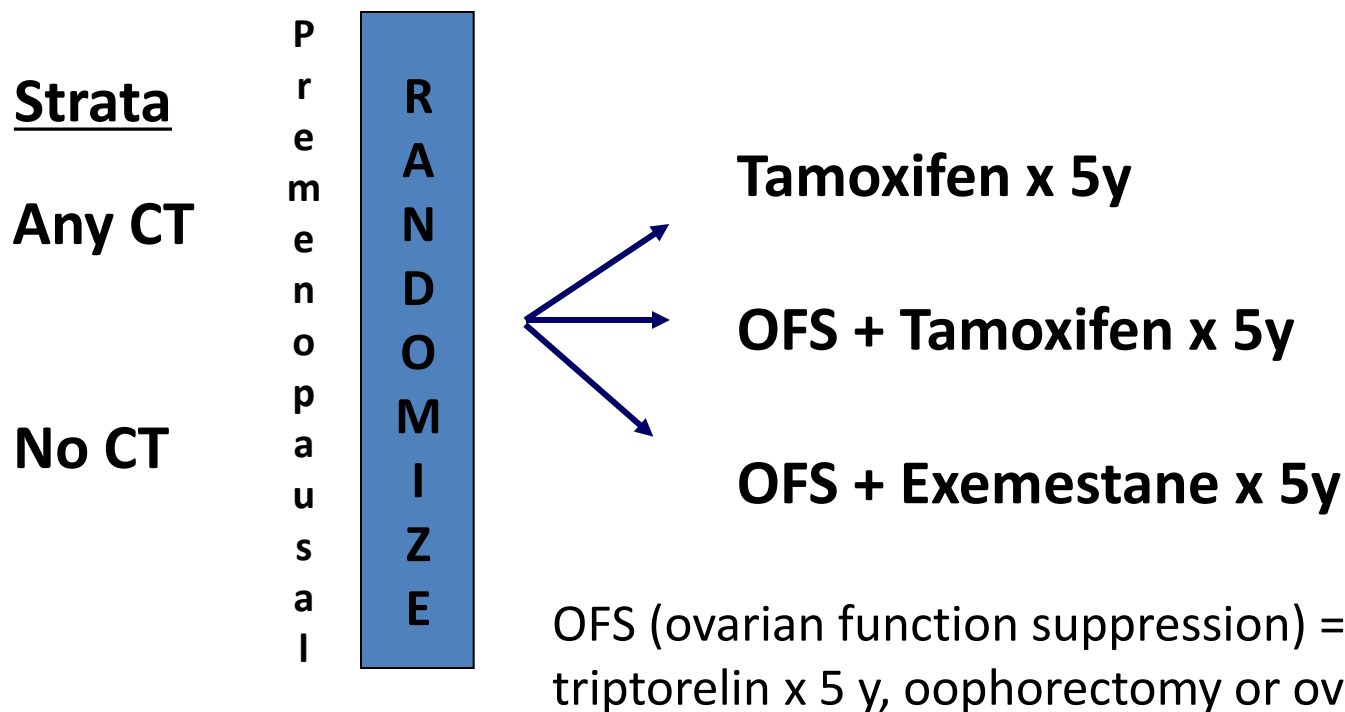
Endocrine Therapy: Establishing Standards for Premenopausal	Yes	No	Abstain
Ovarian function suppression (OFS) should be added to Tam:			
• In all patients?	14.9	80.9	4.2
• In the young (e.g. < 40 yr)?	40.9	50.0	9.1
AI + OFS is a valid option in all patients?	6.3	87.5	6.3

OFS

SOFT [IBCSG 24-02, BIG 2-02]

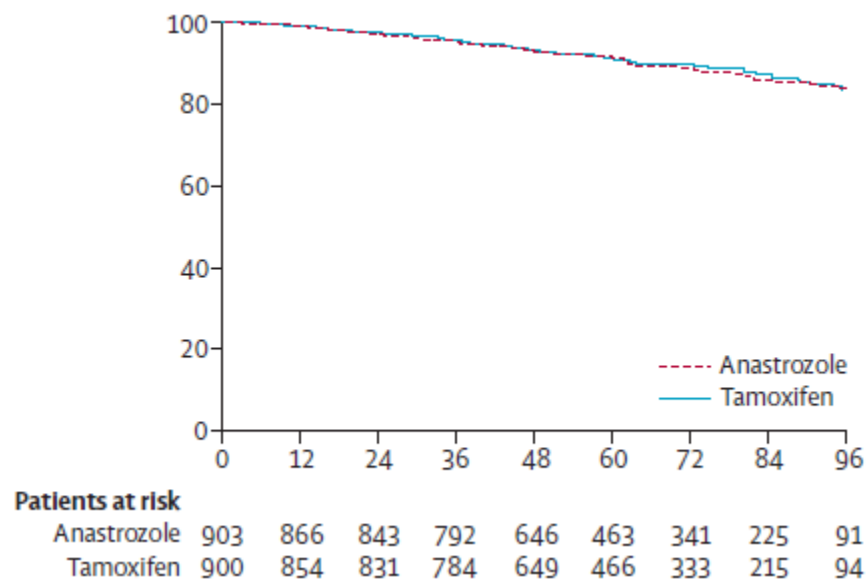
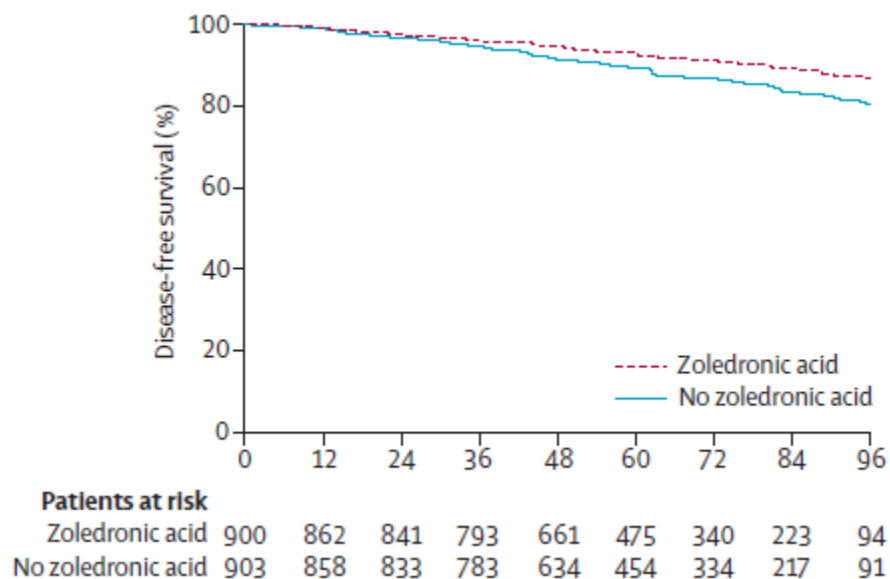
Premenopausal, ER and/or PgR $\geq 10\%$

Patients who remain premenopausal within 6 months after CT, or receive tamoxifen alone as adequate treatment



Ais plus OFS

DFS for women who received adjuvant therapy by zoledronic acid versus no zoledronic acid and tamoxifen vs anastrozole (ABCSG-12)



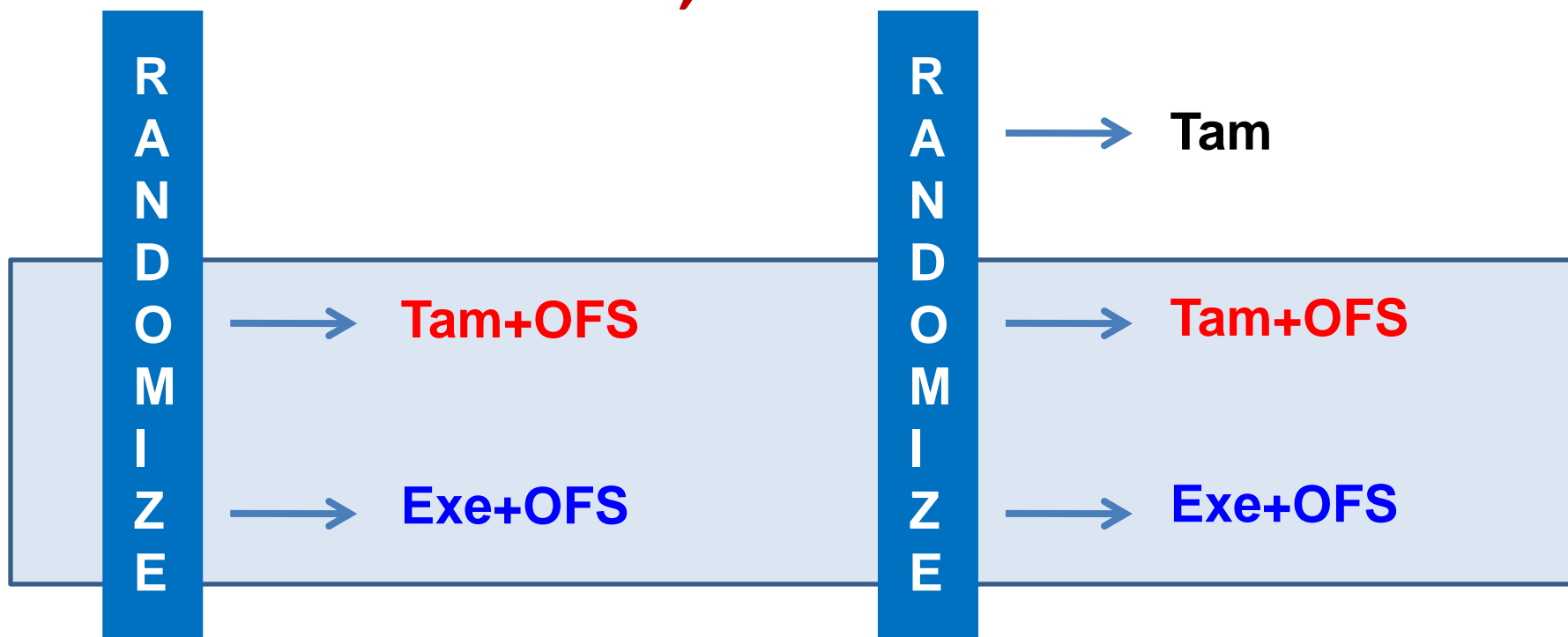
Lancet Oncol 2011; 12: 631–41

Ais plus OFS

TEXT and SOFT

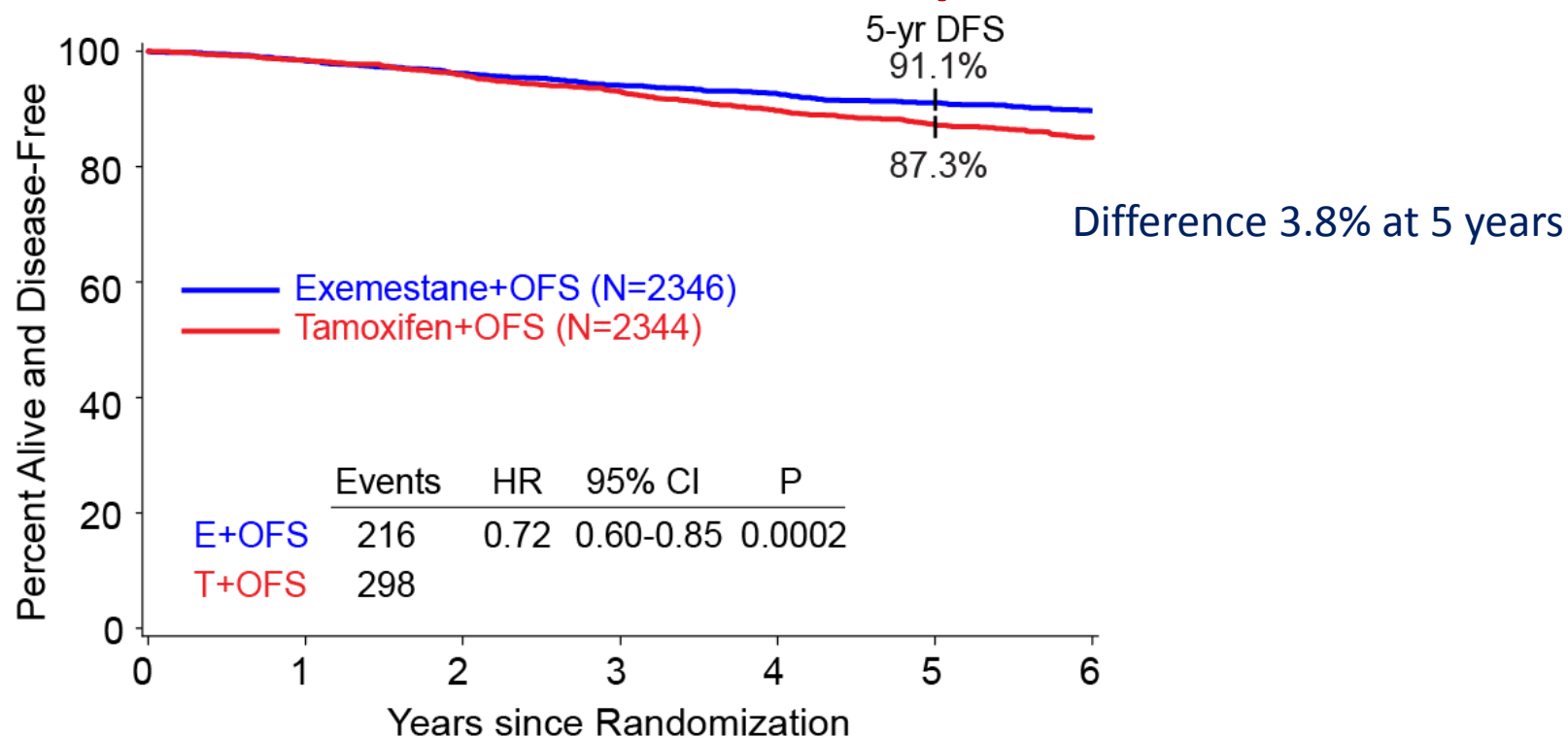
Tamoxifen vs. Exemestane

n=4,717



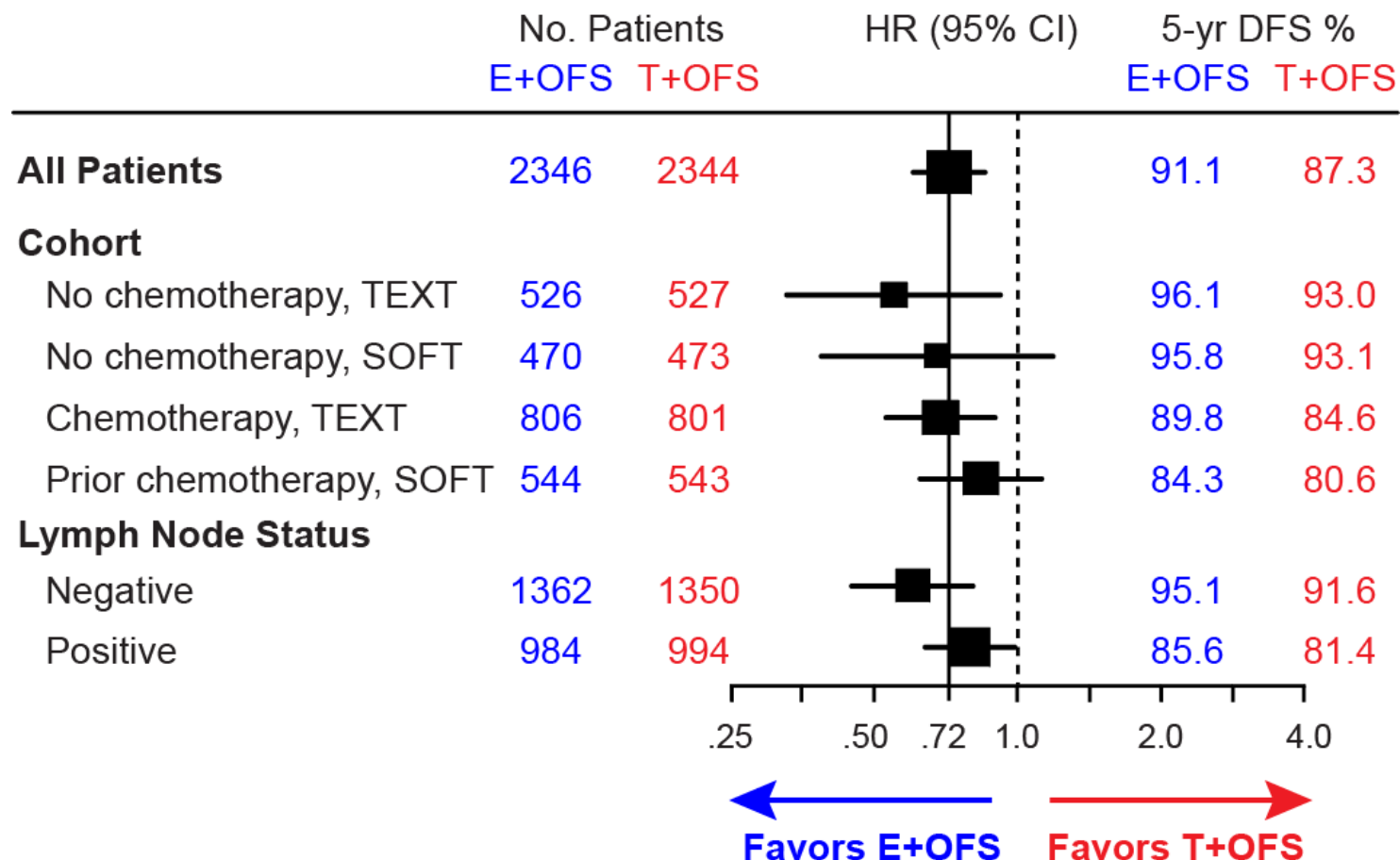
Ais plus OFS TEXT and SOFT

Exemestane+OFS improved DFS



5.7 years median follow-up

Ais plus OFS TEXT and SOFT Exemestane+OFS improved DFS



Ais plus OFS

TEXT and SOFT

Sites of First Failure

Site of First Failure (DFS event)	E+OFS (N=2346)	T+OFS (N=2344)	Overall (N=4690)
<i>All DFS events N (%)</i>	<i>216 (9.2)</i>	<i>298 (12.7)</i>	<i>514</i>
Local	23 (1.0)	28 (1.2)	51
Contralateral breast	9 (0.4)	27 (1.2)	36
Regional ± above	9 (0.4)	30 (1.3)	39
Soft tissue / distant LN ± above	4 (0.2)	6 (0.3)	10
Bone ± above	54 (2.3)	65 (2.8)	119
Viscera ± above	75 (3.2)	105 (4.5)	180
Second (non-breast) malignancy	38 (1.6)	32 (1.4)	70
Death without prior cancer event	2 (0.1)	5 (0.2)	7
Death with recurrence suspected	2 (0.1)	--	2

} 60% distant

Ais plus OFS TEXT and SOFT Conclusions

- Exemestane+OFS, as compared with tamoxifen+OFS, significantly improves DFS, BCFI and DRFI
- It is a new treatment option for premenopausal women with endocrine- responsive operated breast cancer
- No significant difference in overall survival, conclusions premature at this early point in follow-up of endocrine-responsive breast cancer

Treatment duration

Long-term effects of continuing adjuvant tamoxifen by age

Age (yr)	Reduction in event rate	
	Recurrence	Death
< 40	0.56	0.61
40-49	0.71	0.76
50-59	0.66	0.76
60-69	0.55	0.65
>69	0.49	0.63

No evidence of heterogeneity in effect of tamoxifen by age

Panel Voting St Gallen 2013

Endocrine Therapy: Establishing Standards for Premenopausal	Yes	No	Abstain
Tam alone as default?	83.3	16.7	0
Tamoxifen duration should be extended to 10 years in patients remaining premenopausal:			
• For most patients?	42.9	49.0	8.2
• For some patients?	88.9	8.9	2.2

Panel had access to ATLAS publication
But not aTTom ASCO presentation

Adjuvant Endocrine Therapy for Women with Hormone
Receptor-Positive Breast Cancer: ASCO Clinical Practice
Guideline Focused Update

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

- Tamoxifen for an initial duration of 5 years

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

- 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

Conclusion

- Tamoxifen alone or Exemestane plus OFS can be considered as proper endocrine therapies in premenopausal patients
- Despite the lack of conclusive data favoring the combination, exemestane plus OFS might be preferred in premenopausal patients at higher risk
- Some may have similar treatment outcomes with tamoxifen or exemestane plus OFS
- OFS plus tam: wait for SOFT!
- OFS alone inappropriate unless tam contraindicated

Conclusion

- Limited information on tailoring adjuvant treatment for an individual young patient
- The identification of distinct clinical entities is the key achievement for proper management
- Disease extent, host factors, patient preferences, and economic and social factors should impact the choice of therapy