

Optimal adjuvant hormonal therapy in premenopausal women

M. Colleoni

International Breast Cancer Study Group (IBCSG),

Division of Medical Senology,

European Institute of Oncology



Disclosure slide

No relevant financial relationships to disclose



Optimal adjuvant hormonal therapy in premenopausal women

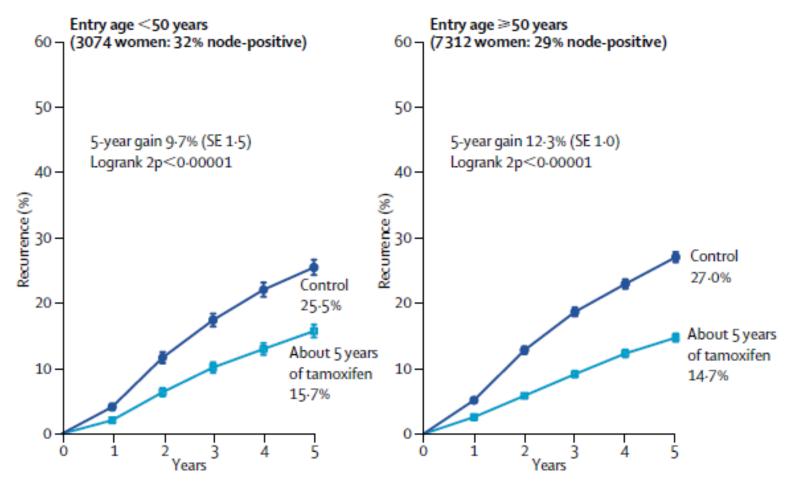
- Healthy, married woman, 40 years old
- Mastectomy +SNB + axillary dissection
- Histology: Ductal invasive carcinoma G2
- pT2 (2.5 cm) pN1a (1/26) ER 90% PgR 90% HER-2 absent KI-67 16%
- No peritumoral vascular invasion



Premenopausal Patients

- Treatment selection
 - Tamoxifen
 - \cdot 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



26-30 September 2014, Madrid, Spain

Lancet 2005; 365: 1687–1717

Tamoxifen

MADRID

2014

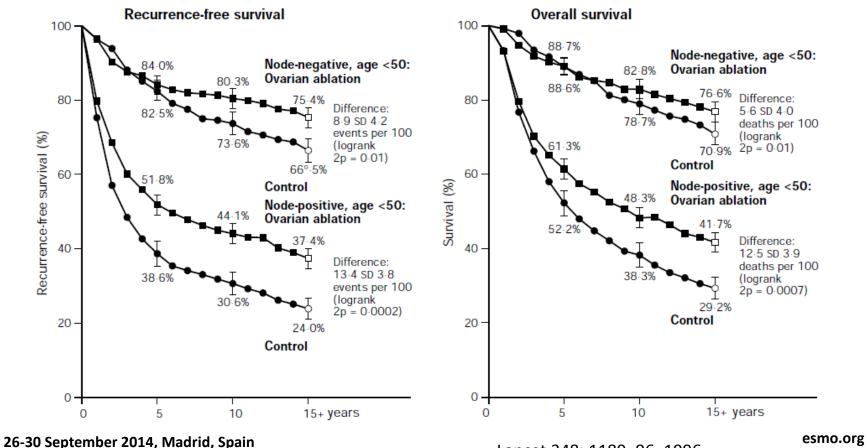
ESM About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease, by entry age Recurrence/woman-years Breast cancer mortality/women

Events/woman-years Tamoxifen events Tamoxifen deaths Deaths/women Ratio of annual death rates Category Allocated Adjusted Logrank Variance Ratio of annual event rates Allocated Adjusted Logrank Variance Category tamoxifen Tamoxifen : Control tamoxifen 0-E of O-E Tamoxifen : Control control 0-E of O-E control (a) Dose of tamoxifen ($\chi^2_2=0.0$; 2p>0.1; NS) (a) Dose of tamoxifen ($\chi^2_2=0.0$; 2p>0.1; NS) 841/30896 1199/27508 -237.8 474.2 0.61 (SE 0.04) 20 mg/day 20 mg/day 561/3550 774/3530 -116.5 311.4 0-69 (SE 0-05) (2·7%/y) (15.8%)(4.4%/y)(21.9%)457/1675 574/1631 0.60 (SE 0.05) -90.5 232.2 0-68 (SE 0-05) 30-40 mg/day 571/16079 742/13540 -1467 2914 30-40 mg/day (27.3%)(35.2%)(3.6%/y) (5·5%/y) (b) Presence or absence of cytotoxics (χ²₂=3·1; p>0·1; NS) (b) Presence or absence of cytotoxics (χ²₂=2·0; p>0·1; NS) Chem with Tam vs 223/3926 270/2979 -54.5 106.3 0.60 (SE 0.08) Chem with Tam vs 168/488 212/462 -41.7 84.7 0.61 (SE 0.09) Chem alone (5·7%/y) Chem alone (45.9%) (9·1%/y) (34.4%)-48.6 133.2 242/8254 Chem then Tam vs 181/1176 -21.3 Chem then Tam vs 319/7682 0.69 (SE 0.07) 142/1204 78.0 0-76 (SE 0-10) (11.8%)(15.4%)Chem alone (2·9%/y) (4·2%/y) Chem alone Tam alone vs 947/34795 1352/30387 -281.4 526.1 0.59 (SE 0.03) Tam alone vs 708/3533 0.69 (SE 0.04) 955/3523 -144.0 381.0 Nil (no adjuvant) (20.0%)(27.1%)Nil (no adjuvant) (2·7%/y) (4·4%/y) (c) Entry age (trend χ²₁=3.8; 2p=0.05) (c) Entry age (trend χ²₁=0·4; 2p>0·1; NS) 113/3231 177/2660 -36.8 63.7 0.56 (SE 0.10) 0-61 (SE 0-12) Age <40 Age <40 74/417 119/398 -21.9 44.0 (3·5%/y) (6·7%/y) (17.7%)(29.9%)0.76 (SE 0.09) 40 - 49275/9461 351/8776 -49.0 143.0 0.71 (SE 0.07) 40 - 49-24.8 173/1119 219/1139 90.3 (2·9%/y) (4·0%/y) (15.5%)(19.2%)0-76 (SE 0-07) 50-59 452/14694 576/13114 -94·5 228·3 0.66 (SE 0.05) 50-59 394/1535 330/1591 -45.2 161.7 (25.7%) (3.1%/v)(20.7%)(4.4%/y)60-69 498/17399 724/14546 60-69 0.65 (SE 0.06) -163.0 270.0 0.55 (SE 0.05) 379/1822 527/1789 -87.3 200.4 (2.9%/y) (5.0%/y) (20.8%)(29.5%) ≥70 70/2105 107/1867 35.2 0.49 (SE 0.12) ≥70 89/286 0-63 (SE 0-15) -25.0 62/266 -13.6 29.9 (3.3%/y)(5·7%/y) (23.3%)(31.1%)Age unknown 6/7 4/10 0.7 0.9 Age unknown 0/100/141412/ 1941/ 0.605 (SE 0.028) 1018/ 1348/ Total -207.0 543.6 0.683 (SE 0.036) -384.5 765.6 Total 46975 41048 5225 5161 2p<0.00001 2p<0.00001 (3·0%/y) (4·7%/y) (26-1%)(19.5%)99% or <>> 95% Cls 0 0.5 1.0 1.5 2.0 0 0.5 1.0 1.52.0 Tamoxifen better Tamoxifen worse Tamoxifen better Tamoxifen worse Lancet 2005; 365: 1687–1717 Treatment effect 2p<0.00001 Treatment effect 2p<0.00001



OFS

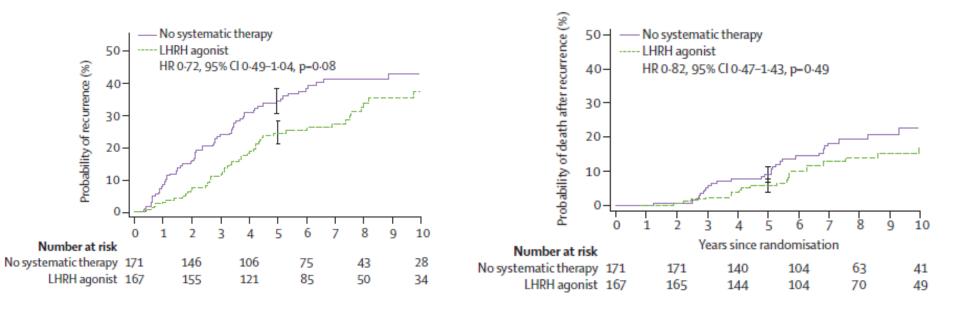
Overview: effects of ovarian ablation in the absence of chemotherapy





Overview: effects of LHRH agonist in the absence of chemotherapy

OFS

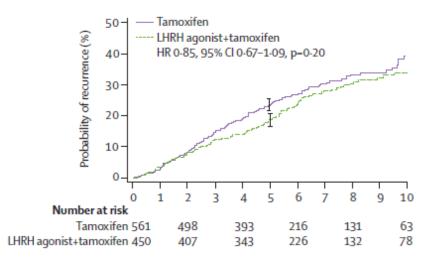


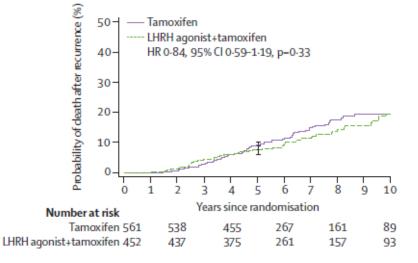
Lancet 369: 1711–23, 2007



Overview: addition of LHRH agonist to tamoxifen

OFS





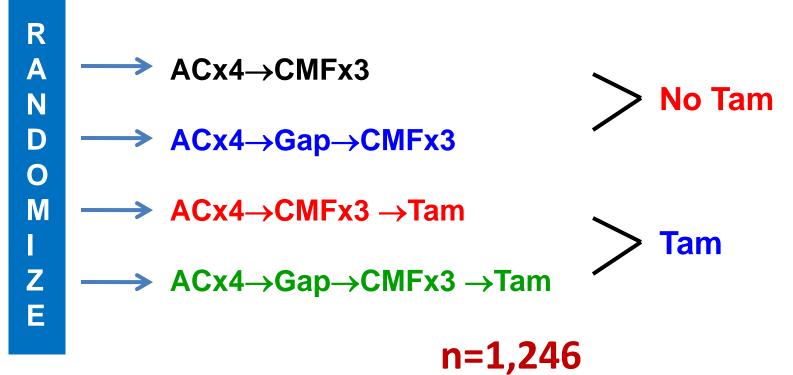
Lancet 369: 1711–23, 2007



IBCSG 13-93 Accrual: 1993-1999

OFS

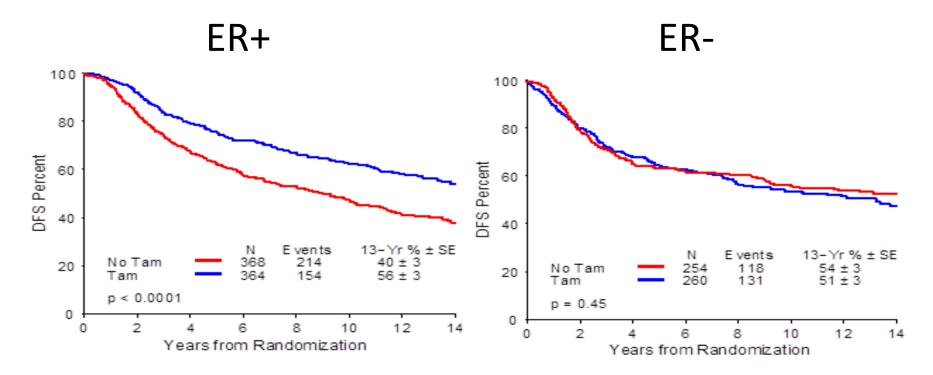
Premenopausal, node-positive breast cancer





Trial 13-93: Tamoxifen Question ER+ and ER-, Disease-Free Survival

OFS



26-30 September 2014, Madrid, Spain

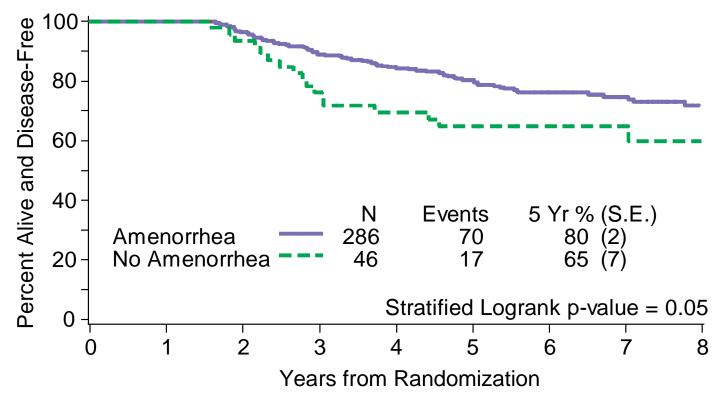
J Clin Oncol. 2006 24:1332-41

esmo.org



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

OFS

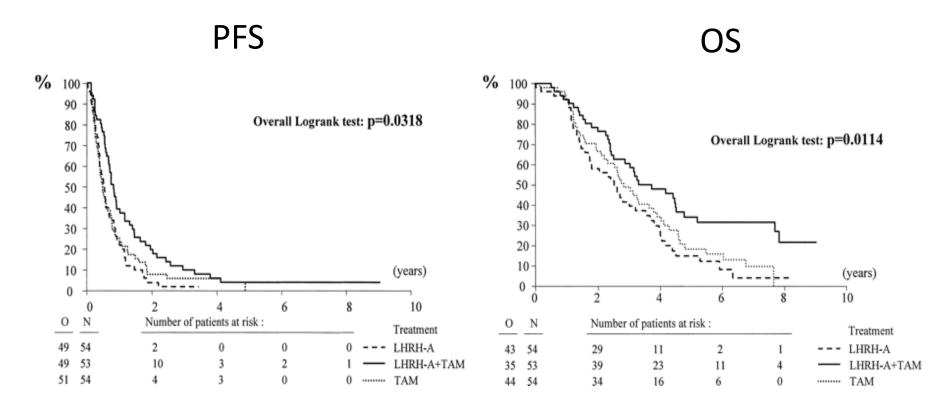


J Clin Oncol. 2006 24:1332-41



LHRH analogue + Tamoxifen advanced disease

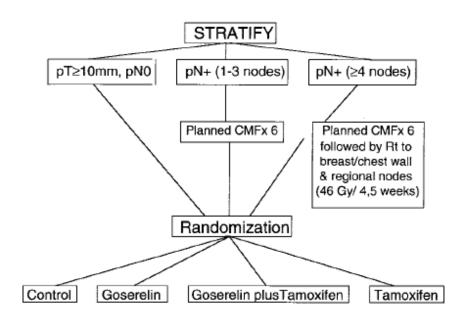
OFS



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



ZIPP Trial Side effects of ovarian function suppression



J Clin Oncol 21: 1836-1844, 2003



Side effects of ovarian function suppression

ZIPP Trial

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

26-30 September 2014, Madrid, Spain

J Clin Oncol 21: 1836-1844, 2003

esmo.org



Panel Voting St Gallen 2013

OFS

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

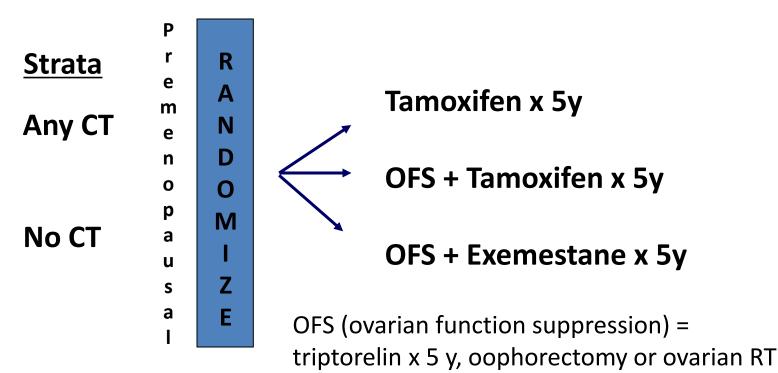




OFS

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

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

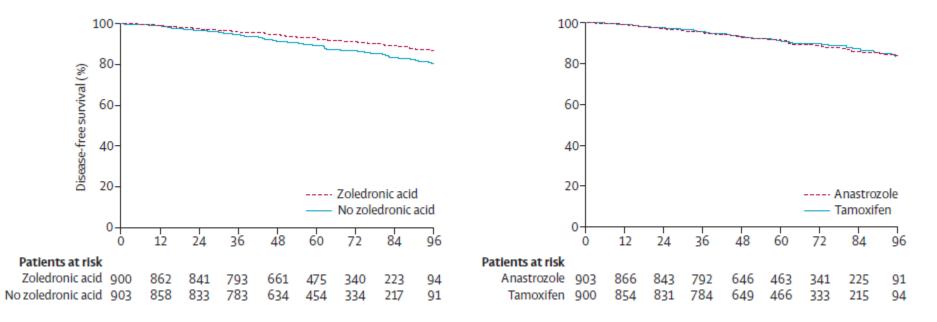


sample size: 3066 patients

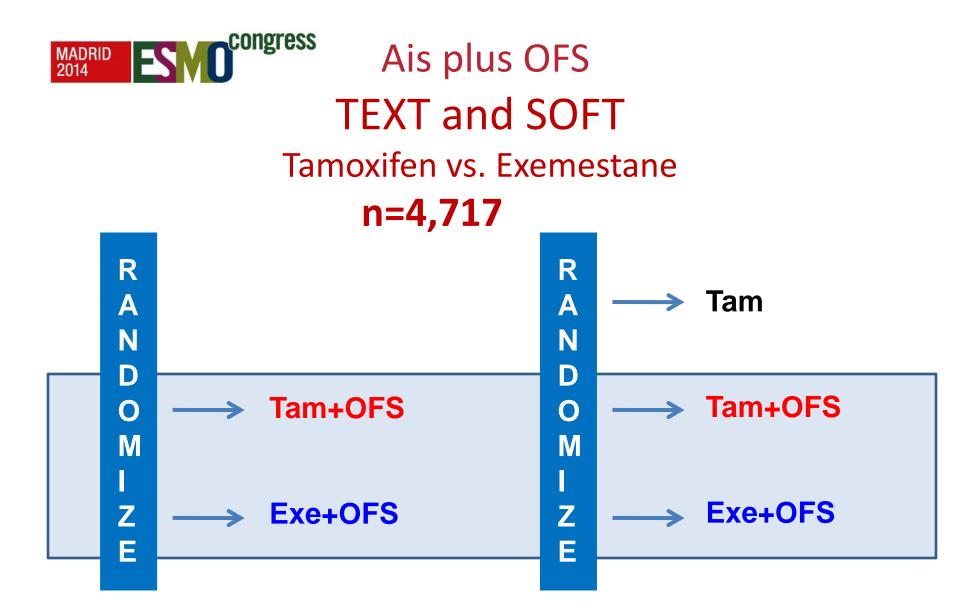


Ais plus OFS

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

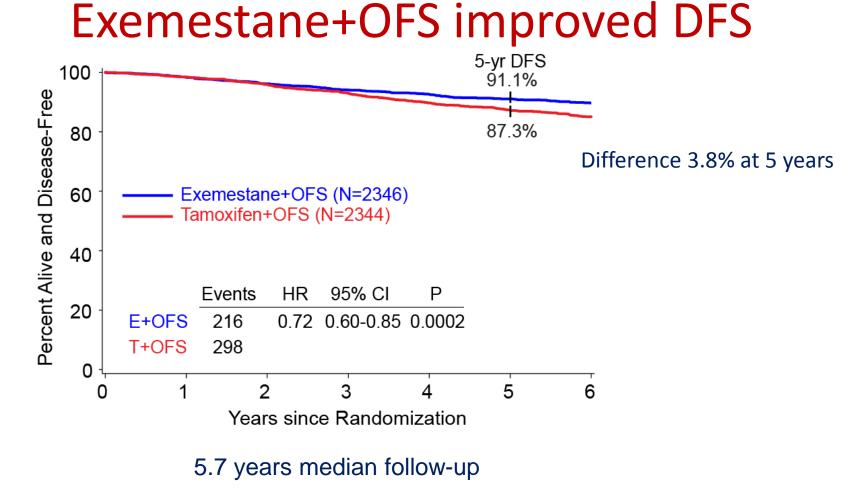


Lancet Oncol 2011; 12: 631–41





Ais plus OFS TEXT and SOFT



Pagani O. et al. NEJM, 2014; 371:107-118

esmo.org



Congress Ais plus OFS TEXT and SOFT Exemestane+OFS improved DFS

	No. Pa E+OFS		HR (95% CI)	5)FS % T+OFS
All Patients	2346	2344	-	91.1	87.3
Cohort					
No chemotherapy, TEXT	526	527 ·	 !	96.1	93.0
No chemotherapy, SOFT	470	473		95.8	93.1
Chemotherapy, TEXT	806	801	- 	89.8	84.6
Prior chemotherapy, SOF	T 544	543	- ∤ ∎∔-	84.3	80.6
Lymph Node Status					
Negative	1362	1350	∎	95.1	91.6
Positive	984	994	-₩-	85.6	81.4
		.25	.50 .72 1.0	2.0	4.0
September 2014, Madrid, Spain 5.7	years		vors E+OFS Fav	vors T+O	► FS

esmo.org

Pagani O. et al. NEJM, 2014; 371:107-118



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)	
All DFS events N (%)	216 (9.2)	298 (12.7)	514	
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	٦
Bone ± above	54 (2.3)	65 (2.8)	119	6
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	

26-30 September 2014, Madrid, Spain

esmo.org

Pagani O et al. NEJM, 2014; 371:107-118



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 endocrineresponsive breast cancer



Treatment duration

Long-term effects of continuing adjuvant tamoxifen by age

	Reduction in event rate			
Age (yr)	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 heterogenity in effect of tamoxifen by age

26-30 September 2014, Madrid, Spain

The Lancet, 381: 805 - 816, 2013

esmo.org



Panel Voting St Gallen 2013

Endocrine Therapy: Establisl Standards for Premenopausal	ning	Yes	No	Abstain
Tam alone as default?		83.3	16.7	0
Tamoxifen duration should be extended				
to 10 years in patients remaining But not aTTom ASCO presentation				
But flot		al Iom ASC	.O presenta	tion
premenopausal:				
 For most patients? 		42.9	49.0	8.2
 For some patients? 		88.9	8.9	2.2
26 20 Contombox 2014 Madrid Chain				esmo org



Treatment duration

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