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

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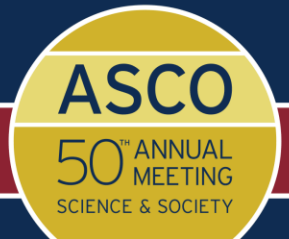
on behalf of the
TEXT and SOFT Investigators and
International Breast Cancer Study Group (IBCSG)



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- Collaboration of the Breast International Group (BIG) and North American Breast Cancer Group (NABCG)

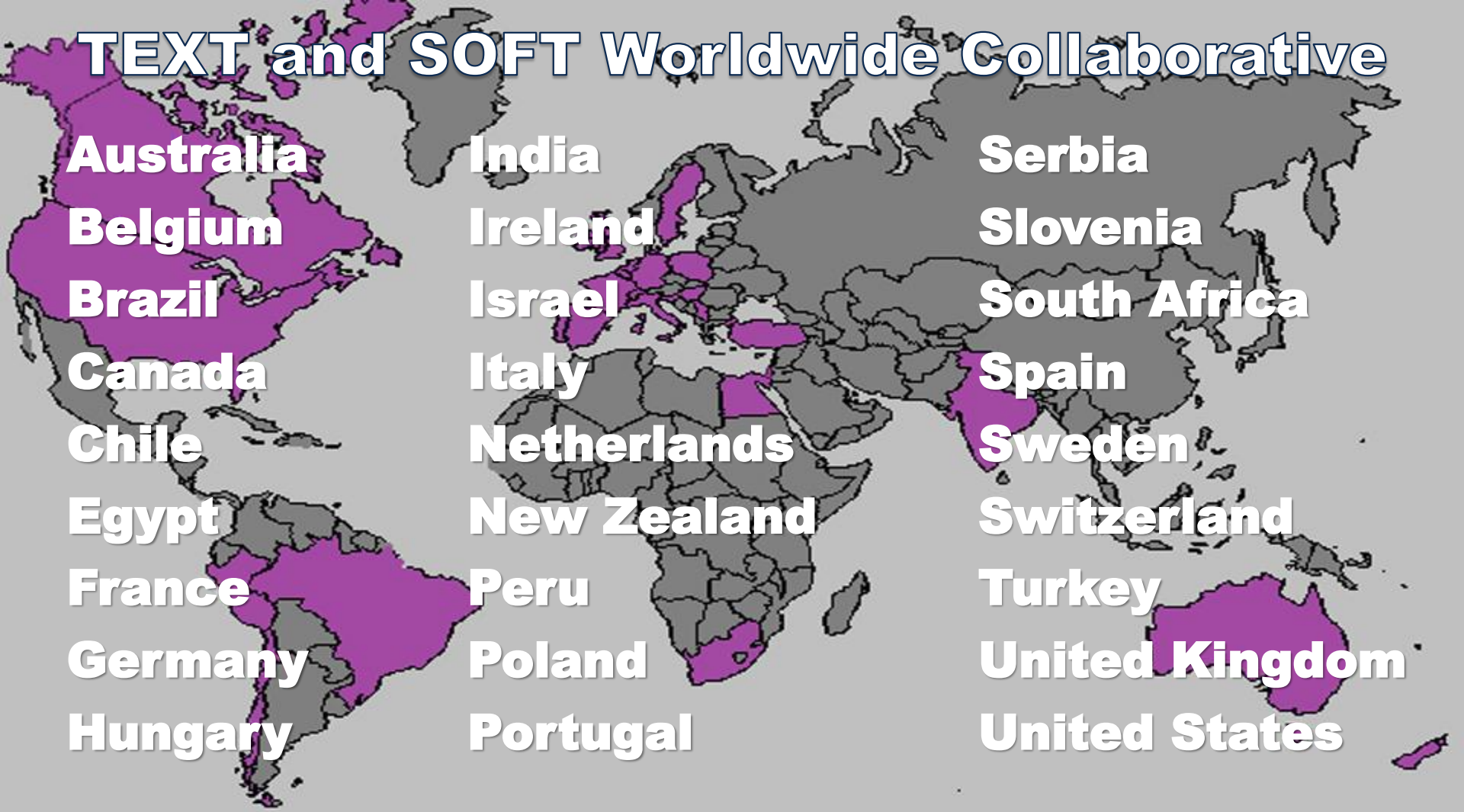
BIG
Breast International Group

NABCG
The North American Breast Cancer Group

- Financial support/drug supply: Pfizer, Ipsen, US NCI

Federally Funded Research

TEXT and SOFT Worldwide Collaborative



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Premenopausal Endocrine Therapy

- Optimal adjuvant endocrine therapy for premenopausal women with HR+ breast cancer is uncertain
- Tamoxifen for at least 5 years is a standard of care
- Ovarian function suppression (OFS) may be given in addition
- IBCSG designed TEXT and SOFT to determine optimal endocrine therapy in premenopausal women with HR+ breast cancer

TEXT - SOFT Trials
Aromatase Inhibitor Question

Does adjuvant therapy with the aromatase inhibitor (AI) exemestane improve disease-free survival relative to tamoxifen in premenopausal women treated with OFS for HR+ breast cancer?

TEXT and SOFT Designs

Enrolled: Nov03-Apr11

- Premenopausal
- ≤12 wks after surgery
- Planned OFS
- No planned chemo *OR* planned chemo

RANDOMIZE

TAMOXIFEN AND EXEMESTANE TRIAL (N=2672)

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

- Premenopausal
- ≤12 wks after surgery
- No chemo

OR

- Remain premenopausal ≤ 8 mos after chemo

RANDOMIZE

SUPPRESSION OF OVARIAN FUNCTION TRIAL (N=3066)

- Tamoxifen x 5y
- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

Joint Analysis (N=4690)

- Tamoxifen+OFS x 5y
- Exemestane+OFS x 5y

Median follow-up 5.7 years

OFS=ovarian function suppression

Eligibility

- Premenopausal women with HR+ (ER and/or PgR≥10%) invasive breast cancer confined to breast +/- axillary nodes
- Proper local-regional treatment with no residual disease
- Randomized within 12 weeks of surgery for all women in **TEXT** and women in **SOFT** who did not receive chemotherapy
- Women in **SOFT** who received prior (neo)adjuvant chemotherapy randomized ≤8 months of chemotherapy completion when premenopausal status demonstrated
  - These patients were permitted to receive oral endocrine therapy prior to randomization

Treatments

Protocol treatment was for 5 years from randomization

- **Ovarian Function Suppression**

  TEXT

  - All women started with GnRH agonist triptorelin (IM q28d)
  - Triptorelin initiated concurrently with chemotherapy, if it was given
  - Bilateral oophorectomy or irradiation as alternatives to triptorelin after 6 months

  SOFT

  - Choice of OFS method

- **Oral endocrine therapy**
  - Exemestane 25 mg daily, or
  - Tamoxifen 20 mg daily
  - In TEXT started 6 to 8 weeks after initiation of OFS, or after chemotherapy if given

Study Procedures

- Adjuvant trastuzumab allowed, if indicated
- Annual mammography and bone densitometry recommended
- Bisphosphonates not permitted unless T-score ≤ -1.5 or participating in a randomized adjuvant trial
- Targeted AEs and other grade 3-5 AEs (CTCAE v3.0)
- Quality-of-life self-assessment of global and symptom-specific indicators

Endpoints

Primary

- Disease-free survival (DFS)
  - Invasive recurrence (local, regional, distant)
  - Invasive contralateral breast cancer
  - Second (non-breast) invasive malignancy
  - Death without prior cancer event

Secondary

- Breast cancer-free interval (BCFI)
  - Invasive recurrence or contralateral breast cancer
- Distant recurrence-free interval (DRFI)
  - Distant recurrence
- Overall survival (OS)
  - Death from any cause

Statistical Considerations

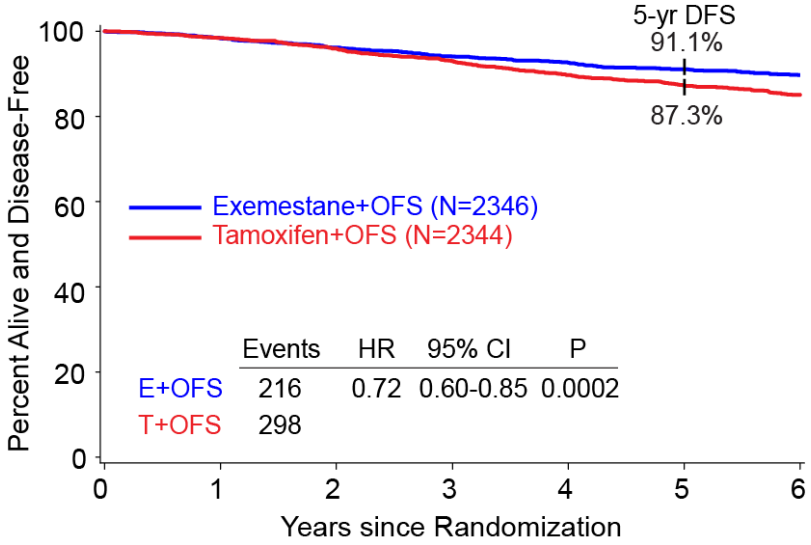
- DFS event rate much lower than anticipated *(Regan et al., The Breast 2013)*
- Protocols amended in 2011 (before efficacy data available):
  - For the E+OFS v. T+OFS comparison, a planned secondary joint analysis of TEXT & SOFT was promoted to become the primary analysis
  - With data cut-off in late-2013 (>5 years median follow-up), power 84% for HR=0.75 (2-sided α=0.05) in the combined analysis
  - No interim analyses
- ITT analysis; stratified by trial, chemotherapy use, nodal status

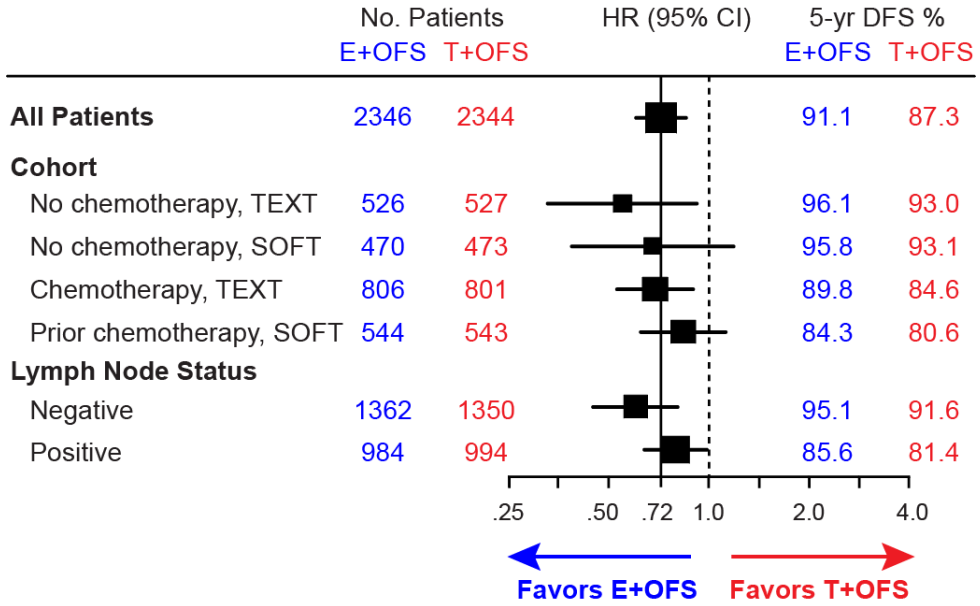
Characteristics

	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

Difference 3.8% at 5 years





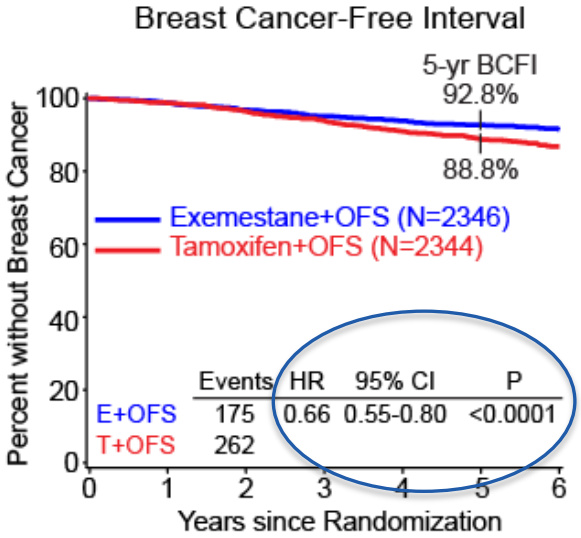
5.7 years median follow-up

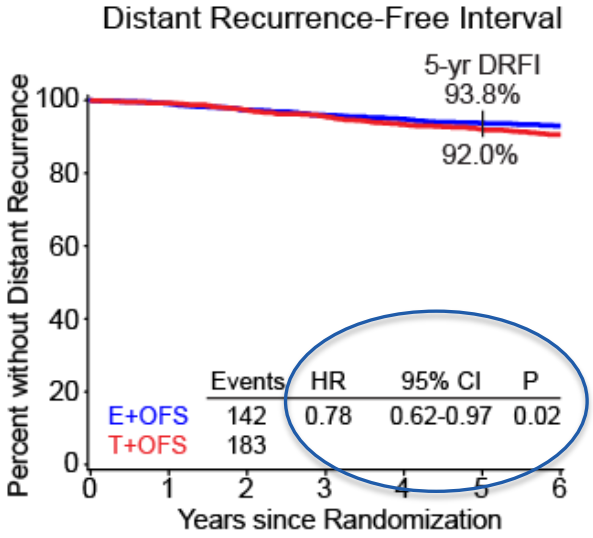
Sites of First Failure

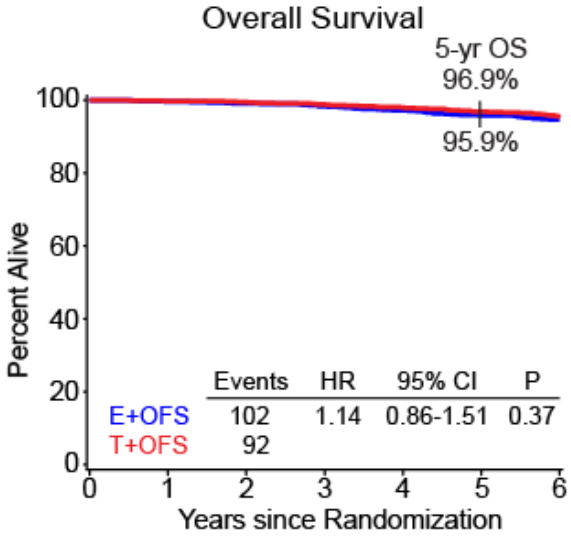
Site of First Failure (DFS event)	E+OFS (N=2346)	T+OFS (N=2344)	Overall (N=4690)
All DFS events N (%)	*216 (9.2)*	*298 (12.7)*	*514*
Local	23 (1.0)	28 (1.2)	51
Contralateral breast	9 (0.4)	27 (1.2)	36
Regional ± above	9 (0.4)	30 (1.3)	39
Soft tissue / distant LN ± above	4 (0.2)	6 (0.3)	10
Bone ± above	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% of first failures involved distant sites

Exemestane+OFS Reduced Recurrence

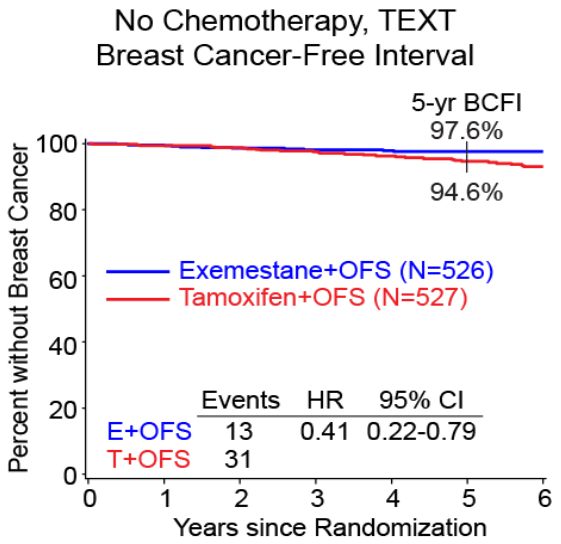






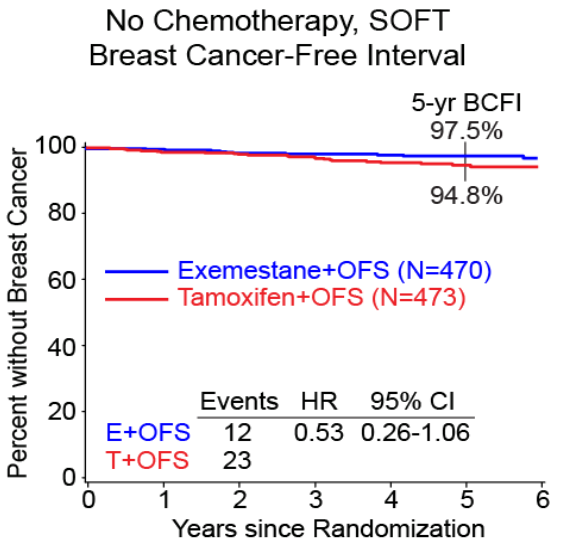
- 4% absolute improvement in 5-yr freedom from breast cancer for exemestane+OFS
- No significant difference in overall survival

Women Who Did Not Receive Chemotherapy



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

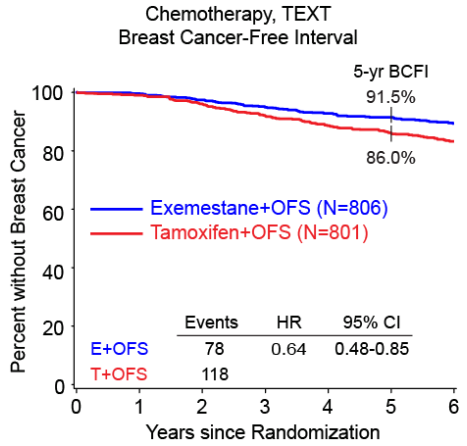
N=1996

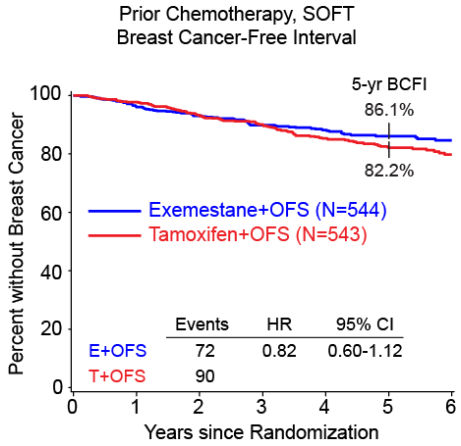


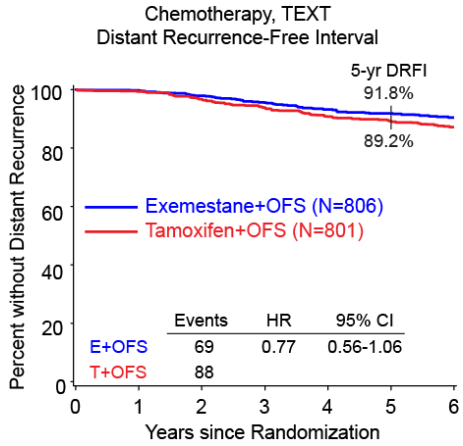
9% <40 years; 15% T-size >2cm; 8% N+

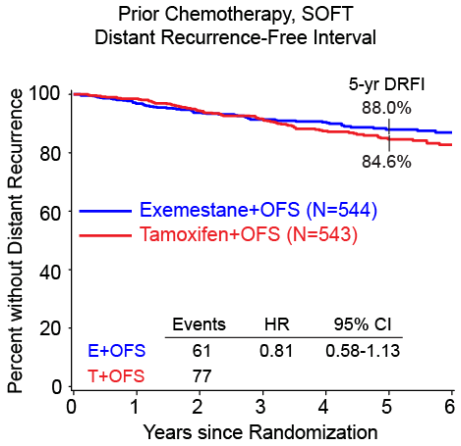
Some women have excellent prognosis with highly-effective endocrine therapy alone
>97% breast cancer-free at 5 years when treated with exemestane+OFS

Women Who Received Chemotherapy









66% N+; 53% T-size >2cm; 30% <40 years

57% N+; 47% T-size >2cm; 49% <40 years

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

Selected Adverse Events

	Exemestane+OFS (N=2318)		Tamoxifen+OFS (N=2325)	
CTCAE v3.0	**Grade 1-4**	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
Depression	50%	3.8%	50%	4.4%
Musculoskeletal	89%	11%	76%	5.2%
Osteoporosis (% T< -2.5)	39% (13%)	0.4%	25% (6%)	0.3%
Fracture	6.8%	1.3%	5.2%	0.8%
Hypertension	23%	6.5%	22%	7.3%
Cardiac ischemia/infarction	0.7%	0.3%	0.3%	0.1%
Thrombosis/embolism	1.0%	0.8%	2.2%	1.9%
CNS ischemia	0.7%	0.3%	0.3%	0.1%
CNS bleeding	0.6%	<0.1%	0.9%	0.1%
Hot flushes/flashes	92%	10%	93%	12%
Sweating	55%	--	59%	--
Vaginal dryness	52%	--	47%	--
Libido decrease	45%	--	41%	--
Dyspareunia	31%	2.3%	26%	1.4%
Urinary incontinence	13%	0.3%	18%	0.3%

Adverse Events and QOL

- AE profiles comparable with postmenopausal women
- Incidence of targeted grade 3-4 AEs similar (31% and 29%)
- Early cessation of all assigned treatments more frequent with exemestane+OFS (16% vs. 11%)
- Patients self-report differential effects, but overall quality of life did not favor either treatment *(Abstract #557)*

Conclusions

- Exemestane+OFS, as compared with tamoxifen+OFS, significantly improves DFS, BCFI and DRFI and is a new treatment option for premenopausal women with HR+ early breast cancer
- No significant difference in overall survival, conclusions premature at this early point in follow-up of HR+ breast cancer
- Side effect profile of exemestane+OFS mirrors that seen with AIs in postmenopausal women
- Some premenopausal women diagnosed with HR+ breast cancer have an excellent prognosis with highly-effective endocrine therapy alone
- Long-term follow-up needed

More from TEXT and SOFT

- Manuscript published online at *New England Journal of Medicine*
- Monday General Poster session:
  - Quality of life — Board #21 (Abstract #557)
  - SOFT-EST estrogen suppression substudy — Board #49 (Abstract #585)
- OFS question from SOFT (tamoxifen+OFS vs tamoxifen) end of 2014

IBCSG Thanks

5,000+ women who participated in the trials

- Physicians, nurses, data and trial coordinators, and pathologists in 510 centers worldwide
- Pfizer and Ipsen for drug supply and financial support
- IBCSG Data Management Center, Coordinating Center, Central Pathology Office, Statistical Center
- STP Steering Committee, DSMC

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