SOFTly:

The Long Natural History of [Trials for] [premenopausal] ER+ Breast Cancer

---

Charles Moertel Lecture

May 12, 2017

Gini Fleming

Charles Moertel

- Founder of NCCTG
- Dedication to high quality clinical research
- With an impact on patient care

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Learning objectives

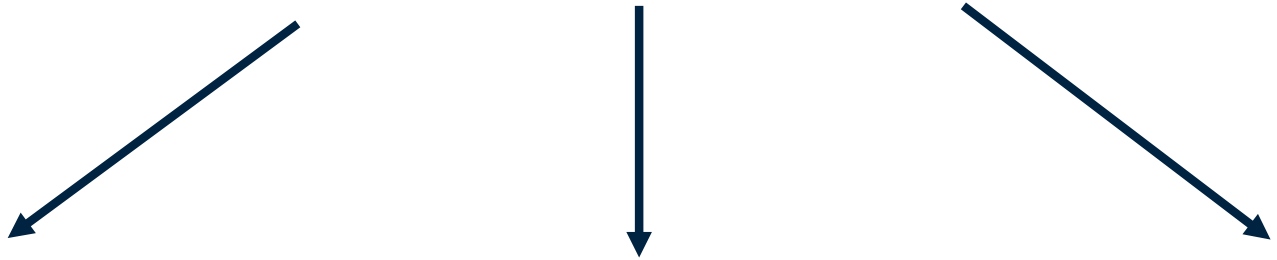
- Develop fascination for complexities of endocrine therapy for breast cancer
- Become ardent supporter of clinical trials
- Describe and implement results of SOFT trial
- Immediately upon return home urge your data managers to update LTFU results of SOFT trial

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

SOFT:

Suppression of Ovarian Function Trial

ER/PR + breast cancer pts who remain premenopausal after completion of chemotherapy or who get no chemotherapy



Tam x 5 yrs

OFS (Triptorelin) +Tam x 5 yrs

OFS + Exemestane x 5 yrs

n = 3000
opens Dec 2003
1st published Jan 2015

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Long term Disease-Free Survival of 826 Women with Node(-) Breast Cancer

Quiet et al
JCO 13:1144, 1995

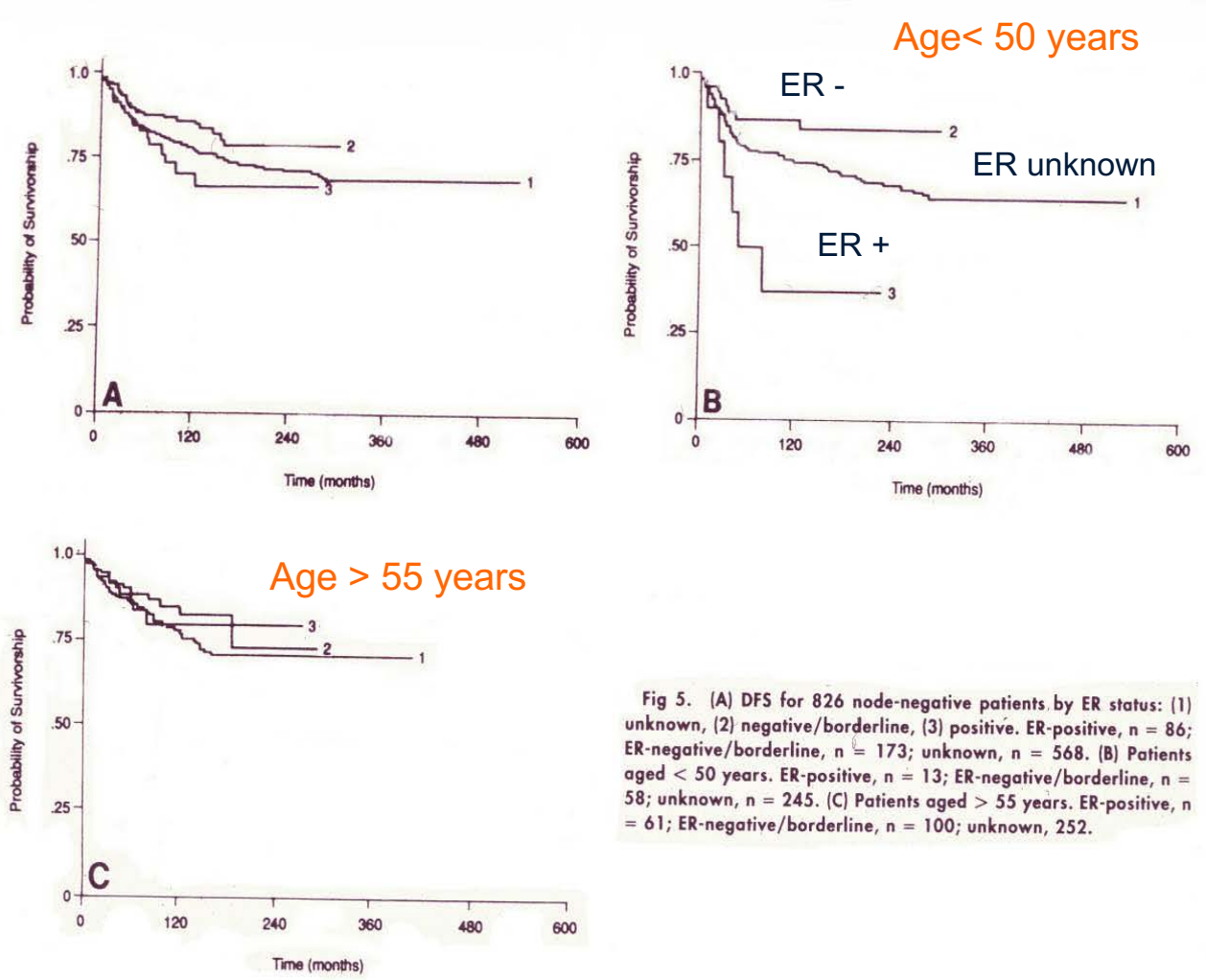
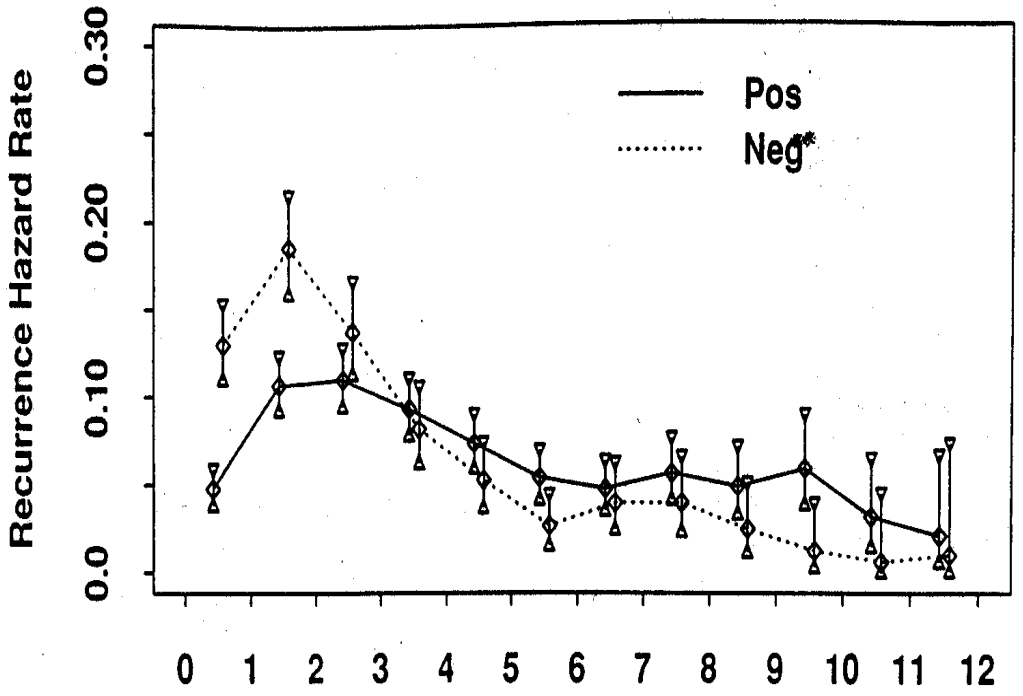


Fig 5. (A) DFS for 826 node-negative patients by ER status: (1) unknown, (2) negative/borderline, (3) positive. ER-positive, n = 86; ER-negative/borderline, n = 173; unknown, n = 568. (B) Patients aged < 50 years. ER-positive, n = 13; ER-negative/borderline, n = 58; unknown, n = 245. (C) Patients aged > 55 years. ER-positive, n = 61; ER-negative/borderline, n = 100; unknown, 252.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

ER+ Breast Cancer Recurs Late

Fig 4. Annual hazard of recurrence of 3,562 patients separated by ER status. The mean follow-up times for ER-positive and ER-negative patients were 8.1 and 8.0 years, respectively. (ER status was missing for 23 patients.)

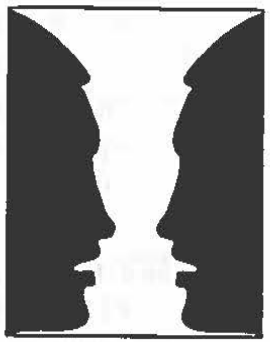


Saphner JCO 1996

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Cancer Investigation, 18(7), 681–684 (2000)

POINT/COUNTERPOINT SERIES

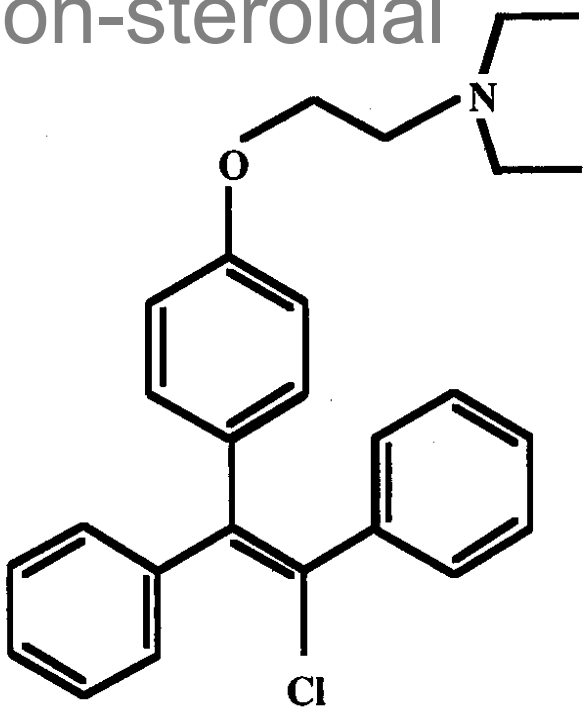


POINT

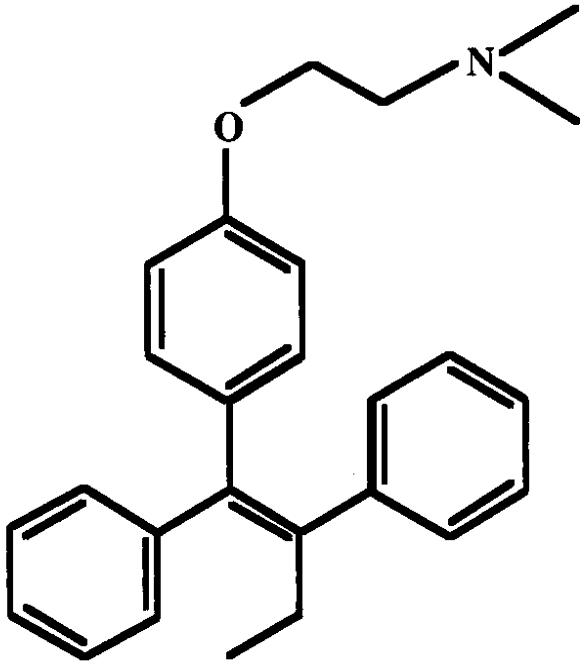
Tamoxifen for Treatment of Premenopausal Women with Breast Cancer

Tamoxifen Structure

- Non-steroidal



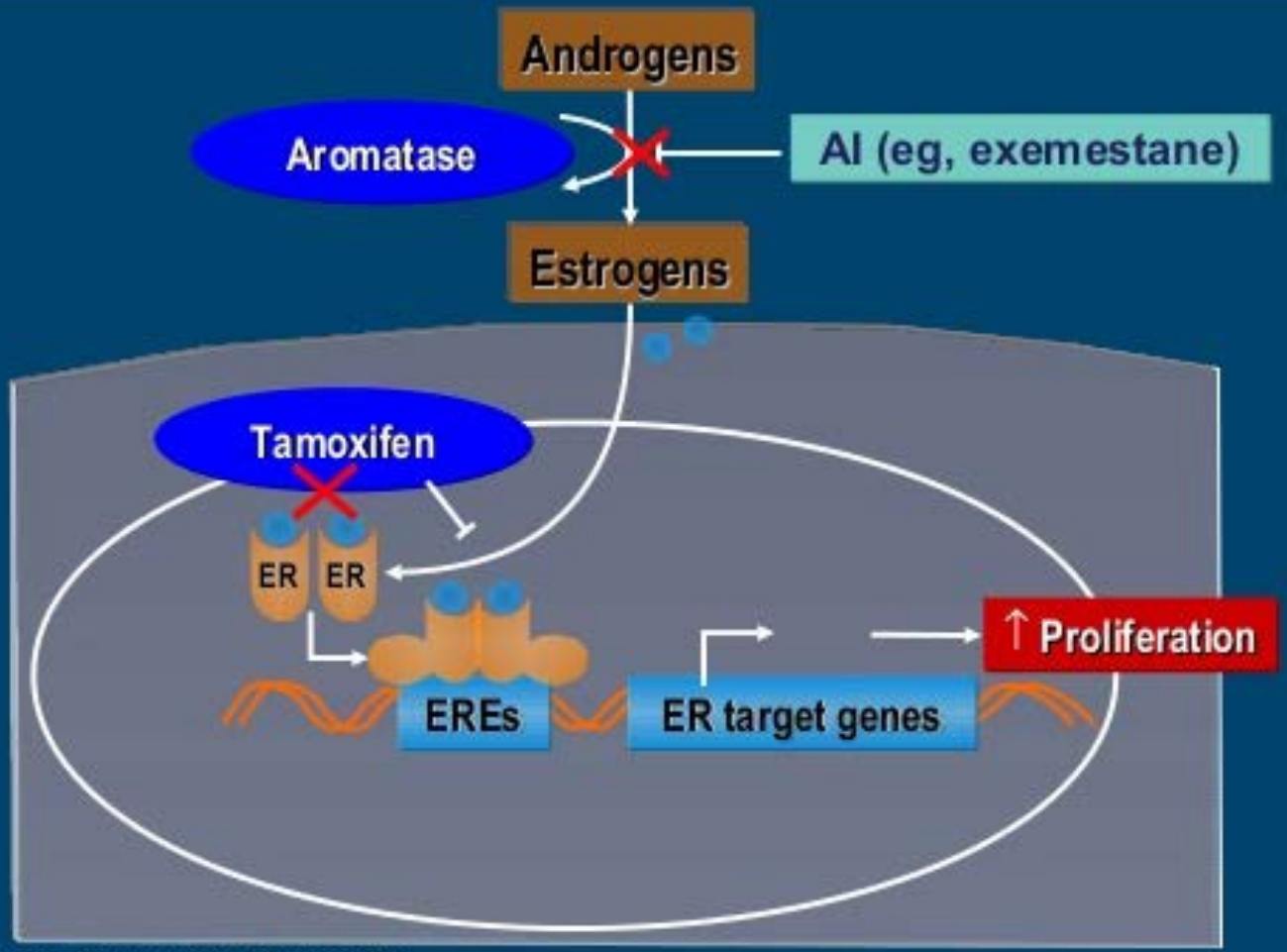
CLOMIPHENE
(mixture of cis and trans isomers)



TAMOXIFEN
(trans isomer only)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Differences in AI and Tamoxifen Mechanism of Action



EREs = estrogen response elements.

Johnston SRD et al. *Nat Rev Cancer.* 2003;3:821-831. Adapted with permission: http://www.nature.com.

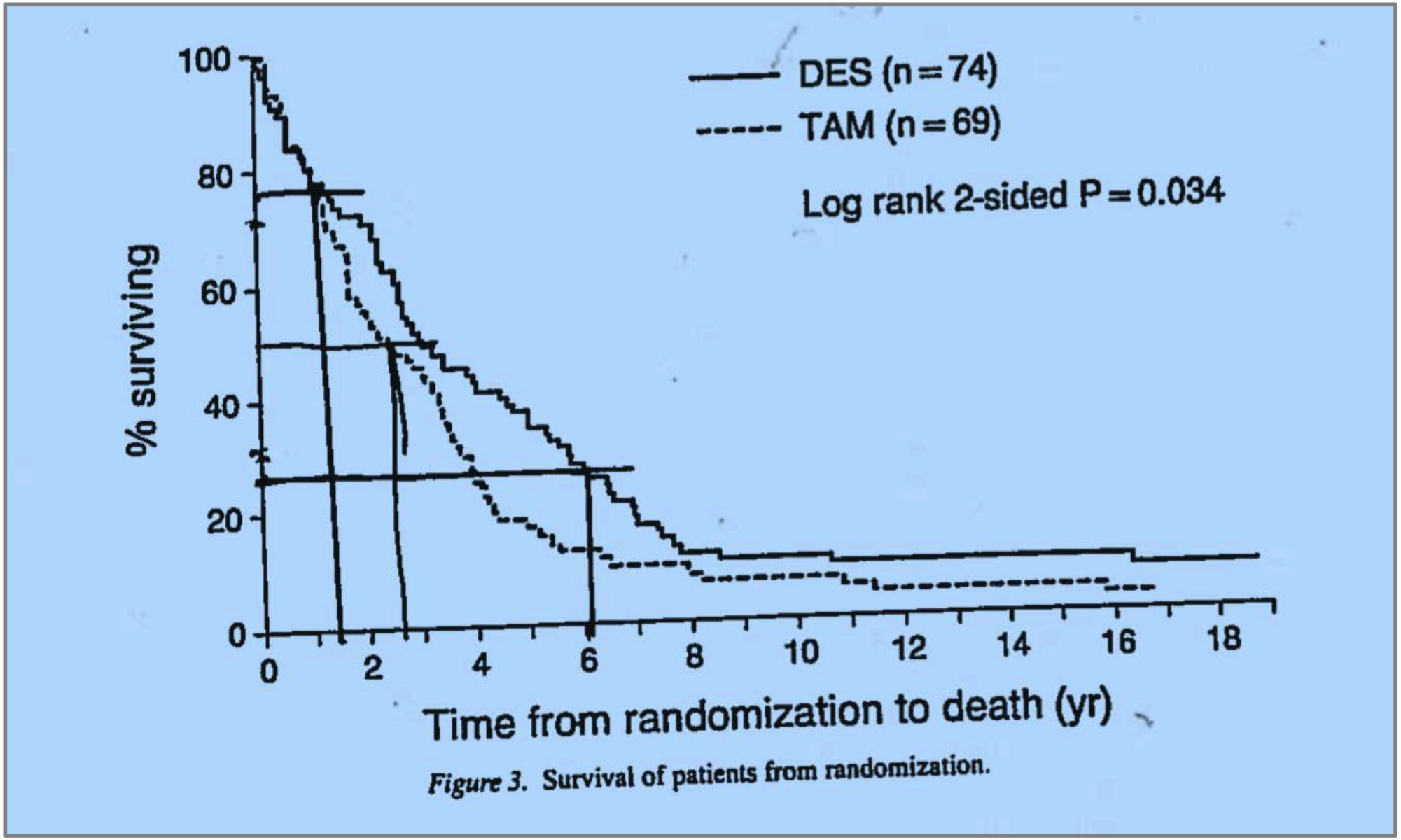


Figure 3. Survival of patients from randomization.

Peethambaram PP, Ingle JN, Suman VJ, Harttmann LC, Loprinzi CL. Randomized trial of diethylstibestrol vs tamoxifen in postmenopausal women with metastatic breast cancer: an updated analysis. Breast Cancer Res Treat 54:117, 1999

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

From: **Lower-Dose vs High-Dose Oral Estradiol Therapy of Hormone Receptor–Positive, Aromatase Inhibitor–Resistant Advanced Breast CancerA Phase 2 Randomized Study**

JAMA. 2009;302(7):774-780. doi:10.1001/jama.2009.1204

Table 4. Treatment Response by Study Group and Contingency for Interaction Between the Presence of a Positive FDG-PET/CT Estradiol Stimulation Test and Response to Estradiol Treatment

	Response		Metabolic Flare onFDG-PET/CT[a]		
	6 mg (n = 34)	30 mg (n = 32)	Yes[b]	No[b]	Total
Complete remission	0	0	NA	NA	NA
Partial response	3 (9)	1 (3)	3	0	3
Stable disease	7 (20)	8 (25)	9	4	13
Progression disease	21 (62)	16 (50)	3	27	30
Not assessable	3 (9)	7 (22)	NA	NA	NA

Abbreviation: FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; NA, not applicable.

[a] Combined data from both groups, $P<.001$.

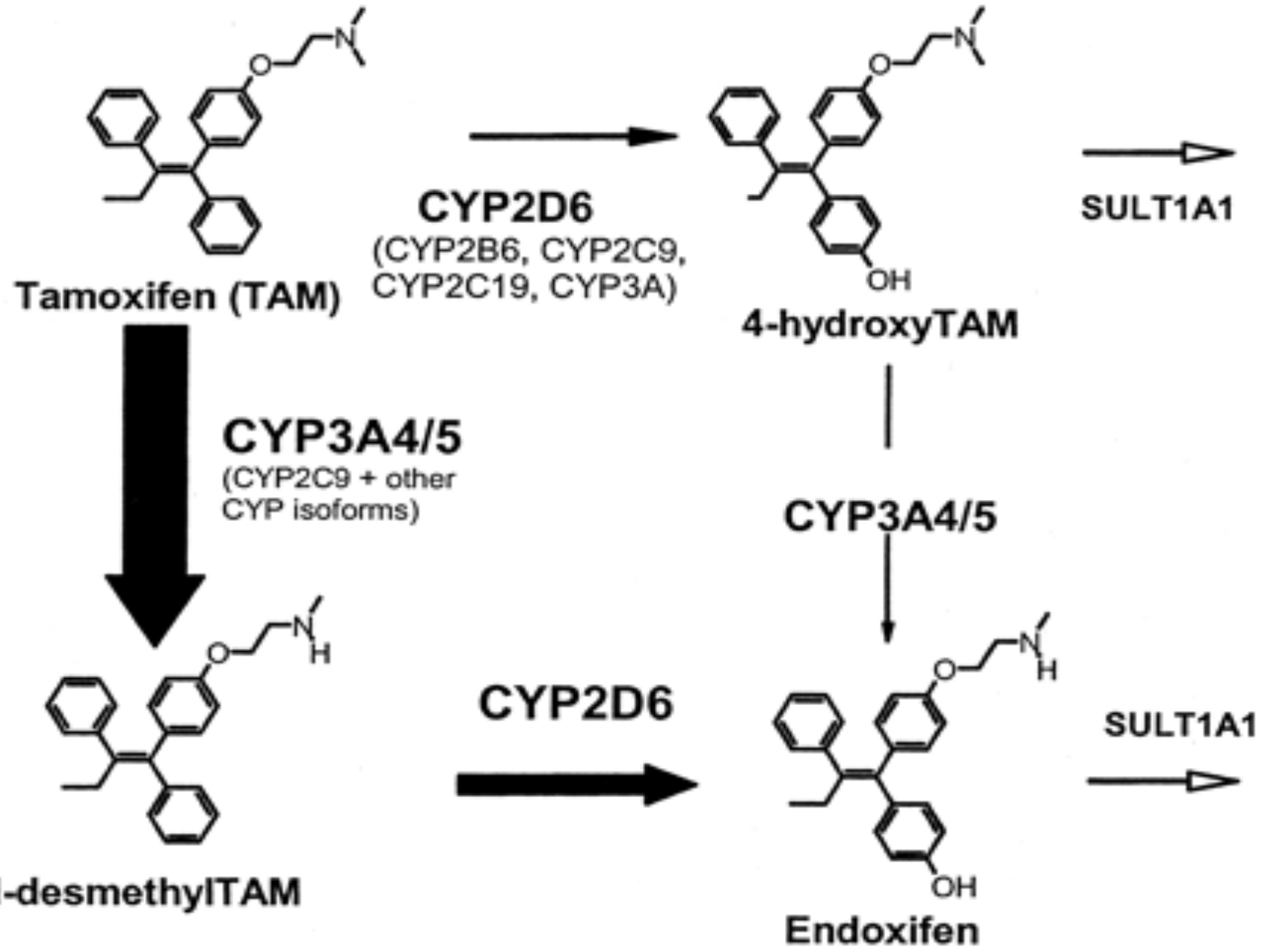
[b] Total yes responses to metabolic flare on FDG-PET/CT, 15; total no responses to metabolic flare on FDG-PET/CT, 31; overall responses, 46.

ShERPAs

- Selective Human Estrogen Receptor Partial Agonsists
  - Mimic actions of E2 in breast cancer therapy
  - Inhibit growth of tamoxifen-resistant breast cancer cell lines
  - Do not cause uterine growth
  - Entering human clinical trials

Xiong it al, J Med Chem 9:219, 2016

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY


Tamoxifen (TAM)
CYP2D6
(CYP2B6, CYP2C9,
CYP2C19, CYP3A)
4-hydroxyTAM
SULT1A1
CYP3A4/5
(CYP2C9 + other
CYP isoforms)
CYP3A4/5
N-desmethylTAM
CYP2D6
Endoxifen
SULT1A1

Alliance A011203

ER+
HER2-
metastatic
BrCA

Mandatory
Biopsy

AI resistant

Post-
menopausal

RANDOMIZE

Tamoxifen 20 mg po daily
f/b
x-over to Endoxifen at
progression

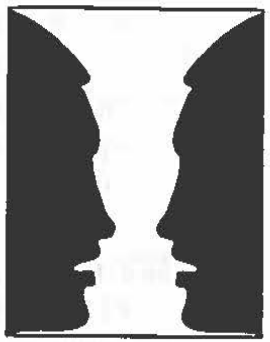
Z-Endoxifen HCL
80 mg po day

Matt Goetz, Chair

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Cancer Investigation, 18(7), 681–684 (2000)

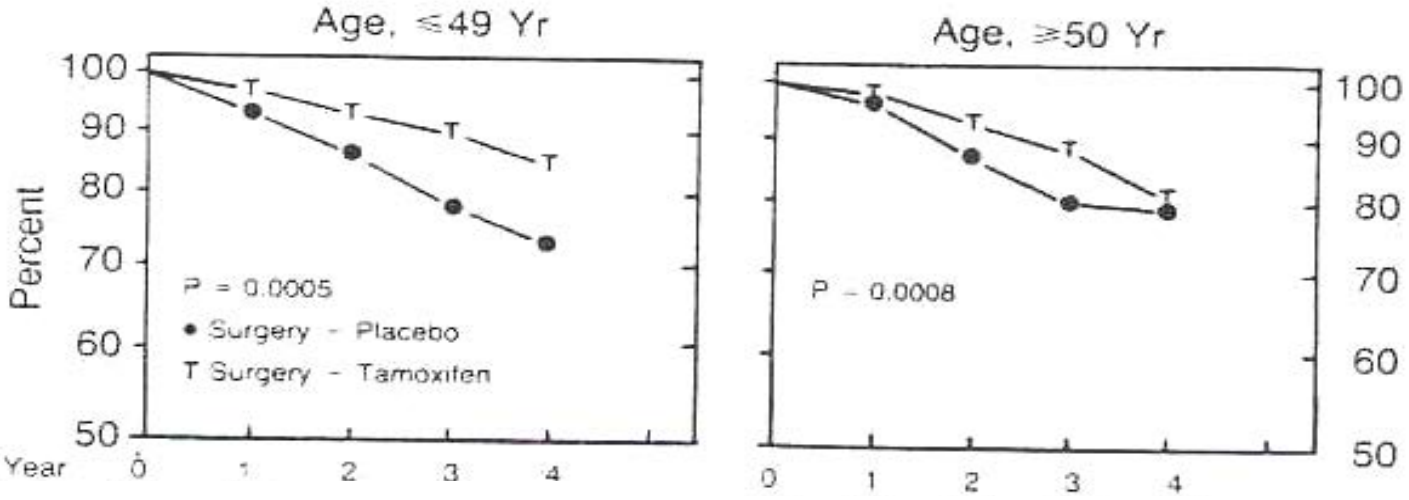
POINT/COUNTERPOINT SERIES



POINT

Tamoxifen for Treatment of Premenopausal Women with Breast Cancer

NSABP B-14: Tamoxifen vs. Placebo in Women With ER+ Node- Tumors



NEJM 320:479, 1989

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Ovarian Overstimulation and Cystic Formation in Premenopausal Tamoxifen Exposure: Comparison between Tamoxifen-Treated and Nontreated Breast Cancer Patients

Ilan Cohen, M.D.,* Arie Figer, M.D.,† Ron Tepper, M.D.,* Jeremiah Shapira, M.D.,‡ Marco M. Altaras, M.D.,* Dror Yigael, M.D.,‡ and Yoram Beyth, M.D.*

*Department of Obstetrics and Gynecology and ‡Medical Oncology Unit, Sapir Medical Center, Kfar-Saba; and †Department of Medical Oncology, Beilinson Medical Center, Petah-Tikva, Affiliated with Sackler Faculty of Medicine, Tel-Aviv University, Ramat-Aviv, Israel

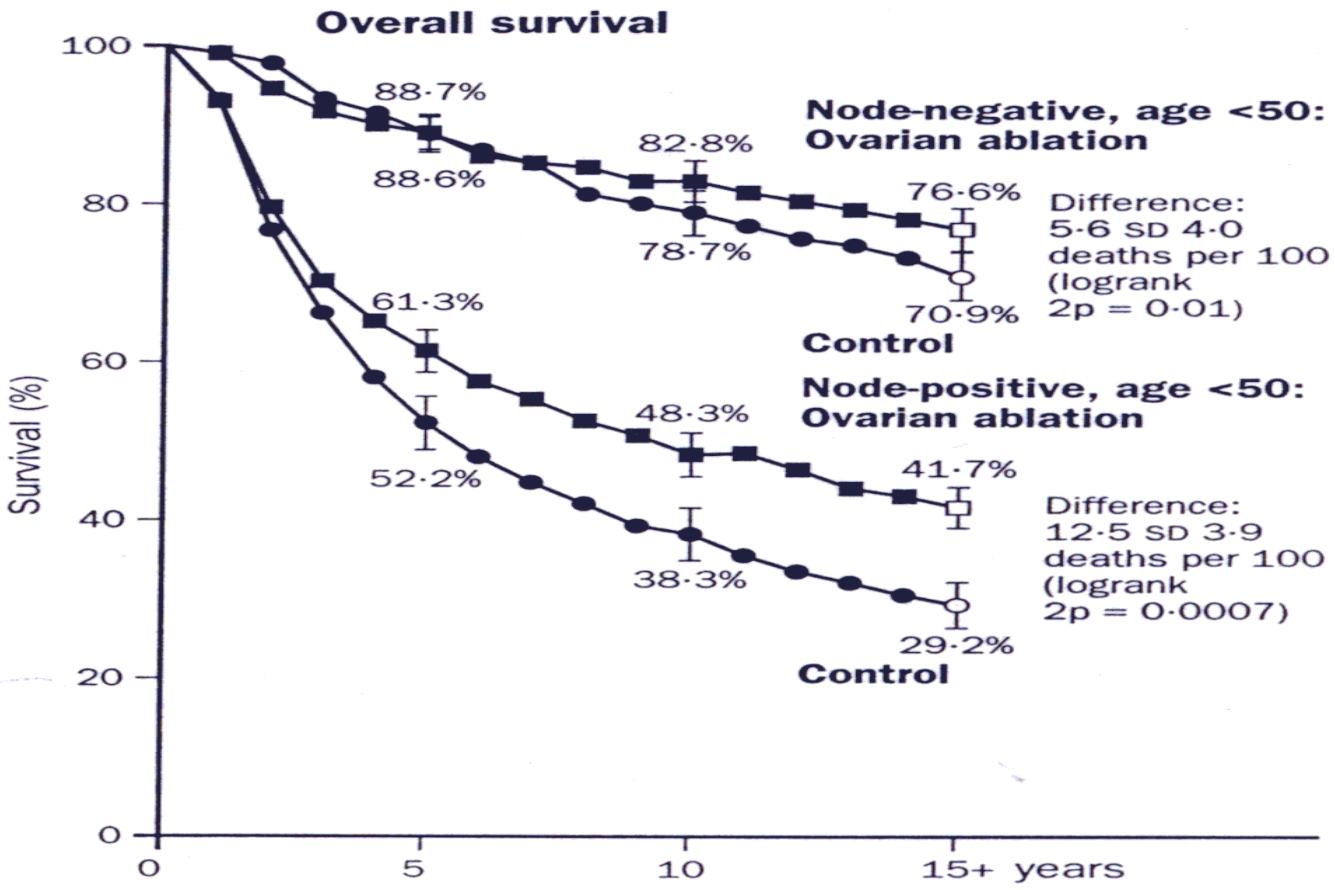
Received February 18, 1998

	Tam	Control	P
Day 3 E2 level (pg/mL)	60.4 +/-71	48	NS
Day 14 E2 level	**757.7 +/-372**	**206.5 +/- 275**	.0012
Day 21 E2 level	300 +/- 135	96.5	.0008

Gynecol Oncol 72:202, 1999

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

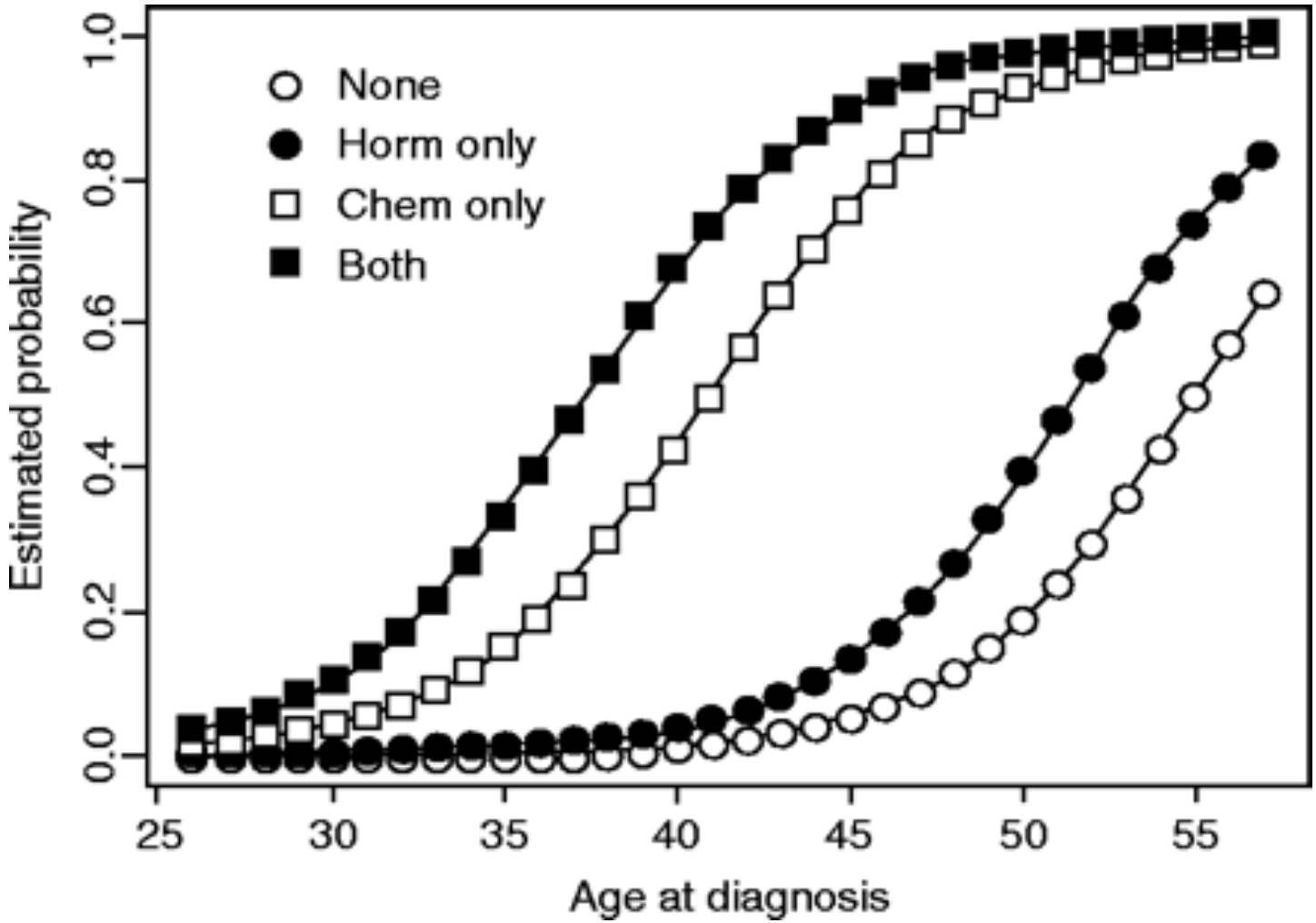
Overall Survival Benefits for Women age <50 with Ovarian Ablation (No Chemotherapy)



EBCTCG
Lancet 348:1189, 1996

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Risk of Menopause During the First Year After Breast Cancer Diagnosis [CMF or CEF]



Goodwin et al

JCO 17:2365, 1999

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

TABLE III – OVERALL EFFECTS OF TAMOXIFEN, AND INDIRECT COMPARISONS OF THE EFFECTS OF TAMOXIFEN (a) AT DIFFERENT DOSES, (b) FOR DIFFERENT DURATIONS, (c) WITHOUT, OR WITH, CONCURRENT CHEMOTHERAPY, (d) IN DIFFERENT NODAL STATUS CATEGORIES, AND (e) IN DIFFERENT OESTROGEN RECEPTOR CATEGORIES

Category of trial or women	No randomised		Typical reduction % (SD) in annual odds of					
			Recurrence or prior death			Death from any cause		
	<50 yr	≥50 yr	<50 yr	≥50 yr	*Any*[a]	<50 yr	≥50 yr	*Any*[a]
All unconfounded trials of tamoxifen vs same treatment without tamoxifen								
Tamoxifen vs no tamoxifen	8012	21 280	12 (4)	29 (2)	*25 (2)*	6 (5)	20 (2)	*16 (2)*
Indirect comparisons between trials of tamoxifen vs no tamoxifen								
(a) Dose of tamoxifen[b]								
20 mg/day vs no tamoxifen	6773	12 291	14 (4)	31 (3)	*27 (2)*	7 (5)	21 (3)	*17 (3)*
30–40 mg/day vs no tamoxifen	1839	8989	5 (8)	27 (3)	*22 (3)*	[2 (9)]	18 (3)	*15 (3)*
(b) Duration of tamoxifen treatment[c]								
Tamoxifen for ≤1 yr vs no tamoxifen	2478	5732	5 (7)	19 (4)	*16 (3)*	4 (8)	13 (4)	*11 (4)*
Tamoxifen for 2 yr vs no tamoxifen	4794	10 490	10 (5)	33 (3)	*28 (2)*	4 (6)	23 (3)	*19 (3)*
Tamoxifen for >2 yr vs no tamoxifen	1311	5067	[43 (11)]	38 (5)	*39 (4)*	[27 (17)]	23 (6)	*24 (6)*
(c) Without, or with, concurrent chemotherapy (CTX)[b]								
Tamoxifen alone vs no adjuvant	2226	13 145	27 (7)	30 (2)	*29 (3)*	[17 (10)]	19 (3)	*19 (3)*
Tamoxifen + CTX vs same CTX alone	6386	8135	7 (4)	28 (3)	*24 (3)*	3 (5)	20 (4)	*16 (3)*
(d) Tamoxifen in different nodal status categories[b]								
Node-negative (by sample or dissection)	3437	9473	22 (8)	28 (4)	*26 (4)*	[19 (12)]	16 (5)	*17 (5)*
Node-positive (all other women)	5175	11 807	11 (4)	33 (2)	*28 (2)*[d]	5 (5)	22 (3)	*18 (2)*[d]
(e) Tamoxifen in different oestrogen receptor (ER) categories[c]								
ER poor (or <10 fmol/mg)	2055	3311	3 (8)	16 (5)	*13 (4)*	[−5 (9)]	16 (6)	*11 (5)*
ER positive (or ≥10 fmol/mg)	4127	10 845	19 (6)	36 (3)	*32 (3)*	13 (8)	23 (4)	*21 (3)*
ER unknown	2401	7153	12 (7)	26 (3)	*22 (3)*	8 (8)	17 (4)	*15 (3)*

EBCTG 1992, The Lancet 1992

ECOG 5188

- Premenopausal
- ER+
- Node +

	CAF	CAF + goserelin	CAF + goserelin + tam
9 year DFS	57%	60%	68%
9 year OS	70%	73%	76%

Davidson et al JCO 2005 23:5973

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

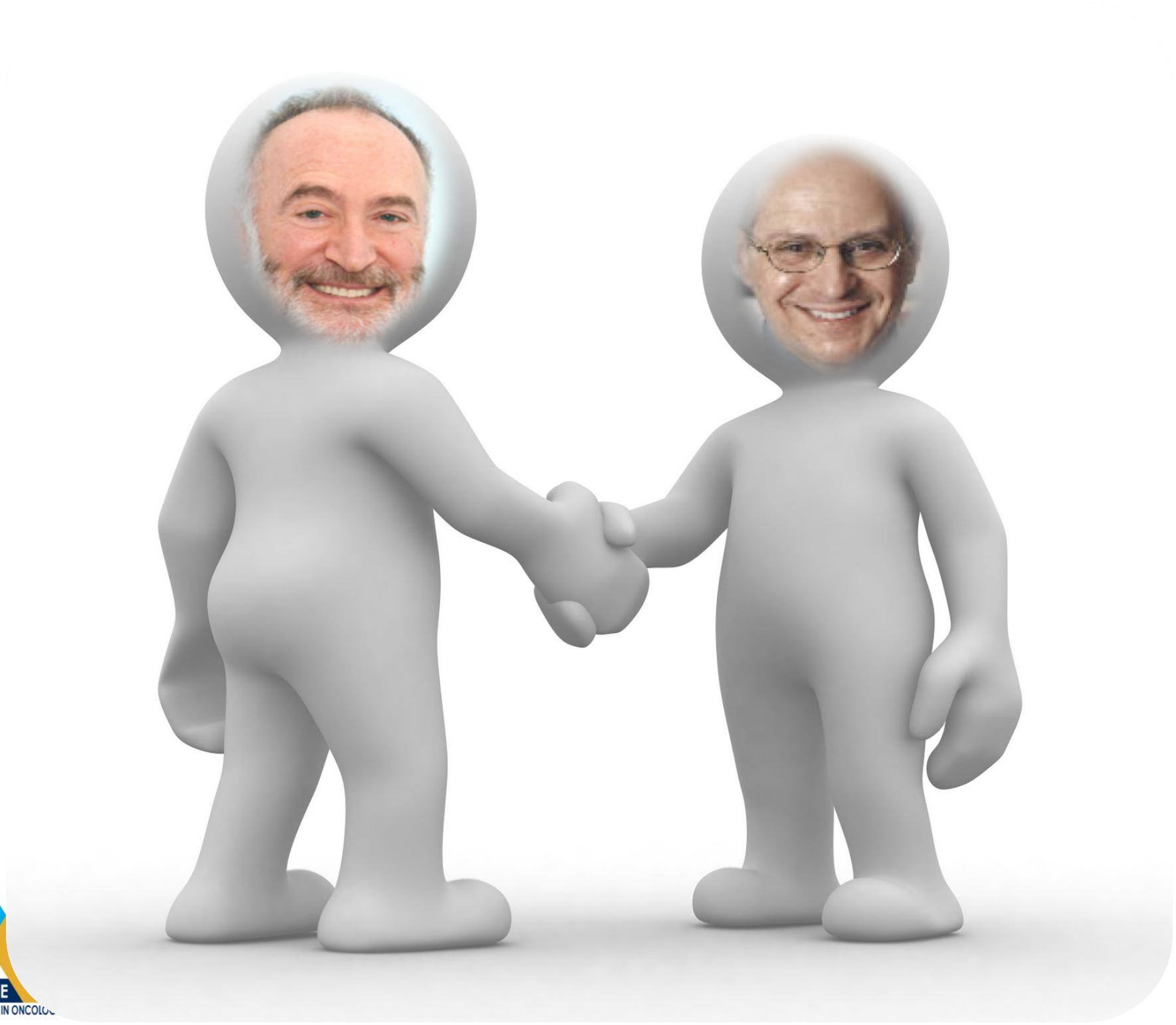
Randomized comparison of adjuvant TAM + OFS versus EXEMESTANE + OFS vs TAM alone in premenopausal women with hormone-receptor-positive (HR+) early breast cancer: The SOFT trial

IBCSG International Breast Cancer Study Group

BIG Breast International Group

NABCG The North American Breast Cancer Group

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY



ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

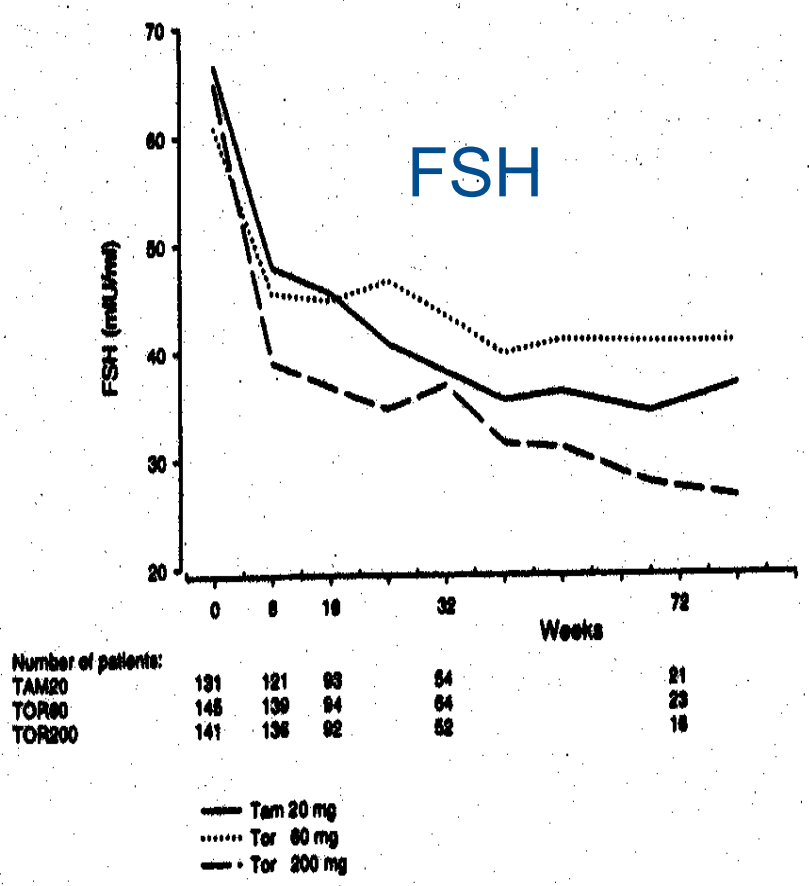
SOFT Eligibility

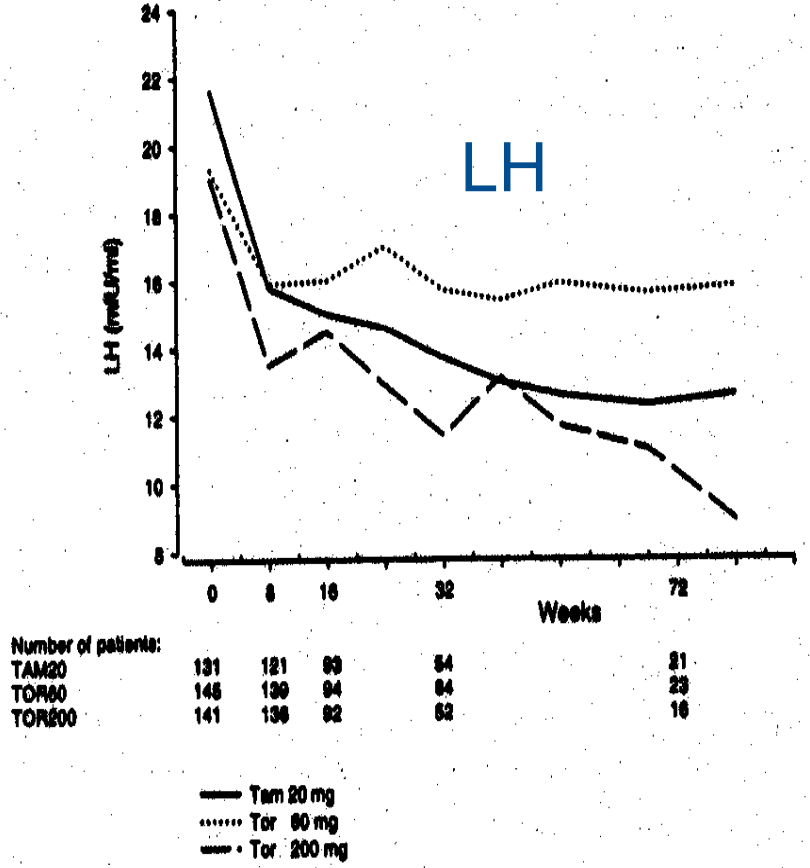
- Premenopausal women with HR+ (ER and/or PR $\geq$ 10%) invasive breast cancer confined to breast +/- axillary nodes
- Randomized $\leq$ 12 weeks from surgery if no chemotherapy
- Women who received prior (neo)adjuvant chemotherapy required premenopausal E_2 level within 8 months of completion; could receive prior tamoxifen

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Postmenopausal Breast Cancer Pts

Tamoxifen decreases FSH and LH measurements





Ellmen Br Ca Res Treat 2003

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Treatments

Treatment for 5 years from randomization with:

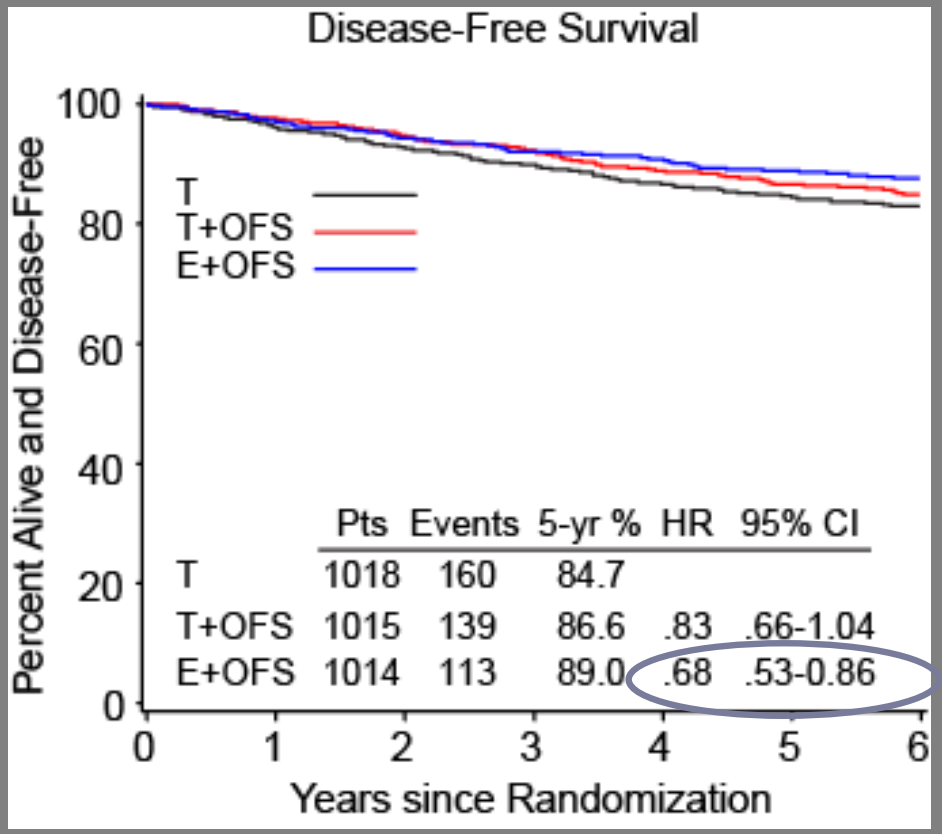
- Tamoxifen 20 mg po daily, or
- Tamoxifen 20 mg po daily + OFS, or
- Exemestane 25 mg po daily + OFS

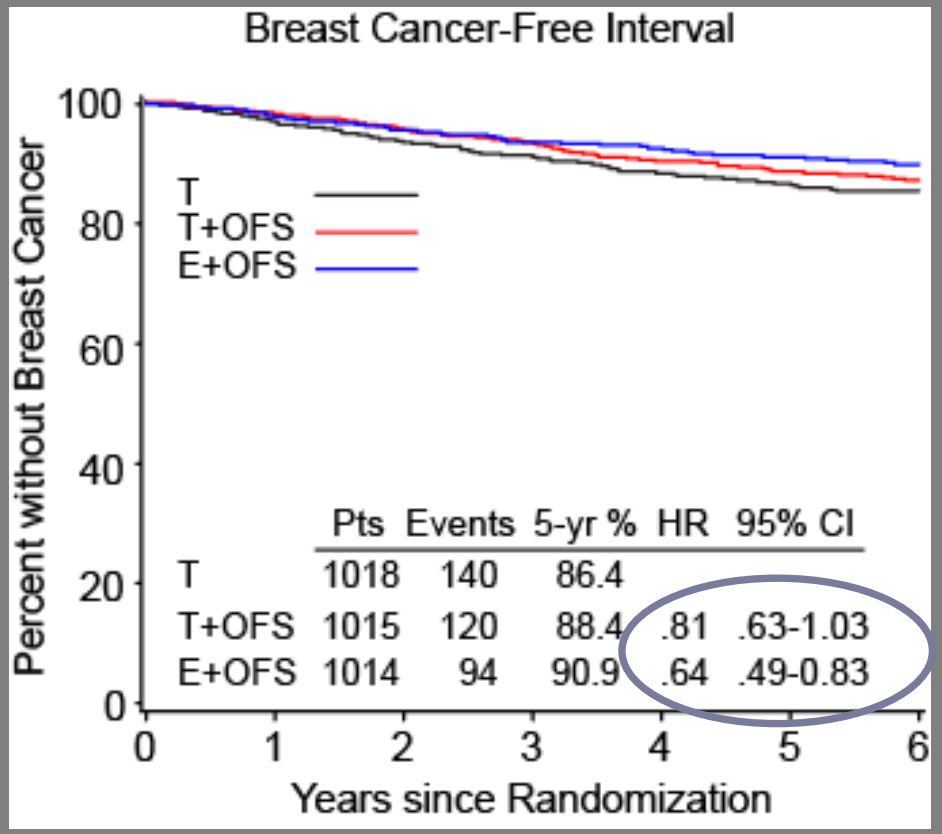
OFS (if assigned) by choice of

- GnRH agonist triptorelin (3.75 mg IM q 28days)
- Bilateral oophorectomy
- Ovarian irradiation

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

SOFT RESULTS



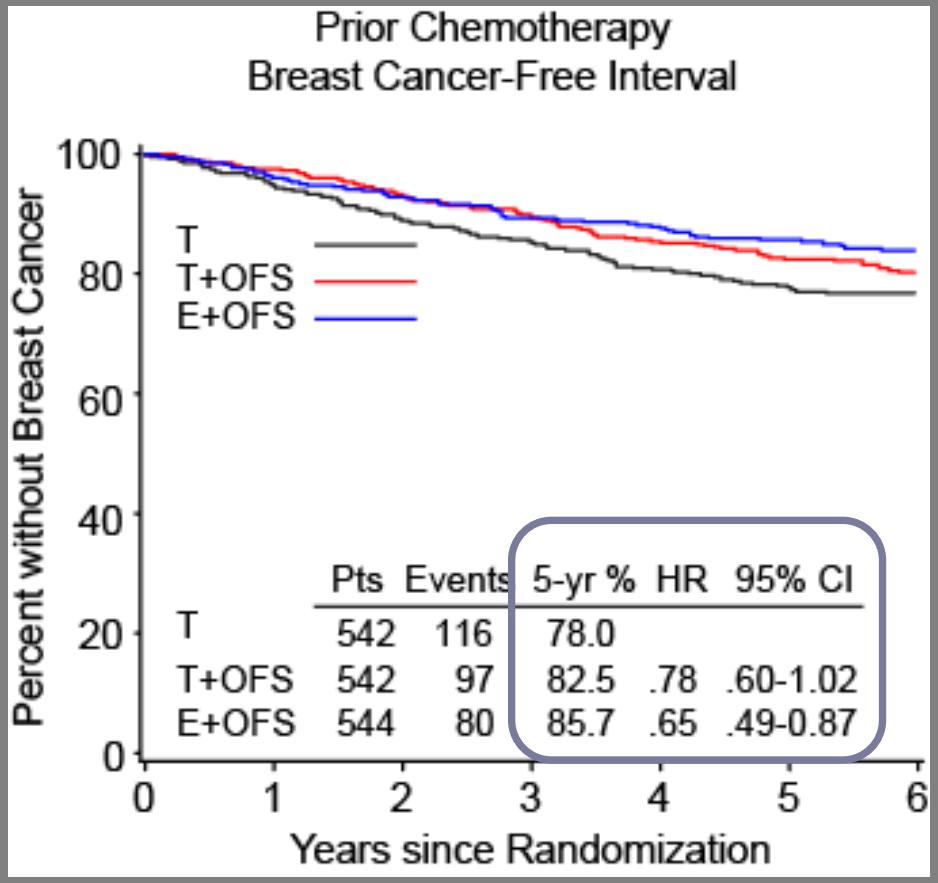


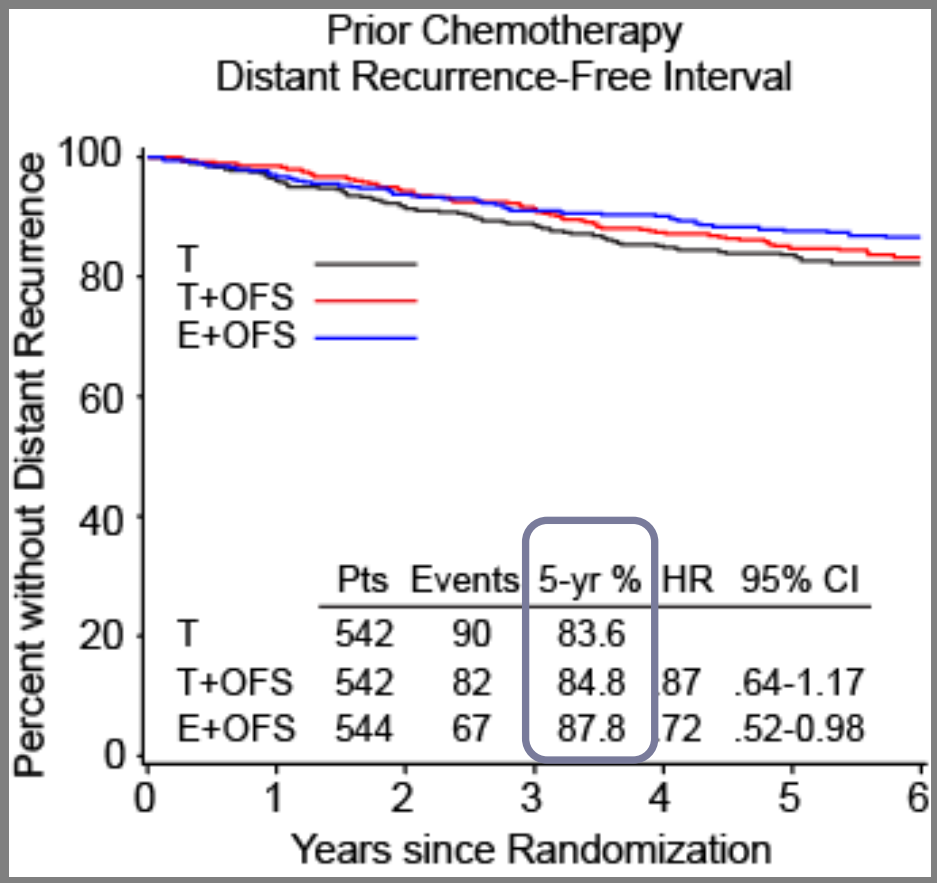
T+OFS v T: 19% relative reduction in BC recurrence, p=0.09

E+OFS v T: 36% relative reduction in BC recurrence

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Premenopausal after Prior Chemotherapy



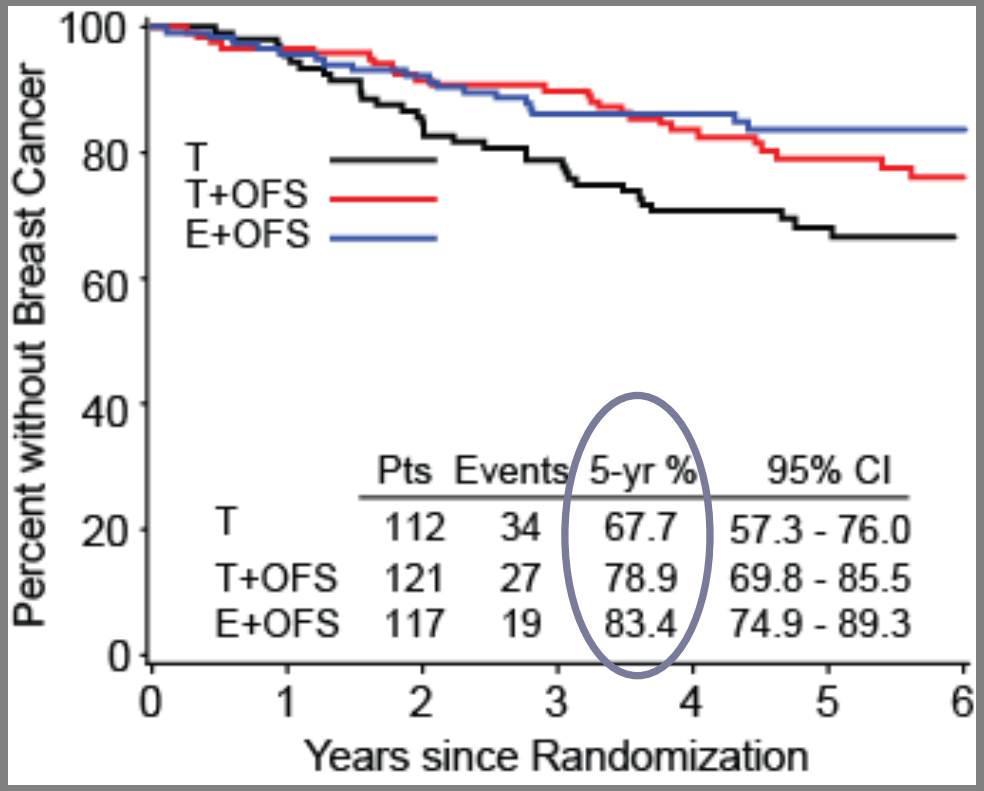


T+OFS v T: Absolute improvement in 5-yr BCFI of 4.5%

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

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

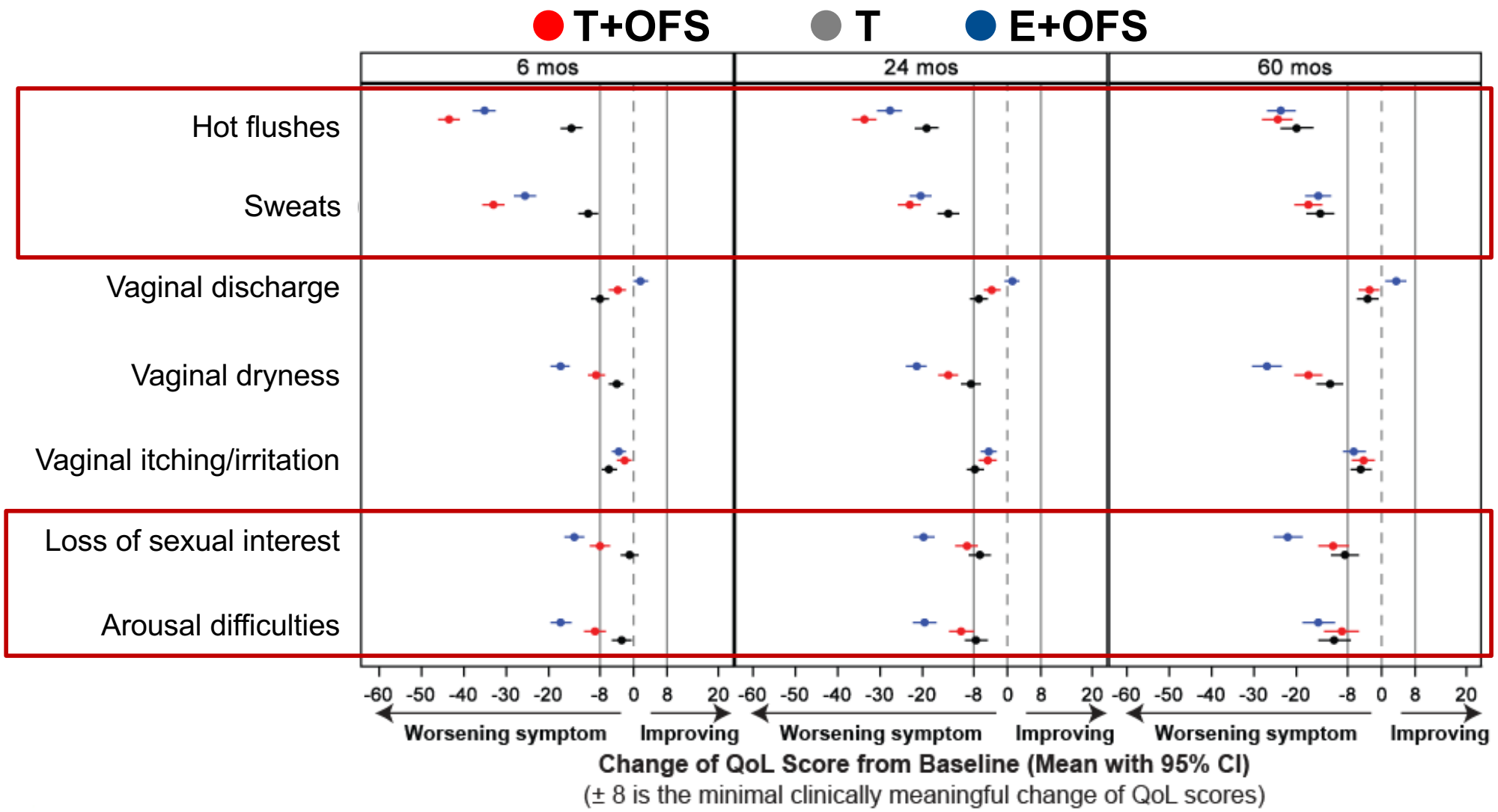
Women < 35 years of age



350 patients (11.5%) under age 35
94% received chemotherapy in this age group

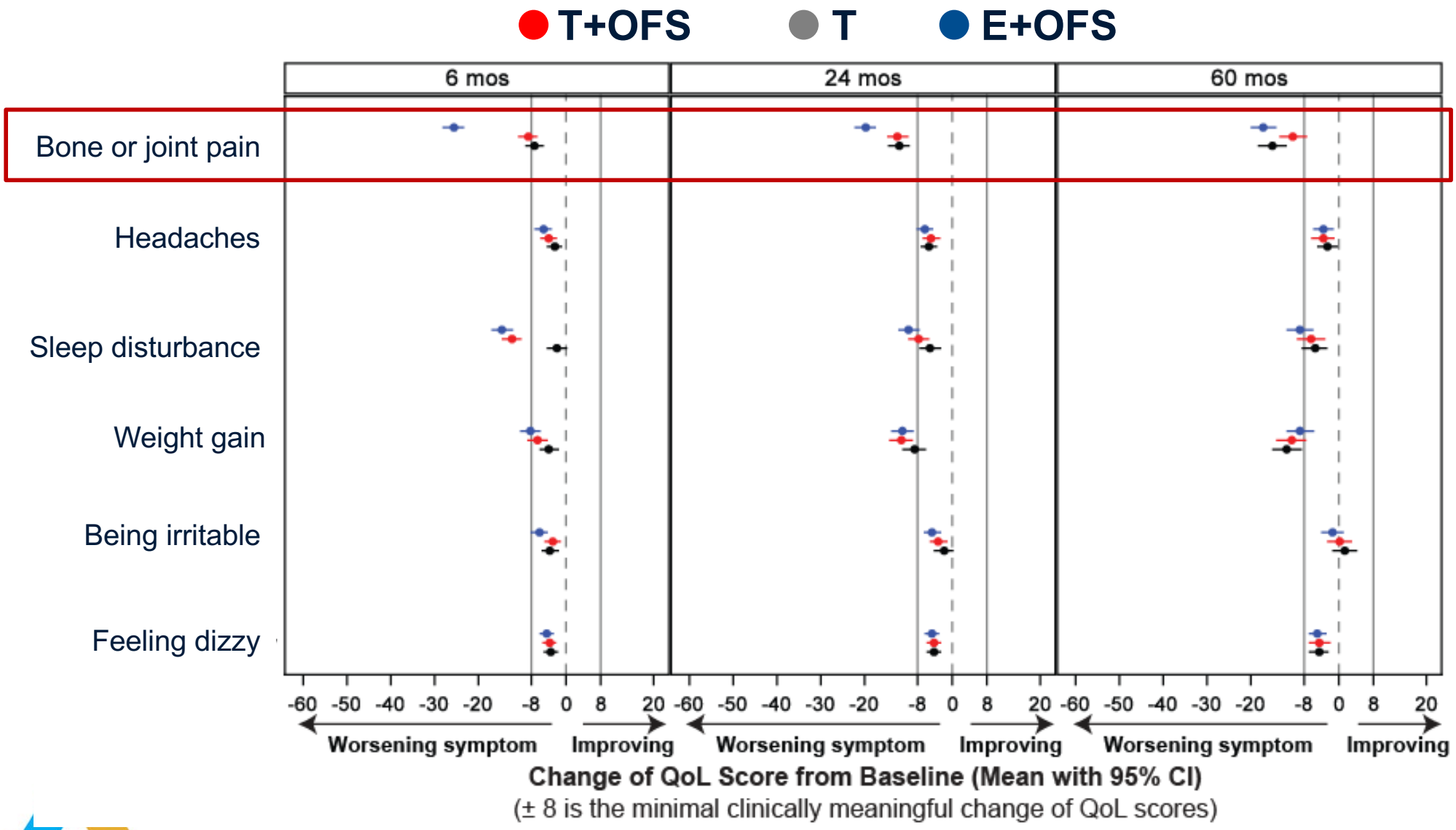
ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Treatment Effect: Symptoms



ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Treatment Effect: Symptoms



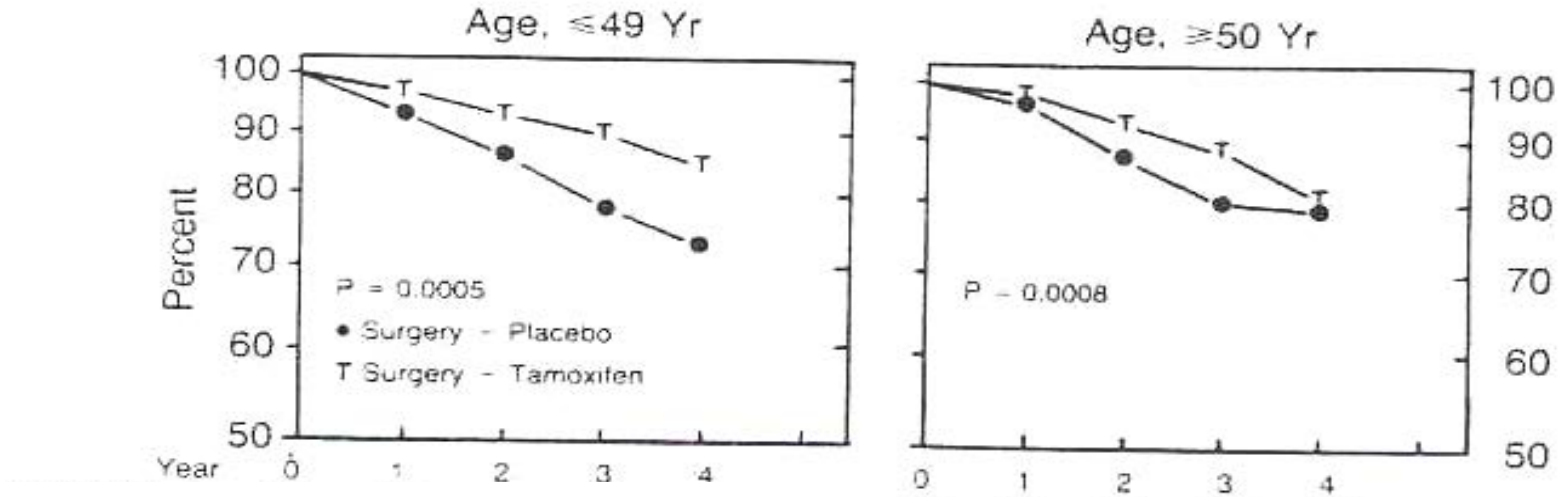
ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

TEXT & SOFT Long-Term Follow-Up

- Follow-up of women randomized in SOFT and TEXT is currently **not mature** and **is insufficient to assess survival outcomes**
- Extended follow-up benefits patients through vital research aims:
  - improve precision of the treatment effects on disease-free survival and recurrence
  - improve power to detect treatment effects on distant recurrence and overall survival endpoints
  - define associated late toxicities and side effects of early menopause.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

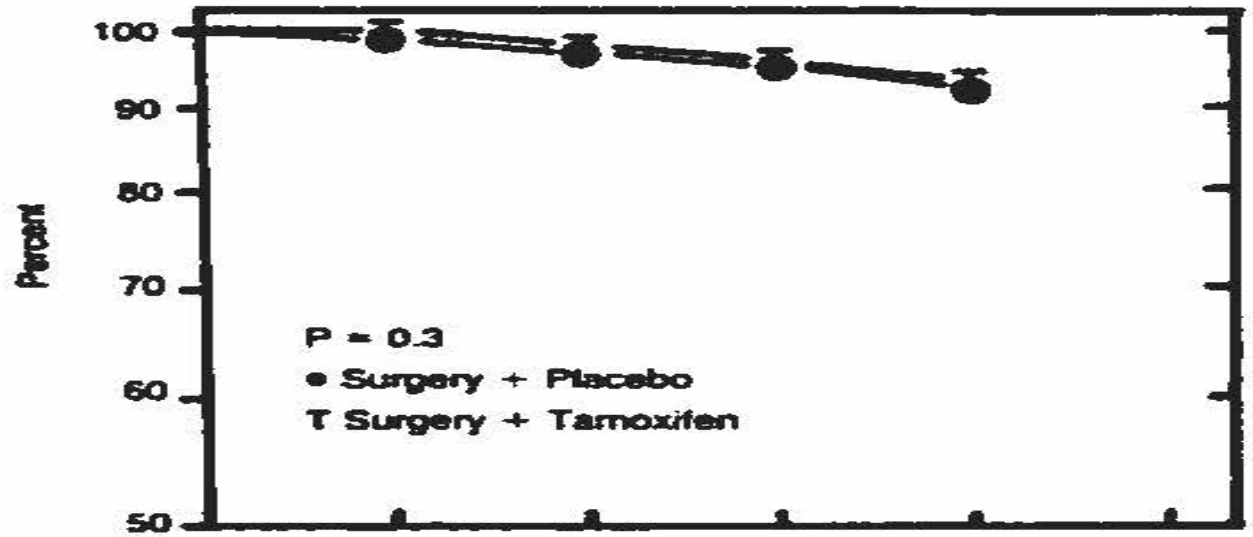
NSABP B-14: Tamoxifen vs. Placebo in Women With ER+ Node- Tumors



NEJM 320:479, 1989

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

NSABP B-14



Year	0	1	2	3	4
No. at Risk •	1326	1037	705	397	206
No. at Risk T	1318	1037	709	419	207
Odds Ratio		4.62	1.82	1.60	1.39
P Value		0.008	0.05	0.06	0.1

• 54 Deaths, T 44 Deaths

Figure 3. Overall Survival According to Treatment Group.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

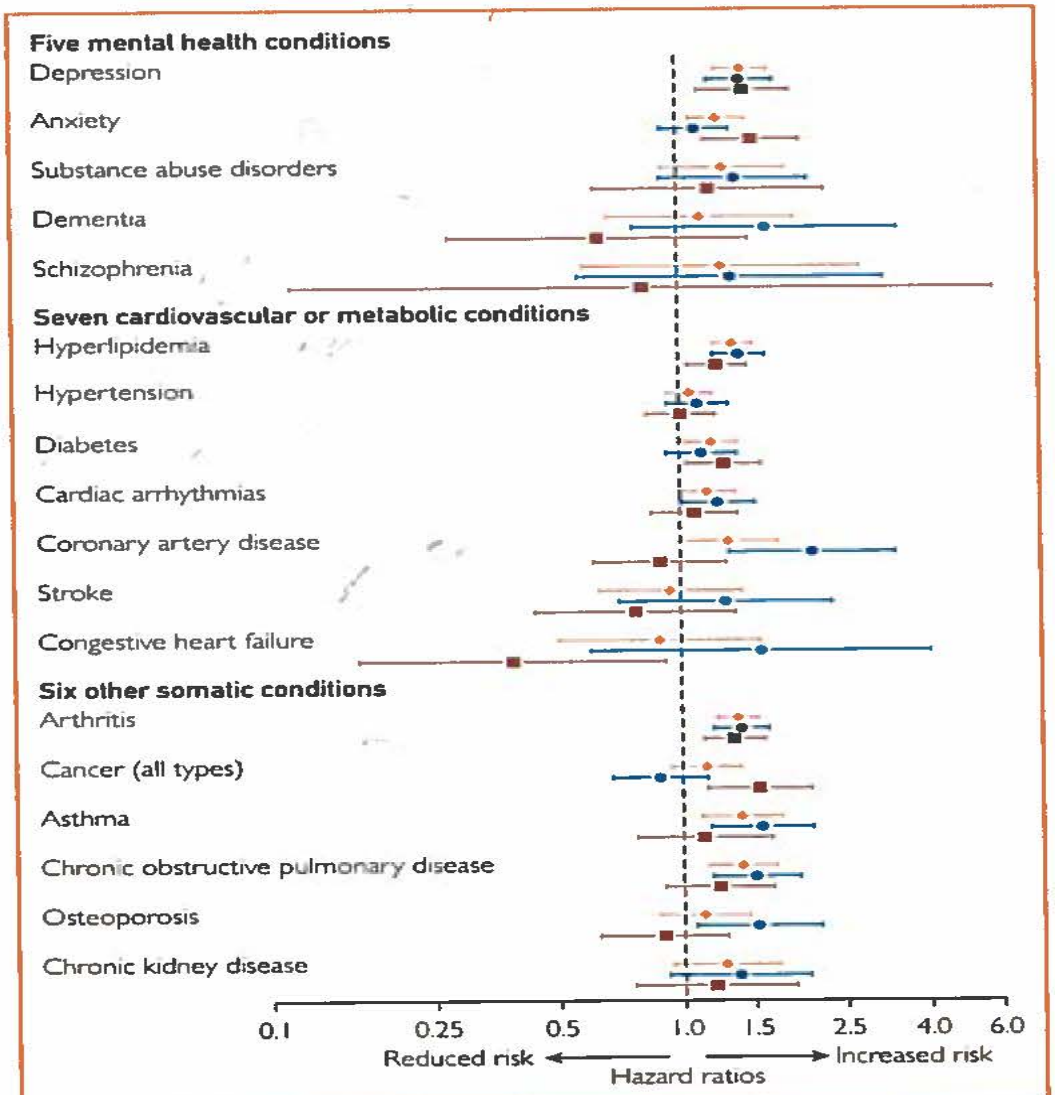
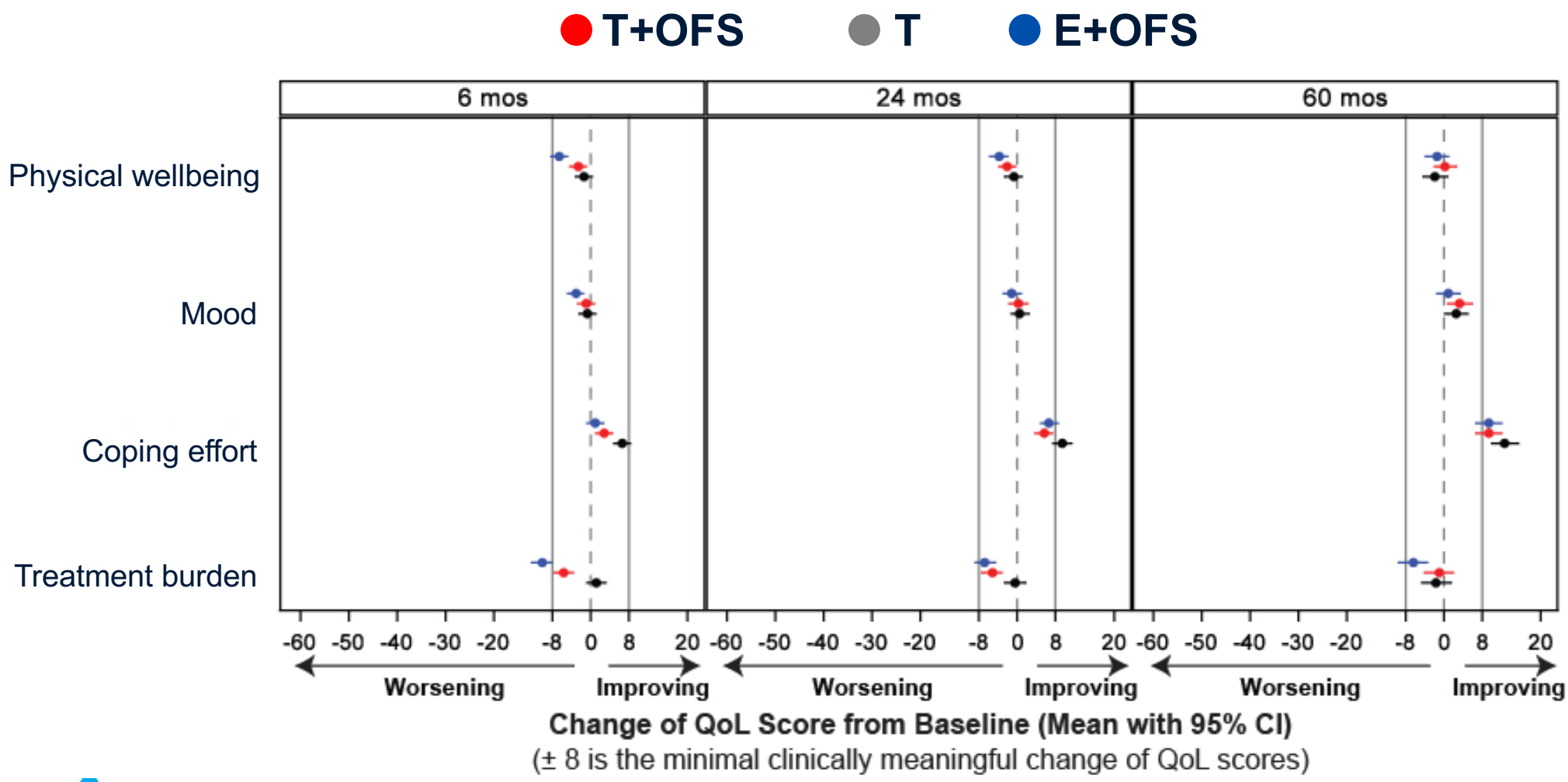


FIGURE 2. Adjusted hazard ratios and 95% CIs for each of the 18 chronic conditions considered separately. Analyses are presented as overall (orange diamonds) and in strata by age at oophorectomy (blue circles for age ≤45 years and brown squares for age 46-49 years). The hazard ratios were calculated using Cox proportional hazards models with age as the time scale and were adjusted for the 18 conditions present at index date, for education, race/ethnicity, body mass index, cigarette smoking, age, and for calendar year using inverse probability weights.

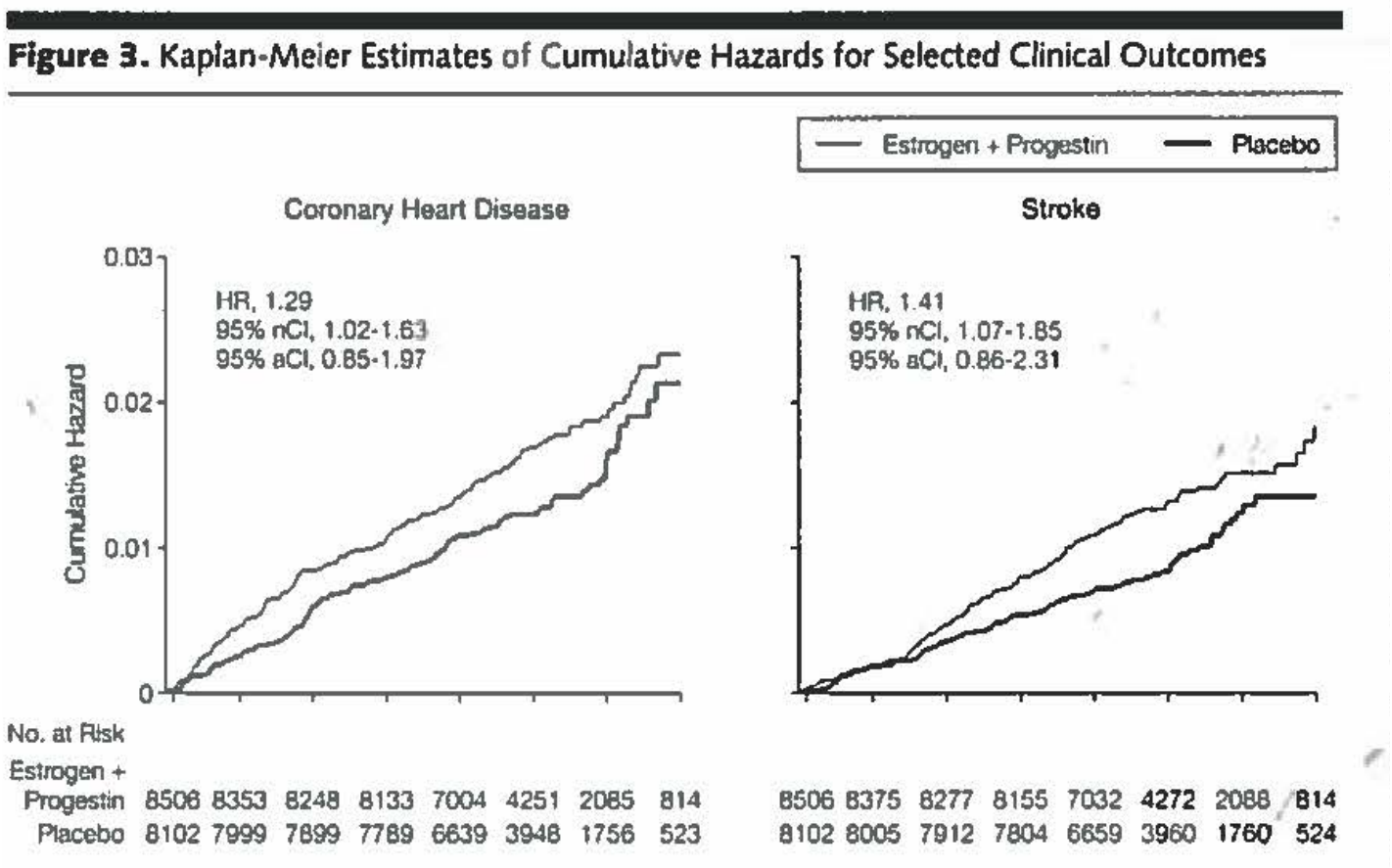
- Rocca et al: Accelerated Accumlation of Multimorbidity after Bilateral Oophorectomy: A Population-Based Cohort Study. Mayo Clin Proc 2016
- Premenopausal women undergoing bilat oophorectomy vs age-matched controls
- BRCA and mutation carriers excluded
- “an elective intervention that causes increased overall mortality and accelerated aging in the entire body is simply not an ethical option” (diff pub of authors)

Treatment Effect: Global QoL



ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Women's Health Initiative



JAMA 288:321, 2002

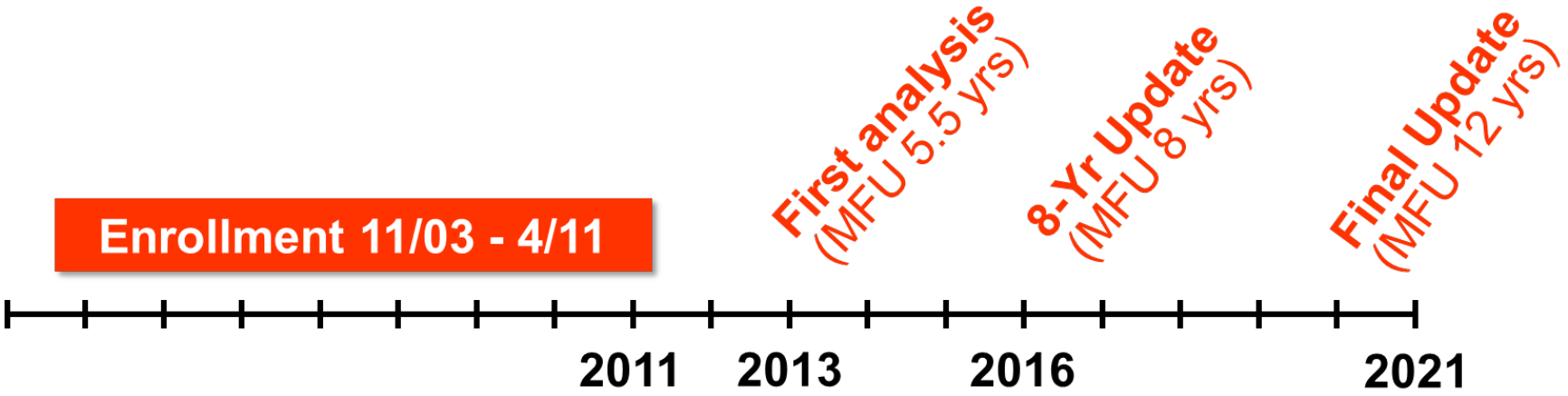
ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

LTFU Data Collection Plans

- Continue yearly visits through Dec 2020
- Annual data collection includes:
  - ✓ Invasive first and subsequent recurrence
  - ✓ Second non-breast malignancy (e.g., endometrial cancer)
  - ✓ In situ cancers
  - ✓ Survival
  - ✓ Late AEs (e.g., cardiovascular, bone fractures)
  - ✓ GYN procedures
  - ✓ Extended adjuvant therapy
  - ✓ Weight
  - ✓ Performance status
  - ✓ Menstrual status
  - ✓ Pregnancy attempts

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

LTFU Analysis/Reporting Plans



- **8-Year update: 6 yr minimum and 8 yr median FU (all patients completed treatment as of Apr 2016)**
- **Final update Dec 2020: 10 yr minimum and 12 yr median FU, roughly doubling the numbers of endpoints events since the first report**
- **Further financial support is critical to reach the final update**

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

SOFT Additional Funding

- NCI approved additional payment for LTFU for SOFT/TEXT patients
- Single payment to cover at least 10 years f/u total for each patient: five additional years @$50 per year or $250 per patient
- Once a patient reaches 6 years since enrollment, only yearly submission of the Follow-Up (E) Form is required.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

SOFT Long term followup

- This dataset will never be replicated
- Please work with your data management staff to prioritize getting the data in

- Thanks!

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY