Lo Studio SOFT

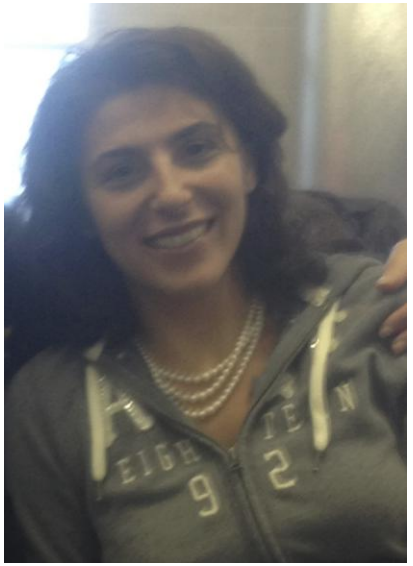
Alessandra Fabi

Valter Torri
"PM"

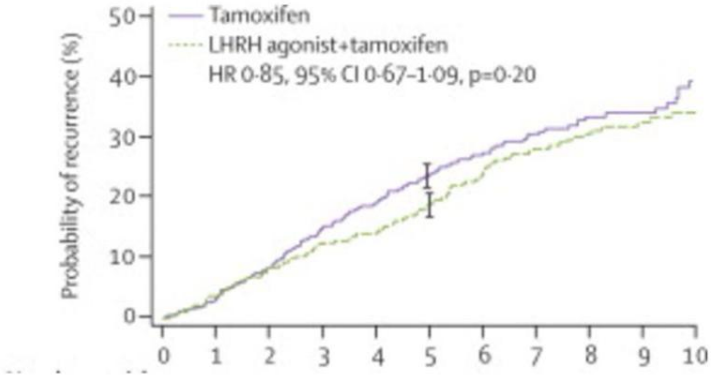
"Giudici"

"Testimone"

"Persona informata sui fatti"

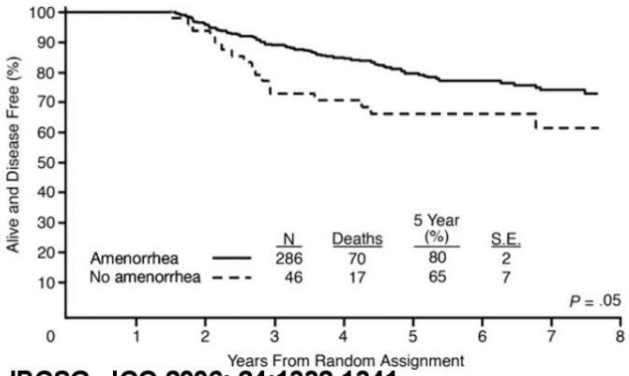


The Paradox of Tamoxifen and OFS



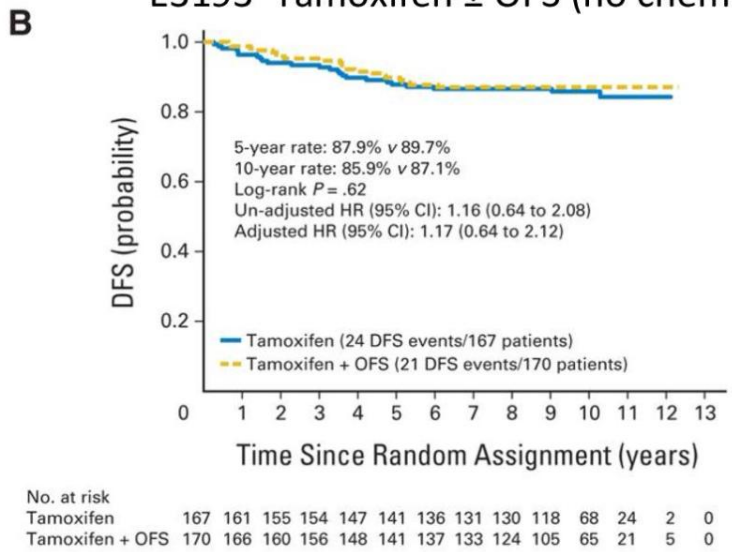
Cuzick J, et al. Lancet 2004;369:1711

IBCSG 13-93



IBCSG, JCO 2006; 24:1332-1341

E3193 Tamoxifen ± OFS (no chemo)

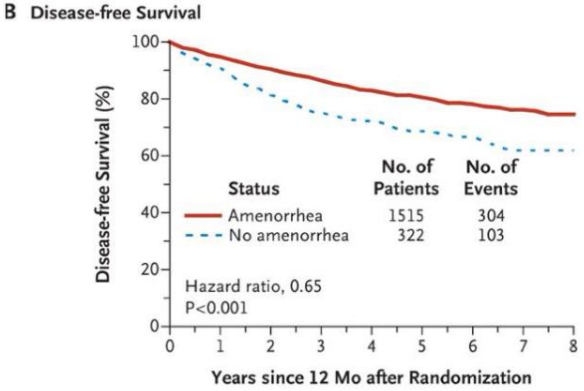


No. at risk

Tamoxifen	167	161	155	154	147	141	136	131	130	118	68	24	2	0
Tamoxifen + OFS	170	166	160	156	148	141	137	133	124	105	65	21	5	0

Tevaarwerk A J et al. JCO 2014;32:3948-3958

NSABP B-30



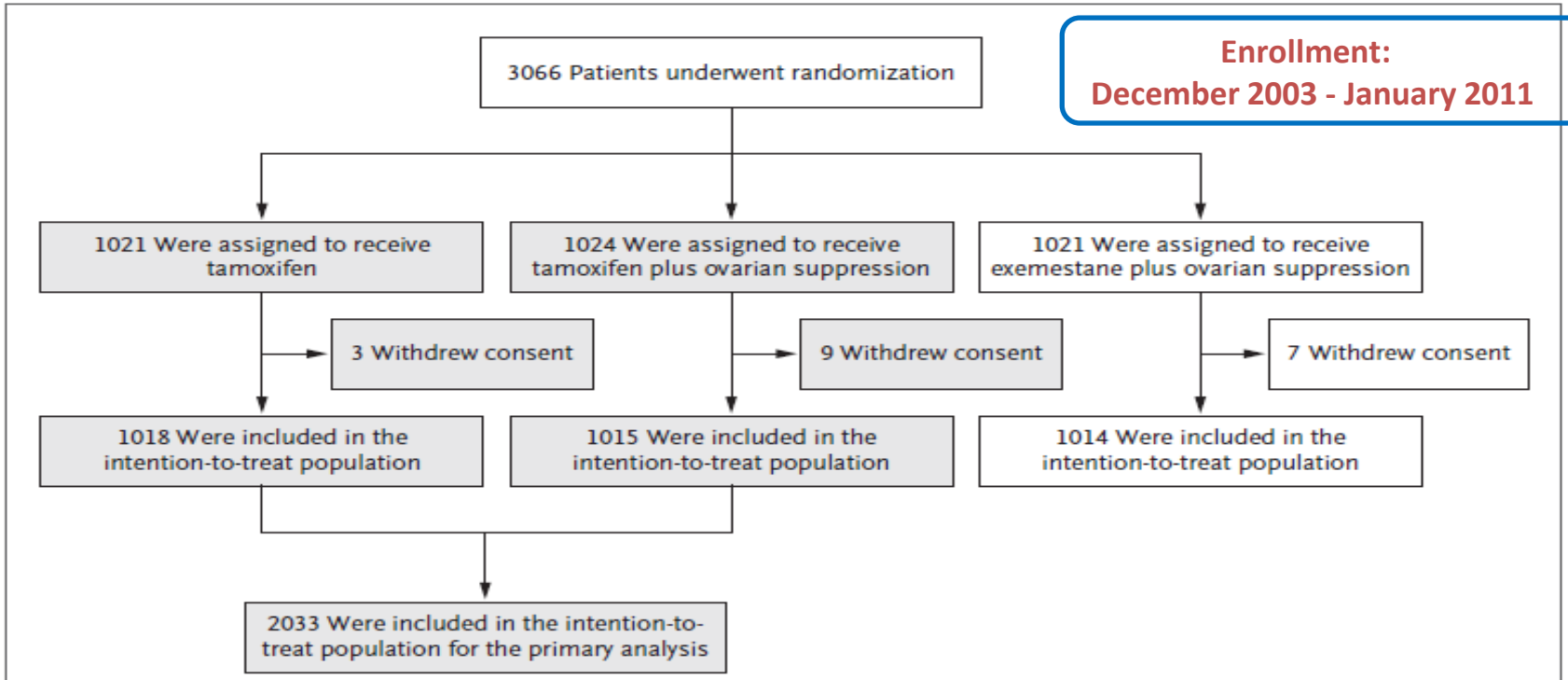
Swain SM et al. N Engl J Med 2010;363:2268-2270.

Burstein SABCS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer



Enrollment:
December 2003 - January 2011

SABCS orally presentation Thursday 11 Dec 2014 hr: 11:00

Published 11 Dec 2014

Francis et al, NEJM 2015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Portugal
Serbia
Slovenia
South Africa
Spain
Sweden
Switzerland
Turkey
United Kingdom
United States

Statistical Considerations

- ITT analysis, stratified by chemo (yes/no), nodal status (-/+)
- Original plan for three pair-wise comparisons to detect HR=0.75 with analysis after 783 DFS events (α=0.0167)
- Enrolled patients older, lower risk, better DFS than anticipated
- Protocol amendment 2011 (before efficacy data)

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Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

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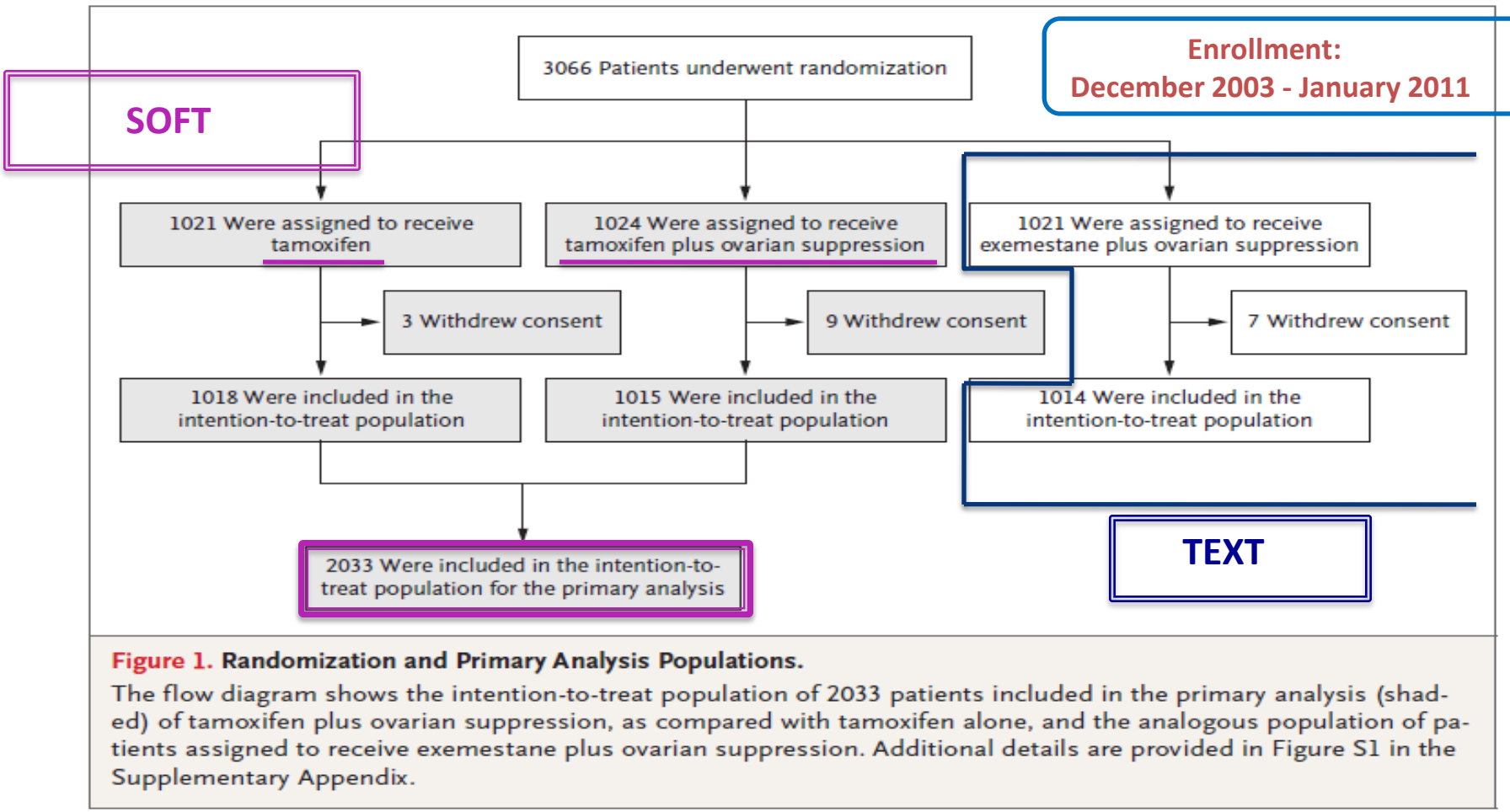

Figure 1. Randomization and Primary Analysis Populations.

The flow diagram shows the intention-to-treat population of 2033 patients included in the primary analysis (shaded) of tamoxifen plus ovarian suppression, as compared with tamoxifen alone, and the analogous population of patients assigned to receive exemestane plus ovarian suppression. Additional details are provided in Figure S1 in the Supplementary Appendix.

Francis et al, NEJM 2015

Statistical Considerations

- ITT analysis, stratified by chemo (yes/no), nodal status (-/+)
- Original plan for three pair-wise comparisons to detect HR=0.75 with analysis after 783 DFS events (α=0.0167)
- Enrolled patients older, lower risk, better DFS than anticipated
- Protocol amendment 2011 (before efficacy data)

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……to SOFT

Statistical Considerations Post-Amendment

- Primary analysis: T+OFS vs T
- After median follow-up of at least 5 years
- Anticipated 186 DFS events, power 80% for HR=0.665 comparing T+OFS vs T (two sided α=0.05)
- Analysis according to use of prior chemotherapy (no/yes) was prospectively planned
- E+OFS vs T became secondary objective

Endpoints

Primary

- Disease – Free Survival
  - Invasive recurrence (local, regional, distant)
  - Invasive contralateral breast cancer
  - Second non-breast invasive malignancy
  - Death without prior cancer event

Secondary

- Breast cancer-free interval
- Distant recurrence-free interval
- Overall Survival

SOFT Study

- Mayor inclusion criteria: premenopausal status, operable breast cancer, positivity for ER e/o PgR (**>10%**).

- Ovarian suppression was achieved by choice of triptorelin [triptorelin acetate] at a dose of 3.75 mg administered by means of im injection every 28 days, bilateral oophorectomy, or bilateral ovarian irradiation

- The patients choice was farmacological in **80.7%** of patients.

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

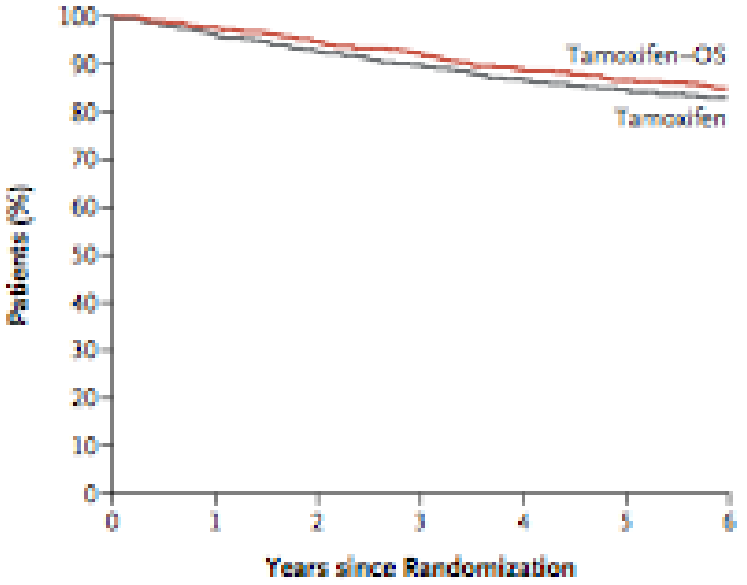
Table 1. Characteristics of Patients in the Primary Analysis, Overall and According to Chemotherapy Cohort.*

Characteristic	No Chemotherapy (N=949)	Prior Chemotherapy (N=1084)	Overall (N=2033)
Age at randomization			
Median — yr	46	40	43
Distribution — no. (%)			
<35 yr	14 (1.5)	219 (20.2)	233 (11.5)
35–39 yr	78 (8.2)	309 (28.5)	387 (19.0)
40–49 yr	702 (74.0)	522 (48.2)	1224 (60.2)
≥50 yr	155 (16.3)	34 (3.1)	189 (9.3)
Lymph-node status — no. (%)			
Negative	861 (90.7)	463 (42.7)	1324 (65.1)
Positive	88 (9.3)	621 (57.3)	709 (34.9)
Tumor size — no. (%)†			
≤2 cm	806 (84.9)	526 (48.5)	1332 (65.5)
>2 cm	136 (14.3)	513 (47.3)	649 (31.9)
Tumor grade — no. (%)‡			
1	389 (41.0)	151 (13.9)	540 (26.6)
2	483 (50.9)	523 (48.2)	1006 (49.5)
3	65 (6.8)	374 (34.5)	439 (21.6)
HER2-positive — no. (%)	40 (4.2)	196 (18.1)	236 (11.6)
Interval from surgery to randomization — mo			
Median	1.8	8.0	3.2
Interquartile range	1.2–2.4	5.8–10.3	1.7–8.33
Endocrine therapy before randomization — no. (%)§	47 (5.0)	475 (43.8)	522 (25.7)

Characteristic	Chemotherapy Stratum				Overall	
	No Chemotherapy		Prior Chemotherapy			
	All		All			
	N	%	N	%	N	%
Other[2]	10	1.1	12	1.1	22	1.1
Prior endocrine therapy[3]						
No	902	95.0	609	56.2	1511	74.3
Yes	47	5.0	475	43.8	522	25.7
HER2-targeted therapy						
Not HER2+	909	95.8	883	81.5	1792	88.1
HER2+, no therapy	39	4.1	61	5.6	100	4.9
HER2-targeted therapy	1	0.1	140	12.9	141	6.9

DFS: Primary Endpoints (all)
median FU 5.6 yrs

A Disease-free Survival

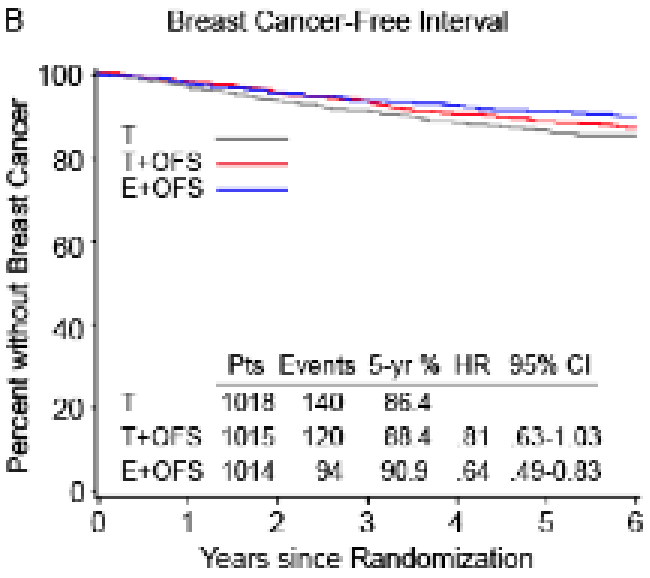


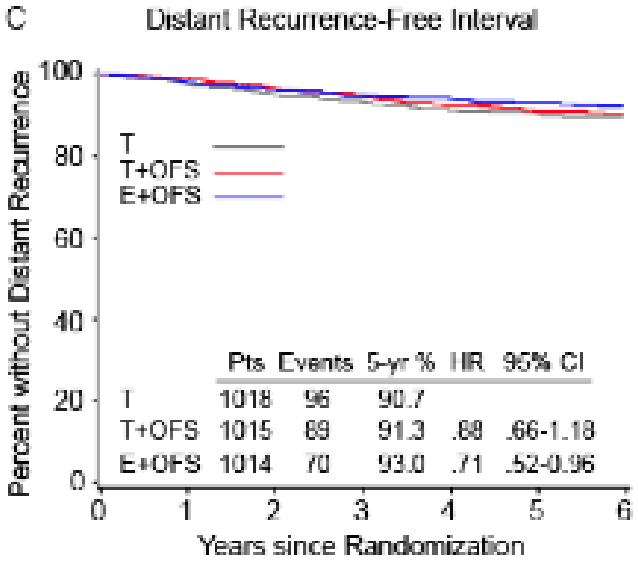
No. at Risk							
Tamoxifen	1018	951	895	847	719	525	309
Tamoxifen–OS	1015	966	927	878	742	556	349

	No. of Patients	No. of Patients with Event	5-Yr Rate %
Tamoxifen	1018	160	84.7
Tamoxifen–OS	1015	139	86.6

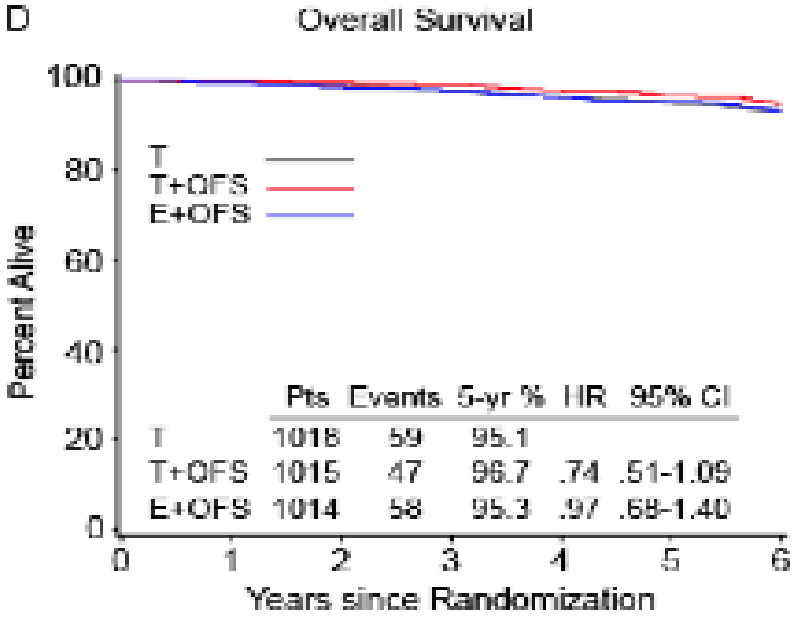
Hazard ratio for recurrence, second invasive cancer, or death, 0.83 (95% CI, 0.66–1.04)
P=0.10

Secondary Endpoints (all)





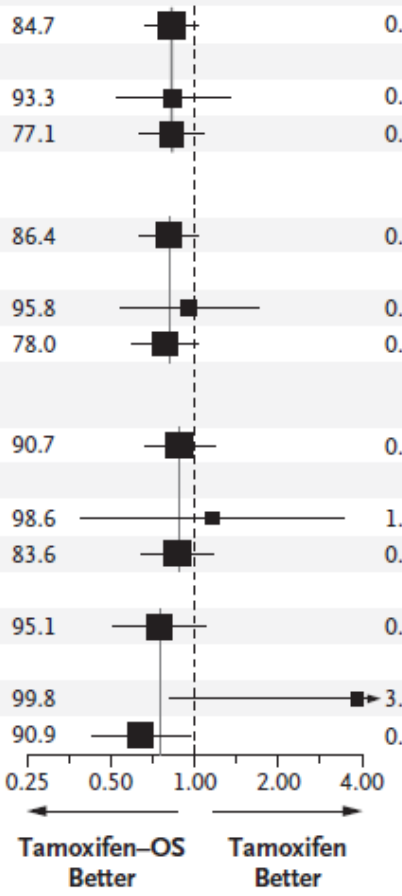
T+OFS v T: 19% relative reduction in BC recurrence, p=0.09
E+OFS v T: 36% relative reduction in BC recurrence, 5y BCFI >90%



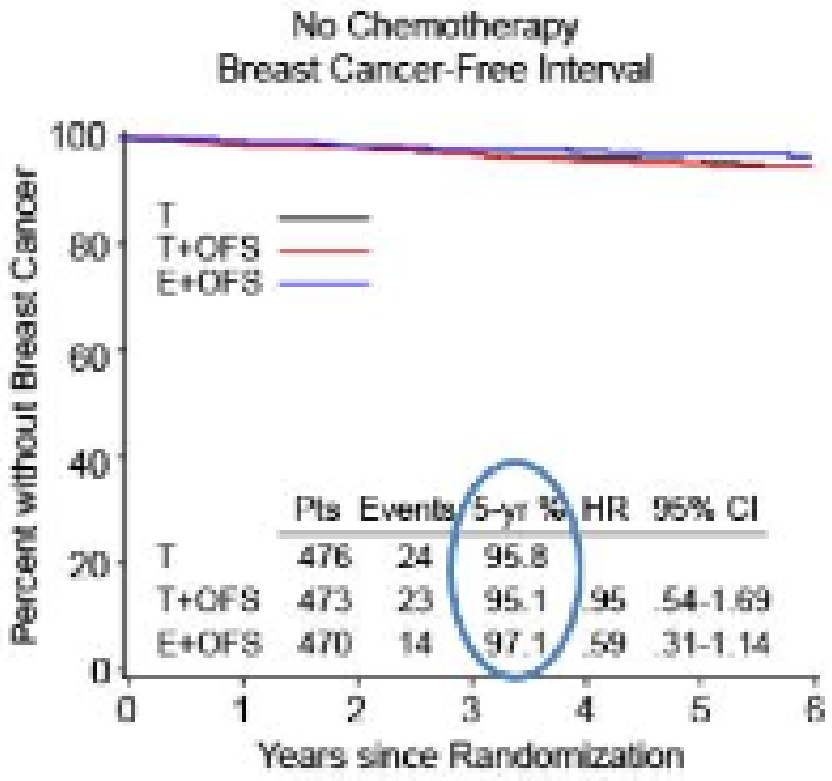
DFS – OS (all)
median FU 5.6 yrs

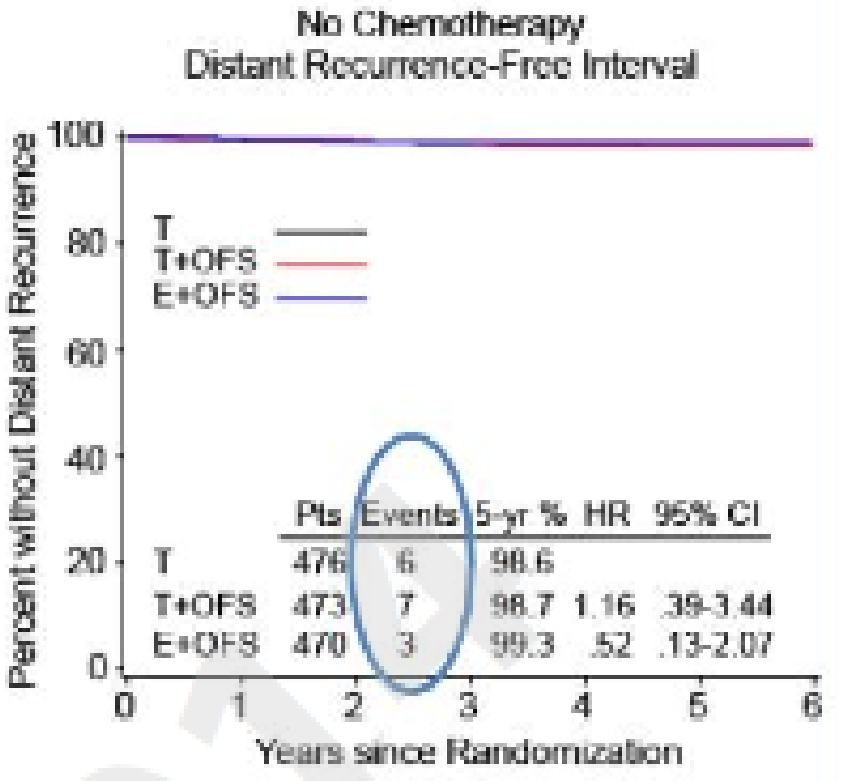
B End Points, Overall and According to Chemotherapy Cohort

End Point	No. of Patients		No. of Patients with Event		5-Yr Rate (%)		Hazard Ratio (95% CI)	P Value
	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen		
Disease-free survival								
All patients	1015	1018	139	160	86.6	84.7	0.83 (0.66–1.04)	0.10
Prior chemotherapy								
No	473	476	32	38	93.4	93.3	0.83 (0.52–1.34)	0.96
Yes	542	542	107	122	80.7	77.1	0.82 (0.64–1.07)	
Freedom from breast cancer								
All patients	1015	1018	120	140	88.4	86.4	0.81 (0.63–1.03)	0.09
Prior chemotherapy								
No	473	476	23	24	95.1	95.8	0.95 (0.54–1.69)	0.54
Yes	542	542	97	116	82.5	78.0	0.78 (0.60–1.02)	
Freedom from distant recurrence								
All patients	1015	1018	89	96	91.3	90.7	0.88 (0.66–1.18)	0.40
Prior chemotherapy								
No	473	476	7	6	98.7	98.6	1.16 (0.39–3.44)	0.62
Yes	542	542	82	90	84.8	83.6	0.87 (0.64–1.17)	
Overall survival								
All patients	1015	1018	47	59	96.7	95.1	0.74 (0.51–1.09)	0.13
Prior chemotherapy								
No	473	476	8	2	99.2	99.8	3.84 (0.81–18.08)	0.03
Yes	542	542	39	57	94.5	90.9	0.64 (0.42–0.96)	



Premenopausal No Chemotherapy





Adjustment for covariates – DFS, stratified according to receipt or not receipt CT and node status

Multivariable Cox proportional-hazards model

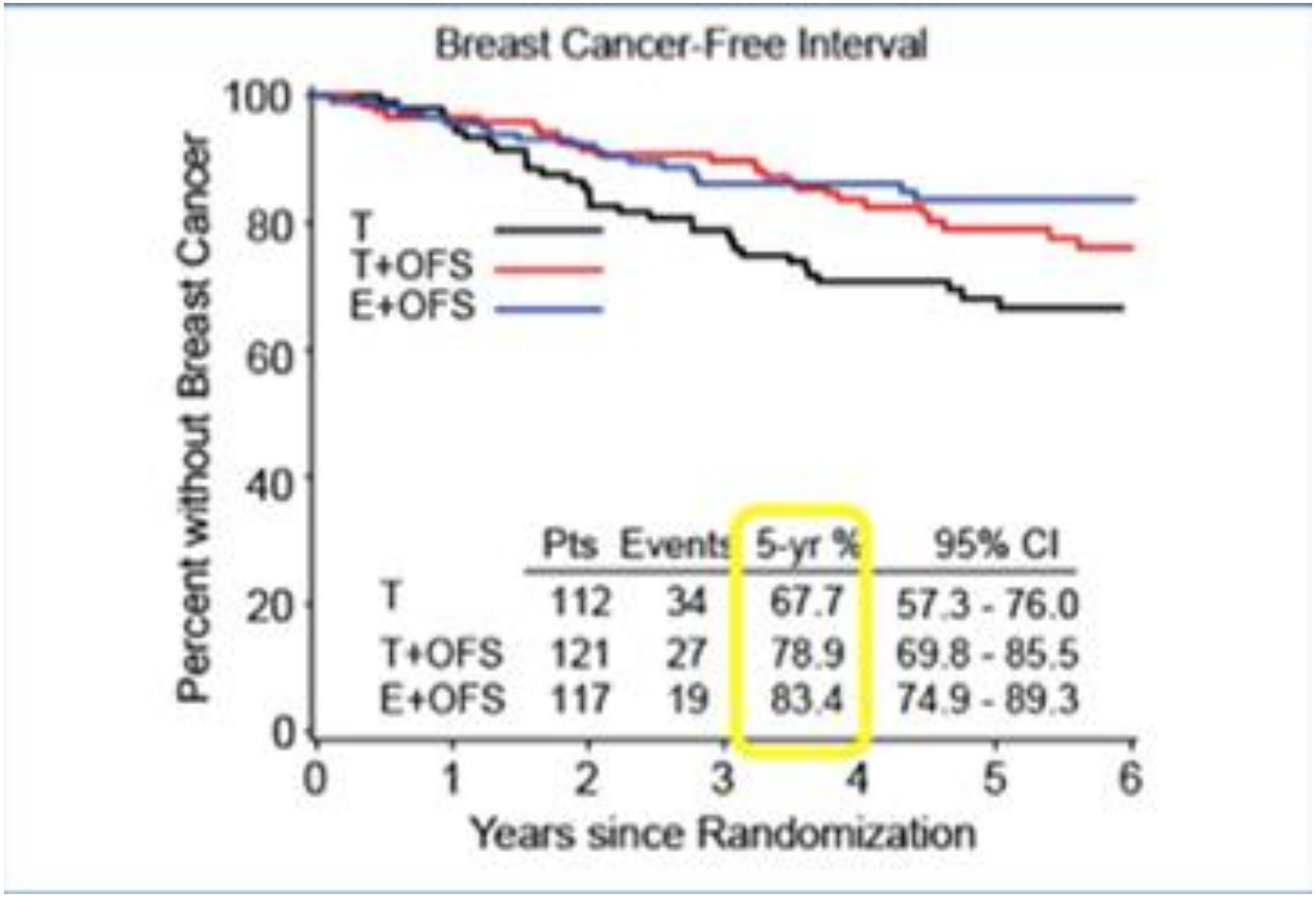
Parameter		Parameter Estimate	SE	Hazard Ratio	95% CI	Wald χ^2 (df)	P-Value (df)[1]
Treatment assignment	*T+OFS vs. T*	*-0.25*	*0.12*	*0.78*	*(0.62, 0.98)*	*4.6 (1)*	*0.03*
Age at randomization	<35	(ref)	-	-	-	13.4 (4)	<0.01
	35-39	-0.34	0.17	0.71	(0.50, 1.00)		
	40-44	-0.51	0.18	0.60	(0.42, 0.85)		
	45-49	-0.54	0.20	0.58	(0.39, 0.87)		
	50+	-0.02	0.25	0.98	(0.60, 1.61)		
Hormone receptor status	ER+ / PgR+	(ref)	-	-	-	6.2 (3)	0.10
	ER+ / PgR-	0.30	0.18	1.35	(0.96, 1.90)		
	ER- / PgR+	0.54	0.27	1.72	(1.00, 2.94)		
	Other	-0.05	0.46	0.95	(0.39, 2.33)		
No. nodes positive[2]	N 0	-	-	-	-	9.1 (1)	<0.01
	N+ 1-3	(ref)	-	-	-		
	N+ 4+	0.50	0.17	1.65	(1.19, 2.30)		
Tumor size	<1cm	(ref)	-	-	-	14.4 (4)	<0.01
	1-2cm	-0.32	0.20	0.73	(0.49, 1.08)		
	>2-5cm	-0.07	0.21	0.93	(0.61, 1.42)		
	>5cm	0.35	0.28	1.42	(0.83, 2.45)		
	Unknown	0.49	0.32	1.64	(0.87, 3.10)		
Tumor grade	1	(ref)	-	-	-	16.7 (3)	<0.001
	2	0.38	0.18	1.47	(1.02, 2.11)		
	3	0.72	0.20	2.06	(1.39, 3.06)		
	Unknown	-0.20	0.46	0.82	(0.33, 2.00)		
Local-regional therapy	Mastectomy, no RT	(ref)	-	-	-	3.3 (3)	0.35
	Mastectomy + RT	0.08	0.19	1.08	(0.74, 1.57)		
	BCS + RT	-0.16	0.16	0.85	(0.62, 1.17)		
	Other	-0.85	1.02	0.43	(0.06, 3.15)		
HER2-targeted therapy	Not HER2+	(ref)	-	-	-	5.3 (2)	0.07
	HER2+, no therapy	0.13	0.24	1.14	(0.71, 1.83)		
	HER2-targeted therapy	-0.50	0.23	0.61	(0.39, 0.95)		

T+OFS significantly reduce hazard of recurrence, second invasive cancer or death

All Women < 35yr

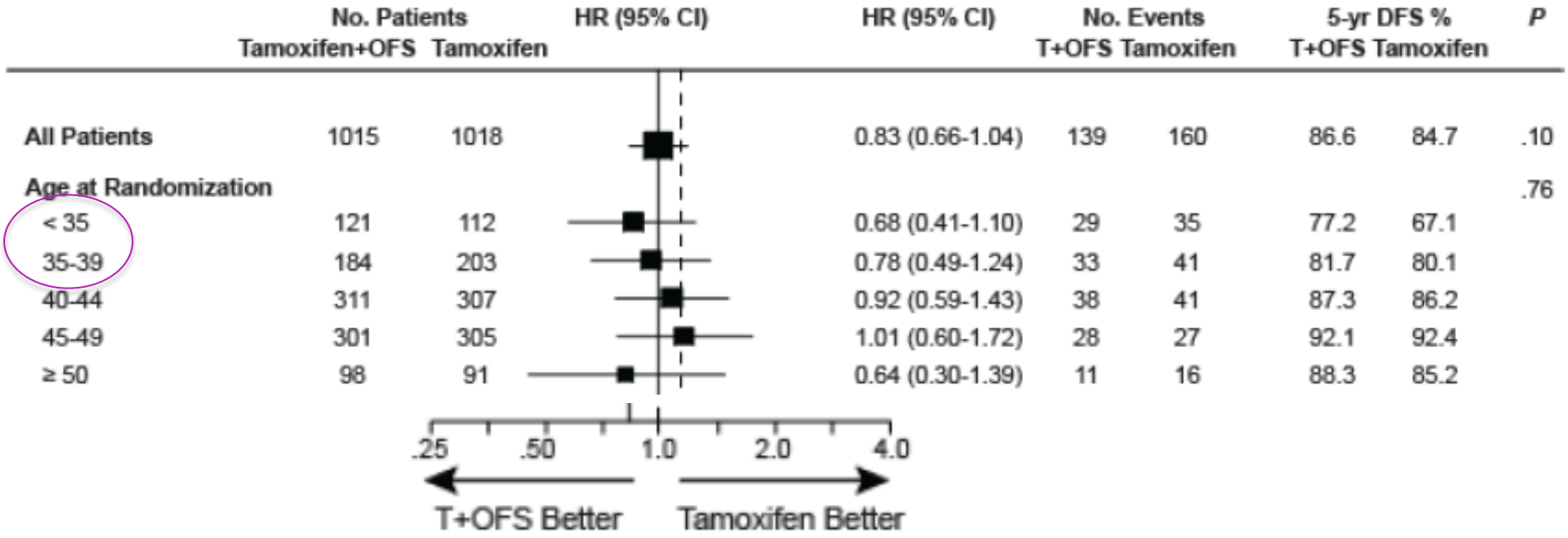
350 patients (11.5% of total pts)

94% received chemotherapy



Tamoxifen alone: 1 in 3 had further breast cancer within 5 yrs
Exemestane+OFS : 1 in 6 had further breast cancer within 5 yrs

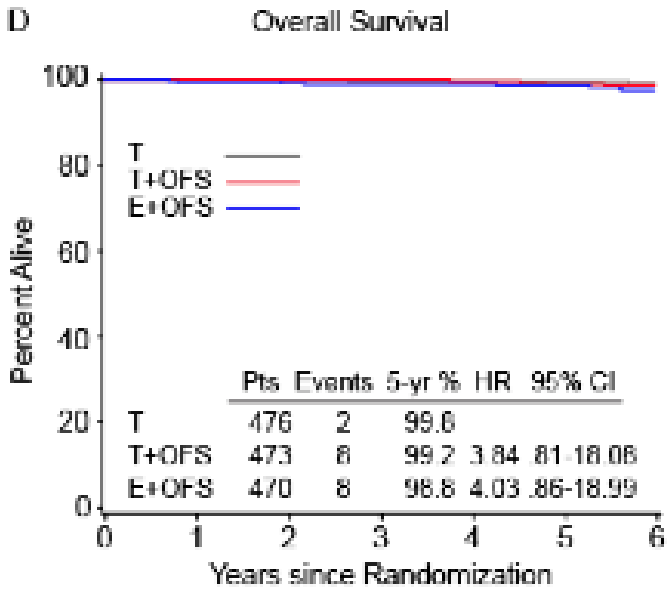
This article was published on December 11 2014, at NEJM.org.



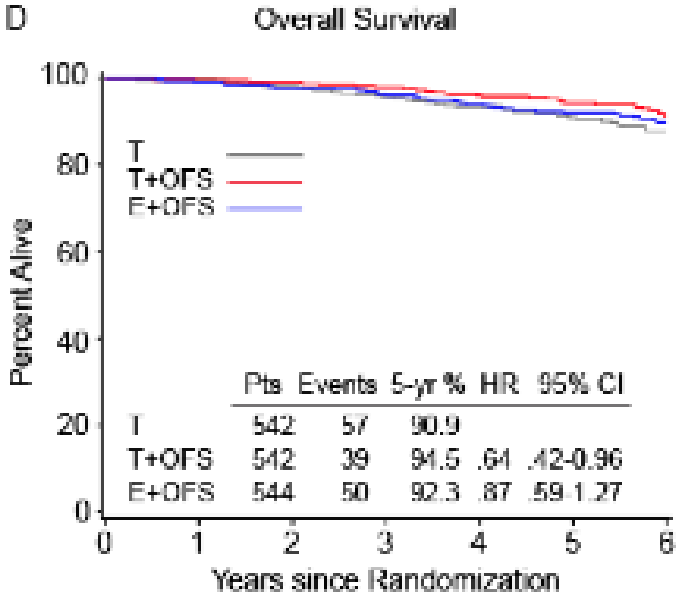
"women younger than 35 years of age, breast cancer recurred within 5 years in approximately one third of the patients assigned to receive tamoxifen alone but in one fifth of those assigned to receive tamoxifene plus ovarian suppression"

Overall Survival

No Chemotherapy



Prior Chemotherapy



90% of the death

SOFT - Safety

Table 2. Key Targeted Adverse Events Reported during Follow-up, According to Treatment Assignment.*

Adverse Event	Tamoxifen (N=1006)				Tamoxifen plus Ovarian Suppression (N=1005)			
	Any Event		Grade 3 or 4 Event		Any Event		Grade 3 or 4 Event	
	no. of patients with event	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*
Hot flushes ☑	803	79.8 (77.2–82.3)	76	7.6 (6.0–9.4)	939	93.4 (91.7–94.9)	133	13.2 (11.2–15.5)
Depression ☑	469	46.6 (43.5–49.8)	38	3.8 (2.7–5.1)	522	51.9 (48.8–55.1)	44	4.4 (3.2–5.8)
Sweating	486	48.3 (45.2–51.4)	—	—	621	61.8 (58.7–64.8)	—	—
Insomnia ☑	466	46.3 (43.2–49.5)	29	2.9 (1.9–4.1)	575	57.2 (54.1–60.3)	46	4.6 (3.4–6.1)
Hypertension ☑	173	17.2 (14.9–19.7)	54	5.4 (4.1–6.9)	233	23.2 (20.6–25.9)	75	7.5 (5.9–9.3)
Musculoskeletal symptoms	694	69.0 (66.0–71.8)	63	6.3 (4.8–7.9)	755	75.1 (72.3–77.8)	55	5.5 (4.1–7.1)
Osteoporosis	124	12.3 (10.4–14.5)	1	0.1 (0.0–0.6)	201	20.0 (17.6–22.6)	3	0.3 (0.1–0.9)
Vaginal dryness	421	41.8 (38.8–45.0)	—	—	500	49.8 (46.6–52.9)	—	—
Decreased libido	427	42.4 (39.4–45.6)	—	—	477	47.5 (44.3–50.6)	—	—
Glucose intolerance†	18	1.8 (1.1–2.8)	3	0.3 (0.1–0.9)	35	3.5 (2.4–4.8)	14	1.4 (0.8–2.3)
Any targeted adverse event‡	959	95.3 (93.8–96.5)	238	23.7 (21.1–26.4)	989	98.4 (97.4–99.1)	315	31.3 (28.5–34.3)

* Data are for the 2011 patients in the safety population who received a protocol-assigned treatment (except for 3 patients who withdrew consent within 1 month after randomization and had no adverse-event data submitted). Targeted adverse events (22 events; see Table S6 in the Supplementary Appendix) and other adverse events of grade 3 or higher were categorized according to the *Common Terminology Criteria for Adverse Events*, version 3.0.[11] A dash indicates that grade 3 or 4 was not a possible grade for the specified adverse event. There was one targeted adverse event of grade 5 (cardiac ischemia or infarction in a patient randomly assigned to tamoxifen).

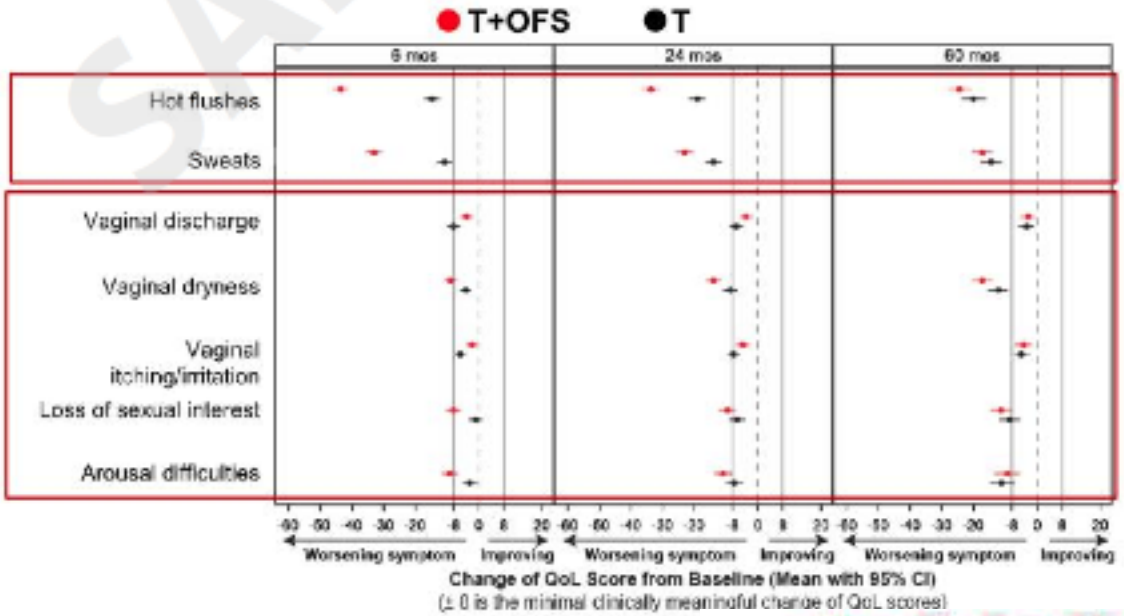
† Glucose intolerance (diabetes) was added as a targeted adverse event in 2011 and therefore may be underreported.

‡ The category of any targeted adverse event includes the 22 targeted adverse events summarized in Table S6 in the Supplementary Appendix.

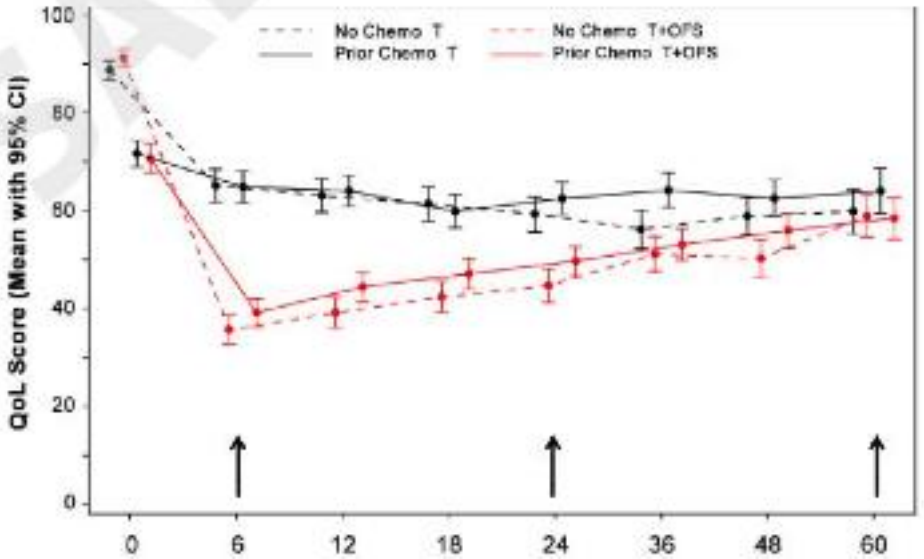
Francis PA et al. N Engl J Med 2014

Treatment Effect: Symptoms

T+OFS vs. T



Treatment Effect: Hot Flushes



Ribi et al, SABCS 2014

Consideration

- In the entire population the addition of OS to adjuvant TAM did not significantly improve DFS

- TAM + OS resulted in a 22% reduction in the relative risk of breast cancer recurrence, a second invasive cancer or death (p=0.03)

- In younger premenopausal patients (< 35 yrs) OS when associate to TAM plays an important role for reducing the risk of breast cancer recurrence

- Longer follow-up is required becouse SOFT is currently underpowered and the overall survival analysis is premature after 5% of patients have died

Advising Patients on Ovarian Suppression: risk stratification

Risk	Higher typically stage II or III, intermediate-high grade		Intermediate Higher anatomic stage, lower risk biology; lower stage, higher risk biology	Lower typically stage I, lower-grade
Age	< 35	40+		40+
Chemo?	Yes	Yes*		No
OFS	Yes	Discuss		No
Tablet	Tamoxifen or AI			Tamoxifen

*more likely to experience chemotherapy-induced amenorrhea

Advising Patients on Ovarian Suppression: risk stratification

Risk	Higher typically stage II or III, intermediate-high grade		Intermediate Higher anatomic stage, lower risk biology; lower stage, higher risk biology	Lower typically stage I, lower-grade
Age	< 35	40+	Variable	40+
Chemo?	Yes	Yes*	±	No
OFS	Yes	Discuss	?	No
Tablet	Tamoxifen or AI		Tamoxifen	Tamoxifen

*more likely to experience chemotherapy-induced amenorrhea

Pagaie Rosa

GRAZIE