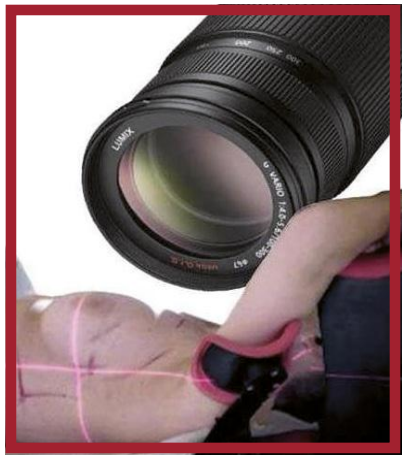
Associazione Italiana Radioterapia Oncologica
Gruppo di Studio per la Patologia Mammaria

V Zoom Journal Club 2015



Non un Congresso "classico" né un Corso, ma un'occasione per concreti aggiornamenti, confronto e dibattito su alcuni "Hot Topics 2015" dalla letteratura relativa alla radioterapia mammaria

Bologna
19 Febbraio 2016

NH Hotel De La Gare

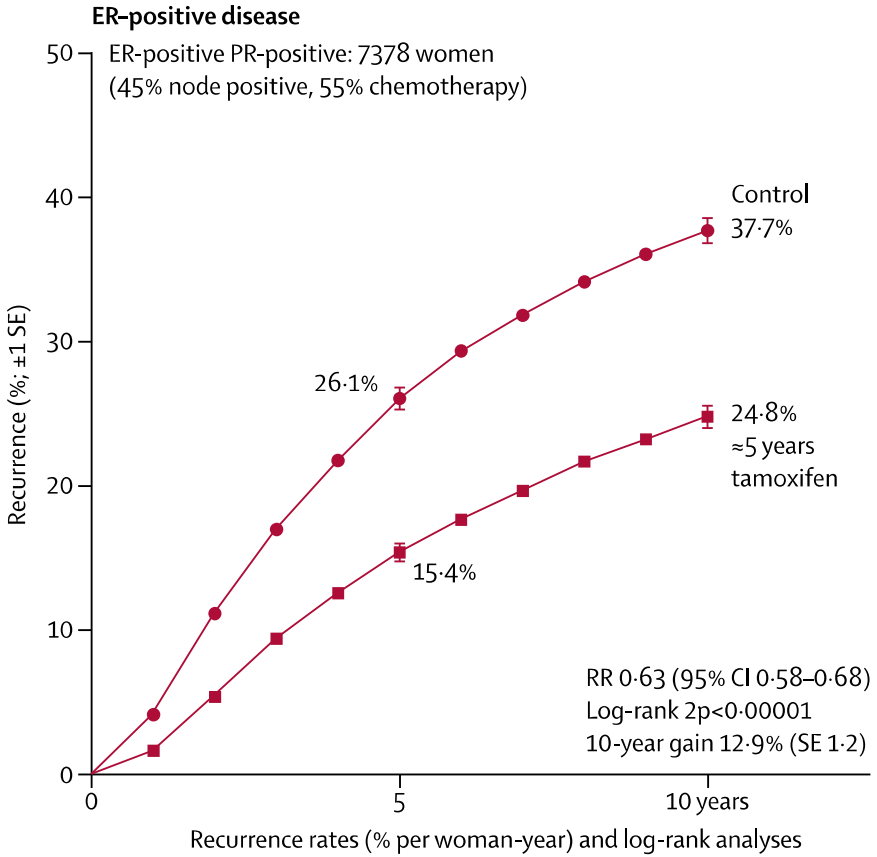
Novità nella terapia delle donne con cancro della mammella in pre-menopausa: studio Text e studio Soft

Grazia Arpino

Universita' di Napoli Fedrico II

Tamoxifen and Aromatase Inhibitors: adjuvant treatment for post menopausal ER+ breast cancer

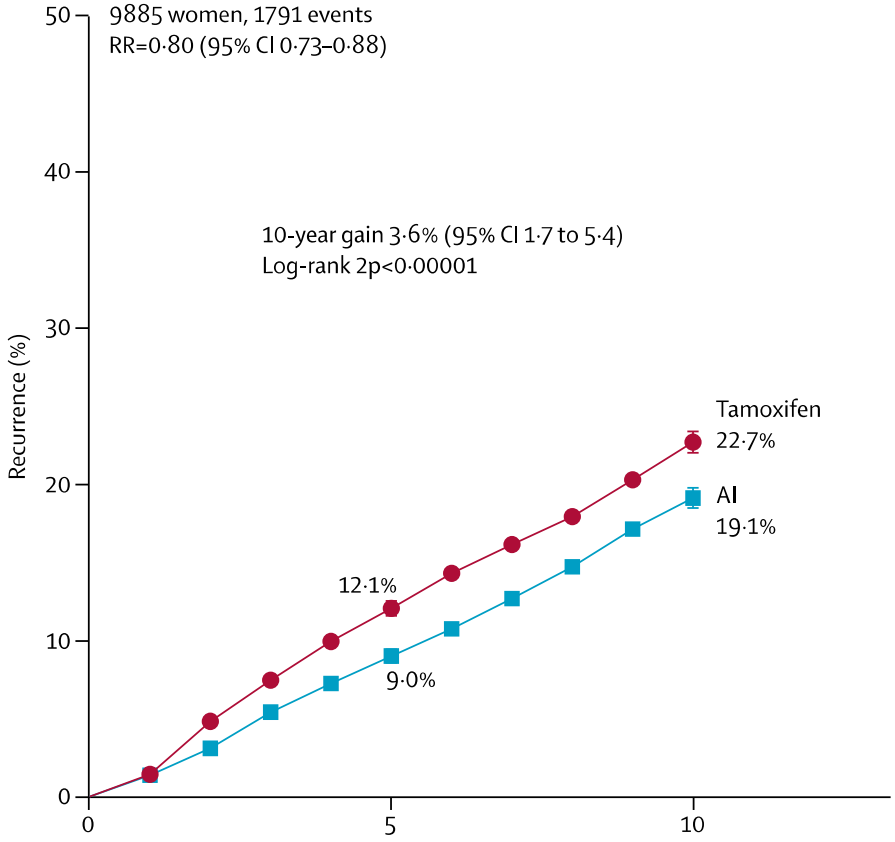
TAMOXIFEN VS. CONTROL



Recurrence rates (% per woman-year) and log-rank analyses

	Years 0–4	Years 5–9	Years 10+
Tamoxifen	3·41 (570/16 701)	2·47 (303/12 248)	2·10 (219/10 446)
Control	6·00 (926/15 432)	3·50 (360/10 295)	2·19 (188/8577)
Rate ratio	0·55 (SE 0·04)	0·68 (SE 0·07)	0·93 (SE 0·10)
(O–E)/V	–209·5/349·4	–60·3/157·1	–6·8/96·4

AIS VS. TAMOXIFEN



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 0–1	Years 2–4	Years 5–9	Year 10+
AI	1·62 (157/9691)	2·14 (285/13 336)	2·33 (365/15 648)	3·23 (20/619)
Tamoxifen	2·41 (230/9542)	2·62 (338/12 906)	2·48 (372/14 985)	4·54 (24/529)
Rate ratio (95% CI)	0·64 (0·52–0·78)	0·80 (0·68–0·93)	0·92 (0·79–1·06)	0·72 (0·39–1·30)
from (O-E)/V	–41·1/92·8	–34·1/149·0	–15·5/177·2	–3·6/10·7

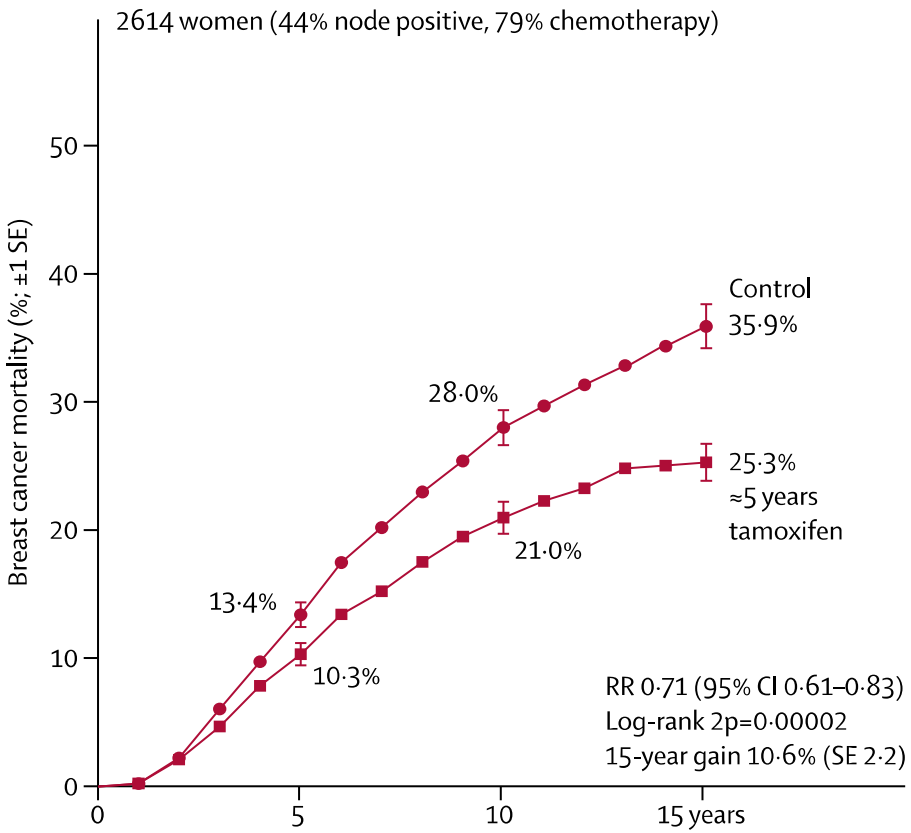
Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*LANCET 2011: LANCET 2015

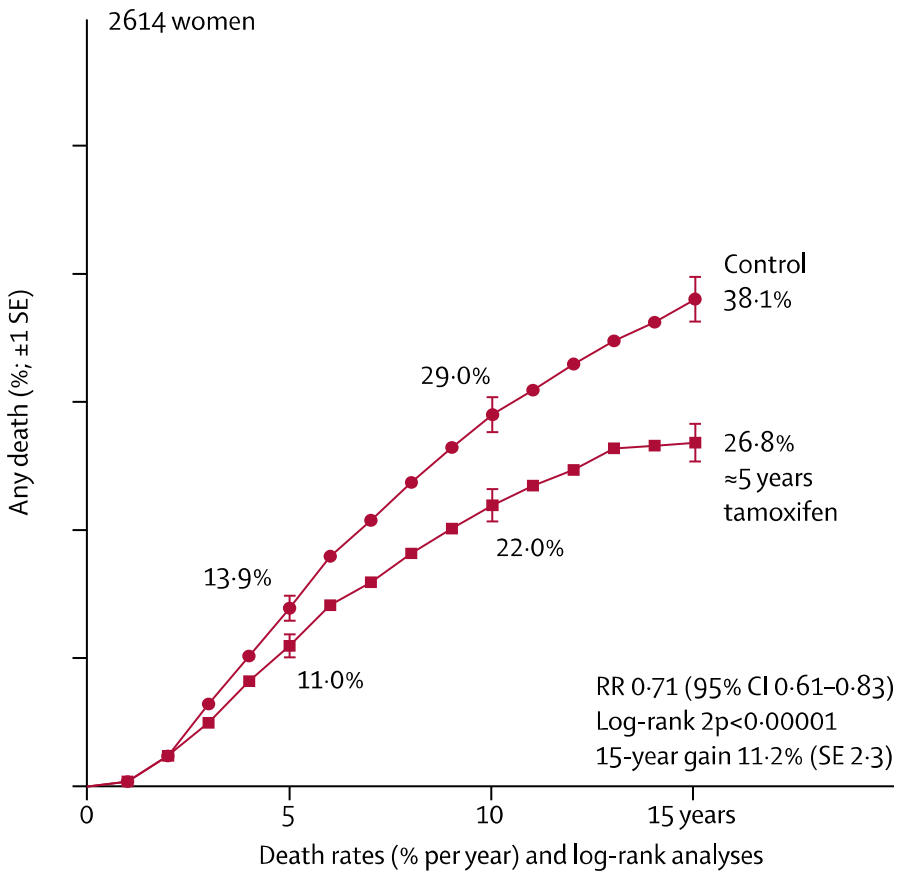
Summary

- In postmenopausal women with ER+ breast cancer, tamoxifen delivered after surgery results in substantial gains in recurrence and survival
- AI's (compared to tamoxifen) further reduce the risk of recurrence and prolong survival

Age <45: Tamoxifen and ER+ Breast Cancer

ER-positive disease only: entry age <45 years



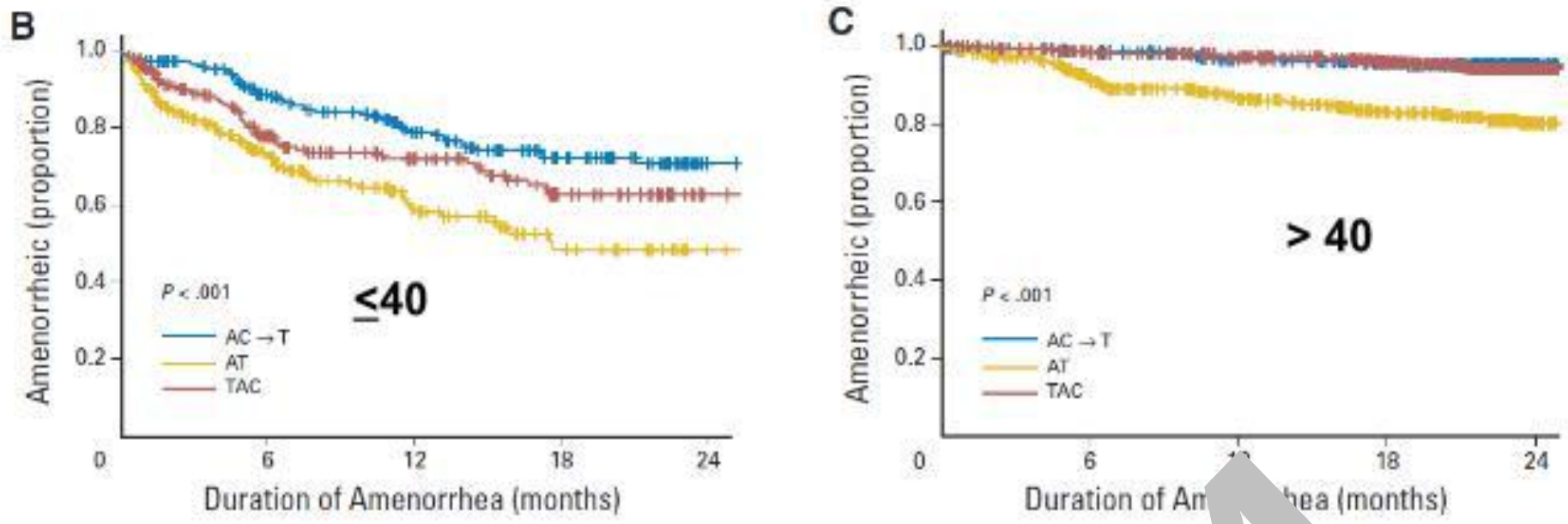


	Years 0–4	Years 5–9	Years 10–14	Year 15+
Tamoxifen	2·15 (SE 0·19)	2·63 (SE 0·25)	1·29 (SE 0·24)	0·98 (SE 0·37)
Control	2·80 (SE 0·21)	3·74 (SE 0·30)	2·39 (SE 0·35)	0·85 (SE 0·38)
Rate ratio	0·76 (SE 0·10)	0·69 (SE 0·10)	0·56 (SE 0·18)	1·07 (SE 0·61)
(O–E)/V	–19·9/71·9	–23·7/63·8	–10·5/18·1	0·2/2·8

Years 0–4	Years 5–9	Years 10–14	Year 15+
2·29 (139/6058)	2·72 (116/4263)	1·52 (33/2167)	1·40 (10/715)
2·91 (178/6109)	3·89 (161/4140)	2·79 (55/1970)	1·52 (9/591)
0·78 (SE 0·10)	0·68 (SE 0·10)	0·56 (SE 0·16)	0·84 (SE 0·43)
–19·1/75·9	–25·2/66·2	–12·5/21·3	–0·8/4·5

Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2011

NSABP B30: Impact of Type of Chemotherapy and Age on Amenorrhea and Outcome



NSABP B30 substudy

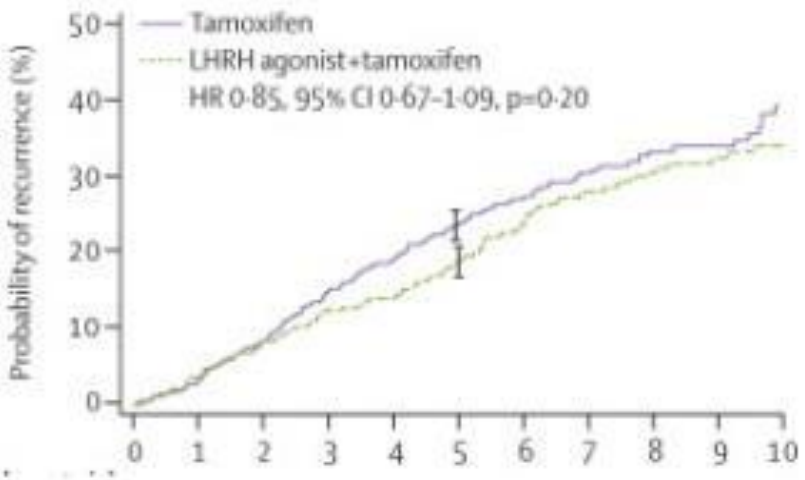
In women with ER+ disease:

amenorrhea for > 6 months predicted

improved OS (HR 0.52, p=0.002 and DFS (0.52 p<0.001)

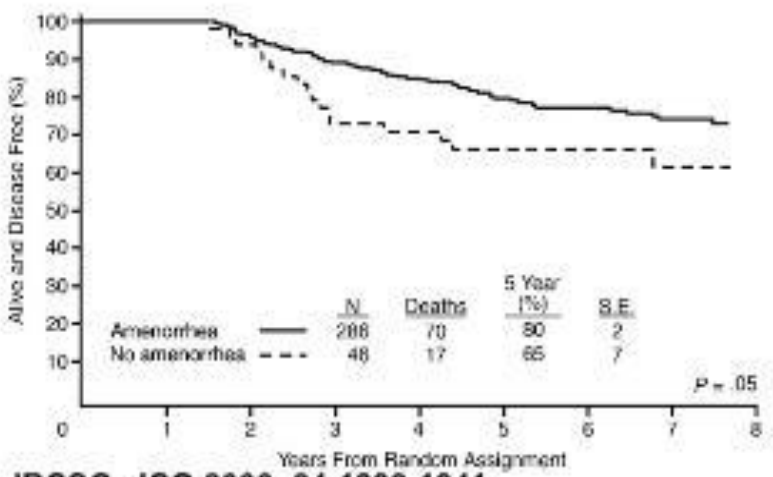
Ganz et al. J Clin Oncol 2011; Swain et al. NEJM 2010

The Paradox of Tamoxifen and OFS



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

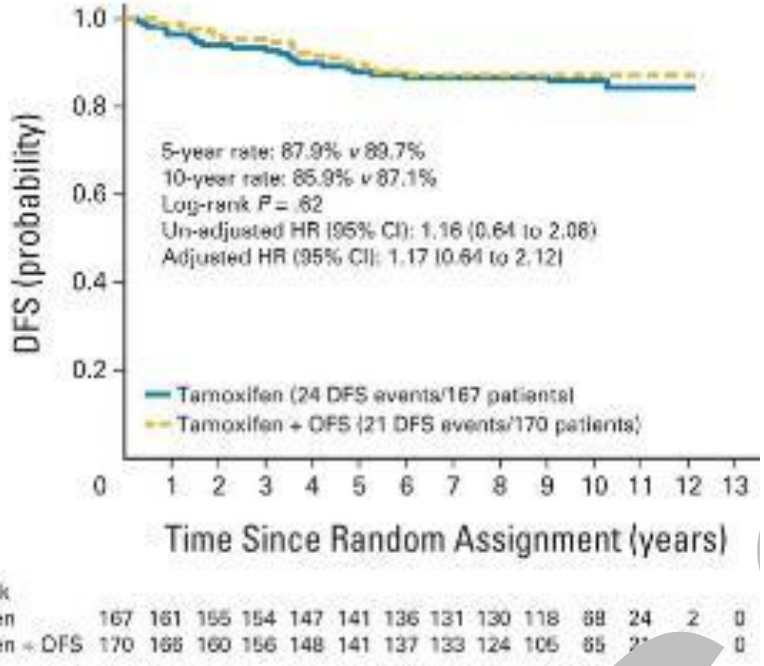
IBCSG 13-93



IBCSG, JCO 2006; 24:1332-1341

E3193 Tamoxifen ± OFS (no chemo)

B



No. at risk

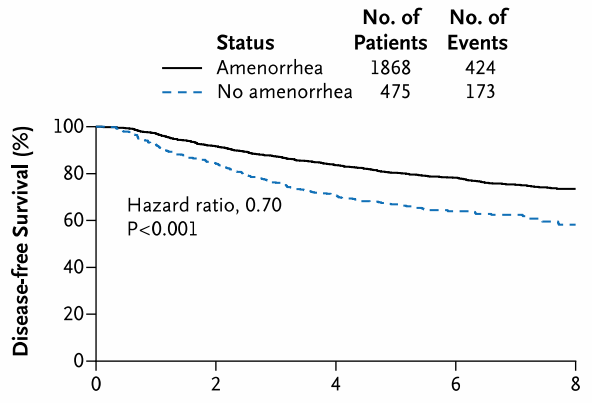
Tamoxifen	167	161	155	154	147	141	136	131	130	118	88	24	2	0
Tamoxifen + OFS	170	168	160	156	148	141	137	133	124	106	65			0

Tevaarwerk A J et al. JCO 2014;32:3948-39

NSABP B-30

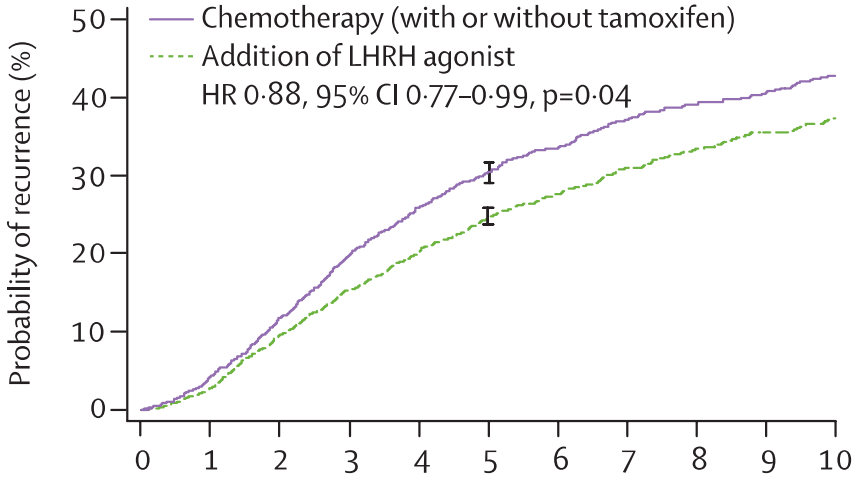
B Disease-free Survival

D



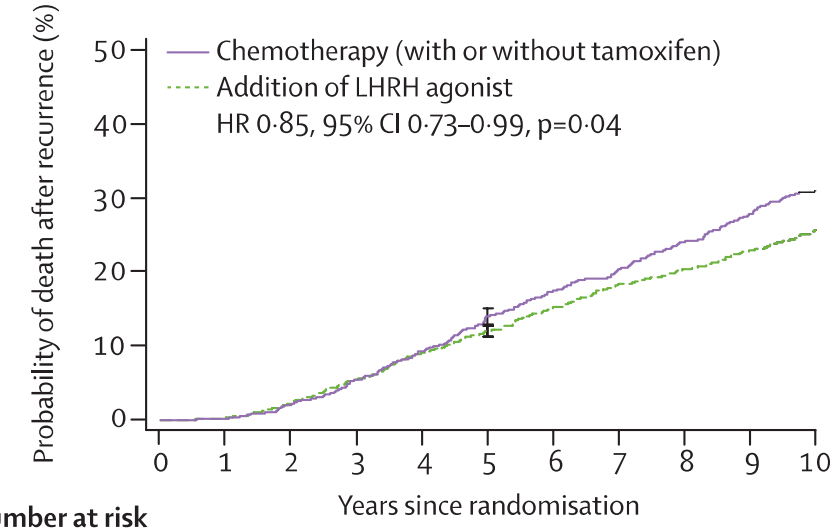
No. at Risk					
Total	2343	2101	1838	974	323
Amenorrhea	1868	1705	1519	797	250
No amenorrhea	475	396	319	177	73

LHRH Agonists: Importance of chemotherapy



Number at risk

Chemotherapy	1371	1187	908	663	476	349
LHRH agonist addition	1370	1217	976	709	505	350



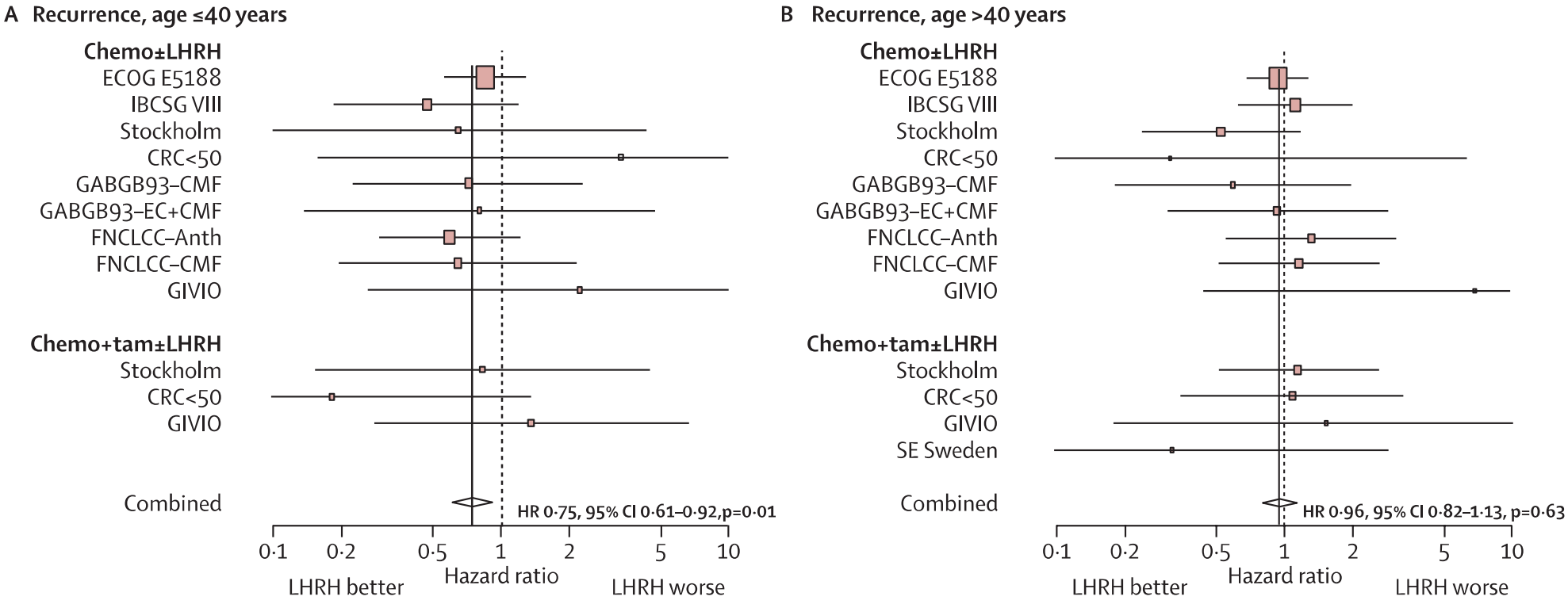
Number at risk

Chemotherapy	1371	1316	1109	827	604	430
LHRH agonist addition	1370	1317	1127	859	637	445

Addition of LHRH agonists to tamoxifen, chemotherapy, or both reduced recurrence and death after recurrence

Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2007

LHRH Agonists: Importance of Age



Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Lancet 2007

LHRH Agonist: Importance of Age

Recurrence risk by age

<= 35 years	**HR 0.66**
35-39 years	**HR 0.77**
• 40-44 years	HR 0.96
• 45-49 years	HR 1.03
• ≥ 50 years	HR 0.85

N=9022

Significant interaction for recurrence of age for addition of LHRH agonist to chemotherapy with or without tamoxifen (p=0.046)

Lancet. 2007;369:1714

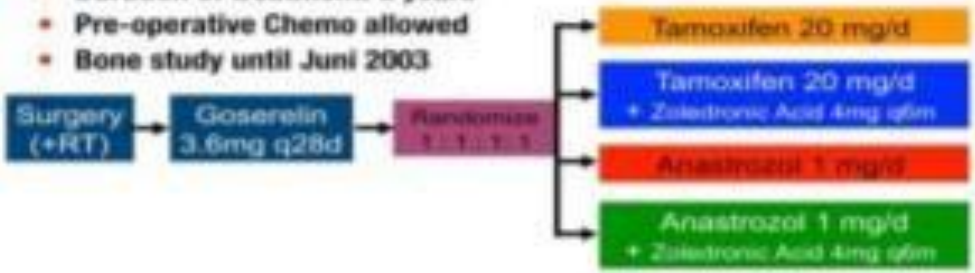
Summary: Tamoxifen and LHRH agonist

- In premenopausal ER+ breast cancer, adjuvant tamoxifen results in substantial gains in terms of recurrence and survival
- LHRH agonists in ER+ breast cancer: Effects appear to be greatest in younger women
- 2007: Questions that remain unanswered:
  - How much does OFS add to tamoxifen in women with intact ovarian function?
  - Does complete estrogen deprivation (OFS + AI) improve outcomes further (compared to tamoxifen alone and tamoxifen + OFS)

ABCSG 12: Tamoxifen, AI's and LHRH agonists

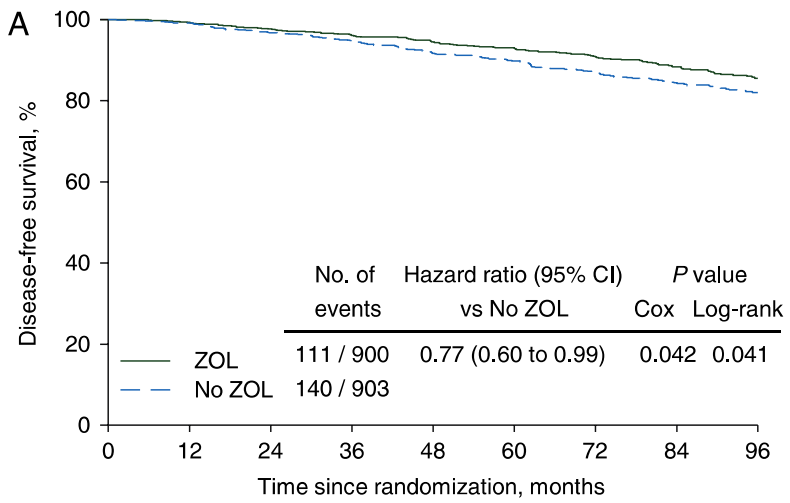
ABCSG-12 Trial Design

- Recruitment 1999-2006
- 1.803 premenopausal patients
- Stage I&II, <10pos nodes, ER+ and/or PgR+
- Duration of treatment: 3 years
- Pre-operative Chemo allowed
- Bone study until Juni 2003



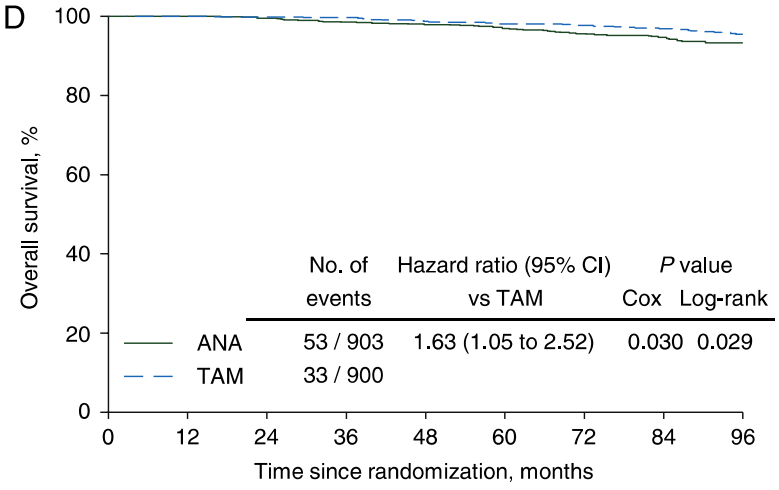
Major Findings:

- Significant improvement in DFS with addition of Zoledronic acid No difference in DFS comparing TAM and Anastrozole
- OS difference related to inadequate OFS?



Patients at risk:

ZOL	900	862	841	822	790	735	648	526	266
No ZOL	903	858	833	805	761	705	617	505	254



Patients at risk:

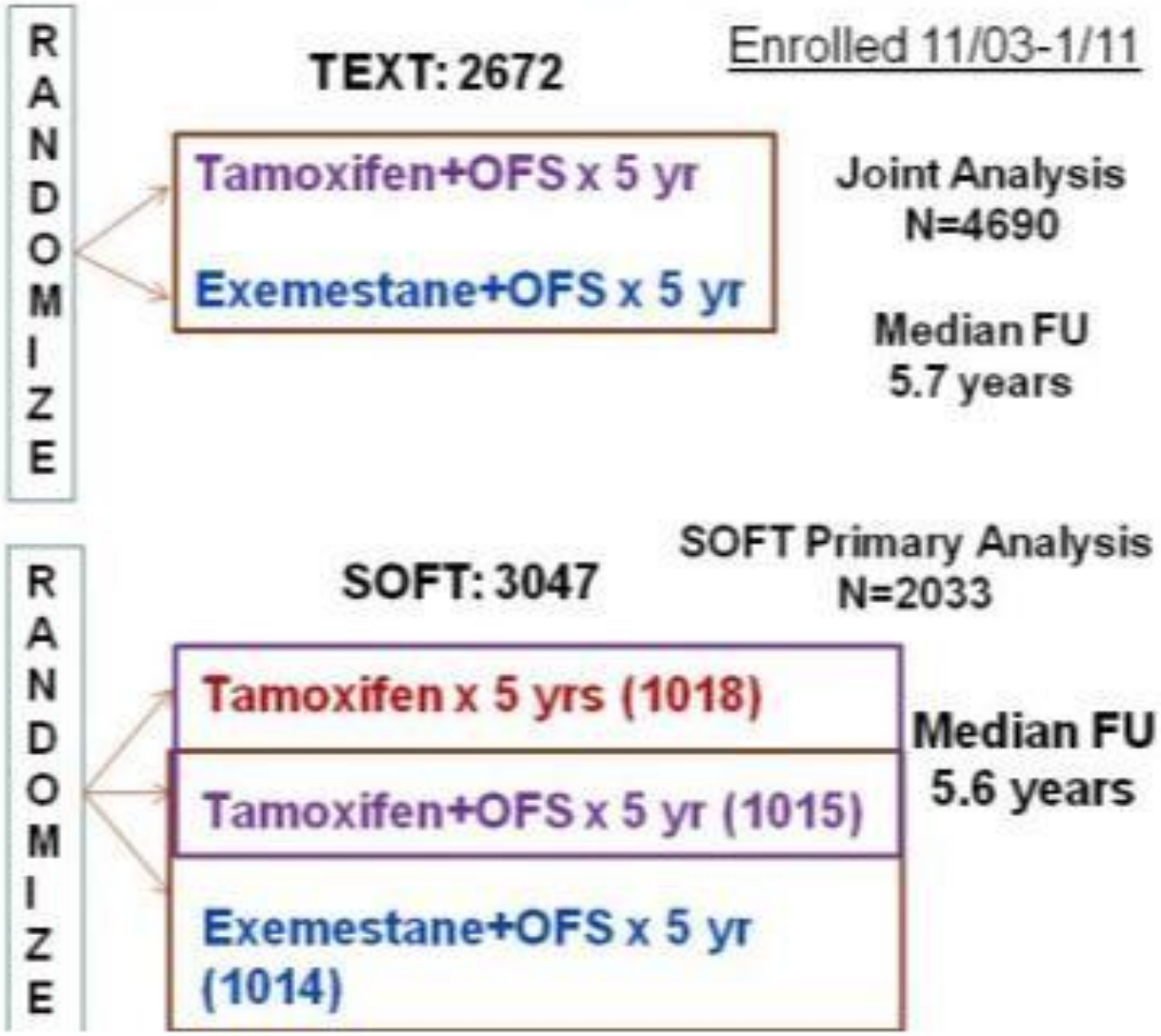
ANA	903	872	864	847	819	772	689	571	288
TAM	900	860	850	841	816	764	690	570	293

M. Gnant et al. Ann Oncol 2015;26:313-320

Summary: ABCSG 12

- No differences in DFS comparing tamoxifen and anastrozole but worse overall survival in the anastrozole arm in ABCSG 12
  - Chance?
  - Inadequate OFS?
  - Unexpected toxic effect of complete estrogen deprivation?

SOFT and TEXT



Pagani et al. NEJM 2014; Francis et al. NEJM 2014

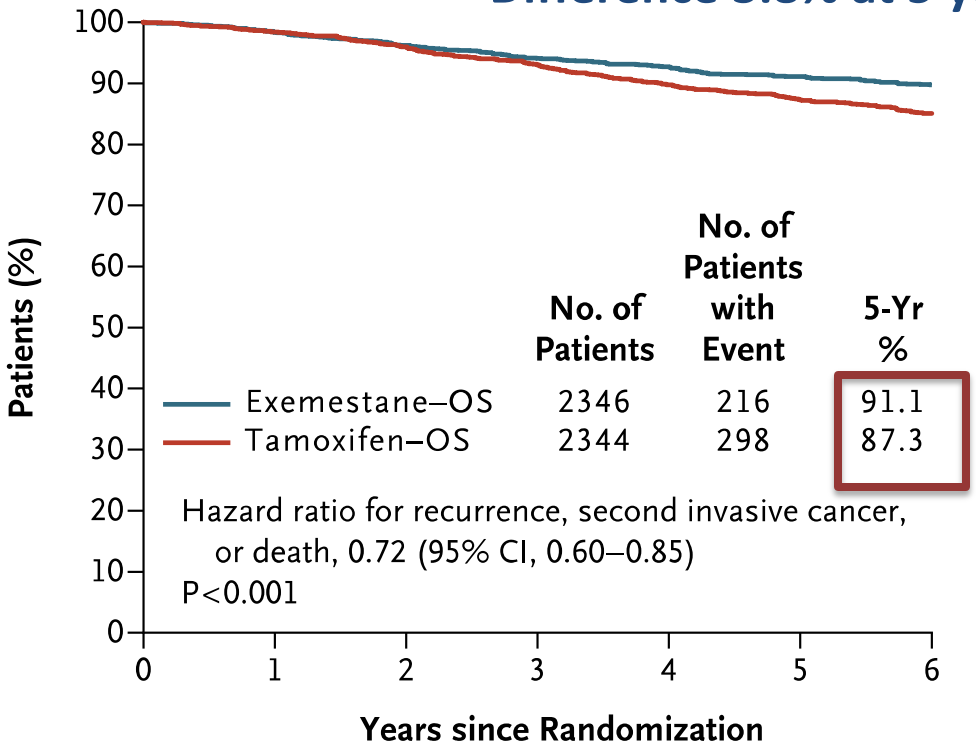
Key Eligibility for SOFT and TEXT

- Premenopausal
- ER or PgR ≥ 10%
- For those who did not receive chemotherapy, randomization within 12 weeks after definitive surgery
- SOFT patients who received chemotherapy underwent randomization within 8 months after completing chemotherapy, once a premenopausal level of estradiol was confirmed

TEXT: Disease-Free Survival

A Disease-free Survival

Difference 3.8% at 5 years



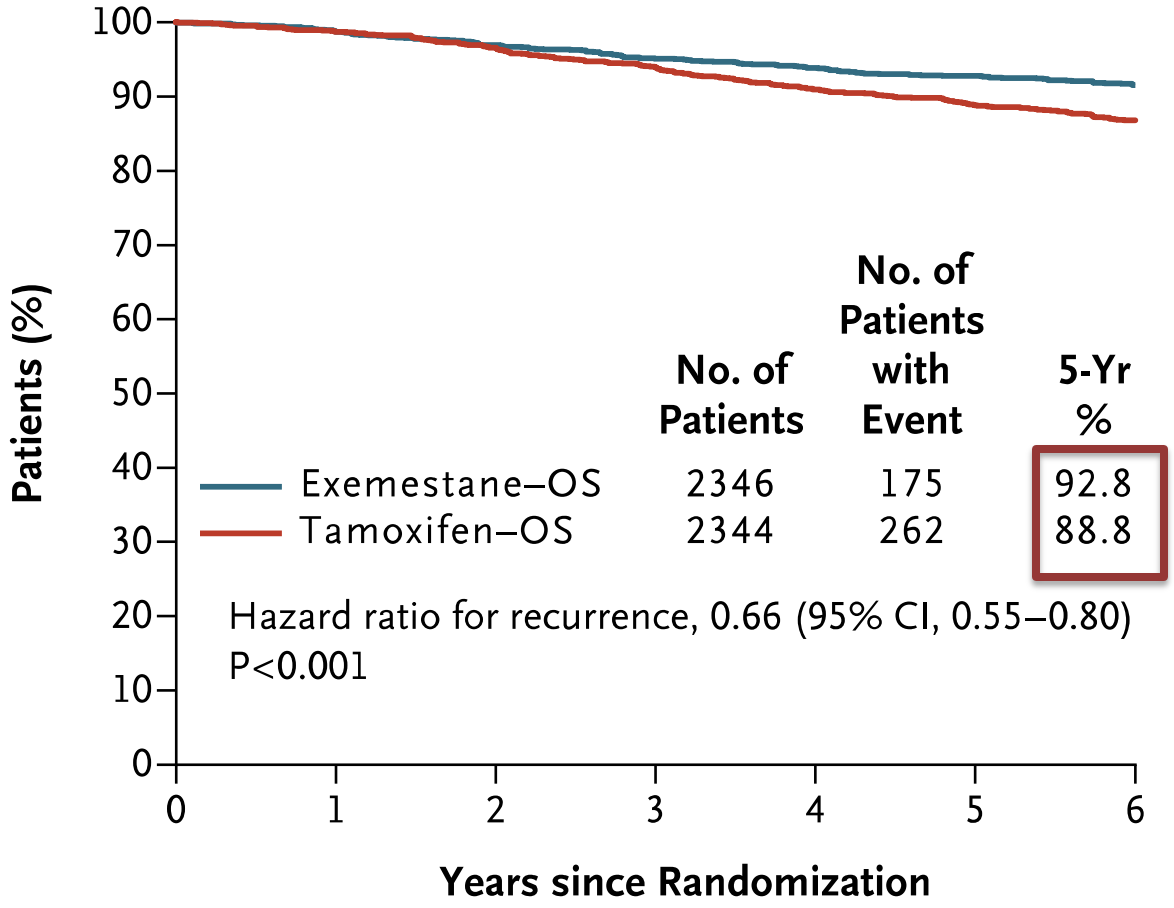
No. at Risk

Exemestane–OS	2346	2217	2128	1848	1517	1289	866
Tamoxifen–OS	2344	2247	2148	1845	1486	1261	834

Pagani et al. NEJM 2014

Text: Freeedom from Recurrence of Breast Cancer

B **Freedom from Breast Cancer**

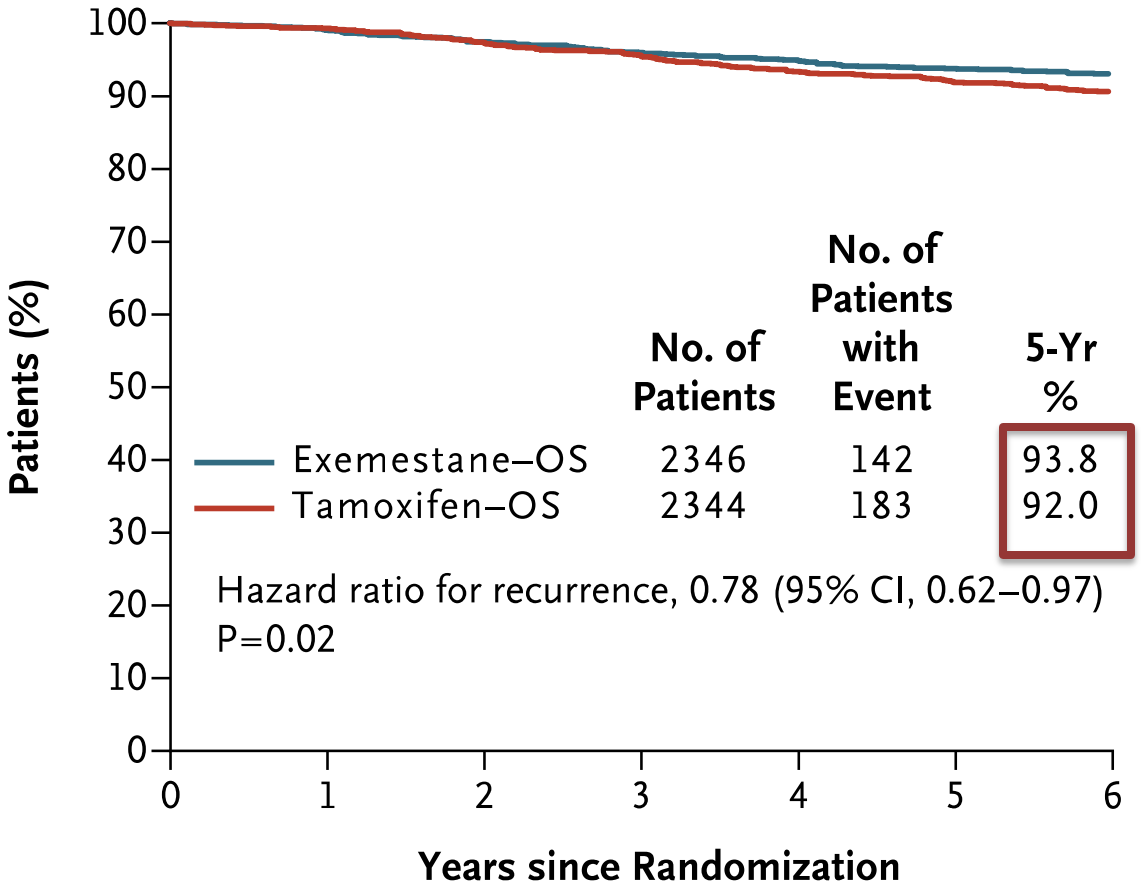


No. at Risk

Exemestane–OS	2346	2223	2138	1863	1534	1309	879
Tamoxifen–OS	2344	2253	2156	1858	1503	1281	844

Text: Freedom from Recurrence of Breast Cancer at a Distant Site

C **Freedom from Recurrence of Breast Cancer at a Distant Site**

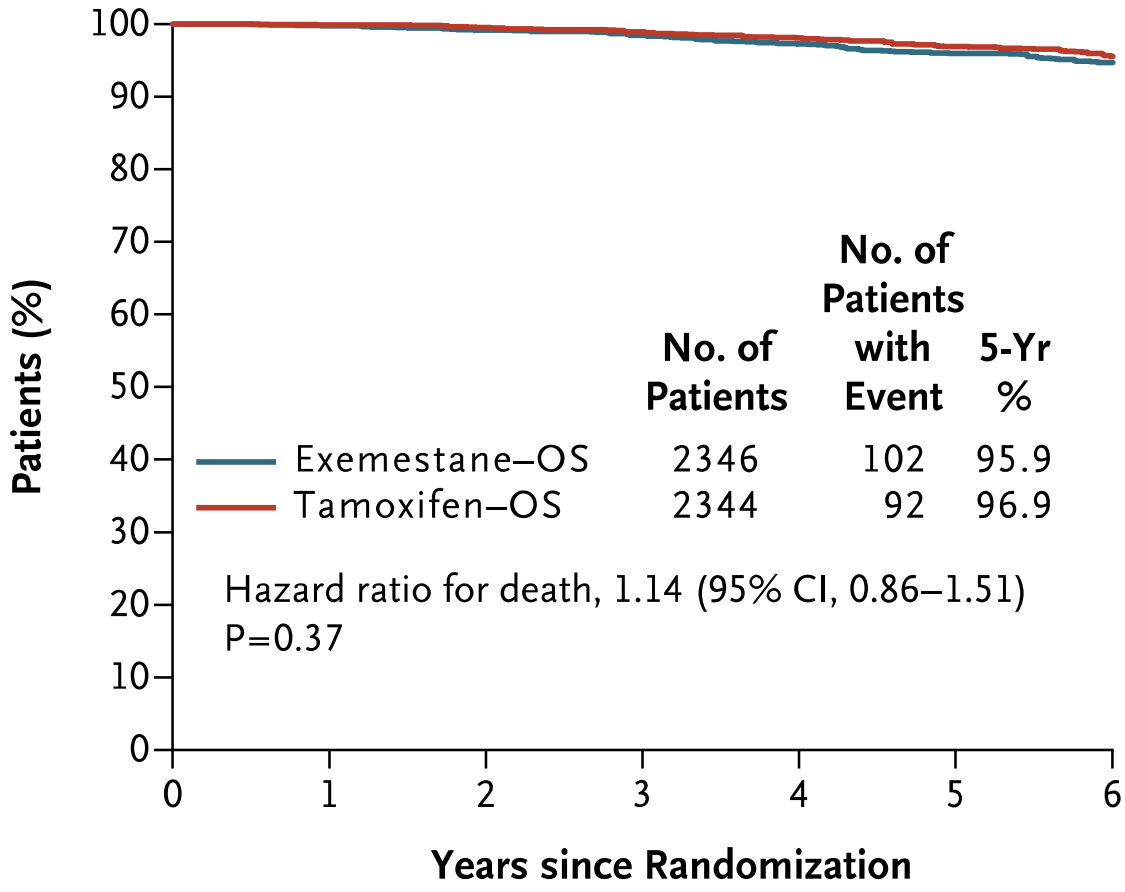


No. at Risk

Exemestane–OS	2346	2232	2150	1879	1548	1318	890
Tamoxifen–OS	2344	2264	2174	1892	1540	1318	874

Text: Overall Survival

D **Overall Survival**



No. at Risk							
Exemestane–OS	2346	2271	2235	1980	1631	1393	938
Tamoxifen–OS	2344	2298	2246	1997	1659	1424	952

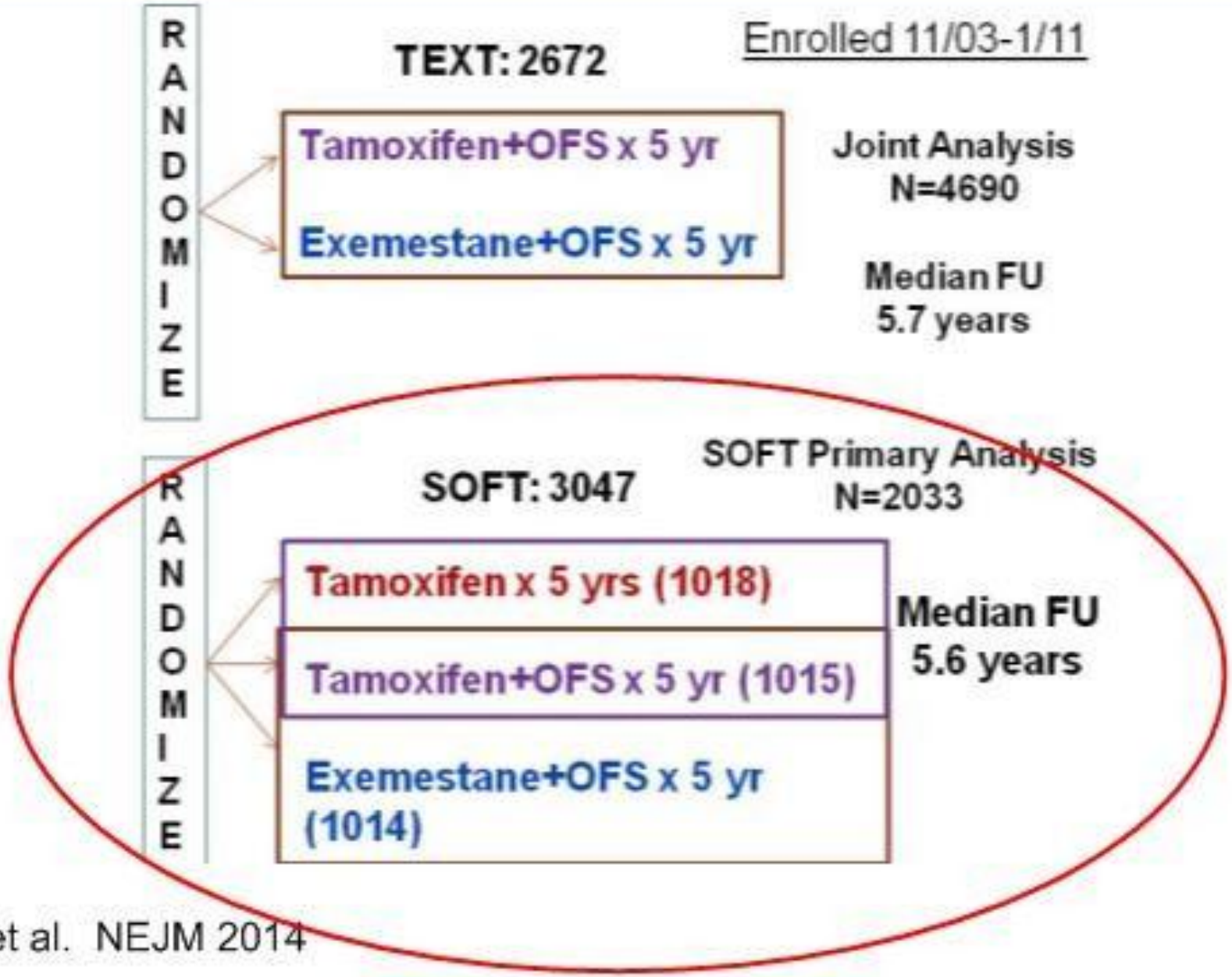
Text: Adverse Events

Adverse Event	Exemestane plus Ovarian Suppression (N=2318)				Tamoxifen plus Ovarian Suppression (N=2325)			
	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)*
Allergic reaction or hypersensitivity	115	5.0 (4.1–5.9)	11	0.5 (0.2–0.8)	107	4.6 (3.8–5.5)	9	0.4 (0.2–0.7)
Injection-site reaction	168	7.2 (6.2–8.4)	1	<0.1 (0.0–0.2)	187	8.0 (7.0–9.2)	1	<0.1 (0.0–0.2)
Hot flushes	2125	91.7 (90.5–92.8)	232	10.0 (8.8–11.3)	2169	93.3 (92.2–94.3)	279	12.0 (10.7–13.4)
Depression	1165	50.3 (48.2–52.3)	87	3.8 (3.0–4.6)	1164	50.1 (48.0–52.1)	102	4.4 (3.6–5.3)
Sweating	1264	54.5 (52.5–56.6)	—	—	1371	59.0 (56.9–61.0)	—	—
Insomnia	1348	58.2 (56.1–60.2)	89	3.8 (3.1–4.7)	1361	58.5 (56.5–60.5)	100	4.3 (3.5–5.2)
Fatigue	1420	61.3 (59.2–63.2)	73	3.1 (2.5–3.9)	1463	62.9 (60.9–64.9)	67	2.9 (2.2–3.6)
Hypertension	527	22.7 (21.0–24.5)	151	6.5 (5.5–7.6)	509	21.9 (20.2–23.6)	169	7.3 (6.2–8.4)
Cardiac ischemia or infarction	16	0.7 (0.4–1.1)	7	0.3 (0.1–0.6)	7	0.3 (0.1–0.6)	3	0.1 (0.0–0.4)
Thrombosis or embolism	24	1.0 (0.7–1.5)	19	0.8 (0.5–1.3)	50	2.2 (1.6–2.8)	45	1.9 (1.4–2.6)
Nausea	721	31.1 (29.2–33.0)	17	0.7 (0.4–1.2)	671	28.9 (27.0–30.7)	13	0.6 (0.3–1.0)
Musculoskeletal symptoms	2057	88.7 (87.4–90.0)	254	11.0 (9.7–12.3)	1766	76.0 (74.2–77.7)	122	5.2 (4.4–6.2)
Osteoporosis	894	38.6 (36.6–40.6)	10	0.4 (0.2–0.8)	586	25.2 (23.5–27.0)	6	0.3 (0.1–0.6)
Fractures	158	6.8 (5.8–7.9)	29	1.3 (0.8–1.8)	120	5.2 (4.3–6.1)	18	0.8 (0.5–1.2)
Vaginal dryness	1214	52.4 (50.3–54.4)	—	—	1101	47.4 (45.3–49.4)	—	—
Decreased libido	1042	45.0 (42.9–47.0)	—	—	950	40.9 (38.9–42.9)	—	—
Dyspareunia	707	30.5 (28.6–32.4)	53	2.3 (1.7–3.0)	601	25.8 (24.1–27.7)	32	1.4 (0.9–1.9)
Urinary incontinence	304	13.1 (11.8–14.6)	6	0.3 (0.1–0.6)	414	17.8 (16.3–19.4)	7	0.3 (0.1–0.6)
CNS cerebrovascular ischemia	5	0.2 (0.1–0.5)	4	0.2 (0.0–0.4)	11	0.5 (0.2–0.8)	8	0.3 (0.1–0.7)
CNS hemorrhage	15	0.6 (0.4–1.1)	1	<0.1 (0.0–0.2)	21	0.9 (0.6–1.4)	2	0.1 (0.0–0.3)
Glucose intolerance†	54	2.3 (1.8–3.0)	11	0.5 (0.2–0.8)	54	2.3 (1.7–3.0)	15	0.6 (0.4–1.1)
Hyperglycemia†	61	2.6 (2.0–3.4)	13	0.6 (0.3–1.0)	80	3.4 (2.7–4.3)	15	0.6 (0.4–1.1)
Any targeted adverse event	2279	98.3 (97.7–98.8)	710	30.6 (28.8–32.6)	2285	98.3 (97.7–98.8)	683	29.4 (27.5–31.3)

Conclusions Regarding TEXT

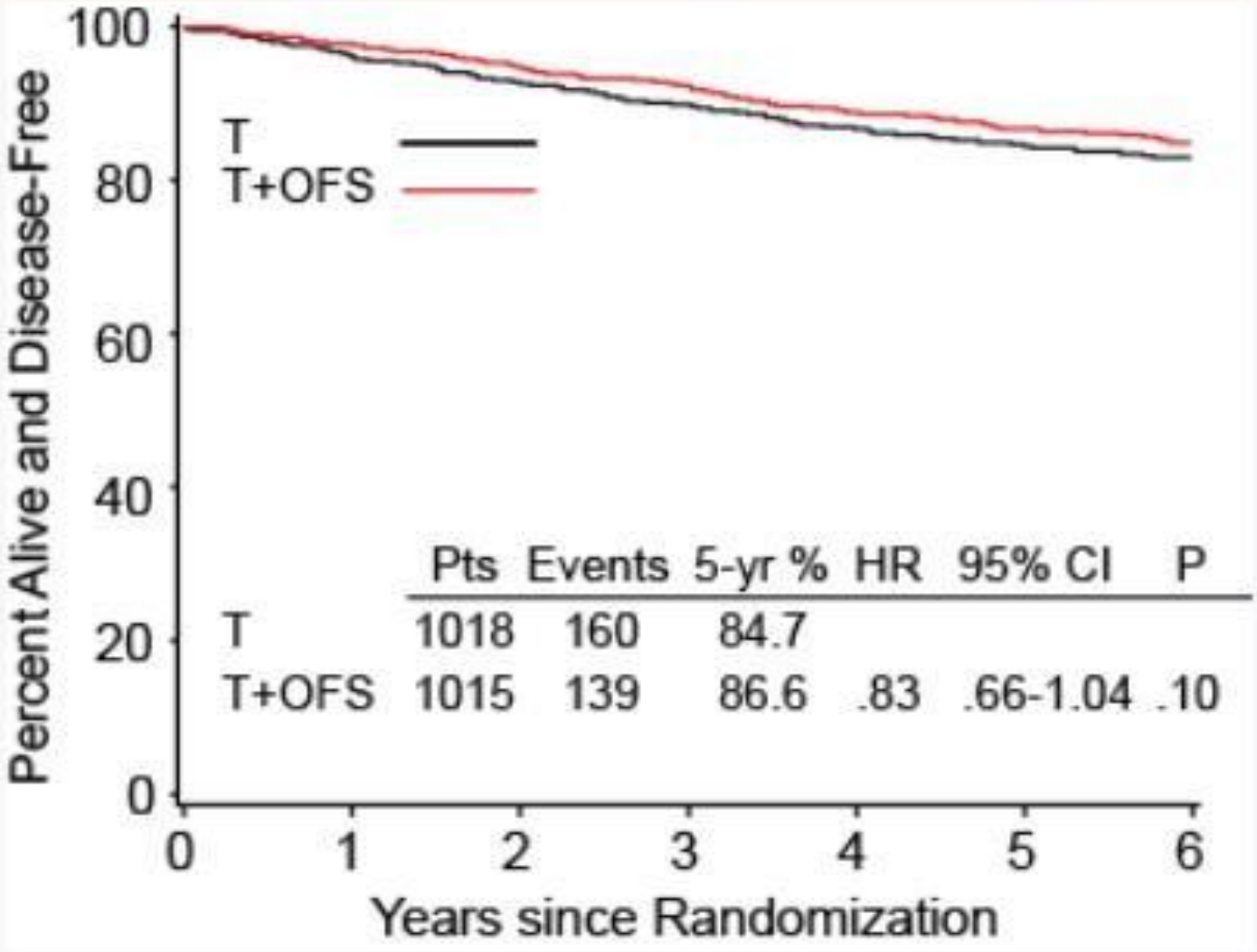
- Exemestane + OFS results in better breast cancer control compared to tamoxifen + OFS
- Unanswered questions
  - What are the long term implications of complete estrogen deprivation in young women?
  - Are there subgroups of patients that do not require OFS?
  - Can we more precisely identify subgroups that could be preferentially treated with one particular regimen?

SOFT



Francis et al. NEJM 2014

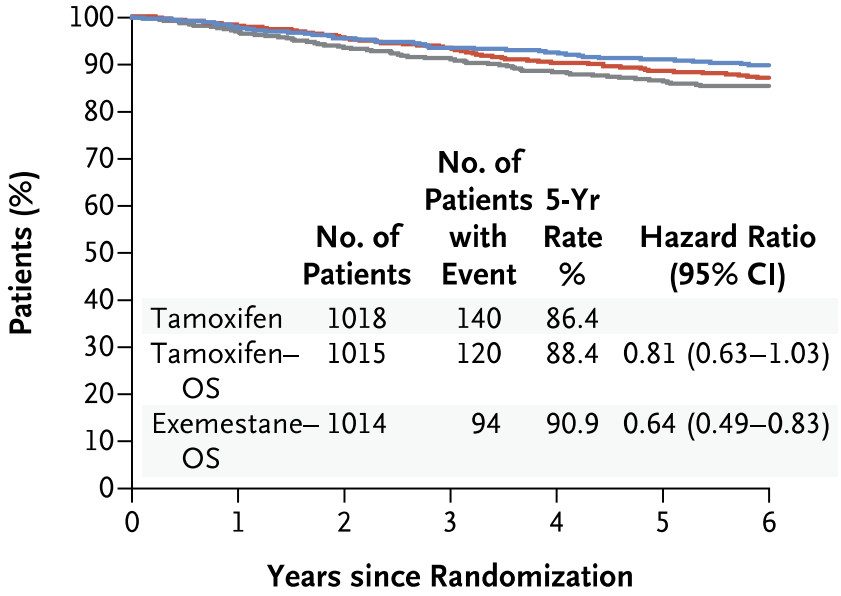
Primary Analysis: Disease-free Survival
5.6 years median follow-up



Francis et al. NEJM 2014

Primary Analysis: freedom from breast cancer and distant recurrence

A Freedom from Breast Cancer

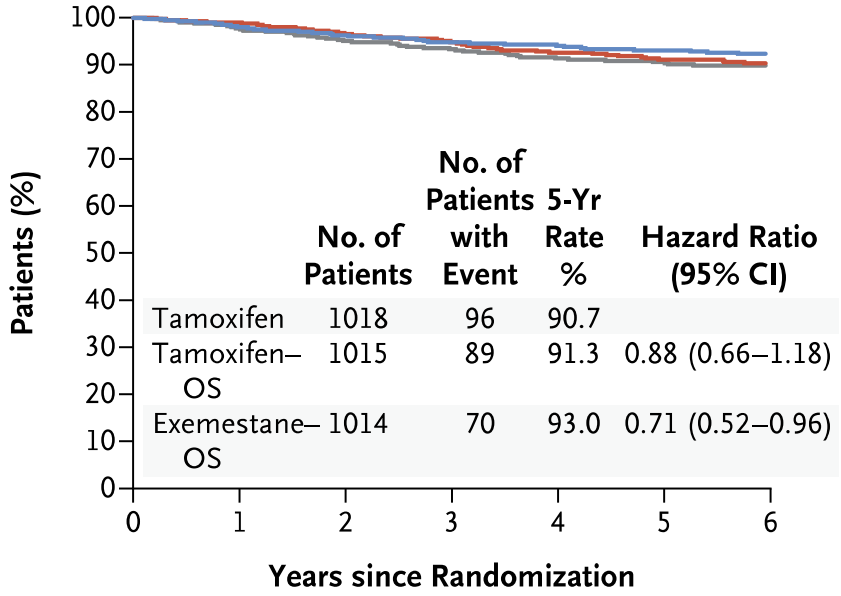


	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	1018	140	86.4	
Tamoxifen–OS	1015	120	88.4	0.81 (0.63–1.03)
Exemestane–OS	1014	94	90.9	0.64 (0.49–0.83)

No. at Risk

Tamoxifen	1018	956	900	855	728	533	314
Tamoxifen–OS	1015	970	932	886	752	568	356
Exemestane–OS	1014	957	912	869	766	550	342

B Freedom from Distant Recurrence



	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	1018	96	90.7	
Tamoxifen–OS	1015	89	91.3	0.88 (0.66–1.18)
Exemestane–OS	1014	70	93.0	0.71 (0.52–0.96)

No. at Risk

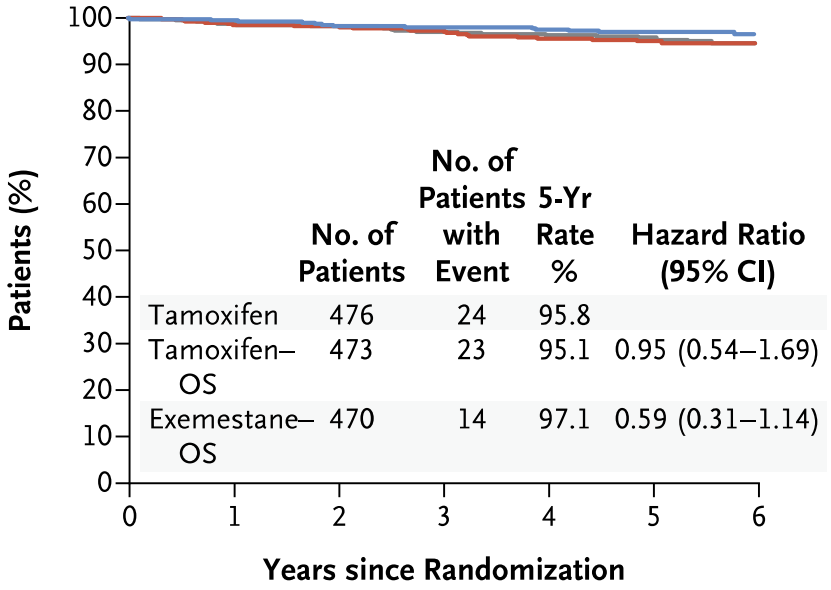
Tamoxifen	1018	966	915	875	755	559	333
Tamoxifen–OS	1015	977	943	901	772	582	363
Exemestane–OS	1014	962	920	882	783	562	352

Francis et al NEJM 2014

SOFT: Premenopausal No Chemotherapy (average age 46 years)

Clinical Assessment Low Risk

C **No Chemotherapy, Freedom from Breast Cancer**

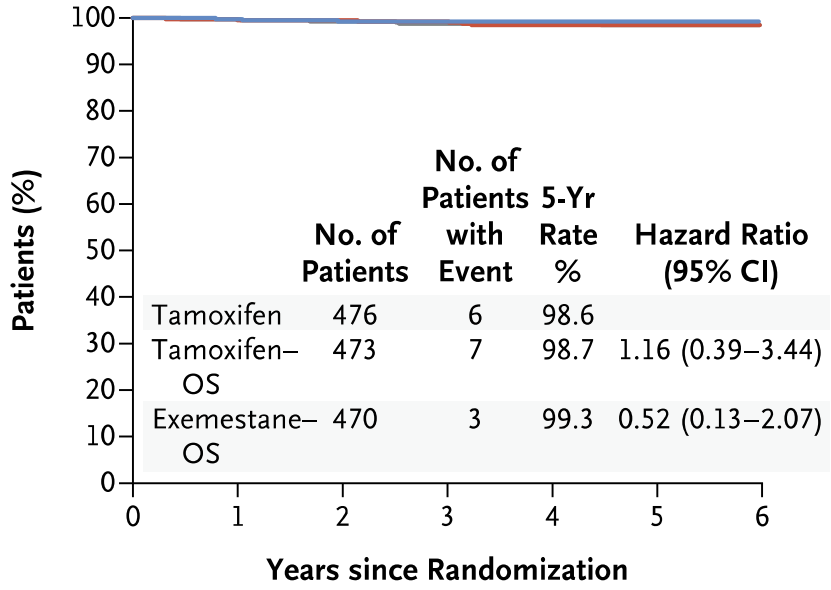


	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	476	24	95.8	
Tamoxifen–OS	473	23	95.1	0.95 (0.54–1.69)
Exemestane–OS	470	14	97.1	0.59 (0.31–1.14)

No. at Risk

Tamoxifen	476	461	445	429	377	277	169
Tamoxifen–OS	473	454	447	429	373	285	179
Exemestane–OS	470	443	425	414	374	278	176

D **No Chemotherapy, Freedom from Distant Recurrence**



	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	476	6	98.6	
Tamoxifen–OS	473	7	98.7	1.16 (0.39–3.44)
Exemestane–OS	470	3	99.3	0.52 (0.13–2.07)

No. at Risk

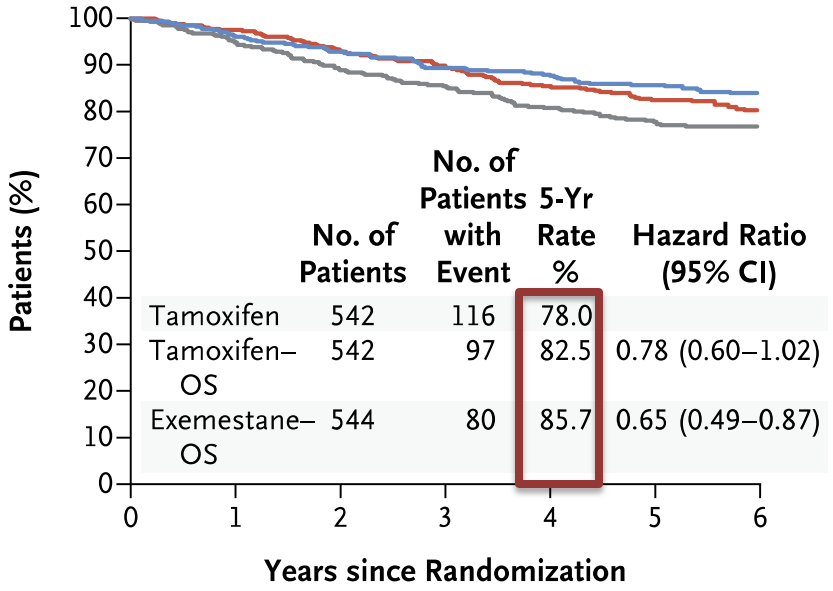
Tamoxifen	476	465	449	436	386	284	176
Tamoxifen–OS	473	458	453	437	385	293	184
Exemestane–OS	470	444	429	419	381	283	180

Francis et al NEJM 2014

SOFT: Premenopausal after Prior Chemotherapy (average age 40 years)

Clinical Assessment High Risk

E **Prior Chemotherapy, Freedom from Breast Cancer**

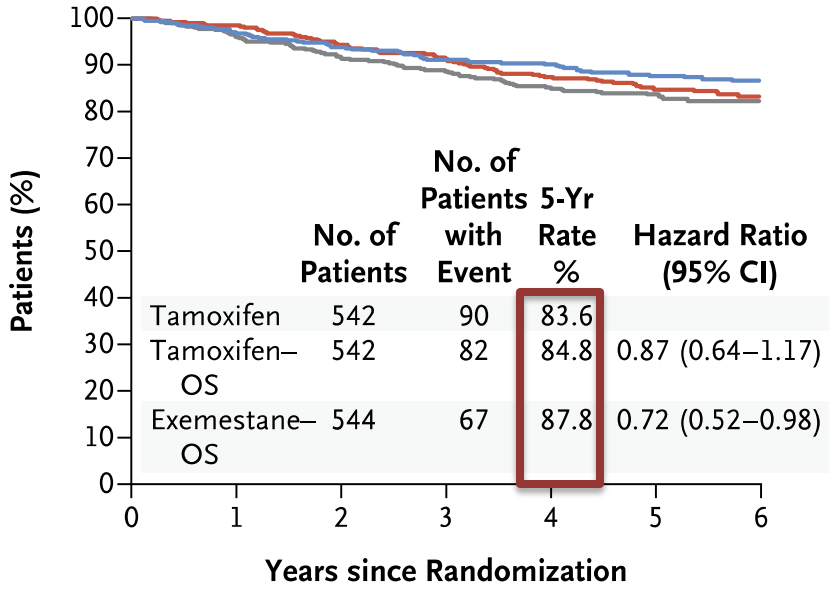


	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	542	116	78.0	
Tamoxifen–OS	542	97	82.5	0.78 (0.60–1.02)
Exemestane–OS	544	80	85.7	0.65 (0.49–0.87)

No. at Risk

Tamoxifen	542	494	455	426	352	255	144
Tamoxifen–OS	542	516	485	456	378	283	176
Exemestane–OS	544	514	487	455	391	273	166

F **Prior Chemotherapy, Freedom from Distant Recurrence**



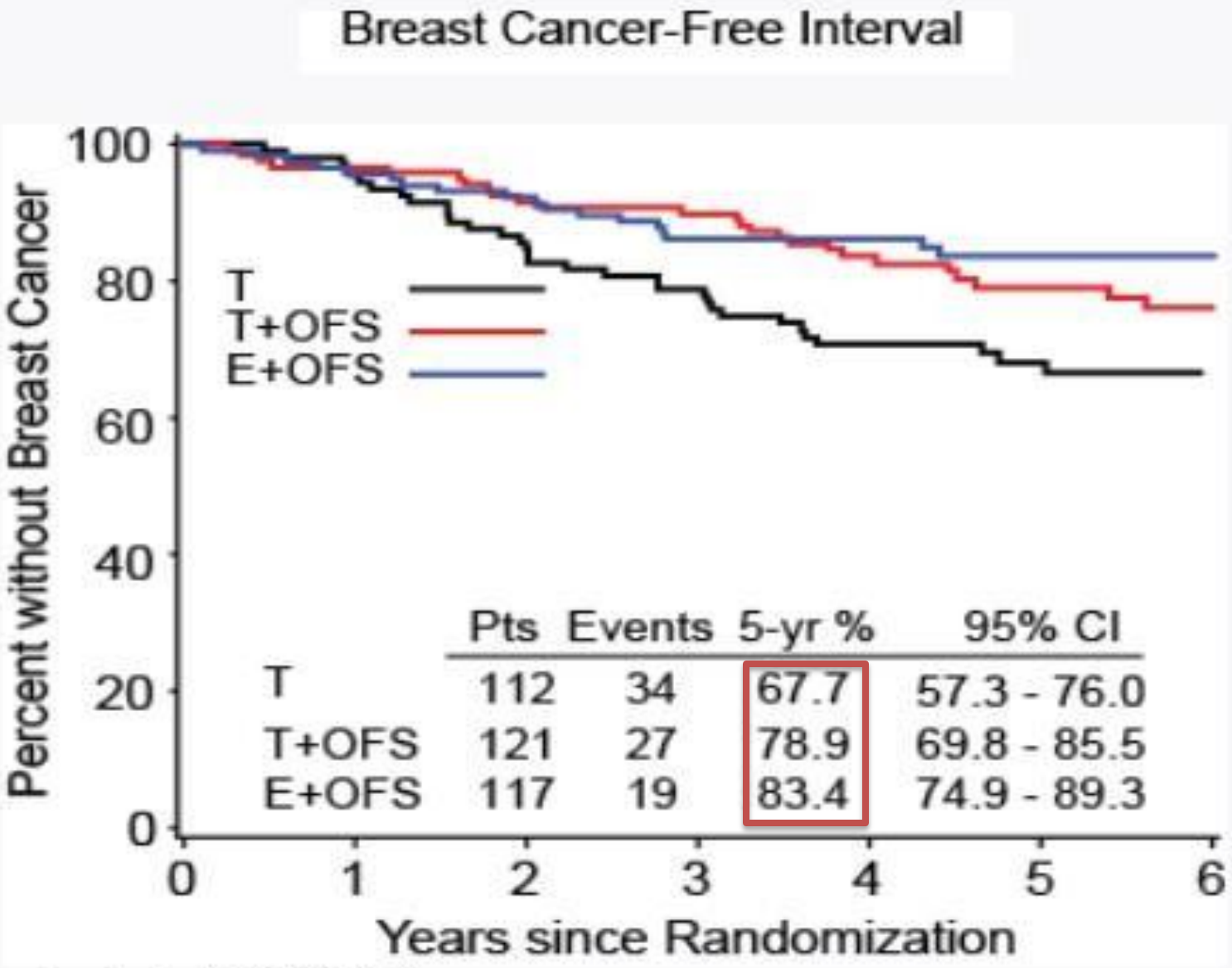
	No. of Patients	No. of Patients with Event	5-Yr Rate %	Hazard Ratio (95% CI)
Tamoxifen	542	90	83.6	
Tamoxifen–OS	542	82	84.8	0.87 (0.64–1.17)
Exemestane–OS	544	67	87.8	0.72 (0.52–0.98)

No. at Risk

Tamoxifen	542	501	466	439	369	274	156
Tamoxifen–OS	542	519	490	463	386	289	178
Exemestane–OS	544	518	491	463	401	280	172

Francis et al NEJM 2014

All women < 35 years of age



Francis et al. NEJM 2014

Biology and Risk Drive Benefit of Ovarian Suppression

- BCFI in premenopausal women who retain ovarian production of estrogen following adjuvant chemotherapy
  - T + OFS > T
  - E + OFS >> T
- This difference is even greater in women < 35 yrs of age

Endpoint		Absolute improvement at 5 years HR (95% CI	
		T + OFS v. T	E + OFS v. T
Premenopausal after chemo	BCFI	4.5% 0.78 (.60-1.02)	7.7% 0.65 (.49-.87)
	DRFI	1.2% 0.87 (,64 17)	4.2% 0.72 (.52-.98)
BCFI in < 35 yo (94% received chemo)		11. %	15.7%

DRFI: distant recu nce e interval BCFI: breast cancer free interval;'

TEXT+SOFT Joint Analysis

		Absolute improvement at 5 years
		E + OFS vs T + OFS
All patients combined	BCFI	4%
	DRFI	1.8%
No chemotherapy (TEXT only)	BCFI	3% (HR 0.41)
		TEXT vs SOFT
Premenopausal after/with chemo	BCFI	5.5 vs 3.9%
	DRFI	3.4 vs 2.6%

- TEXT, no chemotherapy: 21% node positive, 16% < 40, 19% T > 2 cm

SOFT: Adverse Events

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

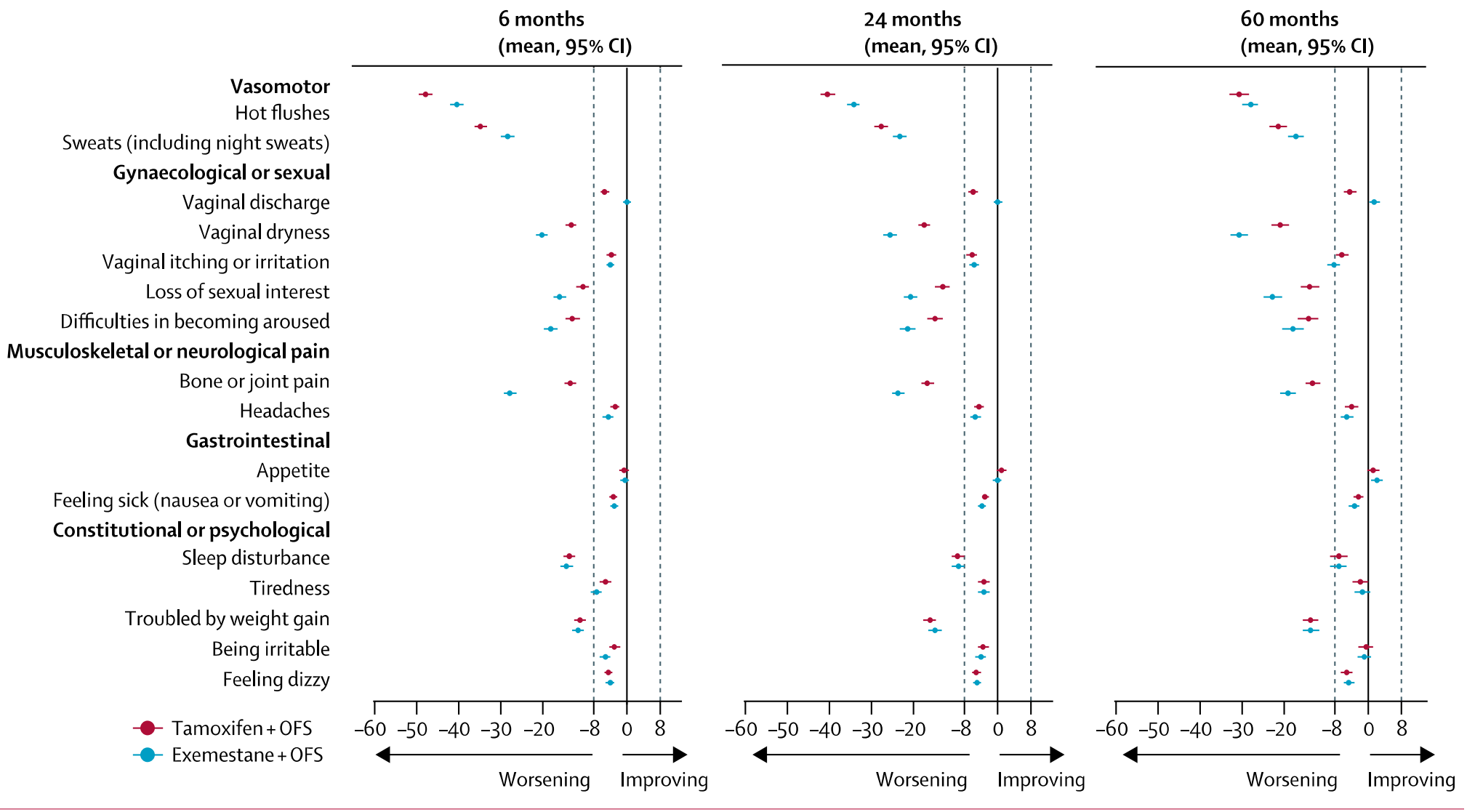
Adverse Event	Tamoxifen (N=1006)				Tamoxifen plus Ovarian Suppression (N=1005)			
	Any Event		Grade 3 or 4 Event		Any Event		Grade 3 or 4 Event	
	no. of patients with event	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (95% CI)*	*no. of patients with event*	*% (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.

Treatment Effect by Cohort



Change in QoL symptom indicator scores from baseline to 6 months, 24 months, and 60 months for overall TEXT and SOFT population according to treatment assignment

Cost of Treatment: Toxicity

- **15% stopped OFS by 2 years, 22% by 3 years.**
- **Provider reported, clinically important**
  - Depression reported in ~ 50%, 4% severe, 5% increase with OFS
  - Increase in menopausal symptoms, osteoporosis, insomnia most marked
- **Patient reported (85% of trial population)**
  - **Pts on tamoxifen plus OFS reported hot flushes and sweats although these symptoms improved over time**
  - **Pts on exemestane plus OFS reported more vaginal dryness, greater loss of sexual interest, and difficulties becoming aroused; these differences persisted over time.**
  - **An increase in bone or joint pain was more pronounced, in patients on exemestane plus OFS than patients on tamoxifen plus OFS.**
  - **Changes in global QoL indicators from baseline were small**

Ribi et al, SABCS 2014

Summary: SOFT

- In the overall population, DFS did not differ comparing tamoxifen with tamoxifen + OFS
- In patients treated with chemotherapy, OFS (with either tamoxifen or exemestane) results in substantial improvements in breast cancer recurrence, most pronounced in young women
- Women whose breast cancers exhibited low risk features had excellent outcomes with tamoxifen monotherapy
- Limited number of deaths so therefore the effect of OFS and exemestane on survival still unknown.

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

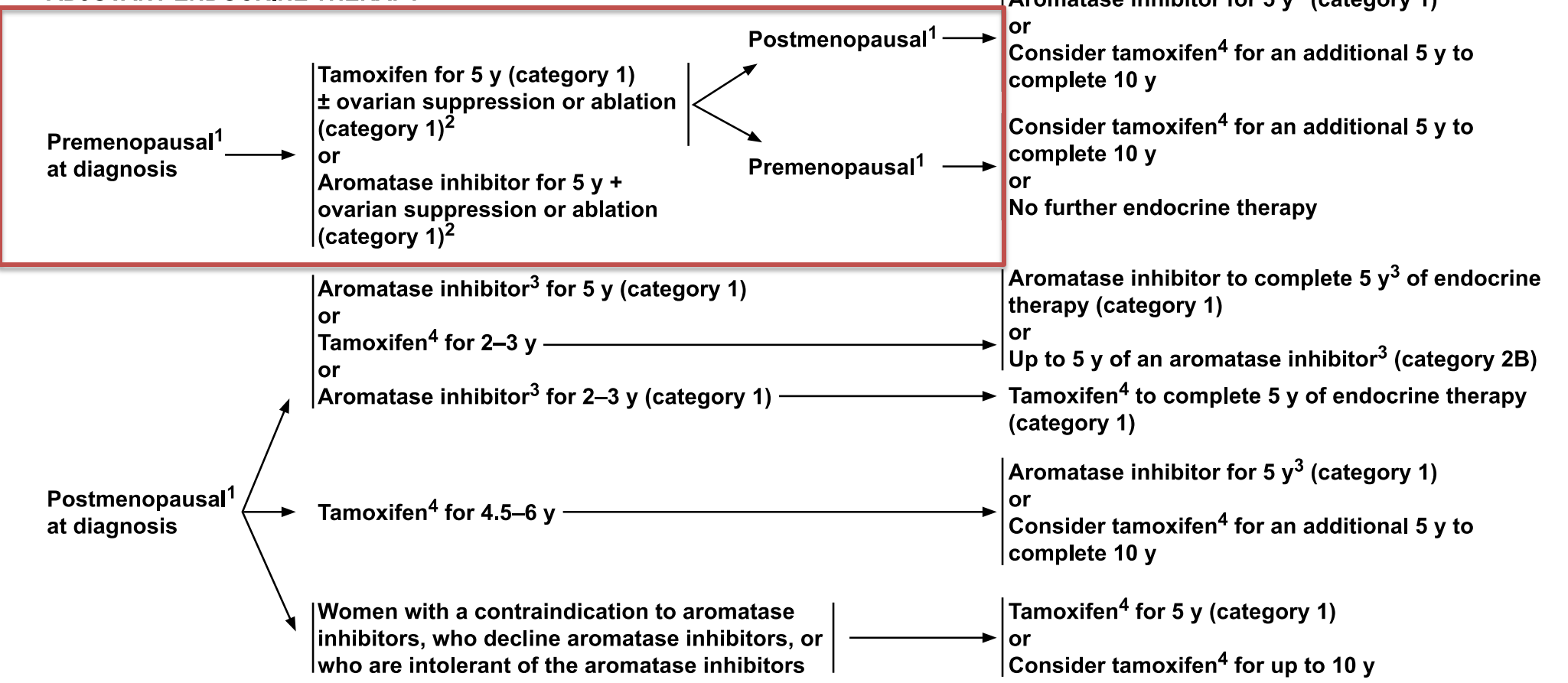
*more likely to experience chemotherapy-induced amenorrhea

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		Ta oxi	Tamoxifen

*more likely to experience chemotherapy-ind ed menorrhea

ADJUVANT ENDOCRINE THERAPY



[1] See Definition of Menopause (BINV-M).
[2] Aromatase inhibitor or tamoxifen for 5 y plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal women at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement, Pagani, NEJM 2014, Prudence, NEJM 2014).Survival data still pending.
[3] The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and preoperative settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.
[4] Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 gene testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Summary

- In premenopausal women with ER+ breast cancer, the addition of OFS to tamoxifen and AI's reduces breast cancer recurrence most notably in younger patients with prior chemotherapy
- AI's (when added to OFS) further reduce breast cancer recurrence and their use is now being considered in young women with high risk features
- Question: Could the short term gains achieved by complete estrogen deprivation be outweighed by potentially long term toxic effects impacting OS? Longer follow-up of SOFT and TEXT will be critical