Terapia ormonale adiuvante in pre-menopausa

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I NUMERI DEL CANCRO IN ITALIA 2015

AIOM Associazione Italiana di Oncologia Medica

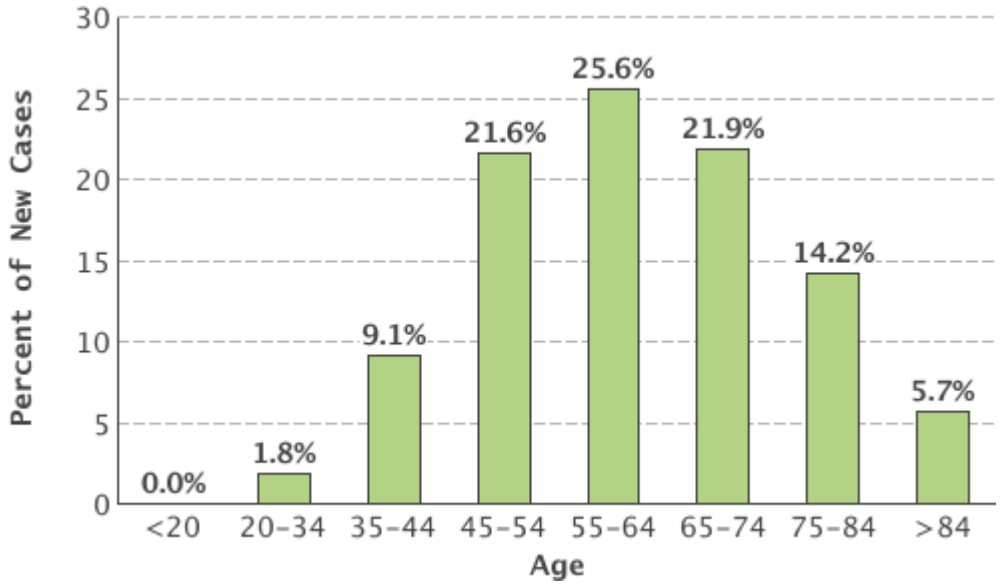
CCM

AIRTUM

TABELLA 3.
Numero di nuovi casi tumorali, totale e per alcune delle principali sedi, stimati per il 2015 (Popolazione italiana residente da previsioni ISTAT – www.demo.istat.it).

Sede	♂ Maschi	♀ Femmine
Vie aerodigestive superiori*	7.000	2.200
Esofago	1.300	600
Stomaco	8.200	5.500
Colon-retto	29.100	22.800
Colon	19.800	16.500
Retto	9.400	6.500
Fegato	8.500	3.800
Colecisti e vie biliari	2.200	2.500
Pancreas	5.900	6.600
Polmone	29.400	11.700
Osso	300	300
Cute (melanomi)	5.900	5.400
Mesotelioma	1.400	500
Sarcoma di Kaposi	600	300
Tessuti molli	1.100	900
Mammella	300	47.900
Utero (cervice)		2.100
Utero (corpo)		8.200
Ovaio		4.800
Prostata	35.200	
Testicolo	2.300	
Rene, vie urinarie**	8.300	4.300
Parenchima	6.800	3.600
Pelvi e vie urinarie	1.200	700
Vescica***	21.100	4.900
Sistema nervoso centrale	3.200	2.500
Tiroide	4.100	11.300
Linfoma di Hodgkin	1.300	1.100
Linfoma non-Hodgkin	7.000	6.000
Mieloma	2.900	2.400
Leucemie	4.800	3.500
Tutti i tumori, esclusi carcinomi della cute	194.400	168.900

Percent of New Cases by Age Group: Breast Cancer

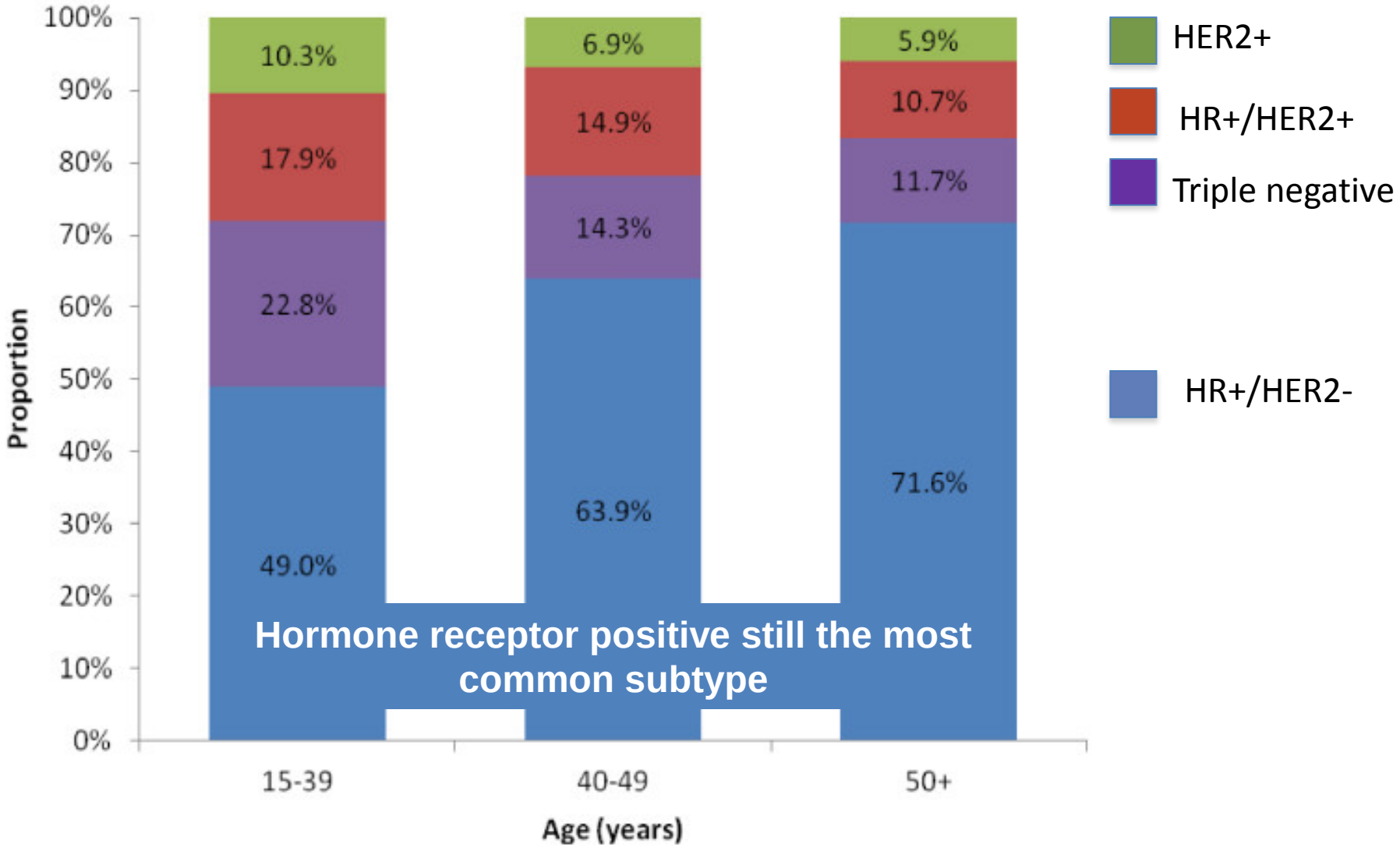


SEER 18 2008-2012, All Races, Females

Breast cancer in young women: specific clinical issues

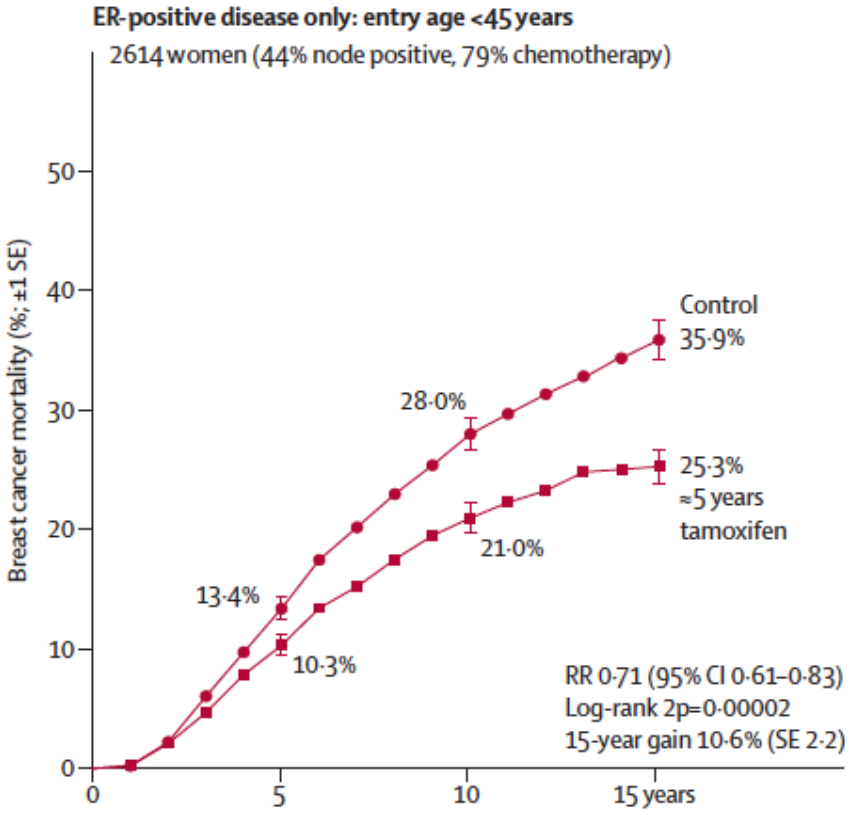
- Risk of hereditary breast cancer
- Optimal endocrine treatment
- Fertility/pregnancy issues

Proportion of Breast Cancer Subtypes by Age



Keegan et al, BCR, 2012

Benefits of 5 years of Tamoxifen: entry age < 45 years and ER+ disease only

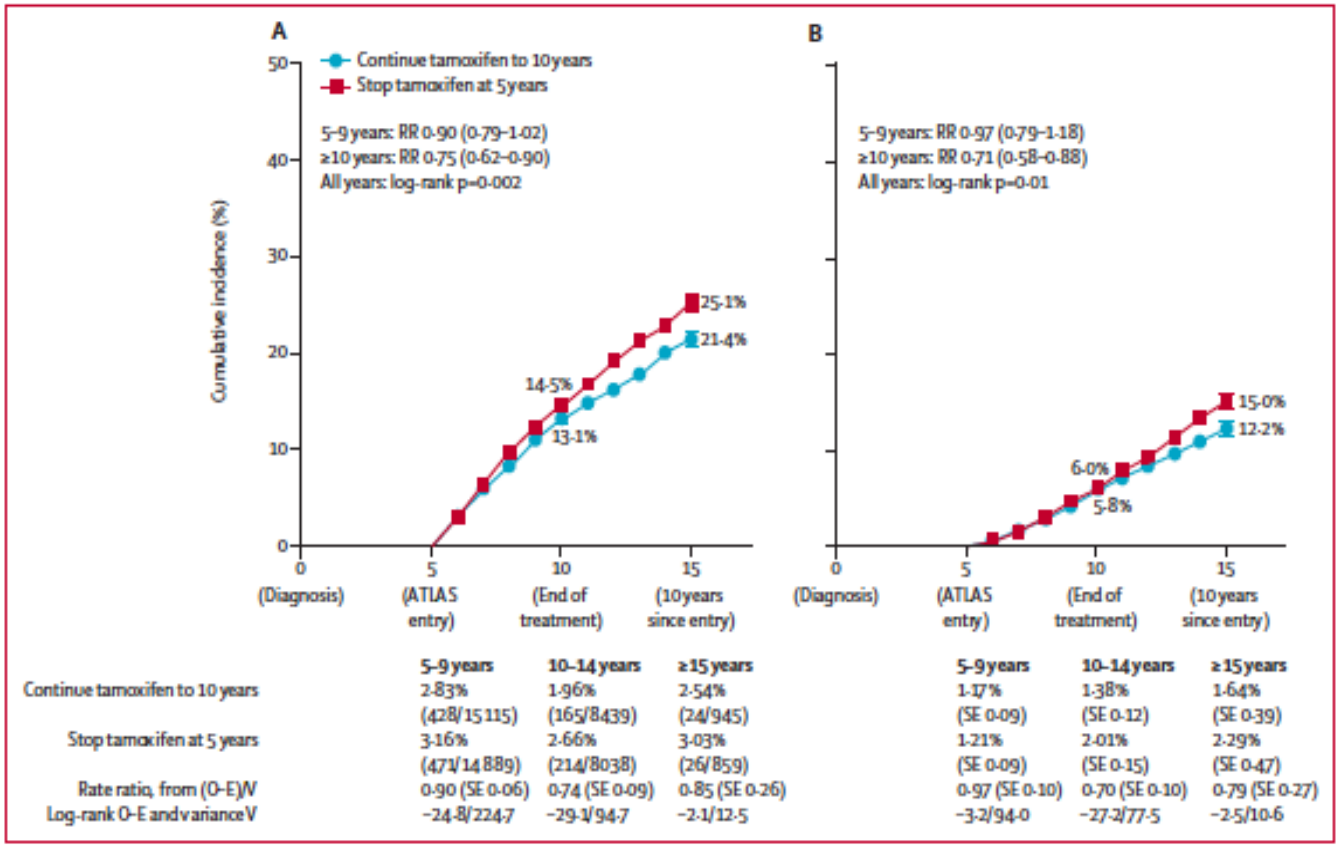


Death rates (% per year: total rate minus rate in women without rcurrence) and log-rank analyses

	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

EBCTCG, Lancet 2011

ATLAS

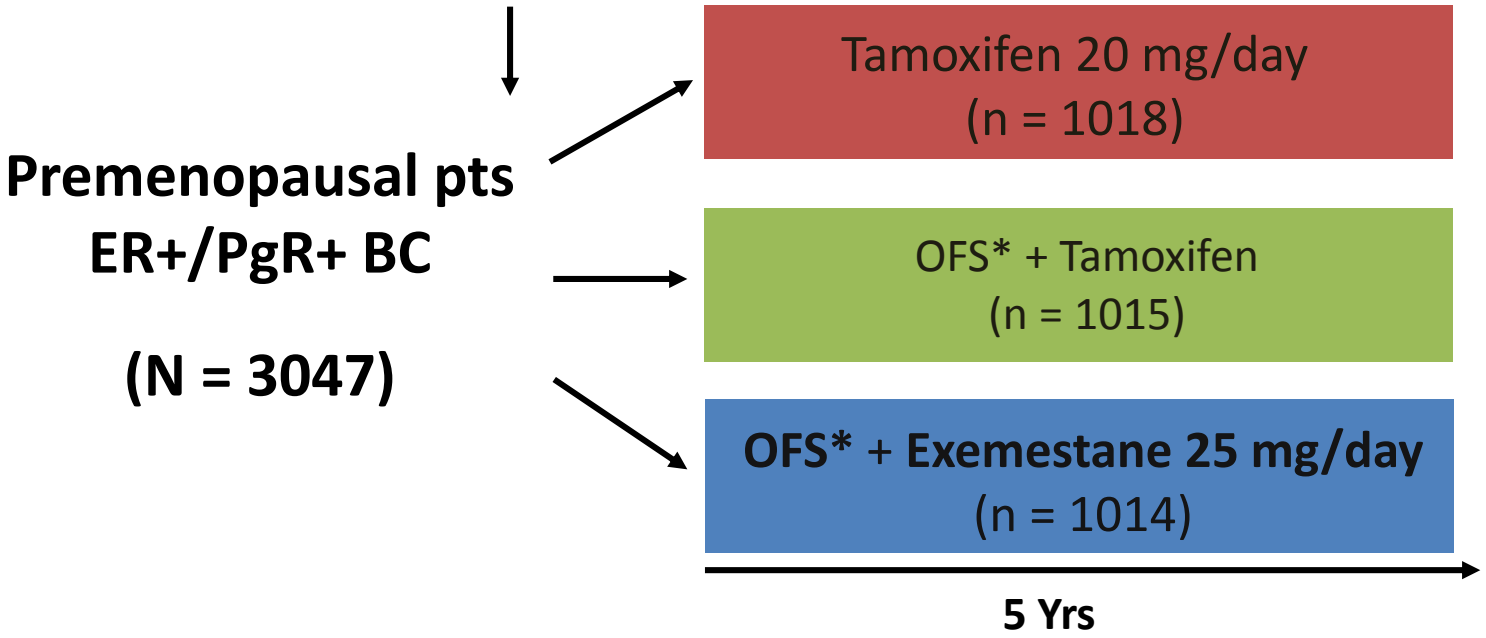


	5–9 years	10–14 years	≥15 years	5–9 years	10–14 years	≥15 years
Continue tamoxifen to 10 years	2·83% (428/15 115)	1·96% (165/8439)	2·54% (24/945)	1·17% (SE 0·09)	1·38% (SE 0·12)	1·64% (SE 0·39)
Stop tamoxifen at 5 years	3·16% (471/14 889)	2·66% (214/8038)	3·03% (26/859)	1·21% (SE 0·09)	2·01% (SE 0·15)	2·29% (SE 0·47)
Rate ratio, from (O–E)/V	0·90 (SE 0·06)	0·74 (SE 0·09)	0·85 (SE 0·26)	0·97 (SE 0·10)	0·70 (SE 0·10)	0·79 (SE 0·27)
Log-rank O–E and variance V	−24·8/224·7	−29·1/94·7	−2·1/12·5	−3·2/94·0	−27·2/77·5	−2·5/10·6

Figure 3: Recurrence (A) and breast cancer mortality (B) by treatment allocation for 6846 women with ER-positive disease
Bars show SE. Recurrence rates are percentage per year (events/patient-years of follow-up). Death rates (overall rate– rate in women without recurrence) are

SOFT

Stratified by prior chemotherapy (yes vs no) and nodal status (+ vs -)



- Primary endpoint: DFS
- Secondary endpoints: BCFI, DRFI, OS

*Triptorelin, oophorectomy, or irradiation

Francis P, et al. SABCS 2014. Abstract S3-08. Francis PA, et al. N Engl J Med. 2014;

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

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

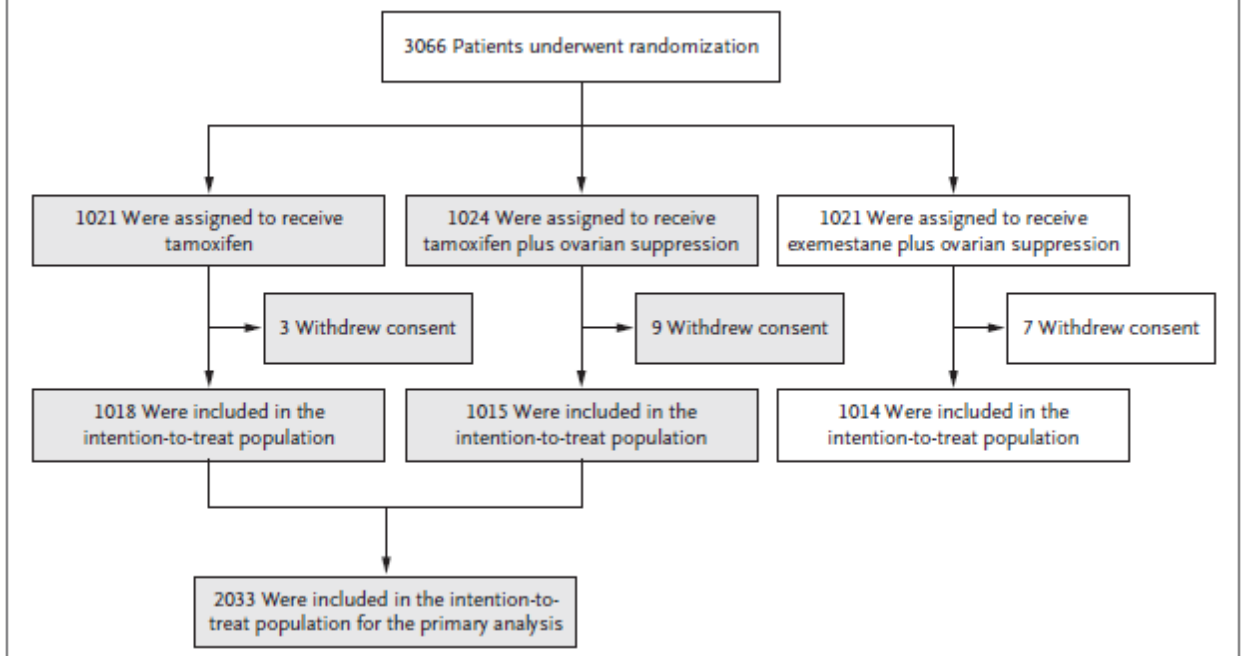
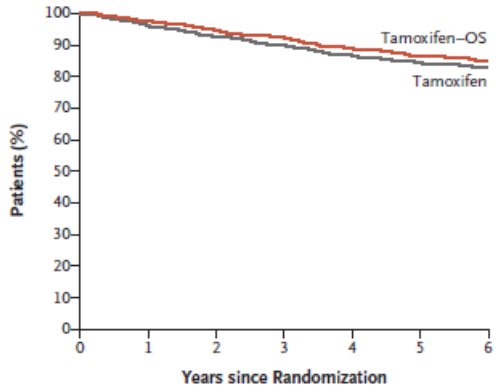


Figure 1. Randomization and Primary Analysis Populations.

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)

A Disease-free Survival



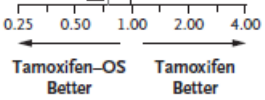
	No. of Patients	No. of Patients with Event	5-Yr Rate %
Tamoxifen	1018	160	84.7
Tamoxifen–OS	1015	139	86.6

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

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

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)	



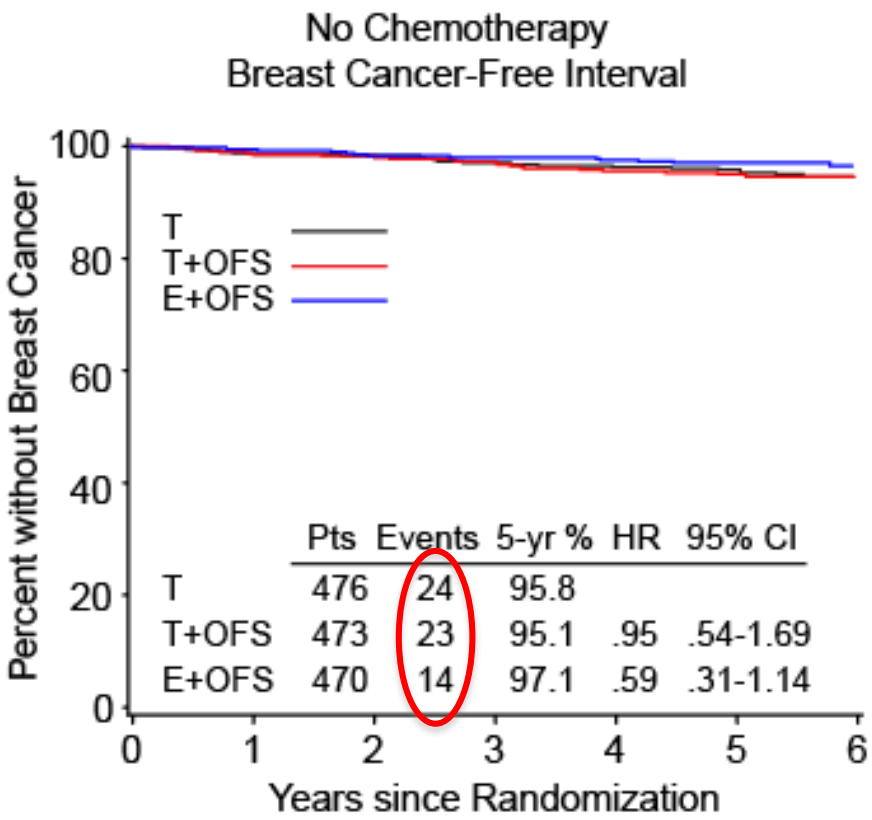
SOFT

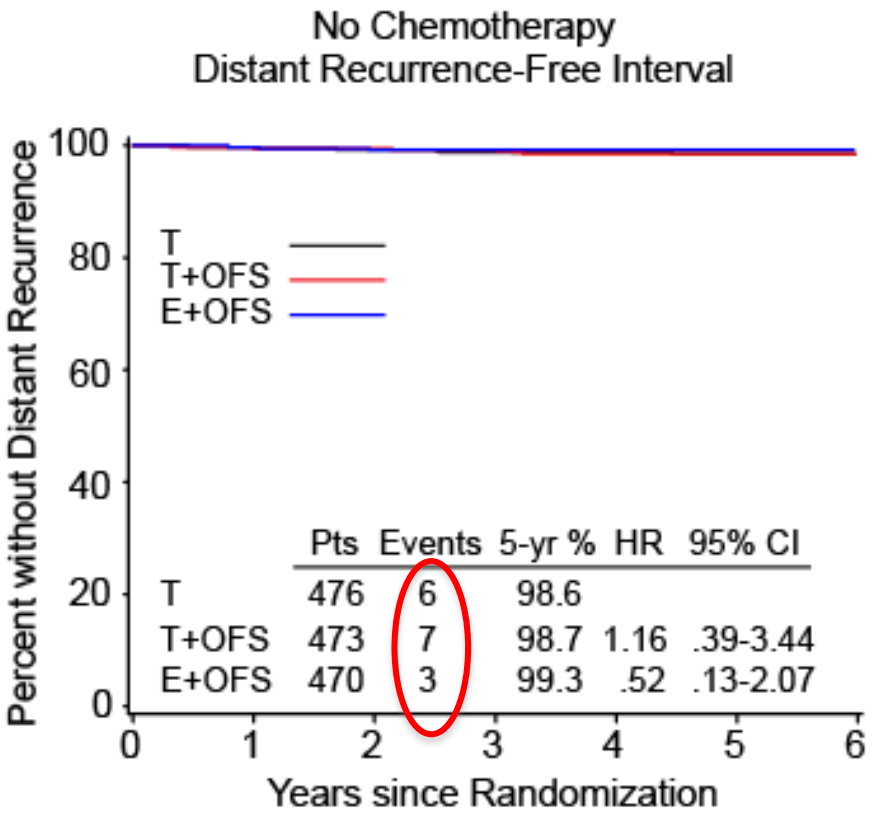
"No chemotherapy" pts had low risk features

- 90% ≥ 40 yrs,
- 91% node negative,
- 85% tumor ≤ 2 cm,
- 41% grade 1

Francis P, et al. SABCS 2014. Abstract S3-08. Francis PA, et al. N Engl J Med. 2014.

Premenopausal No Chemotherapy

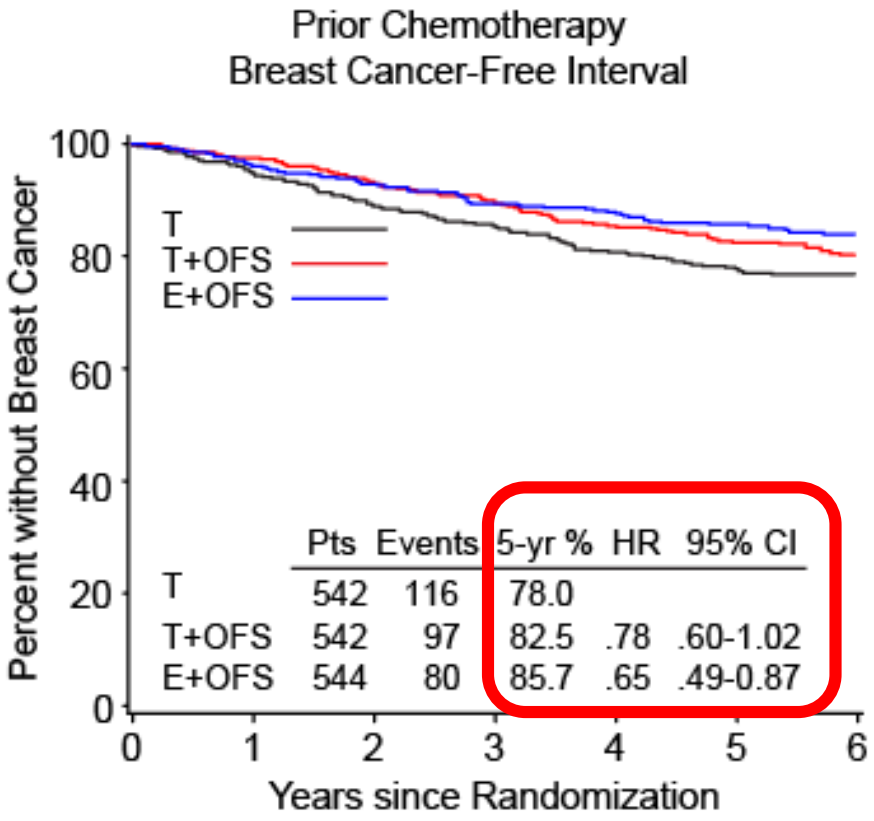


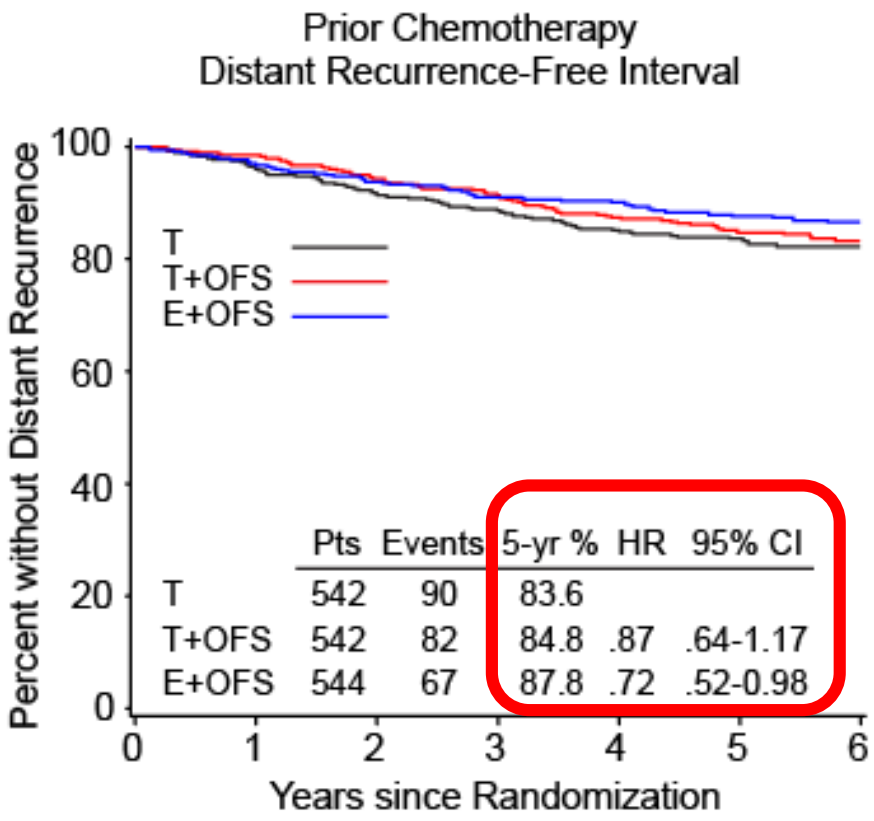


Cohort selected for low risk clinicopathologic features

Francis P, et al. SABCS 2014. Abstract S3-08. Francis PA, et al. N Engl J Med. 2014.

Premenopausal after Prior Chemotherapy





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

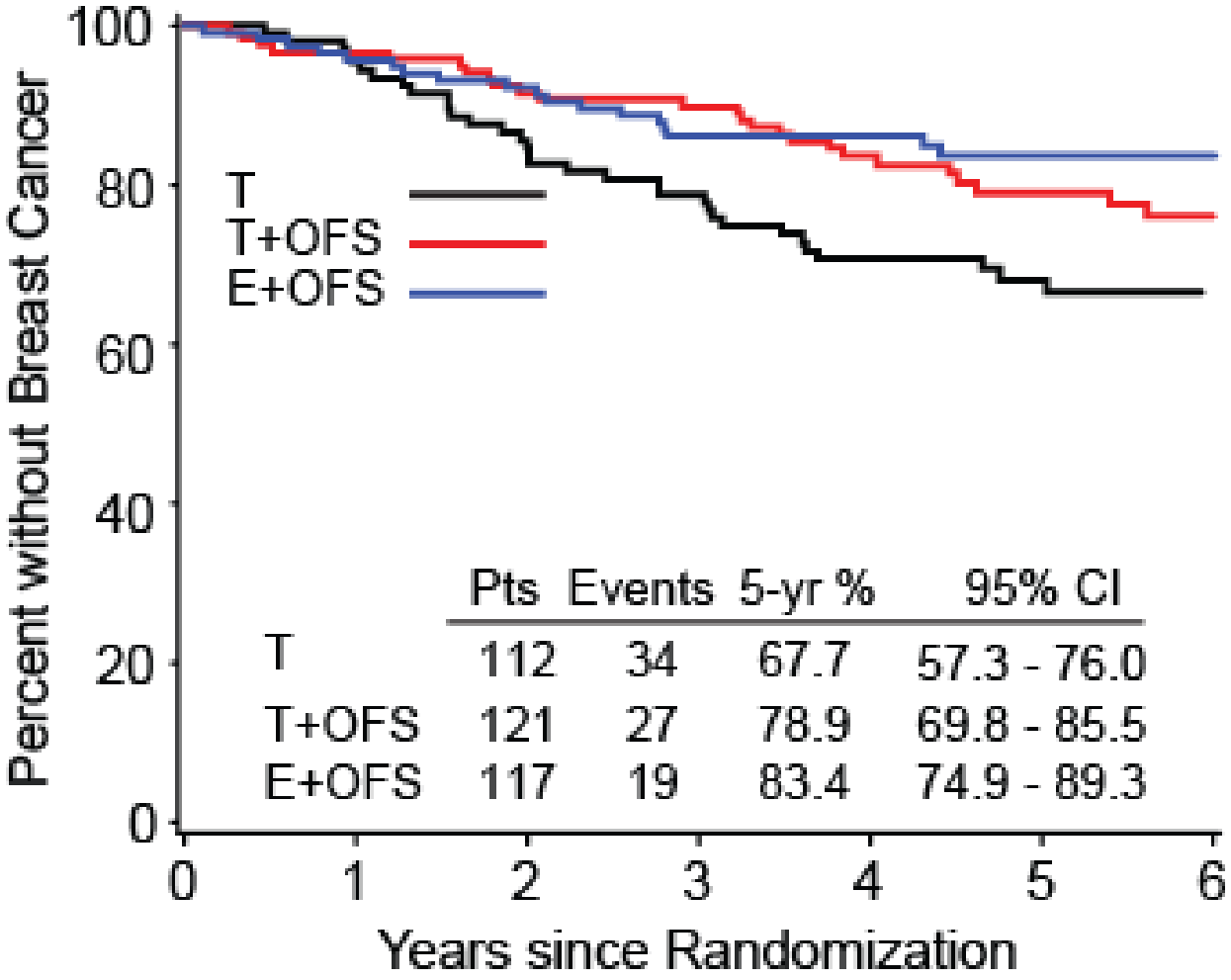
E+OFS v T: Absolute improvement in 5-yr BCFI: 7.7%

E+OFS v T+OFS: Absolute improvement in 5-yr DRFI: 4.2%

Francis P, et al. SABCS 2014. Abstract S3-08. Francis PA, et al. N Engl J Med. 2014.

All women < 35 years of age

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



Francis P, et al. SABCS 2014. Abstract S3-08. Francis PA, et al. N Engl J Med. 2014.

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)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

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

CONCLUSIONS

Adding ovarian suppression to tamoxifen did not provide a significant benefit in the overall study population. However, for women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of ovarian suppression improved disease outcomes. Further improvement was seen with the use of exemestane plus ovarian suppression. (Funded by Pfizer and others; SOFT ClinicalTrials.gov number, NCT00066690.)

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Adjuvant Exemestane with Ovarian Suppression
Premenopausal Breast Cancer

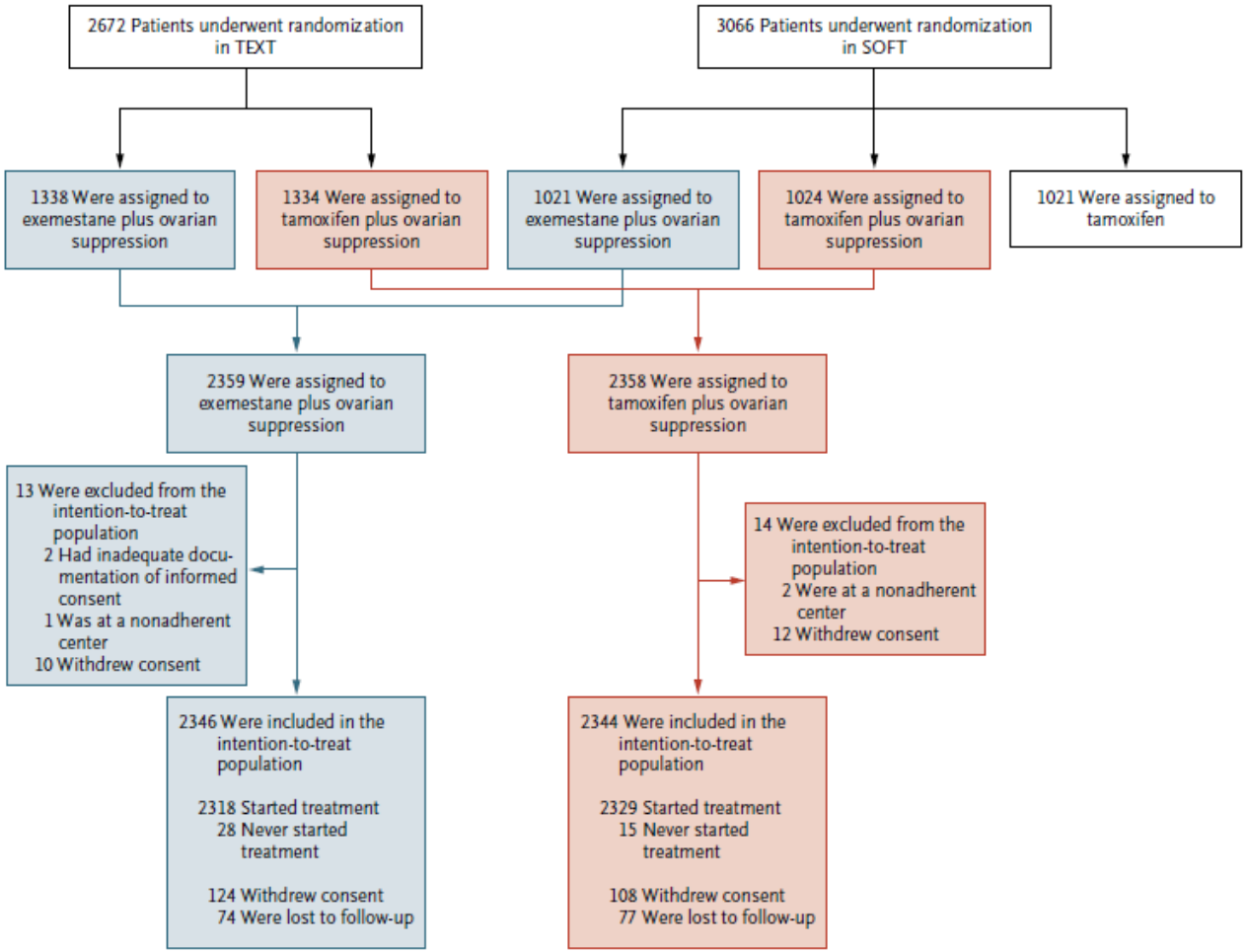
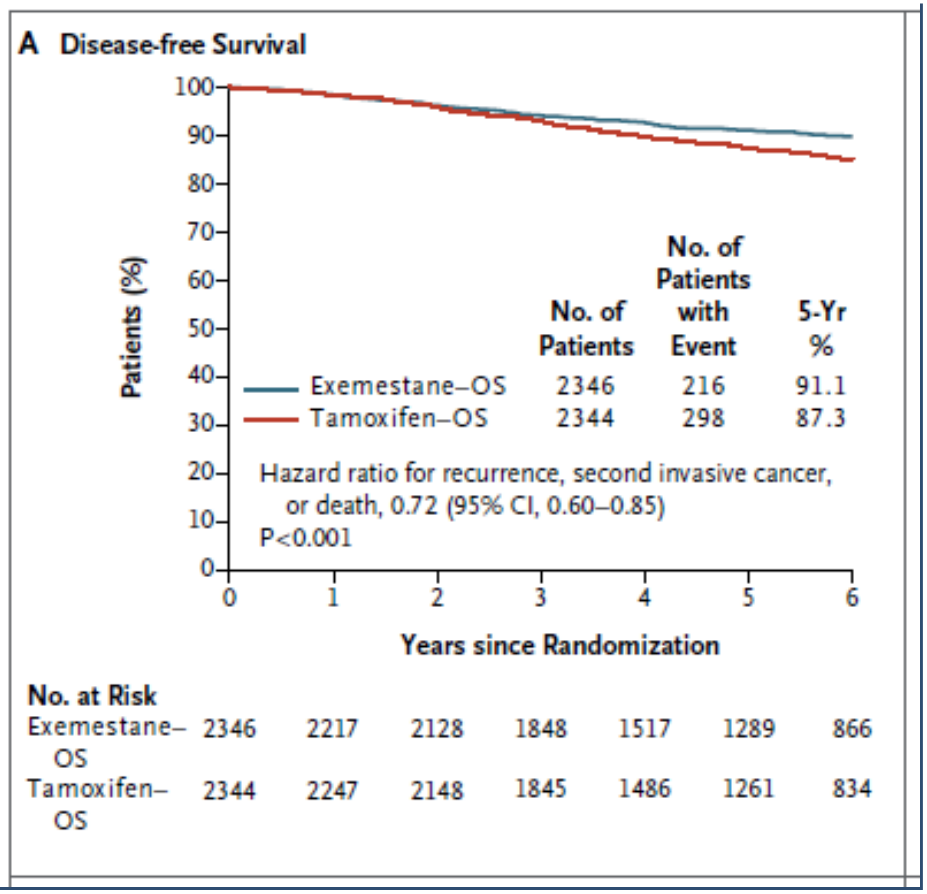


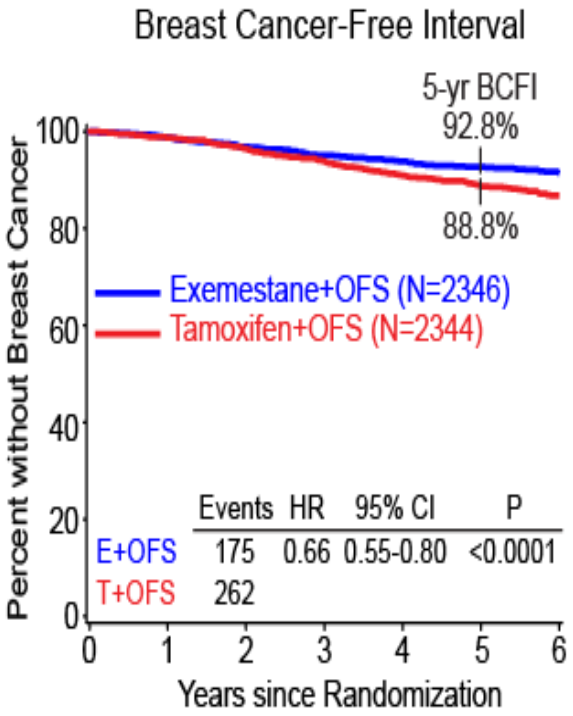
Figure 1. Randomization, Treatment, and Follow-up.

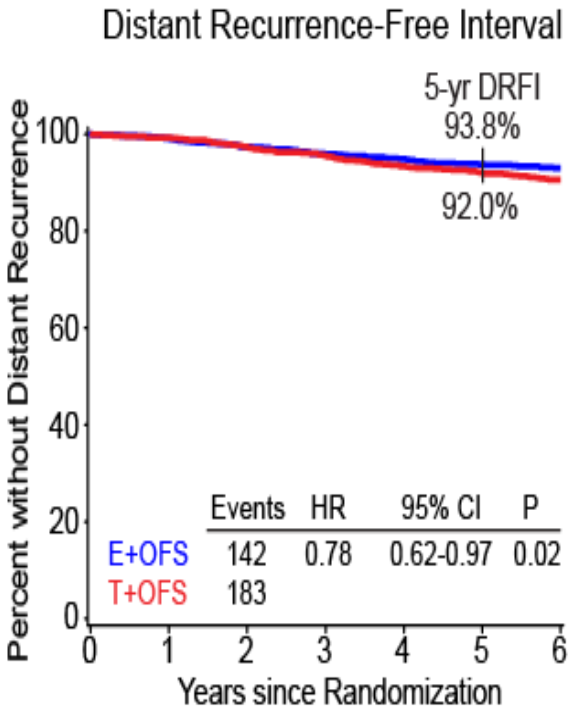
Of the 383 patients who withdrew consent or were lost to follow-up, 150 consented to the continued submission of disease-recurrence and survival status from medical records or such updates are obtainable from tumor and vital registries according to the protocol follow-up schedule. SOFT denotes Suppression of Ovarian Function Trial, and TEXT Tamoxifen and Exemestane Trial.

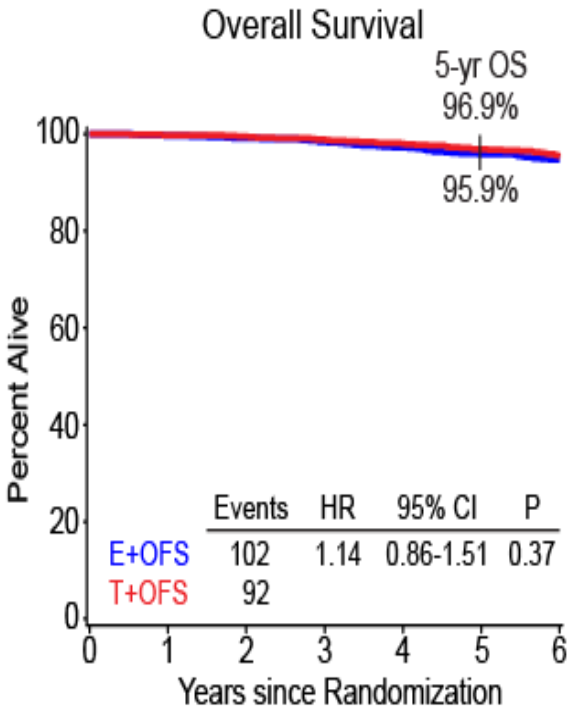
DFS


A Disease-free Survival
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
No. of Patients
No. of Patients with Event
5-Yr %
Exemestane–OS 2346 216 91.1
Tamoxifen–OS 2344 298 87.3
Hazard ratio for recurrence, second invasive cancer, or death, 0.72 (95% CI, 0.60–0.85)
P<0.001
0 1 2 3 4 5 6
Years since Randomization
No. at Risk
Exemestane–OS 2346 2217 2128 1848 1517 1289 866
Tamoxifen–OS 2344 2247 2148 1845 1486 1261 834

Exemestane+OFS Reduced Recurrence

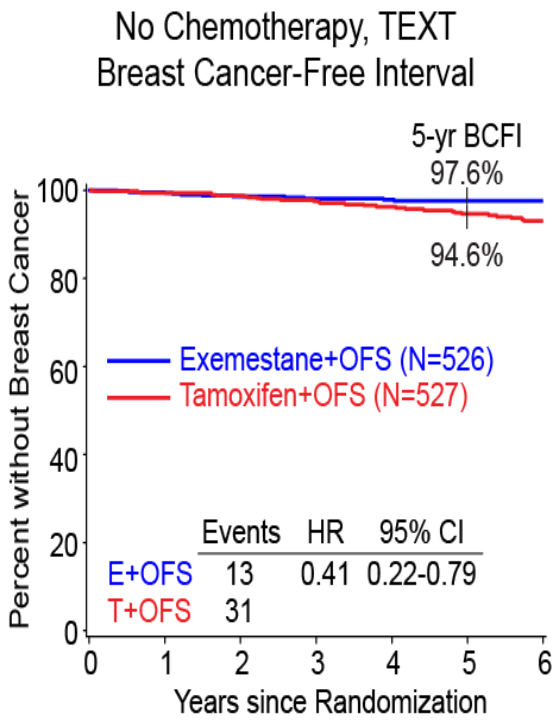




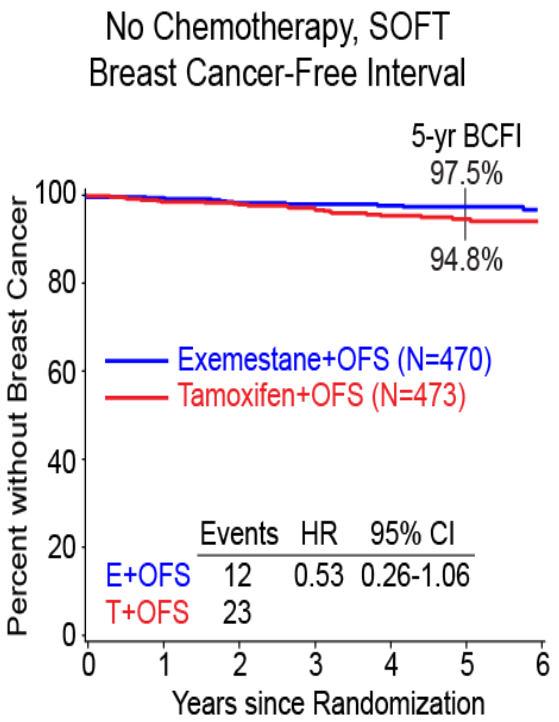


- 4% absolute improvement in 5-yr freedom from breast cancer for Exe+OFS
- 1.8% absolute improvement in 5-yr freedom from distant recurrence for Exe+OFS
- No significant difference in overall survival

Women Who Did Not Receive Chemotherapy



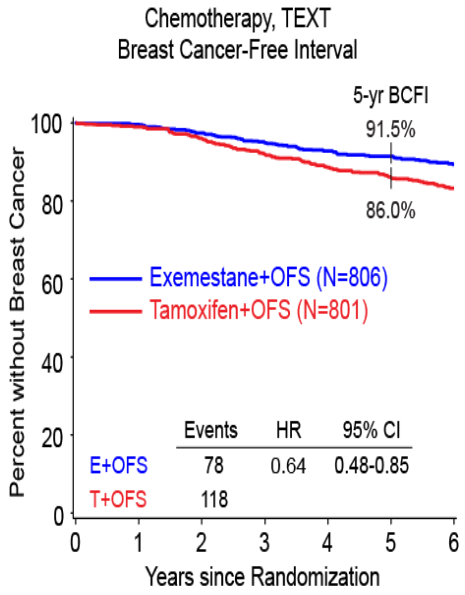
N=1996

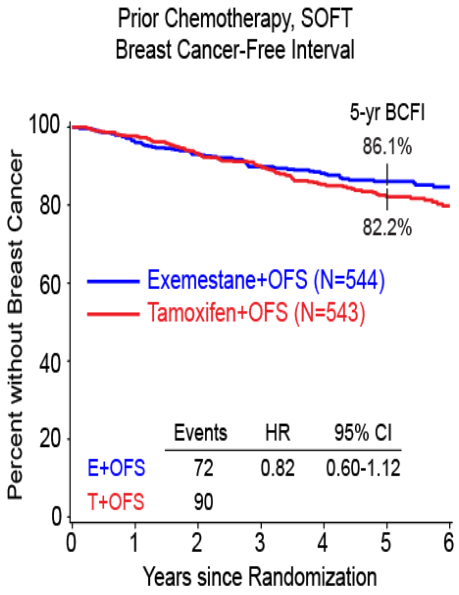


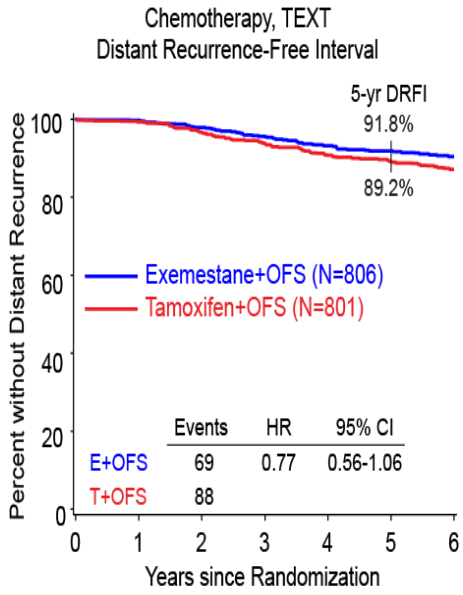
16% <40 years; 19% T-size >2cm; 21% N+

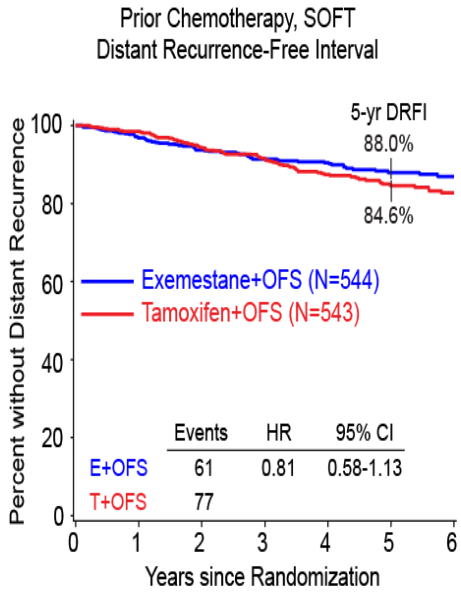
9% <40 years; 15% T-size >2cm; 8% N+

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

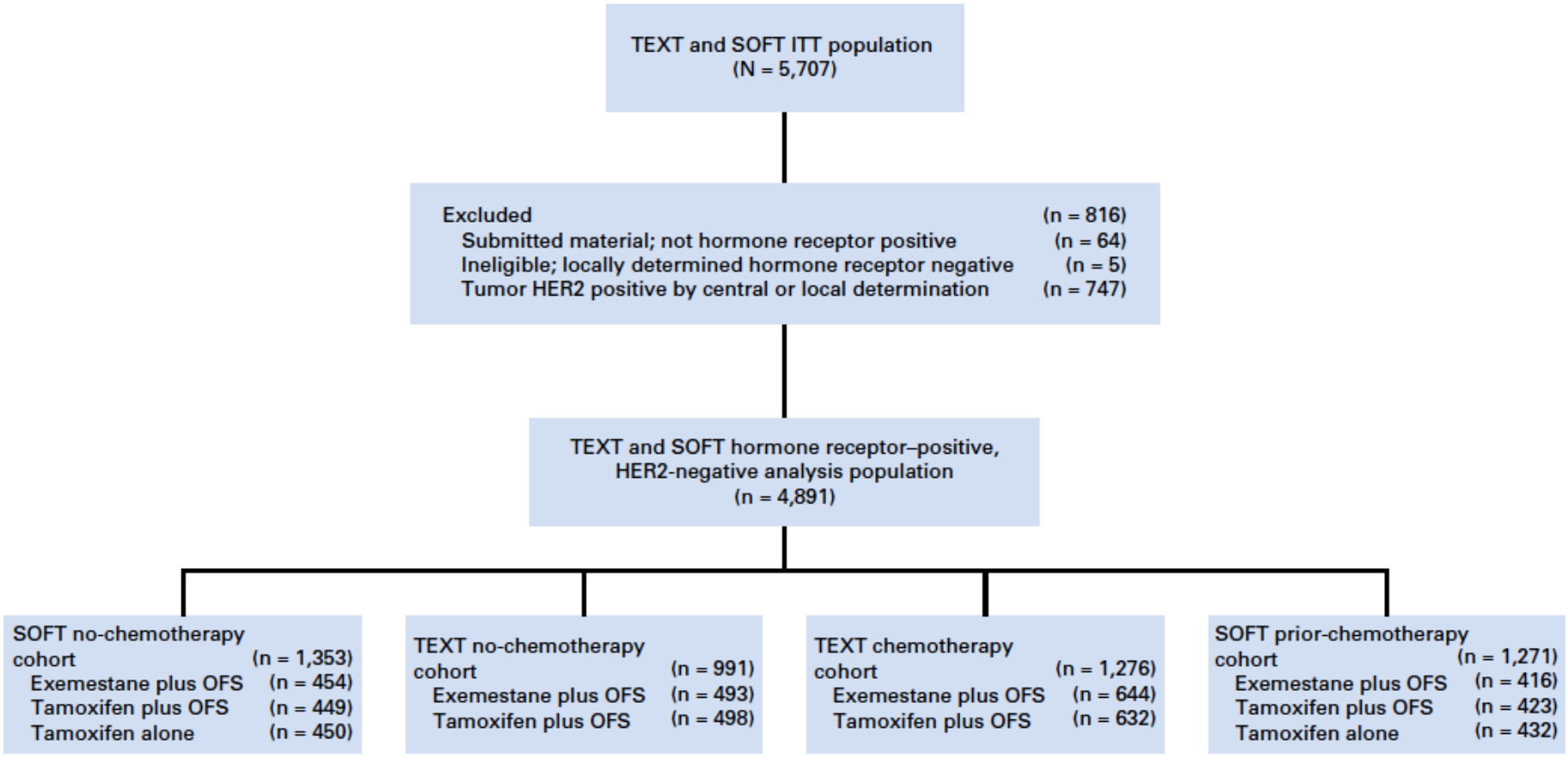
5-yr freedom from breast cancer: 5.5% in TEXT and 3.9% in SOFT

5-yr freedom from distant recurrence: 2.6% in TEXT and 3.4% in SOFT

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

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)

To understand absolute benefit in SOFT/TEXT trials



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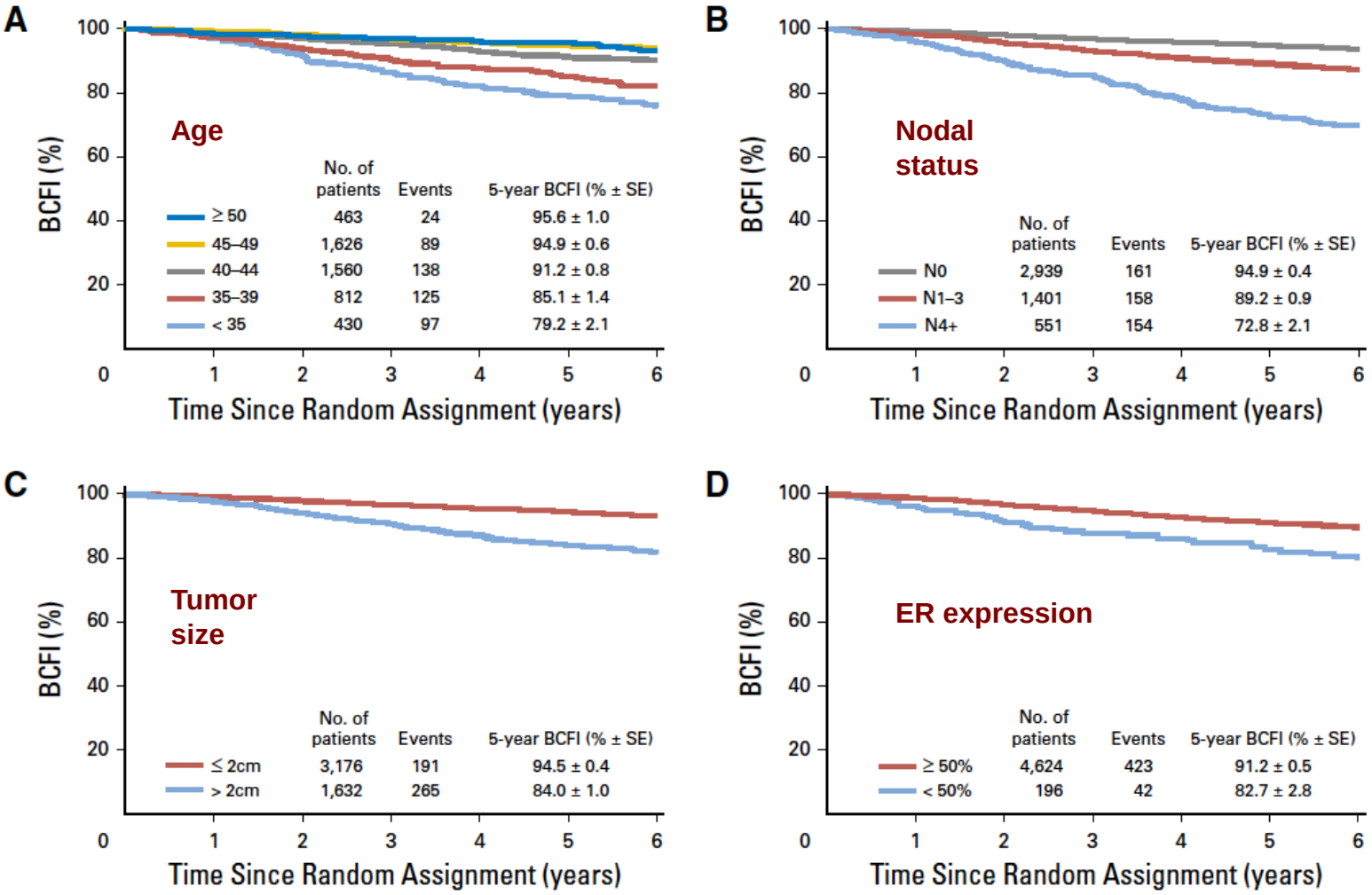
Prognostic factors



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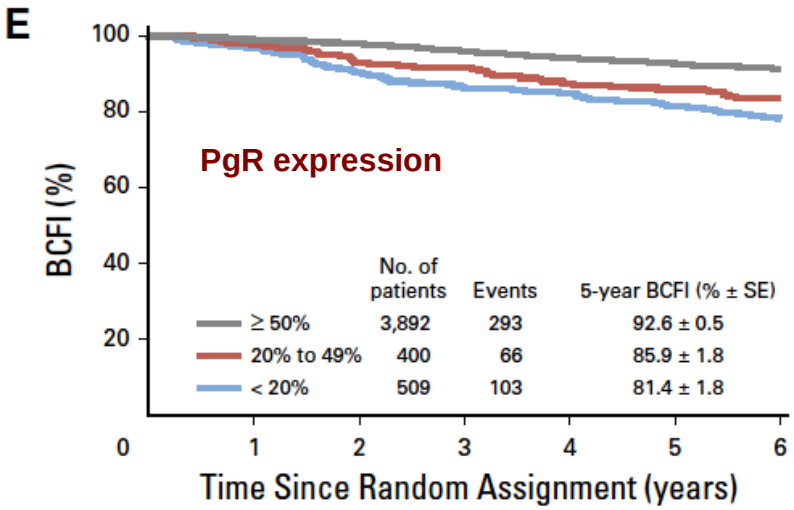
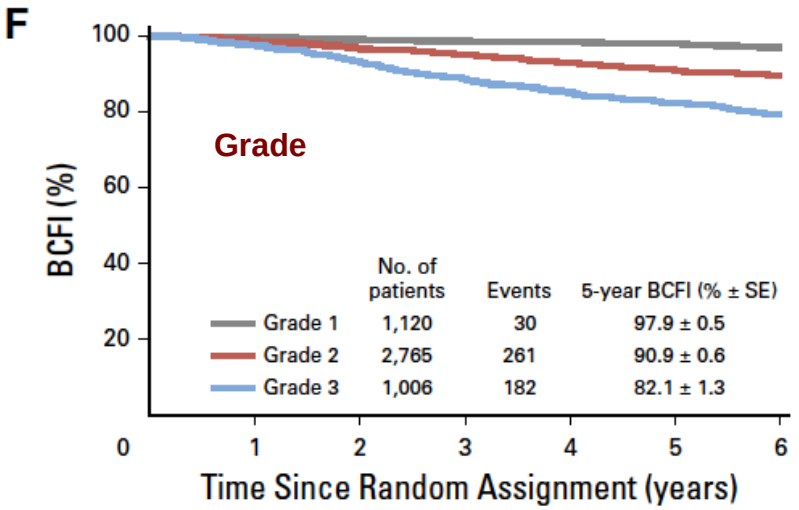
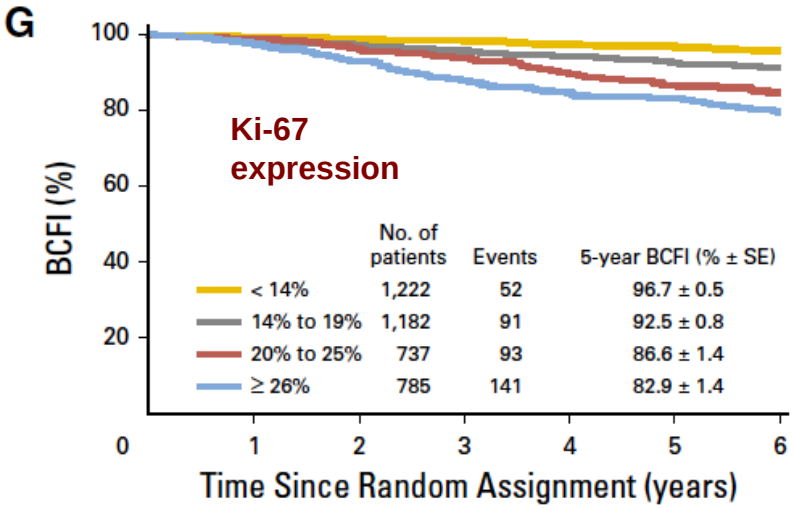
Prognostic factors







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Cox Proportional Hazards Model for Defining the Composite Measure of Recurrence Risk

Parameter	HR	95% CI	P value
Age at random assignment, years			
<35	2.2	1.6-3.1	<0.01
35-39	1.7	1.3-2.3	<0.01
40-44	1.3	1.0-1.7	NS
45-49	Ref	-	-
≥50	1.2	0.7-1.8	NS
No. of positive nodes			
0	Ref	-	-
1-3	1.5	1.1-1.9	<0.01
≥4	3.1	2.4-4.0	<0.01
Tumor grade			
1	Ref	-	-
2	2.5	1.7-3.8	<0.01
3	3.0	1.9-4.9	<0.01

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Cox Proportional Hazards Model for Defining the Composite Measure of Recurrence Risk (cont'd)

Parameter	HR	95% CI	P value
Tumor size, cm			
≤2	Ref	-	-
>2	1.5	1.2-1.9	<0.01
ER expression, %			
<50	1.3	0.9-1.8	NS
≥50	Ref	-	-
PgR expression, %			
<20	1.6	1.2-2.0	<0.01
20-49	1.3	1.0-1.7	0.06
≥50	Ref	-	-
Ki-67 expression, %			
<14	Ref	-	-
14-19	1.1	0.7-1.6	NS
20-25	1.3	0.9-1.9	NS
≥26	1.6	1-2.3	0.03

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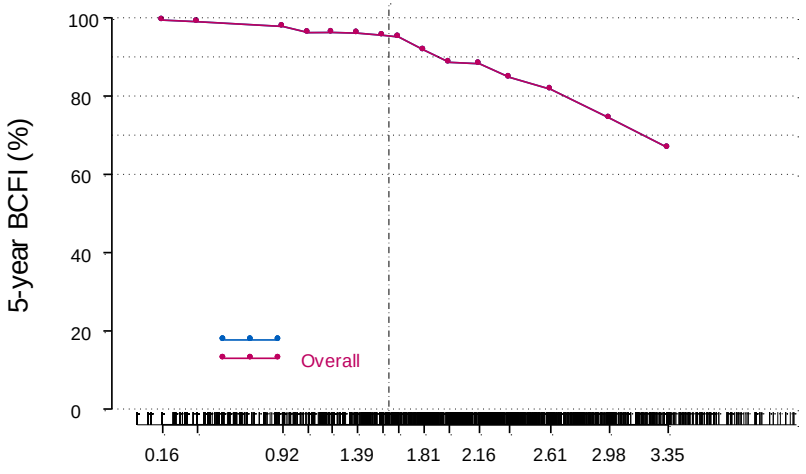
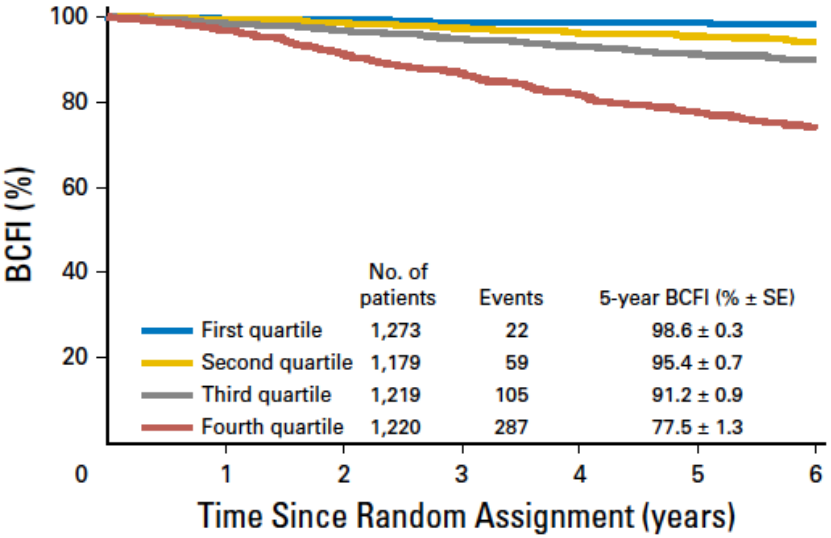
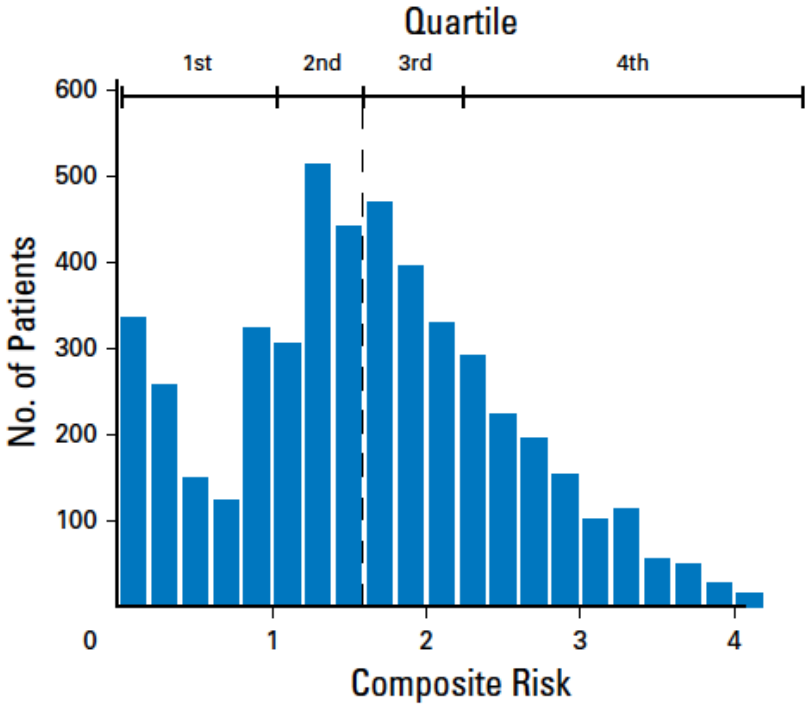
STEPP of 5-year BCFI according to Composite Risk Score: Overall HER2-negative



Median CPRS in Subpopulations





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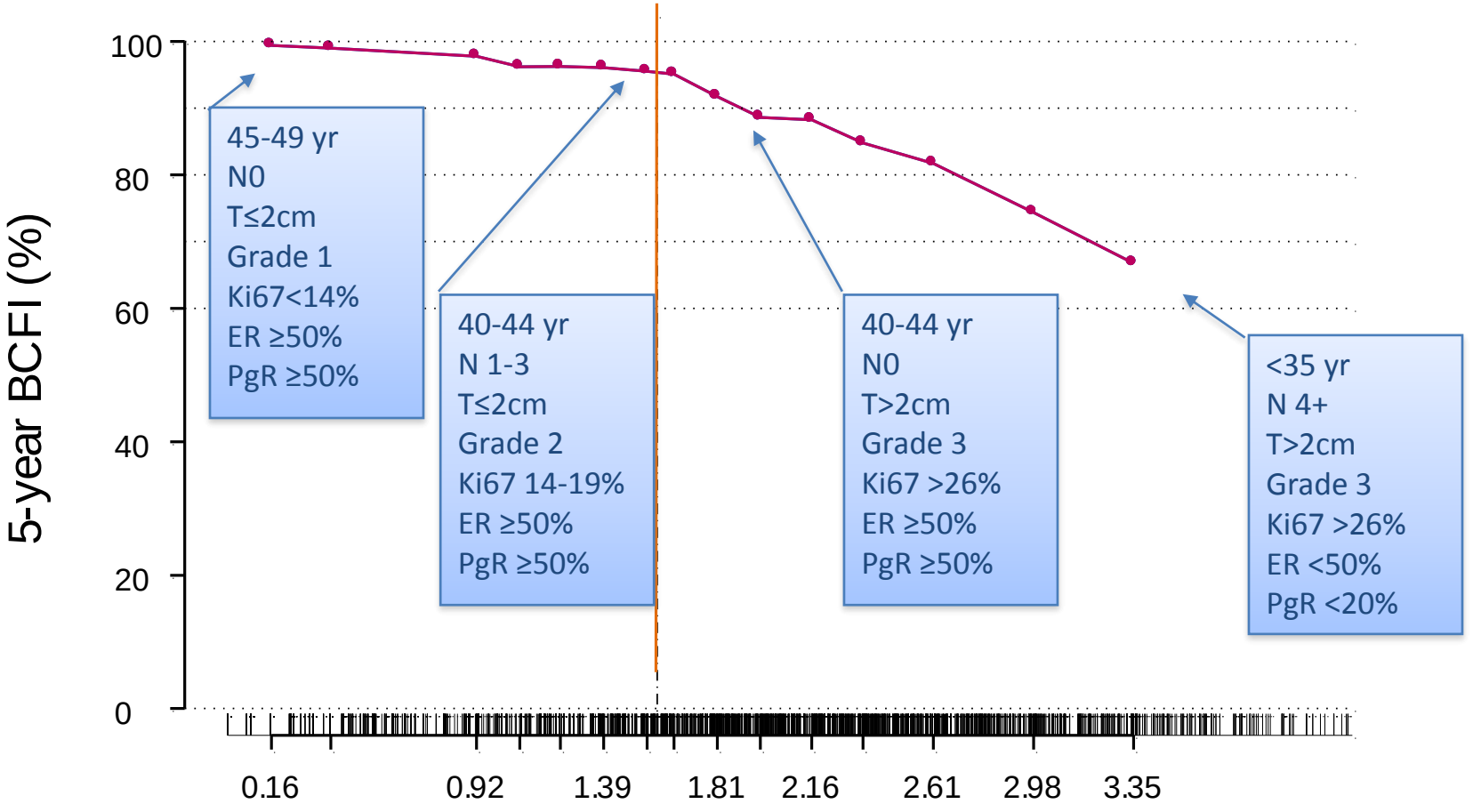
STEPP of 5-year BCFI according to Composite Risk Score: Overall HER2-negative



Median Composite Risk Score in Subpopulations

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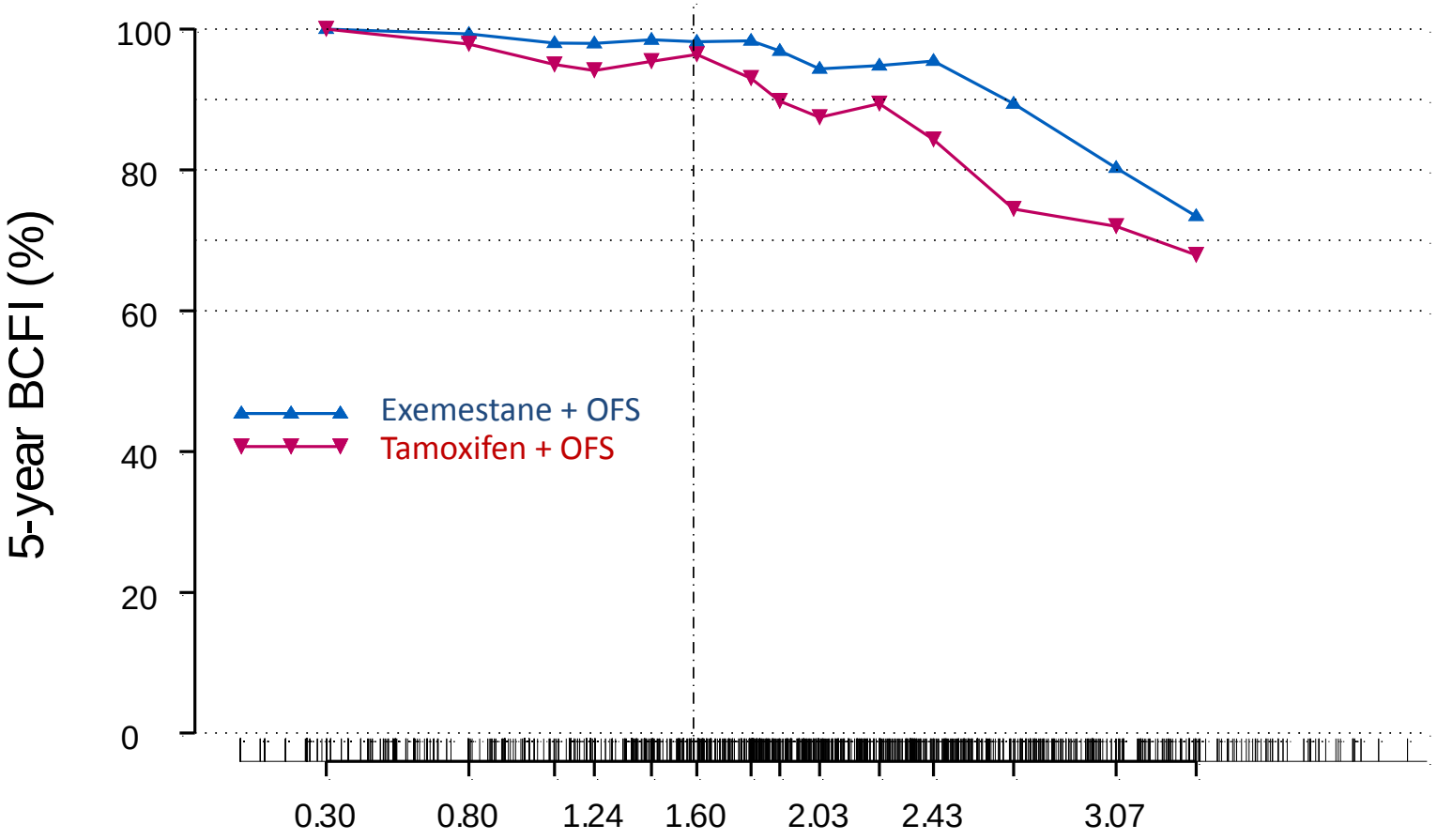
STEPP of 5-year BCFI according to Composite Risk Score: TEXT +/- Chemo



Median Composite Risk Score in Subpopulations

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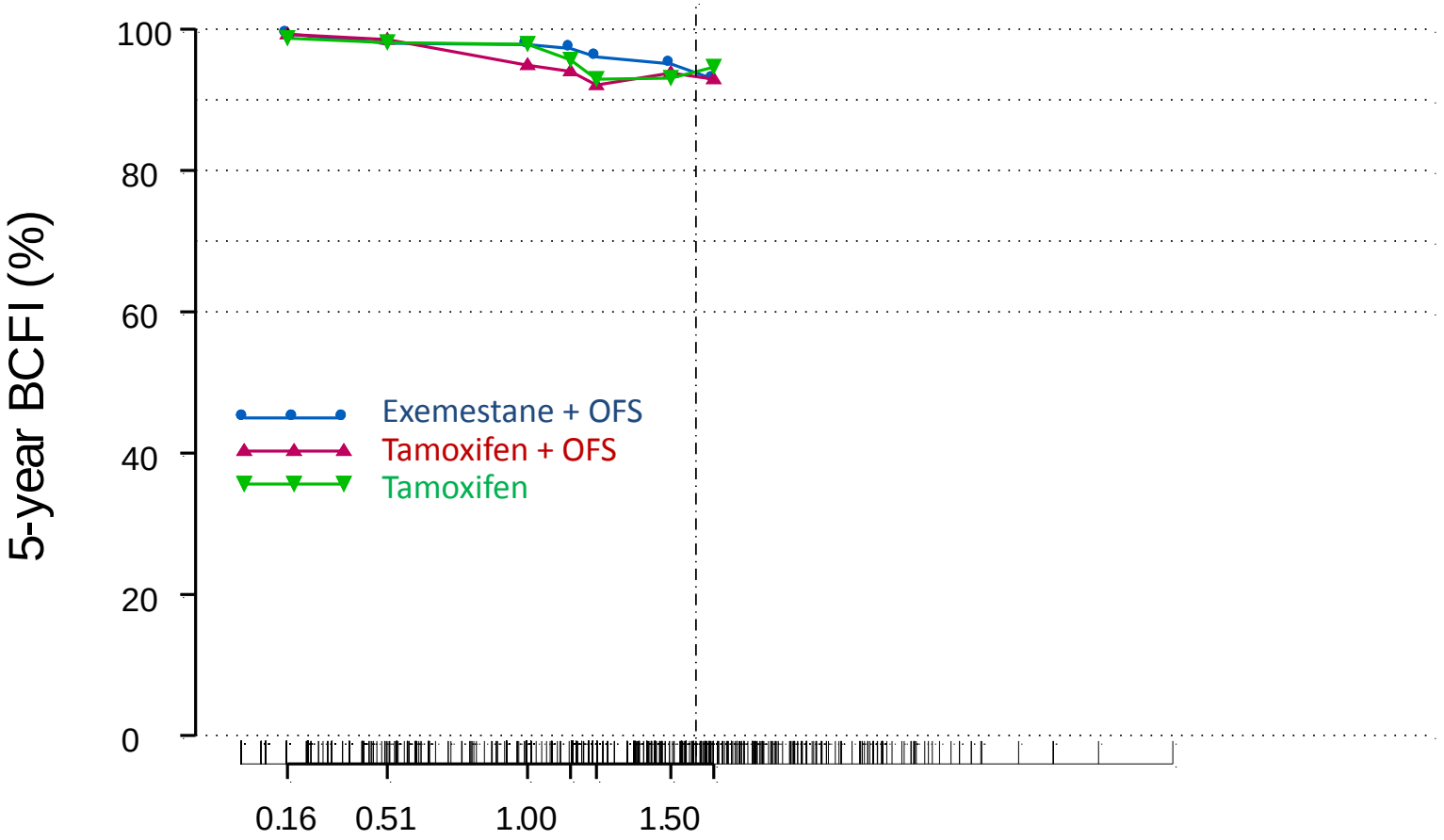
STEPP of 5-year BCFI according to Composite Risk Score: SOFT No Chemo



Median Composite Risk Score in Subpopulations

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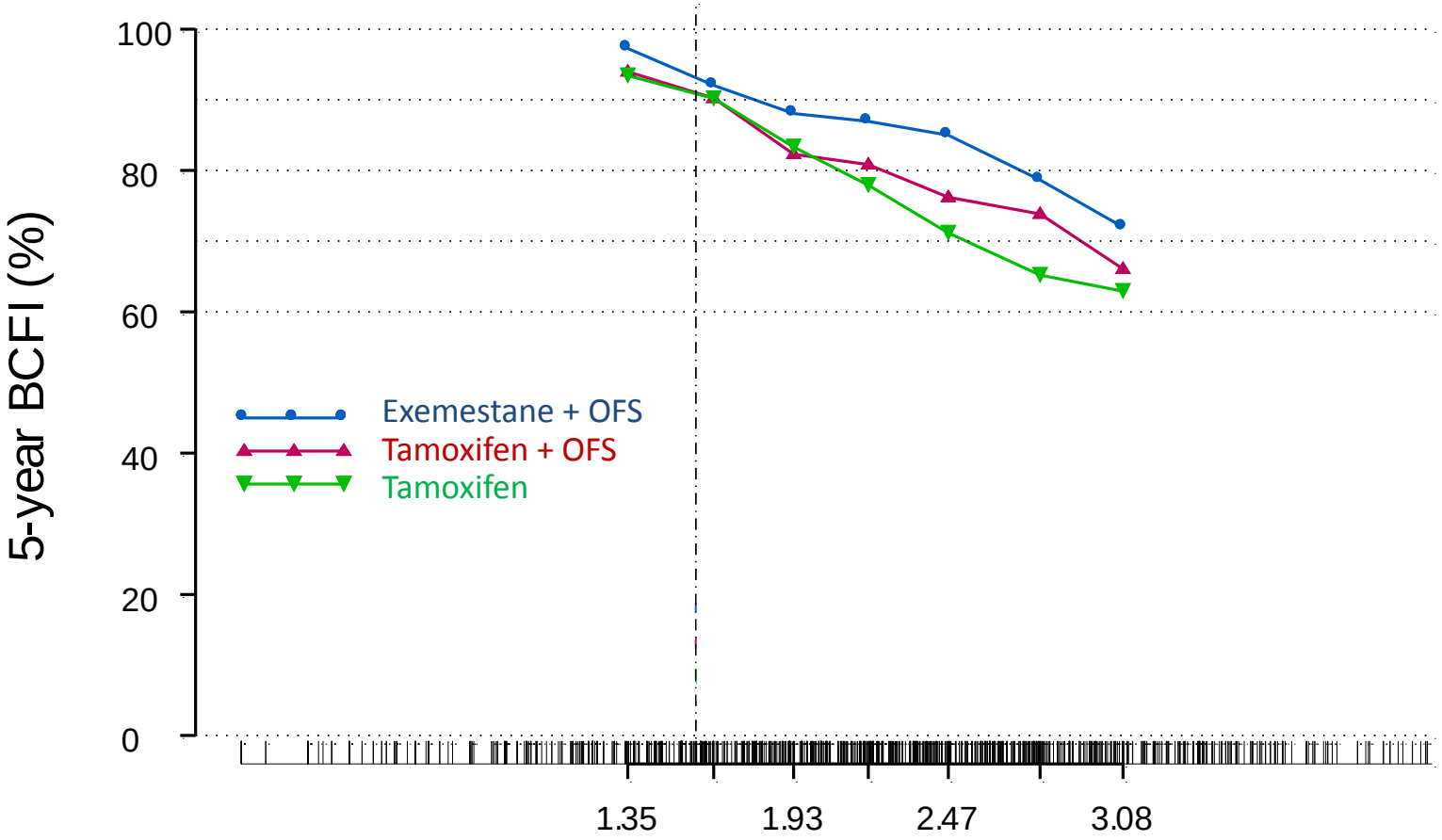
STEPP of 5-year BCFI according to Composite Risk Score: SOFT Prior Chemo



Median Composite Risk Score in Subpopulations

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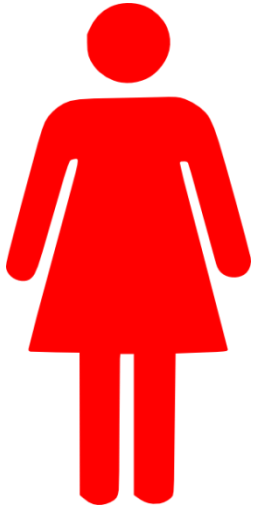
Absolute benefit (AB) in 5-year BCFI and NNT according to clinical scenario

SOFT No-Chemo

5-year BCFI 96.1%

Pts did well with all endocrine therapies

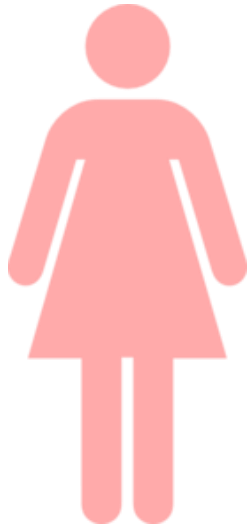


TEXT No-Chemo

OFS + E vs OFS + T (AB 3.6%; NNT 27)

OFS + E vs OFS + T (AB* 10%; NNT 10)

OFS + E vs OFS + T (AB 1%; NNT 100)**

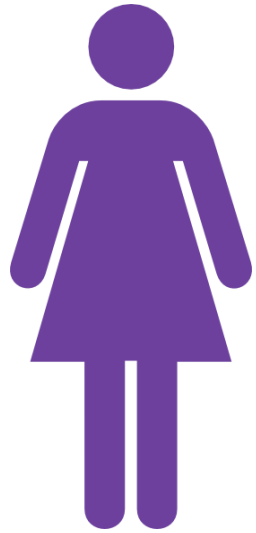


TEXT Chemo

OFS + E vs OFS + T (AB 5.8%; NNT 17)

OFS + E vs OFS + T (AB* 15%; NNT 6)

OFS + E vs OFS + T (AB 5%; NNT 20)**



SOFT Chemo

OFS + E vs OFS + T (AB 5.4%; NNT 18)

OFS + E vs T (AB 7.4%; NNT 13)

OFS + T vs T (AB* 5%; NNT 20)

*high composite risk
**low composite risk

EXPERT REVIEW OF ANTICANCER THERAPY, 2015
http://dx.doi.org/10.1586/14737140.2016.1128327

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REVIEW

Endocrine therapy in premenopausal women with breast cancer: a critical appraisal of current evidence

Filippo Montemurro[a], Lucia Del Mastro[b], Michele De Laurentiis[c] and Fabio Puglisi[d,e]

Table 1. Authors' suggestions on the optimal duration of tamoxifen therapy, the use of OFS, and the choice between tamoxifen plus OFS and exemestane plus OFS.

Which is the optimal duration of tamoxifen therapy?	Well-grounded evidence shows the benefits of prolonging tamoxifen therapy up to 10 years, compared with stopping treatment at 5 years. Prolonged tamoxifen may however be associated with a potentially increased risk of endometrial cancer.
Should OFS be prescribed to all premenopausal patients?	Available evidence shows that the addition of OFS to tamoxifen or exemestane contributes to further reduce the risk of recurrence in moderate- and high-risk patients.
Should exemestane plus OFS be preferred over tamoxifen plus OFS?	Exemestane plus OFS prolongs DFS as compared with tamoxifen plus OFS. However, no advantages in OS were shown. Exemestane plus OFS is a reasonable option for higher-risk patients and for patients for whom tamoxifen should be avoided.

DFS: disease-free survival; OFS: ovarian function suppression.

Grazie per l’attenzione!