Lo studio SOFT

commento alla metodologia

Valter Torri

Istituto 'IRCCS-Mario Negri', Milano

Analisi critica

- Peculiarità e rilevanza del quesito
  - popolazione / interventi / outcomes
- Validità
  - disegno / conduzione / analisi
- Risultati
  - presentazione / interpretazione
- Implicazioni

Peculiarità del quesito

- Terapia adiuvante:
  - Trattamento di pazienti apparente libere da malattia per ridurre il rischio di recidive
- Peculiarità:
  - si applica a *molte pazienti*,
    ma *poche ne trarranno beneficio*

- Ricadute:
  - Disegno (protocol changes)
    sample size (≈1000 pts/arm)
    durata (≈12 yrs)
  - valutazione benefico:rischio

Validità

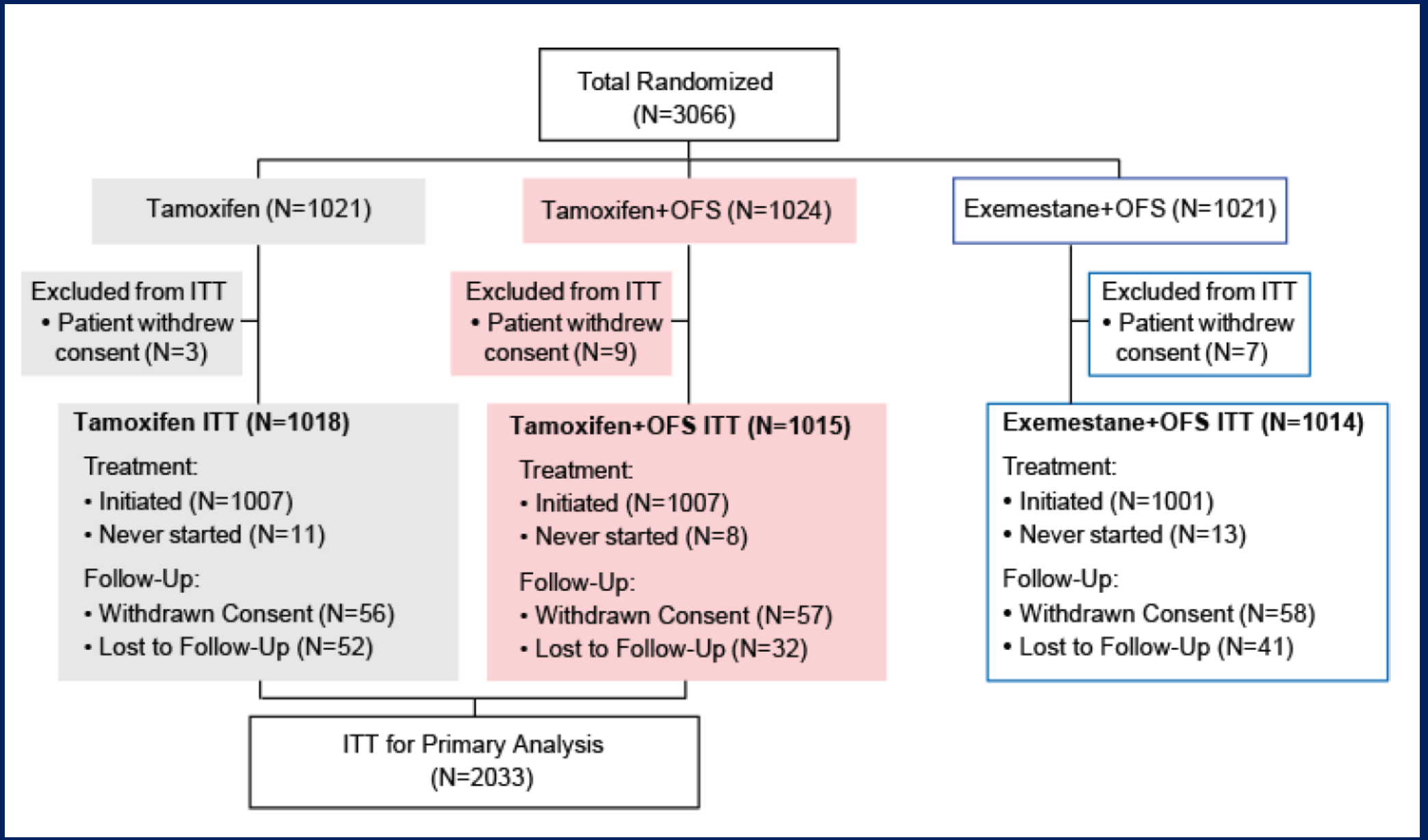
- Disegno
  - Pragmatico, di strategia
    - “all inclusive”: minime restrizioni
    - different option for ovarian ablation/suppression allowed

- Criticità
  - Case-mix differente rispetto all’atteso: pazienti più anziane e a minor rischio

  → Riduzione della potenza statistica

  →Cambio del quesito
    - Esclusione del confronto col braccio con AI exemestane da analisi primaria

CONSORT flow-diagram



Effetti sulla precisione

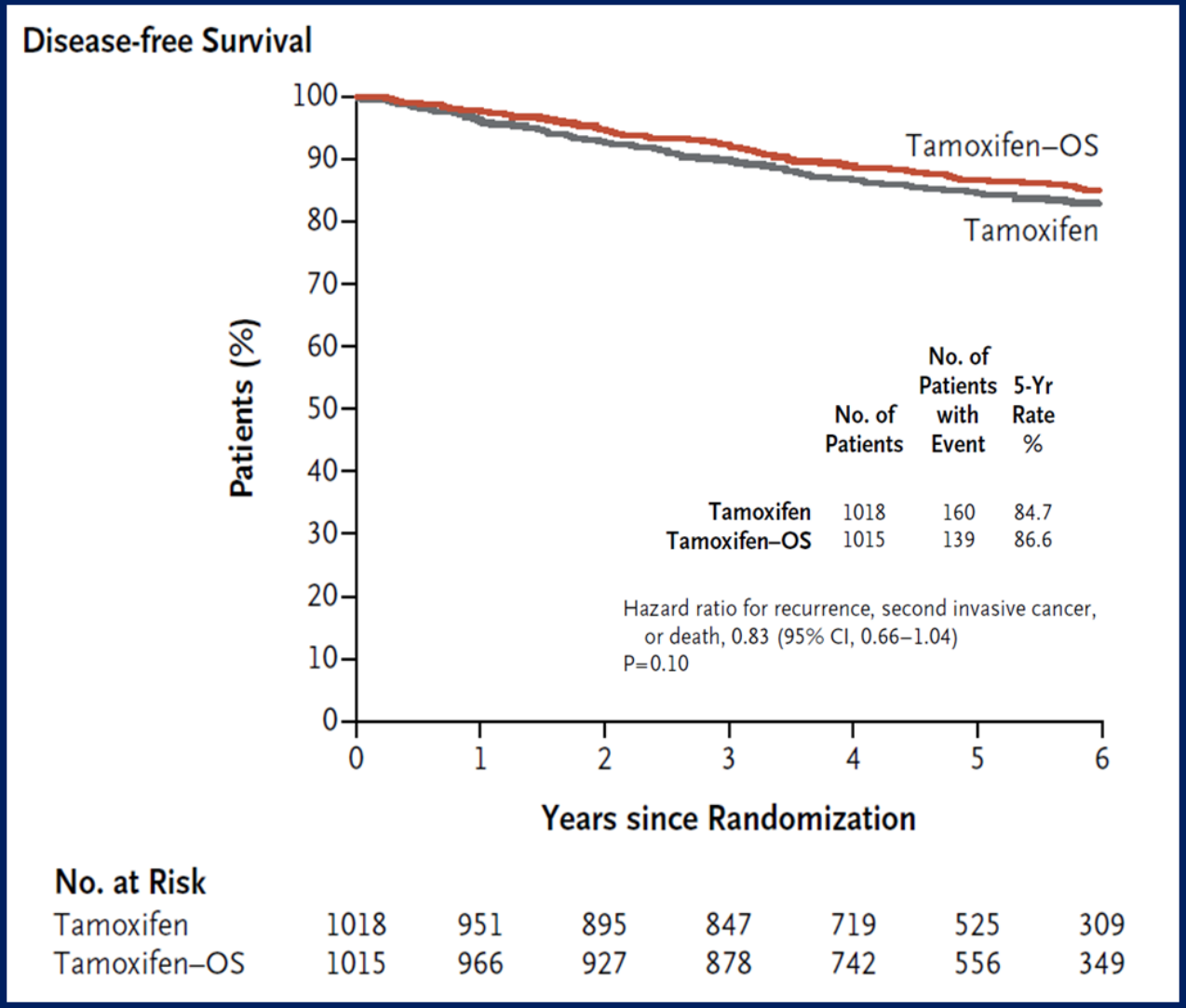
- Da protocollo

  "We calculated that with an estimated 186 events of disease recurrence, second invasive cancer, or death in the two treatment groups after a median follow-up of 5 years, the study would have at least 80%, 69%, and 52% power to detect reductions in risk of 33.5%, 30%, and 25%, respectively, with tamoxifen plus ovarian suppression versus tamoxifen alone, at a two-sided alpha level of 0.05"

- Al momento dello studio: eventi 299

Potenza		Riduzioni del rischio				
prima	dopo	relative	→	assolute 5y	→	NNT
80%	93%	33.5%		5.0%		20
69%	87%	30.0%		4.0%		25
52%	70%	25.0%		3.5%		29

I risultati ottenuti: EP primario DFS



Riduzione

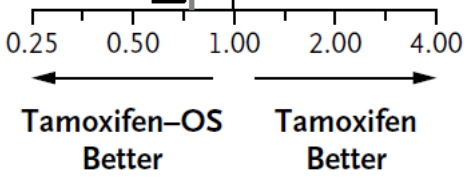
- relativa: 17%
- assoluta 5y: 2%
- NNT: 50

Analisi aggiustata: DFS

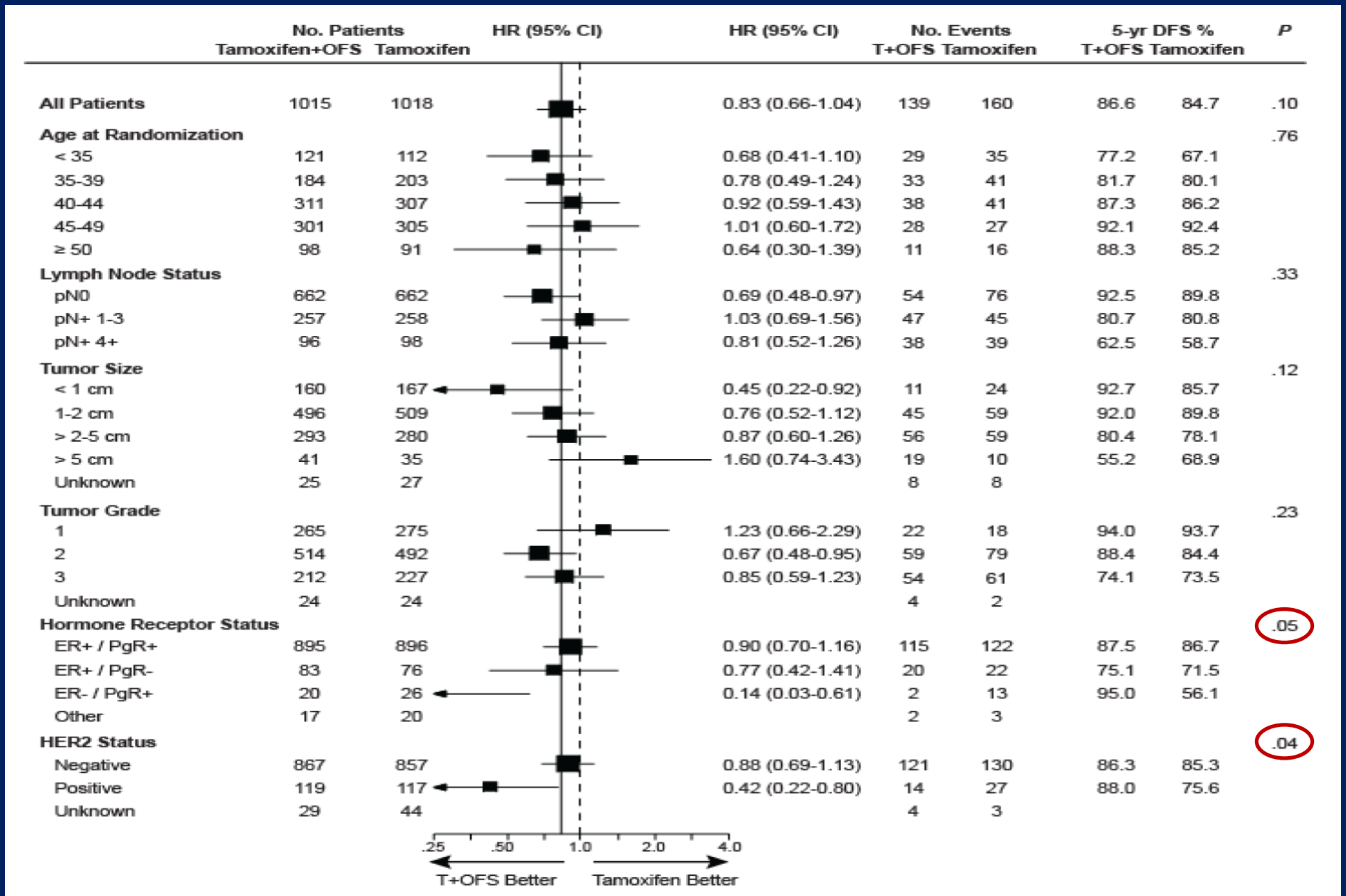
Parameter		Hazard Ratio	95% CI	P-Value (df)[1]
Treatment assignment	*T+OFS vs. T*	*0.78*	*(0.62, 0.98)*	*0.03*
Age at randomization	<35	-	-	<0.01
	35-39	0.71	(0.50, 1.00)	
	40-44	0.60	(0.42, 0.85)	
	45-49	0.58	(0.39, 0.87)	
	50+	0.98	(0.60, 1.61)	
Hormone receptor status	ER+ / PgR+	-	-	0.10
	ER+ / PgR-	1.35	(0.96, 1.90)	
	ER- / PgR+	1.72	(1.00, 2.94)	
	Other	0.95	(0.39, 2.33)	
No. nodes positive[2]	N 0	-	-	<0.01
	N+ 1-3	-	-	
	N+ 4+	1.65	(1.19, 2.30)	
Tumor size	<1cm	-	-	<0.01
	1-2cm	0.73	(0.49, 1.08)	
	>2-5cm	0.93	(0.61, 1.42)	
	>5cm	1.42	(0.83, 2.45)	
	Unknown	1.64	(0.87, 3.10)	
Tumor grade	1	-	-	<0.001
	2	1.47	(1.02, 2.11)	
	3	2.06	(1.39, 3.06)	
	Unknown	0.82	(0.33, 2.00)	
Local-regional therapy	Mastectomy, no RT	-	-	0.35
	Mastectomy + RT	1.08	(0.74, 1.57)	
	BCS + RT	0.85	(0.62, 1.17)	
	Other	0.43	(0.06, 3.15)	
HER2-targeted therapy	Not HER2+	-	-	0.07
	HER2+, no therapy	1.14	(0.71, 1.83)	
	HER2-targeted therapy	0.61	(0.39, 0.95)	

I risultati ottenuti: EP secondari

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)	



I risultati ottenuti: DFS sottogruppi



	No. Patients Tamoxifen+OFS	No. Patients Tamoxifen	HR (95% CI)	No. Events T+OFS	No. Events Tamoxifen	5-yr DFS % T+OFS	5-yr DFS % Tamoxifen	*P*
All Patients	1015	1018	0.83 (0.66-1.04)	139	160	86.6	84.7	.10
Age at Randomization								.76
< 35	121	112	0.68 (0.41-1.10)	29	35	77.2	67.1	
35-39	184	203	0.78 (0.49-1.24)	33	41	81.7	80.1	
40-44	311	307	0.92 (0.59-1.43)	38	41	87.3	86.2	
45-49	301	305	1.01 (0.60-1.72)	28	27	92.1	92.4	
≥ 50	98	91	0.64 (0.30-1.39)	11	16	88.3	85.2	
Lymph Node Status								.33
pN0	662	662	0.69 (0.48-0.97)	54	76	92.5	89.8	
pN+ 1-3	257	258	1.03 (0.69-1.56)	47	45	80.7	80.8	
pN+ 4+	96	98	0.81 (0.52-1.26)	38	39	62.5	58.7	
Tumor Size								.12
< 1 cm	160	167	0.45 (0.22-0.92)	11	24	92.7	85.7	
1-2 cm	496	509	0.76 (0.52-1.12)	45	59	92.0	89.8	
> 2-5 cm	293	280	0.87 (0.60-1.26)	56	59	80.4	78.1	
> 5 cm	41	35	1.60 (0.74-3.43)	19	10	55.2	68.9	
Unknown	25	27		8	8			
Tumor Grade								.23
1	265	275	1.23 (0.66-2.29)	22	18	94.0	93.7	
2	514	492	0.67 (0.48-0.95)	59	79	88.4	84.4	
3	212	227	0.85 (0.59-1.23)	54	61	74.1	73.5	
Unknown	24	24		4	2			
Hormone Receptor Status								.05
ER+ / PgR+	895	896	0.90 (0.70-1.16)	115	122	87.5	86.7	
ER+ / PgR-	83	76	0.77 (0.42-1.41)	20	22	75.1	71.5	
ER- / PgR+	20	26	0.14 (0.03-0.61)	2	13	95.0	56.1	
Other	17	20		2	3			
HER2 Status								.04
Negative	867	857	0.88 (0.69-1.13)	121	130	86.3	85.3	
Positive	119	117	0.42 (0.22-0.80)	14	27	88.0	75.6	
Unknown	29	44		4	3			

I risultati ottenuti: I sede relapse

Sites of First Failure (DFS event)	Chemotherapy Stratum								Treatment Assignment				Overall	
	No Chemotherapy				Prior Chemotherapy									
	Tamoxifen		Tamoxifen +OFS		Tamoxifen		Tamoxifen +OFS		Tamoxifen		Tamoxifen +OFS			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
N Patients	*476*	*100*	*473*	*100*	*542*	*100*	*542*	*100*	*1018*	*100*	*1015*	*100*	*2033*	*100*
N (%) DFS events	38	8.0	32	6.8	122	22.5	107	19.7	160	15.7	139	13.7	299	14.7
Site of First Failure														
Local	6	1.3	3	0.6	15	2.8	9	1.7	21	2.1	12	1.2	33	1.6
Contralat. breast ±above	8	1.7	9	1.9	8	1.5	3	0.6	16	1.6	12	1.2	28	1.4
Regional ±above	4	0.8	5	1.1	10	1.8	5	0.9	14	1.4	10	1.0	24	1.2
Soft tissue / distant lymph nodes ±above	-	-	-	-	3	0.6	3	0.6	3	0.3	3	0.3	6	0.3
Distant bone ±above	4	0.8	2	0.4	27	5.0	35	6.5	31	3.0	37	3.6	68	3.3
Distant viscera ±above	2	0.4	4	0.8	52	9.6	42	7.7	54	5.3	46	4.5	100	4.9
Second (non-breast) invasive cancer*	12	2.5	9	1.9	5	0.9	10	1.8	17	1.7	19	1.9	36	1.8
Death without prior cancer event	2	0.4	-	-	2	0.4	-	-	4	0.4	-	-	4	0.2

Adverse Events

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)

Incremento relativo del rischio: 32%

Incremento assoluto del rischio: 7.6%

NNH: 13

Rapporto R/B

→ 4 AE Gr 3-4 in più per 1 relapse evitato

Conclusioni

- This trial did not support routine use of ovarian suppression in premenopausal breast cancer.

- Nevertheless, there may be some benefit from ovarian suppression in the subgroup of younger patients whose menses return after adjuvant chemotherapy, but also more symptoms.