QUESITO GRADE 3:
Nelle pazienti operate con carcinoma mammario HR+ in premenopausa, il trattamento ormonale adiuvante con exemestane +soppressione ovarica è raccomandato rispetto a tamoxifen + soppressione ovarica?

Jennifer Foglietta
Oncologia medica- Perugia

11/04/2015

Definizione del quesito clinico

- P (popolazione target): pazienti con carcinoma mammario operato HR+ in premenopausa
- I (intervento): exemestane+soppressione ovarica
- C (confronto): tam+soppressione ovarica
- O (outcome): Beneficio: DFS, OS, Distant recurrence

Danno: osteoporosi, fratture, dolori articolari, secchezza vaginale, caldane, ipertensione, stroke emorragico e stroke ischemico, infarto miocardio, tromboembolismo.

Classificazione degli outcome positivi (benefici) e negativi (rischi)

Rating (mediana del voto)	Importanza	Incluso in
7 8 9	Outcome importanti ed essenziali: DFS (9) OS (9) Recidiva a distanza (7) Secchezza vaginale (8) Dolori articolari (8) Ischemia miocardica (7) Stroke ischemico/emorragico (7)	Tabelle sulla qualità delle prove:si Raccomandazione:si
4 5 6	Outcome importanti ma non essenziali: Caldane (5) Osteoporosi (5) Tromboembolismo (4) Fratture (6)	Tabelle sulla qualità delle prove:si Raccomandazione:no
1 2 3	Outcome non importanti Ipertensione (3)	Tabelle sulla qualità delle prove:no Raccomandazione:no

TEXT and SOFT Designs

Joint Analysis
N=4690

Enrolled 11/03-4/11

Premenopausal
≤ 12 weeks after surgery
Planned OFS
No planned chemo
OR planned chemo

RANDOMIZE

TEXT: 2672

- Tamoxifen+OFS x 5 yr
- Exemestane+OFS x 5 yr

Median FU
5.7 years

SOFT Primary Analysis
N=2033

Premenopausal
≤ 12 weeks after surgery
No chemo
OR
Remain premenopausal ≤ 8 mos after chemo

RANDOMIZE

SOFT: 3047

- Tamoxifen x 5 yrs (1018)
- Tamoxifen+OFS x 5 yr (1015)
- Exemestane+OFS x 5 yr (1014)

Median FU
5.6 years

Pagani et al, ASCO 2014 + NEJM 2014, Francis et al, SABCS 2014 + NEJM 2014

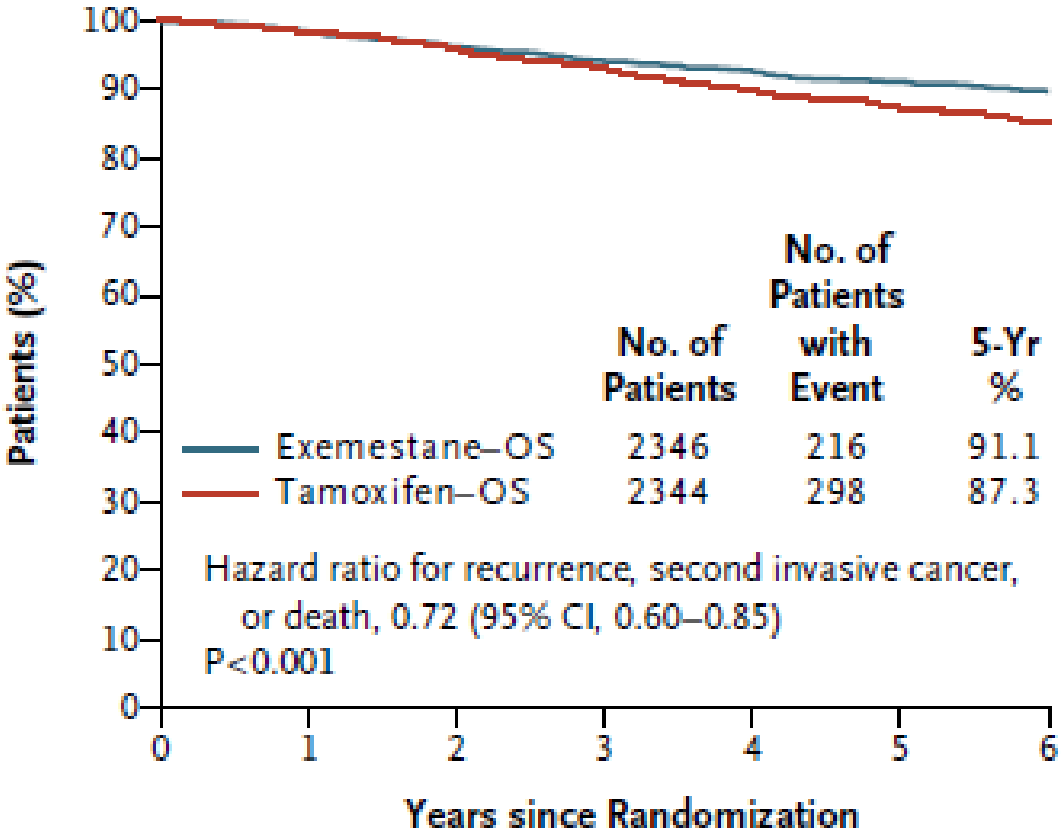
Statistical analysis

- Original statistical analysis plans for TEXT and SOFT were to compare DFS between treatments group within each trial separately.
- However, pts enrolled in the studies had lower-risk characteristics
- 2011 protocol amendements: combined analysis of data from TEXT and SOFT (exemestane+OS vs TAM +OS)

Characteristic	No-Chemotherapy Cohorts		Chemotherapy Cohorts†		Overall (N=4690)
	TEXT (N=1053)	SOFT (N=943)	TEXT (N=1607)	SOFT (N=1087)	
Age at randomization — no. (%)					
<35 yr	41 (3.9)	14 (1.5)	191 (11.9)	224 (20.6)	470 (10.0)
35–39 yr	123 (11.7)	68 (7.2)	289 (18.0)	312 (28.7)	792 (16.9)
40–49 yr	768 (72.9)	690 (73.2)	1048 (65.2)	515 (47.4)	3021 (64.4)
≥50 yr	121 (11.5)	171 (18.1)	79 (4.9)	36 (3.3)	407 (8.7)
Lymph-node status — no. (%)					
Negative	835 (79.3)	865 (91.7)	542 (33.7)	470 (43.2)	2712 (57.8)
Positive	218 (20.7)	78 (8.3)	1065 (66.3)	617 (56.8)	1978 (42.2)
Tumor size — no. (%)‡					
≤2 cm	847 (80.4)	800 (84.8)	738 (45.9)	537 (49.4)	2922 (62.3)
>2 cm	203 (19.3)	139 (14.7)	844 (52.5)	508 (46.7)	1694 (36.1)
HER2 positive — no. (%)	54 (5.1)	30 (3.2)	272 (16.9)	211 (19.4)	567 (12.1)
Interval from surgery to randomization — mo					
Median	1.5	1.8	1.2	8.0	1.6
Interquartile range	1.1–1.9	1.3–2.4	0.9–1.6	5.7–10.1	1.1–2.7
Endocrine therapy before randomization — no. (%)§	—	44 (4.7)	—	453 (41.7)	—

Pagani O. et al NEJM 2014;371:107-118

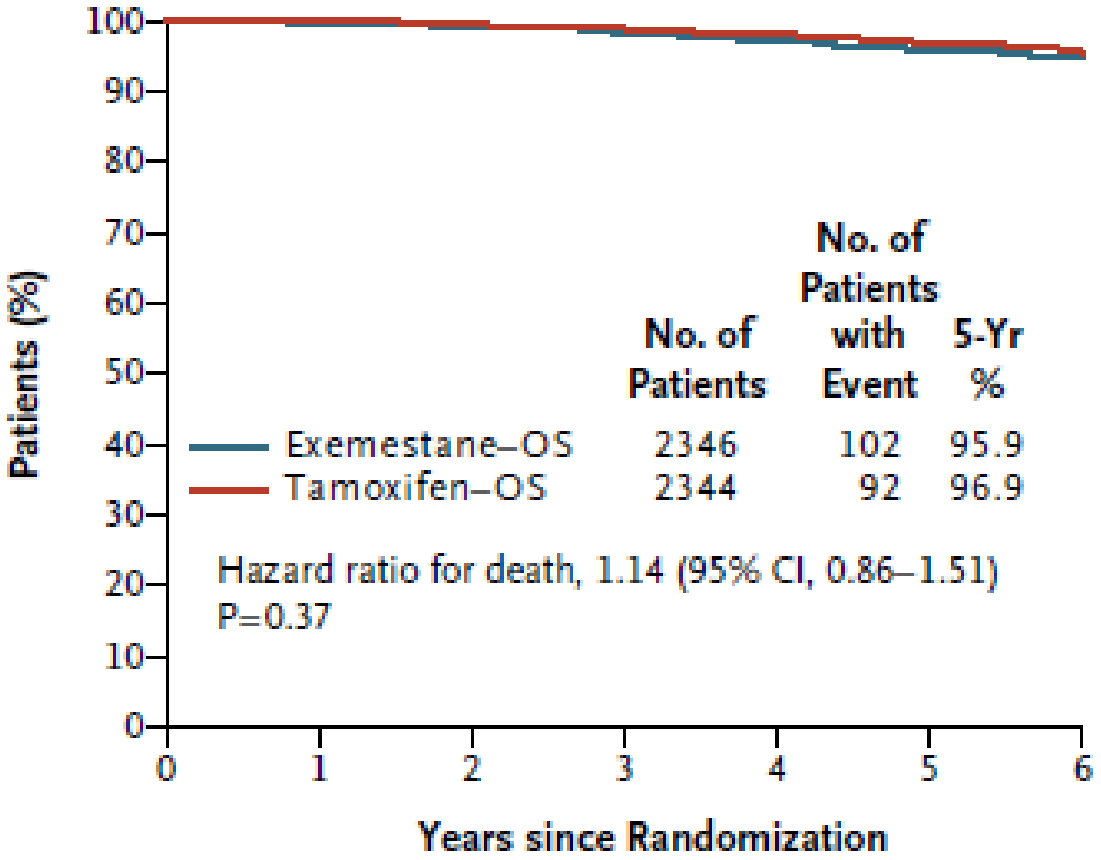
Disease-free Survival



No. at Risk							
Exemestane–OS	2346	2217	2128	1848	1517	1289	866
Tamoxifen–OS	2344	2247	2148	1845	1486	1261	834

Pagani O. et al NEJM 2014;371:107-118

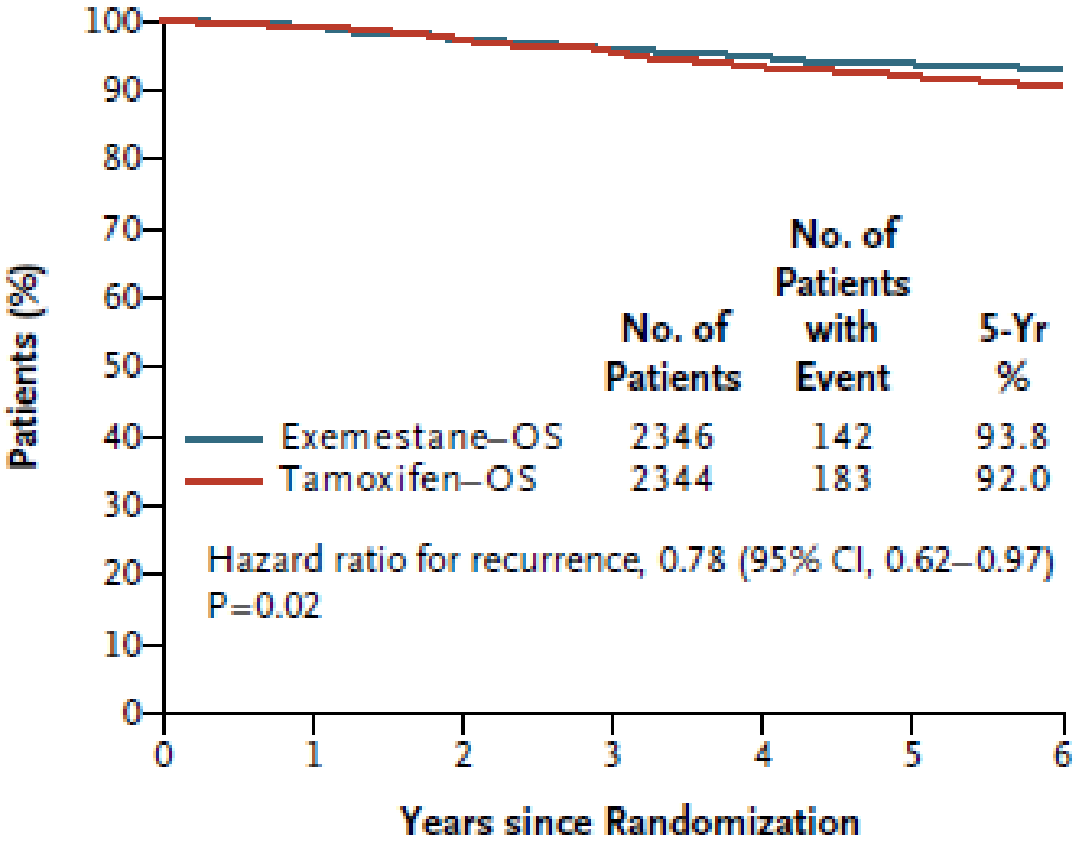
Overall Survival



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

Pagani O. et al NEJM 2014;371:107-118

Freedom from recurrence of breast cancer at a distant site

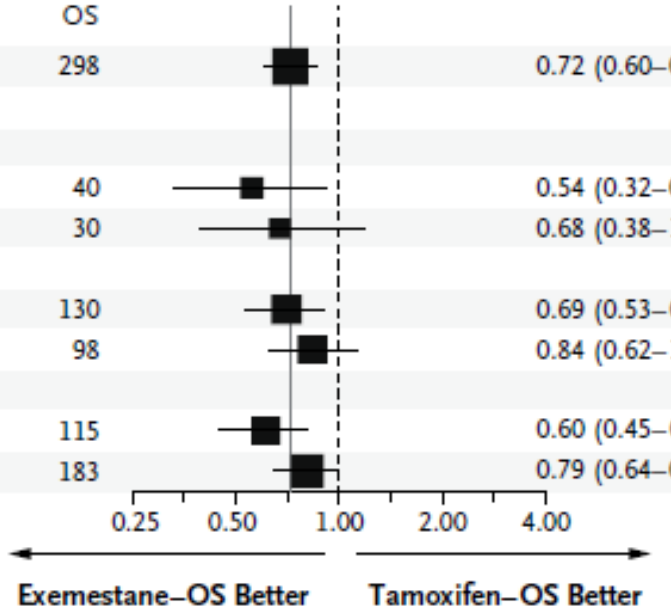


No. at Risk							
Exemestane–OS	2346	2232	2150	1879	1548	1318	890
Tamoxifen–OS	2344	2264	2174	1892	1540	1318	874

Pagani O. et al NEJM 2014;371:107-118

Sottogruppi

Subgroup	No. of Patients		No. of Patients with Event		Hazard Ratio (95% CI)	5-Yr Disease-free Survival (%)	
	Exemestane–OS	Tamoxifen–OS	Exemestane–OS	Tamoxifen–OS		Exemestane–OS	Tamoxifen–OS
All patients	2346	2344	216	298	0.72 (0.60–0.85)	91.1	87.3
Cohort							
No chemotherapy							
TEXT	526	527	22	40	0.54 (0.32–0.92)	96.1	93.0
SOFT	470	473	20	30	0.68 (0.38–1.19)	95.8	93.1
Chemotherapy							
TEXT	806	801	93	130	0.69 (0.53–0.90)	89.8	84.6
SOFT	544	543	81	98	0.84 (0.62–1.13)	84.3	80.6
Lymph-node status							
Negative	1362	1350	70	115	0.60 (0.45–0.81)	95.1	91.6
Positive	984	994	146	183	0.79 (0.64–0.98)	85.6	81.4



Pagani O. et al NEJM 2014;371:107-118

EVENTI AVVERSI

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	38.4 (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)	—	—

Pagani O. et al NEJM 2014;371:107-118

Author(s): MC IC
Date: 2015-03-11
Question: Should LHRH agonist + Exemestane vs LHRH agonist + tamoxifen be used in pre-menopausal hormone-receptor-positive breast cancer patients?
Settings:
Bibliography: Pagani O, NEJM 2014; 371:107-18 Regan MM, The Breast 2013, 22:1094-1100

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LHRH agonist + aromatase inhibitors	LHRH agonist + tamoxifen	Relative (95% CI)	Absolute		
OS - Pagani 2014 (follow-up median 68 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	serious[3]	none	102/2346 (4.3%)	92/2344 (3.9%)	HR 1.14 (0.86 to 1.51)	1 more per 100 (from 1 fewer to 2 more)	ÅÅÅO MODERATE	CRITICAL
DFS - Pagani 2014 (follow-up median 68 months; assessed with: recurrence of invasive breast cancer, second invasive (non-breast) cancer or death)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision	none	216/2346 (9.2%)	298/2344 (12.7%)	HR 0.72 (0.6 to 0.85)	34 fewer per 1000 (from 18 fewer to 49 fewer)	ÅÅÅÅ HIGH	CRITICAL
Distant recurrence - Pagani 2014 (follow-up median 68 months; assessed with: not reported)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision	none	142/2346 (6.1%)	183/2344 (7.8%)	HR 0.78 (0.62 to 0.97)	2 fewer per 100 (from 0 fewer to 3 fewer)	ÅÅÅÅ HIGH	CRITICAL
Thromboembolism (any grade) - Pagani 2014 (follow-up median 68 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision	none	24/2318 (1%)	50/2325 (2.2%)	RR 0.48 (0.3 to 0.78)	1 fewer per 100 (from 0 fewer to 2 fewer)	ÅÅÅÅ HIGH	IMPORTANT
Osteoporosis (any grade) - Pagani 2014 (follow-up median 68 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision	none	894/2318 (38.6%)	586/2325 (25.2%)	RR 1.53 (1.4 to 1.67)	13 more per 100 (from 10 more to 17 more)	ÅÅÅÅ HIGH	IMPORTANT
Fracture (any grade) - Pagani 2014 (follow-up median 68 months)												

2	**randomised trials**	**no serious risk of bias**	**no serious inconsistency**	**no serious indirectness[1,2]**	**no serious imprecision**	**none**	**158/2318 (6.8%)**	**120/2325 (5.2%)**	**RR 1.32 (1.05 to 1.66)**	**2 more per 100 (from 0 more to 3 more)**	**ÅÅÅÅ HIGH**	**IMPORTANT**
Vaginal dryness (any grade) - Pagani 2014 (follow-up median 68 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision	none	1214/2318 (52.4%)	1101/2325 (47.4%)	RR 1.11 (1.04 to 1.17)	5 more per 100 (from 2 more to 8 more)	ÅÅÅÅ HIGH	IMPORTANT
Musculoskeletal symptoms (any grade) - Pagani 2014 (follow-up median 68 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision	none	2057/2318 (88.7%)	1766/2325 (76%)	RR 1.17 (1.14 to 1.2)	13 more per 100 (from 11 more to 15 more)	ÅÅÅÅ HIGH	CRITICAL
Hypertension (any grade) - Pagani 2014 (follow-up median 68 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision	none	527/2318 (22.7%)	509/2325 (21.9%)	RR 1.04 (0.93 to 1.16)	9 more per 1000 (from 15 fewer to 35 more)	ÅÅÅÅ HIGH	NOT IMPORTANT
Myocardial ischemia (any grade) - Pagani 2014 (follow-up median 68 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision[4]	none	16/2318 (0.69%)	7/2325 (0.3%)	RR 2.29 (0.94 to 5.56)	0 more per 100 (from 0 fewer to 1 more)	ÅÅÅÅ HIGH	CRITICAL
Stroke (hemorrhage) (any grade) - Pagani 2014 (follow-up median 68 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision[4]	none	15/2318 (0.65%)	21/2325 (0.9%)	RR 0.72 (0.37 to 1.36)	0 fewer per 100 (from 1 fewer to 0 more)	ÅÅÅÅ HIGH	CRITICAL
Stroke (ischemia) (any grade) - Pagani 2014 (follow-up median 68 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness[1,2]	no serious imprecision[4]	none	5/2318 (0.22%)	11/2325 (0.47%)	RR 0.45 (0.16 to 1.31)	0 fewer per 100 (from 0 fewer to 0 more)	ÅÅÅÅ HIGH	CRITICAL

[1] In the SOFT trial the ovarian function suppression via LHRH chosen in 91% patients
[2] Tha majority of patients received chemotherapy before randomization
[3] 95% confidence interval includes no effect and the upper confidence limit crosses the minimal important difference (MID)
[4] We decided to not downgrade quality of evidence for imprecision due to the low number of events in both arms

Bilancio beneficio/danno: 3 positivi/ 15 incerti

Forza della raccomandazione: 18 debole