GIM GRUPPO ITALIANO MAMMELLA

Riunione Annuale

Le sfide della ricerca sul carcinoma mammario

24 - 25 SETTEMBRE 2019

TRIESTE

Savoia Excelsior Palace Trieste - Starhotels Collezione

Riva del Mandracchio, 4

Ph. Courtesy Andrea Carloni

Adjuvant treatment of HR+/HER2- BC: the path to personalized therapy

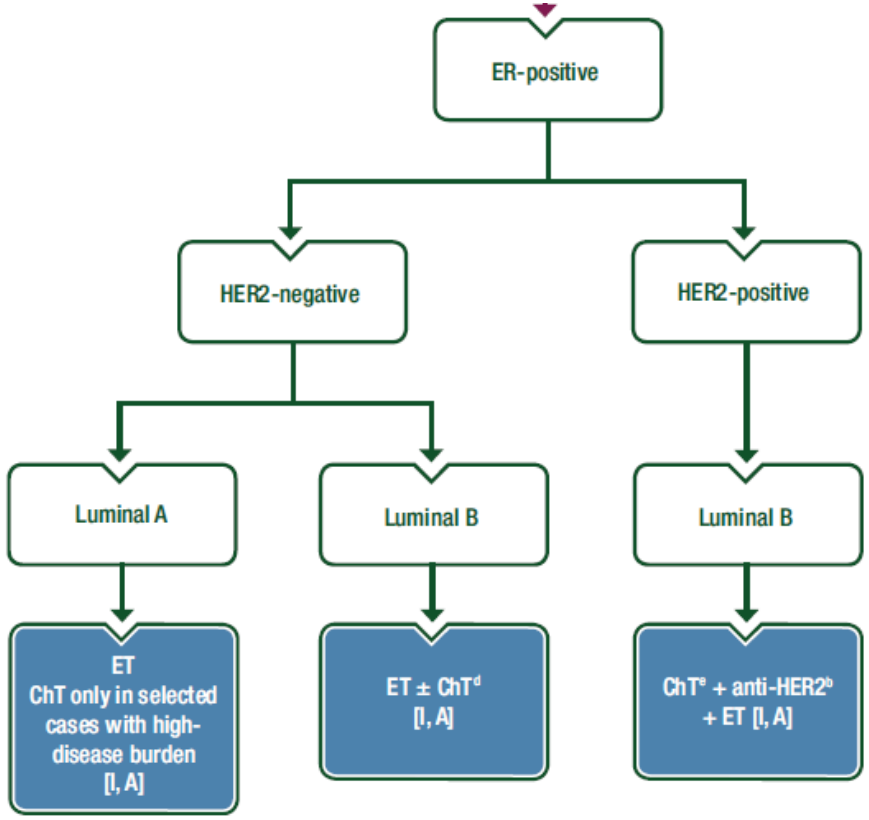
Adjuvant Therapy for Breast Cancer

National Institutes of Health
Consensus Development Conference Statement
November 1-3, 2000

Because adjuvant polychemotherapy improves survival, it should be recommended to the majority of women with localized breast cancer regardless of nodal, menopausal, or hormone receptor status. The inclusion of anthracyclines in adjuvant chemotherapy

Chemotherapy for all

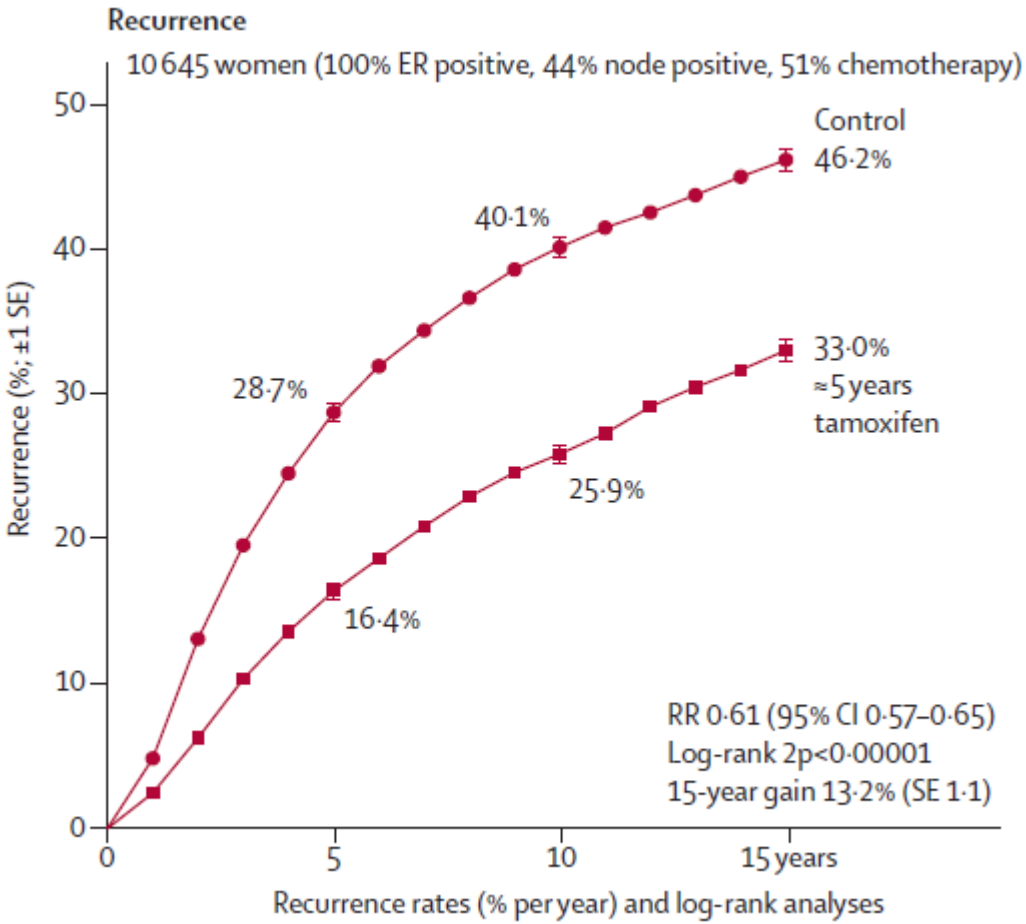
Endocrine therapy for all, chemotherapy for some

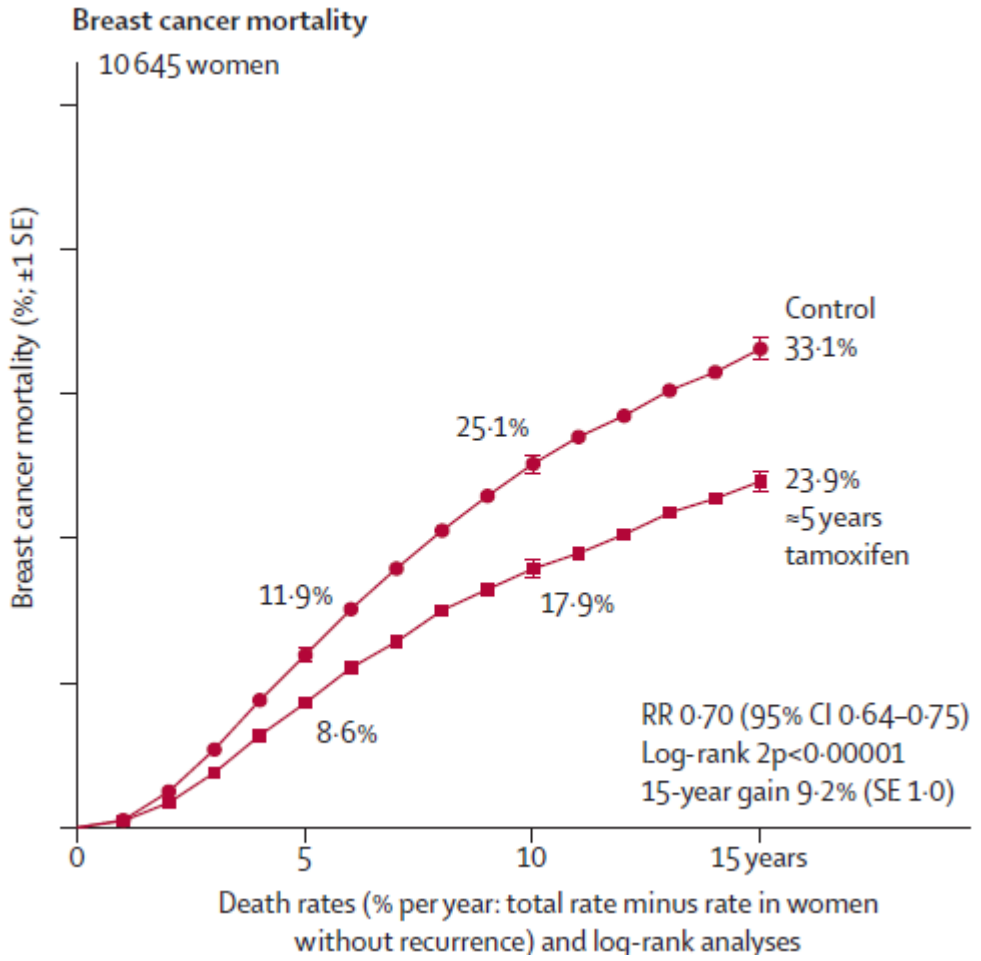


d Depending on level of ER and PgR expression, proliferation, genomically assessed risk, tumour burden and/or patient preference.

ESMO Clinical Practice Guidelines 2019

EBCTCG meta-analyses: tamoxifen vs control

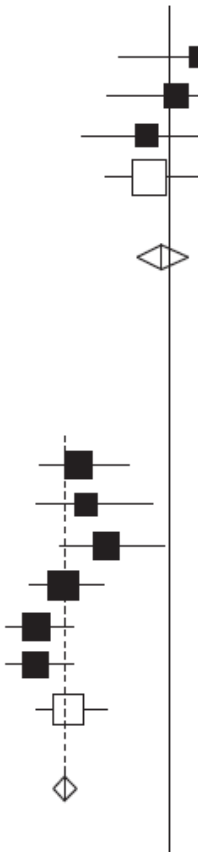




Lancet 2011

EBCTCG meta-analyses: tamoxifen vs control

Category	Events/woman-years (rate [% per year])		Tamoxifen events		Ratio of annual event rates
	Allocated tamoxifen	Allocated control	Log-rank O–E	Variance of O-E	Tamoxifen : control
(a) ER-poor					
ER=0	162/5060 (3·2)	163/5941 (2·7)	7·4	69·5	1·11 (SE 0·13)
ER 1–3	202/6645 (3·0)	192/6357 (3·0)	2·2	85·5	1·03 (SE 0·11)
ER 4–9	185/5490 (3·4)	188/5588 (3·4)	−6·6	77·5	0·92 (SE 0·11)
Other ER-poor	449/9528 (4·7)	451/8995 (5·0)	−14·9	195·5	0·93 (SE 0·07)
(a) Subtotal	**998/26 723 (3·7% per year)**	**994/26 881 (3·7% per year)**	**−12·0**	**428·0**	**0·97 (SE 0·05) 2p=0·6**
Test for trend χ^2_1=1·4; 2p=0·2					
(b) ER-positive by ER measurement					
ER 10–19	232/8173 (2·8)	316/7252 (4·4)	-47·4	120·6	0·67 (SE 0·08)
ER 20–29	158/5104 (3·1)	197/4630 (4·3)	−27·3	76·4	0·70 (SE 0·10)
ER 30–49	235/8107 (2·9)	260/6952 (3·7)	−29·0	112·1	0·77 (SE 0·08)
ER 50–99	293/10 650 (2·8)	361/8973 (4·0)	−69·6	144·8	0·62 (SE 0·07)
ER 100–199	211/8429 (2·5)	344/7376 (4·7)	−80·4	122·8	0·52 (SE 0·07)
ER≥200	216/8279 (2·6)	325/6672 (4·9)	−78·2	119·0	0·52 (SE 0·07)
Other ER+	308/7868 (3·9)	415/6898 (6·0)	−72·9	161·3	0·64 (SE 0·06)
(b) Subtotal	**1653/56 610 (2·9% per year)**	**2218/48753 (4·5% per year)**	**−404·8**	**856·9**	**0·62 (SE 0·03) 2p<0·00001**



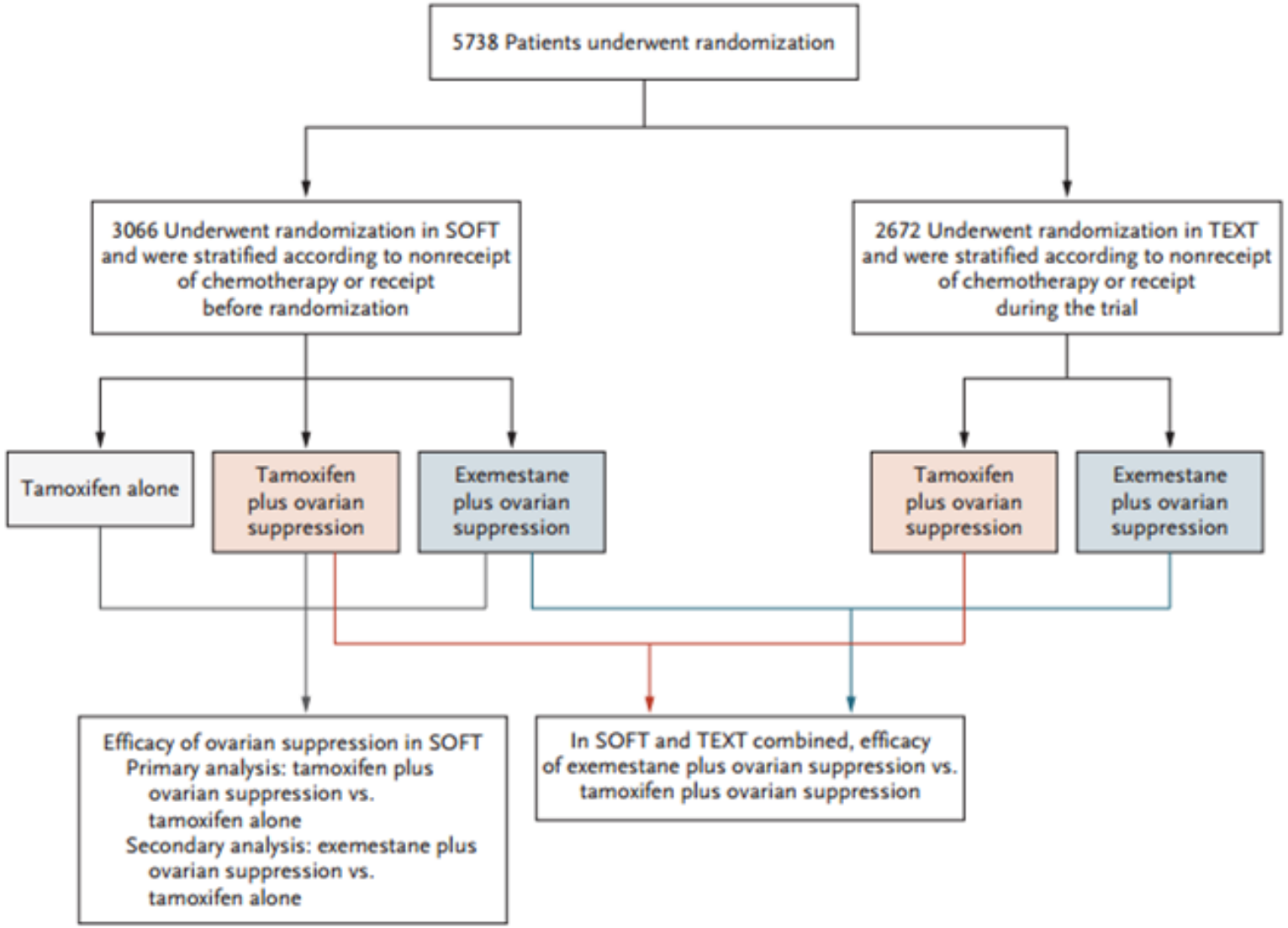
Lancet 2011

Tamoxifen for premenopausal patients

For premenopausal women, tamoxifen for 5-10 years is a standard of care [I, A]

Nelle donne in premenopausa o in perimenopausa, dovrebbe essere considerata in prima istanza una ormonoterapia adiuvante con tamoxifene 20 mg/die per 5 anni

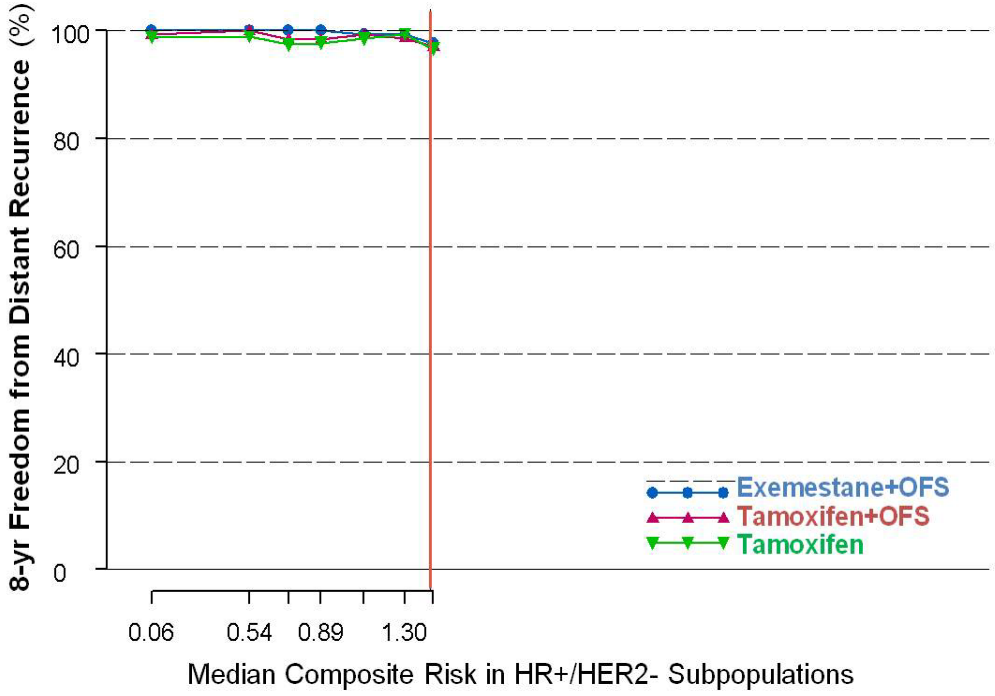
OFS for premenopausal patients: SOFT/TEXT trials



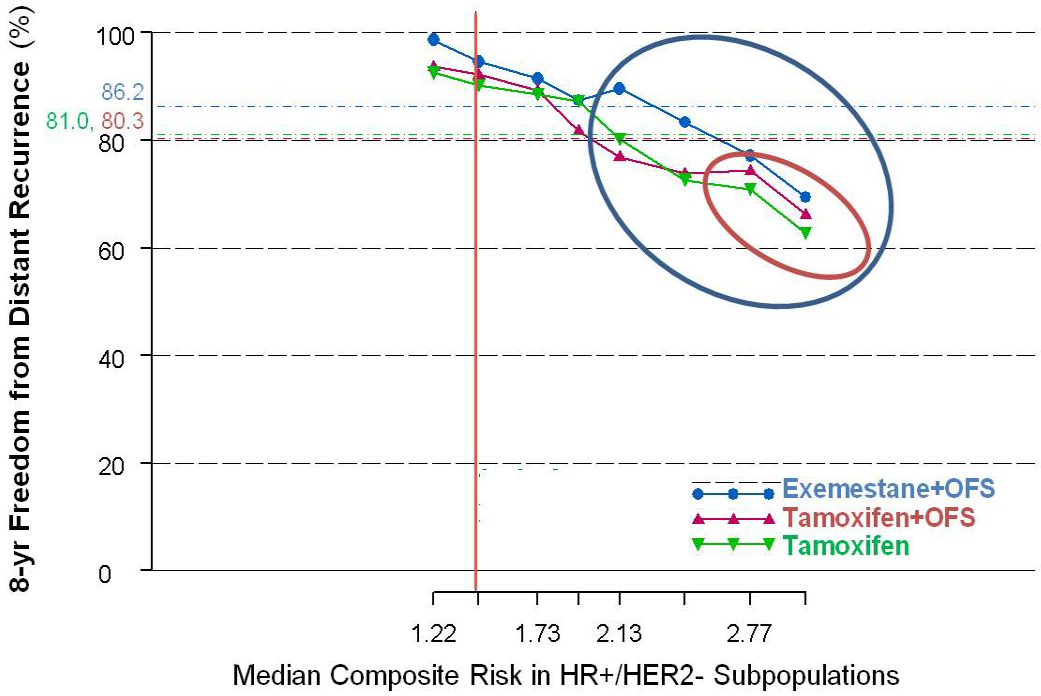
Francis, NEJM, 2018

STEPP of 5-year BCFI according to Composite Risk Score

SOFT No Chemo



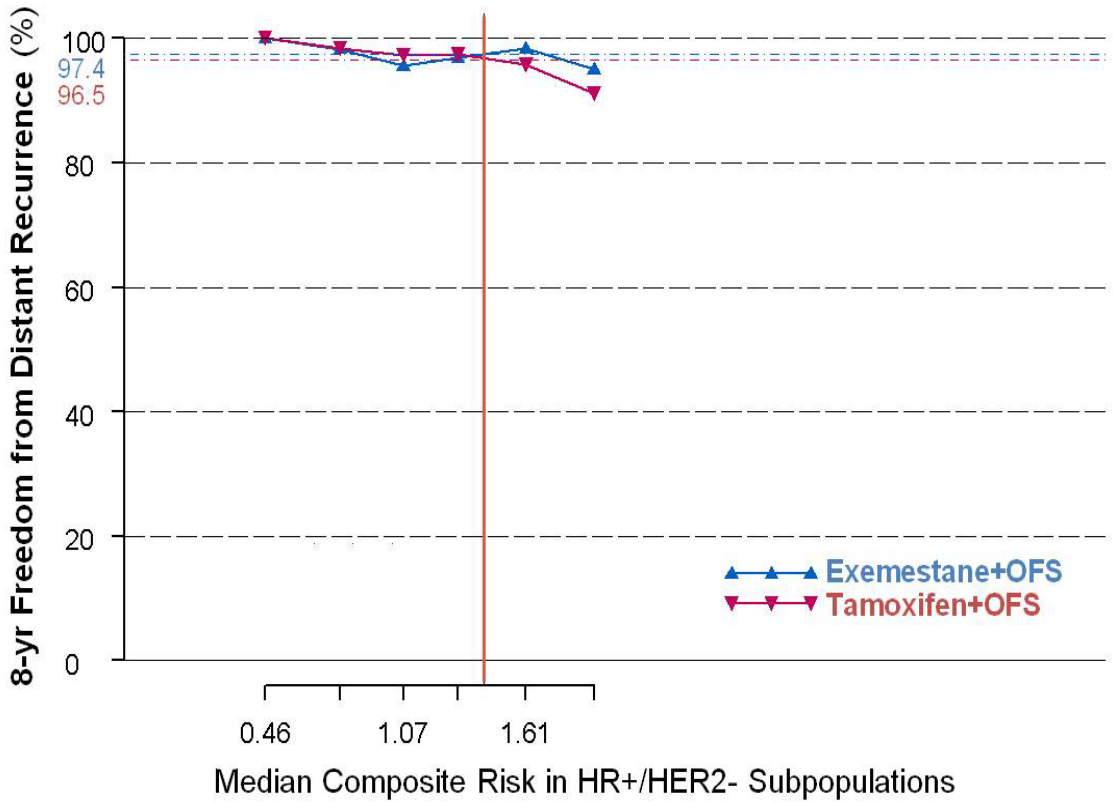
SOFT Prior Chemo



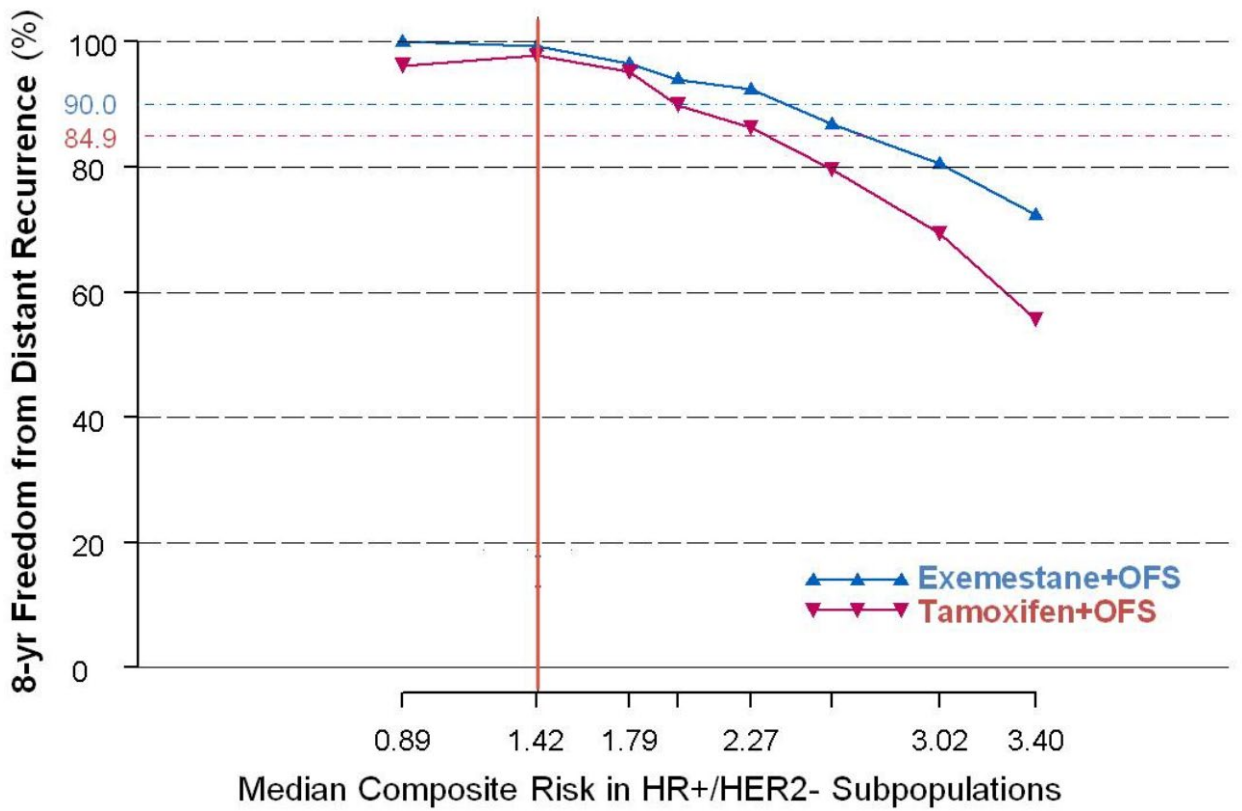
Regan MM et al, J Clin Oncol 2016;34:2221-31. Regan MM et al, ASCO 2018

STEPP of 5-year BCFI according to Composite Risk Score

TEXT No Chemo



TEXT Prior Chemo



Regan MM et al, J Clin Oncol 2016;34:2221-31. Regan MM et al, ASCO 2018

OFS for premenopausal patients

In patients requiring ChT and who recover menses (in particular in the first year but acceptable within the first 2 years), addition of OFS to ET should be strongly considered [I, A].

The role of replacing tamoxifen with an AI can be considered in high-risk patients; if used, it mandates effective OFS, with regular biochemical control of oestrogen levels [I, A].

The role of OFS in patients <35 years not requiring ChT is not clear, but inferior outcomes of young luminal early breast cancer patients suggest the use of the most effective ET (i.e.combination with OFS) [III, A].

OFS for premenopausal patients

Associazione Italiana di Oncologia Medica

TAMOXIFENE + OFS

L'aggiunta della OFS al tamoxifene dovrebbe essere valutata in base al rischio di ripresa di malattia della singola paziente:

- Nelle donne a basso rischio di recidiva l'aggiunta della OFS al tamoxifene NON dovrebbe essere presa in considerazione [negativa debole]
- Nelle donne ad alto rischio di recidiva, l'aggiunta della OFS al tamoxifene DOVREBBE essere presa in considerazione [positiva forte]

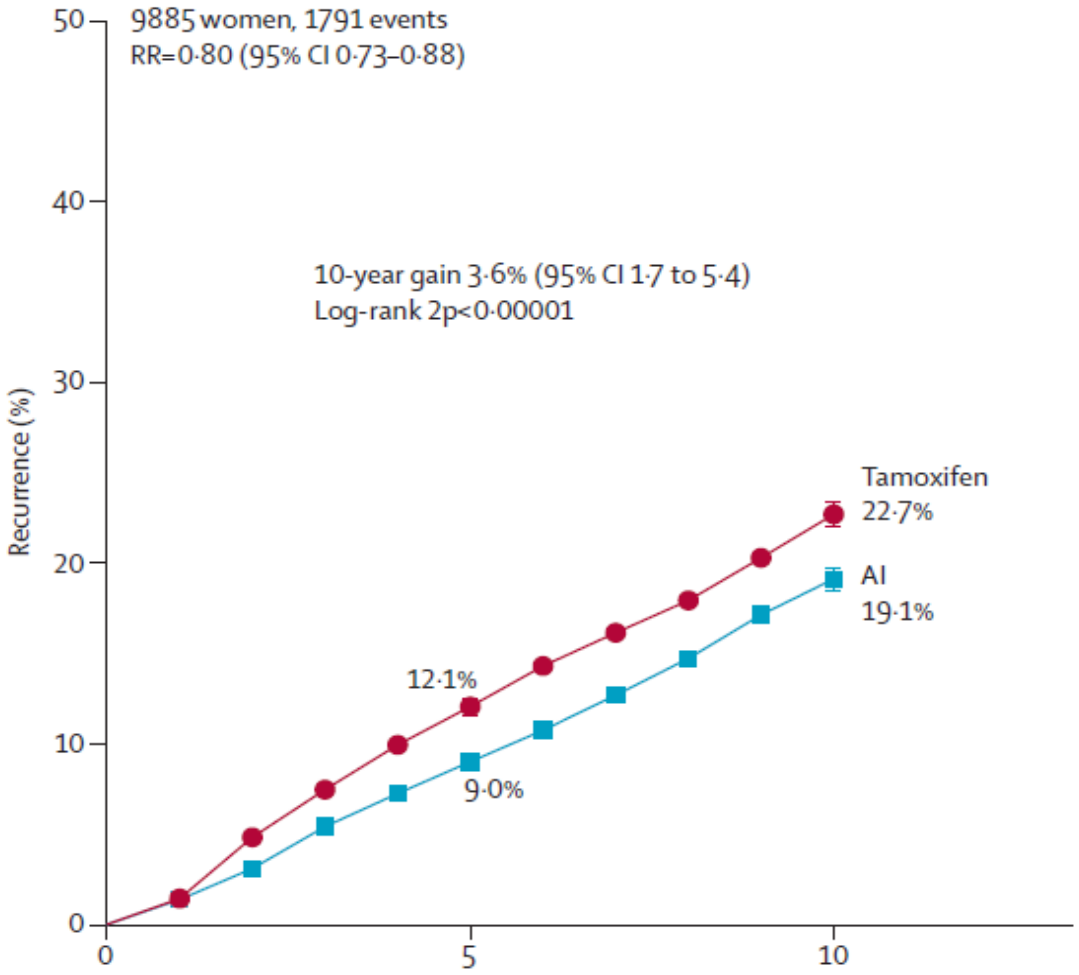
INIBITORE AROMATASI + OFS

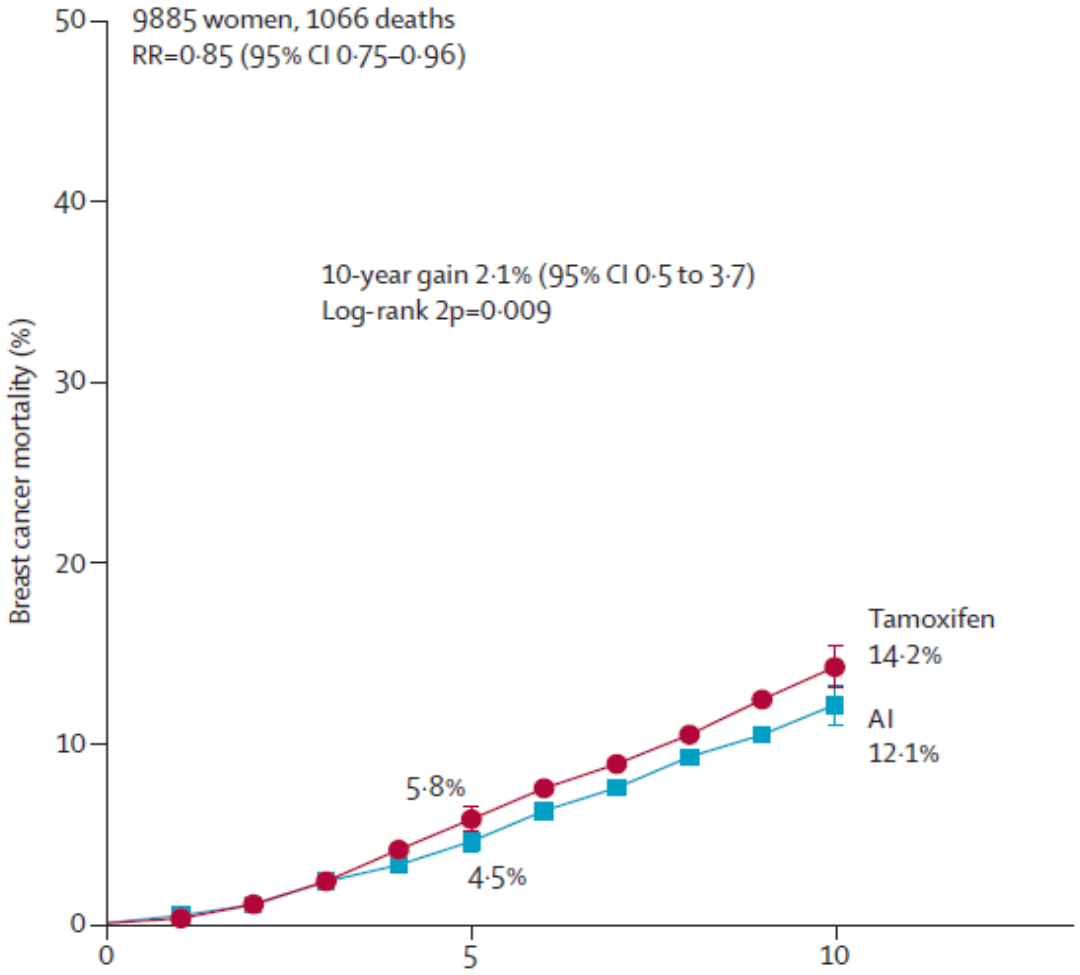
Nelle donne ad alto rischio di recidiva candidate a ricevere OFS, il trattamento con un inibitore dell'aromatasi PUO' essere preso in considerazione rispetto al tamoxifene [positiva debole]

AIs for postmenopausal patients

Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**



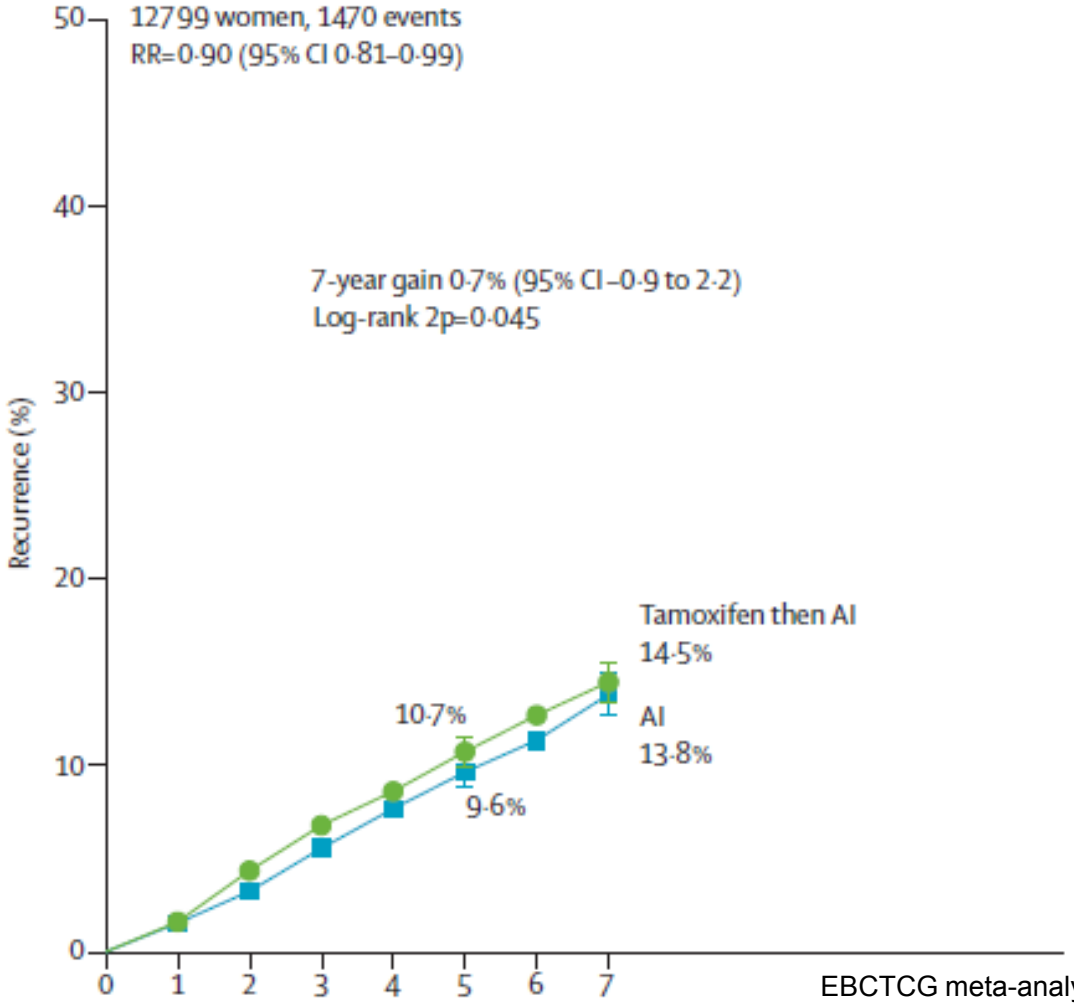


EBCTCG meta-analysis, Lancet 2015

AIs for postmenopausal patients

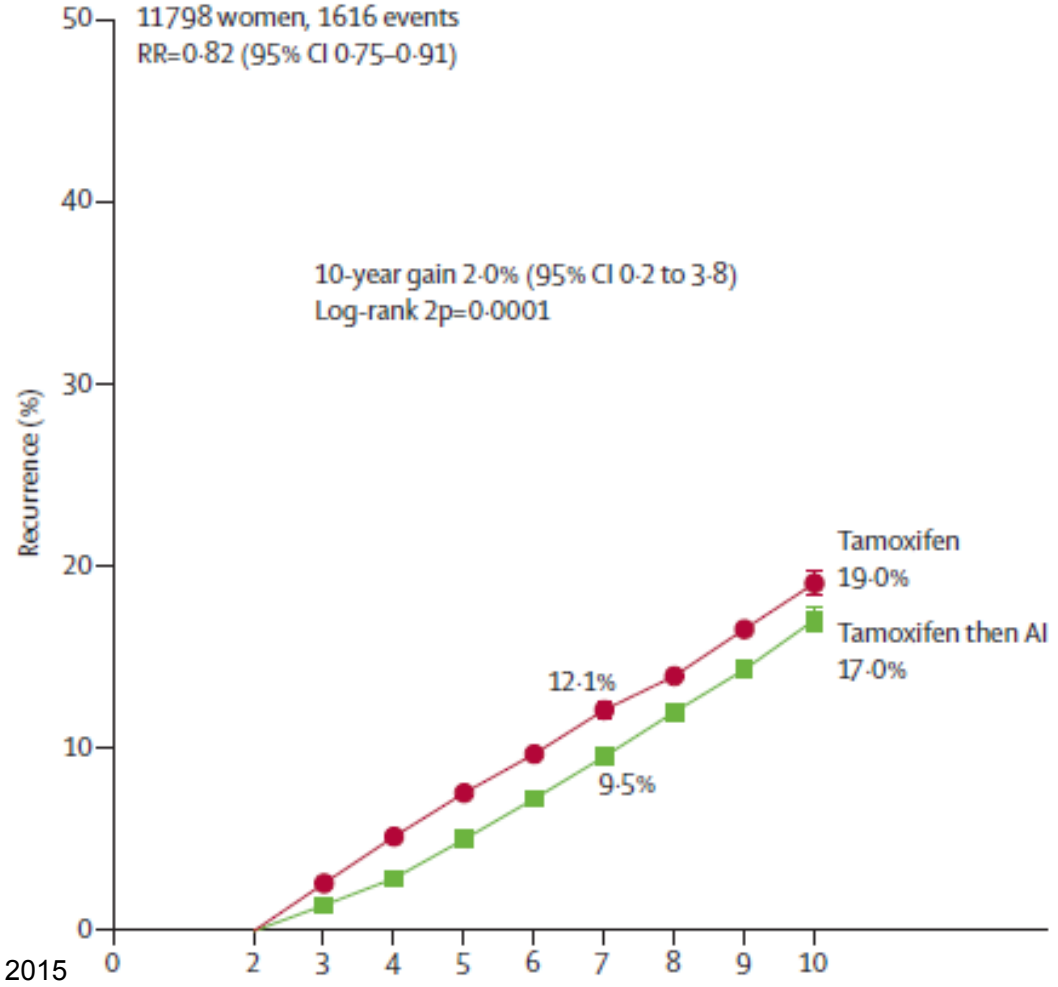
Switch vs AI upfront

BIG 1-98, TEAM, FATA



Switch vs TAM upfront

IES, ABCSG-8, ARNO 95, N-SAS, BC03, ITA



EBCTCG meta-analysis, Lancet 2015

ET for postmenopausal patients

For postmenopausal women, aromatase inhibitors (both non-steroidal and steroidal) and tamoxifen are considered standard treatments [I, A]

AIs can be used (i) upfront, (ii) after 2-3 years of tamoxifen or (iii) as extended adjuvant therapy after 5 years of tamoxifen [I,A]

Associazione Italiana di Oncologia Medica

Nelle donne in post-menopausa candidate a terapia ormonale, dovrebbe essere presa in considerazione una terapia che comprenda inibitori dell'aromatasi [positiva forte]

Nelle donne in cui è controindicato l'uso degli AIs o che sviluppano tossicità gravi (ad esempio di tipo muscolo-scheletrico) o che rifiutano tale trattamento, può essere presa in considerazione una terapia con tamoxifene per 5 anni, oppure la sequenza tamoxifene per 2-3 ani seguito da AI per 3-2 anni

Extended adjuvant therapy: Tamoxifen beyond 5 years

ATLAS + ATTOM combined analysis: 5 vs 10yrs

n=17477 ER+/Unknown (10543 from ATLAS, 6934 from ATTOM)

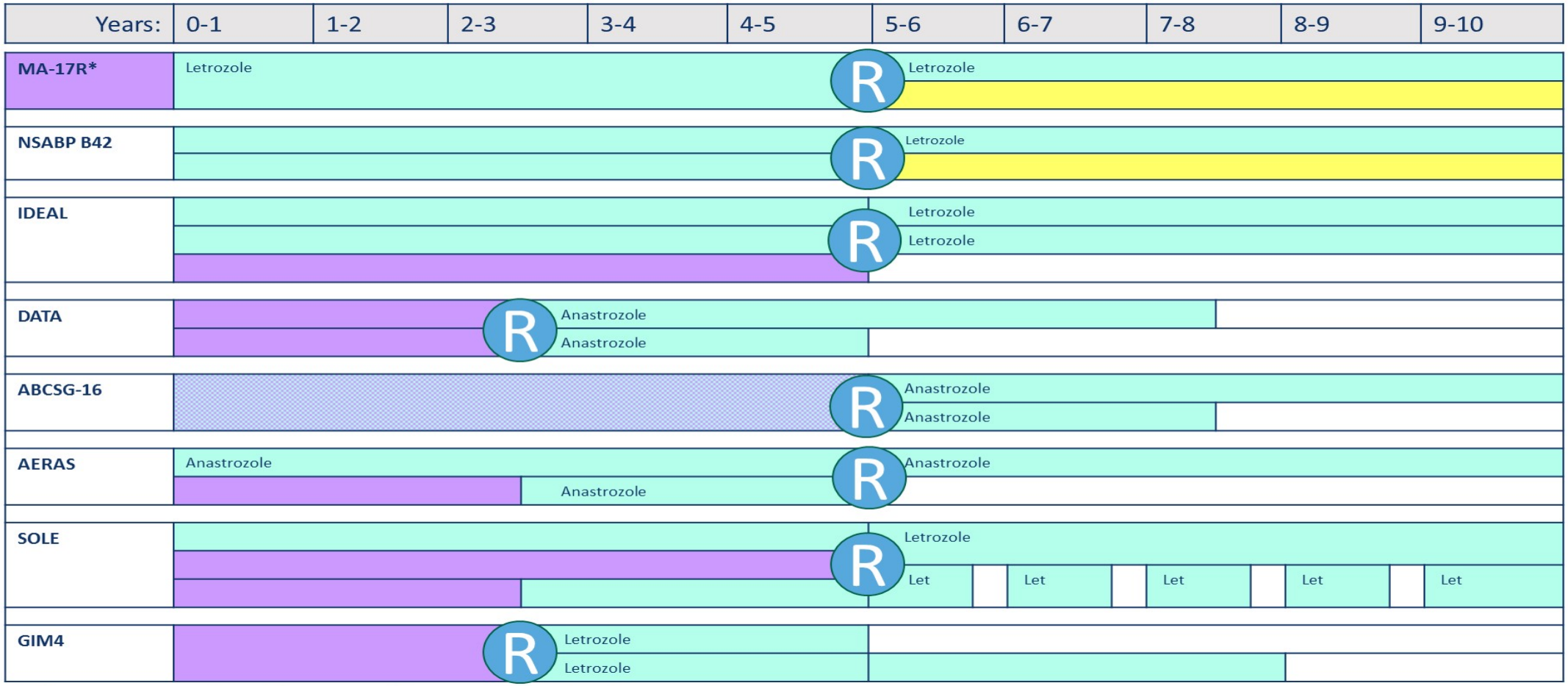
BREAST CANCER MORTALITY	ATLAS*	ATTOM	ATLAS + ATTOM
5-9 yrs	0.92 (0.77-1.09)	1.08 (0.85-1.38)	0.97 (0.84-1.15)
> 10 yrs	0.75 (0.63-0.90) p=0.02	0.75 (0.63-0.90) p=0.07	0.75 (0.65-0.86) p<0.001
All yrs	0.83 0.73-0.94 p=0.04	0.88 (0.74-1.03)	0.85 (0.77-0.94) p=0.001

OVERALL SURVIVAL	ATLAS + ATTOM
5-9 yrs	0.99 (0.89-1.10)
> 10 yrs	0.84 (0.77-0.93) p<0.001
All yrs	0.91(0.84-0.97) p=0.008

*Inverse-variance-weitghted estimate of the effect in ER+

Gray, ASCO 2013

Extended adjuvant therapy: AIs beyond 5 years



*All women received 5 years of tamoxifen prior to year 1

Modified from K Wimmer et al 2017

ET | Tam | AI | Placebo

Extended adjuvant therapy: AIs beyond 5 years

Extending AI Duration Beyond 5 years

	Number (Node+)	Duration ET Duration AI	DFS benefit	OS benefit	New BC benefit
MA-17R	1918 (53%)	10-15 5-10	Yes	No	Yes
NSABP B42	3966 (42%)	5-10 2-10	No	No	Yes
IDEAL	1824 (74%)	7.5-10 2.5-10	No	No	Yes
DATA	1912 (67%)	5-9 3-6	No	No	No
ABCSG-16	3469 (31%)	5-10 7-10	No	No	No
SOLE	4884 (99%)	5-10 5-10 Cont/int	No	No	?
AERAS	1683 (20%)	5-10 5-10	Yes	No	Yes
GIM4	2056 (44%)	5-8 2-5	No	No	No

ET- endocrine therapy, AI- aromatase inhibitor, Cont- continuous, Int- intermittent

Extended endocrine therapy

- In patients becoming post-menopausal during the first 5 years of tamoxifen, a switch to letrozole should be considered, depending on predicted risk of late recurrence [II, A]
- Extended adjuvant therapy should be discussed with all patients, except those with a very low risk of relapse [I,A], but the optimal duration and regimen of adjuvant ET are currently unknown. There is only a minimal benefit for the use of AIs for more than 5 years

Associazione Italiana di Oncologia Medica

- **Pazienti ancora in premenopausa o perimenopausa dopo 5 anni di tamoxifene:** PUO' essere considerata la prosecuzione di tamoxifene per ulteriori 5 anni
- **Pazienti in post-menopausa:** l'estensione della terapia con AI dopo il quinto anno POTREBBE essere presa in considerazione, previa valutazione del rischio beneficio
- **Pazienti in postmenopausa che hanno completato 5 anni di tamoxifene:** l'utilizzo di AIs per 5 anni DOVREBBE (potrebbe) essere preso in considerazione, previa valutazione del rischio/beneficio

Endocrine therapy: summary

- **Several options supported by clinical trials data**

  Tamoxifen, Aromatase Inhibitors, +/- OFS, 5 yy vs extended

- Baseline **risk assessment**
- **Careful discussion** on side effects, life plans, patient expectancies
- Importance of **lifestyle** (BMI, physical activity)

HR+/HER2+ Early BC

Endocrine therapy for ALL

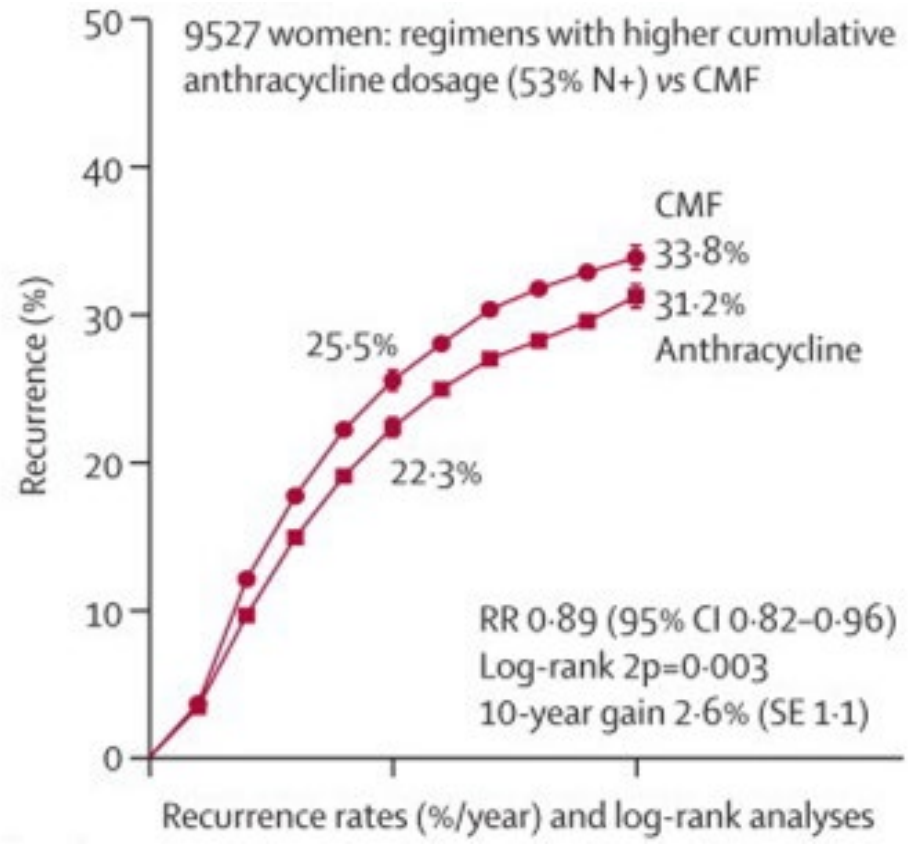
Chemotherapy for some

Choice of CT regimen

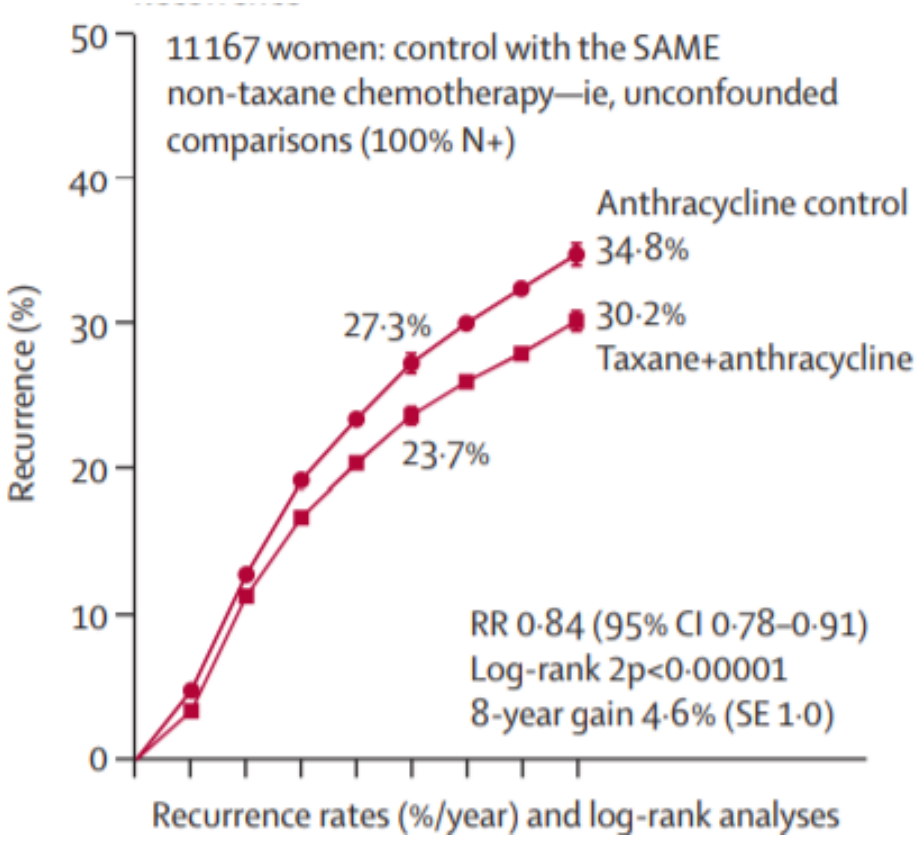
Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Anthracycline-based vs non anthracycline-based CT



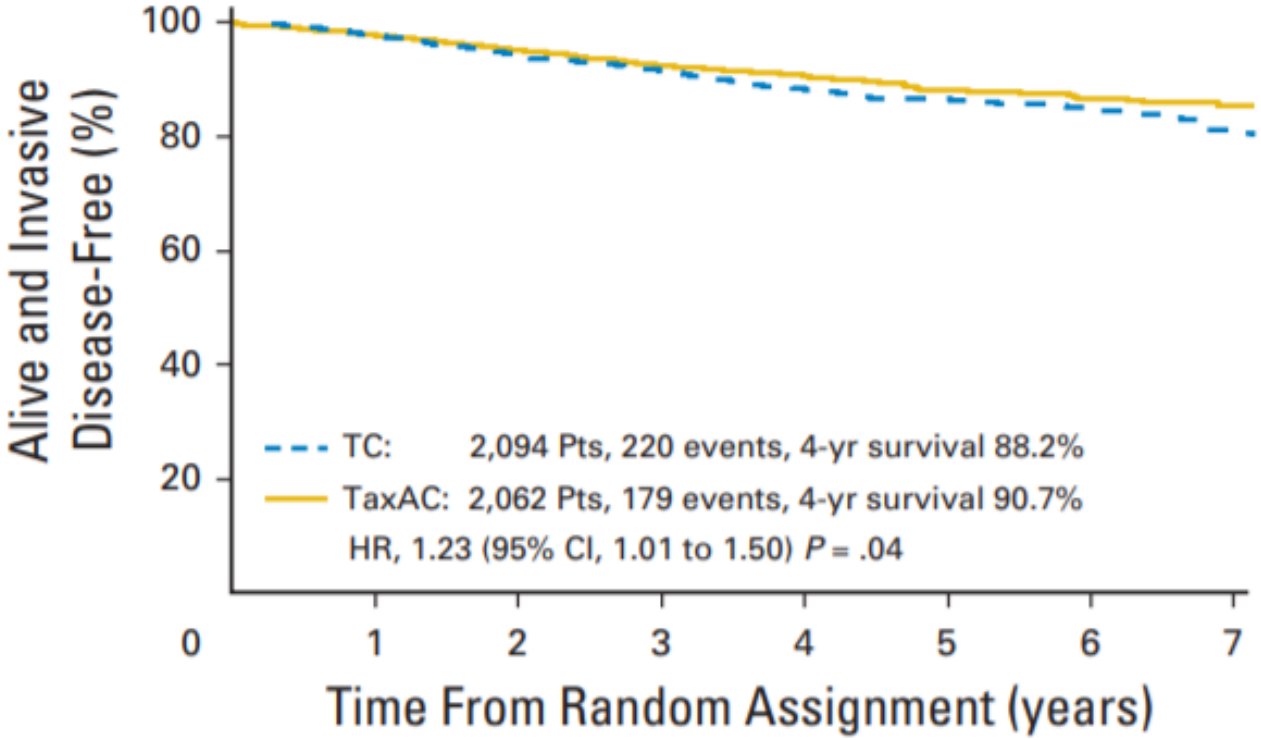
Anthracycline vs anthra+taxane CT

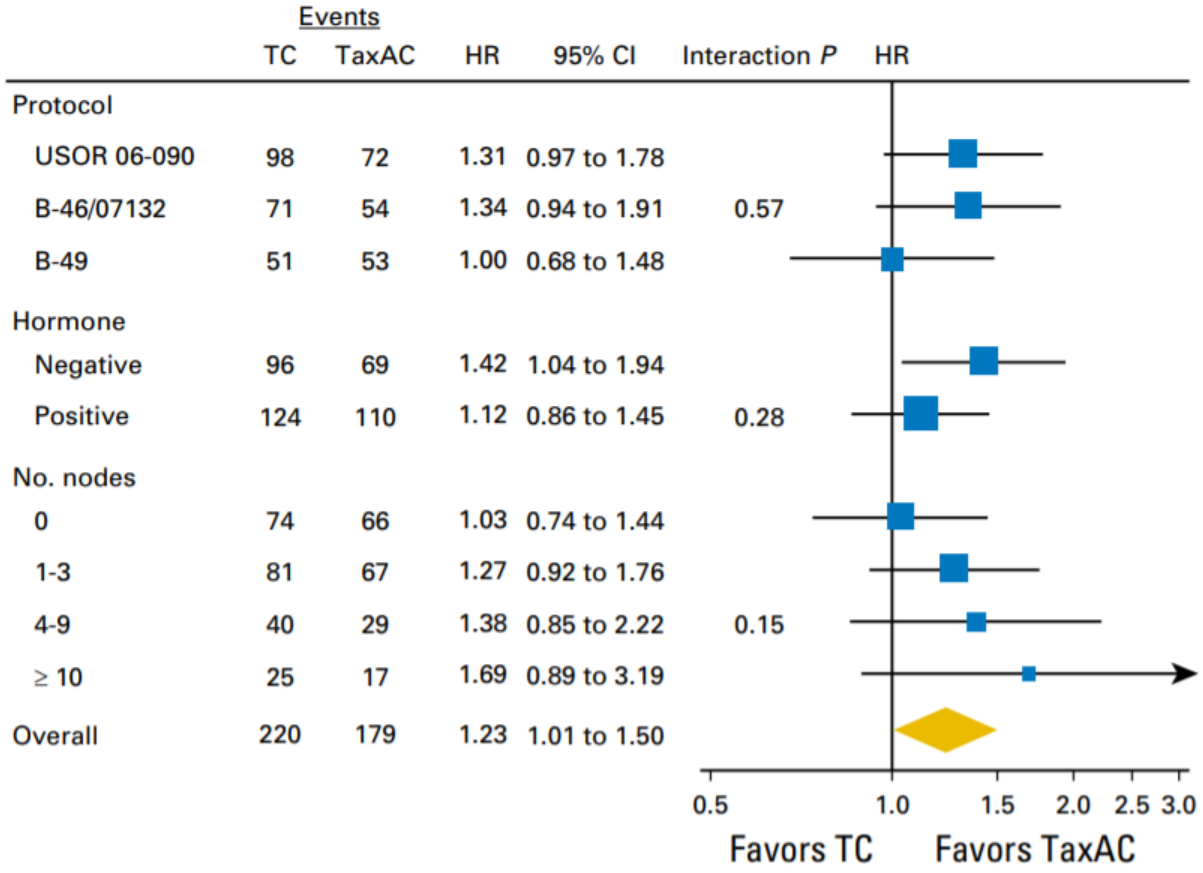


EBCTCG, Lancet 2012

Can we avoid anthracyclines?

Anthracyclines in Early Breast Cancer: The ABC Trials—USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology)



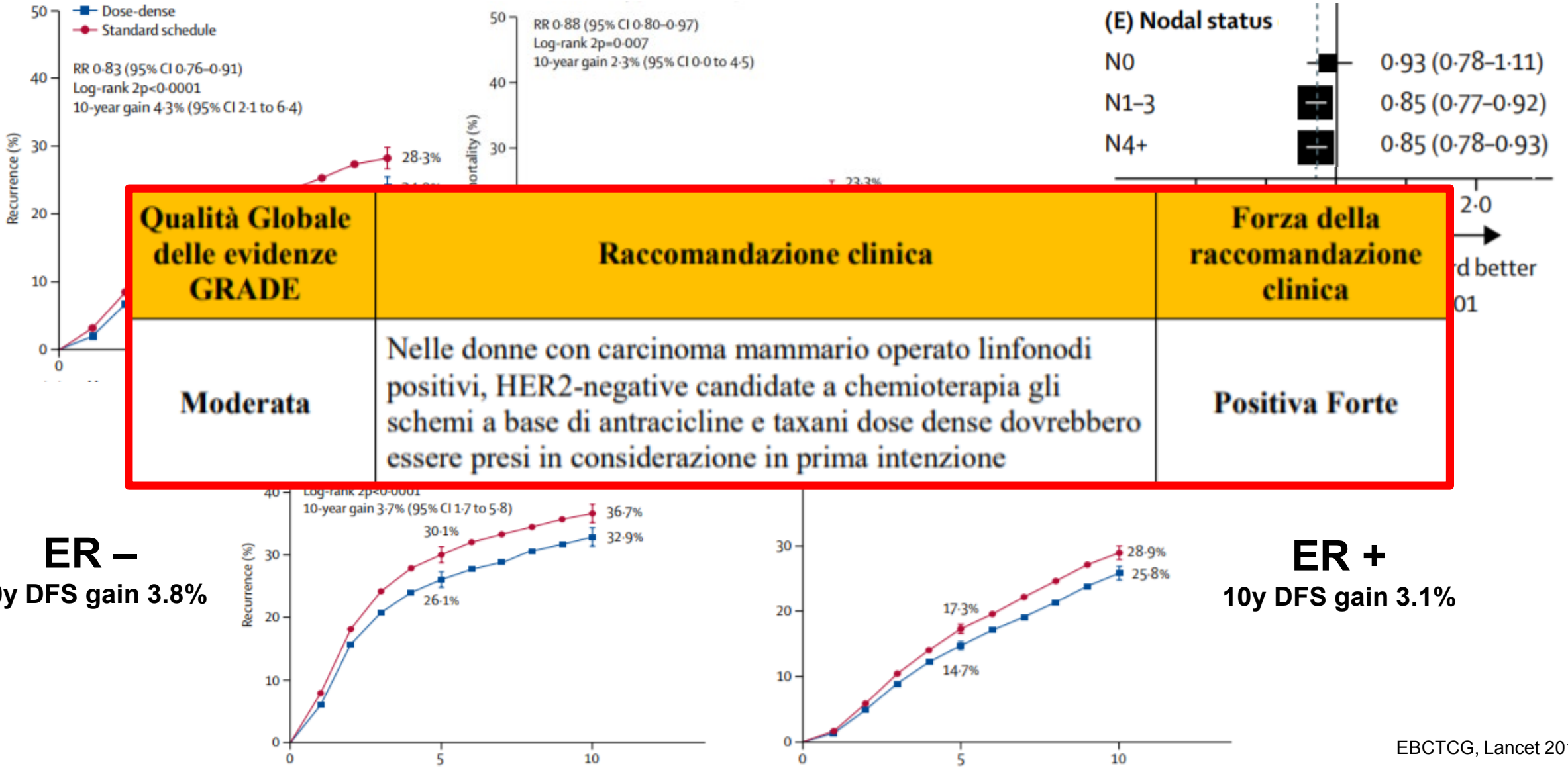


Improvement in iDFS with anthracycline, however the absolute benefit was small.
The benefit appeared to be meaningful in patients with HR- or **HR+ and N+**

Blum, JCO 2016

Dose-dense chemotherapy

Dose-dense (2-weekly) CT versus the same CT given 3-weekly (N=10.004)



Qualità Globale delle evidenze GRADE	Raccomandazione clinica	Forza della raccomandazione clinica
Moderata	Nelle donne con carcinoma mammario operato linfonodi positivi, HER2-negative candidate a chemioterapia gli schemi a base di antracicline e taxani dose dense dovrebbero essere presi in considerazione in prima intenzione	**Positiva Forte**

ER –
10y DFS gain 3.8%

ER +
10y DFS gain 3.1%

EBCTCG, Lancet 2019

Who can be safely spared CT?

Clinical validity

Correlation of score with outcome

Predict baseline prognosis

Clinical utility

Actionable: use results for patient benefit.

Who can be spared chemotherapy?

Prognosis is so good that any relative benefit of adding chemotherapy would translate into a not clinically relevant absolute gain

Multigene signatures can help identify these patients

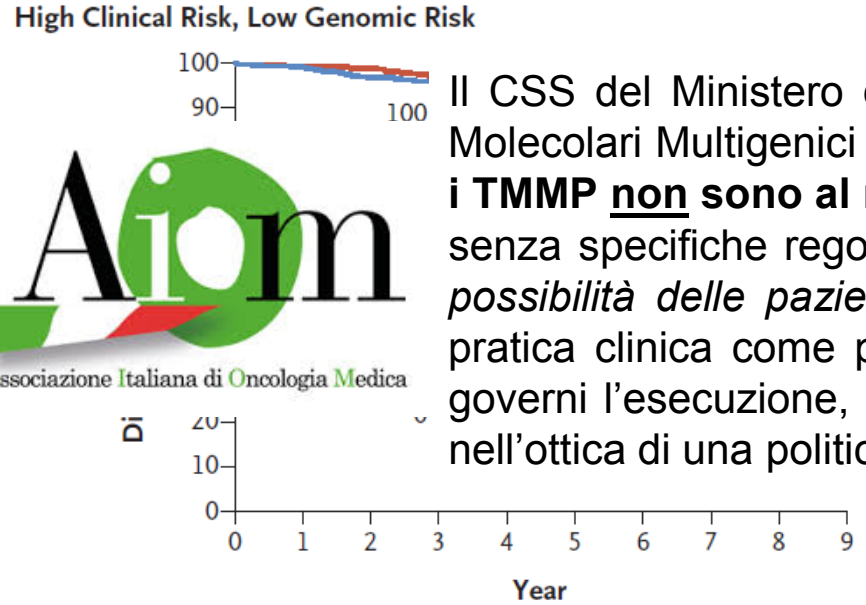
Absolute distant recurrence risk at baseline	Relative risk reduction with CT [a]	Absolute risk reduction from CT [b]	Risk of Fatal, life-threatening, permanent CT toxicity
50-60%	30%	15-20%	2-3%
10-15%	30%	2-3%	2-3%

a) CT produces the same proportional risk reduction in all patients (EBCTCG)
b) This translates into different degrees of absolute benefit, depending on the individual estimate of absolute risk of recurrence.

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 25, 2016 VOL. 375 NO. 8

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

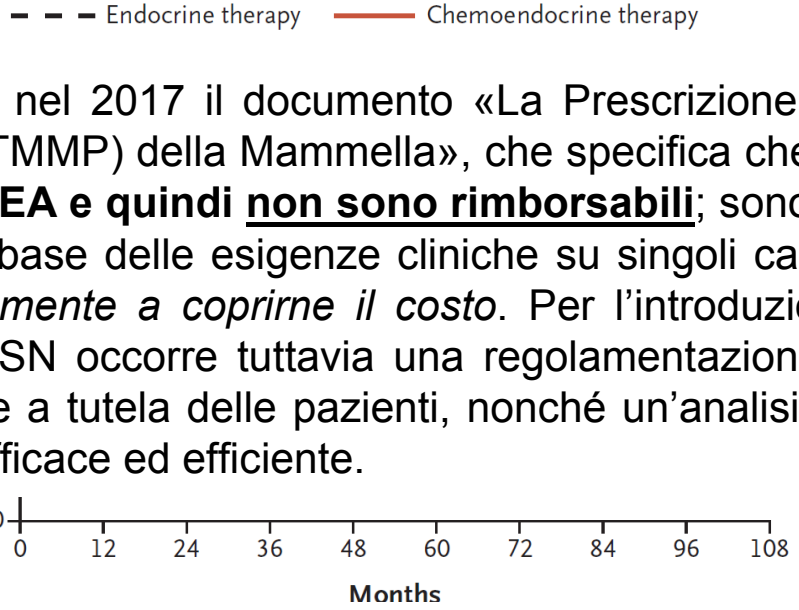
F. Cardoso, L.J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J.-Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A.M. Glas, V. Golfinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P.A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I.T. Rubio, M. Saghatchian, T.J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A.M. Thompson, J.M. van der Hoeven, P. Vuylsteke, R. Bernards, K. Tryfonidis, E. Rutgers, and M. Piccart, for the MINDACT Investigators*



The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 12, 2018 VOL. 379 NO. 2

Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.



Il CSS del Ministero della Salute ha prodotto nel 2017 il documento «La Prescrizione dei Test Molecolari Multigenici Prognostici dei Tumori (TMMP) della Mammella», che specifica che **in Italia i TMMP <u>non</u> sono al momento inseriti tra i LEA e quindi <u>non sono rimborsabili</u>**; sono utilizzati senza specifiche regole istituzionali, ma sulla base delle esigenze cliniche su singoli casi e della *possibilità delle pazienti di provvedere direttamente a coprirne il costo*. Per l'introduzione nella pratica clinica come prestazione offerta dal SSN occorre tuttavia una regolamentazione che ne governi l'esecuzione, la qualità e l'applicazione a tutela delle pazienti, nonché un'analisi dei costi nell'ottica di una politica economico-sanitaria efficace ed efficiente.

LoE1A: results from ≥1 prospective trial specifically designed to test the marker