25-year survival and benefit from tamoxifen therapy by the clinically used breast cancer markers in lymph node-negative and ER-positive / HER2- negative breast cancer

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Background

The clinically used breast cancer markers are known to predict short-term survival, but whether these markers predict long-term (25-year) survival is unclear.

Conclusion

In this randomized trial of n=565 postmenopausal lymph node-negative patients with estrogen receptor (ER)-positive/ HER2-negative breast cancer, our findings indicate that for this selected subgroup tumor size followed by grade are significant long-term prognosticators. Further, a significant long-term benefit from tamoxifen therapy was seen in patients with larger tumor size, lower tumor grade and PR-positive tumors.

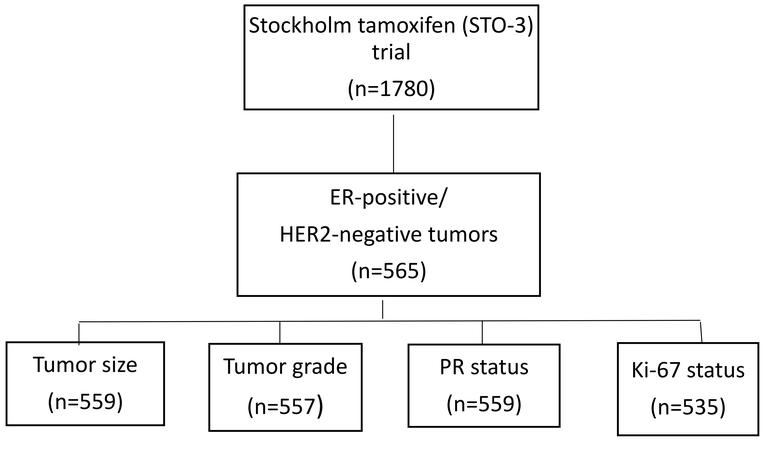


Figure 1. Consort diagram for the STO-3 trial

Secondary analysis of the Stockholm Tamoxifen (STO-3) trial conducted from 1976-1990, randomizing postmenopausal lymph node-negative breast cancer patients to adjuvant tamoxifen therapy.

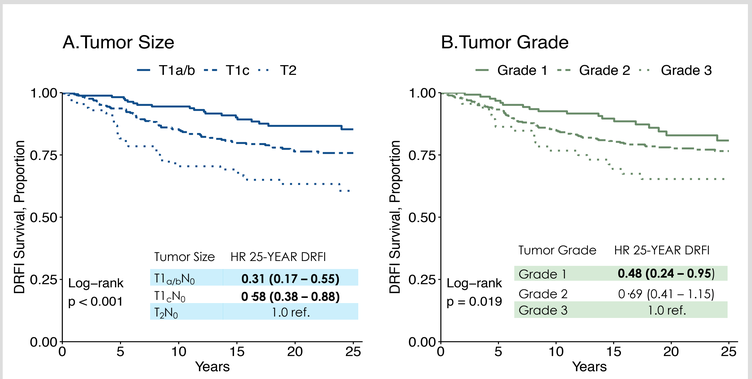
Author disclosures

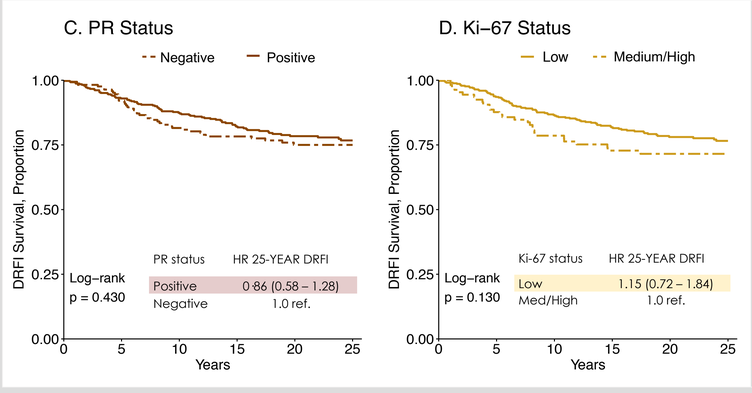
All authors declare there are no conflicts of interest.

Figure 2. Kaplan-Meier analysis of DRFI by Tumor size, grade, PR, and Ki-67 status.

A statistically significant reduced long-term distant recurrence-free interval (DRFI) was seen for patients with (A) smaller tumor size and (B) lower tumor grade as compared to patients with larger (T2) tumor size and grade 3 tumors, respectively.

A statistically significant difference in long-term DRFI was seen not seen by by (C) PR and (D) Ki-67 status.





Research questions

Are the clinically used markers, i.e. tumor size, grade, progesterone receptor (PR), and Ki-67, independent 25-year prognosticators and predictors of tamoxifen therapy benefit?

Table 1: DRFI by treatment stratified by tumor size, tumor grade, PR status, and Ki-67 status

A statistically significant reduced long-term risk was seen for tamoxifen (TAM) treated patients with larger tumor size and lower tumor grade, as compared to untreated patients. Furthermore, treated patients with PR-positive disease had a reduced long-term risk as compared to untreated patients, in contrast to PR-negative patients with no significant long-term benefit of tamoxifen treatment. Finally, treated patients with both Ki-67-medium/ high and Ki-67-low disease had a reduced long-term risk.

	Trial arm	25-year DRFI HR (95% CI)[a,b]
$T1_{a/b}N_0$[b]	TAM Treated	0.39 (0.14 – 1.07)
	Untreated	1.0 ref.
$T1_cN_0$[b]	TAM Treated	**0.53 (0.32 – 0.89)**
	Untreated	1.0 ref.
T_2N_0[b]	TAM Treated	**0.34 (0.16 – 0.73)**
	Untreated	1.0 ref.

	Trial arm	25-year DRFI HR (95% CI)[a,b]
Grade 1[b]	TAM Treated	**0.24 (0.07 – 0.82)**
	Untreated	1.0 ref.
Grade 2[b]	TAM Treated	**0.50 (0.31 – 0.80)**
	Untreated	1.0 ref.
Grade 3[b]	TAM Treated	0.54 (0.21 – 1.38)
	Untreated	1.0 ref.

	Trial arm	25-year DRFI HR (95% CI)[a,b]
PR positive[a,b]	TAM Treated	**0.38 (0.24 – 0.62)**
	Untreated	1.0 ref.
PR negative[a,b]	TAM Treated	0.57 (0.28 – 1.13)
	Untreated	1.0 ref.

	Trial arm	25-year DRFI HR (95% CI)[a,b]
Ki-67 positive[a,b]	TAM Treated	**0.39 (0.17 – 0.92)**
	Untreated	1.0 ref.
Ki-67 negative[a,b]	TAM Treated	**0.45 (0.29 – 0.71)**
	Untreated	1.0 ref.

[a] HR = hazard ratio, CI = confidence interval, TAM = tamoxifen, PR-positivity was defined as ≥10%, and Ki-67 threshold for medium/ high expression was 15% or greater.

[b] Modeled by multivariable Cox proportional hazard analysis adjusting for age at primary diagnosis, calendar period of diagnosis, tumor size, tumor grade, progesterone receptor (PR) status, and Ki-67 status.

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