Prognostic relevance of DNA damage and repair biomarkers in elderly patients with hormone receptor positive breast cancer treated with neo-adjuvant hormone therapy: evidence from the real world setting

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Purpose. The logic behind the outcome of endocrine therapy in breast cancer have long remained roughly characterized. The prognostic role of DNA damage and repair biomarkers (DDR) was explored in postmenopausal, hormone receptor positive breast cancer patients treated with neo-adjuvant hormone therapy (NAHT).

Representative examples of two breast cancer cases with pATR, pATM and γ-H2AX nuclear immunohistochemical expression.

Baseline characteristics of study patients (N=55).

Characteristics		N (%)
Age at diagnosis	Median (min-max) [IQ range]	75.7 (56-88) [68.3-81.7]
cT	1	6 (10.9)
	2	44 (80.0)
	3	5 (9.1)
Histotype	Invasive ductal carcinoma	54 (98.2)
	Lobular carcinoma	1 (1.8)
Subtype	Luminal A	43 (78.2)
	Luminal B	12 (21.8)
Grade	G1	37 (67.3)
	G2	17 (30.9)
	G3	1 (1.8)
ER/PgR at the biopsy	ER+/PgR+	22 (40.0)
	Other+	33 (60.0)
HER2	Negative	51 (92.7)
	Positive	4 (7.3)
Ki67	<14%	45 (81.8)
	≥14%	10 (18.2)
NAHT	Letrozole	22 (40.0)
	Anastrozole	3 (5.5)
	Exemestane	30 (54.5)
Duration of the NAHT	< 6 months	33 (60.0)
	≥ 6 months	22 (40.0)
Clinical Response	CR	4 (7.3)
	PR	41 (74.5)
	SD	8 (14.5)
	PD	2 (3.6)
Adjuvant CT	No Therapy	42 (76.4)
	Anthracycline based	1 (1.8)
	Anthracycline-Taxane Free	8 (14.5)
	Anthracycline+Taxane	4 (7.3)
Adjuvant RT	No	25 (45.5)
	Yes	30 (54.5)
Relapse	No	45 (81.8)
	Yes	10 (18.2)
	Local	1 (10.0)
	Distant	9 (90.0)

cT: Clinically-instrumentally defined primitive tumour size; ER/PgR: Estrogen Receptor/Progesterone Receptor; NAHT: Neoadjuvant therapy: CT: Chemotherapy; RT: Radiotherapy.

Methods. Data on 55 patients were included. The phosphorylated ataxia telangiectasia and Rad3-related protein (pATR), phosphorylated Ataxia Telangiectasia Mutation (pATM) kinase, and the variant of histone H2AX phosphorylated in Ser139, histone (γ-H2AX) were evaluated by immunohistochemistry in paired tissues collected at baseline and following NAHT. Biomarkers were considered both singularly and within signatures. Ki-i-67 percent changes were the primary biomarker endpoint. Classical endpoints were also considered.

Results. The most favorable ki-67 outcome was associated with the γ-H2AX/p-ATM signature (p=0.011). In models of ki-67 reduction, "luminal B" subtype, higher grade of anaplasia, and the γ-H2AX/p-ATM signature tested significant (p<0.05 for all). Results were confirmed in multivariate analysis. No association was observed with pathologic response. An increase of Δ γ-H2AX in paired breast tissues was associated with longer event free survival (p=0.024) and overall survival (p=0.042). In Cox models, both survival outcomes were solely affected by grade of anaplasia, with less favorable prognosis in the highest grades (p<0.05 for both).
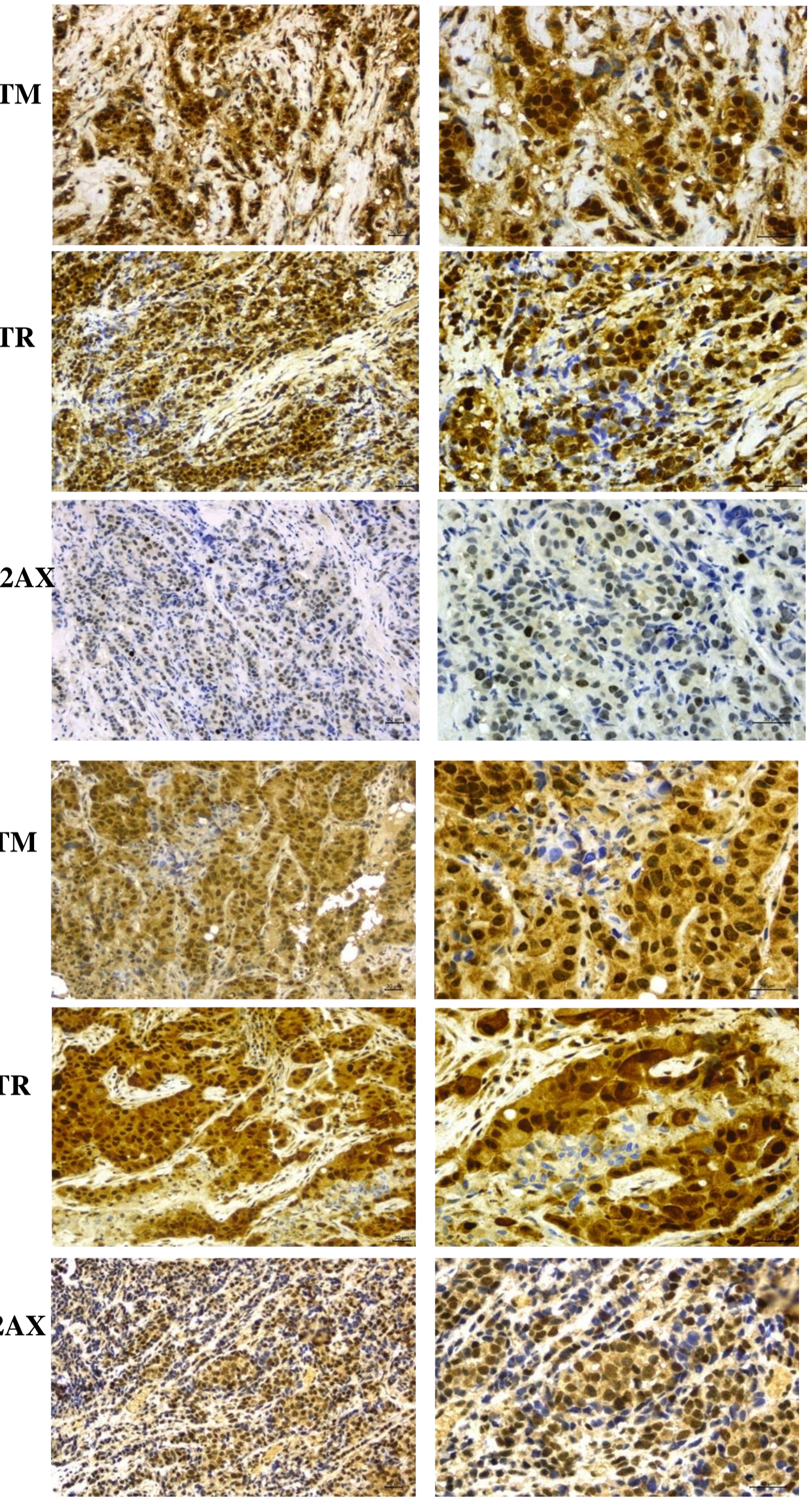
Uni- and multi-variate regression models of factors associated with a ki-67 reduction greater than 5 PT%

		Univariate logistic regression model OR (95%CI)	p-value	Multivariate logistic regression model OR (95%CI)	p-value
Subtype	*Lum. B vs Lum. A	9.33 (1.81-48.24)	0.008	22.87 (3.19-163.74)	0.002
Grade	III-II vs I	3.69 (1.12-12.14)	0.031	6.68 (1.34-33.14)	0.020
γ-H2AX/ p-ATM	γ-H2AX+/ p-ATM+ vs other	9.33 (1.81-48.24)	0.008	17.02 (2.42-119.82)	0.004

*Lum.: Luminal

Association between the biomarkers tested and Ki-67 changes (N:55).

		Ki67 change No change + reduction <5PT% N(%)	Reduction >5PT% N(%)	Increased N(%)	Chi2 Test p-value
γ-H2AX	Negative	20 (58.8)	12 (35.3)	2 (5.9)	0.092
	Positive	6 (28.6)	13 (61.9)	2 (9.5)	
p-ATM	Negative	13 (50.0)	10 (38.5)	3 (11.5)	0.398
	Positive	13 (44.8)	15 (51.7)	1 (3.4)	
p-ATR	Negative	2 (66.7)	1 (33.3)	0 (0.0)	0.746
	Positive	24 (46.2)	24 (46.2)	4 (7.7)	
γ-H2AX/p-ATM	other	24 (55.8)	15 (34.9)	4 (9.3)	0.011
	γ-H2AX+/p-ATM+	2 (16.7)	10 (83.3)	0 (0.0)	
γ-H2AX/p-ATR	other	20 (58.8)	12 (35.3)	2 (5.9)	0.092
	γ-H2AX+/p-ATR+	6 (28.6)	13 (61.9)	2 (9.5)	

Event Free Survival analysis (N=55).
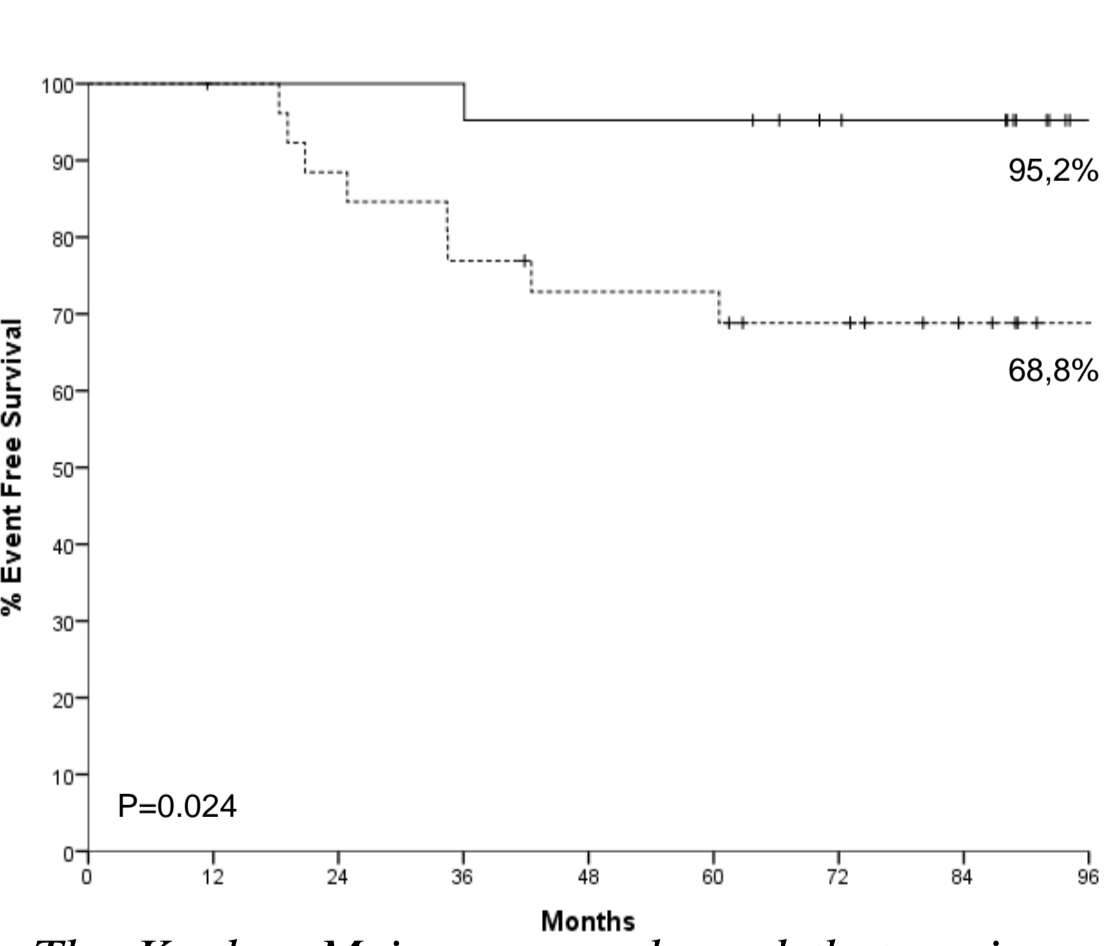
95,2%

68,8%

P=0.024

The Kaplan–Meier curves showed that an increase of Δ γ-H2AX (solid line) in paired breast tissues was associated with a longer time to relapse.

Overall survival by Δ γ-H2AX (N:55).
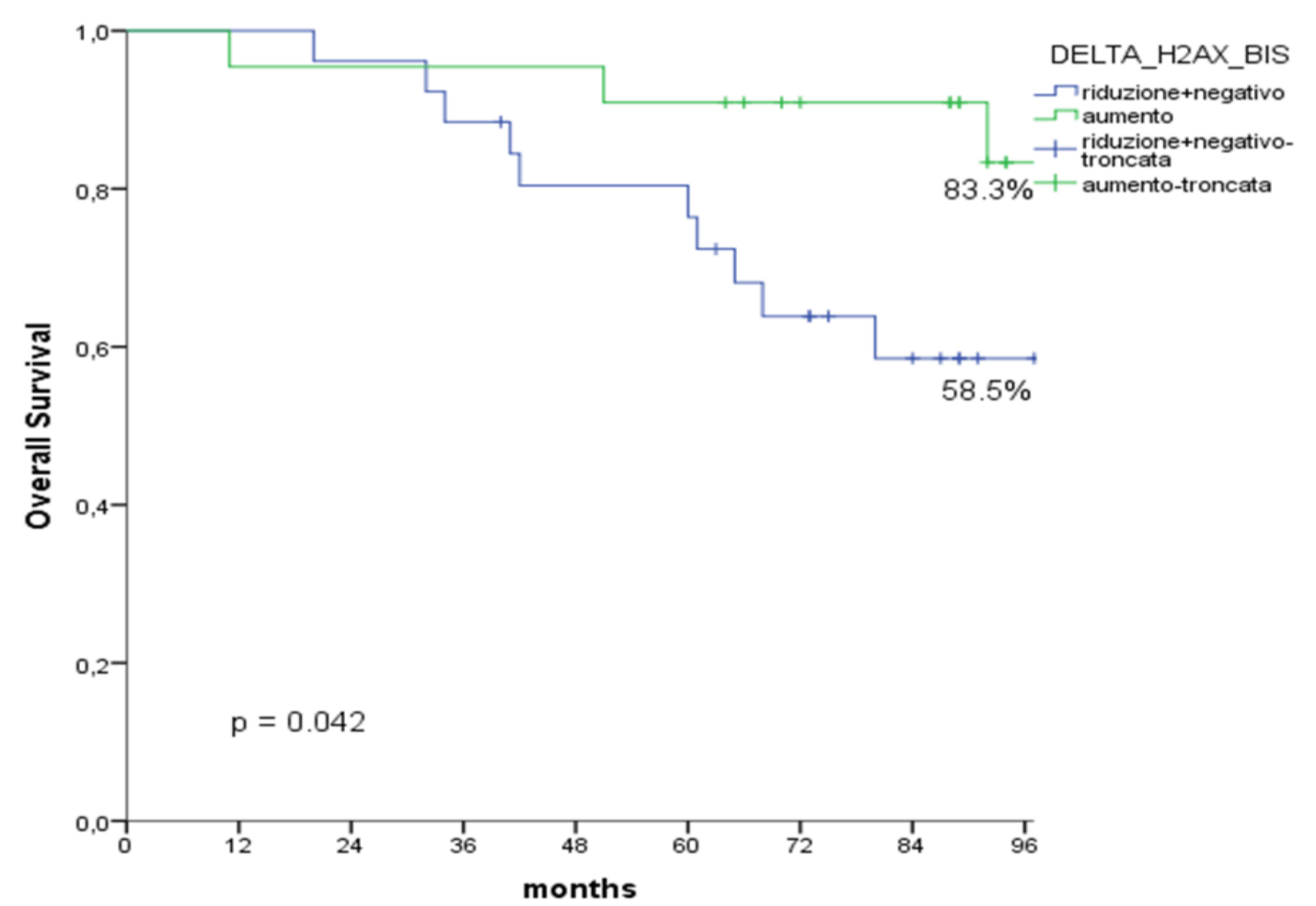
83.3%

58.5%

p = 0.042

The Kaplan–Meier curves showed that an increase of Δ γ-H2AX (solid line) in paired breast tissues was associated with a longer overall survival.

Conclusions. We first report evidence of the prognostic role of DDR biomarkers on patient important outcomes in post-menopausal hormone receptor positive breast cancer patients treated with NAHT. If confirmed in future, adequately sized trials, our results may help inform therapeutic decisions and clarify underlying biological mechanisms.

Selected references (6/34)

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