Patterns of relapse according to breast cancer subtypes in lymph node-negative disease – Results from International Breast Cancer Study Group Trials VIII and IX

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Supplement to "Patterns of recurrence and outcome according to breast cancer subtypes in lymph node-negative disease – Results from International Breast Cancer Study Group Trials VIII and IX"

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Section 1: Pathology assessment

Retrospective central pathology evaluation included ER, PgR, HER2 (immunohistochemistry) and Ki-67 labeling index (LI) performed in the IBCSG Central Pathology Laboratory, European Institute of Oncology, Milan, Italy.

Estrogen receptor (ER) and progesterone receptor (PgR) assessment - Whole tumor sections were incubated with the specific primary mouse monoclonal antibodies to ER (clone 1D5; 1:100 dilution) or PgR (clone 1A6; 1:800 dilution) (both from Dako). ER- and PgR–negative status was defined as < 1% immunoreactive cells

Ki-67 Labeling Index (LI) was assessed using mouse monoclonal antibody MIB-1 (1:200 dilution; Dako, Glostrup, Denmark); the percentage of cells that showed definite nuclear immunoreactivity with MIB-1 among 2,000 invasive neoplastic cells in randomly selected high-power fields (x400) at the periphery of the tumor was recorded.

HER2 immunoreactivity was assessed using a HercepTest kit (Dako), and was scored for the intensity of immunostaining, the completeness of cell membrane staining, and the percentage of immunoreactive neoplastic cells by using a four-tier scale from 0 to 3+. HER2-negative status was defined as immunostaining levels 0, 1+ and HER2-positive was defined as intense and complete membrane staining of >10% of the tumor cells (3+).

Fluorescent in situ hybridization (FISH) was performed on the tissue microarrays (TMAs) using a PathVysion kit (Vysis-Abbott) and considered positive when the HER2: C17 ratio > 2.0. Tissue microarrays were built in the Garvan Institute of Medical Research, Sydney, Australia. The TMAs were produced using the MTA-1 Manual Tissue Arrayer and a 1.0 mm needle to biopsy tumor tissue identified by examination of hematoxylin and eosin (H&E)-stained slides from a standard histological block. Three representative cores were taken from each donor block and deposited in the recipient array block. Each array in Trial VIII comprised 108 (9 ± 12) cores representing about 32 patients. Arrays from Trial IX comprised 96 cores (8 ± 12) representing about 28 patients. An asymmetric template was employed for core orientation. Cores of renal tissue (± 6) were randomly placed within each array to act as orientation markers when scoring. Normal breast cores taken from reduction mammoplasties (± 6) were also placed on each array to allow comparison between immunohistochemical staining in morphological normal breast and invasive breast carcinoma.

Section 2: Hormone receptor status within HER2 subtype

Figure S1: Kaplan-Meier estimates of breast cancer-free interval (BCFI) by hormone receptor status in the HER2 subtype.

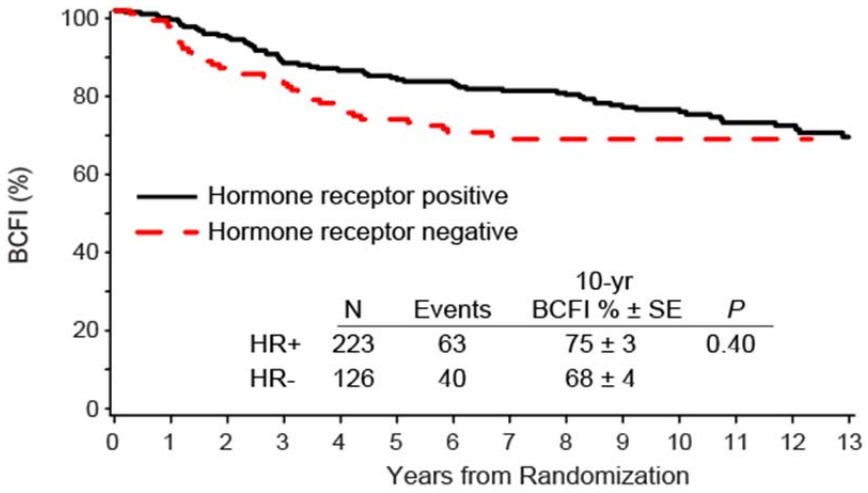

Table S1: 10-year cumulative incidence % ± standard error for HER2+ patients by hormone receptor status

Site of First event	HER2+ hormone receptor + (n =223) No.	10-y%±SE*	HER2+ hormone receptor - (n =126) No.	10-y%±SE*	Gray test p-value
Local	14	5.56±0.02	12	9.63±0.03	0.30
Contralateral breast	7	3.0±0.01	2	1.6±0.01	0.36
Nodal (no CT)	2	2.02±0.01	0	0±0.00	0.28
Nodal (CT)	2	0.88±0.01	5	7.41±0.03	0.05
Bone	11	3.66±0.01	1	0.8±0.01	0.04
Visceral (no CT)**	12	11.35±0.03	13	22.66±0.06	0.08
Visceral (CT)**	15	11.51±0.03	7	10.35±0.04	0.30

Note: Hormone receptor positive (+) is defined as ER-positive and/or PgR-positive and hormone receptor negative is defined as ER-negative and PgR-negative. A total of 20 HER2-positive patients were not included in the analysis due to missing/unknown values of ER and/or PgR.

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