

# BIOLOGICAL THERAPIES FOR BREAST CANCER

## Updates from the 2005 San Antonio Breast Cancer Symposium

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### Top-line summary

Here, *Oncology Exchange* presents an update based on presentations made at the 2005 San Antonio Breast Cancer Symposium (SABCS). These confirmed the unquestionable benefit of trastuzumab, both qualitatively — it works — and quantitatively — it reduces over 40% of breast cancer events in women with HER2-expressing tumours. The symposium also confirmed that other biological therapies such as bevacizumab are on the horizon. Further, the field of molecular markers that may predict benefit of trastuzumab, enabling more precise determination of patients likely to benefit from this expensive therapy, is rapidly advancing.

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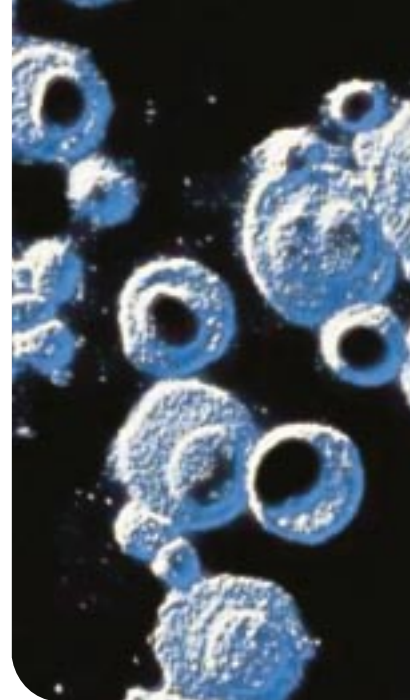
Biological therapies continue to dominate the scene in breast cancer treatment. While most North American cancer care institutions have approved trastuzumab, and guidelines consider it an obligatory component of adjuvant therapy for breast cancer with positive HER2 status, many European institutions have not yet approved this agent for consistent use in the adjuvant setting.

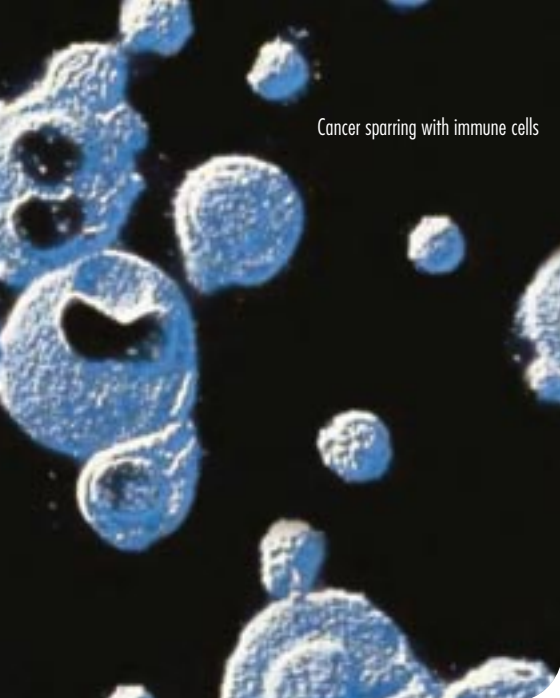
A leading European editorial as recent as November 2005<sup>1</sup> assessed the overall impact of trastuzumab with a great deal of skepticism, being particularly negative about its cost–benefit. This is despite 3 large multicentre randomized trials that independently demonstrated a 40% to 52% reduction of breast cancer recurrences among patients with HER2-expressing tumours,<sup>2,3</sup> and one of these analyses, the NSABP trial B-31, already shows a 33% reduction in mortality at 3 years of followup.<sup>3</sup> Trastuzumab adjuvant therapy received a further boost of acceptance at the 2005 SABCS with results of 2 additional independent trials. The BCIRG group reported on a 3-arm trial, with 2 of the arms given trastuzumab for 1 year, both showing a significant 39% to 51% reduction of recurrences compared to the non-trastuzumab arm in which patients received the same chemotherapy alone.<sup>4</sup> Equally exciting, a Finnish group randomized patients to trastuzumab vs controls receiving no trastuzumab, reproducing a similar magnitude of benefit, this time with just a 9-week short course.<sup>5</sup>

### AVOIDING TRASTUZUMAB-ASSOCIATED CARDIOTOXICITY

A concern with this agent, however, has been its cardiac effects, noted in studies of trastuzumab given to patients with Stage IV disease.<sup>2</sup> The non-anthracycline regimen of docetaxel + carboplatin had previously shown synergy against breast cancer cell lines. The BCIRG 006 study was designed specifically to investigate the combination of this novel regimen with trastuzumab, to avoid the occurrence of cardiac events.<sup>4</sup> The 3222 enrolled patients had HER2-amplified tumours, as evaluated by central fluorescence in situ hybridization (FISH) analysis, and had either positive axillary lymph nodes or high-risk tumours with negative lymph nodes. They were randomized to 3 treatment arms:

- 4 cycles of doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks, followed by 4 cycles of docetaxel 100 mg/m<sup>2</sup> every 3 weeks (AC→T without trastuzumab)
- AC→T with trastuzumab once per week during chemotherapy and every 3 weeks during followup for a year





Cancer sparring with immune cells

SABCS. He reported the first planned interim analysis at 322 events, comprising recurrence of breast cancer, a second primary tumour or death. Median followup was 23 months. Compared to patients receiving the standard treatment, AC→T, the hazard ratio (HR) for disease-free survival in the AC→T with trastuzumab arm was 0.49 ( $p = 0.00000048$ ), translating into a 51% avoidance of recurrences. When the docetaxel + carboplatin + trastuzumab arm was compared to AC→T without trastuzumab, the HR was 0.61 ( $p = 0.00015$ ) (Table 1). These statistics were virtually identical to those seen in the combined NSABP-NCCTG analysis.<sup>3</sup> The difference between the 2 trastuzumab-containing arms was not statistically significant at this early stage of followup, although numerically a greater trastuzumab benefit was apparent when used with prior anthracycline chemotherapy.

Differences related to prior chemotherapy were noted, however, in the analysis of cardiac toxicity (Table 2). When trastuzumab followed anthracycline (e.g. adriamycin) chemotherapy regimens, symptomatic cardiac events (defined as either congestive heart failure, Grade 3–4 ischemia or Grade 3–4

arrhythmias) were substantially increased compared to when trastuzumab therapy was given without the anthracycline regimen. Symptomatic cardiac events were reported in 2.3% of patients treated with AC→T plus trastuzumab, compared to 1.2% of those receiving AC→T without trastuzumab, and 1.2% of those receiving the docetaxel + carboplatin + trastuzumab combination.

These results may be particularly relevant to the majority of women with HER2-overexpressing breast tumours without expression of topoisomerase II alpha (see below). In this subgroup, the breast cancer impact of the cardiotoxicity-sparing docetaxel + carboplatin + trastuzumab regimen were identical to the AC→T plus trastuzumab combination.

**MIGHT 9-WEEKS OF TRASTUZUMAB BE ENOUGH?**

Joensuu et al from Finland reported preliminary results of the European FinHer trial, in which a 2-way randomization permitted both assessment of the impact of trastuzumab and a comparison of docetaxel vs vinorelbine in the adjuvant setting. The 1010 patients received trastuzumab for only 9 weeks, together with chemotherapy. Participants' cancer was either axillary node-positive or node-negative with progesterone receptor-negative tumours > 2 cm. First, they were randomized to receive either 3 cycles of docetaxel 100 mg/m<sup>2</sup> every 3 weeks or 8 cycles of weekly vinorelbine 25 mg/m<sup>2</sup>. Subsequently, patients in both arms received 3 cycles of cyclophosphamide 600 mg/m<sup>2</sup>, epirubicin 60 mg/m<sup>2</sup> and 5-fluorouracil 600 mg/m<sup>2</sup> (CEF) every 3 weeks, and those with hormone receptor-positive tumours took tamoxifen for 5 years. The 232 patients (23%) with tumours that overexpressed HER2, as shown by amplification in chromogen in situ hybridization (CISH) done in 2 central laboratories, were then randomized to receive either 9 weekly cycles of trastuzumab 2 mg/kg, with a first dose of 4 mg/kg, or no trastuzumab.

The results (Table 3, page 8) showed impressive improvements in DFS and distant recurrence, with overall survival

- 6 cycles of docetaxel 75 mg/m<sup>2</sup> + carboplatin AUC6 every 3 weeks, with trastuzumab once per week during chemotherapy and every 3 weeks during followup for a year
- Women with hormone receptor-positive tumours received 5 years of hormonal therapy following chemotherapy.

Dr. Dennis Slamon, who originally discovered the importance of HER2 status in breast cancer<sup>6</sup> and was the lead investigator in the first study to show the impact of trastuzumab in Stage IV breast cancer therapy,<sup>7</sup> presented the study's results at this year's

**TABLE 1. Disease-free survival favouring trastuzumab in 3222 patients in the BCIRG 006 trial**

Treatment arm	hazard ratio vs AC→T* (p-value)
AC→T* with trastuzumab	0.49 ( $p = 0.00000048$ )
docetaxel + carboplatin† + trastuzumab	0.61 ( $p = 0.00015$ )

\* doxorubicin 60 mg/m<sup>2</sup> + cyclophosphamide 600 mg/m<sup>2</sup> q 3 weeks x 4, then docetaxel 100 mg/m<sup>2</sup> q 3 weeks x 4  
 † docetaxel 75 mg/m<sup>2</sup> + carboplatin AUC6 q 3 weeks x 6

**TABLE 2. Rates of cardiac events and decreased left ventricular ejection fraction (LVEF) in BCIRG 006**

	AC→T + trastuzumab	AC→T	docetaxel + carboplatin + trastuzumab	p-value
Symptomatic cardiac events	2.3%	1.2%	1.2%	0.046
LVEF decline > 15%	2.4%	0.6%	0.4%	0.001

approaching statistical significance, indicating that this short duration of trastuzumab therapy is beneficial. At median followup of 38 months, breast cancer events including distant and locoregional recurrences and contralateral breast cancers were significantly reduced in the patients receiving docetaxel and CEF, compared to those taking vinorelbine and CEF (HR 0.58,  $p = 0.0036$ ). Similarly, the HR for distant recurrence was 0.58 ( $p = 0.0087$ ). The effect of the 9-week course of trastuzumab in the HER2-overexpressing patients was also significant, with a 54% reduction of any recurrence (HR 0.46,  $p = 0.0078$ ) (Table 3). Even more impressive was the trastuzumab effect on the reduction of distant recurrences, with 3-year distant recurrence DFS of 93% versus 76% (HR 0.43,  $p = 0.0078$ ). The difference in overall survival was also substantial, but in this short duration of followup it did not quite reach statistical significance, with a HR of 0.43 ( $p = 0.08$ ). Patients tolerated the trastuzumab well, and left ventricular ejection fractions (LVEF) — measured at baseline, after completion of chemotherapy and 12 and 36 months after study entry — remained satisfactory.

## MOLECULAR MARKERS FOR PREDICTING RESPONSE TO TRASTUZUMAB

One of the first indications that molecules other than HER2 could more accurately determine the response to trastuzumab came from Nagata et al,<sup>8</sup> who correlated PTEN loss with a relative refractoriness to trastuzumab in Stage IV breast cancer, and PTEN preservation with a substantial response. The study reported a negligible trastuzumab response (< 10%) in

**TABLE 3. Efficacy of 9 weeks of trastuzumab vs no trastuzumab in 232 patients with HER2-overexpressing tumours in the FinHer trial**

Efficacy measure	hazard ratio (p-value)
any recurrence	0.46 ( $p = 0.0078$ )
distant disease-free survival	0.43 ( $p = 0.0078$ )
overall survival	0.43 ( $p = 0.08$ )

HER2-positive patients with PTEN loss, but a 65% response in HER2-positive patients with preservation of PTEN. Data on the implications of this important PTEN–trastuzumab interaction in the adjuvant treatment setting are pending.

The 2005 San Antonio symposium highlighted 2 other molecules relevant to trastuzumab response: cMYC and topoisomerase II alpha.

## cMYC in NSABP B-31

The cMYC gene has been associated with inferior outcomes in human breast cancer. In a prior search for markers that predict response to trastuzumab, a group of NSABP researchers screened 1900 women with node-positive breast cancer enrolled in NSABP trial B-28 for the presence of gene amplification at 27 gene loci, using FISH. Multivariate analysis showed 3 amplicons (small, replicating DNA fragments) — HER2, cMYC and HTPAP — to be associated with poor prognosis, independent of other known prognostic indicators. Amplification of both HER2 and HTPAP was rare, but coamplification of HER2 and cMYC was seen fairly often and was associated with worse outcome than with either amplification alone.

S. Paik presented a subanalysis of the NSABP B-31 study that investigated trastuzumab's effect according to cMYC expression.<sup>9</sup> NSABP-31 randomized patients to receive adjuvant chemotherapy of doxorubicin + cyclophosphamide for 4 cycles followed by paclitaxel with or without trastuzumab for a year, starting with the first dose of paclitaxel. In this subanalysis, researchers analyzed cMYC amplification in patients with HER2 amplification and treated with trastuzumab, expecting to find that trastuzumab would provide less benefit to women with cMYC amplification. Altogether, 432 (30%) of the 1736 NSABP-31 cases screened for cMYC and HER2 had coamplifications of both genes. The HR for recurrence was 0.63 in the 1078 patients without cMYC amplification vs 0.24 in the 471 with cMYC amplification ( $p = 0.007$ ) (Table 4). The impact of trastuzumab on recurrences and DFS was significantly superior compared to cases without cMYC HER2 coexpression (HR 0.32, and 0.63, respectively,  $p$  for interaction = 0.03). The mortality among patients with HER2-expressing and cMYC-positive tumors was significantly reduced by trastuzumab, (HR 0.36,  $p = 0.037$ ). Treatment with trastuzumab provided 4-year recurrence-free survival of over 90% in patients with coamplification of cMYC and HER2.

These results indicate that the expression of both molecules may be a surrogate for a more powerful HER2 signal, and that in these cases the interruption of the molecular message by trastuzumab may be more evident, resulting in a greater reduction of recurrences than in

**TABLE 4. Outcomes in patients with HER2 amplification, with and without cMYC amplification in the NSABP B-31 trial**

Outcome measure	cMYC not amplified n = 1078	cMYC amplified	interaction p-value n = 471
Recurrences	HR = 0.63	HR = 0.24	$p = 0.007$
Deaths	HR = 0.99	HR = 0.36	$p = 0.037$

cases expressing just HER2 alone without cMYC.

### Topo IIa in BCIRG 006

A similar interaction of HER2 and topoisomerase II alpha was seen in the BCIRG 006 trial, in a subanalysis by M.F. Press et al presented at the 2005 SABCs.<sup>10</sup> The topoisomerase II alpha gene (topo IIa) is located at chromosome band 17q12–q21, close to the HER2 gene.<sup>11,14</sup> In 2000, Jarvinen et al reported frequent coexpression patterns of the HER2 and topo IIa genes, correlating the expression of the 2 molecules with enhanced in vitro and in vivo sensitivity to doxorubicin.<sup>11</sup> The cell lines exhibiting HER2 and topo IIa coamplification, with overexpression of both HER2 and topo IIa proteins, showed an increased 2.9-fold sensitivity to doxorubicin compared to cell lines with deletion of the topo IIa gene, and the latter showed increased resistance to doxorubicin despite preserved amplification of the HER2 gene.

Close to 35% of participants in the BCIRG 006 study had coexpression of HER2 and topo IIa, and for these patients the outcome of AC→T plus trastuzumab was significantly better than that with docetaxel + carboplatin + trastuzumab. In fact, for this group trastuzumab did not improve the outcome of docetaxel + carboplatin + trastuzumab vs AC→T without trastuzumab. On the other hand, among the 65% of the HER2-positive cases without topo IIa coexpression, the survival curve of patients receiving docetaxel + carboplatin + trastuzumab was identical to that of patients receiving AC→T plus trastuzumab — significantly superior in both groups compared to controls treated with AC→T without trastuzumab.

The NSABP cMYC analysis and the BCIRG topo IIa results support an evolving paradigm whereby expression of multiple molecular markers predict the expected impact of trastuzumab. While patient cohorts that will benefit a great deal vs less or not at all from trastuzumab have not yet been identified, it appears that molecules other than HER2 will be essential additional required predictive markers for a more refined selection of trastuzumab ther-

apy recipients — similar to how estrogen and progesterone status are now used to select patients expected to have the best outcomes with endocrine therapy.

### BEVACIZUMAB IN BREAST CANCER TREATMENT

K. Miller et al reported on the multicentre, randomized ECOG E2100 trial testing the impact of bevacizumab plus paclitaxel vs paclitaxel alone in patients with Stage IV breast cancer. Bevacizumab is a monoclonal antibody to vascular endothelial growth factor (VEGF). Data on a negative association of VEGF expression and outcome of breast cancer is accumulating.<sup>15,16</sup>

The ECOG E2100 trial randomized 722 patients with locally recurrent or metastatic breast cancer to receive either paclitaxel 90 mg/m<sup>2</sup> alone on Days 1, 8 and 15 every 4 weeks, or the same dose and schedule of paclitaxel in combination with bevacizumab 10 mg/kg on Days 1 and 8, also every 4 weeks. In this analysis performed at 355 disease-progression events, response rate as determined by Response Evaluation Criteria in Solid Tumors (RECIST) was significantly increased in all patients receiving combination therapy compared to those on paclitaxel alone (28.2% vs 14.2%,  $p = 0.0001$ ). Progression-free survival was 10.97 months vs 6.11 months (HR 0.498,  $p < 0.001$ ) and the HR for overall survival was 0.674,  $p = 0.01$ . Women in the group receiving bevacizumab had a higher incidence of hypertension compared to those taking only paclitaxel (13.5% vs 0%,  $p < 0.0001$ ) of Grade 3–4 proteinuria (2.5% vs 0%,  $p = 0.0003$ ) and of Grade 3–4 neuropathy (28.2% vs 14.2%,  $p = 0.01$ ). Both groups had a similar < 1.5% rate of thromboembolic events and serious bleeding.

These results indicate a more than 50% reduction in breast cancer events, data similar to that first reported for trastuzumab given for Stage IV breast cancer in 2001.<sup>5</sup> Should bevacizumab follow the same pattern as trastuzumab, a potentially major impact in the adjuvant treatment setting may eventually also be seen. The largest adjuvant bevacizumab trial presently underway,

conducted by the ECOG group, randomizes patients to either receive it soon after surgery continuously with dose-dense chemotherapy or delayed (started after 2 months of AC).

### IMPLICATIONS FOR EMERGING TREATMENT

The BCIRG 0006 data confirms that trastuzumab provides a significant benefit in avoiding breast cancer recurrences. Further, it confirms the low cardiotoxicity potential of the novel docetaxel + carboplatin + trastuzumab combination. This observation is particularly appealing for the 65% of HER2-expressing breast cancer cases without topo IIa coexpression, a group in which no difference in outcome was seen after docetaxel + carboplatin + trastuzumab compared to the “gold standard” of anthracycline + taxane + trastuzumab combination. On the other hand, for cases with coexpression of topo IIa, the anthracycline-containing regimen may be required for full trastuzumab effect — the topo IIa expression of these cancers appears to enhance the trastuzumab + anthracycline synergy.

The Finnish trial not only offers confirmation from a different European group that trastuzumab works and that it will avoid over 50% of early breast cancer recurrences, but that it can be restricted to a 9-week course — a very important conclusion relevant to the enormous cost of the 1-year course now becoming standard in North America. The 9-week course will likely also limit cardiotoxicity, although longer followup is required to monitor the full extent of cardiac events.


The observations of enhanced trastuzumab effect among breast cancer cases coexpressing HER2 with other molecular markers such as cMYC or topo IIa indicate that interaction of multiple pathways may be required for the realization of the full effect of trastuzumab, raising the question of which pathways are more and which are less essential. This influences other important decisions about what to do with HER2-expressing cases that lack expression of other HER2 “assistant” molecules, where trastuzumab may be

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## DISCOURSE

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still effective albeit to a lesser degree. The situation is similar to when breast cancers exhibit a medium level of hormonal receptor expression, and will be important to policy and guideline makers and to patients. It is possible that in such situations, the trastuzumab gains to individual patients will still remain potentially very meaningful — albeit not as cost-beneficial on purely fiscal grounds when compared to cases expressing HER2 together with the HER2-assisting molecules. Phase III randomized trials may not be possible to answer all the emerging questions now arising.

Bevacizumab is a more recently developed biological agent, and future trials will be needed to confirm whether its impact in the adjuvant setting will be as profound as seen with trastuzumab, as well as to determine the interaction of the therapies. The question of coexpression of assistant molecules for bevacizumab will likely be even more important than for trastuzumab. The astute use and combination of the existing and emerging biological agents can be expected to further lower the mortality curve and avoid thousands of breast cancer deaths worldwide. 

## References

1. Herceptin and early breast cancer: a moment for caution. Editorial. *Lancet* 2005;366(9498):1673.
2. Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353(11):1074-84.
3. Romond EH, Perez EA, Bryant J et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *NEJM* 2005;353:1673-84.
4. Slamon DJ, Eiermann W, Robert N et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. SABCS 2005. Abstract 1.
5. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P et al. Trastuzumab in combination with docetaxel or vinorelbine as adjuvant treatment of breast cancer: the FinHer Trial. SABCS 2005. Abstract 2.
6. Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-82.
7. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *NEJM* 2001;344:783-92.
8. Nagata Y, Lan KH, Zhou X et al. PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients. *Cancer Cell* 2004;6:117-27.
9. Kim C, Bryant J, Horne Z et al. Trastuzumab sensitivity of breast cancer with co-amplification of HER2 and cMYC suggests pro-apoptotic function of dysregulated cMYC in vivo. Abstract 46.
10. Press MF, Bernstein L, Sauter G et al. Topoisomerase II-alpha gene amplification as a predictor of responsiveness to anthracycline-containing chemotherapy in the Cancer International Research Group 006 clinical trial of trastuzumab (herceptin) in the adjuvant setting. SABCS 2005. Abstract 1045.
11. Jarvinen TA, Tanner M, Rantanen V et al. Amplification and deletion of topoisomerase IIalpha associate with ErbB-2 amplification and affect sensitivity to topoisomerase II inhibitor doxorubicin in breast cancer. *Am J Pathol* 2000;156:839-47.
12. Di Leo A, Gancberg D, Larsimont D et al. HER-2 amplification and topoisomerase IIalpha gene aberrations as predictive markers in node-positive breast cancer patients randomly treated either with an anthracycline-based therapy or with cyclophosphamide, methotrexate, and 5-fluorouracil. *Clin Cancer Res* 2002;8:1107-16.
13. Jarvinen TA, Liu ET. HER-2/neu and topoisomerase IIalpha in breast cancer. *Breast Cancer Res Treat* 2003; 78:299-311.
14. Ragaz J. Impact of HER-2/neu expression on natural history and outcome of human breast cancer. In: *Breast diseases* (Harris J, Morrow M, Lippman M, Osborne K, eds.) Philadelphia, Lippincott Williams and Wilkins, 2004.
15. Konecny GE, Meng YG, Untch M et al. Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients. *Clin Cancer Res* 2004;10:1706-16.
16. Ragaz J, Miller K, Badve S et al. Adverse association of overexpressed vascular endothelial growth factor (VEGF) with survival in early-stage adjuvant chemotherapy in node-positive Stage I-III breast cancer (BrCA). Results from the British Columbia Tissue Microarray Project. *Proc American Soc Clin Oncol* 2004 22;14S. Abstract 524.