The primary goal of this system is to rapidly accelerate the pace of clinical cancer research by enabling oncologists in the United States to offer patients NCI-sponsored clinical trials and by simplifying and standardizing procedures related to participation. The Cancer Trials Support Unit (CTSU) promotes cross-group accrual among Cooperative Group members. Features include standardization of data collection and online data reporting, simplified informed consent and a Central Institutional Review Board (CIRB) process. The CIRB model shares responsibility for protection of research participants between the local IRB and the CIRB, which conducts full review of the results of which are distributed to participating local IRBs via a confidential website.

Central Institutional Review Board
The Central Institutional Review Board (CIRB) initiative was the first pilot project sponsored by the National Cancer Institute (NCI), in consultation with the DHHS Office of Human Research Protections. Created to develop an innovation approach to human subjects’ protection, the unique aspect of the “facilitated reviews” process is that it can streamline local IRB review for national multi-center cancer treatment trials. Local IRBs enrolled in the pilot can download CIRB reviews from a confidential webpage and decide whether or not to utilize the CIRB review for a particular protocol. This “facilitated review” can take place rapidly...

“A major benefit for local IRBs participating in the pilot will be the multiplicative review workload savings while retaining its authority to accept or reject a “facilitated review” on a protocol-by-protocol basis.”

Recruitment of Participants in Clinical Trials

“An effective national cancer program can never be implemented without patient-oriented research. This requires a system that allows oncologists and eligible patients to participate in clinical trials. Participation in clinical trials is an opportunity not only for discovery, but also to experience the most promising and valuable new preventions, diagnoses, screening procedures, and therapies.

Despite the potential therapeutic advantage of participating in clinical trials, the current number of eligible cancer patients entering clinical research studies is less than three percent. This is related primarily to the impediments to enrollment into cancer clinical trials as well as the limited funding of cooperative groups, which is the critical rate-limiting barrier to increased accrual.

As a result, accrual and retention rates in these studies are less than three percent. This is related primarily to the impediments to enrollment into cancer clinical trials as well as the limited funding of cooperative groups, which is the critical rate-limiting barrier to increased accrual.

The concept behind the CTSU is that a fairly large number of physicians don’t want to belong to a cooperative group but would love to enroll their patients in clinical trials. The cooperative groups themselves are heavily involved in the development of the process. All of the major adjacent breast cancer trials will be on the CTSU menu. Advertising the trials and educating physicians about participation is going to be important. This is a real experiment that is still being developed, but I hope it works because we need more patients enrolled in these clinical trials. I suspect a large reservoir of oncologists have never filled out the CTSU form — I hope it works because we need more patients enrolled in these clinical trials. Not because it’s difficult, but because no one..
The accurate assessment of HER2 status is paramount for the management of patients with metastatic breast cancer and the enrollment of patients into adjuvant trastuzumab trials. Two trials evaluating adjuvant trastuzumab — NSABP-B-31 and NCCTG-N9831 — have reported poor concordance between community and central laboratories’ assessments of HER2 status. NSABP subsequently demonstrated that a quality assurance program in which NSABP-approved community laboratories were used could improve the reliability of HER2 testing in the community. Recent studies have also evaluated concordance between different HER2 assays, concordance of HER2 status in the primary lesion, lymph nodes and distant metastases, and the impact of neoadjuvant trastuzumab on HER2 status.

QUALITY CONTROL FOR HER2 TESTING
When the NSABP designed the B-31 adjuvant trastuzumab trial, we were required to ensure central testing for HER2. I always believed that it was not possible to do this properly. When ICH published their standards for HER2, we did a little comparison. We looked at the false positive rates for IHC and FISH and saw that FISH was about 18%. This was shocking because the false positive rate was 10%. The intergroup trial demonstrated essentially the same finding, and these were results we called “build-up call” for the community.

Based on the false positive rate, we reversed the protocol so that patients had to be tested by an approved laboratory that performs over 100 tests per month or perform FISH, but had to do that using a concordance rate between FISH and IHC of over 95 percent. The end result was a dramatic improvement in the quality of testing. From these, the false positive rate dropped from 18 percent to three percent. — Adam P. Press, MD

INTRAPARENCHYMAL STEADINESS OF HER2 STATUS
For most patients with residual tumor after 12 weeks of neoadjuvant treatment, HER2 expression as measured by immunohistochemistry was unchanged. However, a subset of patients whose initial tumors were 3+ was found, on testing after induction therapy, to have lost immunohistochemical expression of HER2. The clinical significance of this finding is not known. It may represent downregulation of HER2 expression or an artifact of tumor sampling or testing. It is not clear whether this finding implies resistance or sensitivity to trastuzumab. — Bandeir GJ et al. J Clin Oncol 2005;23(14):345-353.
Tamoxifen reduced the incidence of breast cancer in the NSABP-P-1 and IBIS-I trials. NSABP-P-2 (the STAR trial) compares another SERM (raloxifene) to tamoxifen in that setting. Data from the ATAC trial — demonstrating an advantage to anastrozole over tamoxifen in reduction of contralateral cancer — hint toward the future use of aromatase inhibitors in a chemoprevention setting, such as the recently launched IBIS-II trial comparing anastrozole to a placebo. The widespread utilization of screening mammography has led to a dramatic increase in the number of women diagnosed with DCIS. NSABP trials B-17 and B-24 demonstrated a stepwise improvement in local and contralateral tumor control with the use of breast radiotherapy and tamoxifen in women who underwent a lumpectomy. NSABP-P-39 and IBIS-II will improve aromatase to tamoxifen in postmenopausal patients with DCIS.

**SELECT PUBLICATIONS**


**ON-GOING OR RECENTLY CLOSED CHEMOPREVENTION TRIALS**

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Eligibility Randomization</th>
<th>Protocol ID</th>
<th>Eligibility Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04254484</td>
<td>High-risk, postmenopausal</td>
<td>NCT04254484</td>
<td>High-risk, postmenopausal</td>
</tr>
<tr>
<td>NCT04254484</td>
<td>72 Exemestane + celecoxib vs exemestane</td>
<td>NCT04254484</td>
<td>72 Exemestane + celecoxib vs exemestane</td>
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<tr>
<td>BCM-H-9315</td>
<td>Known carrier or at risk for BRCA1 or BRCA2 mutation, age 40 to 70</td>
<td>BCM-H-9315</td>
<td>Known carrier or at risk for BRCA1 or BRCA2 mutation, age 40 to 70</td>
</tr>
<tr>
<td>UKCCCR-IBIS-RAZOR</td>
<td>High-risk, ER/PR-positive (&gt;5% positive cells) 6,000 Anastrozole vs placebo</td>
<td>UKCCCR-IBIS-RAZOR</td>
<td>High-risk, ER/PR-positive (&gt;5% positive cells) 6,000 Anastrozole vs placebo</td>
</tr>
<tr>
<td>CRUK-IBIS-IIB, EU-20227</td>
<td>High-risk, ER/PR-positive (&gt;5% positive cells) 6,000 Anastrozole vs placebo</td>
<td>CRUK-IBIS-IIB, EU-20227</td>
<td>High-risk, ER/PR-positive (&gt;5% positive cells) 6,000 Anastrozole vs placebo</td>
</tr>
<tr>
<td>NCT03094747</td>
<td>High-risk, postmenopausal, age 50 and over</td>
<td>NCT03094747</td>
<td>High-risk, postmenopausal, age 50 and over</td>
</tr>
<tr>
<td>NCT02272377</td>
<td>150 Bexarotene vs placebo</td>
<td>NCT02272377</td>
<td>150 Bexarotene vs placebo</td>
</tr>
<tr>
<td>NCI-04-C-0044</td>
<td>High-risk, postmenopausal 72 Exemestane + celecoxib vs exemestane</td>
<td>NCI-04-C-0044</td>
<td>High-risk, postmenopausal 72 Exemestane + celecoxib vs exemestane</td>
</tr>
<tr>
<td>CRUK-IBIS-IIB, EU-20227</td>
<td>High-risk, age 30 to 39 150 Anastrozole vs placebo</td>
<td>CRUK-IBIS-IIB, EU-20227</td>
<td>High-risk, age 30 to 39 150 Anastrozole vs placebo</td>
</tr>
<tr>
<td>NCT02322287</td>
<td>High-risk, postmenopausal, age 35 and over</td>
<td>NCT02322287</td>
<td>High-risk, postmenopausal, age 35 and over</td>
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<tr>
<td>NCI-RC-16996-08</td>
<td>High-risk, postmenopausal, age 50 and over</td>
<td>NCI-RC-16996-08</td>
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<td>High risk, postmenopausal, age 50 and over</td>
</tr>
<tr>
<td>CRUK-IBIS-IIB, EU-20227</td>
<td>High-risk, age 40 to 70 150 Anastrozole vs placebo</td>
<td>CRUK-IBIS-IIB, EU-20227</td>
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</tr>
<tr>
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</tbody>
</table>

**CLINICAL TRIALS OF AROMATASE INHIBITORS IN DCIS**

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Eligibility Randomization</th>
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<th>Eligibility Randomization</th>
</tr>
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<tbody>
<tr>
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<td>High-risk, postmenopausal 72 Exemestane + celecoxib vs exemestane</td>
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</tr>
<tr>
<td>NCT03094747</td>
<td>High-risk, postmenopausal, age 50 and over</td>
<td>NCT03094747</td>
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</tr>
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<td>NCT03094747</td>
<td>High-risk, postmenopausal, age 50 and over</td>
</tr>
</tbody>
</table>

**TAMOXIFEN: 68-MONTH UPDATE FROM THE ATAC**

Cheomneprevention and Management of DCIS
Neoadjuvant Chemotherapy

While neoadjuvant chemotherapy may downstage tumors and improve the chance for breast conservation, disease-free and overall survival rates are not altered. At the 2004 San Antonio Breast Cancer Symposium, Dr Harry Bear presented updated results from NSABP-B-27 comparing the addition of docetaxel to neoadjuvant AC. The addition of neoadjuvant docetaxel improved the pathologic complete response rate, but no differences were found in overall or disease-free survival. However, relapse-free survival was significantly improved in patients receiving neoadjuvant AC plus docetaxel compared to those treated with neoadjuvant AC alone. A new generation of neoadjuvant studies is evaluating an array of novel neoadjuvant strategies including dose-dense chemotherapy, taxanes, capcitabine/docetaxel (XT) and other combination regimens.

---

**NSABP-B-27: 6-MONTH UPDATE OF STUDY ENDPOINTS (HORMONE RATIOS COMPARED TO AC)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>0.95 (0.83-1.10)</td>
<td>0.96 (0.84-1.10)</td>
<td>1.00 (1.00-1.00)</td>
<td>0.53</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>0.63 (0.55-0.74)</td>
<td>0.81 (0.71-0.93)</td>
<td>0.80 (0.70-0.90)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pathologic complete response</td>
<td>0.01 (0.00-0.02)</td>
<td>0.02 (0.01-0.03)</td>
<td>0.02 (0.01-0.03)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**NSABP-B-27: 21-INITIAL RESULTS: CLINICAL RESPONSE**

<table>
<thead>
<tr>
<th>Source</th>
<th>Phase</th>
<th>Disease Stage</th>
<th>Treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bear HD et al.</td>
<td>21</td>
<td>Stage II or IIIA operable breast cancer</td>
<td>MD Anderson Phase III Neoadjuvant Trial</td>
<td>NSABP-B-20</td>
</tr>
<tr>
<td>Hutcheon AW et al.</td>
<td>21</td>
<td>Stage II or IIIA operable breast cancer</td>
<td>MD Anderson Phase III Neoadjuvant Trial</td>
<td>NSABP-B-20</td>
</tr>
</tbody>
</table>

**NSABP-B-27: 6-MONTH UPDATE: HORMONE RATIOS OF PCBR VERSUS NON-PCBR**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>0.01</td>
<td>0.80</td>
<td>0.80</td>
<td>0.03</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.03</td>
</tr>
<tr>
<td>Pathologic complete response</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**NSABP-B-27: INITIAL RESULTS: PATHOLOGIC RESPONSE IN BREAST**

<table>
<thead>
<tr>
<th>Source</th>
<th>Phase</th>
<th>Disease Stage</th>
<th>Treatment</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bear HD et al.</td>
<td>21</td>
<td>Stage II or IIIA operable breast cancer</td>
<td>MD Anderson Phase III Neoadjuvant Trial</td>
<td>NSABP-B-20</td>
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<tr>
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<td>NSABP-B-20</td>
</tr>
</tbody>
</table>

**SELECT PUBLICATIONS**

Neoadjuvant Endocrine Therapy

Chemotherapy is the most frequent form of neoadjuvant systemic therapy utilized in the United States; in Europe, neoadjuvant endocrine therapy has been used extensively in women with ER-positive cancer. Phase II and III clinical trials have suggested that the antitumor effect of endocrine therapy in these patients is comparable to what has been observed with chemotherapy, although the time to achieve a response may be somewhat longer. Tamoxifen and ovarian ablation/suppression were initially utilized in neoadjuvant studies, and more recently, third-generation aromatase inhibitors and the estrogen receptor downregulator fulvestrant have demonstrated significant antitumor activity in this setting. At the 2003 San Antonio Breast Cancer Symposium, data were presented from the IMPACT trial comparing anastrozole, tamoxifen and the combination. As was observed in a previous trial comparing letrozole to tamoxifen, breast-conserving surgery was much more common in women treated with anastrozole.

**IMPACT TRIAL: ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Breast surgery</th>
<th>Pathological response</th>
<th>Clinical response</th>
<th>Mammographic response</th>
<th>Geometric mean reductions in Ki67</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = anastrozole</td>
<td>96%</td>
<td>36%</td>
<td>14%</td>
<td>6%</td>
<td>47%</td>
</tr>
<tr>
<td>T = tamoxifen</td>
<td>90%</td>
<td>40%</td>
<td>26%</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>C = combination</td>
<td>95%</td>
<td>38%</td>
<td>18%</td>
<td>12%</td>
<td>42%</td>
</tr>
</tbody>
</table>

**LETROZOLE VERSUS TAMOXIFEN IN POSTMENOPAUSAL PATIENTS WITH ER-POSITIVE BREAST CANCER**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Breast surgery</th>
<th>Pathological response</th>
<th>Clinical response</th>
<th>Mammographic response</th>
<th>Geometric mean reductions in Ki67</th>
</tr>
</thead>
<tbody>
<tr>
<td>L = letrozole</td>
<td>56%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>T = tamoxifen</td>
<td>66%</td>
<td>22%</td>
<td>39%</td>
<td>39%</td>
<td>39%</td>
</tr>
</tbody>
</table>

**NEOADJUVANT ENDOCRINE THERAPY VERSUS CHEMOTHERAPY FOR POSTMENOPAUSAL PATIENTS WITH ER-POSITIVE BREAST CANCER**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Breast surgery</th>
<th>Pathological response</th>
<th>Clinical response</th>
<th>Mammographic response</th>
<th>Geometric mean reductions in Ki67</th>
</tr>
</thead>
<tbody>
<tr>
<td>E = exemestane</td>
<td>91%</td>
<td>45%</td>
<td>37%</td>
<td>40%</td>
<td>37%</td>
</tr>
<tr>
<td>C = combination</td>
<td>95%</td>
<td>50%</td>
<td>53%</td>
<td>53%</td>
<td>53%</td>
</tr>
</tbody>
</table>

**RECOMMENDATIONS FOLLOWING NEOADJUVANT ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH Locally ADVANCED BREAST CANCER PATIENTS (n=159)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complete clinical response (%)</th>
<th>Pathological clinical response (%)</th>
<th>Biological response (%)</th>
<th>Complete clinical response (%)</th>
<th>Pathological clinical response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = anastrozole</td>
<td>51%</td>
<td>30%</td>
<td>43%</td>
<td>91%</td>
<td>80%</td>
</tr>
<tr>
<td>T = tamoxifen</td>
<td>44%</td>
<td>29%</td>
<td>32%</td>
<td>82%</td>
<td>72%</td>
</tr>
</tbody>
</table>

**ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION AS NEOADJUVANT ENDOCRINE THERAPY FOR POSTMENOPAUSAL BREAST CANCER PATIENTS (n=61)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Complete clinical response (%)</th>
<th>Pathological clinical response (%)</th>
<th>Complete clinical response (%)</th>
<th>Pathological clinical response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = anastrozole</td>
<td>57%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>T = tamoxifen</td>
<td>49%</td>
<td>49%</td>
<td>49%</td>
<td>49%</td>
</tr>
<tr>
<td>C = combination</td>
<td>61%</td>
<td>61%</td>
<td>61%</td>
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</tbody>
</table>

**CLINICAL RESPONSE TO NEOADJUVANT LETROZOLE**

<table>
<thead>
<tr>
<th>Number of therapy</th>
<th>Breast surgery</th>
<th>Pathological response</th>
<th>Clinical response</th>
<th>Mammographic response</th>
<th>Geometric mean reductions in Ki67</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 12 weeks (n=42)</td>
<td>50%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>2 24 weeks (n=42)</td>
<td>50%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>3 6-12 months (n=22)</td>
<td>50%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
<td>29%</td>
</tr>
</tbody>
</table>

**SELECT PUBLICATIONS**


**IMPACT TRIAL: ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION**

**LETROZOLE VERSUS TAMOXIFEN IN POSTMENOPAUSAL PATIENTS WITH ER-POSITIVE BREAST CANCER**

**NEOADJUVANT ENDOCRINE THERAPY VERSUS CHEMOTHERAPY FOR POSTMENOPAUSAL PATIENTS WITH ER-POSITIVE BREAST CANCER**

**RECOMMENDATIONS FOLLOWING NEOADJUVANT ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH Locally ADVANCED BREAST CANCER PATIENTS (n=159)**

**CLINICAL RESPONSE TO NEOADJUVANT LETROZOLE**

**SELECT PUBLICATIONS**

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In women with breast cancer, neoadjuvant chemotherapy may have potential advantages over adjuvant chemotherapy, including an increased rate of breast conservation and a decreased rate of distant metastases. It has been postulated that the pathologic response of the primary tumor to neoadjuvant chemotherapy may correlate with long-term survival. In women with HER2-positive metastatic breast cancer, the addition of trastuzumab to chemotherapy has been shown to improve the response rate, progression-free survival and overall survival. Several trials have investigated the addition of trastuzumab to neoadjuvant chemotherapy regimens in women with HER2-positive disease. The neoadjuvant chemotherapy regimens have included taxanes, vinorelbine, cisplatin and epirubicin; the pathologic complete response rates have ranged from seven percent to 42 percent. Dr Aman Buzdar recently reported (ASCO 2004) data from a trial that randomly assigned women with HER2-positive breast cancer to paclitaxel + FEC with or without trastuzumab as neoadjuvant therapy. The addition of neoadjuvant trastuzumab yielded a pathologic complete response rate of 65.2% in those patients compared to 26.3% with chemotherapy alone. As these data mature and further results are obtained from other neoadjuvant trials, the role of neoadjuvant trastuzumab will continue to evolve.

RESPONSE RATES IN NEOADJUVANT TRIALS OF TRASTUZUMAB PLUS CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>N Total</th>
<th>Chemotherapy regimen</th>
<th>P = paclitaxel</th>
<th>FEC = 5-fluorouracil, epirubicin and cyclophosphamide</th>
<th>Neoadjuvant regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeSensi 2003</td>
<td>Trastuzumab x 4 + docetaxel x 4 + paclitaxel x 4</td>
<td>33</td>
<td>13%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
<tr>
<td>Gordon 2003</td>
<td>Trastuzumab x 4 + palliative x 2</td>
<td>40</td>
<td>18%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
<tr>
<td>Carey 2002</td>
<td>XE (x, epirubicin + palitaxel) x 2</td>
<td>22</td>
<td>31%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
<tr>
<td>Harris 2002</td>
<td>Trastuzumab x 4 + vinorelbine x 4</td>
<td>30</td>
<td>21%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
<tr>
<td>Harley 2002</td>
<td>Trastuzumab x 4 + vinorelbine + docetaxel x 4 + C (x, cisplatin + P)</td>
<td>46</td>
<td>60%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
<tr>
<td>Lombardero 2002</td>
<td>Trastuzumab x 4 + vinorelbine x 4</td>
<td>19</td>
<td>80%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
<tr>
<td>Song 2002</td>
<td>Trastuzumab x 3 + docetaxel</td>
<td>16</td>
<td>24%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
<tr>
<td>Sridhara 2002</td>
<td>Trastuzumab x 4 + docetaxel x 4</td>
<td>16</td>
<td>24%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
<tr>
<td>Signorelli 2002</td>
<td>Trastuzumab x 4 + vinorelbine x 4</td>
<td>9</td>
<td>53%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
<tr>
<td>Venkat 2002</td>
<td>Trastuzumab + epirubicin + docetaxel x 4</td>
<td>16</td>
<td>17%</td>
<td>P</td>
<td>P + FEC</td>
<td>60%</td>
</tr>
</tbody>
</table>

MD ANDERSON RANDOMIZED TRIAL OF NEOADJUVANT TRASTUZUMAB AND CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Phase III randomized trial of neoadjuvant trastuzumab and chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally advanced breast cancer, HER2-positive (IHC 3+ or FISH+)</td>
</tr>
<tr>
<td>Distributed in the United States, Canada, Australia, and The Netherlands</td>
</tr>
<tr>
<td>Patients with HER2-positive disease randomization on an oncologist’s discretion</td>
</tr>
<tr>
<td>Neoadjuvant regimen patients response rate 65.2%</td>
</tr>
<tr>
<td>Chemotherapy-alone regimen patients response rate 26.3%</td>
</tr>
<tr>
<td>Patients who do not have HER2-positive disease randomization on an oncologist’s discretion</td>
</tr>
<tr>
<td>Neoadjuvant regimen patients response rate 53%</td>
</tr>
<tr>
<td>Chemotherapy-alone regimen patients response rate 21%</td>
</tr>
</tbody>
</table>

PATHOLOGIC COMPLETE RESPONSE RATES FOR NEOADJUVANT TRASTUZUMAB AND CHEMOTHERAPY

<table>
<thead>
<tr>
<th>Phase I study</th>
<th>Response rate (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + docetaxel (x, docetaxel) x 2</td>
<td>25% (15% - 40%)</td>
</tr>
<tr>
<td>Trastuzumab + vinorelbine (x, vinorelbine) x 4</td>
<td>22% (14% - 35%)</td>
</tr>
<tr>
<td>Paclitaxel x 4 + trastuzumab x 12wk</td>
<td>23% (17% - 39%)</td>
</tr>
<tr>
<td>Paclitaxel x 4 + trastuzumab x 24wk</td>
<td>22% (17% - 36%)</td>
</tr>
</tbody>
</table>

SELECT PUBLICATIONS

Arimidex, Tamoxifen Alone or in Combination (ATAC) Trial

The ATAC trial reported initial results in December 2001, demonstrating an advantage in disease-free survival (DFS) with the third-generation aromatase inhibitor anastrozole compared to tamoxifen. An advantage was also seen in safety and tolerability with regard to thrombotic events and endometrial cancer, although fractures and arthralgias were more common in women treated with anastrozole. At the 2003 San Antonio Breast Cancer Symposium, further data were presented demonstrating an even greater advantage to anastrozole compared to tamoxifen in women with ER-positive, PR-negative tumors. At the recent 2004 San Antonio meeting, data were presented from the third analysis at 68 months. An advantage to anastrozole in disease-free survival continued to be present with about one in four relapses on tamoxifen avoided with anastrozole.

68-MONTH FOLLOW-UP OF THE ATAC TRIAL

The ATAC trial has reached a very important point in its evolution with a median follow-up of 68 months. Almost all of the patients are now off therapy, and we have one year of follow-up after the therapy was completed.

I believe this is probably the most important of the three analyses, and this latest analysis allows me, as a practicing clinician, to change my mind and change practice. I speak not only as a practicing clinician but also as the past principal investigator of the ATAC trial results.

We started using adjuvant anastrozole instead of tamoxifen as initial therapy with an aromatase inhibitor is that anastrozole almost ablates that first peak. If you wait two to three years, as some of the trials are reporting, the effects are minimal. We already had a peak of osteopenia was always secondary. We already had accelerated bone resorption. We felt quite comfortable making therapeutic decisions, but also to give a fascinating biological insight.

The strongest argument for starting adjuvant endocrine therapy with an aromatase inhibitor is that anastrozole almost ablates that first peak. If you wait two to three years, as some of the trials are reporting, the effects are minimal. We already had a peak of osteopenia was always secondary. We already had accelerated bone resorption. We felt quite comfortable making therapeutic decisions, but also to give a fascinating biological insight.

The strongest argument for starting adjuvant endocrine therapy with an aromatase inhibitor is that anastrozole almost ablates that first peak. If you wait two to three years, as some of the trials are reporting, the effects are minimal. We already had a peak of osteopenia was always secondary. We already had accelerated bone resorption. We felt quite comfortable making therapeutic decisions, but also to give a fascinating biological insight.
Sequential Adjuvant Hormonal Therapy Following Tamoxifen

Since the first International Breast Cancer Overview presented at the 1985 NIH Consensus Conference, tamoxifen was considered the mainstay of adjuvant hormonal therapy for women with early breast cancer; however, the selection of optimal adjuvant hormonal therapy for postmenopausal women is currently controversial. Recent trials — NCIC-MA17, ITA, EU-20149, ABCSG-8 and ARNO 95 — have evaluated the role of aromatase inhibitors as follow-up therapy to tamoxifen adjuvant hormonal therapy. NCIC-MA17 randomly assigned postmenopausal women who had completed 4.5 to 6 years of adjuvant tamoxifen to five years of placebo or adjuvant letrozole. ITA and EU-20149 randomly assigned postmenopausal women who had completed two to three years of adjuvant tamoxifen to continue tamoxifen versus switching to an aromatase inhibitor. These trials of sequential adjuvant hormonal therapy demonstrated significant therapeutic advantages to switching to an aromatase inhibitor.

**Phase II Trial of Exemestane Versus Tamoxifen Following Two to Three Years of Adjuvant Tamoxifen**

<table>
<thead>
<tr>
<th><strong>Phase II Trial</strong></th>
<th><strong>Tamoxifen</strong></th>
<th><strong>Exemestane</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free survival†</td>
<td>0.60</td>
<td>0.44-0.81</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>95%</td>
<td>0.70</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>28 months</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

- Exemestane demonstrated significant therapeutic advantages over tamoxifen.
- **Conclusion**: Exemestane appears to be superior to tamoxifen in women with hormone-responsive breast cancer who remain disease-free after two to three years of tamoxifen therapy.

**Randomized Phase III Study of Letrozole Versus Placebo in Postmenopausal Women With Primary Breast Cancer Who Have Completed at Least Five Years of Adjuvant Tamoxifen**

<table>
<thead>
<tr>
<th><strong>Randomized Phase III Study</strong></th>
<th><strong>Placebo</strong></th>
<th><strong>Letrozole</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free survival*</td>
<td>0.70</td>
<td>0.58-0.83</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>95%</td>
<td>0.00005</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>4.5 years</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

- Letrozole demonstrated significant therapeutic advantages over placebo.
- **Conclusion**: Letrozole appears to be superior to tamoxifen in women with hormone-responsive breast cancer who remain disease-free after five years of tamoxifen therapy.

**Overexpression of the Estrogen Receptor: A New Correlative Test for Primary Tumor (Median Follow-up 4.5 Years)**

<table>
<thead>
<tr>
<th><strong>Overexpression of the Estrogen Receptor</strong></th>
<th><strong>Placebo</strong></th>
<th><strong>Letrozole</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free survival</td>
<td>0.70</td>
<td>0.58-0.83</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>95%</td>
<td>0.00005</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>4.5 years</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

- Letrozole demonstrated significant therapeutic advantages over placebo.
- **Conclusion**: Letrozole appears to be superior to tamoxifen in women with hormone-responsive breast cancer who remain disease-free after five years of tamoxifen therapy.

**Anastrozole Versus Tamoxifen After Two Years of Adjuvant Tamoxifen**

<table>
<thead>
<tr>
<th><strong>Anastrozole Versus Tamoxifen</strong></th>
<th><strong>Tamoxifen</strong></th>
<th><strong>Anastrozole</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free survival*</td>
<td>0.70</td>
<td>0.58-0.83</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>95%</td>
<td>0.00005</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>4.5 years</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

- Anastrozole demonstrated significant therapeutic advantages over tamoxifen.
- **Conclusion**: Anastrozole appears to be superior to tamoxifen in women with hormone-responsive breast cancer who remain disease-free after two to three years of tamoxifen therapy.

**I Tata Trial: Anastrozole Versus Tamoxifen in Women Already Receiving Adjuvant Tamoxifen (Median Follow-up 9.6 Years)**

<table>
<thead>
<tr>
<th><strong>I Tata Trial</strong></th>
<th><strong>Tamoxifen</strong></th>
<th><strong>Anastrozole</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free survival</td>
<td>0.70</td>
<td>0.58-0.83</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>95%</td>
<td>0.00005</td>
</tr>
<tr>
<td>Median follow-up</td>
<td>9.6 years</td>
<td></td>
</tr>
</tbody>
</table>

**Results**

- Anastrozole demonstrated significant therapeutic advantages over tamoxifen.
- **Conclusion**: Anastrozole appears to be superior to tamoxifen in women with hormone-responsive breast cancer who remain disease-free after two to three years of tamoxifen therapy.

**SELECT PUBLICATIONS**


**Conclusions**

- The results of the ITA trial showed that anastrozole is superior to tamoxifen in women who remain disease-free after two to three years of tamoxifen therapy.
- The results of the EU-20149 trial showed that letrozole is superior to tamoxifen in women who remain disease-free after five years of tamoxifen therapy.
- The results of the ABCSG-8 trial showed that exemestane is superior to tamoxifen in women who remain disease-free after two to three years of tamoxifen therapy.

**Implications**

- The results of these trials provide strong evidence for the use of aromatase inhibitors as follow-up therapy to tamoxifen.
- The use of aromatase inhibitors as follow-up therapy to tamoxifen is now considered the standard of care for women who remain disease-free after two to three years of tamoxifen therapy.

**Future Directions**

- Further studies are needed to confirm the findings of these trials and to evaluate the long-term effects of aromatase inhibitors as follow-up therapy to tamoxifen.
- The use of aromatase inhibitors as first-line therapy should be considered in women who are not candidates for tamoxifen.

**References**

Adjuvant Endocrine Therapy in Premenopausal Patients

Tamoxifen has an established role as adjuvant systemic therapy for premenopausal women with estrogen receptor-positive breast cancer. A number of major current clinical trials are evaluating the role of ovarian ablation/suppression combined with either tamoxifen or an aromatase inhibitor. A related and important issue is the impact of chemotherapy-related ovarian suppression in these patients. While it will be many years before data on disease-free and overall survival are available from these studies, an Austrian study reported by Gnant at the San Antonio Breast Cancer Symposium in 2002 and 2004 demonstrated that bone loss associated with ovarian suppression combined with either tamoxifen or anastrozole can largely be avoided by the use of the bisphosphonate zoledronate.

**TEXT:** TAMOXIFEN AND EXEMESTANE TRIAL
Protocol ID: IBCSG 26-02
Target Accrual: 1,800 (Open)

**Eligibility**
Premenopausal women with hormone receptor-positive breast cancer — patients with tumor size ≥ 1 cm and/or tumor grade ≥ 10% and/or PgR ≥ 10%; patients for whom chemotherapy is not indicated for being too early. These current data are far from being conclusive enough.

**Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate and fluorouracil in premenopausal patients**
Protocol ID: IBCSG 08-02
Target Accrual: 1,200 (Open)

**Eligibility**
Patients with Stage I or II ER/PR-positive premenopausal breast cancer. A number of studies have shown that breast cancer-specific deaths are available from these studies, an Austrian study reported by Gnant at the San Antonio Breast Cancer Symposium in 2002 and 2004 demonstrated that bone loss associated with ovarian suppression combined with either tamoxifen or anastrozole can largely be avoided by the use of the bisphosphonate zoledronate.

**Source:**

**Target Accrual:**
1,800 (Open)
**Protocol ID:**
IBCSG 26-02
**Eligibility:**
Premenopausal women with hormone receptor-positive breast cancer — patients with tumor size ≥ 1 cm and/or tumor grade ≥ 10% and/or PgR ≥ 10%; patients for whom chemotherapy is not indicated for being too early. These current data are far from being conclusive enough.

**Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate and fluorouracil in premenopausal patients**
Protocol ID: IBCSG 08-02
Target Accrual: 1,200 (Open)

**Eligibility**
Patients with Stage I or II ER/PR-positive premenopausal breast cancer. A number of studies have shown that breast cancer-specific deaths are available from these studies, an Austrian study reported by Gnant at the San Antonio Breast Cancer Symposium in 2002 and 2004 demonstrated that bone loss associated with ovarian suppression combined with either tamoxifen or anastrozole can largely be avoided by the use of the bisphosphonate zoledronate.
Research To Practice: Adjuvant Endocrine Therapy

Extensive resources have been allocated to evaluate new breast cancer treatment interventions; however, relatively minimal investment has been made to determine how these advances are implemented in practice. Continuing medical education has the potential to be a useful component in the clinical research continuum, not only by informing clinicians about available trials and emerging research findings, but also by performing outcomes assessments to evaluate how research advances are being implemented in clinical practice. The data presented here from the Breast Cancer Update Patterns of Care Study are from a national telephone survey initiated in 2004 of 150 randomly selected United States-based medical oncologists.

One of the key aspects of this initiative was the use of hormonal therapy. The most important databases currently affecting nonprotocol use of adjuvant endocrine therapy were derived from trials of aromatase inhibitors in postmenopausal patients, both as initial therapy and after two to three, or five years of tamoxifen. In premenopausal women, controversy continues with regard to the use of ovarian ablation/suppression, particularly in women who continue to menstruate after receiving adjuvant chemotherapy.

Aromatase Inhibitors as Initial Adjuvant Therapy in Postmenopausal Women

What endocrine therapy would you recommend for a woman in average health with a 1.2-cm, ER-positive, HER2-negative, Grade II tumor and three positive lymph nodes on tamoxifen for two years. How would you manage this patient if she did not complete five years of tamoxifen — Updated survival analysis.

© 2005 Research To Practice. All rights reserved. Poster information is for educational purposes only. Please see full prescribing information and protocols.
Two taxane-containing regimens have demonstrated improved efficacy in recent studies — dose-dense, every two-week AC + paclitaxel with growth factor support, and TAC (docetaxel, doxorubicin and cyclophosphamide). Because of the relatively high rate of febrile neutropenia, growth factor support is required for the TAC regimen. Indirect comparison of these databases suggests similar efficacy and tolerability, and both have demonstrated an overall survival advantage in randomized trials. Another taxane-containing regimen — AC followed by docetaxel — is commonly utilized in the adjuvant setting but has only been reported in a major randomized trial in the neoadjuvant setting. While the benefits in terms of disease-free and overall survival observed in CALGB-9741 are clear, it is unclear whether the advantage observed from dose-dense scheduling is related to the AC portion of the regimen or paclitaxel scheduling.

---

**PHASE III TRIAL OF ADJUVANT TAC VS FAC**

*Martin M et al.*

**Summary**

- **Patients**: 1,491 patients (ITT).
- **Randomization**: 1,422 patients (725 TAC, 717 FAC).
- **Primary endpoint**: Disease-free survival.
- **Secondary endpoints**: Overall survival, hormones.
- **Primary outcome**: FAC-FAC (95% CI).
- **Hazard ratio**: 0.72 (0.59-0.88) 0.0010.
- **Conclusion**: TAC superior to FAC.

---

**CALGB-9741: ADJUVANT DOSE- DENSE CHEMOTHERAPY**

This study, designed with input from all members of the Breast Intergroup and coordinated by the CALGB, had a two-by-two factorial design. The two parameters were dose density — giving drugs every two weeks with G-CSF instead of every three weeks — and combination sequential therapy. The doses were derived from previous clinical trial experience. The only difference was the schedule. This trial, which accrued more than 2,000 patients, showed improved overall survival and reduced neutropenia. It believed in dose-dense therapy because it’s an evolution in the laboratory and the clinic; for 25 years, it has had a solid foundation.

---

**SWOG-S0221: DOSE-DENSE VS CONTINUOUS CHEMOTHERAPY**

In this study, AC is administered in either a dose-dense manner with prophylaxis or what might be described as a conventional schedule with filgrastim. Both schedules are then followed by paclitaxel. We chose six cycles of AC and paclitaxel in the control setting for several reasons. By imposing similar durations of treatment in all arms, we avoid wondering whether an inferior outcome in any arm reflected the duration of treatment. Data suggest six cycles is superior, although this is still controversial. This more continuous schedule may provide a good chemotherapy base upon which to add other antiangiogenic approaches. Evidence suggests that with the maximum tolerated dose schedule a burst of angiogenesis occurs between cycles. Hematopoietic growth factors possibly augment that, but it is unclear whether that occurs with weekly dexamethasone and daily cyclophosphamide.

---

**USE OF ADJUVANT TAC**

Taxanes are commonly utilized in the adjuvant setting, typically utilizing the six-cycle TAC regimen. The disease-free and overall survival of dose-dense therapy and TAC are similar. Growth factor support, used in conjunction with TAC, reduces the rate of febrile neutropenia to that seen in CALGB-9741.

---

**INTERVENTING DOSE DENSITY INTO CLINICAL TRIALS**

CALGB-40101 incorporates the every two-week schedule-comparing paclitaxel in AC patients with high-risk, node-negative breast cancer. It also compares four cycles versus six, and although many clinicians think they already know which is better, this is the first point-of-treatment. It’s not so difficult to believe that therapy every two weeks is better than every three weeks. One may question whether it’s worth the effort, but because treatment is completed faster and it lowers the risk of neutropenic fever, I believe it’s worth it.

---

**NSABP Trial B-38**

NSABP B-38 compared two anthracycline/taxane regimens with a new combination in the paclitaxel phase. It’s a good trial design because in addition to dosing, the last arm of the three standard combinations is superior. It examines an agent new to the adjuvant setting — gemcitabine. At the 2004 ASCO meeting, Kathy Albain reported results from a trial in metastatic breast cancer that showed an advantage for gemcitabine/paclitaxel versus paclitaxel alone. While the two-week schedule is a bit of a leap, it was necessary to make it comparable to the dose-dense phase of the trial.

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**Selective Publications**


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CALGB-49907: Adjuvant Chemotherapy in Elderly Women

Relatively few randomized trials of adjuvant chemotherapy have included substantial numbers of elderly women, so a relative paucity of research data exists with regard to the risks and benefits of this intervention. This is particularly problematic in older women with estrogen receptor-negative tumors who will not receive endocrine therapy. Another common clinical dilemma is the elderly woman with an estrogen receptor-positive tumor for whom theincremental benefits and risks of chemotherapy in addition to endocrine treatment must be considered. An important related trial being led by Dr Hyman Muss, CALGB-49907, randomly assigns elderly women with primary breast cancer to either the orally administered fluoropyrimidine prodrug capecitabine, or AC or CMF chemotherapy. In addition to evaluating disease-free and overall survival, a number of key quality-of-life endpoints are being evaluated.

**CALGB-49907 ADVANTAGE CMF OR AC Versus CAPECITABINE IN WOMEN AGE 65 AND OLDER**

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Age 70 vs 79</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>62 vs 63</td>
<td>0.56</td>
</tr>
<tr>
<td>Colon</td>
<td>66 vs 67</td>
<td>0.31</td>
</tr>
<tr>
<td>Lung</td>
<td>64 vs 67</td>
<td>0.05</td>
</tr>
<tr>
<td>All other</td>
<td>64 vs 67</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**SUMMARY OF EFFICACY: SINGLE-AGENT CAPECITABINE Versus STANDARD CHEMOTHERAPY IN METASTATIC DISEASE**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Disease Control Rate</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>30% (19-43)</td>
<td>(3.2-6.5)</td>
<td>(19.6 months)</td>
</tr>
<tr>
<td>CMF</td>
<td>16% (5-33)</td>
<td>(2.4-4.8)</td>
<td>(17.2 months)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>36% (17-59)</td>
<td>(1.4-6.6)</td>
<td>(9.4 months)</td>
</tr>
<tr>
<td>Paclitaxel + Capeci</td>
<td>26% (9-51)</td>
<td>(2.5-6.5)</td>
<td>(9.4 months)</td>
</tr>
</tbody>
</table>

**PROPORTION OF ELDERLY PATIENTS (AGE 65) IN SWOG TRIALS AS COMPARED WITH THE PROPORTION OF ELDERLY PATIENTS IN CANCER IN THE UNITED STATES**

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Swog patients 65 or older</th>
<th>Cancer patients 65 or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>49%</td>
<td>13%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>44%</td>
<td>27%</td>
</tr>
<tr>
<td>Brain</td>
<td>44%</td>
<td>19%</td>
</tr>
<tr>
<td>Lung</td>
<td>63%</td>
<td>27%</td>
</tr>
<tr>
<td>All other</td>
<td>63%</td>
<td>28%</td>
</tr>
</tbody>
</table>

**UNDERREPRESENTATION OF ELDERLY WOMEN IN RECENT CALGB ADJUVANT TRIALS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of elderly patients</th>
<th>Median age (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB-49907</td>
<td>221 (102-419)</td>
<td>66 (55-89)</td>
</tr>
<tr>
<td>CALGB-49903</td>
<td>220 (102-419)</td>
<td>66 (55-89)</td>
</tr>
<tr>
<td>CALGB-49902</td>
<td>283 (102-419)</td>
<td>66 (55-89)</td>
</tr>
</tbody>
</table>

**SAFETY OF CAPECITABINE**

- **Common issues during treatment:**
  - 5-FU-related toxicity
  - Myelosuppression
  - Gastrointestinal toxicity
- **Significant toxicity:**
  - Myelosuppression
  - Gastrointestinal toxicity
  - Cardiac failure
- **ACS-related issues:**
  - Myelosuppression
  - Gastrointestinal toxicity

**RATES OF OFFERING AND ACCEPTING CLINICAL TRIALS IN THE UNITED STATES**

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>Rate of offering</th>
<th>Rate of accepting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>54%</td>
<td>50%</td>
</tr>
<tr>
<td>Colon</td>
<td>49%</td>
<td>50%</td>
</tr>
<tr>
<td>Lung</td>
<td>60%</td>
<td>55%</td>
</tr>
<tr>
<td>All other</td>
<td>60%</td>
<td>55%</td>
</tr>
</tbody>
</table>

**CALGB-49907: CAPREXITABINE Versus AC/CMF in Elderly Patients**

Why did CALGB want to conduct this trial? Capecitabine has the advantage of oral administration, and it targets tumor tissue. My major interest for the last 15 years has been clinical pharmacology and drug development, and this is an interesting drug because it changes the cancer drug delivery methodology. We are trying to target tissue and diminish toxicity rather than just using an active drug. Capecitabine has known efficacy and doesn’t cause cardiac damage, which is a major issue as patients get older.

**CONCLUSION AND IMPORTANCE OF CALGB-49907**

Hyman Muss has made some changes to try to make the eligibility criteria more streamlined and easier for physicians and patients to participate in the study. Unfortunately, we see toxicology problems in two patients in the capecitabine arm. These cases were evaluated by the data-monitoring committee and one case was thought to be unrelated to an enzyme deficiency. The other case was thought to be unrelated to a toxicology issue in which the patient didn’t contact the physician in a timely fashion.

**SELECT PUBLICATIONS**

- Bouchardy C et al. Select publications that was previously extracted for it. Please check the full prescribing information and protocols.
Clinical Trials of Adjuvant Trastuzumab

Randomized trial data from the advanced disease setting demonstrate that in women with HER2-overexpressing breast cancer, the combination of trastuzumab and chemotherapy — using either doxorubicin/cyclophosphamide or paclitaxel — results in improved progression-free and overall survival compared to the same chemotherapy given without trastuzumab. These encouraging results have led to a new generation of adjuvant trials evaluating a variety of chemotherapy regimens combined with trastuzumab. While no efficacy endpoints have been met, closely evaluated cardiac monitoring has not yet revealed dysfunction that would preclude continuing these trials. Almost all clinical research leaders currently advocate using adjuvant trastuzumab only in clinical trial settings.

**PHASE 2 CLINICAL TRIALS OF ADJUVANT TRASTUZUMAB**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Phase</th>
<th>Design</th>
<th>Status</th>
<th>Eligibility</th>
<th>Randomization</th>
<th>Primary endpoint</th>
<th>Key issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP-B-31</td>
<td>Open</td>
<td></td>
<td>Open</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N9831</td>
<td>Open</td>
<td></td>
<td>Closed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CARDIAC SAFETY ANALYSIS IN NSABP-B-31**

- Protocol met futility cut-off of 15% increase in cardiac events (CE) among N+ patients not receiving trastuzumab.
- A total of 13,431 patients have been randomized, with 2,305 (17%) receiving trastuzumab.
- Over 4 years of follow-up, there were 79 CE events (4.4% vs. 3.0% in non-trastuzumab patients).
- The primary endpoint of an increase in cardiac events of 5% did not occur. A secondary endpoint of an increase of 1% did not occur.
- The HERA and BCIRG-006 studies have finished accruing patients, and the N9831 US Intergroup trial is within eight to 12 months of completing accrual. At our current rate, B-31 would require another three and a half years to complete accrual.
- We are optimistic about the possibility of combining N9831 and B-31 for a joint analysis, which will substantially accelerate the reporting time. We are also due to have our first interim analysis of B-31; the analysis is based on deaths because survival was our primary endpoint.

**MEDICATION**

- Trastuzumab (Herceptin)®
- Adelantado; approved March 2000; interim analysis available for the first quarter of 2006
- 35 patients at risk of 5 years

**Future options with trastuzumab for primary systemic and metastatic breast cancer**

- **New adjuvant strategies for breast cancer:** Meeting the challenge of targeting chemotherapy and trastuzumab (Herceptin).
- **Future clinical trials**
  - Randomized phase III trials evaluating the combination of trastuzumab and chemotherapy in the adjuvant setting.
  - The Z1030 trial is a phase III trial evaluating the combination of trastuzumab and docetaxel in the adjuvant setting.

**SELECT PUBLICATIONS**

- Debu Tripathy, MD
- Sparano JA.
- Perez EA, Rodeheffer R.
- Baselga J et al.
- Tan AR, Swain SM.
The recent emergence of the estrogen receptor downregulator fulvestrant and steroidal and nonsteroidal aromatase inhibitors have complicated the treat-ment algorithm for women with ER-positive metastatic disease. A number of ongoing clinical trials are attempting to evaluate endocrine strategies in women progressing on the usual first-line therapy (nonsteroidal aromatase inhibitors). Other studies are evaluating the combination of aromatase inhibitors with fulves- trant, based on the theoretical advantage of utilizing fulvestrant in a lower-estrogen environment. Biologic agents are also being evaluated in combination with endocrine interventions. These include trials of trastuzumab with aromatase inhibitors and trials of tyrosine kinase inhibitors plus endocrine therapies.

Ongoing Clinical Trials of Hormonal Therapy in Postmenopausal Women with Metastatic Disease

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Phase</th>
<th>Treatment</th>
<th>Eligibility</th>
<th>ARM 1</th>
<th>ARM 2</th>
<th>Target Accrual</th>
<th>Protocol IDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCHE-BO16216</td>
<td>III</td>
<td>Fulvestrant vs exemestane</td>
<td>Postmenopausal women with ER/PR-positive metastatic breast cancer</td>
<td>Fulvestrant</td>
<td>Exemestane</td>
<td>202</td>
<td>ROCHE-BO16216, CWRU-030118, GENENTECH-H2223g, S0226</td>
</tr>
<tr>
<td>CWRU-030118</td>
<td>II/III</td>
<td>Fulvestrant vs fulvestrant + anastrozole vs exemestane</td>
<td>Postmenopausal women with ER/PR-positive metastatic breast cancer</td>
<td>Fulvestrant + Anastrozole</td>
<td>Fulvestrant</td>
<td>250</td>
<td>ROCHE-BO16216, CWRU-030118, GENENTECH-H2223g, S0226</td>
</tr>
<tr>
<td>GENENTECH-H2223g</td>
<td>II/III</td>
<td>Fulvestrant vs exemestane</td>
<td>Postmenopausal women with ER/PR-positive metastatic breast cancer</td>
<td>Fulvestrant</td>
<td>Exemestane</td>
<td>500</td>
<td>ROCHE-BO16216, CWRU-030118, GENENTECH-H2223g, S0226</td>
</tr>
<tr>
<td>SWOG-S0226</td>
<td>III</td>
<td>Anastrozole vs anastrozole + letrozole</td>
<td>Postmenopausal women with ER/PR-positive metastatic breast cancer</td>
<td>Anastrozole</td>
<td>Anastrozole + Letrozole</td>
<td>750</td>
<td>SWOG-S0226</td>
</tr>
</tbody>
</table>

**Phase III Randomized Study of Anastrozole with or without Tamoxifen in Postmenopausal Women with Hormone Receptor-Positive, Locally Advanced, or Metastatic Breast Cancer (EFECT)**

**Study Contact:** Bernd Langer, PhD, Protocol Chair

**Protocol IDs:** ROCHE-BO16216, CWRU-030118, GENENTECH-H2223g, S0226

**Eligibility:** Postmenopausal women with ER/PR-positive, metastatic or locally recurrent breast cancer

**Target Accrual:** 202 (Open)

**Protocol Institutions:** AstraZeneca Pharmaceuticals LP, European Organisation for Research and Treatment of Cancer, Hoffmann-La Roche Inc, European Organisation for Research and Treatment of Cancer

**Study Lead Organization:** European Organisation for Research and Treatment of Cancer

**Study Contact:** Gabriel N Hortobagyi, MD

**Sponsors:** European Organisation for Research and Treatment of Cancer

**Results:***

The trial compared fulvestrant to exemestane in postmenopausal women with ER/PR-positive metastatic breast cancer. The study was stopped early due to efficacy and the superior tolerability of fulvestrant. The results confirmed the efficacy and safety of fulvestrant in this population, providing a new treatment option for hormone receptor-positive metastatic breast cancer.

**Further studies in endocrine therapy:***

- **EFECT Double-blind, placebo-controlled Phase III trial of fulvestrant vs exemestane in postmenopausal women with ER/PR-positive metastatic breast cancer**
- **SoFEA Phase III trial of fulvestrant vs fulvestrant + anastrozole vs exemestane in postmenopausal women with ER/PR-positive metastatic breast cancer**
- **SWOG-S0226 trial of anastrozole vs anastrozole + letrozole in postmenopausal women with ER/PR-positive metastatic breast cancer**

**Conclusion:***

The SoFEA trial will randomly assign 750 patients who have failed therapy with a nonsteroidal aromatase inhibi-tor and who are not fulfilling any of the exclusion criteria. The study will provide an indication of whether fulvestrant is better than exemestane as second-line therapy and whether it's necessary to suppress the levels of estrogen. It is possible to inhibit the aromatase enzyme, without estrogen, to reduce aromatase inhibition. Further studies are needed to establish whether fulvestrant plus anastrozole will be better than fulvestrant alone.

**- Mitchell Dowsett, PhD

**FULVESTRANT VERSUS AROMATASE INHIBITORS IN THE METASTATIC SETTING**

Assuming an aromatase inhibitor and fulvestrant are equivalent in efficacy, the choice of which agent to use may come down to practical considerations. Some of my patients are perfectly happy with a monthly injection while others prefer on an oral agent. For many patients, fulvestrant is financially favorable because of our ancillary reimbursement system. We know that responses can be seen with other sequences—a non-steroidal aromatase followed by fulvestrant or the opposite—but I believe it's important to determine which is superior. I believe the trials of fulvestrant underestimate the efficacy of this agent. The dosing schedule used was probably too high for the time period when the trial was reached, many patients were off study, presumably as a result of the dose. That scenario equates to the addition of aromatase inhibitors and whether it's necessary to suppress the levels of estrogen. Further studies are needed to establish whether fulvestrant plus anastrozole will be better than fulvestrant alone.

**- Mitchell Dowsett, PhD

**SELECT PUBLICATIONS**

Sequence of Hormonal Therapies in Metastatic Disease

As in postmenopausal women with early breast cancer, the sequencing of hormonal therapies in women with metastatic disease has become a topic of considerable interest. Postmenopausal women may now receive not only tamoxifen but also aromatase inhibitors in the adjuvant setting, and the optimal sequencing of hormonal agents for the treatment of metastatic disease is unknown. Fulvestrant, an estrogen receptor downregulator, is a recent addition to the hormonal therapy armamentarium. As second-line therapy in postmenopausal women with advanced breast cancer, fulvestrant and anastrozole have similar efficacy. Fulvestrant has also been compared to tamoxifen as first-line therapy in women with advanced ER/PR-positive disease, and the benefits were comparable. Retrospective analyses of subsequent hormonal agents administered following fulvestrant have demonstrated significant response rates. Future clinical trials are required to determine the optimal sequencing of hormonal therapy options.

**CONSIDERED ANALYSIS OF TWO PHASE III METAT_CENTER TRAILS COMPARING FULVESTRANT TO ANASTROZOLE AS SECOND-LINE THERAPY IN WOMEN WITH ADVANCED BREAST CANCER**

**PHASE III RANDOMIZED TRIAL COMPARING FULVESTRANT TO TAMOXIFEN AS FIRST-LINE ENDocrine THERAPY IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER**

**RESPONSE TO SUBSEQUENT ENDocrine THERAPY IN PATIENTS ENROLLED IN TWO PHASE III TRIALS COMPARING FULVESTRANT AS SECOND-LINE THERAPY: RETROSPECTIVE ANALYSIS**

**SELECT PUBLICATIONS**

**SEQUENCING HORMONAL THERAPY IN POSTMENOPAUSAL WOMEN**

I generally use an aromatase inhibitor in a postmenopausal patient after completion of tamoxifen. Of course, if I see the patient develop disease in the adjuvant setting, I would consider fulvestrant in patients who have failed tamoxifen and an aromatase inhibitor. In my practice, I am seeing patients who have already been treated with fulvestrant in the metastatic setting. I think the results that have been reported are very encouraging, although I think the role of fulvestrant in the metastatic setting is still unclear. It is clear that patients who have failed tamoxifen can still respond to other endocrine therapies (eg, aromatase inhibitors and megestrol acetate).

- **Darrell R. Brollard, MD**

In postmenopausal women whose disease relapses while on adjuvant tamoxifen, I use fulvestrant because I've seen some very long remissions with it. I will use an aromatase inhibitor later because data indicate that patients with disease that progresses on fulvestrant can still respond to other endocrine treatments (eg, aromatase inhibitors and megestrol acetate).

A few reports have evaluated the response to fulvestrant in patients who received an aromatase inhibitor. A small Swiss study reported that about one third of patients with advanced breast cancer who achieved a clinical benefit on fulvestrant in patients who received an aromatase inhibitor.

At ASCO 2003, a compassionate-use trial reported data from about 60 patients treated with fulvestrant as second-line therapy. Fulvestrant had more than a 50 percent clinical benefit rate in those patients.

- **Stephen J. Feng, MD**

Women with breast cancer whose disease fails while on tamoxifen clearly can respond to fulvestrant, and the response rate is equivalent to that seen with anastrozole. Also, in women with disease that has failed an aromatase inhibitor, subsequent therapy with fulvestrant can still lead to a substantial clinical benefit rate of approximately 40 percent. I think the role of fulvestrant in the metastatic setting is still unclear. It is clear that patients who have failed fulvestrant can still respond to other endocrine therapies (eg, aromatase inhibitors and megestrol acetate). In my practice, I am seeing patients who have already been treated with fulvestrant in the metastatic setting. I think the results that have been reported are very encouraging, although I think the role of fulvestrant in the metastatic setting is still unclear. It is clear that patients who have failed tamoxifen can still respond to other endocrine therapies (eg, aromatase inhibitors and megestrol acetate).

- **Robert W. Carlson, MD**
Patient Perspectives on Endocrine Therapy for Metastatic Disease

Two large randomized clinical trials have demonstrated essentially equivalent efficacy and tolerability of anastrozole and fulvestrant in postmenopausal patients with progressive metastatic disease on tamoxifen; however, oncologists in practice generally utilize nonsteroidal aromatase inhibitors prior to fulves- trant because of the perception that patients prefer oral therapy. In a recent telephone survey of 256 women with metastatic breast cancer, a majority stated that they preferred oral endocrine therapy, assuming equal efficacy and side effects; however, about a third of the patients preferred parenteral administration. Patients cited a variety of reasons for this preference, including concerns about compliance, dislike of oral therapy, support received from the oncology office and convenience. In a tandem survey of oncologists and oncology nurses, these professionals estimated that more than one third of their patients with metastatic disease on bisphosphonates would prefer parenteral administration of endocrine therapy. This suggests that these decisions in this palliative setting should be individualized based on patient preference.

**CURRENT AND PRIOR THERAPIES OF PATIENTS PARTICIPATING IN SURVEY**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Percent of patients who received</th>
<th>Mean time spent in oncologist's office (median) (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant</td>
<td>41%</td>
<td>2 hours</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>51%</td>
<td>2 hours</td>
</tr>
<tr>
<td>Oral endocrine therapy</td>
<td>6%</td>
<td>3 hours</td>
</tr>
<tr>
<td>Intramuscular injection</td>
<td>43%</td>
<td>3 hours</td>
</tr>
</tbody>
</table>

**Reasons Cited by Patients for Preferring Parenteral Therapy**

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage of Patients Preferring Parenteral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel time to oncologist’s office</td>
<td>34%</td>
</tr>
<tr>
<td>Active lifestyle</td>
<td>34%</td>
</tr>
<tr>
<td>More effective</td>
<td>34%</td>
</tr>
<tr>
<td>Neutral</td>
<td>8%</td>
</tr>
<tr>
<td>More convenient</td>
<td>8%</td>
</tr>
<tr>
<td>Emotional support received during treatment</td>
<td>8%</td>
</tr>
<tr>
<td>More flexible</td>
<td>8%</td>
</tr>
<tr>
<td>More familiar</td>
<td>8%</td>
</tr>
</tbody>
</table>

**LIFESTYLE DEMOGRAPHICS OF PATIENTS WITH METASTATIC BREAST CANCER**

- Average time spent in oncologist’s office (median): 2 hours
- Active lifestyle: 72%
- More effective: 52%
- More convenient: 70%
- More familiar: 34%
- Emotional support received during treatment: 84%
- More flexible: 84%
- More injectable: 66%

**Healthcare Professionals’ Predictions about Patient Preferences for Oral Versus Intravenous Endocrine Therapy**

- Medical oncologists: 65% prefer oral
- Endocrinologists: 42% prefer oral

**SELECT PUBLICATIONS**


**Patient Perspectives for Oral Versus Intravenous Endothocyn Therapy**

I generally use an aromatase inhibitor in a postmenopausal patient progressing after completion of tamoxifen, but I also present the option of fulvestrant. I think both are reasonable and legitimate options that are equivalent.

As physicians, I think our viewpoint is different than that of patients. To us, oral treatment appears to be more convenient because the patient does not have to come in to the office and it is less expensive; however, some patients prefer an intramuscular injection once a month. Some patients may not be compliant with oral medication. For them, fulvestrant is a good option. Many reasons were cited by women who prefer to receive an injection. One is that they like the interaction with the nurse and feel more cared for in coming in and seeing not only the doctor but also other patients. Another reason is the perception that an intravenous or intramuscular drug is more effective. I see many patients from Asia and Latin America who really believe that injectable drugs are better. That may also be true in the United States.

**Chemotherapy for Metastatic Disease**

Clinical trials of chemotherapeutic agents and regimens in the metastatic setting not only better define clinical care but also provide important clues to future adjuvant therapy strategies. A series of recent studies have resulted in encouraging results with new combinations, including docetaxel/capecitabine, docetaxel/paclitaxel, and gemcitabine/paclitaxel. However, most breast cancer clinical research leaders support nonprotocol therapy with sequential single-agent chemotherapy in the metastatic setting, and the choice of agents is mainly based on prior adjuvant treatment and toxicity considerations.

**Table 1: Phase III Trials Comparing Single-Agent and Combination Therapy for Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th>Trial Description</th>
<th>Drug Combinations</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel vs. Paclitaxel</strong></td>
<td>Docetaxel vs. Paclitaxel</td>
<td>Improved overall survival</td>
</tr>
<tr>
<td><strong>Gemcitabine vs. Paclitaxel</strong></td>
<td>Gemcitabine vs. Paclitaxel</td>
<td>Superior response rate</td>
</tr>
<tr>
<td><strong>Capetitabine vs. Paclitaxel</strong></td>
<td>Capetitabine vs. Paclitaxel</td>
<td>Improved progression-free survival</td>
</tr>
<tr>
<td><strong>Capecitabine vs. Paclitaxel</strong></td>
<td>Capecitabine vs. Paclitaxel</td>
<td>Superior overall survival</td>
</tr>
</tbody>
</table>

**Phase III Trial of Gemcitabine/Paclitaxel Versus Paclitaxel as First-Line Treatment in Patients with Anthracycline-Resistant Metastatic Breast Cancer: Interim Survival Report**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>GT (n=267)</th>
<th>T (n=262)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-Free Survival (95% CI)</strong></td>
<td>11.5 (9.6, 12.7)</td>
<td>12.1 (11.1, 13.0)</td>
<td>0.042</td>
</tr>
<tr>
<td><strong>Overall Survival (95% CI)</strong></td>
<td>21.2 (14.1, 25.5)</td>
<td>22.0 (16.7, 27.1)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

**Capecitabine Plus Paclitaxel in Taxane-Naïve Patients with Metastatic Breast Cancer: Efficacy and Toxicity**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Efficacy</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine</td>
<td>25%</td>
<td>Alopecia 20%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>30%</td>
<td>Alopecia 15%</td>
</tr>
</tbody>
</table>

**Combination Versus Sequential Doxorubicin and Paclitaxel as First-Line Therapy**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Combination (n=34)</th>
<th>Sequential (n=35)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response Rate</strong></td>
<td>70%</td>
<td>30%</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Progression-Free Survival</strong></td>
<td>18.9 months</td>
<td>14.5 months</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Phase III Trial of Docetaxel Monotherapy vs. Intergroup Trial E1193**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Docetaxel</th>
<th>Intergroup Trial E1193</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progression-Free Survival</strong></td>
<td>12.1 months</td>
<td>9.7 months</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Phase II Study of Capecitabine/Docetaxel Versus Docetaxel as First-Line Treatment of Metastatic Breast Cancer**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>C/D (n=37)</th>
<th>T (n=37)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response Rate</strong></td>
<td>50%</td>
<td>40%</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Median Progression-Free Survival</strong></td>
<td>16.5 months</td>
<td>12.1 months</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Conclusion**

The results from these trials have provided valuable insights into the treatment of metastatic breast cancer, highlighting the importance of selecting the most appropriate combination therapy for individual patients. Further studies are needed to confirm these findings and explore the potential for dose intensity and schedule optimization.

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**SELECT PUBLICATIONS**


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Research To Practice: Chemotherapy in Metastatic Disease

The Patterns of Care Study indicates that key factors determining choice of systemic treatment in the metastatic setting are patient age, performance status, site of disease, and ER and HER2 assay results. Endocrine therapy alone is generally utilized in patients with good performance status and ER-positive tumors. Trastuzumab, usually in combination with chemotherapy, is widely utilized as first-line therapy for women with HER2-positive disease. A key issue in selection of chemotherapy is the choice between sequential single agents and combinations. Oncologists often use single agents for patients with good performance status, and the decisions regarding sequencing vary. Side-effect profiles alter choices in individual situations. Anthracycline-based regimens are commonly utilized in patients who have not previously received adjuvant chemotherapy. The combination of docetaxel and capecitabine is frequently utilized in women who have previously received chemotherapy.

**CHEMOTHERAPY FOR ASYMPTOMATIC PATIENTS WITH MALIGNANT PORTAL METASTASES:**
- **Docetaxel**
- **Paclitaxel**
- **Capecitabine**
- **Docetaxel + Capecitabine**
- **Cisplatin + paclitaxel**
- **Paclitaxel + estramustine**
- **Gemcitabine + estramustine**
- **Capecitabine + docetaxel**

**CHEMOTHERAPY FOR SYMPTOMATIC PATIENTS WITH MALIGNANT PORTAL METASTASES:**
- **Docetaxel**
- **Paclitaxel**
- **Capecitabine**
- **Docetaxel + Capecitabine**
- **Cisplatin + paclitaxel**
- **Paclitaxel + estramustine**
- **Gemcitabine + estramustine**
- **Capecitabine + docetaxel**

**TREATMENT OF CHEMOTHERAPY-NAIVE PATIENTS WITH RECEPTOR-NEGATIVE DISEASE**
- **Docetaxel**
- **Paclitaxel**
- **Capecitabine**
- **Docetaxel + Capecitabine**
- **Cisplatin + paclitaxel**
- **Paclitaxel + estramustine**
- **Gemcitabine + estramustine**
- **Capecitabine + docetaxel**

**TREATMENT OF PATIENTS WITH RECEPTOR-NEGATIVE DISEASE AFTER ADJUVANT AC + PRACTIXEL**
- **Docetaxel**
- **Paclitaxel**
- **Capecitabine**
- **Docetaxel + Capecitabine**
- **Cisplatin + paclitaxel**
- **Paclitaxel + estramustine**
- **Gemcitabine + estramustine**
- **Capecitabine + docetaxel**

**SELECT PUBLICATIONS**

Targeting the HER Pathways

The human epidermal growth factor receptor (HER) family has four members: HER1, HER2, HER3, and HER4. These four receptors interact via complex signal transduction pathways, which provide multiple targets for potentially interfering with cellular growth and proliferation. Many biologic agents affecting these pathways are currently being developed and investigated. Preclinical and clinical trials are also evaluating combinations of biologic agents that target the different receptors. The results from ECOG-1100 were disappointing because the combination of trastuzumab and gefitinib did not appear to result in significant antitumor effect. Preclinical data suggest that, perhaps, pan-HER2 blockade with trastuzumab, gefitinib and pertuzumab may prove to be more beneficial.

**ECOG-1100: INTERIM EFFICACY DATA FROM PHASE I/II STUDY OF TRASTUZUMAB AND GEFTINIB IN PATIENTS WITH HER2- OVEREXPRESSING METASTATIC BREAST CANCER**

**HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR (HER) SIGNALING**

The epidermal growth factor receptor (EGFR) family has four members: HER1 (ErbB1 or EGFR), HER2 (ErbB2), HER3, and HER4 (ErbB4). These receptors are all transmembrane tyrosine kinases that function as heterodimers. HER1 and HER2 are the most studied members of the family, as they are overexpressed in many tumors, including breast cancer. HER2 is the target of the anti-HER2 antibody trastuzumab (Herceptin).

**SELECT PUBLICATIONS**

- **Nahta R et al.** Cancer 2004;100:2081-82.

**ECOG-1100 INTERIM ANALYSIS**

The interim analysis of ECOG-1100 suggests no benefit from combining trastuzumab with gefitinib. In addition, the two drugs were well tolerated and patients treated with the combination was shorter than reported with trastuzumab alone; although not a straight comparison. These data highlight the fact that robust preclinical data do not always predict clinical trial results. I know this combination is being used as a bridge in the community, and that needs to be re-examined. This analysis has prompted some questions in the ECOG Breast Care Committee. For example, could we have anticipated these results, avoiding the need for a two-year Phase II study? I believe yes if we had this as a presur-geometric setting, like Dr Chang’s neoadjuvant trial with single-agent agents – we have concluded that this longer study would not be worthwhile.

In an effort to identify the rational partners of trastuzumab, how do we make certain those combinations are at least equivalent or better than trastuzumab alone? One party because of the ECOG-1100 data, we are contemplating a clinical trial plan to identify trastuzumab’s most interfer with the overwhelming choice in the community for HER2-positive, metastatic breast cancer, which is typically trastuzumab. Not only are we ensuring the best opportunity to provide these patients with effective treatment, we are exploring the possibility of using bevacizumab as our next-trastuzumab-partner.

**HER2 INHIBITION**

Work by Kent Odunoglu’s group with mouse xenografts indicates that with a more complete blockade of the HER2 pathway in order to avoid cure. In the mouse xenograft model conducted with HER2-positive metastatic breast cancer, Odunoglu’s group found that when they utilized a pan-HER2 blockade of trastuzumab, gefitinib and pertu- sumab, tumors actually regressed completely and never came back when the combination was stopped. This is extremely exciting and I think we’re moving into an area, where unless we block the HER family completely, you are going to provide the call an escape mechanism.

**PRECLINICAL DATA SUPPORTING SYNERGY OF HER2 ALTERNATIVE INHIBITORS**

“Trastuzumab (Herceptin) and pertuzumab (Omnitarg, 2C4) are monoclonal humoral monoclonal antibodies that target different extracellular regions of the HER2 tyrosine kinase receptor.”

“Combination drug treatment reduced levels of total and phosphorylated HER2-β proteolytic and blocked receptor signaling through Akt but did not affect mitogen-activated protein kinase (MAPK). These results suggest that combining HER2-targeting agents may be a more effective strategy in breast cancer rather than treating with a single HER2 monoclonal antibody.”

Availability of the humanized monoclonal antibody trastuzumab makes it critical to accurately determine HER2 tumor status in all patients with metastatic breast cancer. About three fourths of oncologists accept IHC results of 3+ as HER2-positive, but others require FISH confirmation. The 2004 Patterns of Care demonstrated that, in the first-line metastatic setting, trastuzumab is generally combined with chemotherapy — usually a taxane. Although no randomized clinical trial data are available addressing the questions of continuation of trastuzumab upon disease progression, this is a common practice pattern both in tertiary care centers and community oncology practice. In the adjuvant setting, trastuzumab is rarely utilized outside the context of a clinical trial.

**HER2-TESTING ALGORITHM**

We routinely order IHC on pathology specimens. For patients with metastatic breast cancer, if the IHC is 3+ I do not generally follow up with FISH, provided the tumor stains 3+ in 75 to 100 percent of cells. I sometimes order FISH in IHC 0 cases — not in the adjacent setting when I'm trying to decide between tamoxifen and an aromatase inhibitor, but in metastatic disease, I test everybody. I believe every patient with HER2-positive disease needs one FISH assay in her lifetime. These are not perfect tests by any means, and it is worthwhile to make sure you are comfortable with the results.

— Joyce O'Shaughnessy, MD

I try to find any excuse to order a test. If the IHC is away to 3+, I don't, but if it is 2+, I order FISH. A minority number of tumors are 1+ and FISH-positive but sometimes, for a young patient who has aggressive disease and not many alternatives, I order FISH if the IHC is slightly positive. I will not do that for IHC 0 tumors.

— Gershon Locker, MD

**TREATMENT ALGORITHMS FOR PATIENTS WITH HER2-POSITIVE METASTATIC DISEASE**

I generally use trastuzumab alone for asymptomatic patients with HER2-positive disease. If you recommend chemotherapy to an asymptomatic patient, that patient may become symptomatic. For a highly symptomatic patient who received adjacent AC, I would recommend a taxane plus trastuzumab. I don't think it matters which taxane. I would either use docetaxel every three weeks or weekly paclitaxel, and I would not argue that either is right or wrong.

— Clifford Hudis, MD

I use a combination with weekly paclitaxel as my preferred partner for trastuzumab. Doxorubicin is a reasonable option. In a symptomatic patient I would probably use a platinum/taxane combination. I do not offer trastuzumab plus chemotherapy because most of my patients are not that symptomatic, but for the ones who are, I use a platinum/taxane combination.

Second line, I tend to prefer trastuzumab, but I admit we do not know what the independent contribution of trastuzumab is in that situation. All of the retrospective data does not tell us whether chemotherapy alone would have had the same types of responses that are seen in that setting.

Theoretically, I think trastuzumab still retains the possibility of synergy with other chemotherapy drugs and, therefore, I think a biologic rational exists for continuing it. Also, patients who have not developed toxicities with trastuzumab for some time have a very low risk of additional complications, such as cardiomyopathy, over time. For these reasons, I think it is reasonable to continue trastuzumab. The downside is the cost. It depletes resources, and that is a big issue, especially in fixed-cost medical systems.

— Dulip Mathur, MD

**NONPROTOCOL USE OF ADJUVANT TRASTUZUMAB**

I am somewhat intrigued but very miffed that physicians are not prescribing adjuvant trastuzumab off protocol without high-level evidence that the benefits exceed the long-term toxicities — especially with regard to cardiac toxicity.

This might be a result of the " Bewwoda effect" and physicians' experience with high-dose chemotherapy. Years ago, many community physicians took information that was a little bit disconnected, put it together and concluded that high-dose therapy was superior to standard full-dose therapy. When they eventually were burned by fraudulent trial results, I think many of them paused and thought, "How many women died because of our recommendations, albeit well-intentioned, about how to treat their breast cancer?"

— Robert W Cartan, MD
Partial Breast Irradiation for Primary Breast Cancer

The delivery of larger doses of radiation therapy (RT) to the lumpectomy cavity and a margin of surrounding tissue after breast-conserving surgery, via brachytherapy or external beam radiation techniques, may provide several advantages to appropriately selected patients. Partial breast irradiation (PBI) may improve the documented underutilization of breast-conserving surgery by allowing RT to be completed in four or five days, instead of six to seven weeks, eliminate the acute and chronic toxicities associated with whole breast irradiation (WBI), and improve cosmesis and confer societal economic benefits. Before PBI can be routinely incorporated into clinical practice, several issues must be addressed, including appropriate patient selection, optimal fractionation schedules and PBI techniques. Importantly, it must be established that long-term rates of locoregional control are similar to those achieved with WBI. A matched-pair analysis has demonstrated comparable outcomes for women treated with limited-field irradiation or WBI. Several Phase III clinical trials evaluating these issues are ongoing worldwide.

**SELECT PUBLICATIONS**


**ACTIVE PARTIAL BREAST IRRADIATION TRIALS**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Scorpio (Strasbourg, France)</th>
<th>MammoSite® primary trial</th>
<th>MammoSite® breast trial</th>
<th>MDO® (London, England)</th>
<th>European Institute of Oncology (Milan, Italy)</th>
<th>MDO® breast trial</th>
<th>University of Florida (Gainesville, Florida)</th>
<th>MDO® breast trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>600</td>
<td>300</td>
<td>300</td>
<td>50</td>
<td>100</td>
<td>50</td>
<td>300</td>
<td>50</td>
</tr>
<tr>
<td>Treatment</td>
<td>Partial breast radiation therapy</td>
<td>Partial breast radiation therapy</td>
<td>Partial breast radiation therapy</td>
<td>Partial breast radiation therapy</td>
<td>Partial breast radiation therapy</td>
<td>Partial breast radiation therapy</td>
<td>Partial breast radiation therapy</td>
<td>Partial breast radiation therapy</td>
</tr>
<tr>
<td>Protocol Type</td>
<td>Randomized</td>
<td>Randomized</td>
<td>Randomized</td>
<td>Randomized</td>
<td>Randomized</td>
<td>Randomized</td>
<td>Randomized</td>
<td>Randomized</td>
</tr>
</tbody>
</table>

**FIVE-YEAR ACTUARIAL TREATMENT OUTCOMES FROM MATCHED-PAIR ANALYSIS OF PATIENTS TREATED WITH WHOLE BREAST VS. LIMITED-FIELD RADIATION THERAPY**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Whole breast % (95% CI)</th>
<th>Limited-field % (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral recurrence</td>
<td>1 (0-2.4)</td>
<td>1 (0-2.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>Regional failure*</td>
<td>1 (0-1.5)</td>
<td>1 (0.1-2.1)</td>
<td>0.54</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>95 (94-97)</td>
<td>95 (94-97)</td>
<td>0.26</td>
</tr>
<tr>
<td>Overall survival</td>
<td>90 (87-93)</td>
<td>90 (87-93)</td>
<td>0.23</td>
</tr>
<tr>
<td>Disease-specific survival</td>
<td>97 (95-99)</td>
<td>97 (95-99)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

* Regional failure is defined as the recurrence of cancer in a regional node or bed either before or after the diagnosis of marginal recurrence or distant failure.

**PUBLISHED PBI RESULTS: BRAHCHOTHERAPY**


**RANDOMIZED PHASE III STUDY OF CONFORMAL WHOLE BREAST RADIATION THERAPY VERSUS PBI FOR WOMEN WITH STAGE I-II BREAST CANCER**

- Tufts – New England Medical Center 90 27 4.4
- Florence, Italy 90 27 4.4
- MGH – Massachusetts General Hospital 75 26 4.6
- Nemours – Delaware 70 30 4.4
- University of Virginia 24 37 0
- Turkey – New England Medical Center 23 33 3
- NIO – Hungary 45 60 4.4
- INTRODUCTION

Intraoperative radiation therapy (IORT) is an idea whose time has arrived. The procedure is gaining acceptance, and many competing technologies exist. IORT decreases the thickness of the body that needs to be treated, reduces the amount of time required and the amount of toxicity associated with radiation therapy may increase the rate of breast conservation. IORT is an elegant, simple device that a surgeon can utilize after wide-local excision. In approximately 25 minutes, you can give a boost to the tumor bed and a centimeter beyond in all directions.

**PARTIAL BREAST IRRADIATION**

One of the advantages of PBI is that it can be completed quickly before systemic therapy is initiated. William Beaumont is one of the few institutions that offers IORT with MammoSite® and conformal external beam radiation therapy.

Each technique has its advantages and none of them is applicable to all clinical scenarios. Treatment must be individualized based on factors such as the patient’s access to a radiation facility and the location of the lesion within the breast.

At our institution, the patients who receive PBI, approximately 60 percent are treated with the MammoSite®, 30 percent with conformal external beam radiation therapy and a small percentage with interstitial brachytherapy. Reducing the amount of time required and the amount of toxicity associated with radiation therapy may increase the rate of breast conservation. I am convinced an additional 10 to 20 percent making this decision would select breast-conserving therapy if PBI were an option.
Preliminary data indicate that SLNB has a nine to 10 percent false-negative rate. (SLNB) as an initial staging procedure led to a new generation of trials evaluating sentinel lymph node biopsy. The emergence of sentinel lymph node biopsy (SLNB) has led to attention to axillary dissection in women with pathologically negative or positive nodes. Recently reported results from NSABP-B-32 and the ALMANAC trial support the use of SLNB for women with clinically node-negative disease. Preliminary data indicate that SLNB has a nine to 10 percent false-negative rate. SLNB can also significantly reduce postsurgical arm morbidity.

**SELECT PUBLICATIONS**


**CURRENT STATUS OF SENTINEL LYMPH NODE BIOPSY**

We now have clear data that sentinel lymph node biopsy is the staging procedure of choice for clinically node-negative breast cancer. Over 4,000 cases have been published with a mean follow-up of at least two years and the incidence of isolated axillary failure is ten in one percent, which is very low. Additionally, we now have two randomized trials evaluating the incidence of nodal positivity in women staged by sentinel node biopsy versus axillary dissection.

Sentinel node biopsy provides staging accuracy equivalent to axillary dissection, and the morbidity is clearly less — not only the immediate postsurgical morbidity but also two years later in measurable differences in pain, paraphrenia, arm motion and lymphedema. Additionally, we now know long-term local tumor control is good.

**NSABP-B-32 SENTINEL NODE TRIAL**

The preliminary specificity and sensitivity data from NSABP-B-32 show a nine to 10 percent false-negative rate for detecting positive nodes with the sentinel node method. One can say that surgeons with more experience have a lower rate or that if one examines two or three sentinel nodes, one can lower that rate. However, if one examines four to five nodes, one isn’t really talking about an axillary node dissection.

When we examined some of the older NSABP data to determine how many nodes were necessary to establish positive nodes in the axilla, the number was between six and eight. Any number of nodes below that had a high false-negative rate, while any number above that was superfluous.

I don’t believe questioning the accuracy of axillary node dissection is particularly helpful. In this randomized protocol with over 2,000 women, the false-negative rate with sentinel node biopsy is nine to 10 percent and that’s the inescapable conclusion of this trial.

**THE ALMANAC TRIAL**

The ALMANAC data show a significant decrease in arm morbidity problems and lymphedema with sentinel node biopsy. However, the study unexpectedly underestimated the morbidity experienced by the sentinel node group because 20 percent of those patients actually underwent axillary node dissection for a positive sentinel node or they received axillary radiation. I believe the numbers were skewed against sentinel node biopsy, and that the associated morbidity is probably much lower than these data suggested, which are already much lower than the results seen in the axillary node dissection group.

**Raj-P D, Boccard, PhD**

I was the primary investigator for the quality of life study in the ALMANAC trial, and it was probably the first time since the breast cancer trial that we actually had quality of life as the primary endpoint in a surgical trial. In fact, it was not affected and the quality of life benefits were superior in women who underwent sentinel lymph node biopsy compared to axillary dissection, because they experienced less arm morbidity.

Another important aspect of this study is that, although physicians may be concerned about their patients, often the focus of attention when reviewing clinical trial data is predominantly on non-life-threatening adverse events. For instance, we have one of our patients — surgery, chemotherapy or hormone manipulation — non-life-threatening, but nevertheless significant, side effects can dramatically impair quality of life. Lynch commonly used adjuvant endocrine therapy and the way physicians talk to their patients, often the effects definitely affects one’s ability to function adequately in the home and professional world and in care-taking roles. The ALMANAC trial has at least given us a clear indication that the sentinel lymph node procedure should become the standard of care.
Antiangiogenic Therapy

The importance of angiogenesis in cancer biology has been recognized for decades. One of the first stimulating factors identified was the vascular endothelial growth factor (VEGF). At the 2002 San Antonio Breast Cancer Symposium, Kathy Miller and colleagues reported on the first Phase III randomized trial in breast cancer evaluating the anti-VEGF monoclonal antibody bevacizumab. This ECOG study compared capcitabine alone to capcitabine combined with bevacizumab in heavily pretreated patients with metastatic breast cancer and found a modest response rate advantage to the combination but no improvement in the primary endpoint of time to progression. Another key ECOG study is evaluating bevacizumab combined with paclitaxel in the first-line setting. The hope is that a more significant advantage may be seen in earlier-stage disease, as was observed in the recently reported trial in colorectal cancer in which a marked survival advantage was observed for bevacizumab plus irinotecan and 5-fluorouracil (IFL) compared to IFL alone. The first interim efficacy analysis from the ECOG-2100 trial is expected to be reported in early summer of 2005.

**SELECT PUBLICATIONS**

- Markowitz J et al. Bevacizumab in breast cancer and colon cancer were attributed to the differences in the trial results for bevacizumab in breast cancer and colon cancer were attributable to when patients were treated during the course of the disease — rather than some inherent difference in the biology of the cancers. Our current understanding of the role of bevacizumab in breast cancer is evolving. The CORD-2100 breast cancer trial enrolled patients with breast cancer who had not received previous chemotherapy for metastatic disease but could have undergone adjuvant chemotherapy. Likewise, our CORD-2100 breast cancer trial enrolled patients with breast cancer who had not received chemotherapy for metastatic disease but could have received adjuvant chemotherapy. Patients were randomly assigned to weekly paclitaxel with or without bevacizumab. The primary endpoint for CORD-2100 is time to progression.

**CLINICAL TRIALS EVALUATING THE ANTI-VEGF BIOACTIVE IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS WITH METASTATIC BREAST CANCER**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial Name</th>
<th>Disease</th>
<th>Primary Endpoint</th>
<th>Secondary Endpoint</th>
<th>Treatment</th>
<th>Progression-Free Survival</th>
<th>Overall Survival</th>
<th>Toxicity</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>MSKCC-01008</td>
<td>MBC</td>
<td>Time to progression</td>
<td>Overall survival</td>
<td>Bevacizumab + A/C/T</td>
<td>4.2 months</td>
<td>4.9 months</td>
<td>PE 1.4%</td>
<td>7.4%</td>
</tr>
<tr>
<td>II</td>
<td>UAB-F001009003</td>
<td>MBC</td>
<td>Time to progression</td>
<td>Overall survival</td>
<td>Bevacizumab</td>
<td>6.2 months</td>
<td>6.8 months</td>
<td>PE 0.5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>III</td>
<td>MSKCC-01008</td>
<td>MBC</td>
<td>Progression-free survival</td>
<td>Overall survival</td>
<td>Bevacizumab + A/C/T</td>
<td>10.6 months</td>
<td>16.2 months</td>
<td>PE 3.3%</td>
<td>7.6%</td>
</tr>
<tr>
<td>III</td>
<td>UAB-F001009003</td>
<td>MBC</td>
<td>Progression-free survival</td>
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<td>0.4%</td>
</tr>
</tbody>
</table>

**SELECT PUBLICATIONS**

Adjuvant Bisphosphonates

A number of biologic effects in bone suggest that bisphosphonates have the potential to retard or prevent the clinical onset of metastatic disease. Three randomized adjuvant trials have yielded conflicting results on this question, despite the use of these agents in different standard in patients with known lytic bone metastases. A new generation of adjuvant trials is currently being evaluated whether bisphosphonates will reduce the rate of bone and nonbone metastases and prolong survival.

Promising research strategies actively being discussed is the combination of a bisphosphonate and an aromatase inhibitor, which would not only offer potential reduction in relapse rate but would mitigate bone loss. A data set from Austria presented at the 2002 and 2004 San Antonio Breast Cancer Symposia demonstrated that bone loss from anastrozole in premenopausal women receiving an LH-RH agonist was prevented by the use of zoledronic acid.

ONCOLOGY AND RECENTLY CLOSED ADJUVANT BISPHOSPHONATE TRIALS IN BREAST CANCER

- Gnant M et al. Clodronate versus placebo trial. While we cannot predict which agent will follow up on the NSABP clodronate versus placebo trial. When we will predict the results of the NSABP trial, we believe clodronate will be the winner. Our trial will compare adjuvant clodronate to a more potent oral bisphosphonate and an iv bisphosphonate. We want to see whether these agents can prevent bone metastases and impact disease-free and overall survival.

SELECT PUBLICATIONS


**SELECT PUBLICATIONS**


**ONCOLOGY ON 21-GENE RECURRENCE SCORE ASSAY**

<table>
<thead>
<tr>
<th>recurrence score</th>
<th>10-year BCSS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 18</td>
<td>82.5%</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 31</td>
<td>60.6%</td>
<td></td>
</tr>
</tbody>
</table>

**MULTIGENE RT-PCR ASSAY FOR PREDICTING RECURRENCE IN PATIENTS WITH ER-POSITIVE, NODE-NEGATIVE BREAST CANCER**

Based on literature review and known prognostic factors in breast cancer, approximately 185 genes were selected for a multigene panel and tested in two data sets. Twenty-one genes appeared to predict for outcomes, and these were then confirmed in a subset of patients from the NSABP-B-20 tamoxifen-only arm. NSABP-B-41 tested this multigene panel prospectively in GSKI patients with ER-positive, node-negative breast cancer biopsies, and the panel predicted recurrence risk for 5 years after therapy was started. This assay assigns patients a recurrence score from zero to 100 to assist in deciding on treatment alternatives.

- **Model C A O'Connell, MD

**Predicting Prognosis in Women with Early Breast Cancer**

Tools that accurately predict the prognosis of women with early breast cancer are invaluable to both clinicians and patients when making decisions about adjuvant therapy. In women with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen, a 21-gene assay was recently found by the NSABP to predict the 10-year distant recurrence rate and the benefit associated with adjuvant chemotherapy. The Adjuvant! online computer program, developed by Dr Peter Ravdin, also allows for the prediction of outcomes in women with early breast cancer. In a presentation at ASCO 2004, the predictions from Adjuvant! were found to be very comparable to actual outcomes observed in patients from British Columbia. These and future tools that can predict outcomes should aid in the decision-making process about adjuvant therapies.

**NSABP-B-41 TAM BENEFIT STUDY IN PATIENTS WITH NODE-NEGATIVE, ER-POSITIVE DISEASE**

**SOURCES:**

- Low (RS < 18) 95% 96% 0.76
- Intermediate (RS = 18-30) 89% 90% 0.71
- High (RS ≥ 31) 60% 88% 0.001

**COMPARISON OF OUTCOMES PREDICTED BY ADJUVANT CHEMOTHERAPY AND TAMOXIFEN vs. ACTUAL OUTCOMES OBSERVED BY THE BREAST CANCER OUTCOMES UNIT (BCOU) IN BRITISH COLUMBIA (N=4,083)**

**TABLE 1**: Patients - British Columbia (N=4,083)

<table>
<thead>
<tr>
<th>10-year BCSS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>83.2%</td>
</tr>
<tr>
<td>Low</td>
<td>84.4%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>69.4%</td>
</tr>
<tr>
<td>High</td>
<td>54.3%</td>
</tr>
</tbody>
</table>

**OBJECTIVE:** Determine whether the 21 gene recurrence score assay captures prognosis, response to tamoxifen, or both.

**KAPLAN-MEIER ESTIMATES OF THE 10-YEAR BCSS**

<table>
<thead>
<tr>
<th><em>p</em>-value</th>
<th>10-year BCSS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSABP-B-14</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>NSABP-B-10</td>
<td>≥ 0.05</td>
<td></td>
</tr>
</tbody>
</table>

**SAVING MILLIONS, PREDICTING YEARS**

**REFERENCES:**

Impact of CME on Practice Patterns in Breast Cancer

Surgeon and medical oncologist has the daunting task of keeping up-to-date with the expanding knowledge base in breast cancer medicine. Relatively little is known about the effect of continuing medical education (CME) on oncology practice patterns. As part of the Breast Cancer Update Patterns of Care Study, 200 medical oncologists were surveyed about their participation in various CME activities, and the influence of listening to the Breast Cancer Update audio series on treatment patterns. Compared to nonlisteners, listeners of the BCU audio series were more likely to recommend: dose-dense adjuvant chemotherapy with AC + T, switching a postmenopausal patient who was not tolerating adjuvant therapy to anastrozole fulvestrant as second-line therapy for a woman with asymptomatic ER-positive metastastic disease, and trastuzumab monotherapy for a patient with asymptomatic HER2-positive metastatic disease. Future studies should continue to assess the impact of various CME activities on treatment patterns in medical oncology.

**TIME SPENT IN CONTINUING EDUCATION ACTIVITIES**
- How much time in a typical month do you spend doing the following? (in hours)
  - Reading any type of medical educational materials
  - Listening to any type of medical educational programs on CD or tape
  - Specifically listening to interviews
  - Reading any type of medical educational materials

**WHO IS THE FOLLOWING-JUDGES DO YOU READ OR SKIM EACH MONTH?**
- CME Update
  - ASCO
  - JCO
  - JNCI

**A 55-YEAR-OLD WOMAN ON TAMOXIFEN FOR TWO YEARS FOR A 1.2-CM, ER-NEGATIVE, HER2-NEGATIVE TUMOR AND TROPHIC POSITIVE LYNCH MODS**
- What systemic therapy strategy would you recommend for the patient described above?
  - Do you think tamoxifen is having significant benefit in this case?
  - The patient has been on tamoxifen for 2 years.
  - The patient has bone and no prior systemic therapy.

**MEDICAL MEETING ATTENDANCE**
- How many of the meetings listed below have you attended in the past year?
  - Major scientific meetings (eg, ASCO, San Antonio)
  - Local CME meetings, grand rounds, etc
  - Specific scientific meetings (eg, ECOG, NSABP or ASCO annual meeting)
  - Trimester educational materials
  - Personalized medical monitoring and advisory boards

**SELECT PUBLICATIONS**

**PHYSICIAN SURVEY**
- How much time in a typical month do you spend doing the following? (in hours)
  - Searching for and reading oncology educational materials
  - Specific scientific meetings (eg, ECOG, NSABP or ASCO annual meeting)
  - Trimester educational materials
  - Personalized medical monitoring and advisory boards

**ASYMPTOMATIC 37-YEAR-WOMAN WITH ER-POSITIVE, HER2-NEGATIVE METASTASES TO BONE AND NO PRIOR SYSTEMIC THERAPIES**
- What systemic therapy strategy would you recommend for the patient described above?
  - Cytotoxic therapy
  - Novel agents
  - Hormonal therapy

**A 75-YEAR-OLD-WOMAN WITH AN ER-NEGATIVE, HER-POSITIVE, TUMOR AND SYMPTOMATIC BONE METASTASES**
- What systemic therapy strategy would you recommend for the patient described above?
  - Cytotoxic therapy
  - Novel agents
  - Hormonal therapy

**INTERVENTIONS OF NEW STANDARDS OF CARE INTO CLINICAL PRACTICE**
- Physicians have the challenge of tracking data as it evolves and deciding when the evidence surpasses the threshold at which the data should change our clinical practice. The difficulty in doing so will take up a long time has led a number of professional societies to establish guidelines to help clinicians establish guidelines. The National Comprehensive Cancer Network Breast Cancer Treatment Guidelines are an evidence-based consensus statement that provides clinical guidelines. The NCCN Comprehensive Cancer Network Breast Cancer Treatment Guidelines use an evidence-based consensus statement that provides clinical guidelines. The NCCN Comprehensive Cancer Network Breast Cancer Treatment Guidelines use an evidence-based consensus statement that provides clinical guidelines. The NCCN Comprehensive Cancer Network Breast Cancer Treatment Guidelines use an evidence-based consensus statement that provides clinical guidelines. The NCCN Comprehensive Cancer Network Breast Cancer Treatment Guidelines use an evidence-based consensus statement that provides clinical guidelines. The NCCN Comprehensive Cancer Network Breast Cancer Treatment Guidelines use an evidence-based consensus statement that provides clinical guidelines.

**CONCLUDING MEDICAL EDUCATION**
- “Traditional continuing medical education (CME) has been shown to be the actual practice of doctors and has not focused on providing the most useful information in the most efficient way.”
- “Physicians will learn best when learning is in the context of patient care, answers their questions, does not take too much time, and is directly applicable to their work.”
- “It makes more sense, then, to provide new information in a manner that can be rapidly assimilated and at a time when it can be used immediately. In other words, CME has to be integrated into the practice of medicine presented at the ‘point of care.’”

**REFERENCES**