# Optimal Neoadjuvant Endocrine Therapy

25TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM 11

**Chemotherapy is the most frequent form of neoadjuvant systemic therapy utilized in the United States; while in Europe, preoperative endocrine therapy has been used extensively in women with ER-positive cancers. 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 is somewhat longer with endocrine therapy. Tamoxifen and ovarian ablation/suppression were initially utilized as neoadjuvant therapy, and more recently, studies of third-generation aromatase inhibitors and the estrogen receptor downregulator, fulvestrant, have demonstrated significant antitumor activity. In addition to clinical endpoints, neoadjuvant therapy is also being investigated as an *in vivo* surrogate of tumor response to adjuvant therapy. A current large EORTC randomized trial is evaluating fulvestrant in the preoperative setting.**

### ErbB STATUS AND RESPONSE TO NEOADJUVANT ENDOCRINE THERAPY IN ER+ TUMORS

| Marker status | Letrozole | | Tamoxifen | | p value |
|---|---|---|---|---|---|
| | Responders | % | Responders | % | |
| ErbB-1/2 positive | 15/17 | 88 | 4/19 | 21 | .0004 |
| ErbB-1/2 negative | 55/101 | 54 | 42/100 | 42 | .0780 |

*DERIVED FROM:* Ellis MJ et al. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial.** *J Clin Oncol* 2001;19(18):3808-16.

### INDIRECT COMPARISON OF NEOADJUVANT RESPONSE RATES: CHEMOTHERAPY VERSUS HORMONAL THERAPY

| Study | # Evaluable Patients | Neoadjuvant Therapy | pCR | CR |
|---|---|---|---|---|
| NSABP B-27* | 718<br>1,492 | AC x 4 → T x 4<br>AC x 414% | 26%<br>86% | 91% |
| Aberdeen Trial** | <br><br><br>50<br>47 | CVAP x 4<br>responders<br>randomized<br>→ CVAP x 4<br>→ T x 4 | 15%<br><br><br>31%<br>23% | 66%<br><br><br>64%<br>85% |
| Milla-Santos et al.*** | 74 | Anastrozole | 23% | 83% |
| Ellis MJ et al.**** | 124<br>126 | Letrozole<br>Tamoxifen | —<br>— | 60%<br>41% |

Abbreviations: AC=doxorubicin/cyclophosphamide; T=docetaxel; CVAP=cyclophosphamide/vincristine/doxorubicin/prednisolone; pCR=pathologic complete response; CR=partial and complete clinical response

*NSABP. *Breast Cancer Res Treat* 2001;Abstract 5.

**Smith IC et al. *J Clin Oncol* 2002;20:1456-1466.

***Milla-Santos A et al. *Breast Cancer Res Treat* 2001;Abstract 302.

****Ellis MJ et al. *J Clin Oncol* 2001;19(18):3808-16.

### CLINICAL AND PATHOLOGICAL RESPONSE RATES WITH NEOADJUVANT ANASTROZOLE IN LOCALLY ADVANCED BREAST CANCER

| | n | % |
|---|---|---|
| **Clinical response rates** | | |
| Complete response | 19/74 | 26 |
| Partial response | 42/74 | 57 |
| Objective response | 61/74 | 83 |
| **Pathologic response rates** | | |
| Complete response | 14/74 | 23 |
| Partial response | 47/74 | 64 |

*DERIVED FROM:* Milla-Santos A et al. **Anastrozole as neoadjuvant therapy for hormone-dependent locally advanced breast cancer in postmenopausal patients.** *Breast Cancer Res Treat* 2001;Abstract 302.

### PHASE III RANDOMIZED NEOADJUVANT STUDY OF ICI 182780 IN WOMEN WITH STAGE I OR II PRIMARY BREAST CANCER — Open Protocol

Protocol IDs: BIG-EORTC-10963, EORTC-10963
Projected Accrual: 3,656 patients (1,828 per arm)

**Eligibility:** ER-positive or unknown, pre- or postmenopausal, stage I or II primary operable breast cancer

ARM 1: Fulvestrant IM on day 1
ARM 2: Placebo IM on day 1
→ surgery between days 8 and 29

Patients followed q 3 months x 2 years, q 6 months x 3 years, then annually thereafter.

**Objectives**

I. Determine the inhibitory effect of fulvestrant on the development of metastasis, as measured by disease-free survival and overall survival, in women with operable stage I or II primary breast cancer.
II. Determine toxicity of this regimen in these patients.

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Source: Physician Data Query, October 2002.

### SELECT PUBLICATIONS


Bundred N et al. **ICI 182,780 (Faslodex) an estrogen receptor downregulator reduces cell turnover index more effectively than tamoxifen.** *Proc ASCO* 2001; Abstract 1600.

Dixon JM et al. **The effects of neoadjuvant anastrozole (Arimidex) on tumor volume in postmenopausal women with breast cancer: A randomized, double-blind, single-center study.** *Clin Cancer Res* 2000;6(6):2229-35.

Ellis MJ et al. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial.** *J Clin Oncol.* 2001;19(18):3808-16.

Milla-Santos A et al. **Anastrozole (A) as neoadjuvant (NEO) therapy for hormone-dependent locally advanced breast cancer (LABC) in postmenopausal (PM) patients (pts).** *Breast Cancer Res Treat* 2001; Abstract 302.

NSABP. **The effect on primary tumor response of adding sequential Taxotere to Adriamycin and cyclophosphamide: Preliminary results from NSABP Protocol B-27.** *Breast Cancer Res Treat* 2001; Abstract 5.

Robertson JFR et al. **The pharmacokinetics of single dose Faslodex™ (ICI 182,780) in postmenopausal primary breast cancer — Relationship with estrogen receptor (ER) down regulation.** *Proc ASCO* 2000; Abstract 362.

Smith IC et al. **Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel.** *J Clin Oncol* 2002;20:1456-1466.


#### *RESEARCH BACKGROUND*

*We began studying neoadjuvant systemic therapy about 15 years ago. Our hope was that accurate models of drug action could be derived by taking sequential samples of tumors during treatment. You can obtain a very good idea of what's happening within the tumors by looking at biological markers rather than just clinical endpoints.*

*To determine if we can predict early on whether a patient is going to receive benefit from therapy, we obtain biopsies at 10 to 14 days after treatment and examine effects on proliferation, cell death and a variety of genetic markers. This becomes a potential method to individualize treatment.*

***—J Michael Dixon, MD, FRCS***

#### *NEOADJUVANT AROMATASE INHIBITORS*

*Neoadjuvant therapy allows you to determine in a couple of months whether or not an agent is going to have a favorable impact as opposed to giving a drug blindly for years after local therapy and hoping that it will help. There is a lot of data for chemotherapy, and similar data will emerge for endocrine therapy. The studies in ER-positive, postmenopausal women show a very high degree of antitumor activity in patients treated with aromatase inhibitors. In one trial, anastrozole showed dramatic tumor reductions — more than 80% of the patients had objective shrinkage of their disease, and close to two-thirds of the women were candidates for breast preservation after approximately four months of therapy.*

***—Aman Buzdar, MD***

#### *EFFICACY VERSUS CHEMOTHERAPY*

*Data from trials of neoadjuvant endocrine therapy are impressive and will have important implications for clinical practice. I was impressed by Ellis' study of preoperative letrozole, but the study using anastrozole convinced me to begin utilizing neoadjuvant endocrine therapy. Anastrozole produced the same pathologic complete response rate as AC followed by docetaxel in the NSABP B-27 trial. Previously, when I encountered patients with stage IIIA/B breast cancer, my immediate reaction was to consider which chemotherapeutic regimen to use. Neoadjuvant endocrine therapy appears to be as effective as chemotherapy, and it is much more benign.*

***—Melody A Cobleigh, MD***

#### *EORTC STUDY 10963: FULVESTRANT VERSUS PLACEBO*

*The preoperative EORTC trial evaluates one injection of fulvestrant after the diagnosis of breast cancer but before surgery. The idea is for the fulvestrant injection to cover the operative period as a potent antiestrogen that will lower estrogen receptor levels. We want to test the hypothesis of Bernie Fisher and others that adverse events related to metastases occur during the perioperative period. Hopefully, we can alter that with fulvestrant. The aim is to enroll more than 3,000 women into this study.*

***—Anthony Howell, FRCP***

*Fulvestrant is in a completely new class of antiestrogens. It differs from tamoxifen and other SERMs in that it increases degradation of the estrogen receptor, resulting in dramatic reductions in this protein. It also shuts down both AF1 and AF2 transcription functions, and it appears not to have any estrogenic activity. This agent may be one of the most important new developments in endocrine therapy.*

***—John F Robertson, MD, FRCS***