Neoadjuvant Endocrine Therapy

The most commonly utilized neoadjuvant therapy in the United States is chemotherapy. However, in Europe, preoperative endocrine therapy is used extensively in women with ER-positive breast cancer. A small, randomized neoadjuvant trial demonstrated that the efficacy of the aromatase inhibitors was comparable to chemotherapy in terms of objective and pathologic response rates, local recurrence and breast conservation rates. The IMPACT trial — comparing neoadjuvant anastrozole, tamoxifen or the combination — found that more women receiving anastrozole became eligible for breast-conserving surgery. An upcoming ACOSOG trial will compare the three aromatase inhibitors as neoadjuvant therapy, and an ongoing trial will compare two different doses of fulvestrant.

IMPACT TRIAL: ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION

Eligibility: Postmenopausal, ER-positive breast cancer

Efficacy data (N = 330)	A	T	C
Objective clinical response (caliper)	37%	36%	39%
Patients who became eligible for breast-conserving surgery* after three months of treatment	46%	22%	26%
Geometric mean reductions in Ki-67 after two weeks of treatment†	76%	60%	64%

A = anastrozole; T = tamoxifen; C = combination of A + T

* Of the 220 patients with surgeon's preferred surgery recorded at baseline, 56% were deemed to need a mastectomy.

† The geometric mean suppression of Ki-67 was significantly greater at both two and 12 weeks with anastrozole than with tamoxifen.

INFLUENCE OF HER2 OVEREXPRESSION ON CLINICAL RESPONSE

HER2-positive (n = 34)	Anastrozole	Tamoxifen	Anastrozole + tamoxifen	*p*-value
Clinical response	58%	22%	31%	0.18

SOURCES: Smith IE et al. *J Clin Oncol* 2005;23(22):5108-16. Dowsett M et al. *J Clin Oncol* 2005;23(11):2477-92.

RESPONSE TO NEOADJUVANT ENDOCRINE THERAPY WITH AROMATASE INHIBITORS VERSUS TAMOXIFEN IN POSTMENOPAUSAL WOMEN

Response rate	E[1]	T[1]	A[2]	T[2]
Clinical objective response (%)	76	40	70	44
Mammographic response (%)	64	37	56	36
Ultrasound response (%)	61	37	44	30
Breast-conserving surgery (%)	37	20	42	28

A = anastrozole; E = exemestane; T = tamoxifen

SOURCES: [1] Semiglazov V. et al. *Proc ASCO* 2005;Abstract 530; [2] Semiglazov V. et al. *Proc ASCO* 2003;Abstract 3538.

RANDOMIZED PHASE III STUDY COMPARING NEOADJUVANT EXEMESTANE, LETROZOLE AND ANASTROZOLE IN ER/PR-POSITIVE BREAST CANCER

Protocol ID: ACOSOG Z1031
Target Accrual: 375 (Pending)

Eligibility	Postmenopausal, Stage II/III operable breast cancer ≥2 cm, ER-positive
ARM 1	Exemestane 25 mg qd x 16wk → surgery
ARM 2	Letrozole 2.5 mg qd x 16wk → surgery
ARM 3	Anastrozole 1 mg qd x 16wk → surgery

SOURCE: NCI Physician Data Query, January 2006.

NEOADJUVANT TRIAL OF ENDOCRINE THERAPY VERSUS CHEMOTHERAPY IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE BREAST CANCER: EFFICACY DATA

Efficacy parameter	Chemo*	A	E	*p*-value
Clinical objective response	76.0%	75.6%	81.5%	NR
Mammographic objective response	61.9%	62.1%	71.0%	NR
Pathologic complete response	7.4%	3.3%	6.8%	NR
Breast conservation	23.9%	33.3%	34.0%	0.054
Local recurrence rate	3.2%	3.3%	3.4%	>0.5

A = anastrozole; E = exemestane; NR = not reported
* Chemotherapy = doxorubicin + paclitaxel

SOURCE: Semiglazov V et al. Presentation. ASCO 2004;Abstract 519.

RESPONSE RATES FOLLOWING NEOADJUVANT ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH LOCALLY ADVANCED BREAST CANCER

Clinical response (n = 74)	Response rate
Complete clinical response (cCR)	57%
Partial clinical response (cPR)	26%
Objective response (cCR + cPR)	83%
Pathologic response (n = 61)*	**Response rate**
Complete pathologic response (cPR)	23%
Partial pathologic response (pPR)	77%

* Pathologic response data limited to patients showing an objective response who then underwent a mastectomy.

SOURCE: Milla-Santos A et al. *Anticancer Res* 2004;24(2C):1315-8.

RANDOMIZED PHASE II NEOADJUVANT STUDY OF FULVESTRANT 500 MG VERSUS 250 MG IN POSTMENOPAUSAL WOMEN WITH ER-POSITIVE BREAST CANCER

Protocol IDs: 9238IL/0065, NCT00093002
Target Accrual: 160 (Open)

Eligibility	Postmenopausal; T2-4b, N0-3, M0, ER-positive invasive breast cancer
ARM 1	Fulvestrant 500 mg
ARM 2	Fulvestrant 250 mg

Study contact:
AstraZeneca Cancer Support Network
Ph: 866-992-9276

SOURCES: NCI Physician Data Query, January 2006; www.ClinicalTrials.gov, January 2006.

SELECT PUBLICATIONS

Dixon JM et al. **Surgical issues surrounding use of aromatase inhibitors.** *J Steroid Biochem Mol Biol* 2005;95:97-103.

Dixon JM et al. **Anastrozole demonstrates clinical and biological effectiveness in estrogen receptor-positive breast cancers, irrespective of the erbB2 status.** *Eur J Cancer* 2004;40(18):2742-7.

Dowsett M et al. **Biomarker changes during neoadjuvant anastrozole, tamoxifen, or the combination: Influence of hormonal status and HER-2 in breast cancer — A study from the IMPACT Trialists.** *J Clin Oncol* 2005;23(11):2477-92.

Dowsett M et al. **Ki67 after 2 weeks endocrine treatment predicts relapse-free survival (RFS) in the IMPACT trial.** Poster. San Antonio Breast Cancer Symposium 2005;Abstract 45.

Ellis MJ. **Neoadjuvant endocrine therapy for breast cancer: More questions than answers.** *J Clin Oncol* 2005;23(22):4842-4.

Ellis MJ et al. **Estrogen-independent cell proliferation occurs in the majority of estrogen receptor positive (ER+)/HER2 gene-amplified primary breast cancers: Evidence from a combined analysis of two independent neoadjuvant letrozole studies.** *Proc ASCO* 2005;Abstract 9538.

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Semiglazov V et al. **Anastrozole (A) vs tamoxifen (T) vs combine (A+T) as neoadjuvant endocrine therapy of postmenopausal breast cancer patients.** *Proc ASCO* 2003;Abstract 3538.

Semiglazov V et al. **Exemestane (E) vs tamoxifen (T) as neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer (T2N1-2, T3N0-1, T4N0M0).** *Proc ASCO* 2005;Abstract 530.

Semiglazov V et al. **The relative efficacy of neoadjuvant endocrine therapy vs chemotherapy in postmenopausal women with ER-positive breast cancer.** Presentation. ASCO 2004;Abstract 519.

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Smith et al. **Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: The immediate preoperative anastrozole, tamoxifen, or combined with tamoxifen (IMPACT) multicenter double-blind randomized trial.** *J Clin Oncol* 2005;23(22):5108-16.

ENDOCRINE THERAPY VERSUS CHEMOTHERAPY IN THE NEOADJUVANT SETTING

We're significantly more likely to be successful performing breast-conserving surgery after neoadjuvant endocrine therapy than chemotherapy. One reason for this is that 20 to 30 percent of patients who respond well to neoadjuvant chemotherapy are left with islands of tumor scattered throughout an area of the breast that corresponds to the size of the original tumor, whereas the pattern following neoadjuvant endocrine therapy is that the tumor shrinks and implodes.

The number of patients receiving neoadjuvant endocrine therapy has increased significantly, and many oncologists who have tried this approach and found that it worked have adopted this strategy. I believe more physicians should be utilizing this because it's effective at downstaging some large tumors.

When we treat only patients with ER-rich tumors, meaning Allred scores 6, 7 and 8, the number of patients who progress or actually fail to respond is very small. We have also learned that we can treat patients longer than three or four months with neoadjuvant therapy and see continued response. We've treated patients for up to a year and found that the number of patients with a complete response continues to rise the longer we treat them. If the tumor is shrinking but still not small enough for breast-conserving surgery at three or four months, continuing therapy will give added benefit, and eventually, most of these tumors will become small enough for breast conservation.

— J Michael Dixon, MD.* Breast Cancer Update *2005 (5)

I believe it was a mistake to evaluate chemotherapy rather than endocrine therapy in some of the earlier animal studies. The perioperative phase is critical, and while no evidence indicates that preoperative chemotherapy improves survival, that's nonspecific treatment, and it doesn't mean that neoadjuvant endocrine therapies will fail. I view neoadjuvant endocrine treatment as a biological response modifier, and I believe using the aromatase inhibitors up front might have a greater impact on long-term outcome.

— Michael Baum, MD, ChM.* Breast Cancer Update *2005 (1)

SURROGATE OUTCOMES OF NEOADJUVANT ENDOCRINE THERAPY

A decision regarding neoadjuvant chemotherapy compared with neoadjuvant endocrine therapy would be made easier if there were predictive tests that could select a subpopulation of tumors whose response to the neoadjuvant aromatase inhibitor is in a range of 80 to 90 percent. If such a test also identified a tumor subtype for which chemotherapy did not improve outcomes, then we would have made real progress toward making neoadjuvant endocrine therapy a new standard of care.

— Matthew J Ellis, MB, PhD.* J Clin Oncol *2005;23(22):4842-4.

A short-term biomarker that can predict long-term outcome on a particular therapy for early breast cancer could speed drug development and possibly help select individualised patient treatment. We showed in the IMPACT trial (SABCS 2005) that reduction in Ki67 after 2 weeks was significantly greater in patients treated with anastrozole (A) than with tamoxifen (T) or the combination (C), a result parallel to the greater RFS with A in the ATAC adjuvant trial although Ki67 change was only poorly associated with clinical response. We therefore assessed whether 2-week Ki67 was associated with RFS in this trial… .

On univariate analysis 2-week Ki67 was significantly associated with RFS (hazard ratio 2.13; 95% CI: 1.45 – 3.13, $p<0.001$) for log(2-week Ki67)… . Despite the small number of relapses so far, 2-week Ki67 was a significant predictor of RFS. This provides important further support for Ki67 being a marker of treatment benefit after short-term pre-surgical therapy. Additionally, it suggests that analysis of biomarker profiles may more accurately predict long-term outcome if conducted after short-term in vivo exposure to the treatment of choice.

— Mitchell Dowsett, PhD et al. Poster. San Antonio Breast Cancer Symposium 2005;Abstract 45.