Trials of Hormonal Therapy in Metastatic Disease

The number of hormonal therapy options for postmenopausal women with estrogen receptor-positive metastatic breast cancer expanded with the introduction of the aromatase inhibitors and fulvestrant. Ongoing clinical trials — SoFEA and EFECT — are evaluating endocrine strategies in women whose disease has progressed on the usual first-line therapies (nonsteroidal aromatase inhibitors). Based on the theoretical advantage of utilizing fulvestrant in a lower-estrogen environment, the SoFEA trial and SWOG-S0226 are both investigating the combination of fulvestrant with an aromatase inhibitor. Biologic agents, including trastuzumab, and tyrosine kinase inhibitors are also being assessed in combination with various endocrine interventions.

ONGOING CLINICAL TRIALS OF NOVEL COMBINATIONS OF HORMONAL THERAPIES AND BIOLOGIC AGENTS

Protocol ID	Phase	Trial design
ROCHE-B016216	II/III	**Anastrozole with or without trastuzumab** in postmenopausal women with HER2-overexpressing metastatic breast cancer
GSK-EGF30008	III	**Letrozole with or without lapatinib** in postmenopausal women with Stage IIIB, IIIC or IV breast cancer
3066A1-303	III	**Letrozole with or without temsirolimus** in postmenopausal women with locally advanced or metastatic breast cancer
Biomed 777-CLP-30	III	**Atamestane + toremifene versus letrozole** in postmenopausal women with advanced breast cancer
WSU-C-2876	II	**Lapatinib + tamoxifen** in women with tamoxifen-resistant, locally advanced or metastatic breast cancer
UCLA-0502057-01	II	**Fulvestrant + trastuzumab versus fulvestrant versus trastuzumab** as first-line treatment in postmenopausal women with HER2-overexpressing Stage IV breast cancer
UCLA-0403073-01	II	**Anastrozole with or without lonafarnib** in postmenopausal women with Stage IIIB, IIIC or IV breast cancer
ZD1839US/0713	II	**Anastrozole with or without gefitinib** in postmenopausal women with metastatic breast cancer
NYWCCC-NCI-6205	II	**Fulvestrant + tipifarnib** as second-line therapy in postmenopausal women with inoperable, locally advanced or metastatic breast cancer with progressive disease after prior first-line endocrine therapy
ZD1839IL/0225	II	**Tamoxifen with or without gefitinib** in women with metastatic breast cancer
ECOG-4101	II	**Anastrozole + gefitinib versus fulvestrant + gefitinib** in postmenopausal women with recurrent or metastatic breast cancer
EORTC-10021	II	**Anastrozole with or without gefitinib** in postmenopausal women with locally recurrent or metastatic breast cancer

SOURCE: NCI Physician Data Query, December 2005.

PHASE III STUDY OF SINGLE-AGENT FULVESTRANT

Protocol IDs: D6997C00002, NCT00099437
Target Accrual: 720 (Open)

Eligibility	Postmenopausal Estrogen receptor-positive advanced breast cancer Failure on a previous endocrine treatment
ARM 1	Fulvestrant 500 mg
ARM 2	Fulvestrant 250 mg

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

SOURCE: NCI Physician Data Query, December 2005.

PHASE III STUDY OF FULVESTRANT WITH OR WITHOUT ANASTROZOLE VERSUS EXEMESTANE

Protocol IDs: ICR-CTSU-SoFEA, NCT00253422
Target Accrual: 750 (Open)

Eligibility	Postmenopausal Estrogen and/or progesterone receptor-positive Progression on a nonsteroidal aromatase inhibitor
ARM 1	Fulvestrant (LD) + anastrozole
ARM 2	Fulvestrant (LD)
ARM 3	Exemestane

LD = loading dose (500 mg at day 0, 250 mg at days 14 and 28, then 250 mg qm)

Study chair:
Dr Stephen Johnston, Royal Marsden Hospital,
NHS Trust and Institute of Cancer Research, Ph: 44 (0) 20 7808 2745

SOURCES: Institute of Cancer Research, www.icr.ac.uk/ctsu, December 2005; Gradishar WJ, Sahmoud T. *Clin Breast Cancer* 2005;6(Suppl 1):23-9.

PHASE III STUDY OF ANASTROZOLE WITH OR WITHOUT FULVESTRANT AS FIRST-LINE THERAPY

Protocol IDs: SWOG-S0226, NCT00075764, CAN-NCIC-SWOG-S0226
Target Accrual: 690 (Open)

Eligibility	Postmenopausal Estrogen and/or progesterone receptor-positive
ARM 1	Anastrozole
ARM 2	Anastrozole + fulvestrant (LD)

LD = loading dose (500 mg at day 0, 250 mg at days 14 and 28, then 250 mg qm)

Study contacts:
Rita Mehta, MD, Southwest Oncology Group, Ph: 714-456-5153
Theodore Vandenberg, MD, NCIC-Clinical Trials Group, Ph: 519-685-8640

SOURCES: NCI Physician Data Query, December 2005; Gradishar WJ, Sahmoud T. *Clin Breast Cancer* 2005;6(Suppl 1):23-9.

PHASE III STUDY COMPARING FULVESTRANT AND EXEMESTANE

Protocol IDs: 9238IL/0048, NCT00065325, EFECT
Target Accrual: 660 (Open)

Eligibility	Postmenopausal women Hormone receptor-positive Progression on a nonsteroidal aromatase inhibitor
ARM 1	Fulvestrant (LD)
ARM 2	Exemestane

LD = loading dose (500 mg at day 0, 250 mg at days 14 and 28, then 250 mg qm)

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

SOURCES: NCI Physician Data Query, December 2005; Gradishar WJ, Sahmoud T. *Clin Breast Cancer* 2005;6(Suppl 1):23-9.

SELECT PUBLICATIONS

Burris HA 3rd. **Dual kinase inhibition in the treatment of breast cancer: Initial experience with the EGFR/ErbB-2 inhibitor lapatinib.** *Oncologist* 2004;9(Suppl 3):10-5.

Ellis M. **Overcoming endocrine therapy resistance by signal transduction inhibition.** *Oncologist* 2004;9(Suppl 3):20-6.

Gradishar WJ, Sahmoud T. **Current and future perspectives on fulvestrant.** *Clin Breast Cancer* 2005;6(Suppl 1):23-9.

Howell SJ et al. **The use of selective estrogen receptor modulators and selective estrogen receptor down-regulators in breast cancer.** *Best Pract Res Clin Endocrinol Metab* 2004;18(1):47-66.

Johnston S. **Fulvestrant and the sequential endocrine cascade for advanced breast cancer.** *Br J Cancer* 2004;90(Suppl 1):15-8.

McKeage K et al. **Fulvestrant: A review of its use in hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.** *Drugs* 2004;64(6):633-48.

Perey L et al. **Fulvestrant (Faslodex) as hormonal treatment in postmenopausal patients with advanced breast cancer (ABC) progressing after treatment with tamoxifen and aromatase inhibitors: Update of a phase II SAKK trial.** San Antonio Breast Cancer Symposium 2004;Abstract 6048.

EFECT TRIAL

EFECT is an American and European study that randomly assigns patients who have had disease progression on therapy with a nonsteroidal aromatase inhibitor to fulvestrant or exemestane. Our own study, SoFEA, is slightly different from EFECT because it is based on the observation that the addition of small amounts of estrogen to cells that have been estrogen deprived for a long time reduces the effectiveness of fulvestrant. That scenario equates to the withdrawal of a nonsteroidal aromatase inhibitor and the addition of fulvestrant. Hence, the third arm of our trial includes a nonsteroidal aromatase inhibitor and fulvestrant. I predict fulvestrant alone will probably be better than exemestane, and fulvestrant plus anastrozole will be better than fulvestrant alone.

— *Mitchell Dowsett, PhD.* Breast Cancer Update *2004 (6)*

OPTIMAL SEQUENCING OF AGENTS IN POSTMENOPAUSAL PATIENTS

If you evaluate most of the available data with endocrine agents in the metastatic setting — tamoxifen, steroidal or nonsteroidal aromatase inhibitors or fulvestrant — the question that comes up is whether one sequence enhances patient outcome more than another. This becomes important because if you can demonstrate that one sequence enhances the time to disease progression, it may be built on over time so that overall outcome is improved.

In theory, simply having an improvement in recurrence or progression of metastatic disease impacts quality of life. Patients now typically receive a nonsteroidal aromatase inhibitor — anastrozole or letrozole — as the first treatment. The question then becomes: If patients progress on one of those agents, what would be the next best therapy? Should it be the steroidal aromatase inhibitor exemestane, or should it be fulvestrant? Indirect data evaluating the sequence of a nonsteroidal aromatase inhibitor to fulvestrant suggest that 25 to 30 percent of patients may benefit with that approach.

An important issue is whether fulvestrant 250 mg is optimal. Some of the data suggest that the dose is really on the low end of the curve where you might expect the optimal response rate. Some strategies have evaluated quickly increasing serum levels of fulvestrant, including administering loading doses of 500 mg and within two weeks administering another 250 mg and then proceeding to the monthly schedule. Those strategies are based on mathematical modeling that has shown an ability to achieve steady-state levels much more quickly and consequently achieve a biologically relevant dose of drug circulating much faster.

— *William J Gradishar, MD.* Breast Cancer Update *2005 (4)*

Assuming an aromatase inhibitor and fulvestrant are equivalent in efficacy, the choice of which agent to use may come down to patient preference. Some of my patients are perfectly happy with a monthly injection, while others prefer an oral agent. For many patients, fulvestrant is financially favorable because of our arcane reimbursement system. We know that responses can be seen with either sequence — an aromatase inhibitor followed by fulvestrant or the opposite — but I believe it's important that we determine which is superior.

I believe the trials of fulvestrant underestimate the efficacy of this agent. The dosing schedule used was probably too low, because by the time steady state was reached, many patients were off study, presumably because of progression. In my group, we administer loading doses of 500 mg of fulvestrant followed by 500 mg two weeks later and then 250 mg monthly.

The pharmacokinetics of fulvestrant suggest a loading dose would be beneficial, so it concerns me that the comparison of fulvestrant to anastrozole in a tamoxifen-resistant population might not have revealed the true efficacy of fulvestrant. It showed fulvestrant to be at least as effective as anastrozole, but I expected it to be superior. We may need to repeat some of these studies with a more appropriate dosing schedule.

— *Gabriel N Hortobagyi, MD.* Breast Cancer Update *2004 (9)*