Trials of Hormonal Therapy in Metastatic Disease

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The recent emergence of the estrogen receptor downregulator fulvestrant and steroidal and nonsteroidal aromatase inhibitors have complicated the treatment 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 fulvestrant, 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

Study	Trial design	Fulvestrant dosing/scheduling	Targeted accrual
SAKK	Phase II trial of monthly fulvestrant in postmenopausal women after progression on tamoxifen and a nonsteroidal aromatase inhibitor	250 mg monthly	93
EFECT	Double-blind, placebo-controlled Phase III trial of fulvestrant vs exemestane in postmenopausal women after progression on a nonsteroidal aromatase inhibitor	500 mg day 0, 250 mg days 14, 28 and then monthly	660
SoFEA	Phase III trial of fulvestrant vs fulvestrant + anastrozole vs exemestane in postmenopausal women with ER- and/or PR-positive breast cancer who progressed on anastrozole or letrozole	250 mg monthly	750
SWOG S0226	Phase III randomized study of anastrozole with or without fulvestrant as first-line therapy in postmenopausal women with ER- and/or PR-positive metastatic breast cancer.	250 mg monthly	690
FACT	Phase III trial of anastrozole + fulvestrant vs anastrozole in postmenopausal women with ER- and/or PR-positive metastatic breast cancer or premenopausal women on goserelin	500 mg day 0, 250 mg days 14, 28 and then monthly	558
ECOG 4101	Phase II trial of fulvestrant + gefitinib vs anastrozole + gefitinib in postmenopausal women with ER- and/or PR-positive metastatic breast cancer	250 mg monthly	148

SOURCES: Sahmoud T. **Clinical trial designs for further development of fulvestrant (Faslodex®).** Poster. Lynn Sage Breast Cancer Symposium, September 2003. NCI Physician Data Query, October 2004.

PHASE II/III RANDOMIZED STUDY OF ANASTROZOLE WITH OR WITHOUT TRASTUZUMAB IN POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE HER2-OVEREXPRESSING METASTATIC BREAST CANCER

Protocol IDs: ROCHE-BO16216, CWRU-030118, GENENTECH-H2223g, ROCHE-1100, ROCHE-BO16216E
Target Accrual: 202 patients (Open)

Eligibility	Postmenopausal women with ER- and/or PR-positive, HER2-positive (IHC 3+ or FISH-positive) metastatic breast cancer
ARM 1	Anastrozole qd + trastuzumab qwk
ARM 2	Anastrozole qd

In both arms, treatment continues for at least two years in the absence of disease progression or unacceptable toxicity. During the extension phase of this study, patients in either arm who do not develop disease progression may continue receiving treatment in the arm to which they were originally randomly assigned. Patients in Arm 2 who develop disease progression may receive treatment in Arm 1 during the extension phase in the absence of further disease progression.

Study Contact:
Bernd Langer, PhD, Protocol Chair
Hoffman La Roche Inc
Tel: 41-61-688-0638

SOURCE: NCI Physician Data Query, October 2004.

PHASE II TRIAL EVALUATING A TYROSINE KINASE INHIBITOR IN COMBINATION WITH AN AROMATASE INHIBITOR

Protocol ID: EORTC-10021, IDBBC-10021
Target Accrual: 108 (Open)

Eligibility	Postmenopausal, ER/PR-positive, metastatic or locally recurrent breast cancer
ARM 1	Anastrozole + gefitinib
ARM 2	Anastrozole + placebo

Study Contact:
Emiel Rutgers, MD, PhD, FRCS
European Organization for Research and Treatment of Cancer
Tel: 31-20-512-2551

SOURCE: NCI Physician Data Query, October 2004.

PHASE III RANDOMIZED STUDY OF LETROZOLE WITH OR WITHOUT LAPATINIB IN POSTMENOPAUSAL WOMEN WITH STAGE IIIB OR IV BREAST CANCER

Protocol IDs: GSK-EGF30008, UCLA-0311034-01
Target Accrual: 760 (Open)

Eligibility	Postmenopausal women Stage IIIb or IV, ER- and/or PR-positive breast cancer No prior endocrine therapy for advanced disease
ARM 1	Letrozole + lapatinib
ARM 2	Letrozole + placebo

Study Contact:
Trial Lead Organizations
Acurian Pre-Screening Evaluation Contact
GlaxoSmithKline
Tel: 800-563-6537

SOURCE: NCI Physician Data Query, October 2004.

FULVESTRANT AND EXEMESTANE IN POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR-POSITIVE ADVANCED BREAST CANCER

Protocol IDs: 9238IL/0048, NCT00065325
Target Accrual: 486 (Open)

Eligibility	Postmenopausal women Hormone receptor-positive breast cancer that has progressed on a prior aromatase inhibitor other than exemestane
ARM 1	Fulvestrant
ARM 2	Exemestane

Study Contact:
AstraZeneca Cancer Support Network
AstraZeneca Pharmaceuticals LP
Tel: 866-992-9276

SOURCE: NCI Physician Data Query, October 2004.

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;(Suppl 3):10-5.

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

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.

Kurebayashi J. **Endocrine-resistant breast cancer: Underlying mechanisms and strategies for overcoming resistance.** *Breast Cancer* 2003;10(2):112-9.

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.

Schiff R et al. **Breast cancer endocrine resistance: How growth factor signaling and estrogen receptor coregulators modulate response.** *Clin Cancer Res* 2003;9(1 Pt 2):447S-54S.

TRIALS COMBINING FULVESTRANT WITH AN AROMATASE INHIBITOR

A number of studies are beginning to evaluate combining fulvestrant with aromatase inhibitors. SWOG-S0226 will compare anastrozole to anastrozole plus fulvestrant as first-line therapy in postmenopausal women. In the UK, the SoFEA study will enroll patients who have had disease progression while on an aromatase inhibitor. Those patients will be randomly assigned to fulvestrant, exemestane, or fulvestrant plus anastrozole.

The rationale behind that trial is the data suggesting that estrogen-deprived MCF-7 cells become supersensitive to lower doses of estradiol and, hence, are stimulated again. The third arm of that trial will keep the estradiol levels low and then come in with fulvestrant to determine if that strategy is different from fulvestrant alone without estradiol suppression.

— John F R Robertson, MD

It remains unclear where fulvestrant should be utilized in the sequence of hormonal therapies for metastatic disease. Several new North American trials and the SoFEA trial should help to clarify its role in our armamentarium of hormonal therapies. The SoFEA trial will provide an indication of whether fulvestrant is better than exemestane as second-line therapy and also whether it's necessary to suppress the levels of estrogen. It's possible that by discontinuing the aromatase inhibitor, sufficient estrogen will be produced to circumvent the effects of fulvestrant.

— Anthony Howell, MD

EFECT is an American and European study that will randomly assign patients who have failed 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.

The SoFEA trial will randomly assign 750 patients who have failed therapy with a nonsteroidal aromatase inhibitor to exemestane, fulvestrant alone or fulvestrant plus anastrozole. I predict fulvestrant alone will probably be better than exemestane, and fulvestrant plus anastrozole will be better than fulvestrant alone.

— Mitchell Dowsett, PhD

TRIALS COMBINING TRASTUZUMAB WITH HORMONAL THERAPY

Although controversial, some physicians use the combination of trastuzumab and hormonal therapy as first-line treatment off protocol for women with HER2-positive, hormone receptor-positive metastatic disease. I don't use that strategy. Hormonal therapy is the mainstay of treatment and can produce prolonged responses. It's important to know whether a patient has hormone-sensitive disease. I would not cloud the issue by adding trastuzumab until the ongoing clinical trials indicate a definite advantage for the combination compared to the sequential approach.

A worldwide trial, which has been accruing very slowly, is comparing anastrozole with or without trastuzumab. Approximately 20 percent of tumors are FISH-positive, and of those, perhaps 40 percent are ER-positive — that is less than 10 percent of the overall breast cancer population. The eligibility criteria carve away another few percent. Hence, about seven percent of the overall patient population could potentially be eligible for such trials. It's not surprising that accrual is difficult for these types of trials.

— Charles L Vogel, MD