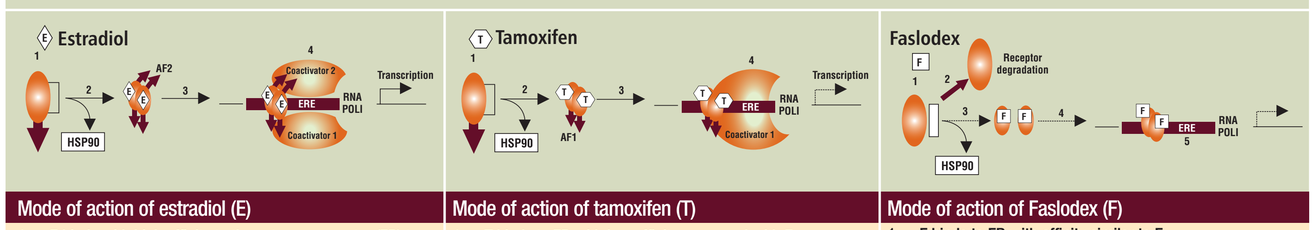
# Fulvestrant: An Endocrine Agent with a Unique Mechanism of Action

25TH ANNUAL San Antonio Breast Cancer Symposium 12

**Many phase III randomized clinical trials have demonstrated the efficacy of selective estrogen receptor modulators (SERMs) in women with increased risk for breast cancer, DCIS and invasive disease in the adjuvant and metastatic setting. Until recently, antiestrogens had minimal impact on patients progressing on tamoxifen, but fulvestrant, a novel agent with a mechanism distinct from SERMs, has now demonstrated efficacy at least equivalent to and perhaps greater than anastrozole in patients with tamoxifen-resistant tumors. Fulvestrant is administered as an intramuscular injection and is well tolerated. The availability of this novel agent raises the issue of the optimal sequence of endocrine agents in the management of postmenopausal women with metastatic breast cancer, and specifically the sequence of fulvestrant, tamoxifen and aromatase inhibitors.**

## MODE OF ACTION




**Mode of action of estradiol (E)**

1. E binds with high affinity to the estrogen receptor (ER) to form an E-ER complex.
2. The E-ER complex pairs with another E-ER complex (dimerizes) and localizes in the cell nucleus. The two transcription activation functions of ER, called AF1 and AF2, are both active.
3. The E-ER dimer binds to estrogen-sensitive genes at the estrogen response element (ERE).
4. The dimer activates transcription of the estrogen-sensitive gene. (AF1 and AF2 interact with coactivators to stimulate the transcription enzyme RNA polymerase II [RNA POL II].)

**Mode of action of tamoxifen (T)**

1. T binds to ER with low affinity compared with E.
2. The T-ER complex dimerizes and localizes in the cell nucleus, and AF1 (but not AF2) is active.
3. The T-ER dimer binds to the gene DNA at the ERE.
4. Transcription of the estrogen-sensitive gene is lessened because AF2 is inactive and coactivator binding is likewise attenuated. AF1 activity results in the partial agonist activity of T.

**Mode of action of Faslodex (F)**

1. F binds to ER with affinity similar to E.
2. F triggers rapid degradation of ER.
3. The F-ER complex results in reduced rate of dimerization and nuclear localization.
4. There is reduced binding of F-ER to ERE on the gene resulting in blocked transcription.

Reproduced with permission. Howell et al. *Cancer* 2000;89:817-825.

## TRIALS 20/21: PHASE III RANDOMIZED STUDY OF ICI 182780 (FULVESTRANT) VERSUS ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER — Closed Protocol

| | |
|---|---|
| **Eligibility** | **Postmenopausal women with metastatic breast cancer progressing on prior endocrine therapy** |
| **ARM 1** | **Fulvestrant 250 mg IM + oral placebo*** |
| **ARM 2** | **Anastrozole 1 mg PO + sham injection*** |

**A third arm in Trial 21, fulvestrant 125 mg, was closed after planned analysis demonstrated that predefined efficacy criteria were not met at that dose. *Only the North American trial (21) had placebo controls.**

## TRIALS 20 AND 21: STUDY DESIGN DIFFERENCES

| | Trial 20 (European) | Trial 21 (North American) |
|---|---|---|
| Receptor unknown | Allowed | Not allowed |
| Double-blind | No | Yes |
| Multi-institutional | Europe, Australia, South Africa | North America |
| Multiple dose levels | No | Yes, initially |
| Dosing | Single injection | Divided injections |
| Evaluations - fulvestrant | Monthly | Monthly |
| Evaluations - anastrozole | Every three months | Monthly |

Adapted from a presentation by Robert W Carlson, MD
Chemotherapy Foundation Meeting, November 2001

## EFFICACY OF FULVESTRANT COMPARED TO ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER PROGRESSING ON PRIOR ENDOCRINE THERAPY

| | Combined Analysis* | | European Trial (0020) | | North American Trial (0021) | |
|---|---|---|---|---|---|---|
| | Fulvestrant (n=428) | Anastrozole (n=423) | Fulvestrant (n=222) | Anastrozole (n=229) | Fulvestrant (n=206) | Anastrozole (n=194) |
| Disease Progression | | | 82.4% | 83.4% | 83.5% | 86.1% |
| Median Time to Progression | 5.4 months | 4.1 months | 5.5 months | 5.1 months | 5.4 months | 3.4 months |
| Treatment Failures | | | 84.7% | 85.6% | 79.6% | 84% |
| Objective Response | 19.6% | 17.3% | 20.7% | 15.7% | 17.5% | 17.5% |
| Clinical Benefit (CR + PR + SD ≥ 24 wks) | 43.7% | 41.1% | 99 (44.6%) | 103 (45.0%) | 87 (42.2%) | 70 (36.1%) |
| Median Duration of Response in Those Responding | 16.7 months | 13.6 months | 15.0 months | 14.5 months | 19.0 months | 10.8 months |

*** In addition to reporting median duration of response (DOR) in those responding, a newly developed statistical analysis of DOR was performed, defined for responders as the time from onset of response to disease progression and for non-responders as zero. In this analysis, DOR was significantly greater (ratio of average response durations = 1.30; 95% CI 1.13 to 1.50; p=0.0003) for fulvestrant versus anastrozole.**

Derived from Osborne CK et al. *J Clin Oncol* 2002;20:3386-95.
Howell A et al. *J Clin Oncol* 2002;20:3396-403.
*Parker LM et al. *Proc ASCO* 2002;Abstract 160.

## SELECT PUBLICATIONS


Bundred N, Howell A. **Fulvestrant (Faslodex): Current status in the therapy of breast cancer.** *Expert Rev Anticancer Ther* 2002;2 (2):151-160.

Carlson RW. **Sequencing of endocrine therapies in breast cancer — integration of recent data.** *Breast Cancer Res Treat* 2002;75 Suppl 1:S27-32; discussion S33-35.

Curran M, Wiseman L. **Fulvestrant.** *Drugs* 2001;61:807-13; discussion 814.

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20:3396-3403.

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20:3386-3395.

Parker LM. **Sequencing of hormonal therapy in postmenopausal women with metastatic breast cancer.** *Clin Ther* 2002;24 Suppl C:C43-57.

Wardley AM. **Fulvestrant: A review of its development, preclinical and clinical data.** *Int J Clin Pract* 2002;56(4):305-309.


### *MECHANISM OF ACTION*

*Tamoxifen and fulvestrant interact differently with the estrogen receptor. Tamoxifen causes receptor dimerization, binding to the estrogen response element and activation of AF-1 but inactivation of AF-2. This causes partial agonistic and partial antagonistic activity, depending on the cell and the gene promoter contact. In contrast, fulvestrant inactivates both AF-1 and AF-2, completely switching off the receptor, and it increases the turnover of the receptors themselves.*

***—Anthony Howell, FRCP***

### *SECOND-LINE METASTATIC TRIALS OF FULVESTRANT VERSUS ANASTROZOLE*

*Similar response rates were found for fulvestrant and anastrozole, but in the North American trial, the response duration was about twice as long for fulvestrant compared to anastrozole.*

*The European and the North American trials are different in their design. The North American trial — which I think has a better design — was a double-blind study. Patients randomized to anastrozole also received placebo injections. Since the all patients were evaluated once a month, there was consistency with regards to patient evaluations.*

*The European trial was not double-blinded. The patients on anastrozole were seen every three months, while the patients on fulvestrant were seen every month. This design had potential bias in terms of identifying patients at the time of progression. Patients in the fulvestrant group of the European trial were seen more often, and conceivably, progression could be identified earlier in those patients than in the patients randomized to anastrozole.*

*Both anastrozole and fulvestrant were well tolerated. The monthly fulvestrant injection did not cause much pain or discomfort. Since fulvestrant does not appear to cross the blood-brain barrier, theoretically, it may not cause hot flashes. The incidence of hot flashes and other side effects with both fulvestrant and anastrozole was very low.*

*Little is known about the effect of fulvestrant on bone and lipids. This pure antiestrogen could theoretically be deleterious. This is not as important in patients with metastatic breast cancer as it will be if this agent moves into adjuvant therapy and prevention.*

***—C Kent Osborne, MD***

### *FULVESTRANT AND THE SEQUENCING OF ENDOCRINE THERAPY IN POSTMENOPAUSAL WOMEN*

*Fulvestrant is equivalent as second-line therapy to our best drugs — the aromatase inhibitors. We now have a choice between treatments that are clearly equivalent. In postmenopausal women, I believe first-line therapy for advanced disease — even in those who have not had adjuvant tamoxifen — is an aromatase inhibitor. I see fulvestrant being used after the aromatase inhibitors.*

***—Anthony Howell, FRCP***

*Currently, this agent is used after aromatase inhibitors, but there are data demonstrating equal or perhaps greater efficacy than aromatase inhibitors for the management of metastatic breast cancer. The different route of administration for fulvestrant is a good thing for some patients, because they won't have to remember to take a tablet on a daily basis. On the other hand, they will have to come to the clinic once a month to receive an intramuscular injection.*

***—Edith Perez, MD***