

Fulvestrant: An Endocrine Agent with a Unique Mechanism of Action



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.

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

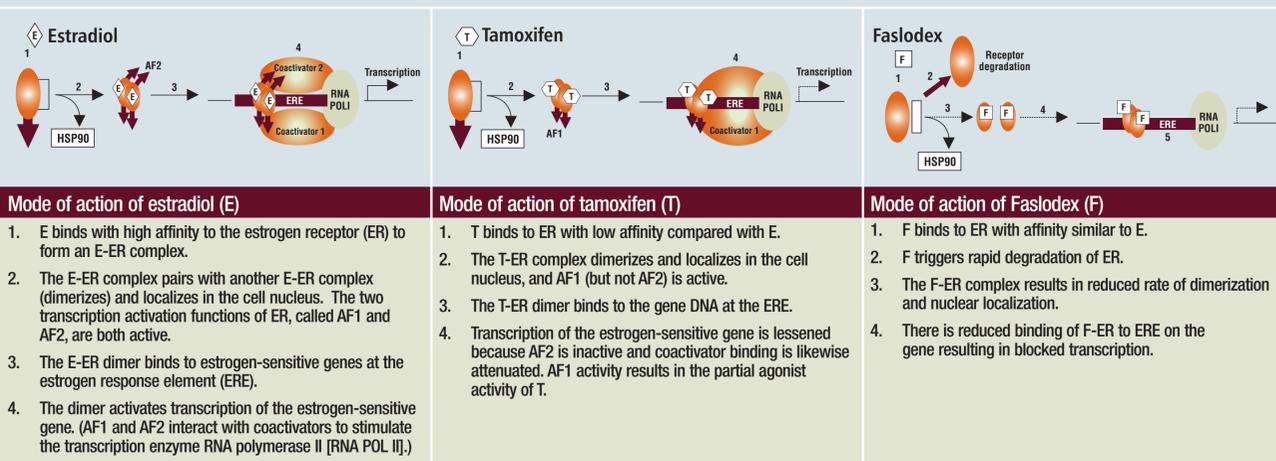
EVOLUTION AND ROLE OF FULVESTRANT

“Fulvestrant (‘Faslodex’), a novel estrogen receptor (ER) antagonist with no known agonist effects that downregulates the ER, is the first in a new class of antiestrogen and is in clinical development for the treatment of advanced or metastatic breast cancer. Fulvestrant does not appear to be cross-resistant with other endocrine therapies making this new antiestrogen an appropriate option for further endocrine treatment in patients who have responded to, but eventually progressed on, previous endocrine therapy...

...Since clinical evaluation of fulvestrant began, a little over a decade ago, evidence has mounted to support this new type of antiestrogen as an effective and well-tolerated treatment for women with advanced breast cancer. The data now appears convincing that fulvestrant is at least as effective as anastrozole in patients with tamoxifen-resistant breast cancer. As many tumors retain hormone sensitivity after disease progression, it is anticipated that in some patients the use of sequential hormone therapies with different mechanisms of action may delay the need for cytotoxic chemotherapy. Fulvestrant is therefore a valuable addition to the current choice of endocrine therapies available for the treatment of advanced breast cancer.”

—Jones SE. *Breast Cancer Res Treat* 2002;75: S19–S21.

MODE OF ACTION



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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

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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.

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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.

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