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Pharmacology of Letrozole

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Presentation

- Mechanism of action of aromatase inhibitors
- Intratumoral aromatase
- Results published after submission of Femara® NDA in 1996

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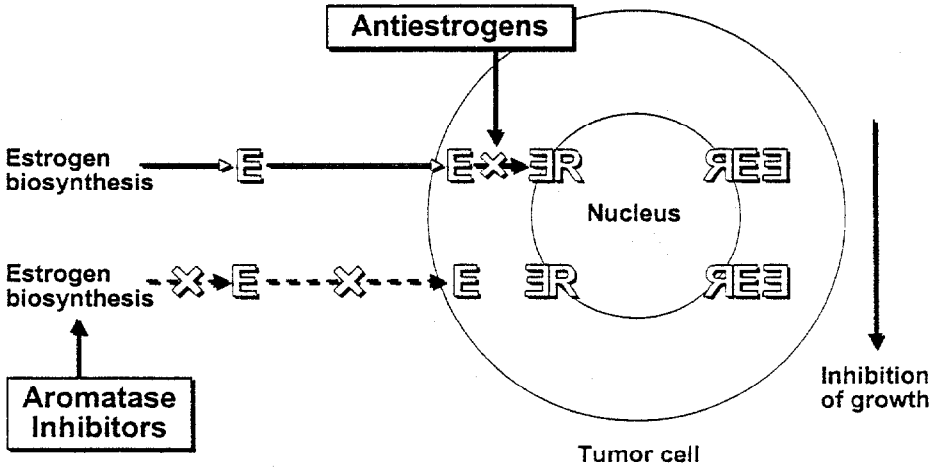
Inhibition of Estrogen-Dependent Growth



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Pharmacologic Profile

Inhibition of aromatase In vitro and in vivo	Selectivity of aromatase inhibition In vitro and in vivo	Efficacy of estrogen deprivation Endocrine and antitumor
In vivo aromatization in humans	Selectivity of aromatase inhibition in humans	Endocrine efficacy in humans

Aromatase inhibition ≡ Estrogen deprivation

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Letrozole

- A highly potent aromatase inhibitor in vitro and in vivo
- Very selective in its inhibition of aromatase
- As effective as oophorectomy in inducing estrogen deprivation
- Shows maximal antitumor efficacy in the DMBA and NMU models
- 1 to 2 orders of magnitude more efficacious than anastrozole in endocrine and antitumor efficacy
- Prevents the appearance of spontaneous mammary tumors in rats

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Commercially Available Aromatase Inhibitors

Aminoglutethimide	Orimeten®	Novartis
Fadrozole	Afema®	Novartis
Letrozole	Femara®	Novartis
Anastrozole	Arimidex®	AstraZeneca
Formestane	Lentaron®	Novartis
Exemestane	Aromasin®	Pharmacia & Upjohn

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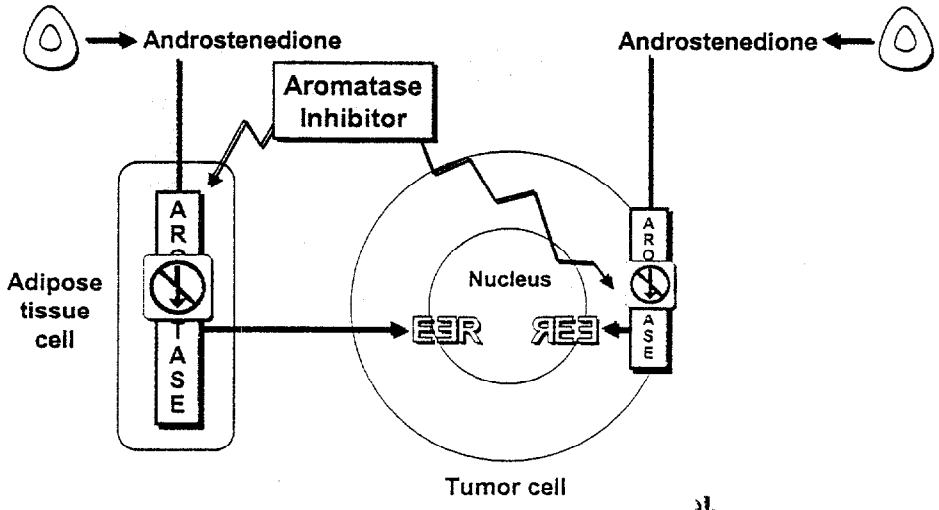
Intracellular Aromatase



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Sources of Aromatase

Placental microsomes	Human, cell-free
Ovarian tissue	Rodent, endocrine, cellular
Breast adipose fibroblasts	Human, endocrine, cellular
MCF-7Ca	Human breast cancer, cellular
JEG-3	Human choriocarcinoma, cellular

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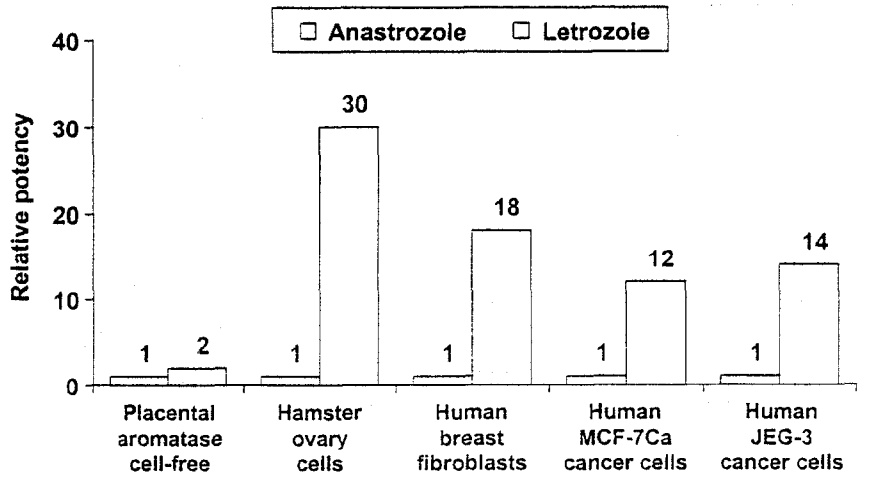
Inhibition of Aromatase in Cell Systems in Vitro



Bhatnagar, et al. JSBMB Symposium 2000.

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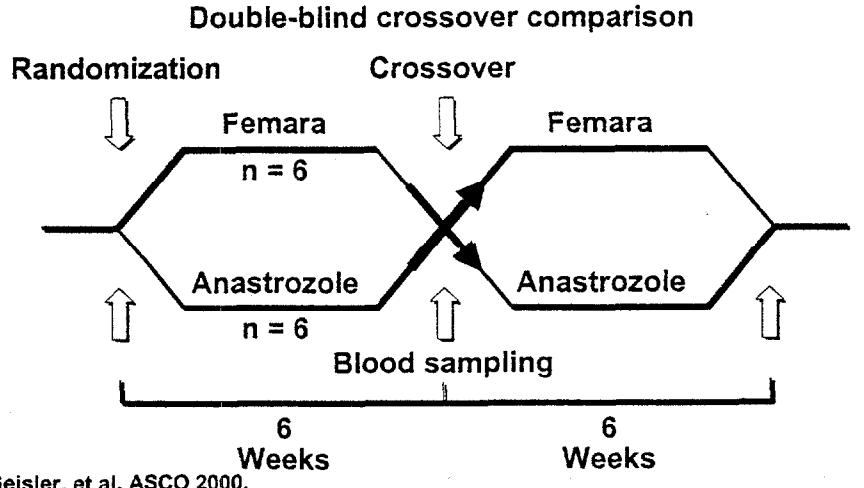
Study Design Femara® Versus Anastrozole



Geisler, et al. ASCO 2000.
Dowsett, et al. EBCC 2000.

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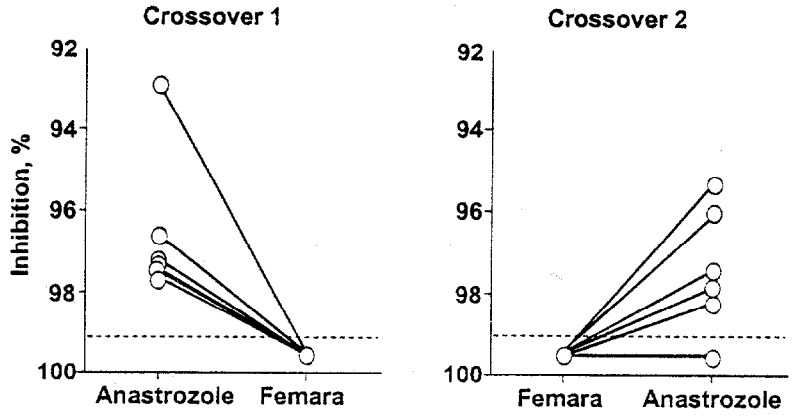
Inhibition of Aromatization by Femara® and Anastrozole



Femara versus Anastrozole, $P = .003$

Dowsett, et al. EBCC 2000.

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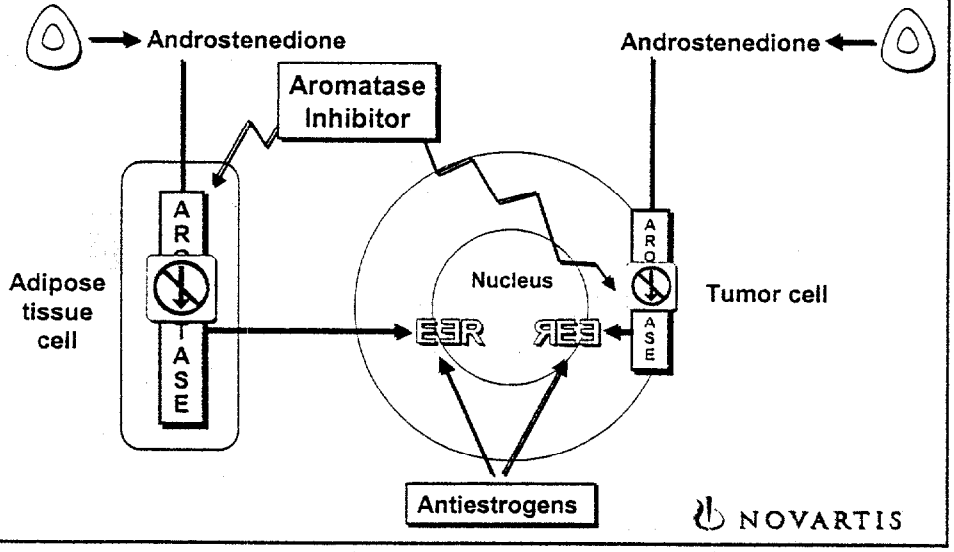
Intracellular Aromatase



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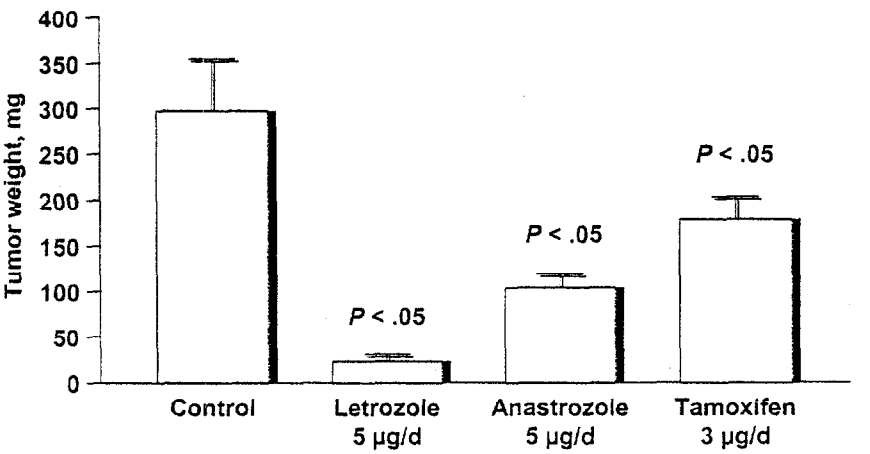
Effect of Letrozole, Anastrozole and Tamoxifen on Tumor Growth of MCF-7 Breast Cancer Cells Transfected With Aromatase Gene in Nude Mice



A Brodie, et al. *Endocrine Rel Cancer.* 1999;6:205-210.

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Conclusions

Letrozole is

- A more potent aromatase inhibitor than anastrozole in the preclinical setting
- A more effective aromatase inhibitor than anastrozole in a human setting
- A more effective anti-tumor agent than both anastrozole and the antiestrogen tamoxifen in an animal tumor model

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