



Role and Sequencing of Fulvestrant in the Treatment of Metastatic Disease

As evident from publication of the NSABP P-1 chemoprevention trial, NSABP B-24 DCIS trial and the ATAC trial, endocrine agents are being utilized in earlier stages of breast cancer. This trend will result in a more heavily pretreated population of patients with advanced breast cancer. The availability of the novel agent fulvestrant raises the issue of the optimal sequencing of endocrine agents in the management of postmenopausal women with metastatic breast cancer, and specifically the sequence of fulvestrant, tamoxifen and aromatase inhibitors. Data presented at the San Antonio Breast Cancer Symposium demonstrate responsiveness to subsequent endocrine therapy in patients treated with fulvestrant..

RETROSPECTIVE EVALUATION OF ENDOCRINE THERAPY AFTER FULVESTRANT

"These data represent the first evaluation of responses to treatment after fulvestrant in patients with advanced disease previously untreated with endocrine therapy...Patients who respond to initial fulvestrant or tamoxifen may retain sensitivity to subsequent endocrine therapy...Aromatase inhibitors such as anastrozole or letrozole produce similar response rates in patients who have progressed on fulvestrant or tamoxifen. The proportion of post-fulvestrant responses reported here are similar to those previously described for second-line aromatase inhibitor therapy in patients who failed on first-line tamoxifen treatment. For example, CB was observed in 99/248 patients treated with anastrozole and in 65/137 patients receiving exemestane...The addition of fulvestrant to the choice of endocrine therapies may extend the opportunity for use of endocrine regimens before reliance upon cytotoxic chemotherapy is necessary.

Fulvestrant is effective in patients progressing on tamoxifen and these data show that after receiving fulvestrant, patients remain sensitive to treatment with other endocrine agents, including tamoxifen and AIs. Fulvestrant therefore provides an additional treatment option that may extend the period of effect of endocrine therapy, before cytotoxic chemotherapy needs to be considered."

— Howell A. *Breast Cancer Res Treat* 2002; Poster/Abstract 251.

POST-FULVESTRANT RESPONSES TO ENDOCRINE THERAPY

Sequencing of fulvestrant is a key issue to be addressed. We have data that you can see responses to aromatase inhibitors after fulvestrant and vice versa. Fulvestrant resistance is not hormone insensitivity.

We do not yet know the mechanism by which cancer becomes resistant to fulvestrant. We do not believe it is an agonistic property. We can see ER expression in patients on fulvestrant — even at the time of resistance. We are studying mechanisms of resistance with sequential biopsies, examining specimens both when patients are responding and when they become resistant.

— John Robertson, FRCS

EMERGENCE OF FULVESTRANT

"The most recent entrant into the new pantheon of drugs for the treatment of breast cancer is the pure antiestrogen fulvestrant. ...Preclinical data suggest fulvestrant may be more effective than tamoxifen, and it might work in patients who are initially resistant to tamoxifen. It is possible that combinations of fulvestrant and aromatase inhibitors will be effective, in contrast to the outcome of the ATAC trial, where there was no advantage to combining tamoxifen and anastrozole."

— I Craig Henderson, MD
J Clin Oncol. 2002;20:3365-3368

FULVESTRANT AND THE SEQUENCING OF ENDOCRINE THERAPY IN POSTMENOPAUSAL WOMEN

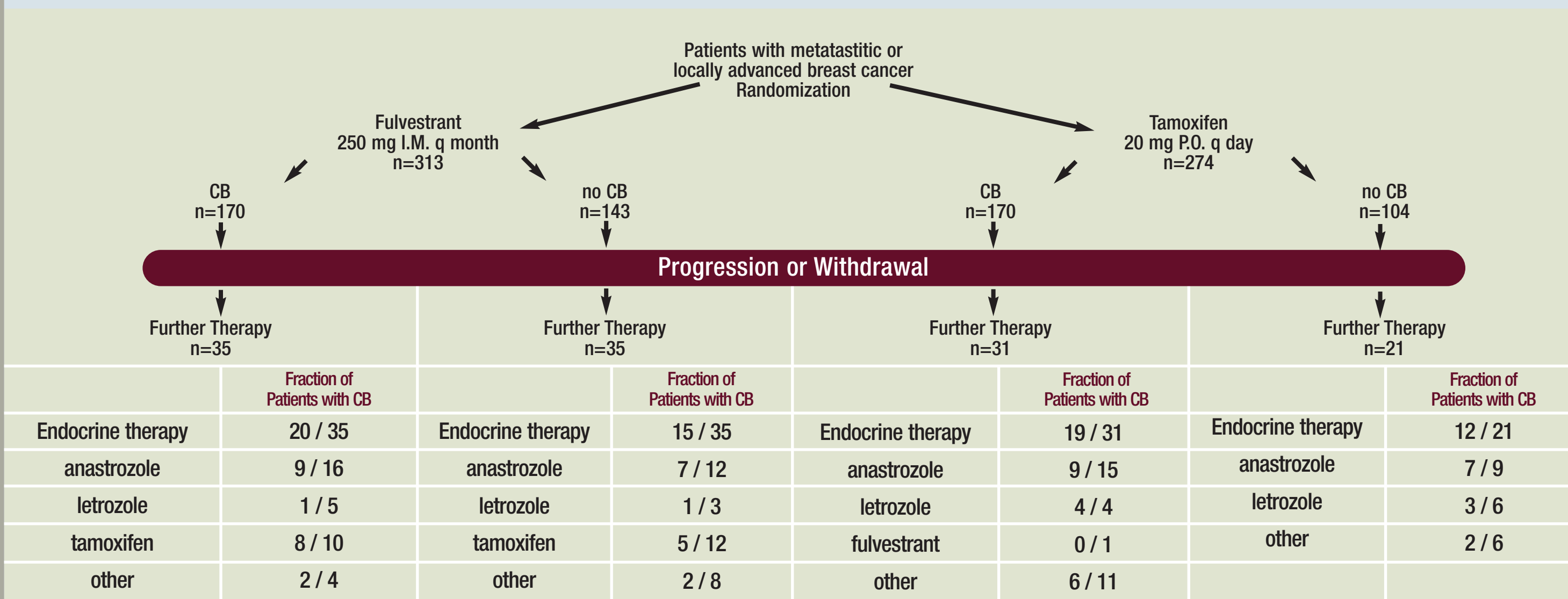
Fulvestrant is equivalent as second-line therapy to our best drugs — the aromatase inhibitors. We now have a choice between treatments that are clearly equivalent. In postmenopausal women, I believe first-line therapy for advanced disease — even in those who have not had adjuvant tamoxifen — is an aromatase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

RESPONSE TO ENDOCRINE THERAPY AFTER FULVESTRANT OR TAMOXIFEN: A RETROSPECTIVE EVALUATION



CB = Clinical Benefit

DERIVED FROM: Howell A. *Breast Cancer Res Treat* 2002;76(supp 1): Abstract 251.

RESPONSE TO ENDOCRINE THERAPY IN PATIENTS IN TRIALS 20 AND 21 WHO DERIVED CLINICAL BENEFIT FROM FULVESTRANT

	Number of patients with clinical benefit			
	PR	SD ≥ 24 weeks	Progression	Total
3rd generation AIs	3	12	24	39
Megestrol acetate	0	2	2	4

DERIVED FROM: Vergote I. *Breast Cancer Res Treat* 2001;69(3):Abstract 446.

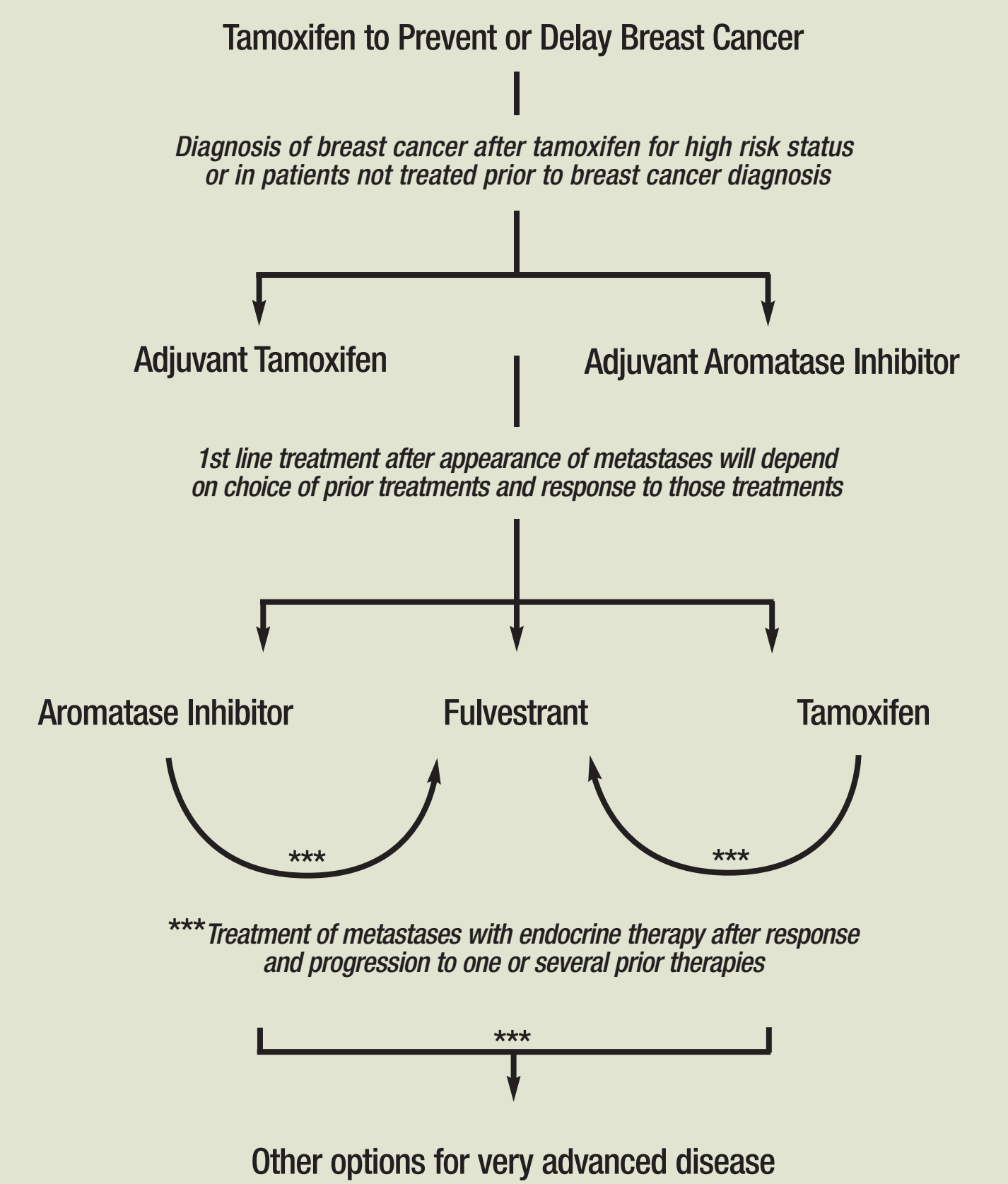
OVERALL RESPONSE RATE TO FULVESTRANT AFTER PROGRESSION ON TAMOXIFEN AND A.I.s IN 32 ELIGIBLE PATIENTS IN THE SAKK TRIAL

	Clinical benefit*	PR	SD ≥ 24 weeks	Disease progression
Number of patients (%)	11(34%)	2(6%)	9(28%)	21(66%)

*PR or SD for ≥24 weeks. AI=aromatase inhibitor; PR=partial response; SD=stable disease

SOURCE: Pery L et al. *Breast Cancer Res Treat* 2002;76(supp 1): Abstract 249.

POSSIBLE LOCATIONS FOR FULVESTRANT IN THE ENDOCRINE CASCADE FOR POSTMENOPAUSAL WOMEN



REPRINTED WITH PERMISSION: Henderson, IC. *J Clin Oncol.* 2002;20:3365-3368.

SELECT PUBLICATIONS

Henderson IC. A rose is no longer a rose. *J Clin Oncol* 2002;20: 3365-3368.

Howell A. Postmenopausal women with advanced breast cancer who progress on fulvestrant or tamoxifen retain sensitivity to further endocrine therapies. *Breast Cancer Res Treat* 2002;76(supp 1): Abstract 251.

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(16):3386-95.

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

Pery L et al. Fulvestrant (Faslodex) as a hormonal treatment in postmenopausal patients with advanced breast cancer progressing after treatment with tamoxifen and non-steroidal aromatase inhibitors: An ongoing phase II SAKK trial. *Breast Cancer Res Treat* 2002;76(supp 1): Abstract 249.

Vergote I. Evidence of continued sensitivity to endocrine agents in postmenopausal women with advanced breast cancer progressing on fulvestrant treatment. *Breast Cancer Res Treat* 2001;69(3):Abstract 446.