Sequencing of Hormonal Therapies in Metastatic Disease

As in postmenopausal women with early breast cancer, the sequencing of hormonal therapies in women with metastatic disease has become a topic of considerable interest. Postmenopausal women may now receive not only tamoxifen but also aromatase inhibitors in the adjuvant setting, and the optimal sequencing of hormonal agents for the treatment of metastatic disease is unknown. Fulvestrant, an estrogen receptor downregulator, is a recent addition to the hormonal therapy armamentarium. As second-line therapy in postmenopausal women with advanced breast cancer, fulvestrant and anastrozole have similar efficacy. Fulvestrant has also been compared to tamoxifen as first-line therapy in women with advanced ER/PR-positive disease, and the benefits were comparable. Retrospective analyses of subsequent hormonal agents administered following fulvestrant have demonstrated significant response rates. Future clinical trials are required to determine the optimal sequencing of hormonal therapy options.

COMBINED ANALYSIS OF TWO PHASE III MULTICENTER TRIALS COMPARING FULVESTRANT TO ANASTROZOLE AS SECOND-LINE THERAPY IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER

Median follow-up 15.1 months	Fulvestrant (n=428)	Anastrozole (n=423)	*p*-value
Complete response rate[1]	4.7%	2.6%	—
Partial response rate[1]	14.5%	13.9%	—
Objective response rate[1]	19.2%	16.5%	0.31
Clinical benefit rate*[1]	43.5%	40.9%	0.51
Estimated median time to progression[1]	5.5 months	4.1 months	0.48
Median follow-up 22.1 months	**(n=84)**	**(n=73)**	***p*-value**
Median duration of response in patients responding[1]	16.7 months	13.7 months	—
Median follow-up 27.0 months	**(n=428)**	**(n=423)**	***p*-value**
Death rate[2]	74.5%	76.1%	—
Median time to death[2]	27.4 months	27.7 months	0.81

* Clinical benefit = complete response + partial response + stable disease ≥24 weeks

SOURCES: [1] Robertson JF et al. *Cancer* 2003;98(2):229-38.

[2] Pippen J et al. Poster. San Antonio Breast Cancer Symposium, 2003;Abstract 426.

RETROSPECTIVE ANALYSIS OF THE PROPORTION OF PATIENTS RESPONDING FOR 1, 1.5 AND 2 OR MORE YEARS IN TWO PHASE III STUDIES OF FULVESTRANT VERSUS ANASTROZOLE

Response	Fulvestrant 250 mg (n=428)	Anastrozole 1 mg (n=423)	*p*-value
Total patients with OR	19.2%	16.5%	0.3070
Patients with OR ≥1y	10.0%	7.1%	0.1627
Patients with OR ≥1.5y	4.0%	3.1%	—
Patients with OR ≥2y	0.9%	0.5%	—
Total patients with CB	43.5%	40.9%	0.5059
Patients with CB ≥1y	19.2%	13.9%	0.0692
Patients with CB ≥1.5y	7.5%	5.7%	—
Patients with CB ≥2y	1.4%	0.9%	—

"This analysis suggests that fulvestrant has benefits over anastrozole in terms of the number of patients with prolonged duration of response. These data support the initial DOR findings in these trials. Fulvestrant is an important new endocrine agent in breast cancer."

OR = objective response; CB = clinical benefit (complete response + partial response + stable disease ≥24 weeks); DOR = duration of response

SOURCE: Jones SE et al. *Breast Cancer Res Treat* 2004;Abstract 6047.

PHASE III RANDOMIZED TRIAL COMPARING FULVESTRANT TO TAMOXIFEN AS FIRST-LINE ENDOCRINE THERAPY IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER

	All patients		Patients with ER/PR-positive tumors	
	Fulvestrant (n=313)	Tamoxifen (n=274)	Fulvestrant (n=247)	Tamoxifen (n=212)
Complete response rate	9.6%	6.9%	8.9%	5.7%
Partial response rate	22.0%	27.0%	24.3%	25.5%
Stable disease ≥24 weeks	22.7%	28.1%	23.9%	31.6%
Objective response rate*	31.6%	33.9%	33.2%	31.1%
Clinical benefit rate†	54.3%	62.0%	57.1%	62.7%

* Objective response indicates a complete or partial response; $p = 0.45$ for all patients; $p = 0.64$ for patients with ER/PR-positive tumors

† Clinical benefit indicates a complete or partial response or stable disease ≥24 weeks; $p = 0.026$ for all patients; $p = 0.22$ for patients with ER/PR-positive tumors

Median time to progression‡	6.8 months	8.3 months	8.2 months	8.3 months
Estimated median survival§	36.9 months	38.7 months	39.3 months	40.7 months

‡ $p = 0.088$ for all patients (upper limit of 95% confidence interval did not satisfy predefined criterion for concluding noninferiority of fulvestrant compared to tamoxifen); $p = 0.39$ for patients with ER/PR-positive tumors

§ $p = 0.04$ for all patients; $p = 0.30$ for patients with ER/PR-positive tumors (upper limit of 95% CI did not satisfy predefined criterion for concluding noninferiority of fulvestrant compared to tamoxifen)

SOURCE: Howell A et al. *J Clin Oncol* 2004;22(9):1605-13.

RESPONSE TO SUBSEQUENT ENDOCRINE THERAPY* IN PATIENTS ENROLLED IN TWO PHASE III TRIALS COMPARING FULVESTRANT TO ANASTROZOLE AS SECOND-LINE THERAPY: RETROSPECTIVE ANALYSIS

	Patients who derived clinical benefit from fulvestrant (n=54)	Patients who did not derive clinical benefit from fulvestrant (n=51)
Partial response	4 (7%)	1 (2%)
Stable disease ≥24 weeks	21 (39%)	17 (33%)
Disease progression	29 (54%)	33 (65%)

* More than 80 percent received an aromatase inhibitor as subsequent endocrine therapy.

SOURCE: Vergote I et al. *Breast Cancer Res Treat* 2003;79(2):207-11.

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SEQUENCING HORMONAL THERAPY IN POSTMENOPAUSAL WOMEN

I generally use an aromatase inhibitor in a postmenopausal patient progressing after completion of tamoxifen, but I also present the option of fulvestrant. I think both are reasonable and legitimate options that are equivalent; however, I think most patients prefer oral therapy and it is less expensive. Some patients prefer an intramuscular injection once a month. Some patients may not be compliant with oral medication. For them, fulvestrant is a good option.

— Debu Tripathy, MD

Most clinicians consider fulvestrant a third-line therapy for patients who have failed tamoxifen and an aromatase inhibitor; however, clinical trials have shown that fulvestrant is equivalent to anastrozole after tamoxifen failure and, in a recently published European study comparing front-line fulvestrant to tamoxifen, I did not view fulvestrant as inferior to tamoxifen. In addition, a Phase III study is underway comparing fulvestrant to exemestane for second-line therapy. I use third-line fulvestrant, but I also use it first line, particularly in women who can't afford an aromatase inhibitor. In addition, I would estimate that approximately 40 percent of my patients prefer a monthly injection to taking a pill every day.

— Adam M Brufsky, MD, PhD

The overall results of Trials 20 and 21 showed no significant difference between anastrozole and fulvestrant, but differences occurred in subset analyses. The duration of response seemed to be longer in patients who responded to fulvestrant, and patients who had visceral disease seemed to respond better than those who did not. I think the takeaway message is that they're equally efficacious; however, there may be subsets of patients in whom you might prefer to use fulvestrant, particularly those for whom compliance may be an issue or those with visceral disease.

The other important point is that anecdotal studies argue that you can use one and switch to the other. Third-line aromatase inhibitors are efficacious after fulvestrant and vice versa.

— Gershon Locker, MD

In postmenopausal women whose disease relapses while on adjuvant tamoxifen, I use fulvestrant because I've seen some very long remissions with it. I will use an aromatase inhibitor later because data indicate that patients with disease that progresses on fulvestrant can still respond to other endocrine treatments (eg, aromatase inhibitors and megestrol acetate).

A few reports have evaluated the response to fulvestrant in patients who received an aromatase inhibitor. A small Swiss study reported that about one third of patients derive clinical benefit from fulvestrant after treatment with tamoxifen or an aromatase inhibitor.

At ASCO 2003, a compassionate-use trial reported data from about 60 patients treated with fulvestrant as second-, third- or fourth-line therapy. Fulvestrant had more than a 50 percent clinical benefit rate in those patients.

— Stephen E Jones, MD

Women with breast cancer whose disease fails while on tamoxifen clearly can respond to fulvestrant, and the response rate is equivalent to that seen with anastrozole. Also, in women with disease that has failed anastrozole, subsequent therapy with fulvestrant leads to a substantial clinical benefit rate of approximately 40 percent. Patients who cross over from fulvestrant to an aromatase inhibitor also show response rates of approximately 40 percent.

Surprisingly, the magnitude of benefit from fulvestrant does not predict whether the cancer will respond to a subsequent hormonal maneuver. One rule of thumb in the past has been that the magnitude and duration of response to the most recent hormonal therapy predicted for the likelihood of response to subsequent hormonal therapies. A small retrospective study suggests that may not be the case with fulvestrant.

— Robert W Carlson, MD