Sequencing of Hormonal Therapies in Metastatic Disease

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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- and/or 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

	Fulvestrant (n=428)	Anastrozole (n=423)	*p*-value
Complete response rate	4.7%	2.6%	—
Partial response rate	14.5%	13.9%	—
Objective response rate	19.2%	16.5%	0.31
Clinical benefit rate*	43.5%	40.9%	0.51
Estimated median time to progression	5.5 months	4.1 months	0.48
Median duration of response in those responding	16.7 months	13.7 months	—
Death rate (median follow-up, n=27.2 months)	74.5%	76.1%	—
Median time to death	27.4 months	27.7 months	0.81

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

SOURCES: Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38.

Pippen J et al. **Fulvestrant (Faslodex) versus anastrozole (Arimidex) for the treatment of advanced breast cancer: A prospective combined survival analysis of two multicenter trials.** Poster. SABCS, 2003;Abstract 426.

RETROSPECTIVE ANALYSIS OF DURATION OF RESPONSE TO FULVESTRANT VERSUS ANASTROZOLE

	Fulvestrant 250 mg, n (%)	Anastrozole 1 mg, n (%)	*p*-value
Total patients with OR	82 (19.2)	70 (16.5)	0.3070
Patients with OR ≥1 year	43 (10.0)	30 (7.1)	0.1627
Total patients with CB	186 (43.5)	173 (40.9)	0.5059
Patients with CB ≥1 year	82 (19.2)	59 (13.9)	0.0692

SOURCE: Jones SE. *Proc ASCO* 2004;Abstract 737.

RESPONSE TO SUBSEQUENT ENDOCRINE THERAPY IN PATIENTS ENROLLED IN A PHASE III TRIAL COMPARING FULVESTRANT TO TAMOXIFEN AS FIRST-LINE THERAPY

	Clinical benefit (CB) with second-line agent	
	No. of patients	%
First-line fulvestrant (n=70)		
Patients who derived CB (n=35)	20	57
Patients who did not derive CB (n=35)	15	43
First-line tamoxifen (n=52)		
Patients who derived CB (n=31)	19	61
Patients who did not derive CB (n=21)	12	57

SOURCE: Howell A. Poster. SABCS, 2002.

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

	All patients		Patients with ER- and/or 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[1]	31.6%	33.9%	33.2%	31.1%
Clinical benefit rate[2]	54.3%	62.0%	57.1%	62.7%
Median time to progression[3]	6.8 months	8.3 months	8.2 months	8.3 months
Estimated median survival[4]	36.9 months	38.7 months	39.3 months	40.7 months

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

[2] 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- and/or PR-positive tumors

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

[4] $p = 0.04$ for all patients; $p = 0.30$ for patients with ER- and/or PR-positive tumors (upper limit of 95% confidence interval [CI] did not satisfy predefined criterion for concluding noninferiority of fulvestrant compared to tamoxifen).

SOURCE: Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *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. **Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy.** *Breast Cancer Res Treat* 2003;79:207-11.

SELECT PUBLICATIONS

Carlson RW, Henderson IC. **Sequential hormonal therapy for metastatic breast cancer after adjuvant tamoxifen or anastrozole.** *Breast Cancer Res Treat* 2003;80(Suppl 1):19-26.

Henderson IC. **A rose is no longer a rose.** *J Clin Oncol* 2002;20:3365-8.

Howell A. **Postmenopausal women with advanced breast cancer who progress on fulvestrant or tamoxifen retain sensitivity to further endocrine therapies.** Poster. SABCS, 2002;Abstract 251.

Lonning PE et al. **Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: A phase II trial.** *J Clin Oncol* 2000;18(11):2234-44.

Perey 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.** Poster. SABCS, 2002;Abstract 249.

Pippen J et al. **Fulvestrant (Faslodex) versus anastrozole (Arimidex) for the treatment of advanced breast cancer: A prospective combined survival analysis of two multicenter trials.** Poster. SABCS, 2002;Abstract 426.

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38.

Vergote I. **Evidence of continued sensitivity to endocrine agents in postmenopausal women with advanced breast cancer progressing on fulvestrant treatment.** Poster. SABCS, 2001;Abstract 446.

SEQUENCING HORMONAL THERAPY IN POSTMENOPAUSAL WOMEN

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 on 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 can clearly 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

In Trials 20 and 21, anastrozole and fulvestrant were equivalent as second-line therapy after tamoxifen failure, but fulvestrant had a significantly longer duration of response in the North American study. In the first-line study, tamoxifen was slightly superior to fulvestrant, which was a very surprising result. In the ER/PR-positive group, fulvestrant was slightly (but not significantly) better than tamoxifen. In other words, it's a drug that is equivalent to anastrozole as second-line therapy and nearly equivalent to tamoxifen as first-line therapy.

We have to ask, "Why wasn't fulvestrant better than tamoxifen?" That's what we expected. The answer may be in the dosing of fulvestrant, because it takes about six months to achieve steady-state levels. Clinical trials will evaluate loading-dose schedules of fulvestrant. Our modeling analyses indicate these approaches will increase the dose of the drug sooner, and then we will be able to investigate whether that is the reason fulvestrant was not better than tamoxifen in the first-line trials.

— Anthony Howell, MD

Many of my patients have received adjuvant tamoxifen, so I typically use first-line aromatase inhibitors and administer fulvestrant upon progression. Subsequently, we may readminister tamoxifen, utilize progestins or try another aromatase inhibitor. Many of our patients with hormone receptor-positive metastatic disease can be maintained on hormonal therapies for several years before we have to treat them with chemotherapy.

— Julie R Gralow, MD

In patients progressing on tamoxifen, tamoxifen binds the estrogen receptors and may actually stimulate growth of the tumor — it certainly is no longer inhibiting it. Treating these patients with an aromatase inhibitor will be ineffective until all the tamoxifen is gone, which takes a couple of months. Fulvestrant, on the other hand, competes with tamoxifen for binding, thus the response may be quicker with fulvestrant than with an aromatase inhibitor in that setting.

— C Kent Osborne, MD