



**High-Dose Fulvestrant for the
Treatment of Postmenopausal
Patients with Hormone Receptor-
Positive Advanced Breast Cancer**

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CME INFORMATION

OVERVIEW OF ACTIVITY

San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year where published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVES

- Identify the clinical efficacy and safety of high-dose fulvestrant in comparison to anastrozole as first-line treatment for advanced breast cancer in postmenopausal patients.
- Assess the efficacy of fulvestrant 250 milligrams versus fulvestrant 500 milligrams as treatment for postmenopausal women with ER-positive advanced breast cancer.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee: AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation; Consulting Agreement and Stock Ownership: Oncimmune Ltd; Paid Research: Amgen Inc, AstraZeneca Pharmaceuticals LP, Bayer Pharmaceuticals Corporation, Oncimmune Ltd; Speakers Bureau: AstraZeneca Pharmaceuticals LP, GlaxoSmithKline.

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Consulting Agreements: Amgen Inc, AstraZeneca Pharmaceuticals LP, Lilly USA LLC, Novartis Pharmaceuticals Corporation, Sanofi-Aventis; Paid Research: Lilly USA LLC; Speakers Bureau: Abraxis BioScience, AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Novartis Pharmaceuticals Corporation.

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IN THIS ISSUE:

- Double-dose [fulvestrant results in a treatment advantage](#) in two randomized trials
- [No benefit](#) to adding fulvestrant to an AI
- [Neoadjuvant research](#) platform predicts the above results

Every year, either at San Antonio or ASCO, I try to meet up for an interview with UK investigator and world-class storyteller Dr John Robertson. When you're in the mood to hear about hormones, you can't do much better than dialing up John, and we again met in San Antonio last month, where he was presenting more from a longstanding series of neoadjuvant endocrine studies.

Unfortunately, and in contrast to the other major biologic target in breast cancer (HER2), there haven't been a whole lot of cool new endocrine therapy developments in recent years. When you consider that approximately two thirds of patients have ER-positive tumors, this troubling dynamic makes you scratch your head at the absence of major Phase III trials looking at up-front endocrine treatment when we can find 8,000 patients already for the ALTTO HER2 trial. Is this drought some kind of industry thing, is it another failure of our "public" programs or have we taken endocrine therapy as far as it can go?

On the enclosed commentary, John pretty much rules out the latter and makes a rather compelling argument that serious consideration should be given to an adjuvant trial that includes double-dose fulvestrant (DDF) — specifically a BIG 1-98-like study that would include different sequences of DDF and an AI. The rationale for this approach is essentially found in the four papers profiled in this issue of 5MJC, and John's hypothesis is that DDF is somehow blocking the emergence of delayed endocrine resistance. When I queried another one of my favorite endocrine mavens about the new data on higher-dose fulvestrant, Rowan Chlebowski told me simply: "This is practice changing." When I asked him if his own practice had changed in that regard, he said, "Yes, since I saw the FIRST trial data in San Antonio last year."

Meanwhile most oncologists use fulvestrant only in very advanced disease and yawn at the topic, maybe because they haven't heard investigators excited about the drug since it was first introduced more than 15 years ago as a new class of hormonal therapy — a

so-called estrogen receptor downregulator. And perhaps there isn't much to be excited about — except that my friend John Robertson is excited, and when that happens, I have learned to pay very close attention.

Next up on 5MJC: The RIBBON 2 trial confirms what oncologists are already doing (using bevacizumab in not only the first-line but also in the second-line metastatic setting).

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High-Dose Fulvestrant for the Treatment of Postmenopausal Patients with Hormone Receptor-Positive Advanced Breast Cancer

Presentations discussed in this issue

Robertson JF et al. **Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: Results from the FIRST study.** *J Clin Oncol* 2009;27(27):4530-5. [Abstract](#)

Di Leo A et al. **CONFIRM: A Phase III, randomized, parallel-group trial comparing fulvestrant 250 mg vs fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer.** SABCS 2009; [Abstract 25](#).

Slides from a journal article and from a presentation at SABCS 2009 and transcribed comments from recent interviews with John F R Robertson, MB, ChB, BSc, MD (12/12/09) and Rowan T Chlebowski, MD, PhD (12/30/09)

Activity of Fulvestrant 500 mg Versus Anastrozole 1 mg As First-Line Treatment for Advanced Breast Cancer: Results From the FIRST Study

Robertson JFR et al.

J Clin Oncol 2009;27(27):4530-35.

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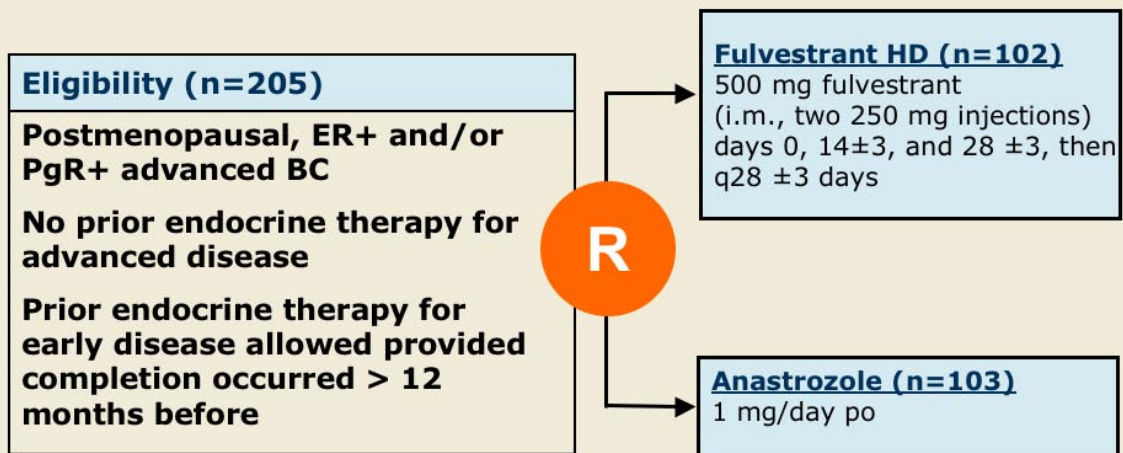
Introduction

- Evidence suggests that doses of fulvestrant higher than the approved dose (AD; 250 mg/month) have greater pharmacological activity (*Oncologist* 2007;12:774).
- Phase II trial NEWEST demonstrated that neoadjuvant fulvestrant high dose (HD; 500 mg/month) is more effective than AD at downregulating the ER pathway in patients with advanced breast cancer (SABCS 2007, Abstract 23).
- Phase III trials have demonstrated that fulvestrant AD is as effective as anastrozole as second-line therapy for advanced breast cancer (*Cancer* 2003;98:229).
- **Current study objective:**
 - Assess the efficacy of first-line fulvestrant HD versus anastrozole in postmenopausal patients with advanced breast cancer (BC).

Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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FIRST: A Phase II, Open-Label Multicenter Trial of Fulvestrant HD Versus Anastrozole



Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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Efficacy Results

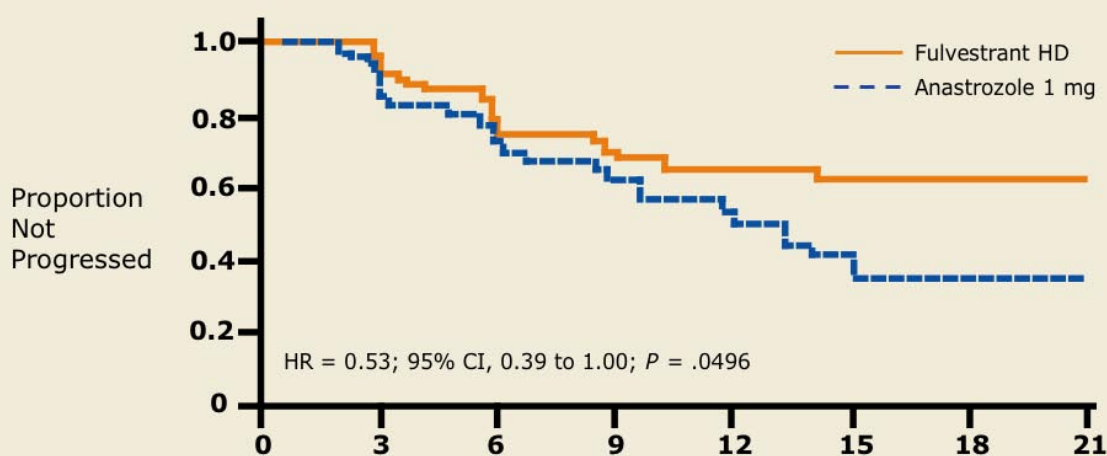
Clinical Response	Fulvestrant HD (n=102)	Anastrozole 1 mg (n=103)	P-value
Clinical benefit rate (CBR)	72.5%	67.0%	0.386
Complete response	0%	1.0%	—
Partial response	31.4%	31.1%	—
Stable disease ≥ 24 wks	41.2%	35%	—
Median duration of response	Not reached	14.2 mos	—
Median duration of clinical benefit	Not reached	Not reached	—
Objective response rate (ORR)*	36.0%	35.5%	0.947

*Fulvestrant HD, n=89; anastrozole, n=93.

Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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Time to Progression (TTP)



Anastrozole median TTP: 12.5 months
Fulvestrant HD median TTP: Not reached

Source: Reprinted with permission. ©2008 American Society of Clinical Oncology. All rights reserved. Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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Prespecified Adverse Events (Safety Population)

Adverse Event*	Fulvestrant HD (n=101)	Anastrozole 1 mg (n=103)	P-value
GI disturbances	27.7%	22.3%	0.420
Hot flashes	12.9%	13.6%	1.000
Ischemic cardiovascular disorders	0%	1.0%	1.000
Joint disorders	13.9%	9.7%	0.391
Urinary tract infections	4.0%	1.0%	0.210
Weight gain	1.0%	0%	0.495

*Only adverse events with incidences > 1% are shown.

Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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Summary and Conclusions

- First-line fulvestrant HD was as effective as anastrozole for the treatment of postmenopausal patients with advanced BC in terms of CBR and ORR.
 - CBR: 72.5% vs 67.0% (p -value=0.386)
 - ORR: 36.0% vs 35.5% (p -value=0.947)
- Median TTP, duration of response and duration of clinical benefit favored fulvestrant HD over anastrozole in this trial setting.
 - The early separation of the Kaplan-Meier curves for TTP suggests that fulvestrant HD may benefit patients who progress early.
 - The longer duration of response and duration of clinical benefit (data not shown) indicate patients' responses are more durable with fulvestrant HD.
- Fulvestrant HD was well tolerated with an adverse event profile comparable to anastrozole.
- CONFIRM trial results (SABCS 2009;Abstract 25) provide additional information on the role of fulvestrant HD for the treatment of advanced BC.

Source: Robertson JFR et al. *J Clin Oncol* 2009;27(27):4530-35.

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CONFIRM: A Phase III, Randomized, Parallel-Group Trial Comparing Fulvestrant 250 mg vs Fulvestrant 500 mg in Postmenopausal Women with Estrogen Receptor-Positive Advanced Breast Cancer

Di Leo A et al.

SABCS 2009;Abstract 25.

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Introduction

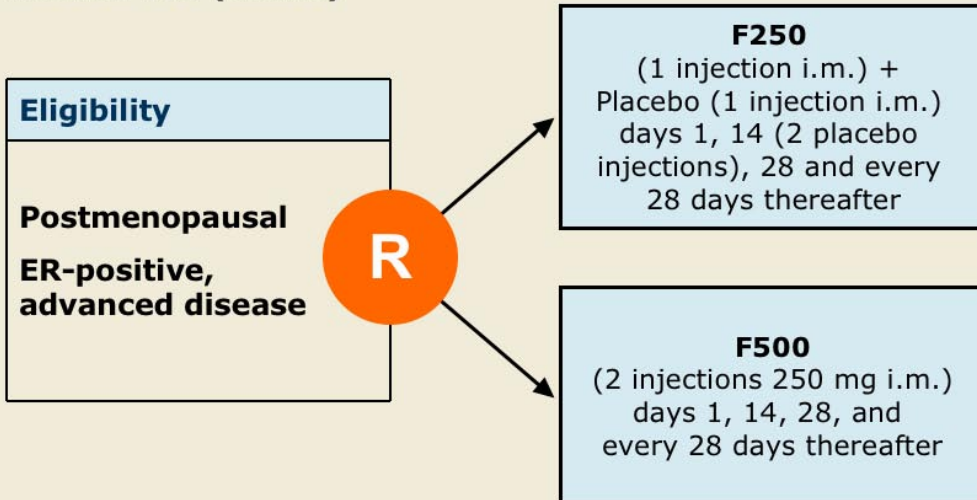
- Fulvestrant is approved for the treatment of postmenopausal women with advanced breast cancer (BC) that have progressed or relapsed following endocrine therapy.
- The efficacy of fulvestrant is well established at the approved dose of 250 mg/month (F250).
- Phase II trials NEWEST¹ and FIRST² have demonstrated that a 500 mg dose of fulvestrant (F500) has improved biological and clinical activities (¹SABCS 2007;Abstract 23, ²JCO 2009;27:4530).
- **Current study objectives:**
 - Compare the biological activity of F250 versus F500 in postmenopausal patients with estrogen receptor (ER)-positive advanced BC.

Source: Di Leo A et al. SABCS 2009;Abstract 25.

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CONFIRM Study Design

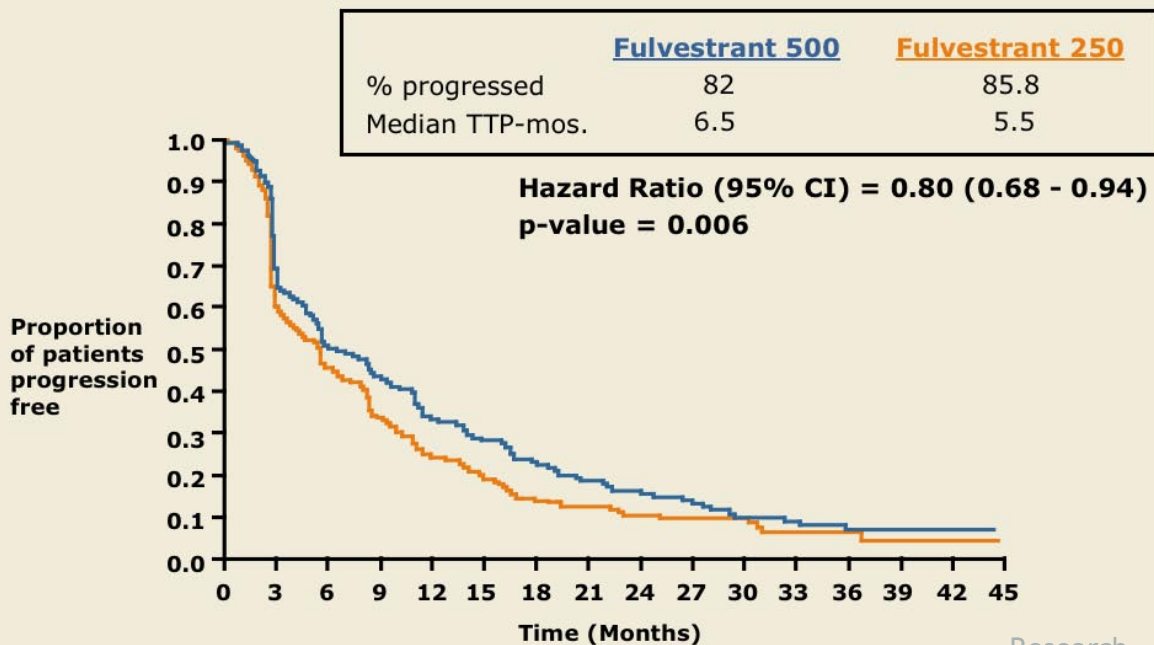
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Source: Di Leo A et al. SABCS 2009;Abstract 25.

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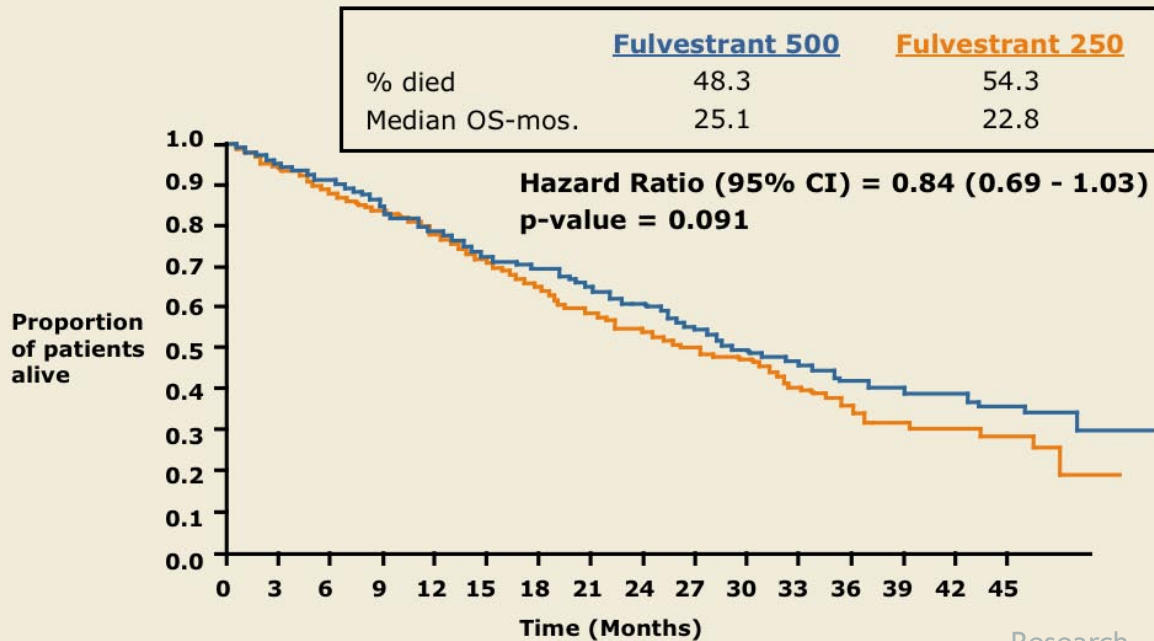
Time to Progression (ITT Analysis)



Source: With permission from Di Leo A et al. SABCS 2009;Abstract 25.

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Overall Survival (50% events)



Source: With permission from Di Leo A et al. SABCS 2009;Abstract 25.

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Objective Response and Clinical Benefit

	F500 (n=362)	F250 (n=374)	Odds ratio (95% CI)
Objective response rate (%)	9.1	10.2	0.94 (0.57 - 1.55)
Complete response (%)	1.1	0.3	—
Partial response (%)	8.0	9.9	—
Clinical benefit rate (%)	45.6	39.6	1.28 (0.95 - 1.71)
Progressive disease (%)	38.7	44.7	—
Median duration of clinical benefit (months)	16.6	13.9	—

Source: Di Leo A et al. SABCS 2009;Abstract 25.

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Pre-specified Adverse Events*

	F500 (n=361)		F250 (n=324)	
	All (%)	≥ Grade 3 (%)	All (%)	≥ Grade 3 (%)
Gastrointestinal disturbances	20.2	2.2	20.3	0.2
Joint disorders	18.8	2.2	18.7	2.1
Injection site reactions	13.6	0.2	13.4	0
Hot flashes	8.3	0	6.1	0
Urinary tract infections	2.2	0.2	2.1	0.2
Ischemic cardiovascular disorders	1.4	0	1.9	0.8
Thromboembolic events	0.8	0.5	1.6	1.0

* Shown are only those adverse events with an incidence of $\geq 1\%$.

Source: Di Leo A et al. SABCS 2009;Abstract 25.

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Conclusions

- TTP was increased in a statistically significant manner with F500 compared to F250.
 - TTP improvement likely a consequence of an increase in the rate of and prolonged duration of disease stabilization.
- The 50% events overall survival analysis appeared to favor F500, although statistical significance has not yet been reached.
 - 75% events overall survival analysis is expected in 2011.
- F500 was well tolerated, with a safety profile consistent with that of F250 and no evidence of dose-dependence for any adverse event.
- Exploratory analyses are underway to identify biologically and clinically defined patient cohorts that might derive the largest benefit from F500 (data not shown).

Source: Di Leo A et al. SABCS 2009;Abstract 25.

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JOHN F R ROBERTSON, MB, ChB, BSc, MD: There has always been some uncertainty in the past as to whether the approved dose of 250 mg/month of fulvestrant was the optimal dose. Data existed that clearly showed that a dose-dependent response for fulvestrant continued up to the 500-mg dose. In addition to that, two studies — studies 20 and 21 — showed that the 250-mg dose of fulvestrant was equivalent to anastrozole in the second-line setting.

In 2009 the results were published from the FIRST study, a study for which Matt Ellis and I were the principal investigators. FIRST showed in the first-line setting that the fulvestrant high dose of 500 mg/month was actually better than anastrozole. Time to disease progression was significantly prolonged in favor of the fulvestrant high dose. When you view the TTP curve, separation did not occur in the curves until just after six months. It is possible that the difference is not in the initial responses, but that acquired resistance is affecting the observed results for the anastrozole arm. It may be that the higher dose of fulvestrant results in greater downregulation of the estrogen receptor and thus there is decreased opportunity for cross talk to occur between the HER2 and EGFR signaling pathways, which play a role in the development of acquired resistance.

DR LOVE: What about using even higher doses of fulvestrant?

PROF ROBERTSON: We don't know if we've reached the top of the dose-response curve yet. In the FIRST trial, we observed that there are no differences in side effects if you increase the dose to 500 milligrams. The time to progression curve is longer — so patients are exposed to the 500-mg dose of fulvestrant longer — yet the side-effect profile is the same. Some arthralgias occur with fulvestrant, but no more than those that occur with aromatase inhibitors.

DR LOVE: Do you think that there is enough clinical evidence to justify examining fulvestrant in the adjuvant setting?

PROF ROBERTSON: I believe that should be done. I do think we are seeing an improved therapy using the higher, 500-mg dose of fulvestrant. We can view the results of the FIRST trial with more confidence in light of the large Phase III CONFIRM trial presented at this meeting that shows that 500 milligrams is better than 250 milligrams. I believe the whole body of evidence should make us move forward with fulvestrant 500 milligrams almost as though it were a new drug. The other thing that makes fulvestrant attractive as a potential adjuvant therapy is that there appears to be no difference in the bone profile for markers of bone resorption or formation in response to fulvestrant. Our own group examined 250 milligrams of fulvestrant over 18 months and saw no difference in the bone profile. The NEWEST study examined the 250-mg and 500-mg doses in the neoadjuvant setting and also observed that the bone profile remained the same.

The design of an adjuvant trial would depend on the question that is being asked. Personally, I favor a crossover strategy by which patients would cross over from treatment with an aromatase inhibitor to fulvestrant 500 milligrams at two or three years. You could include an arm with no crossover, just fulvestrant versus an aromatase inhibitor. Another option is to examine the effect of delayed fulvestrant, administered to patients who have been on aromatase inhibitor therapy for five years. You can compare continuing aromatase inhibitor therapy versus stopping versus crossing over to fulvestrant 500 milligrams. Either of these crossover designs is attractive because we have seen with aromatase inhibitors that as you go out from the time of diagnosis, you get an increase in the hazard ratio. You see a more hormone-sensitive phenotype.

DR LOVE: Are there any situations in which you would use fulvestrant in the adjuvant setting?

PROF ROBERTSON: If the patient is at high risk and has had contraindications to both an aromatase inhibitor and tamoxifen, you could have that discussion. You would have to explain that this was completely off label. I don't think it would be something that you would want to pursue as a policy that you practiced by easy default. We need randomized trials for that.

ROWAN T CHLEBOWSKI, MD, PhD: The CONFIRM trial is a Phase III randomized trial for postmenopausal women with prior hormone exposure. It is comparing the approved dose of fulvestrant, 250 milligrams every 28 days, to that of high-dose fulvestrant, which is 500 milligrams on days one, 14 and 28 followed by 500 milligrams every 28 days. This results in almost a doubling of the dose if you administer over a year's worth of therapy. Prior to this study, the results of the FIRST trial, presented last year, demonstrated a striking result comparing anastrozole to high-dose fulvestrant. Anastrozole had a 12-month time to disease progression, whereas it exceeded 21 months with fulvestrant.

The Phase III study presented by Dr Di Leo had more than 700 patients and met the primary endpoint, which was improvement in time to disease progression. The improvement was modest, 6.5 versus 5.5 months, which was significant at a p -value of 0.006. The overall survival was more interesting in that it was trending in favor of the high-dose fulvestrant, 25.1 months median survival versus 22.8 months, with a p -value of 0.09.

It is also of interest that the duration of clinical benefit was significantly longer with the fulvestrant high dose versus the approved dose. The analyses presented were after 50 percent of the patient population had died. The next analysis will look after an additional 25 percent have died. Knowing that this large proportion of people hadn't experienced disease progression yet on the high-dose fulvestrant arm makes it reasonable to think that, as time goes on, the survival trend may turn out to be significant. I look at this as a positive result.

I believe the study results generate new life into fulvestrant because most postmenopausal patients will be coming off of an adjuvant aromatase inhibitor at some time, either failing on it or following it. This could be a real first-line standard hormonal therapy, especially if it undergoes a label change.

Apparently, this high dose has resulted in a label change in four countries in Europe already, so this is now the standard fulvestrant dose in those countries. This is practice changing. No increase in side effects was seen, and we have been using this dose of fulvestrant for some time in my practice. We haven't had difficulty with patients accepting it, and it can be administered by nurses with ease. However, it will be a problem for routine clinical use if fulvestrant does not undergo a label change.

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