5 Minute JournalClub

Loading Dose Schedule of Fulvestrant Combined with Anastrozole for the Treatment of Patients with Breast Cancer at First Relapse

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual 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 OBJECTIVE

- Identify the clinical efficacy and adverse events associated with combining a loading dose schedule of fulvestrant with anastrozole, versus anastrozole alone, when treating postmenopausal patients with hormone receptor-positive breast cancer at first relapse.

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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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Loading Dose Schedule of Fulvestrant Combined with Anastrozole for the Treatment of Patients with Breast Cancer at First Relapse

Presentation discussed in this issue

Bergh J et al. **First results from FACT — An open-label, randomized Phase III study investigating loading dose of fulvestrant combined with anastrozole versus anastrozole at first relapse in hormone receptor positive breast cancer.** SABCS 2009;**Abstract 23**.

Slides from a presentation at SABCS 2009 and transcribed comments from a recent interview with Rowan T Chlebowski, MD, PhD (12/30/09)

Introduction

- Many patients with advanced hormone-dependent breast cancer develop resistance to aromatase inhibitors such as anastrozole.
- Fulvestrant down regulates estrogen receptors and has similar single agent activity as anastrozole in pre-clinical studies (*Cancer Res* 2008;68:3516).
- The combination of anastrozole (A) and fulvestrant (F) may counteract resistance by increasing the level of estrogen blockade through synergistic modes of action.
- **Current study objectives:**
  - Examine the safety and efficacy of the combination of F + A using a loading dose schedule of F in patients with relapsed hormone receptor positive breast cancer.

Source: Bergh J et al. SABCS 2009;Abstract 23.

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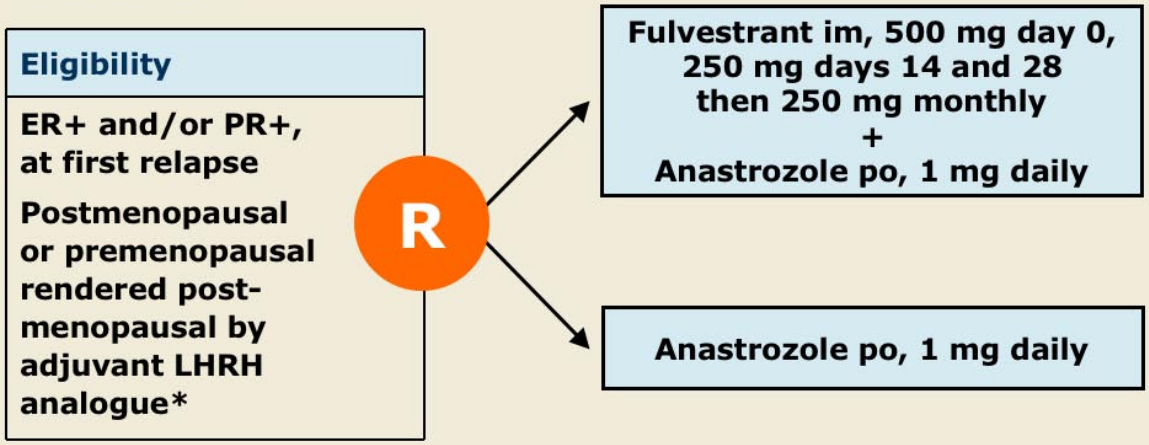
FACT: Phase III, Open-Label, Multicenter Trial of Combined Fulvestrant and Anastrozole Therapy

Accrual: 514



**In these cases, the LHRH analog must be continued throughout the study period*

Source: Bergh J et al. SABCS 2009;Abstract 23.

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Efficacy – Full Analysis Set

Efficacy parameter	F + A (n=258)	A (n=256)	HR (95% CI) *p*-value
Best objective response[1] Complete response (CR) Partial response (PR) Stable disease (SD) ≥ 24 weeks	 1.6% 14.3% 39.1%	 1.6% 13.3% 40.2%	—
Median time to progression (months)	10.8	10.2	0.99 (0.81, 1.20) *p* = 0.91
Overall survival (months)	37.8	38.2	1.00 (0.76, 1.32) *p* = 1.00

[1]*Programmatically derived to RECIST criteria*

Source: Bergh J et al. SABCS 2009;Abstract 23.

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Pre-specified Adverse Events* (Safety Population)

Grouped event type	F + A (n=256)	A (n=254)	*p*-value
GI disturbances	28.9%	25.2%	0.37
Hot flushes	24.6%	13.8%	< 0.01
Joint disorders	26.6%	27.6%	0.84
Thromboembolic events	2.3%	1.6%	0.75
Urinary tract infection	7.8%	5.9%	0.48
Weight gain	2.3%	2.4%	1.00

**Shown are only those adverse events with an incidence of 2% or greater.*

Source: Bergh J et al. SABCS 2009;Abstract 23.

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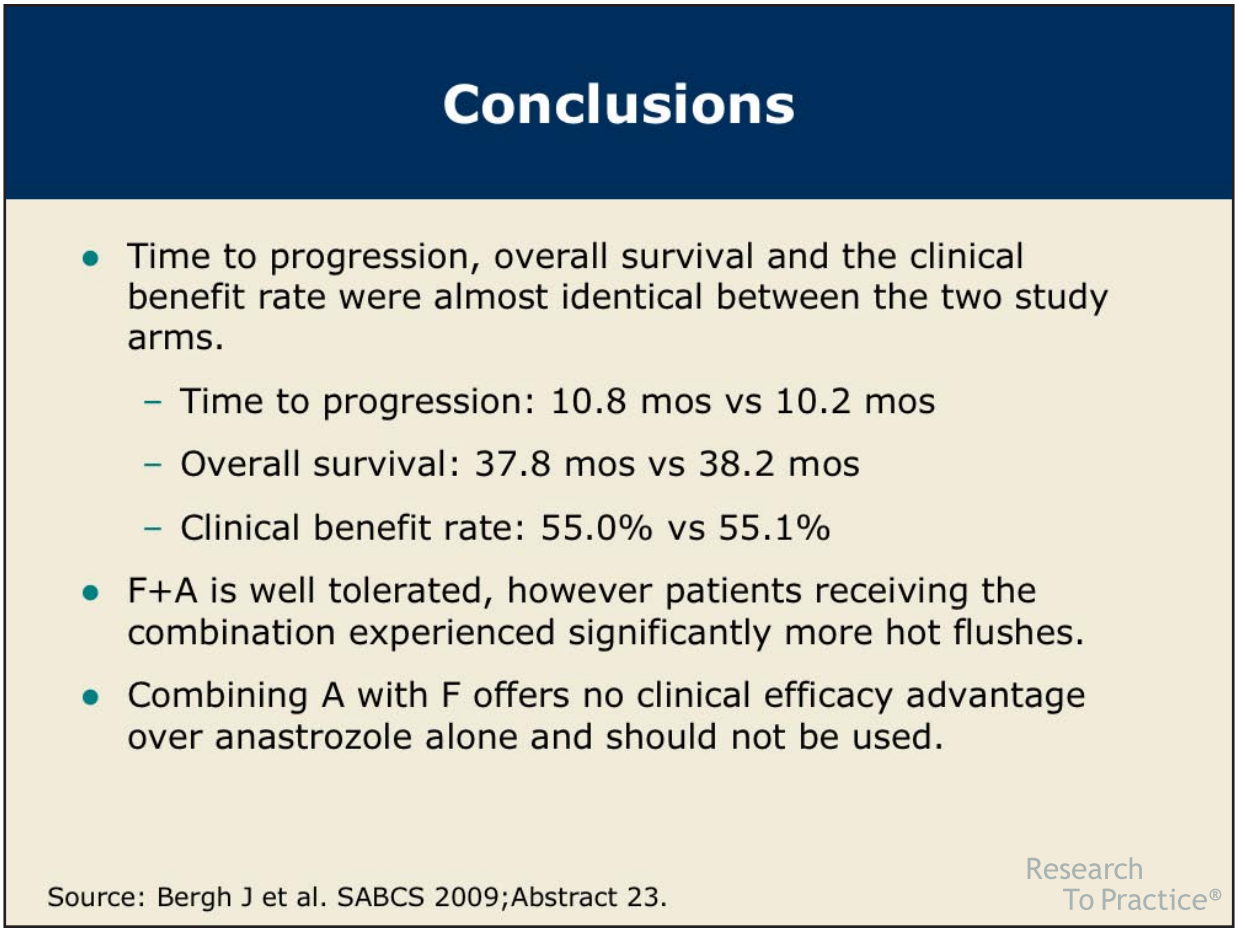

ROWAN T CHLEBOWSKI, MD, PhD: The FACT study is interesting. On the basis of strong preclinical data, a Phase III study was undertaken comparing anastrozole in combination with a loading dose of fulvestrant — 500 milligrams on day one, then 250 milligrams on days 14 and 28 followed by 250 milligrams monthly — to anastrozole alone. The patient population was postmenopausal women with relapsed metastatic breast cancer who had received one prior hormone therapy. Interestingly, with hundreds of patients, the study turned out to be basically negative. No evidence was seen of a difference in time to disease progression or overall survival between the study arms. It's back again to the Aman Buzdar principle with hormone therapy, in which one plus one equals one.

It was a disappointing result. Depending on how one interprets the CONFIRM trial results in terms of high-dose fulvestrant (see presentation 1 of this 5MJC issue), it may be that an inferior dose of fulvestrant was used in the FACT study. The authors conclude that you should not use this regimen, which is easy to agree with.

Dr Chlebowski is Professor of Medicine at the David Geffen School of Medicine at UCLA and Chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center in Torrance, California.