5 Minute JournalClub

Tumor Biomarker Changes After Presurgical Treatment of Patients with Breast Cancer with High-Dose Fulvestrant and Anastrozole

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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 biological activity of fulvestrant 500 milligrams with or without anastrozole versus anastrozole alone for postmenopausal patients with ER-positive primary breast cancer.

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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).

Neil Love, MD
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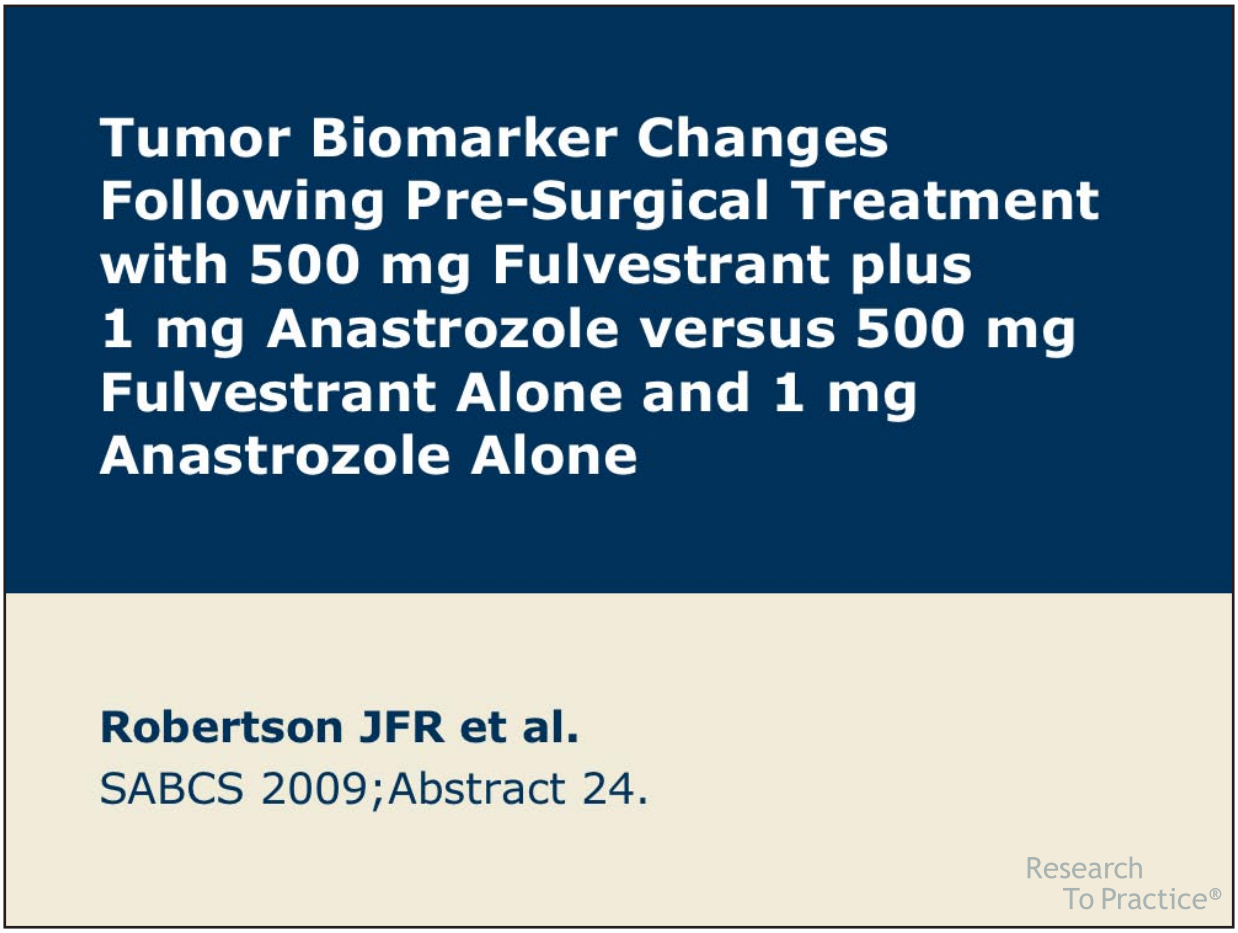
Tumor Biomarker Changes After Presurgical Treatment of Patients with Breast Cancer with High-Dose Fulvestrant and Anastrozole

Presentation discussed in this issue

Robertson JFR et al. **Tumor biomarker changes following pre-surgical treatment with 500 mg fulvestrant plus anastrozole versus 500 mg fulvestrant alone and 1 mg anastrozole alone.** SABCS 2009;**Abstract 24**.

Slides 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)

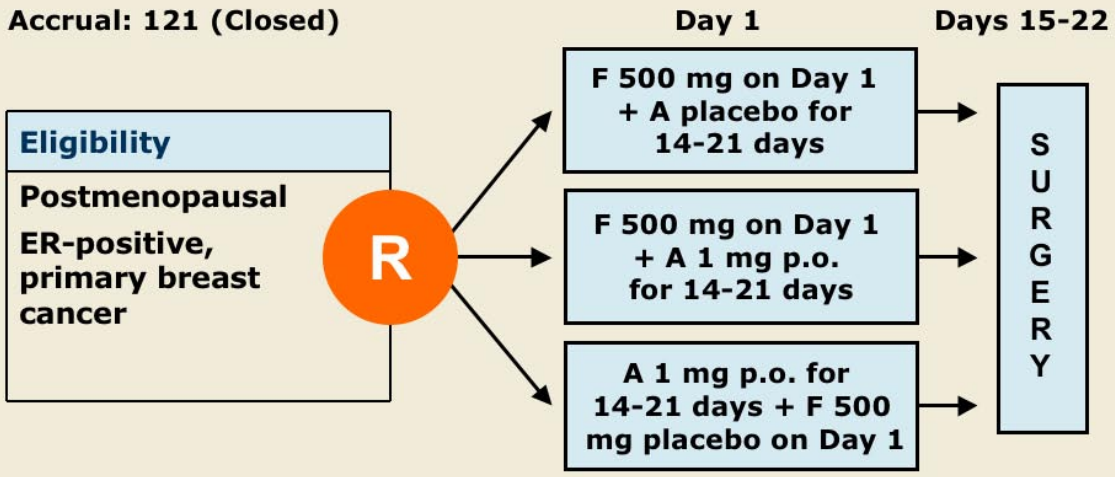


Introduction

- FIRST trial indicated that a high dose of fulvestrant (500 mg) had significantly greater biological activity than the approved dose of 250 mg in the first-line setting (*JCO* 2009;27:4530).
- IMPACT trial demonstrated that the aromatase inhibitor anastrozole is as effective as tamoxifen in postmenopausal women with estrogen receptor-positive (ER+) breast cancer (*JCO* 2005;23:5108).
- FACT trial was underway to assess the efficacy of fulvestrant 250 mg plus anastrozole (SABCS 2009;Abstract 23).
- **Current study objectives:**
  - Compare the biological activity of high dose 500 mg fulvestrant (F) plus anastrozole (A) with 500 mg F alone and A alone in postmenopausal women with ER+ primary breast cancer.

Source: Robertson JFR et al. SABCS 2009;Abstract 24.

Phase II, Double-blind, Multicenter Trial of Higher Dose Fulvestrant plus Anastrozole



Tumor biopsies to measure ER, progesterone receptor (PgR), and Ki67 were taken pre- and post-treatment and analyzed in a blind manner.

Source: Robertson JFR et al. SABCS 2009;Abstract 24.

ER H-score*

	F 500 mg	F 500 mg + A	A
No. of patients	35	31	37
Pre-treatment mean H-score	187.7	184.2	192.2
Post-treatment mean H-score	111.9	115.8	164.2
% change (post-treatment)	**-41%**	**-39%**	**-13%**
Comparison vs baseline	p=0.0001	p=0.0001	p=0.0034

*Changes in ER index were evaluated by non-automated H-score assessment on a scale ranging from 0 to 300.

Source: Robertson JFR et al. SABCS 2009;Abstract 24.

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PgR H-score

	F 500 mg	F 500 mg + A	A
No. of patients*	33	28	33
Pre-treatment mean H-score	145.7	141.7	157.6
Post-treatment mean H-score	97.9	81.1	93.8
% change (post-treatment)	**-34%**	**-45%**	**-37%**
Comparison vs baseline	p=0.0001	p=0.0001	p=0.0001

*Nine patients with a PR H-score of zero at baseline were omitted (F 500 mg n=2; F 500 mg + A n=3; A n=4).

Source: Robertson JFR et al. SABCS 2009;Abstract 24.

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Ki67 Index

	F 500 mg	F 500 mg + A	A
No. of patients	35	31	37
Pre-treatment mean H-score	17.1	17.8	16.2
Post-treatment mean H-score	4.2	3.3	2.6
% change (post-treatment)	**-75%**	**-81%**	**-85%**
Comparison vs baseline	p=0.0001	p=0.0001	p=0.0001

Source: Robertson JFR et al. SABCS 2009;Abstract 24.

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Conclusions

- Addition of anastrozole to fulvestrant 500 mg caused no significant additional decrease in:
  - ER H-score, PgR H-score, Ki67 levels
- Overall incidence of adverse events was similar between study arms (data not shown):
  - F arm (69.2%); F+A arm (66.7%); A arm (71.4%)
- These data extend the FACT study results (SABCS 2009;Abstract 23) at the biological level and suggest the fulvestrant 500 mg + anastrozole combination is unlikely to provide a clinical benefit over fulvestrant 500 mg alone.

Source: Robertson JFR et al. SABCS 2009;Abstract 24.

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JOHN F R ROBERTSON, MB, ChB, BSc, MD: This is a presurgical study examining two to three weeks of fulvestrant 500-mg therapy versus fulvestrant 500 mg in combination with anastrozole versus anastrozole one mg. We used 500 mg because there was already some evidence of a dose response, and we felt that there were ongoing studies evaluating strategies to improve clinical outcomes. We wanted to try the higher dose. We chose to include an arm with anastrozole by itself because in case the combination was better, we wanted to show that the benefit was greater than what you would see with an aromatase inhibitor alone. We also knew from the results from Mitch Dowsett and the IMPACT trial what the effects of anastrozole therapy should be and that arm served as a good control.

We found that ER levels were decreased in all three study arms. The basement levels were similar, and we saw a decrease that was highly significant in all three groups.

What we then saw was that when you did an overall treatment effect, there was a highly significant difference between the groups. The percent change in the downregulation was 41 percent for fulvestrant 500 mg, 39 percent for the combination and 13 percent for anastrozole alone. When you compared the groups, the two fulvestrant groups demonstrated significantly greater downregulation of ER than the anastrozole group did. The combination, however, was not better than fulvestrant alone. The combination did not add to the effects of fulvestrant alone, which is in keeping with the FACT trial.

The differences in levels of ER downregulation in our three study arms point to a difference in mechanism of action between fulvestrant and aromatase inhibitors. I believe that more downregulation of the ER occurs with the antiestrogen fulvestrant. With fulvestrant 500 mg, you have reduced the levels of ER further, whereas the reduction with the aromatase inhibitors is less. The decreased levels of ER would decrease the level of receptor autophosphorylation that occurs and the switching on of the estrogen pathway.

ROWAN T CHLEBOWSKI, MD, PhD: This was a negative study presented by John Robertson. It is a preclinical study that examined the combination of high-dose fulvestrant and anastrozole in the neoadjuvant setting. The study demonstrated that the combination of fulvestrant and anastrozole resulted in the same change in the Ki-67 proliferative index as did anastrozole by itself.

DR LOVE: What are your thoughts regarding the question of whether to bring high-dose fulvestrant into an adjuvant trial?

DR CHLEBOWSKI: I thought for a while that the National Institute of Canada had a slot and was waiting for the results from the FACT study. I don't know if that's still the case. Of course, now you run into the issue of patent life, funding and other similar issues, but it would seem like this would be a reasonable thing to put in an adjuvant

setting. I know some clinicians would use it if they had a patient who couldn't tolerate a standard postmenopausal hormone therapy. Obviously, there are no data to support that type of use.

Prof Robertson is Professor of Surgery and Head of the Academic Division of Breast Surgery at Nottingham City Hospital in Nottingham, United Kingdom.

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.