5 Minute JournalClub

Key SABCS Presentations

Issue 5, 2011

Fulvestrant 500 mg or Anastrozole as First-Line Treatment in Advanced Breast Cancer

For more visit ResearchToPractice.com/5MJCSABCS2011

Research To Practice®

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 in which 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

- Use new research findings to refine or validate current fulvestrant dosing and its sequential placement in the treatment of advanced breast cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentation, read the commentary and complete the Educational Assessment and Credit Form located at CME.ResearchToPractice.com.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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:

Harold J Burstein, MD, PhD
Associate Professor of Medicine
Harvard Medical School
Breast Oncology Center
Dana-Farber Cancer Institute
Boston, Massachusetts

No real or apparent conflicts of interest to disclose.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: Abraxis BioScience Inc, a wholly owned subsidiary of Celgene Corporation, Allos Therapeutics, Amgen Inc, AstraZeneca Pharmaceuticals LP, Aureon Laboratories Inc, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, Lilly USA LLC, Millennium, The Takeda Oncology Company, Myriad Genetics Inc, Novartis Pharmaceuticals Corporation, OSI Oncology, Sanofi-Aventis and Seattle Genetics.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Novartis Pharmaceuticals Corporation and Sanofi-Aventis.

Last review date: February 2011
Expiration date: February 2012

5 MinuteJournalClub

Key SABCS Presentations
Issue 5, 2011

Click here for key papers on endocrine/metabolic issues from the 2010 SABCS

The first targeted therapy for cancer came in the form of an innocuous-appearing pill that for many patients with ER-positive breast tumors was more efficacious than chemotherapy (CT). Thanks to mavens like Craig Jordan, we have known for quite a while that the antitumor effect of tamoxifen (TAM) comes via a metabolite (endoxifen), and thus it made sense that patients with genetic deficiencies of the activating enzyme (CYP2D6) might experience less or no treatment benefit. That being said, prior studies attempting to validate this concept have yielded conflicting results.

Related to this issue, a number of prominent TAM/investigator advocates have hypothesized that the 20 percent reduction in recurrences in trials of adjuvant AIs versus TAM wasn't the result of inherently greater antitumor efficacy but rather because a fraction of women in these studies actually had CYP2D6 deficiency. **Two major presentations** at San Antonio pretty much debunked that theory and added several more nails to the CYP2D6 coffin.

For these studies, investigators accessed available tissue from patients enrolled in two of the largest AI trials — ATAC (anastrozole) and BIG 1-98 (letrozole) — assayed for CYP2D6 genotypes and found no correlation with recurrence rate in patients receiving AIs (as would be expected) or TAM. Although investigators seem ready to abandon CYP2D6 testing in clinical practice outside a protocol setting, it is important to consider that the majority of the available data — including these two new reports — are in postmenopausal subsets. However, TAM is now most commonly used in premenopausal patients, where the hormonal environment (high estrogen levels) is very different. Vered Stearns and ECOG just opened a new trial in metastatic disease to further study this continuing story. Our recent Patterns of Care survey demonstrated that 41 percent of community oncologists have ordered a CYP2D6 assay at least once, and although that practice now seems more questionable than ever, it still makes sense to avoid inhibitors of the enzyme like SSRIs in patients receiving TAM.

We've come a long way in understanding endocrine and metabolic issues in breast cancer in the four decades since TAM first entered oncology practice, and in this issue of *5-Minute Journal Club* we peruse several other interesting related San Antonio papers.

1. **More on 500-mg fulvestrant dosing**

John Robertson presented additional data from the FIRST trial evaluating front-line fulvestrant in metastatic disease, which continues to report benefit with the increased monthly dose after loading. The current data demonstrate a median time to progression of 23.4 months for fulvestrant 500 compared to 13.1 months with anastrozole.

2. **Treatment of breast cancer during pregnancy**

This landmark European registry reported on 313 women diagnosed with breast cancer during pregnancy, including 142 who received CT while still pregnant and 118 who received it immediately after childbirth (with medians of 20 and 28 weeks of gestation, respectively, at the time of diagnosis). Breast cancer and fetal outcomes were similar in the two groups but premature delivery was more common (33 percent) in the delayed group, probably to hasten the time to receive CT. The authors concluded that oncologists should generally use CT during pregnancy rather than expose women and fetuses to the potential complications of premature delivery.

3. **Three papers demonstrating the negative prognostic impact of obesity in the adjuvant setting**

The 2005 presentation by Rowan Chlebowski of the WINS trial demonstrated fewer breast cancer recurrences in women randomly assigned to counseling to reduce dietary fat, and this sparked a series of related analyses along with three new important data sets in San Antonio. Of particular note was an extraordinary presentation by Joe Sparano of data from several recent ECOG randomized trials demonstrating that obese (BMI > 30 kg/m^2) patients had an increased risk of recurrence independent of other factors. This general body of work continues to have important practice and translational research implications.

Next up on this San Antonio highlights series: More on the increasingly complex world of HER2-positive breast cancer.

Neil Love, MD
Research To Practice
Miami, FL

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates each educational activity for a maximum of 0.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in each activity.

This program is supported by educational grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Genomic Health Inc, Novartis Pharmaceuticals Corporation and Sanofi-Aventis.

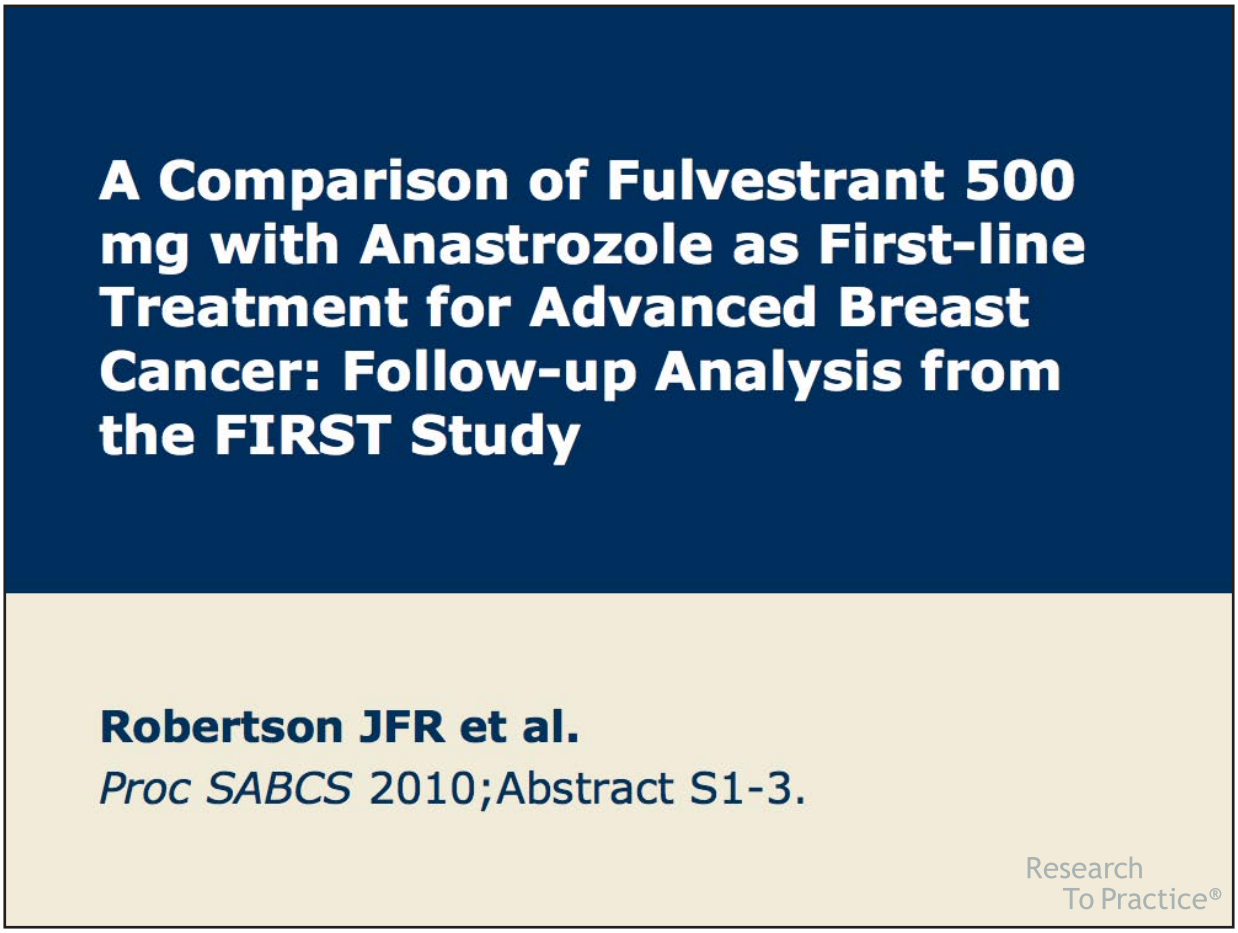
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

Fulvestrant 500 mg or Anastrozole as First-Line Treatment in Advanced Breast Cancer

Presentation discussed in this issue

Robertson JFR et al. **A comparison of fulvestrant 500 mg with anastrozole as first-line treatment for advanced breast cancer: Follow-up analysis from the FIRST study.** San Antonio Breast Cancer Symposium 2010;**Abstract S1-3**.

Slides from a presentation at SABCS 2010 and transcribed comments from a recent interview with Harold J Burstein, MD, PhD (12/22/10)



Methods

- **Objective**
  - To report follow-up data for time to progression (TTP) and time to treatment failure (TTF) from the FIRST study of fulvestrant 500 mg versus anastrozole in the first-line metastatic setting
- FIRST: A Phase II, open-label study
  - **Eligibility**
    - ER-positive
    - Postmenopausal
    - Advanced disease
  - Patients were randomly assigned 1:1 to fulvestrant 500 mg (d0, 14, 28 and then q 4wk) or anastrozole 1 mg daily.

Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

Research To Practice®

FIRST Study Endpoints

- **Primary**
  - Clinical benefit rate
- **Secondary**
  - Objective response rate
  - Time to progression (TTP)
  - Duration of response
  - Duration of clinical benefit
  - Safety
- **Exploratory**
  - Best response to subsequent therapy

These endpoints were planned for the primary data cutoff

Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

Research To Practice®

Clinical Benefit Rate

Fulvestrant 500 mg n = 102	Anastrozole 1 mg n = 103	Odds ratio (95% CI)	Absolute difference (95% CI)
72.5%	67.0%	1.30 (0.72, 2.38)	5.6% (-7.8 to 15.8%)

Robertson JF et al. *J Clin Oncol* 2009;27(27):4530-5.

Research To Practice®

TTP Analysis

Patients experiencing disease progression	Fulvestrant 500 mg n = 102	Anastrozole 1 mg n = 103	Hazard ratio (95% CI)	*p*-value
At primary cutoff[1]	29.4%	41.7%	0.63 (0.39, 0.99)	0.05
Updated analysis[2]	61.8%	76.7%	0.66 (0.47, 0.92)	0.01

Primary analysis median follow-up
Fulvestrant 500 mg - 8.0 months
Anastrozole 1 mg - 5.9 months

Updated analysis median follow-up
Fulvestrant 500 mg - 18.8 months
Anastrozole 1 mg - 12.9 months

[1] Robertson JF et al. *J Clin Oncol* 2009;27(27):4530-5; [2] Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

Research To Practice®

TTP Analysis

Median time to progression	Fulvestrant 500 mg n = 102	Anastrozole 1 mg n = 103	Hazard ratio (95% CI)	*p*-value
At primary cutoff[1]	Not calculable	12.5 months	0.63 (0.39, 0.99)	0.05
Updated analysis[2]	23.4 months	13.1 months	0.66 (0.47, 0.92)	0.01

Primary analysis median follow-up
Fulvestrant 500 mg - 8.0 months
Anastrozole 1 mg - 5.9 months

Updated analysis median follow-up
Fulvestrant 500 mg - 18.8 months
Anastrozole 1 mg - 12.9 months

[1] Robertson JF et al. *J Clin Oncol* 2009;27(27):4530-5; [2] Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

TTF Analysis

Patients experiencing treatment failure[1]	Fulvestrant 500 mg n = 102	Anastrozole 1 mg n = 103	Hazard ratio (95% CI)	*p*-value
Treatment failures	74.5%	84.5%	0.73 (0.54, 1.00)	0.05
Median TTF (months)	17.6	12.7		

Updated analysis median follow-up
Fulvestrant 500 mg - 18.8 months; Anastrozole 1 mg - 12.9 months

[1] Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

Safety

- No significant differences between the groups in pre-specified adverse events[1]:
  - GI disturbances, joint disorders, hot flashes, urinary tract infections, weight gain, endometrial dysplasia, ischemic cardiovascular disorders, osteoporosis, thromboembolic events and vaginitis
- Total of 22 serious adverse events (SAEs) in updated analysis period (n = 14)[2]
  - 12 SAEs in fulvestrant group (n = 7)
  - 10 SAEs in anastrozole group (n = 7)
- No new safety concerns with fulvestrant 500 mg arising from SAEs reported with longer follow-up[2]

[1] Robertson JF et al. *J Clin Oncol* 2009;27(27):4530-5; [2] Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

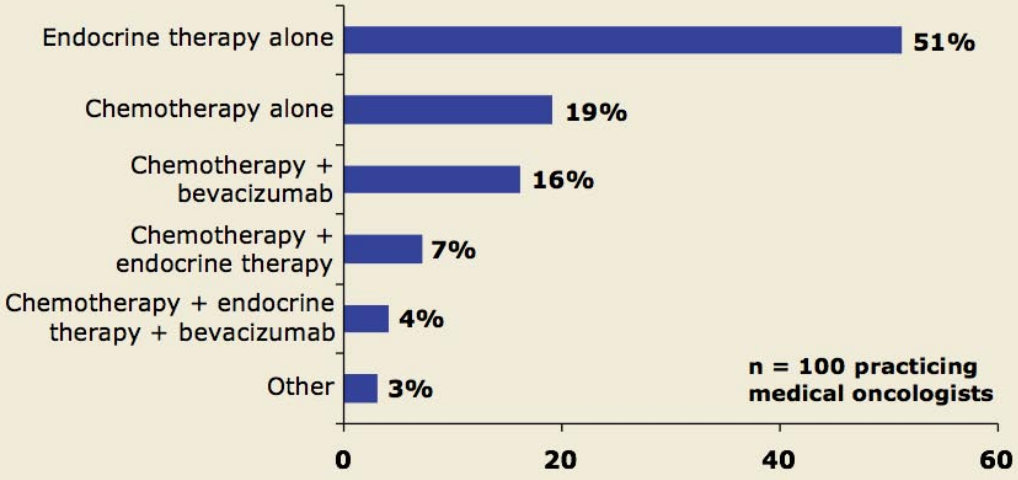
Author Summary

- TTP benefits for fulvestrant 500 mg were significantly greater than those of anastrozole 1 mg with longer follow-up.
  - Patients experiencing disease progression: 61.8% vs 76.7% (p = 0.01)
  - Median TTP: 23.4 months vs 13.1 months (p = 0.01)
- TTP benefit of fulvestrant 500 mg was consistent in all predefined subgroups (data not shown).
- Patients who experience disease progression on either fulvestrant or anastrozole remain sensitive to subsequent endocrine treatments.

Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

A 60-yo postmenopausal woman with a 2.1-cm ER+/PR+/HER2-, node+ IDC treated with ddAC → T followed by anastrozole develops asymptomatic lung and bone mets

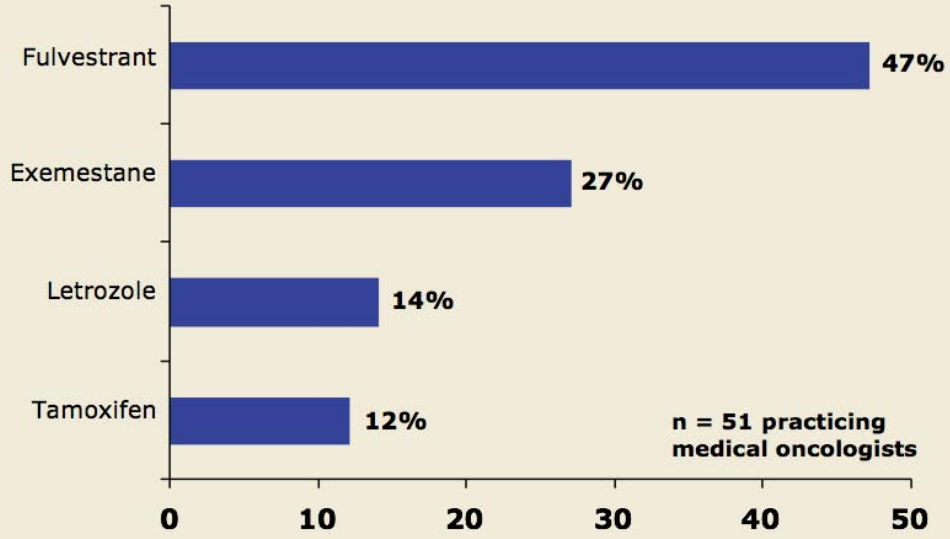
In addition to bisphosphonates, which of the following systemic treatments would you recommend?



Patterns of Care in Breast Cancer, Research To Practice 2010.

Research To Practice®

Which endocrine therapy would you recommend for the previous patient?

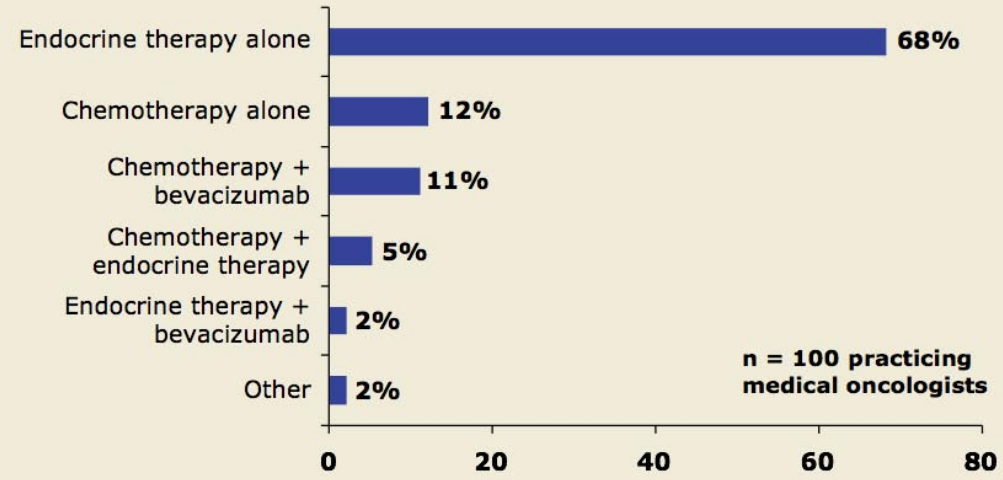


Patterns of Care in Breast Cancer, Research To Practice 2010.

Research To Practice®

A 75-yo woman with a 2.1-cm ER+/PR+/HER2-, node+ IDC treated with ddAC → T followed by anastrozole develops asymptomatic lung and bone mets

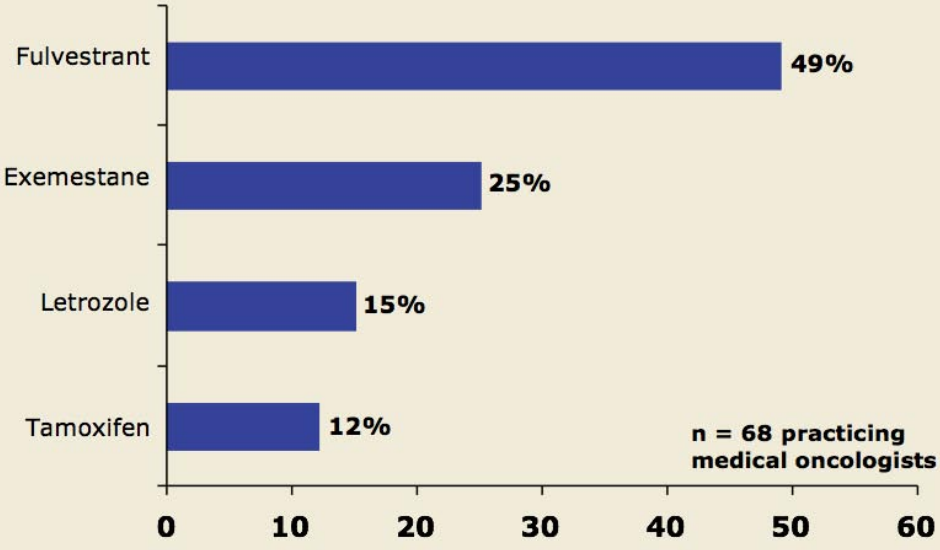
In addition to bisphosphonates, which of the following systemic treatments would you recommend?



Patterns of Care in Breast Cancer, Research To Practice 2010.

Research To Practice®

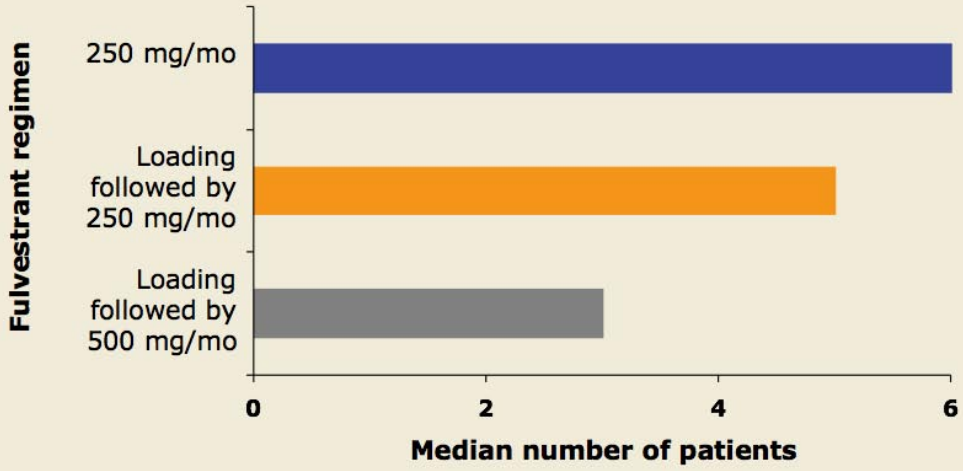
Which endocrine therapy would you recommend for the previous patient?



Patterns of Care in Breast Cancer, Research To Practice 2010.

Research To Practice®

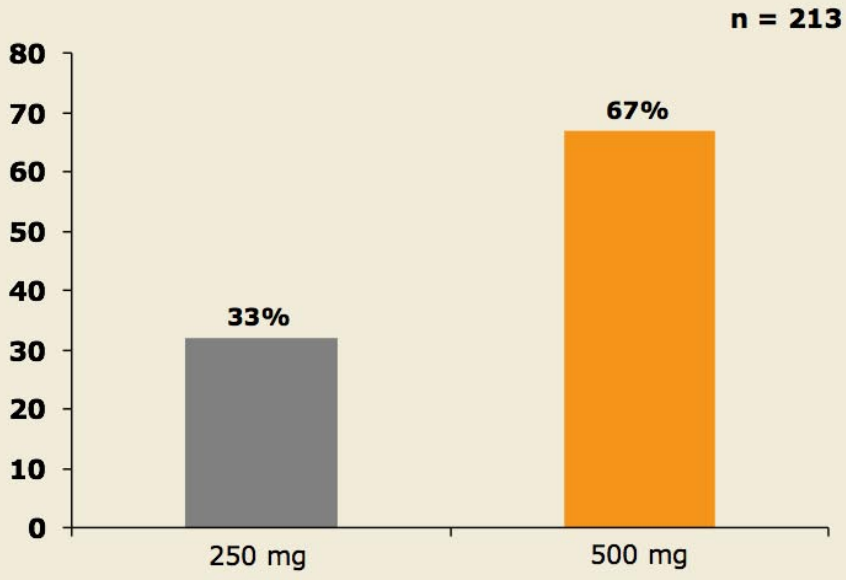
For how many patients have you used the following fulvestrant regimens in the past year?



Patterns of Care in Breast Cancer, Research To Practice 2010.

Research To Practice®

What <u>monthly</u> dose of fulvestrant do you try to use in metastatic BC, regardless of whether you use a loading dose?



Research To Practice Premeeting Survey, *Real-Life Decisions: Practical Perspectives on the Management of Early and Advanced Breast Cancer*, held at SABCS 2010.

Research To Practice®

Investigator Commentary: FIRST Study of First-Line High-Dose Fulvestrant versus Anastrozole

FIRST was a randomized, Phase II trial that compared fulvestrant 500 mg to anastrozole as initial treatment for postmenopausal women with ER-positive metastatic breast cancer. In this medium-sized study, the investigators demonstrated that the higher dose of fulvestrant was at least as good as and maybe better than the aromatase inhibitor, with a median time to disease progression of 13 months for anastrozole and 23 months for fulvestrant. The overall response rates were comparable between fulvestrant and anastrozole.

This study provides an opportunity to use fulvestrant earlier in the treatment of ER-positive metastatic breast cancer, as so many of these patients have already received tamoxifen or an aromatase inhibitor as part of their adjuvant therapy. It's not clear if this study redefines the way we will conventionally use these agents, but it's a nice demonstration that fulvestrant is an active agent.

Interview with Harold J Burstein, MD, PhD, December 22, 2010

Research
To Practice®