JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

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Submitted November 25, 2008; accepted April 16, 2009; published online ahead of print at www.jco.org on August 24, 2009.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).



0732-183X/09/2727-4530/$20.00

DOI: 10.1200/JCO.2008.21.1136

## ABSTRACT

### Purpose
To compare the clinical activity of the pure antiestrogen fulvestrant at 500 mg/mo (double the approved dose) with the aromatase inhibitor anastrozole as first-line endocrine therapy for advanced hormone receptor–positive breast cancer in postmenopausal women.

### Patients and Methods
FIRST (Fulvestrant First-Line Study Comparing Endocrine Treatments) is a phase II, randomized, open-label, multicenter study of a fulvestrant high-dose (HD) regimen (500 mg/mo plus 500 mg on day 14 of month 1) versus anastrozole (1 mg/d). The primary efficacy end point was clinical benefit rate (CBR), defined as the proportion of patients experiencing an objective response (OR) or stable disease for ≥ 24 weeks. The primary analysis was performed 6 months after the last patient was randomly assigned.

### Results
CBR was similar for fulvestrant HD (n = 102) and anastrozole (n = 103), 72.5% *v* 67.0%, respectively (odds ratio, 1.30; 95% CI, 0.72 to 2.38; $P = .386$). Objective response rate (ORR) was also similar between treatments: fulvestrant HD, 36.0%; anastrozole, 35.5%. Time to progression (TTP) was significantly longer for fulvestrant versus anastrozole (median TTP not reached for fulvestrant HD *v* 12.5 months for anastrozole; hazard ratio, 0.63; 95% CI, 0.39 to 1.00; $P = .0496$). Duration of OR and CB also numerically favored fulvestrant HD. Both treatments were well tolerated, with no significant differences in the incidence of prespecified adverse events.

### Conclusion
First-line fulvestrant HD was at least as effective as anastrozole for CBR and ORR and was associated with significantly longer TTP. Fulvestrant HD was generally well tolerated, with a safety profile similar to that of anastrozole.

*J Clin Oncol 27:4530-4535. © 2009 by American Society of Clinical Oncology*

## INTRODUCTION

Fulvestrant (Faslodex, AstraZeneca, Macclesfield, United Kingdom) is an estrogen receptor (ER) antagonist with no known agonist effects[1] and a mode of action distinct from other endocrine agents.[2] The clinical effectiveness of fulvestrant as a treatment for advanced breast cancer has previously been demonstrated at the approved dose (AD; 250 mg/mo) in several phase III clinical trials.[3,4] A fulvestrant loading-dose regimen has also been shown to be effective following nonsteroidal aromatase inhibitor (AI) therapy.[5] However, there is evidence to suggest that doses of fulvestrant higher than 250 mg may have greater pharmacodynamic activity against the ER pathway.[6] It has been observed that ER, progesterone receptor (PgR), and Ki67 are downregulated by fulvestrant in a dose-dependent manner and that the maximum effect on these markers is not reached with the 250-mg dose.[7] In addition, dose-dependent clinical activity has been observed for fulvestrant: for example, in the initial clinical studies, patients receiving fulvestrant at 125 mg/mo showed a lower response rate and shorter time to progression (TTP) than those receiving fulvestrant at the approved dose.[3,6]

The activity of a fulvestrant high-dose (HD; 500 mg/mo) regimen has been investigated in two recent studies. A small, pilot study in Japanese women (n = 20) showed fulvestrant HD to have clinical activity in the treatment of advanced or recurrent breast cancer, to be well tolerated, and to result in plasma levels approximately double those seen with fulvestrant AD.[8] Subsequently, a neoadjuvant study comparing fulvestrant AD and HD

(n = 211) reported that significantly greater Ki67 and ER downregulation was achieved with the HD compared with the AD regimen and that both doses were well tolerated.[9]

Third-generation AIs, such as anastrozole and letrozole, have shown superior efficacy and tolerability compared with tamoxifen and are currently considered standard first-line treatment for advanced breast cancer in postmenopausal women with hormone receptor–positive (HR+) disease.[10,11] Previous phase III trials have demonstrated that fulvestrant AD is at least as effective as anastrozole as a second-line treatment for advanced breast cancer following antiestrogen therapy.[3] The current study (FIRST; Fulvestrant First-Line Study Comparing Endocrine Treatments) examines the efficacy of fulvestrant HD versus anastrozole in the first-line setting. Here, we present the data from the primary analysis of this trial.

## PATIENTS AND METHODS

### Study Design and Treatments

This was a phase II, open-label, randomized, multicenter, parallel-group trial of fulvestrant HD versus anastrozole as first-line treatment for postmenopausal women with advanced breast cancer (http://clinicaltrials.gov/ct2/show/NCT00274469). After enrollment, patients were randomly assigned to receive either fulvestrant HD (500 mg; ie, two 250 mg intramuscular injections on days 0, 14 ± 3, 28 ± 3, and every 28 ± 3 days thereafter) or anastrozole (1 mg/d orally). Anastrozole was dispensed once every 28 ± 7 days; that is, the visit schedule and assessment frequency were symmetric across the study arms. Patients received treatment until they experienced disease progression or another event requiring discontinuation.

The study was performed in accordance with the Declaration of Helsinki and was consistent with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice. The study protocol, patient consent forms, and information sheets were approved by the relevant independent ethics committees and institutional review boards. In North America, the study was conducted under a Food and Drug Administration investigational new drug application.

### Patients

Eligible patients were postmenopausal women with ER+ and/or PgR+ locally advanced or metastatic breast cancer who were not amenable to therapy of curative intent. Prior endocrine therapy for advanced disease was not permitted, but patients could have received adjuvant endocrine therapy for early disease, provided it was completed more than 12 months before random assignment. In addition, patients had to have a WHO performance status of zero to 2 and measurable disease per modified RECIST (Response Evaluation Criteria in Solid Tumors) criteria, or at least one bone lesion with a lytic component (as defined in the protocol).

Exclusion criteria were the presence of life-threatening metastases; current or prior malignancy (except breast cancer or adequately treated skin cancer or in situ carcinoma of the cervix); treatment with a nonapproved or experimental drug in the 4 weeks before being randomly assigned; abnormal laboratory test values; history of bleeding diatheses; long-term anticoagulant therapy; hypersensitivity to excipients of fulvestrant, AIs, or castor oil; or any severe concomitant conditions. All recruited patients provided written informed consent before entering the study.

### Efficacy

The primary end point was clinical benefit rate (CBR), which was defined as the proportion of all randomly assigned patients who had a best overall response of a complete response, a partial response, or stable disease (SD) for at least 24 weeks (SD ≥ 24 weeks). Secondary end points were objective response rate (ORR; the proportion of patients with a best overall response of either a complete response or a partial response), TTP, duration of clinical benefit (DoCB) and duration of response (DoR). TTP was assessed in all randomly assigned patients. DoCB was assessed only for patients who experienced clinical benefit. ORR and DoR were assessed only in evaluable patients; ie, those with measurable disease at baseline for ORR and those with measurable disease who achieved a response for DoR.

Tumor dimensions were assessed by site investigators, and response to treatment was determined according to a modified RECIST scheme, where progression of lytic bone lesions was regarded as a RECIST progression event. Tumor assessment (clinical and radiologic) occurred at the screening visit and then every 12 ± 2 weeks following random assignment until progression. Copies of scans for all patients were collated and reviewed in a blinded manner by an independent radiologist working for a contract services organization (BioImaging Technologies, Leiden, the Netherlands).

### Safety and Tolerability

Assessment of the safety and tolerability of fulvestrant HD and anastrozole was a secondary study end point. Laboratory tests and incidence of adverse events (AEs) were recorded throughout the study. The frequency of 10 prespecified AEs was also evaluated in each treatment group.

**Table 1.** Baseline Patient and Disease Characteristics

| Characteristic | Fulvestrant HD (n = 102) No. | % | Anastrozole 1 mg (n = 103) No. | % |
|---|---|---|---|---|
| Age, years | | | | |
| Median | 66 | | 68 | |
| Range | 40-89 | | 48-87 | |
| ER and PgR status | | | | |
| HR+ | 102 | 100.0 | 103 | 100.0 |
| ER+, PgR+ | 78 | 76.5 | 78 | 75.7 |
| ER+, PgR– | 19 | 18.6 | 19 | 18.4 |
| ER+, PgR unknown | 1 | 1.0 | 3 | 2.9 |
| ER–, PgR+ | 3 | 2.9 | 3 | 2.9 |
| ER unknown, PgR+ | 1 | 1.0 | 0 | |
| HER2 status | | | | |
| 2+/3+ | 19 | 18.6 | 19 | 18.4 |
| Negative | 48 | 47.1 | 49 | 47.6 |
| Unknown | 35 | 34.3 | 35 | 34.0 |
| Disease stage | | | | |
| Locally advanced only | 19 | 18.6 | 18 | 17.5 |
| Metastatic | 83 | 81.4 | 85 | 82.5 |
| Measurable disease | 89 | 87.3 | 93 | 90.3 |
| Metastatic sites | | | | |
| Bone only | 10 | 9.8 | 8 | 7.8 |
| Soft tissue only | 2 | 2.0 | 0 | |
| Any visceral disease | 48 | 47.1 | 58 | 56.3 |
| Any liver metastases | 15 | 14.7 | 14 | 13.6 |
| Any lung metastases | 30 | 29.4 | 42 | 40.8 |
| Prior endocrine treatment* | | | | |
| No prior endocrine treatment | 73 | 71.6 | 80 | 77.7 |
| Completed adjuvant endocrine treatment for early disease > 12 months prior to random assignment | 28 | 27.5 | 23 | 22.3 |
| Prior chemotherapy | | | | |
| Chemotherapy for advanced breast cancer | 0 | 0.0 | 0 | 0.0 |
| Adjuvant chemotherapy received for early breast cancer | 29 | 28.4 | 25 | 24.3 |

Abbreviations: HD, high dose; ER, estrogen receptor; PgR, progesterone receptor; HR, hormone receptor.
*One patient in the fulvestrant HD group received prior adjuvant endocrine treatment within 12 months of being randomly assigned.

**Table 2.** Response to Treatment

| All Randomly Assigned Patients | Best Overall Response | Fulvestrant HD (n = 102) No. | Fulvestrant HD (n = 102) % | Anastrozole 1 mg (n = 103) No. | Anastrozole 1 mg (n = 103) % |
|---|---|---|---|---|---|
| CB | Complete response | 0 | | 1 | 1.0 |
| | Partial response | 32 | 31.4 | 32 | 31.1 |
| | Stable disease ≥ 24 weeks | 42 | 41.2 | 36 | 35.0 |
| | Total with CB | 74 | 72.5 | 69 | 67.0 |
| No CB | Stable disease < 24 weeks | 15 | 14.7 | 12 | 11.7 |
| | Progression | 10 | 9.8 | 20 | 19.4 |
| | Not evaluable | 3 | 2.9 | 2 | 1.9 |
| | Total with no CB | 28 | 27.5 | 34 | 33.0 |

Abbreviation: CB, clinical benefit.

### *Statistical Analysis*

Statistical analyses were performed using SAS software version 8.2 (SAS Institute, Cary, NC). Sample size calculations for this noninferiority trial estimated that 100 randomly assigned patients per treatment group would be required to give 80% power to rule out an absolute deficiency of 20% in CBR for fulvestrant HD with a two-sided 95% CI. The primary analysis was stipulated in the protocol to occur 6 months after the last patient had been randomly assigned.

The primary end point (CBR) was compared in the two groups using a logistic regression model where the absolute differences, odds ratios, and associated 95% CIs and *P* values were reported. The same methods were used for the secondary end point of ORR. Kaplan-Meier plots were produced for TTP, DoR, and DoCB, and a log-rank test was used to generate the hazard ratios, 95% CIs, and *P* values for TTP. Treatment differences in the incidence of prespecified AEs were evaluated using a two-sided Fisher's exact test.

## RESULTS

### *Patients*

In total, 205 patients were randomly assigned: 102 to fulvestrant HD and 103 to anastrozole (Appendix Fig A1, online only). Patients were recruited from 62 centers in nine countries (Brazil, Bulgaria, Czech Republic, France, Italy, Poland, Spain, United Kingdom, and the United States). All randomly assigned patients were included in the primary analysis, although one fulvestrant patient who received no randomly assigned treatment was excluded from the safety population. Overall, 182 patients were assessable for objective response.

Baseline characteristics, including treatment history, were well balanced across the treatment groups (Table 1). Median age was 67 years, the majority of patients (76.1%) were ER+ and PgR+, and 82% had metastatic disease. In total, 153 (74.6%) patients were completely endocrine-therapy naive, whereas 25.4% of patients had previously completed adjuvant endocrine treatment for early disease.

### *Efficacy*

Analysis of the primary end point demonstrated that fulvestrant HD was at least as effective as anastrozole, with CBRs of 72.5% and 67.0%, respectively (odds ratio, 1.30; 95% CI, 0.72 to 2.38; $P = .386$; Table 2). The absolute treatment difference was 5.6% (95% CI, −7.8% to 15.8%). The blinded, independent review of the RECIST data used to determine CBR data resulted in concordance rates of 88.4% for fulvestrant HD and 86.3% for anastrozole.

Fulvestrant HD was also as effective as anastrozole in terms of ORR in evaluable patients (n = 89 for fulvestrant HD and n = 93 for anastrozole), which was virtually identical in the two groups (fulvestrant HD, 36.0%; anastrozole, 35.5%; odds ratio, 1.02; 95% CI, 0.56 to 1.87; $P = .947$). In the overall population, more patients in the fulvestrant HD group (41.2%) achieved a best overall response of SD ≥ 24 weeks compared with patients in the anastrozole group (35.0%), and fewer fulvestrant HD–treated patients showed a best overall response of progressive disease (9.8% *v* 19.4% in the anastrozole group; Table 2). The average time between RECIST assessments was 78 days in the fulvestrant HD group and 74 days in the anastrozole group.

At data cutoff, 29.4% of fulvestrant HD–treated patients had progressed compared with 41.7% of those in the anastrozole group. TTP was significantly longer for fulvestrant HD (hazard ratio, 0.63; 95% CI, 0.39 to 1.00; $P = .0496$; Fig 1). The median TTP for anastrozole was 12.5 months; the median TTP for fulvestrant HD had not been reached at the time of the analysis.

Reflecting the TTP advantage, there were also differences in the DoR and DoCB curves favoring fulvestrant HD (Figs 2A and 2B). The median DoR for anastrozole was 14.2 months. The median DoR for fulvestrant and the median DoCB for both treatments had not been reached at the time of the analysis.

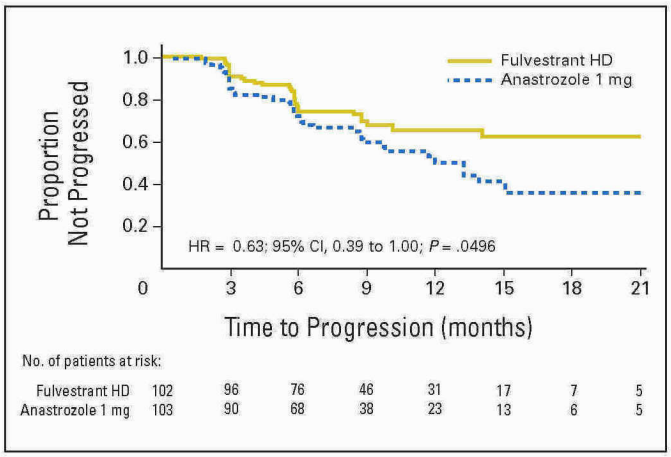


**Fig 1.** Kaplan-Meier plot for time to progression. HD, high dose; HR, hazard ratio.

  

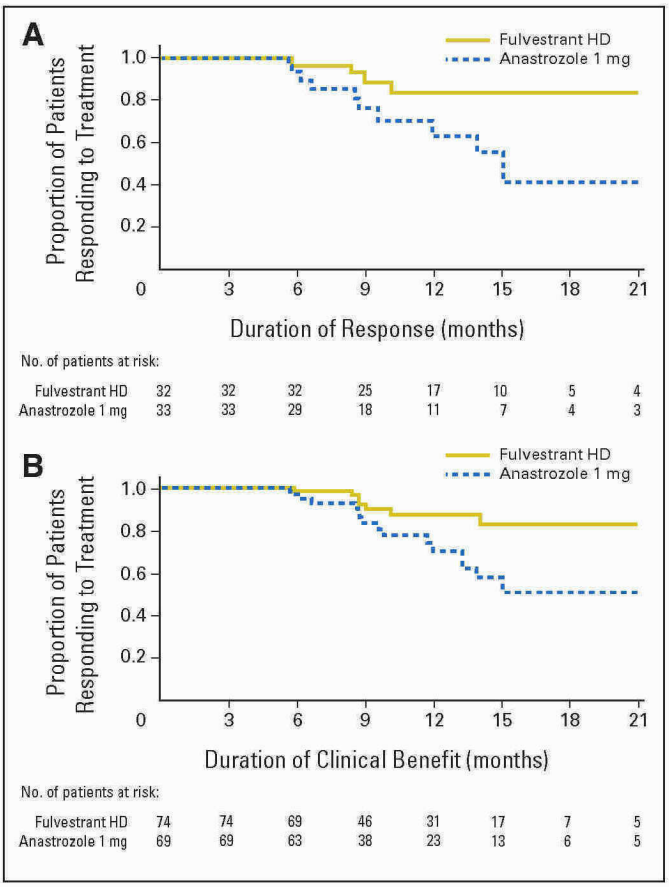


**Fig 2.** Kaplan-Meier plots for (A) duration of response and (B) duration of clinical benefit. HD, high dose.

### *Tolerability*

Median follow-up was 8 months (242.5 days) and 5.9 months (179 days), with median drug exposures of 9.2 months (range, 1 to 20.5 months) in the fulvestrant HD group and 6.1 months (range, 0 to 19.8 months) in the anastrozole group. Follow-up was defined as the number of days between random assignment and either progression or time of last RECIST assessment. The number of patients remaining on randomized treatment at the time of data cutoff was 64 (62.7%) for fulvestrant HD and 53 (51.5%) for anastrozole.

Both fulvestrant HD and anastrozole were well tolerated. A total of 143 (70.1%) patients experienced at least one AE; the incidence of serious AEs was 11.9% with fulvestrant HD and 9.7% with anastrozole. Only three patients in each group (fulvestrant, 3.0%; anastrozole, 2.9%) discontinued treatment because of an AE. Overall, 11 patients (5.4%) died during the study; the predominant cause of death was disease progression. Only one patient (from the anastrozole group) died because of an AE, which was not considered to be treatment-related.

The most common AEs in the fulvestrant HD group were bone pain (13.9%), nausea (10.9%), arthralgia (9.9%), constipation (9.9%), vomiting (8.9%), and dyspnea (8.9%). In the anastrozole group, the most common AEs were hot flashes (13.6%), headache (12.6%), bone pain (9.7%), arthralgia (8.7%), and myalgia (8.7%). Six patients (5.9%) treated with fulvestrant HD reported 14 instances of injection-site pain (1.3% of all administrations; an administration comprises two 250-mg intramuscular injections). The most common treatment-related AEs in the fulvestrant HD group were hot flashes (7.9%), injection-site pain (5.0%), and hyperhidrosis (4.0%); in the anastrozole group, the most common treatment-related AEs were hot flashes (12.6%), arthralgia (5.8%), and headache (5.8%). There were no significant differences between treatments in the incidence of any of the 10 prespecified AEs (Table 3). There were no clinically important changes in hematologic or clinical chemistry parameters with either treatment.

## DISCUSSION

This was an open-label, first-line study of fulvestrant HD versus anastrozole in predominantly endocrine treatment–naive patients with advanced breast cancer. The high CBRs for fulvestrant HD and anastrozole of 72.5% and 67.0%, respectively, confirm the high clinical efficacy of both agents. Furthermore, results from the analysis of the primary end point (CBR) indicated that fulvestrant HD was at least as effective as anastrozole. The secondary end points further confirmed the activity of fulvestrant HD in this setting, most notably median TTP, which was estimated to be 60% longer in patients treated with fulvestrant HD compared with TTP for those treated with anastrozole, a statistically significant difference. DoR and DoCB data also favored fulvestrant HD.

This is the first clinical trial to compare fulvestrant with anastrozole in first-line advanced breast cancer and to show that another endocrine agent may be more effective than a third-generation AI in this setting. Although this was an open-label, phase II study, CBR and ORR data for anastrozole (67.0% and 35.5%, respectively) were consistent with previously reported data for an AI in the first-line advanced disease setting (CBRs of 49% to 59% and ORRs of 28% to 41%).[12-14] There was also a close correspondence between the CBR results derived from the centers and those from the independent review with no evidence of bias. TTP was a secondary end point, and independent review beyond the first 6 months was not scheduled. TTP was therefore based on an open-label assessment by the treating clinician. When a statistically significant increase in TTP was identified in

**Table 3.** Incidence of Prespecified Adverse Events (Safety Population)

| Prespecified Adverse Event | Fulvestrant HD (n = 101) No. | % | Anastrozole 1 mg (n = 103) No. | % | P* |
|---|---|---|---|---|---|
| Endometrial dysplasia | 0 | | 0 | | 1.000 |
| GI disturbances | 28 | 27.7 | 23 | 22.3 | .420 |
| Hot flashes | 13 | 12.9 | 14 | 13.6 | 1.000 |
| Ischemic cardiovascular disorders | 0 | | 1 | 1.0 | 1.000 |
| Joint disorders | 14 | 13.9 | 10 | 9.7 | .391 |
| Osteoporosis | 0 | | 0 | | 1.000 |
| Thromboembolic events | 0 | | 0 | | 1.000 |
| Urinary tract infections | 4 | 4.0 | 1 | 1.0 | .210 |
| Vaginitis | 0 | | 0 | | 1.000 |
| Weight gain | 1 | 1.0 | 0 | | .495 |

Abbreviation: HD, high dose.
*Two-sided Fisher's exact test.

the primary analysis, a retrospective inspection of the number of progression events determined by central review was considered. This was possible only in a subset of patients; nonetheless, the treatment effect remained numerically in favor of fulvestrant in the subset of patients in whom central review of progression was determined.

This study of fulvestrant HD was initiated because of previous clinical and biologic studies that suggested there was a dose response to fulvestrant and that 250 mg might not be the optimal dose. This observation was based on a presurgical study that showed a dose response for three doses of fulvestrant (50 mg, 125 mg, and 250 mg) without reaching a plateau on the biologic effect.[7] Similarly, a phase III clinical study had shown that the hazard ratio for estimating the treatment effect of fulvestrant 125 mg on TTP was inferior to fulvestrant 250 mg. The median TTP for fulvestrant AD (250 mg) was numerically but not statistically greater than that for anastrozole 1 mg.[3] The current study adds to the available data on the dose response of fulvestrant, reporting that the TTP for fulvestrant HD (ie, 500 mg) is statistically longer than that for anastrozole 1 mg.

Numeric benefits in terms of DoR and DoCB have also been observed in previous phase III trials of fulvestrant. In a second-line trial following progression or recurrence on tamoxifen, median DoR was 16.7 months for fulvestrant AD and 13.7 months for anastrozole.[3] Similarly, in a second-/third-line trial following progression or recurrence on a nonsteroidal AI, median DoCB was 9.3 months for a fulvestrant loading-dose regimen versus 8.3 months for exemestane.[5] In a previous first-line trial of fulvestrant AD versus tamoxifen (Trial 0025), fulvestrant did not meet the criteria for noninferiority.[15] However, a relatively large proportion of patients in Trial 0025 had an unknown HR status, and a preplanned subgroup analysis showed that in patients with confirmed HR+ disease, the activity of fulvestrant was similar to that of tamoxifen. In line with this, the FIRST study reported here included only HR+ patients. Indirect cross-trial comparisons between Trial 0025[15] and FIRST suggest that fulvestrant HD may offer higher CBR (from 57.1% to 72.5%) and prolonged TTP (from 8.2 months to approximately 20 months), compared with fulvestrant AD in the same setting, although this remains to be confirmed in direct comparative phase III trials.

The early separation of the Kaplan-Meier curves for TTP suggest that fulvestrant HD may be of benefit for patients who progress early, while the longer DoR and DoCB indicate that patients' responses are more durable during fulvestrant HD treatment. The DoR and DoCB data reported here are supportive of observations in previous fulvestrant studies suggesting that prolonged response may be a consistent benefit of fulvestrant treatment. These observations may be attributable to the distinct mode of action of fulvestrant with downregulation of the ER resulting in less de novo resistance and delayed acquired resistance during fulvestrant treatment. These data are promising and in line with the increased Ki67 and ER downregulation seen for fulvestrant HD versus AD in the recent NEWEST (Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors) study.[9] Collectively, these data provide further support for the improved clinical activity of the fulvestrant HD regimen.

In further agreement with previous studies,[8,9] the fulvestrant HD regimen appeared to be well tolerated, with an AE profile comparable to that of anastrozole and consistent with that previously reported for fulvestrant AD.[3] There were no unexpected AEs and no new safety concerns, and the incidence of injection-site pain with fulvestrant HD (5.9%) was similar to that previously seen with fulvestrant AD (4.6%) despite there being twice as many injections per month with the HD regimen.[3] The relatively high incidence of arthralgia (9.9%) and joint disorders (13.9%), compared with those in previous fulvestrant studies (5% to 14% and 5% to 9%, respectively),[3,5] was noteworthy, and data from the ongoing phase III CONFIRM (Comparison of Fulvestrant in Recurrent or Metastatic Breast Cancer) trial will more fully elucidate the tolerability and efficacy profile of fulvestrant HD versus AD. Nonetheless, the overall tolerability profile of fulvestrant HD reported here is reassuring, particularly in light of the approximately 50% increased exposure in the fulvestrant HD versus anastrozole group because of the improvement in TTP.

In summary, fulvestrant HD is at least as effective as anastrozole in terms of CBR and ORR, is associated with significantly longer TTP, and therefore may offer longer-lasting disease control in the first-line advanced breast cancer setting. The results from FIRST are therefore encouraging. Nonetheless, these data should be interpreted in the context of the limited power provided by a phase II, open-label study. The ongoing CONFIRM trial will provide further clarification of the role of fulvestrant HD in the treatment of patients with advanced breast cancer.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

**Employment or Leadership Position:** Euan Macpherson, AstraZeneca (C); Justin Lindemann, AstraZeneca (C) **Consultant or Advisory Role:** Antonio Llombart-Cussac, AstraZeneca (C); Matthew J. Ellis, AstraZeneca (C) **Stock Ownership:** Euan Macpherson, AstraZeneca; Justin Lindemann, AstraZeneca **Honoraria:** John F.R. Robertson, AstraZeneca; Matthew J. Ellis, AstraZeneca **Research Funding:** John F.R. Robertson, AstraZeneca; John Dewar, AstraZeneca; Matthew J. Ellis, AstraZeneca **Expert Testimony:** None **Other Remuneration:** John F.R. Robertson, AstraZeneca

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