A Good Drug Made Better: The Fulvestrant Dose-Response Story

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Abstract

Sequential use of endocrine therapies remains the cornerstone of treatment for hormone receptor-positive advanced breast cancer, before the use of cytotoxic chemotherapy for unresponsive disease. Fulvestrant is an estrogen receptor (ER) antagonist approved for the treatment of postmenopausal women with ER+ advanced breast cancer after failure of prior antiestrogen therapy. Initially approved at a monthly dose of 250 mg, the recommended fulvestrant dose was revised to 500 mg (500 mg/mo plus 500 mg on day 14 of month 1) after demonstration of improved progression-free survival versus fulvestrant 250 mg. We have reviewed the dose-dependent effects of fulvestrant, both from a retrospective combined analysis of dose-dependent reduction of tumor biomarkers in the presurgical setting (3 previously reported studies: Study 18, Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors, and Trial 57) and from a review of clinical studies for advanced breast cancer in postmenopausal women. Analysis of presurgical data revealed a consistent dose-dependent effect for fulvestrant on tumor biomarkers, with increasing fulvestrant dose resulting in greater reductions in ER, progesterone receptor, and Ki67 labeling index. The dose-dependent biological effect corresponds with the dose-dependent clinical efficacy observed in the treatment of advanced breast cancer after failure of prior antiestrogen therapy. Although it remains to be determined in a phase III trial, cross-trial comparisons suggest a dose-dependent relationship for fulvestrant as first-line treatment for advanced breast cancer. Overall, biological and clinical data demonstrate a strong dose-dependent relationship for fulvestrant, supporting the efficacy benefit seen with fulvestrant 500 mg over the 250 mg dose.

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Introduction

Endocrine therapies provide effective and well-tolerated treatments for postmenopausal women with hormone receptor-positive breast cancer (estrogen receptor-positive [ER+] and/or progesterone receptor-positive [PgR+]), both in the adjuvant setting[1] and for the treatment of advanced disease.[2]

Aromatase inhibitors (AIs), which block production of estrogen through their interaction with the estrogen-producing enzyme aromatase, have demonstrated increased efficacy compared with the ER antagonist tamoxifen in postmenopausal women as first-line endocrine treatment for ER+ advanced breast cancer[3-6] and as adjuvant therapy for postmenopausal women with early breast cancer.[7-9] As such, AIs are now considered the standard of care as adjuvant endocrine therapy for postmenopausal women with hormone receptor-positive breast cancer.

Fulvestrant, a 17β-estradiol analog, is an ER antagonist that competes with endogenous estrogen for binding to the ER.[10] However, unlike tamoxifen, which exhibits partial estrogen agonist activity, fulvestrant has no recognized estrogenic effect. It is thought that this is due to the fact that on binding to the ER, fulvestrant induces a conformational change, leading to degradation of the ER and complete inhibition of ER signaling in animal models.[11]

Unfortunately, resistance to endocrine therapy will eventually develop. Although optimal sequencing of appropriate hormone therapies is the ideal approach, few randomized controlled trials have directly compared the effects of changing the order in which 2 different agents are given.[2] Furthermore, the paucity of data led

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the authors of a recent review to conclude that no definitive recommendations could be made regarding the sequencing of endocrine therapies in patients with advanced breast cancer, and that patients should receive the most efficacious treatment in that setting, while also considering specific side effect issues for that patient.[2] Early preclinical data demonstrated a lack of cross-reactivity between fulvestrant and tamoxifen, with fulvestrant inhibiting the growth of tamoxifen-resistant tumors.[12] Similarly in the clinical setting, many postmenopausal women with advanced breast cancer that responded to first-line fulvestrant remained responsive to further endocrine treatment.[13,14] Furthermore, tumors that have responded to prior treatment with an antiestrogen[15,16] or an AI[17,18] may retain sensitivity to subsequent treatment with fulvestrant.

Presurgical studies provide the opportunity to perform a detailed analysis and comparison of biomarker expression and biomarker response with various experimental drug treatments. As an example, the selective ER modulator tamoxifen was reported to increase PgR levels as a result of its partial estrogen agonist activity.[19] However, downregulation of ER with fulvestrant leads to reduction in PgR protein levels through disruption of ER-dependent transcription of the PgR gene, as shown in a randomized comparison with tamoxifen, highlighting the distinct mechanisms of action of these 2 agents.[20] Reduction in Ki67 expression, a nuclear antigen and marker of cell proliferation, is reported to correlate with treatment response to endocrine therapy in ER+ breast cancer,[21] and Ki67 in short-term neoadjuvant studies has been shown to predict outcome in long-term adjuvant trials.[22]

Clinical efficacy of fulvestrant was demonstrated in postmenopausal women with advanced breast cancer that had progressed or recurred on prior antiestrogen therapy[16,23,24] and was originally approved at a monthly dose of 250 mg. However, a dose-dependent effect was subsequently shown, with improved progression-free survival (PFS) for fulvestrant 500 mg (500 mg/mo intramuscular [IM] injection plus 500 mg on day 14 of month 1) versus the 250 mg dose. This led to approval of the 500 mg dose for the treatment of postmenopausal women with ER+ advanced breast cancer after failure of prior antiestrogen therapy.[25]

This review investigates the dose-dependent effects of fulvestrant more broadly, in terms of both the reduction of tumor biomarkers in the presurgical setting and the clinical efficacy for the treatment of breast cancer.

Biological Rationale for a Dose-Response Relationship for Fulvestrant

Dose-dependent reduction of tumor biomarkers after fulvestrant treatment was first demonstrated in a short-term presurgical study in postmenopausal women with primary breast cancer.[26] After daily injections of a short-acting formulation of fulvestrant, reductions in ER expression and Ki67 labeling index were greater in patients with ER+ breast cancer who received a fulvestrant 18 mg daily injection compared with those who received a fulvestrant 6 mg daily injection.

We now extend the study of dose dependency by presenting a retrospective analysis of tumor biomarker data extracted from 3 previously reported presurgical studies over a fulvestrant dose range of 50 to 500 mg administered using the commercially available long-acting formulation. Data from Study 18,[20] Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors (NEWEST),[27] and Trial 57[28] were combined in this analysis.

Study Designs

Study 18

Study 18 was a randomized, multicenter, partially blinded study that compared placebo, tamoxifen, fulvestrant 50 mg, fulvestrant 125 mg, and fulvestrant 250 mg before surgery in postmenopausal women with previously untreated primary breast cancer.[20] Patients received a single IM dose of fulvestrant 50 mg, 125 mg, 250 mg, or tamoxifen 20 mg daily, or tamoxifen placebo daily for 14 to 21 days before surgery. Only data from patients whose tumors were ER+ or PgR+ have been included in the current analysis. When patients had more than 1 tumor, baseline data from only the primary tumor were included.

NEWEST

NEWEST (ClinicalTrials.gov identifier NCT0093002) was a randomized, multicenter, open-label, phase II study comparing fulvestrant 500 mg (500 mg/mo plus 500 mg on day 14 of month 1) with fulvestrant 250 mg/mo for 16 weeks before surgery in postmenopausal women with ER+ locally advanced breast cancer.[27] Tumor biomarker levels at week 4 have been used in the present analysis for the closest consistency with data from Study 18 and Trial 57.

Trial 57

Trial 57 (ClinicalTrials.gov identifier NCT00259090) was a randomized, multicenter, double-blind, phase II trial comparing fulvestrant 500 mg (single IM dose) plus anastrozole (1 mg orally once daily for 14-21 days), fulvestrant 500 mg plus anastrozole placebo, or anastrozole plus fulvestrant placebo before surgery in postmenopausal women with ER+ primary breast cancer.[28] Before protocol amendment, Trial 57 included a treatment phase in which patients were randomized to receive fulvestrant 250 mg plus anastrozole (n = 6), fulvestrant 250 mg plus anastrozole placebo (n = 6), or anastrozole 1 mg plus fulvestrant placebo (n = 6). Although patient numbers are small and should be interpreted with caution, data for this initial treatment phase have been included for completeness in this analysis.

Tumor Biomarker Expression and Statistical Analyses

ER, PgR, and Ki67 expression were determined in each study by immunochemistry on sections of formalin-fixed, paraffin-embedded tissue. Study 18 used the following antibodies: ER, H222 (Abbott Laboratories, Abbott Park, IL); PgR, KD68 (Abbott); Ki67, MIB-1 (Coulter Electronics, Luton, UK). In NEWEST, the antibodies used were the following: ER, 1D5 (Dako Ltd, Carpinteria, CA); PgR, 636 (Dako Ltd); Ki67, MIB-1 (Coulter Electronics). The antibodies used in Trial 57 were as follows: ER, 6F11 (Novocastra, Newcastle, UK); PgR, 636 (Dako Ltd); Ki67, Clone MIB-1 (Dako Ltd). Antigen retrieval methods and secondary detection methods varied between the studies and have been described.[20,27,28] ER, PgR, and Ki67 expression levels at pre- and post-treatment (14-21 days

Table 1 Change From Baseline in ER H-Score

Treatment	Back-Transformed Least Squares Mean Change From Baseline (%) (95% CI)			
	Study 18	NEWEST	Trial 57 Initial Phase	Trial 57 Main Phase
Placebo	−37.3 (−69.5 to 28.9)			
Tamoxifen	−61.7 (−82.5 to −15.9)			
Fulvestrant 50 mg	−67.6 (−83.7 to −35.5)			
Fulvestrant 125 mg	−75.2 (−87.0 to −52.4)			
Fulvestrant 250 mg	−84.0 (−91.7 to −69.1)	−10.7 (−30.3 to 14.4)	−21.0 (−56.2 to 42.4)	
Fulvestrant 500 mg		−52.9 (−63.0 to −40.1)		−44.6 (−53.9 to −33.4)
Fulvestrant 250 mg plus anastrozole			−43.2 (−68.4 to 2.1)	
Fulvestrant 500 mg plus anastrozole				−48.9 (−58.1 to −37.6)
Anastrozole			5.8 (−41.0 to 89.7)	−14.7 (−29.7 to 3.5)

Abbreviations: CI = confidence interval; ER = estrogen; NEWEST = Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors.

post-treatment in Study 18 and Trial 57 and at week 4 in NEWEST) were determined by manual counting under light microscopy. ER and PgR expression were determined as the H-score, calculated as (0.5 × % ±) + (1 × % +) + (2 × % ++) + (3 × % +++), where % ±, % +, % ++, and % +++ represent the overall percentage positivity of very weak, weak, moderate, and strong staining, respectively. Ki67 expression was determined as the labeling index, derived from the number of positively stained epithelial cells, expressed as a percentage of the total number of cells counted.

Tumor biomarker expression data were analyzed by study using an analysis of covariance (ANCOVA) model (log-transformed ratio of post- to pretreatment) with the log-transformed baseline value and treatment included as factors. The least squares mean and confidence interval (CI) values were back-transformed to the original scale. To assess the impact of fulvestrant dose while allowing for between-study variability, a second ANCOVA model was produced including log-transformed baseline, dose (as a continuous variable), and study as factors. The first ANCOVA included all treatment groups within each trial; the second ANCOVA included only placebo and the fulvestrant 50 mg, 125 mg, 250 mg, and 500 mg treatment groups. For the placebo data to be log-transformed, a dose of 0.5 mg rather than 0 mg was used for the purpose of this analysis.

ER H-Score

In Study 18, NEWEST, and Trial 57, a dose-dependent effect was seen over the dose ranges investigated for reduction in ER expression. In each study, the greatest reduction in ER expression was seen with the highest fulvestrant dose. In Study 18, greater reduction in ER was observed for fulvestrant 250 mg versus tamoxifen, and in Trial 57, greater reduction in ER expression was observed for fulvestrant 500 mg versus anastrozole. In Trial 57, no additional reduction in ER expression was observed for fulvestrant 500 mg plus anastrozole compared with fulvestrant 500 mg alone (Table 1; Figure 1).

PgR H-Score

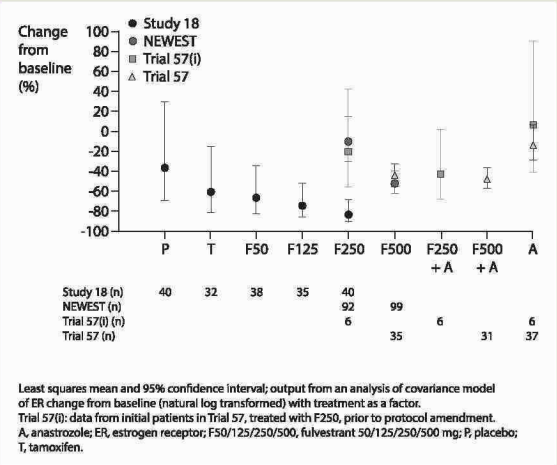
A consistent dose-dependent effect of fulvestrant was also observed in Study 18, NEWEST, and Trial 57 for reduction in PgR expression. The greatest reduction in PgR expression was seen with the highest fulvestrant dose within each study. An increase in PgR expression was seen in the tamoxifen treatment group in Study 18. In Trial 57, no additional reduction in PgR expression was observed for the combination of fulvestrant 500 mg plus anastrozole compared with fulvestrant 500 mg alone or anastrozole alone. Similar reductions in PgR expression were observed for fulvestrant 500 mg alone and anastrozole alone (Table 2; Figure 2).

Ki67 Labeling Index

Ki67 labeling index was reduced after treatment in each fulvestrant treatment group in each study. In Study 18 and NEWEST, the greatest reduction in Ki67 labeling index was seen with the highest fulvestrant dose. In Trial 57, which also included the small initial cohort of patients treated with fulvestrant 250 mg (n = 6), there were no meaningful differences in Ki67 labeling index reduction between the fulvestrant treatment groups (Table 3; Figure 3).

Overall results from the ANCOVA model show a consistent dose-dependent effect for fulvestrant over the dose ranges analyzed for ER and PgR H-score and Ki67 labeling index. Results for the

Figure 1 Change From Baseline in ER Expression



Abbreviation: NEWEST = Neoadjuvant Endocrine Therapy for Women With Estrogen-Sensitive Tumors.

Table 2 Change From Baseline in PgR H-Score

Treatment	Back-Transformed Least Squares Mean Change From Baseline (%) (95% CI)			
	Study 18	NEWEST	Trial 57 Initial Phase	Trial 57 Main Phase
Placebo	40.3 (−25.8 to 165.4)			
Tamoxifen	160.1 (27.7 to 429.8)			
Fulvestrant 50 mg	−62.7 (−80.6 to −28.6)			
Fulvestrant 125 mg	−78.8 (−88.4 to −61.3)			
Fulvestrant 250 mg	−86.4 (−92.8 to −74.2)	−67.3 (−81.0 to −43.7)	−47.5 (−82.8 to 60.3)	
Fulvestrant 500 mg		−91.4 (−95.0 to −85.0)		−63.2 (−77.2 to −40.6)
Fulvestrant 250 mg plus anastrozole			−49.2 (−82.9 to 50.9)	
Fulvestrant 500 mg plus anastrozole				−58.3 (−75.5 to −29.0)
Anastrozole			−65.9 (−88.8 to 4.0)	−59.2 (−75.0 to −33.6)

Abbreviations: CI = confidence interval; NEWEST = Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors; PgR = progesterone.

second ANCOVA, which adjusted for between-study variability, show that increasing fulvestrant dose results in greater reduction in ER and PgR H-score and Ki67 labeling index ($P < .0001$ for the dose-response relationship for each biomarker).

Clinical Evidence of a Dose-Response Relationship for Fulvestrant

Fulvestrant Dose-Response in Second-Line Therapy for Advanced Breast Cancer

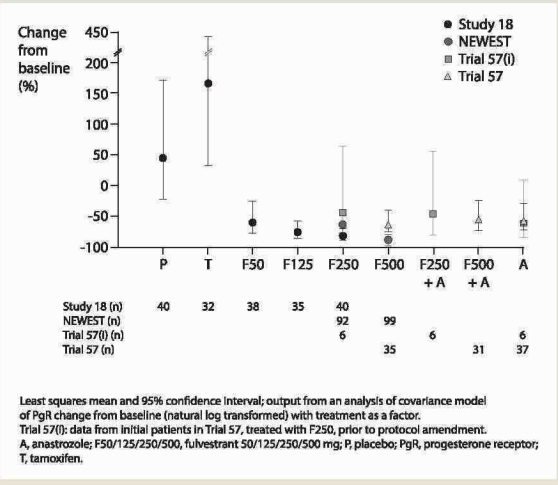
The clinical efficacy of fulvestrant at a dose of 250 mg/mo was established in the registration trials 0020 and 0021, which compared fulvestrant 250 mg with anastrozole for the treatment of postmenopausal women with advanced breast cancer that had progressed or recurred on prior antiestrogen therapy.[23,24] In a combined analysis of data from both studies (fulvestrant, n = 428; anastrozole, n = 423), fulvestrant 250 mg was shown to be at least as effective as anastrozole with respect to time to progression (TTP). Median TTP was 5.5 months for fulvestrant 250 mg compared with 4.1 months for anastrozole (hazard ratio [HR], 0.95; 95.14% CI, 0.82-1.10; $P = .48$).[16] This led to the approval of fulvestrant 250 mg for the treatment of postmenopausal women with advanced breast cancer that had progressed or recurred on prior antiestrogen therapy. However, evidence of dose-dependent clinical efficacy with fulvestrant had already been suggested in these studies, because an initial 125 mg dose was dropped after a planned interim assessment that found no evidence for clinical efficacy at the fulvestrant 125 mg dose. Given the favorable tolerability profile of fulvestrant 250 mg, alternative dosing regimens were investigated.

The phase III COmparisoN of Faslodex In Recurrent or Metastatic breast cancer (CONFIRM) trial was designed to compare fulvestrant 500 mg with fulvestrant 250 mg in patients with hormone receptor-positive, pretreated, advanced breast cancer. Fulvestrant 500 mg significantly prolonged PFS versus fulvestrant 250 mg. Median PFS was 6.5 months in the fulvestrant 500 mg group compared with 5.5 months in the fulvestrant 250 mg group (HR, 0.80; 95% CI, 0.68-0.94; $P = .006$), demonstrating a clear dose-dependent relationship for fulvestrant in this setting (Table 4).[25] Of note, the dose-dependent clinical efficacy seen in CONFIRM was not associated with a dose-dependent increase in toxicity, with no substantial differences between the treatment groups in terms of incidence and severity of adverse events. This increase in therapeutic index led to fulvestrant 500 mg becoming the recommended dose. This benefit was further confirmed in a follow-up analysis performed when approximately 75% of patients had died. Median overall survival was 26.4 months for fulvestrant 500 mg compared with 22.3 months for fulvestrant 250 mg, indicating a clinically relevant difference in overall survival between the treatment groups (HR, 0.81; 95% CI, 0.69-0.96; nominal $P = .016$).[29]

Fulvestrant Dose-Response in First-Line Therapy for Advanced Breast Cancer

Cross-trial comparisons also suggest a dose-response relationship for fulvestrant as first-line therapy for advanced breast cancer. In Trial 25, fulvestrant 250 mg failed to demonstrate noninferiority compared with tamoxifen, the standard of care at the time of the trial, in postmenopausal women with advanced breast cancer previously untreated with endocrine therapy for advanced disease.[30]

Figure 2 Change From Baseline in PgR Expression



Abbreviation: NEWEST = Neoadjuvant Endocrine Therapy for Women With Estrogen-Sensitive Tumors.

Table 3 Change From Baseline in Ki67 Labeling Index

Treatment	Back-Transformed Least Squares Mean Change From Baseline (%) (95% CI)			
	Study 18	NEWEST	Trial 57 Initial Phase	Trial 57 Main Phase
Placebo	3.7 (−18.0 to 31.1)			
Tamoxifen	35.8 (−51.3 to −15.5)			
Fulvestrant 50 mg	−23.3 (−40.6 to −0.9)			
Fulvestrant 125 mg	−46.1 (−58.6 to −29.7)			
Fulvestrant 250 mg	−46.5 (−58.1 to −31.6)	−45.5 (−58.5 to −28.2)	−79.0 (−90.4 to −53.7)	
Fulvestrant 500 mg		−81.2 (−85.8 to −75.0)		−74.4 (−81.5 to −64.5)
Fulvestrant 250 mg plus anastrozole			−91.1 (−96.0 to −80.2)	
Fulvestrant 500 mg plus anastrozole				−83.4 (−88.5 to −76.0)
Anastrozole			−84.4 (−92.9 to −65.6)	−85.0 (−89.1 to −79.4)

Abbreviations: CI = confidence interval; NEWEST = Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors.

Because anastrozole was previously shown to demonstrate improvements in efficacy over tamoxifen,[3] this was considered a surprising outcome for fulvestrant 250 mg. However, with the almost immediate separation of the TTP curves in this trial, it was hypothesized that the 3 to 6 months to steady state for the fulvestrant 250 mg regimen could have led to the underperformance of this treatment group.

In the phase II Fulvestrant fIRst-line Study comparing endocrine Treatments (FIRST) study, fulvestrant 500 mg was compared with anastrozole in postmenopausal women with advanced breast cancer who had not received endocrine therapy for advanced disease. The fulvestrant 500 mg dose regimen, which includes a 500 mg dose at day 14, was shown to be at least as effective as anastrozole in terms of the primary endpoint of clinical benefit rate (fulvestrant, 72.5%; anastrozole, 67.0%), and the secondary endpoint of TTP was significantly longer for fulvestrant 500 mg compared with anastrozole.[31] Safety data indicated that fulvestrant 500 mg has a similar tolerability profile compared with anastrozole 1 mg and is well tolerated as first-line therapy for advanced breast cancer. In a follow-up analysis, which was performed when disease had progressed in approximately 75% of patients, median TTP was 23.4 months for fulvestrant 500 mg compared with 13.1 months for anastrozole (HR, 0.66; 95% CI, 0.47-0.92; $P = .01$).[14] This was the first trial to indicate that an alternative endocrine therapy may be more effective than an AI in the first-line setting for advanced breast cancer and indirectly suggests a dose-response relationship for fulvestrant 500 mg over fulvestrant 250 mg as first-line therapy for advanced breast cancer. Given that fulvestrant 250 mg demonstrated noninferiority to anastrozole (in the second-line setting of the registration trials 0020 and 0021[16,23,24]), the significantly longer TTP with fulvestrant 500 mg versus anastrozole in the first-line setting also was indirect evidence of a dose-response relationship for fulvestrant.

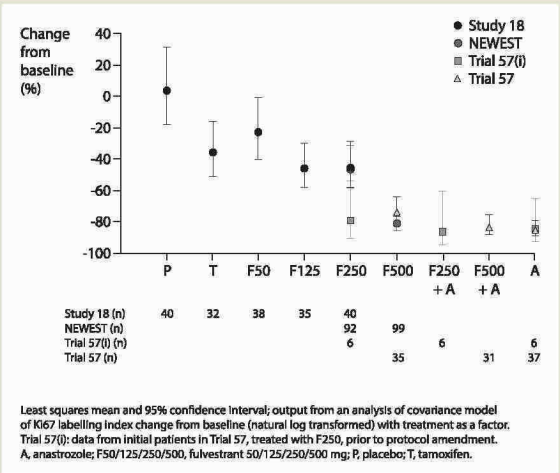
Fulvestrant Dose Response in the Neoadjuvant Setting

NEWEST was the first study to compare the biological and clinical activity of the fulvestrant 500 mg dose regimen versus fulvestrant 250 mg. Although the primary endpoint of NEWEST was biological (change in Ki67 labeling index from baseline to Week 4), the clinical data appeared to correspond with the dose-dependent reduction in tumor biomarkers seen at week 4. The tumor response rate at week 4 was 17.4% for the fulvestrant 500 mg group compared with 11.8% in the fulvestrant 250 mg group (odds ratio [OR], 1.68; 95% CI, 0.77-3.70; $P = .19$). At week 16, tumor response was 22.9% in the fulvestrant 500 mg group compared with 20.6% in the fulvestrant 250 mg group (OR, 1.30; 95% CI, 0.64-2.64; $P = .47$).[27]

Fulvestrant in Combination Therapy

Together with its distinct mechanism of action and reduced risk of cross-resistance with other endocrine treatments, the observation of incomplete ER reduction with fulvestrant 250 mg, in the short,[20] medium, and long term (Agrawal, in press),[32] led to combination therapies being developed, aiming to further reduce ER activity and improve efficacy. The Fulvestrant and Anastrozole Combination Therapy (FACT) study compared the efficacy of a combination of anastrozole plus the fulvestrant 250 mg loading dose (LD) regimen (fulvestrant 250 mg + LD: 500 mg day 0, 250 mg days 14 and 28, 250 mg/mo thereafter) versus anastrozole

Figure 3 Change From Baseline in Ki67 Labeling Index



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