Fulvestrant Revisited: Efficacy and Safety of the 500-mg Dose

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Abstract

Postmenopausal women with hormone receptor-positive advanced breast cancer are candidates for endocrine therapy. As the disease will eventually progress in most patients, it is important to investigate agents with novel modes of action to reduce the likelihood of treatment cross-resistance. Fulvestrant is an estrogen receptor antagonist with no known agonist effects that has been shown to be as effective as anastrozole following failure on tamoxifen, at the approved dose of 250 mg/mo. However, pharmacokinetic modeling and evidence of clinical efficacy in early trials, together with the favorable tolerability profile of fulvestrant 250 mg, led to suggestions that increasing the fulvestrant dose would lead to an improved benefit-risk profile. This review describes the rationale behind the development of a 500 mg/mo higher dose of fulvestrant and details relevant clinical trials, including the pivotal phase III COmparisoN of Faslodex In Recurrent or Metastatic breast cancer (CONFIRM) study. CONFIRM demonstrated a significant improvement in progression-free survival for fulvestrant 500 mg versus 250 mg in postmenopausal patients who had progressed on previous endocrine therapy. Here, we present and discuss a pooled safety analysis of CONFIRM and three further clinical studies demonstrating fulvestrant 500 mg to be well-tolerated with no evidence of dose-related adverse events. Overall, these data indicate an improved benefit-risk profile for fulvestrant 500 mg versus 250 mg following failure on prior endocrine therapy, and suggest that fulvestrant 500 mg may be considered in future as initial endocrine treatment for advanced breast cancer.

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Introduction

Breast cancer is the most common cancer in women in Europe and the United States and, because of a high prevalence of metastatic disease, is the most common cause of cancer death.[1,2] Current treatment options for patients who have breast cancer depend on the extent of the disease, hormone receptor status, and the patient situation in relation to menopause. For postmenopausal women with hormone receptor-positive early breast cancer, the recommended treatment is surgery, with or without radiotherapy, followed by endocrine therapy.[3] Patients with advanced disease are usually treated with a series of hormone therapies that follow one another after progression until the disease is considered endocrine non-responsive. At that point patients become candidates to receive less-tolerable cytotoxic chemotherapy.[4,5]

Steroidal aromatase inhibitors (AIs; exemestane) and non-steroidal AIs (anastrozole and letrozole) have been established as the preferred agents for the treatment of advanced breast cancer due to demonstrated increased efficacy over tamoxifen, and are now used as first-line therapy for advanced disease.[6-9] Despite these improvements, the disease will eventually progress in most patients, leaving a requirement for additional, non–cross-resistant treatment options to provide optimal disease control.[10]

Fulvestrant is a selective estrogen receptor (ER) antagonist that, unlike tamoxifen, which exhibits partial agonist properties (associated with increased risk of endometrial cancer, thromboembolic events, and tumor flare), has no known agonist effects. It has a novel mode of action, binding to the ER causing downregulation and degradation[11]; and tumors resistant to prior endocrine treatment such as tamoxifen and anastrozole remain responsive to treatment with fulvestrant.[12-15] Given as a 250 mg/mo intramuscular injection, fulvestrant was approved for the treatment of postmenopausal women with advanced breast cancer who have progressed or recurred on prior anti-estrogen therapy following the results of registration Trials 0020

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and 0021. Fulvestrant was well-tolerated and efficacious, demonstrating non-inferiority to anastrozole in this setting.[16-18]

Whereas fulvestrant 250 mg/mo was shown to be effective and potentially as good as any other hormone treatment in its licensed setting, its novel mode of action together with early clinical data suggested there may be an opportunity to further enhance efficacy by investigating alternative dosing regimens. This review describes the rationale and subsequent clinical development of a higher 500 mg/mo dose of fulvestrant.

Rationale for Using a Higher Dose of Fulvestrant

The registration Trials 0020 and 0021 established the clinical efficacy and tolerability of fulvestrant 250 mg, but a third arm initially investigating fulvestrant 125 mg was withdrawn from these studies due to lack of clinical benefit. Based on this observation, and with the favorable tolerability profile observed with fulvestrant 250 mg in these trials, the possibility was raised that increasing the dose may improve the benefit-risk profile by further increasing ER downregulation and improving clinical efficacy.[16-18] In addition, Trial 0025 compared fulvestrant 250 mg/mo with tamoxifen as a first-line treatment in postmenopausal women with advanced breast cancer. Although efficacy was similar between treatments, fulvestrant failed to meet the non-inferiority endpoint and patients seemed to progress quicker on fulvestrant than tamoxifen during the first 3 months of therapy. Given that it takes 3 to 6 months for fulvestrant to achieve steady state, the authors hypothesized that the inclusion of a loading dose may also contribute to improve efficacy.[19]

Evidence that increasing the dose of fulvestrant may improve efficacy was available from biological data in early clinical trials. Defriend et al[20] first demonstrated a dose-dependent ER downregulation after fulvestrant administration with a daily dose of either 6 mg or 18 mg fulvestrant (short-acting formulation) before surgery. Study 0018 later demonstrated a dose-response effect across the dose range for both ER and progesterone receptor expression and the Ki67 labeling index, following administration of a single fulvestrant dose of 50, 125, or 250 mg.[19] ER reduction with fulvestrant 250 mg was greater than that achieved with tamoxifen. However, ER expression was not completely suppressed (approximately 70% reduction from baseline) and it was suggested that further increasing the dose of fulvestrant could lead to even greater ER downregulation.

Because of the importance of achieving therapeutic drug levels quickly, pharmacokinetic models were developed to evaluate the effect of both a loading dose component and a high dose (500 mg) of fulvestrant. Reassuringly, the predicted pharmacokinetic model data were shown to closely match the pharmacokinetic data from Trials 0020/0021 with plasma fulvestrant concentrations approximately two-fold higher following repeat administrations of fulvestrant 250 mg versus a single administration, and steady-state plasma concentrations reached at 3 to 6 months with the fulvestrant 250 mg/mo dosing regimen.[21] Subsequently, the model predicted that a 500 mg/mo high-dose regimen could result in higher fulvestrant plasma concentrations (approximately two-fold higher than with fulvestrant 250 mg) and enable steady-state levels to be achieved more quickly (within 1 month) compared with the approved 250-mg dose.[22]

Clinical Evidence To Support a Higher Dose of Fulvestrant

At the approved dose, fulvestrant is administered as a single 250-mg intramuscular injection every 28 days. In the 250-mg loading-dose regimen, referred to here as fulvestrant 250 mg + LD, an initial dose of 500 mg (2 x 250 mg injections) is given on day 0, followed by 250 mg fulvestrant on day 14 and day 28, with the 250-mg dose continuing monthly thereafter. In the high-dose regimen, which also incorporates a loading dose, 500 mg fulvestrant is administered on days 0, 14, 28, and every 28 days thereafter. Several key clinical studies have been conducted to investigate the alternative dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer, and these are summarized in Table 1.[12,23-28]

The phase III Evaluation of Fulvestrant versus Exemestane Clinical Trial (EFECT) was designed to compare the fulvestrant 250 mg + LD regimen with exemestane in women with advanced breast cancer who had progressed on prior non-steroidal AI treatment. The clinical efficacy of fulvestrant 250 mg + LD was confirmed, and median time-to-progression (TTP) was 3.7 months for both treatments [hazard ratio (HR) = 0.963; 95% confidence interval (CI) 0.819, 1.133; $P = .65$]. This study provided the first clinical evidence that steady-state plasma levels were achieved more quickly with the addition of a loading dose and the pharmacokinetic data generated closely matched the previous pharmacokinetic modeling data.[12,29]

The first clinical study to use the fulvestrant high-dose was a phase I trial in Japan, in which 10 patients received the 500-mg dosing regimen.[24] Steady-state fulvestrant plasma levels were shown to be approximately two-fold higher than those achieved with the 250 mg + LD regimen. In addition, the 500-mg fulvestrant dose was shown to be well-tolerated.[24] In a phase II study, Neoadjuvant Endocrine therapy for Women with Estrogen-Sensitive Tumours (NEWEST), the biological activity of fulvestrant 500 mg was compared with fulvestrant 250 mg in the neoadjuvant setting. A significantly greater reduction in Ki67 labeling index was observed at week 4 for fulvestrant 500 mg compared with the 250-mg dose (-78.8% versus -47.3% for the fulvestrant 500-mg and 250-mg groups, respectively; $P < .0001$). ER expression also showed a significantly greater reduction at week 4 for the fulvestrant 500 mg dose compared with the 250-mg dose (-25.0% versus -13.5% for the 500 mg and 250 mg groups, respectively; $P = .0002$).[25] Again, the pharmacokinetic data confirmed that steady-state conditions were reached within the first month of dosing with fulvestrant 500 mg (compared with 3 months for fulvestrant 250 mg) and that steady-state exposures were approximately double those seen with the 250-mg dose.[30]

The phase II Fulvestrant fIRst-line Study comparing endocrine Treatments (FIRST) trial compared fulvestrant 500 mg with anastrozole in the first-line setting. Fulvestrant 500 mg was at least as effective as anastrozole in terms of the primary endpoint with clinical benefit rates of 72.5% and 67.0%, respectively [odds ratio (OR), 1.30; 95% CI, 0.72, 2.38; $P = .386$]. Encouragingly, at the time of the primary analysis, TTP had not been reached for fulvestrant 500 mg compared with 12.5 months for anastrozole (HR, 0.63; 95%

Table 1 Overview of Key Trials Investigating Dosing Regimens of Fulvestrant

Study Name	Study Design and Reference	Indication	Treatment Groups
EFECT (D6997C00048)	Phase III, randomized, double-blind, double-dummy, multicenter[12]	Postmenopausal women with ER+ advanced BC progressing after prior non-steroidal AI	Fulvestrant 250 mg + LD Exemestane 25 mg
Study 062 (D6995C00004)	Phase I, open label, multicenter[24]	Postmenopausal women with ER+, advanced or recurrent breast cancer	Fulvestrant 250 mg + LD Fulvestrant 500 mg
NEWEST (D6997C00003)	Phase II, randomized, open label, parallel group, multicenter[25]	Postmenopausal women with newly diagnosed, ER+, locally advanced BC	Fulvestrant 250 mg Fulvestrant 500 mg
FIRST (D6995C00006)	Phase II, randomized, open label, parallel group, multicenter[28]	Postmenopausal women with advanced BC – first-line treatment	Fulvestrant 500 mg Anastrozole 1 mg
FINDER1 (D6997C0004)	Phase II, randomized, double-blind, parallel group, multicenter[26]	Postmenopausal women with ER+, locally advanced BC recurring or progressing after prior endocrine therapy	Fulvestrant 250 mg Fulvestrant 250 mg + LD Fulvestrant 500 mg
FINDER2 (D6997C00003)	Phase II, randomized, double-blind, parallel group, multicenter[27]	Postmenopausal women with ER+, locally advanced BC recurring or progressing after prior endocrine therapy	Fulvestrant 250 mg Fulvestrant 250 mg + LD Fulvestrant 500 mg
CONFIRM (D6997C0002)	Phase III, randomized, double-blind, parallel group, multicenter[23]	Postmenopausal women with ER+, locally advanced BC recurring or progressing after prior endocrine therapy	Fulvestrant 250 mg Fulvestrant 500 mg

Abbreviations: AI = aromatase inhibitor; BC = breast cancer; ER+ = estrogen receptor-positive; LD = loading dose (500 mg on day 0, 250 mg on day 14).
Fulvestrant 250 mg: 250 mg days 0 and 28, 250 mg/mo thereafter; Fulvestrant 250 mg + LD: 500 mg day 0, 250 mg days 14 and 28, 250 mg/mo thereafter; Fulvestrant 500 mg: 500 mg days 0, 14 and 28, 500 mg/mo thereafter.

CI, 0.39, 1.00; $P = .0496$).[28] In an updated analysis, performed when 79.5% of patients had discontinued study treatment, 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; $P = .01$).[31] Duration of response and duration of clinical benefit were also numerically in favor of fulvestrant 500 mg compared with anastrozole.[28] With FIRST and NEWEST investigating biological and clinical activity for fulvestrant 500 mg in the neoadjuvant and first-line advanced disease settings, the Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) study was designed to elucidate the clinical role of fulvestrant 500 mg in ER-positive (ER+) advanced breast cancer following failure on prior endocrine therapy.

The pivotal phase III CONFIRM study is a randomized, double-blind, placebo-controlled trial that was designed to assess the efficacy and safety of fulvestrant 500 mg versus fulvestrant 250 mg in patients who have progressed following prior anti-estrogen or AI therapy.[23] In total, 736 patients treated at 128 centers in 17 countries were randomized to receive fulvestrant 500 mg (n=362) or 250 mg (n=374). The majority of patients had relapsed or progressed during adjuvant endocrine therapy (48.3% versus 45.2% for the fulvestrant 500-mg and 250-mg groups, respectively) or were progressing on first-line endocrine therapy having previously presented with de novo advanced disease (35.9% versus 33.4% for the fulvestrant 500-mg and 250-mg groups, respectively). No important differences in baseline characteristics were recorded between the groups.

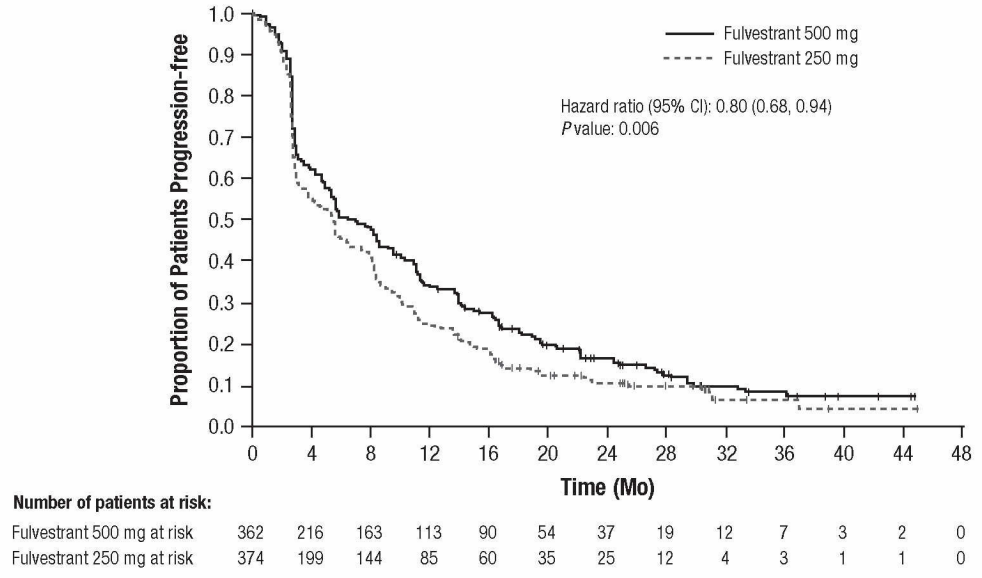
Progression-free survival, which was the primary endpoint of the trial, was 6.5 months in the 500-mg group, compared with 5.5 months for the 250-mg group (HR, 0.80; 95% CI, 0.68, 0.94; $P = .006$), indicating a significant improvement for the higher dose (Fig 1). This is equivalent to a 20% reduction in the risk of progression, clinically meaningful in the proposed indication. There was also a numerical advantage in the secondary endpoints of clinical benefit rate (OR, 1.28; 95% CI, 0.95, 1.71; $P = .100$), overall survival (25.1 versus 22.8 months for the 500-mg and 250-mg treatment groups, respectively; HR, 0.84; 95% CI, 0.69, 1.03; $P = .091$) and duration of clinical benefit (16.6 versus 13.9 months for the 500-mg and 250-mg treatment groups, respectively) for patients receiving fulvestrant 500 mg. The objective response rate in patients with measurable disease at baseline was 33/240 (13.8%) for fulvestrant 500 mg and 38/261 (14.6%) for fulvestrant 250 mg. Duration of response was similar between the two treatment groups (19.4 versus 16.4 months for the 500-mg and 250-mg groups, respectively, calculated from the date of randomization). The pre-planned subgroup analysis showed a consistent treatment effect favoring fulvestrant 500 mg over fulvestrant 250 mg across all subgroups analyzed; the efficacy results were found to be similar, irrespective of whether the patient had progressed on prior anti-estrogen or prior AI therapy (Fig 2).

In addition to the CONFIRM study, the phase II Faslodex InvestigatioN of Dose evaluation in Estrogen Receptor-positive advanced breast cancer (FINDER) 1 and 2 studies were conducted on Japanese and European populations, respectively. Although the relatively small sample sizes did not permit confirmation of improved efficacy for fulvestrant 500 mg in the individual studies, the data allowed concerns of any ethnic differences in the efficacy and tolerability profiles of fulvestrant to be dispelled.[26,27] The efficacy results from all of the described trials, including the phase III CONFIRM trial, definitively demonstrate that fulvestrant 500 mg is associated with increased efficacy over and above the 250-mg dose.

Safety Analysis of Fulvestrant 500 mg

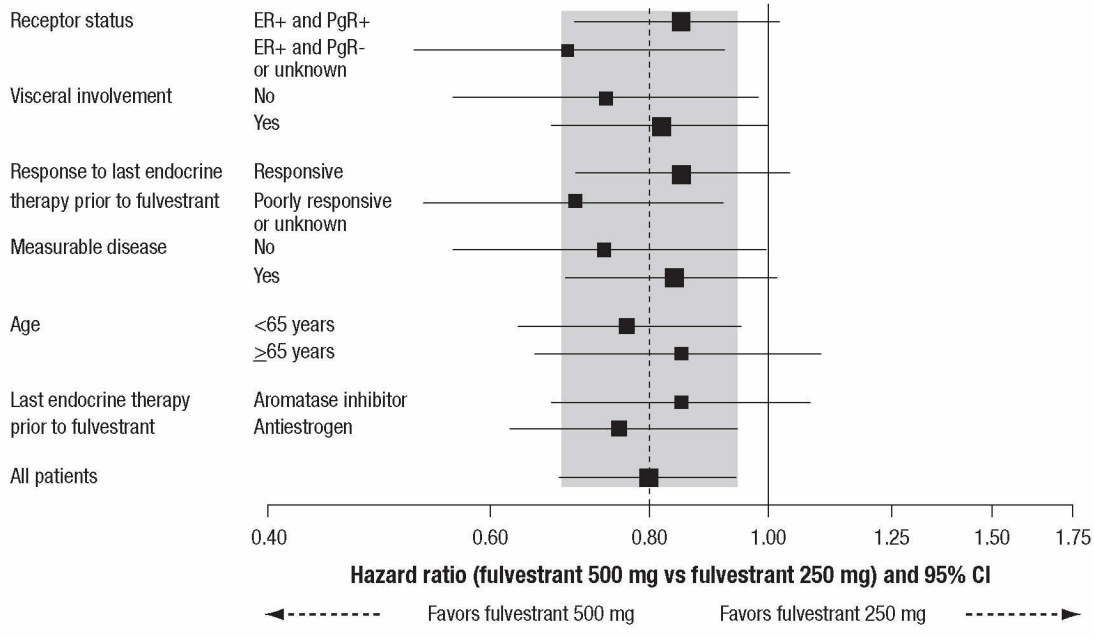
The safety data analysis of fulvestrant 500 mg and 250 mg was conducted on pooled data from four studies – CONFIRM, NEWEST,

Figure 1 Kaplan-Meier Estimates for Progression-Free Survival (CONFIRM Study). Reprinted with permission. ©2008 American Society of Clinical Oncology. All rights reserved[23]



Abbreviation: CI, confidence interval.
Tick marks indicate censored observations.

Figure 2 Forest Plot from CONFIRM Showing Consistent Benefits of Fulvestrant 500 mg Over 250 mg in All Pre-planned Subgroup Analyses. Reprinted with permission. ©2008 American Society of Clinical Oncology. All rights reserved[23]



Abbreviations: CI, confidence interval; ER+, estrogen receptor-positive; PgR+, progesterone receptor-positive; PgR-, progesterone receptor-negative.

Table 2 Summary of Safety Data from Pooled Analysis

Category of AE	Fulvestrant 500 mg n=560 (%)	Fulvestrant 250 mg n=567 (%)
Any AE	393 (70.2)	387 (68.3)
Any AE with Outcome = Death	6 (1.1)	7 (1.2)
Any SAE[a]	48 (8.6)	43 (7.6)
Any SAE with Outcome Other than Death[b]	44 (7.9)	38 (6.7)
Any CTCAE Grade 3 or Higher	84 (15.0)	83 (14.6)
Any AE Leading to Discontinuation of Treatment (DAE)	11 (2.0)	13 (2.3)
Any OAE	0	0

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted in each of those categories.
Abbreviations: AE = adverse event; CTCAE = common terminology criteria for AEs; DAE = discontinuation due to an AE; OAE = other significant AE; SAE = serious adverse event
[a] The "Any SAE" category was not summarized in the NEWEST study.
[b] All patients experiencing an SAE with non-fatal outcome (regardless if they later had a fatal SAE).

FINDER1 and FINDER2 – which included data from 560 patients treated with fulvestrant 500 mg and 567 patients treated with 250 mg. In the CONFIRM and both FINDER studies, patients were postmenopausal women with ER+ advanced breast cancer whose disease had relapsed either while receiving, or within 1 year of receiving, adjuvant endocrine therapy, or who had progressed on first endocrine therapy for advanced disease. However, in the NEWEST study, patients were postmenopausal women with newly-diagnosed ER+ locally advanced breast cancer in the neo-adjuvant setting.

In general, both treatments were well-tolerated across the pooled studies. At least one AE was reported in 70.2% of patients in the 500-mg group and 68.3% of patients in the 250-mg group, respectively. Six patients in the fulvestrant 500-mg group (1.1%) and seven patients in the 250-mg group (1.2%) died due to an AE. Serious AEs were reported in 8.6% of patients in the 500-mg group and 7.6% of patients in the 250-mg group. The incidence of AEs that led to discontinuation of study treatment was low: 2.0% and 2.3% for the 500-mg and 250-mg groups, respectively (Table 2).

In the overall pooled safety data analysis, the most frequently reported AEs were injection-site pain, nausea, hot flush, and headache. There was a small but not significant difference in the occurrence of injection-site pain, which was slightly higher in the 500-mg group (13.9%) than the 250-mg group (10.2%). There was a small increase in patients experiencing anorexia in the 500-mg group (5.7% versus 3.5% for the 500-mg and 250-mg groups, respectively), but this was not associated with any change in mean weight. Incidence of back pain was slightly lower in the 500-mg group (7.1%) than the 250-mg group (9.5%). The number of patients experiencing events classified as Common Toxicity Criteria (CTC) grade 3 or higher was similar between the two groups: 84 (15.0%) in the 500-mg group and 83 (14.6%) in the 250-mg group.

Based on the known safety profile of fulvestrant and the potential safety issues associated with endocrine treatments, pre-specified AE categories were determined. These were endometrial dysplasia; gastrointestinal disturbances; hot flushes; injection-site reactions; ischemic cardiovascular disorders; joint disorders; osteoporosis; thromboembolic events; urinary tract infection; vaginitis; and weight gain. These categories were analyzed using the Mantel-Haenszel test to estimate the overall relative risk (Table 3). Although there were some small numerical differences between the two treatment groups, these were not significant. Additionally, because the higher dose is associated with more injections, a grouped analysis of hypersensitivity reactions was also included using the same analytical approach. Slightly more hypersensitivity reactions were reported in the 500-mg group (5.5% versus 2.8% for the 500-mg and 250-mg groups, respectively) with the risk ratio determined to be 1.66 (95% CI, 0.91, 3.04). However, most reactions were CTC grade 1, and pruritus was the most common pre-specified AE reported (4.1% versus 1.4% for the 500-mg and 250-mg groups, respectively). The occurrence of hypersensitivity reactions is not unexpected with the formulation limitations of fulvestrant requiring two 250 mg 5 mL injections for the high-dose 500-mg regimen.

This large database can therefore provide reassurance that the 500-mg dose has been sufficiently characterized in terms of safety. Fulvestrant 500 mg was well-tolerated with no clinically important differences compared with the 250-mg dose.

Clinical Implications

Treatment with tamoxifen or an AI is associated with a clinically meaningful benefit and an improved tolerability profile over chemotherapy in women with hormone receptor-positive advanced breast cancer. However, most patients with advanced disease will ultimately progress; therefore, there is still a need to improve and build on current therapies.[32] With an increasing number of women treated in the first-line with tamoxifen or an AI, there is a key requirement to develop agents with novel modes of action which improve progression-free survival following failure on these endocrine therapies. Fulvestrant is an ER antagonist with no known agonist effects which has demonstrated efficacy at the currently approved dose of 250 mg following failure on prior endocrine therapy.[18] The findings presented here show that increasing the dose of fulvestrant is associated with improved efficacy, based on a clinically relevant improvement in progression-free survival (20% reduction in the risk of progression for fulvestrant 500 mg versus 250 mg). This appears to be irrespective of the initial type of endocrine treatment received.

It is possible that the higher dose of fulvestrant (500 mg) may lead to a reduction in rate or time to emergence of endocrine resistance. Cross-talk between the ER and the growth factor signaling pathways, such as the epidermal growth factor receptor (EGFR)/human epidermal growth factor receptor 2 (HER2) pathway, is thought to be a mechanism of resistance to endocrine therapy in breast cancer.[33] The greater reduction in available ER seen with fulvestrant 500 mg may therefore reduce or prevent such cross-talk, compared with tumors treated with the fulvestrant 250-mg dose regimen.

With the ultimate aim of endocrine therapy in patients with advanced breast cancer being to prolong progression-free survival and maintain a good quality of life, it is important that any new treatment

Table 3 Relative Risk for Pre-Specified Adverse Events – Pooled Data

Specified AEs[a]	Fulvestrant 500 mg (n=560)		Fulvestrant 250 mg (n=567)		Mantel-Haenszel Relative Risk Estimate and 95% CI[c]
	Events	Event Rate/1000 Patients[b]	Events	Event Rate/1000 Patients[b]	
Exposure (Patient Years)	401.8 years		339.3 years		
Endometrial Dysplasia	0	0	0	0	–
GI Disturbances	119 (21.3%)	299.0	123 (21.7%)	360.1	0.83 (0.65, 1.07)
Hot Flushes	55 (9.8%)	139.0	50 (8.8%)	145.2	0.96 (0.65, 1.40)
Injection-Site Reactions	101 (18.0%)	255.8	82 (14.5%)	240.2	1.07 (0.80, 1.43)
Ischemic Cardiovascular Disorders	6 (1.1%)	14.9	9 (1.6%)	26.6	0.56 (0.20, 1.58)
Joint Disorders	96 (17.1%)	239.8	99 (17.5%)	291.1	0.82 (0.62, 1.09)
Osteoporosis	4 (0.7%)	10.3	0	0	–
Thromboembolic Events	5 (0.9%)	12.6	9 (1.6%)	26.4	0.48 (0.16, 1.42)
Urinary Tract Infection	12 (2.1%)	30.1	9 (1.6%)	26.7	1.13 (0.47, 2.67)
Vaginitis	3 (0.5%)	7.4	1 (0.2%)	3.0	2.47 (0.26, 23.74)
Weight Gain	3 (0.5%)	7.7	4 (0.7%)	11.5	0.66 (0.15, 2.97)

Abbreviations: AE = adverse event; CI = confidence interval; GI = gastrointestinal.
[a] The combined analysis used the Mantel-Haenszel approach to estimate the overall relative risk and 95% CI, stratified by study.
[b] The AE event rate was calculated as the total number of AEs per group relative to exposure, measured as the total number of patient years on treatment, with the resultant rate expressed per 1000 patients.
[c] A Mantel-Haenszel <1.0 indicates a lower event risk in the fulvestrant 500 mg group; relative risk >1 indicates a lower event risk in the fulvestrant 250 mg group.

demonstrating superior efficacy also has a favorable tolerability profile. The lack of evidence for any relevant dose-related AEs when using fulvestrant 500 mg/mo (other than allergic and injection-site reactions, which are expected with the higher dose) therefore makes it an attractive treatment option. Extended tamoxifen use is associated with an increase in endometrial cancer[34] and thrombogenic disease,[35] and the third-generation AIs are associated with increased fractures and joint disorders.[36,37] In contrast, joint disorders do not seem to be associated with fulvestrant, which may be important in some patient populations. The long-term safety of fulvestrant 500 mg, however, is yet to be reported.

Although several hormone therapies are indicated following failure on prior endocrine therapy, there is no clear consensus on the best approach. Until recently, current options were limited to steroidal AIs or fulvestrant 250 mg/mo, both of which have shown similar efficacy.[12] The data described here indicate that fulvestrant 500 mg is associated with an improved benefit-risk profile versus fulvestrant 250 mg, and as such, has recently received approval in Europe and the United States for the treatment of postmenopausal women with locally advanced or metastatic breast cancer failing on prior anti-estrogen therapy. Fulvestrant 500 mg may become the preferred treatment option for patients failing their initial endocrine therapy for early or advanced breast cancer, although no studies comparing fulvestrant 500 mg with exemestane are currently in progress.

Fulvestrant 500 mg/mo may also have a potential impact in women with advanced breast cancer who have not received prior endocrine therapy for advanced disease. Unlike Trial 0025 which failed to demonstrate non-inferiority of fulvestrant 250 mg versus tamoxifen (the standard first-line treatment option at that time),[38] findings from the FIRST study, with a significant improvement in TTP and a greater duration of clinical benefit, suggest that fulvestrant 500 mg is at least as effective as anastrozole, a preferred endocrine therapy in this setting.[28] Indirectly, this suggests an improvement in clinical benefit for fulvestrant 500 mg versus fulvestrant 250 mg as first-line endocrine treatment for advanced breast cancer. Based on the findings from CONFIRM and data from FIRST, one might speculate that fulvestrant 500 mg may also have a role in future first-line treatment of hormone receptor–positive patients with advanced breast cancer, but its role remains to be proven in clinical studies in this setting.

Conclusions

Although the efficacy of fulvestrant 250 mg is well-established, pharmacokinetic modeling and early clinical data suggested that a higher dose may confer additional benefits. This has led to further clinical evaluation of fulvestrant 500 mg in hormone receptor–positive women with advanced breast cancer.

Strong evidence is described here to show that fulvestrant 500 mg is associated with an improved benefit-risk profile and, as such, should replace 250 mg as the preferred dose for postmenopausal women with advanced breast cancer.

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References

1. Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol* 2007; 18:581-92.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59:225-49.

3. Cardoso F, Castiglione M. Locally recurrent or metastatic breast cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2009; 20 (suppl 4):15-8.
4. Guarneri V, Conte PF. The curability of breast cancer and the treatment of advanced disease. *Eur J Nucl Med Mol Imaging* 2004; 31(suppl 1):S149-S161.
5. Harichand-Herdt S, Zelnak A, O'Regan R. Endocrine therapy for the treatment of postmenopausal women with breast cancer. *Expert Rev Anticancer Ther* 2009; 9:187-98.
6. Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001; 19:2596-606.
7. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol* 2008; 26:4883-90.
8. Bonneterre J, Thürlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 2000; 18:3748-57.
9. Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol* 2000; 18:3758-67.
10. Dodwell D, Wardley A, Johnston S. Postmenopausal advanced breast cancer: options for therapy after tamoxifen and aromatase inhibitors. *Breast* 2006; 15:584-94.
11. Wakeling AE, Dukes M, Bowler J. A potent specific pure antiestrogen with clinical potential. *Cancer Res* 1991; 51:3867-73.
12. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol* 2008; 26:1664-70.
13. Ingle JN, Suman VJ, Rowland KM, et al. Fulvestrant in women with advanced breast cancer after progression on prior aromatase inhibitor therapy: North Central Cancer Treatment Group trial N0032. *J Clin Oncol* 2006; 24:1052-6.
14. Neven P, Paridaens R, Pelgrims G, et al. Fulvestrant (Faslodex™) in advanced breast cancer: clinical experience from a Belgian cooperative study. *Breast Cancer Res Treat* 2008; 109:59-65.
15. Perey L, Paridaens R, Hawle H, et al. Clinical benefit of fulvestrant in postmenopausal women with advanced breast cancer and primary or acquired resistance to aromatase inhibitors: final results of phase II Swiss Group for Clinical Cancer Research Trial (SAKK 21/00). *Ann Oncol* 2007; 18:64-9.
16. Howell A, Robertson JFR, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 2002; 20: 3396-403.
17. Osborne CK, Pippen J, Jones SE, et al. A double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of North American trial. *J Clin Oncol* 2002; 20:3386-95.
18. Robertson JF, Osborne CK, Howell A, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. *Cancer* 2003; 98:229-38.
19. Robertson JF, Nicholson RI, Bundred NJ, et al. Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5, (10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. *Cancer Res* 2001; 61:6739-46.
20. DeFriend DJ, Howell A, Nicholson RI, et al. Investigation of a new pure antiestrogen (ICI 182780) in women with primary breast cancer. *Cancer Res* 1994; 54:408-14.
21. Robertson JF, Erikstein B, Osborne KC, et al. Pharmacokinetic profile of intramuscular fulvestrant in advanced breast cancer. *Clin Pharmacokinet* 2004; 43:529-38.
22. Robertson JFR. Fulvestrant (Faslodex) - how to make a good drug better. *Oncologist* 2007; 12:774-84.
23. Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM Phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol* 2010; 28:4594-600.
24. Fujiwara Y, Ohno S, Iwata H, et al. Tolerability of fulvestrant high-dose (HD) in postmenopausal Japanese women with hormone receptor-positive (HR+) advanced (ABC) or recurrent breast cancer (RBC). Abstract 192 presented at the ASCO Breast Cancer Symposium, San Francisco, CA, USA September 7-8, 2007.
25. Kuter I, Hegg R, Singer CF, et al. Fulvestrant 500 mg vs 250 mg: first results from NEWEST, a randomized, phase II neoadjuvant trial in postmenopausal women with locally advanced, estrogen receptor-positive breast cancer. *Breast Cancer Res Treat* 2007; 106(suppl 1):S7 (abstr 23).
26. Ohno S, Rai Y, Iwata H, et al. Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: results from a double-blind, phase II comparative study (FINDER1). *Ann Oncol* 2010; 21:2342-7.
27. Pritchard KI, Rolski J, Papai Z, et al. Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2). *Breast Cancer Res Treat* 2010; 123:453-61.
28. Robertson JFR, Llombart A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. *J Clin Oncol* 2009; 27:4530-5.
29. McCormack P, Sapunar F. Pharmacokinetic profile of the fulvestrant loading dose regimen in postmenopausal women with hormone receptor-positive advanced breast cancer. *Clin Breast Cancer* 2008; 8:347-51.
30. Kuter I, Sapunar F, McCormack P. Pharmacokinetic profile of fulvestrant 500 mg vs 250 mg: results from the NEWEST study. *J Clin Oncol* 2008; 26 (abstr 579).
31. Robertson JFR, Lindemann J, Llombart-Cussac A, 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. *Cancer Res* 2010; 70:76s.
32. Carlson RW, Henderson IC. Sequential hormonal therapy for metastatic breast cancer after adjuvant tamoxifen or anastrozole. *Breast Cancer Res Treat* 2003; 80 (suppl 1):S19-S26.
33. Arpino G, Wiechmann L, Osborne CK, et al. Crosstalk between the estrogen receptor and the HER tyrosine kinase receptor family: molecular mechanism and clinical implications for endocrine therapy resistance. *Endocr Rev* 2008; 29:217-33.
34. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 351:1451-67.
35. Levine MN, Gent M, Hirsh J, et al. The thrombogenic effect of anticancer drug therapy in women with stage II breast cancer. *N Engl J Med* 1988; 318:404-7.
36. ATAC Trialists' Group. Results of the ATAC (arimidex, tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; 365:60-2.
37. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; 349:1793-802.
38. Howell A, Robertson JFR, Abram P, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. *J Clin Oncol* 2004; 22:1605-13.