

Fulvestrant, a new treatment option for advanced breast cancer: tolerability versus existing agents

I. Vergote^{1*} & P. Abram²

¹University Hospitals, Leuven, Belgium; ²Belvoir Park Hospital, Belfast, UK

Received 17 April 2005; revised 10 September 2005; accepted 12 September 2005

Owing to its favourable tolerability profile versus cytotoxic chemotherapy, endocrine therapy is the treatment of choice for postmenopausal women with hormone receptor-positive advanced breast cancer (ABC). However, tolerability concerns associated with some endocrine treatments and the potential for cross-resistance has helped to drive the need for new, effective and better-tolerated agents. Fulvestrant is a new type of oestrogen receptor antagonist with no agonist effects. In phase III trials, fulvestrant has been shown to be at least as effective as the third-generation aromatase inhibitor (AI) anastrozole in the treatment of postmenopausal women with ABC progressing on prior tamoxifen therapy. Fulvestrant is administered as a once-monthly 250 mg intramuscular injection into the gluteus muscle. Here we review the tolerability of fulvestrant in the treatment of postmenopausal women with hormone-sensitive ABC and compare it with that of the four most frequently prescribed endocrine treatments for advanced disease (tamoxifen, anastrozole, letrozole and exemestane). Compared with these agents, fulvestrant is well tolerated and is associated with a lower incidence of joint disorders compared with the non-steroidal AIs and none of the potential androgenic side-effects that are sometimes seen with steroidal AIs. It is also associated with hot flushes compared with tamoxifen. Fulvestrant therefore provides clinicians and patients with a useful, well-tolerated option for the treatment of hormone-sensitive ABC. Integration of such agents into the endocrine treatment sequence may extend the opportunity for using well-tolerated therapies before chemotherapy needs to be considered and thus may improve quality of life for patients with ABC. The overall safety profiles of newer agents such as fulvestrant will become increasingly clear with their ongoing use.

Key words: breast, breast cancer, fulvestrant, hormone, neoplasms, therapy

Introduction

For patients with advanced breast cancer (ABC) in whom palliation of symptoms and maintenance of quality of life are the primary objectives, it is important that any treatment is well tolerated to aid compliance and treatment success. Owing to its favourable tolerability profile, endocrine therapy is the treatment of choice for postmenopausal women with hormone receptor-positive ABC (i.e. about 73% of the total postmenopausal ABC population). Currently available endocrine treatments for advanced disease include the selective oestrogen receptor (ER) modulator tamoxifen, the third-generation, non-steroidal aromatase inhibitors (AIs) anastrozole and letrozole, and the steroidal AI exemestane. The most recent addition to the armamentarium of endocrine agents is fulvestrant, a novel ER antagonist with no agonist effects [1]. It binds, blocks and degrades the ER, thereby downregulating cellular ER levels, which in turn leads to reduced expression of the progesterone receptor.

Here we review the tolerability profile of fulvestrant [250 mg once monthly, intramuscular (i.m.) injection], and compare it with tolerability data from the four most frequently prescribed endocrine treatments for ABC: tamoxifen (20 mg once daily, orally), anastrozole (1 mg once daily, orally), letrozole (2.5 mg once daily, orally) and exemestane (25 mg once daily, orally).

fulvestrant

oestrogen agonist activity

In a phase I trial involving 30 healthy postmenopausal women, volunteers received a single dose of 125 or 250 mg fulvestrant or placebo i.m. followed 2 weeks later by 20 mg/day ethinyloestradiol for 2 weeks. No evidence of agonist activity in the endometrium was observed with fulvestrant [2]. In addition, when compared with placebo, after 21 days of treatment the mean change in oestrogen-stimulated endometrial thickening was prevented using 250 mg fulvestrant (1.5 versus 8.1 mm; $P < 0.001$). Therefore, in contrast to tamoxifen, which has well-known agonist effects in the endometrium, fulvestrant lacks oestrogen agonist effects and so is unlikely to be associated with an increased risk of endometrial cancer with long-term use.

*Correspondence to: Dr I. Vergote, University Hospitals Leuven, Department of Gynecologic Oncology, Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.
Tel: +32-16-34-46-35; Fax: +32-16-34-46-29;
E-mail: Ignace.Vergote@uz.kuleuven.ac.be

comparative tolerability: fulvestrant versus anastrozole

Two phase III studies have shown that fulvestrant is at least as effective as anastrozole in the treatment of postmenopausal women ($n = 851$) with ABC who have progressed or relapsed on prior tamoxifen treatment [3, 4]. This was also borne out in the subgroup of patients with visceral metastases [5].

Study 0020 ($n = 451$) was an open-label, randomised, parallel-group, multicentre study conducted in Europe, South Africa and Australia, in which fulvestrant was delivered in a single 5 ml i.m. injection. The median duration of follow-up in this study was 14.4 months [4]. Study 0021 ($n = 400$) was a double-blind, randomised, multicentre, parallel-group study conducted in North America in which fulvestrant was delivered in two \times 2.5 ml i.m. injections. The median duration of follow-up in this study was 16.8 months [3]. Overall, the median duration of treatment for both studies was 5.5 months (range 0.9–36.8) in the fulvestrant group and 5.5 months (range 0.6–31.4) in the anastrozole group.

Both studies were prospectively designed to allow combined analysis of data [6]. Combined analysis of the safety data showed that both treatments were well tolerated and there was a low incidence of withdrawals due to adverse events (AEs) overall (fulvestrant, 2.8%; anastrozole, 1.9%) and those AEs considered to be drug related (fulvestrant, 0.9%; anastrozole, 1.2%). The most common AEs in these trials were nausea (26% versus 25.3%), asthenia (22.7% versus 27.0%), pain (18.9% versus 20.3%), vasodilatation (dizziness, light-headedness, symptomatic hypotension) (17.7% versus 17.3%) and headache (15.4% versus 16.8%) in the fulvestrant and anastrozole groups, respectively [6]. In these studies, seven AEs considered relevant to endocrine therapy were pre-defined for statistical analysis. In both trials, there was no statistically significant difference between treatment groups in the incidence of weight gain, thromboembolic disease, gastrointestinal disturbance, hot flushes or urinary tract infections (Figure 1). However, there was a significantly lower incidence of joint disorders (including arthralgia, arthrosis and arthritis) with fulvestrant (5.4%) compared with anastrozole (10.6%) ($P = 0.0036$) (Figure 1). The effect of fulvestrant on lipid variables was also monitored as part of laboratory investigations in these trials; no major changes in lipid variables occurred with either treatment (AstraZeneca, data on file). In an extended follow-up for time to death, conducted when 75% of patients had died, no long-term safety concerns were apparent [7].

Fulvestrant i.m. injection was well tolerated locally; in most cases injection-site reactions were non-serious, mild and transient: only 4.6% and 1.1% of fulvestrant i.m. injections in trials 0021 and 0020, respectively resulted in injection-site events. Across the two studies, only two patients (0.5%) in the fulvestrant group withdrew because of injection-site events. In a comparison of fulvestrant and placebo injections in trial 0021, there was no difference in the incidence of injection-site reactions, demonstrating that the fulvestrant i.m. injection is well tolerated in contrast to some other injectable anticancer agents such as the steroidal AI formestane. For example, in a phase II dose-finding study, formestane treatment (500–1000 mg monthly) resulted in injection-site events (abscesses, painful

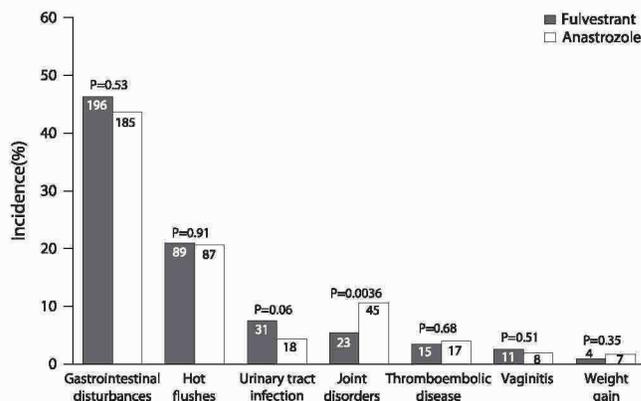


Figure 1. The incidence of predefined adverse events in a combined analysis of two phase III trials comparing fulvestrant with anastrozole as second-line treatments in patients with advanced breast cancer [6]. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

lumps and allergic-type reactions) in 19% of patients [8]. To date, there have been no head-to-head clinical studies comparing fulvestrant with either letrozole or exemestane.

comparative tolerability: fulvestrant versus tamoxifen

A double-blind, double-dummy randomised phase III trial has shown that fulvestrant has similar efficacy to tamoxifen in the first-line treatment of postmenopausal women ($n = 587$) with hormone receptor-positive ABC [9]. The median duration of treatment in this study was 8.3 months (range 0.9–26.5) in the fulvestrant group and 9.3 months (range 0.9–25.1) in the tamoxifen group.

At a median follow-up of 14.5 months, the most frequent AEs in both groups were nausea (20.3% fulvestrant versus 22.5% tamoxifen), asthenia (19.4% versus 20.3%), vasodilatation (14.8% versus 21.4%), pain (13.9% versus 19.2%) and bone pain (13.9% versus 17%) [9]. Most AEs were mild or moderate in severity. A total of 129 (41.6%) patients in the fulvestrant group and 139 (51.3%) patients in the tamoxifen group experienced drug-related AEs. The most frequent drug-related AEs in both treatment groups were vasodilatation, injection-site pain and nausea.

Of the AEs prospectively defined for statistical comparison, there were no significant differences between the two treatment groups for vaginitis and thromboembolic disease. There was a trend for fewer gastrointestinal disturbances (nausea, vomiting, diarrhoea and constipation) with fulvestrant (37.1% versus 43.2%; $P = 0.16$) and the incidence of hot flushes was lower in the fulvestrant group than in the tamoxifen group (17.7% versus 24.7%; $P = 0.05$) (Figure 2). The latter observation may be related to the fact that fulvestrant does not cross the blood–brain barrier (AstraZeneca, data on file).

tamoxifen

Tamoxifen is generally well tolerated, although with long-term use its partial oestrogen agonist properties increase the risk of endometrial cancer. In an overview of the randomised trials of adjuvant tamoxifen including data for 37 000 women, the

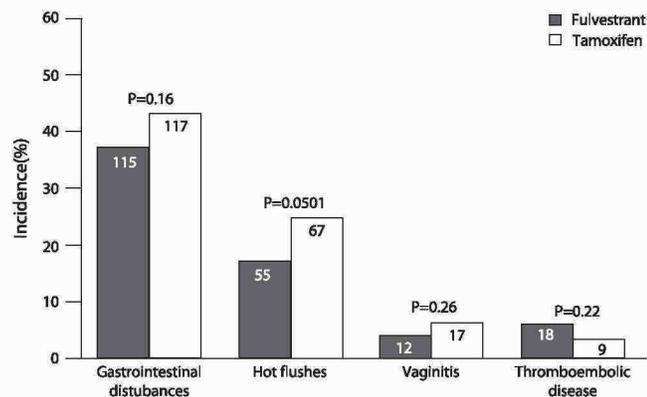


Figure 2. The incidence of predefined adverse events in a phase III trial comparing fulvestrant with tamoxifen as first-line treatments in patients with advanced breast cancer [9]. Reprinted with permission from the American Society of Clinical Oncology.

incidence of endometrial cancer was doubled in trials of 1 or 2 years' treatment and approximately quadrupled in trials of 5 years' tamoxifen [10]. Tamoxifen treatment may stimulate 'tumour flare' subsequent to an initial response and is also associated with hot flushes and an increased risk of stroke and thromboembolic disease. In a trial comparing anastrozole with tamoxifen in the first-line treatment of ABC, tamoxifen was associated with a significantly higher incidence of thromboembolic events (6.5% versus 3.6%; $P = 0.0434$) and vaginal bleeding was also reported in fewer anastrozole-treated patients (2.2% versus 1%) [11]. The incidence of thromboembolic events in a trial comparing tamoxifen with letrozole was 2% and 1%, respectively [12]. The agonist activity of tamoxifen may, however, have beneficial effects on bone mineral density, particularly with long-term treatment, e.g. in the adjuvant setting [13].

aromatase inhibitors

Third-generation AIs are effective and generally well tolerated in the treatment of postmenopausal women with ABC. The selective non-steroidal AIs anastrozole and letrozole have been shown to be at least as effective as tamoxifen in this setting and anastrozole was associated with significantly fewer thromboembolic events than tamoxifen [11, 14]. The AIs inhibit endogenous oestrogen synthesis via aromatase, which in postmenopausal women results in very low plasma levels of oestrogen, and these agents may therefore be associated with some deleterious effects on bone [15].

Joint disorders (e.g. arthralgia) have also been reported for all of the third-generation AIs [6, 16–19]. For example, in a trial comparing the efficacy and tolerability of letrozole and megestrol acetate in patients with ABC, arthralgia was experienced by more letrozole-treated patients (13.2%) compared with those receiving the comparator treatment (7.9%) [16]. However, in a phase III comparative trial of letrozole and tamoxifen there was no difference in the incidence of arthralgia (16% versus 15%, respectively) [14]. As previously stated, significantly more anastrozole-treated patients experienced joint disorders compared with fulvestrant (10.6% versus 5.4%; $P = 0.0036$) in comparative phase III trials [6]. The

steroidal AI exemestane is also associated with arthralgia. In a recent phase III study comparing the efficacy and tolerability of this steroidal AI with tamoxifen, 11% of exemestane-treated patients experienced arthralgia compared with 5% of those treated with tamoxifen [19].

The most common AEs associated with anastrozole are transient gastrointestinal disturbances, generally mild-to-moderate in intensity, headache, asthenia, bone pain and hot flushes [20, 21]. The tolerability profile of letrozole appears to be broadly similar to that of anastrozole with the most commonly encountered AEs also including nausea/vomiting, headache, asthenia, bone pain and hot flushes [16, 22]. In the only study to compare directly the efficacy and tolerability of anastrozole and letrozole, there were no significant differences in the incidence of any AEs [23].

The most frequently reported drug-related AEs with exemestane treatment are hot flushes, nausea and fatigue [24]. Exemestane has weak androgenic properties and has been associated with androgenic side-effects such as weight gain, alopecia and acne, particularly when used at higher doses [25]. In a phase III trial comparing the efficacy and tolerability of exemestane (25 mg/day) and megestrol acetate (160 mg/day), the incidence of grade 3 or 4 weight gain after a median of only 17 weeks' treatment was 8% in the exemestane group and 17% in the megestrol acetate group ($P = 0.001$) [26]. Androgenic side-effects such as hair loss, hypertrichosis, hoarseness and acne are more commonly reported with higher doses of exemestane, occurring in 10% of patients treated with a 200 mg daily dose [27]. In two short-term trials using 25 mg/day exemestane, hypertrichosis and acne were reported in ~2% of patients [28] and grade 2/3 skin disorders were reported in 8% of patients (no reports in the tamoxifen group) [18]. In a recent phase III trial, alopecia was reported in 4% of patients receiving exemestane 25 mg/day compared with 1% of those receiving tamoxifen [19].

Compared with tamoxifen, exemestane treatment was also associated with a higher incidence of increased gamma-glutamyl transferase (33% versus 26%), increased alkaline phosphatase (26% versus 14%), increased bilirubin (11% versus 3%), dyspnoea (17% versus 11%) and AEs of the skin (19% versus 14%), whereas hot flushes (29% versus 24%), bone pain (22% versus 17%), nausea (21% versus 14%) and oedema (20% versus 10%) were all more common in tamoxifen-treated patients [18]. In a subsequent phase III study, exemestane was associated with a higher incidence of weight gain (19% versus 14%), arthralgia/myalgia (11% versus 5%) and diarrhoea (9% versus 3%) compared with tamoxifen. In this study, constipation (13% versus 8%) and vaginal discharge (7% versus 2%) were more commonly seen in patients receiving tamoxifen [19].

summary

More than 1100 postmenopausal women have received fulvestrant during the clinical study programme. This new endocrine agent exhibits a predictable tolerability profile that may offer benefits compared with other agents including tamoxifen and the three currently available AIs: anastrozole, letrozole and exemestane. In all the phase III trials in postmenopausal women with locally advanced or metastatic

breast cancer fulvestrant was well tolerated; AEs were generally mild or moderate in intensity. The higher incidence of joint disorders with the AIs compared with fulvestrant illustrates the value of fulvestrant in a patient population who may be predisposed to musculoskeletal conditions.

Fulvestrant has no proliferative effect on the endometrium [2] and is therefore unlikely to lead to an increased risk of endometrial cancer following long-term exposure such as that produced by tamoxifen [29]. There have been no reports of adverse events that may be attributable to androgenic activity and fulvestrant is associated with a lower incidence of hot flushes compared with tamoxifen. In contrast to other endocrine agents used in the treatment of ABC, fulvestrant is administered as a once-monthly i.m. injection.

In summary, fulvestrant 250 mg once-monthly i.m. injection is a well-tolerated and effective treatment for postmenopausal women with hormone-sensitive ABC. The tolerability profile and route of administration of fulvestrant may also lead to improved patient compliance and thus better patient outcomes, although some patients may prefer to receive their breast cancer treatment orally [30]. The previously demonstrated lack of cross-resistance of fulvestrant with other endocrine treatments along with its favourable tolerability profile means that this agent provides clinicians and patients with a useful additional option for the treatment of hormone-sensitive ABC. Whilst the overall safety profiles of newer endocrine treatments will become increasingly clear with their ongoing use, the integration of agents such as fulvestrant into the endocrine treatment sequence may extend the opportunity for using well-tolerated therapies before chemotherapy needs to be considered and thus may improve quality of life for patients with advanced disease. In addition, the good tolerability profile of fulvestrant may suggest possible benefits for this agent in the adjuvant setting where longer-term use would be anticipated. Although as yet unproven, clinical trials of fulvestrant in the adjuvant setting are being planned.

acknowledgements

Editorial assistance was provided by Dawn Batty PhD, with financial support from AstraZeneca.

references

- Wakeling AE, Dukes M, Bowler J. A potent specific pure antiestrogen with clinical potential. *Cancer Res* 1991; 51: 3867–3873.
- Addo S, Yates RA, Laight A. A phase I trial to assess the pharmacology of the new oestrogen receptor antagonist fulvestrant on the endometrium in healthy postmenopausal volunteers. *Br J Cancer* 2002; 87: 1354–1359.
- Osborne CK, Pippen J, Jones SE et al. 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 a North American trial. *J Clin Oncol* 2002; 20: 3386–3395.
- 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: 3396–3403.
- Mauriac L, Pippen JE, Quaresma Albano J et al. Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials. *Eur J Cancer* 2003; 39: 1228–1233.
- 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: 229–238.
- Pippen J, Osborne CK, Howell A, Robertson JFR. Fulvestrant (Faslodex) versus anastrozole (Arimidex) for the treatment of advanced breast cancer: a prospective combined survival analysis of two multicenter trials. *Breast Cancer Res Treat* 2003; 82 (Suppl 1): S101 (Abstr 426).
- Goss PE, Powles TJ, Dowsett M et al. Treatment of advanced postmenopausal breast cancer with an aromatase inhibitor, 4-hydroxyandrostenedione: phase II report. *Cancer Res* 1986; 46: 4823–4826.
- Howell A, Robertson JFR, Abram P et al. Comparison of fulvestrant v 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: 1605–1613.
- Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 351: 1451–1467.
- Bonnetterre J, Buzdar A, Nabholz JM et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 2001; 92: 2247–2258.
- 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: 2596–2606.
- Fisher B, Costantino JP, Redmond CK et al. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 1994; 86: 527–537.
- Mouridsen H, Gershanovich M, Sun Y et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003; 21: 2101–2109.
- Buzdar A, Robertson JFR, Eiermann W, Nabholz JM. An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole and exemestane. *Cancer* 2002; 95: 2006–2016.
- Dombernowsky P, Smith I, Falkson G et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998; 16: 453–461.
- Donnellan PP, Douglas SL, Cameron DA, Leonard RC. Aromatase inhibitors and arthralgia. *J Clin Oncol* 2001; 19: 2767.
- Paridaens R, Dirix L, Lohrisch C et al. Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Ann Oncol* 2003; 14: 1391–1398.
- Paridaens R, Therasse P, Dirix L et al. First line hormonal treatment (HT) for metastatic breast cancer (MBC) with exemestane (E) or tamoxifen (T) in postmenopausal patients (pts) – A randomized phase III trial of the EORTC Breast group. *Proc Am Soc Clin Oncol* 2004; 23: 6 (Abstr 515).
- Buzdar A, Jonat W, Howell A et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. *Arimidex Study Group. J Clin Oncol* 1996; 14: 2000–2011.
- Wiseman LR, Adkins JC. Anastrozole. A review of its use in the management of postmenopausal women with advanced breast cancer. *Drugs Aging* 1998; 13: 321–332.
- Lamb HM, Adkins JC. Letrozole. A review of its use in postmenopausal women with advanced breast cancer. *Drugs* 1998; 56: 1125–1140.
- Rose C, Vtoraya O, Pluzanska A et al. An open randomised trial of second-line endocrine therapy in advanced breast cancer: comparison of the aromatase inhibitors letrozole and anastrozole. *Eur J Cancer* 2003; 39: 2318–2327.
- Buzdar A. Exemestane in advanced breast cancer. *Anticancer Drugs* 2000; 11: 609–616.

25. Michaud LB, Buzdar AU. Risks and benefits of aromatase inhibitors in postmenopausal breast cancer. *Drug Saf* 1999; 21: 297–309.
26. Kaufmann M, Bajetta E, Dirix LY et al. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. The Exemestane Study Group. *J Clin Oncol* 2000; 18: 1399–1411.
27. Thurlimann B, Paridaens R, Serin D et al. Third-line hormonal treatment with exemestane in postmenopausal patients with advanced breast cancer progressing on aminoglutethimide: a phase II multicentre multinational study. Exemestane Study Group. *Eur J Cancer* 1997; 33: 1767–1773.
28. Jones S, Vogel C, Arkhipov A et al. Multicenter, phase II trial of exemestane as third-line hormonal therapy of postmenopausal women with metastatic breast cancer. Aromasin Study Group. *J Clin Oncol* 1999; 17: 3418–3425.
29. Bergman L, Beelen ML, Gallee MP et al. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of liver and endometrial cancer risk following tamoxifen. *Lancet* 2000; 356: 881–887.
30. Fallowfield L, Atkins L, Catt S et al. Patients' preference for administration of endocrine treatments by injection or tablets: results from a study of women with breast cancer. *Ann Oncol* 2005; doi:10.1093/annonc/mdj044.