Proof of concept review

Arzoxifene: the evidence for its development in the management of breast cancer

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Abstract

Introduction: Endocrine therapy is an important and integral part of breast cancer management. Selective estrogen receptor modulators (SERMs), such as tamoxifen, remain a vital component in the endocrine therapy armamentarium. However the "ideal SERM", which has antagonist effects on the breast and endometrium but beneficial agonistic effects on bone and lipid profile, remains to be found.

Aim: The aim of this review is to examine the evidence for arzoxifene as the "ideal SERM."

Evidence review: Arzoxifene showed initial promise as the "ideal SERM" in preclinical, phase I, and phase II clinical studies. It appeared to have powerful antiestrogenic effects on breast cancer and endometrium, with equally strong favorable estrogenic effects on bone and lipid profile, minimal side effects, and good oral bioavailability.

However, phase III trial data found it to be inferior to tamoxifen, bringing an apparent end to its investigation as a breast cancer treatment.

Clinical potential: Despite early promise as the "ideal SERM", results from a phase III trial have relegated arzoxifene to research in breast cancer prevention and osteoporosis treatment.

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Key words: arzoxifene, selective estrogen receptor modulators (SERM), breast cancer

Core evidence proof of concept summary for arzoxifene in breast cancer

Outcome measure	Emerging evidence
Breast cancer cell growth	Estrogen-stimulated MCF-7 breast cancer cell line proliferation was inhibited by arzoxifene to a degree superior to that with tamoxifen and equivalent to raloxifene
	N-nitrosomethylurea-induced mammary cancer growth in rats inhibited with an ability superior to raloxifene but similar to tamoxifen
Effects on the endometrium	Arzoxifene has no significant estrogenic effect on endometrium
Maintenance of bone density and strength	At least as effective as raloxifene *in vivo*. Evidence of an antiresorptive effect on bone in postmenopausal women
Effects on cholesterol and body weight	Arzoxifene prevents increase in cholesterol to at least same degree as raloxifene; also prevents body weight increase *in vivo*
Endocrine effects	Arzoxifene decreases follicle-stimulating hormone and luteinizing hormone levels with increasing sex hormone-binding globulin levels to similar extent as tamoxifen
	Serum and urine osteocalcin levels decreased *in vivo*
Response rates	Objective response rate (ORR) (defined as CR + PR) achieved in 19.2–40.5% patients with arzoxifene 20 mg/day, and in 7.4–36.4% with 50 mg/day
	Clinical benefit rate (CBR) (defined as CR + PR + stable disease ≥6 months) achieved in 28.8–64.3% for arzoxifene 20 mg/day, and in 20.4–61.4% with 50 mg/day
	ORR rate and CBR rates lower than with tamoxifen 20 mg/day
Time to disease progression	Progression-free survival 4 months with arzoxifene 20 mg/day compared with 7.5 months with tamoxifen 20 mg/day
	Arzoxifene less effective than tamoxifen
Tolerability	Acceptable tolerability profile

CR, complete response; PR, partial response.

Scope, aims, and objectives

Breast cancer remains the most common cancer in women in the Western world (Office for National Statistics 2007; Ries et al. 2007). A significant number of breast cancers are related to exposure to estrogens, either endogenous or exogenous, and more than 75% of breast cancers are hormone receptor positive (Chlebowski et al. 2003; Münster et al. 2006). Hence, manipulation of circulating/local estrogen/progesterone or suppression of the estrogen or progesterone receptors remains an essential part of the treatment and prevention of breast cancer (Early Breast Cancer Trialists' Collaborative Group 1996, 1998, 2005).

A wide range of drugs has been developed since Beatson, in 1896, first reported that breast cancer could be treated by oophorectomy (Beatson 1896). These agents are collectively known as endocrine therapies and can be divided into "ablative" (where the aim is to remove the source of estrogen) and "additive" (where the aim is to interfere with the effect of estrogen on the hormonally dependent cancer cells) (Hayes & Robertson 2002). While ablative therapies were initially delivered via surgical means (e.g. oophorectomy, adrenalectomy, and hypophysectomy), this is now possible through drug treatments such as luteinizing hormone-releasing hormone (LHRH) agonists/antagonists (e.g. goserelin) and the aromatase inhibitors (e.g. anastrazole, letrozole, and exemestane). Additive agents range from androgens (methyl testosterone), estrogenic compounds (diethylstilbestrol, ethinylestradiol), progestins (megestrol acetate, medroxyprogesterone acetate), antiprogestins (mifepristone, onapristone), selective estrogen receptor modulators [(SERMS), such as tamoxifen], and pure antiestrogens (such as fulvestrant).

The success of tamoxifen in the treatment (Early Breast Cancer Trialists' Collaborative Group 1996, 1998, 2005) and prevention (Fisher et al. 1998; Cuzick et al. 2007; Powles et al. 2007) of breast cancer, together with the difference in cost compared with the new aromatase inhibitors, continue to make SERMS the most widely used form of endocrine therapy worldwide. It is well established that tamoxifen has both antagonistic and partial agonistic properties depending on target tissues. Over the years unwanted agonistic side effects of tamoxifen, such as uterine cancer, have become recognized, such that attention has been focused on developing new SERMs with different profiles.

The nonsteroidal SERMS can be categorized into triphenylethylenes (e.g. tamoxifen, toremifene, droloxifene, idoxifene, trichlorophenyethylene, and tribromophenylethylene) and benzothiophenes (e.g. raloxifene and arzoxifene). These modulators have variable estrogenic effects on target tissues dependent upon selective gene coactivator or co-repressor recruitment (Grese et al. 1997; Shang & Brown 2002; Cuzick et al. 2007). Hence, although tamoxifen is antiestrogenic to breast tissue, it has proestrogenic (agonistic) effects on bone and endometrium. While the occurrence of endometrial cancer is clearly undesirable, the increased risk has been perceived as small relative to the substantial benefits that tamoxifen has on reducing breast cancer events (i.e. recurrence and mortality). The aim of SERM development has been to find an "ideal" SERM (Münster 2006), one that has antiestrogenic effects on breast and endometrium, whilst having beneficial estrogenic effects on bone and lipid profiles. In addition, it would be expected not to cause hot flushes or thromboembolic events, nor to be associated with long term exposure tumor dependence as seen with tamoxifen (Gottardis & Jordan 1988; Osipo et al. 2005), which may explain development of tumor resistance (Osborne & Fuqua 1994; Johnston 1997).

Arzoxifene was designed in an attempt to deliver the ideal SERM. The aim of this review is to evaluate the evidence for arzoxifene as the ideal SERM in the management of breast cancer.

Methods

PubMed was searched using the keywords "arzoxifene", "arzoxifene AND breast cancer", and "arzoxifene AND endometrial cancer". The initial search yielded 71 references; adding the keywords "breast cancer" and "endometrial cancer" resulted in 46 and 11 references, respectively, although none were additional to the original 71. A further 33 additional references were added from evidence acquired via the original PubMed search (Table 1).

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	71	0
records excluded	57	0
records included	14	0
Additional studies identified	33	2
Level 1 clinical evidence (systemic review, meta analysis)	19	1
Level 2 clinical evidence (RCT)	1	0
Level ≥3 clinical evidence trials other than RCT case reports	5	0
Nonclinical trial evidence	22	1
Economic evidence	0	0

For definitions of levels of evidence, see Editorial Information on inside back cover or on *Core Evidence* website (http://www.coremedicalpublishing.com).
RCT, randomized controlled trial.

Arzoxifene development

When discussing the development of arzoxifene, it is important to consider results obtained with other SERMs, notably raloxifene.

Benzothiophene SERMs began development in 1980 (Black & Goode 1980), LY-156758 (raloxifene) being one of the first to begin evaluation. It had been noted to have antiestrogenic effects on breast cancer cell lines and endometrial cells, whilst having proestrogenic effects on bone (Palkowitz et al. 1997). However, in a phase II trial in patients with metastatic breast cancer, raloxifene showed little or no therapeutic effect: there were no objective

responses to raloxifene 200 mg daily in 14 patients who had progressed on tamoxifen after initially responding to that agent (Buzdar et al. 1988). Raloxifene, at this stage, was not developed further for breast cancer treatment, with efforts being refocused on its potential use in osteoporosis and breast cancer prophylaxis. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial, in 7705 postmenopausal osteoporotic women randomized to raloxifene or placebo, showed that raloxifene significantly improved bone mineral density in the femoral neck and spine, and significantly reduced the risk of a vertebral fracture [relative risk reduction (RRR) 30–50%] (Ettinger et al. 1999). At early analysis, raloxifene was also reported to be associated with a significant 76% reduction in breast cancer incidence (Cummings et al. 1999). This persisted in long term follow-up with a significant 72% reduction in the incidence of breast cancer, which comprised an 84% reduction in incidence of estrogen receptor-positive breast cancers, with no effect on the incidence of estrogen receptor-negative breast tumors (Cauley et al. 2001). Although raloxifene significantly increased the risk of thromboembolism [relative risk (RR), 3.1], it had no significant effect on the incidence of endometrial cancer. In an extension of the MORE study, women who had been on raloxifene for 4 years were offered a further 4 years of treatment – the Continuing Outcomes Relevant to Evista (CORE) study. This reported a 69% reduction in breast cancer incidence due to raloxifene (Martino et al. 2004). When the MORE and CORE trials were both considered (i.e. analyzing all 8 years of raloxifene therapy) the overall reduction in breast cancer incidence was 66%, with a 76% reduction in estrogen receptor-positive breast cancer. The increased thromboembolism risk persisted (RR=2.17).

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR) phase II trial arose out of the findings of the MORE and CORE studies. STAR was a large, prospective, double-blind, randomized trial in which 19 747 postmenopausal women with a greater than 1.66% 5-year risk of developing breast cancer were randomized to either tamoxifen 20 mg daily or raloxifene 60 mg daily. The NSABP phase I study had already shown tamoxifen to significantly reduce the risk of breast cancer in high risk women by 49% (Fisher et al. 1998). The phase II trial showed raloxifene was equally effective as tamoxifen at preventing invasive breast cancer, which was the primary endpoint of the trial (Vogel et al. 2006). Raloxifene, unlike tamoxifen, did not appear to be effective at preventing *in-situ* cancers (RR 1.4), although this difference was not statistically significant. Other secondary endpoints showed that compared with tamoxifen there were 38% fewer uterine cancers, 30% fewer thromboembolic events, 21% fewer cataracts, and 18% fewer cataract surgeries. Only the incidence of cataract was significantly different between the two SERMs. Raloxifene did not differ from tamoxifen in terms of the incidence of ischemic heart events, strokes, or fractures. Quality of life was also statistically similar for the two drugs (Land et al. 2006). Raloxifene was associated with more musculoskeletal symptoms, dyspareunia, and weight gain, but fewer gynecologic problems, vasomotor symptoms, leg cramps, and bladder control problems (Land et al. 2006). Raloxifene had therefore shown its usefulness in prevention of osteoporosis and vertebral fracture, and at breast cancer prevention. However it had not demonstrated any efficacy as a treatment for established breast cancer.

Arzoxifene was developed as the next generation SERM to determine if the benzothiophenes could still have a role in breast cancer treatment. It is a raloxifene analog with an oxygen modification of raloxifene's carbonyl site. This seemed to increase the estrogen receptor binding affinity and antiestrogenic properties, as well as improving oral bioavailability (Palkowitz et al. 1997; Suh et al. 2001). Arzoxifene offered apparent potent antiestrogenic effects on breast and endometrial cells, whilst having beneficial estrogenic effects on bone and cholesterol metabolism (Palkowitz et al. 1997).

Arzoxifene is rapidly metabolized to desmethylated arzoxifene (LY-335563). The metabolite is active with high estrogen receptor affinity and ability to inhibit breast cancer (MCF-7) cell lines (Freddie et al. 2004). Indeed the metabolite seems to be a more potent inhibitor of MCF-7 cells than both tamoxifen and arzoxifene itself (Freddie et al. 2004). Studies in rats and monkeys show variable extent of metabolism between species (Münster 2006), with prolonged half-lives for parent compound and metabolite in the latter. Fecal elimination predominates, with minimal urinary excretion.

Preclinical studies

Arzoxifene has demonstrated an ability to inhibit breast cancer cell growth in both *in-vitro* and *in-vivo* models. *In vitro*, the parent compound and metabolite show strong inhibition of the estrogen receptor-positive MCF-7 breast cancer cell line, including those demonstrating tamoxifen resistance (Freddie et al. 2004). Estrogen-stimulated MCF-7 breast cancer cell line proliferation was inhibited by arzoxifene to a degree superior to that of tamoxifen and equivalent to raloxifene (Suh et al. 2001). Arzoxifene also displayed inhibition of basal proliferation of these cell lines in the absence of estrogen, whereas tamoxifen stimulated basal proliferation (Suh et al. 2001).

In-vivo arzoxifene inhibited MCF-7 breast cancer xenograft growth in oophorectomized athymic mice (Detre et al. 2003), to a similar degree as tamoxifen. In addition, it prevented mammary cancer growth in rats induced by the carcinogen N-nitrosomethylurea, with an ability superior to raloxifene but similar to tamoxifen (Suh et al. 2001). Some evidence has been found of cross-resistance with tamoxifen (Schafer et al. 2001), with ongoing tumor growth in transplanted athymic mice in one tamoxifen stimulated tumor model (MCF-7), but not in another (T47D).

In the uterus, arzoxifene inhibited the agonistic effect of estrogen on endometrial cell growth (Palkowitz et al. 1997; Sato et al. 1998; Suh et al. 2001), but also did not in itself stimulate uterine hypertrophy or endometrial cell proliferation (Palkowitz et al. 1997; Sato et al. 1998; Suh et al. 2001; Ma et al. 2002). It has also demonstrated an ability to inhibit a tamoxifen-naïve endometrial cancer cell line, but has no effect on tamoxifen- or estrogen-stimulated endometrial tumors (Dardes et al. 2001).

With regard to bone health, arzoxifene maintains bone mineral density in oophorectomized rats, equal to that seen with estrogen

and raloxifene (Sato et al. 1998; Ma et al. 2002). In addition, bone strength and toughness were higher compared with that seen in untreated oophorectomized rats (Ma et al. 2002).

Cholesterol levels were prevented from rising in oophorectomized rats by as much as 59% with arzoxifene (Palkowitz et al. 1997; Sato et al. 1998; Ma et al. 2002), which was an effect at least equivalent to that with estrogen and raloxifene, although arzoxifene demonstrated superior potency achieving the same cholesterol reduction for half the dose of raloxifene (Sato et al. 1998).

Arzoxifene was also reported to prevent body weight increase in oophorectomized rats (Sato et al. 1998; Ma et al. 2002), mainly due to reduced gain of fat mass (Ma et al. 2002). Ovarian cysts were induced by arzoxifene in some species (Münster 2006). Arzoxifene reduced estrogen receptor expression in endometrial cancer cell lines (ECC-1) (Dardes et al. 2001), an effect that was not reproducible in breast cancer cell lines (MCF-7) (Detre et al. 2003). Finally, unlike tamoxifen, long-term exposure in athymic mice did not produce any arzoxifene-stimulated transplantable tumors (Schafer et al. 2001), representing a further apparent advantage over tamoxifen.

These studies set the scene for arzoxifene as a potential candidate for an ideal SERM: inhibition and prevention of breast cancer at least as effective as tamoxifen, no stimulatory effects on the endometrium, maintenance of bone density and strength at least as effective as raloxifene, beneficial effects on cholesterol and weight, and no long-term exposure effects.

Outcomes achieved in clinical development

Phase I trials

With at least raloxifene equivalence and suggestion of superiority over tamoxifen, these promising preclinical data with arzoxifene prompted a phase I trial in women with metastatic breast cancer (Münster et al. 2001). Previous animal studies had shown biological activity at a human equivalent dose of 10 mg/day; furthermore a parallel study in healthy volunteers showed doses of 25 mg/day and 100 mg/day had similar effects on fibrinogen, biochemical bone markers, low density lipoprotein (LDL), cholesterol, and gonadotrophin concentrations (Münster et al. 2001). Hence four dose regimens of 10 mg/day, 20 mg/day, 50 mg/day, and 100 mg/day were chosen for evaluation.

Thirty-two women, all with metastatic estrogen receptor- and/or progesterone receptor-positive breast cancer, were selected: 9% were premenopausal, 47% had liver metastases, median age was 56 years, and the patients had had a median of one prior chemotherapy and two hormonal therapy regimens. All had previously received tamoxifen.

There was a significant decrease in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels, along with an increase in sex hormone-binding globulin (SHBG). Urine osteocalcin (a marker of bone resorption) levels decreased, suggesting a bone health benefit. There were no objective responses (complete, partial, or minor), although 19% of patients had stable disease for ≥6 months [median 7.7 months (range 6–34)].

The plasma concentration of arzoxifene was linear with dose, and there were no dose-limiting toxicities. Hot flushes were the most common (56%) side effect, with no dose-dependent change in frequency. Less frequent were rash (9%), vaginal bleeding (6%), pruritis (6%), and constipation, headache, and stomatitis (3% each). There was no effect on the endometrium based on transvaginal ultrasound (TVU) on 15 patients after 12 weeks' treatment, and no ovarian cysts developed. There was one deep vein thrombosis and one pulmonary embolus, although both occurred in patients with other risk factors for thromboembolic events.

Overall, this trial demonstrated arzoxifene to be safe and well tolerated, with a possible benefit in patients with heavily pretreated metastatic breast cancer.

Further phase I trials (Fabian et al. 2004) evaluated arzoxifene in the preoperative setting. Arzoxifene 10 mg/day, 20 mg/day, or 50 mg/day was used 2–6 weeks prior to surgical resection of an invasive or *in-situ* breast cancer. Although interpretation was limited by the small sample size, arzoxifene appeared to lower proliferation markers including proliferating cell nuclear antigen (PCNA), insulin-like growth factor (IGF)-1 and IGF-binding protein-3 (IGFBP-3), decrease estrogen expression and LH levels, and increase SHBG levels. These effects seemed most pronounced with the 20 mg/day and 50 mg/day doses.

Phase II trials

Breast cancer

The phase I trials set the stage for phase II trials where arzoxifene was compared at two doses (20 mg/day and 50 mg/day) in two separate randomized, double-blind trials in women with hormone-sensitive metastatic breast cancer (Baselga et al. 2003; Buzdar et al. 2003). In the predominantly American trial (Buzdar et al. 2003), 112 women with metastatic breast cancer were recruited, with substratification into tamoxifen-sensitive (no prior tamoxifen exposure or recurrence >12 months postadjuvant tamoxifen completion) or tamoxifen-refractory (relapse or progression whilst on tamoxifen) groups. Treatment continued until disease progression, unacceptable toxicity, or informed consent was withdrawn. Median or mean follow-up time was not stated. In the predominantly European trial (Baselga et al. 2003), 92 women with locally advanced stage IIIB disease (35%) or metastatic disease were recruited for 12 weeks' treatment or until disease progression. Although 9% had prior adjuvant tamoxifen therapy, there was no subcategorization into tamoxifen sensitive or refractory. Average follow-up time was 22 months.

In both trials the objective response rate [ORR; defined as complete response (CR) + partial response (PR)] was numerically higher for arzoxifene 20 mg/day versus 50 mg/day (Table 2); rates were 40.5% versus 36.4% in the European trial (Baselga et al. 2003), and 19.2% versus 7.4% in the American trial (Buzdar et al. 2003). A similar trend was seen for clinical benefit rate

(CBR; defined as CR + PR + stable disease ≥6 months) where the figures were 64.3% for arzoxifene 20 mg/day versus 61.4% with 50 mg/day in the European trial, and 28.8% versus 20.4% in the American trial. ORR and CBR were lower in tamoxifen-refractory patients than in the tamoxifen-sensitive group (Buzdar et al. 2003), with a similar trend of 20 mg performing better than 50 mg (Table 3). In the tamoxifen-sensitive group, ORR was 30.4% and 8.0% for arzoxifene 20 mg and 50 mg, respectively, and CBR was 47.8% and 32.0%. The corresponding rates in the tamoxifen-refractory group were 10.3% with arzoxifene 20 mg/day versus 6.9% with 50 mg/day for ORR, and 13.8% versus 10.3%, respectively, for CBR (Buzdar et al. 2003). Hence 20 mg/day arzoxifene had a numerical (although not statistical) advantage in ORR and CBR over 50 mg/day, and was more effective in tamoxifen-sensitive patients.

Table 2 | Overall efficacy of arzoxifene in metastatic breast cancer in phase II trials [Baselga et al. 2003 (European trial); Buzdar et al. 2003 (American trial)]

Dose	20 mg/day		50 mg/day	
	American	European	American	European
ORR (%)	19.2	40.5	7.4	36.4
CBR (%)	28.8	64.3	20.4	61.4

CBR, clinical benefit rate (ORR + stable disease for ≥6 months); ORR, objective response rate (complete response + partial response).

Table 3 | Arzoxifene efficacy stratified by tamoxifen sensitivity (Buzdar et al. 2003)

	Tamoxifen sensitive		Tamoxifen refractory	
Dose	20 mg/day	50 mg/day	20 mg/day	50 mg/day
ORR (%)	30.4	8.0	10.3	6.9
CBR (%)	47.8	32.0	13.8	10.3

CBR, clinical benefit rate (ORR + stable disease for ≥6 months); ORR, objective response rate (complete response + partial response).

In terms of hormone and bone biomarkers, the European trial showed a significant decrease in FSH and estradiol levels in postmenopausal women, and a significant increase in SHBG levels for both arzoxifene doses, with a significant decrease in LH levels for the 50 mg/day dose only (Baselga et al. 2003), although there was no significant difference between the two dosages. The American trial did not show these changes overall, although when analyzed according to menopausal status there was a decrease in FSH and LH levels, and an increase in SHBG level in post-menopausal women. There was a significant decrease in serum osteocalcin levels in postmenopausal women with both arzoxifene doses in the European trial and only with the 50 mg/day dose in the American trial. In neither trial were there enough premenopausal women to make reliable inferences on biomarker levels.

The top five clinical toxicities in the American trial were hot flushes (46%), nausea (22%), cutaneous side effects (6%), neuromotor toxicity (5%), and weight gain (5%). In the European trial, the most common adverse events were hot flushes (37%), breast pain (23.9%), nausea (16.3%), back pain (15.2%), and dyspnoea (13%), with weight gain next at 11%. In both trials the dose of arzoxifene had no influence on side effects. There was one deep vein thrombosis in the American study, and two in the European study.

In the European study, 52 postmenopausal patients had endometrial assessment (TVU at baseline and at least one follow-up ultrasound at 12 weeks and every 6 months while on arzoxifene), with the majority (83%) showing no change. Only 19% required further investigation. There were no endometrial cancers, and two cases of ovarian cysts (one in each dose arm). In the American study, uterine evaluation involved baseline TVU, and follow-up ultrasound at least every 6 months in the first year and at least yearly thereafter. Sixty postmenopausal patients had baseline evaluation and 46 had at least one follow-up TVU. One patient (in the 20 mg/day arm) had vaginal bleeding attributed to atrophic vaginitis, and five women (all in the 50 mg/day arm) showed increased endometrial thickness. Of these five, only one had further gynecological evaluation, with insufficient tissue obtained for diagnosis. Again, no endometrial cancers were diagnosed.

Overall both trials reached similar conclusions: arzoxifene 20 mg/day showed a numerical advantage over 50 mg/day in efficacy in breast cancer, both doses exhibited satisfactory tolerability, there was no significant estrogenic effect on endometrium, and there was evidence of an antiresorptive effect on bone in postmenopausal women.

Arzoxifene as a chemopreventive agent was also studied in a phase II trial that randomized 199 women considered at high risk of breast cancer to arzoxifene 20 mg/day versus placebo (Fabian et al. 2006; Kimler et al. 2006). Fifty-two percent of patients were premenopausal, whilst 47% of the postmenopausal women were on hormone replacement therapy (HRT). At 6 months, arzoxifene improved two risk biomarkers:

1. Mammographic breast density was significantly reduced ($P<0.001$), both in terms of the total dense area (+3.8 cm^2 versus –12.9 cm^2) and the percent of breast with increased density (+0.8% versus –4.6%) (Kimler et al. 2006)

2. IGF-1:IGFBP-3 ratio was significantly reduced ($P=0.001$) (Fabian et al. 2006).

However, there was no change in a breast epithelial cell cytomorphology risk index score (Masood index), assessed by random periareolar fine-needle aspirate (Fabian et al. 2006). There was a significant reduction ($P=0.002$) in osteocalcin level and no increase in endometrial thickness.

Endometrial cancer

With the preclinical data suggesting arzoxifene did not induce endometrial proliferation (Palkowitz et al. 1997; Sato et al. 1998; Suh et al. 2001; Ma et al. 2002) and in some circumstances would inhibit endometrial cancer cell lines *in vitro* (Dardes et al. 2001), a

phase II open-label trial was conducted using arzoxifene 20 mg/day in recurrent or advanced estrogen receptor- and/or progesterone receptor-positive endometrial cancer (McMeekin et al. 2003). Thirty-four patients were treated, 29 were assessable, and adjuvant chemotherapy was allowed, although not salvage chemotherapy or prior antiestrogen therapy; prior progestogen therapy was permitted. The ORR was 31% (1 CR + 8 PR), CBR was 37.9% (9 responses + 2 stable disease for ≥6 months), and median duration of response was 13.9 months. This was comparable or better than historical controls treated with progestogens with or without tamoxifen. Although encouraging, further use of arzoxifene in this area has not yet been pursued by the manufacturer (Münster 2006).

Phase III trial

The phase II trials in patients with breast cancer had shown arzoxifene to produce results comparable to tamoxifen when it was used in historic phase III trials against other endocrine agents (Münster 2006). These studies had also identified 20 mg/day as the preferred dose to take forward in the development of arzoxifene. The data were thought to be compelling enough to warrant a phase III trial of arzoxifene 20 mg/day versus tamoxifen 20 mg/day in locally advanced/metastatic breast cancer (Deshmane et al. 2007).

The initial trial design aimed to recruit 480 women, aged >50 years, with estrogen receptor- or progesterone receptor-positive (or unknown), locally advanced/metastatic breast cancer. Any previous chemotherapy had to be completed ≥6 months prior to randomization, and patients were either hormone naïve or had endocrine therapy ≥12 months prior to diagnosis of locally advanced/metastatic disease. A planned interim efficacy analysis was performed for the first 200 patients. This suggested arzoxifene had an inferior response compared with tamoxifen (Deshmane et al. 2007) and the data monitoring board recommended trial cessation, which the sponsor accepted. By this time a total of 368 patients had been recruited from 71 centers in 18 countries, with 353 available for final efficacy analysis.

The final efficacy analysis confirmed the interim analysis (Table 4) (Deshmane et al. 2007). Tamoxifen showed a statistically significant advantage over arzoxifene with regards to progression-free survival, time to treatment failure, and on-study progression-free survival. However, there was no significant difference in ORR, CBR, median response duration, or overall survival (Table 4).

Both arzoxifene and tamoxifen significantly reduced total cholesterol, LDL, and high density lipoprotein (HDL) levels from baseline. Both also significantly reduced osteocalcin levels in postmenopausal women.

The most common adverse events were hot flushes, nausea, sweating, and headache, although arzoxifene adverse events were comparable with those from previous phase I and II trials. There was one case of venous thromboembolism on arzoxifene and two on tamoxifen.

Table 4 | Results achieved with arzoxifene compared with tamoxifen in phase III trial in patients with estrogen receptor- or progesterone receptor-positive (or unknown) locally advanced/metastatic breast cancer (Deshmane et al. 2007)

	Arzoxifene	Tamoxifen	*P* value
Progression-free survival (median; months)	4.0	7.5	0.007
Time to treatment failure (median; months)	4.0	6.0	0.029
On-study progression free survival (median; months)	4.0	7.5	0.009
Median response duration (months)	11.9	11.9	0.41
Overall median survival (months)	NA[a]	17.1	0.107
ORR (%)	23.6	27.2	0.46
CBR (%)	33.3	42.8	0.07

[a]Not available due to large proportion (85%) of censored values.
CBR, clinical benefit rate (ORR + stable disease for ≥6 months); ORR, objective response rate (complete response + partial response).

The trial investigators could not offer a definitive explanation for the poorer than expected performance of arzoxifene. There was some speculation made about a higher arzoxifene dose perhaps inducing a better response (in spite of the phase II trial results), or that the longer half-life of tamoxifen or its active metabolite (4-hydroxy-tamoxifen) may have produced a greater than expected antitumor effect (Deshmane et al. 2007). However, on the basis of these data arzoxifene was relegated to investigation for treatment of postmenopausal osteoporosis, with the manufacturer (Ely Lilly & Co.) no longer choosing to pursue the drug as a breast cancer treatment.

Clinical potential

Throughout its development, arzoxifene had shown promise of resurrecting the hopes for benzothiophene SERMs or of possibly outperforming its benzothiophene relative, raloxifene, by becoming what was thought to be the ideal SERM. In both phase I and II studies arzoxifene showed similar endocrine effects of decreasing FSH and LH levels with increasing SHBG levels as had been reported with tamoxifen (Lønning et al. 1995; Kostoglou-Athanassiou et al. 1997). However, with the clinical results of the phase III trial (Deshmane et al. 2007) arzoxifene suffered the same fate as raloxifene, being relegated to investigation as an osteoporosis treatment and breast cancer prophylaxis and no longer considered as a breast cancer treatment. Thus, arzoxifene joins a number of other SERMs such as droloxifene, which was also shown to be inferior to tamoxifen in a phase III trial (Buzdar et al. 2002), or idoxifene (Johnston et al. 2001) and toremifene (Pyrhonen et al. 1999), which were both shown to have similar efficacy and side effect profiles and therefore provided no advantage over tamoxifen.

Currently, the investigators of the phase III trial have not provided a definite explanation for the less than expected performance of arzoxifene. Some speculation has been made about a higher arzoxifene dose or the potential confounding effect of tamoxifen's longer half-life or its active metabolite effects (Deshmane et al. 2007). Meanwhile, other expert commentators (Münster 2006) have only been able to speculate on possible causes. Perhaps there is only a subpopulation of arzoxifene responders, or perhaps indeed the dose used (20 mg/day) was in fact too low despite the phase II data. If the latter is true, then the maximum tolerated dose needs to be found and used (Münster 2006), which could even involve multidose schedules versus once-daily regimes. However, without the support of the manufacturer it would seem unlikely the drug will be resurrected for clinical development in the treatment of established breast cancer.

There are currently two ongoing or recently completed phase III arzoxifene trials: an osteoporosis prevention trial (NCT00085956, completed February 2007), and a study on vertebral fracture and invasive breast cancer prevention in postmenopausal women (NCT00088010, which has now ceased recruiting).

In summary, arzoxifene is a triphenylethylene SERM with a fixed ring structure similar to raloxifene. Initial preclinical and clinical phase I/II data suggested that it might be the ideal SERM with properties that would allow it to replace tamoxifen as the SERM and antiestrogen of choice in the treatment of established hormone receptor positive breast cancer. However, the results of a phase III randomized trial showed arzoxifene to be inferior to tamoxifen in terms of time to progression, which was the primary endpoint. As a result the trial was terminated and the development of arzoxifene for established breast cancer was discontinued. There are currently two remaining ongoing trials that have finished recruitment studying the effect of arzoxifene in the prevention of osteoporosis and breast cancer, respectively. The results of these trials are awaited with interest.

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