Selective oestrogen receptor modulators/new antioestrogens: a clinical perspective

John F.R. Robertson*

Department of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

Summary
Following tamoxifen, the first selective oestrogen receptor modulator (SERM), a number of other antioestrogens have been developed. The first-generation SERMs exhibit cross-resistance with tamoxifen and have agonist effects on the uterus. Toremifene has equal efficacy to tamoxifen and may be useful as a tamoxifen alternative. Efficacy results for droloxifene and idoxifene were disappointing and their clinical development ceased. Response rates for second-generation SERMs such as raloxifene and arzoxifene are also not high, although raloxifene shows promise in the chemoprevention of breast cancer. Paradoxically, high-dose oestrogens are proving to be effective breast cancer treatment with similar responses to tamoxifen in postmenopausal women with advanced disease, although these drugs are not well tolerated. Fulvestrant is a new type of oestrogen receptor (ER) antagonist with no agonist effects, which binds, blocks and degrades the ER. Fulvestrant produces high response rates compared with the SERMs, is not cross-resistant with SERMs or aromatase inhibitors (AIs) and is equally as effective as the AI anastrozole in the treatment of postmenopausal women with advanced breast cancer who have progressed after prior antioestrogen therapy. Pure antioestrogens such as the ER antagonist fulvestrant provide opportunities for therapeutic sequencing with tamoxifen and AIs and offer exciting possibilities for the future treatment of breast cancer.

KEYWORDS
Selective oestrogen receptor modulator; Antioestrogen; Fulvestrant; Breast cancer

Introduction
Oestrogen has a number of important physiological effects on hormone-dependent reproductive tissues. It controls the growth of breast epithelial tissue, regulates the menstrual cycle by promoting endometrial proliferation in the uterus, and regulates circulating cholesterol levels, thereby providing a protective effect on the cardiovascular system. Oestrogen also protects against the loss of bone mineral density (BMD) and cognitive function in elderly women. The biological role of oestrogen is mediated through high-affinity binding to the oestrogen receptor (ER). Breast tumours that express the ER are stimulated by oestrogen and antioestrogen therapy has thus become an established treatment for ER-positive breast cancer.

Treatment decisions for breast cancer can be complicated due to the varied clinical course of the disease and the many different treatments available. Patients with ER-positive tumours in whom hormonal therapy may be indicated include patients with metastatic breast cancer that is not immediately life threatening. In patients with early...
Evolution of antioestrogen therapy

At the end of the 19th century, Beatson first reported that the growth of human breast carcinomas may be associated with ovarian function (i.e. hormones) and antihormonal therapy has been evolving ever since. Pharmacological doses of oestrogens began to be used as treatment for breast cancer in pre- and postmenopausal women in the early 1940s and, second to ovarian ablation, oestrogen therapy is probably the oldest form of hormonal treatment for breast cancer.

The early 1970s saw the development of tamoxifen, the first selective oestrogen receptor modulator (SERM). This new non-steroidal antioestrogen showed a relatively well-tolerated safety profile compared with high-dose oestrogens. Tamoxifen is an oestrogen antagonist in breast tissue. However, in certain other tissues tamoxifen acts as an oestrogen agonist, which provides a protective effect on BMD and serum cholesterol levels. When given post-operatively, tamoxifen reduces the risk of breast cancer recurrence and can prolong survival in women who present with primary operable breast cancer (Fig. 1). However, tamoxifen also causes undesirable side effects, including an increased risk of endometrial cancer and thromboembolic events. Despite these side effects, the net benefit of tamoxifen therapy for patients with breast cancer greatly outweighs the risk, and for the past 30 years tamoxifen has been the ‘gold standard’ against which new antioestrogen therapies are measured.

A number of antioestrogens have been developed since tamoxifen; some with similar structures to tamoxifen and some that are very different. These include several other SERMs and, most recently, fulvestrant, a novel ER antagonist that downregulates the ER and is not associated with tamoxifen-like agonist effects. The clinical usefulness of a new SERM or ER antagonist can be evaluated in a number of different ways: (i) assessment as to whether the new drug is cross-resistant with tamoxifen (ii) comparison of the timelines for the evolution of the antioestrogens. Arrows indicate those drugs that continue to be in clinical use.

<table>
<thead>
<tr>
<th>Date</th>
<th>Steroidal High-dose oestrogens</th>
<th>Pure antioestrogens</th>
<th>Non-steroidal Triphenylethylenes</th>
<th>‘Fixed-ring’</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940s</td>
<td>DES → TCE</td>
<td></td>
<td>Tamoxifen → Raloxifene →</td>
<td></td>
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<tr>
<td>1950s</td>
<td>TCE</td>
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<tr>
<td>1960s</td>
<td>TME</td>
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<tr>
<td>1970s</td>
<td>Fulvestrant →</td>
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<tr>
<td>1980s</td>
<td></td>
<td></td>
<td>Droloxifene → Arzoxifene</td>
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<tr>
<td>1990s</td>
<td></td>
<td></td>
<td>Toremifene → Idoxifene</td>
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</tr>
<tr>
<td>2000s</td>
<td>ERA-923</td>
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<td></td>
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</tr>
</tbody>
</table>

DES, diethylstilboestrol; TCE, triphenylchlorethylene; TME, triphenylmethylethylene.
therapeutic efficacy of the new agent with tamoxifen, particularly in randomised clinical trials (iii) evaluation of the effect of the drug on tissues other than the breast. This paper will review the available data for the SERMs, the high-dose oestrogens, and the novel antioestrogens using these criteria and evaluate these therapies in terms of their clinical usefulness for the treatment of breast cancer.

Non-steroidal SERMs: clinical efficacy versus tamoxifen

First-generation SERMs (triphenylethlenes)

A number of triphenylethylene derivatives have been developed. For each of these antioestrogens, pre-clinical data suggested improved efficacy and safety profiles when compared with tamoxifen.13–15

Toremifene

Toremifene is structurally related to tamoxifen and, due to the high probability of cross-resistance between these two antioestrogens, was developed as an alternative to tamoxifen in the hope that it would produce fewer uterotrophic effects.16–18

Advanced disease

Several studies have confirmed that toremifene is cross-resistant with tamoxifen. In a double-blind, cross-over trial, 66 postmenopausal women were treated with toremifene (240 mg/day) or tamoxifen (40 mg/day). An objective response (OR; complete response + partial response) of 29% (95% confidence interval [CI] 10–41%) versus 42% (95% CI 25–61%) was reported for toremifene and tamoxifen, respectively. At disease progression, 44 patients were crossed over to the alternative treatment. No responses were obtained with either of the second-line treatments.19 In a study conducted in 102 pre- or postmenopausal patients with tamoxifen-refractory breast cancer, an OR of only 5% (95% CI 3–7%) was obtained after treatment with toremifene 200 mg daily.20 Similarly, in another study in 56 tamoxifen-refractory patients, an OR of only 4% was achieved with toremifene.21

Toremifene has been compared with tamoxifen as first-line therapy in hormone-sensitive advanced breast cancer in five phase III trials. In all of these studies, toremifene was similar to tamoxifen for OR, stable disease and time to progression (TTP)22–26 (Table 2). In a meta-analysis of 1421 patients from these trials, median TTP was 4.9 months versus 5.3 months for toremifene and tamoxifen, respectively (p = 0.76). There was no difference between the two treatments for drug-related toxicities.27

Adjuvant therapy

In the adjuvant setting, a study has compared the safety and efficacy of toremifene and tamoxifen in 899 postmenopausal women with node-positive breast cancer. There was no difference in the risk of breast cancer recurrence between the two treatment groups (hazard ratio [HR]: 0.88; 90% CI 0.70–1.09; p = 0.33) (Fig. 2). The incidences of subsequent cancers were also similar, including the incidence of endometrial cancer.28 The side-effect profiles for toremifene and tamoxifen were similar in terms of both adverse events and serious adverse events (Table 3). These studies confirmed that tamoxifen and toremifene are similar for efficacy, safety and tolerability in advanced disease and in the adjuvant setting.

| Table 2 | Toremifene versus tamoxifen: a comparison of phase III studies in advanced disease2 |
|----------|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|          | Toremifene 40–60 mg/day          | Tamoxifen 20–40 mg/day |
|          | n | ORR (%) | TTP (months) | n | ORR (%) | TTP (months) |
| Hayes et al.23 | 221 | 21 | 5.6 | 215 | 19 | 5.8 |
| Pyrhonen et al.22 | 214 | 31 | 7.3 | 201 | 37 | 10.2 |
| Gershunovich et al.24 | 157 | 21 | 4.9 | 149 | 21 | 5.0 |
| Nomura et al.25 | 62 | 24 | 5.1 | 60 | 27 | 5.1 |
| Milla-Santos et al.26 | 106 | 38 | 11.9 | 111 | 32 | 9.2 |
| Meta-analysisa | 725 | 24 | 4.9 | 696 | 25.3 | 5.3 |

ORR, objective response rate; TTP, time to progression.
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a The meta-analysis included the first four studies indicated plus an unpublished German study. The study by Milla-Santos (published in 2001) was not included.
Droloxifene is also structurally similar to tamoxifen, although its relative binding affinity for the ER is between 10- and 60-fold higher than the binding affinity of tamoxifen. In pre-clinical studies, droloxifene not only demonstrated an oestrogenic effect in bone, but also showed a reduced oestrogenicity in the rat uterus compared with tamoxifen, suggesting a potential advantage over tamoxifen.

Advanced disease
A small phase II study showed that droloxifene had some efficacy in patients with advanced breast cancer who had progressed on tamoxifen, suggesting that it may be useful in patients progressing on tamoxifen.

As first-line treatment for advanced disease, a phase III trial was initiated to demonstrate equivalence between droloxifene and tamoxifen. However, in both pre- and postmenopausal women with ER-positive and/or progesterone receptor (PgR)-positive breast cancer, both OR and median TTP were significantly better for tamoxifen compared with droloxifene (OR: 28.6% versus 22.4%, \( p = 0.02 \); median TTP: 228 days versus 183 days; HR: 1.28; 95% CI 1.1–1.4; \( p < 0.001 \) for tamoxifen and droloxifene, respectively). Further clinical development of droloxifene was therefore halted.

Idoxifene
Like droloxifene, idoxifene has an increased binding affinity for the ER compared with tamoxifen and showed reduced agonist effects on the uterus in pre-clinical studies compared with tamoxifen.

Advanced disease
In a small phase I study conducted in 20 women with metastatic breast cancer, 19 of whom had previously been treated with tamoxifen, two patients showed a partial response and four patients had stable disease for between 6 and 56 weeks, suggesting that idoxifene may not be cross-resistant with tamoxifen. However, in a later pre-clinical study conducted in mice with tamoxifen-stimulated tumours, idoxifene demonstrated complete cross-resistance with tamoxifen.

As first-line treatment, a phase III study in 220 postmenopausal women with metastatic breast cancer showed there was no difference in OR (20% [95% CI 12.7–28.2%] versus 19% [95% CI 12.5–28.2%]) or median duration of response (DoR) between idoxifene (40 mg/day) and tamoxifen (20 mg/day) [8.1 months versus 7.3 months for idoxifene and tamoxifen, respectively]. There was also

Table 3: Toremifene versus tamoxifen: summary of adverse events in the adjuvant setting

<table>
<thead>
<tr>
<th>Event</th>
<th>Toremifene (n = 459)</th>
<th>Tamoxifen (n = 440)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweating</td>
<td>247 53.8</td>
<td>225 51.1</td>
<td>0.42</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>237 51.6</td>
<td>209 47.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>193 42.0</td>
<td>156 35.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>120 26.1</td>
<td>117 26.6</td>
<td>0.88</td>
</tr>
<tr>
<td>Itching</td>
<td>118 25.7</td>
<td>119 27.0</td>
<td>0.65</td>
</tr>
<tr>
<td>Depression</td>
<td>112 24.4</td>
<td>119 27.0</td>
<td>0.40</td>
</tr>
<tr>
<td>Rash</td>
<td>90 19.5</td>
<td>75 17.0</td>
<td>0.34</td>
</tr>
<tr>
<td>Nausea</td>
<td>78 17.0</td>
<td>85 19.3</td>
<td>0.39</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>40 8.7</td>
<td>37 8.4</td>
<td>0.91</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>37 8.1</td>
<td>51 11.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Weight increase</td>
<td>23 5.0</td>
<td>19 4.3</td>
<td>0.64</td>
</tr>
</tbody>
</table>

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no difference in gynaecological events between the two treatments and clinical development of idoxifene ceased.\(^{36}\)

**Second-generation SERMs (‘fixed-ring’)**

The development of the ‘fixed-ring’ SERMs in the early 1980s stimulated optimism that these new antioestrogens, with their well-tolerated side-effect profiles, would be of greater clinical usefulness compared with the triphenylethylenes. Structurally, the second-generation SERMs resemble the benzothiophene raloxifene.

**Arzoxifene**

Arzoxifene is a benzothiophene analogue of raloxifene. Pre-clinical studies in immature ovariectomised rats demonstrated arzoxifene to be 30–100 times more potent than raloxifene in preventing the effects of ovariectomy on body weight, serum cholesterol levels and bone, whilst maintaining oestrogen agonist effects on the uterus.\(^{37}\) These results suggested that arzoxifene might have advantages over both tamoxifen and raloxifene in the prevention of bone loss in postmenopausal women.

**Advanced disease**

In a small phase I study in 32 pre- and postmenopausal women with locally advanced or metastatic breast cancer who had previously received endocrine therapy, arzoxifene produced no complete, partial, or minor responses. Stable disease \(\geq 24\) weeks was observed in six (32%) patients with a median DoR of 7.7 months, suggesting some cross-resistance between arzoxifene and tamoxifen.\(^{38}\)

In a phase II study in 119 pre- and postmenopausal women with advanced or metastatic breast cancer, two doses (20 versus 50 mg/day) of arzoxifene were compared in patients who had either tamoxifen-sensitive or tamoxifen-resistant disease. OR rates were low in patients with tamoxifen-resistant disease (6%), although an OR of 26% was obtained in patients with tamoxifen-sensitive disease who had been treated with arzoxifene 20 mg. Curiously, the response rate for 50 mg arzoxifene in tamoxifen-sensitive patients was low (8%).\(^{39}\) A phase III trial was subsequently initiated comparing arzoxifene 20 mg/day with tamoxifen 20 mg/day in postmenopausal women with advanced disease. However, at the interim review, the trial was terminated and development of arzoxifene discontinued for this indication (A Buzdar, personal communication).

**Raloxifene**

Raloxifene was initially developed as LY156758.\(^{40}\) LY156758 showed greater affinity for the ER compared with tamoxifen with a very low level of oestrogenicity in the rat uterus.\(^{40}\)

**Advanced disease**

LY156758, at a dose of 200 mg daily, was evaluated in a small phase II trial in 14 patients with disseminated breast cancer who were resistant to tamoxifen. Although there were no toxicities, there were no complete or partial responses and only one patient showed a minor response, suggesting that raloxifene may be cross-resistant with tamoxifen.\(^{41}\) As first-line treatment of advanced disease, a phase II trial, evaluated LY156758 150 mg twice daily in 21 tamoxifen-sensitive patients with ER-positive metastatic disease. An OR was obtained in four (19%) patients with a median DoR of 22 months.\(^{42}\)

**Raloxifene for the prevention of osteoporosis**

Based on clinical data demonstrating that raloxifene significantly increased BMD in postmenopausal women,\(^{43}\) this agent was subsequently developed for the prevention of osteoporosis. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial randomised over 7700 postmenopausal women with a history of osteoporosis to raloxifene or placebo for 3 years. A prospectively defined secondary endpoint of this trial was the risk of breast cancer. At 4 years’ follow-up, raloxifene reduced the risk of invasive breast cancer by 72% compared with placebo (relative risk [RR]: 0.28; 95% CI 0.17–0.46) and reduced the risk of ER-positive invasive breast cancer by 84% (RR: 0.16; 95% CI 0.09–0.30).\(^{44}\)

**Raloxifene in chemoprevention**

Following the promising results obtained in the MORE trial, the Study of Tamoxifen and Raloxifene (STAR) chemoprevention trial was initiated and will compare raloxifene 60 mg/day with tamoxifen 20 mg/day for 5 years for the reduction in the risk of breast cancer in over 22,000 postmenopausal women \(\geq 35\) years of age who are at high risk of developing the disease. A sub-study to evaluate the effect of raloxifene and tamoxifen on quality of life (QoL) will also be conducted.\(^{45}\)

**ERA-923**

ERA-923 is a second-generation SERM currently under development for the treatment of
tamoxifen-refractory metastatic breast cancer. A randomised, placebo-controlled study evaluated the safety and tolerability of ERA-923 in 50 healthy postmenopausal women. ERA-923 was demonstrated to be safe and well tolerated with no incidence of vaginal discharge or bleeding, suggesting that this agent had no uterotrophic effect on the endometrium.46 An ongoing phase II study will assess the efficacy of two doses of ERA-923 (25 versus 100 mg) as second-line treatment in postmenopausal women with tamoxifen-resistant, ER/PgR-positive breast cancer. A European study is also planned that will evaluate ERA-923 as first-line treatment in ER/PgR-positive metastatic disease. Primary endpoints include TTP, DoR, survival, and QoL.

High-dose oestrogens

Triphenylchlorethylene, triphenylmethylethylene, and stilboestrol were the first synthetic oestrogens to be used to treat carcinoma of the breast, with favourable results.8 It is only relatively recently, however, that high-dose estrogens have been included in the category of SERMs, as it is now apparent that these agents have antioestrogenic effects on breast tumours. It may seem rather paradoxical that both the reduction of oestrogen levels and the administration of high-dose oestrogen can cause tumour regression. Although the mechanism by which high-dose oestrogen induces tumour regression is not entirely understood, this therapy has proven to be effective in breast cancer treatment.

Diethylstilboestrol

Advanced disease

In a trial involving 32 postmenopausal women with advanced breast cancer who had previously been exposed to multiple endocrine therapies (including tamoxifen, aromatase inhibitors [AIs] and megestrol acetate), 10 patients (31%) obtained an OR, demonstrating that diethylstilboestrol (DES) is not cross-resistant with other endocrine therapies.47 As first-line therapy, DES was compared with tamoxifen in a randomised phase III trial conducted in 143 postmenopausal women with advanced breast cancer who had not received any prior hormonal therapy.48 After a follow-up of more than 14 years, median survival was 3.0 years for DES versus 2.4 years for tamoxifen (p = 0.034)

Ethinyloestradiol

Advanced disease

Ethinyloestradiol (EE2) has been compared with tamoxifen in a randomised trial involving 63 postmenopausal women with advanced breast cancer. Response rates were similar for both treatments (OR: 31% versus 33% for EE2 and tamoxifen, respectively). However, similar to that observed with DES, more serious side effects were observed in those patients treated with EE2 compared with those treated with tamoxifen.49

A review of all six studies48–53 that have compared high-dose oestrogens with the SERM tamoxifen (or its cyclical analogue nafoxidine) showed that, overall, similar results had been produced in terms of mean OR rates across all six trials (33% versus 31% for tamoxifen and high-dose oestrogens, respectively).2 However, the side-
Effect profiles were more severe for high-dose oestrogens.

**Fulvestrant: an oestrogen receptor antagonist**

Fulvestrant is the first of a new type of ER antagonist with no known agonist effects, which binds, blocks and degrades the ER. The lack of oestrogen agonist activity was first demonstrated preclinically\(^54\) and confirmed in a study in healthy volunteers.\(^55\) The latter study evaluated the effects of fulvestrant 125 and 250 mg with or without ethinylestrodiol on the endometrium in 30 healthy, postmenopausal volunteers. In addition to blocking the oestrogenic effects of oestradiol, fulvestrant had no oestrogenic effects on the endometrium over the 14-day assessment period, confirming its lack of agonist activity.\(^55\) Fulvestrant therefore offers a potential clinical advantage over the triphenylethylene and ‘fixed-ring’ SERMs.\(^54\),\(^56\)

**Advanced disease**

In a trial involving 19 postmenopausal patients with advanced tamoxifen-resistant breast cancer, a clinical benefit (complete response + partial response + stable disease \(\geq 24\) weeks) rate of 69% was obtained in patients treated with fulvestrant, with a median DoR of 25 months.\(^57\) The level of response with fulvestrant was higher than that previously seen with any of the other SERMs providing strong evidence that fulvestrant is not cross-resistant with tamoxifen.

**Efficacy versus aromatase inhibitors**

Fulvestrant has been evaluated in two randomised phase III trials; trial 0021 conducted in North America and trial 0020 conducted in Europe, Australia and South Africa. Both trials were designed to evaluate the efficacy of fulvestrant versus the AI anastrozole for the treatment of postmenopausal women with advanced disease after progression on prior antioestrogen (mainly tamoxifen). In both trials, fulvestrant was at least as effective as anastrozole for TTP, the primary efficacy endpoint (median TTP: 5.4 months versus 3.4 months; \(p = 0.43\) [trial 21] and 5.5 months versus 5.1 months; \(p = 0.84\) [trial 20] for fulvestrant and anastrozole, respectively)\(^58\),\(^59\). In a prospectively designed combined analysis of the results from both trials \((n = 851)\), median TTP was 5.5 months for fulvestrant versus 4.1 months for anastrozole (HR: 0.95; 95.14% CI 0.82–1.10; \(p = 0.47\))\(^60\) (Fig. 4).

**Tolerability versus aromatase inhibitors**

In both trials, fulvestrant was well tolerated. At the outset of the trials, seven adverse events were considered relevant to endocrine therapy and were pre-defined for statistical analysis. These were: gastrointestinal disturbances, hot flushes, vaginitis, weight gain, thromboembolic disease, urinary tract infection, and joint disorders (including arthralgia, arthrosis, and arthritis). In the combined analysis, the incidences of these pre-defined events were similar for both agents, with the

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**Figure 4** Median TTP for fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer: combined analysis of two multicentre trials.\(^59\) Cancer 2003;98(2):229–238. \(\copyright\)2003 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.
exception of joint disorders, the incidence of which was significantly lower for fulvestrant (5.4% versus 10.6%; *p* = 0.0036) (Table 4). The most common adverse events in both treatment groups, irrespective of relationship to study medication, were nausea (26.0% versus 25.3% for fulvestrant and anastrozole, respectively), asthenia (22.7% versus 27.0%), pain (18.9% versus 20.3%), vasodilatation (17.7% versus 17.3%), and headache (15.4% versus 16.8%).

### Efficacy versus tamoxifen

In a recent phase III, randomised trial, fulvestrant was compared with tamoxifen in 587 postmenopausal women with ER/PgR-positive or ER/PgR-unknown advanced breast cancer who had not previously been treated with endocrine therapy for advanced disease. In an analysis of all randomised patients there was no statistical difference for TTP between the two treatments (median TTP: 6.8 months versus 8.3 months for fulvestrant and tamoxifen, respectively; HR: 1.18; 95% CI 0.98 to 1.44; *p* = 0.08) but the upper limit of the 95% CI (1.44) did not satisfy the predefined criteria for non-inferiority (*≤* 1.25) of fulvestrant compared with tamoxifen. In a prospectively planned analysis of patients with confirmed ER-positive and/or PgR-positive tumours, TTP was similar between the two treatments (median TTP: 8.2 months versus 8.3 months, for fulvestrant and tamoxifen, respectively; HR: 1.10; 95% CI 0.89–1.36; *p* = 0.39). In an analysis of responses to second-line endocrine therapy (where some patients received tamoxifen) after progression on first-line fulvestrant, 57% of eligible patients achieved clinical benefit. This demonstrates that sensitivity to endocrine therapy is maintained after treatment with fulvestrant and confirms that fulvestrant and tamoxifen are not cross-resistant.

### Tolerability versus tamoxifen

In this study both tamoxifen and fulvestrant were well tolerated. The incidence of prospectively defined adverse events of gastrointestinal disturbances (nausea, vomiting, constipation and haemorrhage; 37.1% versus 43.2%, *p* = 0.16), vaginitis (3.9% versus 6.3%, *p* = 0.26) and thromboembolic disease (5.8% versus 3.3%, *p* = 0.22) were similar between fulvestrant and tamoxifen, respectively. However, the incidence of hot flushes was lower in patients treated with fulvestrant compared with those treated with tamoxifen (17.7% versus 24.7%, *p* = 0.0501). The most common adverse events in both treatment groups, irrespective of relationship to study medication, were nausea (20.3% versus 22.5% for fulvestrant and tamoxifen, respectively), asthenia (19.4% versus 20.3%), vasodilatation (14.8% versus 21.4%), pain (13.9% versus 19.2%), and bone pain (13.9% versus 17.0%).

### Optimising treatment: where are we now?

Clinical data for the SERMs have been somewhat disappointing in the advanced disease setting, as the efficacy advantages over tamoxifen seen in preclinical studies have not materialised in patients. However, greater potential may exist in the adjuvant or chemoprevention setting, where beneficial effects on bone, lipid and the endometrium will be of maximum benefit. At present, third-

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**Table 4** Fulvestrant versus anastrozole: summary of predefined adverse events in the second-line treatment of advanced disease

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant (n = 423)</th>
<th>Anastrozole (n = 423)</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal disturbances</strong></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Hot flushes</td>
<td>196</td>
<td>46.3</td>
<td>185</td>
</tr>
<tr>
<td>Joint disorders</td>
<td>89</td>
<td>21.0</td>
<td>87</td>
</tr>
<tr>
<td>Thromboembolic disease</td>
<td>23</td>
<td>5.4</td>
<td>45</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>15</td>
<td>3.5</td>
<td>17</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>31</td>
<td>7.3</td>
<td>18</td>
</tr>
<tr>
<td>Weight gain</td>
<td>11</td>
<td>2.6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>0.9</td>
<td>7</td>
</tr>
</tbody>
</table>


*a* Includes anorexia, constipation, diarrhoea, nausea and vomiting.

*b* Includes arthralgia, arthrosis and arthrits.
generation AIs such as anastrozole and letrozole are the only hormonal therapies that have been demonstrated in double-blind, randomised, controlled trials to be more effective than tamoxifen in advanced disease. In the adjuvant setting, only anastrozole has shown superior efficacy to tamoxifen. This was demonstrated in the ‘Arimidex’, Tamoxifen Alone or in Combination (ATAC) trial, which compared anastrozole with tamoxifen as adjuvant therapy in postmenopausal patients with hormone-sensitive invasive breast cancer. At 3 years’ follow-up, disease-free survival (DFS) was significantly longer with anastrozole compared with tamoxifen. In patients with hormone receptor-positive tumours only, DFS was 91.2% versus 89.3% for anastrozole and tamoxifen, respectively ($p = 0.005$). At a recent update at 4 years’ follow-up, DFS in this patient population was 89.0% and 86.1% for anastrozole and tamoxifen, respectively ($p = 0.03$), demonstrating that the difference in DFS between anastrozole and tamoxifen continues to grow with longer follow-up. These results suggest that AIs are set to become the first-line choice of most clinicians for the treatment of postmenopausal women with both early and advanced breast cancer. The only trial that compared a SERM with an AI in postmenopausal women failing on tamoxifen was terminated after the interim review revealed that the efficacy of anastrozole was substantially higher than that of the SERM (EM-800).2

Given the initial result in tamoxifen-resistant disease (in both phase II and randomised phase III studies), it was surprising that fulvestrant did not demonstrate superiority to tamoxifen in the first-line setting. Not only is fulvestrant as effective as the AIs in second-line therapy of postmenopausal women with advanced disease but also tamoxifen has been shown to be less effective than at least two third-generation AIs (anastrozole and letrozole) as first-line therapy in advanced disease. Nevertheless, the results from the trials in which fulvestrant was as effective as anastrozole are especially significant as these were the first randomised controlled studies in which an antioestrogen was demonstrated to have significant efficacy after tumours had become resistant to tamoxifen. This demonstrates clearly that the mechanism of action of fulvestrant differs from the mechanism of action of the SERMs, which prevents any cross-resistance with prior endocrine therapy.

Toremifene is the only clinically developed SERM other than tamoxifen that remains in use for the treatment of breast cancer. However, cross-resistance between tamoxifen and toremifene precludes the use of toremifene in patients progressing on tamoxifen. Therefore, in tamoxifen-resistant postmenopausal patients, fulvestrant is a good treatment choice. Therapeutic sequencing of different hormonal agents is fast becoming common clinical practice, especially for patients with advanced disease. The selection of antioestrogens, and the sequence in which these therapies are given, requires a rationale that is based not only on the toxicity profile of the drug but also on efficacy. Further evidence of the optimal sequence of the antioestrogens requires additional investigation in order for the most appropriate sequence of hormonal therapy for breast cancer to be established. However, Fig. 5 shows the suggested positions of fulvestrant in the endocrine treatment sequence for postmenopausal patients following treatment with either adjuvant tamoxifen or adjuvant anastrozole based upon currently available data. For premenopausal women, there are fewer treatment options compared with those that are available for postmenopausal patients. For the first-line treatment of premenopausal women, tamoxifen remains, for now, the antioestrogen of choice for most clinicians (with or without ovarian ablation using surgery, irradiation or a luteinising hormone releasing hormone analogue such as goserelin).

The SERMs have not produced the efficacy advantages over tamoxifen that these antioestrogens once promised. However, the development of new and novel antioestrogens continues. GW5638, TAS-108, and ZK 191703 are new antioestrogens currently in development. GW5638 is a tamoxifen analogue, although, like fulvestrant, this agent downregulates the ER. In pre-clinical studies in athymic mice, GW5638 has been compared with fulvestrant and raloxifene. Both GW5638 and fulvestrant were effective in blocking tamoxifen-stimulated breast tumour growth. TAS-108 and ZK 191703 are pharmacologically related to fulvestrant and TAS-108 may have similar effects to fulvestrant on the ER. The development of new drugs that work by downregulation of the ER,

![Figure 5 Suggested treatment schema following first treatment with tamoxifen or anastrozole.](image-url)
rather than selective ER modulation, offers the advantages of a reduced side-effect profile and also provides the option of further treatment choice after failure on tamoxifen. As resistance to tamoxifen may be due, in part, to agonist effects,69 antiooestrogens that use ER downregulation may also delay the emergence of resistance to hormonal therapy.

The impressive developments in breast cancer treatment over the last decade have expanded the treatment options for clinicians both in terms of first-line treatment choice and subsequent therapeutic options. What role the SERMs, the high-dose oestrogens, and the novel antiooestrogens will have in the treatment of breast cancer and where these hormonal therapies will fit into treatment regimens involving third-generation AIs remains to be fully elucidated. At present, an optimum sequence of endocrine agents has not been identified, although on-going studies are addressing this particular issue and these results are awaited with interest.

References

Selective oestrogen receptor modulators/new antioestrogens


59. 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...


