Future Use of Selective Estrogen Receptor Modulators and Aromatase Inhibitors

Anthony Howell
CRC Department of Medical Oncology, University of Manchester, Christie Hospital, Manchester M20 4BX, United Kingdom

Abstract
Selective estrogen receptor modulators (SERMs) may act as estrogens or antiestrogens depending on the cell and tissue targets. The triphenylethylene SERMs are represented by tamoxifen and toremifene and a new agent with a novel carboxylic acid side chain (GW5638). Because of isomerization in the triphenylethylene molecule, “fixed ring” SERMs were introduced. The major one in development is the benzothiophene arzoxifene (LY353381), which is now in Phase III clinical trials versus tamoxifen. A fourth group of SERMs is based on the estrogen molecule and comprises the so-called “pure” antiestrogen ICI 182,780 (fulvestrant, Faslodex) and a new oral analogue just entering trials, SR16234. The steroidal aromatase inhibitors [AIs (40H androstenedione and exemestane)] inactivate aromatase, whereas the triazole AIs (anastrozole and letrozole) inhibit the enzyme via the heme prosthetic group. Thus, there are two groups of AIs that show relative non-cross-resistance in advanced breast cancer and four groups of SERMs that also show a high degree of non-cross-resistance. With six different treatments and six or more clinical situations (prevention, neoadjuvant, adjuvant, and first- and second-line treatments for advanced disease) in which they may be used, the possible combinations of treatment are enormous. At present, we have few clinical pointers to optimal sequence of treatments. Now that most of the appropriate comparative trials have been performed, it may be the time to initiate novel approaches. These include alternating and sequential treatments, preferably with treatments changed before overt progression occurs.

Introduction
Although endocrine therapy has been in use clinically for over 100 years, we still have a great deal to learn concerning the optimal way to use this modality for breast cancer, not only because the appropriate trials to determine the best approach to treatment have not all been performed to date, but also because new endocrine agents are being constantly introduced that require additional studies on how to integrate the new with the old. The two groups of endocrine therapies for which there has been the greatest development recently are the SERMs and the AIs.

SERMs Available or in Development
The first SERMs to be used clinically were pharmacological doses of estrogen analogues, for example, DES (1), dienestrol (2), and ethinylestradiol (3). Randomized trials comparing high-dose estrogens with tamoxifen showed them to be equally active (reviewed in Ref. 3). After long-term follow-up, the largest trial of this type showed a survival advantage for DES compared with tamoxifen (4). We recently reported a study of DES involving 30 patients who had had on average four previous endocrine therapies. Thirty percent of patients responded to DES for a median period of 49 weeks, suggesting that high-dose estrogen therapy may well have been abandoned prematurely as an endocrine treatment (5).

High-dose estrogens were largely replaced by tamoxifen as soon as the latter was shown to be potentially equally active but less toxic (6). Several attempts have been made to introduce more active analogues of tamoxifen, but randomized clinical trials and Phase II studies have not shown superiority for the analogues idoxifene, droloxifene, or TAT 59 compared with tamoxifen, and these have therefore been abandoned for breast cancer treatment (7). Toremifene remains available but shows no advantage over tamoxifen for either adjuvant treatment (8) or the treatment of advanced disease (9). A new triphenylethylene (GW5638), which may be more active than the others because of a novel carboxylic acid side chain, looks promising in preclinical studies and is currently entering clinical trials (Refs. 10 and 11; Fig. 1).

Isomerization around the double bond in the triphenylethylene molecule was thought to be problematical, and thus a series of so-called “fixed ring” structures have been introduced, including raloxifene, EM800 (EM652 is the metabolite), and arzoxifene (LY353381). The activity of these agents in Phase II trials in advanced breast cancer is shown in Table 1. Raloxifene and EM800 are moderately active but have been withdrawn from development for breast cancer treatment, whereas arzoxifene (formerly known as SERM III) looks promising and is in a Phase III trial versus tamoxifen as first-line therapy in advanced disease. A recent Phase II study suggests that arzoxifene may be non-cross-resistant with tamoxifen, although more data are required to be certain (12). Wyeth-Ayerst also have a fixed ring SERM in early clinical development (ERA-923).

Wakeling and Bowler (13) developed the estrogen ana-
High dose 'Oestrogens'

Stilboestrol

Ethinyloestradiol

Triphenyl ethylenes

Tamoxifen

Toremifene

GW 5638

'Refixed ring'

Raloxifene (LY 156,758)

EM 652 (SCH 57068)

Arzoxifene (LY 353,381)

Oestradiol analogues

ICI 182,780

SR 16234

ZK-191703

Fig. 1 Structures of compounds in use or in clinical development in the four classes of SERMs described in the text.

Table 1  First- and second-line treatment with “fixed ring” compounds

<table>
<thead>
<tr>
<th></th>
<th>EM-800 (Ref. 40) (SCH57050) 20 or 40 mg</th>
<th>Raloxifene (Ref. 41) (LY156758) 300 mg</th>
<th>Arzoxifene (Ref. 42) (SERM III)</th>
<th>Arzoxifene (Ref. 12) (LY353381) 20–50 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1</td>
<td>0</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>SD</td>
<td>10</td>
<td>3</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>PD</td>
<td>27</td>
<td>14</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Total response</td>
<td>16/43 (37%)</td>
<td>7/21 (33%)</td>
<td>45/88 (51%)</td>
<td>16/49 (33%)</td>
</tr>
<tr>
<td>Second-line therapy (prior tamoxifen)</td>
<td>43</td>
<td>6</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>All responded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analogue ICI 182,780 (fulvestrant, Faslodex) as a new class of antiestrogen because it was felt that to pursue the development of analogues of triphenylethylenes as breast cancer treatment would not be productive. ICI 182,780 (Fig. 1) has been shown to be non-cross-resistant with tamoxifen and to be equivalent to anastrozole as second-line therapy for advanced breast cancer (14–16). The latter results are promising because all patients in these two Phase III trials had been treated previously with tamoxifen. The results of a trial of tamoxifen versus ICI 182,780 as first-line therapy for advanced disease will be available later.
Table 2  Non-cross-resistance between classes of SERMs

<table>
<thead>
<tr>
<th>Classes of SERMs</th>
<th>Pharmacologic estrogens</th>
<th>Triphenylethylenes—tamoxifen</th>
<th>Fixed ring—Arzoxifene (SERM3)</th>
<th>Steroidal—ICI 182,780</th>
</tr>
</thead>
</table>

Examples of non-cross resistance between classes

- TAM → ICI 182,780 (Ref. 14)
- TAM → Arzoxifene (Ref. 43)
- TAM → Stilbestrol (Ref. 4)

Fig. 2  Two classes of modern AIs: steroidal and nonsteroidal AIs.

Fig. 3 A, 10-year results of the effectiveness of 5 years of adjuvant tamoxifen on relapse-free survival. Just over one-third of relapses are prevented by tamoxifen. B, estimated “clinical benefit” (CR + PR + SD 6/12) after first-, second-, and third-line endocrine therapies for advanced disease.

Many clinical studies indicate that SERMs and AIs show limited cross-resistance. This, together with evidence of non-cross-resistance within the SERM and AI classes, indicates that we have potentially a large number of therapeutic options to explore for the treatment of all stages of breast cancer. However, with six groups of agents (perhaps seven if ovarian ablation is included) and six or seven clinical scenarios (prevention, neo-adjuvant, adjuvant, and first-, second-, and third-line therapy for advanced disease), the problem of finding the optimal sequences or combinations of endocrine agents is enormous.

Effective of Current Treatments

Although we have a pleasing number of endocrine therapies in development, the effectiveness of those in use at present is limited. The results of adjuvant treatment with tamoxifen and commonly used first-, second-, and third-line agents for advanced disease are shown in Fig. 3. Effects are seen in patients with ER+ tumors only because endocrine therapy is clearly ineffective for the 30–40% of patients with ER− tumors, leaving only 60–70% of patients to be treated by this approach. Five years of tamoxifen reduces recurrences from 63% to 76% at 10 years of follow-up (25). This represents a 35% reduction in the proportion of women who relapsed up to 15 years after surgery. Clearly, this means that 65% of women who have a relapse are not helped by tamoxifen or that recurrence is only delayed.
At relapse, a maximum of about 60% of patients respond to the best treatment available at this stage, which appears to be an AI. This 60% includes CRs and PRs (CR + PR) and SD for 6 months or more. SD gives a similar survival benefit as a partial remission and in all modern trials is included as a “response” (26, 27). The overall response (CR + PR + SD) has been called “clinical benefit.” The median duration of response to first-line therapy for advanced disease is about 12–18 months. Nonresponders to endocrine therapy do not usually respond to a second therapy (see exception below) and are usually treated with chemotherapy. Approximately 40% of responders to first therapy will obtain clinical benefit from a second endocrine treatment for a median response duration of about 6–18 months. Approximately 20–30% of responders to second therapy will have clinical benefit from a third therapy for a median of 6–12 months. Some patients can spend many years in multiple remissions, but the majority of patients with relapsed ER+ tumors unfortunately have no benefit or only a temporary benefit from endocrine therapy (Fig. 3).

Mechanisms of Endocrine Responsiveness

With four classes of SERMs and two classes of AIs available, can we improve response rates and response durations in advanced disease and prevent relapse in the adjuvant situation? At this point, it is worth stopping to ask the difficult questions of how endocrine therapies work and why tumors become resistant to them. In particular, it is important to understand potential mechanisms of multiple responses and how we can extend the duration and number of responses. In endocrine-responsive tumors, estrogen is the major mitogenic hormone acting via the ER and stimulates growth through the synthesis of autocrine and paracrine growth factors. In normal breast lobules, ER+ cells do not divide but signal to adjacent ER- ones to do so (28). Early in the malignant process, it appears that ER+ cells acquire the ability to divide, and growth factors that putatively act by a paracrine mechanism in the normal breast may act by autocrine (and paracrine) mechanisms in malignant tumors (29). This change in tumor cells also appears to allow them to adapt to the prevailing estrogen concentrations, whereas there is probable tight regulation of responsiveness in the normal breast. Adaptation to the prevailing estrogen concentrations is seen when ER+ tumors that have an intact receptor grow in the breast and then are detected clinically. At low postmenopausal estrogen concentrations (10^{-11} to 10^{-10} M), normal breast cells do not proliferate, whereas tumors proliferate in response to even such low concentrations. Altering the serum estrogen concentration downward by the AIs (or upward by high-dose estrogens) initially causes inhibition of growth. There is strong evidence that tumors can then adapt to the new estrogen concentration. For example, a response may occur after ovarian ablation: when the tumor regrows, a further response may be obtained by lowering the E2 concentration [E2] further with an AI. When there is a response to high-dose estrogens, a further response may be obtained on progression by simply stopping treatment (30). Such WRs suggest that the tumor gradually adapts to high-dose estrogen and then becomes stimulated by an initially growth-suppressive estrogen concentration (31).

Changes in dose-response curves for E2 can be generated using receptor-positive human tumor cell lines grown in vitro in serum-free media (to remove endogenous hormones and inhibitors found in serum) and give us an indication of the potential in vivo mechanisms of resistance. An early example of such dose-response curves was reported by Reddel and Sutherland (32). They showed maximal stimulation of growth at concentrations of E2 that in vivo would span the range seen in premenopausal women (10^{-10} to 10^{-9} M). Basal cell growth was seen at low E2 concentrations (10^{-11} M), and inhibition of growth was seen at high concentrations, analogous to high-dose estrogen treatment in patients (10^{-5} to 10^{-6} M; Fig. 4). Using MCF-7 cells, Masamura et al. (33) showed that the E2 dose-response curve could be shifted to the left if the cells were grown in serum-free medium as devoid as possible of any E2. The MCF-7 cells initially failed to grow when estrogen was withdrawn, but after a few weeks, they returned to the growth rate of wild-type cells. When the E2 dose-response curve was reassessed, it had shifted markedly to the left. Maximal growth stimulation occurred at 10^{-14} M E2, whereas concentrations of E2 that would be regarded as physiological in vivo (10^{-10} M) were growth inhibitory. These elegant experiments show the enormous range of E2 concentrations under which human receptor-positive cells are able to proliferate (10^{-14} to 10^{-9} M). Given that in vivo tumors can adapt after an initial inhibition of growth by proliferating in the presence of high-dose estrogens, it is likely that the E2 concentrations in which tumors can grow either in vitro or in vivo range from 10^{-14} to 10^{-9} M as shown by Masamura et al. (33) to about 10^{-7} to 10^{-6} M, which is estimated to be the level of estrogen attained during high-dose treatment (Fig. 5).

Reddel and Sutherland (32) also demonstrated a dose-response curve for tamoxifen in T47D cells (Fig. 4). This was very similar to the E2 dose-response curve, with stimulation of...
growth at low concentrations (10⁻⁸ to 10⁻⁷ M) and inhibition at 10⁻⁶ to 10⁻⁵ M, suggesting that under the condition of culture, tamoxifen behaves like an estrogen. Low-dose stimulation of growth in vivo by tamoxifen may account for the tumor flare phenomenon (34). WRs can be demonstrated when, after an initial response to tamoxifen, the drug is stopped at tumor progression, and thus it appears that tumors are capable of adapting to tamoxifen as well as E₂ (31). Tamoxifen stimulation of MCF-7 cell growth can also be demonstrated when these cells are grown in nude mice. After an initial period of growth inhibition, tumor growth is stimulated by tamoxifen and can be reversed by the pure antiestrogen ICI 182,780 (35, 36).

The range of concentrations of estrogen under which tumors can proliferate is illustrated in Fig. 6. Endocrine treatments (e.g., ovarian ablation and aromatase inhibition) shift the concentration of estrogen down, resulting in responses in sensitive tumors. Changes in estrogen dose-response curves (for this purpose, we assume tamoxifen is an estrogen) might change during treatment of a tumor to the left and to the right (Fig. 5). Initially, the tumor grows in response to postmenopausal serum estrogen concentrations, which in the United Kingdom are a geometric mean of about 3 × 10⁻¹¹ M. The tumor is excised surgically and shown to be ER+, and the putative micrometastases are treated with tamoxifen (say, 10⁻⁶ M). After 5 years with no relapse, tamoxifen treatment is stopped, but at, say, 8 years, there is a relapse in bone. These metastases are growing in response to the postmenopausal E₂ concentration of about 3 × 10⁻¹¹ M. The patient is then treated with a potent AI, which reduces E₂ concentration further to 1 × 10⁻¹¹ M. There is a response, but after 18 months, tumor progression occurs at this concentration of E₂, and hence the E₂ concentration is changed to 10⁻⁷ to 10⁻⁶ M with high-dose estrogens. After a further response, the patient is treated either by withdrawal of treatment or with a non-cross-resistant AI and obtains another response. Thus, it is likely that this tumor has had its dose-response curve shifted to the right (tamoxifen and high-dose estrogen) on two occasions and to the left (two AIs) on two occasions. Unusually, it remains sensitive to all these changes. Usually tumors are either resistant de novo (this probability can be assessed by looking at the response rates to preoperative tamoxifen; Ref. 37) or acquire resistance during adjuvant therapy or therapy for advanced disease. For example, approximately 40% of tumors are resistant at relapse; of those that respond, 60% will be resistant to a second endocrine therapy. Thus, as we continually see in the clinic, there is an inexorable trend toward resistance even in initially responsive tumors. Treating patients with endocrine therapy continuously, as is our custom, is likely to be the most rapid way to induce such resistance.

With the new series of endocrine therapies that we now have, we are in a position to investigate ways to minimize the trend toward resistance by using the agents we have creatively and to answer three important questions: (a) can we increase the response rate at relapse; (b) can we increase the duration of response; and (c) can we prevent relapse by using better approaches to adjuvant therapy?

Can We Increase the Response Rate in Advanced Disease?

Tamoxifen has been the first-line treatment for advanced disease for many years, giving clinical benefit in approximately 50% of patients with ER+ tumors. Recent randomized trials in which potent AIs were compared with tamoxifen show that the response rate may be increased a little using either anastrozole, letrozole, or exemestane first line. The results of a trial of ICI 182,780 versus tamoxifen will soon be available, and it is hoped that the pure antiestrogen will also give higher response rates. It is not known why tamoxifen is less effective, but it is possible that some tumors respond to tamoxifen as a growth agonist de novo as first treatment for advanced breast cancer. We and others have reported that there is a small group of tumors that do not respond to first-line tamoxifen treatment but respond to
second-line endocrine therapy, indicating that tamoxifen does not produce responses in all potentially responsive tumors. De novo agonism seems a reasonable explanation for this phenomenon, and the higher response rate to other agents may be because they are not tumor agonists (AIs and ICI 182,780). Given the endocrine therapies available and the ones in development (GW5683, SR16234, and ZK191703), it is unlikely that we can increase the first-line response rate further. In the 40% of tumors that are resistant to therapy, proliferation may be driven by growth factors that act by inducing phosphorylation of ER. The addition of inhibitors of these pathways, e.g., EGF tyrosine kinase inhibitors or HER-2 receptor antibodies, may allow endocrine agents to become active, an approach that warrants additional studies, which are in fact ongoing. Alternatively, synthesis of ER may have been repressed by gene methylation because of the time the original measurement of ER was made on the primary tumor. Treatment with demethylating agents may be effective in reversing endocrine insensitivity.

**Can We Prolong Response Duration in Advanced Disease?**

Even if tumors respond, the median duration of response to first-line endocrine therapy is almost always less than 2 years. A few patients may benefit from multiple responses, but these women must endure the stress of repeated tumor progression and worry whether a further response is attainable. We would wish not only to prolong responses but also to eliminate the progression/response cycle currently seen. This is a difficult problem because we do not have a clear idea of the cellular mechanisms involved, but if this cycle is due to shifts in the estrogen dose-response curve, it is possible that administering endocrine therapy continuously may act to induce endocrine resistance. It may be the fastest way to shift the dose-response curve of the tumor to adapt to the new concentration of hormonal agent. Also, treating until resistance appears may allow about half of tumors to change to complete resistance to endocrine therapy. A reasonable working hypothesis is that resistance may be delayed and duration of response may be prolonged by changing treatment before the tumor adapts to the prevailing concentration of estrogen or, in the case of tamoxifen, anti-estrogen.

Several strategies could be tested in clinical trials in patients with ER+ tumors at first relapse. Treatments that lowered or increased effective estrogen levels could be alternated, say, at 3-month intervals. Alternatively, with the range of available AIs, estrogen concentrations could be lowered in a stepwise fashion or, with estrogen, increased in a stepwise fashion sequentially (Fig. 7). Although we treat patients with large doses of estrogen (DES, 5 mg three times per day in our study), lower doses have not been systematically studied. Many years ago, Stoll (38) reported responses to low-dose components of the oral contraceptive pill (lynestrol), suggesting that a small increase in estrogen concentration might be sufficient to obtain a first response. A report of WRs in four patients who relapsed on HRT after surgery for breast cancer suggests that in postmenopausal women, the small increase in E2 produced by HRT may be adequate adjuvant therapy and may be the reason why case-control studies of the use of HRT after surgery do not appear to show a detrimental effect (39). Fig. 6 shows that the relatively small falls in serum E2 associated with ovarian ablation or AI treatment result in responses. Additive estrogen is usually given at doses that are likely to be near or equivalent to the 10^-6 M concentration of tamoxifen. But there are a whole range of intermediate concentrations from the premenopausal maximum of 10^-9 to 10^-6 or 10^-7 M, which could be explored as therapy in alternating or dose-escalating approaches as described above.

Clinical trials of these approaches will not be easy to mount, not only because of potential patient and investigator resistance, but also because drug companies who finance many of our large randomized trials are unlikely to be interested. Trials of sequential therapy of SERMs and AIs have been performed for many years. We know that ICI 182,780 will be effective after tamoxifen failure (15, 16) and that an AI with a different mechanism of action or greater potency in lowering [E2] will be effective when used sequentially. Changing treatment before progression does not, therefore, seem an enormous step to take. However, the duration of each part of intermittent therapy is an open question. Tumor markers may not be of much use because when they begin to rise it is likely that the tumor has already adapted to the prevailing estrogen concentration. However, they may help with modeling the optimal time to use each treatment. Phase III trials comparing standard sequential (i.e., treatment at progression) with shorter-period sequential therapy will be needed to evaluate this new approach.

**Prevention of Relapse by Better Use of Adjuvant Endocrine Therapy**

As illustrated in Fig. 3, adjuvant endocrine therapy consisting of 5 years of tamoxifen in patients with ER+ tumors gives only modest results. In the 15-year data from the overview (25), 67% of patients in the no-treatment control arm did not
relapse and thus would not have benefited from adjuvant therapy. Of the 33% of patients who relapsed, only just over one-third of these relapses would be preventable with tamoxifen, leaving two-thirds that would not be prevented by treatment. AIs and ICI 182,780 improve a little compared with tamoxifen because they lack agonist activity. However, it may be more appropriate to test sequential approaches. These are being tested by several groups in adjuvant studies in which tamoxifen is changed to an AI after 2–3 years of the 5-year period of adjuvant therapy. The reverse sequence is also being tested. For the reasons outlined above, it is likely that sequential approaches will be superior to the continuous use of a SERM or an AI. A major question is whether shortening the interval between changes of adjuvant therapy to 3–6 months will be superior to our standard approaches.

**Conventional Sequential Therapy: Which Is the Best Sequence?**

The use of estrogens and WRs aside, what might be the optimal sequence for the treatments that are now commonly used or are in late clinical trials? The sequence is different for premenopausal and postmenopausal patients because of the possibility of ovarian ablation for the former group. Also, the sequence may be different according to the point in the course of breast cancer at which therapy is initiated (e.g., prevention, neoadjuvant, adjuvant, or advanced disease). Potential sequences are shown in Table 4. These take into account data from current trials and our knowledge of cross-resistance between and within SERMs and AIs. Clearly the sequences are tentative in the light of the (surprising) paucity of data available.

These data may be summarized as follows:

(a) Tamoxifen and raloxifene are potentially useful preventive agents, particularly in high-risk younger women.

(b) AIs appear to be superior to tamoxifen in downstaging tumors preoperatively.

(c) Five years of tamoxifen still remains the treatment of choice for adjuvant therapy.

(d) AIs are superior to tamoxifen for first-line treatment for advanced disease.

(e) AIs are superior to megestrol acetate for second-line therapy for advanced disease.

(f) ICI 182,780 is equivalent to anastrozole as second-line treatment for advanced disease.

(g) There appears to be little to choose between the new AIs at present.

(h) Little cross-resistance between tamoxifen and ICI 182,780 was seen in two large trials.

The clinical situation will perhaps be clarified when we have the results of the ATAC trial. It is possible that anastrozole will be superior to tamoxifen or the combination of these agents as adjuvant therapy. If this is the case, an AI will become the treatment of choice as adjuvant therapy. Soon we will have the results of a randomized trial of tamoxifen versus ICI 182,780 as first-line treatment for advanced disease. With an AI as optimal treatment for adjuvant disease and possibly ICI 182,780 as optimal treatment for first-line advanced disease, tamoxifen and other AIs may be relegated to second- and third-line therapies for advanced breast cancer together with estrogens.

**Open Discussion**

**Dr. Steven Come:** I wonder what patients would feel like if they were treated with pharmacological doses of estrogens.

**Dr. Howell:** Well, they should feel great because you’re not going to give huge doses. We need to find out what happens between $10^{-10}$ and $10^{-7}$ m. It may well be that you could just give HRT.

**Dr. Per Lonning:** I can add some comments about the high-dose estrogens, because I treated many of these patients myself. There were some striking phenomena. One was that they very often responded very quickly. I still have some patients who are on high-dose estrogens more than 2 years after they got a complete remission.

**Dr. Kent Osborne:** In my minimal experience with it, patients on high-dose DES, 15 mg/day, feel the best of any endocrine therapy. Is that your experience?

**Dr. James Ingle:** Initially. About half will retain fluid, and then you get incontinence in about 40% on long-term high dose. But I think you’re right. If you go up on the dose over about a week, you actually can get around some of the nausea.

**Dr. Osborne:** I think it would be kind of a bumpy ride going from high-dose estrogen down to an AI, and you have to alternate frequently enough to avoid resistance to one pattern or the other.

**Dr. Howell:** Well, that’s right. The question is how much...
you have to give. Going from moderate-dose estrogen down to an AI may well be tolerable. It’s a matter of doing the clinical experiments if you feel that is an approach to take.

Dr. Lonning: When you say that if anastrozole is superior in the ATAC results, it could kill the sequential trial with exemestane, you could say the other way around. If the sequential therapy turns out to be better than tamoxifen, that kills the control arm in the ATAC trial and you have to reject the whole trial.

Dr. Angela Brodie: We have models of these things. These agents all work quite well, actually. If you alternate them back and forth they’re about equivalent. We’ve also tried the on-and-off scheme. However, continuous letrozole treatment was the best and of longest duration in our animals. Once we withdraw letrozole, estradiol is produced again. We were quite surprised to find that giving letrozole a second time actually caused responses. These tumors were also very responsive to fulvestrant, actually even more than to letrozole in this setting.

Dr. Come: How much confidence do we have in these models in terms of predicting?

Dr. Brodie: Well, most of the earlier studies we’ve done have turned out to be predictive in the clinic. The first-line treatment with letrozole, for example, was better than tamoxifen.

Dr. Come: Since we can’t do an infinite number of trials, do we have some really good models that are predictive that will allow us to narrow the questions a great deal and then do a small number of big, meaningful trials with blocks?

Dr. Brodie: We’ll have to do the trials, of course, but these could be focused on predictions from the model.

Dr. Howell: We can’t do every trial.

Dr. Kathleen Pritchard: We want to do the right trials.

References
26. Howell, A., Mackintosh, J., Jones, M., et al. The definition of the “no change” category in patients treated with endocrine therapy and...
4410s SERMs and AIs

Future Use of Selective Estrogen Receptor Modulators and Aromatase Inhibitors

Anthony Howell

_Cancer Res_ 2001;7:4402s-4410s.

---

Updated version

Access the most recent version of this article at:

[http://cancerres.aacrjournals.org/content/7/12_Supplement/4402s](http://cancerres.aacrjournals.org/content/7/12_Supplement/4402s)

---

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.