2. Dombernowsky P, Smith I, Falkson G, *et al*. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998, **16**, 453–461.
3. Kaufmann, M, Bajetta E, Dirix LY, *et al*. Survival advantage of exemestane (AromasinR) over megestrol acetate (MA) in postmenopausal women with advanced breast cancer (ABC) refractory to tamoxifen (tamoxifen): results of a phase III randomized double-blind study. *Proc Am Soc Clin Oncol* 1999, **18**, 109a, (Abstract 412).
4. Howell A, DeFriend D, Robertson J, Blamey R, Walton P. Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer. *Lancet* 1995, **345**, 29–30.
5. Lønning PE. Cross-resistance to different aromatase inhibitors in breast cancer treatment. *Endocrine Rel Cancer* 1999, **6**, 251–257.
6. Lønning PE, Lien E. Mechanisms of action of endocrine treatment in breast cancer. *Crit Rev Oncol/Haematol* 1995, **21**, 158–193.
7. Jones S, Vogel C, Arkhipov A, *et al*. Multicenter, phase II trial of exemestane as third-line hormonal therapy of postmenopausal women with metastatic breast cancer. *J Clin Oncol* 1999, **17**, 3418–3425.
8. Hudis, C, Buzdar A, Munster P, *et al*. Phase I study of a third-generation selective estrogen receptor modulator (SERM3, LY353381.HCl) in refractory, metastatic breast cancer. *Breast Cancer Res Treat* 1998, **50**, 306, (Abstract 442).
9. Lønning PE, Anker G, Taylor PD, *et al*. High-dose estrogen treatment in postmenopausal patients heavily exposed to endocrine treatment for advanced breast cancer. *Breast Cancer Res Treat* 1998, **50**, 305 (Abstract 440).
10. Ingle JN, Suman VJ, Jordan VC, Dowsett M. Combination hormonal therapy involving aromatase inhibitors in the management of women with breast cancer. *Endocrine-Rel Cancer* 1999, **6**, 265–269.
11. Lien EA, Anker G, Lønning PE, Solheim E, Ueland PM. Decreased serum concentrations of tamoxifen and its metabolites induced by aminoglutethimide. *Cancer Res* 1990, **50**, 5851–5857.
12. Dowsett M, Tobias JS, Howell A, *et al*. The effect of anastrozole on the pharmacokinetics of tamoxifen in post-menopausal women with early breast cancer. *Br J Cancer* 1999, **79**, 311–315.
13. Dowsett M, Pfister C, Johnston SRD, *et al*. Impact of tamoxifen on the pharmacokinetics and endocrine effects of the aromatase inhibitor letrozole in postmenopausal women with breast cancer. *Clin Cancer Res* 1999, **5**, 2338–2343.

An overview of the use of non-steroidal aromatase inhibitors in the treatment of breast cancer

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Abstract

A number of potent and selective non-steroidal aromatase inhibitors are now available for the treatment of advanced breast cancer in postmenopausal women. In particular, anastrozole represents a significant advantage over earlier agents, such as aminoglutethimide and formestane, in terms of both efficacy and tolerability. These agents are now established as the second-line therapy of choice in postmenopausal women with advanced disease progressing on tamoxifen and, furthermore, data are now available on the efficacy and tolerability of anastrozole as first-line treatment of advanced breast cancer compared with tamoxifen. The full potential of the new-generation aromatase inhibitors in the treatment of breast cancer is currently being investigated in a large programme of clinical trials, including evaluation as neoadjuvant treatment in postmenopausal women with newly-diagnosed locally-advanced or large operable breast cancers, as first-line treatment of advanced breast cancer in postmenopausal women. Aromatase inhibitors have been available for over 20 years; the ability of these compounds to reduce circulating oestradiol levels has been shown to produce clinical benefit in postmenopausal women with advanced breast cancer. Early aromatase inhibitors, however, such as aminoglutethimide and formestane, were not specific for the aromatase enzyme and resulted in significant side-effects.

Keywords: Breast; Aromatase inhibitors; Treatment

Within the last decade we have seen the development of a new-generation of triazole aromatase inhibitors that are better tolerated with more convenient dosage regimens than these earlier agents. This new class of drugs, which are potent, orally active, non-competitive, selective, non-steroidal aromatase inhibitors, includes anastrozole, the first of these agents to become commercially available for advanced breast cancer in postmenopausal women failing on tamoxifen therapy.

Anastrozole is the most widely used of the new-generation aromatase inhibitors [1], but its use so far has been restricted to the treatment of advanced breast

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cancer in postmenopausal women whose disease has recurred or progressed while on tamoxifen treatment. Anastrozole is well tolerated and, based on the findings of two large, identical, phase III studies comparing anastrozole (1 and 10 mg od) with megoestrol acetate (160 mg qid) as second-line therapy in 764 postmenopausal women with advanced disease, anastrozole has been shown to be associated with significant improvements in both median survival and 2-year survival rates compared with the progestin (hazard ratio (HR) 0.78; $P < 0.25$) [2,3].

Another new-generation aromatase inhibitor, letrozole (2.5 mg daily), which is also now commercially available, was reported as having a significant advantage over megoestrol acetate in terms of objective response ($P = 0.04$), duration of response ($P = 0.02$), and time to treatment failure ($P = 0.04$), although, unlike anastrozole, there was no significant difference in overall survival ($P = 0.15$) [4].

While anastrozole and letrozole have shown clear evidence of benefit over existing agents as second-line treatments, the data regarding fadrozole, which is available only in Japan, and vorozole, which has not progressed beyond phase III clinical development, are more equivocal [5–9]. Neither drug has shown an advantage over existing endocrine agents in terms of efficacy and tolerability.

In addition to becoming established as second-line agents in women progressing on tamoxifen, aromatase inhibitors may have several other potential uses. For example, a study has recently evaluated the use of anastrozole as neoadjuvant therapy in postmenopausal women with newly diagnosed, oestrogen receptor-positive (ER+), locally advanced or large (>3 cm) operable breast cancer [10]. 24 patients in a randomised, double-blind, single-centre study received either 1 mg or 10 mg anastrozole daily over a 3-month period. Of the 17 patients who would have required a mastectomy at initiation of treatment, 15 were suitable for breast conservation following anastrozole treatment, suggesting that anastrozole is highly effective as neoadjuvant therapy in postmenopausal women with ER+ breast cancer. Future neoadjuvant studies should include the comparison of anastrozole with tamoxifen, presently the most commonly used neoadjuvant therapy.

Anastrozole has also recently been shown to be at least as effective as tamoxifen for the first-line treatment of advanced breast cancer in postmenopausal women [11]. In one of the two similar trials carried out, a randomised, double-blind multicentre trial (performed in the US and Canada) designed to demonstrate equivalent efficacy of anastrozole (1 mg daily) relative to tamoxifen (20 mg daily) in ER+ and/or progesterone receptor-positive (PR+) or unknown receptor status patients eligible for endocrine therapy, included a total of 353 patients who were followed for a median of 18 months. Disease progression was observed in 67% of anastrozole patients and 76% of tamoxifen patients. Furthermore, anastrozole showed a significant improvement in time to progression compared with tamoxifen in a retrospective statistical comparison (11.0 months versus 5.6 months, respectively; $P = 0.005$). Clinical benefit rates (complete or partial response, or stable disease for at least 6 months) were 59% for anastrozole but only 46% for tamoxifen. Both treatments were generally well tolerated. This is the first observation of another endocrine agent showing a significant efficacy benefit over tamoxifen, the established treatment of choice in the patient population. The results of the second, similar trial, which was carried out in Europe and rest of the World, is reported by Bonneterre and colleagues [12]. The potential use of anastrozole as adjuvant therapy for early-stage breast cancer in postmenopausal women is also being explored in the ongoing ATAC trial (anastrozole or tamoxifen alone or in combination) [13].

These recent trials indicate that there is clearly an expanding role for the newer aromatase inhibitors in the treatment of endocrine-related breast-cancers, with most of the available data being from trials involving anastrozole. Further studies, together with the data from those still in progress, may provide evidence to support these agents as new and effective alternatives to existing therapies already used to treat all stages of breast cancer in postmenopausal women.

References

1. Wyld DK, Chester D, Perren TJ. Endocrine aspects of the clinical management of breast cancer — current issues. *Endocrine-Related Cancer* 1998, **5**, 97–110.
2. Buzdar A, Jonat W, Howell A, *et al*. Anastrozole, a potent and selective aromatase inhibitor, versus megoestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. *J Clin Oncology* 1996, **14**, 2000–2011.
3. Buzdar AU, Jonat W, Howel A, *et al*. Anastrozole versus megastrol acetate in postmenopausal women with advanced breast cancer: results of a survival update based on a combined analysis of data from two mature phase III trials. *Cancer* 1998, **83**, 1142–1152.
4. Dombernowsky P, Smith I, Falkson G, *et al*. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998, **16**, 453–461.
5. Buzdar AU, Smith R, Vogel C, *et al*. Fadrozole HCL (CGS-16949A) versus megestrol acetate treatment of postmenopausal patients with metastatic breast carcinoma. *Cancer* 1996, **77**, 2503–2513.
6. Thürlimann B, Beretta K, Bacchi M, *et al*. First-line fadrozole HCl (CGS 16949A) versus tamoxifen in postmenopausal women with advanced breast cancer. *Ann Oncol* 1996, **7**, 471–479.
7. Falkson Cl, Falkson HC. A randomised study of CGS 16949A (fadrozole) versus tamoxifen in previously untreated postmenopausal patients with metastatic breast cancer. *Ann Oncol* 1996, **7**, 465–469.
8. Goss P, Wine E, Vogel C, *et al*. Vorozole versus 'Megace' in postmenopausal patients with metastatic breast carcinoma who

had relapsed following tamoxifen. *Proc ASCO* 1997, **16**, 155a, (Abstract 542).
9. Jpistp, SK. 'Rivizor' versus aminoglutethimide (AG) in the second-line endocrine treatment of postmenopausal patients with advanced breast cancer (ABC) following tamoxifen failure. *Breast* 1997, **6**, 244, (Abstracts 0–72).
10. Dixon MJ, Renshaw L, Bellamy C, *et al*. 'Arimidex' as neoadjuvant therapy causes large reductions in tumour volume in postmenopausal women with large operable breast cancers. *Proc ASCO* 1999, **18** (Abstract 345).
11. Buzdar A, Nabholtz JM, Robertson JF, *et al*. Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer (Abc) in postmenopausal (Pm) women — combined analysis from two identically designed multicenter trials. *Proc Am Soc Clin Oncol* **19**, 154a (Abstract 609D).
12. Bonneterre J, Thürlimann BJK, Robertson JFR, On behalf of the 'Arimidex' Study Group; Centre Oscar Lambret, France; St Gallen, Switzerland; Nottingham City Hospital, UK. Preliminary results of a large comparitive multi-centre clinical trial comparing the efficacy and tolerability of Arimidex™ (Anastrozole) and tamoxifen (tamoxifen) in postmenopausal women with advanced breast cancer (ABC). *Eur J Cancer* 1999, **35**(Suppl. 4), S313.
13. Houghton J, Baum M. Arimidex, tamoxifen alone or in combination (ATAC) adjuvant trial in postmenopausal breast cancer. *Eur J Cancer* 1998, **34**(Suppl. 5), S83.

Randomised study of anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women

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Abstract

A total of 668 patients (340 anastrozole and 328 tamoxifen) were randomised in a double-blind, double-dummy multicentre study. Anastrozole was given in a dose of 1 mg once daily and compared with tamoxifen 20 mg daily in postmenopausal patients with tumours that were hormone-receptor positive or of unknown receptor status. The efficacy and tolerability of anastrozole was compared with that of tamoxifen as first-line therapy for advanced breast cancer. The median time to progression was similar for both treatments (8.2 months in anastrozole patients and 8.3 months in tamoxifen patients). Anastrozole was also as effective as tamoxifen in terms of objective response-rate with 33% in the anastrozole group and 32.6% in the tamoxifen group achieving a complete or partial response. Both treatments were well tolerated. However, incidences of thromboembolic events and vaginal bleeding were reported in fewer patients treated with anastrozole than with tamoxifen. In conclusion, these findings indicate that anastrozole can be considered as first-line therapy for postmenopausal women with advanced breast cancer.

Keywords: Breast neoplasms; Aromatase-inhibitors; Anastrozole; Tamoxifen

Since the late 1970's tamoxifen has been accepted as the 'gold' standard first-line treatment for advanced breast cancer in postmenopausal patients. Tamoxifen acts by blocking the binding of the oestrogen receptor (ER) and has an overall response rate of 30–35% when used as first-line therapy for advanced breast cancer [1]. Adverse effects that have been associated with tamoxifen can be classified as either due to its anti-oestrogenic actions (e.g. hot flushes, vaginal bleeding, discharge or dryness), or more general effects (e.g. nausea, vomiting,

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