PERGAMON

European Journal of Cancer 38 Supplement 6 (2002) S61–S62

European Journal of Cancer

www.ejconline.com

Selective oestrogen receptor downregulator

Anthony Howell*

CRC Department of Medical Oncology, University of Manchester, Christie Hospital NHS Trust, Manchester M20 4BX, UK

The non-steroidal anti-oestrogen tamoxifen is well established as an effective treatment for breast cancer, both for metastatic disease and as an adjuvant to surgery for primary breast cancer. In addition, to exerting antagonistic effects on the oestrogen receptor, tamoxifen and its derivatives act as partial agonists on certain tissues. These agonistic effects, for example, endometrial stimulation and stimulation of tumour growth following previous response to tamoxifen, may limit their clinical efficacy. Fulvestrant (ICI 182,780, Faslodex^{TM}) is a novel, steroidal oestrogen antagonist devoid of oestrogen agonist activity in preclinical models. Preclinical and early clinical data suggest that it has a novel mode of action by downregulating the oestrogen receptor which may result in a different tumour response profile from tamoxifen and related compounds with the possibility of more durable tumour responses. The compound was tested in a large number of *in vitro* and *in vivo* preclinical models and its value was assessed clinically when administered before surgery for breast cancer and hysterectomy for benign conditions and after failure of tamoxifen in advanced breast cancer. All data indicated that fulvestrant is devoid of agonist activity in preclinical models and in clinical trials. It inhibits the growth of the breast and endometrium. In animal models, it does not cross the blood-brain barrier and appears to be neutral with respect to lipids and bone. It downregulates the oestrogen receptor and is active in tamoxifen-resistant breast cancer. Fulvestrant was shown to be non-cross resistant with tamoxifen in advanced breast cancer in a small phase II study. These data led to two trials where the pure anti-oestrogen was compared with anastrozole as second-line treatment after tamoxifen failure for advanced breast cancer and a first-line study in comparison to tamoxifen. The results of the two second-line studies, one conducted in Europe, South Africa and Australia (trial 20) and one conducted in North America (trial 21) were presented at the last San Antonio meeting and have been submitted for publication. Essentially the two studies showed that the two endocrine therapies were equivalent. However, in trial 21 there was a duration of response advantage for fulvestrant, but not in trial 20. This may be due to chance, although the trials were quite large with 451 patients entered into 20 and 400 into 21. There were also differences in design. In trial 20 one 5 ml injection was given monthly whereas in trial 21, 2.5 ml injections were given into each buttock and there were also placebo injections and an anastrozole placebo. Tumour assessment was every three months in trial 20 whereas monthly assessments of soft tissue disease were made for the first three months and three monthly thereafter in trial 21. Inclusion and exclusion criteria were identical in the two studies, but patient characteristics differed a little. Trial 21 patients were on average 4 lbs heavier, had fewer patients with an unknown receptor status (14% v 26%) and were more likely to have had previous chemotherapy (62.5% versus 42.5%). There were no major differences in the sites of disease, although trial 21 patients were more likely to have a single site affected (fulvestrant, 45% [trial 20] v 54% [trial 21], anastrozole 38% [trial 20] v 52% [trial 21]). At the time of analysis over 80% of patients had progressed. The hazard ratio for time to progression (TTP) was 0.92 (CL 0.74, 1.14) for trial 21 and 0.98 (CL 0.80, 1.21) for trial 20. The median TTP was 5.4 (fulvestrant) and 3.4 (anastrozole) months for trial 21 and 5.5 and 5.1 months, respectively, for trial 20. Complete Response + Partial Response (CR + PR) was 17.5% (fulvestrant) versus 17.5% (anastrozole) in trial 20 and 20.7% (fulvestrant) versus 15.7% (anastrozole) in trial 21. Clinical benefit was 44.6% versus 45.0% (trial 20) and 42.3% versus 36.1% (trial 21). Median duration of response was 14.3% versus 14.0% (trial 20) and 19.3 months versus 10.5 months (trial 21). There were no significant differences in drug-related adverse events. Pain, inflammation, haemorrhage or hypersensitivity at the injection site in trial 21 was seen in 86 of 1879 (4.6%) of fulvestrant injections and 71 of 1624 (4.4%) placebo injections. In trial 20, 20 of 1898 (1.1%) of injections were associated with an

* Tel.: +44-0161-446-8037; fax: +44-0161-446-8000.
E-mail address: maria.parker@christie-tr.nwest.nhs.uk (A. Howell).

PII: S0959-8049(02)00289-7

adverse event. Thus, in trial 21 there was an increased clinical benefit and a greater duration of response with fulvestrant whereas these differences were not seen in trial 20. The important result is that fulvestrant is at least equivalent and possibly slightly superior to anastrozole despite previous treatment with tamoxifen. fulvestrant specifically downregulates the oestrogen receptor and thus represents the first of a new class of therapeutic agents.

Further reading

1. Howell A, Osborne K, Wakeling A. Faslodex (ICI 182,780). Development of a novel 'pure' antiestrogen. *Cancer* 2000, **89**, 817–825.
2. DeFnend DJ, Howell A, Nicholson RT, *et al*. Investigation of a new pure antiestrogen (ICI 182,780) in women with primary breast cancer. *Cancer Res* 1994, **54**, 408–414.
3. Howell A, DeFriend DJ, Robertson J, *et al*. Response to a specific antiestrogen (ICI 182,780) in tamoxifen resistant breast cancer. *Lancet* 1995, **345**, 29–30.
4. Howell A, Robertson JFR, Quaresma AJ, *et al*. Comparison of efficacy and tolerability of fulvestrant (Faslodex) with anastrozole (Arimidex) in postmenopausai women (PM) with advanced breast cancer (ABC)—preliminary results. *Breast Cancer Research Treatment* 2000, **64**, A6.
5. Osborne CK, Pippen J, Jones SE, *et al*. Faslodex (ICI 182,780) shows longer duration of response compared with arimidex (anastrozole) in postmenopausal (PM) women with advanced breast cancer (ABC). Preliminary results of a phase III North American trial. *Breast Cancer Research Treatment* 2001, **65**, A261.