SUMMARY

ZENECA PHARMACEUTICALS	INDIVIDUAL STUDY TABLE REFERRING TO PART IV OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)

FINISHED PRODUCT:

ACTIVE INGREDIENT:
ICI 182,780 (ZD9238)

Study title (number): A randomised study to evaluate tolerance, pharmacokinetics, and short term efficacy of seven daily doses of the short-acting formulation of ICI 182,780 in women prior to surgery for primary breast cancer (9238HQ/0002)

Clinical phase: II **Time period:** 14 October 1991 to 2 November 1992

Principal Investigator, location and centre number:

Publications: Abstract: Editor Marc E Lippmain (1993) Breast Cancer Research and Treatment
Vol 27: Nos 1/2; 1993 p136

Paper: Defriend DJ, Howell A, Nicholson RI et al
Investigation of a new pure antioestrogen (ICI 182,780) in women with primary breast cancer.
Cancer Research 54:408-414

OBJECTIVES

(a) To demonstrate oestrogen antagonism in malignant human breast tissue with the short-acting formulation of ICI 182,780.

(b) To assess systemic and local tolerability to the short-acting formulation of ICI 182,780 in post-menopausal women with primary breast cancer.

(c) To monitor pre-dose serum concentrations of ICI 182,780 following multiple dosing with the short-acting formulation.

METHODS

Design: Open, randomised, controlled, multicentre study. Patients were randomised 2:1 to either treatment for 7 consecutive days with ICI 182,780 (6 mg or 18 mg) or observation (no treatment for 7 days), followed by surgery for primary breast cancer.

Population: Post-menopausal women with primary breast cancer.

Key inclusion criteria:

(a) Post-menopausal women.

(b) T_2 or T_3 primary breast cancer large enough for core-cut biopsy and no evidence of metastases.

(c) Give informed consent.

Key exclusion criteria:
(a) Aged 76 years or over and weight <40kg or >110kg.
(b) Clinical chemistry, haematology or urinalysis outside the normal range and considered to be clinically significant.
(c) History of drug allergy to similar compounds or parenteral formulations containing the vehicle.
(d) History or presence of hepatic or renal disease, insulin-dependent diabetes, or other conditions known to interfere with absorption, distribution, metabolism or excretion of drugs.
(e) History of disease associated with or affecting steroid metabolism.
Dosage: Once daily injection of either 6 mg or 18 mg ICI 182,780 for 7 consecutive days.

Key assessments:

Efficacy:
(a) Tissue receptor analysis (pS2, Ki67 and oestrogen and progesterone receptors).
Safety:
(a) Safety and tolerability by report of adverse events at each visit;
(b) Tests of haematology, clinical chemistry, and urinalysis at entry and prior to surgery.
(c) Monitoring of serum ICI 182,780 concentrations.
Statistical considerations: No formal statistical analysis plan for the safety and efficacy endpoints, but the data would be summarised by treatment group.

RESULTS: The two randomised groups in this study are ICI 182,780 (irrespective of dose) and to no treatment. The allocation of subjects to different dose levels of ICI 182,780 (6 mg or 18 mg) was based on the time at which patients entered the study.

DEMOGRAPHY: A total of 58 patients with newly diagnosed breast cancer entered the study, 39 randomised to ICI 182,780 (22 received 6 mg and 18 received 18 mg) and 19 randomised to observation. The three groups were well matched with respect to patient age, tumour size, T stage and axillary lymph node status, however the group treated with ICI 182,780 6 mg contained a greater proportion of histological grade III steroid receptor negative tumours than did the control and 18 mg dose groups.

EFFICACY AND SAFETY:

pS2

The mean percentage of cells staining for pS2 decreased following 7 days of treatment. This decrease was slightly greater at the 18-mg dose level compared with 6 mg ICI 182,780.

Ki67

Following 7 days of treatment with ICI 182,780, the percentage of Ki67 positive cells decreased compared with the observation group. The decrease was slightly greater in the 18 mg ICI 182,780 dosed group compared with the 6 mg dosed group.

Progesterone and Oestrogen Receptor

The mean percentage of cells expressing progesterone/oestrogen receptor was lower post-treatment than pre-treatment for the ICI 182,780 group, but higher post-treatment than pre-treatment for the group randomised to no treatment. There was also a greater decrease in percentage of tumour cells expressing the progesterone receptor following treatment with 18 mg ICI 182,780 than with the lower dose of ICI 182,780.

Adverse events

In the treated group, 8 patients (21%) reported at least one adverse event; 5 of these patients received ICI 182,780 6 mg and 3 received ICI 182,780 18 mg. No adverse events were reported in the observation group.

The most frequently reported adverse event was headache (6 patients) with facial oedema, hyperglycaemia and vaginal haemorrhage reported by one patient with hypertension and dyspepsia, each being reported by 1 patient. Only one patient (who received ICI 182,760 6 mg) reported an injection site reaction.

Laboratory variables

All clinically significant out-of-range findings were reported as adverse events. There were no clear trends in minor deviations from the normal ranges in any of the laboratory variables.

Pharmacokinetics

In the ICI 182,780 group who received 6 mg, mean serum concentration was non-detectable pre-dose on Day 1, and rose from Day 2 (2.95 ng/ml) to Day 5 (6.61 ng/ml). Mean concentration rose again from Day 6 to Day 7 (8.23 ng/ml)

In the 18 mg ICI 182,780, serum levels were again non-detectable pre-dose on Day 1. The concentration rose from Day 2 (11.63 ng/ml) to Day 7 (25.95 ng/ml). Again levels were almost the same on Days 5 and 6 (21.50 and 21.78 ng/ml respectively) and Day 6 post-dose and Day 7 (25.41 ng/ml and 25.95 ng/ml respectively).

At each timepoint, the mean serum concentration of ICI 182,780 in the 18 mg group was approximately three times that of the 6 mg group.

DISCUSSION:

This study was the first investigation of the short term administration of ICI 182,780 to women with primary breast cancer. It was found that this short-acting formulation of ICI 182,780 used in this study to be well tolerated, over a 7 day treatment period and to be associated with minimal local or systemic toxicity. The maximum serum levels of ICI 182,780 achieved in this short-term study were of the order of 26 ng/ml. The mean pre-dose concentration of drug increased over the 7 day dosing period showing approximately 3 fold accumulation.

Treatment with ICI 182,780 produced significant decline in the expression of oestrogen receptor and progestrone receptor in the primary breast cancer as determined by immuno-histo-chemistry on pre and post tumour samples. Likewise, treatment showed falls in the oestrogen-stimulated protein, pS2 as measured by cells staining with anti-pS2 anti-bodies in the pre and post treatment samples. Likewise there is also a fall in the antigen represented as Ki67 which is an indicator of cellular-proliferative activity after the treatment period.