AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	ZD6474
Study Code	D4200C00045
Date	05 September 2006

Clinical Study Report Synopsis

A Phase II, double-blind, placebo-controlled, randomised study to assess the efficacy and safety of ZD6474 in combination with ARIMIDEX™, vs ARIMIDEX alone, in patients with hormone-sensitive (ER+ve and/or PR+ve) tumours as second-line treatment for advanced breast cancer (ABC)

Study dates:	First patient enrolled:	21 December 2005
	Last patient completed:	31 July 2006
Phase of development:	Phase II	
Investigators:	See Appendix E for list of Investigators	

This study was performed in compliance with Good Clinical Practice.

A Phase II, double-blind, placebo-controlled, randomised study to assess the efficacy and safety of ZD6474 in combination with ARIMIDEX™, vs ARIMIDEX alone, in patients with hormone-sensitive (ER+ve and/or PR+ve) tumours as second-line treatment for advanced breast cancer (ABC).

ER=oestrogen receptor; PR=progesterone receptor; ARIMIDEX=anastroxole

Early termination of study

The first patient was enrolled into the study on 21 December 2005. A decision was taken and communicated on 12 July 2006 to prematurely terminate the study. Recruitment had been very slow, and this was mainly due to changing treatment practice. Patients recruited into the study were to be postmenopausal, with hormone receptor-positive advanced breast cancer, and were to be either early failures after adjuvant therapy or were to have progressed on or following first-line therapy. The protocol excluded patients with any prior use of aromatase inhibitors, either in early or advanced disease. As aromatase inhibitors have been used increasingly as adjuvant and/or first-line therapy over the last few years, recruitment of suitable patients for this study was very difficult. The study had progression event count as the primary endpoint, so it was important that recruitment proceeded at a reasonable rate so that the required number of progression events was not exceeded before recruitment was completed. It became apparent that an extended recruitment period was inevitable, thus jeopardising the integrity and outcome of the study.

Primary Objective:

The primary objective was to assess the efficacy of ZD6474 in combination with ARIMIDEX (anastrozole) in the treatment of ABC using progression event count methodology.

Secondary Objective:

The secondary objective was to assess the safety and tolerability of ZD6474 in combination with anastrozole in the treatment of ABC by review of adverse events (AEs) and laboratory parameters.

Patients:

A minimum of 64 female patients (from around 10 centres, in approximately 4 countries) were to be randomised to receive either anastrozole plus ZD6474 or anastrozole plus placebo. Only 11 patients were actually randomised, from a total of 5 centres in 4 countries.

Design:

This was a double-blind, placebo-controlled, two-arm, parallel-group study. Following baseline assessments, patients were to be randomised in a 1:1 ratio to receive either 1 mg anastrozole plus 300 mg ZD6474 or 1 mg anastrozole plus placebo. Dose reductions were permitted. Patients were to be followed up every 4 weeks whilst on study treatment until approximately 6 months after recruitment was complete. Patients were permitted to continue with ZD6474, anastrozole, or combination treatment, following the closure of the study.

Outcome Variables:

Efficacy

The primary outcome variable was the number of progression events at data cut-off.
A progression event was defined as the earliest of: Objective disease progression at the data cut-off date (approximately 6 months after the last patient was randomised) as measured using RECIST criteria, or death from any cause

Safety

Safety outcome variables were AEs, clinical chemistry, and haematology.

Results

Summary of patients

The 11 patients randomised had a mean age of 61.5 years (range 49 to 71 years) and were considered to be representative of the broad population of patients with hormone-positive advanced breast cancer. Five patients received anastrozole plus ZD6474, 6 received anastrozole plus placebo.

Ten of the patients had received prior anti-oestrogen adjuvant therapy, 7 patients had received prior chemotherapy (taxane and/or anthracycline), and no patients had received prior trastuzumab (HERCEPTIN®) therapy. One patient (who was enrolled erroneously) had received prior aromatase inhibitor therapy for advanced disease, as well as anti-oestrogen adjuvant therapy and an anthracycline. All patients had bone metastatses and 4 patients were receiving bisphosphonates.

All randomised patients received at least one dose of study treatment, and listings were based on this analysis set. All 4 patients remaining in the combination group at the time of study termination continued with ZD6474 treatment.

Efficacy

Due to the decision to terminate the study early, only 2 patients were followed for more than 2 months. Only 1 patient (receiving anastrozole plus ZD6474) experienced disease progression during the study period. Therefore it was not possible to draw any conclusions regarding efficacy of anastrozole plus ZD6474 versus anastrozole plus placebo.

Safety

Adverse Events

Nine of the 11 patients received less than 2 months treatment (median 46 days). There were 9 AEs in total, of which 1 commenced before treatment started (fluid retention). Four AEs (including fluid retention) were still ongoing at the time the patients discontinued the study.

Two AEs in 2 patients occurred in the anastrozole plus ZD6474 group (rash macular and rash maculo-papular), both of which were considered to be related to ZD6474. Rash macular was the only AE in the study that reached CTCAE grade 3 (Patient E0081002), and this AE led to a dose reduction. Six AEs occurred in 3 patients in the anastrozole plus placebo group (hot flush, arthralgia, headache, hypotension, fatigue, and nausea). Hot flush and nausea were considered to be possibly related to anastrozole.

There were no AEs relating to prolonged QTc interval, hypertension, or other changes in ECG or vital signs.

There were no SAEs, no AEs leading to withdrawal from the study, no AEs leading to permanent discontinuation of ZD6474, and no AEs leading to death. There was one death, which was considered by the investigator to be due to disease progression (see Appendix B).

Laboratory parameters

Laboratory data showed nothing of note in the haematology, creatinine, electrolyte (potassium, sodium, calcium, magnesium) and protein/albumin listings. There were occasional values outside normal laboratory range, but nothing of clinical importance.

There was a tendency for more of the indices of hepatic function (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin) to be above the upper limit of normal during study treatment compared to at screening, in the group that received ansastrozole plus ZD6474 (see Appendix C). This trend was not seen in the anastrozole plus placebo group.