Supplementary Methods

Full Inclusion criteria

The main inclusion criteria for this study were: histologically confirmed invasive adenocarcinoma of the breast with: involvement of at least one axillary lymph node on routine histologic examination; OR ER-negative invasive tumour bigger than 2cm; OR ER-positive invasive tumour bigger than 3cm; standard surgical treatment, consisting either of mastectomy or a standard breast-conserving operation, which included appropriate axillary surgery (sentinel node biopsy or axillary dissection); HER2-normal status (0, or 1+ by immunohistochemistry [IHC] or fluorescence *in situ* hybridization [FISH] non amplified); no evidence of metastatic disease on standard staging investigations; interval between the last surgery for breast cancer and Day 1 of treatment of more than 21 days and less than 84 days, ECOG performance status of 0 or 1. Normal ECG and normal cardiac ejection fraction by echocardiogram (ECHO) or multiple acquisition (MUGA) scan within 3 months prior to registration were required to enter the study. Patients were excluded if they had any clinically significant cardiovascular of cerebrovascular disease, including any history of: symptomatic heart disease or heart disease requiring ongoing treatment; cerebrovascular disease, including transient ischemic attack (TIA), stroke or subarachnoid haemorrhage; ischaemic bowel; myocardial infarction; unstable angina; New York Heart association (NYHA) grade II or greater congestive heart failure; Grade II or greater peripheral vascular disease active at study entry; ongoing anticoagulation therapy; uncontrolled hypertension defined as systolic blood pressure (BP) >145mmHg or diastolic BP >85mmHg, with or without anti-hypertensive medication(s); uncontrolled or clinically significant arrhythmia; non-healing wound or fracture; any history of abdominal fistula, gastrointestinal perforation, or intrabdominal abscess within 6 months prior to randomization. No major surgical procedure was permitted within 21 days of Day 1 of treatment. Patients with inflammatory breast cancer or clinically fixed axillary nodes at diagnosis were excluded. All patients provided written informed consent. The study was conducted according to the principles of Good Clinical Practice, the provisions of the Declaration of Helsinki, and other applicable local regulations.

Treatment scheduling

Study therapy consisted of four cycles of TC (docetaxel 75mg/m2 and cyclophosphamide 600mg/m2 every) and bevacizumab 15mg/kg every administered intravenously every three weeks. After the completion of four cycles of chemotherapy patients received bevacizumab every three weeks for a total of 12 months of therapy, regardless of missed doses. All patients received adjuvant Radiation Therapy (RT) within 4 to 6 weeks following completion of chemotherapy, overlapping with the administration of bevacizumab. RT to chest wall was required when the post-mastectomy microscopic margins were positive, but was at the radiation oncologist's discretion in case of negative post-mastectomy microscopy margins. Protocol mandated that patients with estrogen receptor (ER) positive and/or progesteron (PR) positive tumours should receive a minimum of 5 years of adjuvant endocrine therapy.

Protocol mandated to follow up patients through 5 years (i.e. from the time of registration through to end of Year 5: 1 year of treatment and 4 years follow up). One dose reduction was allowed for both the chemotherapy agents (docetaxel 60mg/m^2 and cyclophosphamide 500mg/m^2). No dose modification was allowed for bevacizumab except for when a patient had a bodyweight change of more than 10%. Bevacizumab was interrupted or discontinued if indicated.

Cardiac safety monitoring

A severe cardiac AE was defined in the study protocol as one of the following conditions: NYHA class III or IV CHF accompanied by a decrease in LVEF of >10% points from baseline and to below 50%; probable cardiac death: sudden unexpected death within 24 hours of clinical presentation without a documented aetiology; definite cardiac death: death due to CHF, myocardial infarction or ischaemis or a documented primary arrhythmia.

Non-severe cardiac adverse events included asymptomatic (NYHA class I) or mildly symptomatic (NYHA class I) CHF accompanied by a decrease in LVEF of >10% points from baseline and to below 50% confirmed after 3 or 4 weeks by a second LVEF assessment.