*T*amoxifen and *E*xemestane *A*djuvant *M*ulticentre trial

An open label, randomised, multicentre, comparative trial of 5 years adjuvant exemestane treatment versus adjuvant tamoxifen followed by exemestane in postmenopausal women with early breast cancer

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2. TEAM STUDY SUMMARY

Title

An open label, randomised, comparative trial of 5 years adjuvant exemestane treatment versus 2.5-3 years adjuvant tamoxifen followed by exemestane treatment in postmenopausal women with early breast cancer.

Study objectives

Primary endpoint

- Disease Free Survival (DFS)

Secondary endpoints

- Overall Survival (OS)
- Incidence of second breast cancer (in contralateral breast)
- Safety and long-term tolerability of both regimens

Differences in outcome based on pathological subgroups will also be analysed and a quality of life (QOL) comparison between the two study arms undertaken (using the FACT-ES questionnaire).

Study design

Phase III, open label, randomised, multicentre, international trial.

Subject numbers

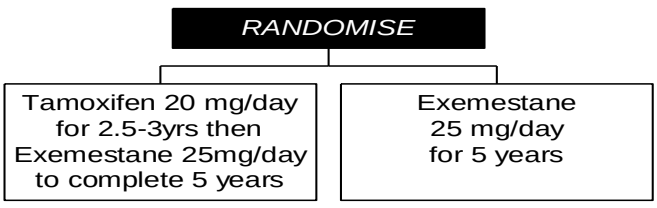
8740 subjects globally, 1240 from the UK/ROI.

Main selection criteria

Women with a histological/cytological diagnosis of early invasive breast carcinoma, completely resected, and who meet the following criteria:

- Postmenopausal
- ER/PgR-positive
- - Any node-positive cancer
  - Any cancer ≥ 3cm
  - Node-negative cancer, grade II or III and ≥ 1cm
- Adequate haematological, renal and hepatic function
- ECOG performance status 0, 1 or 2
- Patients must be randomised within 10 weeks surgery or completion of chemotherapy

Patients who fulfill the eligibility criteria



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3. BACKGROUND AND INTRODUCTION

Preface

The ***TEAM*** trial was designed in 2000/2001 and commenced recruitment in December 2001. The original trial design was to compare tamoxifen for 5 years with exemestane for 5 years in postmenopausal women with early breast cancer. Since the start of the trial a large body of information regarding third-generation aromatase inhibitors in early breast cancer has emerged and in particular data has been published demonstrating a clear Relapse Free Survival (RFS) advantage to a sequential strategy in which exemestane is introduced after 2-3 years of prior tamoxifen. As a result of this data a protocol amendment has been introduced in which patients originally randomised to tamoxifen will be recommended to switch to exemestane after 2.5-3 years of tamoxifen therapy. This protocol has been amended to incorporate this change and contains information concerning the introduction of this protocol change for existing patients recruited to the original trial design and information regarding the conduct of the trial for new patients. The new protocol also contains a number of additional revisions to update the trial conduct in accordance with recent changes in research governance.

3.1. Background - Tamoxifen

Tamoxifen has for many years been the standard hormonal treatment for postmenopausal women following complete resection of primary oestrogen receptor (ER) positive breast cancer. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has performed a meta-analysis of the randomised trials of adjuvant tamoxifen and unequivocally demonstrated the advantage of tamoxifen in improving relapse free and Overall Survival (OS) in women with ER-positive early breast cancer. The magnitude of the benefit increases with increasing duration up to 5 years. Five years of adjuvant tamoxifen reduces risk of recurrence by 47% and risk of breast cancer death by 26%.[1] This finding is supported by randomised comparisons of 2-3 years vs. 5 years of adjuvant tamoxifen, which show a further 18% reduction in risk of relapse when tamoxifen is continued for more than 2-3 years. The impact on survival in these trials requires longer term follow-up but trends towards a survival advantage are seen.[2-4]

Three trials that were designed to investigate duration of tamoxifen beyond 5 years have now reported early results[5-7]. However, the results thus far are contradictory and therefore controversial. The largest study, The National Surgical Adjuvant Breast and Bowel Project (NSABP) B14 trial[6] in node negative patients shows a significant better RFS and OS for the 5 year treatment. The Scottish trial shows a non-significant trend towards better outcome for the 5 year treatment in a population of node-positive and node-negative patients.[5] In contrast the Eastern Cooperative Oncology Group (ECOG) trial[7] has reported a benefit for continued tamoxifen. Further trials are still ongoing which will, in due course, provide definitive information as to the optimal duration of tamoxifen[8]. Based on the current evidence, 5 years of tamoxifen is considered the standard duration of adjuvant tamoxifen monotherapy treatment for postmenopausal patients.

3.2. Background – Third-generation aromatase inhibitors

Tamoxifen acts as a competitive inhibitor of oestradiol, binding directly to the oestrogen receptor (ER), where it acts as a partial agonist. The predominant action in oestrogen-sensitive breast cancer is antagonistic but partial agonist activity is clinically important in postmenopausal women, since it results in preservation of bone mineral density and has a favourable effect on lipid profile. There are however negative aspects to the partial agonist effects since these result in endometrial stimulation. Endometrial pathologies are more common with tamoxifen which leads to adverse gynaecological symptoms such as vaginal discharge, increased incidence of postmenopausal bleeding and increased incidence of endometrial cancer.

An alternative strategy to oestrogen antagonism is to deplete circulating oestrogen levels. Aromatase inhibitors act systemically to inhibit oestrogen synthesis in tissues. These compounds prevent oestrogen biosynthesis by inhibiting the aromatase enzyme, which catalyses the conversion of adrenal and ovarian androgens to oestrogens. Aromatase is most active in adipose, liver and breast tissues. The first aromatase inhibitor, aminoglutethimide (AG), was introduced in the 1970s. Although this first-generation aromatase inhibitor was effective as an adjuvant therapy in breast cancer, [9] it was poorly tolerated and was replaced by the well-tolerated second-generation aromatase inhibitor 4-OH-androstenedione (formestane). This compound however only suppresses plasma oestradiol to a third of baseline levels and requires parenteral administration.[9,10] Some years later, third-generation aromatase inhibitors were developed. They fall into two principal categories (a) non-steroidal, exemplified by fadrozole, vorozole, letrozole and anastrozole and (b) steroidal, exemplified by exemestane, (reviewed in[11-16]). Of these only anastrozole, letrozole and exemestane are commercially available for the treatment of advanced breast cancer. All three drugs have been evaluated as second-line treatment for advanced breast cancer and all have significant advantages to the comparator drug, megestrol acetate, and have become established as endocrine agents of first choice in the treatment of tamoxifen-resistant metastatic breast cancer. Comparative studies of these drugs in this indication have been inconclusive with none of the agents emerging as definitely superior.[17,18] Data is now available from randomised comparisons of all three drugs against tamoxifen as first-line treatment for advanced breast cancer. In the largest study using letrozole a clear statistically significant time to progression advantage for letrozole is apparent.[19] The comparisons with tamoxifen and anastrozole are smaller, however a combined analysis of the hormone receptor-positive subsets of two similar trials shows a significant time to progression advantage for anastrozole[20]. Preliminary data of a comparison between exemestane and tamoxifen demonstrated a borderline significant time to progression advantage for exemestane.[21] Cross- trial comparisons do not suggest that major efficacy differences exist in this setting between these agents, although small but clinically relevant differences may exist.

3.3. Background – Exemestane

Exemestane is a very potent, orally active, selective and long-lasting steroidal, irreversible inactivator of aromatase. In *in vitro* studies exemestane appeared to be 2.8 and 156 times more potent than the steroidal compound formestane and the non-steroidal compound aminoglutethimide respectively in inhibiting human placental aromatase. *In vivo* studies of aromatase inactivation indicate that exemestane, by the oral route, is several times more potent than formestane.[22,23] Exemestane has no noteworthy binding to oestrogen, progesterone, glucocorticoid or mineralocorticoid receptors and only a very low binding to the androgen receptor (Relative Binding Affinity (RBA) 0.2% of dihydrotestosterone (DHT)).[24] However, its metabolite FCE 25071 (17-hydro-exemestane) was found to have a binding affinity to the androgen receptor (100-fold higher than that of exemestane and 0.28% that of DHT, Pfizer Ltd, data on file).

Early hormonal studies in breast cancer patients, using an oestrogen assay subsequently found to suffer from non-specific interactions of exemestane metabolites (Celite-RIA), indicated for exemestane a maximal inhibition of oestrogens up to 30% of baseline levels starting from doses of 2.5-5mg daily.[6,25] However more recent results obtained, using a very specific and sensitive analytical method (HPLC-RIA), indicate that exemestane suppresses plasma oestrogens down to 6-11% of pre-treatment levels,[26,27] thus showing an activity comparable to that observed with third-generation non-steroidal aromatase inhibitors such as letrozole, and significantly more pronounced than that of formestane.

Recent *in vitro* and clinical data on intratumoural and peripheral aromatase inhibition indicate that the drug is a potent inhibitor of the enzyme. *In vitro*, exemestane inhibits the aromatase

enzyme in human placenta, in adipose breast tissue and in tumour tissue, at concentrations of 1000nM, to 5%, 13% and 15% of the baseline values respectively. In patients, the drug inhibits peripheral aromatisation down to 2.2% of the baseline after 8 weeks of treatment with 25mg daily (Pfizer Ltd, data on file), which is considered to be the standard dose. These results are in line with or superior to the ones obtained with other non-steroidal aromatase inhibitors such as anastrozole or letrozole, and are consistent with the efficacy data thus far obtained in phase I and phase II studies.

Exemestane trial results in advanced disease

Phase I studies: In total 137 patients have been treated with exemestane at various daily doses (up to 600 mg) and no Maximum Tolerated Dose (MTD) was determined, whereas 25 objective responses have been observed (18%).

Phase II studies: Four multicentre, multinational, phase II trials in second (tamoxifen failures) or third-line treatment (tamoxifen and megestrol acetate or tamoxifen and aminoglutethimide failures) have been completed, enrolling 437 patients (Pfizer Ltd, data on file).

In total 265 patients were accrued in the two studies (US and European), carried out at the standard dose of 25mg daily, in patients with advanced breast cancer primarily refractory to tamoxifen or progressing after initial response to tamoxifen, and in patients relapsing during or within 12 months of discontinuing adjuvant tamoxifen. Of these, 262 are currently available for response evaluation. Overall, the objective response rate (Complete Response (CR) plus Partial Response (PR)) was 23%; including patients with long-term stabilisation of disease (>24 weeks), 45% of the patients benefited from therapy (Pfizer Ltd, data on file). In the European study, the median duration of objective response was 68 weeks, of overall response (CR, PR or disease stabilisation >24 weeks) 59 weeks and the median Time To Progression (TTP) was 29 weeks; the corresponding figures in the US study were 49, 43 and 24 weeks, respectively (Pfizer Ltd, data on file).

Considering the response rate to exemestane observed in patients failing tamoxifen (21%), this is in the same range as reported in the recent phase III studies for letrozole[28] or vorozole[29], but higher than that recorded with anastrozole (1 mg daily),[30] or formestane.[31]

In a US study assessing the efficacy of exemestane (25mg daily) as third-line treatment after failure of tamoxifen and megestrol acetate, 91 patients were evaluable for response assessment. [32] Response to treatment was observed in 13% of patients with an additional 18% obtaining stable disease, >24 weeks. The median duration of objective response, overall response and TTP are currently 27, 34, and 9 weeks respectively.[32]

In total 78 patients were treated in a study assessing the efficacy of exemestane (200mg daily dose) as third-line treatment of patients progressing on aminoglutethimide, given at a daily dose of >500mg for at least 8 weeks,[33] and all of them are currently available for response evaluation. They include 33 patients unresponsive to aminoglutethimide, 39 patients who had progressed after an initial response to aminoglutethimide, and 6 patients for whom response to prior therapy was either not available or not evaluable. Overall, the objective response rate was 26% (12% in patients refractory to aminoglutethimide and 33% in the responsive ones). Disease stabilisation (>24 weeks) was achieved in an additional 13% of patients (15% of those refractory to aminoglutethimide and 13% of those responsive), the percentage of patients benefiting from therapy thus being 39% in this study. The median duration of objective response (CR plus PR), overall response (CR, PR or disease stabilisation >24 weeks) and TTP were 59, 48, and 21 weeks respectively. These results are very promising considering the fact that the patient population consisted of patients previously treated with at least two hormonal agents and that 55% of them had received, in addition, at least one line of chemotherapy. Furthermore, this study confirms

previous observations of lack of cross-resistance when steroidal aromatase inhibitors are given after non-steroidal aromatase inhibitors. [26,30]

Randomised phase III studies: Exemestane (25mg daily) was evaluated in a phase III, randomised, double-blind, multicentre, multinational, comparative study of postmenopausal women with advanced breast cancer who had disease progression after hormonal treatment with antioestrogens (primarily tamoxifen) for metastatic disease or as adjuvant therapy. Subjects were required to have measurable metastases or lytic bone disease due to breast cancer, reasonable performance, ER/Progesterone Receptor (PgR) status positive or unknown and near-normal organ function. Subjects may also have received prior cytotoxic therapy, either as adjuvant treatment or for metastatic disease. In this study (94 OEXE 018), 769 subjects were randomised to receive exemestane 25 mg once daily (n=366) or megestrol acetate 40 mg four times daily (n=403). Intent-to-treat results for randomised subjects from the study are summarised in Table 1.[34]

Exemestane 25mg/day has been compared to tamoxifen 20mg/day in first-line therapy for advanced breast cancer in the EORTC 10951 randomised phase III study. Preliminary data has been presented showing a significant response rate advantage for exemestane, 46% vs. 31% (p=0.005). Time to progression was also longer, 10 months vs. 6 months, but this was not significant in the primary analysis using a log rank test (p = 0.121) but was significant with a secondary Wilcoxon sensitivity analysis (p=0.028).[21] Exemestane was well-tolerated and comparative toxicity is summarised in Table 5.

Table 1: Efficacy results from a phase III study of postmenopausal women with advanced breast cancer whose disease had progressed after antioestrogen therapy.

Response Characteristics	**Exemestane (n=366)**	**Megestrol acetate (n=403)**	**p value**
Objective Response Rate = CR + PR (%) (95% Confidence Interval)	15.0 (11.5-19.1)	12.4 (9.4-16.0)	
Overall Success = CR + PR + SD ≥ 24 Weeks (%) (95% Confidence Interval)	37.4 (32.3-42.6)	34.6 (29.9-39.6)	
CR (%)	2.2	1.2	
PR (%)	12.8	11.2	
SD (%)	40.7	41.9	
SD ≥ 24 Weeks (%)	21.3	21.1	
PD (%)	35.0	36.2	
Other (%)*	9.3	9.4	
Median Duration of Response (weeks)	76.1	71.0	
Median Duration of Overall Success (weeks)	60.1	49.1	0.025
Median Duration of SD ≥ 24 Weeks (weeks)	48.0	46.6	
Median TTP (weeks) Hazard Ratio (Exemestane-MA) 0.84	20.3	16.6	0.037
Median TTF (weeks)	16.3	15.7	0.042
Median Overall Survival (weeks)	Not reached	123.4	0.039
75% Survival (weeks)† (95% Confidence Interval)	74.6 (59.1-91.0)	55.0 (46.1-70.3)	

*****Includes subjects who were not treated or not evaluable
†25th percentile
Abbreviations: CR = Complete Response, PD = Progressive Disease, PR = Partial Response, SD = Stable Disease (no change), TTP = Time to Tumour Progression, TTF = Time to Treatment Failure

Third-generation aromatase inhibitors in early breast cancer

All three third-generation aromatase inhibitors are the subject of intensive research in the treatment of early breast cancer. A number of studies have now published data on early results from randomised comparisons. These studies have incorporated a range of designs exploring direct comparisons with tamoxifen or combination of drugs or sequences of different drugs. Many trials are currently ongoing. The ATAC (Arimidex, Tamoxifen Alone or in Combination) study was a three-way randomised double-blind comparison of tamoxifen vs. anastrozole vs. the combination of both drugs in women with surgically resected early breast cancer. ATAC randomised over 9000 women to the three arms. This trial reported initially after a median follow-up of 33 months and a small but highly significant difference in RFS was reported with a Disease-Free Survival (DFS) Hazard Ratio (HR) of 0.83 between the tamoxifen and anastrozole arms. [35] The combination arm fared no better than tamoxifen alone and is not considered further. After updated analysis with further follow-up (47 months) the absolute difference remains small, the most pertinent difference being in the large subgroup known to be hormone receptor-positive where the HR for DFS is 0.78 (95% CI, 0.69-0.93) and translates to an absolute difference of 2.9% at 48 months.[36] The toxicity profile is in most respects favourable with fewer gynaecological problems including a reduction in endometrial cancers, fewer thromboembolic complications and fewer hot flushes. Musculoskeletal disorders are more common with anastrozole but most concerning is an increased incidence of clinical fractures compared to tamoxifen. Anastrozole is associated with loss of bone mineral density compared to bone density gain with tamoxifen.[37] At the current time no significant survival difference has emerged in this trial; anastrozole is currently licensed within the UK for the treatment of early breast cancer in women where tamoxifen is contraindicated because of increased thromboembolic risk or endometrial abnormality. In many countries however anastrozole has a much broader adjuvant licence.

Letrozole has been compared to placebo in women who have completed 5 years of adjuvant tamoxifen in the MA17 study. In this study over 5000 women were randomised. The study was terminated early on the recommendation of the data and safety monitoring committee as there was a highly statistically significant difference in RFS in favour of letrozole after a median follow-up of 27 months, HR 0.64 (95% CI, 0.52-0.79). [38] This study has been criticised for the absence of a continued tamoxifen arm, which makes clinical interpretation difficult; and since patients have been permitted to cross-over the long-term toxicity will be difficult to evaluate. Despite short follow-up a numerical but non-significant difference in fractures and osteoporosis has been reported. Letrozole has now been licensed in the UK for the treatment of early breast cancer following adjuvant tamoxifen. Since publication of the first analysis an additional 2.5 months of follow-up data has been analysed and which confirm the original findings and give credibility to the study since more patients had experienced long term exposure. While there remains no overall survival advantage, this analysis has identified a borderline statistically significant survival advantage in the lymph node-positive subgroup (p=0.04).[39]

The Intergroup Exemestane Study (IES) randomised women with early breast cancer, who were disease free after 2-3 years of prior tamoxifen therapy, to either continue to complete 5 years of adjuvant tamoxifen or to commence exemestane 25mg once daily. This double-blind study of over 4,700 patients has recently published interim findings after a median follow-up of 30 months. This study, in a different patient population, has shown a somewhat larger difference than the ATAC study with a hazard ratio of 0.68 which translates to an absolute advantage of 4.7% at 36 months.[40] Within the hormone receptor-positive subgroup the hazard ratio is reduced to 0.64 (95% CI, 0.52-0.79). In IES the majority of patients had completed therapy at the time of analysis, so although follow-up is short the results can be considered as fairly mature. However currently there is no difference in survival between the two groups in either the ATAC or the IES study and further follow-up is required to determine impact on survival. Toxicity differences in

the IES study are similar to ATAC with reduced endometrial and thromboembolic complications. Musculoskeletal complications are more common with exemestane and diarrhoea was also more common (Table 3). There were more fractures in the exemestane group than with tamoxifen but the difference is not statistically significant. A small but significantly increased rate of osteoporosis was however reported with exemestane. A very small Italian study has used the same design as the IES study but used anastrozole rather than exemestane. This study has also reported an advantage to switching to the aromatase inhibitor after 2-3 years.[41]

3.4. Safety of exemestane

An overall safety analysis has been performed on 744 postmenopausal breast cancer patients treated in the exemestane clinical program (phase I and II studies) with fixed doses ranging from 0.5 to 600 mg daily, for a median time of 4 months. Approximately 20% of them received the drug for 1 year or longer (up to 3.5 years). In total 555 patients received the dose of 25mg, which is considered the standard dose.

When events are considered in this safety analysis, that either are drug-related or from indeterminate cause, the overall frequency at the standard dose of 25mg was 49%. Reported events were mainly mild to moderate in severity using the CTC criteria. The most frequent adverse events reported were hot flushes (16%), nausea (12%), fatigue (7%) and dizziness (6%). More detailed data are shown in Table 2.

Table 2: Adverse events, either drug-related or of indeterminate cause, in postmenopausal breast cancer patients treated with exemestane in a daily dose of 25mg.

Adverse Event	**Exemestane 25 mg (n=555)**	
	%	**n**
Any Event	**49**	**274**
Hot flushes	16	88
Nausea	12	65
Fatigue	7	37
Dizziness	6	36
Increased sweating	5	30
Headache	5	29
Insomnia	3	18
Skin Rash	3	18
Anorexia	3	15
Pain	3	15
Abdominal pain	2	14
Alopecia	2	14
Vomiting	2	13
Constipation	2	9
Dyspepsia	2	9
Oedema-peripheral/leg	2	9
Asthenia	1	6
Hypertricosis	1	5
Acne	<1	4
Paresthesia	<1	4
Dysphonia	<1	2

Severe adverse events that were drug-related or from indeterminate cause were reported in only 3% of the overall patient population considered, but increased to 7% in patients treated with the 200mg dose.

Treatment discontinuation due to adverse drug reactions occurred in 1.5% of the patients. Of the 555 patients treated with the 25mg daily dose, 1% discontinued treatment for drug-related adverse reactions and only in two cases for grade 3 adverse reactions (allergic skin reaction in one case and grade 3 nausea in another). The other four patients discontinued treatment for grade 2 nausea (two cases, with concurrent grade 2 depression in one of them), grade 2 dizziness and weakness in one case and elevated liver function test in the last one.

Laboratory tests performed during clinical trials in patients with advanced disease did not indicate major side effects, apart from liver test alterations and decrease in lymphocyte count. Grade 2-3 liver function test abnormalities led to drug discontinuation in one case (0.2%).

When compared to other treatments in comparative trials, the toxicity of exemestane seems to be mild. When compared to megestrol acetate, side effects appear to be comparable or favourable for exemestane. Preliminary results indicate the same when compared with tamoxifen.[34]

Exemestane safety in early breast cancer

The IES study has provided information on the safety and tolerability of exemestane given for 2-3 years after prior tamoxifen therapy (Table 3). In general this is reassuring in comparison to continued tamoxifen, however there is an increase in the incidence of osteoporosis compared to tamoxifen.

Table 3: Adverse events in the IES study significantly different, or different by >1%, or common (>5%)

Adverse events any grade	**Exemestane % (n = 2309)**	**Tamoxifen % (n = 2332)**	**p value**
Arthralgia	5.4	3.6	**0.01**
Diarrhoea	4.3	2.3	**0.001**
Throboembolic AEs	1.0	2.0	0.01
Thromboembolic SAEs	1.3	2.4	0.005
Vaginal bleeding	4.0	5.6	**0.01**
Other gynaecological symptoms	5.8	9.0	**<0.001**
Endometrial cancer	0.21 (5 events)	0.46 (11 events)	Not stated
Other malignancy	22	42	Not stated
Cramp	2.8	4.4	**0.0007**
Sweating	18.6	18.1	
Headache	18.6	16.4	0.09
Dizziness	12.5	12.1	0.93
Visual disturbance	7.4	5.8	**0.04**
Depression	5.2	4.0	
Osteoporosis	7.4	5.7	**0.05**
Clinical fracture	3.1	2.3	0.08

Bone toxicity is clearly an important factor in the use of aromatase inhibitors in early breast cancer. Exemestane has been compared to placebo in a randomised study of postmenopausal women with invasive or pre-invasive breast cancer where the risk of recurrence was considered too small to warrant routine adjuvant treatment. In this study exemestane was associated with a

modest and non-significant difference in Bone Mineral Density (BMD) loss in the lumbar spine over 1 year, 2.2% vs. 1.8%, and a small but statistically different BMD loss at the hip, 2.7% vs. 1.5% (p= 0.02). Bone studies from IES are expected to report shortly. Currently no specific recommendations for the management of bone health in women taking aromatase inhibitors is available, however there is evidence that bone loss in premenopausal women treated with ovarian suppression and zoledronic acid can prevent BMD loss.[42] Women diagnosed with osteoporosis whilst taking aromatase inhibitors would be candidates for bisphosphonate therapy. The field of bone health in women taking adjuvant aromatase inhibitors is the subject of active research: with some patients currently enrolled in the ***TEAM*** study participating in a bone biomarker substudy and BMD studies ongoing in the Netherlands and Germany.

3.5. Safety of tamoxifen

Secondary cancers

The effect of tamoxifen on endometrial tissue has been investigated for many years. Results and conclusions however remain controversial. Effects that appear to be associated with tamoxifen treatment are: uterine fibroids, endometrial polyps, endometriosis and endometrial hyperplasia.[43-47]

Besides this, several reports associate tamoxifen treatment with increased risk of endometrial cancer. Moreover, in a very recent article from the Dutch Comprehensive Cancer Centres' Alert Group, published in The Lancet,[48] it has been reported that the risk of endometrial cancer increased with longer duration of tamoxifen use ($p<0.001$), with relative risks of 2.0 (1.2 – 3.2) for 2-5 years and 6.9 (2.4 – 19.4) for at least 5 years compared to non-users. Moreover, long-term tamoxifen users have a worse prognosis of endometrial cancers, which seems to be due to less favourable histology and higher stage.[49] However, the benefit of tamoxifen on breast cancer survival far outweighs the increased mortality from endometrial cancer.

Other adverse events

Table 4 shows the adverse events reported in the placebo-controlled NSABP B-14 trial. In this study pre- and postmenopausal patients with primary breast cancer and histologically negative axillary nodes with ER-positive tumours were randomised to either an additional 5 years of tamoxifen or 5 years placebo in a double-blind fashion. Hot flushes, vaginal discharge and irregular menses were more frequent in women who were treated with tamoxifen, whereas fluid retention and weight gain were similar in the placebo and tamoxifen treated groups. Thromboembolic phenomena were higher in the tamoxifen treated group (1.2% vs. 0.4%) and two patients in the tamoxifen treated group died of pulmonary emboli. A minority of patients may suffer severe symptoms, but these will diminish with time. Finally, less than 5% of women stop tamoxifen because of side effects.[6]

Table 4: Percentage of women who reported an adverse side effect in the NSABP-14, 5-year tamoxifen trial (20 mg daily), vs. placebo.

Adverse Effects	**Tamoxifen (%) (n = 1424)**	**Placebo (%) (n = 1420)**
Hot flushes	63.9	47.6
Weight gain (> 5%)	38.1	40.1
Fluid retention	32.4	29.7
Vaginal discharge	29.6	15.2
Nausea	25.7	23.9
Irregular menses	24.6	18.8
Weight loss (> 5%)	22.6	18.0
Skin changes	18.7	15.3
Increased blood urea nitrogen (BUN)	18.1	20.2
Diarrhoea	11.2	14.0
Increased serum glutamic-oxaloacetic transaminase (SGOT)	4.8	2.8
Increased alkaline phosphatase	3.0	4.6
Vomiting	2.1	1.7
Increased bilirubin	1.8	1.2
Increased creatinine	1.7	1.0
Thrombocytopenia*	1.5	1.2
Leucopenia**	0.4	1.1
Thrombotic events		
Deep vein thrombosis	0.8	0.3
Pulmonary embolism	0.4	0.
Superficial phlebitis	0.3	0.0

*** Defined as a platelet count of < 100,000/mm^3**
**** Defined as a wbc count of < 3,000/mm^3**

Both pre- and postmenopausal women participated in the study. These are the only side effects noted by the nearly 3,000 women involved in the trial. It should be recognised that all side effects were not experienced by all women.

3.6. Exemestane versus tamoxifen in advanced breast cancer

The largest randomised comparison of adverse events comparing exemestane and tamoxifen comes from a randomised phase III trial conducted by the EORTC Breast Cancer Cooperative Group (EORTC protocol 10951) in postmenopausal patients with metastatic breast cancer who received exemestane or tamoxifen as first line hormonal treatment.[21] Table 5 shows the results.

Table 5: Percentage of women who reported any grade toxicities in EORTC protocol 10951 where these exceed 5% in any arm.

All Grade Toxicities	**% of Patients**	
	Exemestane (n=182)	**Tamoxifen (n= 189)**
Bone pain	33	25
Nausea	17	20
Vomiting	9	7
Contipation	8	13
Diarrhoea/Constipation	9	3
Hot Flushes	36	38
Sweating	11	9
Skin	12	10
Vaginal bleeding	2	5
Vaginal discharge	2	7
Weight gain	19	14

4. TEAM STUDY RATIONALE

The good antitumour activity and safety profile of exemestane, as demonstrated in the phase II and III studies in postmenopausal women with metastatic breast cancer provided a good rationale to investigate the efficacy and safety of adjuvant exemestane in a prospective, randomised study versus the current standard tamoxifen, in postmenopausal women with ER-positive early breast cancer. The publication of the IES study has however undermined the position of tamoxifen for 5 years as the gold standard therapy. Although survival differences have not yet been established for the sequential strategy the size of the hazard ratio and absolute difference in relapse free survival accompanied by the difference in distant relapses provides a powerful rationale for considering a switch to exemestane after 2-3 years prior tamoxifen. The International and UK Steering Groups for the ***TEAM*** trial have taken the view that it is appropriate to offer patients randomised to tamoxifen within the ***TEAM*** study the opportunity to switch to exemestane after 2.5-3 years of tamoxifen. This decision has statistical implications and the trial will continue to recruit patients to achieve a new global target for recruitment.

5. TRIAL OBJECTIVES AND ENDPOINTS

Objectives To compare the efficacy and tolerability of exemestane versus tamoxifen followed by exemestane given in the adjuvant setting in postmenopausal women with ER and/or PgR-positive early breast cancer.

Endpoints

Primary Endpoint

There are 2 co- primary objectives in this study:

- To determine whether adjuvant treatment with exemestane 25 mg once daily improves the disease free survival (DFS) of postmenopausal, receptor positive, node negative or node positive breast cancer patients at 2.75 years compared with adjuvant tamoxifen 20 mg once daily for 2.5 – 3 years, followed by exemestane, 25 mg once daily for 2 – 2.5 years. DFS is defined as the time from randomisation to the earliest recorded documentation of local/regional or distant recurrence of breast cancer, new 2nd primary (contra lateral) invasive breast cancer or death from any cause

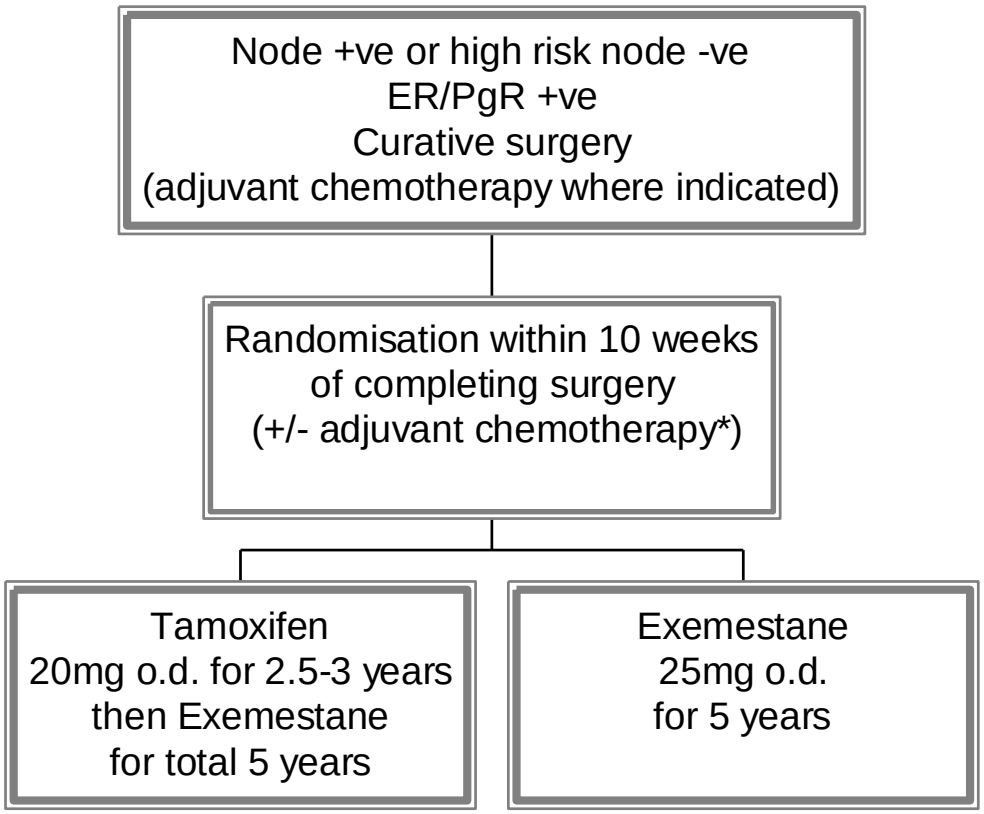
- To determine whether adjuvant treatment with exemestane 25 mg once daily improves the disease free survival (DFS) of postmenopausal, receptor positive, node negative or node positive breast cancer patients at 5 years compared with adjuvant tamoxifen 20 mg once daily for 2.5 – 3 years, followed by exemestane, 25 mg once daily for 2 – 2.5 years

Secondary Objectives

- DFS at 10 years
- Overall Survival (OS)
- The relative safety profiles
- Time from randomisation to new primary breast cancer in postmenopausal women treated with 5 years of exemestane versus tamoxifen therapy for 2.5- 3 years followed by 2.5- 2 years of exemestane.
- Differences in outcome based on pathological subgroups will also be assessed for specified participating centres/countries.
- In the first year of treatment Quality of Life (QOL) assessments in each treatment group will be made.

6. STUDY DESIGN

Phase III, open label, randomised, multicentre, international trial



*Radiotherapy to be given according to normal clinical practice

6.1. Treatment

Treatment must begin within 5 working days after the patient's registration on the study and within 10 weeks of completion of surgery, +/- chemotherapy. Radiotherapy should be given according to local policy.

Subjects will be randomised 1:1 to receive either:

- Tamoxifen, 20mg once daily, until completing at least 2.5 years therapy. Patients will switch to exemestane before completing 3 years of tamoxifen and then complete a total of 5 years endocrine therapy (treatment arm A)

or

- Exemestane, 25 mg once daily, for a minimum of 5 years (treatment arm B)

Both study drugs are registered for breast cancer and will be prescribed by the Investigator. Ongoing studies may provide important information regarding the optimum duration of endocrine therapy. It is therefore proposed to review these data as they emerge and formulate a recommendation for treatment following the 5-year time period. The possibility of a second randomisation may be appropriate.

6.2. Evaluation schedule

After randomisation patients will visit the hospital every 3 months during the first year and according to local policy thereafter, with at least yearly follow-up visits for at least 10 years.

At each visit, adverse effects will be recorded, physical examination will be performed, and concomitant medication will be registered. Mammography, blood chemistry and haematology will be assessed according to local policy.

6.3. Concomitant medication

Treatment of menopausal symptoms may be initiated as per local policy. Systemic oestrogen therapy is not recommended and when required patients should come off study.

6.4. Pathological sub-study

Detailed histopathological studies on tumour tissue will allow for potential analyses addressing the importance of conventional pathological factors (especially ER and PgR status), as well as a number of newer candidate predictive markers. These investigations will use both conventional multivariate techniques and neural network analysis. See Appendix for more information.

6.5. Registration of relapse and death

In the case of any relapse the adjuvant treatment must be stopped, and this is registered as an event. Full details of relapse should be recorded on the trial Case Report Form (CRF) and returned to the CRCTU. A summary of treatment offered at relapse will also be requested. Any malignant contralateral breast cancer will be registered as a second primary, and relapse with supraclavicular disease will be registered as distant relapse, unless otherwise specifically indicated.

'Breast cancer' deaths will be all deaths with breast cancer specified as a cause of death and deaths from any cause following a distant relapse.

All patients will be evaluated for endpoints in the treatment arm to which they were randomised, irrespective of the treatment they actually received. No patient will be removed from the analyses, irrespective of whether she is found to have violated an eligibility criterion after randomisation or to have been withdrawn from trial medication prematurely. Thus analysis will be by "intention-to-treat", including all patients randomised.

6.6. Premature discontinuation

Patients will be withdrawn from the trial if, in the opinion of the Investigator, it is medically necessary or if it is the wish of the patient. If a patient does not return for a scheduled visit every effort should be made to contact the patient. In any circumstance, every effort should be made to document the patient's outcome. Particularly, if a patient requests withdrawal from the trial the patient must be asked whether she accepts that her clinical data will continue to be used for trial purposes (in particular, details of disease-related events and follow-up).

Patients will discontinue study treatment in the case of any relapse. Treatment after relapse is at the discretion of the Investigator. Other reasons for a patient to discontinue treatment will be the withdrawal of consent or experience of unacceptable toxicity. There will be no dose modification and the patient will be discontinued from trial treatment should any unacceptable event occur. Information about discontinuation should be recorded in the CRF, and the CRCTU must be informed. **All patients will continue to be followed-up, irrespective of whether they have discontinued treatment prematurely or not.**

6.7. Quality of life (QOL) sub-study

A quality of life evaluation has been conducted in patients already enrolled in the study and further enrolment in the QOL study is not required.

7. SELECTION OF SUBJECTS

7.1. Inclusion criteria

The study population consists of postmenopausal women diagnosed with resectable breast cancer, meeting all of the following eligibility criteria:

- Histologically/cytologically confirmed early adenocarcinoma of the breast, completely excised by surgery with curative intent (Ro) including:

  -Any node-positive cancer

  -Any cancer ≥ 3cm

  -Node negative cancer, grade II or III and ≥ 1cm

- ER and/or PgR status positive (as defined by local institutional laboratory)
- Postmenopausal defined as:

  Any age: - bilateral surgical oophorectomy

  - amenorrhea ≥ 5 years (any cause)

  - FSH within institutional postmenopausal range

  Age ≥ 50 y: - natural amenorrhea for ≥ 1 year, or fulfilling criteria for <50

  - radiation-induced amenorrhea (radiation completed at least 3 months earlier)

  Age < 50 y: - If amenorrhea < 5 years (any cause) or hysterectomy without bilateral surgical oophorectomy, then FSH must be assayed to confirm postmenopausal status

- Patients on hormone replacement therapy (HRT) which was discontinued at least 4 weeks prior to randomisation are eligible for inclusion
- Adequate haematological, renal and hepatic function (defined as PLT > $100x10^9$/L, WBC> $3x\ 10^9$/L, Creatinine< 1.5 UNL and SGOT (AST) or SGPT (ALT) < 2.5 UNL). Normal hepatic function as defined as normal LFTs, or if LFTs were not normal then liver imaging must be normal
- Accessible for follow-up for the duration of the trial
- ECOG performance status 0, 1 or 2
- Written informed consent (according to ICH/GCP and local IRB guidelines)
- Within 10 weeks of completing surgery +/- adjuvant chemotherapy
- Patient has had a chest X-ray which showed no evidence of metastases (performed prior to randomisation and no more than 1 month before definitive surgery)

7.2. Exclusion criteria

Those patients with:

- Positive supraclavicular nodes
- Evidence of distant metastases (M1)
- Patients whose chemotherapy was started more than 10 weeks after completion of primary surgery
- Patients who have received previous hormonal treatment as adjuvant treatment for breast cancer
- Patients who have received neoadjuvant chemotherapy
- Neoadjuvant hormone therapy > 4 weeks duration prior to surgery
- Severe osteoporosis (bisphosphonates for therapeutic use is not an exclusion criterion)
- Uncontrolled cardiac disease including unstable angina, CHF or arrhythmia requiring medical therapy or with a history of myocardial infarction within the past 3 months or any other serious concomitant disease
- Psychiatric disorders preventing proper informed consent
- Concomitant malignancies except for adequately treated carcinoma *in situ* of the uterine cervix or basal cell carcinoma of the skin. Patients with other malignancies must be disease free for at least 5 years
- Concurrent participation in another clinical study (with the exception of adjuvant cytotoxic chemotherapy trials) involving investigational agents that may interfere with the results of the trial
- Other serious illnesses that may interfere with subject compliance, adequate informed consent or determination of causality of adverse events
- Patients on HRT, which was not discontinued at least 4 weeks prior to randomisation
- Node-negative, grade I cancer < 3cm

8. TRIAL ADMINISTRATION & DATA MANAGEMENT

8.1. Data management

Randomisation

The Investigator must complete a randomisation from prior to randomisation. These details should be phoned or faxed through to the randomisation office at the CRCTU on:

R A N D O M I S A T I O N OFFICE

☎: 0800 371 969 or 0800 731 7625

Fax: 0800 328 6412

(9am-5pm, Monday to Friday)

During the randomisation procedure all eligibility criteria will be confirmed. At the end of the procedure the treatment will be randomly allocated to the patients using a random permuted block method. A sequential Trial Number (TNO) will also be given. This number and the allocated treatment must be recorded on the randomisation form, along with the randomisation date. The randomisation form must be signed by the Investigator and retained in the patient's notes. Confirmation will be sent to the Investigator and the pharmacy of the allocated medication.

Case Report Forms (CRFs) - Data Flow

The CRFs must be completed and signed/dated by the Investigator or one of their authorised staff members as soon as the requested information is available. CRFs will contain common information, but this information will be kept to a minimum. The time between the patient's visit and completion and return of CRF pages should be kept to a reasonable minimum. In all cases it remains the responsibility of the Investigator to check that original CRFs are sent to the CRCTU and to verify that they are completed correctly. The CRFs will be in the form of individual pages, which may be replicated and stored within the Investigator Site File (research folder or patient's notes) and serve as source documents. After completion the original CRF pages must be sent in the prepaid envelope provided to the CRCTU, with copies of the CRFs also stored at site. All sections are to be completed on the CRFs before returning to the CRCTU. If information is not known, this must be clearly indicated by entering NK on the form.

CRFs will include:

- Randomisation form
- On-study form
- Pathology form
- Follow-up forms
- Adverse Event (AE)/Serious Adverse Event (SAE) forms

To enable monitoring, peer review and/or audits from Health Authorities, the Investigator must agree to keep records, including the identity of all participating subjects (sufficient information to link records e.g. CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs and detailed records of drug disposition. To comply with international regulations these records should be retained by the Investigator for 15 years, including assessments such as CT scans.

9. MONITORING

TEAM is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit, at The University of Birmingham according to the current guidelines for Good Clinical Practice. Participating centres will be monitored by CRCTU staff to confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki (Appendix 4).

All clinical Investigators taking part in the trial will be asked to sign a commitment statement and supply a current CV to the CRCTU. All clinic personnel should attend a start-up meeting/initiation visit for training on study procedures and data collection methods. The lead Investigator must submit this protocol, any supporting documentation, and any subsequent amendments to a Local Research Ethics Committee (LREC) and, if locally required, Institutional Review Boards. Investigators must acquire LREC approval and forward a copy of the written LREC approval letter, signed by the Chairman, to the CRCTU before they commence recruitment.

All participating centres will be visited by the CRCTU monitoring team shortly after they begin recruiting, and at the mid- and end-points of the study. The ***TEAM*** Trial Coordinator will be in regular contact with centre personnel (by phone/fax/email/letter) to check on progress and any

queries that they may have. Study staff will check incoming forms for compliance with the protocol, consistent data, missing data and timing. Investigators will allow the monitors access to source documents as requested. If required the monitoring team will visit centres on a more frequent basis. Centres may be barred from further recruitment in the event of serious and persistent non-compliance and/or very poor recruitment.

A pre-study and/or site initiation visit to determine the qualifications of the Investigator(s), to inspect the clinical laboratory facilities, and to fully inform the Investigator of their responsibilities and the procedures for assuring adequate and correct documentation may be conducted on behalf of the UK ***TEAM*** Steering Committee, if deemed necessary.

Monitoring of the individual centres will take place on a regular pre-determined basis, but monitoring will be confined to a minimum.

Data to be verified will include Informed Consent, eligibility, adverse events and outcome. Any major problems identified during monitoring will be reported to the UK ***TEAM*** Steering Committee.

All records will be maintained in accordance with local regulations and in a manner that ensures security and confidentiality.

The completed original CRFs are the sole property of the UK ***TEAM*** Steering Committee and should not be made available in any form to third parties (except for authorised representatives of appropriate Health/Regulatory Authorities) without written permission from the UK ***TEAM*** Steering Committee.

10. ASSESSMENTS AND FOLLOW-UP SCHEDULE

10.1. Pre-randomisation

To be recorded in the patient notes if not included on the CRFs

- Relevant medical history
- Serious acute or chronic conditions
- Cardiac history
- Thromboembolic history
- Rheumatological history
- Demography (date of birth)
- Concomitant medication (description of other medication prescribed for more than 7 days and taken within one month of randomisation)
- Clinical examination including height and body weight
- ECOG performance status

10.2. On-study

To be recorded in the patient notes if not included on the CRFs

- Relevant medical history (relevant surgical resections, conditions that need medical intervention e.g. cardiac ischaemia or arrythmia, COPD, gastric ulcer etc.)
- Clinical examination including vital signs and body weight (Appendix 1)
- WBC with differential and platelet count and blood chemistry (creatinine, bilirubin, AST and/or ALT, calcium, alkaline phosphatase and glucose)

- Concomitant medication (other medication prescribed for more than 7 days) and adverse events
- Mammography (performed according to local policy)
- Other tests at the discretion of the Investigator
- During the first year only (at baseline and months 3 and 12) the QOL questionnaire will be completed (applicable to previously randomised patients only)

10.3. Follow-up evaluation schedule

After randomisation, patients will visit the centre every 3 months for the first year and have long-term follow-up of at least 10 years irrespective of whether they have withdrawn from treatment prematurely. Follow-up data should include sites of recurrence, time of recurrence, subsequent treatment, mortality, and cause of death. Information on second primary breast cancers and other second primary tumours will also be recorded.

During follow-up visits at 1 to 5 years, physical examination will be performed, concomitant medication will be registered and adverse events (if any) will be recorded. Mammography, blood chemistry and haematology will be assessed according to local policy. During follow-up visits at 6 to 10 years patients will be seen according to local policy.

Figure 1: Trial Data Flowchart

Year						**Follow-up (year 1 to 5)**	**Follow-up (year 6 to 10)**
Visit	1	2	3	4	5	6-10	11-15
Within months	0	3	6	9	12	12-60	60 - 120
Medical history	X						
Initial data[1]	X						
Clinical examination	X	X	X	X	X	X	Follow-up should be carried out annually according to local policy
Events (if present)		X	X	X	X	X	
Co-medication[2]	X	X	X	X	X	X	
Adverse Events/SAEs[3]	X	X	X	X	X	X[4]	
Mammography	X					Local policy	
Quality of Life (QOL)	X	X			X		

Notes:

1. Type of primary surgery, tumour pathology and characteristics, pre-existing medical conditions.

2. Any medication **prescribed** and used for more than 7 consecutive days.

3. As described in section 12, 'Adverse Events'.

4. After completion of study treatment, adverse events need only be recorded if they occur within 30 days of the last dose of study medication (section 12).

10.4. Follow-up

All patients should have long-term follow-up, irrespective of whether they have been withdrawn from treatment prematurely. The anticipated follow-up frequency is once every year, unless otherwise clinically indicated. Follow-up after relapse should be according to local policy.

Should a patient be discharged to GP care or another hospital, a Transfer of Follow-up Form must be completed. Thereafter, follow up information must be collected from these sources on an annual basis and sent to the Trials Office. Should the GP or other hospital be unable to provide this information the Trials Office should be informed.

To be recorded:

- Trial events (end-points)
- Survival
- Important information relevant for the trial (unforeseen circumstance that may have led to changes in interpretation of the results, for instance, cause of death)

Note: Disease relapse is defined as the appearance of locoregional recurrence (in a patient with a mastectomy) or distant metastases at any site. Ipsilateral recurrence in a patient treated by lumpectomy or contralateral new breast cancers are not considered as relapses. Time to first locoregional recurrence or distant recurrence will be recorded on separate parts of the CRF. In the event of relapse (locoregional for mastectomy or any distant site), adjuvant hormonal treatment must be stopped. For patients with a lumpectomy and ipsilateral recurrence without distant relapse and for patients with new contralateral breast cancers, adjuvant hormonal treatment may continue at the discretion of the Investigator. All patients must be followed-up, irrespective of whether their recurrence is distant, local or consists of a second (breast) primary. Date of suspicion of relapse, action taken to confirm relapse and date of relapse confirmation will all be recorded on the CRF.

Events that should be recorded are:

- Locoregional recurrence
- Contralateral recurrence (new primary)
- Supraclavicular nodal relapse
- Distant relapse
- Death and cause of death (breast cancer/other)
- Other second malignancies
- (Serious) Adverse Events

10.5. Procedure for introducing protocol change

Patients currently enrolled in the ***TEAM*** trial should be informed of the change in trial design and the reasons for this. All patients currently on allocated study therapy should be provided with the Patient Information Sheet (for current participants). Different Patient Information Sheets are available for patients allocated tamoxifen and those allocated exemestane. All patients should be requested to complete and sign a new Consent Form.

Patients currently taking exemestane will continue their planned therapy without alteration. Patients currently taking tamoxifen should be supplied with exemestane no earlier than 30 months from randomisation and no later than 36 months. Patients who will reach the switch window limit before the next scheduled visit should be recalled early. All other patients should be informed at their next follow-up visit. There is no requirement for additional visits or postal contact, however individual Investigators may wish to contact patients and invite them to discuss the change early.

10.6. End of Study

For the purposes of Clinical Trial Authorisation (CTA) under the European Union Directive 2001/20/EC, the study is deemed to have ended 30 days after the last patient receives the last dose of the Investigational Medicinal Product (IMP).

For the purposes of Multicentre Research Ethics Committee approval, the study end date is deemed to be the 6 months after the date of last data capture.

11. WITHDRAWAL

Patients have the right to withdraw from the study at any time for any reason. The Investigator also has the right to withdraw patients from the study. Full details of the reasons for withdrawal should be recorded on the CRF if clinician initiated, otherwise a simple statement reflecting patient preference will suffice. Withdrawn patients should continue to be followed-up in accordance with the protocol with their permission.

A patient will be withdrawn from the trial if any of the following occur:

- Relapse (appearance of metastatic cancer)
- The patient, in the opinion of the treating physician, is unable to tolerate the toxicity resulting from the hormonal treatment
- Non-adherence with protocol/treatment
- Refusal and/or reservations of the patient to continue treatment or withdrawal of consent.
- Patient lost to follow-up

The date and reason for discontinuation must be recorded on the CRF. Every effort should be made to complete the appropriate assessments.

12. ADVERSE EVENTS: DEFINITIONS AND REPORTING

12.1. Procedures for collecting Adverse Events

All medical occurrences (which meet any of the following definitions) from the first dose of Investigational Medicinal Product (IMP) to 30 days after the last dose of IMP should be reported as adverse events and must be accurately recorded on the appropriate trial CRF and sent to the ***TEAM*** study office.

In addition, any known untoward event that occurs subsequent to the adverse event-reporting period that the Investigator assesses as possibly related to the IMP should also be considered an adverse event and reported accordingly.

Toxicities will be reviewed using the National Cancer Institute Common Toxicity Criteria (NCI CTC version 2.0). Appendix 5 shows a selection of the NCI CTC; a full list can be found in your Investigator Site File or you can request a copy from the CRCTU. Any toxicities incurred but not categorised by the NCI CTC should be graded by the physician and be recorded on the CRF using a scale of (1) mild, (2) moderate or (3) severe (as defined in Appendix 6). For each sign/symptoms, the highest grade observed since the last visit should be recorded.

Please note the following:

- **A pre-existing condition should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event-reporting period**
- **Symptoms of the targeted cancer or relapse with breast cancer (relapse being a study endpoint) should not be reported as adverse events**

12.2. Adverse event definitions

Adverse Event (AE)

An Adverse Event (AE) is defined as any unfavourable and unintended sign, symptom or disease in a clinical trial subject temporarily associated with the use an Investigational Medicinal Product (IMP); the event need not have a causal relationship to the IMP.

Adverse Reaction (AR)

An Adverse Reaction (AR) is defined as all untoward and unintended responses to an IMP related to any dose administered. An AR is therefore an adverse event where a possible causal relationship between the IMP and the adverse event cannot be ruled out.

Unexpected Adverse Reaction (UAR)

An Unexpected Adverse Reaction (UAR) is defined as an AR that in nature or severity is not consistent with the applicable product information (e.g. is not listed as a known toxicity in the protocol, the Consent Form, the package insert, the Investigator File, Investigator Brochure or Summary of Product Characteristics).

Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) is defined as any medical occurrence that at any dose is fatal or life-threatening (i.e. results in an immediate risk of death); is permanently or substantially disabling; requires or prolongs hospitalisation (only if related to an unexpected complication); or is a congenital anomaly, a new primary cancer (excluding breast cancer) or medication overdose. This category also includes any other event the Investigator judges to be serious or which would suggest a significant hazard, contra-indication, side effect or precaution.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is defined as a SAR that has not been previously documented in the product literature, the nature and severity not being consistent with the product information.

12.3. Recording and reporting Serious Adverse Events

In the case of a SAE (SAR/SUSAR) the Investigator must **immediately** on becoming aware of the event:

- **Complete a 'Serious Adverse Event Form'**. This should contain all of the information known at the time of the report
- **Fax** within 24 hours of becoming aware of the event the signed and dated 'Serious Adverse Event Form' to the ***TEAM*** study office at the CRCTU, Birmingham: **UK Fax: 0800 328 6412**

- **Telephone** (on day of awareness) the ***TEAM*** study office at the CRCTU, Birmingham in the case of death or life-threatening events: ☎: **0121 414 3797** (**Mon-Fri, 9am –5pm)**
- In addition, send by post the original copy of the SAE form and ensure that the reporting clinician has signed/dated it.

The ***TEAM*** study office will inform Pfizer UK who will notify the relevant regulatory authorities (MHRA/IMB). The ***TEAM*** study office (with the consultation of the Chief Investigator) will inform the Multicentre Research Ethics Committee (MREC), each centre should inform their Local Research Ethics Committee (LREC) of SAEs. The annual report (detailed in section17 - Ethical Requirements) contains details of SAEs; this report will be sent to MREC and participating centres, which should then send this report to their LREC as soon possible.

12.4. Follow-up of AEs/SAEs

All AEs will be recorded on the CRFs until 30 days after the last treatment dose on study or until the start of other anti-cancer treatment, whichever occurs first. Additionally, all AEs deemed possibly related to the trial medication (exemestane or tamoxifen) will be followed until resolution, or the Investigator assesses them to be chronic or stable, or initiation of other anti-cancer therapy, whichever occurs first**.**

In the case of a SAE, the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Follow-up information can be added to the original (or copies) of the initial SAE form. Extra annotated information and/or copies of test results may be provided separately.

13. DRUG SUPPLIES

Tamoxifen prescribing should be initiated by the Investigator, and continued supply arranged according to normal local practice.

Exemestane treatment should be initiated by the Investigator, with drug supply for the entire treatment period arranged through the participating hospital pharmacy. In the first year of treatment the patient will receive three monthly supplies of exemestane, corresponding to the frequency of follow-up visits required. Thereafter the patient will be given up to six months supply of exemestane at a time. The medication will be commercial stock in standard packaging. The pharmacist should label the drugs on receipt.

14. DETERMINATION OF EFFICACY

Patients on both treatment arms are followed-up at specified intervals and evaluated for evidence of relapse. Required evaluations at each time-point are specified in Section 10.3 of this protocol.

14.1. Disease-Free Survival (DFS)

Disease-Free Survival (DFS) is defined as the time from randomization to the earliest recorded documentation of local/regional or distant recurrence of breast cancer, new 2nd primary (contralateral) invasive breast cancer or death from any cause. Patients who have not had any such event (relapse or death) at the time of data analysis will be censored at 2.75 years for the first co-primary endpoint and at the last date they were known to be event-free for the 2nd co-primary endpoint and the secondary endpoints. Kaplan-Meier estimates of the survival curves for each treatment arm (including medians and 95% confidence intervals) as well as the result of the log-rank test will be presented.

14.2. Overall Survival (OS)

OS is defined as the time from first trial drug administration to date of death. In the absence of confirmation of death, survival time will be censored to last date of follow-up.

15. STATISTICAL CONSIDERATIONS

15.1. Organisation of the TEAM trial

The ***TEAM*** trial is a single trial consisting of 7 separately managed country-specific trials within 8 participating countries. Each country has its own protocol, CRFs and database. The trials are very similar to each other in design, with efforts made to ensure that data are compatible. The countries have their own sub-studies asking questions which will be answered with their own patients. Each countries trial data will be collated by the Central Data Centre and primary and secondary efficacy analyses and safety analyses will be carried out centrally. Each country-specific trial has a Chief Investigator and a Country Trial Steering Committee.

The overall trial is managed by an International Steering Committee consisting of all of the Chief Investigators, a statistician from the Central Data Centre and representatives from Pfizer Inc. There is an Independent Data Monitoring Committee consisting of a biostatistician and 4 oncologists, 2 each from Europe and North America who meet regularly to evaluate the progress of the trial and make recommendations on whether to continue. There is also a sub-committee of the Steering Committee called the Data Management Committee, which consists of 4 of the Chief Investigators, the biostatistician from the Central Data Centre and representatives of Pfizer Inc.

The Central Data Centre is located at the Leiden University Medical Centre in the Netherlands. Data from all countries involved is collected in/transferred to the central database on a regular basis prior to DMC and Steering Committee meetings.

15.2. Hypothesis and sample size

In the amended protocol (27th October 2004), patients in the tamoxifen arm are assumed to switch to exemestane after 2¾ years (range from 2½ -3 years) of treatment with tamoxifen. The main goals of this study are to compare the DFS among patients who received either exemestane 25 mg or tamoxifen for 2.5- 3 years followed by 2.5- 2 years of exemestane for 2.75 years (i.e. 33 months), and for 5 years. Overall survival and DFS at 10 years will be evaluated. The safety for both arms at 2.75 years and 5 years will also be assessed.

The ATAC paper provided updated information comparing tamoxifen and anastrozole.[36] The 3-year DFS rate was estimated to be approximately 90% for the tamoxifen arm (i.e., Arm B before switch). If the hazard ratio of DFS is assumed to be 1.28 between the two treatment arms (Arm B / Arm A), **723 events** will achieve 87% power to detect the corresponding difference in DFS with a two-sided significance level of 0.0298. Assuming constant exponential rates in both groups with a hazard ratio of 1.28), **9300 patients (4650 in each group) are sufficient in order to observe these 723 events after each subject is followed for 2.75 years.** The Independent Data Monitoring Committee, as part of their evaluation of the progress of the trial, will review an interim analysis at the time 50% of the events are reported for the first co-primary endpoint, at or before 2.75 years form the time of randomization.

The entire TEAM trial will accrue a total of 9300 patients in order to observe 723 DFS events at 2.75 years (33 months). UK will contribute approximately 1200 patients.

Timing of the first primary analysis of DFS: approximately 2¾ years after the last patient has been enrolled when there will be at least 723 events. Based on this, the following hypotheses are stated:

A: under the null-hypothesis (H_0) if there is no difference between the two treatments, assuming the 3-year DFS is 90%, then: treatment arm A (tamoxifen) and treatment arm B (exemestane) will show a 3 years DFS of 90%.

B: under the alternative hypothesis (H_1) the HR is 1.28 for the first 2¾ years and hence (H_0) is rejected.

15.3. Rationale for type of analysis and trial organisation

This country-specific study is designed to be a part of a larger group of studies that will be pooled in order to test DFS and OS. A total of 723 events are needed in order to test for a reduction in the DFS between the two treatment arms when the true hazard ratio is 1.28.

The rationale for testing using multiple studies and testing using a pooled analysis as opposed to conducting one large multi-national study is that many additional questions of interest that do not require such a large sample size can be answered. The reporting of one study's main objective will not be delayed while waiting for the other studies to finish and therefore, not delaying the release of important clinical results. In addition, the CRFs will be more manageable and data clean up will be simplified.

The data from all the trials will be collected periodically throughout the trial and stored in a central database located at the Leiden University Medical Center in the Netherlands. Interim and final analyses for the combined trial will be conducted in this central location.

There are six major areas in which a meta-analysis might lead to misinterpretation: study design, combinability, heterogeneity of studies, statistical analysis, sensitivity analysis and control of bias. The confidence one places in the results of any such meta-analysis is limited by the combinability of the studies; that is inherent differences in design, sample, and endpoints. Thus, the greater the similarities of the studies with regard to those points, the greater the confidence one may have in the results of a meta-analysis.

The ***TEAM*** trial, of which this trial is a part, is different from trials usually analysed with meta-analytic methods. The data in this trial can be pooled because the studies will all be similar in patient population, design, duration, endpoints, and will use similar forms for data collection. Care will be taken to test for heterogeneity of studies and to incorporate any such heterogeneity into the statistical analysis. As this is a pre-specified pooling it will not be subject to the usual issues facing a meta-analysis such as publication bias (the phenomenon in which studies with positive results are more likely to be published than studies with negative results), which is often the largest bias of meta-analysis results.

15.4. Efficacy analysis

15.4.1 First co-primary efficacy analysis

The first co-primary efficacy endpoint will be the DFS at 2.75 years post-treatment (before tamoxifen arm switching to exemestane), as estimated from the Kaplan-Meier curves for each

treatment arm. The difference in DFS will be assessed using the log-rank test at the 5% significance level, with a 90% power to detect absolute differences of 2%-3%.

15.4.2 Second co-primary efficacy analysis

The second co-primary efficacy endpoint will be DFS at 5 years post-treatment as a point estimate obtained from the Kaplan-Meier survival estimates of the two treatment arms. The difference in 5-years DFS between the treatment arms will be reported, along with its standard error (SE) and an associated 95% confidence interval. . In addition, patients will be followed up for a minimum of 10 years and long term outcomes will be reported.

15.4.3 Secondary efficacy analysis

The secondary efficacy endpoints will be 5 and 10 years overall survival and 10 years disease free survival, comparing exemestane vs. tamoxifen followed by exemestane as estimated from the Kaplan-Meier curves for each treatment arm. The difference in 5 and 10 overall survival and 10 years disease free survival between the treatment arms will be reported, along with its standard error (SE) and an associated 95% confidence interval. In addition, patients will be followed up for a minimum of 10 years and long term outcomes will be reported.

For the primary efficacy analyses, Cox regression models will be used to explore the influence of stratification and prognostic factors on DFS. Each factor will be evaluated for inclusion in the multivariate model, and only factors significant at the 10% level will be considered. The secondary efficacy analysis, i.e. the results of the patients who received both medications sequentially due to the "cross-over" design, will be analysed on an exploratory basis since the proportional hazards model may not be appropriate for these patients.

15.5. Safety analysis

Safety analyses will include all randomised subjects who received at least one dose of study medication. Adverse events will be recorded and graded according to the CTC classification system (Appendix 5 shows a selection).

The frequency and percentage of patients experiencing a specific adverse event will be tabulated by treatment group. Adverse events will be summarised by worst CTC grade and reported relationship with study group. In the cases that the adverse events or event frequencies are judged to be clinically important, a Chi-square test will be used to analyse the difference between the treatment groups.

15.6. Interim Analysis

The entire TEAM trial will accrue a total of 9300 patients in order to observe 723 DFS events in the first co-primary endpoint at 2.75 years. Safety analyses will be reported to the Independent Data Monitoring Committee (IDMC) every 6 months without evaluation of efficacy. The number of efficacy events will be monitored centrally every 3 months and reported to the IDMB. One interim efficacy analysis is planned for the first co-primary endpoint, to be reviewed by the IDMC. As part of their evaluation of the progress of the trial, they will review an interim analysis of the combined TEAM trial at the time 50% of the events are reported for the first co-primary endpoint, at or before 2.75 years form the time of randomization when half of the required number of DFS events for the first co-primary endpoint have occurred. These unblinded data will only be reviewed by IDMC members. The primary objective of the interim analysis is the early detection of either alarming side effects, intolerability to the treatment regimens, or of large differences in treatment effects.

The overall alpha-level for the first co-primary analysis will be maintained at 0.0302

using an O'Brien-Fleming-type alpha-spending function. The levels of significance at the interim analysis and at the final analysis for the first co-primary endpoint are 0.0012 and 0.0298, respectively.**15.7 Stratification**

At randomisation, patients will be stratified by the following groups:

- **Nodal status:** node-negative, 1-3 positive nodes, 4 plus positive nodes
- **Prior chemotherapy:** none, anthracyclines, taxanes, other

16. DATA AND SAFETY MONITORING COMMITTEE (DSMC)

The analyses will be supplied to an independent International DSMC who will be asked to give advice on whether the accumulated data from this trial, together with the results from other relevant trials, justifies the continuing recruitment of further patients. This committee will meet annually; depending on the rate of accrual and events rates. The DSMC will monitor recruitment to the trial and protocol compliance as well as tolerability and SAEs. The main outcomes will be analysed as stated in the analysis plan (Section 15).

17. ETHICAL REQUIREMENTS

17.1. Ethical conduct of the study

This study will be carried out in accordance with the World Medical Association (WMA) Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments (Appendix 4). The declaration of Helsinki can be found on the World Medical Association website: http://www.wma.net

The protocol will be approved by a Multicentre Research Ethics Committee (MREC). Before entering patients into the study, the responsible Investigator must ensure that the protocol has also the approval of the relevant Local Research Ethics Committee (LREC).

The ***TEAM*** study office will send an annual trial update report to the MREC, which will also be forwarded to each participating centre, together with details of their individual recruitment. It will be the responsibility of each study site to send a copy of this report onto their LRECs.

17.2. Informed Consent

It is the responsibility of the Investigator to obtain written Informed Consent (Appendices 7 & 8) in compliance with national requirements from each subject prior to entering the trial or, where relevant, prior to evaluating the subject's suitability for the study. The Patient Information Sheets will be available in electronic format from the CRCTU to enable individual hospitals to copy onto their headed paper.

Patient identification data (patient name and hospital number) will be required at randomisation to assist with long-term follow-up. The ***TEAM*** Steering Committee will preserve the confidentiality of patients taking part in this study.

17.3. Protocol amendment

Any variation in procedure from that specified in the ***TEAM*** protocol may lead to the results of the trial being questioned and in some cases rejected. Any proposed protocol change must therefore be submitted in writing to the ***TEAM*** Steering Committee. All agreed protocol amendments will be documented by the CRCTU and will be submitted to the MREC for approval prior to submission to all LRECs. Changes not pre-approved by the TEAM Steering Committee will be considered as protocol deviations. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interests of individual patients.

18. PUBLICATION POLICY

The results of the pooled analysis will be published in the name of the ***TEAM*** trial in a peer reviewed journal on behalf of all collaborators. All presentations and publications, including abstracts, relating to the main trial must be authorised by the ***TEAM*** Steering Committee. The individual countries will be allowed to publish their efficacy results, however, the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the ***TEAM*** Steering Committee decides otherwise.

Individual countries will be encouraged to publish the results of their side-studies as soon as the data are mature. The Chief Investigator and Country Trial Steering Committee will have the responsibility to make decisions about publications of these results and authorship.

19. CONCURRENT STUDIES

In the experience of the CRCTU, patients can be successfully randomised into multiple studies and, accordingly, ***TEAM*** patients can be offered the opportunity to participate in other appropriate randomised studies providing these have been approved by the appropriate Steering Committees. All Investigators will be kept up to date with information about ongoing national peer-reviewed studies.

20. SPONSORSHIP AND INDEMNITY

The University of Birmingham is the sponsor for the ***TEAM*** study.

TEAM is co-ordinated by the CRCTU at The University of Birmingham. The CRCTU does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. As this is a clinician-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry will not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available in the event of clinical negligence being proven.

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APPENDIX 1: ECOG PERFORMANCE STATUS

Status	Description
0	Asymptomatic, fully active and able to carry out all pre-disease performance without restriction.
1	Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature e.g. light housework, office work
2	Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day.
3	Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bed-ridden.
4	Completely disabled. Cannot undertake any self-care. Totally bed-ridden.

APPENDIX 2: Royal College of Pathologists Guidelines

National recommendations for assessment of steroid hormone positivity by immunostaining.

Suggested scoring system

Score for proportion staining		Score for staining intensity	
0	No nuclear staining	0	No staining
1	<1% nuclei staining	1	Weak staining
2	1–10% nuclei staining	2	Moderate staining
3	11–33% nuclei staining	3	Strong staining
4	34–66% nuclei staining		
5	67–100% nuclei staining		

Adding the two scores together gives a maximum score of 8.

(J Clin Pathol 2000; 53:634-635)

APPENDIX 3: Pathological Marker Study

Consenting Patients

Patients who consent to participation in ***TEAM*** should also be made aware that, as an integral part of this trial, tissue removed at surgery will be used in research. It will be made clear in the Consent Form that this tissue will be used only for research and such use will in no way compromise or alter the patient's diagnosis or treatment. The total amount of tissue used in this research will be less than 1 g (approximately 30-50 mg). Tissue will be used for research related to the ***TEAM*** trial as defined in the following sections. At all times results from research studies will not be linked to patient notes.

HER-2 analysis

HER-2 expression will be analysed using conventional immunohistochemistry (DAKO herceptest) on conventional tissue sections taken from the tissue block submitted by the local pathologist to the central laboratory. Sections will also be analysed for gene amplification using fluorescent in situ hybridisation. The results of the HER-2 analysis will be communicated back to the local hospital as this marker is now central to the management of many breast cancer patients.

Construction and analysis of tissue arrays and tissue sections

For each patient a representative tumour-containing fixed tissue block will be requested from the appropriate pathology laboratory. Given the amount of tissue required for these studies it is not foreseen that removal of tissue will in anyway compromise the future diagnostic evaluation of patient samples. In cases where the block sent is the only sample available from the patient, consultation with the consultant pathologist of record will be undertaken to ensure that sufficient material remains to allow future diagnostic procedures to be performed. In the rare event that there is concern that removal of cores may compromise future diagnostic testing on the patients' tumour the patient will be excluded from the pathological study. The tissue will be sent by post to the reference (banking) laboratory. On receipt each tissue block will receive a unique study identification code. Tissue from individual tumours will be stored in tissue arrays and also as standard tissue sections before the blocks are returned, if required, to the referring pathologist.

This tissue will be used to construct tissue arrays as show diagrammatically in Figure 1. Briefly, a section of tissue will be stained using Haematoxylin & Eosin (H&E) to identify areas of tumour. Three tumour areas will be selected and 6 x 0.6 mm^2 cores of tumour tissue will be removed in total from each block. These cores of tumour tissue will be transferred to multiple (6) recipient blocks (100-300 cores per block) to form tissue arrays. From each tissue array up to 300 x 5μm sections will be taken for analysis of biomarkers.

In addition, up to 20 serial 5μm tissue sections will be taken for evaluation of factors such as microvessel density and lymphocytic infiltration gene mutation analysis (on extracted DNA) etc. for which use of tissue arrays is inappropriate.

Biological Analysis of tissues

The aim of the biological studies associated with the ***TEAM*** trial is to define the underlying molecular events which relate to patient response or failure to respond to the therapies applied in the trial. Further, we will use this dataset to further our understanding of the basic molecular events in breast tumours. Our central hypothesis is that molecular modification of signal transduction pathways (e.g.HER2/EGFr) modify responsiveness of breast tumours to oestrogens and anti-oestrogens. However, future studies to elucidate molecular mechanisms relating to the

actions of exemestane on aromatase and other aspects of the steroid biosynthetic pathway are also envisaged.

Tissue arrays and sections will be analysed using immunohistochemistry (IHC) and fluorescent in situ hybridisation (FISH), to determine protein expression and gene expression respectively, using standard methodologies and commercially available reagents. Factors that we intend to evaluate include steroid receptors and genes activated via steroid receptor pathways, growth factor receptors (e.g. the HER1-4 type I receptor tyrosine kinase pathway) and modifiers of signal transduction pathways (e.g. RAS, PI3KCA, AKT etc.), factors associated with neovascularisation (vascular endothelial growth factors (VEGFs) and their receptors FLK-1 etc). Research in these areas is developing rapidly and it is not at present possible to provide an inclusive list of the factors involved and which will be relevant to this area of study.

ERα ER□, PgR and steroid receptor pathways

A key aspect of the ***TEAM*** study is the relative effect of the two agents being tested on the activation of the oestrogen receptor (ER) pathway. Oestrogen receptor status and progesterone(PgR)receptor status are key indicators of potential response to tamoxifen. Activation of these pathways may be modified by factors such as AIB1 (Amplified in Breast cancer 1) which may alter response to anti-oestrogens. This aspect of the studies would be targeted at elucidating the effects of such molecules on the activation of steroid response in treated patients.

Receptor tyrosine kinases (HER-2, EGFR etc.)

The type I receptor tyrosine kinases (HER1-4) include the most significant molecular prognostic markers identified to date in breast cancers (HER2/c-erbB-2 and HER1/EGFr). Increasing evidence from both clinical and laboratory studies suggests that modification of ER via direct phosphorylation may explain the marked difference in the impact of these factors in ER-positive and ER-negative patients. In patients treated with tamoxifen, phosphorylation of ER via HER2 may promote the agonist effects of tamoxifen and cause proliferation. Many factors in the HER signal transduction pathway (hRAS etc.) are amplified in breast cancers and may have similar effects to alterations of HER1-2. Investigation of these pathways in the context of this clinical trial may significantly improve our understanding of the mechanisms at work in patients who fail to respond to anti-oestrogenic therapies yet respond to aromatase blockade. Future studies of factors such as c-SIS and platelet derived growth factor receptor-□ (PDGF□) may provide further information on this important axis.

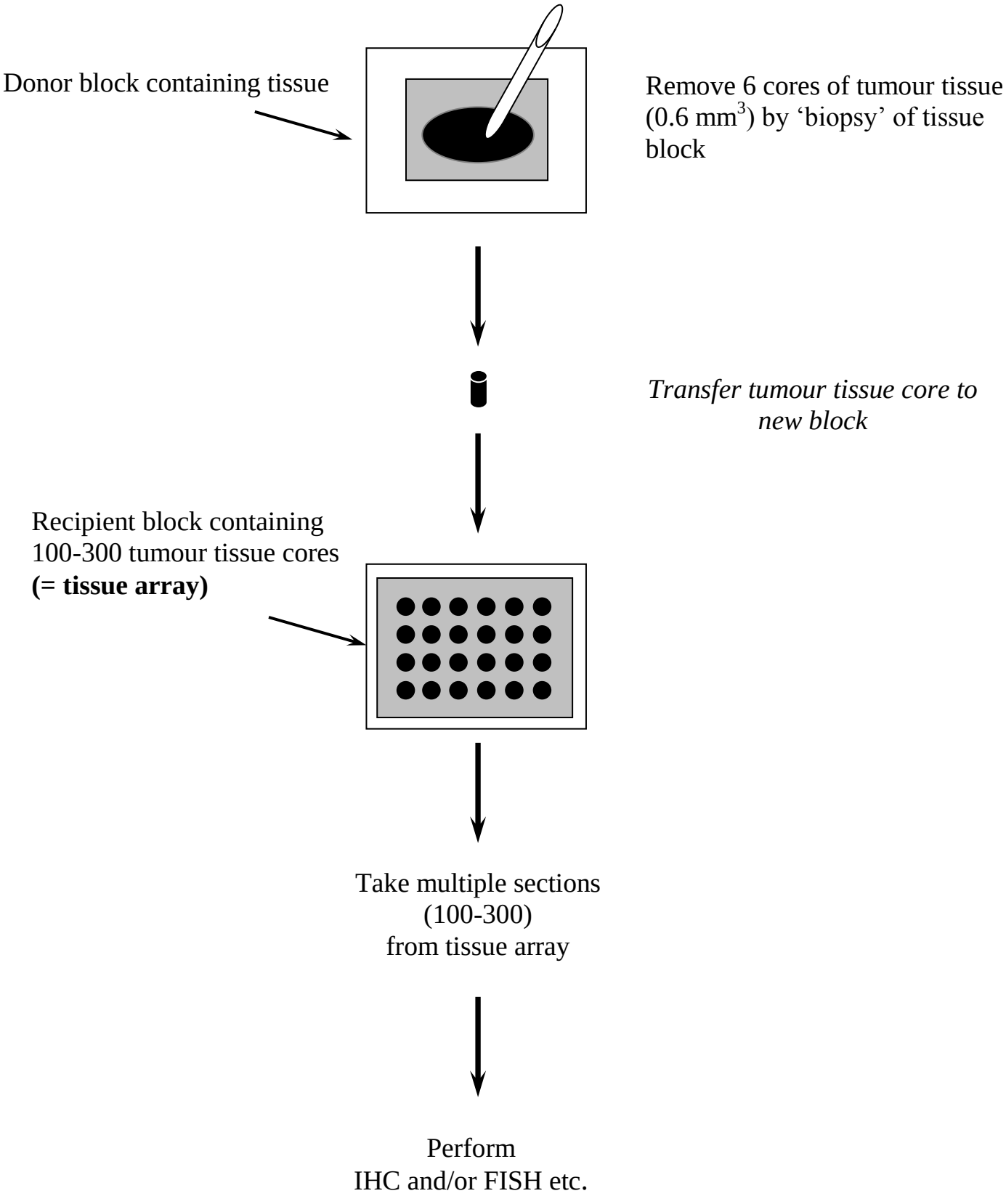
Neovascularisation associated factors. (VEGF/VEGFR)

Neovascularisatin is emerging as a crucial controller of tumour progression. New blood vessels not only supply oxygen and nutrients to tumours but promote metastasis due to their "leakiness" resulting from incomplete formation of basement membranes etc. Promotion of neovascularisation is complex involving host and tumour responses. Evidence for involvement of the HER type I receptor tyrosine kinases as well as inflammatory events mediated by tumour infiltrating lymphocytes exists. Our aim would be to elucidate the relative involvement of neovascularisation in tumour response within the context of the ***TEAM*** trial by evaluation of microvessel density using novel objective methods developed in our laboratories and by assessing expression of VEGFs and related factors known to promote new vessel formation.

Central to all of the biological studies will be the requirement to evaluate these studies in the context of patient response data. The clinical trials database held in the CRCTU will include the unique tumour identifier used for construction of the tissue arrays in the tumour-banking laboratory. Relevant patient information (response data, follow-up etc.) available at the close of

the trial will be linked to the appropriate tissue array and/or tissue section via this unique study identification code **without** the transfer of unique patient identifiers (i.e. name, hospital number etc.) held within the trials database. This will ensure that the data from pathological studies remains viable in terms of the clinical outcome of the patients whilst ensuring that those involved in pathological studies remain blinded to patient identifiers and preserving patient anonymity. Only the HER2 status, a clinical diagnostic assay, will be communicated to the clinician managing the patient.

FIGURE 1: Construction and analysis of tissue arrays



APPENDIX 4: Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October, 1975
35th WMA General Assembly, Venice, Italy, October, 1983
41st WMA General Assembly, Hong Kong, September, 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October, 1996
52nd WMA General Assembly, Edinburgh, Scotland, October, 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate,

approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly

available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix 5: Common Toxicity Criteria (CTC)

This is a selection of the CTC, the full list can be found in your Investigator folder, or you can receive a full copy by contacting the CRCTU.

Toxicity Grade	0	1	2	3	4
Cardiovascular					
Cardiac dysrhythmias	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥10% but < 20% of baseline value; shortening fraction ≥24% but <30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting LVEF ≥ 20% of baseline value; <24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
Cardiac ischaemia/ infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST + T-wave changes suggesting ischaemia	angina without evidence for infarction	acute myocardial infarction
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	with physiologic consequences	tamponade (drainage or pericardial window required)
Hypotension	none	changes, but not requiring therapy (incl. transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalisation; no physiologic consequences present	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidaemia and impairing vital organ function due to tissue hypoperfusion)
Phlebitis (superficial)	none	--	--	--	--
Thrombosis/ embolism	none	--	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Dermatological					
Alopecia	normal	mild hair loss,	pronounced hair loss	--	--
Skin (rash/desquamation)	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering <50% of body surface or localised desquamation or other lesions covering <50% of body surface area	symptomatic generalised erythroderma or macular, papular, or vesicular eruption or desquamation covering ≥50% of body surface area	generalised exfoliative dermatitis or ulcerative dermatitis
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	--
Gastrointestinal					

Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring i.v. fluids	--
Vomiting	none	1 episode in 24 hrs over pre-treatment	2-5 episodes in 24 hrs over pre-treatment	≥ 6 episodes in 24 hrs over pre-treatment, or need for i.v. fluids	requiring parenteral nutrition; or physiologic consequences requiring intensive care; haemodynamic collapse
Diarrhoea	none	increase of <4 stools/day over pre-treatment	increase of 4-6 stools /day, or nocturnal stools	increase of ≥7 stools/day, or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or haemodynamic collapse
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Stomatitis	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, oedema, or ulcers but can swallow	painful erythema, oedema, or ulcers, requiring i.v. hydration	Severe ulceration requires prophylactic intubation
Oesophagitis/ dysphagia	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring i.v. hydration	complete obstruction (cannot swallow saliva); requiring enteral or parenteral or perforation
Weight gain	< 5%	5 – <10%	10 – <20%	≥ 20%	--
Weight loss	< 5%	5 – <10%	10 – <20%	≥ 20%	--
Haematological					
WBC $\times 10^9$/L	WNL	3.0 – <LLN	≥2.0 – <3.0	≥1.0 – <2.0	< 1.0
Platelets $\times 10^9$/L	WNL	75 – <LLN	≥50 - <75	≥10 – <50	< 10
Haemoglobin g/dL g/L mmol/L	WNL WNL WNL	10.0 – <LLN 100 – <LLN 6.2 – <LLN	8.0 - <10.0 80 – <100 4.95 – <6.2	6.5 – <8.0 65 – <80 4.0 – <4.9	< 6.5 < 65 <4.0
Neutrophils/ granulocytes $\times 10^9$/L	WNL	≥1.5 – <2.0	≥1.0 – <1.5	≥0.5 – <1.0	< 0.5
Lymphocytes $\times 10^9$/L	WNL	1.0 – <LLN	≥0.5 - <1.0	<0.5	--
Infection/ fever					
Infection in absence of neutropenia	none	mild, no active treatment	moderate, localised infection, requiring local or oral treatment	severe, systemic infection, requiring i.v. antibiotic or antifungal treatment, or hospitalisation	life-threatening sepsis (e.g. septic shock)
Fever in absence of neutropenia	none	38.0 – 39.0°C	39.1 – 40.0°C	> 40°C for < 24 hrs	> 40°C for > 24hrs,
Chills	none	mild, requiring symptomatic treatment (e.g. blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	--
Myalgia/ arthralgia	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

			living		
Liver					
Transaminase SGOT/AST & SGPT/ALT	WNL	>ULN-2.5 × ULN	>2.5 – 5.0 × ULN	>5.0 – 20.0 × ULN	> 20.0 × ULN
Neurological					
Neuropathy - sensory	normal	loss of deep tendon reflexes or paraesthesia (incl. tingling) but not interfering with function	objective sensory loss or paraesthesia (incl. tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paraesthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Mood alteration (anxiety/depression)	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living transient	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Taste disturbance	normal	slightly altered	markedly altered	--	--
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	Moderate (e.g. decrease in performance status by 1 ECOG level or 20% Karnofsky or Lansky) or causing difficulty performing some activities	severe (e.g. decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or Lansky) or loss of ability to perform some activities	bedridden or disabling
Ocular					
Conjunctivitis/ keratitis	none	abnormal opthalmological changes, but asymptomatic or symptomatic without visual impairment (*i.e.* pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	Symptomatic and interfering with activities of daily living	(keratitis) unilateral or bilateral loss of vision (blindness)
Pulmonary					
Dyspnoea	normal	--	dyspnoea on exertion	dyspnoea at normal level of activity	dyspnoea at rest or requiring ventilator support
CO diffusion capacity (DL_{CO})	≥ 90% of pre-treatment or normal value	≥75 – <90% of pre-treatment or normal value	≥50 – <75% of pre-treatment or normal value	≥25-<50% of pre-treatment or normal value	< 25% of pre-treatment or normal value
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring O_2	requiring assisted ventilation
Pneumonitis/ pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	Radiographic changes and requiring steroids or diuretics	Radiographic changes and requiring O_2	Radiographic changes and requiring assisted ventilation

Pleural effusion	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g. requiring intubation)
Adult respiratory distress syndrome (ARDS)	absent	--	--	--	present
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	--
Renal/ genitourinary					
Haematuria	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterisation or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Sexual/ reproductive					
Libido	normal	decrease in interest	severe loss of interest	--	--
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering activities of daily living	disabling
Hot flushes	none	mild or no more than 1 per day	moderate, > 1 per day	--	--

WNL: Within Normal Limits: LLN: Lower Limit of Normal; UNL: Upper Limit of Normal

APPENDIX 6:

Classifications of severity and relationship to therapy for adverse events

Relatedness
A determination of relatedness (yes/no) to Pfizer investigational or trial medication, concomitant trial specific and other medication is required for all SAEs reported in clinical trials.

The criteria applied are a determination of whether there is a reasonable possibility that the event is related to the investigational product. Note that a "reasonable possibility" does not include cases where there is only a remote or unlikely possibility that the SAE may have been caused by the product.

All SAEs should be reviewed by a Local Pfizer Office (MC) physician before sending to GDS and the CPL. The MC physician is encouraged to comment on the SAE in order to assist the CPL/GDS in reaching the final corporate determination of relatedness although the MC physician is not required to provide her/his own personal relatedness determination. When a MC physician is not available during the required timeframe the SAE report should be immediately sent to CPL/GDS by designated MC personnel.

Severity
Adverse events will be reviewed using the National Cancer Institute Common Toxicity Criteria (NCI CTC) (Appendix 5). Any adverse events incurred but not categorised by the NCI CTC should be graded by the physician and be recorded using a scale of (1) mild, (2) moderate, (3) severe or (4) life threatening on the case report form, as defined below:

MILD	Does not interfere with subject's usual function
MODERATE	Interferes to some extent with subject's usual function
SEVERE	Interferes significantly with subject's usual function
LIFE THREATENING	Resulting in risk of death, organ damage or disability

Note the distinction between the gravity and the intensity of an adverse event. **Severe** is a measure of intensity; thus, a **severe** reaction is not necessarily a **serious** reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria that define serious events.

APPENDIX 7: Patient Consent Form **Version 3: 27/10/2004**

TEAM

An open label, randomised, multicentre, comparative trial of 5 years adjuvant Exemestane treatment versus 2.5 years adjuvant Tamoxifen followed by Exemestane in postmenopausal women with early breast cancer: a research study

Patient Consent Form

- I have read and understood the Patient Information Sheet (Version 4: 27/10/2004). **Yes / No**
- I have had the opportunity to ask questions and discuss the study. **Yes / No**
- I understand that I am free to choose not to participate in the study, or to withdraw from it at any time, without prejudicing my care. **Yes / No**
- I understand that the doctors in charge of this study may close the study, or stop my participation in it at any time, without my consent. **Yes / No**
- I give permission for my GP to be informed of my participation and sent details of the trial. **Yes / No**
- I give permission for my name to be given to the trials office when I am registered on the ***TEAM*** study. **Yes / No**
- I give permission for a tissue sample to be taken from my tumour. **Yes / No**
- I understand that confidential data which identifies me by name may be looked at by responsible individuals from the trials office, pharmaceutical companies, or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. However, I understand that I will not be identified by name in any reports or publications resulting from this study **Yes / No**
- I also understand that data collected about me for this study is covered under the Data Protection Act and stored electronically in a secure encoded format. **Yes / No**
- I have had the opportunity to discuss all of the above with my Doctor. **Yes / No**
- I agree to take part in this study. **Yes / No**

Patient…….	
Signed…….	
Name……	Date…….
Witness…….	
Signed…….	
Name……	Date…….
Doctor…….	
Signed…….	
Name……	Date…….

APPENDIX 8: Patient Re-Consent Form **Version 1: 27/10/2004**

TEAM	**An open label, randomised, multicentre, comparative trial of 5 years adjuvant Exemestane treatment versus 2.5 years adjuvant Tamoxifen followed by Exemestane in postmenopausal women with early breast cancer: a research study**

Patient Re-Consent Form

- I have read and understood the ***TEAM*** trial ***Current Participant Patient Information Sheet***. (Version 1. 27/10/2004). **Yes / No**
- I have had the opportunity to ask questions concerning the revised trial design and the implications for my treatment within the trial. **Yes / No**
- I understand that I am free to withdraw from the ***TEAM*** trial at any time, without prejudicing my care. **Yes / No**
- I give permission for my GP to be informed of my continued participation and sent details of the trial revision. **Yes / No**
- I have had the opportunity to discuss all of the above with my Doctor. **Yes / No**

- I agree to continue to take part in this study in its revised form. **Yes / No**

Patient…….	
Signed…….	
Name……	Date…….
Witness…….	
Signed…….	
Name……	Date…….
Doctor…….	
Signed…….	
Name……	Date…….

APPENDIX 9: NEW Patient Information Sheet **Version 4: 27/10/2004**

TEAM

A randomised comparison of 5 years adjuvant Exemestane versus 5 years adjuvant Tamoxifen for 2.5-3 years followed by Exemestane treatment of postmenopausal women with early breast cancer: a research study

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*This sheet provides some written information about a **clinical research trial**, and is intended to supplement your discussions about the trial with your doctor and nurses. Having read it you may well have further questions, and these should be discussed with your consultant or one of the doctors on the team.*

You have recently had surgical treatment for your breast cancer and this has now been examined by the pathologist. The breast cancer has been removed and lymph glands under the arm have also been examined. The surgery has successfully removed all visible cancer. We know that despite apparently successful surgery there is a possibility of the breast cancer recurring in the future. We cannot tell if this will happen in your case but for many women we can reduce the risk of a recurrence using hormonal treatments. Your breast cancer shows features indicating that hormonal treatment should be recommended for you. This trial is trying to find out if a new form of hormonal drug treatment called exemestane is any better than a recent combination treatment using two different drugs (tamoxifen and exemestane) in sequence over 5 years.

What is tamoxifen?

Tamoxifen is a drug taken orally once a day, which prevents the natural hormone oestrogen from encouraging breast cancer cells to grow by blocking the effects of oestrogen in cells. When taken after surgery for breast cancer we know that it reduces the risk of a breast cancer recurrence. Breast cancer recurrence can happen near the original cancer (local relapse) or at distant sites such as bones or liver (distant relapse). Tamoxifen reduces the risk of this happening. We know that tamoxifen should be taken for at least 5 years to gain maximum benefit. Tamoxifen is a very valuable treatment and is saving many lives when used after breast cancer surgery. Tamoxifen given for 5 years after surgery remains an appropriate treatment for many women with oestrogen receptor-positive breast cancer and is an effective way to reduce, but not eliminate, the risk of recurrence. Tamoxifen can cause a very long list of side effects but the commonest side effects are menopausal type hot flushes. Tamoxifen also helps maintain bone strength. Although some women experience vaginal discharge or even vaginal bleeding, this is uncommon and you should always tell your doctor if this happens. Tamoxifen increases the risk of developing cancer of the womb lining (endometrial cancer). Tamoxifen also increases the risk of blood clots in the legs (deep vein thrombosis) and blood clots on the lung (pulmonary embolus). These increased risks are very small and are greatly outweighed by the benefits of taking tamoxifen.

What is Exemestane?

Exemestane is a new drug that until very recently has been used only for the treatment of breast cancer after tamoxifen has stopped working in patients with relapsed or advanced breast cancer. New trial information now shows that if we introduce exemestane after 2 or 3 years of tamoxifen

this reduces the risk of breast cancer recurrence. We do not yet know about the long term effects of this combination on chances of survival but since the treatment reduces the risk of breast cancer recurrence by about a third many doctors now think this sequential treatment is the right treatment for some patients with early breast cancer. Exemestane has now been compared to tamoxifen as treatment for advanced breast cancer and is slightly more effective than tamoxifen. We now want to study how well exemestane works when given as an 'adjuvant therapy' immediately after surgery rather than after a period of time on tamoxifen.

Exemestane works by preventing the formation of oestrogen. It only works in women who have gone through the change and are no longer having menstrual periods (postmenopausal women). Exemestane is taken orally, once per day. Exemestane also has a long list of possible side effects including hot flushes, nausea and fatigue. For most people these side effects are mild. We do not know if exemestane is a better hormone treatment to use after surgery and the ***TEAM*** study is designed to find out if exemestane is better than tamoxifen or not.

Differences between tamoxifen and exemestane

	Tamoxifen	**Exemestane**
Mechanism	Blocks oestrogen action	Blocks oestrogen production
Effectiveness after surgery	Reduces risk of relapse by about 40% if taken for 5 years	Reduces risk even more than tamoxifen when introduced after 2-3 years of prior tamoxifen
Effectiveness after recurrence	Can work well but eventually stops working. Limited information suggests that exemestane could be better (ongoing research)	Slightly more effective than tamoxifen but also eventually stops working. Effective after tamoxifen failure
Main side effect	Hot flushes and sweats	Hot flushes and sweats
Other recognised common side effects (only experienced by a minority of patients)	Postmenopausal bleeding/discharge Nausea Dizziness	Nausea Dizziness Diarrhoea
Bone density	Preserves bone density	Increased risk of osteoporosis compared to tamoxifen
Cholesterol	Reduced	Unchanged
Blood clots	Increased risk (small)	Reduced risk compared to tamoxifen.
Endometrial (womb) cancer	An increased risk of this rare cancer is far outweighed by benefit	Reduced risk compared to tamoxifen

What happens if I go into the study?

If you agree to take part in this study we will ask you to sign a consent form and we will then register your details with the trial centre and check that you are suitable for the trial. The trial centre will allocate your treatment, which will either start with exemestane or tamoxifen. If you start tamoxifen you will be switched to exemestane after you have had at least 2.5 years tamoxifen. If you are allocated exemestane you will continue this for the entire 5-year period. Starting treatment is allocated at random so there is an equal chance of being allocated initially to tamoxifen or exemestane. We will see you in a follow-up clinic on a regular basis and check on how you are getting on. We will record any adverse medical events and check you are still taking your medication. We do not usually need any extra tests for this study but we need to check that you have had a recent chest X-ray and that your blood test results are satisfactory (tests from around the time of surgery or chemotherapy are usually sufficient). In some cases we need a blood test to confirm that you are postmenopausal.

Extra research on your cancer tissue

If you are entered into the ***TEAM*** study we would like to do some further research on your breast cancer tissue. With your permission we would like to send a part of your breast cancer to a central laboratory where we can analyse the tissue for some special molecular features or proteins (molecular markers). One test we would like to do is the HER-2 test, which might be important in predicting the effectiveness of hormone treatments. This information will be sent back to your hospital and may be helpful in the future if you need further treatment and is already tested routinely in many but not all hospitals. We would also like to retain a tiny piece of your breast cancer tissue and use this in the future for research to help understand more about breast cancer and hormone treatments. After removing this sample we will return the rest of the cancer tissue to your hospital if requested. The tissue would be stored in such a way that it would not be identifiable. We do not yet know precisely which molecular markers or genes we will be looking at but the tissue we collect could be analysed for the presence of up to three hundred different proteins and genes inside the breast cancer cells. We will be looking at proteins or genes that we think might help improve our ability to treat breast cancer and in particular to help predict if some cancers are best treated with different types of hormone therapy. Because the samples are not identifiable results of this research will have no influence on your treatment but doctors taking part in the study will be informed of the general findings of this research. If you do not want your tissue used in this way please tell us. You can still take part in the trial.

Tumour material collected during this study will not be sold to third parties or used for commercial gain. Intellectual property rights that may arise as a result of findings from this research could be exploited commercially. The rights to any intellectual property will reside with the Investigators.

What we will do with information about you

With your agreement, your GP and any other doctors who may treat you will be informed that you are taking part in this trial. All information collected about you for this study is strictly confidential and will be covered under the Data Protection Act. With your permission, your doctor will give us your name when s/he telephones to register you on the study. However, all other information about you which leaves the hospital will refer to you only by a unique trial number allocated to you, or by your initials. All information will be securely stored at the trials office on paper and electronically in an encoded format. We may need to check clinical information from your medical records. This will be done by clinical staff or designated trials office personnel, and possibly by responsible individuals from the pharmaceutical companies mentioned above, or from government regulatory agencies. Under no circumstances will you be identified in any way in any report arising from the trial. The results of the research may be published in medical journals, but this will not include any reference to individual patients. Your medical records may be reviewed by the trial monitor or authorised persons from regulatory bodies, in which case your confidentiality will be maintained at all times.

If during the course of this trial we become aware of any new information which may have a bearing on your treatment or continued participation in this study we will inform you and invite you to discuss the implications of this information.

What about other treatments?

Depending on your individual circumstances you may be recommended for other treatment such as radiotherapy or chemotherapy. These treatments will form part of your normal treatment and will not be effected by taking part in the trial. Most doctors now start hormone treatment after chemotherapy treatment is completed so if you are having chemotherapy your hormone treatment will not start until your chemotherapy has been completed.

Tamoxifen alone
At the present time in the UK and Republic of Ireland the majority of patients are treated with tamoxifen only. The information regarding exemestane after tamoxifen is new and has not yet become standard treatment in most hospitals and associated GP practices. There are still unresolved questions about the long term effects of exemestane especially effects on bone health. Exemestane is also more expensive than tamoxifen. You should ask what your current standard treatment is for your particular cancer. Over the next few years new information will emerge and your hospital policy could chance, your doctor may in the future recommend a change in therapy even if the current recommendation is tamoxifen for 5 years. For some patients tamoxifen is associated with a high risk of complications and tamoxifen is not recommended. If this is the case for you, you should not take part in this study.

Other aromatase inhibitors
Hormone treatment for breast cancer is becoming increasingly complicated. Other drugs are available for the treatment of breast cancer and you may hear or read about anastrozole. At the moment anastrozole is licensed to treat early breast cancer in women at risk of complications from tamoxifen. This drug has been shown to be more effective than tamoxifen alone. Anastrozole not only increases the risk of bone loss but is associated with a small but definite increased fracture risk compared to tamoxifen. We do not know if tamoxifen followed by exemestane is better or worse than anastrozole alone and we do not know if exemestane alone is better than anastrozole alone. With as many questions as answers about hormone treatment for breast cancer, further research such as the ***TEAM*** study is important. You should discuss the available options that your doctor thinks are appropriate to your individual situation. You may also read or hear about letrozole, which is yet another aromatase inhibitor. At the present time we know that letrozole is an effective treatment to introduce after completing a 5-year course of tamoxifen. Trials of letrozole given earlier are being conducted.

What if I do not want to go into the study?
If you do not want to take part in the study we will still recommend hormone therapy. The treatment you will be recommended will depend on local hospital policy and the precise characteristics of your cancer.
Participation in this study is entirely voluntary. If you decide not to participate, this will not affect your routine treatment in any way. Also if you decide to participate, and then change your mind at a later date, you may withdraw from the study. This will not affect your routine treatment or your relationship with your doctor.

Compensation
The ***TEAM*** study is a clinician-initiated and clinician-led study. The study is being run by the Cancer Research UK Clinical Trials Unit (CRCTU) in Birmingham and by other research groups in Holland, France and the USA. Financial support is being provided by Pfizer Ltd. the pharmaceutical company that makes exemestane. Neither the CRCTU nor the supporting pharmaceutical company hold insurance against claims for compensation for injury caused by participation in this trial and they cannot offer any indemnity. However, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is only available in the event of clinical negligence being proven. There are no specific arrangements for compensation made in respect of any serious adverse events occurring through your participation in this study, whether side effects listed above, or others as yet unforeseen.

Thank you for reading this information leaflet. If you have any problems or questions now or during your treatment, please do not hesitate to get in touch. Please use one of the following contact numbers.

Dr _____Tel_____

Research nurse_____Tel_____

A regional research ethics committee and your local research ethics committee have approved this study

APPENDIX 10: **Version 1. 27/10/2004**

CURRENT PARTICIPANT: Patient Information Sheet (for patients randomised to tamoxifen)

TEAM

Formerly:
A randomised comparison of 5 years adjuvant Exemestane versus 5 years adjuvant Tamoxifen treatment of postmenopausal women with early breast cancer: a research study

Now:
A randomised comparison of 5 years adjuvant Exemestane versus 2.5-3 years adjuvant Tamoxifen treatment followed by Exemestane to complete 5 years hormone therapy in postmenopausal women with early breast cancer: a research study

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This sheet provides some important written information about new results from research involving tamoxifen and exemestane. You should read this carefully as it may alter your future hormonal treatment.

You very kindly agreed to take part in the ***TEAM*** study some time ago and were allocated tamoxifen. You will remember that this was being compared to a new drug called exemestane and the aim was to find out if exemestane was better than tamoxifen. We undertook to inform you about any new information if this became available.

New information from exemestane studies
A large study has recently been published in which women who had been taking tamoxifen for 2-3 years and were well, were either switched to exemestane or continued on their tamoxifen. The results show that the risk of a breast cancer recurrence are reduced by about a third if you switch to exemestane instead of tamoxifen. At the moment we don't yet know if there is any difference in long term survival because the study has not been running long enough. Because of this new information we have decided that it is appropriate to change the ***TEAM*** study and **offer all women taking tamoxifen in the *TEAM* study the opportunity to switch over to exemestane**. There are however some important side effect differences you should understand before you decide what to do.

Side effect differences between tamoxifen and exemestane
Because you are already taking tamoxifen you will know how it is currently affecting you. You may get different side effects on exemestane. In the trial mentioned above there were fewer reports of gynaecological problems such as vaginal bleeding or cancer of the womb in women switching to exemestane. There were also fewer episodes of thrombosis or stroke. Switching to exemestane was however associated with an increase in diarrhoea and in joint pains. Visual disturbances were also slightly more common. More women switching to exemestane developed osteoporosis (thinning of the bones) although it is not yet clear if this results in a definite increase in bone fractures.

What is Exemestane?

To remind you, exemestane is a new drug that is currently used to treat breast cancer after tamoxifen has stopped working in patients with relapsed or advanced breast cancer. Exemestane has been compared to tamoxifen as treatment for advanced breast cancer, exemestane is more effective in shrinking breast cancers and keeps advanced breast cancer under control for a little longer.

Exemestane works by preventing the formation of oestrogen. It only works in women who have gone through the change and are no longer having menstrual periods (postmenopausal women). Exemestane is taken orally, once per day. Exemestane also has a long list of possible side effects including hot flushes, nausea and fatigue. For most people these side effects are mild. Although we now know that switching to exemestane reduces risk of breast cancer recurrence we do not know if this is the best strategy and we would still like to find out if starting exemestane straight away is the best way to use this drug.

Differences between tamoxifen and exemestane

	Tamoxifen	Exemestane
Mechanism	Blocks oestrogen action	Blocks oestrogen production
Effectiveness after surgery	Reduces risk of relapse by about 40% if taken for 5 years	Unknown at the start but more effective than continuing tamoxifen after 2-3 years
Effectiveness after recurrence	Can work well but eventually stops working. Exemestane slightly more effective	Also effective but also eventually stops working. Effective after tamoxifen failure
Main side effect	Hot flushes	Hot flushes
Other recognised side effects	Sweating Postmenopausal bleeding/discharge Nausea Dizziness	Sweating Fatigue Nausea Dizziness Diarrhoea
Bone density	Preserves bone density	Increased osteoporosis compared to tamoxifen
Cholesterol	Reduced	Unchanged
Blood clots	Increased risk (small)	Reduced risk
Endometrial (womb) cancer	An increased risk of this rare cancer is far outweighed by benefit	Reduced risk

What happens if I agree to switch?

If you are happy to switch to exemestane when you have completed at least 2.5 years of tamoxifen we will supply you with exemestane from the hospital pharmacy to complete 5 years of hormone treatment. You will continue to be followed-up in exactly the same way as before. We would like you to switch before 3 years are up but if for some reason you have taken tamoxifen for more than 3 years you should switch as soon as possible.

We are asking all women in the ***TEAM*** study to sign a new consent form confirming that you have been given the updated information and are still happy to be included in the trial.

What if I get bad side effects?

Clearly if you have bad side effects we will have to decide how to deal with them on an individual basis, but going back to tamoxifen is an option.

What can be done about osteoporosis?

A lot of research is currently ongoing to help understand who is at risk of osteoporosis and if we can identify people who are not at risk. You should discuss your individual circumstances with your

study doctor as there are a lot of different factors that may be involved in osteoporosis risk. It is not yet clear if all patients should have tests for osteoporosis and currently we are not requiring these for all patients in the trial. Osteoporosis is a condition that can usually be treated effectively, although we do not yet have a lot of information about treating osteoporosis in women taking exemestane. It is possible that during the course of this trial our understanding and approach to handling osteoporosis may change. Osteoporosis is only painful if you develop a fracture as a result of this condition and should not be confused with joint pains that are experienced by some women when taking exemestane.

What if I do not want to take exemestane?
Although we have recommended that you switch to exemestane you are under no obligation to do so and you may choose to stay on tamoxifen. We would like to continue to monitor you and supply the trial centre with trial-related information about you. If you start exemestane and then change your mind you should come back and discuss things again with your study doctor. If you want to switch back to tamoxifen you will be able to do this. Even if you decide to stay on tamoxifen we would like you to sign our new consent form.

Compensation
The ***TEAM*** study is a clinician-initiated and clinician-led study. The study is being run by the Cancer Research UK Clinical Trials Unit (CRCTU) in Birmingham and by other research groups in Holland, France Germany and the USA. Financial support is being provided by Pfizer Corporation, the pharmaceutical company that makes exemestane. Neither the CRCTU nor the supporting pharmaceutical company hold insurance against claims for compensation for injury caused by participation in this trial unless this occurs as a result of negligence. NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is only available in the event of clinical negligence being proven. There are no specific arrangements for compensation made in respect of any serious adverse events occurring through your participation in this study, whether side effects listed above, or others as yet unforeseen.

Thank you for reading this information leaflet. If you have problems or questions now or during your treatment, please do not hesitate to get in touch. Please use one of the following contact numbers.

Dr _____Tel_____

Research nurse_____Tel_____

A regional research ethics committee and your local research ethics committee have approved this study

APPENDIX 11: **Version 1. 27/10/2004**

CURRENT PARTICIPANT: Patient Information Sheet (for patients randomised to exemestane)

TEAM

Formerly:
A randomised comparison of 5 years adjuvant Exemestane versus 5 years adjuvant Tamoxifen treatment of postmenopausal women with early breast cancer: a research study

Now:
A randomised comparison of 5 years adjuvant Exemestane versus 2.5-3 years adjuvant Tamoxifen treatment followed by Exemestane to complete 5 years hormone therapy in postmenopausal women with early breast cancer: a research study

---

This sheet provides some important written information about new results from research involving tamoxifen and exemestane. Please read this carefully as it contains new information about tamoxifen and exemestane in women with early breast cancer.

You very kindly agreed to take part in the ***TEAM*** study some time ago and were allocated exemestane. You will remember that this was being compared to tamoxifen and the aim was to find out if exemestane was better than tamoxifen. We undertook to inform you about any new information if this became available.

New information from exemestane studies
A large study has recently been published in which women, who had been taking tamoxifen for 2-3 years and were well, were either switched to exemestane or continued on their tamoxifen. The results show that the risk of a breast cancer recurrence is reduced by about a third if you switch to exemestane instead of tamoxifen. At the moment we don't yet know if there is any difference in long term survival because the study has not been running long enough. Because of this new information we have decided that it is appropriate to change the ***TEAM*** study and offer all women taking **tamoxifen** in the ***TEAM*** study the opportunity to switch over to exemestane after they have been taking tamoxifen for more than 2.5 years.

What does this mean for me?
As you are already taking exemestane this will not affect you directly and we would like you to continue taking exemestane for 5 years.
In the trial mentioned above there were fewer reports of gynaecological problems such as vaginal bleeding or cancer of the womb in women switching to exemestane. There were also fewer episodes of thrombosis or stroke. Switching to exemestane was however associated with an increase in diarrhoea and in joint pains. Visual disturbances were also slightly more common. More women switching to exemestane developed osteoporosis (thinning of the bones) although it is not yet clear if this results in a definite increase in bone fractures.

Exemestane, a reminder and update

To remind you, exemestane is a new drug that is currently used to treat breast cancer after tamoxifen has stopped working in patients with relapsed or advanced breast cancer. Exemestane has been compared to tamoxifen as treatment for advanced breast cancer, exemestane is more effective in shrinking breast cancers and keeps advanced breast cancer under control for a little longer.

Exemestane works by preventing the formation of oestrogen. It only works in women who have gone through the change and are no longer having menstrual periods (postmenopausal women). Exemestane is taken orally, once per day. Exemestane also has a long list of possible side effects including hot flushes, nausea and fatigue. For most people these side effects are mild. Although we now know that switching to exemestane reduces the risk of breast cancer recurrence we do not know if this is the best strategy. We would still like to find out if starting exemestane straight away is the best way to use this drug which is why we would like you to continue taking exemestane. We will still compare how women in your group compare with the women switching to exemestane. The table below has been updated from our original information leaflet.

Differences between tamoxifen and exemestane

	Tamoxifen	**Exemestane**
Mechanism	Blocks oestrogen action	Blocks oestrogen production
Effectiveness after surgery	Reduces risk of relapse by about 40% if taken for 5 years	Unknown at the start but more effective than continuing tamoxifen after 2-3 years
Effectiveness after recurrence	Can work well but eventually stops working. Exemestane slightly more effective	Also effective but also eventually stops working. Effective after tamoxifen failure
Main side effect	Hot flushes	Hot flushes
Other recognised side effects	Sweating Postmenopausal bleeding/discharge Nausea Dizziness	Sweating Fatigue Nausea Dizziness diarrhoea
Bone density	Preserves bone density	Increased osteoporosis compared to tamoxifen
Cholesterol	Reduced	Unchanged
Blood clots	Increased risk (small)	Reduced risk
Endometrial (womb) cancer	An increased risk of this rare cancer is far outweighed by benefit	Reduced risk

What can be done about osteoporosis?

A lot of research is currently ongoing to help understand who is at risk of osteoporosis and if we can identify people who are not at risk. You should discuss your individual circumstances with your study doctor as there are a lot of different factors that may be involved in osteoporosis risk. It is not yet clear if all patients should have tests for osteoporosis and currently we are not requiring these for all patients in the trial. Osteoporosis is a condition that can usually be treated effectively although we do not yet have a lot of information about treating osteoporosis in women taking exemestane. It is possible that during the course of this trial our understanding and approach to handling osteoporosis may change. Osteoporosis is only painful if you develop a fracture as a result of this condition and should not be confused with joint pains that are experienced by some women when taking exemestane.

Continuing exemestane
We do not think this new information should affect your participation in the ***TEAM*** trial. We will continue to prescribe exemestane for you, provided you are happy to continue with the drug. We will however ask you to sign a new consent form confirming your willingness to continue in the trial.

What if I now do not want to take exemestane?
If as a result of this new information you no longer wish to take exemestane you should discuss the available alternatives with your study doctor. We do not have any information on the effectiveness of other hormone therapies after exemestane in early breast cancer. Even if you stop taking exemestane we would like to continue to collect information about you and would like you to sign our new consent form indicating you agree to this.

Compensation
The ***TEAM*** study is a clinician-initiated and clinician-led study. The study is being run by the Cancer Research UK Clinical Trials Unit (CRCTU) in Birmingham and by other research groups in Holland, France, Germany and the USA. Financial support is being provided by Pfizer Corporation, the pharmaceutical company that makes exemestane. Neither the CRCTU nor the supporting pharmaceutical company hold insurance against claims for compensation for injury caused by participation in this trial unless this occurs as a result of negligence. NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is only available in the event of clinical negligence being proven. There are no specific arrangements for compensation made in respect of any serious adverse events occurring through your participation in this study, whether side effects listed above, or others as yet unforeseen.

Thank you for reading this information leaflet. If you have problems or questions now or during your treatment, please do not hesitate to get in touch. Please use one of the following contact numbers.

Dr _____Tel_____

Research nurse_____Tel_____

A regional research ethics committee and your local research ethics committee have approved this study

APPENDIX 12: GP LETTER: FOR CURRENT PARTICIPANTS **Version 1. 27/10/2004**

TEAM

Formerly:
A randomised comparison of 5 years adjuvant Exemestane versus 5 years adjuvant Tamoxifen treatment of postmenopausal women with early breast cancer: a research study

Now:
A randomised comparison of 5 years adjuvant Exemestane versus 2.5-3 years adjuvant Tamoxifen treatment followed by Exemestane to complete 5 years hormone therapy in postmenopausal women with early breast cancer: a research study

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Dear Dr

Your Patient _____

Has been participating in the ***TEAM*** trial. Recent data has caused the trial organisers and investigators to introduce a substantial revision to this trial. The original design comprised a simple comparison of 5 years of adjuvant tamoxifen versus 5 years of the steroidal aromatase inhibitor exemestane. Since this trial commenced several important studies using aromatase inhibitors in early breast cancer have been published.

The Anastrozole, Tamoxifen, Alone or in Combination study (ATAC)[1,2] has compared 5 years of anastrozole with 5 years of tamoxifen. This study has shown a reduction in risk of relapse by 22% with immediate use of anastrozole alone in hormone receptor-positive cancers. The published results have not analysed survival and a survival analysis is expected soon. In the UK anastrozole is currently only licensed for women with early breast cancer where tamoxifen is contraindicated. The main concern with adjuvant anastrozole being loss of bone mineral density compared to tamoxifen, with an associated significant but small increase in fractures observed.

Exemestane has been examined in a different trial design, the Intergroup Exemestane Study (IES),[3] where women with early breast cancer completing between 2 and 3years of tamoxifen were randomly allocated to complete a standard 5-year course of tamoxifen or to switch to exemestane. This study demonstrated an advantage in favour of the aromatase inhibitor in reducing risk of relapse in oestrogen receptor-positive women by 36%. Survival analysis is as yet too immature to show an impact. There are therefore two competing strategies, aromatase inhibitor from the outset and a sequential approach. Which strategy is the most effective is currently unknown.

After considerable deliberation the ***TEAM*** trial has been amended so that women randomised to tamoxifen will be offered the opportunity to switch to exemestane after they have completed at least 2.5 years of tamoxifen therapy. The new design will allow us to determine the best way of using exemestane, which now has an established role. This does however require a larger sample size. It has been possible to introduce this change effectively for all patients since the first patients entered the trial less than 3 years from the change.

All patients in ***TEAM*** will be informed about this change and will all be re-consented. Women who are happy to switch from tamoxifen to exemestane will start to receive trial stock exemestane from their hospital pharmacy at the appropriate scheduled visits and should stop tamoxifen after they have their exemestane prescribed. Some patients may prefer to stay on tamoxifen in which case they will come ‘off study’ but we will continue to follow these patients and perform an intent to treat analysis. For women allocated exemestane there are no direct consequences to this change and they will continue to be treated with exemestane as now. Patients experiencing difficulty with exemestane should be referred back to hospital for advice.

We now have comparative toxicity data from the IES trial (Table 1), which demonstrates some differences between exemestane and tamoxifen. Fewer gynaecological complications are evident with exemestane but more arthralgia was reported. A higher incidence of osteoporosis and a non-significant increase in clinical fractures was recorded on exemestane. We also know that compared to placebo exemestane results in a small increase in bone mineral density loss. We do not currently advise any osteovigilance strategy but substudies within the ***TEAM*** trial and elsewhere will help clarify this. Calcium and vitamin D supplementation is permitted within the trial but we have no data on efficacy with exemestane. At the end of the 5-year treatment period it will be necessary to review the available data on duration of endocrine therapy after 5 years to determine what further treatment, if any, is appropriate. You may be aware of yet more recent research demonstrating a relapse-free survival advantage for women taking letrozole following 5 years of adjuvant tamoxifen.[4] We do not have data to indicate if this 'extended adjuvant therapy' is effective in women exposed to aromatase inhibitors during the earlier part of hormonal therapy.

Table 1: Adverse events in the IES study significantly different, or different by >1%, or common (>5%) adverse events.

Adverse events any grade	**Exemestane % (n = 2309)**	**Tamoxifen % (n = 2332)**	**P value**
Arthralgia	5.4	3.6	**0.01**
Diarrhoea	4.3	2.3	**0.001**
Throboembolic AEs	1.0	2.0	0.01
Thromboembolic SAEs	1.3	2.4	0.005
Vaginal bleeding	4.0	5.6	**0.01**
Other gynaecological symptoms	5.8	9.0	**<0.001**
Endometrial cancer	0.21 (5 events)	0.46 (11 events)	Not stated
Other malignancy	22	42	Not stated
Cramp	2.8	4.4	**0.0007**
Sweating	18.6	18.1	
Headache	18.6	16.4	0.09
Dizziness	12.5	12.1	0.93
Visual disturbance	7.4	5.8	**0.04**
Depression	5.2	4.0	
Osteoporosis	7.4	5.7	**0.05**
Clinical fracture	3.1	2.3	0.08

References

1: The ATAC Trialists Group: Lancet 359:2131-9, 2002
2: The ATAC Trialists Group: Cancer 98:1802-10, 2003
3: Coombes RC, Hall E, Gibson LJ, et al:N Engl J Med 350:1081-92, 2004
4: Goss PE, Ingle JN, Martino S, et al: N Engl J Med 349:1793-802, 2003

We hope this letter is helpful, if you need additional information or wish to discuss this trial further please do not hesitate to get in touch with the Cancer Research UK Clinical Trials Unit in Birmingham on 0121 414 3797.

Appendix 13: GP Letter for NEW Patients

Version 2: 27/10/2004

TEAM

A randomised comparison of 5 years adjuvant Exemestane versus 2.5-3 years adjuvant Tamoxifen followed by Exemestane treatment of postmenopausal women with early breast cancer

Dear Dr

Your Patient _____

Has been identified as eligible for the above study and has been requested to consider taking part in the study.

Tamoxifen is firmly established as an effective adjuvant therapy for women after treatment for early stage breast cancer. Randomised trials have established that adjuvant tamoxifen taken for five years reduces the risk of breast cancer recurrence by 40% in women with tumours expressing significant levels of oestrogen receptor. Emerging data from randomised clinical trials indicates a role for the new third-generation aromatase inhibitors, which inhibit oestrogen synthesis rather than antagonise at the receptor level. The Anastrozole, Tamoxifen Alone or in Combination study (ATAC)[1,2] has compared 5 years of anastrozole with 5 years of tamoxifen and has shown a reduction in risk of relapse by 22% with immediate use of anastrozole alone in hormone receptor-positive cancers. The published results have not analysed survival and a survival analysis is expected soon. In the UK anastrozole is currently only licensed for women with early breast cancer where tamoxifen is contraindicated. The main concern with adjuvant anastrozole being loss of bone mineral density compared to tamoxifen, with an associated significant but small increase in fractures observed. Another third-generation aromatase inhibitor exemestane has been examined in a different trial design, the Intergroup Exemestane Study (IES),[3] where women with early breast cancer completing between 2 and 3years of tamoxifen were randomly allocated to complete a standard 5-year course of tamoxifen or to switch to exemestane. This study demonstrated an advantage in favour of the aromatase inhibitor in reducing risk of relapse in oestrogen receptor-positive women by 36%. There are therefore two competing strategies, aromatase inhibitor from the outset and a sequential approach. Which strategy is the most effective is currently unknown.

In the ***TEAM*** study women with receptor-positive early breast cancer are randomised to treatment with tamoxifen for 2.5-3 years followed by exemestane to complete 5 years of treatment or treatment with exemestane for 5 years.

This trial is a multinational, multicentre, trial with a recruitment target of 8740 patients. The trial is being run from the Cancer Research UK Clinical Trials Unit in Birmingham for UK participants. The primary endpoint for the study is relapse-free survival with secondary endpoints of overall survival and tolerability. We have completed a quality of life analysis and will also be performing a pathological correlate study.

Patients will be followed-up every three months for one year after which follow-up reverts to a minimum of annual review. No additional investigations will be required. Patients experiencing suspected adverse drug reactions should be referred back to breast clinic immediately. We may ask you to provide information regarding the status of patients lost to follow-up. Patients randomised to tamoxifen therapy will be supplied with ongoing medication in the normal way. When they are due to commence exemestane this will be dispensed from hospital pharmacies. Patients randomised to exemestane therapy will receive drug supply direct from their hospital pharmacy.

You will be informed of the treatment allocation for your patient and we ask that you continue to prescribe adjuvant tamoxifen only to patients allocated to tamoxifen up to the time they switch to exemestane. At the end of the 5 year treatment period it will be necessary to review the available data on duration of endocrine therapy after 5 years to determine what further treatment if any is appropriate. You may be aware of yet more recent research demonstrating a relapse-free survival advantage for women taking letrozole following five years of adjuvant tamoxifen[4]. We do not have data to indicate if this 'extended adjuvant therapy' is effective in women exposed to aromatase inhibitors during the earlier part of hormonal therapy.

Exemestane is currently used to treat advanced breast cancer and is generally well tolerated. We now have comparative toxicity data from the IES trial (Table 1), which demonstrates some differences between exemestane and tamoxifen. In early breast cancer exemestane results in fewer gynaecological complications including reduced risk of endometrial cancer compared to tamoxifen but is associated with more arthralgia, which may need drug treatment. Higher incidence of osteoporosis was seen in the IES study with a non-significant increase in reported clinical fractures. We also know that compared to placebo exemestane results in a small increase in bone mineral density loss. We do not currently advise any osteovigilance strategy but substudies within the ***TEAM*** trial and elsewhere will help clarify this. Calcium and vitamin D supplementation is permitted within the trial but we have no data on efficacy with exemestane.

Table 1: Adverse events in the IES study significantly different, or different by >1%, or common (>5%) adverse events.

Adverse events any grade	**Exemestane % (n = 2309)**	**Tamoxifen % (n = 2332)**	**P value**
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Vaginal bleeding	4.0	5.6	**0.01**
Other gynaecological symptoms	5.8	9.0	**<0.001**
Endometrial cancer	0.21 (5 events)	0.46 (11 events)	Not stated
Other malignancy	22	42	Not stated
Cramp	2.8	4.4	**0.0007**
Sweating	18.6	18.1	
Headache	18.6	16.4	0.09
Dizziness	12.5	12.1	0.93
Visual disturbance	7.4	5.8	**0.04**
Depression	5.2	4.0	
Osteoporosis	7.4	5.7	**0.05**
Clinical fracture	3.1	2.3	0.08

References

1: The ATAC Trialists Group: Lancet 359:2131-9, 2002
2: The ATAC Trialists Group: Cancer 98:1802-10, 2003
3: Coombes RC, Hall E, Gibson LJ, et al:N Engl J Med 350:1081-92, 2004
4: Goss PE, Ingle JN, Martino S, et al: N Engl J Med 349:1793-802, 2003

We hope this letter is helpful, if you need additional information or wish to discuss this trial further please do not hesitate to get in touch with the Cancer Research UK Clinical Trials Unit in Birmingham on 0121 414 3797.

ABBREVIATIONS AND DEFINITION OF TERMS

ABPI	The Association of the British Pharmaceutical Industry
AE	Adverse Event
AG	Aminoglutethimide
ALT	Alanine aminotransferase
AST	Aspartate transaminase
BC	Breast Cancer
BUN	Blood Urea Nitrogen
CHF	Chronic Heart Failure
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRCTU	Cancer Research UK Clinical Trials Unit (UK National Data Centre)
CRF	Case Report Form
DHT	Dihydroxytestosterone
DSMC	Data and Safety Monitoring Committee
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECOG	Eastern cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ER	Oestrogen Receptor
FCE	17- Hydro-exemestane (exemestane metabolite)
FISH	Fluorescent In-Situ Hybridization
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
Hb	Haemoglobin
HPLC	High Performance Liquid chromatography
HR	Hazard Ratio
HRT	Hormone Replacement Therapy
IBCSG	International Breast Cancer Study Group
ICCG	The International Collaborative Cancer Group
IRB	Institutional Review Board
ICH	International Conference of Harmonization
IHC	Immunohistochemistry
LFTs	Liver Function Tests
LREC	Local Research Ethics Committee
MREC	Multicentre Research Ethics Committee
MTD	Maximum Tolerated Dose
NCI-CTC	National Cancer Institute Common Toxicity Criteria
NSABP	The National Surgical Adjuvant Breast and Bowel Project
OS	Overall Survival
PgR	Progesterone Receptor
PLT	Platelets
PR	Partial Response
RBA	Relative Binding Affinity
DFS	Disease Free Survival
RIA	Radio immuno-assay
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TNO	Trial Number
TTF	Time to Treatment Failure
TTP	Time To Progression
TWIST	Time Without Symptoms or Toxicity
UNL	Upper Normal Limit
WBC	White Blood Cell Count
WMA	World Medical Association

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