Study Of Faslodex

with or without concomitant Arimidex vs Exemestane

following progression on non-steroidal Aromatase inhibitors

A partially-blind phase III randomised trial of Fulvestrant (Faslodex™) with or without concomitant Anastrozole (Arimidex™) compared with exemestane in postmenopausal women with ER+ve locally advanced/metastatic breast cancer following progression on non-steroidal aromatase inhibitors

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**The SoFEA trial has been scientifically approved
by the Clinical Trials Awards and Advisory Committee (CTAAC)
of Cancer Research UK and the Medical Research Council (February 2003)
and is thus part of the NCRN/NCRI portfolio of breast cancer trials.
The trial meets the criteria for R&D support as outlined
in the Statement of Partnership on Non-Commercial R&D in the NHS in England.**

SoFEA TRIAL - FINAL PROTOCOL
Approved by:

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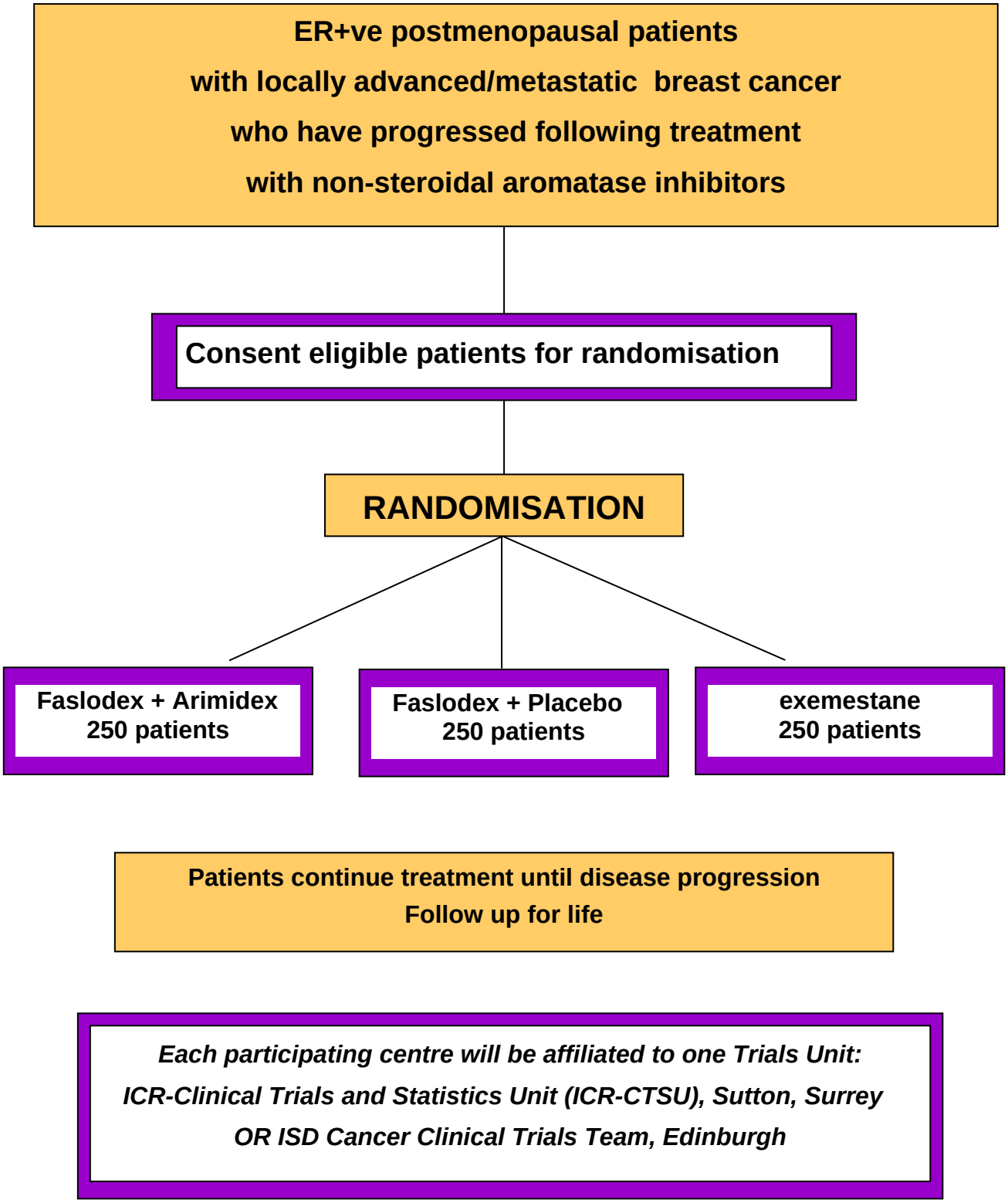
TRIAL SCHEMA



TRIAL SUMMARY

TITLE:

A Partially-Blind Phase III Randomised Trial of Fulvestrant (Faslodex™) with or without concomitant Anastrozole (Arimidex™) compared with exemestane in postmenopausal women with ER+ve locally advanced / metastatic breast cancer following progression on non-steroidal aromatase inhibitors (NSAIs).

OBJECTIVES:

Primary:

1. To compare the progression-free survival of patients treated with Faslodex plus concomitant Arimidex (F+A) versus Faslodex (F) alone.
2. To compare the progression-free survival of patients treated with Faslodex (F) alone versus those treated with the current standard, exemestane (E).

Secondary:

1. To assess the objective tumour response rate (CR [Complete Response] + PR [Partial Response]), duration of response, clinical benefit rate (CR/PR + Stable Disease (SD) ≥6 months), duration of clinical benefit, time to treatment failure, and overall survival of patients treated with Faslodex plus concomitant Arimidex (F+A) compared with Faslodex (F) alone.
2. To assess the objective response rate, duration of response, clinical benefit rate, duration of clinical benefit, time to treatment failure, progression-free and overall survival of patients treated with Faslodex (without concomitant Arimidex) compared with exemestane.
3. In the case that concomitant use of Arimidex with Faslodex provides *equivalent* outcome to Faslodex alone, to compare the progression-free survival of all Faslodex treated patients with those treated with exemestane.
4. To determine the tolerability of Faslodex with or without concomitant Arimidex, and compared with exemestane.

Exploratory:

To establish in accessible tumour biopsies from as many patients as possible relapsing on NSAIs: tumour oestrogen receptor (ER) expression and activation status (i.e. phosphorylation status); tumour epidermal growth factor (EGFR) / transmembrane human epidermal growth factor receptor (HER2) expression and activation of the intracellular signalling pathways.

TRIAL DESIGN:

A partially-blind, randomised, multicentre phase III trial of Faslodex plus concomitant Arimidex versus Faslodex plus Arimidex-Placebo versus exemestane in postmenopausal locally advanced / metastatic breast cancer patients who have progressed on NSAIs.

Randomisation to Faslodex ± Arimidex / Arimidex-Placebo or exemestane will be open (1:1:1). For Faslodex treated patients the randomisation to Arimidex or Arimidex-Placebo will be double-blind.

TYPE AND NUMBER:	Patients will be postmenopausal women with measurable / evaluable oestrogen receptor positive (ER+ve) and / or progesterone receptor positive (PgR+ve) locally advanced / metastatic breast cancer who have progressed during treatment with an NSAI either as adjuvant therapy or as first-line treatment for locally advanced / metastatic disease, and who are suitable for further endocrine therapy. A total of 750 patients will be recruited. There will be 250 patients treated with Faslodex plus Arimidex, 250 patients treated with Faslodex + Arimidex-Placebo, and 250 patients treated with exemestane.
TRIAL TREATMENT:	**Patients randomised to Faslodex:** A loading dose of 500 mg intramuscular (i.m.) Faslodex on Day 1, followed by 250 mg i.m. on days 15 and 29, and thereafter continued at 250 mg i.m. monthly. In addition, all Faslodex patients will be randomised (double-blind) to either Arimidex 1mg orally once daily or matching Arimidex-Placebo orally once daily. **Patients randomised to exemestane:** Patients will receive exemestane 25 mg orally once daily, continuously.
DURATION OF TREATMENT:	Until evidence of disease progression, or withdrawal of treatment due to any drug related serious adverse event or patient choice.
PRIMARY ENDPOINTS:	Progression-free survival (PFS)
SECONDARY ENDPOINTS:	Objective Tumour Response Rate (CR + PR) Duration of Objective Tumour Response Clinical Benefit Rate Duration of Clinical Benefit Time to Treatment Failure Overall Survival Tolerability of Faslodex (± Arimidex) and exemestane In the case that the primary endpoint analysis of Faslodex versus Faslodex plus Arimidex shows equivalence (section 9.2) then a secondary analysis comparing the PFS of all Faslodex treated patients with that of exemestane treated patients will be performed.
EXPLORATORY ENDPOINTS:	Correlative Biological Studies of ER, EGFR / HER2 and mitogenactivated protein kinases (MAPK) / externally reglulated kinases (ERK) / insulin-like growth factor receptor (IGFR) and (product of the normal gene homologue of v-*akt)* AKT signalling in tumour biopsies at randomisation.

1. Background

1.1 Clinical Setting

Non-steroidal aromatase inhibitors (NSAIs) such as Anastrozole (Arimidex™), or letrozole (Femara™) are standard endocrine therapy for postmenopausal women with oestrogen receptor positive (ER+ve) advanced breast cancer who relapse after previous tamoxifen therapy [1] [2]. Recent randomised trials have shown that NSAIs are superior to tamoxifen as first-line therapy in metastatic disease [3] [4], while in the adjuvant setting preliminary data from the ATAC trial in ER+ve postmenopausal primary breast cancer have shown improved disease free survival for Arimidex in comparison with tamoxifen [5]. As a consequence it is likely that an increasing number of ER+ve postmenopausal women may be treated with an aromatase inhibitor (AI) as their initial endocrine therapy of choice.

Breast cancer cells can adapt to the low levels of oestrogen induced by long-term oestrogen deprivation (LTED) with AIs, such that eventually patients relapse with resistant disease. If these patients still exhibit clinical features suggestive of hormone sensitivity at the time of relapse (e.g. retained tumour ER expression, durable response as first-line therapy or long disease-free interval in the adjuvant setting, soft-tissue indolent disease at subsequent progression, etc.), several questions arise. Firstly, are such patients suitable for further endocrine therapy after failure of an NSAI? At a clinical level, third-line responses have been recorded with the steroidal AI exemestane, although the mechanism for any partial non-cross resistance with the non-steroidal aromatase inhibitor is currently unclear [6]. Secondly, what would the endocrine therapy of choice be following failure of AIs - is there evidence they might respond to an antioestrogen? In addition to understanding mechanisms of acquired resistance, endocrine therapies which are effective following AIs are needed.

1.2 Acquired Resistance to Aromatase Inhibitors

There are emerging data which suggest that endocrine sensitivity may not only be maintained but also enhanced following acquired resistance to long-term oestrogen deprivation (LTED) with AIs. In the laboratory, data suggest that hormone sensitive MCF-7 breast cancer cells treated by LTED eventually adapt and become hypersensitive to the very low levels of oestradiol (E2) [7-9]. In part this is caused by an adaptive increase in ER expression and function [10]. In addition there is evidence for “cross-talk” between various growth factor receptor signalling pathways and ER at the time of relapse, with ER becoming activated and super-sensitised by a number of different intracellular kinases, including mitogen-activated protein kinases (MAPKs) and the insulin-like growth factor (IGF) / AKT pathway [11-13].

While ER may be expressed and hypersensitive in breast cancer cells which become resistant to LTED, there is evidence that they are cross-resistant with tamoxifen [14]. Indeed such cells may perceive tamoxifen as an agonist, being stimulated rather than growth inhibited. In contrast, ER dependent growth and gene transcription in these LTED resistant cells was dramatically inhibited by the non-agonist antioestrogen ICI 182780 (Faslodex) [10] [14]. The ability of Faslodex to downregulate ER levels and its associated lack of any agonist activity may be central to its mechanism of action in this scenario.

As such it is envisaged that Faslodex could be an effective treatment option for ER+ve breast cancer following acquired resistance to LTED as a consequence of AI therapy. There are pharmacological reasons (relating to concentrations required to occupy ER) which suggest that Faslodex might be more effective in an environment of continued low oestrogen. Likewise, growth of breast cancer cells resistant to LTED and hypersensitive to oestrogen could become enhanced upon subsequent release from oestrogen deprivation (i.e. clinically equivalent to removal of the AI at the time of relapse / progression and restoration of physiological postmenopausal E2 levels). Although Faslodex can reduce the growth of resistant LTED cells in-vitro, it is clear that added oestrogen may reduce its growth inhibition. As such, the effectiveness of Faslodex following failure of AIs may be critically dependent on the background E2 levels.

1.3 Pre-clinical Pharmacology of Faslodex

Faslodex (fulvestrant or ICI 182780) is a pure steroidal antioestrogen devoid of agonist oestrogen-like activity both in breast and uterine tissues [15]. In-vitro Faslodex's binding affinity for the ER is approximately 100-fold greater than tamoxifen, and in ER+ve MCF-7 breast cancer cells Faslodex, unlike tamoxifen, is a pure antagonist of oestrogen-regulated gene expression (Cathepsin D and pS2) [16]. ER expression is suppressed and downregulated by Faslodex, without any concomitant rise in epidermal growth factor receptor (EGFR) or transforming growth factor (TGF alpha) expression [17]. Other important anti-proliferative effects of Faslodex on hormonally-regulated breast cancer cells include suppression of insulin-like growth factor receptor (IGF-1R) signalling [18] [19].

In vitro studies have demonstrated that tamoxifen-resistant breast cancer cell lines remained sensitive to growth inhibition by Faslodex [20-22], while in vivo studies in athymic mice showed that Faslodex suppressed the growth of established MCF-7 xenografts for twice as long as tamoxifen and significantly delayed the onset of resistant tumour growth [23]. Taken collectively, these pre-clinical data suggest that Faslodex could be a more effective oestrogen antagonist than tamoxifen, and that the lack of adverse agonist effects on breast cancer cells may be advantageous in the endocrine-resistant setting.

1.4 Clinical Development of Faslodex

1.4.1 Phase I / II Studies

Initial clinical trials of Faslodex were undertaken with administration of a short acting, propylene glycol-based, formulation by daily intramuscular (i.m.) injections. In an open randomised study 56 postmenopausal patients with operable breast cancer were randomised to seven consecutive daily i.m. injections of either 6 mg or 18 mg Faslodex, or to no active treatment (observation control), for 1 week prior to surgery [24]. Faslodex resulted in a reduction in tumour cell proliferation as measured by Ki67 labelling index and a reduction or absence of expression of ER and progesterone receptors (PgR) in ER+ve tumours [24] [25]. In a much larger pre-operative study, 221 patients were randomised to receive either Faslodex over a range of doses (50, 125 or 250 mg i.m.) or tamoxifen (20 mg/day) or matching tamoxifen placebo for 14-21 days prior to surgery [26] [27]. A significant dose-dependent reduction in the levels of ER expression was observed across all three doses of Faslodex compared with placebo and with tamoxifen when given at the 250mg i.m. dose [26].

The clinical efficacy of Faslodex in women with tamoxifen-refractory advanced breast cancer was shown in a small phase II trial in 19 patients who received the monthly i.m. formulation starting with 100mg in the first month, increasing to 250mg for the second and subsequent months [28]. Seven patients demonstrated a partial response in their tumour and six patients stable disease for at least 6 months. Overall the median duration of clinical benefit for the 13 patients was 25 months. These data clearly confirmed the lack of cross-resistance with tamoxifen which had been suggested in pre-clinical studies, supporting a mechanism of action distinct from tamoxifen. Subsequently a comparison with a well-matched historical control group of patients treated with the progestin megestrol acetate suggested a longer duration of response for patients receiving Faslodex (26 months vs 14 months) [29].

1.4.2 Phase III studies

Two phase III studies have compared the efficacy and tolerability of Faslodex (250mg administered once monthly) with Arimidex (1mg daily), in postmenopausal women whose disease had progressed on or after tamoxifen [30] [31]. The North American trial was a double-blind randomised trial and recruited 400 patients, whilst the second Rest of the World (ROW) trial was an open label randomised study. The median time to disease progression was numerically longer for Faslodex compared with Arimidex for both the North American (5.4 vs. 3.4 months) and ROW (5.5 vs. 5.1 months) trials, but was not statistically significant. The objective response rates were not significantly different in either trial (17.5% for both arms in the North American trial, and 20.7 vs.15.7 % for Faslodex and Arimidex respectively in the

ROW trial). In those patients who responded, median duration of response to Faslodex and Arimidex was 19.3 months and 10.5 months, respectively, in the North American trial and 14.3 months and 14.0 months, respectively, in the ROW trial. Overall, the incidence of adverse events was low, and in the double-blind double-dummy North American trial which included a placebo intra-muscular injection in the Arimidex treatment group, there was no difference in injection site reactions compared to the Faslodex treated patients [30]. This suggested that the drug itself does not induce any specific local reactions at the site of injection.

1.5 Scientific Rationale for Study

The hypothesis to be tested in this study is that breast cancers which relapse after an NSAI such as Arimidex or letrozole (Femara™) contain enhanced and activated ER, and that an ER downregulator such as Faslodex is an effective treatment for such patients. Because these cancer cells may be hypersensitive to E2, it is hypothesised that Faslodex could be more effective in an environment of continued "low" compared with "normal physiological" postmenopausal E2 levels. Therefore the first primary aim of the study will be to compare, in a double-blind randomised trial, the progression-free survival of such patients following NSAI failure treated with Faslodex plus concomitant Arimidex (F+A) versus Faslodex alone (F + matching Arimidex-Placebo). A third arm will give a randomised reference control arm for the trial. This will be exemestane, the current endocrine treatment of choice for those who progress following NSAI [6]. (The results of a recent UK survey concluded that 60% of oncologists would prescribe exemestane for patients who progress after response to Arimidex for 1st line metastatic breast cancer (unpublished)). The second primary aim of the study is, therefore, to compare Faslodex alone against the current standard treatment, exemestane. The two primary aims are therefore independent and distinct. This strategy allows any additional benefit by combining Faslodex with Arimidex to be set within the context of the relative efficacy of Faslodex and exemestane.

An exploratory aim described in the associated translational correlative science studies will be to collect accessible tumour biopsies from as many patients as possible relapsing on NSAIs (Appendix A).Molecular, biochemical and cytological assessments will be made in tumour samples / cells of ER expression and activation status, together with studies of activated growth factor signalling pathways. The aim will be to substantiate that ER+ve breast cancers resistant to NSAIs contain upregulated / hypersensitive ER signalling, and that this together with the circulating E2 levels may determine the response to Faslodex.

It is anticipated that this clinical study will establish a clear rationale for the sequential use of Faslodex in women with ER+ve breast cancer who relapse after NSAIs. It is likely that the majority of patients will have received Arimidex which is the most widely used NSAI in the UK, although some centres use letrozole (Femara™). There are no randomised clinical trials of Faslodex in this setting - a small Phase II study has been started by the SAKK group in Switzerland, and in 17 patients they have reported 2 responses and 7 patients with stable disease for >24 weeks [32]. A Regulatory trial will be conducted outside the UK (by AstraZeneca) simply comparing Faslodex directly with exemestane. However this trial will not study the effect of Faslodex in the continuing presence of an aromatase inhibitor, providing a low-oestrogen environment. It is felt that the pre-clinical findings in resistant LTED cells of an activated and hypersensitive ER, together with resistance to tamoxifen yet retained sensitivity to Faslodex, strongly support a clinical trial being started now to define the clinical role of Faslodex in this setting, together with the optimal way of delivering the drug (i.e. with or without concomitant Arimidex).

2. Aims of study

2.1 The primary aims of the study

- To compare the progression-free survival of patients treated with Faslodex plus concomitant Arimidex (F+A) versus Faslodex (F) alone.
- To compare the progression-free survival of patients treated with Faslodex (F) alone versus those treated with the current standard, exemestane (E).

2.2 The secondary aims of the study

- To assess the objective tumour response rate (CR + PR), duration of response, clinical benefit rate (CR/PR + SD $\geq$6 months), duration of clinical benefit, time to treatment failure, and overall survival of patients treated with Faslodex plus concomitant Arimidex (F+A) compared with Faslodex (F) alone.
- To assess the objective response rate, duration of response, clinical benefit rate, duration of clinical benefit, time to treatment failure, progression-free and overall survival of patients treated with Faslodex (without concomitant Arimidex) compared with exemestane.
- In the case that concomitant use of Arimidex with Faslodex provides *equivalent* outcome to Faslodex alone, to compare the progression-free survival of all Faslodex (F and F+A) treated patients with those treated with exemestane (E).
- To determine the tolerability of Faslodex with or without concomitant Arimidex, and compared with exemestane.

2.3 The exploratory aims of the study

- To establish in accessible tumour biopsies from as many patients as possible relapsing on NSAIs: tumour ER expression and activation status (i.e. phosphorylation status); tumour EGFR / HER2 expression and activation of the MAPK / ERK / IGFR / AKT signalling pathways.

3. Study Design

3.1 Study treatments

This is a partially-blind, randomised, multicentre study for eligible patients with locally advanced / metastatic breast cancer who have progressed on the non-steroidal aromatase inhibitors (Arimidex or letrozole (Femara™)). The study will compare the progression-free survival of patients treated with Faslodex plus concomitant Arimidex (F+A) versus Faslodex (F) alone. All Faslodex treated patients will take either an Arimidex or an Arimidex-Placebo tablet once daily, and both patients and clinicians will be blinded to this treatment option (i.e. double-blind). A reference control arm will be included with the steroidal aromatase inhibitor exemestane (E) which is the current endocrine treatment of choice for such patients.

Eligible patients will be randomised in a ratio of 1:1:1 to either:

Faslodex plus Arimidex-Placebo
Faslodex will be administered in the first month using a loading dose schedule of 500mg i.m. on day 1, followed by 250 mg i.m. on days 15 and day 29, and 250 mg i.m. monthly thereafter (section 7.0). Patients will also receive Arimidex-Placebo 1mg orally once daily.

Faslodex plus Arimidex
Faslodex will be administered in the first month using a loading dose schedule of 500mg i.m. on day 1, followed by 250 mg i.m. on days 15 and day 29, and 250 mg i.m. monthly thereafter (section 7.0). Patients will also receive Arimidex 1mg orally once daily.

Exemestane
Patients allocated to exemestane in the reference control arm will receive a 25mg tablet of exemestane once daily (section 7.0).

For all patients, treatment should continue until evidence of disease progression, or withdrawal of treatment in the event of any drug related serious adverse events (SAEs) or patient choice (patients are only considered as withdrawn from the trial if consent is relinquished).

3.2 **When to stop previous NSAI treatment**

Breast cancer cells that are resistant to LTED and are hypersensitive to oestrogen could become enhanced upon subsequent release from oestrogen deprivation i.e. removal of NSAI (Arimidex or letrozole (Femara™)) at the time of relapse / progression and restoration of physiological postmenopausal E2 levels (oestradiol).

The effectiveness of Faslodex following failure of NSAI may be critically dependant on the background E2 levels i.e Faslodex might be more effective in an environment of continued low oestrogen.

An important part of the trial is to assess the effectiveness of Faslodex with or without Arimidex i.e. Faslodex alone versus Faslodex + Arimidex, therefore it is important **not** to stop previous NSAI, until the patient has been randomised and has started their allocated treatment.

In patients who have consented to have blood samples taken for research, this effect will also be investigated by comparing E2 levels before and after 3 months of trial treatment.

4. Patient Selection and Eligibility

4.1 Source of patients

Postmenopausal patients with ER and/or PgR +ve locally advanced / metastatic breast cancer will be recruited from clinics within UK (and possibly European) centres. Patients previously entered into trials of adjuvant therapy are eligible for inclusion in this trial.

4.2 Number of patients

A total of 750 patients will be required.

4.3 Inclusion Criteria

- Female postmenopausal patients defined as:
  - i Age ≥ 60 years **or**
  - ii Aged 45-59 with intact uterus and amenorrhoeic for at least 12 months **or**
  - iii Any age having had a bilateral oophorectomy.
- Histologically or cytologically confirmed adenocarcinoma of the breast.
- Patients with original ER+ve and/or PgR+ve breast cancer which has relapsed or progressed during endocrine therapy with a single agent non-steroidal aromatase inhibitor (NSAI) given as either:
  - adjuvant treatment where the patient received at least 12 months therapy, **or**
  - first-line therapy for locally advanced / metastatic disease. Patients treated with an NSAI as first-line therapy must have had either an objective response (CR/PR) or stabilisation of disease for at least 6 months.
- Sites of metastatic disease which are measurable / evaluable (according to Response Evaluation Criteria in Solid Tumours (RECIST)) should be assessed and followed as either:
  - **Measurable disease:** *must include at least one target marker lesion* ***OR:***
  - **Non-measurable disease (ie evaluable disease):** *must include at least one non-target marker lesion*
- Patients with bone only metastases are eligible provided they have evaluable site of bone metastases that can be followed by Xray or MRI / CT scanning.
- Patients already established on bisphosphonate therapy for at least 6 months may continue on bisphosphonates;
  - Patients who will be started on bisphosphonates for bone metastases must have concurrent soft tissue / visceral sites of disease as the measurable / evaluable target marker lesion(s)
- WHO performance status 0, 1 or 2.
- Prior therapy permissible:
  - Tamoxifen given in the adjuvant or neo-adjuvant setting only.
  - Prior chemotherapy in the adjuvant or neo-adjuvant setting.
  - Prior chemotherapy as first-line treatment for metastatic breast cancer followed by NSAI alone for at least 6 months.
- Adequate haematological function defined by haemoglobin ≥10 g/dl, neutrophil count ≥1.5 x 10^9/l and platelets ≥ 100 x 10^9/l.
- Adequate hepatic function defined by AST and ALT ≤ 2.5 x upper limit of normal. Alkaline phosphatase ≤ 5 x upper limit of normal, unless bone metastases in the absence of liver disease. Renal function adequate defined by creatinine <175 mmol/l.
- Life expectancy of >3 months and suitable for further endocrine therapy.
- Have given written informed consent and are available for prolonged follow-up.

4.4 Exclusion Criteria

- Patients whose primary breast cancer was classified as:
    i. ER -ve and PgR NK
    ii. ER -ve and PgR -ve
    iii. ER NK
- Rapidly progressive visceral disease (i.e. lymphangitis carcinomatosa, diffuse hepatic involvement).
- Patients with malignancies (other than breast cancer) within the last 5 years, except for adequately treated in situ carcinoma of the cervix or basal cell / squamous cell carcinoma of the skin.
- Systemic corticosteroids for > 15 days within the last 4 weeks.
- Investigational drugs given within the previous 4 weeks.
- Patients known to be on any unlicensed non-cancer investigational agent.
- Patients with thrombocytopaenia (platelets <100 x 10^9/l or on anti-coagulant therapy (contra-indicated due to risk of bleeding with i.m. injection of Faslodex).

5. Randomisation

5.1 Randomisation Procedures

Patients are randomised by telephone through the affiliated Clinical Trials Unit:

- ICR Clinical Trials and Statistics Unit (ICR-CTSU), Section of Clinical Trials, The Institute of Cancer Research (Sutton, Surrey) **Tel: 020 8643 7150 (09.00 – 17.00 Monday to Friday)**
- ISD Cancer Clinical Trials Team (Edinburgh)
  Tel: 0131 275 7276 (09.00 – 17.00 Monday to Friday)

Prior to randomisation an eligibility checklist must be completed by the clinician / research nurse.

The following information will be required at randomisation:

- Name of cancer centre (if applicable), name of hospital, consultant and person randomising patient.
- Confirmation that patient is eligible for the trial by completion of the eligibility checklist.
- Confirmation that patient has given written informed consent for randomisation.
- Ascertainment whether the patient has given written informed consent for blood samples and / or tumour biopsies to be taken for research purposes.
- Patient's full name, hospital number, date of birth, NHS number.
- Date and site of first relapse.
- Date NSAI first prescribed and type i.e. Anastrozole (Arimidex^{TM}) or Letrozole (Femara^{TM}).
- Confirmation that the patient is continuing on NSAI.
- Ascertainment whether NSAI has been given:
  i) as adjuvant treatment or
  ii) for locally advanced / metastatic disease.

The caller will be given the patient's unique trial identification number (Trial ID) and will be told whether the patient has been allocated to either:

i) a Faslodex containing treatment **or**
ii) exemestane.

5.2 Stratification

At randomisation, patients will be stratified by:

- centre
- whether previous NSAI treatment was given for adjuvant or locally advanced / metastatic disease.

Since the use of a particular NSAI (i.e. Arimidex or letrozole (Femara^{TM})) is determined at a centre level, stratification by centre will additionally ensure balance for type of previous treatment.

5.3 Following randomisation

- For patients allocated to one of the Faslodex containing treatments the relevant pharmacy department will be sent a fax confirming patient details and Trial ID together with instructions on dispensing the patient's individual treatment. *(*section 7.4.1*)*

For patients allocated to exemestane the clinician should then write a prescription as in routine clinical practice.

6. Trial Evaluations

6.1 At Baseline

- Relevant past medical history and clinical examination.
- Haematology and biochemistry.
- Corecut or excision biopsy for assessment of ER, EGFR / HER2 & signalling pathways (Appendix A) in patients with accessible tumour who are willing to give consent to a biopsy.
- 9 ml blood sample for baseline endocrine evaluation (oestradiol or oestrone) whilst patient still taking NSAI - in patients willing to give consent.

  NB Declining provision of blood samples for research does not exclude a patient from entry into the trial.

  Tumour staging either by CT scan thorax and abdomen, chest X-ray, bone scan and / or skeletal survey, clinical photograph, etc. (Appendix B for definitions of evaluable sites of disease, and criteria for response assessment by RECIST).

6.2 During Study

- Clinical assessment: monthly during the first 6 months, and every 3 months thereafter providing that disease is stable / responding and treatment continues.

  A nurse or qualified person delegated by the Principal Investigator may carry out the monthly treatment evaluation which <u>may</u> be completed as a telephone assessment (i.e. for patients randomised to exemestane).

  Telephone Assessments
  To avoid bias in toxicity reporting, monthly assessment (excluding 3 monthly assessment) may be carried out via telephone. However these must be consistent with clinic visits i.e. exactly the same toxicity questions should be asked in the same manner according to the CRF format. This will enable comparable assessments of all treatments.
- Tumour evaluation every 3 months during treatment, and at time of discontinuation / withdrawal from treatment. Tumour assessment to be conducted by the same imaging technique used to evaluate the indicator lesions at baseline.

  (The investigator must complete the **<u>3 monthly assessment of treatment evaluation</u>** and the patient must be present at these assessments).
- Haematology and biochemistry every 3 months.
- 9 ml blood sample taken for endocrine evaluation (oestradiol or oestrone) at 3 months (or at disease progression if relapse is prior to 3 months).

6.3 Patient follow up following progression or withdrawal from treatment.

Following progression / withdrawal patient will be seen as part of routine clinical practice and details of death will be recorded on CRFs.

6.4 Schema of Trial Evaluations

Time points / Investigations	Screening – within 28 days prior to randomisation	Before treatment begins	Visit 1 Day 1 (Should occur within 7 days of randomisation)	Day 15	Month 1 Day 29 (Monthly assessment form)	Month 2 Day 57 (3 - Monthly assessment form)	Month 3 Day 85 (3 - Monthly assessment form)	Month 4 Day 113 (Monthly assessment form)	Month 5 Day 141 (Monthly assessment form)	Month 6 Day 169 (3 - Monthly assessment form)	Month 9 and every 3 months thereafter (3 - Monthly assessment form)	Withdrawal/ Disease Progression
Histology and WHO performance status	✓ (Eligibility Checklist)	×	×	×	×	×	×	×	×	×	×	×
Details of Primary disease	×	✓ Initial Clinical Data (Form 1a)	×	×	×	×	×	×	×	×	×	×
Details of treatment for locally advanced/metastatic disease	×	✓ Relapse details (locally advanced or metastatic) (Form 1b)	×	×	×	×	×	×	×	×	×	×
Tumour assessment (Clinical examination / X-ray / Ultrasound / MRI / CT Scan / Other – same method to be used for each tumour site)	×	✓ Baseline Evaluation (Form 1c)	×	×	×	×	✓	×	×	✓	✓	✓ (Tumour Evaluation at discontinuation / withdrawal from treatment form)
Haematology / Biochemistry evaluation	✓ (Eligibility Checklist)	✓ (Form 1c)	×	×	×	×	✓	×	×	✓	✓	×
Toxicity reporting	×	×	×	×	✓	✓	✓	✓	✓	✓	✓	✓
Treatment given												
Faslodex	×	×	✓ (Initial Assessment of Faslodex Treatment form)	✓ (Initial Assessment of Faslodex Treatment form)	✓ - Patient to continue on Faslodex monthly →							×
Arimidex/ placebo	×	×	✓ - Patient to continue on Arimidex / Arimidex-Placebo - prescribed every 3 months →									×
OR Exemestane	×	×	✓ - Patient to continue on Exemestane - prescribed as per routine practice →									×
Tissue samples (see Appendix A - only if patient has consented)	For all blood samples complete 'Blood sample form for Biological Studies' (see Site Information File) and send samples to Royal Marsden Hospital by courier (DHL).											
Blood sample for endocrine evaluation (9mls)	×	✓	×	×	×	×	✓	×	×	×	×	✓ Only if relapse is prior to 3 months.
Biopsy of accessible tumour (see Appendix A)	×	✓	×	×	×	×	×	×	×	×	×	×

N.B. CRFs to be completed are given in parentheses.

7. Trial Treatment

Treatment must begin within 7 days following randomisation.

7.1 Drug Administration: Route and Dose Schedule

7.1.1 Faslodex

Must be administered according to the manufacturers Summary of Product Characteristics (SmPC).

Faslodex is to be administered by intramuscular (i.m.) injection into the gluteus maximus muscle by staff specifically trained to do so (section 7.3). Each injection must be administered slowly over at least 2 minutes. A small number of patients have reported minor discomfort following the injection. This may be relieved by gentle massage over the injection site. It is recommended that the patient lies on the opposite side from the injection site in bed on the night following the injection to prevent discomfort from pressure on the injection site. Some redness at the injection site has occasionally been reported which has resolved without treatment. No specific treatment is recommended but, if necessary, symptoms can be treated according to local hospital procedures.

7.1.2 Faslodex Dose Schedule

Faslodex will be administered in the first month using a loading dose schedule of 500 mg i.m. on day 1, delivered as 1 x 5 ml injection in left buttock and 1 x 5 ml injection in right buttock. This will be followed by a 250 mg i.m. injection (5 ml) on days 15 (+/- 3 days) and day 29 (+/- 3 days), and 250 mg i.m. injection (5 ml) monthly thereafter (- 10 days to + 3 days) – until disease progression or withdrawal from treatment.

Treatment Delays

In the event that treatment cannot be given on the scheduled date, it is preferable to give treatments earlier rather than later, this is to ensure that blood levels are maintained. The next cycle should also be timed from the actual date of injection, not the proposed date i.e. if the loading dose is given on 1st March (500 mg) and the next dose on the 15th March (250 mg) the next dose will be due on the 29th March but if this dose is brought forward to the 26th March (250 mg), the dosing continues monthly from the 26th and not the 29th.

7.1.3 Arimidex / Arimidex-Placebo Tablets

Must be taken according to the manufacturer's SmPC for Arimidex.

Patients treated with Faslodex will also receive either 1 mg Arimidex or 1 mg Arimidex-Placebo tablets orally once daily (assigned in a double-blind fashion [section 7.3.1]) – until disease progression or withdrawal from the study.

7.1.4 Exemestane

Must be taken according to the manufacturer's SmPC.

Patients allocated to exemestane should be prescribed 25 mg exemestane to be taken orally once daily until disease progression or withdrawal from the study. Exemestane should be prescribed according to local practice; this is usually either dispensed from the hospital pharmacy or initially from the hospital pharmacy and thereafter prescribed via the patient's GP.

7.2 Formulation, Presentation and Storage

7.2.1 Faslodex

Faslodex will be supplied as a 5% oily solution in pre filled syringes for single dose use. Each pre filled syringe will contain 250 mg of Faslodex (LA ICI 182780) in 5 mls, (i.e. at a concentration of 50 mg/ml), designated as Faslodex 5% w/v injection, formulation number F6521. The syringes must be stored between 2-8^{o}C (not frozen) in a secure location in a pharmacy and protected from light.

Temperature excursions should be minimised and comply with the manufacturer's storage statement. Departure from the recommended storage conditions has a cumulative effect on the product quality if the upper or lower limits are exceeded for a cumulative period of no more than 28 days over the duration of the claimed shelf life.

Fridge breakdowns

In the event of a fridge breakdown the pharmacist should notify ICR-CTSU of the event for advice.

7.2.2 Arimidex

Arimidex will be supplied as pots of 112 tablets. Each tablet is white and film coated containing 1 mg Anastrozole and inactive substances Lactose, Povidone, Sodium Starch, Glycollate and Magnesium Stearate. Arimidex should be stored below 30^{o}C.

7.2.3 Arimidex-Placebo

Arimidex-Placebo will be supplied as pots of 112 tablets. Each tablet is white and film coated containing only the inactive substances Lactose, Povidone, Sodium Starch, Glycollate and Magnesium Stearate. Storage conditions are as for Arimidex in order to maintain the Arimidex-Placebo blind.

7.2.4 Exemestane

For patients allocated exemestane, this will be prescribed by the investigator and dispensed as per routine practice (i.e. following the initial prescription from hospital pharmacy, clinicians may prefer patients to obtain further supplies via their GP).

Each coated tablet contains 25 mg exemestane. Exemestane should be stored below 25°C and protected from light.

7.3 Drug labelling

7.3.1 Arimidex / Arimidex-Placebo

In addition to the supply of Faslodex, each hospital pharmacy department will be sent a supply of Arimidex / Arimidex-Placebo tablets in pots containing 112 tablets sufficient for a 3 month supply for each patient and allowing for some overage. Each pot of tablets will have been labelled with the name of the trial and 'For Clinical Trials use only' and will bear two tear off slips. Each will specify that the contents are Arimidex / Arimidex-Placebo 'Treatment A' or Arimidex / Arimidex-Placebo 'Treatment B'.

Following randomisation, fax confirmation will be sent to pharmacy by the appropriate Trials Unit with patient details and allocated treatment as exemestane or Faslodex and 'Treatment A' or Faslodex and 'Treatment B'.

Following appropriate assignment of Arimidex / Arimidex-Placebo ('Treatment A' or 'Treatment B') the pharmacist must then complete details on the tear off labels as indicated. The 1st tear off slip must be detached and filed as in routine practice within the pharmacy department. The 2nd tear off slip should be attached to the patient's prescription.

The label on the pot as seen by the patient will contain information that conforms to standard detail requirements such as quantity, storage information, expiry date, batch number and any other pharmacy instructions. Each hospital pharmacist must also insert the name of the PI or hospital specific code by which the PI can be identified. Contents will only be stated as '112 Arimidex tablets 1mg or Placebo to match'.

7.3.2 Faslodex

Faslodex has been labelled to include standard detail requirements such as quantity, storage information, expiry date, batch number and any other pharmacy instructions.

There are two labels to each 5 ml syringe box. The pharmacist must complete both labels and then detach the tear off slip and file as in routine practice within the pharmacy department.

7.3.3 Exemestane

Should be labelled and dispensed according to standard local practice for medication dispensed within a clinical trial, but must include a 'For clinical trial use only' label.

7.4 Prescriptions

The type of prescription used in this trial will be as is standard routine practice within each hospital. There is no special prescription for SoFEA.

7.5 Code Breaking

Unblinding is restricted to emergency situations and should only be used under circumstances where knowledge of the treatment is necessary for the proper clinical care of the patient. If the treatment code is broken, the pharmacist must complete a patient code break form clearly stating the reason for the code break. The form must then be signed, dated and returned to the appropriate Trials Unit.

Each hospital pharmacy will be issued with one code break envelope which will specify treatment 'A' or 'B' as being Arimidex or Arimidex-Placebo. This must only be broken by the pharmacist. Details divulged to the clinician must only be in regard to specific treatment for the patient for whom the code is broken and no details should be given as to whether the specific patient was allocated to Treatment 'A' or Treatment 'B' i.e. clinicians must not find out which drug corresponds to treatment 'A' / 'B'.

7.6 Drug Accountability

AstraZeneca are providing the supplies of Faslodex and Arimidex / Arimidex-Placebo free of charge to all participating centres via their drug handling company 'DHP'. ICR-CTSU will liaise closely with AstraZeneca and have prior agreement as to the specific contents of the bottles.

As soon as each participating centre has Site Specific Approval (SSA), R&D approval and the contract agreement between the centre and the appropriate Trials Unit has been signed, ICR-CTSU will fax DHP the details required to ensure that the initial supplies of both Faslodex (6 or 12 pre-filled syringes, depending upon recruitment) and Arimidex / Arimidex-Placebo (6 or 12 pots) are despatched without delay to the relevant hospital pharmacy department. DHP will also notify ICR-CTSU that such deliveries have been despatched.

Records must be kept for all deliveries and a copy of the order / delivery note placed in the Trial Information pack and kept within the pharmacy department as in routine practice. At the end of the trial, it must be possible to reconcile supply and usage of stock. Account must be given of any discrepancies and certificates of delivery and return must be signed.

Each of the pharmacy departments must designate a responsible person for ensuring that:

- investigational products are handled and stored safely and properly;
- investigational products are dispensed only to trial patients and in accordance with the protocol;
- that there is a sufficient supply of investigational products for patients' continued treatment, and in a timely manner, contact ICR-CTSU for re-supply of stock;
- investigational products expiry dates are monitored and are used in order of expiry date order i.e. earliest expiry first;
- and that any unused products are returned or destroyed locally.

8. Pharmacovigilance

For the purpose of this trial, any detrimental change in the patient's condition that occurs after randomisation and within 30 days of the last administration of randomised treatment, which is not due to progression of disease (breast cancer), should be considered either as an AE or SAE.

8.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a drug; the event does not necessarily have a causal relationship with the treatment or usage.

Whenever one or more signs and / or symptoms correspond to a disease or well-defined syndrome only the main disease / syndrome should be reported. For each sign/symptom the highest grade observed since the last visit should be reported.

8.1.1 Adverse Reaction

Any untoward and unintended response in a patient to an investigational medicinal product which is related to any dose administered to that patient.

For the purpose of the trial, AEs that are considered as 'expected' Adverse Reactions are listed below (these are a sub-set of reactions that are specified in individual drug SmPCs):-

Drug	Very common	Common	Uncommon
Faslodex (Fulvestrant)	▪ Hot flushes	▪ Gastrointestinal disturbance including nausea, vomiting, diarrhoea and anorexia ▪ Rash ▪ Urinary tract infections ▪ Headache ▪ Asthenia ▪ Back pain	▪ Leucorrhoea
Arimidex (Anastrozole)	▪ Hot flushes	▪ Asthenia ▪ Joint pain / Stiffness ▪ Vaginal dryness ▪ Hair thinning ▪ Rash ▪ Nausea ▪ Diarrhoea ▪ Headache	▪ Anorexia ▪ Hypercholesterolaemia ▪ Vomiting ▪ Somnolence
Aromasin (exemestane)	▪ Hot flushes ▪ Nausea ▪ Fatigue ▪ Increased sweating and dizziness	▪ Headache ▪ Insomnia ▪ Pain ▪ Skin rash ▪ Abdominal pain ▪ Anorexia ▪ Vomiting ▪ Depression ▪ Alopecia ▪ Peripheral or leg oedema ▪ Constipation ▪ Dyspepsia	

The side effects of combining Faslodex and Arimidex are not known, but it is not expected that they will be any more severe than with either drug on its own. It is also not expected that there would be any greater risk of developing blood clots with either Faslodex, Arimidex or with the combination of the two medications than with any of the treatments that the patient has been prescribed previously.

8.2 Serious Adverse Events (SAE)

ICH GCP defines an SAE as any untoward medical occurrence that:

- Results in death.
- Is life-threatening*.
- Requires inpatient hospitalisation** or prolongation of existing hospitalisation** (excluding hospital admissions for study drug administration, or admission for palliative care, terminal care or elective surgery).
- Results in persistent or significant disability / incapacity.
- Is a congenital anomaly / birth defect
- (Any untoward medical occurrence requiring medical intervention to prevent permanent impairment or damage).

N.B. Details given above in parentheses are an expansion of the SAE definition by ICR-CTSU

* The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure, for continued observation. **Hospitalisation for a pre-existing condition or for further disease progression, including elective procedures, which has not worsened, does not constitute a serious adverse event.**

In addition the following will also be included as an SAE within the SoFEA trial:

- Incidence of second primaries regardless of whether they **occur during or at anytime after treatment**.

Other important medical events that may not result in death, are not life threatening, or do not require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (excluding cancer or result of overdose).

Signs and Symptoms of metastatic disease as determined by the Principal Investigator are not Serious Adverse Events.

Hospitalisation or death due to disease progression should not be reported as an SAE.

8.3 Recording and Reporting of Serious Adverse Events

Refer to flow diagram given in section 8.8

An AE classified as an SAE under the definition given in section 8.2 **must be reported within 24 hours of the Principal Investigator or designated representative becoming aware of the event** using the specific SAE form. The form must be sent by FAX to:

ICR Clinical Trials and Statistics Unit (ICR-CTSU), Section of Clinical Trials,
The Institute of Cancer Research **SAE safety desk on 020 8722 4368.**

At the same time centres affiliated to the ISD Cancer Clinical Trials Team must **also FAX a copy to ISD Cancer Clinical Trials Team on 0131 275 7512.**

These **must** be completed, signed and dated by the Principal Investigator or designated representative.

8.4 Follow up of Serious Adverse Event

The patient must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Information on final diagnosis and outcome of SAE which may not be available at the time the SAE was initially reported should be completed on the relevant part of the original SAE form within 15 days of the initial report and faxed to ICR-CTSU (Centres affiliated to the ISD Cancer Clinical Trials Team must also FAX a copy to ISD Cancer Clinical Trials Team on 0131 275 7512).

8.5 Review of Serious Adverse Event

Once the SAE has been received by ICR-CTSU it will be forwarded to the Chief Investigator (CI) or designated representative for review.

Centres should respond immediately (within 6 days) to requests from the CI or designated representative (via ICR-CTSU) for further information that maybe required for final assessment.

The CI or designated representative will assess the SAE in respect to the following definitions:

Serious Adverse Reactions (SARs) are those SAEs, which are considered to be possibly/probably/definitely related to the trial treatment.

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SARs, which are not classified as "expected".

SUSARs require expedited reporting by trial sponsor (i.e. CI with ICR-CTSU) to MHRA and main REC, therefore every effort should be made to notify Trial Unit/s within the timeframe shown in section 8.3.

8.6 Reporting of SUSARs to MHRA and the Main REC

If an SAE is defined as a SUSAR and is fatal or life threatening, ICR-CTSU will report this to the MHRA and Main REC within 7 days from the date of definition.

If an SAE is defined as a SUSAR and is **not** fatal or life threatening, ICR-CTSU will report this to the MHRA and Main REC within 15 days.

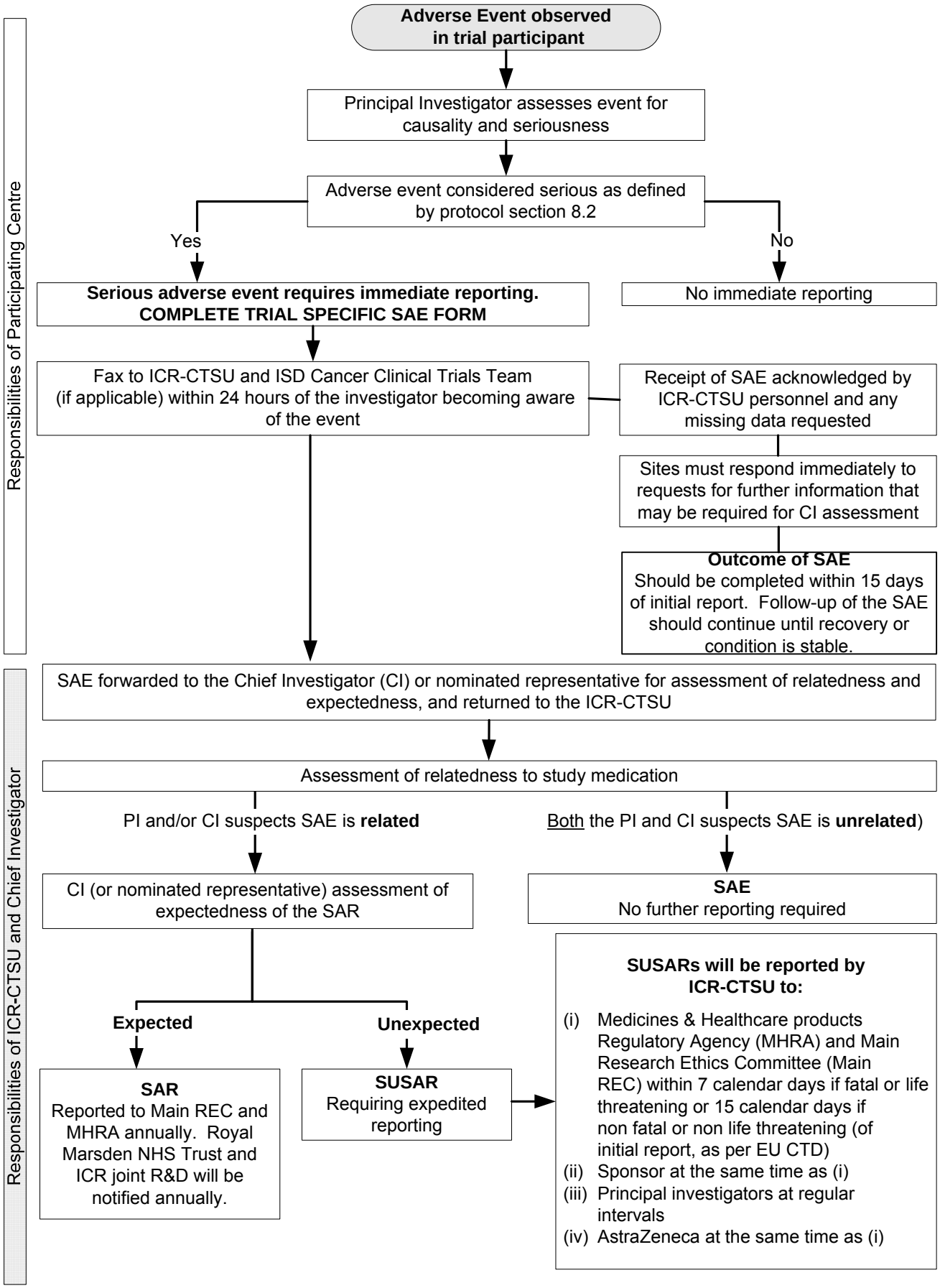
Additional relevant information may be requested from centres, to make the assessment, this should then be sent to ICR-CTSU within 6 days.

8.7 Annual Reporting of Serious Adverse Events

An annual report will be provided to the MHRA and the Main REC after the end of the reporting year. This will be defined as one year after the date when the Clinical Trials Authorisation (CTA) was obtained. This report will be in the form specified by the MHRA and COREC.

8.8 Flow diagram of SAEs reporting, and action following the report.

Flow diagram for SAE reporting, and action following report



9 Statistical Considerations

9.1 Stratification

At randomisation, patients will be stratified by:

- centre
- whether previous NSAI treatment was given for adjuvant or locally advanced / metastatic disease

Since the use of a particular NSAI (i.e. Arimidex or letrozole [Femara™]) is determined at a centre level, stratification by centre will additionally ensure balance for type of previous treatment.

Patients will be identified by a unique identifier (Trial ID) comprising centre number, patient number and appropriate stratification. Once a Trial ID has been assigned, no attempt should be made to use that number again if, for example, a patient withdraws, or if a Trial ID has been incorrectly allocated. No patient should be randomised more than once into the trial.

The randomisation process incorporates a computer generated programme for producing randomly balanced permuted blocks.

9.2 Sample size

This trial will be undertaken in postmenopausal patients with advanced breast cancer who have failed an NSAI and has two primary aims. The sample size has been calculated to allow these two distinct analyses to be carried out independently.

Faslodex plus Arimidex-Placebo (F) versus Faslodex plus concomitant Arimidex (F+A)

The first primary aim of the trial is to detect an improvement in median progression-free survival (PFS) from 5.5 to 7.5 months in patients allocated to F+A compared with F. Patients entering this study will either be “first-line” having progressed on an NSAI in the adjuvant setting, or “second-line” having progressed in the advanced disease setting on first-line NSAI therapy. It is estimated that approximately 20% patients will be first-line, and 80% second-line. From previous published studies the median progression free survival for F was 166 days for second-line patients in trials 0020 and 0021 [30, 31]. It should be noted that patients in these previous Faslodex trials were tamoxifen-treated patients, but for the purpose of power calculations assumptions have been made that similar progression-free intervals will exist for patients who have failed NSAI therapy.

In order to detect a hazard ratio of ≤ 0.73 for F +A compared to F, approximately 440 events are required to have occurred in the trial. Using an estimated accrual of just over 25 patients per month for 24 months, and a minimum follow-up of 6 months, approximately 250 patients will be required for each of the F+A and F groups. This would yield the 440 events required in order to detect a hazard ratio of ≤ 0.73 at a significance level of 5% (two sided) with 90% power.

Faslodex (F) alone versus exemestane (E)

The second primary aim of the trial compares the PFS of patients allocated to F with those allocated to the current standard therapy for these patients, E.

In a Phase II study following failure of previous NSAI the median PFS with E (given mainly as 3rd line therapy) was 90 days [6]. Due to the fact that these patients will have received NSAI as first-line therapy the anticipated median PFS for E treated patients may be higher than that seen in Lonning’s study [6]. If the median PFS is in fact 4 months, then 208 events per arm

would be required to compare it with the expected median PFS of 5.5 months in the F treated patients (translating to a hazard ratio of ≤0.73; α=0.05 (2 sided); 90% power). Approximately 250 patients will therefore be allocated to E.

Consequently, approximately 750 patients in total will be required for this trial, with the primary analysis occurring after 440 patients have progressed in the F+A and F groups.

The AstraZeneca Regulatory study of Faslodex (EFECT) versus exemestane therapy in patients progressing on a first-line NSAI will recruit a total of 660 patients randomised 1:1 between the arms. The results from this study will be compared with those from the current (SoFEA) protocol in a meta-analysis type overview undertaken after the completion of both studies.

Conditional analysis of all Faslodex treated patients with exemestane

If evidence is observed that the PFS of F and F+A is in fact approximately equivalent (two sided and as defined by the observed Δ and its associated precision) then an analysis of all patients allocated to receive F versus those allocated to E will be conducted. The chosen value of Δ will be defined in conjunction with the independent Data Monitoring and Ethics Committee (DMEC). This therefore represents a closed testing procedure and thus does not impact on the significance of the primary endpoint.

9.3 Analysis methods

Objective tumour response rate and clinical benefit rate will be analysed using logistic regression. Duration of response and duration of clinical benefit, measured from the date of randomisation, will only be summarised. Time to progression and time to death will be analysed using the Logrank test and Cox proportional hazards models. Subgroup analyses will be performed according to response to prior NSAI therapy (i.e. for those who received NSAI for advanced disease and achieved a CR / PR), and also according to ER or EGFR / HER2 expression and MAPK / ERK / IGF / AKT activation at the time of relapse in those where this has been analysed in excision biopsies. The prognostic value of disease free interval prior to randomisation will be investigated. For tolerability, all adverse events, serious and non-serious, will be recorded. In addition, data will be collected on weight gain, hot flushes, and injection site reactions.

9.4 Data monitoring and interim analyses

An independent Data Monitoring and Ethics Committee (DMEC) will be established to oversee the safety and interim efficacy of the trial. This committee will be constituted according to MRC Good Clinical Practice (MRC GCP). The DMEC will meet on a regular basis as they see fit, but no less than annually. Following each meeting, the DMEC will report their findings and recommendations to the Trial Steering Committee (TSC) and to the Trial Management Group (TMG). Interim analysis (split by treatment group) of side-effects, tolerability, progression-free survival, objective tumour response rate (CR + PR), duration of response, clinical benefit rate (CR/PR + SD ≥6 months), duration of clinical benefit, time to treatment failure, and overall survival for all randomised patients will be supplied in strict confidence by the trial statisticians to the DMEC together with any other analyses that the DMEC may request. The complete DMEC reports will remain confidential to the DMEC members and statisticians providing the report, however the Chief Investigator and Trial Coordinators will receive subsets of the report as seen fit by the DMEC (e.g. accrual, compliance, data completeness). Basic accrual data and safety reports, aggregated across the two treatment groups will be produced at appropriate periodic intervals and distributed to the TMG and to AstraZeneca.

The main criterion for early stopping of the trial by the TSC upon suggestion from the DMEC will be that evidence from the trial and from other sources suggests a) proof beyond reasonable doubt that for all, or for some types of patient, one treatment regimen is clearly indicated or contra-indicated in terms of a net difference in PFS and b) evidence that might

reasonably be expected to influence routine clinical practice. Criteria for the above will usually be a difference in PFS significant at $p<0.001$ by overall log-rank analysis. No results on PFS will be made available to participants or AstraZeneca until the DMEC consider the results to be clinically and statistically informative.

9.5 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 remaining on treatment receives the last dose of the investigational medicinal product (IMP).

Follow-up of all randomised patients will continue in the post-treatment phase.

For the purposes of Main REC approval, the study end date is deemed to be the date of the last data capture.

9.6 Analyses for Publication

Unless the DMEC advises otherwise, it is expected that the first analyses for publication / presentation will be performed when the required number of events is reached. All trial data are owned by the Trial Management Group (TMG).

9.7 Publishing policy

All publications and presentations relating to the trial will be authorised by the TMG. A writing committee may be appointed. Authorship will include the principal investigators, statisticians and trial coordinators. Further authorship will be determined by centre accrual. The trials offices who have undertaken the data management and all participating centres will be acknowledged in the final manuscript according to patient accrual.

Participants will only present data separately to the total data available, with the permission of the TMG, and not less than 6 months after publication of the main results.

AstraZeneca has the right to review all abstracts, papers, or other research communications prior to their submission to journals, meetings, or conferences and all such communications will be circulated to the Trial Steering Committee (TSC) for their information and comment. AstraZeneca may request removal of propriety information and may suggest editorial changes in the papers to the TMG. The TMG has final authority over the content of all publications.

10. Research Governance

10.1 Trial Administration

Sponsorship activities and delegated responsibilities are shared between the employer of the Chief Investigator (The Royal Marsden NHS Foundation Trust) and The Institute of Cancer Research in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments and in line with the Research Governance Framework for Health and Social Care and the principles of GCP. Both parties agree to allow inspection of sponsors' premises by the competent authorities.

The Institute of Cancer Research is responsible for administering, funding and co-ordinating any required legal agreements and investigator statements.

10.1.1 Chief Investigator responsibilities include:-

- Trial authorisation (including responsibility for protocol, submissions to MHRA / COREC, informing ICR-CTSU of centres that have Site-Specific assessment (SSA), selection of investigators);
- Ensuring that the trial is conducted in accordance with Good Clinical Practice – delegating responsibilities noted below to ICR-CTSU;
- Pharmacovigiliance – The Chief Investigator or, in his absence, a designated representative is responsible for a prompt decision as to which serious adverse events are SUSARs, and for prompt reporting to ICR-CTSU. Other responsibilities noted below are delegated to ICR-CTSU.

10.1.2 ICR-CTSU responsibilities

The Chief Investigator has delegated responsibility to ICR-CTSU for the trial conduct as specified in the agreement between the centre and ICR-CTSU / ISD Clinical Trials Team.

ICR-CTSU has overall responsibility for facilitating and coordinating the conduct of the trial and is also responsible for collating data obtained, and undertaking and reporting interim and final analyses.

10.1.2 Trials Units responsibilities:-

The day to day management of the trial is being undertaken jointly by ICR-CTSU (Sutton) and ISD Cancer Clinical Trials Team (Edinburgh). All data will be entered onto a database at ICR-CTSU, and one at ISD Cancer Clinical Trials Team.

The responsibilities of ICR-CTSU and / or ISD Cancer Clinical Trials Team for the day-to-day management of the trial will include the following:

- Trial initiation visits to selected centres and early visits to the remainder;

  It is important that the investigator and their relevant personnel are available during these visits and that sufficient time is devoted to the process
- communication with / submission to local ethics committees;
- randomising patients;
- submission of monthly accrual figures to the ICR-CTSU within the first week of each month;
- receiving completed CRFs from the hospitals;
- raising and resolving queries with local investigators;
- logging data received; raising queries;
- monitoring of centres at agreed frequency;

- informing ICR-CTSU (in writing) of Serious Adverse Events, code breaks, protocol violations;
- requesting drug supply via ICR-CTSU;
- circulating unexpected drug related SAEs and safety reports to centres.

10.1.3 Site-Specific responsibilities:-

Local sites should conduct the trial in accordance with the clinical trials agreement, SOPs, principles of GCP and current trial protocol.

10.2 Data Management

10.2.1 Case Report Forms (CRFs)

Case Report Forms (CRFs), which are in the form of a booklet, should be completed for all patients and should not be made available to third parties.

CRFs are in duplicate. The top copy must be sent by the designated staff member i.e. Data manager or Research nurse to the affiliated Trials Unit (either ICR-CTSU or ISD Cancer Clinical Trials Team) as soon as they are due. The bottom copy must be retained in the booklet and held by the investigator. All sections are to be completed on the form before sending or submitting to the affiliated Trials Unit. If information is not known it must be clearly stated.

10.3 Protocol Compliance

SoFEA is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the EU Directive and principles of GCP.
Staff from centres that have attended either the Investigator meeting and/or Nurses training day will not require start-up visits unless there is a specific request.

All staff who are to administer Faslodex will require training (section 7.3).

10.4 Data Acquisition and On-site Monitoring / Auditing

By participating in the SoFEA trial the Principal Investigators at each centre are confirming agreement with his / her local NHS Trust to ensure that:

- sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs;
- source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits;
- all staff at their centre who are involved with the trial will meet the requirements of the EU Directive;
- original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent;
- copies of CRF's are retained for 15 years to comply with international regulations;
- staff will comply with the Trial Guidance Notes for SoFEA.

The affiliated Trials Unit will monitor receipt of CRFs and evaluate incoming CRFs for compliance with the protocol, inconsistencies and missing data.

Participating centres may be monitored by the Trials Unit and possibly by Health Authorities. Monitoring by Trials Units will confirm compliance with the protocol and source data verification (SDV).

Site auditing/monitoring will be conducted at a proportion of participating centres at least once during the course of the trial. If a monitoring visit is required the Trials Unit will contact the centre to discuss dates of proposed visit. Once a date has been confirmed a list of names of patients whose notes will be monitored / audited during the visit will be sent to the centre. This list will be sent out in advance to give sufficient time for the notes to be made available. (The Trial Statistician will decide what percentage of patients are to be monitored / audited).

If any problems are detected in the course of the monitoring / auditing visits then the Principal Investigator and the Trials Unit will work together to resolve queries to determine the centre's future participation in the study.

10.5 Financial Matters

SoFEA is an investigator designed and led trial that has been subjected to independent peer review and approved by the Clinical Trials Awards and Advisory Committee (CTAAC) of Cancer Research (UK) and thus meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

Research costs (to the Trials Units) are being funded via an educational grant provided by AstraZeneca. Faslodex and Arimidex / Arimidex-Placebo are provided free of charge by Astra Zeneca. If additional financial support is received from any other source, this will be made apparent to the Main REC and CTAAC, but will not require a protocol amendment.

No individual per patient payment will be made to trusts or investigators, but NCRN (or regional equivalent) network resources should be made available as the trial is part of the NCRI trials portfolio by virtue of its approval by CTAAC.

11. Clinical Risk Assessment

Generic Risk Assessment Hazards to patients, study and organisation have been performed for the SoFEA Trial and have been considered low risk.

12. Confidentiality and Liability

12.1 Liability / Indemnity / Insurance

This study is an investigator-led trial endorsed by the Clinical Trials Awards and Advisory Committee (CTAAC) of Cancer Research UK and the UK Medical Research Council. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

12.2 Patient Confidentiality

The patient's full name, date of birth, hospital number and NHS number (or Community Health Index and / or hospital number in Scotland) will be collected at randomisation to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential, and to preserve each subject's anonymity, only their initials and date of birth will be recorded on subsequent Case Report Forms.

The investigator must keep a separate log of patients' trial numbers, names, addresses and hospital numbers. The investigator must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The investigator must ensure that patient' confidentiality is maintained.

ICR-CTSU / ISD Cancer Clinical Trials Team will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the Trials Units will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. (In the case of special problems and / or government queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected).

12.3 Ethics Issues

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

It is the responsibility of the investigator to obtain approval of the trial protocol and any subsequent amendment from the Main REC. All correspondence relating to Research Ethics committees should be filed by the Investigator. Copies of the Main REC approval should be forwarded to ICR-CTSU by the Chief Investigator.

It is the responsibility of the investigator to give each patient, prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. Patients must be informed about their right to withdraw from the trial and the possible risk involved. Written patient information must be given to each patient before enrolment. The written patient information is an approved patient information sheet according to national guidelines. It is the responsibility of the investigator to obtain signed informed consent from all patients prior to inclusion in the trial.

The patient information sheet provided in the SoFEA trial should be provided in addition to the standard hormone therapy patient information sheet that is provided by the centre and used in routine practice.

Patient identification data will be required at randomisation to assist with long-term follow-up.

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APPENDIX A -Translational Correlative Science Studies associated with SoFEA

AIM

To conduct molecular, cytological and biochemical analyses in tissue and blood and to establish a scientific rationale for the use of the pure anti-oestrogen Faslodex in women with endocrine-sensitive breast cancer following failure of aromatase inhibition.

Material for Study

a) Acquisition of primary tumour specimen blocks for centralised assessment.
b) Acquisition of metastatic tissue specimens at initiation of trial therapy.
c) Creation of tissue microarrays.

a) Acquisition of primary tumour specimen blocks for centralised assessment.

Rationale

Blocks of the primary tumour will be retrieved to assess baseline measurements of hormone and growth factor receptors and signal transduction components. These factors may predict for primary response to endocrine treatment, and it is hypothesised that acquired changes (particularly in growth factors) may account for the development of resistance [1, 2]. Therefore patterns of expression will be compared with metastatic tissue at relapse (see below) to gain insight into mechanisms of resistance to aromatase inhibitors (AIs).

Practical aspects

Details of the primary tumour will be collected on the initial clinical data form in the CRFs, which will include:

- Date of original diagnosis
- Name of reporting pathologist
- Histology number
- Location of paraffin blocks

At the end of trial recruitment all paraffin-embedded blocks from the original primary tumour surgical specimen from as many patients as possible (who have given consent), will be requested by the Trials Unit to be sent by post to the Academic Department of Biochemistry, Royal Marsden NHS Foundation Trust, London SW3 6JJ. In previous trials blocks have been acquired from up to 80% of trial patients. Up to 10 sections from a representative tumour block will be cut and stained by immuno-histochemistry (IHC) for hormone receptors (ER, PgR), peptide growth factor receptors (HER2, EGFR) and total/activated components of the MAPK and AKT signal transduction pathways. Antibodies for IHC use against phosphorylated (activated) kinases (ie P-ERK1/2, P-p38MAPK, P-Akt) are in regular use in Professor Dowsett's laboratory. Three x 600µm cores will be taken for the construction of tissue microarrays for the analysis of other molecular markers. All blocks will be returned to the referring centre / pathology laboratory.

b) Acquisition of metastatic tissue specimens at initiation of trial therapy.

Rationale

When available this tissue will be analysed with respect to the biomarkers and pathways discussed above. Fresh frozen tissue will be used for gene expression profiling. The tumour phenotype at relapse after aromatase inhibitor will be compared with the primary sample retrieved above, and will also be correlated with clinical response to treatment in the SoFEA trial. This may enable the identification of the molecular profiles / phenotypes at relapse on AIs which predict for sensitivity to Faslodex.

Practical aspects

Wherever possible accessible metastatic deposits (such as skin nodules, locally advanced breast tumours or lymph nodes) will be sampled prior to trial initiation by core biopsy or surgical excision. Specific written informed consent will be sought from patients for these biopsies. From previous studies it is estimated that such tissue will be available in between 20-25% of patients eligible for the SoFEA trial. Tissue will be split equally between fresh frozen (for mRNA and protein studies) and formalin fixation for IHC studies. The fresh frozen tissue should be stored in liquid nitrogen and transferred to Academic Department of Biochemistry, Royal Marsden NHS Foundation Trust, London SW3 6JJ on cardice. The formalin-fixed tissue should be sent to the same address at ambient temperature.

The mRNA extracted from frozen tissue will be used for cDNA microarray gene expression studies. Where indicated from the cDNA arrays or other parallel studies, real-time (quantitative) PCR of specific highlighted genes will be performed. In addition protein extracts will be used to measure activated ER, activated ERK 1/2 and Akt, and IGFR / IRS signalling pathways by Western blotting. At present antibodies against activated phosphorylated ER (ie at sites such as Ser^{118} and Ser^{167}) are available for Western blot analysis only (in due course assays may be developed to study these by IHC in fixed tissues).

Formalin-fixed metastatic pre-treatment tissue will be analysed by IHC for hormone receptors (ER, PgR), peptide growth factor receptors (HER2, EGFR) and total/activated components of various signal transduction pathways (i.e. P-ERK1/2, P-p38MAPK, P-Akt), and comparison made with primary breast cancer samples from the same patients. This will allow an unique study of the intra-patient change in ER and growth factor signalling associated with acquired resistance to aromatase inhibitors, and will determine in-vivo whether cross-talk activation of ER accounts for resistance, and in particular whether this predicts for response to Faslodex in the context of the randomised trial.

c) Creation of tissue microarrays.

Rationale

Tumour specimens will also be used to create tissue microarrays as a resource for future studies. As antibodies against new biomarkers from various signal transduction pathways are discovered, these can be analysed retrospectively in the constructed tissue arrays from this treatment cohort.

Practical aspects

These tissue arrays will be created from available primary and metastatic blocks of tumour using protocols in routine use at the Academic Department of Biochemistry, Royal Marsden NHS Foundation Trust, **London SW3 6JJ.** . Previous tissue microarrays from over 800 patients have been constructed as part of the national adjuvant TACT (Taxotere as Adjuvant Chemo Therapy) trial, as well as a pre- and post-tamoxifen resistance array from 56 patients with advanced breast cancer.

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APPENDIX B - Response Evaluation Criteria in Solid Tumours (RECIST)

Quick Reference

Eligibility

Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques and:-

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumours of the chest, abdomen and pelvis. Head and neck tumours and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumour lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumour evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumour response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumour markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g. after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumour.

- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR):	Disappearance of all target lesions.
* Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
* Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level.
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits.
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. ($^{+}$)

($^{+}$) Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target lesions	**Non-Target lesions**	**New Lesions**	**Overall response**
CR	CR	No	CR
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumour types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.