N-SAS BC 05

National Surgical Adjuvant Study of Breast Cancer

CSPOR

Comprehensive Support Project for Oncology Research (CSPOR)

National Surgical Adjuvant Study of Breast Cancer (N-SAS BC)

Randomized Study to Assess the Efficacy of a Further 5 Years of Anastrozole Treatment for Postmenopausal Women with Breast Cancer After Completing 5 Years of Anastrozole Treatment-Containing Adjuvant Endocrine Therapy

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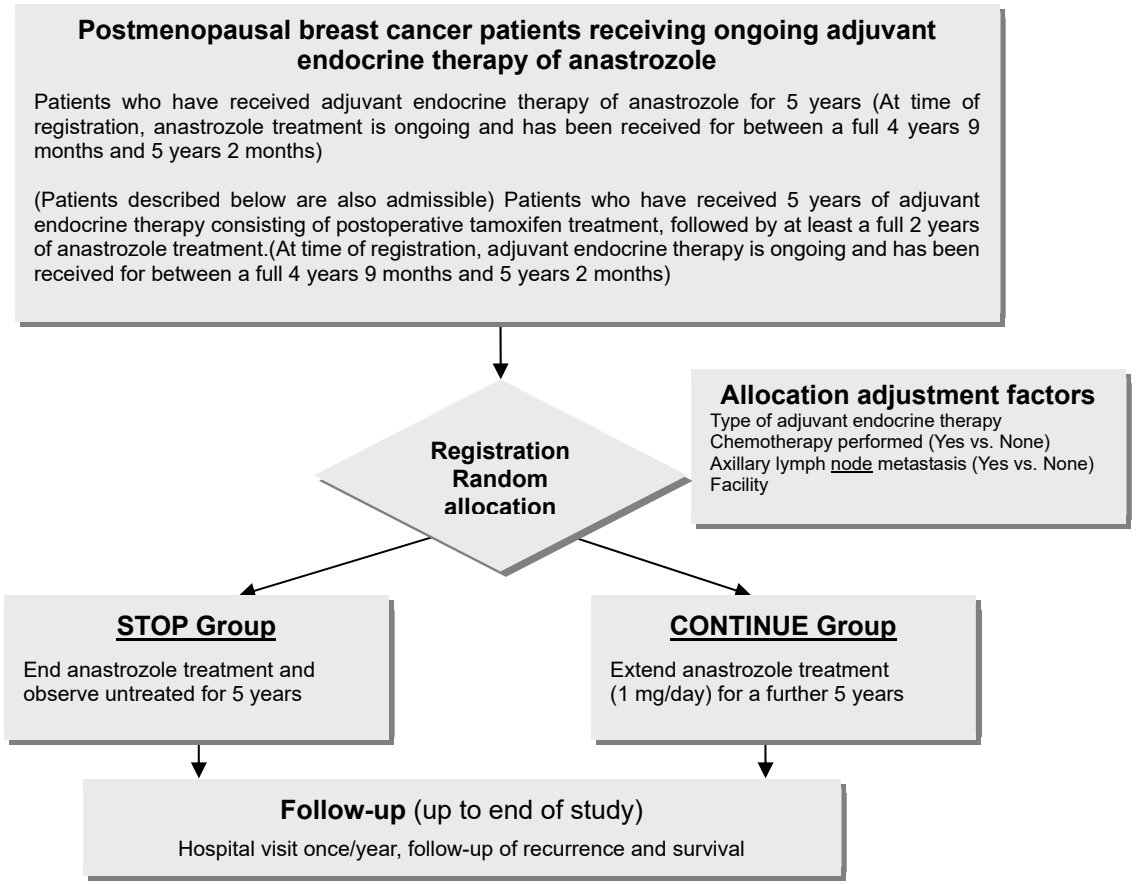
0 Overview

0.1 Trial schema



Abbreviated Study Title: AERAS (Arimidex Extended adjuvant Randomized Study)

0.2 Study design

This is a multicenter, open label, randomized, parallel-group study.

0.3 Objectives

1) To demonstrate the superiority of treatment efficacy in the CONTINUE group against the STOP group in terms of disease-free survival.
   To also evaluate overall survival and distant disease-free survival.
2) To evaluate the safety of a 5-year extension of anastrozole treatment.
3) To evaluate health-related quality of life (HRQOL) and cost-effectiveness (utility).
4) To establish and expand information networks enabled by the participation of general practitioners specializing in breast cancer in clinical trials.

Primary endpoint: Disease-free survival (DFS)

Secondary endpoints: Overall survival (OS), distant disease-free survival (DDFS), adverse events, HRQOL, cost-effectiveness (utility)

Other endpoints: Bone density, joint symptoms

0.4 Selection criteria

Patients will meet all the criteria below.

1) Patient has been diagnosed histologically with invasive breast cancer, has undergone surgery on the primary female breast cancer, and is menopausal at registration.
   The requirement for being menopausal is to meet at least one of the criteria below.
   a) ≥55 years of age
   b) ≥45 years of age with amenorrhea for 2 years or more, and has not undergone a hysterectomy
   c) Has undergone bilateral oophorectomy
2) The patient has not used LH-RHa and any of the below criteria applies regarding adjuvant endocrine therapy.
   a) Initial therapy of anastrozole treatment for 5 years and ongoing (ANA)
      (At time of registration, anastrozole treatment that is ongoing and has been received for between a full 4 years 9 months and 5 years 2 months will be admissible)
   b) Initial therapy of tamoxifen treatment followed by at least a full 2 years of anastrozole treatment, comprising adjuvant endocrine therapy of a total of 5 years that is ongoing. (TAM→ANA)
      (At time of registration, adjuvant endocrine therapy that is ongoing and has been received for between a full 4 years 9 months and 5 years 2 months will be admissible)
3) TNM staging at first examination (before surgery) of T1-3, N0-2, M0 (3.1 Clinical stage

classification)

4) Positive for at least one of hormone receptors, estrogen receptor or progesterone receptor.
5) PS (ECOG) 0, 1 (3.3 Performance status evaluation)
6) Aged ≤80 years at time of registration.
7) Neither recurrence nor contralateral breast cancer found on examination within 6 months prior to registration.

   Only either a bilateral mammogram or breast ultrasound (one-sided in patients with mastectomy) is required for this examination. Examination of areas other than the breasts (chest, abdomen, bones, etc.) will be performed according to the normal examination policies of each facility.
8) Patient has adequate organ function.

   Meets all the criteria below (according to laboratory test results from within 3 months prior to registration).

   a) Leukocyte count: ≥3,000/mm^3
   b) Platelet count: ≥100,000/mm^3
   c) Hemoglobin: ≥9.0 g/dl
   d) Total bilirubin: ≤1.5 mg/dl
   e) GOT and GPT ≤2.5 times the facility upper limit of normal
   f) Creatinine: ≤1.5 mg/dl
   g) No history of myocardial infarction or congestive heart failure
   h) No ischemic heart disease or valvular disease that requires treatment
9) Consent for study participation obtained in document form from the patient herself

0.5 Exclusion criteria

Patients meet any of the criteria below.

1) Patient has a metachronous or synchronous bilateral breast cancer
2) Patient has invasive cancer of another organ within 5 years after the end of treatment
3) Medical history of deep vein thrombosis
4) Medical history of bone fracture attributed to osteoporosis, and has symptoms of osteoporosis at time of registration
5) Patient is receiving ongoing treatment in the form of hormone replacement therapy or a selective estrogen receptor modulator (SERM)
6) Currently participating in another clinical trial with the objective of preventing the postoperative recurrence of breast cancer
7) Patient is deemed unsuitable for study participation by an attending physician

0.6 Treatment

Patients are allocated randomly to either the STOP group or CONTINUE group.

STOP group: Observation untreated for 5 years

CONTINUE group: 5-year extension of anastrozole treatment (once daily, 1 mg/day, oral administration)

0.7 Scheduled number of patients and study period

Scheduled number of patients: 1250 in each group and 2500 patients in total.

Registration period: 5 years (from registration of first patient)

Study period: 10 years

Scheduled follow-up period: 5 years (maximum of 10 years)

1 Objectives

This randomized study will be performed in patients who have completed 5 years of adjuvant endocrine therapy for hormone-responsive breast cancer, which will compare the current standard treatment period for adjuvant endocrine therapy of 5 years (STOP group) with a 5-year extension of endocrine therapy in the form of anastrozole treatment (CONTINUE group).

The objectives of this study are as described below.

1) To demonstrate the superiority of treatment efficacy in the CONTINUE group against the STOP group in terms of disease-free survival (DFS).
   To also evaluate overall survival (OS) and distant disease-free survival (DDFS).

2) To evaluate the safety of a 5-year extension of anastrozole treatment.

3) To evaluate health-related quality of life (HRQOL) and cost-effectiveness (utility).

4) To establish and expand information networks enabled by the participation of general practitioners specializing in breast cancer in clinical trials..

1.2 Primary endpoint

Disease-free survival (DFS)

1.3 Secondary endpoints

Overall survival (OS), distant disease-free survival (DDFS), adverse events, HRQOL, cost-effectiveness (utility).

1.4 Other endpoints

Bone density, joint symptoms

2 Background

2.1 Standard adjuvant endocrine therapy for postmenopausal breast cancer patients

An examination of data on postmenopausal breast cancer patients by the Japanese Breast Cancer Society (JBCS) in 2004 found that postmenopausal breast cancer accounted for approx. 60% of all female breast cancers in Japan, and that over 70% of all breast cancers were hormone responsive breast cancers. Consequently, improving the prognosis for postmenopausal, hormone responsive breast cancers will lead to an overall improvement in breast cancer prognosis.

The use of tamoxifen (TAM) as a adjuvant endocrine therapy has resulted in a marked improvement in prognosis, and 5 years of TAM treatment has been the recommended standard therapy in hormone responsive patients (St Gallen, 2003[1]). However, TAM use entails problems such as cancer recurrence and adverse reactions including endometrial cancer and venous thrombosis, and for these reasons has not been a fully adequate solution (EBCTCG 1998[2]).

Aromatase inhibitors (AIs) have the potential to control breast cancer by lowering the concentration of tumor and systemic female hormones. The mid-1990s saw the appearance of third generation drugs, anastrozole (ANA) and letrozole, and there was a substantial change from the exclusive use of TAM as adjuvant endocrine therapy. After reports emerged of results showing the efficacy of these AIs as first line treatments[3] and even secondary treatments[4] for advanced recurrent breast cancer, a number of clinical trials were performed with the expectation that these AIs could be applied as postoperative endocrine therapies, and in turn the results of those clinical trials have been presented. Regarding the question as to whether to chose TAM or AIs as the initial treatment for adjuvant endocrine therapy, the ATAC trial[5] and BIG1-98 trial[6] were conducted. With regard to the question as to whether AI should replace TAM for patients receiving TAM currently, the ITA trial and IES trial[7] were conducted. In all studies, the results from AI treatment surpassed those of TAM treatment.

In 2004 and in light of these trial results, ASCO that was previously extremely wary of changing treatment away from TAM also decided to recommend AIs as adjuvant endocrine therapy for hormone responsive postmenopausal breast cancer (ASCO Technology Assessment 2004[8]).

2.1.1 The usefulness of anastrozole (ANA) as postoperative adjuvant therapy

The usefulness and safety of third generation AIs (anastrozole, exemestane and letrozole) has been demonstrated against TAM treatment in randomized studies. Below are the results of major clinical studies that examined ANA use and distinguished between “Initial Therapy” which uses AI as an initial therapy after surgery and “Switching Therapy” which uses TAM for 2-3 years then switching to an AI.

(1) Clinical study of AI as initial therapy after surgery (Initial Therapy)

Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial[9]

9366 postoperative patients with postmenopausal, invasive cancer were allocated randomly to one of three groups, an (1) ANA + placebo group, (2) TAM + placebo group, and (3) ANA + TAM group. The groups were compared for recurrence-free survival and adverse events. By December 2001, at a median duration of observation of 33 months, an academic report described the usefulness of treatment in the ANA group already having been demonstrated in hormone responsive patients. A debate ensued concerning how to manage the rest of the study. At the same time, results in the concomitant treatment group were not superior to those in the TAM group, and so treatment of concomitant treatment group was discontinued. By a median observation period of 68 months, the Disease-Free Survival (DFS) was significantly higher in the ANA group than in the TAM group with the hazard ratio (HR) of 0.83 (P=0.005) for hormone responsive patients. However, there was no significant difference in the Overall Survival (OS) with a HR of 0.97.

Results at this point also showed significantly fewer drug-related adverse events in the ANA group at 4.7%, compared to 9.0% in the TAM group (P<0.0001) demonstrating superior safety in the ANA group.

(2) Clinical study of 2-3 years of TAM treatment followed by ANA (Switching Therapy)

1) **Italian Tamoxifen Anastrozole trial**[10]

448 postmenopausal patients (with lymph node metastasis and hormone responsiveness) receiving ongoing TAM treatment were divided into (1) a group that continued TAM treatment and (2) another that switched to ANA treatment. Both groups received treatment for 5 years each in total. By a median observation period of 36 months, in terms of DFS the HR of 0.35 (P=0.001) demonstrated a significantly more favorable result in the group that switched to ANA treatment.

2) **ABCSG trial and ARNO 95 trial**[11]

Two clinical trials have been conducted in patients with postmenopausal, hormone responsive breast cancer who completed two years of TAM treatment. The two trials were analyzed together and the result was reported. Approx. 1600 patients were registered to each group, consisting of a group switched to ANA treatment and a group that continued TAM treatment while treatment was unblinded. By a median observation

period of 28 months, in terms of DFS the HR of 0.60 (*P*=0.0009) demonstrated a significantly more favorable result in the treatment-switching group.

2.1.2 The safety of anastrozole as postoperative adjuvant therapy

In the ATAC trial, the frequency of adverse events when using ANA as adjuvant therapy was lower relative to TAM. In particular, the frequency of events such as gynecological adverse events including endometrial cancer, thrombosis, and hot flush was significantly lower.

Conversely, the adverse events, bone fracture and arthralgia, were significantly more frequent with ANA treatment, observed at respective frequencies of 11% and 35%. Based on these results, 5 years of ANA treatment is safer than TAM and is not problematic in terms of safety. However, incidence of adverse events is unknown beyond 5 years of use, care must be taken to observe mainly for bone-related adverse events.

2.1.3 Extension of endocrine therapy

The use of TAM as endocrine therapy has been compared for administration periods of 1, 2, 5 years and longer. Up to a period of 5 years, the longer treatment is performed the better the effect becomes. Since the effects of TAM continue for a period of time after stopping treatment, long-term observation is required to determine the relation between the duration of TAM treatment and the efficacy. The results of comparative trials of treatment for 5 or more years, such as NSABP B-14[12], show no efficacy in extending the treatment period past 5 years and, consequently, in current clinical practice the standard period of treatment is 5 years.

An EBCTCG[13] meta-analysis of TAM treatment for 5 years in estrogen receptor positive (and unknown) breast cancer patients found recurrence and mortality remained significantly reduced in the TAM treatment group after 15 years of follow-up relative to the group not treated with TAM. This result is evidence of the usefulness of adjuvant endocrine therapy. However, the cumulative rate of breast cancer recurrence in the TAM group was 15.1% at 5 years, 24.7% at 10 years and 33.2% at 15 years, showing that recurrence occurs dependent on time after the completion of 5 years of TAM treatment, and indicating a need to extend the period of endocrine therapy in estrogen receptor positive breast cancer patients.

Because of the existence of trial results that show for a small sample group the efficacy of extending TAM treatment past 5 years cannot be ruled out (ECOG trial[14]), and the results to two additional clinical trials (ATLAS, aTTom) that explored the efficacy of extended treatment with tamoxifen, based on these results a new judgment will be reached.

The MA17 trial[15] demonstrates the additional effect of using an AI (letrozole) to extend endocrine therapy after 5 years of TAM treatment. After completing 5 years of TAM treatment, more than 5000 patients were allocated to receive letrozole or a placebo for a further 5 years. By a median observation period of 30 months, the prognosis in terms of DFS in the letrozol group had improved significantly

(HR=0.58, *P*<0.01). The results showed no difference in overall survival, but when considering only patients with lymph node metastasis there was a significant reduction in mortality in the letrozole group (HR=0.61, *P*=0.04). In light of the above results, it may be efficacious to extend endocrine therapy by changing to an AI after completing 5 years of TAM treatment.

2.2 Study design rationale

Since both the initial therapy and switching therapy regimes, using ANA described above have resulted in a favorable prognosis relative to 5 years of TAM treatment only, both 5-year treatment methods have been chosen as the standard arm of this study. Although the MA17 trial only suggests the usefulness of extending endocrine therapy using an AI (letrozole) after completing 5 years of TAM treatment, there is no data on using an AI to extend endocrine therapy past 5 years when using an AI either from the start of treatment or switching to an AI during the first 5 years of treatment. An NSABP trial that is currently ongoing is being performed in patients who are in just this position, and randomly allocates patients to either 5 years of letrozole treatment or a placebo (NSABP B-42). The present study differs from the NSABP trial in being able to collect data on using the endocrine therapy ANA as its third generation AI, in limiting pre-study AI treatment to ANA and collecting data on more than 5 years of additional ANA treatment, and collecting data over an extended period of ANA treatment lasting 10 years. By incorporating at least 5 years and up to 10 years of ANA treatment, this study will not only demonstrate the effects of extended endocrine therapy, but can also be used to analyze the efficacy and safety of ANA treatment for a period that exceeds 5 years.

2.3 Patients eligible for registration

In August 2006, a questionnaire was sent to 170 supervising physicians of 158 facilities registered with the CSPOR concerning patients currently receiving postoperative treatment with an aromatase inhibitor. A response was obtained from 111 facilities.

Responses detailed approximately 3700 patients in total in all facilities who had received initial treatment with ANA after surgery and would complete 5 years of ANA treatment in the next 2 years. Approx. 60 facilities showed interest in the study and stated consent for participation could be obtained, which was deemed to account for over 2000 patients. No survey was taken of the number of patients who had switched treatments, but after adding an estimated figure for those patients to the previous total it was supposed that in a 2-year period between 2000-3000 patients could be registered to the study. It was estimated that a scheduled number of 2500 patients could be obtained.

2.4 Summary of anticipated benefits and risks (disadvantages) to study participants

Protocol treatment in the STOP group will consist of ending anastrozole treatment 5 years after surgery identical to normal medical care, and in the CONTINUE group will consist of extending ANA treatment by a further 5 years. The effect of treatment observed in the CONTINUE group is expected to be superior to that in the STOP group, but since there is currently no evidence relating to administration of 10 years of postoperative treatment in support of this hypothesis the medical benefits of study participation are not clear. In addition, all medical costs in this study, including drugs and investigations, will be paid under the health insurance of the patient or as patient out-of-pocket expenses. Medical examinations and investigations will be performed during the study period at a frequency similar to that of normal medical care, so the consequent burden posed by medical examinations and investigations (including invasive investigations) will not increase by participation in this study. However, this study does require surveys pertaining joint symptoms, QOL and medical economics be performed in some patients, which may be an additional burden faced by those patients.

The environment created by the regular medical examinations and investigations and contact with attending physicians and CRCs, amongst other parties, performed during the period of study participation will make consultation and advice easier to obtain for patients, and the resulting intimate level of medical care may be an overall benefit of study participation when compared with non-participation in the study.

2.5 Significance of this study

2.5.1 Determining the effects of extended endocrine therapy and the optimum period of postoperative anastrozole treatment

Since the publication of the 2001 ATAC trial, 5-year ANA treatment has become a common postoperative therapy in Japan in patients with postmenopausal, hormone responsive breast cancer. Japanese patients who have completed the 5 years of ANA treatment have therefore existed since March 2007. Similarly, we expect to encounter increasing numbers of patients who have completed a total of 5 years of endocrine therapy and switched to ANA treatment after 2-3 years of TAM treatment. From this point on, data must be obtained on whether it is possible to control and what degree of control is possible over late-stage recurrence after the completion of 5 years of treatment, including AI treatments. Extending endocrine therapy with AI treatment has been cited as a way of improving on the prognosis seen in patients after 5 years of TAM treatment, and it may be possible to further improve prognosis in these patients by administering further additional AI treatment. This study is capable of demonstrating the efficacy and safety of continued ANA treatment for more than 5 years, and will provide new information on the effect of extended adjuvant endocrine therapy and the optimum period of postoperative ANA treatment. The results of this study will be immediately reflected in normal clinical practice and are of great importance.

Assuming this study is started in 2007, the results can be investigated as part of the 2015 EBCTCG meta-analysis.

2.5.2 Significance of HRQOL evaluation

From the perspective of evaluating the total benefit a patient can obtain from a cancer treatment, it is very important to obtain an evaluation of the HRQOL-based patient-reported outcome alongside the the evaluation of the objective indicator of survival time. It is normal that QOL be included as a primary or secondary endpoint in large-scale trials of adjuvant chemotherapies performed in breast cancer patients. Since a QOL evaluation is also essential in when considering the treatment objectives of postoperative adjuvant endocrine therapy, this study will demonstrate the effects of extending anastrozole treatment on QOL relative to untreated patient observations.

2.5.3 Significance of the evaluation of medical economics (cost-benefit performance)

The focus of interest of an evaluation of economy of medical care is not only to compare the costs of the therapeutic drugs, but also the drugs used to alleviate adverse drug reactions and the cost of outpatient visits. A diverse evaluation of (disease-free) survival, QOL and economy of medical care, including a comparison of quality-adjusted life year (QALY) that is the cost of survival with good QOL for one year and an estimation of the cost of extending one year of survival with good QOL (incremental cost/QALY) relative to the untreated group can make a substantial contribution not only in terms of potential therapeutic options for clinical practice, but also in terms of social significance.

2.6 Comprehensive Support Project for Oncology Research

In the year 2000, the Public Health Research Foundation commenced a “comprehensive support project for the development of therapy including psychosocial intervention for the purpose of improving the quality-adjusted life years (QALY) of breast cancer patients”. The Public Health Research Foundation is a designated public interest corporation that was established in 1984 with the Ministry of Health, Labour and Welfare as its supervisory government agency. It was established with the objective of “Making a contribution to the maintenance and improvement of public health by conducting research on the impact of stress on physical and mental health and implementing the results of this research in areas of disease prevention and health promotion of the Japanese people”. While the prevalence of breast cancer is on the rise as a consequence of changes in lifestyle, patient awareness towards QOL is also increasing. The biological characteristics of cancer are also being revealed and new therapies are rapidly being developed in light of these new findings. The implementation of researcher-led clinical studies that include a QOL evaluation aspect is essential in the creation of an evidence-based system of standard treatment, and in creating treatment choices that value the QOL of each individual patient. However, the infrastructure to facilitate large-scale multicenter studies in Japan is immature. In light of these circumstances, the comprehensive support project will carry out the following operations aimed at improving the quality of breast cancer clinical research and the QOL of breast cancer patients in Japan:

1) Planning and implementation of researcher-led breast cancer clinical research.
2) Investigative research pertaining to the QOL of breast cancer patients.
3) Education of Clinical Research Coordinators (CRCs).
4) Utilizing the Internet to provide information to breast cancer patients, physician researchers and CRCs.

The English name of this project is the “Comprehensive Support Project for Oncological Research”, abbreviated to CSPOR. The present study is conducted as part of the Comprehensive Support Project for Oncology Research.

2.7 N-SAS BC

The National Surgical Adjuvant Study of Breast Cancer (N-SAS BC) was inaugurated in 1993 and is affiliated with the “Anti-Cancer Drug Post-Marketing Research Team” (leader at the time: Kaoru Abe, National Cancer Center President), which belongs to the Ministry of Health’s (now Ministry of Health, Labour and Welfare) “Drug Epidemiological Technique Examination Project” Contract Research Organization. Its English name is the National Surgical Adjuvant Study of Breast Cancer and is abbreviated to the N-SAS BC. The “N-SAS BC 01” multicenter study conducted by the National Surgical Adjuvant Study of Breast Cancer included 732 registered patients from 45 medical facilities nationwide between October 1996 and March 2001. Continuing form this study, the “N-SAS BC 02” study commenced in December 2001, the “N-SAS BC 03” study in November 2002, and the “N-SAS BC 04” study commenced in September 2003 and is currently ongoing. In order to make use of the knowledge, experience and know-how developed during the N-SAS BC studies performed to date, and to continue in the format of a national-scale multicenter study research group, the research group has adopted the English name and abbreviation of “National Surgical Adjuvant Study of Breast Cancer” (N-SAS BC) with the present study being named “N-SAS BC 05”.

3 Criteria and definitions used in this study

3.1 Clinical stage classification

"Breast Cancer Management (2004, 15th Ed.)" will be used.

The UICC-TNM classification (2002, 6th Ed.) is adopted for stage classification.

3.1.1 T: Primary tumor[Note 1)]

		Size (cm)	Chest wall fixation [Note 2)]	Edema of the skin, ulcer/ satellite skin nodule
TX		Not evaluable		
Tis		Non-invasive carcinoma or Paget's disease where no tumor mass is observed		
T0		No primary tumor observed [Note 3,4)]		
T1 [Note 5)]		≤2.0	−	−
T2		>2.0 ≤5.0	−	−
T3		>5.0	−	−
T4	a	Any size	+	−
	b		−	+
	c		+	+
	d	Inflammatory breast carcinoma [Note 6)]		

Note 1: T1 is determined comprehensively by clinical breast examination and diagnostic imaging.

Note 2: Chest wall refers to the ribs, sternum, intercostal muscle and serratus anterior muscle, and does not include the pectoral muscle.

Note 3: The primary tumor cannot be determined by clinical breast examination or diagnostic imaging (mammography, ultrasound).

Note 4: Patients with nipple discharge, calcification on mammography, etc. will not be diagnosed as T0 and instead classification will be deferred. These patients will be classified as Tis, T1 mic, etc. according to a final pathological diagnosis.

Note 5: Subclassification as "a" (≤0.5), "b" (>0.5, ≤1.0) and "c" (>1.0, ≤2.0).
Histological radius of invasion of ≤0.1 cm will be described as T1mic.

Note 6: Inflammatory breast carcinoma indicates diffuse redness, edema and induration when a normal tumor mass is not found.

Note 7: In the event of multiple tumor masses in the mammary gland, the highest T classification will be used.

3.1.2 N: Regional lymph nodes [Note 1)]

	Ipsilateral axillary lymph node		Parasternal lymph nodes [Note 2)]	Ipsilateral subclavicular lymph node	Ipsilateral supraclavicular lymph node
	Movable	Fixed (in surrounding tissue or between lymph nodes)			
NX	Not evaluable				
N0	−	−	−	−	−
N1	+	−	−	−	−
N2 a	−	+	−	−	−
N2 b	−	−	+	−	−
N3 a	+/−	+/−	+/−	+	−
N3 b	+ Or +		+	−	−
N3 c	+/−	+/−	+/−	+/−	+

Note 1: Diagnosis of lymph node metastasis is by palpation, diagnostic imaging, etc.

Note 2: Taken as (-) if parasternal lymph node metastasis not found.

3.1.3 M: Distant metastasis

MX Cannot be evaluated

M0 No distant metastasis

M1 Distant metastasis present

3.1.4 TNM classification

		T0	T1	T2	T3	T4
M0	N0		I	IIA	IIB	IIIB
	N1	IIA	IIA	IIB	IIIA	IIIB
	N2	IIIA	IIIA	IIIA	IIIA	IIIB
	N3	IIIC	IIIC	IIIC	IIIC	IIIC
M1		IV	IV	IV	IV	IV

Stage 0: Tis noninvasive cancer

: Not applicable

State I-IV: Invasive cancer

White potion without shading is subject to examination in this study

3.2 Histological classification

"Breast Cancer Management (2004, 15th Ed.)" will be used.

1 Non-invasive carcinoma
- 1a. Non-invasive ductal carcinoma
- 1b. Lobular carcinoma in situ

2 Invasive carcinoma
- 2a. Invasive ductal carcinoma
  - 2a 1 Papillotubular carcinoma
  - 2a 2 Solid-tubular carcinoma
  - 2a 3 Scirrhous carcinoma
- 2b. Special-types
  - 2b 1 Mucinous carcinoma
  - 2b 2 Medullary carcinoma
  - 2b 3 Invasive lobular carcinoma
  - 2b 4 Adenoid cystic carcinoma
  - 2b 5 Squamous cell carcinoma
  - 2b 6 Spindle cell carcinoma
  - 2b 7 Apocrine carcinoma
  - 2b 8 Carcinoma with cartilagous and/or osseous metaplasia
  - 2b 9 Tubular carcinoma
  - 2b 10 Secretary carcinoma (Juvenile carcinoma)
  - 2b 11 Others

3 Paget's disease

3.3 Performance Status evaluation

The Japanese translation of the ECOG scale[16] will be used.

Grade	Performance Status
0	Symptomless, able to carry out social activities without restriction similarly to pre-disease performance.
1	Mild symptoms, restricted in physically strenuous activity but ambulatory and able to carry out light physical labor and sedentary work. For example, light housework and office work.
2	Ambulatory and capable of all self-care but sometimes requires assistance. Unable to carry out light labor but moving for more than 50% of waking hours.
3	Capable of limited self-care but often requires assistance. Confined to bed or chair more than 50% of waking hours.
4	Completely incapable of self-care and requires constant assistance. Totally confined to bed or chair.

4 Inclusion and exclusion criteria

4.1 Selection criteria

Patients who meet all the criteria below will be eligible for this study.

1) Patient has been diagnosed histologically with invasive breast cancer, undergone surgery on the primary female breast cancer, and is menopausal at time of registration to this study.
   The condition for being menopausal is to meet at least one of the criteria below.
   a) ≥55 years of age
   b) ≥45 years of age with amenorrhea for at least 2 years, and has not undergone a hysterectomy
   c) Has undergone bilateral oophorectomy

2) The patient has not used LH-RHa and any of the criteria below applies regarding adjuvant endocrine therapy.
   a) Initial therapy of anastrozole treatment for 5 years and ongoing (ANA)
      (At time of registration, anastrozole treatment that is ongoing and has been received for between a full 4 years 9 months and 5 years 2 months will be admissible)
   b) Initial therapy of tamoxifen treatment followed by at least a full 2 years anastrozole treatment, comprising adjuvant endocrine therapy of a total of 5 years that is also ongoing (TAM→ANA)
      (At time of registration, adjuvant endocrine therapy that is ongoing and has been received for between a full 4 years 9 months and 5 years 2 months will be admissible)

3) TNM staging at first examination (before surgery): T1-3, N0-2, M0 (3.1 Clinical stage classification)

4) Positive for at least either ER hormone receptor or PR hormone receptor.

5) PS (ECOG) 0, 1 (3.3 Performance status evaluation)

6) Aged ≤80 years at time of registration.

7) Neither recurrence nor contralateral breast cancer found at examination within 6 months prior to registration.
Only either a bilateral mammogram or breast ultrasound (one-sided in patients with mastectomy) is required for the examination. Examination of areas other than the breasts (chest, abdomen, bones, etc.) will be performed according to the normal examination policies of each facility.

8) Patient has adequate organ function.
Meets all the criteria below (according to clinical test results form within 3 months prior to registration).
   a) Leukocyte count: ≥3,000/mm^3
   b) Platelet count: ≥100,000/mm^3
   c) Hemoglobin: ≥9.0 g/dl
   d) Total bilirubin: ≤1.5 mg/dl
   e) GOT and GPT ≤2.5 times the facility upper limit of normal
   f) Creatinine: ≤1.5 mg/dl
   g) No history of myocardial infarction or congestive heart failure.
   h) No ischemic heart disease or valvular disease that requires treatment.

9) Consent obtained for study participation in document form from patient herself.

4.2 Exclusion criteria

Patients who meet any of the criteria below will not be eligible for this study, regardless of whether all selection criteria are met.

1) Patient has a metachronous or synchronous bilateral breast cancer.

2) Patient has invasive cancer of another organ within 5 years of the end of treatment.

3) Medical history of deep vein thrombosis.

4) Medical history of bone fracture attributed to osteoporosis, and has symptoms of osteoporosis at time of registration.

5) Patient is receiving ongoing treatment in the form of hormone replacement therapy or a selective estrogen receptor modulator (SERM).

6) Currently participating in another clinical trial with the objective of preventing the postoperative recurrence of breast cancer.

7) Patient is deemed unsuitable for study participation by an attending physician.

5 Registration and allocation

5.1 Registration procedure

5.1.1 Sending of patient registration forms

Attending physicians will confirm that patients meet the selection criteria (4.1) and do not meet any of the exclusion criteria (4.2), fill in all items to be investigated at registration (8.1.1) in the “patient registration form” (Appendix B) and fax the “patient registration form” to the CSPOR Data Center.

CSPOR Data Center
Fax: 03-5298-8536
Tel: 03-3254-8029
Open: Weekdays 10 am to 5 pm (except on weekends and national holidays)

5.1.2 Registration and allocation

The CSPOR Data Center will confirm the eligibility of patients based on the “patient registration form”. Eligible patients will be registered and allocated randomly (5.2).

5.1.3 Notification of registration and allocation results

The CSPOR Data Center will fax a “registration confirmation form” (Appendix B) to the fax number of the attending physician noted on the “patient registration form”.

5.1.4 Initiation of protocol treatment

Attending physicians will check the allocation result (treatment group) noted in the “registration confirmation form” received from the CSPOR Data Center and initiate the prescribed protocol treatment (6 Treatment plan).

5.2 Random allocation and allocation adjustment factors

Patients will be allocated randomly to the STOP group and CONTINUE group at a ratio of nearly 1-to-1. Random allocation will be performed dynamically using the adjustment factors below. The allocation algorithm will be determined by the person responsible for biostatistical analysis.

1) Type of treatment prior to study (adjuvant endocrine therapy) (Anastrozole/Tamoxifen→Anastrozole)
2) Preoperative or postoperative chemotherapy (Yes/None)
3) Axillary lymph node metastasis (Yes/None)
   Negative for isolated tumor cells (ITC)
4) Facility (By facility)

5.3 Registration confirmation and reporting commencement of the study

After the CSPOR Data Center has faxed the “registration confirmation form” (Appendix B) to the attending physician, it will also be posted to the attending physician in the mail. The CSPOR Data Center will register eligible patients for electronic data capture (EDC).

An attending physician or CRC, etc. will submit a “commencement of study report” (Appendix B) to the CSPOR Data Center via EDC within one month of initiation of protocol treatment.

Study registration will take place at the CSPOR Data Center according to the prescriptions below.

1) Patients will not be registered if their patient registration form is not fully complete.
2) Once registered, patient registration may not be rescinded (erased from the database).
3) In the event of a duplicate registration, the prior registration information will be used (patient registration number, allocation group).
4) Because a special procedure is required for dealing with an erroneous or duplicate registration in the database, when an erroneous or duplicate registration comes to light at a facility it will promptly be reported to the Data Center.

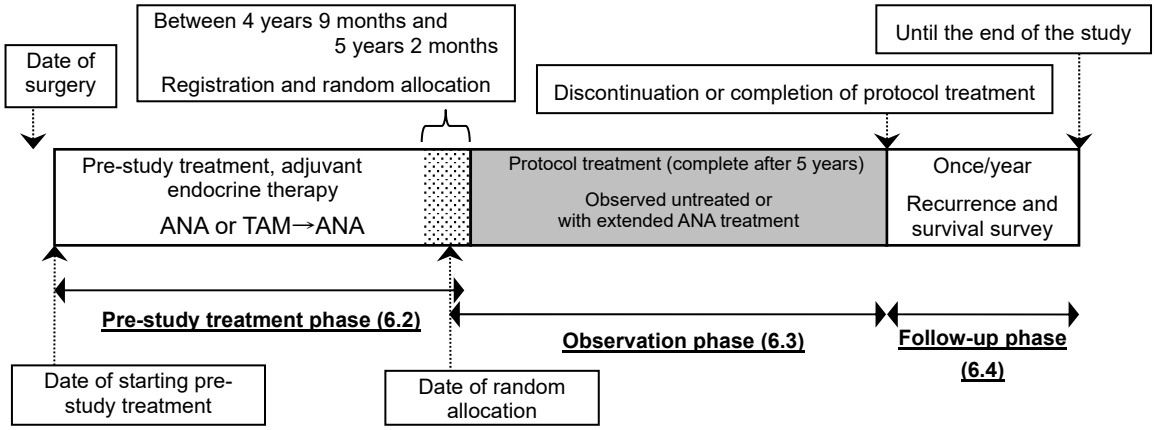
5.4 Discontinuation prior to commencement of the study

Following registration, a “commencement of study report” and “progress report” will be collected for every patient, even patients for whom participation is discontinued prior to the initiation of protocol treatment. For patient discontinuations that occur prior to the initiation of protocol treatment due to withdrawal of consent or cancelled visits, background information and the progress report at the time of withdrawal will be collected, and no further observations, examinations or investigations will be carried out.

6 Treatment plan

6.1 Definition of study periods

Study periods are defined as shown below.



6.2 Pre-study treatment phase

In this study the 5 years of adjuvant endocrine therapy initiated after surgery will be called “pre-study treatment”, and this period will be termed the “pre-study treatment phase”.

6.2.1 Pre-study treatment and registration

Attending physicians will register patients to this study who are receiving ongoing pre-study treatment and who are at a point between a full 4 years 9 months and 5 years 2 months into the pre-study treatment phase (5.1). Pre-study treatment will not include use of LH-RHa and will apply to the use of any of the postoperative endocrine therapies shown below (4.1 Selection criteria). Registration will, whenever possible, be carried out at the time of completion of 5 years of pre-study treatment and will be followed by the immediate initiation of protocol treatment (6.3.1).

1) Initial therapy of 5 years of anastrozole treatment that is ongoing (ANA)
   (At time of registration, anastrozole treatment that is ongoing and has been received for between a full 4 years 9 months and 5 years 2 months)
2) Initial therapy of tamoxifen treatment followed by at least a full 2 years of anastrozole treatment, comprising adjuvant endocrine therapy of a total of 5 years that is ongoing. (TAM→ANA)
   (At time of registration, adjuvant endocrine therapy that is ongoing and has been received for between a full 4 years 9 months and 5 years 2 months)

6.2.2 Ending pre-study treatment

Attending physicians will end pre-study treatment in patients according to the provisions below.

1) When the period of pre-study treatment is between 4 years 9 months and less than 5 years at time of registration:
   Pre-study treatment will be continued until the full 5 years then ended.
2) When the period of pre-study treatment is between a full 5 years and 5 years 2 months at time of registration:
   Pre-study treatment will be ended at time of registration.

6.3 Observation phase

The “protocol treatment” described below will be initiated after the end of pre-study treatment and observations will be continued for 5 years from the date of initiation. The immediate initiation of protocol treatment after the end of pre-study treatment is desirable, though transition to protocol treatment will be completed within 90 days of the end of pre-study treatment.

The prescribed observations, examinations and evaluations (8.1) will be performed during the observation phase and reported in a “progress report” (Appendix B).

6.3.1 Protocol treatment

Protocol treatment is defined as the treatment administered to the two groups below, into which patients are allocated randomly at registration.

STOP group: 5 years of observation without treatment

CONTINUE group: Extension of anastrozole treatment for 5 years (1 dose/day, 1 mg/day, oral administration)

The date of initiation of protocol treatment will be reported in a “commencement of study report” (Appendix B).

6.3.2 End of protocol treatment

Reasons for ending protocol treatment will be classified as shown below.

The end date and reasons will be reported in a “progress report” (Appendix B).

1) Completion of 5 years of protocol treatment. (Also reported as completion of observation (6.3.6).)
2) Discontinuation of protocol treatment due to an event (recurrence)
3) Discontinuation of protocol treatment due to an event (death). (Also reported as discontinuation of observation (6.3.6).)
   This classification will not be applicable in the event protocol treatment is ended for another reason prior to patient death
4) Protocol treatment discontinued by an attending physician due to an adverse event
5) Discontinuation of protocol treatment due to the wishes of the patient (for reasons related to the occurrence of adverse events)
6) Discontinuation of protocol treatment due to the wishes of the patient (for reasons not related to the occurrence of adverse events)
   This classification will only be applicable in the event a relationship with an adverse event can be ruled out.
7) Discontinuation of protocol treatment due to medical facility transfer
8) Discontinuation of protocol treatment due to other reasons (initiation of a prohibited concomitant treatment, protocol violations, etc.)

Note: The prescribed observations, examinations and evaluations (8.1) will continue in the event of discontinuation of protocol treatment. If observation becomes impossible to perform simultaneous to the end of protocol treatment, it will be reported as “discontinuation of observation (6.3.6)”.

Only investigations of survival, HRQOL (EQ-5D only) and economy of medical care will be continued after a recurrence occurs.

6.3.3 Concomitant treatments prohibited during participation in the study

Concomitant use of the treatments below is prohibited. If a prohibited concomitant treatment is used, the date the treatment was initiated and details of the treatment will be reported in a “progress report” (Appendix B).

1) Anticancer treatments other than the protocol treatment (chemotherapy, endocrine therapy, antibody therapy, surgery, irradiation, etc.).
2) Hormone replacement therapy.
3) Treatment with a selective estrogen receptor modulator (SERM).

6.3.4 Concomitant treatments during study participation: Treatment for reduced bone density

Attending physicians will advise patients to take care to take in calcium everyday as part of a balanced diet. Treatment will be performed as described below in the event of reduced bone density during protocol treatment.

(1) Criteria for initiation of treatment

Treatment will be administered if the young adult mean (YAM) or T score of the bone mineral density (BMD) of the lumbar vertebra (mean of L1-4, or mean of L2-4), femur, radius or second metacarpal meets the criteria below.

Initiation of treatment will be recommended regardless of the T score if a previous vertebral body fracture that is suspected to be non-traumatic is observed at X-ray examination of the thoracic vertebra or lumbar vertebra at the time of registration.

1) T score of ≤-2.5 or YAM of <70% (osteoporosis) → Initiate treatment (required)
2) T score ≤-2.0 or YAM of <80% (decrease in bone mass) → Recommend treatment (if possible)

(2) Treatment method

See the treatment methods described below.

1) First choice:
   Bisphosphonate preparation (any of the preparations noted below is recommended)
   • Alendronate (35 mg, once/week)
   • Risedronate (17.5 mg, once/week)
2) Second choice: If a bisphosphate preparation cannot be administered
   Active vitamin D (0.25 μg, once/day, taken after evening meal is recommended)
3) Concomitant use of 1) and 2) will be recommended if patient is 70 years of age or older

6.3.5 Treatment after the end of protocol treatment

This study does not prescribe any treatment to be given after the end of protocol treatment.

6.3.6 Completion or discontinuation of observations

Performance of the prescribed observations, examinations and evaluations (8.1) during the protocol treatment phase for the prescribed 5 years will be termed “completion of observation”, and if they cannot be performed for the prescribed 5 years will be termed “discontinuation of observation”. Prescribed observations, examinations and evaluations will be performed in the event of either completion or discontinuation of observations, and the date of final observation and reasons for ending observation (following categories) will be reported in a “progress report” (Appendix B).

1) Completion of 5 years of observation:
   The follow-up phase (6.4) occurs after the completion of observation.
2) Discontinuation of observation due to an event (recurrence):
   Also reported as recurrence (8.2).
   Only investigations of survival, HRQOL (EQ-5D only) and economy of medical care will be continued after a recurrence occurs.
3) Discontinuation of observation due to an event (death):
   This classification is not applied if observation is discontinued for another reason prior to death:
   The cause of death will be described.
4) Discontinuation of observation by an attending physician due to adverse events.
5) Discontinuation of observation due to the wishes of the patient (for reasons related to the occurrence of adverse events):
   The reasons will be described.
6) Discontinuation of observation due to the wishes of the patient (for reasons not related to the occurrence of adverse events).
   This classification will only be applied in the event a relationship with the adverse event can be ruled out:
   The reasons will be described
7) Discontinuation of observation due to medical facility transfer:
   The destination medical facility will be recorded.
8) Discontinuation of observation due to other reasons

6.4 Follow-up phase

The period between the completion of observation and the end of the study (completion of the overall study) will be defined as the “follow-up phase”. During the follow-up phase, attending physicians will examine patients once per year whenever possible to performed prescribed observations, examinations and evaluations (8.1.4).

If a patient cannot be examined, the attending physician will investigate from the facility by whatever means possible (by phone, by documents sent through the post, etc.), in particular, obtaining information on survival and recurrence whenever possible.

The date of follow-up investigations and investigation results will be recorded in a “follow-up report” (Appendix B) for each follow-up examination performed. If follow-up is ended, the date of the final follow-up investigations, reasons for ending follow-up and results will be reported.

7 Treatment Drug

A summary of the drugs used in this study based on the drug package inserts is shown below. See the package inserts (Appendix D) for details. The latest information on each drug will always be used and the latest version of the package inserts of each drug can be found on the Pharmaceutical and Medical Devices Agency web site (http://www.info.pmda.go.jp/).

7.1 Anastrozole (Arimidex® tablet 1 mg)

Generic name: Anastrozole, ANA

Product name: Arimidex tablet 1 mg (AstraZeneca K.K.)

7.1.1 Contraindications and careful administration

(1) Contraindications

Pregnancy, possible pregnancy, or breast-feeding.

A history of hypersensitivity to drug ingredients.

(2) Careful administration

Severe liver or kidney damage.

7.1.2 Main adverse drug reactions

(1) Severe adverse drug reactions

1) Stevens-Johnson syndrome (<0.1%)
2) Anaphylactic reaction, angioedema, hives

(2) Other adverse drug reactions

1) ≥10%: Hot flush
2) 1 to <10%: Headache, asthenia, fatigue, malaise, nausea, alopecia, genital bleeding
3) <1%: Anorexia, vomiting, diarrhea, somnolence, rash, arthralgia, stiffness, vaginal dryness
4) Unknown frequency: GOT/GPT/AL-P/γ-GTP increased, carpal tunnel syndrome, osteoporosis, fracture, hypercholesterolemia

7.1.3 Drug interactions

Anastrozole inhibits activity of CYP1A2, CYP2C9 and CYP3A4 in *in vitro* tests, but during clinical trials that investigated interaction with antipyrine, warfarin and tamoxifen this inhibitory action was confirmed to be clinically non-problematic.

7.1.4 Metabolism and excretion

The main metabolites on single oral administration of the drug in healthy, postmenopausal women were triazole, glucuronic acid conjugates, and glucuronic acid conjugates of anastrozole hydroxide. By 336 hours after administration at least 70% of the drug was excreted in urine and at least 75% of the drug was deemed to have disappeared due to hepatic metabolism.

8 Observation, examination and evaluation

8.1 Observation, examination and evaluation schedule

	Visit	Clinical examination	Height	Breast exam: Palpation and visual examination	Breast exam: Mammography	Laboratory tests	X-ray of lumbar and thoracic vertebra	Adverse events	Bone density and urinary NTx	Joint symptoms (patient survey form)	HRQOL**	Economy of medical care**
At registration*	1	○	○	◎		○	○	Investigated during all phases/periods		●‡	●	●
At initiation of protocol treatment†	2	○	○	○	○				○			
6 months after initiation	3	○		○								
After 1 year	4	○	○	○	○				○	○	○	○
After 1 year 6 months	5	○		○								
After 2 years	6	○	○	○	○				○	○	○	○
After 2 years 6 months	7	○		○								
After 3 years	8	○	○	○	○				○	○	○	○
After 3 years 6 months	9	○		○								
After 4 years	10	○	○	○	○				○	○	○	○
After 4 years 6 months	11	○		○								
At completion of observation (after 5 years) Or at discontinuation of observation	12	○	○	○	○				○	○§	○§	○§
After 6 years (1 year after start of follow-up)	13	△		△	△					△	△	△
After 7 years (2 years after start of follow-up)	14	△		△	△							

◎：Recurrence and contralateral breast cancer not observed in examinations performed within 6 months before registration (4.1 Selection criteria).

Only bilateral mammography or breast ultrasound (one-sided in patients with mastectomy) is required.

Examination of areas other than the breasts (chest, abdomen, bones, etc.) will be performed according to the normal examination policies of each facility.

●：Performed after consent is obtained and before faxing the patient registration form.

△：Performed whenever possible.

＊ Data at registration will refer to data obtained within 3 months prior to registration (8.1.1).

† Data at initiation of protocol treatment will refer to data obtained within 3 months prior to initiation

of protocol treatment (8.1.2).

‡ Patient investigations will be carried out at registration, and physician evaluation will be carried out by the initiation of protocol treatment (8.5).

§ Only survival, HRQOL (EQ-5D only) and economy of medical care will continue to be investigated after recurrence.

＊＊ See “11 Evaluation of HRQOL and economy of medical care”.

8.1.1 Investigations at registration (Visit 1 in Table 8.1)

The matters below will be investigated at registration. If no other specific provisions apply, data will be used from examinations within 3 months prior to registration.

1) Height, body weight, date of surgery, date of initiation of pre-study treatment, scheduled date of initiation of protocol treatment
2) Selection criteria check (4.1 Selection criteria)
   a) Menopausal
   b) Type of pre-study treatment (adjuvant endocrine therapy); ANA / TAM→ANA
   c) TNM staging at first examination (before surgery) (3.1 Clinical stage classification)
   d) Hormone receptors (estrogen receptor, progesterone receptor)
   e) PS (3.3 Performance Stats evaluation)
   f) Age at time of registration
   g) Recurrence and contralateral breast cancer (based on examination within 6 months prior to registration)
   h) Organ function: Laboratory tests (leukocyte count, platelet count, hemoglobin, total bilirubin, GOT, GPT, creatinine), medical history of and complicating heart disease
   i) Consent obtained in document form
3) Exclusion criteria check (4.2 Exclusion criteria)
   a) Metachronous and synchronous bilateral breast cancer
   b) Invasive cancer of another organ within 5 years of the end of treatment
   c) Medical history of deep vein thrombosis
   d) Medical history of bone fracture attributed to osteoporosis (symptoms present at time of registration)
   e) Receiving ongoing hormone replacement therapy or a SERM
   f) Deemed unsuitable for study participation by an attending physician
4) Presence/absence of axillary lymph node metastasis (number of metastases if present) Negative for isolated tumor cells (ITC).
5) Use/nonuse of (preoperative or postoperative) chemotherapy
6) X-ray examination of thoracic vertebra and lumbar vertebra (check for vertebral fracture)
7) Joint symptoms (patient survey form), HRQOL, economy of medical care.

   Investigations at registration will be performed after consent is obtained and before faxing the patient registration form. After completion will be entered into the registration form.

8.1.2 Investigation at initiation of protocol treatment (Visit 2 in Table 8.1)

The matters below will be investigated at initiation of protocol treatment. Data obtained within 3 months prior to initiation of protocol treatment will be used for test values (the same data may be used as that used at time of registration if the test was performed within 3 months prior to initiation of protocol

treatment).

In the event of patient discontinuation after registration and prior to initiation of protocol treatment, background information will be collected and investigations at discontinuation will be carried out but no further observation, examination or investigation will be performed.

1) Date of initiation of protocol treatment
2) Confirmation of discontinuation prior to initiation of treatment
3) Patient background
4) Surgical findings
5) State of breast cancer prior to registration
6) Concomitant treatments
7) Recurrences, metastases and secondary cancers
8) Bone evaluation: PS, height, bone density test, urinary NTx, bone fracture
9) Complications: Presence/absence of chronic rheumatism, joint symptoms, symptoms, signs and diseases that are not the primary disease that are present prior to the start of this study

8.1.3 Investigation between 6 months and 5 years after initiation of protocol treatment (Visits 3-12 in Table 8.1)

According to the schedule (8.1), the following items will be investigated.

1) Date of observation: Date of final observation and reasons at discontinuation or completion of observation (6.3.6)
2) Protocol treatment: Date of ending treatment and reasons if protocol treatment has been ended since the previous investigation (6.3.2)
3) Concomitant treatments
4) Survival status
5) Recurrences, metastases and secondary cancers
6) Bone evaluation: PS, height, bone density test, urinary NTx, bone fracture
7) Adverse events
8) Joint symptoms (patent survey form), HRQOL, economy of medical care

Only survival, HRQOL (EQ-5D only) and economy of medical care will continue to be investigated after recurrence.

8.1.4 Investigation during follow-up phase (Visits 13 and 14 in Table 8.1)

The matters below will be investigated once/year during the follow-up phase. If a medical examination is not feasible the attending physician will report details of investigations performed by remote contact with the patient.

1) Discontinuation and continuation of follow-up: Date of the final follow-up investigation and reasons if follow-up was ended
2) Survival status
3) Recurrences, metastases and secondary cancers
4) Adverse events

   Adverse events that occur anew during the follow-up phase, and the outcome of adverse events that occurred during the observation phase.

In addition to the above, whenever possible HRQOL, economy of medical care and joint symptoms (patient survey form) will be investigated only after 1 year of follow-up (Visit 13 in Table 8.1). Also, only survival, HRQOL (EQ-5D only) and economy of medical care will be investigated after recurrence.

8.2 Evaluation of recurrence

8.2.1 Tests for recurrence

Tests for recurrence will be carried out after the commencement of observation according to the prescribed schedule (8.1). If recurrence is suspected the necessary examinations will be performed to obtain a definite diagnosis (8.2.3 Diagnosis of recurrence).

8.2.2 Definition and classification of recurrence (parts 1-18 of Breast Cancer Management, 15th edition)

Recurrence refers to a re-emergence of cancer after temporary clinical disappearance due to breast cancer treatment (surgery, radiotherapy, chemotherapy, etc.) that is confirmed histologically (cellularly). Multiple cancers are excluded from this definition. Recurrence is classified as follows according to the site.

1) Conserved breast recurrence
2) Local recurrence (affected breast wall)

   The breast wall refers to an area contained by the lower edge of the clavicle as upper boundary, the costal arch as lower boundary, the midline of the sternum as inner boundary and the anterior border of the latissimus dorsi as outer boundary. Cases that occur close to a boundary that are difficult to determine will be included under cases of local recurrence.
3) Regional lymph node recurrence
4) Distant recurrence

The following symbols will be used for distant organs in accordance with the TNM classification.

Contralateral breast	:CBR	Lymph node	:LYM
Lung	:PUL	Bone marrow	:MAR
Bone	:OSS	Pleural	:PLE
Liver	:HEP	Skin	:SKI
Brain	:BRA	Other	:OTH

8.2.3 Diagnosis of recurrence

Below are stipulated the criteria for a definite diagnosis of recurrence.

1) Conserved breast recurrence

   Determined as recurrence when definite diagnosis is obtained from biopsy or cytological examination.
2) Local recurrence (affected breast wall)

   Determined as recurrence when definite diagnosis is obtained from biopsy or cytological examination.
3) Regional lymph node recurrence (LLYM)

   Determined as recurrence when definite diagnosis is obtained from biopsy, cytological

examination or diagnostic imaging.

4) Distant organ metastasis

a) Contralateral breast (CBR)

Determined as recurrence when definite diagnosis of breast cancer from cytological examination or biopsy is obtained and diagnosed as clearly a metastasis either clinically or pathologically. A diagnosis of metachronous bilateral breast cancer will be referred to as secondary cancer (double cancer) and not recurrence.

b) Distant lymph node (DLYM)

Determined as recurrence when definite diagnosis is obtained from biopsy, cytological examination or diagnostic imaging.

c) Lung (PUL)

Determined as recurrence when multiple nodular shadows consistent with lung metastasis are observed in diagnostic imaging (plain chest x-ray, CT, etc.).

Determined as recurrence when a solitary nodule difficult to differentiate from primary lung cancer appears afresh, appropriate differential diagnosis is carried out and the results show metastasis.

The onset of primary lung cancer will be treated as a “secondary cancer complication” rather than “recurrence”.

d) Bone marrow (MAR)

Determined as recurrence when definite diagnosis is obtained from bone marrow aspiration.

e) Bone (OSS)

Determined as recurrence when osteolytic or osteoblastic changes are observed in bone x-ray or when abnormalities are observed in bone scintigraphy or bone MRI, etc. and other conditions can be ruled out.

f) Pleural (pleural effusion) (PLE)

Determined as recurrence when positive cytological examination or pleural biopsy results are obtained.

g) Meninges

Determined as recurrence when definite diagnosis is obtained from cytological examination.

h) Ascites (peritoneal), pericardial effusion

Determined as recurrence when definite diagnosis is obtained from biopsy or cytological examination.

i) Eye

Determined as recurrence when diagnosis is obtained from fundoscopy, CT or MRI.

j) Liver (HEP)

Determined as recurrence when diagnosis is obtained from ultrasonography, CT or MRI.

k) Skin (SKI)

Determined as recurrence when definite diagnosis is obtained from biopsy or cytological examination.

l) Brain (BRA), spinal cord

Determined as recurrence when diagnosis is obtained from CT or MRI.

m) Other (OTH)

Determined as recurrence when definitive diagnosis is obtained from biopsy or histological examination or non-definitive diagnosis from biopsy or histological examination where other conditions are ruled out.

5) Diagnosis of recurrence from tumor markers

a) An increase in tumor markers alone will not result in a diagnosis of recurrence.

b) The likelihood of recurrence is extremely high in cases where there is an increase in multiple tumor markers above a certain proportion during the same period or a continuous increase in a single tumor marker over time and therefore appropriate diagnostic imaging shall be carried out in such cases to properly diagnose recurrence.

8.2.4 Determination of the date of recurrence

The date of recurrence will be the date recurrence was first confirmed, that is, either the date specimens were collected for biopsy and cytological examination or the date of the imaging exam (determined based on the “First Evidence Principle”).

8.3 Evaluation of adverse events

In this study adverse events will be all undesirable signs and symptoms that occur in a patient (including abnormal laboratory test values) regardless of causal relationship to the study drug. However, the recurrence of breast cancer during the study period will be deemed worsening of the primary disease and not an adverse event. When an adverse event occurs attending physicians will promptly take necessary measures (examinations, treatment of adverse event, discontinuation of protocol treatment, etc.) and endeavor to ensure patient safety.

Adverse events will be named and Grade determined according to Common Terminology Criteria for Adverse Events (CTCAE) v3.0 - August 9, 2006 (Japanese translation JCOG/JSCO Edition – March 8, 2007) (Appendix F).

8.3.1 Timing of evaluation and adverse events subject to evaluation

1) All adverse events that occur during the observation phase will be investigated (including exacerbation of complications).

Adverse events subject to evaluation will be grouped as shown below in the progress report. Determination of grade and the naming of adverse events that are “other” will be carried out according to the CTCAE.

		CTCAE		
		Major classification	Name of adverse event	
Hot flush	⇒	Endocrine	Hot flush (flushed face)	Hot flashes/flushes
Fracture	⇒	Musculoskeletal /Soft tissue	Fracture	Fracture
Osteoporosis	⇒	Musculoskeletal /Soft tissue	Osteoporosis	Osteoporosis
Stiffness	⇒	Musculoskeletal /Soft tissue	Joint function	Joint-function
Arthritis	⇒	Musculoskeletal /Soft tissue	Arthritis (nonseptic)	Arthritis（non-septic）
Arthralgia	⇒	Pain	Pain-choice: Joint	Pain-Select: Joint
Headache	⇒	Pain	Pain-choice: Headache	Pain-Select: Head/headache
Other	⇒	According to CTCAE		

2) Adverse events that occur anew during the follow-up phase, and the outcome of adverse events that occurred during the observation phase will be investigated.

8.3.2 Known and unknown adverse events

Adverse events that appear as adverse drug reactions on drug package inserts will be known adverse events, and those that do not appear will be unknown adverse events.

8.4 Evaluation of bone density

Periodic observation of bone condition is recommended as an important basic precaution on the anastrozole package insert (Appendix D). Since all patients of this study will be exposed to anastrozole, an evaluation of bone density is deemed necessary and the tests below will be performed.

Attending physicians will measure bone density at visits made at the initiation of protocol treatment, at 1 year after initiation of protocol treatment and at 2 years, 3 years, 4 years and 5 years. The measurement method, measurement site and results will be reported in a progress report (Appendix B). Measurement will be carried out according to the items below and treatment in the event of reduced bone density will be carried out according to “6.3.3 Treatment for reduced bone density”.

1) Bone density measurements will, whenever possible, be carried out by dual X-ray absoptiometry (DXA). If a facility is unable to perform DXA the next-preferred measurement methods are CXD (MD) and DIP. (CXD: computed X-ray densitometry, MD: microdensitometry, DIP: digital image processing). Measurement results obtained from other medical institutions are permitted, but the same measurement method will be used for the same patient for the duration of the study.
2) Measurement sites in order of preference are lumbar vertebra>femur>radius>second metacarpal.
   The mean of L1-L4 or the mean of L2-L4 will be used for the lumbar vertebra.
3) DXA measurement results will be recorded as BMD (g/cm^2) and percentage relative to T score or YAM. CXD (MD) and DIP measurement results will be recorded as (mm AI) and percentage relative to YAM.
4) Urinary NTx (urinary cross-linked N-telopeptides of type-I collagen) will be measured as a predictive factor of bone fracture independent of BMD. NTx will be measured by a noninvasive method of urine collection as opposed to blood collection.
   Although the collection of second morning urine is optimal, whenever possible urine will be collected during at same time period (morning or afternoon) in the same patient, given what is feasible.

In addition, considering that height loss may be related to reduced bone density, height will be measured at each visit.

8.5 Evaluation of joint symptoms

The below investigations will be performed since anastrozole treatment is reported to cause arthalgia and stiffness.

Attending physicians will use CTCAE v3.0 to evaluate arthralgia as an adverse event at visits in all patients, and report the results in a progress report (Appendix B).

In addition, patients subject to HRQOL investigations will be requested to fill in a patient survey form (Appendix C) pertaining to joint symptoms with the same schedule as the HRQOL investigations (at registration, after 1 year, 2 years, 3 years, 4 years, 5 years and 6 years [1 year after starting follow-up]) (investigation of joint symptoms will end in the event of breast cancer recurrence). The patient survey form will include the following.

1) Presence/absence and grade of arthralgia (CTCAE v3.0 modified for patient use).
2) Figures to identify sites of arthralgia in the body and a VAS scale showing the severity of pain at the site where it is most severe.
3) Presence/absence and grade of joint stiffness (CTCAE v3.0 modified for patient use).
4) Figures to identify sites of joint stiffness in the body and a survey of timing of onset and change in symptoms.

8.6 Evaluation of HRQOL and economy of medical care

(See “11 Evaluation of HRQOL and economy of medical care”.)

9 Data collection

9.1 Data submission

In this study most data collection will be carried out via electronic data capture (EDC). The attending physician or Clinical Research Coordinator (CRC) will submit data to the CSPOR Data Center in accordance with the progress of the study up until its completion for all patients registered to this clinical study. When a CRC completes a form or enters data he/she will obtain confirmation from the attending physician.

Types of survey forms, means of sending and submission of survey forms and timings are shown below.

No.	Type	Method and timing of sending form	Method and timing of submitting form
1	Normal laboratory test values	Posting of EDC Immediately after facility registration	EDC entry 1 week prior to start of registration
2	Patient registration form (Appendix B)	Mailed in advance to participating facilities	Faxed at time of registration
3	Commencement of study report (Appendix B)	(Included in EDC)	EDC entry Within 1 month after initiation of protocol treatment
4	Progress report (Appendix B) Protocol treatment, concomitant treatment, survival, recurrence, evaluation of bone, adverse events	(Included in EDC)	EDC input Within 1 month of timing of each survey
5	Follow-up report (Appendix B) Recurrence, state of survival	(Included in EDC)	EDC input Within 1 month after implementation
6	Patient survey form; joint symptoms (Appendix C)	Mailed in advance to facilities performing the investigation	Mailed Within 1 month after implementation
7	Lifestyle and cost questionnaire(Appendix C)	Mailed in advance to facilities performing the investigation	Mailed Within 1 months after implementation
8	Copies of statements of medical expenses and outside prescription (paper or electronic media)	Stipulated for each facility performing the investigation	Submitted once/year
9	Adverse event emergency contact form (Appendix B)	Medical facility's style of form can also be used Mailed in advance to participating facilities	Faxed within 72 hours of learning of occurrence

9.2 Data management

The CSPOR Data Center will, in accordance with a separately prescribed data management plan (SOP and manual), send reminders concerning unsubmitted data, scrutinize submitted data and make inquiries, amend data based on the results of said inquiries and manage the database. In addition, the Data Center will also create documents based on the input data for monitoring purposes, which the Data Center will conduct together with the Executive Committee. The Data Center will also create analysis data sets for statistical analysis.

10 Reporting of adverse events

If any of the following adverse events that must be reported occur, the physician in charge will make a report to the secretariat. Note that when a serious adverse event (serious according to the definition of ICH E2A) with a causal relationship to the drug that cannot be ruled out occurs, reports made according to the Safety Information Report System for Drugs, etc. (Pharmaceutical Affairs Law Article 77-4 No.2-2) and communications with the relevant marketing authorization holder with the purpose of obtaining cooperation in spontaneous reports of adverse drug reactions by the marketing authorization holder (Pharmaceutical Affairs Law Article 77-4 No.2-1) will be carried out appropriately in accordance with the provisions of each medical facility and under the responsibility of the physician in charge.

10.1 Adverse events requiring emergency reporting

The following adverse events will be subject to emergency reporting via the adverse event emergency contact form (Appendix B).

1) All deaths during the protocol treatment or within 30 days following the date of the final protocol treatment

   Deaths will be subject to emergency reporting regardless of causal relationship to the protocol treatment. In addition, in the event protocol treatment is discontinued and posttreatment has already begun, deaths within 30 days after the date of the final protocol treatment will also be subject to emergency reporting.

2) Unknown grade 4 non-hematological toxicity (adverse events that are not classified under the blood or bone-marrow classification according to CTCAE).

   “Unknown adverse events” refer to events not described on the drug package insert.

10.2 Adverse events requiring normal reporting

Adverse events subject to normal reporting are shown in “8.3 Evaluation of adverse events”.

10.3 Reporting obligations of the physician in charge and reporting procedures

10.3.1 Emergency reporting

If an adverse event requiring emergency reporting (10.1) occurs, the attending physician will promptly inform the physician in charge. In the event the physician in charge cannot be contacted, the attending physician must assume the responsibilities of the physician in charge. If an adverse event requiring emergency reporting is observed, the physician in charge must immediately report the situation to the head of the medical facility, and report the situation to the secretariat orally within 24 hours. The physician in charge must also fill in the prescribed items of an “adverse event emergency contact form” (the medical facility’s own style of form can also be used) and fax it to the CSPOR Data Center (fax: 03-5298-8536) **within 72 hours** of knowledge of the adverse event. In addition, the physician in charge will create a case report (A4 free format) as a separate document that describes the adverse event in further detail and fax it to the CSPOR Data Center **within 15 days** of both parties becoming aware of the adverse event.

10.3.2 Normal reporting

The physician in charge will fill out the prescribed items in a “progress report” (Appendix B) that corresponds to the timing of onset of the adverse event and send it to the CSPOR Data Center within the time of submission for the progress report.

10.4 Responsibilities of the secretariat

10.4.1 Determination of the necessity to suspend registration and emergency notification of participating medical facilities

In the event the secretariat receives a report from a physician in charge, he/she will seek the judgment of the principal investigator (or the person acting on his/her behalf) with regard to the degree of urgency, importance and effects of the report and, if necessary, take measures such as temporary suspension of registration (by contacting the CSPOR Data Center and all participating medical institutions) and urgently inform participating facilities of the matters in the report.

In addition, the secretariat will also strongly encourage the physician in charge at the reporting facility to cooperate in making a report according to the Safety Information Report System for Drugs, etc. and spontaneous reports of adverse drug reactions by marketing authorization holders based on the Pharmaceutical Affairs Law.

10.4.2 Reporting to the Independent Monitoring Committee

If the principal investigator deems an adverse event that has been reported by a medical facility via normal reporting or via emergency reporting is an “adverse event that requires reporting”, the principal investigator will make a report in document form to the Independent Monitoring Committee within 15 days after learning of the adverse event. At the same time, the principal investigator’s opinion concerning the relevant adverse event and a review of the appropriateness of the response to the adverse event will also be requested.

10.5 Investigation by the Independent Monitoring Committee

The Independent Monitoring Committee will review the content of reports and recommend an ongoing response to the principal investigator in document form that will cover the handling of the subject and whether to continue registration.

11 Evaluation of HRQOL and economy of medical care

11.1 Evaluation of HRQOL

11.1.1 Objectives

HRQOL from the subjective perspective of the patient will be evaluated and compared as a secondary endpoint of this study.

1) HRQOL will be compared over a period of disease-free survival in patients who have completed 5 years of adjuvant endocrine therapy for postmenopausal breast cancer after either ending treatment or after extension of anastrozole treatment for 5 years.
2) An investigation of utility, used to evaluate economy of medical care (11.2) will also be carried out at the same time.

11.1.2 Measures (survey form)

The survey forms below will be used as measures to evaluate HRQOL (Appendix C).

1) SF-36 (Medical Outcome Study Short-Form 36-Item Health Survey): The Japanese translation of SF-36v2™[17, 18], a survey form and comprehensive measure of HRQOL, will be used.
2) FACT-ES[19, 20] subscale: Additional measure for evaluation of endocrine-related symptoms (subscale only)
3) EQ-5D (EuroQol 5 Dimension)[21-23]: This is a scale based on preference and will be used to measure utility for evaluation of economy of medical care (5th only, excluding VAS).

11.1.3 Investigation schedule

Investigations will be undertaken at the time of registration, 1 year after registration, 2 years, 3 years, 4 years, 5 years and 6 years (1 year after start of follow-up). Investigation at time of registration will take place between after obtaining consent and before faxing the patient registration form. The acceptable window for conduct of other investigations will be within ±6 months of each time point. The investigation at 6 years after initiation of observation (1 year after starting follow-up) will be performed whenever possible. Investigations will continue as long as a patient is alive and does not refuse the investigation. In the event of recurrence the SF-36 and FACT-ES surveys will end and only the EQ-5D survey will be continued.

11.1.4 Investigation methods

Attending physicians will obtain the survey forms by post in advance. Attending physicians will distribute the survey form to patients subject to the HRQOL investigation and request the patient fill in and submit the survey form at each time point. Submission of survey forms will take place by the retrieval of survey forms by the attending physician and postage to the Data Center within the prescribed window of time. Patients may submit forms by post directly to the Data Center, in which case the attending physician will check compliance with submission.

If a patient is unable to fill in a survey form due to exacerbation of an illness or the like, a third party that may be a family member or a CRC may read the survey form to the patient and fill it in on the patient's behalf. In this case the fact this method has been used will be described on the survey form. See Appendix C for precautions during the completion of the survey by third parties and how to respond in the event of missing data and the like.

11.1.5 Number of patients

From the experience of the N-SAS BC 03 study, the number of patients required for HRQOL analysis is deemed to be approx. 150 in each group. In this study the planned number of patients for use in the evaluation of HRQOL is 150 patients in each group starting from the first enrolled patient, with a total of 300 patients in all.

11.1.6 Data analysis method

The SF-36, FACT-ES and EQ-5D scores obtained will be collected by treatment group to produce a pattern of change over time, summarized by a few statistical variables as necessary and compared between treatment groups using an analysis of variance technique. The EQ-5D score will be used to calculate the QALY and QADFY for an evaluation of economy of medical care (11.2). Note that the details of the analytical plan will be described in detail in a separate analysis plan.

11.2 Evaluation of economy of medical care

11.2.1 Objective

To compare the economics of ending treatment and of a 5-year extension of anastrozole treatment in patients who have completed 5 years of adjuvant endocrine therapy for postmenopausal breast cancer.

11.2.2 Variables subject to evaluation

(1) Direct medical costs

1) Facilities subject to evaluation

Participating medical institutions that are capable of implementing the HRQOL investigation and a survey of statements of medical expenses (medical practitioners' receipts for health insurance claim). This will be approx. 10 facilities.

2) Number of patients

Approx. 100 patients.

(2) Indirect costs and direct non-medical costs

The same 300 patients participating in the HRQOL investigation will be surveyed.

11.2.3 Method

1) Analytical method

A cost-utility analysis (Note 1) will be performed.

If outcomes are equivalent, a cost minimization analysis will be performed.

2) Frame of reference

Analysis will be from a societal perspective (Note 2).

3) Outcome indicators

Quality adjusted life year (QALY)

The survival time (overall survival, OS) and QOL (evaluated using a scale where 1 is full health and 0 is death) are required to calculate QALY. The secondary endpoint overall survival will be used for survival time and QOL will be obtained from the HRQOL investigation.

Quality adjusted disease free year (QADFY)

QADFY will be calculated using the primary endpoint disease-free survival (DFS) and QOL.

4) Cost variables (Note 3)

Costs will be summarized from a societal perspective in terms of direct cost and indirect cost.

Direct cost

Direct medical cost

Medical cost associated with treatment and intervention for treatment of adverse drug reactions.

Direct non-medical cost

Travel cost of medical examination

Disease-related adaptive devices (supportive devices, pads, wigs, etc.).

Indirect cost

Work loss associated with treatment.

5) Discounting (Note 4)

Discounting will be implemented at a yearly rate of discount of 3% of costs and outcomes[24].

6) Presentation of results (Note 5)

Cost-utility ratio (CUR)

The CUR is the cost of obtaining 1 QALY (or 1 QADFY) in either the untreated group or the extended anastrozole treatment group. The cost of obtaining the same unit of QALY (or QADLY) will be compared and the group with the smaller cost-utility ratio determined as the more efficient method of treatment. If outcomes are equivalent between the groups, a cost-minimization analysis will be performed by comparison of cost only and the cost-utility ratio will not be calculated.

Incremental cost-utility ratio (ICUR)

The ICUR is the cost required to obtain an additional 1 QALY (or 1 QADFY) in the extended anastrozole treatment group relative to the untreated group. This will determine whether introducing a 5-year extension of anastrozole treatment corresponds with additional cost.

If the therapeutic effect is higher in the extended anastrozole treatment group relative to the untreated group and cost is lower, the extended anastrozole treatment group is “dominant” and the incremental cost-utility ratio will not be calculated.

7) Sensitivity analysis

A sensitivity analysis will be performed that changes the values of parameters using to calculated both cost and outcome. A sensitivity analysis will also be carried out using a discount rate of between 0%-7%.

11.2.4 Data collection

1) Outcome

Disease-free survival (DFS)

The primary endpoint of this study and as such used in the clinical trial results.

QOL (Note 6)

Investigated using a QOL survey form. Evaluation of economy of medical care will use the QOL evaluation results calculated based on the EQ-5D form.

2) Cost

Direct medical cost

Direct medical cost will use data from medical practitioners' receipts for health insurance claims (receipts) and data from outside prescriptions for facilities that issue prescriptions to be filled at external pharmacy services. Copies of receipts printed for invoicing purposes and outside prescriptions that are issued will be collected on an annual basis. Electronic data pertaining to direct medical cost is allowed. The standard data collection procedure will be as described below. Since receipts occur in two types, paper receipts and electronic receipts, the procedure for submission of receipts will be decided in advance after discussion between the relevant medical institution and the Data Center.

a) Request for cooperation is made to a medical institution.

b) Provisions are created pertaining to the facility and data collection methods.

c) Commencement of data collection

d) Copies are made of the receipts and outside prescriptions of relevant patients, and after redacting patient names and other information the study registration number is added to the copies and the copies are sent to the Data Center.

e) The receipts and outside prescriptions are checked at the Data Center and data is entered.

Direct non-medical cost

To investigate direct non-medical cost, a questionnaire survey (Appendix C) will be implemented in patients subject to the HRQOL investigation with the same schedule as HRQOL investigations (at time of registration, 1 year after registration, 2 years, 3 years, 4 years, 5 years and 6 years [1 year after start of follow-up]). The acceptable window of time for surveys is within ±6 months of each time point. Investigations will continue as long as a patient is alive and does not refuse the investigation, and in the event of recurrence the investigation will continue to be implemented using the same survey form.

Indirect cost

The investigation of indirect cost will be included in the investigation of direct non-medical cost.

11.2.5 Data processing

1) Outcome

QALY will be calculated for each relevant patient using survival time and QOL evaluation results.

2) Cost

Direct medical cost will be entered with costs grouped by type as clinical exams, administered drugs, injections, medical procedures, surgeries, tests, diagnostic imaging, hospitalizations and diet. The medical cost of each medical practice will be calculated as well as overall medical cost.

Direct non-medical cost and indirect cost will be calculated per relevant patient for each treatment method after the data has been entered at the Data Center.

3) Statistical analysis

Details of the analytical plan will be prescribed in a separate analysis plan.

An analysis of the years of disease-free survival can be performed using only the data collected in this study. An analysis of the overall years of survival will require additional information on cost after occurrence of metastasis and the like, and is difficult to perform using only the data obtained in this study. Because of this, analysis will be conducted using a medical treatment model.

Note 1: Cost-utility analysis

Normal methods of evaluating the economy of medical care include cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). Each of these involves a comparison of multiple treatment methods and uses data both on cost and outcome to investigate efficiency, and is classified as a full economic evaluation[25].

The CMA is used when outcome is identical between the treatment methods being compared. The CMA only compares cost where the method of least cost is determined the most efficient. The CEA is the most commonly deployed analytical method and defines one primary outcome indicator and compares the calculated cost of obtaining a single unit of outcome. Life years gained is often used as the outcome indicator for CEA. The CUA uses a utility value as an indicator of outcome, which is a measure that takes into account extension of years of survival and the relative QOL between those years. QALY is often used as the unit of reference for CUA. QALY is evaluated using a scale that takes total health as “1” and death as “0”. Consequently, 1 QALY refers to one year of survival in a fully healthy state. The CBA converts all the effects obtained from treatment into a monetary value and evaluates the results. In addition to comparing the calculated benefit obtained per input cost, the CBA also compares the calculated net benefit that is the benefit minus cost.

Note 2: Analytical perspective

When conducting an evaluation of the economy of medical care, it is important to define from whose perspective the evaluation is being performed. In terms of outcome the objective is an improvement in the health status and QOL of the patient, but changing from whose perspective analysis is performed will result in differing scopes of costs that must be included in the analysis. Potential perspectives include the patient, medical institution, insurance-paying party and government. For example, from the perspective of the patient, costs will include payments made at the medical institution and travel costs incurred due to clinical exams. From the perspective of the medical institution, cost will include the labor costs, materials costs, expenditures, etc. incurred in providing medical care for the illness. From the perspective of the party paying the insurance claim, costs will include remuneration paid to the medical institution. A societal perspective includes all these perspectives and in so doing encompasses all perspectives that pertain to a disease.

Note 3: Classification of cost

There are various methods of classifying cost for the evaluation of economy of medical care. What follows is an explanation of the difference between direct and indirect cost. Direct cost is the cost paid to receive treatment for a particular disease while items included in the direct cost will vary from an analytical perspective. Normally, direct cost is divided in to the costs incurred at the medical institution and pharmacy (direct medical cost) and other payments (direct non-medical cost). Indirect cost is calculated as the opportunity cost of loss of work that arises from the change in becoming unable to perform activities of daily living associated with a disease or treatment. No actual payments are made, but indirect cost is important for an evaluation of economy of medical care from the perspective of loss of resources.

Note 4: Discount

Discounting is a method of converting cost arising across a number of years into a valuation at a single point in time. People generally have a time preference, where a sum of money has a higher valuation in the present time relative to its valuation at a point of time in the distant future. Discounting is carried out to convert a future cost into a current valuation. A number of discount rates have been proposed. There is a dispute about whether to also discount for outcomes, with many suggesting that outcome should be discounted to the same extend as cost.

Note 5: Cost-utility ratio and incremental cost-utility ratio

The results of evaluations of economy of medical care are often represented as the cost of obtaining a single unit of outcome. This is the cost-utility ratio (called the cost-utility ratio or cost-benefit ratio depending on the analytical method). The cost-utility ratio is calculated by taking the cost of each treatment method as the numerator and the effect obtained as the denominator.

Taking the respective cost of treatments A and B as cost(A) and cost(B) and the respective effects as effectiveness(A) and effectiveness(B), the cost-effectiveness ratio is calculated as:

Compared to this, the incremental cost-effectiveness ratio is calculated using the incremental cost or effect of a treatment method relative to the more common treatment method or the lower cost treatment of the treatments being compared:

This represents the cost incurred to obtain an additional single unit of effect relative to the treatment method taken as the control method.

Note 6: QOL evaluation for an evaluation of economy of medical care

The QOL evaluation used in the cost-utility analysis uses a scale between 1 and 0 where 1 represents full health and 0 represents death. Direct methods of QOL evaluation include the visual analogue scale, time trade-off and standard gamble. An indirect method of QOL evaluation includes calculating a QOL evaluation value using a conversion formula obtained from a scale based on preference (for example, the ED-5Q that evaluates a scale of 5 dimensions and 3 stages, and the HUI of 8 dimensions).

12 Endpoints

12.1 Primary endpoint

12.1.1 Disease-free survival (DFS)

(1) Definition

Period of time from date of random allocation to the date when the first event occurs.

(2) Event

An event will be defined as occurrence of any of the below.

1) A diagnosis of conserved breast recurrence, local (affected chest wall) recurrence, regional lymph node recurrence or distant organ metastasis (8.2)
2) A diagnosis of metachronous breast cancer or secondary cancer (not including cutaneous basal cell carcinoma, squamous cell cancer or endometrial intraepithelial carcinoma)
3) All deaths (regardless of cause)

(3) Cut-off

1) The last confirmed date of an absence of the above events
2) For surviving patients, the last confirmed date of survival

12.2 Secondary endpoints

12.2.1 Overall survival (OS)

(1) Definition

Period of time from date of random allocation to the date of death, regardless of cause of death

(2) Event

All deaths (regardless of cause)

(3) Cut-off

1) For surviving patients, the last confirmed date of survival
2) For patients lost to follow-up, the last confirmed date of survival

12.2.2 Distant disease-free survival (DDFS)

(1) Definition

Period of time from date of random allocation to the date when the first event occurs

(2) Event

An event will be defined as occurrence of any of the below.

1) A diagnosis of distant organ metastasis (8.2)
2) All deaths (regardless of cause)

(3) Cut-off

1) The last confirmed date of an absence of the above events
2) For surviving patients, the last confirmed date of survival

12.2.3 Adverse events

Adverse events will be termed and classified by Grade according to the JCOG Edition Japanese translation of CTCAE v3.0 (Appendix F).

The rate of occurrence of adverse events will be calculated by taking the total number of patients in whom observation is initiated (patients evaluable for safety) as the denominator and the number of patients in whom one or more adverse events is observed after commencement of observation as the numerator. In addition, the rate of occurrence of the most severe Grade of each adverse event will be calculated for each group.

12.2.4 Evaluation of HRQOL and economy of medical care

(See “11 Evaluation of HRQOL and economy of medical care”.)

12.3 Other endpoints

12.3.1 Evaluation of bone density

Bone density will be evaluated in registered patients in whom the mean BMD (g/cm^2) is measured in L1-L4 or in L2-L4. Taking the commencement of observation as baseline, the mean rate of change (percentage change) in BMD and the T score in each year will be compared in the CONTINUE group and the STOP group. The temporal change in urinary NTx will be evaluated in patients in whom urinary NTx is measured.

Bone density results obtained by methods other than DXA will be used for evaluating adverse events and determining the commencement of treatment (6.3.3 Treatment for reduced bone density).

12.3.2 Evaluation of joint symptoms

Joint symptoms will be valuated in patients in whom the below items are investigated according to the provisions of section “8.5” of this protocol. CTCAE v3.0 evaluation results will be used to calculate rate of occurrence of each Grade and a comparison made between the CONTINUE group and STOP group. The pain score measured in terms of distance from a zero score indicating no pain according to the VAS evaluation, will be used to calculate basic statistics and make a comparison between the groups.

1) Joint pain-related CTCAE v3.0 (pain-musculoskeletal-joints) evaluation (patient and physician)
2) Sites of joint pain throughout body (patient)
3) VAS evaluation of site of strongest joint pain (patient)
4) Joint stiffness-related CTCAE v3.0 (musculoskeletal-joint function) evaluation (patients and physician)
5) Sites of joint stiffness (patient)
6) Duration of joint stiffness (patient)
7) Change in joint stiffness (patient)

13 Statistical matters

13.1 Rationale for primary hypothesis and the number of patients

The hypothesis for this study is that “If the rate of disease-free survival is 91% in patients who complete 5 years of endocrine therapy (ANA or TAM→ANA) followed by no treatment for 5 years, the rate of disease-free survival in patients who receive a 5-year extension of ANA treatment will be 94% or higher”.

An EBCTCG meta-analysis[13] of 15 years of long-term follow-up including 5 years of TAM treatment in ER positive (including unknown) breast cancer patients reports that patients who transitioned to untreated observation after 5 years of TAM treatment had a cumulative rate of breast cancer recurrence of 15.1% after 5 years, 24.7% after 10 years, and 33.2% after 15 years. In addition, an ATAC trial that obtained 68 months of data reports a difference of a little under 3% in recurrence rate between patients treated with ANA or TAM after 5 years of endocrine therapy. Even considering the carry over effect, based on the previously mentioned EBCTCG results the estimated recurrence rate for a group transitioned to 5 years of no treatment after receiving ANA treatment will be 9%.

Consequently, the results observed in patients who receive TAM→ANA treatment are assumed to be almost identical to those who receive ANA monotherapy, and the estimated rate of recurrence in the STOP group of this study is estimated at 9%.

Although no results are available from direct investigations into the potential recurrence rate in the CONTINUE group, the results of the MA17 trial[15] of an additional 4 years of LET treatment after 5 years of TAM treatment showed a difference in DFS of ≥4%. Consequently, it has been assumed that an improvement in DFS of ≥3% will be evidence of clinical effectiveness.

13.2 Scheduled number of patients and follow-up period

With a DFS rate of 91% for untreated observation (STOP group) and 94% in the population that receives a 5-year extension of ANA treatment (CONTINUE group), an enrollment period of 2 years is chosen, a follow-up period of 5 years, a type I error of 5%, and a statistical power of 80%.

The number of patients required has been calculated assuming a patient dropout rate of 0%, 5% and 10% in the STOP group and 0% and 5% in the CONTINUE group (according to the SAS 9.1.3 STAT Power procedure).

STOP group Dropout rate	CONTINUE group Dropout rate	Number of patients/group
0	0	1002
0	0.05	1098
0.05	0	1068
0.05	0.05	1159
0.1	0	1144
0.1	0.05	1231

In this study of the 5 years that follow standard treatment, assuming slightly more dropouts in the STOP group compared to the CONTINUE group with respective dropout rates of 10% and 5%, the required number of patients is 1231. For reference purposes only, when the required number of patients was calculated using the Freedman and Schoenfeld formulae, not taking into account a dropout rate or registration period, the two methods gave results of 1214 and 1178 patients, respectively.

Consequently, the required number of patients will be 1250 per group.

13.3 Handling of patients and analysis sets

The analysis set will include all patients who are allocated randomly after consent is obtained.

13.4 Aggregation of patient registration status

Patients who discontinue or drop out from the study will be aggregated in accordance with the handling guidelines and the cumulative discontinuation and drop out rate will be calculated using the Kaplan-Meier method. Aggregation of patient registration status in terms of a scoring of each patient background factor will be carried out and the difference between the groups will be tested with the purpose of examining the balance amongst the groups with regards to distribution of discontinuation and dropout cases.

13.5 Aggregation and comparison of treatment compliance

Aggregation of treatment compliance will be carried out in accordance with the handling guidelines, and the reasons for treatment discontinuation will be gathered and summarized.

13.6 Analyses of each survival times

Rates of DFS will be compared amongst the groups by constructing a Kaplan-Meier curve and applying a Log-rank test. The test will be two-sided with a significance level of 5% and the two-sided 95% confidence interval will be calculated.

Interaction between the factors used during allocation will be examined using a chi-square test and a diagrammatic representation of confidence intervals for subgroups. In particular, since patients eligible for this study will have received an endocrine therapy of either ANA or TAM→ANA, whether a difference in treatment method on entry has an effect on prognosis will be examined.

In addition, this study will evaluate whether to continue or discontinue ANA treatment. Since patients have already received 5 years of treatment, analysis (sensitivity analysis) will take into account carry-over effects of the prior treatment and results will be examined for corresponding influences.

See the separately prepared analysis plan for more details.

13.7 Supplemental analysis of each survival time

Cox regression analysis will be performed to examine each survival time with the use of adjustment factors.

13.8 Analysis of adverse events

The rate of adverse events in each group will be summarized and evaluated.

13.9 Other analyses

Other analyses will be decided during the period until the conduct of data analysis, and included on preparation of the analysis plan.

13.10 Monitoring and review under blinding

The Executive Committee will conduct appropriate monitoring and review of the matters below.

- Enrollment
- Recurrence of beast cancer and occurrence of adverse events (examination of annual number of events only)

The need to reexamine the number of patients and the timing of interim and final analyses will be determined based on information gained through monitoring and review and new findings obtained until that point in time. This information will also be examined for the appropriateness of the timing of publication of results.

The Executive Committee will also provide recommendations to the Clinical Study Sub-Committee and the Independent Monitoring Committee in the event the protocol requires amendment, and amendments will require review and approval by the Clinical Study Sub-Committee and the Independent Monitoring Committee.

Note the blind review required to determine the particulars of the analysis plan, such as to examine the variables used in the Cox regression analysis, will be performed prior to interim analysis.

13.11 Interim analysis

Calculation of the rate of DFS in the STOP group will be performed based on the EBCTCG meta-analysis. In addition, an interim analysis will be performed due to a lack of evidence in Japanese patients. To maintain a two-sided type I error of 5% for the whole study at interim analysis, the Lan & DeMets α consumption function will be used to adjust for redundancy in analysis of the primary endpoint. The O'Brian & Fleming α consumption function will be used.

Interim analysis will be carried out by the Independent Monitoring Committee. The prospective number of events according to the Freedman equation is 232. Interim analysis will be carried out when 50%-60% of events have occurred.

If the therapeutic effects are sufficient and rate of cancer recurrence is higher than supposed in the STOP group according to results at interim analysis, the disbenefit of not receiving treatment will have been demonstrated adequately. Recalculated based on therapeutic effects evidenced up to the point of interim analysis, if the number of required patients differs substantially from the initial calculation the discontinuation or change of the study will be examined from a statistical viewpoint and a recommendation will be made to the Executive Committee.

In addition, the Independent Monitoring Committee will carry out an interim analysis of safety at 1 year and 2 years after commencing registration. The Independent Monitoring Committee will examine treatment compliance and occurrence of adverse events, and if it deems discontinuation or change of the study necessary will make a recommendation to the Executive Committee.

14 Ethics

14.1 Patient Protection

All researchers involved with this study will conduct this study in conformance with the Declaration of Helsinki (Appendix E) and the “Ethical Guidelines for Clinical Research” (http://www.imcj.go.jp/rinri/index.html) of the Ministry of Health, Labour and Welfare.

14.2 Informed Consent

14.2.1 Explanation to patients

Prior to registration, the attending physician will provide the patient with explanatory documents (Appendix A explanatory documents revised by each facility) approved by the facility’s Ethical Review Committee (or Institutional Review Board; IRB) and give the patient a detailed oral explanation of the following content.

1) An explanation of the disease
2) That the study is a clinical trial
3) The study design and rationale (study significance, scheduled number of patients, necessity, objectives, etc.).
4) Details of the protocol treatment
   Drug names, treatment methods, doses, phases, etc.
5) Expected effects of protocol treatment
6) Anticipated adverse events and treatment methods
7) Burden of cost and compensation
   The burden of cost and compensation will be equivalent to normal medical care. I.e., the cost of treatment will be covered by the patient’s system of insurance and in the event of damage to patient health compensation will be consistent with normal medical care.
8) Alternative methods of treatment
   Alternative methods of treatment that are currently common treatments.
9) The anticipated benefits and possible disadvantages of participation in the study
10) Checking of the patient’s medical history by auditors
    Explanation of the patient’s acceptance of audit
11) Refusal of consent and withdrawal of consent
    That the patient is free to refuse consent before participating in the study, and once consent has been given the patient is still free to withdrawal consent, and will be put at no unreasonable medical disadvantage as a result.
12) Human rights
    Utmost efforts will be made to protect the name and personal information of the patient.
13) Secondary use of data
    Data may be put to secondary uses in such a way that it may not be linked to personally

identifying information.

14) Freedom to ask questions

The patient will be given a document with the contact details of the attending physician and principal investigator (or study secretariat), and given the freedom to ask questions about the study or treatment.

14.2.2 Consent

Patients will be asked to participate in this study after having the study explained to them and after it has been confirmed they fully understand the content of the study. In the event a patient consents to participation in the study, a consent form in a format prescribed by the facility will be used to record the name and signature of the physician who provided the explanation, the patient who received the explanation and consents to participation in the study, and the date of consent.

Two copies of this consent form will be made, one copy given to the patient and one copy retained by the facility. The original will be stored in the patient's medical record.

14.2.3 Timing of obtaining consent

Consent will be obtained prior to registration.

14.3 Patient identification and protection of privacy

The names of registered patients will not be made known to the Data Center by participating facilities. Identification of and queries regarding registered patients will be carried out using their patient registration number issued at the time of registration, initials and date of birth and no information that would allow a third party to directly identify patients such as patient names, etc. will be registered in the database of the Data Center.

To maintain confidentiality of patient information the "day" section of the date and patient initials may be masked, but an "x" mark will be placed next to the affected place.

Exchange of patient data between facilities, the Data Center and the secretariat will be conducted by the methods described below.

1) Patient registration, queries to be expedited, emergency adverse event reporting: By fax.

2) EDC system: Electronic data transfer employing encryption.

3) Paper survey forms: Mailed through the post or passed hand-to-hand.

14.4 Protocol compliance

The researchers participating in this study will comply with this study protocol insofar as compliance does not compromise patient safety and human rights.

14.5 Facility Ethical Review Committee (or Institutional Review Board: IRB) approval

14.5.1 Approval at commencement of study participation

Upon commencing participation in this study, each facility's Ethical Review Committee or IRB must approve this study protocol and the patient explanatory documents. If IRB approval is obtained, a copy of the IRB approval form will be sent to the CSPOR Data Center. The original IRB approval forms will be retained by each facility and copies retained by the CSPOR Data Center.

14.5.2 Yearly re-approval by the IRB

The regulations of each facility will dictate whether yearly review and re-approval of this study protocol and the patient explanatory documents by their Ethical Review Committee or IRB will be necessary.

15 Monitoring and auditing

15.1 Monitoring

15.1.1 Objective

To confirm whether the study is being conducted safely and in accordance with this protocol and whether data is being collected accurately.

15.1.2 Central monitoring (in-house monitoring)

The Executive Committee and Data Center will cooperate in monitoring the content of EDC data and HRQOL survey forms collected at the CSPOR Data Center using the processing results of digitized data as a reference. There is no plan to carry out monitoring by visiting participating facilities.

15.1.3 Items (on patient basis)

1) Eligibility
2) Protocol treatment status
3) Adverse events; serious adverse events and their reporting status in particular
4) Follow-up status after completion of the protocol treatment; survival in particular
5) Other items

15.1.4 Items (on by-group accumulated results basis)

1) Patient accumulation status
2) Eligibility
3) Protocol treatment status
4) Incidence of adverse events
5) Follow-up
6) Other items

15.2 Auditing

15.2.1 Objective

To confirm whether this study is being conducted appropriately and verify the reliability of the data obtained.

15.2.2 Auditing Committee

An Auditing Committee will be established within the Japan Clinical Research Support Unit (J-CRSU) in order to conduct auditing. The Auditing Committee will be composed of physicians or professionals with similar qualifications who possess experience and insight in clinical trial research and are not directly responsible for patients that are subject to auditing. A chairperson will be selected from amongst the members.

15.2.3 Duties of the Auditing Committee

1) The Auditing Committee will conduct audits to verify whether the registration of eligible patients, drug administration, observation and follow-up examinations, etc. are being carried out in accordance with the provisions of this clinical study protocol.

2) The Auditing Committee will create auditing plans (SOP and manual) and visit the CSPOR Data Center and participating medical facilities to conduct audits in accordance with these auditing plans.

3) Visit and audit of medical facilities
The Auditing Committee will sequentially visit all participating medical facilities to inspect clinical study-related documents and source documents related to registered patients (medical records, diagnostic images, etc.) with the purpose of confirming whether this study is being conducted in adherence with the principles of ICH-GCP and this clinical study protocol.

4) CSPOR Data Center auditing
The auditing team will conduct auditing to confirm whether duties of the CSPOR Data Center are being carried out in accordance with the SOP and provide guidance.

5) Creation of audit reports
The Auditing Committee will perform their duties, create audit reports to record matters confirmed in audits that have been conducted, create audit certificates to prove that audits have been conducted and submit these documents to the principal investigator.

15.2.4 Protection of privacy

Attention will be given to the protection of records that disclose the identity of the patients in this study and confidential medical information.

15.2.5 Extramural review by the Auditing Committee

The Auditing Committee will conduct an extramural review of cases of recurrence, death and serious or unexpected adverse events and report their results to the principal investigator. The principal investigator and Executive Committee will examine the necessity of facility monitoring based on these results and conduct facility monitoring if necessary.

16 Announcement of research results

Research results will be published in line with policy created by the Clinical Study Sub-Committee. Study-related announcements will be made at the study planning report, interim report, and final report stages of the study. These announcements will be within the format of academic conferences and article submissions to journals. The study planning report will be announced at an appropriate time as an outline of this study that will be based on this protocol. The interim report will be announced promptly at the first opportunity if results are obtained from an interim analysis performed according to the previous study plan that should be announced. As long as the study does not end early, the final report (report of results of primary endpoint confirmatory analysis) will be made at the completion of the follow-up phase.

The listing of authors and their listing order will be carried out in accordance with the above-mentioned Clinical Study Sub-Committee policy and be reviewed and authorized by the Clinical Study Sub-Committee and Independent Monitoring Committee prior to announcement of the relevant results at both academic conference presentations and in submissions to journals.

17 Conflicts of interest and research funding

There are no potential conflicts of interest relating to the planning, conduct or announcement of this study. A conflict of interest refers to a vested interest that affects research results and includes financial and personal relationships.

The conduct of this study is funded by the Comprehensive Support Project for Oncology Research (CSPOR). The secretariat of the CSPOR will undertake clerical activities but will have no part in decisions related to the planning, conduct or announcement of the study. Decisions relating to the planning, conduct and announcement of the study will be undertaken by the Executive Committee.

18 Clinical trial registration

This study will be registered to and information published on the UMIN Clinical Trials Registry (UMIN-CTR, http://www.umin.ac.jp/ctr/index-j.htm). Registration will occur prior to enrollment of the first patient to the study, and registration will be carried out by the CSPOR.

UMIN-CTR is a registry organization that meets the requirements of the internationally supported clinical trial registration system. The necessity for the registration of clinical trials has been debated since the 1970s. In September 2004, the International Committee of Medical Journal Editors (ICMJE) declares a policy that made the advance registration of clinical trials a condition of their publication[26, 27], advancing the establishment of a system of registration. In addition, the World Health Organization (WHO) launched the International Clinical Trials Registry Platform, and in April 2005 implemented a system of WHO guidance that stipulated standards for registration[28]. In light of this, in June 2005 the UMIN-CTR was initiated as Japan's first clinical trial registration organization. UMIN-CTR is recognized as an acceptable registry by the ICMJE, and cooperates with the WHO.

19 Accompanying research

The “Breast cancer patient multipurpose cohort study 05” will be carried out as accompanying research.

The study protocol will be prescribed separately.

20 Study organization

This study is one of the clinical studies carried out as part of the Public Health Research Foundation's Comprehensive Support Project for Oncological Research. The first committee listed here is the Executive Committee, which is an organization unique to this study. Next, committees, etc. that are common across the support project are listed.

20.1 N-SAS BC05 Executive Committee

Chairperson (principal investigator)

Takuji Iwase (Department of Breast Oncology, The Cancer Institute Hospital of JFCR Ladies Center)

Study statistician (person responsible for biostatistical analysis)

Hiroshi Ohtsu (Department of Clinical Trial Data Management, Graduate School of Medicine, The University of Tokyo)

Committee members (in order of Japanese syllabary)

Yoshifumi Komoike (Department of Breast and Endocrine Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases)

Shigehira Saji (Department of Oncology, Saitama Medical University International Medical Center)

Hiroyuki Takei (Department of Breast Surgery, Saitama Cancer Center)

Hiroshi Yagata (Department of Breast Surgery, St. Luke's International Hospital)

Adviser

Toshitaka Nakamura (Bone Metabolism Adviser: Department of Orthopaedic Surgery, University of Occupational and Environmental Health)

20.1.1 Mission of the N-SAS BC05 Executive Committee

- To carry out coordination work related to the implementation of the study with the secretariat and Data Center
- To report the study implementation status to the Clinical Research Committee
- Matters necessary for quality control and quality assurance of the entire study
- Quality evaluation of the facilities participating in the study
- To support the Data Center in data management
- To support the study statistician in statistical analysis
- Report creation
- Other matters necessary for the smooth and efficient implementation of the study

20.2 Management Committee

Chairperson

Yasuo Ohashi (Graduate School of Medicine, The University of Tokyo)

Vice chairperson

Kojiro Shimozuma (College of Life Sciences, Department of Science and Engineering, Ritsumeikan University)

Management Committee members

Toru Watanabe (Hamamatsu Oncology Center)

Tadashi Ikeda (Department of Surgery, School of Medicine, Teikyo University)

Masakazu Toi (Department of Breast Surgery, Kyoto University Hospital)

Takuji Iwase (Department of Breast Oncology, The Cancer Institute Hospital of JFCR Ladies Center)

Yuichi Takatsuka (Department of Surgery, Japan Labour Health and Welfare Organization Kansai Rosai Hospital)

Shinzaburo Noguchi (Department of Breast and Endocrine Surgery, Faculty of Medicine, Osaka University)

Shinji Ohno (Department of Breast Oncology, National Hospital Organization Kyushu Cancer Center)

Hiroji Iwata (Department of Breast Oncology, Aichi Cancer Center Central Hospital)

Seiichiro Yamamoto (Center for Cancer Control and Information Services, National Cancer Center)

20.2.1 Mission of the Management Committee

- To formulate long-term project plans and annual project plans and report activities to the Public Health Research Foundation
- To formulate budget proposals for project implementation and report balance sheets to the Public Health Research Foundation
- To establish/abolish various sub-committees in order to carry out the project and appoint sub-committee members
- To oversee the activities of sub-committees
- Any other matters necessary to achieve the aims of the project

20.3 Advisory Committee

Members

Shigemitsu Takashima (Department of Breast and Endocrine, National Hospital Organization Shikoku Cancer Center)

Hiroki Koyama (Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular

Diseases)

Tomoo Tajima (Breast Clinic, Department of Surgery, Tokai University Tokyo Hospital)

Hiroshi Obata (Public Health Research Foundation)

20.3.1 Mission of the Advisory Committee

- To oversee the activities of the Management Committee and respond to inquiries of the Public Health Research Foundation
- To advise the Management Committee and sub-committees
- Other matters necessary to ensure transparency of the project and guarantee consistency with its purpose

20.4 Clinical Study Sub-Committee

Chairperson

Masakazu Toi (Department of Breast Surgery, Kyoto University Hospital)

Vice chairperson

Tetsuya Taguchi (Department of Breast and Endocrine Surgery, Osaka University Hospital)

Members

Toru Watanabe (Hamamatsu Oncology Center)

Takuji Iwase (Department of Breast Oncology, The Cancer Institute Hospital of JFCR Ladies Center)

Takuhiro Yamaguchi (Department of Clinical Trial Data Management, Graduate School of Medicine, The University of Tokyo)

Shinji Ohno (Department of Breast Oncology, National Hospital Organization Kyushu Cancer Center)

Hiroji Iwata (Department of Breast Oncology, Aichi Cancer Center Central Hospital)

Observers

Yasuo Ohashi (Graduate School of Medicine, The University of Tokyo)

Kojiro Shimozuma (College of Life Sciences, Department of Science and Engineering, Ritsumeikan University)

Hirokuni Amari (Visiting Researcher, Public Health Research Foundation)

20.4.1 Mission of the Clinical Study Sub-Committee

- To make decisions on new clinical studies and associated research and, in the event a public appeal for research is made, make decisions on the guidelines of the public appeal and adopt research
- To appoint Executive Committee members for each clinical study and associated research

- To oversee the implementation of each clinical study and associated research
- To approve oral presentations and the publication of papers related to clinical studies and associated research
- Any other matters necessary for the smooth implementation of the clinical studies and associated research conducted under this project and coordination between studies

20.5 Epidemiological Study Sub-Committee

Chairperson

Katsumasa Kuroi (Department of Surgery, Tokyo Metropolitan Komagome Hospital)

Vice chairperson

Hiroji Iwata (Department of Breast Oncology, Aichi Cancer Center Central Hospital)

Members

Motoki Iwasaki (Research Center for Cancer Prevention and Screening, National Cancer Center)

Kojiro Shimozuma (College of Life Sciences, Department of Science and Engineering, Ritsumeikan University)

Tomotaka Sobue (Center for Cancer Control and Information Services, National Cancer Center)

Kaoru Hirose (Aiichi Prefectural Institute of Health)

Observer

Yasuo Ohashi (Graduate School of Medicine, The University of Tokyo)

20.5.1 Mission of the Epidemiological Study Sub-Committee

- To make decisions on new epidemiological studies, and in the event a public appeal for research is made, make decisions on the guidelines of the public appeal, select research, and report the selected research to the Management Committee
- To appoint Executive Committee members for each apidemiological study
- To oversee the implementation of each epidemiological study
- To approve oral presentations and the publication of papers related to epidemiological studies
- Any other matters necessary for the smooth implementation of the epidemiological studies conducted under this project and coordination between studies

20.6 Education and Training Sub-Committee

Chairperson

Toru Watanabe (Hamamatsu Oncology Center)

Vice chairperson

Kojiro Shimozuma (College of Life Sciences, Department of Science and Engineering, Ritsumeikan University)

Members

Yasuo Ohashi (Graduate School of Medicine, The University of Tokyo)

Keiichi Fujiwara (Department of Gynecologic Oncology, Saitama Medical University International Medical Center)

Yuko Saito (Clinical Study Support Laboratory, Shizuoka Cancer Center)

Hirofumi Mukai (Department of Chemotherapy, National Cancer Center Hospital East)

Noriyuki Katsumata (Department of Internal Medicine, National Cancer Center Hospital)

Eriko Aotani (Research Center for Clinical Pharmacology, The Kitasato Institute)

Miki Fukutani (Research Center for Clinical Pharmacology, The Kitasato Institute)

Noriko Yamashita (Division of Clinical Trials and Treatment Development, National Cancer Center Hospital)

Tatsuhiko Ichiki (EPS Corporation)

Shigeru Takagi (TAIHO PHARMACEUTICAL CO., LTD.)

Yoshitake Tamaoka (Novartis Pharma K.K.)

20.6.1 Mission of the CRC Support/Education Sub-Committee

- To plan and implement seminars for physician and CRC education
- To collaborate with internal and external organizations conducting physician and CRC education
- To report activities to the Management Committee
- Other matters necessary for the improvement in quality and vitalization of physician and CRC education

20.7 Public Relations Sub-Committee

Chairperson

Atsushi Fukuuchi (Department of Breast and Endocrine Surgery, Mitsui Memorial Hospital)

Vice chairperson

Seigo Nakamura ((Department of Breast Surgery, St. Luke's International Hospital)

Members

Kojiro Shimozuma (College of Life Sciences, Department of Science and Engineering, Ritsumeikan University)

Shigeru Murakami (Department of Breast Surgery, Hiroshima University Hospital)

Mitsuru Miyauchi (BREAST SERVICE Co., Ltd.)

20.7.1 Mission of the Public Relations Sub-Committee

- To provide information for the implementation of clinical studies supported by the project
- To examine the content of the Japan Comprehensive Cancer Network, Breast (JCCNB)
- To establish working groups for the actual provision of information and oversee their activities
- Public relations activities related to the project (media, academia, patient groups)
- To report activities to the Management Committee
- Other activities that contribute to the provision of useful information to breast cancer patients and the smooth implementation of breast cancer research

20.8 Independent Monitoring Committee (Clinical Study Protocol Review Committee)

Chairperson

Tomoo Tajima (Breast Clinic, Department of Surgery, Tokai University Tokyo Hospital)

Members

Suketami Tominaga (Aichi Cancer Center)

Fujio Kasumi (Breast Center, Juntendo Universtiy Hospital)

Eiko Uchida (NPO Bougainvillea)

Nobuo Seo (Lawyer, Tokyo Hatchobori Law Office)

20.9 Data Management Committee

Chairperson

Yasuo Ohashi (Graduate School of Medicine, The University of Tokyo)

Member

Yuko Saito (Clinical Study Support Laboratory, Shizuoka Cancer Center)

Katsumasa Kuroi (Department of Surgery, Tokyo Metropolitan Komagome Hospital)

Koji Oba (Kyoto University Graduate School of Medicine)

Hiroshi Ohtsu (Department of Clinical Trial Data Management, Graduate School of Medicine, The University of Tokyo)

Harumi Kaba (National Cancer Center)

Shigeru Hayase (Japan Clinical Research Support Unit)

Naohito Fukui (Japan Clinical Research Support Unit)

Akio Ohta (Japan Clinical Research Support Unit)

20.10 CSPOR Data Center

The CSPOR Data Center carries out patient registration, clinical study progress management, monitoring and data management.

NPO Japan Clinical Research Support Unit (J-CRSU)

Representative (Head of Data Center)

Yasuo Ohashi (Graduate School of Medicine, The University of Tokyo)

Address: 5F Nishiyama-kogyo Ochanomizu Building. 1-2-13 Yushima, Bunkyo Ward, Tokyo 113-0034

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E-mail: support@csp.or.jp

20.11 Comprehensive Support Project for Oncological Research Secretariat

Department Chief

Hitoshi Masuda

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Public Health Research Foundation

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E-mail: info@csp.or.jp

21 Amendment of the study protocol / discontinuation of the study

21.1 Change to the protocol

21.1.1 Classification of protocol content changes

Changes to the study protocol following approval by the Clinical Study Review Committee will be classified as either “amendments” or “revisions”. The definition and treatment of “amendments” and “revisions” are as follows.

(1) Amendment

Amendments include partial changes to the protocol that may increase risk to the patients participating in this clinical study or changes that are related to the primary endpoint.
Review and approval of the Independent Monitoring Committee and Ethical Review Committee of each facility is required for amendments.
The date of Independent Monitoring Committee approval will be listed on the cover page of the protocol.

(2) Revision

Revisions include changes to the protocol that do not increase risk to the patients participating in this clinical study and are not related to the primary endpoint.
Independent Monitoring Committee review is not required for revisions; however approval of the chairperson of the Executive Committee and reporting to the Independent Monitoring Committee is required. The regulations of each facility will dictate whether review and approval by their Ethical Review Committee is required.
The date of Executive Committee chairperson approval will be listed on the cover page of the protocol.

21.1.2 Approval of the of the Ethical Review Committee of each facility at the time of protocol amendment/revision

In the event this study protocol or the patient explanatory documents are amended during this study with the approval of the Independent Monitoring Committee, the amended study protocol and/or the amended patient explanatory documents must also be approved by each facility’s Ethical Review Committee (or IRB).
In the event a revision, not an amendment, is made, the regulations of each facility will dictate whether review and approval by their Ethical Review Committee (or IRB) is required.
In the event IRB approval is obtained for an amendment, the facility coordinator of each facility shall send a copy of the IRB approval form to the secretariat. The original IRB approval form will be retained by the CRC and a copy retained by the secretariat.

21.2 Discontinuation of the study

The Independent Monitoring Committee will examine the validity of continuing the study based on interim analyses of safety and efficacy. If continuation of the study is not deemed to be appropriate, the Independent Monitoring Committee will recommend the discontinuation or suspension of the study to the Executive Committee. If the Executive Committee decides to discontinue the study in accordance with this recommendation, the principal investigator will inform the physicians in charge of the discontinuation, reason for the discontinuation and method of supporting patients participating in the study as soon as possible. Physicians in charge will report the circumstances surrounding the discontinuation to their IRB and provide appropriate support for patients participating in the study in accordance with the directions of their IRB and the principal investigator.

22 List of participating medical facilities

Facility name	Department	Physician in charge

See http://www.csp.or.jp/ for the most recent list of participating medical institutions.

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