The randomized-controlled trial is widely accepted as a clinical trial to decide a standard therapy. It remains to be concluded whether or not patients benefit from participation itself in a randomized-controlled trial. This study was aimed at comparing prognoses between trial participants and participation-refusers. Concerned randomized trials are ‘selection of effective chemotherapy for breast cancer’ (SELECT BC) and its successor trial, SELECT BC-CONFIRM. Study subjects are all of metastatic breast cancer patients who are requested by their doctors to participate in these two trials. This trial is a hitherto exceptional prospective study and is suitable to clarify the effects of participation per se in such a trial on prognosis when compared with previous two studies.

Key words: metastatic breast cancer – prospective cohort study – SELECT BC – SELECT BC-CONFIRM

INTRODUCTION

At the present time, the randomized-controlled trial is a widely accepted procedure to establish a standard therapy. In 1985, Davis et al. (1) compared participants and non-participants in a randomized-controlled trial in postoperative non-small cell lung cancer patients, reporting a significantly better survival in the trial participants. Similarly, as reported in 2000 by Gnant (2), participants in nine randomized-controlled trials showed a longer overall survival than non-participants among patients with Stage I or II early breast cancer.

Therefore, participation itself has the potential to improve patients’ prognoses in the randomized-controlled trial. On the other hand, Peppercorn et al. (3) reviewed 26 reports on comparison of clinical trial participants and non-participants, concluding that there was no evidence enough to definitely favor the prognosis of the participants. Furthermore, in 2009, a similar comparative study was performed by Tanai et al. in Japanese advanced lung cancer patients. These investigators found no significant difference in prognosis between participants and non-participants in a randomized-controlled trial (4). As mentioned above, it has not been concluded yet whether or not participation per se in a randomized-controlled trial provides a better prognosis to patients. If non-participants include patients who are in such a bad condition that they do not meet entry criteria of a trial, non-participants have logically worse prognoses. Additionally, a trial may have the following effects and biases: effects of protocol therapy per se, care effects, Horson effects and placebo effects; and patient selection biases, clinical doctor selection biases and movement biases (5). Unless these biases are well controlled and minimized, it cannot be clarified whether or not participation per se in a randomized-controlled trial benefits participants.

This is an accompanying study of ‘selection of effective chemotherapy for breast cancer’ (SELECT BC) and its successor, SELECT BC-CONFIRM (6). The SELECT BC and
SELECT BC-CONFIRM trials are one of the largest scale randomized-controlled trials that are now ongoing in Japan in metastatic or recurrent breast cancer patients (Fig. 1).

This study has been designed so that study subjects are all patients who meet the eligibility criteria of SELECT BC as well as SELECT BC-CONFIRM trials and are requested for participation by attending doctors to compare prognoses between participants and participation-refusers. Since therapeutic agents that are to be administered to participants in both trials have been already approved, it is expected that participants and participation-refusers receive almost identical therapy except for orders of agent administration.

Treatment methods, examinations to be performed during therapy and observation methods of participants of both trials take a practical approach, and so care seems to be scarcely different in its effects between both trials. It is also expected that backgrounds of the participants and participation-refusers are eventually similar, because study subjects have to meet the eligibility criteria of both trials and are free to participate or refuse. Accordingly, this study is more suitable for clarifying effects of participation itself in randomized-controlled trials on prognosis than previous studies. Moreover, this study is a rare prospective study of great significance.

**DIGEST OF THE STUDY PROTOCOL**

**PURPOSE**

To prospectively perform a prognostic study of participants and participation-refusers of SELECT BC and SELECT BC-CONFIRM trials to compare their life prognoses.

**RESOURCES**

This study was funded by Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation. The research fund was provided to CSPOR by Taiho Pharmaceutical Co., Ltd. Taiho Pharmaceutical took no part in this study other than providing information relevant to proper use of the study drug. All decisions concerning the planning, implementation and publication of this study were made by the executive committee of this study.

**ENDPOINT**

The endpoint is overall survival.

**ELIGIBILITY CRITERIA**

All patients that were proposed to participate in SELECT BC and SELECT BC-CONFIRM trials are study subjects of SELECT BC ECO. A participation-refuser is defined as ‘a person who meets the eligibility criteria of SELECT BC and SELECT BC-CONFIRM but refuses to participate on their own will’. The inclusion and exclusion criteria of both trials are described below.

**INCLUSION CRITERIA**

(i) Women with a histologically confirmed diagnosis of breast cancer.

(ii) One of the following conditions has to be met for a diagnosis of metastatic breast cancer:

(a) At presentation, the patient has distant metastasis.

(b) The patient has breast cancer that has worsened or recurred in association with distant metastasis after treatment (after surgery and preoperative and postoperative treatment); however, local recurrence is excluded.

(iii) The presence of at least one assessable lesion. However, sites treated by radiotherapy are not considered assessable lesions.

(iv) No chemotherapy with anticancer drugs since the diagnosis of metastatic breast cancer.

(v) An age of 20–75 years.

(vi) A performance status of 0–1 according to the Eastern Cooperative Oncology Group scale.

(vii) Either of the following conditions has to be met concerning previous treatment with taxane derivatives (paclitaxel or docetaxel):

(a) Not administered previously.

(b) If such drugs have been administered as preoperative or postoperative adjuvant chemotherapy, at least 6 months (168 days, 24 weeks) should have elapsed since the final day of treatment.

(viii) Either of the following conditions has to be met concerning a history of treatment with oral 5-fluorouracil (5-FU) derivatives:

(a) Not administered previously.

(b) If such drugs have been administered as preoperative or postoperative adjuvant chemotherapy, at least 6 months (168 days, 24 weeks) have elapsed since the final day of treatment.

(ix) Both of the following conditions have to be met concerning preceding treatment:

**Figure 1.** Study design of SELECT BC and SELECT BC-CONFIRM.
(a) Hormone therapy: At least 7 days have elapsed since the final day of drug treatment (irrespective of the details of treatment).

(b) Radiotherapy: At least 14 days have elapsed since the final dose of radiation.

(x) Resistance to hormone therapy is defined as any of the following:

(a) Estrogen receptors or progesterone receptors are negative on examination of the primary lesion or recurrent lesion(s). However, if both the primary lesion and recurrent lesion(s) are examined and the results differ, the results for the recurrent lesion(s) will apply.

(b) Hormone therapy is ineffective after recurrence.

(c) Recurrence occurs during postoperative adjuvant hormone therapy or within 6 months after the final dose.

(xi) All of the following conditions have to be met regarding organ function (within 21 days before registration):

(a) A neutrocyte count (stab cells + segmented cells) of 1500/mm³ or higher, or a white cell count of 3000/mm³ or higher.

(b) A platelet count of 100 000/mm³ or higher.

(c) A total bilirubin concentration of not more than 2.5 times the upper limit of normal at the laboratory where the test was performed.

(d) Aspartate aminotransferase (AST, GOT) and alanine aminotransferase concentrations (ALT, GPT) of not more than 2.5 times the upper limit of normal at the laboratory where the test was performed.

(e) A serum creatinine concentration of not more than the upper limit of normal at the laboratory where the test was performed.

(xii) At least one of the following conditions has to be met for cardiac function:

(a) No cardiac disease: absence of fatigue, palpitations, shortness of breath and anginal pain during daily activities as confirmed by interview.

(b) Cardiac disease is present, but exercise restriction is not required, and the absence of fatigue, palpitations, shortness of breath and anginal pain during daily activities can be confirmed, and is expected to be maintained during treatment.

(xiii) Written informed consent has been obtained directly from the subject.

The requirement of informed consent as in the above inclusion criteria is not applied to participation-refusers.

EXCLUSION CRITERIA

(i) Women who are pregnant, nursing infants or intend to become pregnant.

(ii) Overexpression of HER2 (Her2/neu, Erb B2), or the results of fluorescence in situ hybridization are positive.

(iii) A past history of hypersensitivity to the protocol treatment drugs or their solvents.

(iv) The presence of other active cancers (synchronous double cancers or metachronous double cancers with a disease-free interval of 5 years or less).

(v) The presence of brain metastasis requiring treatment because of increased intracranial pressure or emergency brain irradiation.

(vi) The presence of extensive liver metastasis or lymphatic pulmonary metastasis associated with dyspnea.

(vii) The presence of only one assessable lesion located at a previously irradiated site.

(viii) The presence of pleural effusion, ascites or pericardial effusion requiring emergency treatment.

(ix) Concurrent active infections.

(x) The presence of interstitial pneumonia or pulmonary fibrosis.

(xi) Positive test results for HBs antigen.

(xii) Patients with diabetes mellitus that is poorly controlled or being treated with insulin.

(xiii) Participation in the study is precluded by mental disease or psychological symptoms.

(xiv) Other reasons that preclude participation in the study as judged by the investigator.

TREATMENT

TAXANE ARM

For the taxane arm, one of the three regimens described below will be selected. Before the start of treatment, the treatment regimen will be selected at the discretion of the investigator. The same regimen will be used for the duration of first-line treatment. The reason for selecting the regimen will be reported in the ‘Follow-up Report’.

(i) Docetaxel 60–75 mg/m² administered at 3- or 4-week intervals. Treatment will be repeated until tumor progression or for at least six courses (18 or 24 weeks).

(ii) Paclitaxel 175 mg/m² administered at 3- or 4-week intervals. Treatment will be repeated until tumor progression or for at least six courses (18 or 24 weeks).

(iii) Paclitaxel 80–100 mg/m² administered every week. Weekly treatment for three consecutive weeks, followed by a 1-week rest period will comprise one course. Treatment will be repeated until tumor progression or for at least six courses (24 weeks).

ANTHRACYCLINE ARM

One of the following regimens will be selected at the discretion of the attending physician, and treatment will be repeated until disease progression or for at least six courses.

(i) Doxorubicin 40–60 mg/m² + Cyclophosphamide 400–600 mg/m² given at 3- or 4-week intervals.

(ii) Epirubicin 60–90 mg/m² + Cyclophosphamide 400–600 mg/m² given at 3- or 4-week intervals.
(iii) Fluorouracil 500 mg/m² + Doxorubicin 40–50 mg/m² + Cyclophosphamide 500 mg/m² given at 3- or 4-week intervals.

(iv) Fluorouracil 500 mg/m² + Doxorubicin 60–100 mg/m². Cyclophosphamide 500 mg/m² given at 3- or 4-week intervals.

**TS-1 ARM**

TS-1 will be administered orally in doses of 40–60 mg twice daily for 28 consecutive days. The dose will be assigned according to body weight. Treatment will be followed by a 14-day rest period to complete one course. Treatment will be repeated until tumor progression or for at least four courses (24 weeks).

Participating doctors must send each patient’s information to the CSPOR Data Center for registering patients to this study. Detailed information, for example, why patients refused to participate in the original clinical trial ‘SELECT-BC, SELECT-BC CONFIRM’, will be gathered afterward with a submitted Case Report Form. This study has been ongoing completely in parallel with the original prospective study.

Treatment methods for participation-refusers are not defined.

**PERIOD OF THIS STUDY**

This study ends when both SELECT BC and SELECT BC-CONFIRM trials end.

**STATISTICAL ANALYSIS**

Ratios of participants to participation-refusers in this study are assumed to fall between 1 to 2 and 2 to 1. Two groups of participants and refusers are examined by the Kaplan–Meier method for cumulative survival rates. In addition, the log–log plot is applied to Kaplan–Meier curves of both groups to confirm inter-group proportionality of hazards.

In both SELECT BC and SELECT BC-CONFIRM trials, the following items are used as allocation adjustment factors: (1) institution, (2) the presence or absence of liver metastasis, (3) the presence or absence of hormone sensitivity, (4) administration or non-administration of taxanes, (5) oral administration or non-administration of 5-FU agents and (6) period from surgery to recurrence. If there is a significant difference in these allocation adjustment factors in comparison of the two groups, adjustment is made before the analysis.

**Funding**

This study was funded by Comprehensive Support Project for Oncology Research (CSPOR) of Public Health Research Foundation.

**Conflict of interest statement**

None declared.

**References**


