Open-label Phase II Study of Everolimus Plus Endocrine Therapy in Post-Menopausal Women with ER+, HER2- Metastatic Breast Cancer : Chloe trial

312 Tip

Tadahiko Shien[1], Akihiko Shimomura[2], Yukari Uemura[3], Hiroaki Kato[4], Masahiro Kitada[5], Yuichiro Kikawa[6], Eiichi Shiba[7], Tatsuya Yoshida[8], Takashi Morimoto[9], Tetsuya Toyama[10], Tomohiko Aihara[11], Hirofumi Mukai[12].

1.Department of Breast and Endocrine Surgery, Okayama University Hospital. 2.Department of Breast and Medical Oncology, National Cancer Center Hospital. 3.Division of Biostatistics,Clinical Research Support Center,Tokyo University Hospital 4.Department of Thoracic Surgery, Teine Keijinkai Hospital 5.Department of Surgery, Asahikawa Medical University, Asahikawa. 6.Department of Breast Surgery, Kobe City Medical Center General Hospital 7.Osaka Breast clinic. 8.Department of Breast Surgery, Kanagawa Cancer Center. 9.Department of Breast Surgery, Yao Municipal Hospital 10.Department of Oncology, Immunology and Surgery, Nagoya City University, Graduate School of Medical Science. 11.Keimeikai-Aihara Hospital 12.Division of Breast and Medical Oncology, National Cancer Center Hospital East.

tshien@md.okayama-u.ac.jp

Background

For patients with metastatic or recurrent hormone receptor-positive breast cancer who are not in a life-threatening condition, it is common to treat with endocrine therapy prior to chemotherapy so as to preserve their quality of life (QOL) (N Engl J Med, 1998; 339:974-84). Since drug resistance develops during endocrine therapy in patients with hormone receptor-positive breast cancer, several methods for overcoming such resistance have been investigated. Current counter-measures to these drug-resistance phenomena include switching to chemotherapy while also continuing hormone therapy. In terms of the latter, endocrine therapies which utilize different mechanisms of action, along with agents that suppress altered signaling pathways causing drug-tolerance, are considered at present. It has been previously reported that application of an mTOR inhibitor (everolimus) to endocrine therapy-resistant breast cancer cells restored their sensitivity to endocrine therapy (Clin Cancer Res, 2005; 11 (14): 5319-28). The BOLERO-2 trial showed a statistically significant difference in PFS between the group treated with the combination of everolimus and exemestane (7.8 months) and the group treated with exemestane alone (3.2 months) ($p<0.0001$); the hazard ratio was 0.45 with 95% confidence intervals of 0.38-0.54. Accordingly, both preclinical and clinical studies have demonstrated that everolimus was effective in overcoming resistance to endocrine therapy. Furthermore, a recent preclinical study demonstrated the improvement of dependency of estrogen receptors to genomic pathway by the application of a PI3K inhibitor or an mTOR inhibitor (rapamycin) to hormone receptor-positive breast cancer cells, suggesting the possibility that mTOR inhibitors potentiate the effect of endocrine therapy（Sci Transl Med, 2015 Apr 15;7（283）:283ra51）. Since endocrine therapy generally causes few adverse events, the patient's QOL may be maintained for a long time if the introduction of chemotherapy can be postponed. Therefore, we planned this study to examine whether concomitant administration of everolimus with endocrine therapy further prolongs PFS in patients with breast cancer whose hormone sensitivity still remains. At present, a Phase II study (BOLERO-4 trial; NCT 01698918) is ongoing abroad to evaluate the efficacy and safety of combined use of everolimus with letrozole as initial therapy for metastatic ER-positive HER2-negative breast cancer. However, patients in this study are administered everolimus from the beginning of study regardless of their hormone sensitivity. Since our study will be conducted with patients whose hormone sensitivity remains, the subject background is different between the BORELO-4 trial and our study. If our Phase II study supports the hypothesis that additional administration of everolimus to patients whose hormone sensitivity remains can prolong the administration period of AI agents through postponing the acquisition of drug-resistance, we have planned a subsequent Phase III study to confirm the usefulness of everolimus in respect of cost-effectiveness and cost-utility due to prolongation of the entire period of hormone therapy by early administration of everolimus to ER-positive aromatase-sensitive breast cancer. Therefore, we plan to assess QOL in this Phase III study after confirmation of the core hypothesis.

Objectives

This study is conducted on patients with recurrent metastatic cancer with the following three objectives:

1, To examine whether additional administration of everolimus significantly prolongs progression-free survival period in post-menopausal patients with ER-positive HER2-negative metastatic breast cancer who showed a positive response to an aromatase inhibitor (AI agent) as a primary endocrine therapy.
2, To examine the effect on the incidence of adverse events from the additional administration of everolimus to an AI agent.
3, To explore the biomarkers related to the efficacy of everolimus.

Eligibility criteria

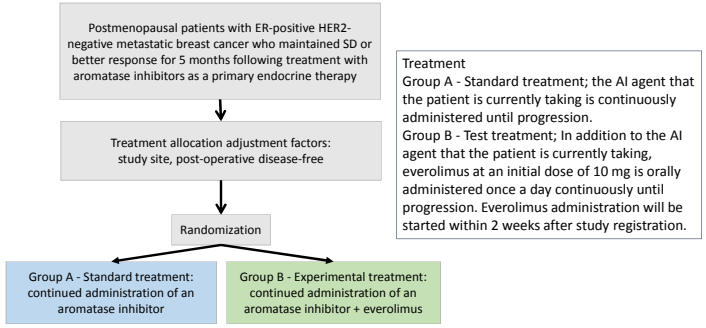
Inclusion criteria

1, Patients who are histologically diagnosed as having breast cancer.
2, The cancer is immunohistochemically ER-positive (>10%) and HER2- negative (0/1+) (or HER2-negative based on ISH testing).
3, Patients who have one or more measurable lesions according to RECIST (Ver 1.1).
As for bone lesions, patients who have measurable osteolytic or osteolytic osteoblastic lesions by CT or MRI (≥ 1cm in length) are eligible.
4, Patients with metastatic breast cancer that satisfy one of following two conditions:
1) Patients with remote metastasis judged not to be indicated for surgical resection at the first visit.
2) Patients with metastatic breast cancer except for local recurrence (the term local here refers to the chest wall surrounded by the following areas: upward to subclavian margin, downward to costal arch, inward to medial sternal margin and outward to the frontal margin of latissimus dorsi muscle). Patients with local recurrence which is not indicated for surgical resection due to diffuse lesions are eligible.
5, If patients received post-operative endocrine therapy, a 12 month or longer period must have passed since the end of the last administration. History of post-operative chemotherapy and elapsed time from chemotherapy, as well as the regimen of post-operative endocrine therapy, do not matter.
6, Among patients who start the treatment with an AI agent within 5-7 months previously. Patients who have not received chemotherapy or received just 1 regimen of chemotherapy.
7, Patients who have no history of treatment with everolimus. 8, Patients who are post-menopausal women.
9, Patients with ECOG performance status (PS) of 0 or 1. Patients with PS2 due to bone metastasis is allowed.
10, If patients have received radiation therapy, a 14 day or longer period must have passed since the end of the last radiation session.
11, Adequate organ functions. 12. Written informed consent.

Exclusion criteria

1, Patients who have active double cancer (simultaneous double cancer or metachronous double cancer within 5 years of disease-free period). Carcinoma in situ (intraepithelial carcinoma and mucosal carcinoma) that is judged to be already cured will not be classified as active double cancer
2, Patients who have a history of serious drug hypersensitivity.
3, Patients who have serious concomitant diseases (including pulmonary fibrosis or interstitial pneumonia, uncontrollable diabetes, serious cardiac dysfunction, renal failure, hepatic insufficiency, cerebrovascular disease and ulcer(s) requiring a blood transfusion).
4, Patients who have an active infectious disease requiring systemic treatment.
*Patients who are HBs antigen positive and HBc antibody positive, and/or HBs antibody positive.
*Patients who are infected with HCV or have a history of HCV infection.
5, Patients who have active hemorrhagic diathesis or who are being treated with an oral vitamin K antagonist.
6, Patients with cerebral metastasis that is symptomatic or requires treatment.
7, Patients who have been administered medicines known as potent CYP3A inhibitors or CYP3A inducers (rifabutin, rifampicin, clarithromycin, ketoconazole, itraconazole, voriconazole, ritonavir, or telithromycin).
8, Patients who have been treated with hormone replacement therapy.
9, Patients who have a mental disorder that affects the informed consent process.
10, Patients who are judged to be inappropriate to participate in this study on the basis of physician's assessment.

Study design



Endpoints & Statistical Methods

Primary endpoint
Progression-free survival (PFS)

Secondary endpoints
Overall survival (OS); response rate (RR); disease control rate (DCR); adverse events; time to treatment failure (TTF); and the proportion of patients who continued administration of AI agents for 1 year after the randomized allocation.

Study Hypothesis
The clinical hypothesis of this study is that the test treatment group (continuous administration of an AI agent + everolimus) is superior to the standard treatment group (continuous treatment of an AI agent alone) in regard to PFS.
- Median progression free survival (PFS) of ER+ HER2- MBC in general, 12 months
- Assumed median PFS in standard arm after randomization, 10 months
- 5.4 months prolongation expected by additional everolimus (hazard ratio, 0.65)

Sample size and follow-up period
- Planned number of patient registrations: 130 patients (65 patients in each group)
- One-sided alpha, 0.1; power, 0.8
- Registration period: From July 2016 to June 2018
- Study period: From July 2016 to June 2020 (2 years after the final patient registration) Total study period: 4 years
- The protocol will not be revised in case of prolongation of study period within 6 months.

This study will be conducted under the framework of a CSPOR-BC (Comprehensive Support Project for Oncological Research of Breast Cancer) project.