

Embargoed for Release: 7 a.m. CT, Dec. 11, 2019

To interview Masakazu Toi, contact contact Julia Gunther at julia.gunther@aacr.org or 215-446-6896. For a photo of Toi, click [here](#).

Addition of S-1 to Post-operative Endocrine Therapy Improves Outcomes for Patients with Hormone Receptor-positive, HER2-negative Breast Cancer

SAN ANTONIO — A post-operative combination of S-1, an oral [fluoropyrimidine](#)-based drug, with endocrine therapy significantly increased invasive disease-free survival (iDFS) and improved five-year iDFS estimates in patients with [hormone receptor \(HR\)-positive, HER2-negative](#) breast cancer, according to results from a [phase III study](#) presented at the [San Antonio Breast Cancer Symposium](#), held Dec. 10-14.

“Although we have made remarkable progress with systemic therapy for breast cancer, many patients still experience disease recurrence,” said [Masakazu Toi, MD, PhD](#), professor of breast surgery at Kyoto University Hospital.

HR-positive, HER2-negative breast cancer, also referred to as luminal breast cancer, is the most common breast cancer subtype, accounting for approximately [67 percent](#) of cases. Patients with this subtype are often treated with endocrine therapies, which work in various ways to prevent hormones from activating cancer growth. Although this subtype is associated with a favorable [five-year relative survival rate](#), there is a risk of disease recurrence several years after treatment, explained Toi. “Because of the risk of recurrence, there is interest in identifying novel post-operative adjuvant therapies to be used in conjunction with endocrine therapy,” said Toi.

S-1 is a combination drug composed of tegafur, which is a 5-fluorouracil prodrug that inhibits DNA synthesis and cell division, and gimeracil and oteracil, which promote tegafur activity and prevent gastrointestinal toxicity, respectively. Previous studies suggested that combining tegafur with endocrine therapy could improve anti-tumor efficacy.

In this study, Toi and colleagues examined the efficacy of S-1 in combination with adjuvant endocrine therapy in patients. The study enrolled 1,939 patients with stage I-III HR-positive, HER2-negative breast cancer with intermediate or higher risk of recurrence in the full analysis set. The study included patients from 139 centers in Japan. Patients were randomized to receive either S-1 and endocrine therapy or endocrine therapy alone as adjuvant treatment.

The median follow-up after treatment was 51.4 months. Among the 957 patients in the S-1 arm, 101 experienced disease recurrence (iDFS events), compared to 155 of the 973 patients in the control arm (10.6 percent versus 15.9 percent). The estimated five-year iDFS was 86.9 percent for patients in the S-1 arm compared to 81.6 percent in the control arm.

“We found that the postoperative adjuvant use of S-1 in combination with standard endocrine therapy significantly reduced iDFS events and improved five-year iDFS estimates in patients with HR-positive and HER2-negative breast cancer,” said Toi. Furthermore, the S-1 treatment was well tolerated and manageable, according to Toi. Major toxicities associated with S-1

treatment included signs of bone marrow suppression, such as decreased neutrophil counts; gastrointestinal toxicities, such as nausea and diarrhea; hyperpigmentation; and fatigue.

“Our findings support the addition of S-1 to standard endocrine therapy in the post-operative adjuvant setting for patients with HR-positive, HER2-negative disease and an intermediate or higher risk of recurrence,” said Toi.

A limitation of the study is that it only included patients from Japan, and the toxicity profile may be slightly different between Asian and non-Asian patients, explained Toi.

The study was sponsored by the Comprehensive Support Project of the Public Health Research Foundation and Taiho Pharmaceutical. Toi has served advisory roles for Kyowa Kirin, Bristol-Myers Squibb, Daiichi Sankyo, Genomic Health, and Konica Minolta. Toi has received honoraria from Taiho, Chugai, Takeda, Pfizer, Kyowa-Kirin, Eisai, Daiichi-Sankyo, AstraZeneca, Eli Lilly, Genomic Health, Novartis, Konica Minolta, and Shimadzu. Toi has received research grants from Taiho, Kyowa Kirin, AstraZeneca, Shimadzu, AFI Technology, and Astellas. Toi has received additional funds from Chugai, Pfizer, Nippon Kayaku, Terumo, JBCRG Association, and the Kyoto Breast Cancer Research Network.

ABSTRACT

Publication Number: GS1-09

Addition of S-1 to endocrine therapy in the post-operative adjuvant treatment of hormone receptor-positive and human epidermal growth factor receptor 2-negative primary breast cancer: A multicenter, open-label, phase 3 randomized trial (POTENT trial)

Masakazu Toi¹, Shigeru Imoto², Takanori Ishida³, Yoshinori Ito⁴, Hiroji Iwata⁵, Norikazu Masuda⁶, Hirofumi Mukai⁷, Shigehira Saji⁸, Akira Shimizu¹, Takafumi Ikeda¹, Hironori Haga¹, Toshiaki Saeki⁹, Kenjiro Aogi¹⁰, Tomoharu Sugie¹¹, Takayuki Ueno⁴, Takayuki Kinoshita¹², Yuichiro Kai¹³, Masahiro Kitada¹⁴, Yasuyuki Sato¹⁵, Kenjiro Jimbo¹⁶, Nobuaki Sato¹⁷, Hiroshi Ishiguro¹⁸, Masahiro Takada¹, Yasuo Ohashi¹⁹ and Shinji Ohno⁴. ¹Kyoto University Hospital, Kyoto, Japan²Kyorin University Hospital, Mitaka, Japan³Tohoku University, Sendai, Japan⁴Cancer Institute Hospital, Tokyo, Japan⁵Aichi Cancer Center Hospital, Nagoya, Japan⁶NHO Osaka National Hospital, Osaka, Japan⁷National Cancer Center Hospital East, Kashiwa, Japan⁸Fukushima Medical University, Fukushima, Japan⁹Saitama Medical University International Medical Center, Hidaka, Japan¹⁰NHO Shikoku Cancer Center, Matsuyama, Japan¹¹Kansai Medical University Hospital, Hirakata, Japan¹²NHO Tokyo Medical Center, Tokyo, Japan¹³Ueo Breast Surgery Clinic, Oita, Japan¹⁴Asahikawa Medical University Hospital, Asahikawa, Japan¹⁵NHO Nagoya Medical Center, Nagoya, Japan¹⁶National Cancer Center Hospital, Tokyo, Japan¹⁷Niigata Cancer Center Hospital, Niigata, Japan¹⁸International University of Health and Welfare Hospital, Nasushiobara, Japan¹⁹Chuo University, Tokyo, Japan

BACKGROUND) Although long-term prognostic outcomes of primary breast cancer (PBC) patients have been improved remarkably in recent years, the disease recurrence remains a serious problem. We have previously investigated a role for oral fluoropyrimidines in postoperative adjuvant treatments. In this study, we aimed to verify the usefulness of S-1 in combination with adjuvant endocrine therapy for PBC patients having luminal disease.

PATIENTS AND METHODS) This open-label, randomized, phase 3 trial was carried out in 139 centers in Japan. Stage III PBC patients, who had hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative status and intermediate or higher risk of recurrence were randomly assigned (1:1) to receive standard endocrine therapy alone (control arm) or endocrine therapy plus S-1 (S-1 arm). Recurrence risk assessment was performed using anatomical stage, pathological findings such as histologic grade, and centrally confirmed proliferative marker status. S-1 was administered postoperatively in combination with standard endocrine therapy. For patients who underwent multi-drug postoperative adjuvant or preoperative neoadjuvant chemotherapy, S-1 was administered following the multi-drug

Addition of S-1 to Post-operative Endocrine Therapy Improves Outcomes for Patients with Hormone Receptor-positive, HER2-negative Breast Cancer

Page 3 of 3

chemotherapy. Cases having no residual cancer in the breast and axillary node after the preoperative chemotherapy were excluded from this study. The S-1 dosage was chosen among 80 mg/day, 100 mg/day, and 120 mg/day according to the body surface area of each patient, and S-1 was administered for one year with a 2 weeks on/1 week off administration schedule. The primary endpoint was invasive disease-free survival (iDFS), defined as time from randomization to invasive disease recurrence, occurrence of second invasive cancer event, or death, and was analyzed on an intent-to-treat basis. Secondary endpoints included DFS, distant DFS, overall survival, and safety profile. RESULTS) From Feb 2012 to Feb 2016, 1959 patients were enrolled and 1932 patients were included in the full analysis set (control arm, 973; S-1 arm, 959). The results of the prespecified interim analysis met the primary end point, and this trial was terminated early. Median follow-up was 51.4 months. S-1 significantly reduced invasive events; 153 iDFS events were reported in the control arm and 99 iDFS events were reported in the S-1 arm [hazard ratio, 0.63 (95%CI, 0.49-0.81); p-value, 0.0003]. The 5-year iDFS estimate was 81.5% in the control arm and 86.9% in the S-1 arm. Distant recurrence as the first disease event was observed in 6.8% of patients in the S-1 arm and in 9.5% of those in the control arm. The safety data in patients treated with S-1 was consistent with the known profile of S-1. The S-1 treatment was well tolerated and manageable.

CONCLUSIONS) It was concluded that the postoperative adjuvant use of an oral fluoropyrimidine S-1 significantly reduced iDFS events and improved 5-year iDFS estimate in PBC patients having HR-positive and HER2-negative disease, in the combination with standard endocrine therapy, with a feasible safety profile.

Funding: This study was funded by the Comprehensive Support Project (CSP) of the Public Health Research Foundation. The research fund was provided to CSP by Taiho Pharmaceutical Co., Ltd. This trial was conducted as a study of 'Advanced Medical Care,' the Ministry of Health, Labour and Welfare, Japan. JRCT ID: jRCTs051180057, UMIN000003969

###

Follow the meeting on Twitter: [@SABCSSanAntonio](https://twitter.com/SABCSSanAntonio) and [#SABCS19](https://twitter.com/SABCS19)

About SABCS®

Since 1977 the San Antonio Breast Cancer Symposium® (SABCS®) has been the leading scientific conference for basic scientists, physician-scientists, clinical investigators and breast care providers, and advocates seeking an exchange of new information in experimental biology, etiology, prevention, diagnosis, and therapy of premalignant breast disease and breast cancer. Founded, owned, and operated by UT Health San Antonio, the symposium has grown to a five-day event attended by an international audience of academic investigators and private physicians from over 80 countries to attain information through abstract presentations, panel discussions, research findings, and state-of-the-art educational sessions. [UT Health San Antonio](http://www.utmsd.edu), the [American Association for Cancer Research](http://www.aacr.org) (AACR), and [Dan L Duncan Comprehensive Cancer Center at Baylor College of Medicine](http://www.danl.com) support SABCS, which provides education and accessibility to the latest information regarding the prevention, diagnosis, and treatment of premalignant breast cancer and breast disease. For more information about the symposium, please visit www.sabcs.org.