Adjuvant S-1 plus endocrine therapy for oestrogen receptor-positive, HER2-negative, primary breast cancer: a multicentre, open-label, randomised, controlled, phase 3 trial

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For the Chinese translation see Online for appendix 1

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Summary

Background Oral fluoropyrimidines, such as S-1, have been shown to have a role in controlling disease progression in metastatic breast cancer. We examined adjuvant treatment with S-1 in patients with oestrogen receptor (ER)-positive and HER2-negative primary breast cancer.

Methods We did a multicentre, open-label, randomised, controlled, phase 3 trial in 139 sites (137 hospitals and two clinics). Eligible patients were women aged 20–75 years with histologically diagnosed stage I to IIIB invasive breast cancer (intermediate to high risk of recurrence). Patients were temporarily registered at participating institutions and biopsy or surgical samples were collected and sent for central pathological assessment. Patients received 5 years of standard adjuvant endocrine therapy (selective oestrogen receptor modulators with or without ovarian suppression and aromatase inhibitors) with or without 1 year of S-1. Oral S-1 80–120 mg/day was administered twice a day for 14 days with 7 days off. Randomisation (1:1) using the minimisation method was done with six stratification factors (age, axillary lymph node metastasis at surgery or sentinel lymph node biopsy, preoperative or postoperative (neoadjuvant or adjuvant) chemotherapy, preoperative endocrine therapy, proportion of ER-positive cells, and study site). The primary endpoint was invasive disease-free survival, in the full analysis set (all randomly assigned patients, excluding those with significant protocol deviations). The safety analysis set consisted of all patients who received at least one dose of study treatment. Here, we report the results from the interim analysis at the data cutoff date Jan 31, 2019. This trial is registered with Japan Registry of Clinical Trials, jRCTs051180057, and the University hospital Medical Information Network, UMIN000003969.

Findings Between Feb 1, 2012, and Feb 1, 2016, 1930 patients were enrolled in the full analysis set, 957 (50%) received endocrine therapy plus S-1 and 973 (50%) received endocrine therapy alone. Median follow-up was 52·2 months (IQR 42·1–58·9). 155 (16%) patients in the endocrine therapy alone group and in 101 (11%) patients in the endocrine therapy plus S-1 group had invasive disease-free survival events (hazard ratio 0·63, 95% CI 0·49–0·81, p=0·0003). As the primary endpoint was met at interim analysis, the trial was terminated early. The most common grade 3 or worse adverse events were decreased neutrophil count (72 [8%] of 954 patients in the endocrine therapy plus S-1 group *vs* seven [1%] of 970 patients in the endocrine therapy alone group), diarrhoea (18 [2%] *vs* none), decreased white blood cells (15 [2%] *vs* two [<1%]), and fatigue (six [<1%] *vs* none). Serious adverse events were reported in nine (1%) of 970 patients in the endocrine therapy alone group and 25 (3%) of 954 patients in the endocrine therapy plus S-1 group. There was one (<1%) possible treatment-related death in the endocrine therapy plus S-1 group due to suspected pulmonary artery thrombosis.

Interpretation These data suggest that this combination of S-1 with endocrine therapy could be a potential treatment option for this intermediate and high-risk group of patients with ER-positive, HER2-negative primary breast cancer.

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Introduction

In 2012, there were approximately 1700 000 cases of newly developed primary breast cancer worldwide,[1] which increased to 2 088 849 in 2018, representing 11·6% of all cancers and 24·2% of all cancers in women.[2] This increasing trend is apparent in many countries, particularly in Asian countries such as Japan.[3,4] Patients with oestrogen receptor (ER)-positive and HER2-negative primary breast cancer account for approximately 70% of all cases of breast cancer.[5]

In the past three decades, survival outcomes of patients with primary breast cancer have notably improved, mainly due to early detection of the disease and advances in adjuvant treatments such as endocrine therapy, chemotherapy, and anti-HER2 therapy. For example, postoperative adjuvant endocrine therapy with 5 years of

Research in context

Evidence before this study

We searched PubMed for any reports published before Dec 31, 2019 (the cutoff date) in any language using the search terms "S-1", "endocrine", "breast cancer", and "HER2-negative". Although S-1 has been evaluated in breast cancer as first-line monotherapy or in combination with chemotherapy, no trials examining a combination of adjunctive S-1 with endocrine therapy were identified.

Added value of this study

To our knowledge, this is the first trial to show an improved clinical benefit for patients with ER-positive, HER2-negative breast cancer receiving concurrent S-1 treatment. Fewer invasive disease-free survival events were reported in the endocrine therapy plus S-1 group than in the endocrine therapy alone group, and the overall safety profile of S-1 was manageable.

Implications of all the available evidence

Our results suggest a treatment advantage of S-1 with endocrine treatment in patients with ER-positive and HER2-negative breast cancer and suggest the potential importance of this combination within the current treatment algorithms. As the therapeutic effect appeared to be unaffected by common clinicopathological factors, S-1 plus endocrine therapy might provide benefit for many patients with ER-positive and HER2-negative breast cancer. Further long-term studies to evaluate the impact of this treatment regimen on overall survival outcomes are warranted.

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tamoxifen, an aromatase inhibitor, or both sequentially have shown significant decreases in recurrence and cancer-related mortality.[6]

ER-positive and HER2-negative luminal disease is extremely heterogeneous with respect to genetic abnormality, growth speed, disease progression (including metastasis), and therapeutic sensitivity to endocrine treatment.[7] To further improve survival outcomes of this disease, a variety of approaches have been investigated, such as extension of adjuvant endocrine therapy, combinations of multi-agent chemotherapy and endocrine therapy, and combination treatment including other drug classes.[8]

Oral fluoropyrimidines such as S-1, tegafur-uracil, and capecitabine have been evaluated for both adjuvant therapy and treatment of metastatic breast cancers.[9–11] S-1, a combination of tegafur, gimeracil (a fluorouracil inactivated enzyme inhibitor that is more potent than uracil), and oteracil potassium (to reduce the gastrointestinal toxicity), has shown efficacy similar to that of docetaxel in the treatment of metastatic breast cancer.[12] S-1 is associated with a relatively low frequency of adverse reactions and is administered orally, potentially allowing dosing without compromising patient quality of life.[13] Additionally, there are considerable data supporting the usefulness of fluorouracil-containing compounds with or without endocrine therapy in ER-positive and HER2-negative breast cancer.[9–11] According to a study[14] examining the efficacy of adjuvant capecitabine, a significant reduction in disease recurrences and deaths was associated with capecitabine use.[14] The results were more marked in the hormone receptor-negative and HER2-negative subpopulation, but a trend towards improved outcomes was also seen in the ER-positive and HER2-negative subpopulation. However, it must be noted that, historically, the combination of adjuvant chemotherapy and endocrine therapy has been discouraged; furthermore, this combination strategy has not been recommended in treatment guidelines for advanced disease.[15]

The objective of this study was to investigate whether the concurrent administration of standard postoperative endocrine therapy with S-1 increases the recurrence-inhibitory effect compared with standard postoperative endocrine therapy alone in women with ER-positive and HER2-negative primary breast cancer.

Methods

Study design and participants

We did a multicentre,open-label, randomised, controlled, phase 3, trial in 139 sites (137 hospitals, including 48 university hospitals and 15 cancer centers, and two clinics) in Japan.

Eligible patients were women aged 20–75 years with histologically diagnosed stage I to IIIA and stage IIIB invasive breast cancer (positive or negative for axillary lymph node involvement), had undergone radical surgery, had an intermediate to high risk of recurrence (defined in the appendix 2 p 6), and had an Eastern Cooperative Oncology Group performance status of 0 or 1. Tumours were required to be ER-positive (≥1% by immunohistochemistry) and HER2-negative (0 or 1+ by immunohistochemistry, or *HER2/CEP* ratio <1·8 by fluorescence in-situ hybridisation). At temporary registration, patients were required to undergo laboratory tests to ascertain major organ functions and obtain laboratory test values, and provide biopsy or surgical samples for confirmation of the percentage of ER-positive cells, Ki67 and histologic grade by central pathologic assessment. The main exclusion criteria were active secondary cancer; bilateral breast cancer or inflammatory breast cancer; 2 weeks or more of previous treatment with oral fluorouracil; or any clinically serious complication or medical history. The full inclusion and exclusion criteria are listed in the appendix 2 (p 5).

See **Online** for appendix 2

The trial was designed by the Kyoto University Project Secretariat and the Protocol Development Committee and overseen by the institutional review board at each study site (appendix 2 p 2). The trial protocol (appendix 2

pp 21–140) was approved by the institutional review board of each study site. The study was done in accordance with the principles of the Declaration of Helsinki. All patients provided written, informed consent.

During recruitment, the planned sample size was increased from 1400 to 1860 patients, to allow an increase in power from 80% to 90% for hypothesis testing. Subsequently, the protocol and informed consent form were amended Dec 2, 2014 (version 2.1), to indicate that the study registration period was prolonged by 6 months from the original specification to reach the larger planned sample size.

Randomisation and masking

The trial was open-label, with patients randomly assigned (1:1) to a treatment group using the Viedoc system (Swedish Pharma Consulting Group AB, Uppsala, Sweden) using minimisation method. Randomisation was done to balance cases within each treatment group (endocrine therapy plus S-1 or endocrine therapy alone) according to six specified stratification factors: age (≤54 *vs* ≥55 years), axillary lymph node metastasis at surgery or sentinel lymph node biopsy (yes or no), preoperative or postoperative (neoadjuvant or adjuvant) chemotherapy (yes or no), preoperative endocrine therapy (yes or no), proportion of ER-positive cells (1–9% or ≥10%), and study site. If the allocation in each stratification layer was balanced, the next patient was allocated with an equal probability (50%), and if not balanced, the patient was allocated to the group that needed to be balanced with a probability of 75%. A random number was generated for each patient to determine the treatment allocation group; the probability of the generated number allocating a patient to a specific treatment group was based on the balance within each stratum.

Procedures

Patients in the endocrine therapy plus S-1 group and the endocrine therapy alone group received standard endocrine therapy, with 5 years of follow-up planned. In premenopausal women, endocrine therapy consisted of 5 years of treatment with tamoxifen 20 mg/day or toremifene 40–120 mg/day. In postmenopausal women, endocrine therapy consisted of 5 years of treatment with an oral aromatase inhibitor: anastrazole 1 mg/day, letrozole 2·5 mg/day, or exemestane 25 mg/day. Tamoxifen 20 mg/day or toremifene 40–120 mg/day were specified if aromatase inhibitors were unsuitable (appendix 2 p 6). Patients in the endocrine therapy plus S-1 group also received concurrent S-1 administered twice a day orally after breakfast and dinner for 14 consecutive days with 7 days off; this 21-day cycle was repeated for 1 year. The dosing schedule was selected based on a previous study of S-1 in head and neck cancer, in which the 14 days on 7 days off schedule was found to reduce gastrointestinal toxicity and improve compliance compared with a 28 days on 14 days off schedule.[16] The 1-year duration was selected based on the ability to deliver at least 80% of the scheduled dose to ensure efficacy. A previous study[17] indicated that the prognosis for patients with gastric cancer treated with S-1 was good as long as 70% or more of the scheduled dose could be administered; we considered that even if the dose of S-1 was decreased by one level, patients would receive 80% of the scheduled dose as long as treatment continued for 1 year.

The S-1 dose was calculated according to body surface area, and was 80–120 mg/day in patients with normal renal function (creatinine clearance ≥80 mL/min), and 60–100 mg/day in patients with impaired renal function (creatinine clearance ≥50 to <80 mL/min). As S-1-derived fluorouracil concentrations and the development of adverse reactions are affected by renal function, treatment was started at the normal dose specified in the package insert in patients with a creatinine clearance of ≥80 mL/min or more and decreased by one level in patients with impaired renal function. Creatinine clearance was measured using 24-h pooled urine; if there was no measured value, an estimate was calculated using the Cockcroft-Gault formula. The dose of S-1 could be reduced in any of the following circumstances: white blood cell count lower than 1000/μL; neutrophil count lower than 500/μL; platelet count lower than 25000/μL; haemoglobin lower than 7·0 g/dL; total bilirubin lower than 3·0 mg/dL; aspartate aminotransferase or alanine aminotransferase higher than 150 international units per L; and anorexia, nausea, vomiting, or diarrhoea grade 2 or higher. The endocrine therapy can be adjusted or discontinued according to the investigator's decision.

Patients were discontinued from the study if consent was withdrawn, or due to protocol deviation, death, or loss to follow-up (ie, transfer to another hospital). Radiographic assessments consisted of compulsory mammography once a year; and chest-abdominal CT, bone scintigraphy, and other assessments at the doctor's discretion. Patients were assessed for recurrence by radiological or pathological examination at participating institutions according to the General Rules for Clinical and Pathological Recording of Breast Cancer (16th edition). Adverse events (classified using the Common Terminology Criteria for Adverse Events; version 4.0 Japanese translation, including laboratory test abnormalities) that developed during the period from the initiation of the study to the completion of the post-treatment observation period (30 days after the last administration of the study drug) or the start of the next treatment after protocol treatment, whichever was earlier, were collected in all patients who consented.

To assess the risk of recurrence, evaluation of clinicopathological factors such as histological tumour size, nodal status and lymphovascular invasion, histologic grade, and Ki-67 labelling index (Ki-67 LI) were incorporated into the study design.[18,19] Oncotype DX (Genomic Health Inc, Redwood, CA, USA) was used in a subpopulation of the patients to quantify recurrence risk.[9,18,20]

Outcomes

The primary endpoint was investigator assessed invasive disease-free survival, defined as the period from the treatment allocation date to the confirmed recurrence date (excluding non-invasive ductal carcinoma, non-invasive lobular carcinoma, and all other intraepithelial carcinoma), confirmed development of cancerous lesions other than recurrence, or the date of death from any cause, whichever was the earliest. The period from the date of surgery was also examined as a reference analysis. The secondary endpoints were overall survival (defined as the period from the date of allocation to the date of death from any cause), distant disease-free survival (defined as the period from the date of allocation to the date on which the patient was diagnosed with distant recurrence, but not including death from any cause), disease-free survival (defined as the period from the date of treatment allocation to the date on which recurrence was confirmed, the date on which the development of cancerous lesions other than recurrence was confirmed, or the date of death from any cause, whichever was the earliest), relationship of tumour growth factors and biomarkers with the recurrence-inhibitory effect of S-1, and safety.

Statistical analysis

The target sample size was 1860 patients (930 patients in the endocrine therapy alone group and 930 patients in the endocrine therapy plus S-1 group), allowing for a power of 90% for hypothesis testing, which was calculated based on 5-year recurrence-free survival reported in previous trials.[9–11] 5-year invasive disease-free survival was assumed to be 83% in the control group and the hazard ratio (HR) 0·70 (5-year invasive disease-free survival of 87·8% in the S-1 endocrine therapy plus S-1 group); with a follow-up period of 5 years, a two-sided α value of 0·05 and β value of 0·1, the necessary sample size was 915 patients per group. The target sample size was set at 930 patients per group to allow for dropouts.

The analysis groups comprised the full analysis set (all randomly assigned patients, excluding those with significant protocol deviations) and the safety analysis set (all patients who received at least one dose of study treatment). Protocol deviations were defined as non-conformance to the inclusion or exclusion criteria, taking prohibited concomitant drugs or therapies (appendix 2 p 7), or withdrawal of consent.

An interim analysis was planned to determine whether the trial should be terminated early for efficacy or futility, when approximately two-thirds of the number of events required for the validation of the primary endpoint (332 events) were observed. As such, the interim analysis was done when 235 events were collected. The primary endpoint of invasive disease-free survival was estimated by the Kaplan-Meier method, and the CI for survival rate estimated using Greenwood's formula. The log-rank test was used in the evaluation of hypotheses, (two-sided test with an α value of 0·05). The superiority of the trial was calculated with the Haybittle-Peto method, and early termination for efficacy was considered when the overall type I error rate was less than 0·05. The Bayesian probability of trial failure was calculated, and if the prediction probability was lower than 10%, treatment futility discontinuation of the trial was considered. As a result of the interim analysis, the primary endpoint was met, and study discontinuation was recommended by the Independent Data Monitoring Committee. As a result of the proportional hazards test based on Schoenfeld residuals, the hypothesis that the proportional hazards are valid was not rejected (p=0·2606).

The primary endpoint of invasive disease-free survival was also assessed in a prespecified subgroup analysis using important prognostic factors considered at allocation and newly revealed important prognostic factors: age (≤54 years *vs* ≥55 years), axillary lymph node involvement at surgery or sentinel-node biopsy (yes *vs* no), preoperative or adjuvant chemotherapy (yes *vs* no), preoperative endocrine therapy (≥4 months; yes *vs* no), percentage of ER-positive cells (1–9% *vs* ≥10%), and Ki67 (<14% *vs* ≥14%).

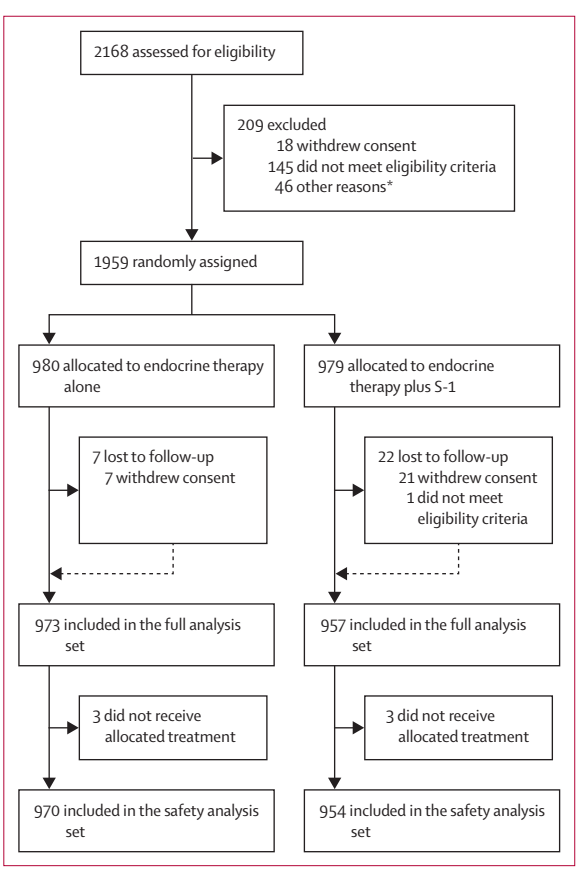

Figure 1: **Trial profile**

*Reason for exclusion unknown or not documented (n=36), physician request (n=3), patient met the exclusion criteria (n=3), duplication of patient identification code (n=2), and lack of pathological specimens or laboratory test values for analysis (n=2).

	Endocrine therapy only group (n=973)	Endocrine therapy plus S-1 group (n=957)
Age, years		
Median (IQR)	51·0 (45·0–61·0)	52·0 (45·0–61·0)
≤54 years	557 (57%)	544 (57%)
≥55 years	416 (43%)	413 (43%)
Bodyweight, kg		
Median (IQR)	55·4 (50·0–63·0)	55·1 (50·0-61·7)
Menopausal status		
Premenopausal	480 (49%)	457 (48%)
Postmenopausal	493 (51%)	500 (52%)
Histological grade		
Grade 1	106 (11%)	109 (11%)
Grade 2	585 (60%)	587 (61%)
Grade 3	264 (27%)	249 (26%)
Unknown or missing	18 (2%)	12 (1%)
Lymph node metastases		
Positive	616 (63%)	612 (64%)
Negative	357 (37%)	345 (36%)
Number of nodes involved		
1–3	313 (32%)	344 (36%)
≥4	109 (11%)	80 (8%)
Unknown or missing	194 (20%)	188 (20%)
Invasive diameter without preoperative therapy (includes chemotherapy* or endocrine therapy), cm		
<2	299 (31%)	298 (31%)
2 to <3	237 (24%)	256 (27%)
≥3	198 (20%)	173 (18%)
Unknown or missing	6 (1%)	1 (1%)
Lymphovascular invasion		
Positive	431 (44%)	453 (47%)
Negative	333 (34%)	299 (31%)
Unknown or missing	209 (22%)	205 (22%)
Ki67, %		
<14	523 (54%)	527 (55%)
≥14 to <30	305 (31%)	299 (31%)
≥30	128 (13%)	120 (13%)
Unknown (missing)	17 (2%)	11 (1%)
Proportion of oestrogen receptor-positive cells		
1% to <10%	12 (1%)	11 (<1%)
≥10%	961 (99%)	946 (99%)
Previous therapy for breast cancer		
Adjuvant chemotherapy	346 (36%)	338 (35%)
Neoadjuvant chemotherapy	197 (20%)	195 (20%)
Neoadjuvant endocrine therapy	36 (4%)	34 (4%)
Surgery		
Total mastectomy	523 (54%)	488 (51%)
Partial mastectomy	450 (46%)	469 (49%)

Data are presented as n (%) or median (IQR). *Permitted chemotherapy was prespecified in the protocol.

Table 1: **Baseline demographic characteristics (full analysis set)**

Overall survival, distant disease-free survival, and disease-free survival were analysed in the same way as the primary endpoint, including prespecified analysis of prognostic factors. Relationship of tumour growth factors and biomarkers with the recurrence-inhibitory effect of S-1 was analysed using the tumour cell Ki-67 labelling index. Ki67 analysis was performed as a prespecified subgroup analysis. Adverse events and adverse drug reactions are described for each treatment group, and the worst grade in each patient was also derived for each adverse events. Statistical analyses were done using SAS (version 14.1). This study is registered with the Japan Registry of Clinical Trials, number jRCTs051180057; and the University hospital Medical Information Network, number UMIN000003969.

Role of the funding source

The Public Health Research Foundation was involved in the design and conduct of the trial, data collection and analysis, preparation of the manuscript, and in the decision to submit for publication. Taiho Pharmaceutical had no role in study design, data collection, data analysis, or interpretation, or writing of the report, but did provide information on proper use of the study drug. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication.

Results

Patients were recruited between Feb 1, 2012, and Feb 1, 2016. 1959 (90%) of 2168 patient assessed for eligibility were randomly assigned to treatment. Of the 1959, there were 29 protocol deviations: 28 patients (1%) withdrew consent and one (<1%) was found not to meet eligibility criteria after allocation to the treatment group; thus, the full analysis set comprised 1930 patients: 957 in the endocrine therapy plus S-1 group and 973 in the endocrine therapy alone group. Three patients per group did not receive the allocated treatment and were excluded from the safety analysis set, which thus comprised 1924 patients (954 in the endocrine therapy plus S-1 group and 970 in the endocrine therapy alone group; figure 1).

Baseline characteristics are outlined in table 1 and a summary of endocrine therapies given is shown in the appendix 2 (p 8). Treatment compliance rates and S-1 dose ratios are provided in the appendix 2 (pp 9–10).

The data cutoff date for this interim analysis was Jan 31, 2019. The trial was terminated early because the primary endpoint was met at the interim analysis. Thus, in this analysis, invasive disease-free survival events were reported in 155 (16%) patients in the endocrine therapy alone group and in 101 (11%) patients in the endocrine therapy plus S-1 group (HR 0·63, 95% CI 0·49–0·81; p=0·0003; figure 2A; table 2). The 5-year invasive disease-free survival estimate was 82% (95% CI 79–84) in the endocrine therapy alone group and 87% (84–89) in the endocrine therapy plus S-1 group (median follow-up time 52·2 months; IQR 42·1–58·9). The invasive disease-free survival results according to subgroup analysis are shown in figure 3. Kaplan-Meier plots of subgroup analysis, prespecified analyses, and post-hoc analyses, of

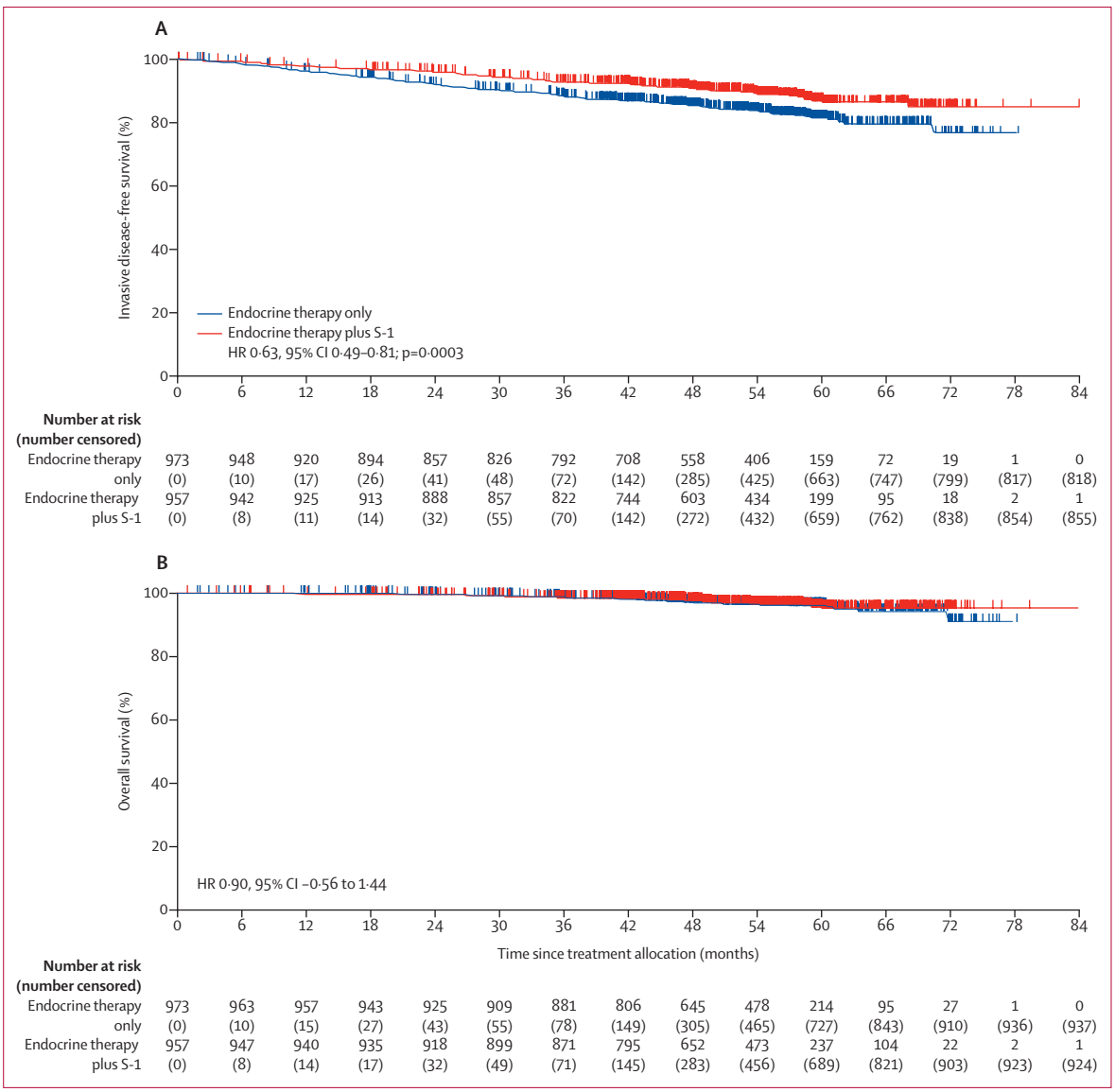

Figure 2: **Invasive disease-free survival (A) and overall survival (B) according to treatment**
HR=hazard ratio.

invasive disease-free survival are shown in the appendix 2 (pp 14–19).

68 (4%) of 1930 patients died (36 [4%] of 973 patients in the endocrine therapy alone group and 32 [3%] of 957 patients in the endocrine therapy plus S-1 group). Most deaths were due to primary disease progression or new breast lesions (33 [92%] of 36 patients in the endocrine therapy alone group and 30 [94%] of 32 patients in the endocrine therapy plus S-1 group). The other reasons for death were cardiac arrest in one patient (<1%) and other primary cancers in two patients in the endocrine therapy alone group; the remaining two deaths in the endocrine therapy plus S-1 group were treatment-related pulmonary thrombosis in one (<1%) patient and unknown in one (<1%) patient. Overall survival was similar between treatment groups (HR 0·90, 95% CI –0·56 to 1·44; figure 2B), and across all prognostic factors (appendix 2 p 21). Distant recurrence as the first disease event was observed in 66 (7%) of 957 patients in the endocrine therapy plus S1 group and in 93 (10%) of 973 in the endocrine therapy alone group. Disease-free survival events occurred in 101 (11%) in the endocrine therapy plus S-1 group and 155 (16%) patients in the endocrine therapy alone group. Kaplan-Meier curves of distant disease-free survival and disease-free survival are shown in the appendix 2 (p 20). The relationship between invasive disease-free survival and the Ki-67 labelling index (appendix 2 p 17) was the only analyses done on the potential relationship between tumour growth factors and biomarkers with the recurrence-inhibitory effect of S-1.

During the study period, 293 (31%) of 954 patients required a reduction in the dose of S-1; in 283 (97%) of 293 patients, the reason for the dose reduction was the occurrence of adverse events. 217 (22%) of 970 in the endocrine therapy alone group and 182 (19%) of 954 patients in the endocrine therapy plus S-1 group changed their endocrine treatment while on study. In the endocrine therapy alone group, 158 (16%) of 970 patients discontinued endocrine therapy; the main reasons were primary disease recurrence or development of new lesions in 120 (76%) of 158 patients, transfer to another hospital in 16 (10%) of 158 patients, and patient request in 12 (8%) of 158 patients. In the endocrine therapy plus S-1 group, 113 (12%) of 954 patients discontinued endocrine therapy; the main reasons were primary disease recurrence or development of new lesions in 72 (64%) of 113 patients, transfer to another hospital in 16 (14%) of 113 patients, and physician discretion in ten (9%) of 113 patients. In the 198 (21%) of 954 patients who discontinued S-1 therapy, the main reasons were patient request in 89 (45%) of 198, physician discretion in 57 (29%) of 198, and occurrence of adverse events requiring S-1 withdrawal for more than 28 days in 27 (14%) of 198 patients.

769 (79%) of 970 in the endocrine therapy alone group and 944 (99%) of 954 in the endocrine therapy plus S-1 group had an adverse event (table 3); a full list of grade 3–5 adverse events occurring in more than one patient overall is provided in the appendix 2 (p 12–13). The most common grade 3 or worse adverse events were decreased neutrophil count (72 [8%] of 954 patients in the endocrine therapy plus S-1 group *vs* seven [1%] of 970 patients in the endocrine therapy alone group), diarrhoea (18 [2%] *vs* none), decreased white blood cells (15 [2%] *vs* two [<1%]), and fatigue (six [<1%] *vs* none;

	Endocrine therapy only group (n=973)	Endocrine therapy plus S-1 group (n=957)
Patients with events	155 (16%)	101 (11%)
Recurrence	125 (13%)	80 (8%)
Breast recurrence	5 (<1%)	0
Local recurrence*	18 (2%)	6 (1%)
Regional lymph nodes	31 (3%)	17 (2%)
Distant organ metastasis	80 (8%)	62 (7%)
Contralateral breast	0	1 (<1%)
Distant node	13 (1%)	12 (1%)
Lung, liver	45 (5%)	30 (3%)
Bone marrow	42 (4%)	32 (3%)
Other	10 (<1%)	10 (1%)
Cancer lesions other than recurrence	28 (3%)	19 (2%)
Metachronous cancer	8 (1%)	7 (1%)
Secondary cancer	20 (2%)	12 (1%)
Death	2 (<1%)	3 (<1%)

Data are n (%).*Chest wall.

Table 2: **Invasive disease-free survival events in the full analysis set**

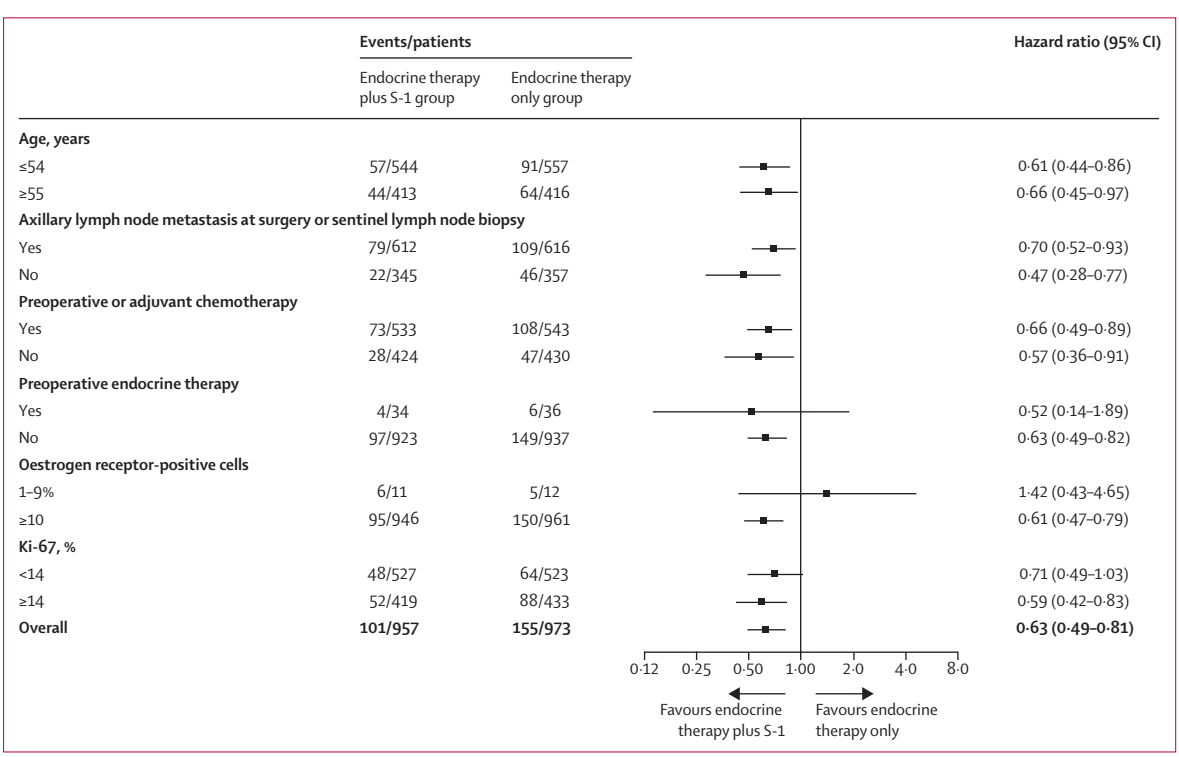

Figure 3: **Subgroup analysis of invasive disease-free survival**
As Oncotype DX breast recurrence score could only be evaluated in 20 patients, this subgroup analysis is not presented.

	Endocrine therapy only group (n=970)				Endocrine therapy plus S-1 group (n=954)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
White blood cells decreased	275 (28%)	2 (<1%)	0	0	504 (53%)	12 (1%)	3 (<1%)	0
Hyperpigmentation	33 (3%)	0	0	0	480 (50%)	0	0	0
Alanine aminotransferase increased	187 (19%)	9 (2%)	1 (<1%)	0	403 (42%)	6 (1%)	0	0
Neutrophil count decreased	110 (11%)	3 (<1%)	4 (<1%)	0	329 (35%)	67 (7%)	5 (1%)	0
Bilirubin increased	66 (7%)	3 (<1%)	0	0	379 (40%)	10 (1%)	0	0
Fatigue	88 (9%)	0	0	0	367 (39%)	6 (<1%)	0	0
Aspartate aminotransferase increased	129 (13%)	5 (1%)	0	0	367 (39%)	1 (<1%)	0	0
Anaemia	151 (16%)	0	0	0	330 (35%)	3 (<1%)	0	0
Nausea	35 (4%)	0	0	0	327 (34%)	2 (<1%)	0	0
Diarrhoea	24 (3%)	0	0	0	290 (30%)	18 (2%)	0	0
Platelet count decreased	79 (8%)	2 (<1%)	2 (<1%)	0	302 (32%)	4 (<1%)	1 (<1%)	0
Anorexia	36 (4%)	0	0	0	271 (28%)	3 (<1%)	0	0
Oral mucositis	34 (4%)	0	0	0	257 (27%)	4 (<1%)	0	0
Creatinine increased	136 (14%)	1 (<1%)	0	0	134 (14%)	0	0	0
Maculopapular rash	32 (3%)	0	0	0	122 (13%)	1 (<1%)	0	0
Dysgeusia	2 (<1%)	0	0	0	101 (11%)	0	0	0

Data are n (%). Adverse events reported by 10% or more of patients in either treatment group.

Table 3: **Adverse events in the safety analysis set**

table 3). Serious adverse events are listed in the appendix 2 (p 11); those occurring in more than one patient in either group were diarrhoea (six [1%] in the endocrine therapy plus S-1 group *vs* none in the endocrine therapy alone group), pneumonitis (three [<1%] in each group), and fracture (two [<1%] *vs* one [<1%]).

Discussion

In this study, administration of S-1 with adjuvant endocrine therapy significantly reduced invasive disease-free survival events and improved 5-year invasive disease-free survival estimates for patients with ER-positive, HER2-negative, primary breast cancer.

To our knowledge, no data have shown the usefulness of adjuvant S-1 combined with endocrine therapy in this particular setting. The clinical benefit of capecitabine, another oral fluoropyrimidine, has previously been shown in patients with HER2-negative, residual invasive breast cancer after neoadjuvant chemotherapy.[14] In 910 patients receiving standard treatment after surgery with or without capecitabine, the primary endpoint of disease-free survival was significantly longer in the capecitabine group than in the endocrine therapy alone group (74% *vs* 68% at 5 years; HR 0·70, 95% CI 0·53–0·92; p=0·01).[14] The prespecified subgroup analysis of that study indicated a therapeutic advantage for the ER-negative and HER-2 negative subpopulation, but the benefits for ER-positive and HER2-negative luminal disease were less notable.[14] With regard to other fluoropyrimidines, the ACETBC trial[21] showed greater effectiveness with tegafur plus uracil in combination with tamoxifen than with tamoxifen alone as adjuvant therapy in women with early ER-positive breast cancer.[21] Results were better with the combination therapy in patients positive for lymph node metastasis and in patients who were premenopausal.[21] However, it must be noted that the recommended duration of adjuvant therapy at that time was shorter than the duration in use today. In another study[11] of 733 women with node-negative, high-risk breast cancer, the efficacy of adjuvant oral tegafur plus uracil was similar to that of cyclophosphamide, methotrexate, and fluorouracil (HR 0·98, 95% CI 0·66–1·45; p=0·92 for relapse-free survival; 0·81, 0·44–1·48, p=0·49 for overall survival).[11] Furthermore, in a subsequent integrated analysis of two tegafur plus uracil trials, non-inferiority of tegafur plus uracil to cyclophosphamide, methotrexate, and fluorouracil in patients with ER-positive breast cancer 50 years and older was confirmed.[9] The use of chemotherapy plus endocrine therapy for advanced breast cancer has generally been discouraged,[15] and recent data have not shown any definitive benefit from such combinations;[22,23] thus, the placement of this type of regimen within the treatment algorithm remains open to question.

The improvement in invasive disease-free survival observed in this study is notable. The therapeutic effect appeared to be unaffected by major clinicopathological factors, suggesting that S-1 plus endocrine therapy might provide benefit for many patients with ER-positive and HER2-negative breast cancer.

The American Society for Clinical Oncology guidelines were updated as a result of the TAILORx trial,[24] which used Oncotype DX to determine the need for chemotherapy in patients with hormone receptor-positive, axillary node-negative breast cancer.[25] In our study, we were able to use Oncotype DX for only a very small number of cases (<1% of the trial population), which did

not allow us to draw any meaningful conclusions from the data; therefore, it could be useful to do additional studies to evaluate the role of Oncotype DX in this study population and its potential to predict the efficacy of adjuvant S-1 therapy.

S-1 treatment was well tolerated and adverse events were manageable. Several adverse events were haematological and only a small proportion were grade 3 or worse; of these, neutrophil count and white blood cells decrease, diarrhoea, and fatigue, were more common in the endocrine therapy plus S-1 group. The safety data from this study are generally consistent with the known safety profile of S-1.[12] To maintain patient adherence and maximise response (because reduced adherence is associated with worse outcomes),[26] oncologists must minimise toxicity by carefully monitoring patients receiving S-1.

We acknowledge that there are some limitations of this study. S-1 gastrointestinal side-effects are less likely to occur in Asian populations, and this should be considered when extrapolating our results to other populations. According to a pharmacokinetics study[27] previously done in patients from the USA and Japan, the area under the curve (AUC) of fluorouracil concentration adjusted by body surface area was similar between patients from Japan and the USA.[27] Nevertheless, adverse events such as gastrointestinal toxicities were observed more frequently in patients from the USA than in patients from Japan, suggesting that as yet unidentified mechanisms might have a role in the development of gastrointestinal disorders. In this regard, the role of the CYP2A6 genotype has been investigated, but it was not found to affect the AUC of fluorouracil.[28] Nonetheless, it remains possible that the pharmacokinetics of S-1 might differ by population; in one study,[29] although there was no difference in exposure (AUC) with fluorouracil, dose-normalised $AUC_{0–48h}$ for tegafur (p=0·05) and gimeracil (p=0·04) were found to be higher in East Asian patients than in white patients, and $AUC_{0–48h}$ of fluoro-b-alanine was higher in white patients (p=0·04). However, this aspect requires further study for definitive confirmation. Additionally, information about the use of bone-targeted drugs such as bisphosphonates should be collected and analysed, although the adjuvant use of these drugs is not currently indicated in Japan. Studies with longer observational periods are warranted to evaluate the effect of this treatment regimen on overall survival outcomes. A meta-analysis on adjuvant therapy with oral fluorouracil could be needed to expand and validate our results.

We postulate that continuous oral treatment with S-1 could have an additional therapeutic application as a metronomic drug. Previous experimental studies have shown the usefulness of this therapeutic concept for controlling breast cancer progression.[30] S-1 has a relatively low incidence of adverse drug reactions and a comparatively low cost, but additional research into predictive markers for prognosis and adverse events will be required to further improve clinical outcomes using this drug.

Recently, a potential role for cyclin-dependent kinase inhibitors for luminal disease has been shown in the metastatic breast cancer setting, and cyclin-dependent kinase inhibitors are being extensively investigated in the adjuvant setting.[8] The results of several trials (NCT02513394, NCT03155997, NCT01864746) are expected soon, and, if positive, the resulting data could change the landscape of adjuvant treatment for this patient population. To improve survival outcomes, novel therapeutic combinations and the individualisation of treatment are necessary.

In conclusion, in patients with primary ER-positive and HER2-negative breast cancer and intermediate-risk to high-risk disease, adjuvant administration of the oral fluoropyrimidine S-1 concurrently with standard endocrine therapy significantly reduced invasive disease-free survival events and improved the 5-year invasive disease-free survival. Adverse events were manageable and consistent with previous reports of S-1.

Contributors

MTo, SI, Tis, YI, HIw, NM, HM, SS, AS, TIk, TSu, TU, HIs, MTa, YO, and SO designed the study. YI, NM, HM, AS, TIk, HH, TSa, KA, TSu, TU, TK, YK, MK, YS, KJ, NS, MTa, and SO collected data. YO interpreted the data. MTo interpreted the data and wrote the report. All authors revised the manuscript for critically important content and approved the final version for submission.

Declaration of Interests

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Data sharing

Deidentified patient data will be made available upon reasonable request. Requests for data access should be made in writing, including details of how the data will be used, and addressed to the corresponding author, and approval will be considered based on the scientific merit, feasibility, and timeliness of the request.

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