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ORIGINAL ARTICLE

The efficacy and safety of gemcitabine plus paclitaxel combination first-line therapy for Japanese patients with metastatic breast cancer including triple-negative phenotype

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Abstract
Purpose Gemcitabine (GEM)–paclitaxel combination therapy has been confirmed as a standard therapy for metastatic/recurrent breast cancer (MBC) in Western countries. This study was conducted to assess the efficacy and safety of GEM–paclitaxel combination therapy in Japanese MBC patients.
Methods Patients were administered paclitaxel 175 mg/m^2 on day 1, and GEM 1,000 or 1,250 mg/m^2 on days 1 and 8 of 21-day cycle. The primary endpoint of this study was overall response rate; secondary endpoints were duration of response, time to progression, survival time and rate.
Results Paclitaxel 175 mg/m^2 plus GEM 1,250 mg/m^2 was determined as the recommended dose. A total of 56 patients received 506 cycles of treatment (median: 7.5 cycles) with a relative dose intensity of 79.6% for GEM and 85.8% for paclitaxel. The response rate was 44.6% (25/56 patients), median time to progression 8.6 months and median survival time 27.1 months. In triple-negative patients, the response rate was 35.7% (5/14 patients), and the median time to progression was 6.0 months. The most frequent grade ≥ 3 toxicities were neutropenia (82.1%), leukopenia (62.5%) and ALT increase (14.3%).
Conclusions This study confirmed the efficacy and safety of GEM–paclitaxel combination therapy in Japanese MBC patients.

Keywords Anthracycline-pretreated metastatic breast cancer · Triple negative · Gemcitabine · Paclitaxel · Phase I/II trial

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Introduction

Since 1990, the age-standardized breast cancer death rate has declined in many developed countries [1]; however, the mortality rate is still increasing in Japan [2].

Metastatic breast cancer remains an incurable disease despite progress in current treatment that has resulted in improved survival rates and quality of life. Chemotherapy is currently the treatment of choice for women with Her2/neu negative, endocrine-resistant MBC, or for women with extensive visceral localizations or life-threatening disease. The most used drugs are anthracyclines, taxanes, alkylating agents, anti-metabolites, and vinca-alkaloids. Anthracycline-based combinations remain the standard first-line treatment for MBC, but despite objective response rates in 50–60% of patients, median survival period does not exceed 2–3 years [3–5].

Combination first-line chemotherapy usually provides a higher response rate and longer progression-free survival compared with single-agent chemotherapy [6]. However, due to the availability of very effective second-line, third-line, or even fourth-line chemotherapy along with the recent development of effective molecular targeted therapy, very few trials show overall survival benefit for a combination strategy [7]. One of the exceptions is the combination of an anti-metabolite such as capecitabine or gemcitabine (GEM) with taxane.

Combination therapy with GEM (a nucleoside analog) and taxane offers specific advantages because of their distinct mechanisms of action with no overlapping toxicity, including lack of cardiotoxicity [8]. GEM has demonstrated synergistic effects with taxanes in preclinical tumor models [9, 10], and the two-drug combination of GEM–paclitaxel was studied in various other malignant conditions including non-small cell lung cancer [11], bladder [12], ovarian [13], and breast cancer [14]. In recent years, two phase III randomized clinical trials [15, 16] have shown the beneficial effects of combined therapy with GEM and taxane for the treatment of MBC. Further, an analysis of the global QoL endpoint favored the GEM–paclitaxel combination therapy over paclitaxel monotherapy despite an increase in myelosuppression [17]. Consequently, GEM in combination with paclitaxel has been approved in several countries including the United States and the European Union for the treatment of unresectable, locally recurrent, or metastatic BC in patients following anthracycline-based adjuvant/neoadjuvant chemotherapy.

Japanese patients are known to suffer from more bone marrow toxicity compared with patients from Western countries when treated with a paclitaxel containing regimen [18]. Although paclitaxel 175 mg/m^2 plus GEM 1,250 mg/m^2 has been established as a standard regimen for MBC in Western countries, the optimal dose, schedule, and sequence of administration still need to be determined in Japanese MBC patients. The present phase I/II clinical study was thus conducted using the same regimen to assess the efficacy and safety of GEM–paclitaxel combination therapy in Japanese MBC patients.

Patients and methods

Study design

This study was a multicenter, non-randomized, open-label, phase I/II study conducted in Japanese patients with metastatic/recurrent breast cancer (MBC) to assess the efficacy and safety of the GEM–paclitaxel combination therapy. This study consisted of two steps. At Step 1, the officially approved GEM dose for other cancers in Japan (GEM 1,000 mg/m^2) was administered with paclitaxel 175 mg/m^2 to the first group of patients as the initial dose of the study treatment. After confirmation of the safety at GEM 1,000 mg/m^2 plus paclitaxel 175 mg/m^2, an escalated dose of GEM 1,250 mg/m^2 plus paclitaxel 175 mg/m^2 was administered to a second group of patients. This specific dose was chosen because the combination of GEM 1,250 mg/m^2 and paclitaxel 175 mg/m^2 has been recommended in countries other than Japan according to the results from a phase III study [15].

Six patients were enrolled for each group in Step 1. Paclitaxel 175 mg/m^2 was administered intravenously over 3 h on day 1 and GEM 1,000 mg/m^2 was given intravenously over a 30-min infusion on days 1 and 8 in a 3-week cycle, 2 consecutive administration weeks followed by a 1-week rest period. If dose-limiting toxicity (DLT) occurred in less than 2 out of 6 patients at GEM 1,000 mg/m^2, the dose was increased to GEM 1,250 mg/m^2 and paclitaxel 175 mg/m^2, and then administered to a second group of patients.

In Step 2, an additional 50 patients were enrolled and evaluated for the efficacy and safety at the recommended dose determined in Step 1. Treatment was repeated every 21 days until disease progression, intolerable toxicity or patient withdrawal.

Patients

Female patients with histologically or cytologically confirmed MBC or inoperable locally advanced BC were enrolled in the study. All MBC patients had relapsed after receiving anthracycline-based chemotherapy regimen in a neo-adjuvant/adjuvant setting, but no prior chemotherapy for metastatic disease. Neo-adjuvant/adjuvant chemotherapy

including taxanes must have been completed more than 12 months before registering in this study. Other inclusion criteria were as follows: good performance status (ECOG) 0 or 1, at least one bidimensionally measurable lesion, adequate function of major organs [hemoglobin $\geq$ 9.0 g/dL, neutrophils $\geq$ 2,000/mm^3, platelets $\geq$ 100,000/mm^3, AST/ALT $\leq$ 2.5 times upper limit of normal (ULN), ALP $\leq$ 2.5 times ULN, $\leq$ 5.0 times ULN for patients with liver or bone metastases] and an estimated life expectancy of at least 12 weeks. Written informed consent was obtained from all patients enrolled in the study.

This study was conducted in compliance with the guideline of good clinical practice and the Declaration of Helsinki, and the study protocol was approved by the local institutional review boards. The Efficacy and Safety Evaluation Committee, an independent review board, was consulted if any efficacy or safety issues arose in the study.

Efficacy measures

The primary objective of this study was to confirm that the lower limit of the 95% confidence interval (CI) of the response rate at the recommended dose exceeded the threshold response rate of 25%. Tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST 2000). Responder was defined as a patient who met either the complete response (CR) or partial response (PR) criteria for overall response assessment. CR or PR was confirmed at least 4 weeks after first observation of the response.

Secondary objectives included the median duration of response, time to progression, median survival time, and 1- and 2-year survival rates. The duration of response was the period from the day when the patient first satisfied either the CR or PR criteria to the day when the patient first met the criteria of progressive disease (PD). Time to progression (TTP) was defined as the period from the registration day to the time when any indication of disease progression (including increased size of tumor, identification of a new lesion, death, and aggravation of symptoms) was observed. Survival time was defined as the period from the date of registration to the date of death (regardless of the cause of death). Patients alive at the end of the follow-up period were treated as censored cases.

Safety measures

The safety evaluation included the type and incidence of adverse events. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.0; toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

DLT was defined as a toxicity occurring in cycle 1 that met one of the following criteria: neutropenia of $\geq$grade 3 with a fever of $\geq$38.0°C, thrombocytopenia of <25,000/mm^3 or thrombocytopenia with bleeding that required platelet transfusion(s), non-hematotoxicity of $\geq$Grade 3 (excluding nausea, vomiting, anorexia). A delay in the start of cycle 2 was also classified as a DLT if cycle 2 could not be started within 42 days after the initiation of cycle 1 due to study drug toxicity.

Statistics

All patients who received at least one dose of the study drug were included in the efficacy and safety analysis. The primary efficacy endpoint was response rate. A statistical test against the null hypothesis of "the response rate is less than 25%" was performed by obtaining an exact *P*-value based on the binomial distribution with a significance level of 2.5% (one-sided). The other efficacy endpoints of duration of response, time to progression (TTP), survival time and 1- and 2-year survival rates were estimated using the Kaplan–Meier method. Two-sided 95% CIs for all endpoints were obtained.

The sample size was determined by reference to the results of a global phase III study [15]. The expected response rate of the GEM–paclitaxel combination treatment and the threshold response rate were set at 45% and 25% respectively. Assuming that the true response rate is 45%, the number of 48 subjects is needed to achieve 80% power when the statistical test is applied based on the binomial distribution with a significance level of 2.5% (one-sided). As this was the first time of the GEM–paclitaxel combination treatment to Japanese patients with MBC, given adequate consideration for feasibility, it was necessary to treat at least 55 patients with the recommended dose to evaluate the safety profile.

Results

Patient disposition and characteristics

This study was carried out from June 2006 to August 2009 at 24 study centers in Japan. Sixty-two female patients were enrolled into this study. At Step 1, 12 patients were divided into two groups of 6 patients each and administered paclitaxel 175 mg/m^2 plus GEM 1,000 mg/m^2 or GEM 1,250 mg/m^2 to determine the recommended dose for Step 2. At Step 2, an additional 50 patients were enrolled at the recommended dose of GEM plus paclitaxel 175 mg/m^2.

The mean age was 58.2 years (range 51–63) in the GEM 1,000 mg/m^2 dose group and 54.4 years (range 30–73) in the GEM 1,250 mg/m^2 dose group. All 62 patients had a history of prior chemotherapy; 27 were anthracycline and taxane pretreated patients and 35 anthracycline pretreated patients. Fifty-five patients had metastases: 32 lung, 25 bone, 22 liver and 20 lymph nodes (Table 1).

Table 1 Baseline demographic and characteristics of patients

	G 1000 group	G 1250 group
Patient number (%)	6 (100.0)	56 (100.0)
Age: mean (SD)	58.2 (4.5)	54.4 (8.7)
Height (cm): mean (SD)	153.5 (8.0)	154.7 (6.2)
Body weight (kg): mean (SD)	57.2 (15.3)	55.8 (8.7)
PS (ECOG)		
0	4 (66.7)	50 (89.3)
1	2 (33.3)	6 (10.7)
Metastatic sites		
Patients without metastases	1 (16.7)	6 (10.7)
Patients with metastases	5 (83.3)	50 (89.3)
Lung	3 (50.0)	29 (51.8)
Bone	1 (16.7)	24 (42.9)
Liver	2 (33.3)	20 (35.7)
Brain	0 (0.0)	2 (3.6)
Lymph node	2 (33.3)	18 (32.1)
Skin	0 (0.0)	4 (7.1)
Other sites	1 (16.7)	14 (5.0)
Estrogen receptor status		
Positive	1 (16.7)	35 (62.5)
Negative	5 (83.3)	21 (37.5)
Progesterone receptor status		
Positive	1 (16.7)	26 (46.4)
Negative	5 (83.3)	30 (53.6)
Her2/neu expression status		
0	4 (66.7)	19 (33.9)
1+	2 (33.3)	22 (39.3)
2+	0 (0.0)	1 (1.8)
3+	0 (0.0)	9 (16.1)
Unknown	0 (0.0)	5 (8.9)
Prior therapy		
Surgical therapy	3 (50.0)	42 (75.0)
Chemotherapy	6 (100.0)	56 (100.0)
Radiotherapy	2 (33.3)	25 (44.6)
Hormonal therapy	1 (16.7)	33 (58.9)
Other	2 (33.3)	16 (28.6)
Prior chemotherapy		
Anthracycline plus taxane	2 (33.3)	25 (44.6)
Anthracycline	4 (66.7)	31 (55.4)

PS performance status, *ECOG* Eastern cooperative oncology group, *Her2* human epidermal growth factor receptor 2

Triple-negative patients were defined as those with negative estrogen receptor (ER) and progesterone receptor (PR) status and an Her2/neu status of 0 or 1+. Fourteen of the 56 patients in the GEM 1,250 mg/m^2 dose group met the triple-negative criteria.

Patients were also classified by hormone receptor subtype: 27 patients with ER+ or PR+ and HER2−, 7 patients with ER+ or PR+ and HER2+, 2 patients with ER− and PR− and HER2+.

Dose-limiting toxicity (DLT)

Two DLTs were observed: grade 3 ALT increase (1 patient at 1,000 mg/m^2) and grade 3 fatigue (1 patient at 1,250 mg/m^2). Therefore, GEM 1,250 mg/m^2 plus paclitaxel 175 mg/m^2 was determined as the recommended dose of this study.

Drug exposure

A total of 506 cycles were administered (median 7.5 cycles, range 1–37 cycles) at the GEM 1,250 mg/m^2 dose level. Relative dose intensities were 79.6% for GEM and 85.8% for paclitaxel.

Efficacy

The response rate was 44.6% at the GEM 1,250 mg/m^2 dose level, median duration of response was 7.9 months (95% CI: 5.6, 11.0), and the median TTP was 8.6 months (95% CI: 6.5, 10.3) (Table 2). The 1-year survival rate was 78.6% (95% CI: 67.8, 89.3). The 2-year survival rate was 58.9% (95% CI: 46.0, 71.8), with 30 out of 56 patients surviving at the time of the 2-year survival analysis. The median survival time was 27.1 months (95% CI: 22.9, incalculable) at the median follow-up time period of 24.8 months (Figs. 1, 2).

Among the 14 triple-negative patients, the response rate was 35.7% with 5 patients achieving PR. The median TTP in the triple-negative patients was 6.0 months (95% CI: 1.4, 7.3) compared with 9.6 months (95% CI: 7.4, 13.6) in the non-triple-negative patients (Table 2). The 27 patients with ER+ or PR+ and HER2− hormonal receptor subtype achieved a 59.3% response rate and a median TTP of 9.3 months (95% CI: 7.4, 15.4).

Safety

All 62 patients reported at least one adverse event, and hematological toxicity was commonly observed at the GEM 1,250 mg/m^2 dose level. The most common grade ≥ 3 drug-related adverse events were neutropenia

Table 2 Tumor response and time-to-event (RECIST criteria)

	N	Tumor response *n* (%)						Time to event median (months) (95% CI)	
		CR	PR	SD	PD	NE	RR (95% CI)	DOR	TTP
G 1250 group	56	0 (0.0%)	25 (44.6%)	14 (25.0%)	11 (19.6%)	3 (5.4%)	44.6% (31.3, 58.5)	7.9 (5.6, 11.0)	8.6 (6.5, 10.3)
Triple negative	14	0	5	4	5	0	35.7%	4.5 (2.8, 9.3)	6.0 (1.4, 7.3)
Non-triple negative	42	0	20	13	6	3	47.6%	8.2 (7.3, 13.2)	9.6 (7.4, 13.6)

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *RR* response rate, *DOR* duration of response, *TTP* time to progression, 95% CI: 95% confidence interval

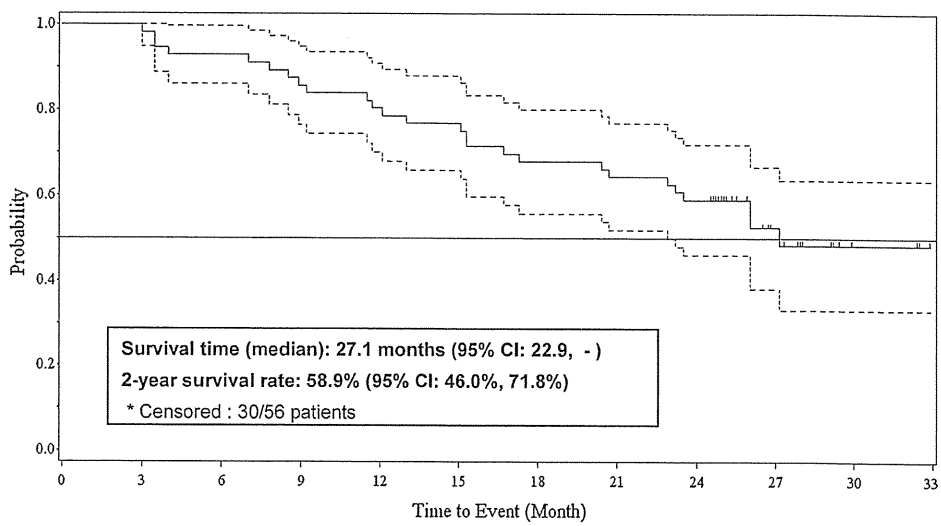

Fig. 1 Kaplan–Meier survival curve

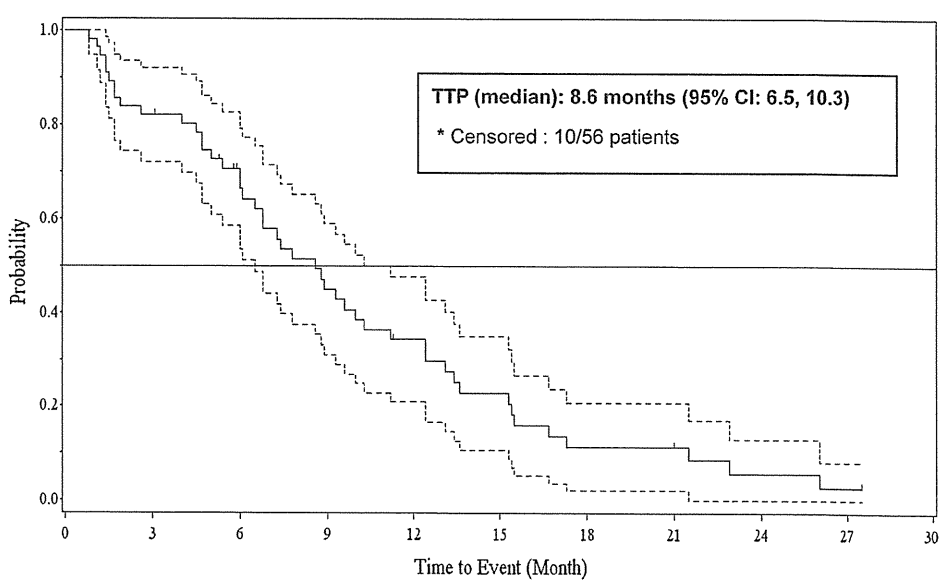

Fig. 2 Kaplan–Meier time to progression (*TTP*) curve

(82.1%), leukopenia (62.5%), lymphopenia and alanine transaminase (ALT) increase (14.3% each). The incidence of grade 3 non-hematological toxicity was low (Table 3). Fourteen of 56 patients (25.0%) reported peripheral neuropathy, but with no grade 3 or 4 toxicities. The incidence of neutropenia was 82.1%; however, no case of febrile neutropenia was reported. Prophylactic use of G-CSF was not allowed in this study, and only 10 patients (10/56, 17.9%) received G-CSF during the 2-year follow-up period. No patients required platelet transfusions.

Table 3 Adverse reactions (CTC grade 2, 3 or 4 toxicities)

Parameters	Toxicity grade[a] ($N = 56$)					
	Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%
Hematologic						
Neutrophil count decreased	7	12.5	18	32.1	28	50.0
White blood cell count decreased	12	21.4	30	53.6	5	8.9
Lymphocyte count decreased	18	32.1	4	7.1	3	5.4
ALT increased	24	42.9	7	12.5	0	0.0
Hemoglobin decreased	21	37.5	4	7.1	0	0.0
Platelet count decreased	8	14.3	5	8.9	0	0.0
AST increased	8	14.3	4	7.1	0	0.0
Red blood cell count decreased	13	23.2	3	5.4	0	0.0
GGT increased	3	5.4	2	3.6	0	0.0
Blood albumin decreased	4	7.1	0	0.0	0	0.0
Febrile neutropenia	0	0.0	0	0.0	0	0.0
Non-hematologic						
Alopecia	25	44.6	0	0.0	0	0.0
Malaise	9	16.1	1	1.8	0	0.0
Pain in extremity	9	16.1	1	1.8	0	0.0
Rash	9	16.1	0	0.0	0	0.0
Arthralgia	8	14.3	1	1.8	0	0.0
Peripheral neuropathy	7	12.5	0	0.0	0	0.0
Constipation	6	10.7	0	0.0	0	0.0
Diarrhea	4	7.1	2	3.6	0	0.0
Myalgia	4	7.1	1	1.8	0	0.0
Fever	4	7.1	1	1.8	0	0.0
Vomiting	4	7.1	0	0.0	0	0.0
Nausea	3	5.4	0	0.0	0	0.0
Anorexia	2	3.6	1	1.8	0	0.0

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma glutamyltransferase, *ALP* alkaline phosphatase

[a] Toxicity was graded according to CTCAE v3.0

Discussion

This phase I/II, multicenter study was conducted to evaluate the efficacy and safety of GEM plus paclitaxel combination therapy in Japanese MBC patients who had received prior chemotherapy with anthracycline.

Selection of combination versus serial single chemotherapy in the metastatic setting has been debated. The concepts of non-overlapping resistance mechanisms and toxicity profile have been the guiding principle for modern combination chemotherapy such as used in lymphoma, certain leukemia, and testicular germ cell cancers, but the validity of this concept has not been consistently shown in MBC. In randomized trials where single-agent and combination chemotherapy for MBC were compared, only a few multidrug therapies (capecitabine plus docetaxel or GEM plus paclitaxel) were associated with improvement in overall survival [15, 19], possibly because effective first-line chemotherapy can mask the true efficacy of second or later-line chemotherapy. In a phase III study that compared the GEM–paclitaxel combination with paclitaxel monotherapy, randomized patients were required to have had a history of anthracycline containing chemotherapy, and thus fewer patients in the monotherapy arm responded to paclitaxel monotherapy. In that study, more than 90% of the patients had prior anthracycline therapy resulting in a lower response rate for paclitaxel monotherapy [15].

Although therapy with serial single agents is a reasonable and often preferred alternative to combination regimens, combination therapy may be a more appropriate first-line choice, especially for symptomatic patients or those with rapidly progressive visceral metastases because of the greater likelihood of an objective response. Furthermore, analysis of the global QoL endpoint from a phase III study favored the GEM–paclitaxel combination therapy over paclitaxel monotherapy. The benefits of this combination as shown by QoL differences and mean global QoL scores rated by the Rotterdam Symptom Checklist (RSCL) indicated significant improvement of patients in GEM–paclitaxel combination arm versus paclitaxel monotherapy arm [17]. Capecitabine and docetaxel share hand–foot syndrome as an overlapping toxicity. Retrospective analysis of 1,000 Japanese breast cancer patients showed that the incidence of grade 2 or higher hand–foot syndrome with docetaxel was 16%, which increased to 40% with the docetaxel–capecitabine combination [20]. Results from another phase III study have also suggested that GEM may be a better option than capecitabine in combination with docetaxel for the treatment of advanced BC [16].

The present study also revealed that GEM–paclitaxel therapy was well tolerated in Japanese patients with 19 of 56 patients able to continue the study treatment for more than 10 cycles, adverse events that occurred in this study were manageable with appropriate treatment. The most common clinically significant adverse events encountered with this combination therapy were related to myelosuppresion such as neutropenia (82.1%), leukopenia (62.5%) and lymphocytopenia (12.5%). However, patients were able to continue the treatment over 506 cycles administered in 56 patients (median 7.5 treatment cycles, range 1–37). Grade 3 ALT increases were reported in 7 patients (12.5%); however, the study protocol allowed patients with liver metastases to enroll. At study entry, 20 patients had liver metastases and elevated liver enzymes associated with symptomatic aggravation. Results obtained in the present study were similar to those obtained in an earlier randomized phase III global trial [15] which demonstrated significant benefit of the GEM–paclitaxel combination therapy

over paclitaxel alone in the treatment of advanced breast cancer. Indeed, RR (44.6%) as well as TTP (8.6 months) observed in the present study were numerically better than the results (41.4% and 6.1 months, respectively) reported in the global trial. The 1- and 2-year survival rates observed in the present Japanese study (78.6 and 58.9%, respectively) were also greater than the survival rates (71 and 41%) observed in the global trial. The median survival time in this study was 27.1 months (95% CI: 22.9, incalculable) with more than half the patients were surviving after the 2-year follow-up period. This clearly demonstrates the beneficial effect of the GEM–paclitaxel combination on survival.

The response rate in the present study was similar to the other GEM–paclitaxel combination phase II first-line study [21]. Response rates for MBC in that study were 40–50%, while Delfino et al. reported a higher response rate of 66.7% (30/45 patients, 10 CR and 20 PR) in their phase II study [22]. This might be due to differences in patients' background in that more than half of the patients (53.3%) had no history of prior chemotherapy in the Delfino study.

Another important observation made in the present study relates to the effects of the GEM–paclitaxel combination therapy on patients with triple-negative breast cancer (TNBC). It is estimated that over 1 million women worldwide will be diagnosed annually for breast cancer and that 15% of them are likely to be classified as patients with TNBC [23, 24], with 30% of these patients developing metastatic disease [25]. TNBC usually exhibits an aggressive clinical course unlike hormone receptor-positive breast cancer and previously had not been a candidate for target therapy such as HER-2-positive breast cancer. Therefore, patients with TNBC are more likely to develop distant metastasis in locations like the brain earlier than non-TNBC patients, and have shorter overall survival [26]. Lin et al. reported that close to 50% of TNBC develop brain metastasis, and one-third of which were at first site of recurrence [27].

Until recently, the subset of breast cancer patients with triple-negative disease lacked a distinct therapeutic approach, despite this accounting for 15% of breast cancer patients. For patients with TNBC, anti-estrogen therapy and HER2 targeted agents are not useful options, and strategies utilizing both standard cytotoxic agents and novel targeted therapy have evolved [28]. A recent randomized phase II study on the efficacy of a PARP (poly ADP ribose polymerase) inhibitor in combination with GEM and carboplatin in patients with TNBC has shown that the median PFS was 6.9 months [29]. In comparison, combination therapy with GEM–paclitaxel at the recommended dose level (GEM 1,250 mg/m^2) resulted in a 7.9 month median duration of response for the 25 responding patients in this study. It was also found that TTP in triple-negative patients was 6.0 months versus 9.6 months in non-triple-negative patients.

Hormone receptor-positive patients have longer progression-free survival compared with triple-negative (TN) type patients. In the E2100 trial, where paclitaxel was compared with the paclitaxel plus bevacizumab, the PFS of TN patients was shorter compared with hormone receptor-positive patients in the paclitaxel arm (5.3 vs. 10.6 months) [30]. Although cross-trial comparison is limited by many biases and our study used tri-weekly paclitaxel, our results also showed a similar trend (TN 6.0 vs. non-TN 9.6 months). Since weekly administration of paclitaxel has an advantage over tri-weekly administration [31], the combination of GEM with weekly paclitaxel, possibly incorporating bevacizumab might result in better tumor control. This is being tested in ongoing clinical trial [32].

Even though the efficacy of combination therapy in the treatment of TNBC needs to be further studied, the results from the present study are in agreement with similar observations made in the earlier global trial [15] and indicate that GEM–paclitaxel combination therapy would be effective and well tolerated in Japanese patients with MBC.

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Conflict of interest statement The following authors disclose relationships with Eli Lilly Japan: TF and JF are employed by Eli Lilly and MT contributed in an advisory role.

Appendix

The following institutions participated in this study.

Sapporo Breast Surgical Clinic, Iwate University Hospital, Gunma Prefectural Cancer Center, Saitama Red Cross Hospital, Chiba Cancer Center, Kameda General Hospital, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, St Luke's International Hospital, Tokai University Hospital, Seirei Hamamatsu General Hospital, Aichi Cancer Center Hospital, Osaka National Hospital, Osaka Medical Center for Cancer and Vascular Diseases, Osaka Breast Clinic, Kinki University Hospital, Sakai Municipal Hospital, Kure Medical Center and Chugoku Cancer Center, Shikoku Cancer Center, Fukuoka University Hospital, Kyushu Cancer Center, Kumamoto Municipal Hospital, Breastpia Namba Hospital, and Sagara Hospital.

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Ki67 index changes, pathological response and clinical benefits in primary breast cancer patients treated with 24 weeks of aromatase inhibition

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Aromatase inhibitor shows efficacy for hormone receptor positive postmenopausal breast cancer. We evaluated the activity of 24 weeks of aromatase inhibition with exemestane for primary breast cancer in a neoadjuvant setting. Patients with stage II/IIIA invasive breast cancer with estrogen receptor (ER) and/or progesterone receptor (PgR)-positive status were eligible. Primary endpoints were objective response rate (ORR) and safety. A steroidal aromatase inhibitor exemestane of 25 mg/day was administered for 16 weeks with an 8-week extension. Secondary endpoints were rates of breast-conserving surgery (BCS), and change of Ki67 index and ER/PgR expression in central laboratory analyses. Between March 2006 and December 2007, 116 patients were enrolled. Among those, 102 patients completed 24 weeks of administration. The ORR was 47% (55/116) at Week 16 and 51% (59/116) at Week 24, respectively. No serious toxicity was seen. ORR was associated with ER Allred scores but not with PgR scores. The significant reduction in Ki67 index was confirmed. No progression was experienced in tumors with less than 15% Ki67 index. Pathological response was observed in 28 (30%) of 94 evaluated cases. No statistical correlation between pre-treatment Ki67 index and pathological response was detected; however, a trend of correlation was found between the post-treatment preoperative endocrine prognostic index (PEPI), a prognostic score and the pathological response. At diagnosis, 59 patients (51%) would have required mastectomy but 40 patients were converted to BCS, showing an increase in the rate of BCS (77%). The 24-week aromatase inhibition provided preferable clinical benefits with significant reduction in Ki67 index. More precise mechanisms of the response need to be investigated. (*Cancer Sci* 2011; 102: 858–865)

Many studies of neoadjuvant chemotherapy for breast cancer have been conducted. These studies have revealed that neoadjuvant chemotherapy allows more women to undergo breast-conserving surgery (BCS) rather than total mastectomy, and prolongs the survival of patients who achieved pathological complete response (pCR).[1–3] However, it has been described that neoadjuvant chemotherapy has a limited effect in hormone receptor-positive patients in terms of pCR rates, and raises safety concerns for elderly patients.[4–7] Therefore, as a treatment strategy, the efficacy and safety of neoadjuvant hormone therapy using aromatase inhibitors (AI) is being assessed in several trials in postmenopausal breast cancer patients.[8–11]

In a phase II randomized study in which neoadjuvant hormone therapy and neoadjuvant chemotherapy were compared in hormone receptor-positive patients, no significant difference in the clinical response rate was observed between these two groups. Notably, the rate of BCS tended to be higher, and the incidence of adverse events was generally lower in the neoadjuvant hormone therapy group than in the neoadjuvant chemotherapy group.[12] These results suggest the benefit of neoadjuvant hormone therapy in hormone-sensitive postmenopausal breast cancer patients.[13] Therefore, it seems that neoadjuvant hormone therapy offers an alternative to neoadjuvant chemotherapy.

However, there are some concerns surrounding the use of neoadjuvant hormone therapy that need to be addressed. First, tumor regression is slower with neoadjuvant hormone therapy than with chemotherapy. In fact, a study investigating the response rate to 6-month neoadjuvant hormone therapy using exemestane reported that the objective response rate (ORR: complete response [CR] + partial response [PR]) continued to increase even after 4 months of treatment.[14] Another concern is that there is no established index for evaluating the efficacy of neoadjuvant hormone therapy. In neoadjuvant chemotherapy, the pCR rate can be used as a surrogate marker for the prognosis of patients.[2] However, it has been reported that, in estrogen receptor (ER)-positive patients, the proportion of patients who achieved a pCR was not significantly correlated with overall survival (OS) or disease-free survival (DFS).[15] In addition, several Phase II studies of neoadjuvant hormone therapy reported that pCR rates were from 0 to about 3%, which were remarkably lower than those expected from the benefit observed in adjuvant hormone therapy.[8,11,12] Therefore, in hormone receptor-positive breast cancer patients, pCR is unlikely to be a useful marker for assessing efficacy or prognosis. A possible alternative marker for neoadjuvant hormone therapy is the percentage of MIB1/Ki67-positive cells (MIB-1/Ki67 labeling index), a cell proliferative index. The Ki67 index after neoadjuvant hormone therapy was shown to correlate with the recurrence rate.[16,17] However, the usefulness of the Ki67 index has not been fully evaluated.

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Clinical Trial Registration Number
UMIN Clinical Trial ID; C000000345.

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Table 1. Patient characteristics

Factor	*n* (%)
Age, years (median, range)	64 (55–79)
Prior treatment	None
Tumor stage	
T2	110 (95)
T3	6 (5)
Nodal status	
N0	91 (78)
N1	23 (20)
Unknown	3 (2)
Clinical stage	
IIA	89 (77)
IIB	23 (20)
IIIA	4 (3)
Tumor diameter, mm (median, range)	
Caliper	32 (12–74)
Ultrasound	27.3 (15–102)
ER status	
ER+	116 (100)
ER–	0
PgR status	
PgR+	80 (69)
PgR–	36 (31)
HER2 status	
HER2+	3 (3)
HER2–	101 (87)
Not evaluated	12 (10)

ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

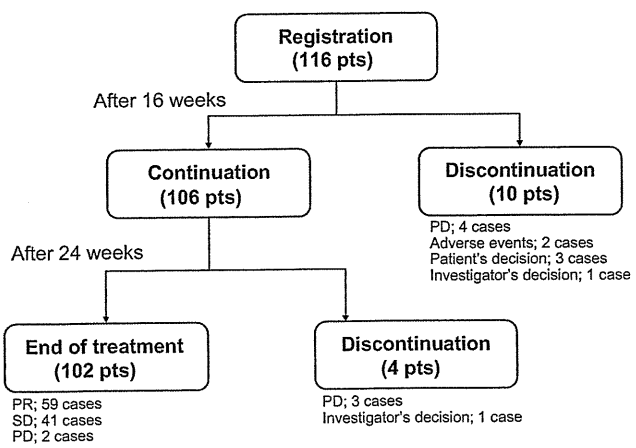

Fig. 1. Patient registration and the treatment flow of 24 weeks. PD, progressive disease; pts, patients; PR, partial response; SD, stable disease.

From these circumstances, we conducted the present study in Japanese patients with hormone receptor-positive postmenopausal breast cancer who received neoadjuvant hormone therapy using exemestane for 24 weeks to assess tumor response and safety of the treatment. We also evaluated the Ki67 index and expression of hormone receptors to determine its potential use as a marker to predict clinical and histopathological response in a central laboratory. Preoperative endocrine prognostic index (PEPI),[16] a prognostic index, was determined in each individual and the relationship with clinical and pathological responses was investigated.

Table 2. Clinical response after 16 weeks and 24 weeks of treatment

After 16 weeks evaluation (number of patients)		After 24 weeks evaluation (number of patients)	
PR	45	PR	59
SD	14		
PR	7	SD	41
SD	34		
PR	1	PD	4
SD	3		
PR	2	Not evaluated	12
SD	3		
PD	4		
Not evaluated	3		
Total		116	

PR, partial response; SD, stable disease; PD, progressive disease.

Patients and Methods

Patients. Postmenopausal women aged 55–75 years with operable, Stage II or IIIA, histologically confirmed invasive breast cancers were enrolled. Patients were confirmed positive for ER or progesterone receptor (PgR) by immunohistochemical staining (≥10% nuclear staining was defined as positive). Expression of human epidermal growth factor receptor 2 (HER2) was determined immunohistologically with the Herceptest (Dako, Glostrup, Denmark). Positive in HER2 status was defined as either 3+ or 2+ with confirmed *c-erbB2* gene amplification by the FISH test. All patients were judged by their primary physicians as having a good performance status (PS; 0–1) and an indication for neoadjuvant hormone therapy after consideration of other treatment options such as surgical therapy and neoadjuvant chemotherapy.

This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research of the Ministry of Health, Labour and Welfare of Japan. Approval was obtained from the institutional review board at each study center. Written informed consent was obtained from all patients before enrolment.

Treatment scheme. The patients' lesions were measured by palpation, ultrasound and computed tomography or magnetic resonance imaging. Surgical procedures were determined based on the initial examination; axillary lymph node metastasis was also assessed.

Patients were initially treated with 25 mg of exemestane (Aromasin®; Pfizer Inc. Tokyo, Japan) once daily, orally, for 16 weeks. Clinical response was assessed by comparing the longest diameter of the target lesions with the baseline measurement based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Patients with progressive disease (PD) were withdrawn from the study and the remainder continued to receive exemestane for a further 8 weeks, for a total treatment period of 24 weeks. At Week 24, the clinical response was re-evaluated using the same criteria as at Week 16. Patients classified as showing CR, PR or stable disease (SD) at Week 24 underwent surgery as appropriate; patients classified as PD either underwent surgery or commenced another treatment. After surgery, patients classified as CR, PR or SD continued to receive exemestane for postoperative adjuvant hormone therapy for ≥5 years, including the neoadjuvant treatment period. Radiotherapy and drug therapy other than hormone therapy could be given concomitantly at the investigator's discretion. Postoperative treatment was not pre-specified for patients with PD.

Study end points. The primary end points were objective response rates (ORR) and safety after 16 and 24 weeks of

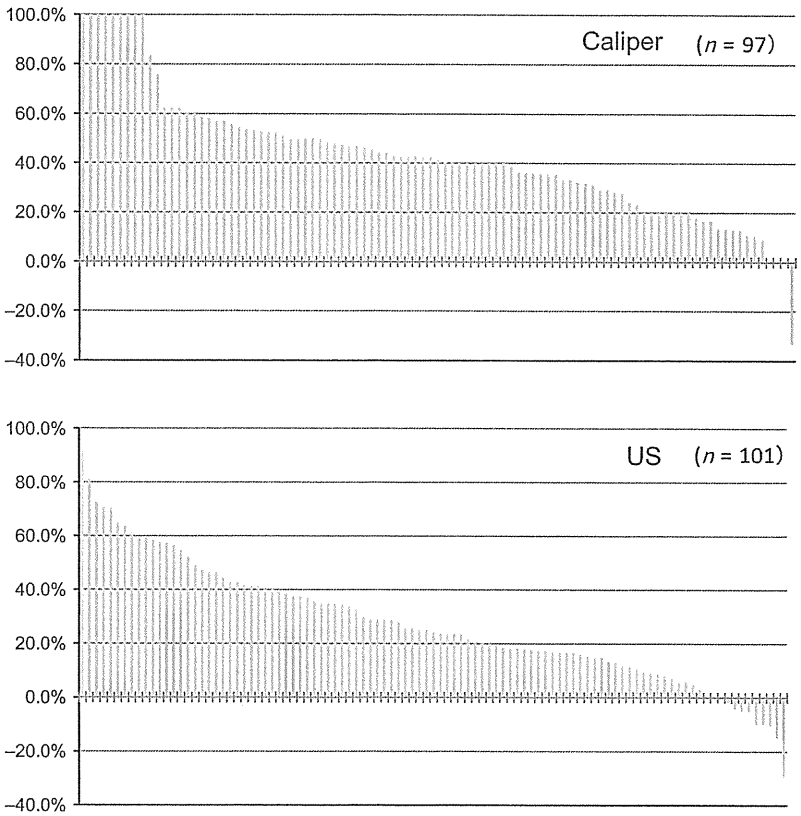

Fig. 2. Waterfall plot analysis of clinical response at 24 weeks evaluated by caliper and ultra sound (US). Horizontal axis indicates data from each patient and vertical axis, the reduction rate of tumor size evaluated by indicated modality. Negative values on vertical axis indicates tumor progression.

Table 3. Rates of breast conserving surgery in pre-treatment estimation and surgery undergone after treatment

		Post treatment (underwent)			Total
		Mastectomy	BCS	Without surgery	
Estimation pre-treatment	Mastectomy	14	40	5	59 (50.9%)
	BCS	5	49	3	57 (49.1%)
Total		19 (16.4%)	89 (76.7%)	8 (6.9%)	116

BCS, breast conserving surgery.

treatment in intent to treatment analysis. Secondary end points were rates of breast-conserving surgery and mastectomy, nodal status, biomarker changes, pathological response and Allred score. Correlations between the pre-treatment Ki67 labeling index and its changes by treatment and therapeutic effects were also investigated.

Safety assessments. Adverse events (defined as the development of a new medical condition or the deterioration of a pre-existing medical condition) were recorded every 4 weeks, and were graded according to the National Cancer Institute, Common Toxicity Criteria version 3.0. Pre-specified adverse events were hot flushes, sweating, headache, dizziness, fatigue, nausea/vomiting, appetite loss, weight gain, hypertension, vaginal bleeding, joint pain and bone fracture.

Central biomarker analysis. In order to determine the suitability for further immunohistochemical (IHC) analyses and then for the evaluation of pathological response, initially, one 4-μm section of each submitted paraffin blocks of pre- and post-treatment specimens of 107 patients who underwent surgery were stained with H&E to verify an adequate number of invasive breast carcinoma cells and the quality of fixation for this study. Serial tissue sections were then prepared from selected blocks and immunohistochemistry was performed to immunolocalize ER, PgR, HER2 and Ki67 as described previously.[18–20] In brief, IHC staining was performed by streptavidin–biotin amplification method using a Histofine Kit (Nichirei, Tokyo, Japan). The Ki67 was stained after overnight preparation using the following antibody dilution: 1:100 (Dako). The ER, PgR and HER2 were stained automatically (Ventana, Tucson, Arizona, USA). The immunostained slides were independently evaluated by three of the authors (NC, TS, HS) who were blinded to clinical outcome of individual patients. The immunoreactivity of ER and PgR was scored by assigning proportion and intensity scores according to Allred's procedure.[18] The membrane staining pattern was estimated in HER2 immunostaining and scored on a scale of 0–3.[19] Evaluation of Ki67 was performed by counting 1000 carcinoma cells or more from each patient and the percentage of immunoreactivity was subsequently determined by a labeling index.[20]

Pre-operative endocrine prognostic index (PEPI). According to an algorithm proposed by Ellis's group, we calculated the total PEPI score for each patient. Briefly, the PEPI score is the sum of the risk points derived from the pathological T stage, pathological nodal stage, Ki67 level and ER Allred score status of the surgical specimen.[16] High PEPI scores correlate with high risk of relapse.

Statistical analysis. The target sample size of this study (110 patients) was calculated based on clinical data obtained in previous studies of aromatase inhibitors and assumptions regarding the expected number of dropouts. Tumor response was evaluated by summary statistics and calculated together with 95% confidence intervals. The distribution of adverse events was summarized and their incidence rates calculated for each grade of severity (grades 1–4). Univariate and multivariate analyses

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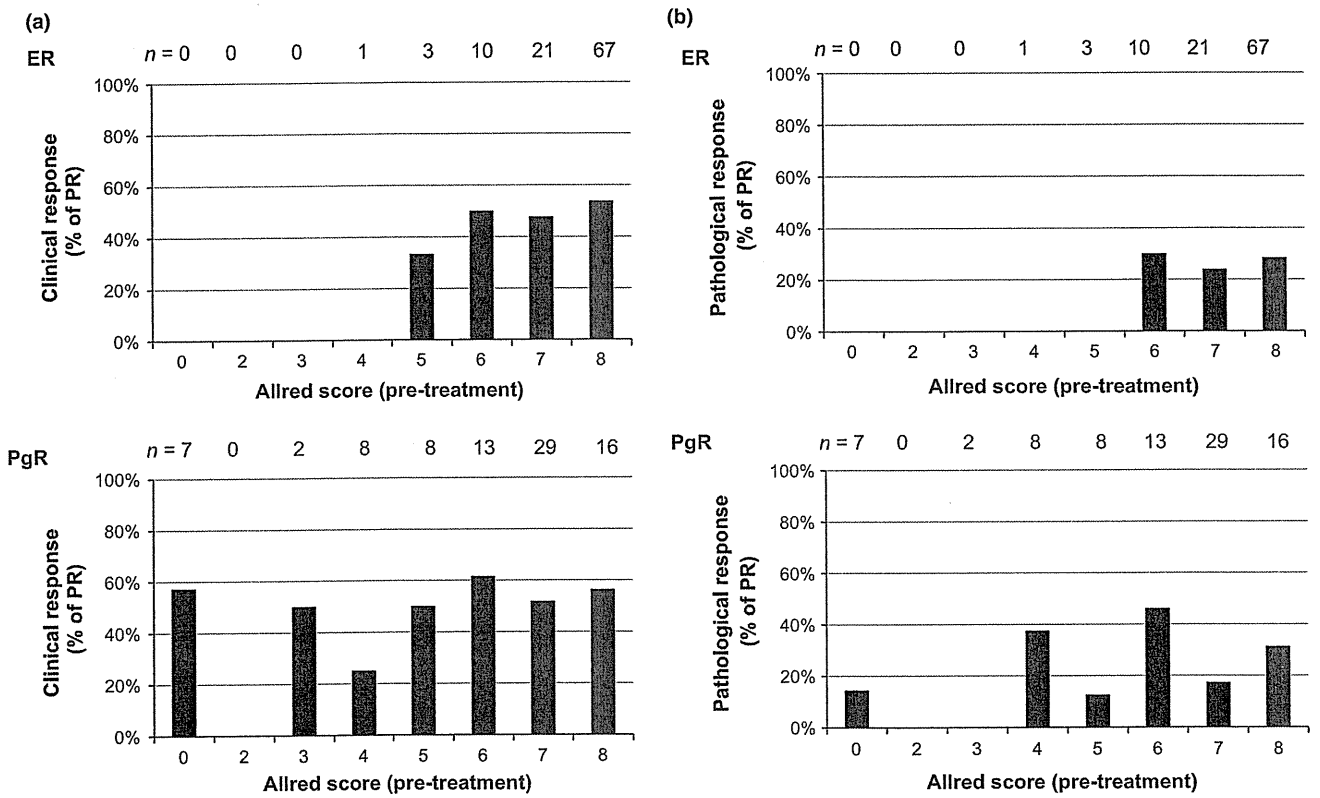

Fig. 3. (a) Clinical response rates and centrally evaluated ER and PgR Allred scores. Numbers above the graph indicate total patient counts in each Allred score group. (b) Pathological response rates and centrally evaluated ER and PgR Allred scores. Numbers above the graph indicate total patient counts in each Allred score group.

were performed with a logistic regression model, Pearson's chi-squared test and multiple logistic regression models, respectively.

Results

Patients. Between March 2006 and December 2007, 116 patients were enrolled; their baseline characteristics are displayed in Table 1. All patients were defined as ER-positive; 80 (68.9%) were PgR-positive and 3(2.5%) were HER2-positive by investigator evaluation. During the first 16 weeks, ten patients discontinued neoadjuvant exemestane treatment because of PD (four patients), investigator decision (one patient), adverse events (two patients, one of whom was not evaluable at Week 16), or the patient's decision (three patients, two of whom were not evaluable at Week 16) (Fig. 1). A total of 106 patients were included in the 8-week extension and 102 patients completed 24 weeks of exemestane neoadjuvant treatment. Of 102 patients who completed the extension study, 99 underwent surgery.

Clinical response. The clinical response was determined by the investigators evaluation based on the combination of caliper measurement and other image modalities such as ultrasound (US), computed tomography (CT) and MRI as defined by protocol. In intent to treat (ITT) analysis with 116 patients, at Week 16, 55 patients (47.4%) achieved PR and 54 patients (46.6%) showed SD. Four patients (3.4%) were considered to have PD (Table 2). The ORR at Week 24 analysis was 50.9%. In detail, no patient achieved CR, 59 (50.9%) achieved PR, 41 (35.3%) had SD and PD was noted in eight patients (6.9%), including four PD cases at Week 16. There was no significant difference in ORR between Weeks 16 and 24 ($P = 0.54$, McNemar's test). As a reference, ORR in patients who could complete the 24-week exemestane course was 57.8% (59/102). Although ORR at 24 weeks treatment was about 50%, most patients experienced shrinkage of the tumor with no regard to the evaluation with caliper or ultrasound as shown in the Waterfall plot analysis (Fig. 2).

Rate of conversion to breast conserving surgery (BCS). Based on assessments before neoadjuvant hormone therapy, 59 (50.9%) and 57 (49.1%) of 116 patients were indicated for total mastectomy and BCS, respectively (Table 3). At Week 24, 19 (16.4%) and 89 (76.7%) patients underwent total mastectomy and BCS, showing an increase in the rate of BCS. Of the 59 patients originally indicated for total mastectomy, 14 underwent total mastectomy, 40 were converted to BCS and five received no surgical treatment because of multiple reasons as already described. Of the 57 patients originally indicated for BCS, 49 underwent BCS, five underwent total mastectomy and three received no surgical treatment, respectively. Among five patients whose surgery were converted from BCS to mastectomy after neoadjuvant treatment, four were due to the patient's preference for mastectomy rather than BCS, and one patient showed progression of the primary tumor.

Safety. The most frequently seen adverse events were an abnormal increase in liver enzyme levels (SGOT, SGPT, ALP), hot flushes, joint pain, hypoalbuminuria and elevated creatinine and bilirubin levels. None of these adverse events was deemed to be severe in intensity. The only Grade 3 adverse events were elevated liver enzymes in four cases. No other adverse events of Grade 3 or 4 were noted in this study. Overall, two patients discontinued the study during the initial 16-week phase because

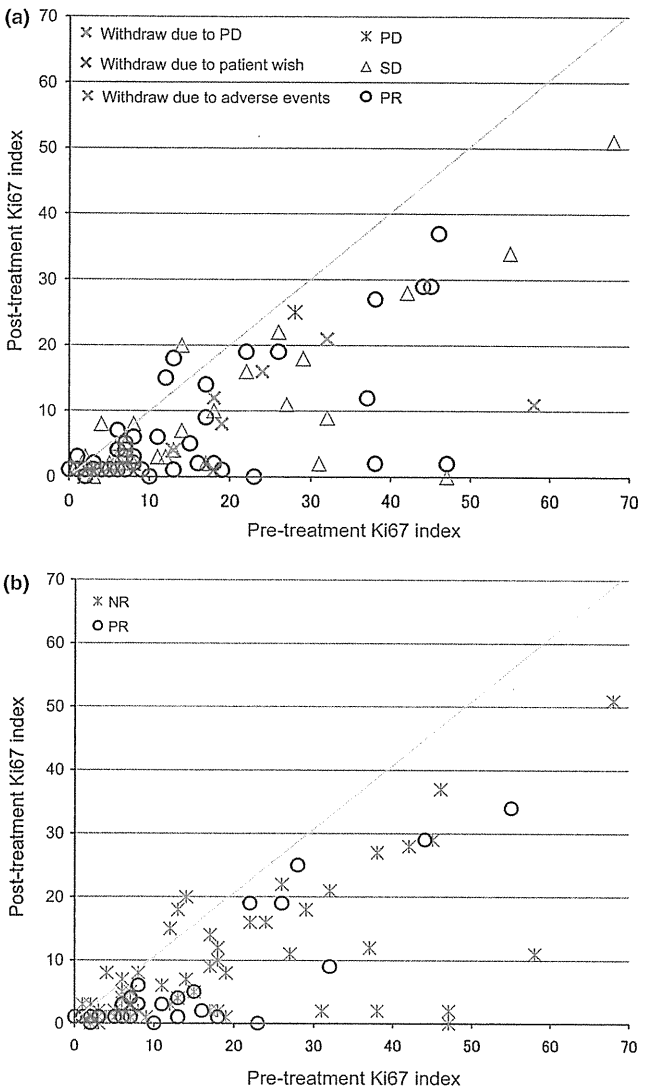

Fig. 4. (a) Correlation between pre- and post-treatment Ki67 index and clinical response. PD, progressive disease; PR, partial response; SD, stable disease (n = 93). (b) Correlation between pre-and post-treatment Ki67 index and pathological response. NR, non-response; PR, Partial response (n = 90).

of adverse events. One patient had Grade 3 AST and ALT elevations, and the other patient had Grade 2 AST and Grade 3 ALT elevations. No patient discontinued the study during the 8-week extension because of adverse events. Details are described in a Data S1.

Centrally evaluated pathological response. Tissue sections from 94 patients among 107 surgical specimens, from pretreatment core needle biopsies and final surgical specimens, were available to be assessed for changes in cellularity and degree of fibrosis in H&E stained slides. Pathological response was categorized using the modified criteria previously described by Miller *et al.*,[21] and assessed as follows: complete when there was no evidence of malignant cell at the original tumor site, partial response when histological decrement in cellularity and/or increment in fibrosis was detected, or no change/non-response. All of the pathological responders were partial response 28 cases (29.8%) while non-responders comprised 66 cases (70.2%).

Centrally evaluated ER/PgR Allred scores and Ki67 labeling index. Paraffin embedded slides for biomarker studies were submitted to the Department of Pathology, Tohoku University School of Medicine, which served as the central laboratory as described in Patients and Methods. Allred scores of ER and PgR staining before treatment (102 samples and 83 samples, respectively, were available from 116 enrolled patients) were analyzed for evaluating the correlation to clinical response. Clinical objective response was observed in patients with score 5 or greater in ER expression, and had a tendency to increase in higher score group (Fig. 3a). However, it was shown that in any PgR score patients could have a favorable clinical response.

Allred scores of ER and PgR staining of the same population were also assessed for correlation to pathological response (Fig. 3b). For ER, there was the same tendency that pathological responses were observed in higher Allred score group such as 6 or more. In PgR evaluation, there was no obvious correlation of pathological response to PgR score. Ninety-three pairs of core needle biopsies before treatment and tumor tissues after surgery were applied to Ki67 index evaluation.

Figure 4a shows the scatter plot of pre-treatment and post-treatment Ki67 indices with information of clinical response. Plots located under the curve of $y = x$ indicate the tumors that Ki67 decreased by neo-adjuvant exemestane treatment. At first, there was no correlation between the pre-treatment Ki67 index and clinical responses (PR versus others, $P = 0.52$). Overall, significant reduction in the Ki67 index was observed at Week 24 compared to the baseline (Median [range]: pre, 11 [0–68]; post, 3 [0–51], $P < 0.0001$, paired Student's t-test). Analysis of the Ki67 index according to clinical response revealed that the Ki67 index was significantly decreased in patients with both PR and SD ($P < 0.0001$ for both). In patients who achieved PR, the median Ki67 index decreased from 9 (range 0–47) to 2 (range 0–37) after neoadjuvant treatment with exemestane, while that in patients with SD decreased from 8 (range 1–68) to 3 (range 0–51). No association was observed between changes in Ki67 index and clinical responses. A noteworthy observation in Figure 4a was that there were no PD patients during the 24-week treatment period, if pretreatment tumor expressed a Ki67 index of 15% or less.

Correlation of Ki67 index to pathological response was also evaluated in the same manner (Fig. 4b). In patients who achieved pathological partial response (PR), the median Ki67 index decreased from 10 (range 0–55) to 2 (range 0–34) after neoadjuvant treatment, while that in patients with NR decreased from 12 (range 1–68) to 4 (range 0–51). Statistically, the Ki67 index dropped significantly in both pathological responders and non-responders ($P < 0.0001$). There was no statistical correlation between pre-treatment Ki67 index and pathological response. Nevertheless, all cases that showed increases of Ki67 index after the treatment were evaluated as pathological non-responders.

The results of univariate and multivariate analysis with respect to clinical and pathological response are summarized in Table 4. Young age, small tumor size and high ER score were associated with clinical response: PR + SD versus PD.

The relationship between the PEPI score and responses is described in Table 5. There was no correlation between PEPI score and clinical response ($P = 0.99$, chi-squared test). Nevertheless, a trend was found that that patients with PEPI score of 4 or more unlikely to have pathological response ($P = 0.053$, chi-squared test).

Discussion

The objectives of neoadjuvant hormone therapy for breast cancer are to increase the likelihood for patients to undergo

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Table 4. Univariate and multivariate analysis with respect to clinical and pathological response

(a) Outcome = clinical response (PR versus SD + PD)

Variables	Univariate analysis				Multivariate analysis (full model)				Multivariate analysis (stepwise)			
	P-value	Odds	95%CI		*P*-value	Odds	95%CI		*P*-value	Odds	95%CI	
Age	0.233	0.963	0.904	1.024	0.295	0.959	0.884	1.037	0.233	0.963	0.904	1.024
T	0.516	0.550	0.088	3.428	0.726	0.683	0.071	6.507				
N (N2–3 *vs* N0)	0.892	0.944	0.413	2.159	0.308	1.726	0.609	5.166				
ER (score)	0.356	1.253	0.777	2.071	0.269	1.360	0.790	2.422				
PR (score)	0.769	1.030	0.842	1.261	0.901	0.986	0.783	1.232				
HER2 (positive versus negative)*	0.189				0.200	5553.597	0.000	0.000				
Ki67 index	0.254	0.984	0.956	1.011	0.358	0.983	0.000	0.000				
Model *P*-value					0.617				0.233			
Model R2					0.050				0.009			

(b) Outcome = clinical response (PR + SD versus PD)

Variables	Univariate analysis				Multivariate analysis (full model)				Multivariate analysis (stepwise)			
	P-value	Odds	95%CI		*P*-value	Odds	95%CI		*P*-value	Odds	95%CI	
Age	0.067	0.900	0.794	1.007	0.227	0.903	0.741	1.063	0.072	0.867	0.717	1.012
T	0.008	0.108	0.015	0.758	0.023	0.032	0.001	0.608	0.006	0.019	0.001	0.306
N (N2–3 *vs* N0)	0.010	0.176	0.041	0.754	0.389	0.436	0.056	2.935				
ER (score)	0.024	2.227	1.117	4.558	0.009	3.318	1.339	11.136	0.002	4.046	1.674	12.841
PR (score)	0.161	1.225	0.915	1.603	0.649	1.095	0.708	1.579				
HER2 (positive versus negative)*	0.668				0.699	2242.634	0.000	0.000				
Ki67 index	0.050	0.959	0.920	1.000	0.085	0.952	0.000	0.000	0.102	0.958	0.905	1.009
Model *P*-value					0.008				0.001			
Model R2					0.367				0.353			

(c) Outcome = pathological response

Variables	Univariate analysis				Multivariate analysis (full model)				Multivariate analysis (stepwise)			
	P-value	Odds	95%CI		*P*-value	Odds	95%CI		*P*-value	Odds	95%CI	
Age	0.337	0.965	0.893	1.038	0.498	0.969	0.879	1.062				
T	0.252	0.000			0.206	0.000	0.000	3.280				
N (N2–3 *vs* N0)	0.058	0.297	0.080	1.101	0.274	0.466	0.000	0.000	0.046	0.297	0.065	0.979
ER (score)	0.329	1.325	0.767	2.545	0.282	1.453	0.000	0.000				
PR (score)	0.510	1.081	0.864	1.409	0.771	1.040	0.000	0.000				
HER2 (positive versus negative)	0.156	5.000	0.434	57.547	0.581	2.447	0.000	0.000				
Ki67 index	0.555	0.991	0.957	1.021	0.428	0.982	0.000	0.000				
Model *P*-value					0.379				0.046			
Model R2					0.087				0.035			

PR, partial response; SD, stable disease; PD, progressive disease. *All HER2 positive cases (n = 2) were PR, so that odds calculation could be unstable.

Table 5. Association between tumor response and preoperative endocrine prognostic index

Response	PEPI			*P* value (chi-squared test)
	0	1–3	4–	
Pathological responder	9	11	3	$P = 0.112$
Pathological non-responder	14	26	21	(0–3 *vs* 4–:0.053)
Clinical PR	13	22	12	$P = 0.988$
Clinical SD	10	17	10	(0–3 *vs* 4–: 0.88)

PEPI, preoperative endocrine prognostic index; PR, partial response; SD, stable disease.

BCS rather than mastectomy, and to expect benefits from a drug that is used in adjuvant therapy. With the introduction of third-generation AI such as anastrozole, exemestane and letrozole, the response rate in hormone-sensitive breast cancer patients has increased. In addition, several clinical studies have reported that neoadjuvant hormone therapy using AI improves the rate of BCS. For example, in the P024 study,[9] 4 months of neoadjuvant hormone therapy using letrozole was compared with tamoxifen in 337 postmenopausal patients with hormone receptor-positive early breast cancer. The ORR and the rate of BCS were significantly higher in the letrozole group (55% and 45%, respectively) than in the tamoxifen group (36% and 35%, respectively). Similarly, in the large-scale PROACT study, 314 patients received only neoadjuvant hormone therapy with anastrozole or tamoxifen for 3 months, and the ORR and rate of BCS were significantly higher in the anastrozole group (49.7% and 43.0%, respectively) than in the tamoxifen group (39.7% and 30.8%, respectively).[10] In the ABCSG-17 study, which used exemestane,[8] the ORR was 34% in hormone receptor-positive breast cancer patients who received 4 months of neoadjuvant treatment with exemestane, and the rate of BCS was 76%.

In the present study, the ORR for exemestane was 47.4% at Week 16 and 50.9% at Week 24 in ITT analysis, which were comparable with the results of the previous studies. Although the response rate at Week 24 was slightly higher than that at Week 16, this difference was not significant. Notably, of the 55 patients with PR at Week 16, 45 patients maintained PR at Week 24 and, of the 54 patients with SD at Week 16, 14 had PR at Week 24 and 35 had SD. These results suggest that 24 weeks of continuous treatment with exemestane induces sustained tumor regression. The response rate in patients who could complete 24 weeks of exemestane was 57.8%.

The proportion of patients suitable for BCS was 49.1% in the evaluation performed before treatment, but improved to 76.7% after 24 weeks of neoadjuvant hormone therapy. Notably, among 59 patients who are initially candidates for mastectomy, 40 patients (67.8%) could undergo BCS. This observation is almost identical to the recent phase II study in which 30 (65%) of 46 patients who were initially marginal for BCS underwent BCS after 16–24 weeks of treatment with letrozole.[22] These improvements seem to be due to universal tumor shrinkage in the majority of the patients, as shown in the Waterfall plot analysis. Toxicity was acceptable. Therefore, treatment with exemestane for 24 weeks was effective in promoting tumor regression and improving BCS rates, with an acceptable tolerability. It has also been reported that continuing letrozole in responding patients beyond 3–4 months achieves further clinical reduction in tumor size.[23] A treatment period of 24 weeks is considered to achieve the efficacy and safety levels required for neoadjuvant therapy.

The ER status is an established predictive factor for the response to endocrine therapy. In the central laboratory evaluation of ER IHC, there was a tendency for higher ER Allred scores in a tumor to correlate with preferable response both for clinical and pathological outcomes. Limitation of this finding was all patients enrolled to this study were above score 4 in the ER evaluation and 65.7% were at score 8. Progesterone receptor expression before treatment predicted neither clinical response nor pathological response. Although further studies are required with a central laboratory determination, this result indicates that tumors with lower or absent expression of PgR should not be excluded from neoadjuvant AI treatment.

The percentage of MIB1/Ki67-positive cells (Ki67 index) is considered to be a prognostic factor for breast cancer patients. In the P024 study, although no correlation was observed between the Ki67 index before neoadjuvant hormone therapy and the recurrence rate, the Ki67 index after neoadjuvant hormone therapy (at surgery) was correlated with the recurrence rate.[16] The Ki67 index and progression free survival (PFS) has also been studied in patients receiving neoadjuvant hormone therapy with anastrozole, with reported similar findings.[17] Miller *et al.*[21] evaluated 63 postmenopausal breast cancer patients after 3 months of neoadjuvant hormone therapy with letrozole and reported that the clinical response rate was 85% (41 of 48) in patients with a ≥40% decrease in the Ki67 index, and that a ≥40% decrease in Ki67 index was observed in 11 (70%) of 15 patients with SD.

In the present study, the Ki67 index decreased significantly between baseline and endpoint but the change ratio showed no significant correlation with clinical objective response. As in previous reports, the pretreatment Ki67 index had no predictive value for the probability of clinical objective response and pathological response, indicating that patients who have higher Ki67 tumors still may achieve clinical and/or pathological responses with neoadjuvant exemestane treatment. On the other hand, there were no clinical PD patients during the 24-week treatment period (patients withdraw due to PD and PD, Fig. 4a), if a primary tumor expressed a Ki67 index of 15% or less. In addition, an increase of Ki67 index after treatment, even among tumors with of Ki67 index less than 15%, meant no chance of pathological response. The prognostic impact of clinical non-responders and of pathological non-responders is not fully understood yet, and these are crucial issues to be investigated with a long-term follow-up.[24,25] In this study, a PEPI score[16] was used as a prognostic indicator, and correlation to clinical and pathological responses was investigated. The results implied that pathological non-response might correlate to the poor prognosis, which was shown as a PEPI score of 4 or higher. In future studies, the relationship between pathological response and biomarker changes will be assessed on survival outcomes.

From our investigation of the Ki67 index, monitoring of changes in Ki67 index during treatment, as well as primary treatment stratification with the initial Ki67 index, is essentially important to identify a more appropriate combination of neoadjuvant hormone therapy and chemotherapy, and also to realize the selection of an optimal regimen for each individual patient. For the future, it is warranted to analyze hormone receptor associations and crosstalks with other growth axes such as the HER family in further depth.

In conclusion, this study revealed that 24 weeks of neoadjuvant treatment with exemestane is safe and effective in patients with postmenopausal, hormone receptor-positive breast cancer, achieving ORR values of 50.9%. Furthermore, the number of patients considered candidates for BCS was increased by neoadjuvant treatment. The Ki67 index decreased significantly in patients with PR and SD after treatment. The treatment of hormone responsive breast cancer patients will be personalized with clinical and/or pathological response and biomarker determinations for greater efficacy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Adverse events (number of patients).

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EPIDEMIOLOGY

Economic evaluation of the 70-gene prognosis-signature (MammaPrint®) in hormone receptor-positive, lymph node-negative, human epidermal growth factor receptor type 2-negative early stage breast cancer in Japan

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Abstract The 70-gene prognosis-signature is validated as a good predictor of recurrence for hormone receptor-positive (ER+), lymph node-negative (LN−), human epidermal growth factor receptor type 2-negative (HER2−) early stage breast cancer (ESBC) in Japanese patient population. Its high cost and potential in avoiding unnecessary adjuvant chemotherapy arouse interest in its economic impact. This study evaluates the cost-effectiveness of including the assay into Japan's social health insurance benefit package. An economic decision tree and Markov model under Japan's health system from the societal perspective is constructed with clinical evidence from the pool analysis of validation studies. One-way sensitivity analyses are also performed. Incremental cost-effectiveness ratio is estimated as ¥3,873,922/quality adjusted life year (QALY) (US$43,044/QALY), which is not more than the suggested social willingness-to-pay for one QALY gain from an innovative medical intervention in Japan, ¥5,000,000/QALY (US$55,556/QALY). However, sensitivity analyses show the instability of this estimation. The introduction of the assay into Japanese practice of ER+, LN−, HER2− ESBC treatment by including it to Japan's social health insurance benefit package has a reasonable chance to be judged as cost-effective and may be justified as an efficient deployment of finite health care resources.

Keywords Adjuvant therapy · Breast cancer · Cost-effectiveness · Gene diagnosis · 70-gene prognosis-signature

Introduction

Oestrogen receptor-positive (ER+) diseases have a large share in breast cancer, which amount to 76.9% in Japan [1]. And among those, 61.0% of them are node-negative (LN−) and human epidermal growth factor receptor type 2-negative (HER2−) diseases [1]. After the primary surgery on these cases, a difficult clinical decision must be made about whether to add systemic chemotherapy to standard adjuvant endocrine therapy. Whereas the effectiveness of adjuvant endocrine therapy has been established [2], the use of adjuvant chemotherapy in ER+, LN−, HER2− diseases is still under debate [3].

The 70-gene prognosis-signature (MammaPrint®) is a prognostic tool, which was developed to predict the recurrence in LN− diseases [4] and individualise adjuvant therapy for early stage breast cancer (ESBC) patients. The usefulness of the tool has been validated in several studies of retrospective patients [5–7] including Japanese patients [8]. Patients classified as at low risk of recurrence by the assay may need adjuvant endocrine therapy only, while those at high risk may require additional treatment with chemotherapy. The assay was cleared for younger patients by the US Food and Drug Administration in 2007, of which age indication has been later extended to older patients [9].

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And it has been included in St Gallen consensus statement since 2009 [3].

One of the notable attributes of the assay is its high cost: ¥380,000 (US$4,222; US$1 = ¥90). Coupled with its potential cost-saving effect by avoiding expensive and highly toxic chemotherapy, the economic evaluation of the assay has aroused great interests among health managers and oncologists. A cost-effectiveness analysis regarding ER+, LN− diseases among younger and older patients was reported from The Netherlands [10], which found the use of the assay cost-effective to guide adjuvant treatment decision compared to both St Gallen consensus and Adjuvant! Online software (http://www.adjuvantonline.com). Another cost-effectiveness analysis regarding ER+, LN− diseases among younger patients was reported from the US [11], which also found the use of the assay cost-effective compared to Adjuvant! Online software. However, no cost-effectiveness study has been reported from Japan or Asian countries, although the clinical utility of the assay has been validated in corresponding population [8].

In this study, we analyse the cost-effectiveness of introducing the assay into Japanese practice of ER+, LN−, HER2− ESBC treatment. In the current Japanese context, an introduction with limited indication such as ER+ and HER2− diseases is an agendum for health managers and oncologists, since ER− and HER2+ diseases may have clearer indication for adjuvant chemotherapy and anti-HER2 therapy, respectively, without the use of 70-gene prognosis-signature. The results would be of help in considering the inclusion of the assay in the benefit package of Japan's social health insurance, as well as interesting to health managers and oncologists in Asian countries.

Methods

We conduct a cost-effectiveness analysis of introducing the 70-gene prognosis-signature into the current Japanese practice of ER+, LN−, HER2− ESBC treatment with decision tree and Markov modelling including sensitivity analysis from the societal perspective. Since we have already developed an economic model depicting the courses followed by the target patients elsewhere [12, 13], which are economic evaluations of the 21-gene signature (Onco*type* DX®), we combine this model with clinical evidence depicting treatment decision changes among target patients. We also carry out a deliberate literature survey to find out the best available clinical evidence. The PubMed database and Igaku Chuo Zasshi (Japana Centra Revuo Medicina), a Japanese medical literature database, are accessed with combinations of relevant terms such as 70-gene prognosis-signature, MammaPrint, etc.

Treatment decision change and recurrence

We assume that the current Japanese practice of ESBC treatment is according to St Gallen 2009 criteria without the use of multigene assays based on a survey of Japanese experts practice [14] and current consensus guidelines [15], in which the use of Adjuvant! Online software is not recommended. Then we search for reports on clinical outcomes of target patients to make a comparison between St Gallen criteria-guided treatment without multigene assays and the 70-gene prognosis-signature-guided treatment. We assume 100% usage of the gene signature when it is included into the Japanese social health insurance benefit package. However, data of such comparison is not available in the Japanese validation study [8]. It reports the distant metastasis-free survival rates according to the 70-gene prognosis-signature, but not according to St Gallen 2009 criteria. And we have no access to the data to implement further analysis for our economic modelling. However, Retèl et al. [10] is a unique report of the comparison, which presents the results of a pooled prognosis analysis of three validation studies [5–7, 10]. Table 1 shows the 5-year distant recurrence rates by St Gallen criteria-guided treatment and the 70-gene prognosis-signature-guided treatment. In St Gallen criteria-guided treatment, 89.84% of the patients are classified as at high risk of distant recurrence and are given adjuvant chemotherapy, while 10.16% are classified as at low risk and are treated with adjuvant endocrine therapy only. Their 5-year incidence rates of distant recurrence for the first 5 years and the second 5 years are 10.95 and 7.79% in patients at high risk and 3.23 and 10.0% in patients at low risk, respectively. In the 70-gene prognosis-signature-guided treatment, 46.23% of the patients are classified as at high risk and are given adjuvant chemotherapy, while 53.77% are classified as at low risk and are treated with adjuvant endocrine therapy only. Their 5-year incidence rates of distant recurrence for the first 5 years and the second 5 years are 17.73 and 10.35% in patients at high risk and 3.66 and 6.33% in patients at low risk, respectively. The reduction of the use of chemotherapy using the 70-gene prognosis-signature instead of St Gallen criteria is 43.61%.

Patient cohort

ER+, LN−, HER2− ESBC patient cohort at the age of 55 is targeted for our base-case analysis. The age, 55 years old, is chosen according to the average age of equivalent patient population in a Japanese nationwide cancer registry [1].

Decision tree and Markov model

Our economic model shown in Fig. 1 incorporates clinical courses followed by ER+, LN−, HER2− ESBC patients,