Table 3 Costs

	Base-case value	Range tested in sensitivity analyses	Source
21-gene RT-PCR[a] assay (Oncotype DX® Breast Cancer Assay)	¥450,000	Change by ±50%	[15, 17]
Adjuvant therapy			
Endocrine therapy, per year	¥534,610	Change by ±50%	[15, 17, 27, 28]
Chemotherapy	¥343,001	Change by ±50%	[15, 17, 27, 28]
Trastuzumab, per year	¥3,105,120	Change by ±50%	[15, 17, 27, 28]
Treatment for toxicity			
Major	¥173,352	Change by ±50%	[15, 17, 27–30]
Monitoring			
After adjuvant therapy without recurrence, per year	¥25,340	Change by ±50%	[15, 17, 27, 28]
Treatment for distant recurrence			
Endocrine therapy and chemotherapy, per year	¥558,458	Change by ±50%	[15, 17, 27, 28]
Trastuzumab, per year	¥3,105,120	Change by ±50%	[15, 17, 27, 28]
End-of-life, per year	¥1,315,143	Change by ±50%	[15, 31]

[a] Reverse transcriptase-polymerase chain reaction

other regimens. These cost ¥343,001 (US$3,430) per year. Adjuvant trastuzumab costs ¥3,105,120 (US$31,051) per year, of which administration is assumed to be 1 year.

There are three levels of toxicity in the decision tree. However, the cost of major toxicity only is estimated as ¥173,352 (US$1,734), which includes an unplanned hospitalisation for 1 month in two fifths of the cases and rescue treatment at outpatient clinic in three fifths of the cases [29, 30]. For minor toxicity, from which 60% of patients suffer, the cost is included in the cost of adjuvant chemotherapy, since prophylactic use of antiemetic, for example, is routinely applied these days. And the clinical course of fatal toxicity is so diverse and not fit to costing by modelling here, therefore, its cost is assumed to be the same as the end-of-life treatments cited from the literature [31].

After the completion of adjuvant therapy, patients are assumed to visit their physician twice a year for the purpose of monitoring, which costs ¥25,340 (US$253) per year.

There are various options of treatments for the distant recurrence depending on regimens used in the adjuvant therapy. Yet, we assume crossover endocrine treatments followed by capecitabine within the 1st year as typical 1st line and 2nd line therapies for our hypothetical cohort, which cost ¥558,458 (US$5,585) per year. We further assume that this cost is applicable to 2nd year and thereafter. For HER2+ patients, trastuzumab is administered continuously, so the cost comes up as the same as the adjuvant therapy, ¥3,105,120 (US$31,051) per year.

The cost of the end-of-life treatments are ¥1,315,143 (US$13,151) per year [15, 31], which is also used as the cost of treating fatal toxicity.

Costs are also discounted at a rate of 3% [26].

Comparison of scenarios

Incremental cost-effective ratios (ICER) are calculated for two scenarios:

$$\mathrm{ICER} = \frac{\mathrm{Cost}_{\mathrm{RS-guided\ treatment}} - \mathrm{Cost}_{\mathrm{St\ Gallen\ 2009\ criteria-guided\ treatment}}}{\mathrm{Effect}_{\mathrm{RS-guided\ treatment}} - \mathrm{Effect}_{\mathrm{St\ Gallen\ 2009\ criteria-guided\ treatment}}}$$

Sensitivity analysis

In order to appraise the stability of ICERs against assumptions made and uncertainty of adopted values of probabilities, utility weights, and costs in our economic model, one way sensitivity analyses are performed. The age of cohort is changed to 45 and 65 years old. DFRS5s and DFRS10s shown in Table 1 are changed according to the reported 95% confidence interval. The use of adjuvant chemotherapy in St Gallen 2009 criteria-guided treatment is changed from 0 to 100% of no definitive indication cases. The propensity to alter treatment among patients classified as intermediate scores by RS criteria reclassification is changed from 100 to 50%. As shown in Table 2,

Table 4 Results of cost-effectiveness analysis

Scenario	Treatment	Cost (¥)	Incremental cost (¥)	Effect (QALY[a])	Incremental effect (QALY)	Incremental cost-effectiveness ratio (¥/QALY)
Indication for LN−	St Gallen 2009 criteria-guided	3,627,193		19.48		
	RS criteria-guided	3,867,876	240,683	20.11	0.63	384,828
Indication for LN−/+	St Gallen 2009 criteria-guided	3,818,952		18.82		
	RS criteria-guided	4,088,987	270,035	19.29	0.47	568,533

[a] Quality adjusted life year

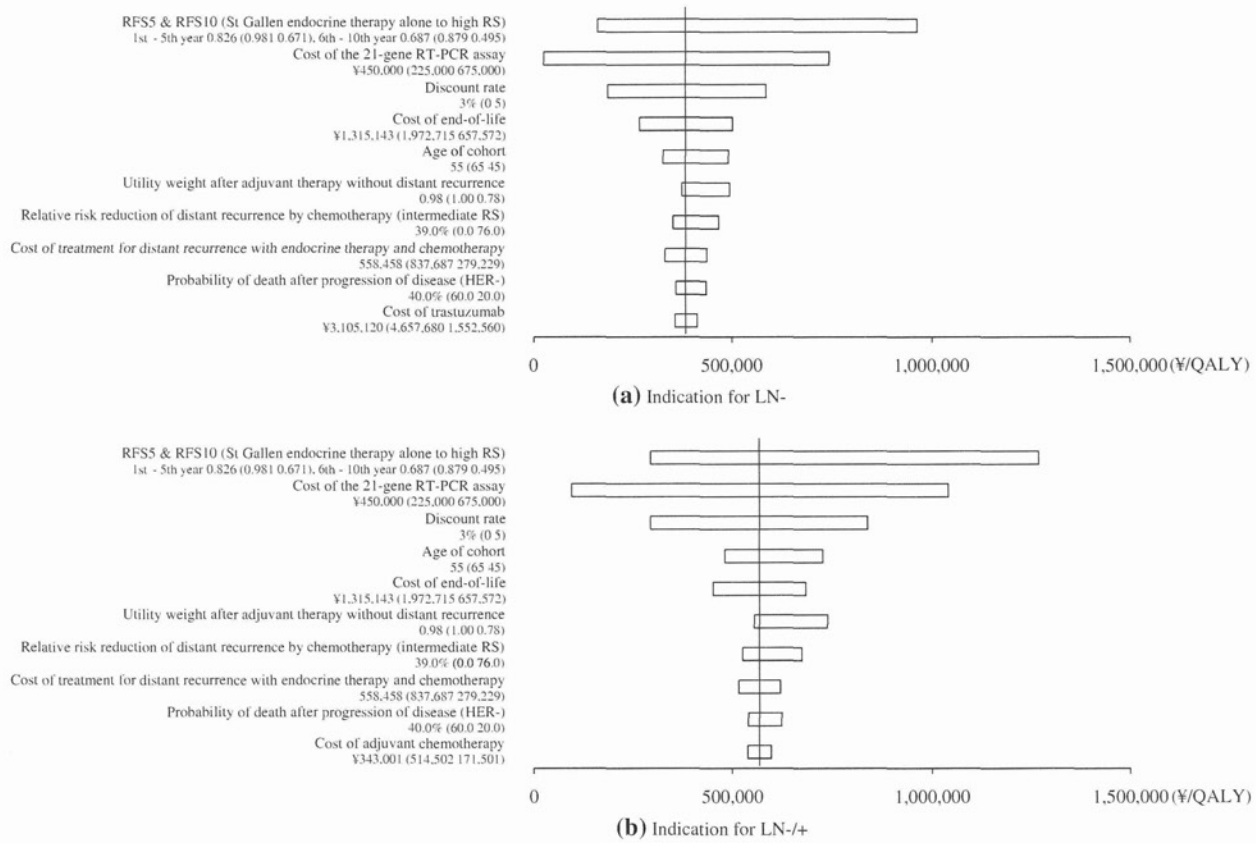

Fig. 2 Results of sensitivity analyses. **a** Indication for LN−, **b** Indication for LN−/+. *RT-PCR* reverse transcriptase-polymerase reaction, *RS* recurrence score

probabilities other than the relative risk reductions are changed by ±50%, while the relative risk reductions are changed according to the reported 95% confidence intervals of each value. The effectiveness of adjuvant trastuzumab is extended to 5 years. Utility weights are all changed by ±20%. And as shown in Table 3, costs are all changed by ±50%. Discount rate is also changed from 0 to 5%.

Additionally, in order to simulate the effect of limiting the indication of the assay to HER2− cases, we calculate the ICER with the probability of HER2+, 0%. This simulation assumes that the risk of recurrence and the benefit from chemotherapy are indifferent between HER2+ cases and HER2− cases.

Results

Cost-effectiveness

Table 4 shows the result of the cost-effective analysis of the 21-gene RT-PCR assay. As to the indication for

LN− scenario, the cost of RS criteria-guided treatment, ¥3,867,876 (US$38,679), exceeds that of St Gallen 2009 criteria-guided treatment, ¥3,627,193 (US$36,272), which results in a positive incremental cost of ¥240,683 (US$2,407). The effect in QALYs of RS criteria-guided treatment, 20.11 year, exceeds that of St Gallen 2009 criteria-guided treatment, 19.48 year, which results in a positive incremental effect of 0.63 year. The ICER is calculated as ¥384,828 (US$3,848) per QALY.

As to the indication for LN−/+ scenario, the cost of RS criteria-guided treatment, ¥4,088,987 (US$40,890), exceeds that of St Gallen 2009 criteria-guided treatment, ¥3,818,952 (US$38,190), which results in a positive incremental cost of ¥270,035 (US$2,700). The effect in QALYs of RS criteria-guided treatment, 19.29 year, exceeds that of St Gallen 2009 criteria-guided treatment, 18.82 year, which results in a positive incremental effect of 0.47 year. The ICER is calculated as ¥568,533 (US$5,685) per QALY.

Stability of ICER

Figure 2 shows the results of one way sensitivity analyses. Ten items of each of the two scenarios are listed by the order of the magnitudes of ICER change in terms of yen per QALY.

Items with the largest ICER change up to the third largest are common between the indication for LN− scenario and the indication for LN−/+ scenario. ICER is most sensitive to the change of DRF5 & DRFS10 of patients who are reclassified as high RS by the assay from endocrine therapy alone by St Gallen 2009 criteria, which ranges from ¥161,716 (US$1,617) to ¥964,027 (US$9,640), and from ¥295,348 (US$2,953) to ¥1,270,006 (US$12,700), respectively. Second, it is sensitive to the cost of the assay, which ranges from ¥25,660 (US$257) to ¥743,997 (US$7,440), and from ¥95,586 (US$956) to ¥1,041,480 (US$10,415), respectively. The ranges of ICER changed by the discount rate are ¥398,773 (US$3,988) and ¥543,714 (US$5,437), respectively.

The ranges of ICER changed by the items featured are less than ¥250,000 (US$2,500). Items include costs such as the cost of end-of-life, the cost of treatment for distant recurrence with endocrine therapy and chemotherapy, the cost of trastuzumab, and the cost of adjuvant chemotherapy. They also include outcomes related items such as relative risk reduction of distant recurrence with endocrine therapy and chemotherapy, and the probability of death after progression of disease. Age of cohort and utility weight after adjuvant therapy without distant recurrence are also included in the 10 items.

Overall, the range of ICERs by the change of assumptions and values is limited between ¥25,660 (US$257) and ¥964,027 (US$9,640) for the indication for LN− scenario and between ¥95,586 (US$956) and ¥1,270,006 (US$12,700) for the indication for LN−/+ scenario.

Additionally, Table 5 shows the results of simulation of limiting indication to HER2− cases. Incremental costs both for the indication for LN− scenario and LN−/+ scenario increased slightly compared to the base-cases results, while incremental effects are about the same. These increased ICER slightly to ¥434,096 (US$4,341) for the indication for LN− scenario and to ¥614,765 (US$6,148) for the indication for LN−/+ scenario.

Discussion

We evaluate the cost-effectiveness of the 21-gene RT-PCR assay under Japan's health care system with two scenarios of including it into the benefit package of Japan's social health insurance: the indication for LN− scenario, under which the assay is made available for LN−, ER+, ESBC patients and the indication for LN−/+ scenario, under which the assay is made available for LN−/+, ER+, ESBC patients. Our economic model indicates that the use of the assay gains more in terms of outcomes but costs more at the same time. The estimated ICERs, ¥384,828 (US$3,848) per QALY for the indication for LN− scenario and ¥568,533 (US$5,685) per QALY for the indication for LN−/+ scenario are not more than a suggested social willingness-to-pay for one QALY gain from an innovative medical intervention in Japan, ¥5,000,000/QALY (US$50,000 QALY) [32]. Sensitivity analyses show that

Table 5 Results of simulation of limiting indication to HER2− cases

Scenario	Treatment	Cost (¥)	Incremental cost (¥)	Effect (QALY[a])	Incremental effect (QALY)	Incremental cost-effectiveness ratio (¥/QALY)
Indication for LN−	St Gallen 2009 criteria-guided	3,280,456		19.48		
	RS criteria-guided	3,553,750	273,294	20.10	0.63	434,096
Indication for LN−/+	St Gallen 2009 criteria-guided	3,437,132		18.81		
	RS criteria-guided	3,731,159	294,027	19.28	0.48	614,765

[a] Quality adjusted life year

this result is plausibly robust, since ICERs do not exceed the threshold by various changes of assumptions made and values employed. In this sense, the assay has good value for money.

The results of the indication for LN−/+ scenario is the first economic evidence of the assay in the literature to include LN+ cases. Compared to the indication for LN− scenario, the ICER for LN−/+ scenario is found less favourable. The incremental effect of the indication for LN−/+ scenario is less than the indication for LN− scenario, which may correlate with the poorer prognosis of LN+ cases than that of LN− cases. Although the proportion of cases who undergo adjuvant chemotherapy reduce more, 8.2%, under the indication for LN−/+ scenario than 6.8% under the indication for LN− scenario, the incremental cost is found more, which could be explained by the higher risk of recurrence of LN+ cases. The treatment of such cases would consume substantial resources.

Our simulation of foreseeable limited indication for HER2− cases suggests the same conclusion as our base-cases analysis, that is, the use of the assay is cost-effective. This depends on the assumption that the risk of recurrence and the benefit from chemotherapy are indifferent between HER2+ cases and HER2− cases. However, the proportion of HER2+ cases among the patient population under consideration, 9.3%, is relatively small. We consider our simulation is reasonable.

Our sensitivity analysis reveals that the cost-effectiveness of the assay depends on the change of DRF5 & DRFS10 of patients who are reclassified as high RS by the assay from endocrine therapy alone by St Gallen 2009 criteria. This suggests that the clinical benefit of the assay to prolong outcomes is brought by identifying patients who would have missed the benefit from adjuvant chemotherapy without the assay. And as anticipated, the cost of the assay is found to be influential to the cost-effectiveness. ±50% changes of the value result in neither cost-saving nor cost-ineffectiveness.

Comparing the results of this study with our last study, the estimated ICERs, ¥384,828 (US$3,848) per QALY for the indication for LN− scenario is more favourable than our previous estimation, ¥1,239,055 (US$12,391) per QALY. The difference is attributable to the difference in patient populations examined in the U.S. validation study, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 study [33], and the Japanese validation study, JBCRG-TR03 study [16]. Arguably, the patient population in JBCRG-TR03 study represents Japanese patients' population under consideration better than NSABP B-14 study. We think that the results of this study confirmed the cost-effectiveness of the assay in Japanese context with a more sound estimation of ICER.

However, this study has its own limitations. First, as to the benefit from adjuvant chemotherapy, our estimation of outcomes still depends on the validation study carried out in the U.S. [5]. Although the evidences adopted are considered as the best available to date, it is needless to say that there are differences in population and cancer care practice between the U.S. and Japan. Secondly, utility weights adopted are also derived from Western countries due to the unavailability of data from Japan. Thirdly, our model does not include potentially costly clinical stages such as local recurrence or contralateral breast cancer due to the lack of data in validation studies. In regards to these shortcomings, reports that allow us to refine our model are awaited.

Now that the clinical usefulness of the assay is confirmed by the Japanese validation study [16], Japanese health manager inevitably needs to decide how to fit the assay to the health care system. The results of this study imply the possibility of coverage by the social health insurance reimbursement. If the manager gives much importance to fiscal policy or cost containment, the selective indication of the assay for higher risk patients, which results in an avoidance of adjuvant chemotherapy without additional use among lower risk patients, might be a potential option. Further analysis incorporating such scenarios may be useful.

In conclusion, the routine use of the 21-gene RT-PCR assay for LN−/+, ER+, ESBC is indicated as cost-effective in Japan. The results could inform health managers in developed countries where diffusion of the assay is under consideration.

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Conflict of interest None.

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FcγR2A and 3A polymorphisms predict clinical outcome of trastuzumab in both neoadjuvant and metastatic settings in patients with HER2-positive breast cancer

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Background: Antibody-dependent-mediated cytotoxicity (ADCC) is one of the modes of action for trastuzumab. Recent data have suggested that fragment C γ receptor (FcγR) polymorphisms have an effect on ADCC. This prospective phase II trial aimed to evaluate whether these polymorphisms are associated with clinical efficacies in patients who received trastuzumab.

Patients and methods: Patients in a neoadjuvant (N) setting received Adriamycin and cyclophosphamide followed by weekly paclitaxel/trastuzumab. Patients in a metastatic (M) setting received single trastuzumab until progression. In total, 384 distinct single nucleotide polymorphisms of different FcγR, HER2, and fucosyltransferase loci were assessed.

Results: Fifteen operable and 35 metastatic HER2-positive breast cancer patients were enrolled in each of the N and M settings, respectively. The FcγR2A-131 H/H genotype was significantly correlated with the pathologically documented response (pathological response) ($P = 0.015$) and the objective response ($P = 0.043$). The FcγR3A-158 V/V genotype was not correlated with the pathological response, but exhibited a tendency to be correlated with the objective response. Patients with the FcγR2A-131 H/H genotype had significantly longer progression-free survival in the M setting ($P = 0.034$).

Conclusion: The FcγR2A-131 H/H polymorphism predicted the pathological response to trastuzumab-based neoadjuvant chemotherapy in early-stage breast cancer, and the objective response to trastuzumab in metastatic breast cancer.

Key words: ADCC, FcγR, trastuzumab

introduction

The humanized HER-2/*neu* immunoglobulin G (IgG) 1 monoclonal antibody (mAb) trastuzumab is an effective treatment of HER-2/*neu*-positive breast cancer. However, large differences in clinical outcome remain among patients treated with trastuzumab. Identifying molecular markers that can select patients who are to benefit from trastuzumab treatment is crucial for avoiding chemotherapy toxicity and reducing treatment costs.

Antibody-dependent cytotoxicity (ADCC) mediated by fragment C γ receptor (FcγR) on immune cells such as macrophages and natural killer cells plays an important role in the antitumor effect of IgG1 antibodies [1]. Genetic polymorphisms have been identified in genes encoding the activating receptors FcγR2A and 3A. A histidine (H)/arginine (R) polymorphism at position 131 for FcγR2A and a valine (V)/phenylalanine (F) polymorphism at position 158 for FcγR3A are two polymorphisms that affect the affinity of the receptors to human IgG [2–4]. Clinical studies have shown that FcγR2A-131 H/H and FcγR3A-158 V/V genotypes are associated with better clinical outcomes following the administration of rituximab as a first-line treatment of follicular lyoma [5, 6] and diffuse large lyoma [7] and cetuximab as a first-line treatment of metastatic colorectal cancer [8].

FcγR-deficient mice show a significantly reduced antitumor effect after trastuzumab treatment, with wild-type mice [9]. HER-2/*neu*-positive breast cancer cell lines are susceptible to ADCC in the presence of trastuzumab [10–12]. The activity of trastuzumab *in vivo* has also been correlated with a significant increase in the numbers of peritumoral lyomonocytes and *in vitro* ADCC [13]. In a clinical trial, Musolino et al. [14]

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demonstrated that a better response to trastuzumab-based therapy in metastatic breast cancer (MBC) was associated with the above two genotypes. In contrast, a recent large prospective trial (BCIRG006) [15] showed that the two FcγR single nucleotide polymorphisms (SNPs) did not predict disease-free survival in early breast cancer or progression-free survival (PFS) in MBC after trastuzumab-based therapy. Most of the previous studies reporting that FcγR SNPs are correlated with outcome [5–8, 14] have been under-powered, with the exception of BCIRG006. However, this inconsistency might have been influenced by the different modalities of therapeutic use [i.e. adjuvant and metastatic (M) settings] or the combinations of cytotoxic agents.

The goal of our prospective study was to determine the predictive values of these two SNPs as biomarkers in predicting the objective response to the single use of trastuzumab and to these predictive values with other SNPs in FcγR, HER2 or fucosyltransferase in MBC patients. We also analyzed their potential as a predictive marker of pathological complete response (pCR) in a neoadjuvant (N) setting with trastuzumab-based chemotherapy.

materials and methods

eligibility criteria

Eligible patients had histologically confirmed breast cancer, operable stage II–IIIA disease (tumor size > 3 cm) in an N setting or stage IV disease in an M setting (recurrent disease after curative surgery was also eligible), HER2-positive (IHC 3+ or FISH positive), chemotherapy, measurable disease, age ≥ 20 years, Eastern Cooperative Oncology Group performance status of 0–2, and adequate organ function (white blood cell count ≥ 4000/μl, platelet count ≥ 100 000/μl, hemoglobin concentration ≥ 9.0 g/dl, serum bilirubin ≤ 2.0 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤ 100 IU/l, serum creatinine ≤ institutional upper limit of normal range, PaO_2 ≥ 60 mmHg, baseline left ventricular ejection fraction >50%). The main exclusion criteria were active concomitant malignancy, congestive heart failure, uncontrolled angina pectoris, arrhythmia, symptomatic infectious disease, severe bleeding, pulmonary fibrosis, obstructive bowel disease or severe diarrhea, symptomatic peripheral or cardiac effusion, and symptomatic brain metastasis. This study was conducted according to a protocol approved by the institutional review board/independent ethics committee, and informed consent was obtained from all patients for the use of blood samples and the analysis of clinical information.

analysis of FcγR, HER2, and fucosyltransferase polymorphisms

In a previous study [14], the authors focused only on the hot spot of SNPs at FcγR2A-131 and FcγR3A-158. However, other loci of FcγR, including 2B-232 I/T, have already been reported [16] as potential markers for predicting the response to trastuzumab. Additionally, FUT8 is known to transfer a fucose residue to N-linked oligosaccharides on glycoproteins [17], and we reported that FUT8 plays an important role in ADCC activity [18]. Goldgate Genotyping is a novel technique that can be used to determine 384 SNPs quickly and simultaneously. Based on these backgrounds, 384 SNPs harboring FcγR1, R2, R3, HER2, and fucosyltransferase (FUT8) loci were custom designed using Goldgate Genotyping [19] (Illumina Co., CA) in this study. Among them, 67 SNPs were designed in exons. Genomic DNA was purified from peripheral blood using QIAamp Micro kits (QIAGEN K.K., Tokyo, Japan). Genomic DNA was isolated from specimens using QIAamp Micro kits. Genomic DNA (250 ng) was hybridized using a bead array and the Goldgate Genotyping Assay manual [20]. The presence of SNPs was analyzed using a bead array reader. Gene clustering was carried out automatically using a software algorithm (Beadstudio) several times, and all the spots were confirmed by visual inspection. When the separation of the clustering was poor or when some samples provided inconsistent data, the assay was repeated to confirm the results. We also combined standard DNA (HapMap) with the assay as a control. Molecular data were independently interpreted by two biologists (FK and KN) who were blinded to the clinical outcomes of the study participants.

treatment and assessment

Treatment in the N setting consisted of Adriamycin and cyclophosphamide (60/600 mg/m^2) × 4 i.v. every 3 weeks followed by paclitaxel (80 mg/m^2) with trastuzumab (4 mg/kg followed by 2 mg/kg) × 12 i.v. every week. Treatment of MBC consisted of trastuzumab (8 mg/kg, followed by 6 mg/kg) every 3 weeks until disease progression. Routine clinical and laboratory assessments were carried out every 3 weeks, and a CT or echo examination of the target lesion was carried out every 2 months. The pathologically documented response (pathological response) after N therapy was assessed using the histopathological criteria of the Japanese Breast Cancer Society [21]. The objective response was evaluated every month using the Response Evaluation Criteria in Solid Tumors guidelines [22]. All the adverse effects that occurred during treatment were reported, and the severity of each adverse effect was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0.

statistical analysis

The association of each polymorphism with either the pathological response for the N setting or the objective tumor response for the M setting was the primary end point of the analysis. The association of each polymorphism with the PFS for the M setting and with a linkage analysis between FcγR2A and 3A were the secondary end points. First, all genotypes (wild, hetero and homo) of the 384 SNPs were assessed as to whether or not a difference in the primary end points was present with a statistical power <0.1. Second, the pathological responses and objective tumor responses of the patients were according to the selected FcγR polymorphisms using a two-tailed Fisher's exact test [23], chi-square test [23], linear correlation test [24], and analysis of variance (ANOVA) test [24]. Linkage disequilibrium was determined using a Fisher's exact test, chi-square test, and linear correlation test. The PFS was calculated as the length of time between the first day of trastuzumab treatment and the first observation of disease progression or death from any cause. If a patient had not progressed or died, the PFS was censored at the time of the last follow-up examination. The association of each polymorphism with PFS was analyzed using Kaplan–Meier curves [25] and the log-rank test [26]. All tests of statistical significance were two-tailed. The analyses were carried out using the SAS statistical package, version 9.0 (SAS Institute Inc., Cary, NC).

results

patient characteristics

Between December 2005 and August 2008, 40 and 36 patients were prospectively screened for N and M settings, respectively. Out of the 40 patients in the N setting, 15 (37.5%) patients were diagnosed as being HER2-positive using tissue samples obtained during a core needle biopsy. One patient in an M setting was ineligible because of an incorrect diagnosis of breast cancer. The clinical and pathologic features of the patients are presented in Table 1.

genotypic frequencies of the polymorphisms

A total of 384 SNPs harboring FcγRI, RII, RIII, HER2 and FUT8 loci were custom designed and analyzed in all 50 patients (15 in an N setting and 35 in an M setting). After a study to establish the correlations between the genotypes of these SNPs and the clinical outcome, we found that only two hot spots, FCγR2A-131 H/H and FCγR3A-158 V/V, among the 384 loci were predictive markers of the response to trastuzumab-based therapy. Forty-four percent (22 of 50) of the patients were homozygous for the FCγR2A-131 H allele, 48% (24 of 50) were heterozygous (H/R), and 8% (4 of 50) were homozygous(R/R) for the 131R allele (Tables 3 and 4). Forty-four percent (22 of 50) of the patients were homozygous for the FCγR3A-158 F allele, 46% (23 of 50) were heterozygous carriers (F/V), and 10% (5 of 50) were homozygous for the 158V allele. The distribution of genotypes between the N and M settings was similar and was not significantly different from that would be expected if each group was in Hardy–Weinberg equilibrium.

Table 1. Patient characteristics

Characteristics	N setting		M setting	
	No.	%	No.	%
No. of patients	15	100	35	100
Median age, years	44		58	
Range	23–66		28–76	
Menopausal status				
Pre	9	60	14	40
Post	6	40	21	60
Eastern Cooperative Oncology Group performance status				
0	12	80	18	51
1	3	20	16	46
2	0	0	1	3
Stage				
II	11	73	0	0
III	4	27	0	0
IV (+recurrence)	0	0	35	100
Histological grade				
1	3	20	2	6
2	5	33	9	26
3	7	47	24	68
Estrogen receptor status				
Positive	6	40	12	34
Negative	9	60	23	66
Progesterone receptor status				
Positive	5	33	7	20
Negative	10	67	28	80
Number of axillary lymph node				
1	10	67	–	–
1–3	5	33	–	–
≧4	0	0	–	–
Number of metastatic sites				
1	–	–	16	46
2	–	–	12	34
≧3	–	–	7	20

N, neoadjuvant; M, metastatic.

clinical response to trastuzumab therapy and FcγR polymorphisms

The pCR rate for the N setting was 33% [95% confidence interval (CI), 11.6% to 61.6%] (Table 2). No significant difference in the pretreatment features was observed between the FCγR2A and R3A genotypes. The FcγR2A-131 H/H genotype was significantly correlated with the pathological response [71% (5/7) for H/H versus 0% (0/8) for H/R + R/R; $P = 0.015$, Fisher's exact test; $P = 0.007$, chi-square test; $P < 0.05$, both linear correlation test and ANOVA test; Table 3]. The FcγR3A-158 V/V genotype was not correlated with the pathological response.

The objective response rate for the M setting was 23% (95% CI, 10.4% to 40.1%), and the disease control rate was 66% (95% CI, 47.8% to 80.9%) (Table 2). The median duration time of stable disease ($n = 15$) was 9.5 (5.3–17.7) months. A significant difference in the objective response rate was observed between patients with FcγR2A-131 H/H and those with either the 131 H/R or the 131 R/R genotype ($P = 0.043$, Fisher's exact test; $P < 0.05$, both linear correlation test and ANOVA test; Table 4). Although this difference did not reach the level of statistical significance, patients with FcγR3A-158 V/V also showed an overall higher response rate than the other two FcγR3A-158 genotypes [40% (6/15) for V/V versus 10% (2/20) for F/V + F/F; $P = 0.053$, Fisher's exact test; $P = 0.051$, chi-square test].

PFS analysis according to FcγR polymorphisms

The median follow-up times for the N and M settings were 24.8 and 22.6 months, respectively. Six patients (four local, two distant) had already relapsed as of July 2010. The PFS was assessed at 1 year after the last patient's enrollment in the study.

Table 2. Responses of patients in M or N settings

Response	No.	%
Neoadjuvant setting ($n = 15$)		
Grade 3[a] (pathological CR)	5	33
Grade 2 (marked response)	5	33
Grade 1b (moderate response)	3	20
Grade 1a (mild response)	2	14
Grade 0 (no response)	0	0
Pathological CR rate	5	33
95% CI	11.6–61.6	
M setting ($n = 35$)		
Compete response	1	3
Partial response	7	20
Stable disease	15	43
Progressive disease	12	34
Objective response rate	8	23
95% CI	10.4–40.1	
Disease control rate	23	66
95% CI	47.8–80.9	

[a]Grade refers to the histopathological criteria for the assessment of therapeutic response [21].

N, neoadjuvant; M, metastatic; CR, complete response; CI, confidence interval.

Table 3. FcγR polymorphisms and pathological responses to trastuzumab in an N setting

Polymorphism	Patients	Pathological response (grade)							
		1a		1b		2		3 (pCR)	
		No.	%	No.	%	No.	%	No.	%
FcγR2A									
H/H	7	0	0	0	0	2	29	5	71
H/R	6	1	17	3	50	2	33	0	0
R/R	2	1	50	0	0	1	50	0	0
Fisher's exact test: *P*				*0.015*					
Chi-square test (pCR versus others): *P*[a]				*0.007*					
Linear correlation test: *P*				*0.0076*					
ANOVA test: *P*				*0.0088*					
FcγR3A									
V/V	7	0	0	1	14	2	29	4	57
F/V	6	1	17	2	33	2	33	1	17
F/F	2	1	1	0	0	1	1	0	0
Fisher's exact test: *P*				*0.45*					
Chi-square test (pCR versus others): *P*[a]				*0.12*					
Linear correlation test: *P*				*0.069*					
ANOVA test: *P*				*0.16*					

[a]Comparison of H/H versus R carrier (H/R + R/R) or V/V versus F carrier (F/V + F/F).

N, neoadjuvant; FcγR, fragment C γ receptor; pCR, pathological complete response; ANOVA, analysis of variance.

Table 4. FcγR polymorphisms and tumor responses to trastuzumab in an M setting

Polymorphism	Patients	Response					
		CR/PR		SD		PD	
		No.	%	No.	%	No.	%
FcγR2A							
H/H	15	6	40	7	47	2	13
H/R	18	2	12	8	44	8	44
R/R	2	0	0	0	0	2	100
Fisher's exact test: *P*				*0.043*			
Chi-square test (CR/PR versus SD/PD): *P*[a]				*0.051*			
Linear correlation test: *P*				*0.0077*			
ANOVA test: *P*				*0.029*			
FcγR3A							
V/V	15	6	40	5	33	4	27
F/V	17	1	6	10	59	6	35
F/F	3	1	33	0	0	2	67
Fisher's exact test: *P*				*0.053*			
Chi-square test (CR/PR versus SD/PD): *P*[a]				*0.051*			
Linear correlation test: *P*				*0.12*			
ANOVA test: *P*				*0.16*			

[a]Comparison between H/H versus R carrier (H/R + R/R) or V/V versus F carrier (F/V + F/F).

M, metastatic; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FcγR, fragment C γ receptor; ANOVA, analysis of variance.

The median PFS time was 6.4 months (95% CI, 3.9–8.6 months). The PFS of patients with FcγR2A-131 H/H was significantly longer than that of patients with 131 H/R or R/R. (Figure 1A: 9.2 versus 3.5 months, $P = 0.034$). In contrast, no statistical difference in the PFS of patients with FcγR3A-158 V/V and that of patients with 158 F/V or F/F was observed (Figure 1B: 8.5 versus 5.3 months, $P = 0.37$). Linkage disequilibrium analyses were conducted among the two FcγR polymorphisms (Table 5). The incidence of the FcγR2A-131 genotype was associated with that of the FcγR3A-158 genotype according to a Fisher's exact test, a chi-square test, and a linear correlation test.

discussion

The overexpression of HER2 protein is observed in ~20–30% of patients with breast cancer and is correlated with a poor clinical outcome. Trastuzumab is an IgG1-type humanized HER2 mAb that has been shown to exhibit significant clinical efficacy as a treatment of MBC [27] and as an adjuvant treatment of operable breast cancer [28]. However, the clinical effectiveness of trastuzumab is somewhat limited: the response rate to single-agent trastuzumab as a first-line treatment is 20–30%; the pCR rate to neoadjuvant therapy including trastuzumab is ~30%. A substantial numbers of HER2-positive tumors exhibit *de novo* resistance to trastuzumab; therefore, the development of biomarkers to select patients who might benefit from trastuzumab is warranted, as a way of decreasing toxicity and reducing unnecessary cost.

The principal mechanism of action of trastuzumab is HER2 blockade with the inactivation of the signal transduction pathway, leading to apoptosis. ADCC is another not insignificant and generally accepted mechanism of trastuzumab action. In ADCC, the cytotoxicity of mAbs that target tumor cells, is mediated by immune effector cells that express FcγR. Recently, two FcγR gene polymorphisms have been identified that affect the binding affinity of IgG, thus changing the effectiveness of ADCC and affecting tumor response. FcγR3A-158 V/V, either alone or in combination with the FcγR2A-131 H/H genotype, was significantly associated with a better response and PFS among patients with follicular lyoma [5, 6] and among MBC patients [14] treated with rituximab- or trastuzumab-based therapy, respectively. Inconsistent data have been reported in metastatic colorectal cancer patients who had not responded to previous irinotecan- or oxaliplatin-based therapy and were subsequently treated with single-agent cetuximab [29]. The

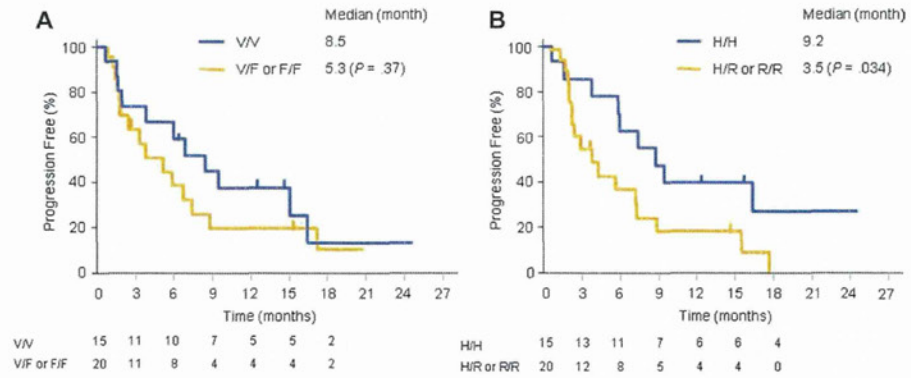

Figure 1. Progression-free survival for patients with metastatic breast cancer receiving single-agent trastuzumab categorized according to fragment C γ receptor (FcγR) polymorphisms. (A) Progression-free survival (PFS) curves were plotted for FcγR2A-131 H/H and H/R or R/R carriers. (B) PFS curves were plotted for FcγR3A-158 V/V and F/V or F/F carriers. V, valine allele; F, phenylalanine allele; H, histidine allele; R, arginine allele.

Table 5. Linkage analysis between FcγR2A and 3A alleles

	Patients	FcγR3A					
		V/V		F/V		F/F	
		No.	%	No.	%	No.	%
FcγR2A							
H/H	22	13	59	9	41	0	0
H/R	24	8	33	13	54	3	13
R/R	4	1	25	1	25	2	50
Total	50	22	44	23	46	5	10
Fisher's exact test: *P*				*0.030*			
Chi-square test (V/V versus F carrier) *P*[a]				*0.020*			
Linear correlation test: *P*				*0.0067*			

[a]Comparison between H/H versus R carrier.
FcγR, fragment C γ receptor.

influence of cytotoxic agents in combination with antibody therapy or the retrospective natures of these analyses might explain the previous inconsistencies. In the present prospective study, the FcγR2A-131 H/H genotype was significantly associated with a stronger tumor response and a longer PFS, and the FcγR3A-158 V/V genotype tended to be correlated with the tumor response after single-agent trastuzumab therapy.

Metastatic cancer patients mostly have suppressed immune function. Thus, early-stage breast patients treated with trastuzumab might be more sensitive to ADCC activity. In the current study, we have demonstrated for the first time that the FCγR2A-131 H/H genotype was significantly correlated with the pathological response after neoadjuvant trastuzumab-based treatment. Our data suggest that this genotype was correlated with not only the pCR rate but also the gradation of the response based on a precise assessment of pathological responses using established histopathological criteria (grade 1a–3; Table 3). A recent large adjuvant trial with trastuzumab-based therapy [15] has raised questions regarding the usefulness of the two FcγR SNPs as predictive biomarkers for recurrence. The sample size of this trial was relatively large; thus, the results seemed to be confirmatory. However, one possible explanation for this difference is that ADCC might be influenced by the existence of a target tumor volume. Another possible explanation is that the cytotoxic agents might influence outcome. Theoretically, the clinical efficacy of trastuzumab is based on both the direct blockade of signal transduction and its indirect effect, ADCC. On the other hand, the efficacy of cytotoxic agents is based on the direct DNA damaging effect and not on ADCC. Thus, the change in ADCC induced by different SNPs might be diluted in cases where trastuzumab and cytotoxic agents are combined, with cases in trastuzumab is used singly.

In this study, we examined 384 SNPs at FcγRI, RII, RIII, HER2 and FUT8 loci. Our findings demonstrated that only two SNP hot spots were correlated with the clinical efficacy of trastuzumab, indicating a high specificity. Our finding that the incidences of the two FCγR2A-131 H/H and FcγR3A-158 V/V genotypes were moderately linked with each other is inconsistent with a previous report [14]. One possible explanation for this discrepancy might be ethnical differences in SNP frequency. Zhang et al. [29] showed that the FCγR2A-131 H/H and FcγR3A-158 V/V genotypes were more frequent among Asian populations than among Western populations. Statistical approaches, including a linear correlation or ANOVA test, suggested that heterozygosity for the two SNPs might have a minimal effect on ADCC activity. Additional studies evaluating the relationship between ADCC activity and the SNP status are needed.

In conclusion, this study supports the hypothesis that FcγR polymorphisms play a role in trastuzumab-mediated ADCC and can predict the clinical outcome of patients with both early and MBC in Asian populations.

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disclosure

The authors declare no conflict of interest.

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ORIGINAL REPORT

Phase III Trial Comparing Oral S-1 Plus Carboplatin With Paclitaxel Plus Carboplatin in Chemotherapy-Naïve Patients With Advanced Non–Small-Cell Lung Cancer: Results of a West Japan Oncology Group Study

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This study is registered with University Hospital Medical Information Network Clinical Trial Registry (http://www.umin.ac.jp/ctr/index.htm, identification number UMIN000000503).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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ABSTRACT

Purpose
The primary goal of this open-label, multicenter, randomized phase III trial was to determine whether treatment with carboplatin plus the oral fluoropyrimidine derivative S-1 was noninferior versus that with carboplatin plus paclitaxel with regard to overall survival (OS) in chemotherapy-naive patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
A total of 564 patients were randomly assigned to receive either carboplatin (area under the curve, 5) on day 1 plus oral S-1 (40 mg/m^2 twice per day) on days 1 to 14 or carboplatin (area under the curve, 6) plus paclitaxel (200 mg/m^2) on day 1 every 21 days.

Results
At the planned interim analysis, with a total of 268 death events available, the study passed the O'Brien-Fleming boundary of 0.0080 for a positive result and noninferiority of carboplatin and S-1 compared with carboplatin and paclitaxel was confirmed for OS (hazard ratio, 0.928; 99.2% CI, 0.671 to 1.283). Median OS was 15.2 months in the carboplatin and S-1 arm and 13.3 months in the carboplatin and paclitaxel arm, with 1-year survival rates of 57.3% and 55.5%, respectively. Rates of leukopenia or neutropenia of grade 3/4, febrile neutropenia, alopecia, and neuropathy were more frequent in the carboplatin and paclitaxel arm, whereas thrombocytopenia, nausea, vomiting, and diarrhea were more common in the carboplatin and S-1 arm. The carboplatin and S-1 arm had significantly more dose delays than the carboplatin and paclitaxel arm.

Conclusion
Oral S-1 with carboplatin was noninferior in terms of OS compared with carboplatin and paclitaxel in patients with advanced NSCLC, and is thus a valid treatment option.

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INTRODUCTION

Lung cancer is the leading cause of death related to cancer worldwide,[1] with non–small-cell lung cancer (NSCLC) accounting for 85% of lung cancer cases. For individuals with advanced or metastatic NSCLC, platinum-based chemotherapy is the mainstay of first-line treatment on the basis of the moderate improvement in survival and quality of life it affords compared with best supportive care alone.[2-5] Thus, there is still a need for new treatment regimens to ameliorate symptoms and prolong survival in patients with advanced NSCLC in a manner that is both convenient and safe.

S-1 (TS-1; Taiho Pharmaceutical Co Ltd, Tokyo, Japan) is an oral fluoropyrimidine agent that consists of tegafur, 5-chloro-2,4-dihydroxypyridine, and potassium oxonate in a molar ratio of 1:0.4:1.[6,7] A phase II trial of oral S-1 as a single agent for the treatment of advanced NSCLC yielded a response rate of 22% and a median survival time of 10.2 months in 59 patients without prior chemotherapy.[8] We previously performed a phase I/II study of carboplatin/S-1 combination therapy and found that administration of S-1 (40 mg/m^2 twice per day) on days 1 to 14 in combination with carboplatin (area under the curve [AUC], 5) on day 1 of every 3-week cycle yielded efficacy results similar to those of other platinum doublets.[9] The carboplatin and S-1 combination had a more favorable toxicity profile than that typically seen with platinum-based regimens,

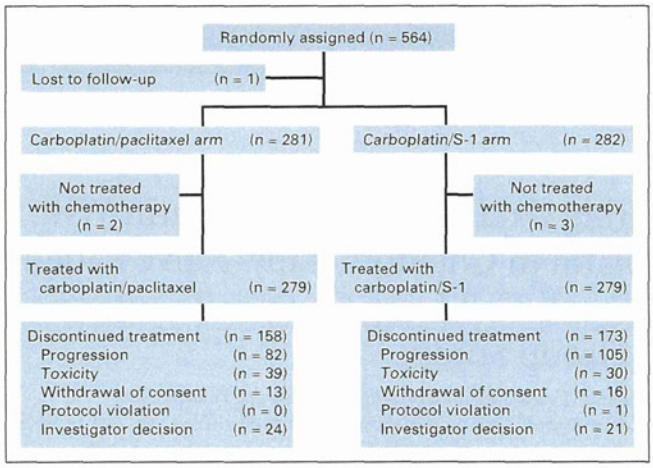

Fig 1. CONSORT diagram for the study.

especially with regard to neutropenia, febrile neutropenia, neuropathy, and alopecia.[9] In addition, replacement of paclitaxel with oral S-1 in combination therapy with carboplatin avoids the need for premedication to ameliorate paclitaxel-induced hypersensitivity and the 3-hour infusions required for paclitaxel administration. We therefore undertook and now report the results of the LETS (Lung Cancer Evaluation of TS-1) study, a multicenter, randomized, phase III, noninferiority trial of carboplatin and S-1 in comparison with carboplatin and paclitaxel combination therapy in chemotherapy-naive patients with advanced NSCLC.

PATIENTS AND METHODS

Patients

The criteria for patient eligibility included a diagnosis of NSCLC confirmed either histologically or cytologically; a clinical stage of IIIB not amenable to curative treatment or of stage IV; a measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST)[10]; no prior chemotherapy; an age of 20 to 74 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and a projected life expectancy of at least 3 months. Patients had adequate bone marrow reserve and organ function including a calculated creatinine clearance of $\geq$ 60 mL/min based on the standard Cockcroft and Gault formula. Radiation therapy for metastatic disease was permitted if it was completed at least 2 weeks before random assignment. Main exclusion criteria included active concomitant malignancy, symptomatic brain metastasis, interstitial pneumonia, watery diarrhea, heart failure, uncontrolled diabetes mellitus, active infection, and a past history of drug allergy. These inclusion and exclusion criteria are consistent with those of previous studies involving carboplatin and paclitaxel treatment.[11] Written informed consent was obtained from all patients, and the study protocol was approved by the institutional ethics committee of each of the participating institutions.

Treatment Plan

Eligible patients were randomly assigned to receive either carboplatin (AUC, 6) plus paclitaxel (200 mg/m^2) on day 1[11] or carboplatin (AUC, 5) on day 1 plus oral S-1 (40 mg/m^2 twice per day) on days 1 to 14. Chemotherapy was repeated every 3 weeks for a maximum of six cycles unless there was earlier evidence of disease progression or intolerance of the study treatment.

End Points

The primary objective of this open-label, multicenter, randomized phase III trial was to establish the noninferiority of S-1 plus carboplatin compared with paclitaxel plus carboplatin as first-line therapy in terms of overall survival (OS) in patients with advanced NSCLC. Secondary end points included tumor response, treatment safety, quality of life (QOL), and progression-free survival (PFS).

Baseline and Follow-Up Assessments

Baseline evaluations included medical history, physical examination, ECG, tumor status, ECOG performance status, and laboratory analyses. During treatment, blood counts and biochemical tests were performed at least biweekly. A computed tomography scan was performed for tumor assessment within 14 days of initiation of study treatment and was repeated after every 1 to 2 months of planned therapy. All responses were defined according to RECIST. If a patient was documented as having a complete response (CR) or a

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Carboplatin/Paclitaxel (n = 281) No.	Carboplatin/Paclitaxel (n = 281) %	Carboplatin/S-1 (n = 282) No.	Carboplatin/S-1 (n = 282) %	*P*
Age, years					
Median	63		64		.510
Range	36-74		38-74		
Sex					
Male	215	76.5	217	77.0	.902
Female	66	23.5	65	23.0	
ECOG PS					
0	90	32.0	86	30.5	.695
1	191	68.0	196	69.5	
Histology					
Adenocarcinoma	195	69.4	195	69.1	.560
Nonadenocarcinoma	86	30.6	87	30.9	
Clinical stage					
IIIB	68	24.2	68	24.1	.981
IV	213	75.8	214	75.9	
Smoking status					
Smoker	229	81.5	230	81.6	.984
Nonsmoker	52	18.5	52	18.4	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

partial response (PR), a confirmatory evaluation was performed after an interval of 4 weeks. Disease control was defined as the best tumor response among CR, PR, or stable disease that was confirmed and sustained for 6 weeks or longer. Patients were evaluated for adverse events during therapy and until 42 days after administration of the last dose of the study treatment. Toxicity was evaluated according to the National Cancer Institute Cancer Common Toxicity Criteria, version 3. QOL was assessed with the lung cancer subscale of the Functional Assessment of Cancer Therapy–Lung (FACT-L)[12] and the neurotoxicity subscale of the FACT/Gynecology Oncology Group-Neurotoxicity (GOG-Ntx) version 4.[13] In addition, alopecia was evaluated on the basis of the single item "I have been bothered by hair loss," which was included in the former version of FACT-L. The maximum attainable scores on the lung cancer subscale, neurotoxicity subscale, and alopecia item were 28, 44, and 4, respectively, with which the patient was considered to be asymptomatic. Patients were asked to complete each instrument at the time of enrollment and at 6 and 9 weeks after initiation of treatment.

Statistical Analysis

Eligible patients were randomly assigned according to a 1:1 ratio to receive either carboplatin and paclitaxel or carboplatin and S-1. After a check of patient eligibility, random assignment was performed centrally at the West Japan Oncology Group data center by minimization with stratification factors including disease stage (IIIB *v* IV), type of histology (adenocarcinoma *v* nonadenocarcinoma), sex (male *v* female), and investigator center. The intent-to-treat (ITT) patient population included all patients who underwent random assignment. The per-protocol (PP) population was defined as the ITT population minus patients considered to have major violations of inclusion or exclusion criteria and those who did not receive any protocol treatment. The safety population was defined as all patients receiving at least one dose of study drugs. The primary end point of the study was OS, which was analyzed in the ITT population by estimation of the hazard ratio (HR) and two-sided 95% CI derived from a Cox regression model with adjustment for the stratification factors with the exception of investigator center. Median OS in both treatment arms was assumed to be 14 months on the basis of data from previous clinical trials.[11] Noninferiority of carboplatin and S-1 was to be concluded if the upper limit of the 95% CI of the HR was lower than 1.33; that is, the null hypothesis that the median OS of the carboplatin and S-1 group would be up to 3.48 months shorter than that of the carboplatin and paclitaxel group was analyzed. Demonstration of noninferiority with a statistical power of 85% at a two-sided significance level of .05 and 2 years of follow-up after 2.5 years of accrual would require 263 patients in each treatment group. Given the possibility of variance inflation due to censoring, the sample size was set at 560 (280 per arm). One interim analysis was planned when all the patients had been enrolled. For analysis of the primary end point, adjustment for multiple comparisons was handled by the method of Lan and DeMets, with the use of the O'Brien-Fleming type α spending function. The significance level was set at .008 for the interim analysis, taking the numbers of observed events (n = 268) and expected events (n = 442) into account. Survival curves (PFS and OS) were analyzed by the Kaplan-Meier method and were compared between groups by the Cox regression model. The 95% CI for median PFS and OS was calculated by the method of Brookmeyer and Crowley. Planned subgroup analyses for OS were performed to examine the interaction effect of treatment arm with each of performance status, sex, disease stage, type of histology, and smoking status. Patient characteristics (ie, sex, ECOG PS, histology, clinical stage, and smoking status) as well as response and toxicity incidence were compared between the two treatment arms by the χ^2 test, and age was compared by the Wilcoxon test. Longitudinal QOL data were analyzed with a linear mixed-effects model. All *P* values were two sided. Statistical analyses were performed with SAS for Windows, release 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

From August 2006 to May 2008, 564 patients from 30 institutions were enrolled in the study. One patient was excluded from the carboplatin and paclitaxel arm because of loss to follow-up. The ITT population thus consisted of 563 patients: 281 individuals randomly assigned to the carboplatin and paclitaxel group and 282 individuals randomly assigned to the carboplatin and S-1 group (Fig 1). The baseline demographic and disease-related characteristics of the study subjects were well-balanced between the two treatment arms (Table 1). Two patients in the carboplatin and paclitaxel arm and three patients in the carboplatin and S-1 arm did not receive any chemotherapy, with the result that 558 patients were eligible for safety analysis (Fig 1).

Delivered Chemotherapy

The number of treatment courses administered was 1,037 in the carboplatin and paclitaxel arm (median, 4; range, 1 to 6) and 987 in the carboplatin and S-1 arm (median, 4; range, 1 to 6). Dose reductions occurred in 90 (8.7%) of the carboplatin and paclitaxel courses and in 49 (5.0%) of the carboplatin and S-1 courses. Carboplatin and paclitaxel dose reductions were mainly due to neuropathy, whereas those for carboplatin and S-1 were most commonly attributable to thrombocytopenia. Dose delays occurred in 47.9% of carboplatin and paclitaxel courses and 68.5% of carboplatin and S-1 courses. Delays due to

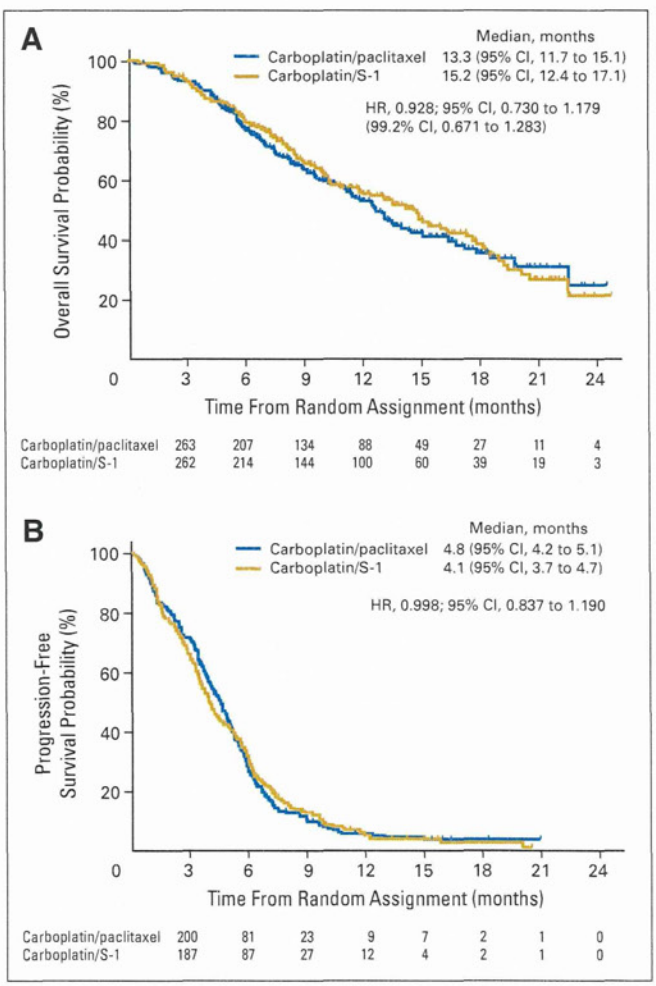

Fig 2. (A) Overall survival and (B) progression-free survival for the intent-to-treat population (n = 563). HR, hazard ratio.

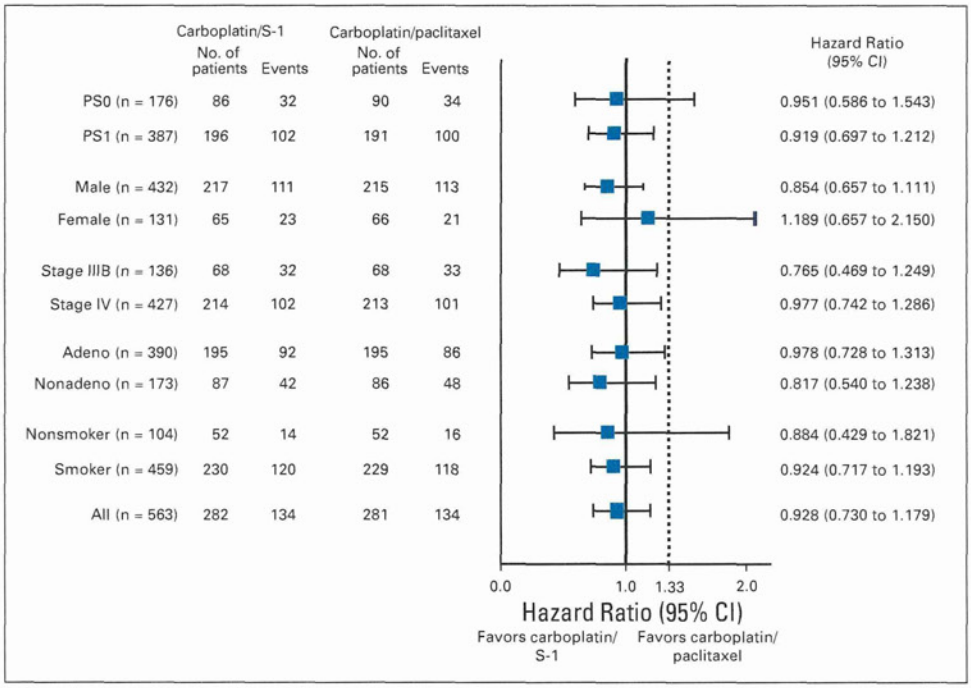

Fig 3. Subgroup analysis of overall survival in the intent-to-treat population (n = 563). PS, performance status; Adeno, adenocarcinoma; Nonadeno, nonadenocarcinoma.

hematologic toxicity occurred in a higher proportion of carboplatin and S-1 courses (51.6%) than carboplatin and paclitaxel courses (9.6%). S-1 was administered for the planned 14 days without interruption in 89.1% of carboplatin and S-1 courses. The median relative dose intensities were high for both carboplatin and paclitaxel (89.6% and 87.6%, respectively) and carboplatin and S-1 arms (83.3% and 94.3%, respectively). The most frequent reason for discontinuation of therapy was disease progression in both arms. Treatment was withdrawn before completion from a similar proportion of patients in each group (13.6% for carboplatin and paclitaxel and 10.7% for carboplatin and S-1) because of adverse events.

Efficacy

At the interim analysis planned for when patient enrollment was completed, 268 death events were available in total. The study passed the O'Brien-Fleming boundary of 0.0080 for a positive result with a *P* value of .002. The HR for OS (carboplatin and S-1 *v* carboplatin and paclitaxel) in the ITT population was 0.928, with a two-sided 99.2% CI after adjustment for multiplicity due to interim analysis of 0.671 to 1.283 (Fig 2A). Noninferiority of carboplatin and S-1 therapy was thus confirmed at the interim analysis by the upper limit of the CI being less than the protocol-specified margin of 1.33. The crude (unadjusted) 95% CI of the HR for OS of 0.928 was 0.730 to 1.179 in the ITT population, and an HR for OS of 0.931 (95% CI, 0.732 to 1.186) was obtained with the PP population. Median OS was 15.2 months (95% CI, 12.4 to 17.1) in the carboplatin and S-1 arm and 13.3 months (95% CI, 11.7 to 15.1) in the carboplatin and paclitaxel arm, with the 1-year survival rates being 57.3% and 55.5%, respectively. Subgroup analysis of OS in the ITT population according to stratification variables and other baseline characteristics were consistent with the primary analysis. A significant interaction effect between treatment arm and subgroups was not observed. The 95% CI for the HR in each subgroup included 1.00 (Fig 3).

The median PFS was 4.1 months in the carboplatin and S-1 arm and 4.8 months in the carboplatin and paclitaxel arm in the ITT population, with a corresponding HR of 0.998 and 95% CI of 0.837 to 1.190 (Fig 2B). In the PP population, the median values of PFS were 4.2 and 4.8 months for the carboplatin and S-1 and carboplatin and paclitaxel arms, respectively, with a corresponding HR of 0.992 and 95% CI of 0.832 to 1.184. Response to treatment was assessed in 279 patients (99.3%) of the carboplatin and paclitaxel group and in 279 patients (98.9%) of the carboplatin and S-1 group. For overall response (CR + PR) rate, carboplatin and paclitaxel was superior to carboplatin and S-1 (29.0% *v* 20.4%; $P = .019$, χ^2 test), whereas the overall disease control (CR + PR + stable disease) rate was similar in both treatment groups (73.5% *v* 71.7%, respectively; $P = .635$).

Safety

The incidence of leukopenia or neutropenia of grade 3 or 4 was significantly lower for patients in the carboplatin and S-1 arm than for those in the carboplatin and paclitaxel arm (leukopenia, 5% *v* 33%; neutropenia, 21% *v* 77%, respectively), as was the incidence of febrile neutropenia (1% *v* 7%; Table 2). Conversely, treatment with carboplatin and S-1 was associated with a higher rate of thrombocytopenia of grade 3 or 4 than was that with carboplatin and paclitaxel (33% *v* 9%, respectively). Platelet transfusion was also necessary for more patients in the carboplatin and S-1 arm than in the carboplatin and paclitaxel arm (8% *v* 2%, respectively; $P = .002$). The overall rates of neuropathy and alopecia were much lower in the carboplatin and S-1 arm (neuropathy, 16% *v* 81%; alopecia, 9% *v* 77%), whereas nausea, vomiting, and diarrhea occurred more frequently in the carboplatin/S-1 arm (Table 2). Death as a result of toxicity occurred in two patients; one death in the carboplatin and S-1 arm was associated with gastrointestinal hemorrhage, and another patient in the carboplatin and paclitaxel arm died of febrile neutropenia and pneumonia.

Table 2. Incidence of Drug-Related Toxicities in Randomly Assigned and Treated Patients

Toxicity	Regimen by Grade (%)						*P*	
	Carboplatin/Paclitaxel (n = 279)			Carboplatin/S-1 (n = 279)				
	All	3	4	All	3	4	All	3 or 4
Hematologic								
Leukopenia	86.0	29.7	2.9	55.4	5.0	0.4	< .001	< .001
Neutropenia	89.6	31.9	44.8	58.3	18.3	2.9	< .001	< .001
Anemia	82.4	14.3	2.5	86.7	15.5	3.6	.165	.680
Thrombocytopenia	63.1	7.2	2.2	87.4	19.4	13.3	< .001	< .001
Nonhematologic								
Febrile neutropenia	7.2	6.8	0.4	1.1	1.1	0	< .001	< .001
Nausea	49.1	2.2	0	62.4	1.8	0	.002	.475
Vomiting	23.7	1.1	0	34.1	1.8	0	.007	.837
Diarrhea	20.8	1.1	0	32.6	3.2	0	.002	.302
Neuropathy: sensory	81.0	2.9	0	15.8	0.4	0	< .001	.668
Arthralgia	67.4	2.5	0	7.9	0	0	< .001	.357
Alopecia	76.7			9.3			< .001	

NOTE. Differences between the two arms were evaluated by the χ^2 test.

QOL

At random assignment, 99.6% of patients (562 of 564) completed baseline questionnaires, with the questionnaire completion rates being 93.4% at 6 weeks and 90.1% at 9 weeks. Compliance rates were not significantly different between the treatment arms. QOL data were missing in 38 surveys due to death or severe impairment of the patient's general condition, which accounted for 2.3% of the total number of the surveys scheduled. There was no significant difference in the lung cancer subscale of FACT-L between the treatment arms (Fig 4). Scores on the neurotoxicity subscale of FACT/GOG-Ntx had decreased significantly in the carboplatin and paclitaxel arm after two cycles of chemotherapy (Fig 4); the adjusted mean scores at 6 and 9 weeks were 41.2 and 41.0 for the carboplatin and S-1 arm and 38.2 and 37.1 for the carboplatin and paclitaxel arm. The alopecia score was also significantly worse in the carboplatin and paclitaxel arm than in the carboplatin and S-1 arm ($P < .001$, analysis of variance), with the adjusted means at 6 and 9 weeks being 3.8 and 3.7 for carboplatin and S-1 and 1.7 and 1.9 for carboplatin and paclitaxel ($P < .001$ at both 6 and 9 weeks, Tukey-Kramer multiple-comparison test).

Poststudy Treatment

There were no major differences in poststudy treatment between the two arms. Overall, 69.4% of carboplatin and paclitaxel patients and 75.5% of carboplatin and S-1 patients received an additional line of therapy ($P = .103$, χ^2 test). Docetaxel was administered in 43.4% and 52.0% of patients and epidermal growth factor receptor tyrosine kinase inhibitors were administrated in 24.0% and 27.2% of patients in the carboplatin and paclitaxel and carboplatin and S-1 arms, respectively.

DISCUSSION

Our phase III study is the first to evaluate the efficacy of an S-1–containing regimen in comparison with standard platinum-doublet chemotherapy for first-line treatment of patients with advanced NSCLC. The primary objective of the study—determination of the noninferiority of carboplatin and S-1 compared with carboplatin and paclitaxel in terms of OS—was met at the planned interim analysis.

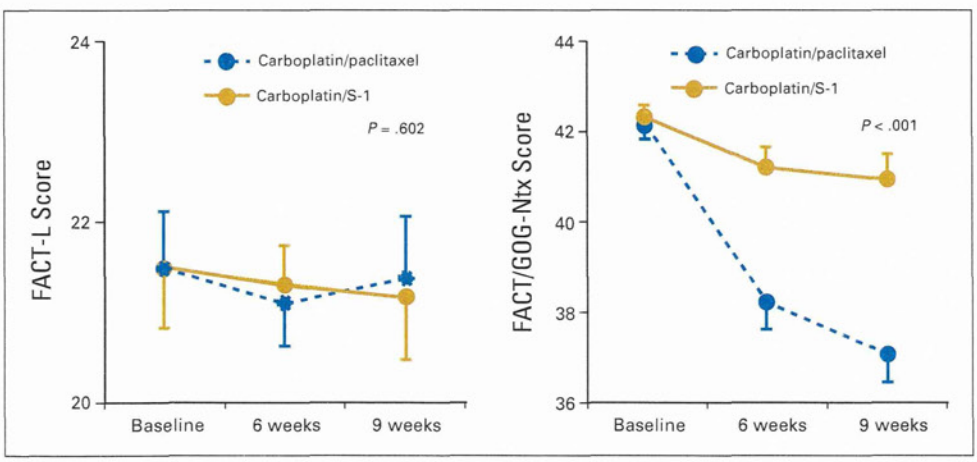

Fig 4. Quality of life assessments with the (left) seven-item Functional Assessment of Cancer Therapy–Lung (FACT-L) and (right) 11-item FACT/Gynecology Oncology Group-Neurotoxicity (GOG-Ntx) scales. Data are least square means ± 95% CI. Higher scores indicate better quality of life. *P* values shown were determined by analysis of variance, with *P* being less than .001 for comparison of FACT/GOG-Ntx scores between the two arms at both 6 and 9 weeks by the Tukey-Kramer multiple-comparison test.

Analysis of OS in the ITT and PP populations as well as in subgroups of the study subjects demonstrated the noninferiority of carboplatin and S-1. Although there was a significant difference in response rate favoring carboplatin and paclitaxel, disease control rate and PFS were similar for carboplatin and S-1 and carboplatin and paclitaxel. Given that subsequent therapies after discontinuation of the study treatment were well-balanced between the treatment groups, it is unlikely that poststudy therapy confounded survival results. Collectively, our secondary data indicate that the findings of the main analysis are robust. Although the protocol-specified noninferiority margin of 1.33 may be large, the survival curves themselves mostly coincided for the two treatment arms and median OS in the carboplatin and S-1 group was noteworthy at approximately 15 months.

The profile of adverse events associated with carboplatin and S-1 and carboplatin and paclitaxel was as expected, but there were marked differences in the incidence of some of these events. Carboplatin and paclitaxel treatment resulted in a typically high incidence of neutropenia of grade 3 or 4 (76.7%) as well as of febrile neutropenia (7.2%), compared with incidences of only 21.1% and 1.1%, respectively, for carboplatin and S-1. These rates of neutropenia associated with carboplatin and paclitaxel treatment are consistent with those observed in previous studies of Japanese patients.[11,14] Carboplatin and S-1 treatment showed a significantly higher rate of thrombocytopenia, which was the most frequent reason for dose delays in the carboplatin and S-1 group. However, this condition was considered manageable because it was associated with bleeding of grade 3 in only one patient. With regard to nonhematologic toxicities, neuropathy, arthralgia, and alopecia were much less frequent in patients treated with carboplatin and S-1 than in those receiving carboplatin and paclitaxel. Consistent with these results, carboplatin and S-1 treatment showed a clinically relevant improvement in QOL as assessed by the FACT/GOG-Ntx scale and alopecia score. Despite these QOL benefits with carboplatin and S-1, however, there was no significant difference in FACT-L score between carboplatin and S-1 and carboplatin and paclitaxel, possibly because of other more toxic effects of carboplatin and S-1. The incidence of nausea, vomiting, and diarrhea of any grade was higher in patients assigned to the carboplatin and S-1 arm than in those assigned to carboplatin and paclitaxel, although grades 3 or 4 of these toxicities were uncommon ($< 4\%$) in both groups. The relative dose intensity of S-1 was 94.3% in the carboplatin and S-1 arm (median of four cycles administered), and treatment was discontinued in only approximately 10% of patients in this arm because of adverse events. Overall, these data indicate that carboplatin and S-1 was well-tolerated, with continuation of treatment as specified in the protocol not being a problem. According to our previous phase I/II study of carboplatin and S-1,[9] this study excluded elderly (≥ 75 years old) patients. Given its efficacy and favorable toxicity profile, the combination of S-1 and carboplatin warrants further evaluation in elderly patients.

In conclusion, our present study demonstrates the noninferiority of carboplatin and S-1 relative to carboplatin and paclitaxel in terms of OS for patients with advanced NSCLC. Carboplatin and S-1 is therefore a valid therapeutic option for the first-line treatment of patients with advanced NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Prospective Study Evaluating the Plasma Concentrations of Twenty-six Cytokines and Response to Morphine Treatment in Cancer Patients

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Abstract. *Cytokine signaling is involved in pain and opioid-receptor signaling. In this prospective study, we studied the plasma cytokine levels in order to identify candidate biomarkers for predicting resistance to morphine treatment in a cohort of opioid-treatment-naïve cancer patients. We analyzed pain rating and the plasma concentrations of 26 cytokines at baseline and after morphine treatment using a multiplex immunoassay system for the following cytokines: eotaxin, colony stimulating factor, granulocyte (G-CSF), colony stimulating factor granulocyte-macrophage (GM-CSF), interferon α2 (IFN-α2), IFN-γ, interleukin 1α (IL-1α), IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17, IP-10, monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α), MIP-1β, tumor necrosis factor-α (TNF-α) and TNF-β. No correlation was observed between the clinical characteristics and the numerical rating scale for pain at baseline or among patients who developed resistance to morphine treatment. Interestingly, the plasma concentration of MIP-1α significantly decreased during morphine treatment (day 8 vs. baseline, p=0.03). Regarding the baseline plasma cytokine concentrations, none of the cytokine levels were correlated with the numerical rating scale for pain at baseline; however, the baseline plasma concentrations of eotaxin, IL-8, IL-12 (p40), IL-12 (p70), MIP-1α and MIP-1β were significantly lower in patients who required a high dose of morphine or who developed resistance to morphine treatment. In conclusion, this is the first report revealing that the plasma concentrations of several cytokines were significantly modulated during treatment and were correlated with treatment outcome of morphine. Our results suggest that plasma cytokine levels may be promising biomarkers for morphine treatment and that they warrant further study.*

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Approximately 80% of advanced-stage cancer patients suffer from pain as a result of their disease, and more than 10 million cancer patients are thought to be treated with opioids worldwide (1). Therefore, controlling chronic, severe pain caused by cancer is considered a very important issue for improving the quality of life of cancer patients. Since the degree of pain sensation and the outcome of morphine treatment varies widely among individuals, pharmacogenetic, pharmacokinetic and pharmacodynamic biomarkers of opioid treatment, such as genetic determinants, have been investigated intensively to improve the effectiveness of morphine treatment (2). Several genetic variants associated with varying pain sensitivity have been identified in the general population, including of the genes for μ-opioid receptor (*OPRM1*); δ-opioid receptor (*OPRD1*); catecholamine-O-methyltransferase (*COMT*); guanosine

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