ANTICANCER RESEARCH *38*: 379-383 (2018)
doi:10.21873/anticanres.12233

Safety and Efficacy of Low-dose Nanoparticle Albumin-bound Paclitaxel for HER2-negative Metastatic Breast Cancer

TSUTOMU TAKASHIMA[1], HIDEMI KAWAJIRI[2], TAKEO NISHIMORI[3], SEIKA TEI[4], SHIGEHIKO NISHIMURA[5], SHIGEHITO YAMAGATA[4], SHINYA TOKUNAGA[6], YOKO MIZUYAMA[7], TAKESHI SUNAMI[8], KENJI TEZUKA[9], KATSUMI IKEDA[6,10], YOSHINARI OGAWA[10], SHINICHIRO KASHIWAGI[1], SATORU NODA[1], NAOYOSHI ONODA[1], TETSURO ISHIKAWA[11], SHINZOH KUDOH[12], MINORU TAKADA[13], KOSEI HIRAKAWA[1] and MASAICHI OHIRA[1]

[1]*Department of Surgical Oncology, Osaka City University Graduate School of Medicine, Osaka, Japan;*
[2]*Department of Breast Surgery, Ishikiri Seiki Hospital, Osaka, Japan;*
[3]*Department of Surgery, Ikuwakai Memorial Hospital, Osaka, Japan;*
[4]*Department of Surgery, Seichokai Fuchu Hospital, Osaka, Japan;*
[5]*Department of Surgery, Sumitomo Hospital, Osaka, Japan;*
[6]*Department of Clinical Oncology, Osaka City General Hospital, Osaka, Japan*
[7]*Department of Surgery, Ohno Memorial Hospital, Osaka, Japan;*
[8]*Department of Surgery, Izumi Municipal Hospital, Osaka, Japan;*
[9]*Department of Surgery, Kishiwada City Hospital, Osaka, Japan;*
[10]*Department of Breast Surgery, Osaka City General Hospital, Osaka, Japan;*
[11]*Department of Surgery, Kashiwara Municipal Hospital, Osaka, Japan;*
[12]*Department of Internal Medicine, Osaka Socio-Medical Center Hospital, Osaka, Japan;*
[13]*Hanwa Daini Senboku Hospital, Osaka, Japan*

Abstract. *Background/Aim: Nab-paclitaxel (nab-PTX) is an albumin-bound paclitaxel formulation. Although nab-PTX has shown superior efficacy compared to conventional paclitaxel (PTX) in metastatic breast cancer (MBC), chemotherapy-induced peripheral neuropathy (CIPN) was more frequently observed in nab-PTX. In this study, we aimed to estimate the feasibility of the nab-PTX 175 mg/m^2/3weeks regimen. Patients and Methods: Patients having metastatic or inoperable HER2-negative breast cancer received 175 mg/m^2 of nab-PTX every three weeks. The primary endpoint was safety and the secondary endpoints were response and survival. Results: Seventeen patients were enrolled with a median age of 64 years. Ten patients had estrogen receptor positive disease and seven had triple-negative disease. CIPN was observed in seven patients (41%) however, grade 3 CIPN was only seen in one patient (6%). Objective response rate was 41% and progression-free survival was 23 weeks. Conclusion: Nab-PTX 175 mg/m^2/3wks regimen has a good safety profile and less frequent CIPN. This regimen can contribute to the strategy of MBC treatment.*

Correspondence to: Tsutomu Takashima, Department of Surgical Oncology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi Abeno, Osaka 5458585, Japan. Tel: +81 666453838, Fax: +81 666466450, e-mail: tsutomu-@rd5.so-net.ne.jp

Key Words: Metastatic breast cancer, HER2-negative breast cancer, nanoparticle albumin-bound paclitaxel, safety, chemotherapy, peripheral neuropathy.

The prognosis for patients with human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC) has improved significantly, however, overall survival of patients with endocrine-resistant HER2-negative MBC remains only three years (1). As MBC is currently incurable, the goals of therapy are to prolong survival, palliate symptoms, and improve quality of life (QoL) (2). The current guidelines suggest using a single agent to optimize both treatment length and QoL, except in the case of immediately life-threatening disease (2, 3).

Recently, nanoparticle albumin-bound paclitaxel (nab-PTX) that is a solvent-free formulation in which paclitaxel is delivered as a suspension of albumin nanoparticles came to provide for MBC treatment. It can be administered as a high dose of paclitaxel (PTX) without steroid premedication in only 30 min. This formulation does not contain alcohol and cremophor. No premedication is required because it is less allergenic, and it can be used safely for alcohol intolerance patients. It does not require polyvinyl chloride free infusion line (4). The CA012 trial comparing solvent-based PTX of

175 mg/m^2/3 weeks dose with nab-PTX 260 mg/m^2/3 weeks dose for MBC demonstrated a significantly superior response rate and progression free survival (PFS) in the nab-PTX arm, compared to the PTX arm. However, this study could not show a survival benefit of nab-PTX (overall survival; 65.0 *vs.* 55.7 weeks) and grade 3 or higher chemotherapy induced peripheral neuropathy (CIPN) was more frequently observed in the nab-PTX arm than those in the PTX arm (10.5% *vs.* 2.2%). This higher incidence of grade 3 CIPN in nab-PTX arm was considered as dose limitation toxicity of this agent (5). By observing the recent guidelines for MBC treatment, nab-PTX does not seem to be suitable for MBC treatment at the standard 260 mg/m^2/3 weeks dose because it is difficult to maintain QoL due to severe neurotoxicity.

From a pharmacological perpective, nab-PTX should have at least an equal effect in comparison with the same dose of PTX. To date, only one phase II trial (CA002-0LD) is conducted outside Japan. In this study, low dose tri-weekly nab-PTX 175 mg/m^2 showed good ORR (39.5%) and no CIPN of grade 3 or higher (6). Therefore, we conducted a feasibility study of nab-PTX using the 175 mg/m^2/3 weeks dose in Japanese patients.

Patients and Methods

Patients. Key inclusion criteria included: female patients with histologically confirmed HER2-negative MBC; aged ≥20 and <80 years; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; having measurable lesion(s) based on the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 (7); and adequate bone marrow, liver, renal, and lung functions. Key exclusion criteria included: hypersensitivity to taxane or albumin; systemic infection; uncontrolled pleural effusion/ascites or pericardial effusion; symptomatic brain tumor; serious complications, active concomitant malignancy; pregnancy (including possible pregnancy) of premenopausal women. Patients who were considered ineligible by the investigator were also excluded.

Study design. This was a single-arm, multicenter trial conducted at eight sites in Japan. The study protocol and all amendments were approved by local ethics committees or the institutional review board at each study site. This trial was conducted in accordance with the Japanese Guidelines for Clinical Research of the Ministry of Health, Labor and Welfare and the Declaration of Helsinki, as well as other applicable regulatory requirements. All participants provided written informed consent prior to study entry. The present trial has been registered with the University Hospital Medical Information Network (UMIN) Center (ID: UMIN000013275). This was an investigator-initiated clinical trial that was not supported by any industry funding, nor requested by any organization.

Nab-PTX was administered intravenously, without any premedication, at a dose of 175 mg/m^2 over 30 min on days 1 of a 21-day cycle. Study treatments continued until disease progression, unacceptable toxicity, or the patient requested to withdraw from the study. Concomitant use of other anticancer therapy (*e.g.*, hormone therapy, targeted therapy, immune therapy, and chemotherapy other than nab-PTX) and any local therapy was prohibited. Concomitant use of bone modifying agents was permitted if the agents had been used since prior to the study entry. Use of granulocyte colony-stimulating factor was permitted, but not for prophylactic administration, by decision of the investigator based on the clinical practice guidelines (8).

The primary efficacy outcome was safety. The secondary endpoints included overall response rate (ORR), defined as the proportion of patients who achieved a complete response (CR) plus those who achieved a partial response (PR), time to treatment failure (TTF) and overall survival (OS).

Assessment. The information on patients' characteristics at baseline was collected within 28 days prior to the initiation of nab-PTX administration. Baseline tumor assessments by radiographic evaluation were also performed within 28 days prior to the initiation of nab-PTX administration, and tumor assessments were performed by the same methods at least every 3 months. For safety, hematology and biochemistry assessments were performed before the start of each treatment cycle. All adverse events were assessed at every visit and were graded according to the Common Terminology Criteria for Adverse Events ver. 4.0 (9). Tumor assessments were analyzed based on the RECIST ver. 1.1 (7) and classified as CR, PR, stable disease (SD), progressive disease, or not evaluable. TTF was defined as the time from initiation of nab-PTX to treatment discontinuation for any reason (*e.g.*, disease progression, treatment toxicity, patient preference, or death), OS was defined as the time from initiation of ab-PTX to death from any cause.

Statistical analysis. The safety analysis was also conducted in the full analysis set which included all patients who received at least one dose of nab-PTX. Efficacy outcome (proportion of patients who achieved CR or PR for at least four weeks) was assessed in the full analysis set. In addition, clinical benefit rate (CBR) was defined as the proportion of patients who achieved CR, PR, or SD for at least 24 weeks. The median values for TTF and OS curves were estimated with the Kaplan-Meier method.

Results

Patients. A total of 17 patients with inoperable or recurrent breast cancer were enrolled in the study, to be treated with low dose nab-PTX from October 2011 to September 2014; none were excluded from our primary analysis. The characteristics of the patients at baseline are summarized in Table I. The median age was 64 years (range=43-79 years), and the all patients had ECOG PS 0 or 1. Thirteen patients (76%) had recurrent disease and four patients (24%) had inoperable disease at the presentation. Ten patients (59%) were hormonal receptor-positive. Median number of prior chemotherapy was one regimen (range=0-7 regimens). Disease free interval of the patients who had recurrent disease was 38 months. Four patients (24%) had less than two years disease free interval. Seven patients (41%) had received taxane before nab-PTX. The median number of nab-PTX administration was 6 (range=2-16). Patients were followed-up for a median of 75 weeks (range=6-203 weeks).

Table I. *Patient characteristics*.

Age, median (range)	64 (43-79)
ECOG PS, n	
0	9
1	6
2	2
Menopausal status	
Pre	2
Post	15
Prior Chemotherapy, n	
Taxane	7
Anthracycline	7
Hormonal receptor, n	
positive	10
Negative	7
Metastatic sites, n	
Visceral	9
Non-visceral	8
Stage, n	
Recurrence	13
Inoperable	4
Disease free interval, months	38 (9-127)
<2yrs	4
>=2yrs	9
without surgery	4
No. of prior chemotherapy, median (range)	1 (0-7)
0	4
1	6
2	2
3	1
4 or more	4
Treatment Cycles, median (range)	6 (2-16)

Table II. *Adverse events*.

Adverse events	All grade (n)	Grade3/4 (n)
CIPN	7	1
Myalgia	9	0
Arthralgia	3	0
Fatigue	7	0
Appetite loss	5	0
Nausea	3	0
Vomiting	1	0
Skin rash	2	0
Alopecia	17	-
Leukopenia	7	2
Neutropenia	5	3
Anemia	5	0
Thrombocytopenia	4	0
Aspartate aminotransferase	5	0
Alanine aminotransferase	3	0
Alkaline phosphatase	1	0
Lactate dehydrogenase	9	0
γ-glutamyltransferase	1	0
Blood urea nitrogen	3	0

Table III. *Efficacy*.

Response	n
CR	0
PR	7
SD >24 weeks	1
SD	6
PD	3

Safety analysis. Observed adverse events are shown in Table II. CIPN was observed in seven patients (41%); three were grade 1, three were grade 2 and only one patient (6%) developed grade 3 sensory neuropathy. The most commonly reported non-hematological adverse events other than CIPN were alopecia (17 patients; 100%), followed by myalgia (9 patients; 53%), fatigue (7 patients; 41%), and appetite loss (5 patients; 29%).

Regarding hematological toxicity, two patients (12%) showed grade 4 and one (6%) showed grade 3 neutropenia. Mild anemia up to Grade 2 was observed in five and also mild thrombocytopenia appeared in four patients. Febrile neutropenia was not reported in this series.

No patient discontinued low dose nab-PTX therapy due to adverse events.

Abnormal values in biochemical parameters were reported as follows: aspartate aminotransferase (5 patients; 29.4%), alanine aminotransferase (3 patients; 17.6%), gamma-glutamyl transpeptidase (2 patients; 11.8%), alkaline phosphatase (1 patients; 5.9%). All non-hematologic toxicities were Grade 1. There were no serious adverse events reported.

Efficacy analysis. No patient achieved CR, seven patients (41%) showed PR, and 7 patients showed SD (one patient longer than 24 weeks and six patients shorter than 24 weeks).

The ORR was 41% (95%CI=17.8-64.5), CBR was 47% (95%CI=23.3-70.8) (Table III).

The median PFS was 23 weeks (95%CI=15.7-30.3) and median OS was 79 weeks (Figure 1).

Discussion

The current study was to investigate the safety and efficacy of low-dose nab-PTX for HER2-negative MBC in Japanese patients.

Overall, the safety of low-dose nab-PTX was acceptable, and no patient discontinued therapy due to adverse events. The majority of non-hematological adverse events were mild in severity. Grade 3 sensory neuropathy, which might lead to discontinuation of nab-PTX therapy, was reported in only one

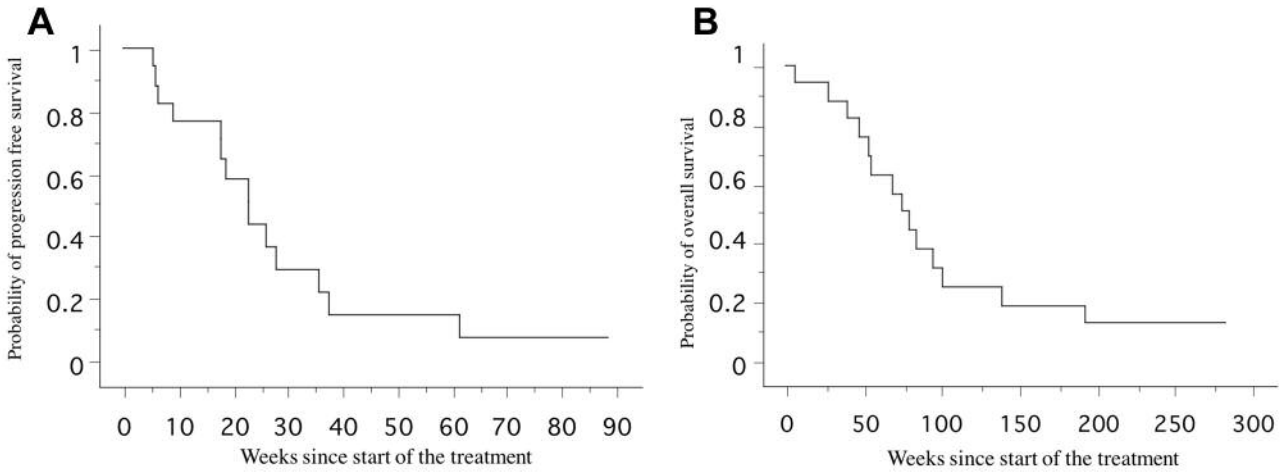

Figure 1. *(A) Progression-free survival. (B) Overall survival.*

(6%) patient. Among hematological adverse events, grade 3 or 4 neutropenia was reported in only three patients (one grade 3 and two grade 4). The proportion of patients who experienced severe adverse events after initiation of low dose nab-PTX was relatively low. Thus, many patients treated with low dose nab-PTX might not experience deterioration of their QoL due to severe adverse events. With the aspect of the efficacy, this study demonstrated that the ORR was 44% and PFS was 23 weeks. It is comparable to efficacy of other key drugs for MBC treatment (10-12). CA002-0LD, a small single arm phase 2 study including 43 MBC patients, was conducted as a part of the clinical researches for the development of nab-PTX. This trial has not been published, however, tri-weekly nab-PTX at 175 mg/m^2 dose demonstrated a good objective response rate (39.5%) without grade 3 or higher CIPN (6). Recently, results were reported from a phase II trial, that tested for low dose nab-PTX at 180 mg/m^2/3 weeks. No grade 3-4 peripheral sensory neuropathy occurred in this trial (13).

Nab-PTX is a solvent-free formulation in which paclitaxel is delivered as a suspension of albumin nanoparticles and additionally, drug transport into tumors may be enhanced by albumin receptor and caveolae-mediated transport across endothelial cells (4). Therefore, it should have at least equal efficacy in comparison with the same dose of solvent-based PTX which has been used as a key drug for MBC. Tri-weekly regimen of solvent-based PTX at 175 mg/m^2 dose was tested in late 1990's to early 2000's, mainly as the control arm of many clinical trials (5, 10, 12, 14, 15). They demonstrated four to six months PFS or TTF and around 30% of ORR. Grade 3 or 4 CIPN was observed only in 2 to 7 % of the patients. A standard dose of nab-PTX (260 mg/m^2/3w) was in fact superior to solvent-based PTX of 175 mg/m^2/3w dose in ORR (33% *vs.* 19%) and time to progression (23.0 *vs.* 16.9 weeks) in the CA012-0 trial, however there was no difference in overall survival, and grade 3 CIPN occurred more frequently in the nab-PTX arm.

Weekly administration of nab-PTX was tested in a randomized phase III trial, GeparSepto-GBG 69, that compared nab-PTX at the dose of 150 mg/m^2/week with solvent-based PTX in neoadjuvant setting. However, grade 3 or 4 CIPN occurred in 15% of the patients treated with weekly nab-PTX. Eventually, the weekly nab-PTX dose was reduced after enrolment of 464 participants to 125 mg/m^2 due to increased treatment discontinuation and sensory neuropathy (16). In the phase III CALGB 9840 trial of breast cancer comparing weekly PTX at 80 mg/m^2 dose with tri-weekly PTX at 175 mg/m^2 dose, there was significantly less grade 3 or 4 CIPN in the tri-weekly arm (12% *vs.* 19%) (17). The incidence of CIPN seemed to depend on not only dosage, but also treatment schedules and a tri-weekly schedule might be superior to a weekly one.

In the recent consensus, the goal of MBC treatment is prolonging OS with maintaining good QoL, it is never cure (2, 3). Severe CIPN is one of the most common causes of QoL deterioration due to impairment of daily life activity and we don't have any effective way to control it. Therefore, we believe a standard dose of nab-PTX is not appropriate as a regimen for metastatic setting and 175 mg/m^2/3w dose of nab-PTX is enough to control the disease with less adverse events.

In conclusion, our results suggest low dose nab-PTX at 175 mg/m^2/3 weeks could contribute as a part of MBC treatment sequence. However, since the number of patients included in this study was very small, caution is required for interpretation of the results.

To investigate the appropriate dose of nab-PTX in a metastatic setting, a randomized phase II trial (ABROAD trial) is now being conducted in Japan (protocol ID: UMIN000012429) (18). It compares PFS of three different doses of tri-weekly nab-PTX

(180 mg/m^2 *vs*. 220 mg/m^2 *vs*. 260 mg/m^2) in patients with MBC. This trial will provide some speculation about the balance between dose, efficacy and adverse events.

Acknowledgements

The Authors would like to express their deepest gratitude to the women who participated in this trial and their family members, in addition to the investigators and all staff members at the study sites for their contribution to the study.

References

1 Takashima T, Mukai H, Hara F, Matsubara N, Saito T, Takano T, Park Y, Toyama T, Hozumi Y, Tsurutani J, Imoto S, Watanabe T, Sagara Y, Nishimura R, Shimozuma K and Ohashi Y: Taxanes *versus* S-1 as the first-line chemotherapy for metastatic breast cancer (SELECT BC): an open-label, non-inferiority, randomised phase 3 trial. Lancet Oncol *17*: 90-98, 2016.

2 Partridge AH, Rumble RB, Carey LA, Come SE, Davidson NE, Di Leo A, Gralow J, Hortobagyi GN, Moy B, Yee D, Brundage SB, Danso MA, Wilcox M and Smith IE: Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol *32*: 3307-3329, 2014.

3 Cardoso F, Costa A, Norton L, Senkus E, Aapro M, André F, Barrios CH, Bergh J, Biganzoli L, Blackwell KL, Cardoso MJ, Cufer T, El Saghir N, Fallowfield L, Fenech D, Francis P, Gelmon K, Giordano SH, Gligorov J, Goldhirsch A, Harbeck N, Houssami N, Hudis C, Kaufman B, Krop I, Kyriakides S, Lin UN, Mayer M, Merjaver SD, Nordström EB, Pagani O, Partridge A, Penault-Llorca F, Piccart MJ, Rugo H, Sledge G, Thomssen C, Van't Veer L, Vorobiof D, Vrieling C, West N, Xu B and Winer E: ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Ann Oncol *25*: 1871-1888, 2014.

4 Henderson IC and Bhatia V: Nab-paclitaxel for breast cancer: a new formulation with an improved safety profile and greater efficacy. Expert Rev Anticancer *7*: 919-943, 2007.

5 Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, Hawkins M and O'Shaughnessy J: Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol *23*: 7794-7803, 2005.

6 Ibrahim NK, Samuels B, Page R, Guthrue T, Ramakrishnan G, Doval D, Patel K, Rao S, Nair M, Digumarti R and Hortobagyi GN: Nanoparticle paclitaxel (ABI-007) in metastatic breast cancer (MBC): efficacy and evidence of dose dependent activity in two multicenter phase II studies. ASCO Proc Am Soc Clin Oncol Orleans, USA *21*: 53a, 2002.

7 Eisenhauer EA1, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours. Revised RECIST guideline (version 1.1). Eur J Cancer *45*: 228-247, 2009.

8 Dale DC: Updated ASCO recommendations for the use of white blood cell growth factors. Clin Adv Hematol Oncol *4*: 664-666, 2006.

9 Cancer Therapy Evaluation Program (CTEP). Common Terminology Criteria for Adverse Events (CTCAE) v4.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. [Accessed Aug 8, 2017].

10 Sledge GW, Neuberg D, Bernardo P, Ingle JN, Martino S, Rowinsky EK and Wood WC: Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An Intergroup Trial (E1193). J Clin Oncol *21*: 588-592, 2003.

11 Katsumata N, Watanabe T, Minami H, Aogi K, Tabei T, Sano M, Masuda N, Andoh J, Ikeda T, Shibata T and Takashima S: Phase III trial of doxorubicin plus cyclophosphamide (AC), docetaxel, and alternating AC and docetaxel as front-line chemotherapy for metastatic breast cancer: Japan Clinical Oncology Group trial (JCOG9802). Ann Oncol *20*: 1210-1215, 2009.

12 Jones SE1, Erban J, Overmoyer B, Budd GT, Hutchins L, Lower E, Laufman L, Sundaram S, Urba WJ, Pritchard KI, Mennel R, Richards D, Olsen S, Meyers ML and Ravdin PM: Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol *23*: 5542-5551, 2005.

13 Yamamoto S, Maeda N, Nagashima Y, Kubo H, Sato Y, Matsui H, Inoue Y, Shindo Y, Kanekiyo S, Sakamoto K, Suzuki N, Takeda S, Ueno T, Yoshino S, Hazama S, Oka M and Nagano H: A phase II, multicenter, single-arm study of tri-weekly low-dose nanoparticle albumin-bound paclitaxel chemotherapy for patients with metastatic or recurrent breast cancer. Breast Cancer *24*: 783-789, 2017.

14 Nabholtz JM, Gelmon K, Bontenbal M, Spielmann M, Catimel G, Conte P, Klaassen U, Namer M, Bonneterre J, Fumoleau P and Winograd B: Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol *14*: 1858-1867, 1996.

15 Winer EP, Berry DA, Woolf S, Duggan D, Kornblith A, Harris LN, Michaelson RA, Kirshner JA, Fleming GF, Perry MC, Graham ML, Sharp SA, Keresztes R, Henderson IC, Hudis C, Muss H and Norton L: Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: Cancer and Leukemia Grup B Trial 9342. J Clin Oncol *22*: 2061-2068, 2004.

16 Untch M, Jackisch C, Schneeweiss A, Conrad B, Aktas B, Denkert C, Eidtmann H, Wiebringhaus H, Kümmel S, Hilfrich J, Warm M, Paepke S, Just M, Hanusch C, Hackmann J, Blohmer JU, Clemens M, Darb-Esfahani S, Schmitt WD, Dan Costa S, Gerber B, Engels K, Nekljudova V, Loibl S and von Minckwitz G: Nab-paclitaxel *versus* solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol *17*: 345-356, 2016.

17 Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, Gipson G, Burstein H, Lake D, Shapiro CL, Ungaro P, Norton L, Winer E and Hudis C: Randomized phase III trial of weekly compared with every 3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol *26*: 1642-1649, 2008.

18 Hara F, Takashima T, J Tsurutani, Saito T, Taira N, Kashiwabara K, Aihara T and Mukai H: Randomized, Optimal Dose Finding, Phase II Study of Tri-Weekly Nab- Paclitaxel in Patients with Metastatic Breast Cancer (ABROAD). J Clin Trials *6*: 267, 2016.

Received October 9, 2017
Revised November 3, 2017
Accepted November 6, 2017