Phase I and Pharmacokinetic Study of ABI-007, Albumin-bound Paclitaxel, Administered Every 3 Weeks in Japanese Patients with Solid Tumors

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Objective: ABI-007 is a novel Cremophor® EL-free nanoparticle albumin-bound paclitaxel. This Phase I study was designed to evaluate tolerability and determine recommended dose for Japanese patients when ABI-007 was administered in every-3-week schedule. Pharmacokinetics of paclitaxel was also assessed.

Methods: Patients with advanced solid tumors refractory to standard therapy received a 30 min intravenous infusion of ABI-007 every 3 weeks without pre-medications at 200, 260 or 300 mg/m², respectively. Tolerability and recommended dose were determined by the standard ‘3 + 3’ rule.

Results: No dose-limiting toxicity was observed, despite the dose escalation. In another cohort, 260 mg/m² was re-evaluated and resulted in no dose-limiting toxicity. Grade 3 or 4 neutropenia was reported for the majority of patients (n = 8) but no incidence of febrile neutropenia. Non-hematological toxicities were generally mild except for Grade 3 sensory neuropathy (n = 3). Pharmacokinetic study demonstrated the area under the curve of paclitaxel increased with increasing the dosage, and comparable pharmacokinetic parameters to the western population. Partial response was observed in three non-small cell lung cancer patients. Two of whom had received docetaxel-containing chemotherapy prior to the study.

Conclusions: ABI-007 administered in every-3-week schedule was well tolerated up to 300 mg/m², and recommended dose was determined at 260 mg/m² in consideration of efficacy, toxicities and similarity of pharmacokinetic profile in western studies. Additional studies of single-agent ABI-007 as well as platinum-based combinations, particularly in patients with non-small cell lung cancer, are warranted.

Key words: nanoparticle albumin-bound paclitaxel – ABI-007 – Phase I – pharmacokinetic – Japanese

INTRODUCTION

ABI-007 (Abraxane®; Abraxis Bioscience, Los Angeles, CA, USA) is a novel Cremophor® EL (polyoxyethyalted castor oil)-free albumin-bound nanoparticle formulation of paclitaxel. This formulation allows for a higher paclitaxel concentration in the suspension, serving to reduce the administration volume and time. No pre-medication to prevent the Cremophor® EL-induced hypersensitivity reaction is needed. In addition, non-polyvinyl chloride infusion system and in-line filtration are not necessarily applied given no leaching of plasticizers (1,2).
In the Phase I study of every-3-week (Q3W) schedule conducted in the USA, the dose of ABI-007 was escalated from 135 to 375 mg/m², and maximum tolerated dose (MTD) and recommended dose (RD) were established at 300 mg/m². It was exceedingly higher than that of solvent-based paclitaxel (Taxol™; Bristol–Myers Squibb, Princeton, NJ, USA), 175 mg/m² (1). Dose-limiting toxicities (DLTs) were keratitis, blurred vision, sensory neuropathy, stomatitis and neutropenia. Maximum concentration ($C_{\text{max}}$) and the area under the curve from time zero to infinity (AUClinf) of paclitaxel increased linearly over the ABI-007 dose range of 135–300 mg/m² administered over 30 min. Volume of distribution of ABI-007 is characterized by the larger distribution than solvent-based paclitaxel, indicating extensive extravascular distribution of the drug (3). $C_{\text{max}}$ and AUClinf values for individual patients correlated well with toxicities.

In the Phase III pivotal study of 454 patients with metastatic breast cancer, Q3W schedule of ABI-007 260 mg/m² produced the superior outcome to the same schedule of solvent-based paclitaxel, 175 mg/m²: significantly higher response rate and prolonged time to progression [33% vs. 19% ($P < 0.001$) and 23.0 vs. 16.9 weeks ($P = 0.006$), respectively] and significantly lower incidence of Grade 4 neutropenia, despite a 49% higher paclitaxel dose [9% vs. 22% ($P < 0.001$)] (4). The dosage and schedule used in this Phase III study lead to the approved labeling worldwide.

According to the clinical utility and study data reported overseas, ABI-007 seems to be an effective treatment. This Phase I study aimed to evaluate tolerability, DLT and RD in Japanese patients with solid tumors when administered in Q3W schedule. Efficacy, toxicity and pharmacokinetics (PK) were also evaluated as secondary objectives, followed by the evaluation on ethnic difference in PK.

### PATIENTS AND METHODS

**Patient Eligibility**

Patients aged 20–74 years with histologically or cytologically diagnosed malignant solid tumors refractory to standard therapies or for which there was no effective treatment were eligible. They had to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, and a life expectancy of ≥60 days. Eligibility criteria also included adequate renal, liver and bone marrow function, defined as serum creatinine (Cr) $\leq 1.5$ mg/dl, serum total bilirubin (TB) $\leq 1.5$ mg/dl, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 100$ IU/l, respectively, serum albumin $\geq 3.0$ g/dl, white blood cell count $\leq 12 000$/mm³, absolute neutrophil count $\geq 2000$/mm³, platelets $\geq 100 000$/mm³ and hemoglobin $\geq 9.0$ g/dl. Patients with prior exposure to taxanes were eligible for the study. Key exclusion criteria included the following: (i) surgery within 4 weeks; (ii) chemotherapy within 3 weeks; (iii) radiotherapy within 3 weeks; (iv) history of radiation to more than 30% of hematopoietic marrow; (v) pre-existing sensory neuropathy $\geq$ Grade 2; (vi) pleural effusion and ascites that required drainage; (vii) brain metastasis showing symptoms or requiring treatment; (viii) hepatitis B or C virus or human immunodeficiency virus infection; (ix) chronic steroid treatment; (x) pregnancy, lactation, suspicion of being pregnant; (xi) serious pre-existing medical conditions such as uncontrolled infections, pulmonary fibrosis, diabetes, severe heart disease and psychogenic disorders.

This study was approved by the Institutional Review Board at the National Cancer Center and conducted according to Japanese Good Clinical Practice guidelines. All patients provided written informed consent prior to study entry.

### STUDY DESIGN AND TREATMENT

This Phase I, open label, dose-finding study was conducted at National Cancer Center and National Cancer Center East.

ABI-007 was supplied by TAIHO Pharmaceutical Co., Ltd, Tokyo Japan. Each vial contained 100 mg of paclitaxel and $\sim 900$ mg of frozen-dried Albumin Human (United States Pharmacopeia). The prescribed dose of ABI-007 was prepared in 5 mg (paclitaxel)/ml of physiological saline as a suspension. The drug was administered via 30 min i.v. without pre-medications and in-line filtration.

Evaluated dose levels were 200, 260 or 300 mg/m², as shown in Table 1, repeated every 3 weeks. The rationale for selected dose range was the following: the upper level, 300 mg/m²—MTD determined in a US Phase I study; the middle level, 260 mg/m²—the approved dose in the US/EU, and the lower level, 200 mg/m²—one dose level below MTD examined in the foregoing Phase I study. The dose range also factored in PK: linear PK of ABI-007 over the dose range 80–300 mg/m² and the same level and activity of CYP2C8 and CYP3A4 between Japanese and Caucasians (5). Dose escalation was capped at 300 mg/m². In the event that MTD exceeded the cap, further steps in investigation would be discussed among study sponsor, principal investigator and medical experts.

The dose escalation followed the standard ‘3+3’ rule. Three patients were evaluated at the first dose level, and in the absence of DLTs, three additional patients were entered at the next dose level. If one of the three patients encountered a DLT, another cohort was to be added at the same dose level. The MTD was defined as the dose level at which two out of three to six patients experienced DLT. The RD

| Level | Dose (mg/m²) | No. of patients entered | No. of courses |
|-------|-------------|------------------------|---------------|
| 1     | 200         | 3                      | 9             |
| 2     | 260         | 6                      | 23            |
| 3     | 300         | 3                      | 14            |

Table 1. Dose levels
was defined as the dose level that is one level below MTD, and consequently, a total of six patients were to be treated at RD to further evaluate the safety profile.

DLTs were pre-defined as any of the following drug-related toxicities that had occurred during the first course: (i) Grade 4 thrombocytopenia; (ii) Grade 3 thrombocytopenia requiring platelet transfusion; (iii) Grade 4 neutropenia over 4 days; (iv) Grade 3 or 4 febrile neutropenia; and (v) Grade 3 or 4 non-hematologic toxicity. Dose was reduced by one level when DLT occurred in the first course, and reduction was allowed when the toxicities corresponding to DLT or Grade 2 neuropathy occurred in the second course or later.

**Patient Evaluation**

Pre-treatment evaluation included a complete history and physical examination, a complete blood count with differential, serum chemistry profile, urinalysis including pregnancy test, chest X-ray and electrocardiogram. Serum chemistry profile included electrolytes, Cr, urea nitrogen, TB, AST, ALT, lactic dehydrogenase, alkaline phosphatase, total protein, albumin and C-reactive protein. Baseline imaging studies and serum tumor marker levels were obtained at the discretion of treating physician. Toxicity assessment, physical examination and all blood tests except serum tumor markers were repeated on a weekly basis.

Toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Patients were considered evaluable for toxicity if they received at least one dose of the study drug. Objective response to therapy was assessed every 4–6 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0 (6).

**Blood Sampling and PK Analysis**

Whole blood samples of 7 ml each were collected in 6 ml of heparinized tube and 1 ml of K3-EDTA tube to determine the PK of ABI-007 at time points: 0, 0.25, 0.5 (end of infusion), 0.75, 1, 1.5, 2, 4, 10, 24, 48 and 72 h. Heparinized samples were immediately centrifuged at 1000 g for 15 min in 4°C and resultant plasma was stored in aliquot, whereas K3-EDTA samples were softly mixed in normal temperature. These samples were stored at less than or equal to −20°C until analyzed. The sample was analyzed for paclitaxel using liquid chromatography/tandem mass spectrometry in Alta Analytical Laboratory (El Dorado Hills, CA, USA). The \( C_{\text{max}} \) of paclitaxel was obtained directly from experimental data. The elimination constant (\( \lambda_z \)) was obtained by log-linear regression analysis of the terminal phase of the whole blood/plasma concentration vs. time profile. The elimination half-life (\( t_{1/2} \)) was determined by taking the ratio of natural log of 2 and \( \lambda_z \). The \( \text{AUC}_{\text{inf}} \) was estimated by summing the areas from time zero to the last measured concentration—time point (\( \text{AUC}_{0-\text{inf}} \)), calculated using the linear-logarithmic trapezoidal method, and the extrapolated area. The dose–area relationship (i.e. total ABI-007 dose divided by \( \text{AUC}_{\text{inf}} \)) was used to determine total body clearance (CL). The volume of distribution (Vz) was determined by taking the ratio between CL and \( \lambda_z \).

| Characteristics | No. of patients |
|-----------------|-----------------|
| Total no. of patients | 12 |
| Male/female | 10/2 |
| Age (years) | |
| Median | 61 |
| Range | 45–69 |
| ECOG performance status | |
| 0 | 3 |
| 1 | 9 |
| Tumor type | |
| NSCLC | 6 |
| Parotid gland | 1 |
| Ovary | 1 |
| Bladder | 1 |
| Pharyngeal and esophageal | 1 |
| Colon | 1 |
| Thymoma | 1 |
| Prior treatment | |
| Surgery | 9 |
| Radiotherapy | 3 |
| Chemotherapy | 12 |
| No. of prior chemotherapy | |
| 1 | 1 |
| 2 | 4 |
| ≥3 | 7 |
| Prior taxane therapy | |
| Yes | |
| Solvent-based paclitaxel | 1 |
| Docetaxel | 5 |
| Solvent-based paclitaxel and docetaxel | 2 |
| No | 4 |

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.
Descriptive statistics were used for baseline characteristics, safety assessment, and PK variables. Regression analysis of individual C\text{max}, and AUC\text{inf} vs. dose was performed to gain an appreciation of PK linearity. The SAS software package (ver8.2, SAS Institute, Inc., NC, USA) was used for statistical analysis.

RESULTS

PATIENTS AND TREATMENT

Between August 2006 and June 2007, 12 patients were enrolled and treated in this study at two participating centers in Japan. Patient characteristics are summarized in Table 2. Most patients were male (83%) with a median age of 61 (range, 45–69) years and all patients were ECOG PS 0–1. The predominant type of tumor was non-small cell lung cancer (NSCLC). Nine patients had surgery for primary tumors, seven had received more than three prior chemotherapy regimens and eight had received prior taxane-containing chemotherapy.

The patients were treated at the following dose levels: 200 mg/m\textsuperscript{2} (Level 1, \( n = 3 \)), 260 mg/m\textsuperscript{2} (Level 2, \( n = 6 \)) and 300 mg/m\textsuperscript{2} (Level 3, \( n = 3 \)). All were evaluable for safety and PK, and 11 for efficacy (one had no adequate measurable lesions for RECIST criteria).

DLT, TOLERABILITY AND RD

No DLTs were observed through the dose escalation to the highest Level 3; therefore, the MTD was not reached methodologically. To decide on the potential RD, study sponsor, medical advisor and principal investigators jointly reviewed the reference data in the foreign studies (1,4,7) and favored 260 mg/m\textsuperscript{2} from tolerability and safety perspectives, particularly the development of cumulative neurotoxicity. Additional three patients were then accrued to 260 mg/m\textsuperscript{2} cohort to repeat the assessment. None of DLTs being experienced by the additional patients, 260 mg mg/m\textsuperscript{2}, was established as RD.

SAFETY

A total of 46 courses of ABI-007 was administered, and the median number of courses administered per patient was 3 (range, 1–11). No acute hypersensitivity reactions were observed during the infusion period. The most common toxicities were neutropenia, leucopenia, lymphopenia, alopecia and sensory neuropathy. The incidences of hematologic toxicities by dose level are shown in Table 3. Grade 3 or 4 neutropenia was often experienced in more than half of patients throughout the study; however, no febrile neutropenia was observed. The median time to onset of Grade 3 or 4 neutropenia was 15.0 (range, 8–34) days, and the median time to recovery to <Grade 2 was 6.5 (range, 3–14) days. There were no episodes of ≥Grade 2 or greater thrombocytopenia, and anemia was mostly mild. Frequent non-hematologic toxicities were sensory neuropathy, alopecia, arthralgia/myalgia and rash (Table 4). The sensory neuropathy was manifested by paresthesia in a symmetric, stocking/glove distribution, and the median time to the first indication or exacerbation from the baseline was 7 days. The severity of non-hematologic toxicities was generally mild except for three cases of Grade 3 sensory neuropathy at Level 2 (\( n = 1 \)) and Level 3 (\( n = 2 \)), which cumulatively exacerbated from Grade 1 observed in the first week of the first course (range, 3–6 days from the administration) to Grade 3 during the third or later course (range, 3–11 courses from the administration). Among the three patients who experienced Grade 3 sensory neuropathy, one patient had received taxane-containing chemotherapy prior to the study. A variety of ocular toxicities including superficial keratopathy reported in the initial Phase I study of USA were not observed in this study. Treatment delay occurred in one patient at each Levels 2 and 3 due to the neurotoxicity, dose reduction occurred in two patients at each Levels 2 and 3 due to the neurotoxicity, and treatment was discontinued in three patients at each Levels 2 and 3, comprising five patients with treatment-related neurotoxicity and one patient with unrelated neutropenia.

| Dose levels | Level 1 (200 mg/m\textsuperscript{2}) | Level 2 (260 mg/m\textsuperscript{2}) | Level 3 (300 mg/m\textsuperscript{2}) | All |
|-------------|-------------------------------------|-------------------------------------|-------------------------------------|-----|
| No. of patients (no. of courses) | \( n = 3 \) (9) | \( n = 6 \) (23) | \( n = 3 \) (14) | \( n = 12 \) (46) |
| CTCAE grade | 1–2 | 3 | 4 | 1–2 | 3 | 4 | 1–2 | 3 | 4 |
| Leucopenia | 2 | 0 | 0 | 3 | 2 | 0 | 3 | 0 | 0 | 8 | 2 | 0 |
| Neutropenia | 1 | 1 | 0 | 1 | 3 | 1 | 1 | 2 | 0 | 2 | 6 | 2 |
| Anemia | 1 | 0 | 0 | 2 | 0 | 0 | 1 | 0 | 0 | 4 | 0 | 0 |
| Thrombocytopenia | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 0 | 0 |

CTCAE, Common Terminology Criteria for Adverse Events.
Eleven of 12 patients were evaluable for anti-tumor response (Table 5). Partial responses were observed in three NSCLC patients. Of them, two of whom had received docetaxel-containing chemotherapy prior to the study. The first patient, entered at Level 1, had received 6 courses of ABI-007, and the second and third patients, entered at Level 2, 11 and 6 courses, respectively. The both responders in Level 2 attained disease control until the treatment discontinuation due to the sensory neuropathy.

**PHARMACOKINETICS**

Blood samples for PK analysis were available from all of 12 patients following the first course of treatment. A semi-log plot of the mean values of paclitaxel concentration for each dose level vs. time is shown in Fig. 1. After 30 min infusion of ABI-007, the concentration of paclitaxel began to decrease immediately upon cessation of the infusion with $t_{1/2}$ of 17.3–27.3 h in the whole blood, which is nearly comparable with that of standard dose of solvent-based paclitaxel (6), and the decline of paclitaxel concentration from maximum was multiphasic.

The mean PK parameters of paclitaxel are summarized in Table 6. $C_{\text{max}}$, $AUC_{0-\text{t}}$, and $AUC_{\text{inf}}$ of paclitaxel when administered as a 30 min infusion of ABI-007 increased with increasing dosage. CL and Vz of the blood sample showed the small inter-patient variability, and the mean ± SD values (CV%) for CL and Vz at the dose level of 260 mg/m² were $18.1 \pm 2.33$ (12.9 CV%) (l/h/m²) and $510 \pm 96.8$ (19.0 CV%) (l/m²), respectively. These values slightly decreased with increased dosage. It was considered that there was no remarkable difference in calculated values of PK parameters between whole blood and plasma. Regression analysis suggested the dose-proportionality of ABI-007 within the dose range in this study ($R^2$ of $C_{\text{max}} = 0.4470$, $R^2$ of

| Tumor type               | Prior taxane therapy | Response |
|--------------------------|----------------------|----------|
| Level 1 (200 mg/m²) NSCLC| +                    | PD       |
| NSCLC                    | +                    | PR       |
| Parotid gland            | +                    | PD       |
| Level 2 (260 mg/m²) NSCLC| +                    | PD       |
| NSCLC                    | –                    | PR       |
| Ovary                    | +                    | PD       |
| NSCLC                    | +                    | PR       |
| Colon                    | –                    | PD       |
| Thymoma                  | –                    | SD       |
| Level 3 (300 mg/m²) Bladder| –                    | SD       |
| NSCLC                    | +                    | NE       |
| Pharyngeal and esophageal| +                    | SD       |

PD, progressive disease; PR, partial response; SD, stable disease; NE, not evaluable.

**Table 5. Anti-tumor response**

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AUC_{inf} = 0.7177); however, it was difficult to establish the linearity due to those narrow dose range and small data size.

**DISCUSSION**

In the Phase I study where ABI-007 was administered in Q3W schedule in Japanese patients, no DLT occurred at any dose level of 200, 260 and 300 mg/m². Because MTD was not reached by the 3 + 3 rule, selection of RD was attributed to the consideration of reasonable tolerability, toxicities and PK profile. Since paclitaxel treatment was characterized for the cumulative neurotoxicity, dose selection also took into account the development of sensory neuropathy throughout the study. Consequently, 260 mg/m² was reassessed as potential RD and established as RD in the absence of applicable DLT. Outcome of sensory neuropathy in all treatment courses also provided the justification for the feasibility of 260 mg/m² (Table 7). Among 260 and 300 mg/m² cohorts, every patient experienced neuropathic events, in which Grade 3 or 4 event was more frequent in 300 mg/m² (two out of three patients) than in 260 mg/m² cohorts (one out of six patients). Moreover, all the three patients in 300 mg/m² cohort discontinued the treatment due to neuropathic events as opposed to two out of six patients in 260 mg/m² cohort.

In terms of treatment-related toxicities, Grade 3 or 4 neutropenia was experienced in 15 of 46 treatment courses (32%). Nonetheless, no febrile neutropenia was observed. Median duration of recovery from Grade 3 or 4 to <Grade 2 was 6.5 days (range, 3–14). No treatment delay was caused by neutropenia. In addition, platelet decrease ≥Grade 2 was not observed throughout the study. On the whole, hematological toxicities were mild. In regard to sensory neuropathy, the median time to the first indication or exacerbation from the baseline was 7 days, which
was relatively early to that of solvent-based paclitaxel. Especially for Grade 3 sensory neuropathy, the indication or exacerbation fell within the first week of the first course, ranging from 3 to 6 days; the time to improve from Grade 3 to Grade 2 or 1 was 21, 26 and 46 days in the respective cases. Although the improvement tended to delay when compared with median 22 days in a previous Phase III study (4), it still remains controversial because of the great difference in the sample sizes between the two studies. Meanwhile, other non-hematological toxicities including mucositis—the DLT of the US Phase I study—were generally mild to moderate up to 300 mg/m².

PK profiles of ABI-007 have revealed the small inter-patient variability, and the AUC and $C_{\text{max}}$ of paclitaxel increased with increasing the dosage. In whole blood samples, there was a significant correlation between the doses and PK parameters. The linearity was uncertain in the face of wide confidence interval (CI) with small sample size, however, presumable from the other reported data showing the linearity over a wide dose range: 80–300 mg/m² (2) and PK equality between Japanese and western population (3).

Anti-tumor response was demonstrated in the patients with NSCLC including the patients who had received prior taxane-containing therapy.

Multiple previous studies of ABI-007 also reported the promising data in the patients with NSCLC. In a Phase II trial, 260 mg/m² of ABI-007 was administered alone in the same Q3W schedule as our study in the first-line setting, overall response rate was 16.3% (95% CI, 5.24–27.31%) and the disease control rate was 48.8% (95% CI, 33.90–63.78%) (8). More recently, weekly (QW) schedule of ABI-007 was also reported: 125 mg/m² of ABI-007 was administered in monotherapy on days 1, 8 and 15 every 4 weeks, the response rate was 30% (95% CI, 16–44%) and the disease control rate was 50% (95% CI, 35–66%) (9). Despite the higher incidence of Grade 3 neutropenia and sensory neuropathy relative to the Q3W schedule, QW schedule was well tolerated and active.

In conclusion, no DLT observed at any dose levels, and ABI-007 was well tolerated up to 300 mg/m² in Japanese

### Table 6. PK parameters of paclitaxel

| Dose (mg/m²) | 200 mg/m² (n = 3) | 260 mg/m² (n = 6) | 300 mg/m² (n = 3) |
|-------------|------------------|------------------|------------------|
| $C_{\text{max}}$ (ng/ml) | 9430 ± 28.3 | 11 635 ± 13.0 | 13 833 ± 15.3 |
| $\text{AUC}_{\text{inf}}$ (ng h/ml) | 10 360 ± 22.0 | 14 593 ± 13.7 | 19 138 ± 12.2 |
| $t_{1/2}$ (h) | 24.3 ± 10.9 | 19.5 ± 7.9 | 18.3 ± 1.9 |
| CL (L/h/m²) | 19.9 ± 21.6 | 18.1 ± 12.9 | 15.8 ± 11.2 |
| $V_z$ (L/m²) | 689 ± 15.3 | 510 ± 19.0 | 417 ± 9.7 |

PK, pharmacokinetic; CV, coefficient of variation; $C_{\text{max}}$, maximum concentration; $\text{AUC}_{\text{inf}}$, area under the concentration–time curve up to $\infty$ hours; $t_{1/2}$, terminal elimination half-life; CL, clearance; $V_z$, volume of distribution based on terminal phase.

### Table 7. Grade change in sensory neuropathy (all courses)

| Level | Case | Before administration | Course no. |
|-------|------|----------------------|------------|
|       |      |                      | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Level 1 | 1-2 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1* | — | — | — | — |
| Level 2 | 2-1 | 1 | 2 | — | — | — | — | — | — | — | — | — | — |
|        | 2-2 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 3* | — |
|        | 2-3 | 0 | 0 | 1 | — | — | — | — | — | — | — | — | — |
| Level 3 | 3-1 | 0 | 1 | 1 | 2 | 2 | 2 | 3* | — | — | — | — | — |
|        | 3-2 | 0 | 1 | 1 | 1 | 2 | 2* | — | — | — | — | — | — |
|        | 3-3 | 0 | 2 | 2 | 3* | — | — | — | — | — | — | — | — |
| Level 2 | 2-4 | 0 | 1 | 1 | 1 | 2 | 2 | 2* | — | — | — | — | — |
|        | 2-5 | 0 | 1 | — | — | — | — | — | — | — | — | — | — |
|        | 2-6 | 0 | 1 | 1 | — | — | — | — | — | — | — | — | — |

—, end of study.

*Study-off due to sensory neuropathy.
patients. RD in this schedule was determined to be 260 mg/m² in consideration of efficacy, toxicities and similarity of PK profile in the western studies. Additional studies of single-agent ABI-007 and platinum-based combinations are warranted.

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Conflict of interest statement

Hironobu Minami and Tomohide Tamura receive remuneration for the lectures from Taiho Pharmaceutical (Tokyo, Japan).

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