Palonosetron has higher affinity for the serotonin receptor and a longer half-life in plasma than previous 5-$HT_3$ receptor antagonists [6, 7]. In a phase II, dose-ranging randomized study, Eisenberg et al. [8] reported that 3 and 10 μg/kg i.v. palonosetron (equivalent to fixed doses of 0.25 and 0.75 mg) were the lowest effective doses to prevent CINV in patients treated with HEC. In this phase II study, palonosetron was used without corticosteroid therapy: at that time the use of dexamethasone as a concomitant antiemetic was not part of clinical practice.

In a phase III trial carried out in Europe and in the United States, palonosetron was given at single doses of 0.25 and 0.75 mg and compared with a single 32-mg dose of ondansetron to prevent nausea and vomiting induced by HEC [9]. Dexamethasone, the use of which has now been introduced in clinical practice [10–13], was allowed, at the discretion of the investigators only as a single administration before chemotherapy: under these conditions dexamethasone was administered to 67% of patients. Patients pretreated with 0.25-mg palonosetron plus dexamethasone had significantly higher complete response (CR) rates than those receiving ondansetron plus dexamethasone during both the delayed (42.0% versus 28.6%) and overall (40.7% versus 25.2%) phases. In all patients, palonosetron showed CR rates similar to ondansetron at three observation periods: acute, delayed, and overall phases (0–24, 24–120, and 0–120 h, respectively). No clinically relevant differences were noted between the two doses (0.25 and 0.75 mg) in either efficacy or safety.

No 5-$HT_3$ receptor antagonists have yet been approved in Japan for both acute and delayed CINV. A phase I trial of palonosetron in healthy Japanese volunteers showed similar pharmacokinetic profiles in Japanese and US populations [6]. The present randomized, double-blind phase II trial sought to determine the fully effective and safe dose range of palonosetron in patients in Japan receiving HEC with three fixed doses (0.075, 0.25, and 0.75 mg) combined with dexamethasone. Safety was assessed for 14 days after palonosetron administration. The pharmacokinetic profile of palonosetron was assessed in a subgroup of patients.

## materials and methods

The study was conducted according to the Declaration of Helsinki, and written approval was obtained from the institutional review boards at each site before study commencement. All patients provided written informed consent before enrollment. A total of 34 Japanese hospitals were involved from April to October 2005.

### patient population

The study enrolled patients 20–79 years old with confirmed diagnoses of cancer. Subjects were either naive to chemotherapy or had received only low or minimally emetogenic chemotherapies. They had an Eastern Cooperative Oncology Group performance status of zero or one and were scheduled to receive one cycle of HEC (including ≥50 mg/$m^2$ cisplatin, >1500 mg/$m^2$ cyclophosphamide or dacarbazine). Adequate hepatorenal function (white blood cell ≥3000/$mm^3$, aspartate aminotransferase <100 IU/l, alanine aminotransferase <100 IU/l, and creatinine clearance ≥60 ml/min) was required. Exclusion criteria included severe, uncontrolled complications; unstable metastases in the brain; a history of convulsions requiring anticonvulsant agents; uncontrolled pleural effusion or ascites; gastrointestinal obstruction; vomiting or ≥ grade 2 nausea [the National Cancer Institute—Common Terminology Criteria for Adverse Events v3.0 (CTCAE)]; corrected QT interval >450 ms; hypersensitivity to other 5-$HT_3$ receptor antagonists or dexamethasone; or other investigational agents within 3 months of entering the study.

### study design

This phase II study was conducted at multiple centers. Eligible patients were randomized to one of three fixed, single doses of palonosetron. Dose groups were stratified at randomization by gender and by paclitaxel (Taxol, Bristol-Myers K.K., Japan; which needs a higher premedication dose of dexamethasone). Thirty minutes before HEC, patients received a single, 30-s i.v. infusion of 0.075, 0.25, or 0.75 mg palonosetron. The low dose of 0.075 mg was decided on to enable adequate comparisons since placebo would not be ethically acceptable. We injected 12–16 mg dexamethasone i.v. within 45 min before the palonosetron. This dose was increased to 24 mg for those patients who received concomitant paclitaxel to prevent anaphylaxis [14, 15]. Another 8 mg of dexamethasone was administered i.v. to all patients 24–26 h after chemotherapy and a last dose of 4–8 mg was given i.v. 48–50 h after chemotherapy. The doses of dexamethasone used in this study were determined based on the doses employed by previous Japanese clinical studies [16, 17] and on the doses used in clinical practice in Japan.

### assessment

All patients were hospitalized at least until the next day following the administration of palonosetron. Efficacy was assessed starting from administration of HEC up to 5 days. Patients recorded the date and time of episodes of emesis and the degree of nausea in diaries. An emetic episode was defined as one episode of vomiting or a sequence of episodes in very close succession not relieved by a period of relaxation of at least 1 min; any number of unproductive emetic episodes (retching) in any given 5-min period; or an episode of retching lasting <5 min combined with vomiting not relieved by a period of relaxation of at least 1 min [18]. Nausea was classified into four grades (0, none; 1, mild; 2, moderate; and 3, severe). Any use of rescue medication was recorded, including drug name, dose, and time of administration. Rescue medication could be administered for an emetic event or nausea or by patient request. Descriptions in diaries were confirmed daily by physicians or nurses, or both.

### efficacy parameters

The primary end point was the proportion of patients with a CR (no emesis and no rescue medication) during the acute phase (0–24 h) after chemotherapy. The secondary end points were (i) proportion of patients with CR during the delayed phase (24–120 h) and overall phase (0–120 h) and daily CR rates after administration of chemotherapy; (ii) proportion of patients with complete control (CC: no emetic episode, no rescue medication, and no more than mild nausea) during the acute, delayed, and overall phases; and (iii) time to treatment failure (TTF: time to first emetic episode or first administration of rescue medication).

### safety parameters

Vital signs, physical exam, 12-lead electrocardiogram, blood tests, and urinalysis were assessed on days 2, 8, and 15. Safety was also assessed by recording adverse events (AEs) up to 14 days. AEs were assessed using CTCAE by the investigators for intensity and possible association with palonosetron.

### pharmacokinetic analysis

Accurate pharmacokinetic evaluation of palonosetron and its N-oxide metabolite (metabolite M9) required at least six patients in each dose group. Over 6 ml of whole blood was collected from patients in the

pharmacokinetic study into heparinized vacuum tubes before study drug administration and then at 0.25, 0.5, 1, 2, 4, 8, 24, 48, 72, 120, and 168 h from then. Plasma was separated from whole blood by centrifugation and stored at −20°C or less until analysis. Palonosetron and metabolite M9 in plasma were determined by liquid chromatography–tandem mass spectrometry after solid-phase extraction. The lower limits of quantification (LLOQ) were 0.05 ng/ml for palonosetron and 0.01 ng/ml for metabolite M9. For pharmacokinetic analysis, the maximum plasma concentration ($C_{max}$), area under the plasma concentration–time curve (AUC), terminal half-life ($t_{1/2}$), total clearance ($CL_{tot}$), and volume of distribution in the terminal phase ($Vd_\beta$) of individual subjects were calculated to obtain means and standard deviations according to dose groups. All pharmacokinetic parameters were calculated as actual times after administration.

### statistical analyses

A number of 72 patients were needed in each group, i.e. 216 patients in total, to obtain 80% statistical power to confirm the dose–response relationship of palonosetron assuming CR rates of 45%, 65%, and 65%, for the 0.075-, 0.25-, and 0.75-mg dose groups, respectively, in the acute phase.

A relationship between dose and response in the acute phase was found using the Cochran–Armitage trend test, with an upper significance level of 2.5%. Based on previous reports, dose–response contrast coefficients of −2, 1, and 1 were assumed for the dose groups [8]. The full analysis set (FAS), defined as patients who received palonosetron and HEC on day 1, was used to assess efficacy. For secondary efficacy end points, CR and CC rates, up to 120 h after HEC, were evaluated every 24 h by groups using 95% confidence intervals (CIs). Generalized estimating equations (GEEs) were applied to the logistic models to evaluate dose response in consideration of all CR assessments carried out every 24 h after administration of HEC. Contrast coefficients were assigned to dose groups in the model to test dose response. TTF was evaluated using the Kaplan–Meier method with estimation of quartiles and 95% CIs among different dose groups. The number of emetic episodes and frequency of nausea events were summarized every 24 h until 120 h after HEC. Safety was evaluated in the safety analysis group: all patients received palonosetron and underwent at least one safety evaluation. Analyses were made with SAS version 8.0 (SAS Institute, Cary, NC).

In statistical analysis of pharmacokinetic parameters, the dose proportionality for AUC and $C_{max}$ was evaluated using linear and log–log (power) regression models. One-way analysis of variance was used to examine the effect of dose on pharmacokinetic parameters. All parameters were converted to natural logarithms, and AUC and $C_{max}$ were adjusted with dose normalization.

## results

### patients

A total of 233 patients were enrolled. Two patients were not administered palonosetron because of infection. Palonosetron was therefore given to 231 patients, two of whom withdrew consent for study participation or transferred to another hospital. Subsequent analyses were based on 231 patients given the projected study medication, as the FAS. Baseline characteristics of patients were similar across treatment groups. Approximately 95% of patients had lung cancer (Table 1). All patients were administered cisplatin at highly emetogenic doses: only one patient (treated with 0.075 mg) received cisplatin and paclitaxel.

**Table 1.** Baseline demographic and clinical characteristics (full analysis set, $N = 231$)

| Characteristic | 0.075 mg $N = 76$ | 0.25 mg $N = 77$ | 0.75 mg $N = 78$ |
|---|---|---|---|
| Gender, *n* (%) | | | |
| Male | 56 (73.7) | 56 (72.7) | 57 (73.1) |
| Female | 20 (26.3) | 21 (27.3) | 21 (26.9) |
| Age, years | | | |
| Mean ± SD | 61.7 ± 8.9 | 62.1 ± 8.8 | 62.0 ± 9.8 |
| Height, cm | | | |
| Mean ± SD | 161.78 ± 8.20 | 163.14 ± 8.73 | 162.74 ± 7.23 |
| Weight, kg | | | |
| Mean ± SD | 58.30 ± 9.41 | 59.50 ± 10.52 | 58.74 ± 7.75 |
| PS, *n* (%) | | | |
| 0 | 35 (46.1) | 39 (50.6) | 44 (56.4) |
| 1 | 41 (53.9) | 38 (49.4) | 34 (43.6) |
| Tobacco use, *n* (%) | | | |
| Nonsmoker | 19 (25.0) | 15 (19.5) | 14 (17.9) |
| Ex-smoker before 180 days | 21 (27.6) | 16 (20.8) | 19 (24.4) |
| Ex-smoker within 180 days | 19 (25.0) | 26 (33.8) | 28 (35.9) |
| Smoker | 17 (22.4) | 20 (26.0) | 17 (21.8) |
| Alcohol use, *n* (%) | | | |
| No | 26 (34.2) | 32 (41.6) | 21 (26.9) |
| Rarely | 11 (14.5) | 2 (2.6) | 8 (10.3) |
| Occasionally | 13 (17.1) | 8 (10.4) | 15 (19.2) |
| Regularly | 26 (34.2) | 35 (45.5) | 34 (43.6) |
| Cisplatin, mg/m$^2$ | | | |
| Mean ± SD | 74.0 ± 9.4 | 73.1 ± 10.1 | 71.6 ± 10.4 |
| Cancer, *n* (%) | | | |
| Non-small-cell lung cancer | 66 (86.8) | 56 (72.7) | 53 (67.9) |
| Small-cell lung cancer | 6 (7.9) | 19 (24.7) | 21 (26.9) |
| Others | 4 (5.3) | 2 (2.6) | 4 (5.1) |

SD, standard deviation; PS, performance status.

### primary efficacy end point

The CR rates during the first 24 h (acute phase) were 77.6%, 81.8%, and 79.5% in the 0.075-, 0.25-, and 0.75-mg dose groups, respectively (Table 2 and Figure 1). Differences of the CR rates among three dose groups were not significant (upper side $P = 0.2858$).

### secondary efficacy end point

CR rates during the delayed and overall phases were higher both in the 0.25- and 0.75-mg groups than in the 0.075-mg group. The CR rates were 40.8%, 53.2%, and 56.4% in the 0.075-, 0.25-, and 0.75-mg groups, respectively, in the delayed phase, and 38.2%, 49.4%, and 56.4%, respectively, in the overall phase (Table 2). The elevation in CR rates with increases in palonosetron doses indicated statistically significant differences among the doses with the given coefficients of −2, 1, and 1 (upper side $P = 0.0142$ and 0.0108 in delayed and overall phases, respectively). Both the 0.25- and 0.75-mg CR rates were >10% higher than in the 0.075-mg group.

**Table 2.** Complete response rates (full analysis set, $N = 231$)

| Period (h) | | 0.075 mg ($N = 76$) | | | 0.025 mg ($N = 77$) | | | 0.75 mg ($N = 78$) | | | $P$ value[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $n$ | % | 95% CI | $n$ | % | 95% CI | $n$ | % | 95% CI | |
| Acute | 0–24 | 59 | 77.6 | 66.6–86.4 | 63 | 81.8 | 71.4–89.7 | 62 | 79.5 | 68.8–87.8 | 0.2858 |
| Delayed | 24–120 | 31 | 40.8 | 29.6–52.7 | 41 | 53.2 | 41.5–64.7 | 44 | 56.4 | 44.7–67.6 | 0.0142 |
| Overall | 0–120 | 29 | 38.2 | 27.2–50.0 | 38 | 49.4 | 37.8–61.0 | 44 | 56.4 | 44.7–67.6 | 0.0108 |

[a]Cochran–Armitage test for trend using $Z$ score approximation with contrast coefficients in each dose group −2,1, and 1, respectively.
CI, confidence interval.

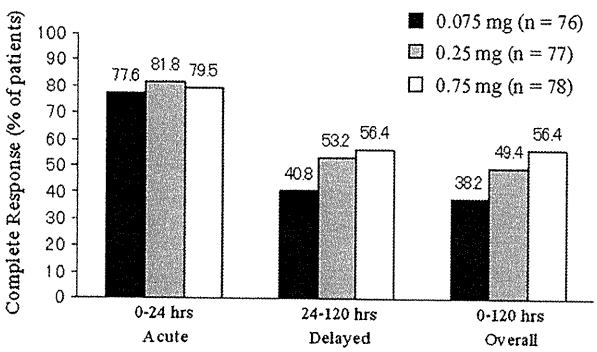


**Figure 1.** Patients with a complete response in acute emesis (first 24 h after chemotherapy), delayed emesis (24–120 h), and overall emesis (0–120 h). Black bars: 0.075 mg ($n = 76$); gray bars: 0.25 mg ($n = 77$); outlined bars: 0.75 mg ($n = 78$).

Dose–response relationship in consideration of all CR assessments carried out every 24 h after HEC was evaluated using the GEE logistic model with contrast coefficients assigned to dose groups. Dose response was significant with contrast coefficients of −2, 1, and 1, indicating a statistically significant difference between the 0.075-mg group and the two higher dose groups (Table 3).

CC rates in each group were similar with CR rates (data not shown).

TTF was significantly longer in the 0.75-mg group than in the 0.075-mg group ($P = 0.0376$, Figure 2). The 0.075-mg group had significantly shorter TTF than the combined 0.25- and 0.75-mg groups ($P = 0.0491$). Median TTFs were 82.0, 117, and >120 h in the 0.075-, 0.25-, and 0.75-mg groups, respectively.

## safety

Safety was assessed in all 231 patients who received palonosetron. All patients experienced at least one AE during the 14-day period after palonosetron, but the majority of these (~60%) were judged to be unrelated or unlikely related to palonosetron, being instead associated with cancer or chemotherapy. Of those patients who suffered from AEs thought to be related to palonosetron, the maximum intensity of the events was mild or moderate in almost all (>90%). AEs related to palonosetron are shown in Table 4, the most frequent AEs being constipation and headache. The incidence, intensity, and relation of AEs to palonosetron were similar among the

**Table 3.** Test of dose–response relationship in consideration all CR assessment over 0 to 120 h using GEE logistic model with contrast coefficients

| Contrast coefficient for three dosage groups (0.075, 0.25, 0.75 mg) | $P$ (two sided) |
|---|---|
| −2, 1, 1 | 0.048 |
| −1, 0, 1 | 0.071 |
| −1, −1, 2 | 0.247 |

CR, complete response; GEE, generalized estimating equation.

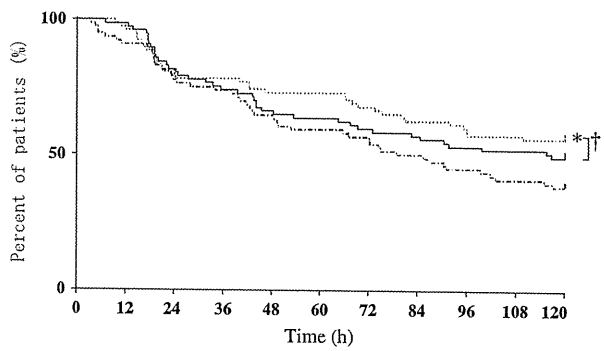


**Figure 2.** Kaplan–Meier curves for time to treatment failure. *$P = 0.0376$ for 0.075 versus 0.75 mg; †$P = 0.0491$ for 0.075 versus 0.25 mg plus 0.75 mg. Broken line: 0.075 mg ($n = 76$); solid line: palonosetron 0.25 mg ($n = 77$); dotted line: 0.75 mg ($n = 78$).

**Table 4.** Patients with adverse events related to palonosetron (safety cohort, $N = 231$)

| | 0.075 mg $N = 76$ | | 0.25 mg $N = 77$ | | 0.75 mg $N = 78$ | |
|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | $n$ | % |
| Constipation | 5 | 6.6 | 9 | 11.7 | 11 | 14.1 |
| Headache | 3 | 3.9 | 5 | 6.5 | 2 | 2.6 |
| Hiccup | 2 | 2.6 | 2 | 2.6 | 0 | 0 |
| Rash | 1 | 1.3 | 1 | 1.3 | 2 | 2.6 |
| Diarrhea | 1 | 1.3 | 1 | 1.3 | 1 | 1.3 |
| Cold sweat | 0 | 0 | 2 | 2.6 | 0 | 0 |
| Angiopathy | 2 | 2.6 | 0 | 0 | 0 | 0 |

Adverse events judged by the investigator to be related, probably related, possibly related to the study drug.

three dose levels. No relevant clinical differences were found among the three dosage groups with respect to laboratory test results, vital signs, or electrocardiographic findings.

### pharmacokinetics

The pharmacokinetics of palonosetron was examined in 24 eligible patients (Table 5). The mean time-to-concentration profiles of palonosetron in plasma for the three dosage groups are illustrated in Figure 3A. The concentration of palonosetron declined relatively rapidly to 6 h and then gradually at an elimination half-life of ~40 h thereafter. The concentrations of metabolite M9 were much lower than that of palonosetron (Figure 3B).

Pharmacokinetic parameters are shown in Table 6. Inspection of individual concentration–time profiles estimated the terminal elimination phase for palonosetron as 24 h after administration or later. The $t_{1/2}$, $CL_{tot}$, and $Vd_{\beta}$ could be calculated for only one patient in the 0.075-mg group because most data in the terminal phase were under the LLOQ. The data indicated a prolonged effective concentration and extensive systemic distribution. Linear and log–log (power) models revealed that AUC and $C_{max}$ were proportional to doses from 0.075 to 0.75 mg. One-way analysis of variance found no significance for any parameter among the three dose levels, suggesting that the pharmacokinetics of palonosetron was proportional to dose.

## discussion

We set out to determine whether palonosetron, given on the first day of HEC, in combination with dexamethasone provided dose-dependent antiemetic effects. During the acute phase (day 1), no significant difference was observed in the CR rates among the three dose groups of palonosetron. In contrast to the acute phase, a significant difference in CR rate was observed between the 0.075-mg group and other two dose groups (0.25 and 0.75 mg) by applying a logistic model with the GEE method for the period from 0 to 120 h. The TTF at the highest dose was significantly longer than at the lowest dose.

While in previous studies in Western populations, dexamethasone was not used [8], patients in the present study received dexamethasone from days 1 to 3. This is due to the evolution of recommendations updated in the currently available guidelines [19–22]: dexamethasone is now recognized to have an additive antiemetic effect on CINV [10–13]. The results reflect the current clinical practice whereby 5-$HT_3$ receptor antagonists and dexamethasone are given in combination.

**Table 5.** Baseline demographic of patients for pharmacokinetic study ($N = 24$)

| | 0.075 mg $N = 9$ | 0.25 mg $N = 6$ | 0.75 mg $N = 9$ |
|---|---|---|---|
| Gender | | | |
| Male | 5 | 6 | 5 |
| Female | 4 | 0 | 4 |
| Age, years | | | |
| Mean ± SD | 63.2 ± 4.9 | 56.5 ± 5.1 | 54.9 ± 9.2 |
| Weight, kg | | | |
| Mean ± SD | 54.0 ± 7.6 | 66.2 ± 17.4 | 52.9 ± 8.1 |
| Height, cm | | | |
| Mean ± SD | 160.7 ± 10.1 | 169.3 ± 6.1 | 159.5 ± 6.6 |

SD, standard deviation.

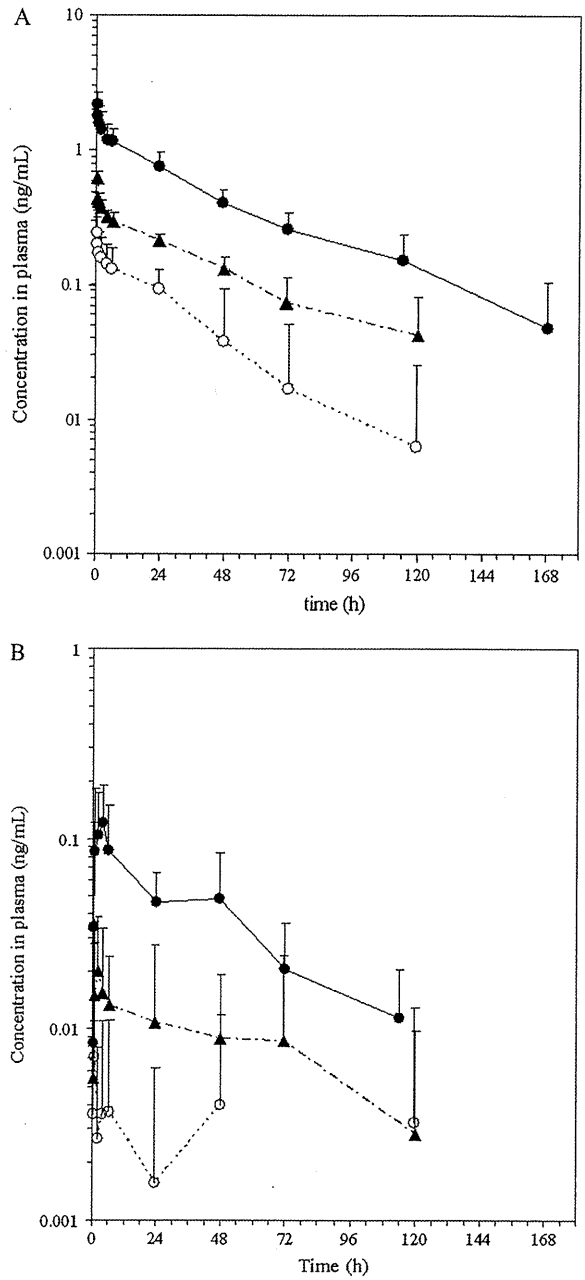


**Figure 3.** (A) Mean plasma concentration–time profiles of palonosetron. Open circles: 0.075 mg ($n = 9$); filled triangles: 0.25 mg ($n = 6$); black dots: 0.75 mg ($n = 9$). (B) Mean plasma concentration–time profiles of M9. Open circles: 0.075 mg ($n = 9$); filled triangles: 0.25 mg ($n = 6$); black dots: 0.75 mg ($n = 9$).

**Table 6.** Pharmacokinetic characteristics of palonosetron ($N = 24$)

| | 0.075 mg | | 0.25 mg | | 0.75 mg | |
|---|---|---|---|---|---|---|
| | Mean ± SD | *n* | Mean ± SD | *n* | Mean ± SD | *n* |
| $C_{max}$ (ng/ml) | 0.245 ± 0.113 | 9 | 0.625 ± 0.072 | 6 | 2.277 ± 0.589 | 9 |
| $t_{1/2}$ (h) | 53.1 | 1 | 43.3 ± 13.7 | 5 | 41.6 ± 13.1 | 9 |
| $AUC_{0-24}$ (ng·h/ml) | 2.90 ± 1.26 | 9 | 6.71 ± 0.89 | 6 | 25.1 ± 6.28 | 9 |
| $AUC_{0-last}$ (ng·h/ml) | 4.87 ± 4.68 | 9 | 14.3 ± 3.24 | 6 | 59.5 ± 18.22 | 9 |
| $AUC_{0-inf}$ (ng·h/ml) | 20.53 | 1 | 20.16 ± 3.78 | 5 | 66.38 ± 19.28 | 9 |
| $CL_{tot}$ (l/h) | 3.65 | 1 | 12.8 ± 2.57 | 5 | 12.1 ± 3.34 | 9 |
| $Vd_{\beta}$ (l) | 280 | 1 | 766 ± 141 | 5 | 695 ± 191 | 9 |
| AUC ratio M9/Palonosetron | 0.263 ± 0.148 | 3 | 0.070 ± 0.069 | 5 | 0.080 ± 0.051 | 9 |

Palonosetron concentrations in plasma increased with dose, and the dose proportionality of its pharmacokinetics was verified in the patient population of this study. Palonosetron has a much longer $t_{1/2}$ than other 5-$HT_3$ receptor antagonists, as measured both in Western and Japanese patients [6]. $Vd_{\beta}$, which generally reflects tissue distribution, was higher than that of other 5-$HT_3$ receptor antagonists [6]. Thus, a prolonged pharmacological effect can be expected in patients in Japan, as already observed in Western population.

AEs were found in all patients, although the majority was unrelated or unlikely to be related to palonosetron. The main AEs related to palonosetron were constipation and headache, at frequencies of <15% and they were not dose dependent. No serious AE was related to palonosetron, and no patients died during the observation period of this study. The types of AEs were similar to those reported in previous trials [8, 9, 18, 23].

Our results demonstrated that single 0.25- and 0.75-mg doses of palonosetron given on the first day of HEC, combined with dexamethasone (on three consecutive days beginning on day 1 of treatment), exhibited antiemetic effects in a dose-dependent manner, especially in the overall and delayed observation periods. Both the 0.25- and 0.75-mg doses of palonosetron were identified as effective and tolerated well by patients in Japan. The 0.075 mg dose appeared to be insufficient to completely prevent CINV. Comparison of the effects of palonosetron with those of other 5-$HT_3$ receptor antagonists in combination with dexamethasone is under investigation. Further studies are required to clarify the best method to administer palonosetron to prevent nausea and vomiting associated with emetogenic chemotherapy.

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# Twenty-Seven Years of Phase III Trials for Patients with Extensive Disease Small-Cell Lung Cancer: Disappointing Results

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## Abstract

***Background:*** Few studies have formally assessed whether treatment outcomes have improved substantially over the years for patients with extensive disease small-cell lung cancer (ED-SCLC) enrolled in phase III trials. The objective of the current investigation was to determine the time trends in outcomes for the patients in those trials.

***Methods and Findings:*** We searched for trials that were reported between January 1981 and August 2008. Phase III randomized controlled trials were eligible if they compared first-line, systemic chemotherapy for ED-SCLC. Data were evaluated by using a linear regression analysis. Results: In total, 52 trials were identified that had been initiated between 1980 and 2006; these studies involved 10,262 patients with 110 chemotherapy arms. The number of randomized patients and the proportion of patients with good performance status (PS) increased over time. Cisplatin-based regimens, especially cisplatin and etoposide (PE) regimen, have increasingly been studied, whereas cyclophosphamide, doxorubicin, and vincristine–based regimens have been less investigated. Multiple regression analysis showed no significant improvement in survival over the years. Additionally, the use of a PE regimen did not affect survival, whereas the proportion of patients with good PS and the trial design of assigning prophylactic cranial irradiation were significantly associated with favorable outcome.

***Conclusions and Significance:*** The survival of patients with ED-SCLC enrolled in phase III trials did not improve significantly over the years, suggesting the need for further development of novel targets, newer agents, and comprehensive patient care.

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## Introduction

Lung cancer is a leading cause of cancer-related mortality in many industrialized countries. Small-cell lung cancer (SCLC), which accounts for about 15% of all lung cancer cases, is categorized into two clinical stages: limited disease (LD) and extensive disease (ED). For patients with ED-SCLC, combination chemotherapy is the mainstay of treatment.

In the 1980s, the most widely used combination of drugs for initial treatment of ED-SCLC was cyclophosphamide, doxorubicin, and vincristine (CAV), which produced a median survival time of 9 to 11 months [1]. In the late 1980s, a combination regimen of cisplatin and etoposide (PE) was introduced, and an alternating regimen of PE and CAV has been widely investigated in randomized controlled trials [2].

In 1999, the results of a systemic review indicated a modest improvement over the years in the survival time of patients with ED-SCLC treated with chemotherapy between 1972 and 1994 [3]. This improvement was potentially attributable to (i) introduction of the PE regimen in the late 1980s and (ii) improvements in the supportive care and general management of the patients. However, this included just North American trials and would provide some justification for looking at the world-wide result.

A decade has passed since that systemic review, and recent clinical trials have investigated newer antineoplastic agents such as irinotecan and topotecan. Thus, we performed a literature search to determine whether patient outcomes have improved in the treatment of ED-SCLC.

## Materials and Methods

### Searching

We searched for trials that were reported between January 1981 and August 2008. To avoid publication bias, we identified both published and unpublished trials through a computer-based search of the PubMed database and abstracts from past conferences of the American Society of Clinical Oncology (1998–2008). We used the following search terms: *lung neoplasm, carcinoma, small-cell, chemotherapy,* and *randomized controlled trial.* The search was guided by a

thorough examination of reference lists from original articles, review articles, relevant books, and the Physician Data Query registry of clinical trials.

### Selection

Phase III randomized controlled trials were eligible for inclusion in this study if they compared first-line, systemic chemotherapy for ED-SCLC that contained cytotoxic agents, providing the year of trial initiation. Trials were excluded if they only investigated immunotherapy regimens, or if they enrolled only responders to the initial chemotherapy. Trials initially designed to assess combined-modality treatment, including radiotherapy and surgery concurrently undergone with the initial chemotherapy, were also ineligible, but those optionally designed to conduct these therapies or prophylactic cranial irradiation (PCI) sequentially after the induction chemotherapy were allowed. Some phase III trials incorporated patients with both LD-SCLC and ED-SCLC. These were considered eligible only if survival data for patients with ED-SCLC could be solely obtained. We acknowledge that the definitions for LD-SCLC and ED-SCLC vary somewhat in the different groups compared, and we could not strictly reallocate each patient because we were unable to access the individual patient databases. Instead, we applied the definition described in each original report to this study. If no relevant descriptions were documented, we considered that the definition in that trial would have been based on the guidelines in existence at the time of that trial initiation [4,5]. The control arms in each of the phase III trials were identified based on statements in each trial.

### Validity Assessment

To avoid bias in the data abstraction process, four medical oncologists (I.O., N.O., Y.F., and K.H.), one of whom (K.H.) holds a board certificate for medical oncology, independently abstracted the data from the trials and subsequently compared the results. All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators.

### Data Abstraction

The following information was obtained from each report: year of trial initiation (i.e., year when the first patient was accrued); number of patients enrolled and randomized; median age of patients; proportion of patients with good performance status (PS); proportion of patients who were male and who had brain metastasis; chemotherapy regimen; definition of ED; description of the administration of sequential thoracic irradiation, surgery, or PCI as one of the trial designs; and median survival time (per treatment arm).

### Study Characteristics

All studies included were phase III randomized controlled trials of first-line systemic chemotherapy for ED-SCLC. The study outcomes were median survival time. Variation in study characteristics and clinical heterogeneity between studies were adjusted statistically (see below).

### Quantitative Data Synthesis

Data from phase III trials were evaluated by using multiple, stepwise regression analysis (with the following stepping method criteria: probability of F to enter the model, $<0.05$; to remove from the model, $>0.10$). The data analyzed included year of trial initiation, use of PE regimen, maximal age of patients, proportion of patients with good PS, proportion of male patients, and definition of PCI settings. These data were used to determine whether each factor had an independent impact on the survival of patients with ED-SCLC who were treated in the phase III studies over time. All $P$ values corresponded to 2-sided tests, and significance was set at $P<0.05$.

## Results

### Trial Flow/Flow of Included Studies

Figure 1 shows a flow chart of this study. In total, 52 trials for ED-SCLC were identified as a result of the computer-based and manual searches for relevant articles, abstracts, and references

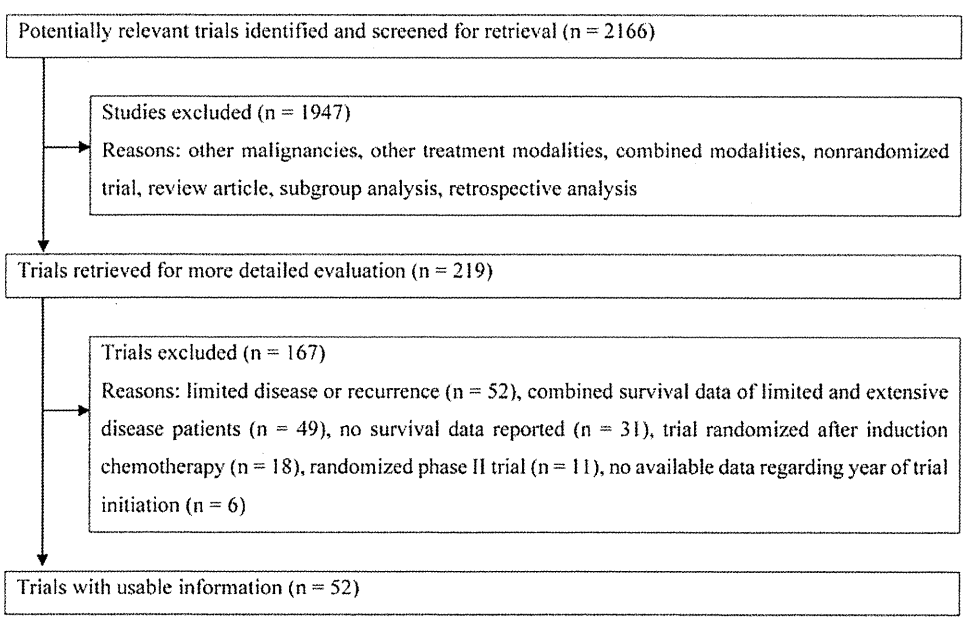


**Figure 1. Flow chart showing the progress of trials through the review.**
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(Please see File S1). A total of 10,262 patients had been allocated randomly to 110 chemotherapy arms.

## Study Characteristics

Table 1 lists the baseline characteristics of the trials. Trials were initiated between 1980 and 2006. The number of randomized patients and the proportion of patients with good PS increased over time (13.9 patient increase/year, $P<0.001$; and 1.32% increase/year, $P<0.001$, respectively; Figures 2A and 2B), whereas the proportion of male patients remained consistent (0.47% decrease/year, $P=0.114$; Figure 2C). In 19 trials that assigned PCI, it was planned that patients who achieved a complete response (CR) or CR/partial response (PR) after induction chemotherapy would receive PCI. Thirteen (25%) of the 52 phase III trials showed a statistically significantly difference in survival time. Of these, eight were in favor of the patient cohort that received the experimental therapy compared with the control group, while the remaining five were in favor of that in the control group.

**Table 1.** Characteristics of the 52 Randomized Trials.

| Variable | Value |
|---|---|
| No. of trials | 52 |
| (No. of randomized patients in all trials 10262) | |
| No. of treatment arms | |
| 2 | 47 |
| 3 | 4 |
| 4 | 1 |
| Year of trial initiation | |
| Median (range) | 1990 (1980–2006) |
| No. of randomized patients (%) | |
| <100 | 35 |
| 100–200 | 25 |
| 200–300 | 29 |
| >300 | 11 |
| Median (range) | 158 (34–786) |
| Proportion of patients with good performance status† (%) | |
| <80 | 50 |
| 80–90 | 42 |
| >90 | 8 |
| Median percentage (range) | 80 (35–100) |
| Male Patients (%) | |
| <80 | 54 |
| 80–90 | 35 |
| >90 | 11 |
| Median percentage (range) | 75 (56–93) |
| Trials assigning PCI for those with CR or CR/PR to the initial chemotherapy | |
| Yes | 37 |
| No | 63 |
| Trials with a statistically significant difference in overall survival time (%) | |
| Yes | 25 |
| No | 65 |
| Not recorded | 10 |

†Defined as a performance status of 0 or 1.
Abbreviations; PCI, prophylactic cranial irradiation; CR, complete response; PR, partial response.
doi:10.1371/journal.pone.0007835.t001

## Types of Chemotherapy Arms

There were 110 chemotherapy treatment arms in the 52 phase III trials (Table 2). Cisplatin-based regimens were the most frequently investigated. The PE regimen, currently considered as the standard treatment for patients with ED-SCLC, has increasingly been studied (Figure 1). As expected, the CAV alternating PE regimen was extensively examined in the 1980s, but this decreased in the 1990s.

## Trends in Patient Survival

Data on patient survival were available from all 52 trials and 110 chemotherapy arms and analyzed by treatment arm. A scattergram of the two parameters (year of trial initiation and median survival time) revealed that the slope of the fitted line was 0.021, indicating a 0.021 month (0.63 day) increase in median survival time per year ($P=0.272$; Figure 3). Multiple regression analysis, adjusting for several confounding trial characteristics, also showed no significant association between the two parameters (regression coefficient for year of trial initiation $=0.011$, 95% confidence interval $=-0.36$–$0.38$, $P=0.950$; Table 3). In this setting, the proportion of patients with good PS was significantly associated with a favorable outcome. The multiple regression analysis also showed a significant influence of PCI setting on survival prolongation. This finding is partly supported by a recent report on the survival advantage of PCI in ED-SCLC patients who responded to initial chemotherapy [6].

# Discussion

Our results demonstrate no significant improvement in patient outcomes over the years in phase III trials of systemic chemotherapy for ED-SCLC, with an increase of 0.021 months (0.63 days) per year (univariate analysis; $P=0.272$; Figure 3) confirmed in the multivariate model ($P=0.950$; Table 3). However, the proportion of patients with good PS and the trial design of assigning PCI for those with CR or CR/PR significantly influenced survival (Table 3).

The introduction of multiple drug regimens has been a great advance in the treatment of ED-SCLC; indeed, the CAV regimen yielded a survival time approximately twice as long as that of the single-agent therapy frequently used in the early 1970s [1,7]. However, the survival benefit from chemotherapy has reached somewhat of a plateau, even with the introduction of the PE regimen in recent clinical trials, as compared with the CAV regimen or CAV alternating PE [2,8,9,10]. In addition, most of newer antitumour agents introduced after PE (e.g., irinotecan and topotecan) failed to substantially prolong survival in the first-line setting over the standard PE regimen [11,12,13,14,15]. Thus, based on these findings, our main results demonstrate no significant improvement in survival since 1980. In contrast, a 1999 study showed a significant increase in overall survival time [3]. This difference in the time trend in overall survival is mainly attributable to differences in the study period (year of trial initiation: 1972–1994 vs. 1980–2006 in the earlier and present study, respectively; [3]).

In Figure 3, trials between 2000 and 2005 appeared to show extensive clustering with median survival time of around ten months. It would be attributable to some common characteristics among these trials, such as relatively uniformed chemotherapeutic regimens (cisplatin-based ones) and larger number of the registered patients. In contrast, there were other trial arms that yielded the

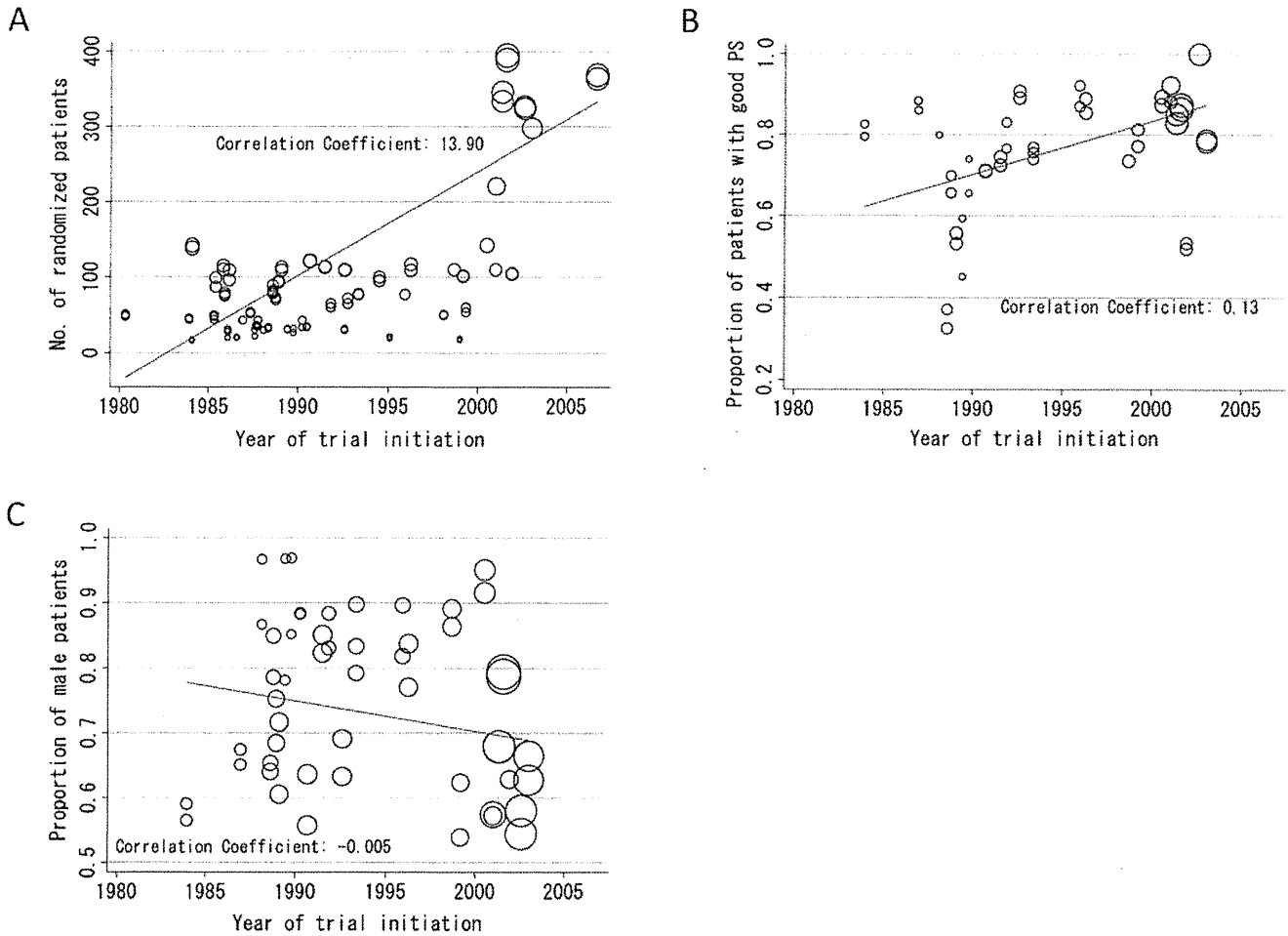


**Figure 2. Trends in trial characteristics.** These charts show the associations between year of trial initiation and number of randomized patients (A), proportion of patients with good PS (B), and proportion of male patients (C) in each trial. The size of solid circles represents data weighted on the basis of the number of randomized patients. Abbreviations: PS, performance status.
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longest versus shortest survival times (14–15 months versus 5–6 months). These included less number of the enrolled patients, which possibly resulted in a wide-range distribution in the Figure.

We investigated a similar issue previously [16], namely trends in prognosis over the years in chemo-naïve patients with advanced non-small cell lung cancer (NSCLC) enrolled in phase III trials.

**Table 2.** Types of Chemotherapy Arms and Treatment Outcomes (Per Treatment Arm).

| Chemotherapy Arm | No. of Arms (%) | MST [range], months | |
|---|---|---|---|
| Total no. of arms | 110 | 9.3 | [4.9–14.5] |
| Platinum-based regimens | 78 (70.9) | 9.5 | [4.9–14.5] |
| Cisplatin-based | 64 (58.2) | 9.6 | [5.8–14.5] |
| CAV alternating PE | 16 (14.5) | 9.5 | [5.8–14.5] |
| PE | 16 (14.5) | 9.4 | [7.0–10.2] |
| Other Cisplatin-based | 32 (29.1) | 9.8 | [6.7–12.8] |
| Nonplatinum regimens | 32 (29.1) | 8.5 | [5.0–13.0] |
| CAV-based | 10 (9.1) | 9.1 | [7.5–13.8] |
| Non-CAV-based combination therapy | 19 (17.3) | 8.2 | [5.0–13.0] |
| Non-CAV-based monotherapy | 3 (2.7) | 8.3 | [6.0–9.3] |

Abbreviations: MST, median survival time; CAV, cyclophosphamide, doxorubicin, and vincristine; PE, cisplatin and etoposide.
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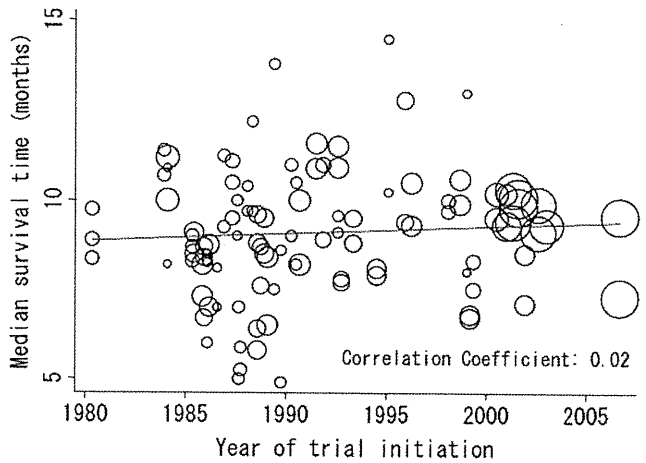


**Figure 3. Relationship between year of trial initiation and median survival time.** Analysis was weighted by the number of randomized patients. Each trial is represented by a circle; the size of each circle is proportional to the sample size of randomized patients in the given trial.
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**Table 3.** Multiple Stepwise Linear Regression Analysis of Overall Survival (Per Treatment Arm).

| Factor | Regression Coefficient* | SE | P† |
|---|---|---|---|
| Year of trial initiation | Excluded | | |
| Use of PE regimen (y or n) | Excluded | | |
| Proportion of patients with good PS | 6.65 | 1.30 | <0.001 |
| Proportion of male patients | Excluded | | |
| Median age of patients | Excluded | | |
| Design of the PCI setting (y or n) | 2.14 | 0.742 | 0.009 |
| Description of definition for ED (y or n) | Excluded | | |

*Threshold F values for entering and removing from the model were 0.05 and 0.10, respectively.
†$P<0.05$ was considered significant. This multivariate stepwise regression model excluded the factors "Year of trial initiation," "Use of PE regimen," "Proportion of male patients," "Median age of patients," and "Description of definition for ED" from the model.
Abbreviations: PE, cisplatin and etoposide; PS, performance status; PCI, prophilactic cranial irradiation; ED, extended disease.
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The analysis similarly revealed a very small increase in patient survival (3.61 days per year) but one that was statistically significant in the multiple regression model ($P<0.001$; ([16]). There may be several potential factors behind such differences in statistical results in SCLC and NSCLC settings. The most important is that new active agents such as taxanes appeared in the treatment of NSCLC [17,18] and few novel agents, including molecular-targeted agents, did in the treatment for SCLC [11,19,20,21] in these study periods. Another hypothesis is that advanced NSCLC might be more influenced than SCLC by lead time bias through early detection with improved imaging techniques, mainly because the growth rate of NSCLC is generally less rapid than that of SCLC throughout its natural history [22]. Progress in supportive care practices would lead to improvements in survival among patients with advanced NSCLC. Those with advanced NSCLC usually have less rapid disease progression and, thus, would likely benefit from its advancement. Finally, the statistical difference between our NSCLC and SCLC studies could have arisen from differences in sample size (number of trials), indicating that the current study may have lacked adequate power to accurately evaluate the association between the year of trial initiation and patient outcome.

The potential influence of second-line chemotherapy should also be considered in assessing the effect of first-line chemotherapy because it may contribute to recent improvements in survival [23]. The trials analyzed here rarely provided information about second-line treatment, and we can not assess its exact effect in this setting. There are few positive phase III trials of second-line treatments, and thus it is unlikely that such therapy can significantly confound patient prognosis after the initiation of first-line chemotherapy [24].

In conclusion, the results of our analysis suggest that, regardless of the reason, the survival of patients with ED-SCLC who were enrolled in phase III trials did not improve significantly over the years. Thus, the development of novel targets, newer agents, and comprehensive patient care will be essential in the future fight against lung cancer.

## Supporting Information

**File S1**
Found at: doi:10.1371/journal.pone.0007835.s001 (0.05 MB DOC)

## Author Contributions

Conceived and designed the experiments: KH. Performed the experiments: KH. Analyzed the data: IO KH. Wrote the paper: IO KH KK NO NT YF MT MT.

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original article

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# A phase II dose-ranging study of palonosetron in Japanese patients receiving moderately emetogenic chemotherapy, including anthracycline and cyclophosphamide-based chemotherapy

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**Background:** The 5-$HT_3$ receptor antagonists (RAs) help maintain the standard of care, in various combinations with other agents, for prevention of chemotherapy-induced nausea and vomiting (CINV). Palonosetron is a new generation 5-$HT_3$ RA with indication not only acute but also delayed nausea and vomiting induced by moderately emetogenic chemotherapy (MEC). This study was carried out to determine the optimal dosage of palonosetron in combination with dexamethasone in patients in Japan.

**Patients and methods:** This study evaluated the efficacy and safety of palonosetron in patients receiving MEC combined with dexamethasone. Patients received single doses of 0.075, 0.25, or 0.75 mg of palonosetron before MEC. Dexamethasone was infused before palonosetron, at 20 mg for the patients receiving paclitaxel (Taxol) and 8 mg for the patients not receiving paclitaxel. The primary end point was complete response (CR: no emetic episodes and no rescue medication) in the acute phase (0–24 h).

**Results:** In total, 204 patients (88 men, 116 women; 96 with paclitaxel, 108 without paclitaxel) were assessable for efficacy. No dose–response relationship was observed regarding the CR rate in the acute phase. CR rates increased dose dependently for delayed (24–120 h) and overall (0–120 h) phases in patients receiving anthracyclines and cyclophosphamide combination (AC/EC, $n = 80$); however, the difference in CR rates among doses was not statistically significant. The most commonly reported adverse events related to palonosetron were constipation and headache, confirming the class safety profile.

**Conclusion:** This study indicates a statistically nonsignificant trend for the dose–response relationship for antiemetic protection in the delayed and overall phases in AC/EC patients (the regimen currently considered to be more emetogenic than MEC).

**Key words:** chemotherapy-induced nausea and vomiting, 5-$HT_3$ receptor antagonist, palonosetron

## introduction

Chemotherapy-induced nausea and vomiting (CINV) are among the most common significant side-effects of cancer chemotherapy. CINV can become a major problem both for patients receiving highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC), especially in patients receiving a combination of anthracyclines and cyclophosphamide [1, 2]. Inadequate control of CINV can have a considerable negative impact on all aspects of patient quality of life and may lead patients to refuse to continue chemotherapy [1]. It is clear today that serotonin plays an important role in the development of CINV [3]. Control of acute nausea and vomiting improved significantly in the 1990s when 5-$HT_3$ receptor antagonists (RAs) were introduced into clinical practice. Combined with various agents, the 5-$HT_3$ RAs are now considered a standard of care [4–6]. The dose to be used varies in different settings. However, the effectiveness of

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previously developed 5-$HT_3$ RAs such as ondansetron, dolasetron, granisetron, and tropisetron, in preventing delayed nausea and vomiting (with symptoms occurring later than 24 h after chemotherapy) is considered less than optimal. In fact, patients still experience CINV when undergoing HEC or MEC even when multiple 5-$HT_3$ RAs are administered [7, 8].

Palonosetron is a new highly potent and selective 5-$HT_3$ RA. It has a receptor binding affinity that is ~100 times higher than previously developed 5-$HT_3$ RAs [9] and it has a significantly longer plasma elimination half-life, ~40 h [10] compared with other agents in this class [11, 12]. Results from three phase III trials [13–15] and one phase II study, conducted in the Western patients [16], indicated in a recommended dosage of 0.25 mg for palonosetron, administered as a single i.v. dose 30 min before chemotherapy. In the phase II study to determine the most appropriate dose of palonosetron (0.3–90 μg/kg) for patients receiving HEC, the two lowest effective doses were reported to be 3.0 and 10 μg/kg (reported to be equivalent to fixed doses of 0.25 and 0.75 mg per body, respectively) [16]. These two fixed doses of palonosetron were then compared with single i.v. doses of ondansetron 32 mg [15] and dolasetron 100 mg [14] in two phase III trials conducted in patients receiving MEC. In these trials, 0.25 mg of palonosetron was proven to control CINV with a clinically relevant better efficacy than ondansetron and dolasetron, at all times studied (acute, delayed, and overall phases). The difference in complete response (CR; no emesis and no rescue medication) rates between 0.25 mg palonosetron and comparator was around 15% in the delayed and overall phases. Both studies failed to show any advantage for patients who received 0.75 mg palonosetron. Of note, these studies included a minority of patients receiving corticosteroids. In contrast to the other 5-$HT_3$ RAs, palonosetron is given as a single injection to patients receiving MEC on the day of chemotherapy, to prevent CINV in the overall period following chemotherapy administration (1–5 days) [14, 15]. These data prompted the Food and Drug Administration (FDA) to grant palonosetron approval for the prevention of acute and delayed CINV in patients receiving MEC. Palonosetron is also approved for the prevention of CINV in European Union (EU) countries.

The current phase II, dose-ranging, randomized, double-blind, multicenter study was conducted on patients receiving MEC in Japan to identify the most effective dose of palonosetron when combined with fixed doses of dexamethasone. The additional objective was safety assessment, in the evaluated dose range.

## patients and methods

### patient selection

MEC was defined as chemotherapy based on the administration of a single agent (or a combination of agents) of emetogenicity level 3 or 4 of the National Comprehensive Cancer Network (NCCN) 2004 guidelines [17] [i.e. any dose of carboplatin, epirubicin, idarubicin, ifosfamide, or irinotecan; or cyclophosphamide (≤1500 mg/$m^2$), doxorubicin (≥20 mg/$m^2$), or cisplatin (<50 mg/$m^2$, infused over 1–4 h)]. Patients with diagnosis of cancer who were naive to chemotherapy and who satisfied the following inclusion criteria were scheduled to receive their first dose of MEC and enrolled in this dose-ranging study of palonosetron. Patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of one or less, age between 20 and 79 years, and adequate bone marrow (white blood cell count ≥ 3000/$mm^3$), hepatic (serum aspartate aminotransferase and alanine aminotransferase levels < 100 IU/l each), and renal (creatinine clearance level estimated by the Cockcroft–Gault formula [18] ≥60 ml/min) function. Exclusion criteria included severe, uncontrolled, concurrent illness other than cancer; symptomatic brain metastasis; evidence of seizure disorder requiring anticonvulsants; pleural effusion or ascites that required drainage; gastric or intestinal obstruction; vomiting, retching, or ≥grade 2 nausea [National Cancer Institute—Common Terminology Criteria for Adverse Events v3.0 (CTCAE)]; corrected QT interval >450 msec on 12-lead electrocardiogram (ECG); known hypersensitivity to other 5-$HT_3$ RAs or dexamethasone sodium phosphate; no consent to practice adequate contraception; and participation in another study of investigational agents within 3 months. Patients were excluded if they were scheduled to receive level 4 or more emetogenic agents according to the NCCN 2004 guidelines or radiotherapy within the period of observation of efficacy (5 days). Administration of any antiemetics, sedatives, or corticosteroids (other than dexamethasone as a study medication) was not permitted within 24 h preceding palonosetron.

### study design and treatment regimen

This was a phase II, randomized, double-blind, dose-ranging, multicenter study conducted in Japan from April to November 2005. Eligible patients were randomly assigned to receive a single i.v. dose of palonosetron of 0.075, 0.25, or 0.75 mg over 30 s, administered 30 min before the first dose of MEC or AC/EC regimen on day 1. Patients were stratified at randomization by gender and administration of paclitaxel (Taxol, Bristol-Myers K.K., Japan) using a minimization method. Dexamethasone 8 mg was also i.v. administered within 45 min before palonosetron administration. In case of MEC including paclitaxel, 20 mg dexamethasone, combined with 50 mg oral diphenhydramine and 20 mg i.v. famotidine or 50 mg i.v. ranitidine, was administered as premedication to prevent anaphylaxis at least 30 min before paclitaxel administration [19]. This study was approved by the Institutional Review Board at each participating institution and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from each patient before they were enrolled in the trial.

### efficacy parameters

The primary end point of this study was the proportion of patients who achieved a CR, defined as no emetic episode and no use of rescue medication during the first 24 h (acute phase) following administration of study chemotherapeutic agents. An emetic episode was defined as one episode of vomiting or a sequence of episodes in very close succession not relieved by a period of relaxation of at least 1 min, any number of unproductive emetic episodes (retching) in any given 5-min period, or an episode of retching lasting <5 min combined with vomiting not relieved by a period of relaxation of at least 1 min [15]. Secondary end points included CR rates from 24 to 120 h (delayed phase) and 0 to 120 h (overall phase); complete control (CC) rates, which was defined as no emetic episode, no need for rescue medication, and no more than mild nausea; time to treatment failure (first emetic episode or first need of rescue medication, whichever occurred first); number of emetic episodes; severity of nausea; and patient global satisfaction with antiemetic therapy as measured on a visual analogue scale.

### study assessment procedures

Each consenting patient was screened for study eligibility within 7 days before being enrolled. Baseline assessment procedures included past medical history, vital sign measurements, concomitant medications, ECOG

PS, physical examination, 12-lead ECG, and laboratory tests (complete blood count with differential, blood chemistry, urinalysis, and estimated creatinine clearance). All patients were required to be hospitalized at least until completing assessment on day 2. In addition, follow-up assessment was conducted on day 8 (permissible range days 6–10) and on day 15 (days 14–20) for each patient. Assessment procedures included vital sign measurements, physical examination, 12-lead ECG, and laboratory tests. Evaluation of daily emetic episodes, severity of nausea, and patient global satisfaction until day 5 were reported by the patient in a diary. Use of rescue medication was recorded on each patient's medical chart. Safety was assessed using CTCAE until day 15. All adverse events were reported, irrespective of study medications.

### statistical analyses

In this dose-ranging study of palonosetron, CR rates in acute phase were assumed to be 67%, 85%, and 85% in the 0.075, 0.25, and 0.75 mg palonosetron dose groups, respectively. This assumption was based on the following: (i) the CR rate in acute phase was reported to plateau at a palonosetron dose ≥0.25 mg in two earlier phase III studies of MEC in Western patients [14, 15]; (ii) concurrent use of dexamethasone (8 or 20 mg) in all patients in the present study would contribute a 10%–20% increase of CR rates [20]; and (iii) the CR rate in the lowest dose of 0.075 mg was estimated to be ~40% higher than the CR rate in the lowest dose group (24% in the 0.3 μg/kg dose group) of the preceding phase II study of HEC in Western patients [16] because the present study enrolled patients receiving MEC and all patients were administered dexamethasone with palonosetron. For the Cochran–Armitage trend test (contrast coefficient score setting: −2 at the 0.075 mg and 1 at the 0.25 and 0.75 mg dose groups), a sample size of 189 assessable patients was required to ensure a one-sided α level of 2.5% with a statistical power of 80%. Assuming five dropout patients per dose group, 204 patients were needed in this study.

Statistical analyses were carried out using SAS software version 8.0 (SAS Institute, Inc., Cary, NC). The Cochran–Armitage trend test was used to determine the significance of differences in dose–response parameters (i.e. CR or CC rates) between dose groups. The $\chi^2$ test or Fisher's exact probability test was used to compare proportions of categorical variables. The difference in mean values of baseline characteristics was tested using one-way analysis of variance. The number of emetic episodes, severity of nausea, and patient global satisfaction were compared between dose groups using the Kruskal–Wallis test. Time-to-event distributions were calculated using the method of Kaplan and Meier, and differences between these distributions were assessed using the log-rank test.

Analyses of efficacy end points were carried out for the full analysis set (FAS) population, which was defined as those of patients receiving both palonosetron and level 3 or 4 emetogenic chemotherapy agents on day 1. Furthermore, additional efficacy analyses were carried out for the subgroup patients receiving combination chemotherapy of AC/EC, which is considered to be more emetogenic than MEC agents. Safety data for all patients receiving palonosetron were tabulated and summarized descriptively.

## results

### patient baseline demographics

We enrolled 211 patients in this study from 19 institutions. Patients were randomly assigned to one of the three palonosetron dose groups. Efficacy and safety analyses were carried out for the FAS population (67, 68, and 69 patients, respectively, in the 0.075, 0.25, and 0.75 mg palonosetron dose groups) because seven patients who had never received palonosetron were excluded (three patients each in the 0.075 and 0.25 mg dose groups and one patient in the 0.75 mg dose group).

Baseline demographic data and characteristics of patients in the FAS cohort are presented in Table 1. There were no differences between the groups in the distribution of patients by gender, age, height, weight, or ECOG PS. The most common types of tumor cancer were non-small-cell lung cancer ($n = 108$) followed by breast cancer ($n = 82$) and small-cell lung cancer ($n = 9$). The most common chemotherapeutic agents administered on day 1 were carboplatin ($n = 112$), paclitaxel ($n = 96$), cyclophosphamide ($n = 83$), epirubicin ($n = 45$), and doxorubicin ($n = 36$). Eighty patients received a combination of anthracyclines and cyclophosphamide (AC/EC). There were no differences in the proportion of cancer types or chemotherapy agents administered in individual palonosetron dose groups.

**Table 1.** Patient baseline demographics

| | Palonosetron dose | | | *P* value |
|---|---|---|---|---|
| | 0.075 mg (*N* = 67), *n* (%) | 0.25 mg (*N* = 68), *n* (%) | 0.75 mg (*N* = 69), *n* (%) | |
| Gender | | | | |
| Male | 31 (46.3) | 28 (41.2) | 29 (42.0) | 0.822 |
| Female | 36 (53.7) | 40 (58.8) | 40 (58.0) | |
| Age (years)[a] | 57.0 ± 11.2 | 58.2 ± 11.4 | 59.3 ± 10.2 | 0.474 |
| Height (cm)[a] | 160.5 ± 8.0 | 160.0 ± 7.6 | 157.7 ± 8.7 | 0.105 |
| Weight (kg)[a] | 60.1 ± 9.5 | 57.3 ± 8.9 | 56.8 ± 9.7 | 0.085 |
| ECOG PS | | | | |
| 0 | 54 (80.6) | 48 (70.6) | 53 (76.8) | 0.390 |
| 1 | 13 (19.4) | 20 (29.4) | 16 (23.2) | |
| Tobacco use | | | | |
| Nonsmoker | 32 (47.8) | 38 (55.9) | 34 (49.3) | 0.642 |
| Ex-smoker 180 days prior | 13 (19.4) | 9 (13.2) | 17 (24.6) | |
| Ex-smoker within 180 days | 10 (14.9) | 12 (17.6) | 14 (20.3) | |
| Current smoker | 12 (17.9) | 9 (13.2) | 4 (5.8) | |
| Alcohol use | | | | |
| None | 31 (46.3) | 27 (39.7) | 34 (49.3) | 0.414 |
| Rarely | 9 (13.4) | 8 (11.8) | 9 (13.0) | |
| Occasionally | 11 (16.4) | 13 (19.1) | 11 (15.9) | |
| Regularly | 16 (23.9) | 20 (29.4) | 15 (21.7) | |
| Cancer type | | | | |
| Lung non-small cell | 34 (50.7) | 36 (52.9) | 38 (55.1) | Not done |
| Breast | 28 (41.8) | 27 (39.7) | 27 (39.1) | |
| Lung small cell | 4 (6.0) | 3 (4.4) | 2 (2.9) | |
| Other | 1 (1.5) | 2 (2.9) | 2 (2.9) | |
| Chemotherapy agent | | | | |
| Carboplatin | 37 (55.2) | 37 (54.4) | 38 (55.1) | Not done |
| Paclitaxel | 32 (47.8) | 32 (47.1) | 32 (46.4) | |
| Cyclophosphamide | 28 (41.8) | 27 (39.7) | 28 (40.6) | |
| Epirubicin | 15 (22.4) | 16 (23.5) | 14 (20.3) | |
| Doxorubicin | 11 (16.4) | 12 (17.6) | 13 (18.8) | |

[a]Mean ± standard deviation.

ECOG PS, Eastern Cooperative Oncology Group performance status.

## primary efficacy analysis

The CR rates in the acute phase were 85.1%, 82.4%, and 92.8%, respectively, for the 0.075, 0.25, and 0.75 mg palonosetron dose groups (Figure 1A). There was no significant dose–response relationship found with the Cochran–Armitage trend test (contrast coefficients: −2 at the 0.075 mg and 1 at the 0.25 mg and 0.75 mg dose groups; $P = 0.2499$), where age (<65 or ≥65 years) and gender were included as stratification factors because they were identified as covariates on blind review.

## secondary efficacy analysis

For the delayed (24–120 h) and overall (0–120 h) periods, the CR rates increased in a dose-dependent way, although not with clinical relevance (62.7%, 66.2%, and 71.0% for the delayed and 59.7%, 64.7%, and 69.6% for the overall period in the 0.075, 0.25, and 0.75 mg palonosetron dose groups, respectively; Figure 1A), and a similar increase was observed in CR rate among the three dose groups for the cumulative periods (Table 2) as well as successive 24-h periods (24–48, 48–72, 72–96, and 96–120 h; data not shown). The CC rates for the acute, delayed, and overall periods were similar to those in the CR evaluation (data not shown). In addition, the number of emetic episodes, severity of nausea as assessed by the four-point Likert scale, and patient global satisfaction did not differ among the three palonosetron dose groups (data not shown).

Cumulative CR rates in patients who received a combination of anthracyclines (doxorubicin or epirubicin) and cyclophosphamide (AC/EC, $n = 80$) are shown in Figure 1B and Table 2. In this subgroup of patients who received less corticosteroids, a dose-dependent increase in CR rates was observed, with increases of >10%, showing better efficacy in the 0.75 mg dose group. These differences did not reach statistical significance. CR rates in patients receiving agents other than the AC/EC regimen, mainly carboplatin and paclitaxel, were 95.1%–100.0% in the acute phase and 76.2%–78.0% in the delayed phase (Figure 1C).

The time to treatment failure in the FAS population and AC/EC subgroup are shown in Figure 2A and B ($n = 203$ and $n = 80$, respectively). One patient in the 0.25 mg palonosetron dose group discontinued the study and was excluded from the FAS for this analysis. The median time to treatment failure in the FAS population was >120 h in all three dose groups, with first quartile times of 41.8, 44.3, and 72.2 h, respectively, in the 0.075, 0.25, and 0.75 mg palonosetron dose groups. In the AC/EC subgroup analysis, the median time to treatment failure was 36.2, 55.8, and >120 h, respectively, in the 0.075, 0.25, and 0.75 mg palonosetron dose groups. However, these differences did not reach statistical significance.

## safety evaluation

Of the total 204 patients evaluated for safety, 67 (100%), 67 (98.5%), and 69 (100%) experienced at least one adverse event, in the 0.075, 0.25, and 0.75 mg palonosetron dose groups, respectively. Adverse drug reactions appeared in 22 (32.8%), 17 (25.0%), and 16 (23.2%) patients in the 0.075, 0.25, and 0.75 mg palonosetron dose groups, respectively. In addition, serious adverse events were reported in 10 (4.9%) patients, all of which were assessed as not related to palonosetron. A list of

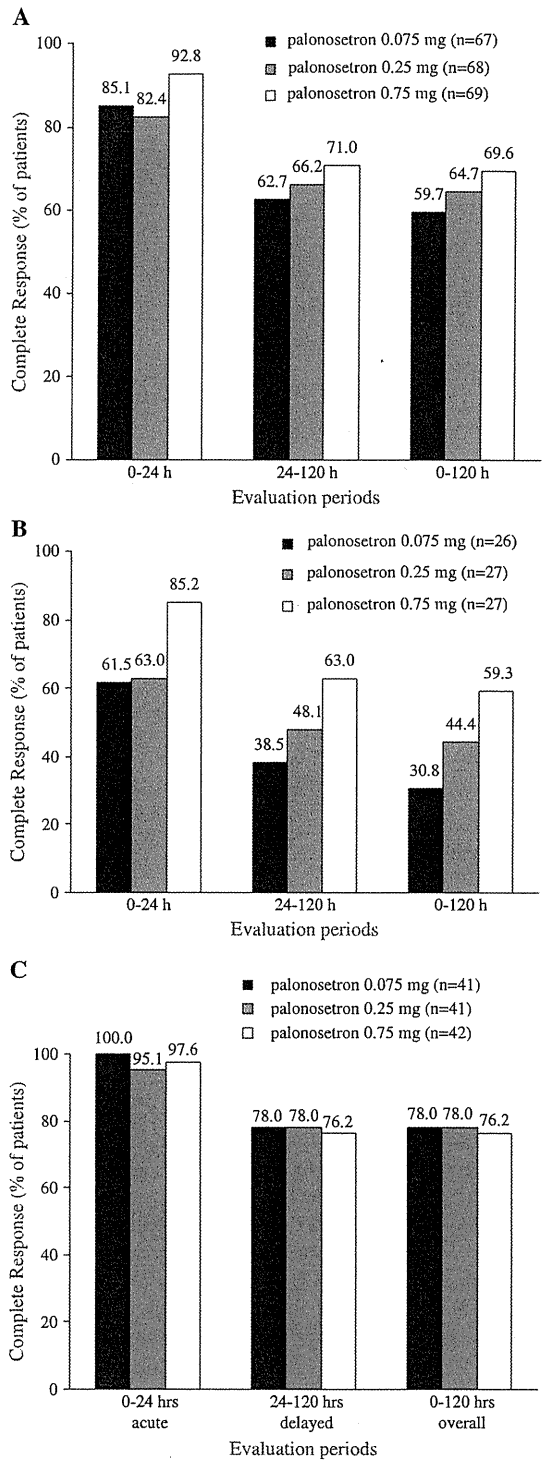


**Figure 1.** (**A**) Complete response rates after administration of moderately emetogenic chemotherapy in pooled patients population ($n = 204$). (**B**) Complete response rates in AC/EC subgroup ($n = 80$). (**C**) Complete response rates in non-AC/EC subgroup ($n = 124$). AC/EC, anthracyclines and cyclophosphamide combination.

**Table 2.** Complete response rate in the FAS (A) and complete response rates in AC/EC subgroup (B)

| Period (h) | *n* | % | 95% CI | *n* | % | 95% CI | *n* | % | 95% CI |
|---|---|---|---|---|---|---|---|---|---|
| A | | | | | | | | | |
| | 0.075 mg ($N = 67$) | | | 0.25 mg ($N = 68$) | | | 0.75 mg ($N = 69$) | | |
| 0–24 | 57 | 85.1 | 74.3–92.6 | 56 | 82.4 | 71.2–90.5 | 64 | 92.8 | 83.9–97.6 |
| 0–48 | 45 | 67.2 | 54.6–78.2 | 50 | 73.5 | 61.4–83.5 | 56 | 81.2 | 69.9–89.6 |
| 0–72 | 43 | 64.2 | 51.5–75.5 | 45 | 66.2 | 53.7–77.2 | 51 | 73.9 | 61.9–83.7 |
| 0–96 | 41 | 61.2 | 48.5–72.9 | 44 | 64.7 | 52.2–75.9 | 48 | 69.6 | 57.3–80.1 |
| 0–120 | 40 | 59.7 | 47.0–71.5 | 44 | 64.7 | 52.2–75.9 | 48 | 69.6 | 57.3–80.1 |
| 24–120 | 42 | 62.7 | 50.0–74.2 | 45 | 66.2 | 53.7–77.2 | 49 | 71.0 | 58.8–81.3 |
| B | | | | | | | | | |
| | 0.075 mg ($N = 26$) | | | 0.25 mg ($N = 27$) | | | 0.75 mg ($N = 27$) | | |
| 0–24 | 16 | 61.5 | 40.6–79.8 | 17 | 63.0 | 42.4–80.6 | 23 | 85.2 | 66.3–95.8 |
| 0–48 | 9 | 34.6 | 17.2–55.7 | 15 | 55.6 | 35.3–74.5 | 18 | 66.7 | 46.0–83.5 |
| 0–72 | 9 | 34.6 | 17.2–55.7 | 12 | 44.4 | 25.5–64.7 | 16 | 59.3 | 38.8–77.6 |
| 0–96 | 8 | 30.8 | 14.3–51.8 | 12 | 44.4 | 25.5–64.7 | 16 | 59.3 | 38.8–77.6 |
| 0–120 | 8 | 30.8 | 14.3–51.8 | 12 | 44.4 | 25.5–64.7 | 16 | 59.3 | 38.8–77.6 |
| 24–120 | 10 | 38.5 | 20.2–59.4 | 13 | 48.1 | 28.7–68.1 | 17 | 63.0 | 42.4–80.6 |

AC/EC, anthracyclines and cyclophosphamide combination; CI, confidence interval.

common treatment-related adverse events is given in Table 3. The most common adverse events related to palonosetron were constipation ($n = 20$) and headache ($n = 9$). Neither the incidence nor the severity of these events was dependent on dose. In this study, safety assessments were similar to what was reported in the safety profile observed in previous phase III trials [13–15] conducted in Western patients.

## discussion

Palonosetron has been approved for CINV induced by MEC both in United States and EU at 0.25 mg i.v. Its peculiar characteristics are high affinity for the receptor and prolonged duration of action. The FDA approved palonosetron for both acute and delayed emesis (i.e. up to 120 h of observation).

The present dose-ranging study was conducted in patients receiving MEC in Japan. At the time this study was planned, the AC/EC regimens were considered MEC. Eighty of 204 patients (39.2%) received such regimens.

A slight but not clinically relevant dose–response relationship for antiemetic efficacy was observed in the FAS patient population between the three tested doses in the acute, delayed, and overall phases. Interestingly, in the subgroup of patients receiving AC/EC, the CR rates for the delayed and overall phases appeared to increase with dose and showed the highest efficacy in the 0.75 mg dose group. The lowest dose appeared to be suboptimal in the delayed (CR = 38.5%) and overall (CR = 30.8%) periods. The 0.75 mg dose appeared to be at least 20% more efficacious in the acute phase (CR = 85.2%) in comparison to 0.075 mg (CR = 61.5%) and 0.25 mg (CR = 63.0%). In the delayed period, it was ~15% better than the dose of 0.25 mg (CR, respectively, of 63.0% and 48.1%), while in the overall phase, CR accounted, respectively, for 59.3% and 44.4%, showing another difference of 15%. The difference of 15% between the two doses shows numerically higher CR rates for the 0.75 mg dose with overall safety similar

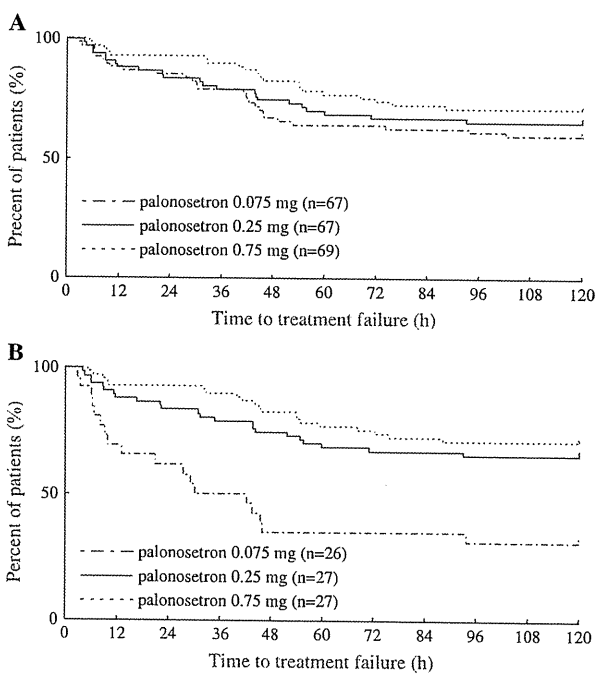


**Figure 2.** (A) Time to treatment failure of treatment of all patients ($n = 203$). (B) Time to treatment failure of treatment of AC/EC subgroup ($n = 80$). AC/EC, anthracyclines and cyclophosphamide combination.

to other dose groups and shows the same clinical difference found between palonosetron and comparators in the pivotal clinical phase III studies conducted in Europe and the United States, that included regimens of cyclophosphamide and/or anthracyclines [14, 15]. The highest dose level was shown to better protect from CINV those patients who received a regimen of AC/EC. On the other hand, CR rates in the patients receiving agents other than AC/EC showed no

**Table 3.** Common adverse events related to treatment

| | Palonosetron dose | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.075 mg ($N = 67$), $n$ (%) | | | | 0.25 mg ($N = 68$), $n$ (%) | | | | 0.75 mg ($N = 69$), $n$ (%) | | | |
| | Grade | | | | Grade | | | | Grade | | | |
| | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Constipation | 6 (9.0) | 2 (3.0) | 0 | 0 | 3 (4.4) | 2 (2.9) | 0 | 0 | 7 (10.1) | 0 | 0 | 0 |
| Headache | 3 (4.5) | 0 | 0 | 0 | 3 (4.4) | 0 | 0 | 0 | 2 (2.9) | 1 (1.4) | 0 | 0 |
| Rash | 2 (3.0) | 0 | 0 | 0 | 2 (2.9) | 4 (5.9) | 0 | 0 | 0 | 0 | 0 | 0 |
| ALT increased | 4 (6.0) | 0 | 0 | 0 | 2 (2.9) | 0 | 0 | 0 | 2 (2.9) | 0 | 0 | 0 |
| Blood bilirubin increased | 2 (3.0) | 0 | 0 | 0 | 2 (2.9) | 1 (1.5) | 0 | 0 | 2 (2.9) | 0 | 0 | 0 |
| ECG QT prolongation | 3 (4.5) | 1 (1.5) | 1 (1.5) | 0 | 1 (1.5) | 0 | 0 | 0 | 0 | 0 | 1 (1.4) | 0 |

ALT, alanine aminotransferase; ECG QT, electrocardiographic QT intervel.

significant difference among the three dose groups in the acute, delayed, and overall periods. This subgroup population included mainly patients receiving paclitaxel combined with carboplatin and they were given high-dose dexamethasone (20 mg), diphenhydramine, and histamine $H_2$-RA (famotidine or ranitidine) as premedication to prevent anaphylaxis. The CR rates in this subgroup were most likely influenced by the concomitant use of dexamethasone and diphenhydramine, which are also listed as antiemetic agents in the guidelines [21, 22]. This may also possibly have resulted in the absence of dose response through the efficacy evaluation period in this subgroup population.

Palonosetron was well tolerated in all the dose groups. Incidences, frequencies, intensities, and drug relationships of AEs appeared to be equally distributed among the three dose groups with no apparent relationship to dose. In another Japanese phase II study, conducted in patients receiving HEC, no differences were apparent in protection from CINV for 0.25 and 0.75 mg doses. Also in this trial, no differences in safety profile were evident between the two dose groups [23].

In conclusion, the trends for better efficacy and the excellent safety profile of palonosetron in this trial and the phase II HEC trial indicate that 0.75 mg could be the recommended dose of palonosetron for future studies in the Japanese population.

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# Cooperative Group Research Efforts in Thoracic Malignancies 2009: A Review From the 10th Annual International Lung Cancer Congress

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## Abstract

Critical advances in the treatment of patients with lung cancer have occurred in the past few years. The cooperative groups in North America and internationally have played crucial roles in these advances. The leaders of the groups meet on a regular basis to review the progress of their trials. However, they rarely have a chance to discuss all ongoing and planned trials, except at the annual Lung Cancer Congress held each June. This article captures this exchange from the 10th Annual Lung Cancer Congress held in June 2009. Exciting efforts are ongoing for all stages of non–small-cell lung cancer, small-cell lung cancer, and mesothelioma. A major focus of the groups at this time is a push toward more personalized medicine, as reflected in the selection criteria for many of the trials, along with planned correlates to better define populations most likely to benefit. Agents targeting the vascular endothelial growth factor (VEGF) pathway, including many tyrosine kinase inhibitors against the VEGF receptor, and those targeting the epidermal growth factor receptor pathway, are under extensive development with many combination trials ongoing.

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## Introduction

Progress in therapy for thoracic malignancies has been increasing dramatically in recent years. We have known for some time that chemotherapy improves survival and quality of life compared with best supportive care for advanced-stage disease.[1] Guidelines published by the American Society of Clinical Oncology (ASCO) and the American College of Chest Physicians endorse either a platinum or nonplatinum doublet as initial therapy for patients with good performance status (PS) with newly diagnosed advanced-stage non–small-cell lung cancer (NSCLC).[2,3] For early-stage NSCLC that has been resected, both ASCO and the National Comprehensive Cancer Network endorse cisplatin-based adjuvant chemotherapy for resected stage II and IIIA NSCLC, with controversy surrounding therapy of stage I disease and the use of postoperative radiation therapy.[4-6]

For advanced-stage disease, efforts to add a third drug to the standard 2-drug doublet regimens had not met with success until recent trials that have included bevacizumab and cetuximab, both antibodies targeted to pathways now known to be important in NSCLC.[7-9] These pathways include the vascular endothelial growth factor (VEGF) pathway critical for angiogenesis targeted by bevacizumab and the epidermal growth factor receptor (EGFR) pathway targeted by cetuximab. The benefit of the addition of bevacizumab to chemotherapy was first demonstrated by E4599, a phase III trial led by one of the large cooperative oncology research

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