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ORIGINAL ARTICLE

# Phase I study of larotaxel administered as a 1-h intravenous infusion every 3 weeks to Japanese patients with advanced solid tumours

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**Abstract** Larotaxel (XRP9881, RPR109881), a novel semi-synthetic taxoid that shares a mode of action with the taxanes docetaxel and paclitaxel, was active in preclinical studies against a broad spectrum of tumour cells and tumour models refractory/resistant to taxanes, and have demonstrated clinical activity in taxane pre-treated/resistant metastatic breast cancer (MBC) patients. The current phase I dose-escalation study sought to define in Japanese patients with advanced solid tumours the maximum tolerated dose (MTD) and recommended dose (RD) of larotaxel administered as a 1-h intravenous infusion every 3 weeks. Eighteen patients were treated in total with 11 of those (61%) having previously received a docetaxel- or paclitaxel-based regimen. The MTD was defined as 90 mg/m$^2$ following the occurrence of dose-limiting toxicities (DLTs) in two of five patients treated at this dose level including grade 4 neutropenia lasting >7 days or febrile neutropenia. The RD for phase II was consequently 75 mg/m$^2$ q3w, with no DLTs in the six patients treated. The principal toxicity and DLT was neutropenia, with or without neutropenic complications. Partial responses were reported for 2 of 18 (11%) treated patients and a further 8 achieved stable disease (44%). The clearance 19.1–31.9 L/h was similar to that observed in Caucasian subjects with value of 33.0 ± 10.7 L/h. In conclusion, larotaxel 75 mg/m$^2$, administered as a 1-h infusion every 3 weeks, appeared to be clinically tolerable in this Japanese patient population and showed early indications of activity.

**Keywords** Larotaxel · XRP9881 · Japanese · Solid tumour · Taxane · Phase I

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## Introduction

For several decades, cancer has remained the most common cause of death in Japan [1]. While improved prevention and screening programmes will most likely contribute to a reduction in the frequency of such deaths in the future, the development of new anticancer drugs will remain as a key component of integrated strategies to minimise the mortality associated with this disease. Conventional cytotoxic agents achieve cancer cell specificity by targeting most effectively proliferating over non-proliferating cells. The commercially available taxanes, docetaxel and paclitaxel are amongst the most efficacious and safe anticancer agents used for the treatment of a wide range of advanced tumours, including non-small cell lung, breast, prostate, gastric, head and neck and ovarian cancer. In in vivo studies, taxanes enhance microtubule polymerisation and stabilise microtubules against depolymerisation [2, 3]. During cell division, taxane action results in the disruption of the functioning of the mitotic spindle, which leads to cell cycle arrest in the G2/M phase, which in turn triggers apoptotic cell death [4, 5].

The initial or ultimate failure of a chemotherapeutic agent or regimen rests on the intrinsic or acquired resistance of clones of the tumour cell population to that treatment. As with all agents, the usefulness of taxanes can, therefore, be limited due to development of drug resistance that is often a consequence of the high-level expression of the ABCB1 gene, which encodes the 170 kDa, energy-dependent drug efflux pump, P-glycoprotein [6]. This fact coupled with the clinical success of docetaxel and paclitaxel therefore spurred the search for new taxane compounds that might show a broader spectrum of activity against taxane-resistant tumours [7, 8] by overcoming P-glycoprotein-mediated drug resistance while improving the safety profile.

Larotaxel (XRP9881, RPR109881) is synthesized as a single diastereomer by partial synthesis from 10-deacetyl baccatin III, the major natural taxoid that can be extracted from the needles of the European yew tree, *Taxus baccata*. The mechanism of action of larotaxel is similar to the existing taxanes in that it efficiently stabilises microtubules against cold-induced depolymerisation ($IC_{50} = 0.21$ μM) and has been shown to be equipotent to docetaxel in docetaxel-sensitive tumour models. Larotaxel demonstrated in vitro and in vivo activities in a range of taxane-resistant tumour models and was active when administered orally or intravenously. It was also able to cross the blood–brain barrier, with marked antitumour activity demonstrated in nude mice bearing early stage intracranial glioblastomas [9].

Several phase I studies have been carried out which have sought to define the dose-limiting toxicity (DLT), the maximum tolerated dose (MTD), and recommended dose (RD) of larotaxel administered intravenously on various schedules in Japanese, European and North American patients [10–15]. Of these schedules, a 1-h infusion of larotaxel 90 mg/m$^2$ administered every 3 weeks was selected as an appropriate dose for phase II testing [16]. In a similar study of 19 Japanese patients with advanced solid tumours, the MTD for patients receiving a 1-h i.v. infusion of larotaxel every 3 weeks was reached at 75 mg/m$^2$, and the RD in this population was defined as 60 mg/m$^2$ [12]. Neutropenias with or without neutropenic complications were common DLTs in both of these studies. However, the criterion for defining DLT in the Japanese study in relation to neutropenia differed from the European and other studies in that grade 4 neutropenia for ≥3 days was considered to be a DLT, compared with the more commonly used definition of grade 4 neutropenia for more than 7 days. The current phase I dose-escalation study was, therefore, designed primarily to re-assess the MTD and RD of larotaxel on this schedule in Japanese patients at different institutions from the previous study using the more commonly accepted DLT definition of grade 4 neutropenia lasting for more than 7 days which is equivalent to that used in European and other studies. The different DLT criterion is considered one of the causes for the different MTD/RD obtained in Japanese studies and European and other studies.

## Materials and methods

### Major eligibility criteria

Patients aged 20–74 years of age with a histologically or cytologically proven diagnosis of metastatic or advanced solid tumour malignancy with no available standard curative measures were eligible. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and life expectancy of at least 12 weeks and were to have recovered to grade ≤1 (according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [CTCAE v.3.0]) from all clinically significant toxic effects (excluding alopecia) of any prior surgery, radiotherapy, hormonal therapy, immunotherapy, therapeutic antibody or other molecularly targeted non-cytotoxic therapy, or chemotherapy. Prior hormonal or molecularly targeted non-cytotoxic therapy should have been completed ≥3 weeks before first administration of the study treatment dose and all prior chemotherapy, immunotherapy, antibody therapy and radiotherapy should have been completed ≥4 weeks before the first administration of study drug.

Patients were also required to have adequate organ function as follows: absolute neutrophil count $\geq 1.5 \times 10^9$ L$^{-1}$; platelet count $>100 \times 10^9$ L$^{-1}$; haemoglobin ≥9.0 g/dL; albumin ≥3.5 g/dL; creatinine <1.5 × upper limit of normal (ULN); total bilirubin within normal limits, serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≤2.5 × ULN (if alkaline phosphatase was ≤2.5 × ULN) or ≤1.5 × ULN (if alkaline phosphates was >2.5 to ≤5.0 × ULN).

Patients were ineligible if they were breastfeeding or if they had received more than two prior chemotherapy regimens for advanced disease, radiation therapy to >25% bone marrow area, or if they had a history of hypersensitivity to taxanes, polysorbate-80 or alcohols. They were also excluded if they had brain or leptomeningeal disease, interstitial pneumonitis, peripheral neuropathy grade ≥2 or a serious illness or medical condition that could deter participation in the study.

### Study design and treatment

This was a two-centre, phase I dose-escalation study of larotaxel administered as a 1-h intravenous (i.v.) infusion every 3 weeks to patients with advanced solid tumours until the occurrence of disease progression, unacceptable toxicity

or withdrawal of consent or investigator decision. The primary objective of the study was to determine the DLT and MTD of larotaxel administered according to this schedule. Secondary objectives were to establish the RD of larotaxel for future phase II trials, to investigate the general safety profile, tolerability and pharmacokinetics (PKs) of larotaxel and to assess for evidence of antitumour activity.

Within 30–60 min prior to each dose of larotaxel, patients received prophylactic premedications for hypersensitivity reactions which included: dexchlorpheniramine 5 mg, diphenhydramine 25 mg or other antihistamines (H1 blocker), i.v. (or p.o.); ranitidine 50 mg, i.v.; dexamethasone 8 mg or an equivalent steroid, i.v. Anti-emetic prophylaxis with ondansetron or granisetron was also recommended.

Six dose levels of larotaxel (−1, 1, 2, 3, 4, 5) were planned, including 45, 60, 75, 90, 105 and 120 mg/m$^2$, respectively. The starting dose of 60 mg/m$^2$ (dose level 1) was chosen on the basis of previous phase I studies in Japanese and Caucasian patients [12, 13]. Starting at 60 mg/m$^2$, cohorts of three to six patients were treated at each dose level and observed for DLT over the first treatment cycle. Initially, up to three patients were enrolled at each dose level. If none of these patients developed a DLT, the dose was escalated to the next level. If one patient experienced a DLT, a further three patients were recruited to that dose level. If no further DLT developed at the first cycle, dose was escalated. Prior to dose escalation, all three or six patients should have completed the first cycle and been observed for toxicity for at least 3 weeks. If two or more patients developed a DLT at a dose level, dose escalation was discontinued and this dose level was defined as the MTD. Once the MTD had been defined, an additional three patients were recruited at the dose level immediately below the MTD (unless six had already been treated). If less than two patients developed DLT at this dose level, it was defined as the RD for phase II studies. If two patients experienced DLT at dose level 1 (60 mg/m$^2$), patients were to be subsequently enrolled in dose level −1 (45 mg/m$^2$). Intrapatient dose escalation was not allowed and patients who were not evaluable for DLT during the first cycle as a consequence of allergic reaction were to be replaced.

National Cancer Institute CTCAE v.3.0 was used to evaluate toxicities. DLT was defined as the occurrence in the first cycle of any of the following toxicities: neutropenia, grade 4 for more than 7 days; platelets, grade 4; grade 4 anorexia, fatigue, nausea or vomiting, despite prophylaxis and/or treatment with anti-emetics; any other grade 3 or 4 toxicity (including febrile neutropenia and neutropenic infection), except hypersensitivity reaction, nausea, vomiting, fatigue or anorexia, unless the investigator and sponsor concluded that these toxicities were acceptable.

## Pharmacokinetic analysis

The PK evaluations were performed in patients in the first treatment cycle. Blood samples (2 mL) for the analysis of plasma concentrations of larotaxel and its metabolite (RPR206205) were collected immediately prior to infusion, 30 min after beginning of infusion, immediately before the end of infusion and 10, 20, 30, 60 and 90 min and 2, 4, 6, 8, 24, 48, 72, 96 and 120 h post-infusion and at a time point between day 20 and the next infusion in cycle 2 (or discontinuation day, if the patient was withdrawn from the study). Plasma was separated from heparinised blood samples by centrifugation at 4°C for 10 min at 2,200 g, transferred to a fresh tube and stored at −20°C until analysis. Not more than 1 h was allowed between blood collection and plasma sample freezing. Urine samples were collected for the analysis of larotaxel and RPR206205 ≤24 h prior to the start of infusion and at the following time intervals: 0–6, 6–24, 24–48, 48–72, 72–96 and 96–120 h from the start of larotaxel infusion. For each interval, the total volume of urine was measured and a 10 mL aliquot collected and stored at −20°C until analysis.

Drug concentrations in plasma and urine were determined using liquid chromatography–tandem mass spectrometry. The lower limit of quantitation (LOQ) in each case was 1 ng/mL for a 200 μL sample. PK parameters were calculated using a non-compartmental model. PK parameters for larotaxel and RPR206205 were calculated using WinNonlin Professional Edition software, version 4.1 (Pharsight Corp, Mountain View, CA). Variables determined included maximum plasma concentration ($C_{max}$), area under the concentration–time curve (AUC), elimination half-life ($t_{1/2}$), total plasma clearance (CL), volume of distribution at steady state ($V_{ss}$) and urinary excretion rate.

## Statistical methods and considerations

The primary study variable was the number of DLTs occurring at the first treatment cycle at each dose level. Safety variables included the number and severity of toxicities and the number of discontinuations due to toxicities. The primary efficacy variable was overall tumour response, assessed according to RECIST guidelines for unidimensional evaluation [17]. At baseline, all known and suspected sites of disease were imaged radiologically (computed tomography or magnetic resonance imaging scans) and lesions were classified as either measurable (accurately measurable in at least one dimension) or non-measurable. Responses (complete or partial) had to be confirmed by repeat radiological imaging and clinical assessment performed 4–6 weeks after the criteria for response were first met. For stable disease, follow-up measurements had to

meet the stable disease criteria at least once after study enrolment, at a minimum interval of 6 weeks.

The study was conducted according to good clinical practice and the ethical principles described in the International Conference on Harmonization ICH E6 Guideline (Guideline for Good Clinical Practice). Informed written consent was obtained from all patients prior to the initiation of any study-related procedures. The study protocol was approved by Institutional Review Board of each institution.

## Results

### Patients and treatment compliance

Eighteen Japanese patients who had all previously received chemotherapy were enrolled and treated with larotaxel. In 11 instances, prior chemotherapy (61%) included a taxane-based regimen: nine patients had been treated with docetaxel, included one who received this as adjuvant therapy, and two had received paclitaxel. The most common primary malignancies were stomach and lung adenocarcinoma (each in three patients), followed by oesophageal squamous cell carcinoma and colon adenocarcinoma (each in two patients). The first patient was enrolled on 6 October 2004 and the last completed observation on 9 March 2007. Seven, six and five patients were treated at the dose levels of 60, 75 and 90 mg/m$^2$, respectively. Baseline demographic characteristics were similar between patients in these treatment groups (Table 1).

The 18 patients received a median of 4, 3 and 6 treatment cycles and achieved relative dose intensities of 1.0, 0.94 and 0.92 in the 60, 75 and 90 mg/m$^2$ dose groups, respectively. Dose reductions occurred in 9 of 72 (13%) cycles as a result of the occurrence of drug-related haematological (five cases), non-haematological (three cases), and haematological and non-haematological (one case). Delays occurred in 13 of 72 (18%) administered cycles, most commonly due to study drug-related haematological toxicity (9/72 cycles, 13%). Study discontinuations were due to progressive disease in 14 patients and to toxicities in 4 patients. In three of these four patients, the toxicities leading to discontinuation were thought to be related to study treatment: grade 3 of pulmonary suppuration (one patient at 60 mg/m$^2$); grade 3/2 of elevated ALT/AST (one patient at 75 mg/m$^2$); and grade 3 of enteritis and sepsis (one patient at 90 mg/m$^2$).

### Dose-limiting toxicity

The incidence of DLT is summarised in Table 2. One patient from the 60 mg/m$^2$ treatment cohort was excluded from the DLT evaluation by the study's Safety and Efficacy Evaluation Committee because it was difficult to judge whether the patient's fever (lower than 38.5°C) was affected by the concomitant use of an antipyretic. Of the remaining six patients treated at this dose level, only one experienced DLT (grade 4 neutropenia for more than 7 days) and in accordance with the study design, the dose was escalated. No DLTs developed in six patients treated at 75 mg/m$^2$ and the dose level was elevated to 90 mg/m$^2$. DLTs occurred in two of five patients treated at this dose level. These included grade 4 neutropenia for more than 7 days, grade 3 infection with neutropenia, grade 3 diarrhoea, in one patient and grade 3 febrile neutropenia, grade 3 AST/ALT elevation, and grade 3 sodium decrease in another patient. Therefore, the MTD of larotaxel administered as a 1-h intravenous infusion every 3 weeks in Japanese patients with advanced solid tumours was determined to be 90 mg/m$^2$. Given that none of the six patients treated at 75 mg/m$^2$ experienced DLT, the RD was established as 75 mg/m$^2$.

### Safety

All 18 patients received at least one administration of larotaxel and were, therefore, evaluable for safety. The most common toxicities at any grade were fatigue (18 patients, 100%), neutropenia and leukopenia (each 17 patients, 94%), alopecia and sensory neuropathy (each 16 patients, 89%, all events grade 1 or 2) and haemoglobin decreased and anorexia (each 15 patients, 83%). Two patients experienced allergic/hypersensitivity reactions, but these were moderate at grade 2. Four patients (22%) experienced oedema of the limb (in three cases, grade 1; in one case, grade 2) and two (11%) oedema of the head and neck (grade 1). Grade 1 nail changes were noted for one patient.

Summarised in Table 3, the most common grade 3/4 toxicities were haematological, with the majority of patients experiencing neutropenia (16/18, 89%), lasting a median of 8 days, which reached grade 4 in 12 instances (67% of patients). Febrile neutropenia occurred in three of five patients receiving 90 mg/m$^2$. The frequency of occurrence of non-haematological toxicities was relatively low, with the most common being anorexia, elevated ALT and fatigue, each occurred in four patients (22%). Elevated AST, grade 3 was also reported in three patients (17%).

There were nine deaths during the follow-up period due to progression of the malignant disease. All occurred more than 31 days after the final administration of larotaxel and none were thought to be related to the study treatment.

### Efficacy

Response was evaluated according to RECIST guidelines in all 18 patients. Partial responses were observed for two

**Table 1** Demographic and disease characteristics at baseline

| Characteristic | Number (%) or summary statistics | | | |
|---|---|---|---|---|
| | 60 mg/m$^2$ ($N = 7$) | 75 mg/m$^2$ ($N = 6$) | 90 mg/m$^2$ ($N = 5$) | Total ($N = 18$) |
| Gender | | | | |
| Male | 3 (43) | 5 (83) | 3 (60) | 11 (61) |
| Female | 4 (57) | 1 (17) | 2 (40) | 7 (39) |
| ECOG performance status | | | | |
| 0 | 5 (71) | 3 (50) | 3 (60) | 11 (61) |
| 1 | 2 (29) | 3 (50) | 2 (40) | 7 (39) |
| Age (years) | | | | |
| Median (range) | 57.0 (28–63) | 51.0 (43–67) | 58.0 (26–69) | 56.5 (26–69) |
| Body surface area (m$^2$) | | | | |
| Median (range) | 1.530 (1.45–1.79) | 1.765 (1.56–1.98) | 1.690 (1.32–1.93) | 1.690 (1.32–1.98) |
| Primary lesion | | | | |
| Stomach, AC | – | 1 | 2 | 3 |
| Lung, AC | 1 | 1 | 1 | 3 |
| Oesophageal, SCC | – | 2 | – | 2 |
| Colon, AC | 1 | 1 | – | 2 |
| Head and neck | 1 | – | 1 | 2 |
| SCC | 1 | – | – | 1 |
| Nasopharynx | – | – | 1 | 1 |
| Others | 4 | 1 | 1 | 6 |
| Prior treatments | | | | |
| Surgery | 5 (71) | 4 (67) | 2 (40) | 11 (61) |
| Chemotherapy | 7 (100) | 6 (100) | 5 (100) | 18 (100) |
| Immunotherapy | 1 (14) | – | – | 1 (6) |
| Molecularly targeted therapy | 4 (57) | 1 (17) | 1 (20) | 6 (33) |
| Radiotherapy | 1 (14) | 1 (17) | 2 (40) | 4 (22) |
| Number of prior chemotherapy regimens | | | | |
| 1 | 2 (29) | 3 (50) | 4 (80) | 9 (50) |
| 2 | 5 (71) | 3 (50) | 1 (20) | 9 (50) |

*ECOG* Eastern Cooperative Oncology Group, *AC* adenocarcinoma, *SCC* squamous cell carcinoma, *LCC* large cell carcinoma, *NOS* not otherwise specified

patients (11%) at the 90 mg/m$^2$ dose level. Both patients had previously received taxane-based chemotherapy. The primary disease for these patients was a lung adenocarcinoma in one case and in the other, a squamous cell carcinoma of the head and neck. In addition, disease stabilisation was achieved from a further eight patients (44%).

## Pharmacokinetics

Plasma and urine samples were collected from all 18 patients at the first cycle and the concentrations of larotaxel and its metabolite (RPR206205) were measured by liquid chromatography–tandem mass spectrometry. The mean plasma concentration–time curves of these compounds are shown in Fig. 1. PK parameters were calculated using a non-compartmental model (Table 4). Across the dose range of 60–90 mg/m$^2$, the mean value for CL was 19.1–31.9 L/h m$^2$, the $V_{ss}$ was large, at 596.8–807.8 L/m$^2$, mean AUC ranged from 2592.1 to 3347.3 ng h/mL and the half-life of larotaxel in the final phase was long, at 32.1–35.9 h. Dose proportionality of AUC was not statistically evaluated across the dose range of 60–90 mg/m$^2$. The AUC of RPR206205 was less than 10% of that of larotaxel. Larotaxel showed a long half-life of 33–36 h. The urinary excretion rate of larotaxel and RPR206205 until 120 h after i.v. infusion was 0.34–1.28 and 0.02–0.77% of dose, respectively.

**Table 2** Dose-limiting toxicity

| Initial dose level (mg/m$^2$) | Evaluable patients (*N*) | Patients with DLT (*N*) | Dose-limiting toxicity |
|---|---|---|---|
| 60 | 6[a] | 1 | Neutropenia grade 4 for >7 days |
| 75 | 6 | 0 | |
| 90 | 5 | 2 | Neutropenia grade 4 for >7 days<br>Infection with neutropenia: grade 3<br>Enteritis with diarrhoea: grade 3<br>Febrile neutropenia: grade 3<br>AST/ALT elevation: grade 3<br>Sodium decrease: grade 3 |

*DLT* dose-limiting toxicity, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

[a] One enrolled patient in the initial cohort of seven patients was excluded from the DLT evaluation by the Safety and Efficacy Evaluation Committee

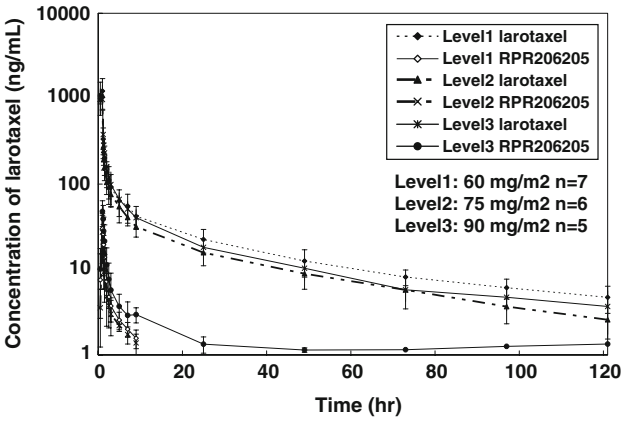


**Fig. 1** Mean plasma concentration–time curves of larotaxel and its metabolite, RPR206205

## Discussion

The novel taxoid larotaxel has particular characteristics that suggest that its continued development might widen the clinical spectrum of the existing taxanes. In particular, it appears to be cytotoxic to P-glycoprotein-expressing cell lines with a multidrug-resistance phenotype [9]. Furthermore, and most likely as a consequence of its low affinity for P-glycoprotein, larotaxel has been shown to cross the blood–brain barrier, and intracranial anticancer activity has been noted not only in murine model systems, but also in the brain metastasis of a lung cancer patient [13].

A previous phase I study defined the MTD and RD of larotaxel administered as a 1-h infusion every 3 weeks to Japanese patients to be 75 and 60 mg/m$^2$, respectively. Using a conventional definition of neutropenia-associated DLT, the MTD of larotaxel in Japanese patients was reached in the current study at the higher dose of 90 mg/m$^2$ and the RD was consequently defined as 75 mg/m$^2$. This is closer to the MTD of 105 mg/m$^2$ and RD of 90 mg/m$^2$ reported for this administration schedule in European patients [13]. Indeed, given that the prophylactic administration of haematopoietic colony-stimulating factors may allow an increase in the dose intensity of chemotherapy regimens known to be associated with myelotoxicity [18]

**Table 3** Grade 3/4 adverse events occurring in two or more patients

| Adverse event | Number (%) | | | |
|---|---|---|---|---|
| | 60 mg/m$^2$ (*N* = 7) | 75 mg/m$^2$ (*N* = 6) | 90 mg/m$^2$ (*N* = 5) | Total (*N* = 18) |
| Neutropenia | 6 (86) | 5 (83) | 5 (100) | 16 (89) |
| Leukopenia | 5 (71) | 4 (67) | 5 (100) | 14 (78) |
| Lymphopaenia | 3 (43) | 1 (17) | 3 (60) | 7 (39) |
| Elevated ALT | – | 2 (33) | 2 (40) | 4 (22) |
| Anorexia | – | 2 (33) | 2 (40) | 4 (22) |
| Fatigue | – | 3 (50) | 1 (20) | 4 (22) |
| Elevated AST | – | 1 (17) | 2 (40) | 3 (17) |
| Febrile neutropenia | – | – | 3 (60) | 3 (17) |
| Hyponatraemia | 2 (29) | – | 1 (20) | 3 (17) |
| Dyspnoea | 1 (14) | 1 (17) | – | 2 (11) |
| Elevated Gamma–GTP | – | 1 (17) | 1 (20) | 2 (11) |
| Haematocrit decreased | 2 (29) | – | – | 2 (11) |
| Haemoglobin | 2 (29) | – | – | 2 (11) |
| Thrombocytopenia | 1 (14) | – | 1 (20) | 2 (11) |
| Vomiting | – | – | 2 (40) | 2 (11) |

**Table 4** Pharmacokinetic parameters of larotaxel

| Dose | $C_{max}$ (ng/mL) | $t_{1/2}$ (h) | AUC (ng h/mL) | CL (L/h m$^2$) | $V_{ss}$ (L/m$^2$) |
|---|---|---|---|---|---|
| 60 mg/m$^2$ ($N = 7$) | | | | | |
| Mean | 1265.2 | 35.9 | 3347.3 | 19.1 | 596.8 |
| Range | 442.4–1807.4 | 31.9–40.0 | 2148.2–4711.5 | 12.3–27.9 | 345.5–996.2 |
| CV (%) | 38.6 | 7.7 | 29.0 | 28.3 | 36.6 |
| 75 mg/m$^2$ ($N = 6$) | | | | | |
| Mean | 1166.3 | 32.1 | 2592.1 | 30.1 | 690.0 |
| Range | 883.2–1494.4 | 27.5–35.3 | 1866.6–3243.7 | 23.1–40.2 | 585.3–811.8 |
| CV (%) | 22.9 | 9.8 | 21.1 | 29.0 | 11.8 |
| 90 mg/m$^2$ ($N = 5$) | | | | | |
| Mean | 1168.2 | 33.4 | 2933.9 | 31.9 | 807.8 |
| Range | 845.0–1515.2 | 27.0–40.0 | 2301.3–3756.4 | 24.0–39.1 | 568.4–1011.1 |
| CV (%) | 26.4 | 14.4 | 22.1 | 21.3 | 22.6 |

$C_{max}$ maximum plasma concentration, *AUC* area under the concentration–time curve, $t_{1/2}$ elimination half-life, *CL* total plasma clearance, $V_{ss}$ volume of distribution at steady state, *CV* coefficient of variation

and that a second DLT, diarrhoea, may also be to some extent manageable using loperamide or octreotide [19], it is possible that 90 mg/m$^2$ will also be a feasible dose for phase II studies in Japanese patients.

As in the earlier phase I studies [12, 13], the principal toxicity in the current study was neutropenia, with 16/18 (89%) patients experiencing grade 3/4 events (12/18, 67%; grade 4). Febrile neutropenia was reported for three of five patients treated at the highest dose. Neutropenia with or without neutropenic complications was also the main DLT. The most common grade 3/4 non-haematological AEs were elevated ALT, anorexia and fatigue (each, 4/18 patients, 22%). Elevated ALT was noted as a grade 3/4 event in the previous phase I study of Japanese patients, as was fatigue [12]. Grade 3/4 hypersensitivity reactions were not reported, although grade 2 reactions occurred in two patients. Similarly, grade 3/4 oedema was not reported, with occurrences being generally mild. Sensory neuropathy, an adverse event commonly associated with paclitaxel [20], was common in the current study, but reached only grade 1 or 2.

Three patients withdrew from the study due to larotaxel-related toxicities. No deaths were thought to be related to study treatment. Based on these results larotaxel, administered as a 1-h i.v. infusion of 75 mg/m$^2$ every 3 weeks, can be considered to be clinically tolerable in Japanese patients with advanced solid tumours. Early indications of activity were demonstrated with one patient with lung cancer and one with head and neck cancer (2/18, 11%) achieving partial responses and a further 8/18 patients (44%) showing disease stabilisation. This is particularly noteworthy given that 11 patients including both those achieved a partial response had previously failed taxane-based therapy prior to study entry.

With regard to PK data, including urinary excretion, there were no relevant differences observed between parameter values for the Japanese patients in the current study and European and Japanese patients previously enrolled in phase I studies [12, 13].

In summary, in Japanese patients with advanced solid malignancies, the MTD of larotaxel administered as a 1-h i.v. infusion every 3 weeks was 90 mg/m$^2$ and the RD for phase II studies 75 mg/m$^2$. The RD was considered to be clinically tolerable in this patient population and showed early indications of activity. The clearance 19.1–31.9 L/h was similar to that observed in Caucasian subjects with value of 33.0 ± 10.7 L/h.

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## References

1. Yamaguchi K (2002) Overview of cancer control programs in Japan. Jpn J Clin Oncol 32(Suppl):S22–S31
2. Gligorov J, Lotz JP (2004) Preclinical pharmacology of the taxanes: implications of the differences. Oncologist 9(Suppl 2):3–8
3. Yvon AM, Wadsworth P, Jordan MA (1999) Taxol suppresses dynamics of individual microtubules in living human tumor cells. Mol Biol Cell 10:947–959
4. Fabbri F, Carloni S, Brigliadori G et al (2006) Sequential events of apoptosis involving docetaxel, a microtubule-interfering agent: a cytometric study. BMC Cell Biol 7:6
5. Woods CM, Zhu J, McQueney PA et al (1995) Taxol-induced mitotic block triggers rapid onset of a p53-independent apoptotic pathway. Mol Med 1:506–526
6. Fojo T, Menefee M (2007) Mechanisms of multidrug resistance: the potential role of microtubule-stabilizing agents. Ann Oncol 18(Suppl 5):v3–v8
7. Bissery MC (2001) Preclinical evaluation of new taxoids. Curr Pharm Des 7:1251–1257

8. Engels FK, Sparreboom A, Mathot RA et al (2005) Potential for improvement of docetaxel-based chemotherapy: a pharmacological review. Br J Cancer 93:173–177
9. Bissery M-C, Vrignaud P, Combeau C et al (2004) Preclinical evaluation of XRP9881A, a new taxoid. In: Proceedings of the 95th annual meeting of the American association for cancer research, p 45 (abstr 5430)
10. Barthier S, Dieras V, Kalla S et al (1998) A phase I and pharmacokinetics (PK) study of RPR 109881A given as 6-h iv infusion in patients (pts) with advanced solid tumors. Proc Am Soc Clin Oncol 16:(abstr 747)
11. Gelmon KA, Latreille J, Tolcher A et al (2000) Phase I dose-finding study of a new taxane, RPR 109881A, administered as a 1-h intravenous infusion days 1 and 8 to patients with advanced solid tumors. J Clin Oncol 18:4098–4108
12. Kurata T, Shimada Y, Tamura T et al (2000) Phase I and pharmacokinetic study of a new taxoid, RPR 109881A, given as a 1-h intravenous infusion in patients with advanced solid tumors. J Clin Oncol 18:3164–3171
13. Sessa C, Cuvier C, Caldiera S et al (2002) Phase I clinical and pharmacokinetic studies of the taxoid derivative RPR 109881A administered as a 1-h or a 3-h infusion in patients with advanced solid tumors. Ann Oncol 13:1140–1150
14. Slaughter M, Pazdur R, Hoff PM et al (1998) Phase I trial of RPR 109881A (RPR), a novel taxoid derivative, administered as a 24-h continuous infusion. Proc Am Soc Clin Oncol 16:(abstr 748)
15. Vernillet L, Semiond D, Vergniol JC et al (1998) Pharmacokinetics of a new taxoid (RPR 109881A): comparison of five different administration schedules. Proc Am Soc Clin Oncol 16:(abstr 749)
16. Dieras VC, Limantani SA, Lortholary A et al (2003) A multicentre, non randomized phase II study with RPR 109881A in metastatic breast cancer (MBC) patients (pts). Proc Am Soc Clin Oncol 22:(abstr 565)
17. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
18. Smith TJ, Khatcheressian J, Lyman GH et al (2006) 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 24:3187–3205
19. Benson ABIII, Ajani JA, Catalano RB et al (2004) Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol 22:2918–2926
20. Mielke S, Sparreboom A, Mross K (2006) Peripheral neuropathy: a persisting challenge in paclitaxel-based regimes. Eur J Cancer 42:24–30