Safety, Efficacy and Pharmacokinetics of Neratinib (HKI-272) in Japanese Patients with Advanced Solid Tumors: A Phase I Dose-escalation Study

Yoshinori Ito1,*, Mitsukuni Suenaga1, Kiyohiko Hatake1, Shunji Takahashi1, Masahiro Yokoyama1, Yusuke Onozawa2, Kentaro Yamazaki2, Shuichi Hironaka2, Kiyoshi Hashigami3, Hirotaka Hasegawa3, Nobuko Takenaka4 and Narikazu Boku2

1Department of Medical Oncology, The Cancer Institute of the Japanese Foundation for Cancer Research, Tokyo, 2Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, 3Department of Oncology, Clinical R&D, Pfizer Inc, Tokyo and 4Department of Clinical Pharmacology, Clinical R&D, Pfizer Inc, Tokyo, Japan

*For reprints and all correspondence: Yoshinori Ito, Breast Cancer Division, Department of Medical Oncology, The Cancer Institute of the Japanese Foundation for Cancer Research, 3-8-31 Ariake Koto-ku, Tokyo 135-8550, Japan. E-mail: yito@jfcr.or.jp

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Objective: Neratinib (HKI-272), a potent, irreversible, small-molecule, orally administered, pan-ErbB inhibitor that blocks signal transduction via inhibition of three epidermal growth factor receptors [ErbB1, ErbB2 (Her2) and ErbB4], is being developed for the treatment of solid tumors, including breast cancer. This Phase I dose-escalation study assessed the safety, tolerability, maximum-tolerated dose, antitumor activity and pharmacokinetics of neratinib in Japanese patients with advanced solid tumors.

Methods: Patients received neratinib 80, 160, 240 or 320 mg orally; each patient enrolled in only one dose cohort. Patients received a single dose in week 1, followed by daily continuous doses. Blood samples collected were on days 1 and 21 for pharmacokinetic analyses.

Results: Twenty-one patients were enrolled (3 breast cancer; 17 colorectal cancer; 1 gastric cancer). Neratinib-related adverse events (all grades) included diarrhea (20 patients), fatigue (14 patients), nausea and abdominal pain (9 patients each) and anorexia (8 patients). Grade ≥3 neratinib-related adverse events in two or more patients were diarrhea and anorexia (two patients each). Dose-limiting toxicities were diarrhea and anorexia (two patients, 320 mg dose). The maximum-tolerated dose and recommended dose was neratinib 240 mg once daily. Of 21 evaluable patients, 2 with breast cancer had partial response, 3 had stable disease ≥24 weeks, 7 had stable disease ≥16 weeks and 9 had progressive disease. Pharmacokinetic analyses indicated that neratinib exposures increased with dose.

Conclusions: The safety, efficacy and pharmacokinetic profiles of neratinib are consistent with those reported for non-Japanese patients and warrant further investigation of neratinib in Japanese patients with solid tumors.

Key words: ErbB2 – maximum-tolerated dose – neratinib – Phase I clinical trial – treatment efficacy

INTRODUCTION

Dysregulation of growth factor signaling due to hyperactivation of the epidermal growth factor receptor (EGFR/ErbB) family of tyrosine kinase receptors has been observed in several cancer types (1) and is associated with increased proliferation, angiogenesis, metastasis and decreased apoptosis (2). Due to its implication in tumorigenesis, inhibition of
this family of kinase receptors may be a novel and viable treatment option for patients who are intolerant to chemotherapy or those refractory to the current standard of care.

Several drugs have been developed and marketed that selectively inhibit the ErbB receptor kinases, such as the small-molecule, reversible, adenosine triphosphate-competitive inhibitors erlotinib and gefitinib, which target ErbB1 (3,4), and lapatinib, which targets both ErbB1 and ErbB2 (Her2) (5). Monoclonal antibodies have also demonstrated antitumor activity, such as trastuzumab, which binds to ErbB2 (6), and panitumumab and cetuximab, which bind to ErbB1 (7,8).

There are, however, various limitations to the safety and efficacy of these drugs. For example, gefitinib and erlotinib provide progression-free survival (PFS) times of only 9–13 months in patients with non-small cell lung cancer showing EGFR mutations. Likewise, trastuzumab is associated with response rates of only 15–26% when given as monotherapy (9,10) and 42% in combination with paclitaxel for the treatment of patients with metastatic breast cancer (11). Trastuzumab is also associated with cardiac toxicity, particularly in patients previously treated with anthracyclines (12,13).

Neratinib (HKI-272) is a potent, orally administered, small-molecule, pan-ErbB inhibitor that irreversibly blocks signal transduction via inhibition of ErbB1, ErbB2 and ErbB4 (14–16). Neratinib has shown promising antitumor activity in a variety of solid tumors, including breast cancer and non-small cell lung cancer (17,18). In addition, neratinib can potentially overcome the acquired resistance of the EGFR ‘gatekeeper’ T790M mutation. This mutation typically develops in the tumors of lung cancer patients that harbor the EGFR kinase domain-sensitizing mutation after treatment with reversible inhibitors such as gefitinib or erlotinib and subsequent disease progression (19–22).

In the Phase 1, first-in-human dose-escalation study of neratinib in patients with solid tumors that was conducted in the USA, the maximum-tolerated dose (MTD) of neratinib was found to be 320 mg once daily (17). In addition, neratinib exposure was dose-dependent and the pharmacokinetic (PK) results favored a once-daily dosing regimen (17). Neratinib was also clinically active in patients with advanced and/or metastatic ErbB2-positive breast cancer, even under conditions of trastuzumab resistance, and was well tolerated as a once-daily orally dosed agent (17). However, due to the primary dose-limiting toxicity (DLT) of diarrhea, the therapeutic dose was limited to 240 mg once daily in later Phase 2 studies. In patients with advanced ErbB2-positive breast cancer, the 16-week PFS rates were 59 and 78% for patients with prior trastuzumab and no prior trastuzumab treatments, respectively, and the objective response rates (ORRs) were 24 and 56%, respectively (18).

Because the efficacy and safety of drugs, such as gefitinib and sunitinib, can vary between Western and Asian populations (23), we assessed the safety and tolerability, and determined the MTD of oral neratinib in Japanese patients with solid tumors in this Phase 1 study. The preliminary antitumor activity and the PK profile of neratinib in the same patient population were also evaluated.

### PATIENTS AND METHODS

#### STUDY DESIGN

This was a multicenter, open-label, Phase 1, ascending single and multiple oral dose study conducted in Japan to determine the safety, tolerability, MTD, antitumor activity and PK of neratinib in Japanese patients with advanced solid tumors. Each patient participated in only one dose cohort (three to six patients) and received a single dose of neratinib. After a 1-week observation period, patients received neratinib as a continual oral daily dose for up to 6 months (six cycles), or longer at the same dose level if neratinib was well tolerated and the patient showed no evidence of progressive disease (PD).

This study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the ethical principles that have origins in the Declaration of Helsinki. The study protocol was approved by an Institutional Review Board and written informed consent was obtained from all patients before their enrollment in this study.

#### PATIENT ELIGIBILITY

Patients were eligible for enrollment if they were ≥20 years of age and had a histologic/cytologic diagnosis of metastatic or advanced cancer that had failed to respond to standard effective therapy or for which no standard effective treatment was available, a life expectancy of ≥12 weeks and a measurable lesion as defined by modified Response Evaluation Criteria in Solid Tumors guidelines. Other key inclusion criteria were a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale, an absolute neutrophil count of ≥1.5 × 10^9/l, platelet count ≥100 × 10^9/l, creatinine level ≤1.5 × the upper limit of normal and total bilirubin ≤1.5 × the upper limit of normal.

The main exclusion criteria were the following: anticancer chemotherapy, radiotherapy, immunotherapy or investigational agents within 4 weeks before treatment day 1; prior treatment with anthracyclines with a cumulative dose of doxorubicin or equivalent >400 mg/m²; automatic electrocardiogram (ECG)-corrected QT (QTc) interval reading at screening >470 ms; left ventricular ejection fraction (LVEF) below the institutional range of normal as measured by echocardiogram; significant gastrointestinal disorders with diarrhea as a major symptom; and a history of clinically significant cardiac disease, including congestive heart failure, myocardial infarction and significant arrhythmia.

#### DOSE ESCALATION

Neratinib was administered orally once daily with food, preferably in the morning. After administration of the single dose and a 1-week observation period, patients were treated at the same dose level with continual oral daily doses in 28-day cycles. Dose cohorts consisted of neratinib 80, 160, 240 and 320 mg. The starting dose was based on the results...
of the Phase 1, first-in-human study of neratinib in patients with solid tumors that was conducted in the USA, in which neratinib-related Grade 3 adverse events (AEs) were not reported at doses ≤ 80 mg (17). The decision to proceed to the next dose level was made after the last patient in a cohort had been evaluated through ~14 days of continuous daily administration. Enrollment at the next dose level occurred according to the following criteria: if no patients experienced a DLT, then three–six patients were enrolled at the next dose level; if one patient experienced a DLT, then an additional six patients were treated at the same dose level and the dose escalated if no more than one of those patients had a DLT. If two or more patients at a dose level experienced a DLT by day 14 of continuous daily dosing, dose escalation stopped and the previous dose level was considered the MTD. If a patient in any dose cohort had a toxicity that met the definition of DLT, then the patient’s dose was reduced by one dose level, and if the patient experienced a second DLT, then the dose was further decreased by one dose level. No more than two dose reductions were allowed for any patient.

A DLT was defined as any neratinib-related non-hematologic Grade 3 or any Grade 4 AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, with the exception of Grade 3 nausea, vomiting, diarrhea or rash, unless the patient was receiving appropriate medical therapy. Additional DLTs included Grade 2 or 3 diarrhea lasting ≥ 2 days, for which the patient was receiving appropriate medical therapy or for that which was associated with fever or dehydration. DLTs were assessed during the first 21 days following the administration of the first dose in the continual single-dose period.

**Evaluation of Patients**

Safety evaluations were based on the incidence and severity of AEs, the DLTs at each dose level and changes in clinical laboratory test results over time. AEs were monitored and recorded continuously during the study, while laboratory evaluations were conducted at screening; on day 1 of the single-dose period; on days 1, 7, 14 and 21 of cycle 1 of the continuous dosing period; on days 1 and 14 of cycles 2 through 6; and at the final evaluation (30 days after the last dose). Other safety assessments included vital signs, interim history, radiographs, cardiac evaluations, echocardiogram and ECGs. The efficacy population included all patients who received ≥ 2 weeks of neratinib therapy and underwent ≥ 1 tumor assessment ~8 weeks after starting continual daily neratinib administration. In addition, patients with disease progression prior to receiving 14 days of neratinib therapy were considered evaluable for efficacy.

**PK Analyses**

Timed blood samples for PK analyses of neratinib were collected on day 1 and on day 14 (study day 21) of continual daily dose administration. Samples were collected at 0 h (pre-dose) and at 1, 2, 4, 6, 8 and 24 h after dose administration. Samples were also collected at 48 h after dose administration on day 1 of the single-dose period. Plasma neratinib concentrations were measured using a validated liquid chromatography/tandem mass spectrometry method. PK analyses were performed for each patient using non-compartmental methods (24) with WinNonLin® Enterprise application, version 5.1 (Pharsight Corporation, CA, USA). The parameters determined included the following: observed maximum concentration (Cmax), area under the concentration–time curve (AUC) from time zero extrapolated to infinite time (AUC0–∞), AUC at steady state (AUCss), AUC from time 0–24 h (AUC0–24h), time of maximum concentration (tmax), terminal-phase elimination half-life (t1/2), the apparent volume of distribution for the terminal disposition phase (V/F) and the apparent oral clearance (CL/F).

The preliminary assessment of dose proportionality was evaluated by the following power model:

\[
C_{\text{max}}, \quad \text{AUC}_{0-\infty} \quad \text{or} \quad \text{AUC}_{\text{ss}} = \alpha \times \text{dose}^\beta
\]

where \(\alpha\) is the coefficient and \(\beta\) is the exponent of the linear-regression model on log-transformed parameters, \(C_{\text{max}}, \quad \text{AUC}_{0-\infty}, \quad \text{AUC}_{\text{ss}}\) and dose. The 95% confidence intervals (CIs) for the exponents were also calculated. The validity of the power model was evaluated by performing a lack-of-fit test. A P-value for the lack-of-fit test of < 0.05 would imply that there was a significant lack of fit in the power model and that the point estimate derived from the power model was not valid.

**Determination of Sample Size**

Approximately 28 patients were to be enrolled in this study. This estimate was based on a maximum of 6 patients per dose cohort over approximately four dose levels and enrolling 4–7 additional patients (total 10 patients) at the recommended dose. The actual number of patients enrolled was dependent on the tolerability of neratinib and the number of dose levels required to attain the MTD.

The sample size for this study was determined by clinical rather than statistical considerations. With cohort sizes of three to six patients, if the true underlying rates of DLT were 0.1, 0.2, 0.3, 0.4 and 0.5, there would be 0.91, 0.71, 0.49, 0.31 and 0.17 chances, respectively, of escalating to the next higher dose level. If the frequencies of AEs of Grade ≥3 were 0.1, 0.25 and 0.5, the probabilities of detecting one or more such events in six patients receiving neratinib would be 0.469, 0.822 and 0.984, respectively, and the probabilities of detecting one or more such events in 10 patients would be 0.651, 0.944 and 0.999, respectively.
RESULTS

PATIENT CHARACTERISTICS

A total of 21 patients (median age: 61 years; range: 39–78 years) were enrolled in this study from March 2007 to March 2009. The baseline characteristics of the 21 patients are presented in Table 1. Seventeen patients had a primary diagnosis of colorectal cancer, three had a diagnosis of breast cancer and one had a diagnosis of gastric cancer. All 21 (100%) patients had an ECOG performance status of 0 or 1. All patients had received prior cancer-related surgery and chemotherapy and four had received prior radiotherapy.

Dose Escalation of Neratinib

Diarrhea and anorexia were the only reported DLTs for two (40%) patients in the 320 mg dose cohort in this study; one patient had Grade 3 diarrhea and Grade 3 anorexia, and the other patient had Grade 2 diarrhea and Grade 3 anorexia. Neratinib 240 mg was determined to be the MTD and was thus used for the expanded MTD cohort. Therefore, the 240 mg cohort was expanded to include an additional seven patients to confirm the safety and tolerability of the MTD of neratinib.

SAFETY

All 21 (100%) patients completed the single-dose period and then started the continual daily dose period. The median duration of treatment in the continual daily dose period was 14.9 weeks (range: 2.1–39.9 weeks). The median relative dose intensity was 1.00 for each dose level (range in 240 mg: 0.75–1.00), indicating that patients received close to the initial scheduled daily dose.

All 21 patients experienced AEs that were considered neratinib-related (Table 2). The most common neratinib-related AEs were: diarrhea (20 patients, 95%); fatigue (14, 67%); nausea and abdominal pain (9, 43%
increased aspartate aminotransferase levels, increased blood alkaline phosphatase levels, decreased hemoglobin levels and anorexia (8, 38% each); and increased alanine aminotransferase levels, decreased blood albumin levels and decreased weight (7, 33% each). Anorexia and diarrhea were the most common Grade ≥3 neratinib-related AEs (2, 10% each; Table 2). The median onset of diarrhea was 10.0 days and the median duration was 2.0 days. Even though all diarrhea AEs were considered neratinib-related, no patient had a Grade ≥4 event. Diarrhea was managed by dose interruption, dose reduction and appropriate medication and resolved in 90% of the patients. Cardiovascular AEs were reported for one patient who had an LVEF that decreased from normal at baseline to 50%. However, the decrease in LVEF was related to the patient’s underlying disease of sinus bradycardia and was considered not related to neratinib therapy by the treating investigator.

Serious AEs were reported for six patients; anorexia and fatigue (two patients each); hydronephrosis, nausea, dysphagia, esophageal varices and dyspnea (one patient each). One neratinib-related serious AE, esophageal varices, was reported for a patient in the 240 mg cohort. No patient discontinued treatment and was withdrawn from this study due to an AE, and no deaths were reported during the study or within 30 days after the last dose was administered.

A total of three (14%) patients had dose reductions due to AEs; two patients in the 320 mg cohort had diarrhea and anorexia, and one patient in the 240 mg cohort had diarrhea. All AEs that led to dose reductions were considered neratinib-related.

### Antitumor Activity

All 21 patients were considered evaluable for efficacy (Table 3). Two of the three patients with primary diagnoses of breast cancer had a partial response (PR). ErbB2 status was positive for one of these two patients but unknown for the other patient; both patients had received a prior trastuzumab-containing regimen. Three patients had stable disease (SD) ≥24 weeks, seven patients had SD ≥16 weeks and nine patients had PD. The ORR [complete response (CR) + PR] for all patients was 9.5% (95% CI: 1.2–30.4%

### Table 2. Neratinib-related adverse events of all grades that occurred in ≥15% of patients and of Grade ≥3 that occurred in one or more patients from screening visit until 30 days after last dose of neratinib

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Dose cohorts, mg neratinib</th>
<th>80 (n = 3)</th>
<th>160 (n = 3)</th>
<th>240 (n = 10)</th>
<th>320 (n = 5)</th>
<th>Total (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td></td>
<td>2</td>
<td>3</td>
<td>10</td>
<td>5</td>
<td>20 (95)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>4</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td></td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Increased</td>
<td></td>
<td>Grade ≥3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Blood alkaline phosphatase</td>
<td></td>
<td>Increased</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td></td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td></td>
<td>Increased</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Blood albumin decreased</td>
<td></td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td></td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td></td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>6 (29)</td>
</tr>
<tr>
<td>Blood creatine phosphokinase</td>
<td></td>
<td>Increased</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td></td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td></td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Grade ≥3</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

### Table 3. Best overall response in the evaluable population

<table>
<thead>
<tr>
<th>Response</th>
<th>Dose cohorts, mg neratinib</th>
<th>80 (n = 3)</th>
<th>160 (n = 3)</th>
<th>240 (n = 10)</th>
<th>320 (n = 5)</th>
<th>Total (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, n</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR, n</td>
<td></td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>ORR, %</td>
<td></td>
<td>0</td>
<td>0</td>
<td>10.0</td>
<td>20.0</td>
<td>9.5</td>
</tr>
<tr>
<td>SD, n</td>
<td>≥16 weeks</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>≥24 weeks</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>CBR, %</td>
<td></td>
<td>0</td>
<td>0</td>
<td>30.0</td>
<td>40.0</td>
<td>23.8</td>
</tr>
<tr>
<td>PD, n</td>
<td></td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; ORR, objective response rate (CR + PR); SD, stable disease; CBR, clinical benefit rate (CR + PR + SD ≥24 weeks); PD, progressive disease.
and the clinical benefit rate (CR + PR + SD/C2124 weeks) was 23.8% (95% CI: 8.2–47.2). Durations of response for the two patients with PR were 16.1 and 32.3 weeks, respectively. The median duration of SD was 16.7 weeks (95% CI: 16.3–24.1) among 10 patients with SD. The median time to progression was 16.1 weeks (95% CI: 8.4–17.0) for all patients.

PHARMACOKINETICS

Plasma samples for PK analyses were available for all 21 patients who received neratinib doses ranging from 80 to 320 mg. Samples collected within 5 days after dose reduction were not included in the PK analysis. The PK parameters are summarized in Table 4. Following single doses of neratinib from 80 to 320 mg on study day 1, the absorption of neratinib was relatively slow with a median $t_{\text{max}}$ of 4–6 h and mean $t_{1/2}$ for the 160–320 mg dose cohorts ranged from 11 to 16 h (percent coefficient of variation, 13–28%). Multiple-dose exposure was 1.2- to 1.5-fold greater than single-dose exposure across the entire dose range, as assessed by the mean accumulation ratio ($R$, $AUC_{\text{ss}}$ on study day 21 to $AUC_{\text{0–24h}}$ on study day 21); NC, not calculated; NA, not applicable.

A comparison of our PK results in our Japanese patients versus patients in the neratinib study that was conducted in the USA (17), using our in-house data, is presented in Fig. 2. Although the variability in $C_{\text{max}}$, $AUC_{\text{0–1}}$ and $AUC_{\text{ss}}$ is large, there is overlap of the PK exposures between the Japanese and US studies. This comparison suggests that there are no relevant differences in the PK between Japanese patients and those patients (92% white) in the US study.

DISCUSSION

In this Phase 1 study, neratinib as a single agent was administered to Japanese patients with advanced solid tumors. The reported DLTs were Grades 2 and 3 diarrhea and Grade 3 anorexia for two patients in the 320 mg dose cohorts; therefore, the MTD of neratinib for Japanese patients was determined to be 240 mg once daily. In comparison, the MTD was found to be 320 mg once daily in the Phase 1 study.
A study of neratinib that was conducted in the USA in 72 patients (92% white, 6% black or Hispanic, 1% Asian and 1% Middle Eastern) with advanced solid tumors; the DLT was Grade 3 diarrhea [1 (17%) patient in the neratinib 180 mg dose group and 5 (83%) patients in the 400 mg dose group] (17). However, due to gastrointestinal AEs, the recommended dose in ongoing Phase 3 studies is 240 mg once daily. Although diarrhea was expected in this study and was reported in 20 (95%) patients, no patients were withdrawn from the study or had a serious AE of diarrhea. Diarrhea was managed by dose interruption, dose reduction and appropriate anti-diarrhea medication.

Neratinib demonstrated promising efficacy results in Japanese patients with advanced solid tumors: PR was observed in two (10%) patients with breast cancer; three (14%) patients had SD/C21 24 weeks and seven (33%) patients had SD/C21 16 weeks.

PK analyses revealed that after single and multiple oral doses of neratinib, exposures (C\text{max}, AUC\text{0–1} and AUC\text{ss}) increased in a dose-dependent manner from 80 to 320 mg. Multiple-dose exposures were 1.2- to 1.5-fold greater than single-dose exposures across the entire dose range, thus suggesting that there was no major accumulation of neratinib after repeated daily administration of neratinib in cancer patients. The mean elimination t\text{1/2} on day 1 at the recommended dose of 240 mg was 14.3 h and supports a once-daily dosing regimen. Our PK data are also consistent with that reported for the US Phase 1 study of neratinib and suggest that there are no relevant differences in the PK profiles between Japanese and white patients with cancer.

This study investigated doses of neratinib from 80 to 320 mg daily. The starting dose was chosen based on information from Phase 1 study conducted in the USA (17). In the US study, diarrhea was the main DLT, with five patients in the 400 mg cohort reporting Grade 3 diarrhea. The MTD

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**Figure 1.** Individual and mean (SD) plasma neratinib exposures versus dose on study day 1 (a) C\text{max} versus dose and (b) AUC\text{0–1} versus dose, and study day 21 (c) C\text{max} versus dose and (d) AUC\text{ss} versus dose. Patients with advanced solid tumors received single ascending oral doses of neratinib once daily. SD, standard deviation; C\text{max}, peak concentration; AUC\text{ss}, area under the concentration–time curve from time zero extrapolated to infinite time.

**Figure 2.** Comparison of neratinib exposures on study day 21: Japan versus US studies. Patients with advanced solid tumors received single ascending oral doses of neratinib once daily; (a) C\text{max} versus dose and (b) AUC\text{ss} versus dose. C\text{max}, peak concentration; AUC\text{ss}, area under the concentration–time curve at steady state.
in the US study was, therefore, established as 320 mg. In the US study, neratinib-related Grade 3 AEs were not reported at doses \( \leq 80 \) mg. Therefore, a starting dose level of 80 mg was chosen for the current study. Based on the results of preclinical toxicity studies, this starting dose (80 mg/body = 48 mg/m^2 based on 1.65 m^2 human body surface area) is one-fifth of the highest non-severely toxic dosage of 45 mg/kg/day (266 mg/m^2/day, with conversion factor of 5.9), which was the highest dose used in a 4-week rat study (data on file). This dose did not elicit severe or life-threatening toxicity. This clinical dose is also supported by dosages [up to 6 mg/kg/day or 107 mg/m^2 (conversion factor of 17.9)] that did not elicit severe or life-threatening toxicity in a 4-week study in dogs (data on file).

The mean steady-state exposure of the doses at which two patients achieved PR were above the minimum efficacious dose exposure (431 ng/C20 h/ml) in nude mice. In addition, the mean steady-state exposure at the therapeutic dose of 240 mg was \( \sim 2.6 \) -fold higher than the minimum efficacious dose exposure. However, there was no clear correlation between the dose or exposure and the severity of major AEs (i.e. diarrhea, fatigue, nausea or abdominal pain) because of the small number of patients in this study.

Irreversible inhibition of the EGFR kinase is desirable because such inhibition can occur in the presence of ATP within the cell and can only be overcome by new synthesis of EGFR. Several ATP-competitive EGFR tyrosine kinase inhibitors have been developed and investigated in clinical trials for the treatment of cancer. First-generation irreversible inhibitors include agents such as pelitinib (EKB-569). A US Phase I study showed no major antitumor responses at the MTD of pelitinib (25), although two patients in a Japanese Phase I study with advanced non-small cell lung cancer with EGFR mutations and acquired gefitinib resistance showed radiographic tumor regression (26). However, as pelitinib showed limited activity in Her2-dependent tumor models, the development of irreversible inhibitors with improved activity toward Her2-expressing tumors continued (16). It was discovered that attaching a large lipophilic group to the molecule resulted in improved potency for Her2 kinase inhibition (16). Thus, the structure of the second-generation irreversible pan-Her inhibitor neratinib is similar to the structure of pelitinib, but with this different aniline headpiece. The binding model for neratinib at the ATP site of Her2 indicates that the aniline portion of the molecule fits into a long lipophilic pocket. The nature and placement of these groups most likely gives neratinib its improved Her2 activity compared with pelitinib.

In conclusion, the MTD of oral neratinib was determined to be 240 mg once daily in Japanese patients with advanced solid tumors. Neratinib 240 mg was safe and well tolerated, and demonstrated encouraging antitumor activity in this patient population. We therefore recommend that this dose is used for subsequent studies in Japanese patients. The results of this Phase I study are consistent with those observed in white patients and warrant further investigation of neratinib in Japanese patients with solid tumors.

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Conflict of interest statement

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