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Combination neratinib (HKI-272) and paclitaxel therapy in patients with HER2-positive metastatic breast cancer

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Introduction: Neratinib is a potent irreversible pan-ErbB tyrosine kinase inhibitor that has demonstrated antitumour activity and an acceptable safety profile in patients with human epidermal growth factor receptor (HER)-2-positive breast cancer and other solid tumours.

Methods: This was a phase I/II, open-label, two-part study. Part 1 was a dose-escalation study to determine the maximum tolerated dose (MTD) of neratinib plus paclitaxel in patients with solid tumours. Part 2 evaluated the safety, efficacy, and pharmacokinetics of the combination at the MTD in patients with HER2-positive breast cancer.

Results: Eight patients were included in the dose-escalation study; no dose-limiting toxicities were observed, and an MTD of oral neratinib 240 mg once daily plus intravenous paclitaxel 80 mg m⁻² on days 1, 8, and 15 of each 28-day cycle was determined. A total of 102 patients with HER2-positive breast cancer were enrolled in part 2. The overall median treatment duration was 47.9 weeks (range: 0.1–147.3 weeks). Common treatment-emergent adverse events (all grades/grade ≥3) included diarrhoea (92%/29%; none grade 4), peripheral sensory neuropathy (51%/3%), neutropenia (50%/20%), alopecia (46%/0%), leukopenia (41%/18%), anaemia (37%/8%), and nausea (34%/1%). Three (3%) patients discontinued treatment due to an adverse event (mouth ulceration, left ventricular ejection fraction reduction, and acute renal failure). Among the 99 evaluable patients in part 2 of the study, the overall response rate (ORR) was 73% (95% confidence interval (CI): 62.9–81.2%), including 7 (7%) patients who achieved a complete response; an additional 9 (9%) patients achieved stable disease for at least 24 weeks. ORR was 71% among patients with 0/1 prior chemotherapy regimen for metastatic disease and no prior lapatinib, and 77% among those with 2/3 prior chemotherapy regimens for metastatic disease with prior lapatinib permitted. Kaplan–Meier median progression-free survival was 57.0 weeks (95% CI: 47.7–81.6 weeks). Pharmacokinetic analyses indicated no interaction between neratinib and paclitaxel.

Conclusion: The combination of neratinib and paclitaxel was associated with higher toxicity than that of neratinib as a single agent, but was manageable with antidiarrhoeal agents and dose reductions in general. The combination therapy also demonstrated a high rate of response in patients with HER2-positive breast cancer. A phase III trial is ongoing to assess the benefit and risk of this combination in the first-line setting.

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The long-term survival of patients with metastatic breast cancer is traditionally low (Jemal *et al*, 2010). Human epidermal growth factor receptor (HER)-2 represents an important target for the treatment of breast cancer, as increased HER2 expression is observed in approximately 20–30% of breast cancers and has been shown to correlate with more aggressive tumours (Slamon *et al*, 1987). The introduction of HER2-targeted therapies, such as trastuzumab and lapatinib, has improved outcomes for patients with advanced HER2-positive breast cancer (Slamon *et al*, 2001; Burstein *et al*, 2008; Cameron *et al*, 2008; Di Leo *et al*, 2008; Toi *et al*, 2009). However, not all patients respond to anti-HER2 agents, whereas others develop drug resistance, shown by limited times to progression and overall survival in clinical studies (Eiermann, 2001; Slamon *et al*, 2001; Marty *et al*, 2005; Geyer *et al*, 2006; Robert *et al*, 2006; Burstein *et al*, 2007; Cameron *et al*, 2008; Di Leo *et al*, 2008; Blackwell *et al*, 2010; Andersson *et al*, 2011). Therefore, the development of new potent and selective anti-HER2 agents is needed, particularly for patients whose prior treatment has failed. Further, antitumour activity may be achieved with a regimen that includes anti-HER2 therapy in combination with chemotherapy or other targeted agents, if the combination is tolerable at therapeutic dose levels.

Neratinib (HKI-272) is a potent, orally administered irreversible tyrosine kinase inhibitor of the ErbB family of receptors (epidermal growth factor receptor (EGFR)/HER1, HER2, and HER4) that covalently binds to the cytoplasmic domain of ErbB receptors, thereby preventing downstream signalling (Rabindran *et al*, 2004; Tsou *et al*, 2005). Neratinib has the ability to irreversibly inhibit multiple ErbB receptors and effectively inhibits the proliferation of EGFR- and HER2-expressing cells that are resistant to treatment with first-generation ErbB receptor tyrosine kinase inhibitors (e.g., gefitinib; Kwak *et al*, 2005). Neratinib has demonstrated anti-tumour activity in phase I and II clinical studies in patients with HER2-positive breast cancer, including ones with or without prior exposure to trastuzumab, as well as in patients with other solid tumours (Wong *et al*, 2009; Burstein *et al*, 2010).

Potential antitumour activity of neratinib in combination with paclitaxel is suggested from *in vitro* and *in vivo* data demonstrating that gefitinib (EGFR inhibitor) combined with paclitaxel (taxane) yields inhibition and apoptosis of EGFR-expressing non-small-cell lung cancer cell line and xenograft tumour models (Sirotnak *et al*, 2000; Van Schaeybroeck *et al*, 2006). This phase I/II, open-label, two-part study determined the maximum tolerated dose (MTD) of neratinib in combination with paclitaxel and assessed the safety, efficacy, and pharmacokinetics of this combination in patients with HER2-positive metastatic breast cancer.

MATERIALS AND METHODS

Patient population. Adults aged 18 years and older were eligible for enrolment. In part 1 of the study, patients were required to have confirmed diagnosis of a solid tumour. In part 2, patients were required to have confirmed diagnosis of stage IV HER2-positive breast cancer (confirmed with fluorescent *in situ* hybridisation or immunohistochemistry score of ≥ 3) and prior trastuzumab therapy in the neoadjuvant, adjuvant, or metastatic setting (unless trastuzumab was contraindicated or unavailable); no more than three prior cytotoxic chemotherapy regimens in the metastatic setting were permitted. Patients in both study parts were required to have at least one measurable lesion by modified Response Evaluation Criteria In Solid Tumors (RECIST) guidelines, version 1.0; an Eastern Cooperative Oncology Group Performance Status score of 0 or 1; left ventricular ejection fraction within normal limits; adequate haematologic, hepatic, and renal laboratory values; and, for women of child-bearing potential, a negative pregnancy

test result and willingness to use contraceptives. Full inclusion and exclusion criteria are summarised in Supplementary Table A1.

This study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study participation, and the protocol was approved by the institutional review board at each study site.

Study design. This was a phase I/II, open-label, two-part study. Part 1 was a dose-escalation study of a standard 3 + 3 design in which successive cohorts of three to six patients with advanced solid tumours were evaluated for safety and determination of the MTD of combination treatment. Patients were administered ascending daily oral doses of neratinib (either 160 or 240 mg) in combination with intravenous paclitaxel (80 mg m⁻²) on days 1, 8, and 15 of each 28-day cycle. Each cohort of three to six patients was assessed for safety and dose-limiting toxicities (DLTs) over 28 days before the escalation to the next dose level. If one of three patients experienced a DLT, the cohort was expanded to six patients. The MTD was defined as the highest dose at which no more than one patient experienced a DLT; therefore, if two or more patients experienced a DLT, dose escalation was stopped and the prior dose level was considered the MTD. A DLT included any of the following treatment-related events occurring during the first 28 days of therapy: grade 3/4 non-haematologic toxicity (except grade 3 asthenia unless lasting >3 days, grade 3 nausea or vomiting unless on optimal medical therapy, and grade 3 diarrhoea unless lasting >2 days on optimal medical therapy (Benson *et al*, 2004) or associated with fever or dehydration); grade 4 neutropenia lasting at least 7 days or associated with fever; grade 3/4 infection in the context of grade 3/4 neutropenia; and delayed recovery to grade 0/1 toxicity that requires treatment interruption of more than 3 weeks.

Part 2 of this study evaluated the efficacy, safety, and pharmacokinetics of neratinib plus paclitaxel in patients with HER2-positive breast cancer at the MTD and schedule established in part 1. The patients were divided into two groups based upon prior anticancer therapy: group A included patients who had received no more than one prior cytotoxic chemotherapy regimen for metastatic disease and no prior lapatinib exposure, whereas group B included patients who had received no more than three prior cytotoxic chemotherapy regimens for metastatic disease with prior lapatinib exposure permitted. The primary objective for part 2 was to estimate the probability of overall response (complete + partial responses). The secondary objectives of part 2 were to confirm the MTD identified in part 1 of the study, to obtain safety and pharmacokinetic information, and to assess additional efficacy parameters, including the probability of clinical benefit (complete/partial response + stable disease ≥ 24 weeks), the probability of progression-free survival (PFS) at week 16, and duration of response.

Study assessments. Safety was assessed by physical exams, laboratory assessments, and adverse event reporting. Adverse events were reported at each study visit and graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Serious adverse events were reported until 28 days after the last dose of study treatment and were followed until resolution.

Tumour assessments were performed at baseline and then every two cycles (8 weeks) throughout the study, or as clinically indicated (based on protocol amendment). Measurable (target) and non-measurable (non-target) lesions were documented by computed tomography or magnetic resonance imaging scans and followed using the same assessment method throughout the study. Response was assessed by the investigators based on modified RECIST guidelines, with complete and partial responses requiring confirmation by a repeat assessment at least 4 weeks after initial

documentation of the response. Stable disease could first be assessed no sooner than 8 weeks after the first dose of study drug.

For pharmacokinetic assessments, blood samples were collected predose and at 1, 2, 4, 6, 8, and 21–24 h post-dose on day 15 of cycle 1 for analyses of neratinib plasma concentrations. Pharmacokinetic analyses were performed using a noncompartmental method.

Statistical analyses. In part 1, the sample size was determined by clinical rather than statistical considerations. Considering the true DLT rates were 0.1, 0.2, 0.3, 0.4, and 0.5 for the cohort sizes of three to six patients, there would be probabilities of 91%, 71%, 49%, 31%, and 17%, respectively, for escalation to the next full dose. In part 2, the uninteresting overall response rate (ORR) was set at 35% and the sufficiently promising ORR was set at 50%, based on previously reported data from phase III studies of trastuzumab plus paclitaxel and lapatinib plus paclitaxel in HER2-positive breast cancer (Di Leo *et al*, 2008; Seidman *et al*, 2008). The overall probability of accepting neratinib plus paclitaxel for further study under the null hypothesis was approximately 0.10. To compensate for the expected dropout or nonevaluable rate of 15%, approximately 60 patients were to be enrolled in group A, providing approximately 79% power to detect an ORR of 50%. An additional 25 patients were to be enrolled in group B to evaluate the safety and efficacy of neratinib in pretreated patients.

All patients who received at least one dose of neratinib were included in the safety analysis. Patients who completed at least one post-baseline tumour assessment and received at least 2 weeks of neratinib treatment and two doses of paclitaxel were evaluable for efficacy; efficacy was also evaluated in the intent-to-treat (ITT) population, which included all enrolled patients. Categorical variables (i.e., response) were presented as counts and percentages along with associated 95% confidence intervals (CIs), whereas continuous variables were presented using descriptive statistics. Time-to-event end points (i.e., PFS, duration of response) were analysed using the Kaplan–Meier method; median PFS and the corresponding 95% CI were calculated. PFS was calculated from the date of first dose of study drug administered until the date of first documentation of recurrence/progression or death due to any cause; patients were otherwise censored at the last evaluation. The duration of response was calculated from the date of first documented response until the first date of disease progression.

RESULTS AND DISCUSSION

Patients. A total of 110 patients with solid tumours ($n=8$) or HER2-positive breast cancer ($n=102$; including 71 in group A and 31 in group B) were enrolled in the study. The baseline

Table 1. Patient demographic and baseline disease characteristics

Characteristic	Part 1		Part 2		Total (N = 110)
	Neratinib 160 mg + paclitaxel (n = 3)	Neratinib 240 mg + paclitaxel (n = 5)	Group A ^a (n = 71)	Group B ^b (n = 31)	
Median age (range), years	61 (40–68)	44 (37–64)	49 (20–76)	51 (36–63)	50.5 (20–76)
< 65 Years, n (%)	2 (67)	5 (100)	67 (94)	31 (100)	105 (95)
≥ 65 Years, n (%)	1 (33)	0	4 (6)	0	5 (5)
Female sex, n (%)	1 (33)	2 (40)	71 (100)	31 (100)	105 (95)
Ethnicity, n (%)					
Asian	2 (67)	2 (40)	48 (68)	25 (81)	77 (70)
White	0	3 (60)	22 (31)	5 (16)	30 (27)
Other	1 (33)	0	1 (1)	1 (3)	3 (3)
Stage III/IV disease at diagnosis, n (%)	2 (67)	3 (60)	36 (51)	12 (39)	53 (48)
ER/PR-positive disease, n (%)	1 (33)	0	36 (51)	20 (65)	57 (52)
ECOG performance status, n (%)					
0	2 (67)	3 (60)	31 (44)	22 (71)	58 (53)
1	1 (33)	2 (40)	40 (56)	9 (29)	52 (47)
No. of prior chemotherapy regimens,^c n (%)					
0	0	0	15 (21)	0	15 (14)
1	2 (67)	2 (40)	30 (42)	0	34 (31)
2	1 (33)	0	20 (28)	9 (29)	30 (27)
3	0	1 (20)	4 (6)	15 (48)	20 (18)
> 3	0	2 (40)	2 (3)	7 (23)	11 (10)
Prior radiotherapy, n (%)	2 (67)	3 (60)	40 (56)	20 (65)	65 (59)
Prior trastuzumab therapy, ^c n (%)	0	1 (20)	18 (25)	12 (39)	31 (28)
Prior lapatinib therapy, ^c n (%)	0	1 (20)	0	14 (45)	15 (14)
Prior endocrine therapy, ^c n (%)	0	0	24 (34)	16 (52)	40 (36)
Prior taxane therapy, ^c n (%)	1 (33)	2 (40)	34 (48)	30 (97)	67 (61)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; PR = progesterone receptor.

^aGroup A allowed ≤ 1 prior cytotoxic chemotherapy regimen for metastatic disease.

^bGroup B allowed ≤ 3 prior cytotoxic chemotherapy regimens for metastatic disease, with prior lapatinib permitted.

^cIncludes treatment regimens used in the neoadjuvant, adjuvant, or metastatic setting.

demographic and disease characteristics for patients in both parts of the study are shown in Table 1. This patient population includes those who received study treatment in both the first-line setting and in the second-line and greater settings.

Dose escalation (part 1). Eight patients with solid tumours were enrolled in part 1 of the study, including three patients enrolled in the initial cohort for neratinib 160 mg plus paclitaxel and five patients enrolled in the subsequent cohort for neratinib 240 mg plus paclitaxel. There were no DLTs observed in either cohort, and both dose regimens were well tolerated; therefore, the MTD was determined to be oral neratinib 240 mg once daily plus intravenous paclitaxel 80 mg m⁻² on days 1, 8, and 15 of each 28-day cycle, corresponding to the full recommended dose previously determined for neratinib as monotherapy (Burstein *et al*, 2010) and a paclitaxel dose commonly used in other combination regimens (Perez *et al*, 2005; Furukawa *et al*, 2006; Gasparini *et al*, 2007; Han *et al*, 2009; Horiguchi *et al*, 2009; Andre *et al*, 2010). This combination was further evaluated at the MTD in part 2.

Treatment summary (parts 1 and 2). Treatment summaries for parts 1 and 2 are shown in Table 2. Overall, 90 patients discontinued treatment; reasons for stopping treatment included disease progression (*n* = 75 (68%)), patient request (*n* = 7 (6%)), death (*n* = 3 (3%)), adverse event (*n* = 2 (2%)), investigator request (*n* = 2 (2%)), and other (*n* = 1 (1%)). The median treatment duration of neratinib (parts 1 and 2) was 47.9 weeks (range: 0.1–147.3 weeks), with a median dose intensity of neratinib 239.6 mg per day (range: 100.5–241.1 mg per day). The median treatment duration of paclitaxel was 29.6 weeks (range: 1.0–97.1 weeks), with a median dose intensity of paclitaxel 213.5 mg m⁻² per cycle (range: 78.7–245.1 mg m⁻² per cycle). Dose reductions of neratinib and paclitaxel, respectively, were required by 21 (19%) and 41 (37%) patients and temporary dose delays were required by 58 (53%) and 71 (65%) patients.

Safety and tolerability (parts 1 and 2). The most common non-haematologic treatment-emergent adverse events during the study (including three patients from part 1 who received neratinib 160 mg per day plus paclitaxel) were diarrhoea (92%), peripheral sensory neuropathy (51%), alopecia (46%), and nausea (34%); common haematologic adverse events included neutropenia (50%), leukopenia (41%), and anaemia (37%; Table 3). The most common grade 3/4 treatment-emergent adverse events (≥5% of patients) were diarrhoea (29%), neutropenia (20%), leukopenia (18%), and anaemia (8%). The median time to onset of diarrhoea was 3 days (range: 1–583 days). Events of diarrhoea were typically transient in nature, with a median cumulative duration of diarrhoea of 35.5 days (range: 1–737 days) and a majority (73%) of patients who reported diarrhoea experiencing resolution of their diarrhoea as of the time of this analysis. There were no grade 4 events of diarrhoea reported and none of the patients discontinued treatment due to diarrhoea. On treatment, 6 (5%) patients experienced a prolonged QTc interval greater than 500 ms and 19 (17%) patients experienced a QTc interval increased greater than 60 ms from baseline.

Throughout the study, 45% of patients required a dose reduction of neratinib and/or paclitaxel due to an adverse event and 72% of patients required a temporary interruption of study medication due to an adverse event. Adverse events leading to dose reduction/temporary interruption in at least 5% of patients included neutropenia (16%/26%), diarrhoea (13%/24%), leukopenia (8%/17%), peripheral sensory neuropathy (6%/4%), and decreased weight (7%/0%). Three (3%) patients discontinued treatment due to an adverse event (mouth ulceration, left ventricular ejection fraction reduction, and acute renal failure). A total of six (5%) patients died during treatment or within 28 days of the last dose of study medication; one patient in part 1 (neratinib 240 mg dose) and three patients in part 2 group A died due to disease progression, and two patients in part 2 group A died due to an adverse event (pneumonia and pulmonary embolism).

Table 2. Treatment summary

Parameter, <i>n</i> (%)	Part 1		Part 2		Total (<i>N</i> = 110)
	Neratinib 160 mg + paclitaxel (<i>n</i> = 3)	Neratinib 240 mg + paclitaxel (<i>n</i> = 5)	Group A ^a (<i>n</i> = 71)	Group B ^b (<i>n</i> = 31)	
Median neratinib treatment duration (range), weeks	12.3 (8.1–24.3)	15.0 (4.3–63.4)	48.1 (0.1–144.4)	52.3 (7.7–147.3)	47.9 (0.1–147.3)
Median paclitaxel treatment duration (range), weeks	11.1 (7.1–23.1)	15.0 (3.0–46.9)	31.0 (1.0–81.0)	30.0 (3.0–97.1)	29.6 (1.0–97.1)
Median neratinib dose intensity (range), mg per day	160.0 (150.7–160.0)	239.5 (166.7–240.0)	239.6 (152.9–241.1)	240.0 (100.5–240.0)	239.6 (100.5–241.1)
Median paclitaxel dose intensity (range), mg m ⁻² per cycle	225.8 (207.4–244.1)	211.9 (158.1–237.5)	212.4 (78.7–245.1)	226.2 (131.1–244.9)	213.5 (78.7–245.1)
Neratinib dose modification					
Dose delay	1 (33)	3 (60)	42 (59)	12 (39)	58 (53)
Dose reduction	0	1 (20)	13 (18)	7 (23)	21 (19)
Due to adverse event	0	1 (20)	10 (14)	5 (16)	16 (15)
Other/not stated	0	0	7 (10)	2 (6)	9 (8)
Paclitaxel dose modification					
Dose delay	1 (33)	5 (100)	46 (65)	19 (61)	71 (65)
Dose reduction	1 (33)	2 (40)	25 (35)	13 (42)	41 (37)
Due to adverse event	1 (33)	2 (40)	25 (35)	12 (39)	40 (36)
Other/not stated	0	0	0	1 (3)	1 (1)

^aGroup A allowed ≤1 prior cytotoxic chemotherapy regimen for metastatic disease.
^bGroup B allowed ≤3 prior cytotoxic chemotherapy regimens for metastatic disease, with prior lapatinib permitted.

Overall, the combination of neratinib plus paclitaxel was associated with a safety and tolerability profile generally characteristic of each agent given as monotherapy. Although the safety analyses included patients from both parts 1 and 2 of the study, only three patients received a dosage lower than the MTD (i.e., neratinib 160 mg per day plus paclitaxel). Neratinib has previously been associated with incidences of gastrointestinal events (i.e., diarrhoea, nausea, and vomiting), fatigue, and rash, (Wong *et al*, 2009; Burstein *et al*, 2010) with incidences similar to those observed in the current study. Although diarrhoea was the most common adverse event and grade 3/4 adverse event observed with neratinib treatment in this study (92% all grades; 29% grade 3/4) and in previous studies (88%–93%; 21%–32%), it typically occurred early (median time to onset of 2–8.5 days across studies) and was managed with dose adjustments and/or anti-diarrhoeal medications (Wong *et al*, 2009; Burstein *et al*, 2010). In addition, no patients stated diarrhoea as their primary reason for treatment discontinuation in this study, and it has only rarely been associated

with treatment discontinuation in prior neratinib monotherapy studies (Wong *et al*, 2009; Burstein *et al*, 2010).

Paclitaxel monotherapy has been associated with haematologic events (i.e., neutropenia, anaemia, and leukopenia), peripheral sensory neuropathy, alopecia, and gastrointestinal events (Wiseman and Spencer, 1998), and, as expected, these events were also seen with combination neratinib plus paclitaxel in the current study. Comparison of adverse events across multiple studies is difficult due to differences in patient population and study design (including treatment duration); however, the incidence (all grades; grade 3/4) of adverse events observed in the current study compare favourably with those previously reported for combination studies of weekly paclitaxel 80 mg m⁻² plus other anti-HER2 agents (i.e., trastuzumab or lapatinib): neutropenia (50% in current study vs 44–87% in prior studies; 20% vs 22–52%), anaemia (37% vs 43–47%; 8% vs 0–6%), leukopenia (41% vs 41–92%; 18% vs 11–31%), peripheral sensory neuropathy (51% vs 25–86%; 3% vs 0–6%), and alopecia (46% vs 89–94%; 0% vs 0–14%; Perez *et al*, 2005; Furukawa *et al*, 2006; Gasparini *et al*, 2007; Han *et al*, 2009; Horiguchi *et al*, 2009; Jagiello-Gruszfeld *et al*, 2010). In addition, comparison of adverse events with those reported for paclitaxel monotherapy is difficult given that reported data are primarily for a different dose and schedule (i.e., paclitaxel 175 mg m⁻² every 3 weeks; Wiseman and Spencer, 1998).

Overall, no unexpected toxicity was observed in patients receiving neratinib plus paclitaxel, with a safety profile that suggests no additional (i.e., synergistic) toxicity. Although toxicities previously associated with neratinib and/or paclitaxel were observed in the current study, few patients discontinued treatment due to toxicity.

Antitumour activity (part 2). A total of 99 patients from part 2 of the study were evaluated for antitumour activity. The ORR for all evaluable patients was 73% (95% CI, 62.9%–81.2%), and included seven (7%) patients who achieved a complete response and 65 (66%) who achieved a partial response (Table 4). ORR rates were high among patients in both group A (71%) and group B (77%), including 23 of 33 (70%) patients who received treatment in the first-line setting (Table 5). Among those who responded, the overall median duration of response was 73.0 weeks (range; 9.0–136.4 weeks); median duration of response in group A was 77.1 weeks and in group B was 56.3 weeks. An additional nine (9%) patients achieved stable disease for at least 24 weeks, for a clinical

Table 3. Treatment-emergent adverse events reported by ≥10% of patients, any causality

Adverse event, n (%)	Total (N = 110) ^a	
	All grades	Grade ≥3
Diarrhoea	101 (92)	32 (29)
Peripheral sensory neuropathy	56 (51)	3 (3)
Neutropenia	55 (50)	22 (20)
Alopecia	51 (46)	0
Leukopenia	45 (41)	20 (18)
Anaemia	41 (37)	9 (8)
Nausea	37 (34)	1 (1)
Rash	32 (29)	1 (1)
Vomiting	29 (26)	2 (2)
Decreased appetite	28 (25)	1 (1)
Fatigue	23 (21)	4 (4)
Peripheral oedema	23 (21)	1 (1)
Pyrexia	23 (21)	0
Cough	21 (19)	0
Asthenia	20 (18)	1 (1)
Stomatitis	20 (18)	0
ALT increased	17 (15)	4 (4)
Urinary tract infection	17 (15)	0
AST increased	14 (13)	3 (3)
Dyspnea	14 (13)	4 (4)
Decreased weight	13 (12)	1 (1)
Dyspepsia	13 (12)	0
Headache	13 (12)	0
Dizziness	12 (11)	1 (1)
Hypokalemia	12 (11)	3 (3)
Upper abdominal pain	12 (11)	0
Abdominal pain	11 (10)	0
Pain in extremity	11 (10)	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

^aIncludes three patients from part 1 of the study who received neratinib 160 mg per day plus paclitaxel, who experienced grade 3/4 events of anaemia (n = 1), abdominal discomfort (n = 1), and diarrhoea (n = 1).

Table 4. Best overall response and clinical benefit, evaluable patients (part 2)

Investigator assessment, n (%)	Group A ^a (n = 68)	Group B ^b (n = 31)	All patients (n = 99)
Overall response rate (95% CI)	48 (71) (58.3–81.0)	24 (77) (58.9–90.4)	72 (73) (62.9–81.2)
Complete response	6 (9)	1 (3)	7 (7)
Partial response	42 (62)	23 (74)	65 (66)
Clinical benefit rate ^c	56 (82)	25 (81)	81 (82)
Stable disease			
<24 Weeks	6 (9)	3 (10)	9 (9)
≥24 Weeks	8 (12)	1 (3)	9 (9)
Progressive disease	3 (4)	3 (10)	6 (6)
Not determined	3 (4)	0	3 (3)

Abbreviation: CI = confidence interval.

^aGroup A allowed ≤1 prior cytotoxic chemotherapy regimen for metastatic disease.

^bGroup B allowed ≤3 prior cytotoxic chemotherapy regimens for metastatic disease, with prior lapatinib permitted.

^cClinical benefit rate = complete response + partial response + stable disease ≥24 weeks.

benefit rate of 82% (95% CI: 72.8–88.9%; Table 4). Few patients had a best overall response of progressive disease ($n=6$ (6%)). Kaplan–Meier median PFS was 57.0 weeks (95% CI: 47.7–81.6 weeks) among all evaluable patients, and was similar between groups A and B (Figure 1).

The three patients from the ITT population ($n=102$) who were not included in the evaluable population did not achieve a complete or partial response, or did they maintain stable disease for at least 24 weeks. Thus, the response rates in the ITT population were 7% ($n=7$) for complete response and 64% ($n=65$) for partial response, with an ORR of 71% (95% CI: 60.7–79.2%). An additional 9% ($n=9$) of patients maintained

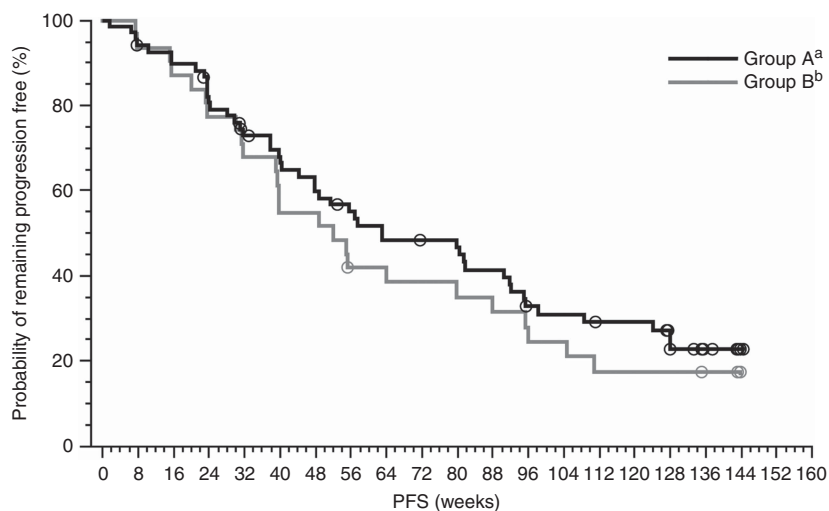
stable disease for at least 24 weeks, leading to a clinical benefit rate of 79% (95% CI: 70.3–86.8%).

In the evaluable population, the ORR (73%) for neratinib plus paclitaxel in the current study was noticeably higher than that observed for neratinib monotherapy in patients with advanced HER2-positive breast cancer (32–40%); among responders, the median duration of response was 73.0 weeks vs 20.9–52.4 weeks, respectively (Wong *et al*, 2009; Burstein *et al*, 2010). The median time to PFS was also longer in the current study (57.0 weeks vs 15.7–39.6 weeks; Wong *et al*, 2009; Burstein *et al*, 2010). Although many of the patients in the prior studies were heavily pretreated (≥ 4 prior treatments; more similar to group B of the current study),

Table 5. Overall response rate, efficacy subsets (part 2)

Efficacy subsets	n	Overall response rate		Progression-free survival	
		n (%)	95% CI	Median (weeks)	95% CI
Hormone receptor status					
ER/PR +	55	46 (84)	71.2–92.2	64.0	52.1–92.1
ER/PR –	44	26 (59)	43.2–73.7	47.7	29.9–91.9
Prior therapy status					
First-line therapy	33	23 (70)	51.3–84.4	57.0	44.1–90.4
Prior HER2-directed therapy	38	27 (71)	54.1–84.6	63.1	47.7–95.4
Prior trastuzumab therapy	28	20 (71)	51.3–86.8	94.9	55.1–NE
Prior lapatinib therapy	14	10 (71)	41.9–91.6	44.3	23.4–64.0
Prior endocrine therapy	39	32 (82)	66.5–92.5	52.1	39.7–81.4
Prior taxane therapy	62	50 (81)	68.6–89.6	55.6	40.4–87.7

Abbreviations: CI = confidence interval; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NE = not estimable; PR = progesterone receptor.



No. of patients at risk	
Group A	68 63 60 53 46 42 37 33 29 28 27 24 18 17 15 15 12 5 1 0 0
Group B	31 29 27 24 21 17 17 12 12 11 10 9 8 7 5 5 5 2 0 0 0

Efficacy subsets	n	Median PFS	95% CI
All patients	99	57.0 weeks	47.7–81.6
Group A	68	63.1 weeks	47.7–92.1
Group B	31	52.1 weeks	39.0–87.7

Figure 1. PFS, evaluable patients (part 2). Kaplan–Meier median PFS was based on investigator assessments. Abbreviation: CI, confidence interval. ^aGroup A allowed ≤ 1 prior cytotoxic chemotherapy regimen for metastatic disease. ^bGroup B allowed ≤ 3 prior cytotoxic chemotherapy regimens for metastatic disease, with prior lapatinib permitted.

Table 6. Summary of neratinib pharmacokinetic parameters

Parameter, mean (CV%)	Neratinib 240 mg + paclitaxel 80 mg m ⁻² (n = 22)	Monotherapy of neratinib 240 mg (n = 3) (Wong <i>et al</i> , 2009)
C _{max} , ng ml ⁻¹	68.6 (47)	73.5 (37)
AUC ₀₋₂₄ , ng h ml ⁻¹	1027 (49)	939 (34)

Abbreviations: AUC₀₋₂₄ = area under the curve from treatment initiation to 24 h; CV% = coefficient of variation; C_{max} = maximum plasma concentration.

the antitumour activity observed for group B (ORR, 77%; median PFS, 52.1 weeks) still compares favourably with the previous reports of neratinib monotherapy.

In the current study, secondary analyses indicated that the ORR and Kaplan–Meier median PFS were higher among patients with hormone receptor–positive disease (84% and 64.0 weeks) compared with those with hormone receptor–negative disease (59% and 47.7 weeks; Table 5). The ORR remained high among patients with prior endocrine therapy (82%), although Kaplan–Meier median PFS was shorter among patients with prior hormonal therapy (52.1 weeks) compared with those without (79.7 weeks).

Of 38 evaluable patients exposed to prior HER2-directed therapy in the current study, 27 responded (ORR, 71%), including 20 of 28 (71%) patients treated with prior trastuzumab and 10 of 14 (71%) patients treated with prior lapatinib (Table 5). However, Kaplan–Meier median PFS among patients with prior HER2-directed therapy was 63.1 weeks (95% CI: 47.7–95.4 weeks), whereas those without prior HER2-directed therapy was 52.1 weeks (95% CI: 39.7–81.4 weeks). A high rate of response (ORR, 81%) and long Kaplan–Meier median PFS (55.6 weeks) was also observed in patients with prior taxane therapy.

The data suggest good clinical activity among subsets of patients with prior endocrine, HER2-directed, and/or taxane therapies who received neratinib plus paclitaxel in the current study. However, as the number of patients in each prior treatment subset was small in this study, these subset results should be interpreted with caution. A prior study of neratinib monotherapy in patients with HER2-positive breast cancer with and without prior trastuzumab treatment indicated that neratinib had greater activity in those who were trastuzumab naive (ORR, 24% vs 56%; PFS, 22.3 vs 39.6 weeks, respectively; Burstein *et al*, 2010). Similarly, in a study of trastuzumab plus paclitaxel, response rates were lower among patients with prior taxane therapy compared with the overall study population (ORR, 37.7% vs 20.0%; Furukawa *et al*, 2006). In contrast, in the current study, response rates and median PFS for patients with prior HER2-directed therapy (trastuzumab and/or lapatinib) as well as prior taxane therapy were similar to those of the overall patient population.

Pharmacokinetics. In this study, the maximum plasma concentration (C_{max}) and area under the curve (AUC) from treatment initiation to 24 h (AUC₀₋₂₄) of neratinib given in combination with paclitaxel were 68.6 ng ml⁻¹ and 1027 ng h ml⁻¹ (Table 6). These neratinib exposures were similar to those previously observed for neratinib monotherapy in patients with solid tumours (Wong *et al*, 2009), suggesting that there is no interaction between neratinib and paclitaxel when administered in combination.

CONCLUSIONS

The combination of neratinib (240 mg per day) and paclitaxel (paclitaxel 80 mg m⁻²) was associated with apparently higher

toxicity than that of neratinib as monotherapy but was manageable with anti-diarrhoeal agents and dose reductions. Diarrhoea was the most common treatment-emergent adverse event (all grades and grade 3); however, it typically occurred early, was transient, and did not lead to treatment discontinuation. Despite the absence of interaction between neratinib and paclitaxel from pharmacokinetics, careful clinical monitoring of the treatment-emergent side effects is necessary. This combination also demonstrated a high rate of response in patients with HER2-positive breast cancer, including patients in both the first-line setting and the second-line or greater setting. The benefit and risk should be carefully evaluated in the future studies.

Nevertheless, results from this study support the further evaluation of neratinib combined with paclitaxel for the treatment of patients with HER2-positive breast cancer. A phase III trial is currently ongoing to study the combination of neratinib plus paclitaxel compared with trastuzumab plus paclitaxel in the first-line setting. Other ongoing or recently completed trials are assessing the activity of neratinib in combination with trastuzumab (Swaby *et al*, 2009), capecitabine (Saura *et al*, 2009), vinorelbine (Staroslawska *et al*, 2010), and temsirolimus (Gandhi *et al*, 2011) in HER2-positive breast cancer or other solid tumours.

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CONFLICT OF INTEREST

SG has served as an advisor/consultant for Pfizer. RA and MLV are employees of Pfizer and AF and YZ are former employees of Pfizer; YZ and RA additionally own stock in Pfizer. The remaining authors (LC, BX, and IB) declare no conflict of interest.

AUTHOR CONTRIBUTIONS

LW-CC, YZ, and RA assisted with the conception and design of the study. LW-CC, BX, AF, RA, MLVV, and IB collected and assembled data for the study, and all authors assisted in the analysis and/or interpretation of the data. All authors have participated in the writing and/or critical revision of this manuscript and have approved the final manuscript for publication.

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