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GENERIC DRUG NAME / COMPOUND NUMBER: Neratinib / WAY-179272

PROTOCOL NO.: 3144A1-2206 (B1891017)

PROTOCOL TITLE:

A Phase 1/2, Open-Label Study of Neratinib (HKI-272) in Combination With Capecitabine in Subjects With Solid Tumors and ErbB-2 Positive Metastatic or Locally Advanced Breast Cancer

Study Centers:

Thirty-three (33) centers took part in the study: 10 in the United States, 5 in Russia, 4 in Spain, 4 in China, 3 in Republic of Korea, 2 in Hungary, 2 in Australia, 1 each in Brazil, Hong Kong, and Croatia.

Study Initiation Date and Final Completion Date:

Study Initiation Date: 09 December 2008

Final Completion Date: Not applicable

Data cut-off date was 27 September 2011.

Phase of Development:

Phase 1/2

Study Objectives:

Primary Objectives:

- Part 1: To assess the safety and tolerability, and to define the maximum tolerated dose (MTD) of neratinib in combination with capecitabine in subjects with advanced solid tumors.

- Part 2: To confirm the MTD identified in Part 1 by collecting further data on the safety and tolerability of the combination of neratinib and capecitabine at the MTD in subjects with erythroblastic leukemia viral oncogene homolog (erbB-2) positive breast cancer.

Secondary Objectives:

- Part 1: To obtain preliminary anti-tumor activity for neratinib in combination with capecitabine.

- Part 2: To obtain pharmacokinetic (PK) information, and to assess additional efficacy parameters including objective response rate (ORR) (ORR = complete response [CR] + partial response [PR]), progression-free survival (PFS), clinical benefit rate (CR + PR + stable disease [SD] ≥24 weeks), and duration of response for the combination of neratinib plus capecitabine.

METHODS

Study Design:

This was a Phase 1/2, multicenter, open-label study of neratinib in combination with capecitabine in subjects with solid tumors and breast cancer. The study was conducted in 2 parts. Part 1 was a dose escalation study to establish the MTD for neratinib in combination with capecitabine. Part 2 was intended to confirm the MTD established in Part 1 and provide preliminary data on the clinical anti-tumor activity of neratinib in combination with capecitabine in subjects with erbB-2 positive metastatic or locally advanced breast cancer.

Part 1

In Part 1 of the study, 5 dose combinations (3 dose levels of neratinib and 2 dose levels of capecitabine) were planned for initial enrollment of 3 to 9 subjects/dose group, with each subject participating in a single group. Dose levels planned for initial enrollment were as follows (Figure 1):

Dose Level 1: 160 mg neratinib plus 750 mg/m^2 twice daily (BID) capecitabine

Dose Level 2: 240 mg neratinib plus 750 mg/m^2 BID capecitabine

Dose Level 3: 240 mg neratinib plus 1000 mg/m^2 BID capecitabine

Dose Level 4: 200 mg neratinib plus 1000 mg/m^2 BID capecitabine

Dose Level 5: 160 mg neratinib plus 1000 mg/m^2 BID capecitabine

A sixth dose level, specifying an intermediate dose of 200 mg neratinib plus 750 mg/m^2 capecitabine, was planned in the event that dose level 1 was tolerated but dose level 2 was not.

Part 1 was an ascending dose study whereby subjects were only enrolled at the next dose level after all subjects evaluable for dose escalation were evaluated for 21 days of the first treatment cycle. Subjects evaluable for dose escalation were defined as those that either:

- Experienced a dose limiting toxicity (DLT) within the first 21 days, regardless of the number of doses of treatment received, or

- Received ≥75% of planned doses of both neratinib and capecitabine.

Enrollment at the next higher dose level were based on the tolerability of the preceding dose level in accordance with the following criteria:

- If none of the evaluable subjects at a given dose level experienced a DLT by Day 21, then the dose was escalated, and ≥3 evaluable subjects were treated at the next higher dose level.

- If 1 evaluable subject at a given dose level experienced a DLT by Day 21, then a total of 6 evaluable subjects were treated at the same dose level. The dose was then escalated if only 1 evaluable subject (out of a total of 6) had a DLT.

- If ≥2 of 3 to 6 (≥33%) or ≥3 of 9 (≥33%) evaluable subjects at a dose level experienced a DLT by Day 21, dose escalation was stopped and the prior dose level was considered the MTD.

Subjects enrolled in Part 1 and withdrawn from the study for a reason other than a DLT might have been replaced. Intra-subject dose escalation was not permitted. Additional subjects could be included at any dose level to further assess the safety and tolerability at that dose level.

Figure 1. Overview of Part 1 Study Design

NERATINIB (mg)			
	160	Dose Level 1	Dose Level 5
	200	NE[a]	Dose Level 4
	240	Dose Level 2	Dose Level 3
		750 BID (1500)	1000 BID (2000)
		CAPECITABINE	

BID = bis in die (twice a day); NE = not enrolled; MTD = maximum tolerated dose.

[a]If dose level 1 was tolerated, but dose level 2 was not tolerated, the protocol specified an intermediate dose level at 200 mg neratinib in combination with 750 mg/m^2 BID (1500 mg total) capecitabine could be investigated for MTD.

Part 2

In Part 2 of the study, enrollment of approximately 80 female subjects with locally advanced erbB-2 positive breast cancer were planned at the MTD of the neratinib and capecitabine combination determined in Part 1. Enrollment in Part 2 of the study was conducted with the purpose of generating 2 planned analysis groups: subjects with no prior lapatinib exposure (30 to 60 subjects), and subjects with prior exposure to lapatinib (maximum of 20 subjects).

Number of Subjects (Planned and Analyzed):

The planned number of lapatinib naïve subjects to be enrolled was contingent upon the MTD established in Part 1. Specifically, if the MTD in Part 1 equaled the maximum dose level (level 3), 20 to 30 lapatinib-naïve subjects were to be enrolled in Part 2. In case of any lower dose level identified as the MTD, 50-60 lapatinib-naïve subjects were to be enrolled. Depending on the safety and activity profile observed during the dose escalation phase, the dose selected for Part 2 was adjusted, if appropriate. In cases where 1 test article of the combination was discontinued due to intolerance, the other test article was administered alone.

A total of 105 subjects were enrolled in the study and received neratinib. All enrolled subjects were analyzed for safety in the study. A total of 98 subjects comprised the evaluable population in Part 1 and Part 2.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Subjects enrolled in Part 1 of this study were males or females aged ≥18 years, with a confirmed pathologic diagnosis of a solid tumor that was not curable with available therapies for which neratinib plus capecitabine was a reasonable treatment option, ≥1 measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 guidelines, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and screening laboratory values and left ventricular ejection fraction (LVEF) within normal limits.

Subjects enrolled in Part 2 of this study were females aged 18 or older with a histologically and/or cytologically confirmed diagnosis of breast cancer, metastatic or locally advanced, erbB-2 gene amplified tumor, disease progression on or following at least 1 prior trastuzumab containing treatment regimen (≥6 weeks) for metastatic or locally advanced disease, prior treatment with a taxane in the neoadjuvant, adjuvant, locally advanced, and/or metastatic disease treatment setting, ≥1 measurable lesion as defined by the RECIST v1.0 guidelines, an ECOG performance status of 0 to 2, and screening laboratory values and LVEF within normal limits.

Main Exclusion Criteria:

- Subjects enrolled in Part 2 were not to have received prior treatment with capecitabine, lapatibine (excluding 20 subjects enrolled with prior treatment lapatinib) or any erbB-2 targeted agents except trastuzumab. Treatment with erbB-2 targeted therapy had to exceed 2 weeks (14 days) in order to be exclusionary.

- Subjects enrolled in Part 2 were not to have received prior treatment with anthracyclines with a cumulative dose of doxorubicin of >400 mg/m^2, epirubicin dose of >800 mg/m^2, or the equivalent dose for other anthracyclines.

- Major surgery, chemotherapy, radiotherapy, any investigational agents, or other cancer therapy within 2 weeks of treatment Day 1.

- Subjects with bone as the only site of disease.

- Active uncontrolled or symptomatic central nervous system (CNS) metastases, as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Subjects with a history of CNS metastases or cord compression are allowable if they have been considered definitively treated, and are off anti-convulsants and steroids for ≥4 weeks before the first dose of test article.

- Family history of congenital long or short QT syndrome, Bruganda syndrome or subjects with a QT/QTc (corrected QT interval) >0.45 second or known history of QTc prolongation, or Torsade de Pointes.

Study Treatment:

Subjects received a daily oral dose of neratinib tablets by mouth with food preferably in the morning or with the first solid meal of the day to be eaten at a relatively regular time. On days when PK samples were drawn, subjects received neratinib (with food) and capecitabine (with water) concurrently with breakfast after drawing the predose PK samples on Day 1 of Cycle 1. On all other days, neratinib was taken either before or after capecitabine. Daily doses of capecitabine were administered in 2 divided doses, orally, with water, on Days 1 to 14 of a 21-day cycle. On days when PK samples were drawn, subjects received capecitabine concurrently with neratinib in the morning after drawing the predose PK samples on Day 1 of Cycle 1 and prior to drawing the first PK samples on Day 14 of Cycle 1. On all other days, capecitabine was taken either before or after neratinib.

Efficacy and Pharmacokinetic Endpoints:

Primary Efficacy Endpoints: Preliminary evidence of the antitumor activity of neratinib and capecitabine was assessed based on tumor assessments performed for all subjects at Screening and done every 2 cycles, ie, every 6 weeks ± 4 days during the treatment period. Tumor response was evaluated per RECIST v1.0 criteria.

Secondary Efficacy Endpoints: PFS was defined as the interval from the date of randomization until the earliest date of disease recurrence, progression (per RECIST v1.0 criteria) or death due to any cause. Symptomatic deterioration was considered as progressive disease (PD). Subjects without documented progression or death were censored at the date of last valid tumor assessment.

Duration of response was measured from the first date of CR or PR until the first date of PD, symptomatic deterioration, or death. Subjects with confirmed CR or PR and without documented PD were censored at the date of last valid tumor assessment.

Clinical benefit included a confirmed response of CR, PR, or (SD) for ≥24 weeks (in case of SD, the last valid tumor assessment with overall response of SD or better ≥22 weeks from date of first dose, taking into account the time window for tumor assessments) per RECIST v1.0 criteria. Clinical benefit rate was defined as the proportion of subjects demonstrating a clinical benefit during the study.

Pharmacokinetic Endpoints: Blood samples (3 mL whole blood) were only to be taken from subjects participating in Part 2 of the study and at the following time points: predose on

Day 1 of Cycle 1, at 1, 2, 4, 6, 8, and 21 to 24 hours postdose on Day 14 of Cycle 1. Evaluation of multiple dose PK parameters of neratinib and its metabolites (WAY_193575, WYE_121529, and WYE_121592) in combination with capecitabine was a secondary endpoint of the Part 2 study at the MTD. Among the parameters to be estimated were the observed maximum concentration of neratinib (C_{max}), time of maximum concentration (T_{max}), and area under the concentration-time curve (AUC). Plasma concentrations of neratinib and its metabolites were determined using sponsor approved and validated liquid chromatography/tandem mass spectrometry assays.

The following PK parameters were calculated for each subject by non-compartmental analysis of concentration-time data (Table 1). Nominal sample collection time was used for the PK analyses.

Table 1. Pharmacokinetic Parameters

Parameter	Definition	Method of Determination
AUC_τ	For steady state data: area under the concentration versus time curve from 0time to τ, the dosing interval (24 hours)	Linear/ Log trapezoidal method
C_{av}	Average plasma concentration at steady state	AUC_τ/τ
C_{max}	Maximum plasma concentration at steady state	Observed
C_{min}	Minimum plasma concentration at steady state	Observed
C_{last}	Plasma concentration for last quantifiable plasma concentration	Observed
C_{trough}	Concentration prior to dose	Observed
T_{max}	Time for C_{max}	Observed
T_{last}	Time of C_{last}	Observed
CL/F	Clearance after oral administration	$Dose/AUC_\infty$ or $Dose/AUC_\tau$

Pharmacokinetic parameter values were calculated using electronic noncompartmental analysis (eNCA, Version 2.2.3).

Safety Evaluations:

Safety assessments included adverse events (AEs), laboratory tests, physical examinations, vital signs, and 12-lead electrocardiograms (ECGs). Other safety assessments included LVEF, ECOG performance status, pulmonary function tests, and pulse oximetry.

Statistical Methods:

Part 1 was intended to determine the safety, tolerability, and MTD of neratinib administered in combination with capecitabine. No formal statistical analysis was planned for this portion of the study. Efficacy analyses were based on the evaluable and intent-to-treat (ITT) populations. Those Part 1 subjects who took MTD dose and were eligible for Part 2 were combined with Part 2 subjects for some efficacy analyses. Primary efficacy analysis was to calculate ORR, exact 80% and 95% confidence intervals (CI) based on the evaluable subjects of Part 2. The ORR and 95% CI were also computed based on the ITT population. The ITT population consisted of all subjects enrolled in the study. The evaluable population was defined as all subjects who met all inclusion and none of the exclusion criteria, received ≥2 weeks of neratinib plus capecitabine (date of last dose – date of first dose + 1 ≥14), and underwent valid tumor assessment at Baseline and ≥1 post-baseline time

point. Post-baseline tumor assessment was not required for subjects who died or had symptomatic deterioration before the second scheduled post-baseline tumor assessment.

Subjects who received ≥1 dose of test article were included in the safety population. Safety data were evaluated using descriptive statistics. All AEs were summarized as of the data cutoff date. The incidence of AEs was summarized by system organ class, preferred term, and treatment. AEs resulting in dose hold, dose reduction, DLT, and withdrawal from the study were summarized. AEs were also summarized by toxicity grade (National Cancer Institute Common Terminology Criteria v3.0), by relationship to test article, and by seriousness. Laboratory results, vital signs results, and 12-lead ECG results of potential clinical importance were summarized by treatment.

RESULTS

Subject Disposition and Demography:

A total of 147 subjects were screened for entry into this study, and 42 subjects were considered screen failures. The combined enrollment for Part 1 and Part 2 was 105 subjects. A total of 33 subjects were enrolled across the 5 dosing cohorts in Part 1 of the study and a total of 72 female subjects with erbB-2 positive breast cancer were enrolled and treated at the MTD in Part 2. In Part 2, 65 lapatinib-naive and 7 subjects with prior lapatinib exposure were enrolled at the MTD of 240 mg of neratinib combined with 750 mg/m² of capecitabine, as determined in Part 1.

At the time of the data cutoff, 20 subjects (19.0%) were still participating in the study, and 85 subjects (81%) had discontinued from the study. The reasons why subjects discontinued from the study included disease progression (60 subjects; 57.1%), other (11 subjects; 10.5%), subject request (5 subjects, 4.8%), death (7 subjects; 6.7%), and Investigator request (2 subjects, 1.9%).

A total of 105 subjects were included in the safety population; 105 subjects were included in ITT population; and 98 subjects were included in the evaluable population for efficacy.

Demography of the subjects is summarized in Table 2 below.

Table 2. Summary of Demographics (Safety Population)

Characteristics	Part 1					Part 2			
	Dose Level 1 N160 + C1500 (N=6)	Dose Level 2 N240 + C1500 (N=8)	Dose Level 3 N240 + C2000 (N=4)	Dose Level 4 N200 + C2000 (N=6)	Dose Level 5 N160 + C2000 (N=9)	N + C MTD (No Prior Lap) (N=65)	N + C MTD (Prior Lap) (N=7)	N + C MTD Total (N=72)	Total (Part 1 + Part 2) (N=105)
Age (years)									
N	6	8	4	6	9	65	7	72	105
Mean	49.7	53.3	56.3	59.0	55.7	51.5	50.9	51.4	52.4
Standard Deviation	11.50	10.42	17.15	10.88	10.64	10.48	10.65	10.42	10.77
Minimum	37	38	39	39	41	33	38	33	33
Maximum	69	69	80	69	70	79	61	79	80
Median	46.0	56.5	53.0	63.0	52.0	52.0	56.0	52.0	53.0
Age Range									
<65	5 (83.3)	7 (87.5)	3 (75.0)	3 (50.0)	7 (77.8)	59 (90.8)	7 (100)	66 (91.7)	91 (86.7)
≥65	1 (16.7)	1 (12.5)	1 (25.0)	3 (50.0)	2 (22.2)	6 (9.2)	0	6 (8.3)	14 (13.3)
Sex									
Female	4 (66.7)	5 (62.5)	3 (75.0)	3 (50.0)	6 (66.7)	65 (100)	7 (100)	72 (100)	93 (88.6)
Male	2 (33.3)	3 (37.5)	1 (25.0)	3 (50.0)	3 (33.3)	0	0	0	12 (11.4)
Race									
Asian	0	0	0	0	0	25 (38.5)	3 (42.9)	28 (38.9)	28 (26.7)
Black or African American	1 (16.7)	0	0	0	0	2 (3.1)	0	2 (2.8)	3 (2.9)
White	5 (83.3)	8 (100)	4 (100)	6 (100)	9 (100)	38 (58.5)	4 (57.1)	42 (58.3)	74 (70.5)
Height (cm)									
N	6	8	4	6	8	64	7	71	103
Mean	168.88	167.68	163.87	169.56	168.74	160.38	159.86	160.33	162.73
Standard deviation	8.619	12.173	7.979	13.864	8.911	7.239	7.515	7.213	8.946
Height									
Minimum	157.0	153.7	154.5	153.0	157.0	146.0	149.0	146.0	146.0
Maximum	177.8	178.6	174.0	191.8	181.6	182.0	171.0	182.0	191.8
Median	169.05	166.00	163.50	167.00	167.39	160.00	160.00	160.00	162.00
Missing	0	0	0	0	1	1	0	1	2
Weight (kg)									
N	6	8	4	6	9	65	7	72	105
Mean	79.64	67.47	74.24	65.19	73.71	66.80	58.89	66.03	67.84
Standard deviation	30.684	10.338	11.741	19.746	24.158	14.982	12.820	14.893	16.934

Table 2. Summary of Demographics (Safety Population)

Characteristics	Part 1					Part 2			
	Dose Level 1 N160 + C1500 (N=6)	Dose Level 2 N240 + C1500 (N=8)	Dose Level 3 N240 + C2000 (N=4)	Dose Level 4 N200 + C2000 (N=6)	Dose Level 5 N160 + C2000 (N=9)	N + C MTD (No Prior Lap) (N=65)	N + C MTD (Prior Lap) (N=7)	N + C MTD Total (N=72)	Total (Part 1 + Part 2) (N=105)
Minimum	51.0	55.8	60.2	48.6	37.9	44.2	40.0	40.0	37.9
Maximum	126.6	83.0	88.2	102.5	111.9	110.0	79.0	110.0	126.6
Median	69.17	66.60	74.28	61.60	63.50	62.00	58.00	61.00	63.00

C = capecitabine; C1500 = capecitabine 1500 mg/m^2; C2000 = capecitabine 2000 mg/m^2; Lap = lapatinib; MTD = maximum tolerated dose; N = neratinib; N160 = neratinib 160 mg; N200 = neratinib 200 mg; N240 = neratinib 240 mg.

Efficacy and Pharmacokinetic Results:

A total of 4 of 7 (57.1%) subjects with prior lapatinib exposure in the evaluable population from Part 2 achieved CR or PR while receiving neratinib + capecitabine MTD. A total of 40 of 63 (63.5%) lapatinib-naïve subjects in the evaluable population from Part 2 and Part 1 achieved CR or PR. The ORR for the evaluable population was statistically significantly >the 24% ORR of historical controls (p<0.0001). For the ITT population who were lapatinib-naïve, a total of 41 of 67 (61.2%) Part 2 and eligible Part 1 subjects achieved CR or PR. Primary efficacy (ORR) and secondary efficacy results (PFS, duration of response and clinical benefit) are summarized in Table 3, Table 4, Table 5, Table 6, Table 7 and Table 8 below.

Table 3. Overall Response Rate

Investigator Assessment[a]	Evaluable Population			ITT Population	
	Prior Lapatinib Subjects	Lapatinib-Naïve Subjects		Lapatinib-Naïve Subjects[b]	
	MTD (Part 2) (N=7)	MTD (Part 2) (N=61)	MTD (Part 2 + Part 1)[c] (N=63)	MTD (Part 2) (N=65)	MTD (Part 2+Part 1)[c] (N=67)
No. subjects with CR or PR, n (%)	4 (57.1)	39 (63.9)	40 (63.5)	40 (61.5)	41 (61.2)
80% CI for Rate	(27.9, 83.0)	(55.0, 72.2)	(54.7, 71.6)	(52.9, 69.7)	(52.6, 69.2)
95% CI for Rate	(18.4, 90.1)	(50.6, 75.8)	(50.4, 75.3)	(48.6, 73.3)	(48.5, 72.9)
One sided p-value[d]		<0.0001	<0.0001		

CI = confidence interval; CR = complete response; MTD = maximum tolerated dose; N = number of subjects; No = number; PR = partial response.

a. Disease assessment is based on review of radiographic and clinical data by the Investigator.
b. All subjects with prior exposure to lapatinib were included in evaluable population.
c. Combined group with Part 2 subjects and Part 1 subjects who took MTD dose and would be eligible for Part 2.
d. One-sided p-value from Z-test comparing with 24% Overall Response Rate of historical controls.

Table 4. Best Overall Response

Investigator Assessment[a]	Evaluable Population			ITT Population	
	Prior Lapatinib Subjects	Lapatinib-Naïve Subjects		Lapatinib-Naïve Subjects[b]	
	MTD (Part 2) (N=7)	MTD (Part 2) (N=61)	MTD (Part 2+Part 1)[b] (N = 63)	MTD (Part 2) (N=65)	MTD (Part 2+Part 1)[c] (N=67)
Complete Response, n (%)	1 (14.3)	7 (11.5)	7 (11.1)	7 (10.8)	7 (10.4)
Partial Response, n (%)	3 (42.9)	32 (52.5)	33 (52.4)	33 (50.8)	34 (50.7)
Stable Disease <24 weeks, n (%)	2 (28.6)	12 (19.7)	12 (19.0)	13 (20.0)	13 (19.4)
Stable Disease ≥24 weeks, n (%)	1 (14.3)	5 (8.2)	6 (9.5)	5 (7.7)	6 (9.0)
Progressive Disease, n (%)	0	5 (8.2)	5 (7.9)	5 (7.7)	5 (7.5)
Unknown, n (%)	0	0	0	2 (3.1)	2 (3.0)

ITT = intent-to-treat; MTD = maximum tolerated dose; N = number of subjects; n = percentage of subjects.

a. Disease assessment is based on review of radiographic and clinical data by the Investigator.
b. All subjects with prior exposure to lapatinib were included in evaluable population.
c. Combined group with Part 2 subjects and Part 1 subjects who took MTD dose and would be eligible for Part 2.

Table 5. Duration of Response

Investigator Assessment[a]	Evaluable Population			ITT Population	
	Prior Lapatinib Subjects	Lapatinib-Naïve Subjects		Lapatinib-Naïve Subjectsb	
	MTD (Part 2) (N=7)	MTD (Part 2) (N=61)	MTD (Part 2+Part 1) c (N = 63)	MTD (Part 2) (N=65)	MTD (Part 2+Part 1)c (N = 67)
No. subjects with follow-up tumor assessment or early PD, n (%)	7 (100)	61 (100)	63 (100)	64 (98.5)	66 (98.5)
No. subjects with BOR=CR or PR, n (%)	4 (57.1)	39 (63.9)	40 (63.5)	40 (61.5)	41 (61.2)
No. subjects with PD or death, n (%)	3 (75.0)	21 (53.8)	21 (52.5)	22 (55.0)	22 (53.7)
No. of censored subjects, n (%)	1 (25.0)	18 (46.2)	19 (47.5)	18 (45.0)	19 (46.3)
Median duration in weeks[d] (80% CI)	48.3 (30.0, 61.0)	46.3 (36.4, NE)	46.3 (36.4, NE)	42.0 (34.7, NE)	42.0 (36.4, NE)
Median duration in weeks[d] (95% CI)	48.3 (30.0, 61.0)	46.3 (30.1, NE)	46.3 (30.1, NE)	42.0 (30.1, NE)	42.0 (30.1, NE)
Range (min, max)	43.0 (18.0, 61.0)	79.0 (11.1,90.1)	79.0 (11.1, 90.1)	79.0 (11.1, 90.1)	79.0 (11.1, 90.1)

BOR = best overall response; CI = confidence interval; CR = complete response; ITT = intent-to-treat; min = minimum; max = maximum; MTD = maximum tolerated dose; NE = not estimable; No. = number; PD = progressive disease; PR = partial response.

a. Disease assessment is based on review of radiographic and clinical data by the investigator.
b. All subjects with prior exposure to lapatinib were included in evaluable population.
c. Combined group with Part 2 subjects and Part 1 subjects who took MTD dose and would be eligible for Part 2.
d. Kaplan-Meier method used to estimate median and confidence intervals.

Table 6. Clinical Benefit Rate

Investigator Assessment[a]	Evaluable Population			ITT Population	
	Prior Lapatinib Subjects	Lapatinib-Naïve Subjects		Lapatinib-Naïve Subjects[b]	
	MTD (Part 2) (N=7)	MTD (Part 2) (N=61)	MTD (Part 2+Part 1)[c] (N=63)	MTD (Part 2) (N=65)	MTD (Part 2+Part 1)[c] (N=67)
No. subjects with CR, PR or SD ≥24 weeks, n (%)	5 (71.4)	44 (72.1)	46 (73.0)	45 (69.2)	47 (70.1)
80% CI for Rate	(40.4, 92.1)	(63.5, 79.6)	(64.6, 80.3)	(60.7, 76.8)	(61.8, 77.5)
95% CI for Rate	(29.0, 96.3)	(59.2, 82.9)	(60.3, 83.4)	(56.6, 80.1)	(57.7, 80.7)

CI = confidence interval; CR = complete response; ITT = intent-to-treat; MTD = maximum tolerated dose; No. = number PR = partial response; SD = stable disease.

a. Disease assessment is based on review of radiographic and clinical data by the Investigator.
b. All subjects with prior exposure to lapatinib were included in evaluable population.
c. Combined group with Part 2 subjects and Part 1 subjects who took MTD dose and would be eligible for Part 2.

Table 7. Duration of Stable Disease

Investigator Assessmenta	Evaluable Population			ITT Population	
	Prior Lapatinib Subjects	Lapatinib-Naïve Subjects		Lapatinib-Naïve Subjectsb	
	MTD (Part 2) (N=7)	MTD (Part 2) (N=61)	MTD (Part 2+Part 1)c (N=63)	MTD (Part 2) (N=65)	MTD (Part 2+Part 1)c (N=67)
No. subjects with follow-up tumor assessment or early PD, n (%)	7 (100)	61 (100)	63 (100)	64 (98.5)	66 (98.5)
No. subjects with BOR=SD, n, (%)	3 (42.9)	17 (27.9)	18 (28.6)	18 (27.7)	19 (28.4)
No. subjects with PD or death, n (%)	2 (66.7)	10 (58.8)	11 (61.1)	10 (55.6)	11 (57.9)
No. of censored subjects, n (%)	1 (33.3)	7 (41.2)	7 (38.9)	8 (44.4)	8 (42.1)
Median duration in weeks[d] (80% CI)	23.8 (18.0, 29.6)	24.1 (16.9, 42.0)	36.3 (18.0, 72.0)	24.1 (16.9,42.0)	36.3 (18.0, 72.0)
Median duration in weeks[d] (95% CI)	23.8 (18.0, 29.6)	24.1 (12.1, 72.0)	36.3 (16.9, 72.0)	24.1 (12.1,72.0)	36.3 (16.9, 72.0)
Range (min, max)	23.4 (6.1, 29.6)	76.9 (6.4, 83.3)	76.9 (6.4, 83.3)	77.6 (5.7, 83.3)	77.6 (5.7, 83.3)

BOR = best overall response; CI = confidence interval; ITT = intent-to-treat; min = minimum; max = maximum; MTD = maximum tolerated dose; No. = number; PD = progressive disease.

a. Disease assessment is based on review of radiographic and clinical data by the Investigator.
b. All subjects with prior exposure to lapatinib were included in evaluable population.
c. Combined group with Part 2 subjects and Part 1 subjects who took MTD dose and would be eligible for Part 2.
d. Kaplan-Meier method used to estimate median and confidence intervals.

Table 8. Progression-Free Survival

Investigator Assessment[a]	Evaluable Population			ITT Population	
	Prior Lapatinib Subjects	Lapatinib-Naïve Subjects		Lapatinib-Naïve Subjects[b]	
	MTD (Part 2) (N=7)	MTD (Part 2) (N=61)	MTD (Part 2+Part 1)[c] (N=63)	MTD (Part 2) (N=65)	MTD (Part 2+Part 1)[c] (N=67)
No. subjects with PD or death, n (%)	6 (85.7)	37 (60.7)	38 (60.3)	40 (61.5)	41 (61.2)
No. of censored subjects, n (%)	1 (14.3)	24 (39.3)	25 (39.7)	25 (38.5)	26 (38.8)
Median PFS in weeks[d] (80% CI)	35.9 (18.9, 60.1)	40.3 (36.1, 48.3)	42.0 (36.1, 51.0)	39.0 (35.0, 47.6)	40.3 (35.7, 47.6)
Median PFS in weeks[d] (95% CI)	35.9 (18.9, 60.1)	40.3 (30.3, 66.0)	42.0 (35.0, 72.0)	39.0 (30.1, 51.0)	40.3 (30.1, 66.0)
Range (min, max)	47.9 (18.0, 65.9)	93.0 (3.1, 96.1)	93.0 (3.1, 96.1)	96.0 (0.1, 96.1)	96.0 (0.1, 96.1)

CI = confidence interval; ITT = intent-to-treat; MTD = maximum tolerated dose; PD = progressive disease; min = minimum; max = maximum; No. = number; PFS = progression-free survival.

a. Disease assessment is based on review of radiographic and clinical data by the Investigator.
b. All subjects with prior exposure to lapatinib were included in evaluable population.
c. Combined group with Part 2 subjects and Part 1 subjects who took MTD dose and would be eligible for Part 2.
d. Kaplan-Meier method used to estimate median and confidence intervals.

Pharmacokinetic Results: After daily oral administration of neratinib for 14 days in combination with capecitabine (1500 mg/m^2/day), median T_{max} was 4 hours (range 1.0 to 8.0 hours) for neratinib and its metabolites (Table 9). Mean C_{max} was 92.0, 27.2, 12.8, and 22.2 ng/mL for neratinib, WAY_193575, WYE_121529, and WYE_121592, respectively. Observed mean plasma AUC_{τ} was 1175.0, 305.7, 119.9, and 240.9 ng•hr/mL for neratinib, WAY_193575, WYE_121529, and WYE_121592, respectively. Mean neratinib CL/F was observed to be 267.6 L/hour.

Table 9. Pharmacokinetic Parameters of Neratinib and Its Metabolites (Subjects With ≥4 Consecutive Days of Neratinib Dosing Prior to Pharmacokinetic Sample Collection)

Drug (Metabolite) Parameter	B1891017 (Study 3144A1-2206-WW) Mean (CV%) (Median)	Historical Data[a]		
		Study 3144A1-102-US Mean (CV%)	Study 3144A1-1116-US Mean (STD)	Study 3144A1-104-JA Mean (STD)
HKI_272				
N	59	NR	20	10
T_{max} (hr)[b]	4.0 (1.0-8.0)	3.0 (2.0-5.0)	6.0 (4.0-8.0)	4.0 (2.0-7.9)
C_{max} (ng/mL)	92.0 (49) (90.3)	73.5 (37)	73.1 (25.5)	81.5 (45.9)
AUCτ (ng•hr/mL)	1175.0 (51) (1115.4)	939 (34)	1060 (262)	1110 (660)[c]
CL/F (L/hr)	267.6 (57) (215.2)	4.42 (21)[d]	NR	317 (222)[c]
C_{avg} (ng/mL)	49.0 (51) (46.5)	NR	NR	N/A
WAY_193575				
N	59	N/A	20	N/A
T_{max} (hr)[b]	4.0 (1.0-8.0)	N/A	6.0 (4.0-8.0)	N/A
C_{max} (ng/mL)	27.2 (54) (26.4)	N/A	28.3 (8.2)	N/A
AUCτ (ng•hr/mL)	305.7 (49) (287.5)	N/A	350 (72.5)	N/A
C_{avg} (ng/mL)	12.7 (49) (12.0)	N/A	NR	N/A
WYE_121529				
N	55	N/A	20	N/A
T_{max} (hr)[b]	4.0 (1.0-8.0)	N/A	4.0 (2.0-6.0)	N/A
C_{max} (ng/mL)	12.8 (53) (11.6)	N/A	15.4 (5.5)	N/A
AUCτ (ng•hr/mL)	119.9 (62) (104.8)	N/A	162 (54.5)	N/A
C_{avg} (ng/mL)	5.0 (62) (4.4)	N/A	NR	N/A
WYE_121592				
N	57	N/A	20	N/A
T_{max} (hr)[b]	4.0 (1.0-8.0)	N/A	4.0 (2.0-8.0)	N/A
C_{max} (ng/mL)	22.2 (70) (17.6)	N/A	19.6 (12.6)	N/A
AUCτ (ng•hr/mL)	240.9 (73) (194.0)	N/A	233 (135)	N/A
C_{avg} (ng/mL)	10.0 (73) (8.1)	N/A	NR	N/A

Parameters defined in Table 1.
Study 3144A1-102-US (An Ascending Single and Multiple Dose Study of the Safety,Tolerability, Pharmacokinetics, and Pharmacodynamics of HKI-272 Administered Orally to Subjects With HER-2/neu or HER-1/EGFR-Positive Tumors).
Study 3144A1-1116-US (A Double-Blind, Sponsor-Unblinded, Randomized, Multiple-Dose, Parallel Group Study to Characterize the Occurrence of Mild to Moderate Diarrhea after Administration of Neratinib Either 240-mg Once Daily or 120-mg Twice Daily for 14 Days to Healthy Subjects).
Study 3144A1-104-JA (An Ascending Single and Multiple Dose Study of the Safety, Tolerability and Pharmacokinetics of HKI-272 Administered Orally to Japanese Subjects With Advanced Solid Tumor).
CV = coefficient of variation; N = number of subjects; N/A = not applicable; NR = not reported; PK = pharmacokinetic; STD = standard deviation.
a.Neratinib administered as monotherapy.
b.Median (Range).
c.A subject was not included for the calculation of these parameters (N=9).
d.L/hr/kg; for a 70 kg person the value would be: 309 L/hr.

Safety Results:

Death and Serious Adverse Events: There were 13 deaths (12.4%) during this study, including 6 deaths (5.7%) within 28 days of the last dose. All deaths were attributed by the Investigator to disease progression, except a single case of hemorrhagic shock and a single death with cause classified by the Investigator as 'it was not clear'. This death was likely related to disease progression based on the clinical profile of the subject. Among subjects

who died within 28 days of the last dose, 5 (4.8%) died due to disease progression while 1 subject (1.0%), died from hemorrhagic shock. A total of 36 subjects (34.3%) had an SAE in the study. The most common SAE was diarrhea (4 subjects; 3.8%).

Adverse Events: A total of 103 subjects (98.1%) reported ≥1 treatment-emergent AE (TEAE; all causalities) in the study. The most common TEAEs were diarrhea (93 subjects; 88.6%), palmar-plantar erythrodysesthesia syndrome (57 subjects; 54.3%), nausea (42 subjects; 40%), vomiting (36 subjects; 34.3%), and decreased appetite (32 subjects; 30.5%). A total of 66 subjects (62.9%) had a TEAE of Grade 3 or higher. The most common TEAEs of Grade 3 or higher were diarrhea (24 subjects; 22.9%), palmar-plantar erythrodysesthesia syndrome (13 subjects; 12.4%), and asthenia (6 subjects; 5.7%). TEAEs reported in safety evaluable population are included in Table 10 below.

Table 10. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events Reported in ≥10% of Subjects Overall (Safety Population)

	Part 1					Part 2			
System Organ Class[a] Preferred Term	**Dose Level 1 N160 + C1500 (N = 6)**	**Dose Level 2 N240 + C1500 (N = 8)**	**Dose Level 3 N240 + C2000 (N = 4)**	**Dose Level 4 N200 + C2000 (N = 6)**	**Dose Level 5 N160 + C2000 (N = 9)**	**N + C MTD [No Prior Lap.] (N = 65)**	**N + C MTD [Prior Lap.] (N = 7)**	**N + C MTD Total (N = 72)**	**Total [Part 1 + Part 2] (N = 105)**
Any adverse event	6 (100)	8 (100)	4 (100)	6 (100)	9 (100)	63 (96.9)	7 (100)	70 (97.2)	103 (98.1)
Blood and lymphatic system disorders	2 (33.3)	2 (25.0)	1 (25.0)	3 (50.0)	5 (55.6)	16 (24.6)	1 (14.3)	17 (23.6)	30 (28.6)
Neutropenia	0	0	0	1 (16.7)	2 (22.2)	10 (15.4)	1 (14.3)	11 (15.3)	14 (13.3)
Gastrointestinal disorders	4 (66.7)	8 (100)	4 (100)	6 (100)	8 (88.9)	61 (93.8)	7 (100)	68 (94.4)	98 (93.3)
Abdominal pain	1 (16.7)	2 (25.0)	0	2 (33.3)	1 (11.1)	8 (12.3)	0	8 (11.1)	14 (13.3)
Constipation	0	2 (25.0)	0	1 (16.7)	1 (11.1)	8 (12.3)	2 (28.6)	10 (13.9)	14 (13.3)
Diarrhea	4 (66.7)	6 (75.0)	4 (100)	6 (100)	8 (88.9)	59 (90.8)	6 (85.7)	65 (90.3)	93 (88.6)
Dyspepsia	0	2 (25.0)	0	0	1 (11.1)	10 (15.4)	2 (28.6)	12 (16.7)	15 (14.3)
Nausea	2 (33.3)	4 (50.0)	2 (50.0)	3 (50.0)	3 (33.3)	24 (36.9)	4 (57.1)	28 (38.9)	42 (40.0)
Stomatitis	0	0	0	1 (16.7)	0	12 (18.5)	0	12 (16.7)	13 (12.4)
Vomiting	1 (16.7)	6 (75.0)	2 (50.0)	1 (16.7)	3 (33.3)	19 (29.2)	4 (57.1)	23 (31.9)	36 (34.3)
General disorders and administration site conditions	5 (83.3)	7 (87.5)	3 (75.0)	5 (83.3)	9 (100)	42 (64.6)	3 (42.9)	45 (62.5)	74 (70.5)
Asthenia	1 (16.7)	4 (50.0)	2 (50.0)	2 (33.3)	4 (44.4)	11 (16.9)	0	11 (15.3)	24 (22.9)
Fatigue	1 (16.7)	3 (37.5)	1 (25.0)	1 (16.7)	4 (44.4)	12 (18.5)	1 (14.3)	13 (18.1)	23 (21.9)
Mucosal inflammation	0	3 (37.5)	1 (25.0)	2 (33.3)	0	9 (13.8)	0	9 (12.5)	15 (14.3)
Pyrexia	4 (66.7)	2 (25.0)	1 (25.0)	1 (16.7)	2 (22.2)	5 (7.7)	0	5 (6.9)	15 (14.3)
Infections and infestations	2 (33.3)	2 (25.0)	2 (50.0)	2 (33.3)	6 (66.7)	25 (38.5)	1 (14.3)	26 (36.1)	40 (38.1)
Upper respiratory tract infection	0	0	1 (25.0)	0	2 (22.2)	8 (12.3)	1 (14.3)	9 (12.5)	12 (11.4)
Investigations	3 (100)	1 (14.3)	4 (100)	5 (83.3)	4 (50.0)	28 (43.1)	3 (42.9)	31 (43.1)	48 (48.0)
Alanine aminotransferase increased	2 (66.7)	0	1 (25.0)	1 (16.7)	2 (25.0)	10 (15.4)	2 (28.6)	12 (16.7)	18 (18.0)
Aspartate aminotransferase increased	2 (66.7)	0	1 (25.0)	1 (16.7)	2 (25.0)	9 (13.8)	2 (28.6)	11 (15.3)	17 (17.0)

Table 10. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events Reported in ≥10% of Subjects Overall (Safety Population)

	Part 1					Part 2			
System Organ Class[a] Preferred Term	**Dose Level 1 N160 + C1500 (N = 6)**	**Dose Level 2 N240 + C1500 (N = 8)**	**Dose Level 3 N240 + C2000 (N = 4)**	**Dose Level 4 N200 + C2000 (N = 6)**	**Dose Level 5 N160 + C2000 (N = 9)**	**N + C MTD [No Prior Lap.] (N = 65)**	**N + C MTD [Prior Lap.] (N = 7)**	**N + C MTD Total (N = 72)**	**Total [Part 1 + Part 2] (N = 105)**
Any adverse event	6 (100)	8 (100)	4 (100)	6 (100)	9 (100)	63 (96.9)	7 (100)	70 (97.2)	103 (98.1)
Metabolism and nutrition disorders	0	6 (75.0)	4 (100)	5 (83.3)	2 (22.2)	27 (41.5)	3 (42.9)	30 (41.7)	47 (44.8)
Decreased appetite	0	2 (25.0)	3 (75.0)	4 (66.7)	2 (22.2)	19 (29.2)	2 (28.6)	21 (29.2)	32 (30.5)
Nervous system disorders	1 (16.7)	3 (37.5)	0	2 (33.3)	3 (33.3)	22 (33.8)	4 (57.1)	26 (36.1)	35 (33.3)
Dizziness	1 (16.7)	3 (37.5)	0	0	0	6 (9.2)	1 (14.3)	7 (9.7)	11 (10.5)
Headache	0	0	0	0	2 (22.2)	10 (15.4)	0	10 (13.9)	12 (11.4)
Psychiatric disorders	1 (16.7)	4 (50.0)	1 (25.0)	1 (16.7)	0	11 (16.9)	0	11 (15.3)	18 (17.1)
Insomnia	0	4 (50.0)	0	0	0	9 (13.8)	0	9 (12.5)	13 (12.4)
Respiratory, thoracic and mediastinal disorders	4 (66.7)	1 (12.5)	2 (50.0)	0	3 (33.3)	22 (33.8)	1 (14.3)	23 (31.9)	33 (31.4)
Dyspnea	1 (16.7)	0	0	0	3 (33.3)	8 (12.3)	0	8 (11.1)	12 (11.4)
Skin and subcutaneous tissue disorders	3 (50.0)	3 (37.5)	3 (75.0)	2 (33.3)	4 (44.4)	52 (80.0)	5 (71.4)	57 (79.2)	72 (68.6)
Palmar-plantar erythrodysesthesia syndrome	2 (33.3)	2 (25.0)	3 (75.0)	1 (16.7)	4 (44.4)	40 (61.5)	5 (71.4)	45 (62.5)	57 (54.3)
Rash	0	1 (12.5)	0	1 (16.7)	0	11 (16.9)	2 (28.6)	13 (18.1)	15 (14.3)

Note: Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
C1500 = capecitabine 1500 mg/m^2; C2000 = capecitabine 2000 mg/m^2; N160 = neratinib 160 mg; N200 = neratinib 200 mg; N240 = neratinib 240 mg;
Lap = lapatinib; MTD = maximum tolerated dose; N = neratinib; C = capecitabine
a. Totals for the number of subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different AEs within the higher level category.

Discontinuations due to Adverse Events: A total of 14 subjects (13.3%) withdrew from the study due to an AE. TEAEs reported were breast neoplasm, decrease in weight, wound infection pseudomonas, increase in blood bilirubin, abnormal liver function test, hemorrhagic shock, diarrhea, nausea, vomiting, palmar plantar erythrodysesthesia syndrome, fatigue, ataxia and thrombocytopenia. Breast neoplasm, wound infection pseudomonas and abnormal liver function test were considered not related to the test article; while other reported TEAEs were considered to be related to the test article.

CONCLUSIONS:

- The MTD of neratinib (240 mg) in combination with capecitabine (1500 mg/m^2) was safe and well-tolerated in subjects with advanced solid tumors (Part 1).

- Treatment with neratinib in combination with capecitabine demonstrated encouraging efficacy and acceptable tolerability in subjects with erbB-2 positive metastatic or locally advanced breast cancer (Part 2).

- The efficacy observed in lapatinib-naïve subjects (evaluable population, Part 2 and eligible Part 1 subjects) (ORR, 63.5%) suggests that the combination of neratinib + capecitabine may be beneficial as an early line of treatment for advanced breast cancer.

- Neratinib + capecitabine combination therapy also demonstrated good efficacy as measured by tumor shrinkage (ORR, 57.1%) in a limited number of subjects in the evaluable population who had received prior lapatinib therapy, indicating that it may also be an important option for subjects who are intolerant or resistant to lapatinib.

- The most common treatment-emergent treatment-related AE observed in Part 2 of the study was diarrhea; 5 of 105 subjects (4.8%) discontinued treatment due to diarrhea.

- Based on neratinib multiple dose PK analyses, neratinib PK parameters such as T_{max}, C_{max}, AUC_{τ}, and CL/F were observed to be similar to previously reported multiple dose PK of neratinib administered as a single therapy. Another study concluded that there were no apparent differences in the PK of neratinib and capecitabine between monotherapy and combination therapy. The data suggested that the PK of neratinib when co-administered with capecitabine did not change compared to when it was administered as a single therapy.