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GENERIC DRUG NAME AND COMPOUND NUMBER: Neratinib / PF-05208767

PROTOCOL NO.: 3144A1-2204-WW (B1891015)

PROTOCOL TITLE:

A Phase 1/2 Study of HKI-272 in Combination With Vinorelbine in Subjects With Solid Tumors and Metastatic Breast Cancer

Study Centers:

The study was conducted at 29 centres in Belgium, China, France, Hong Kong, Netherlands, Poland, Spain, Sweden, Taiwan, United Kingdom, and the United States.

Study Initiation Date and Final Completion Date:

29 April 2008 and 25 October 2011 (for efficacy results) and to 27 September 2011 (for safety results). This is an interim study results synopsis.

Phase of Development:

Phase 2

Study Objectives:

Primary Objectives:

- Part 1: To assess the safety, tolerability, and to define the maximum tolerated dose (MTD) of HKI-272 (neratinib) in combination with vinorelbine in subjects with advanced solid tumors.
- Part 2: To estimate the objective response rate (ORR) for subjects with human epidermal growth factor receptor (ErbB) -2-positive breast cancer treated at the MTD of HKI-272 (neratinib) in combination with vinorelbine.

Secondary Objectives:

- Part 1: To obtain preliminary data describing antitumor activity for the combination of HKI-272 (neratinib) with vinorelbine.
- Part 2: To confirm the MTD identified in Part 1 of the study to obtain safety and pharmacokinetic (PK) information, and to assess additional efficacy parameters including clinical benefit rate (ie, CBR = complete response [CR] + partial response

[PR] + stable disease [SD] ≥24 weeks), progression-free survival (PFS) rate, and duration of response to HKI-272 (neratinib) in combination with vinorelbine.

METHODS

Study Design:

This was an open-label, Phase 2 study of ascending multiple oral doses of neratinib in combination with intravenous (IV) vinorelbine in subjects with solid tumors and ErbB-2-positive metastatic breast cancer (MBC). The study was being conducted in 2 parts. In Part 1, 3 to 6 subjects with advanced solid tumors were to be enrolled in each dose group. Adverse events (AEs) and dose-limiting toxicities (DLTs) were assessed from the first dose of the study medication through Day 21. Subjects enrolled in Part 1 and withdrawn from the study for a reason other than a DLT could be replaced. Intrasubject dose escalation was not permitted.

In Part 2, up to an additional 80 subjects with metastatic ErbB-2-positive breast cancer were to be enrolled at the dose determined to be the MTD. Two (2) subject groups were to be analyzed separately in Part 2:

- Arm A: Subjects with no prior lapatinib exposure (approximately 60 subjects); and
- Arm B: Subjects with prior lapatinib exposure (maximum of 20 subjects).

Number of Subjects (Planned and Analyzed):

It was planned to enroll 12 to 15 subjects during Part 1 (dose escalation) and 80 subjects in Part 2 (approximately 60 subjects without prior exposure to lapatinib and a maximum of 20 subjects previously exposed to lapatinib were planned to be enrolled). A total of 92 subjects were enrolled, 91 subjects were treated and analyzed.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Subjects enrolled into Part 1 of had confirmed pathologic diagnosis of a solid tumor not curable with available therapies for which neratinib plus vinorelbine was a reasonable treatment option. Subjects enrolled into Part 2 had a confirmed pathologic diagnosis of ErbB-2-positive breast cancer (current stage 4) in female subjects for which vinorelbine plus neratinib was a reasonable treatment option. Subjects in Part 2 also had ≤1 prior antineoplasic chemotherapy treatment regimen for metastatic disease or relapsed under adjuvant treatment, and had ≤1 prior treatment with a trastuzumab-containing regimen for ≤6 weeks for metastatic disease or relapsed under adjuvant treatment. Subjects in Part 2 also had ErbB-2 gene amplified tumor(s) as detected by fluorescence in situ hybridization or chromogenic in situ hybridization. All subjects had ≥1 measurable lesion as defined by Response Evaluation Criteria in Solid Tumors guidelines and Eastern Cooperative Oncology Group status of 0 to 2.

Main Exclusion Criteria: Subjects were excluded from the study if they had known >2 prior antineoplastic treatment regimens (excluding hormonotherapy) for metastatic disease, subjects who relapsed under adjuvant treatment were not to receive >1 line of chemotherapy

for metastatic disease (Part 2 only), subjects consumed prior treatment with vinorelbine for metastatic setting, or prior treatment with any ErbB-2 targeted agents except trastuzumab (Part 2 only) and up to 20 subjects with ErbB-2-overexpressing MBC who had been previously exposed to lapatinib but were not refractory to lapatinib may be enrolled in Part 2, subjects had prior treatment with anthracyclines with a cumulative dose of doxorubicin of >400 mg/m^2, or of epirubicin dose of >800 mg/m^2, or the equivalent dose for other anthracyclines or derivatives (Part 2 only).

Study Treatment:

Part 1: Three (3) to 6 subjects with advanced solid tumors were to be enrolled in each of the 2 neratinib and vinorelbine combination dose groups (ie, 160 mg and 25 mg/m^2, or 240 mg and 25 mg/m^2) to define the MTD.

Four (4) neratinib 40 mg tablets, or a 240 mg tablet, were to be administered daily for Cycles 1 through 12 (and beyond, if appropriate) beginning on Day 1 through Day 15 (ie, 1 cycle) in Part 1. Neratinib was to be taken with food, preferably in the morning. IV infusions of vinorelbine (25 mg/m^2) occurred on Days 1 and 8 (±2 days) for Cycles 1 through 12 (and beyond, if appropriate) in Part 1.

Part 2: After establishing the MTD of neratinib and vinorelbine up to 80 subjects with metastatic ErbB-2-positive breast cancer are being treated with the MTD combination treatment (ie, 240 mg neratinib tablet and 25 mg/m^2 vinorelbine infusion). In Part 2, neratinib was not administered on Day 1 of Cycle 1 but on Day 2 of Cycle 1. IV infusions of vinorelbine (25 mg/m^2) occurred on Days 1 and 8 (±2 days) for Cycles 1 through 12 (and beyond, if appropriate) in Part 2, as it occurred in Part 1.

PK Samples in Part 2: The 1 day delay in neratinib administration allowed for PK samples of vinorelbine to be collected over a 24-hour period on Day 1 Cycle 1 in Part 2. PK sample collection on Day 8 of Cycle 2 allowed for PK samples of the combination treatment to be collected over a 24-hour period.

Neratinib Montherapy: Subjects who discontinued vinorelbine therapy (after ≥2 doses) because of toxicity may have continued on neratinib as monotherapy, after consultation with the Sponsor, and if neratinib treatment was well-tolerated and there was no evidence of disease progression.

Efficacy, Pharmacokinetics and Pharmacogenomic Endpoints:

The primary efficacy endpoint was the ORR determined for the MBC subjects in Part 2 of the study. It was assessed for those subjects with no prior lapatinib exposure (ie, approximately 60 subjects) among the evaluable population. Secondary efficacy endpoints included clinical benefit (CR + PR + SD ≥24 weeks), PFS rate, and duration of response of neratinib in combination with vinorelbine. Secondary efficacy parameters were assessed during Part 2 for subjects with no prior lapatinib exposure.

Pharmacokinetic Evaluations: Plasma concentration of neratinib/its metabolites and vinorelbine were evaluated to assess whether liver function test (LFT) elevations were

associated with study drug plasma concentrations and to determine if any drug-drug interactions were present.

Pharmacogenomic Evaluations: Since overexpression of the ErbB-2 gene has been correlated with a worse overall prognosis, a more aggressive tumor phenotype, and faster relapse times in subjects with MBC, a confirmed pathologic diagnosis of ErbB-2-positive status was required for entry into the study. Subjects who had a negative ErbB-2 status at Screening were considered screen failures.

Safety Evaluations:

Safety evaluations included collection of treatment-emergent adverse events (TEAEs), physical examinations, electrocardiograms, vital signs measurements, Eastern Cooperative Oncology Group performance status, left ventricular ejection fractions, and clinical laboratory measurements (ie, hematology, LFT, blood chemistry, coagulation, and urinalysis parameters). Pregnancy testing also occurred multiple times during the study for women of childbearing potential.

AEs were reported by type, incidence, severity, timing, seriousness, and relatedness to treatment.

Statistical Methods:

There were 2 efficacy populations: The modified intent-to-treat (mITT) and the evaluable populations. The mITT population consisted of all subjects enrolled in the study who received at least 1 dose of neratinib or vinorelbine. The evaluable population consisted of all subjects who met the eligibility criteria, received at least 2 weeks of neratinib and at least 2 doses of vinorelbine, and underwent at least 1 follow-up tumor assessment at approximately Cycle 2 (ie, ~6 weeks after starting study medication).

Analysis of the ORR used the efficacy evaluable population for those subjects enrolled in Part 2 with no prior lapatinib exposure. The point estimate of the ORR and corresponding 95% exact confidence interval (CI) was computed. Tumor assessments of target and non-target lesions were used to determine the clinical activity of the MTD cohort. Tumor responses were determined using 2 methods: the site Investigator's tumor assessment data and an independent radiologist's tumor assessments provided by a central vendor.

All analyses of secondary efficacy variables used the mITT population for subjects enrolled in Part 2 with no prior lapatinib exposure. The CBR (CR + PR + SD ≥24 weeks) was estimated in the same fashion as ORR (eg, point estimate and corresponding 95% CI). The Kaplan-Meier method was used to determine the duration of response, and the PFS rate.

RESULTS

Subjects Disposition and Demography:

A total of 92 subjects were enrolled in the study and all but 1 subject were treated (91/92, 98.9%). The majority of subjects were evaluable for efficacy (78/92, 84.8%). Subject disposition is summarized in Table 1 and discontinuations from the study are summarized in Table 2.

Table 1. Neratinib and Vinorelbine Subject Disposition – mITT Population

No. (%) of Subjects	Treatment					
	Part 1 (Advanced Tumors)		Part 2 (Metastatic ErbB-2+ Breast Cancer)			
	Nera (160 mg) + Vin (N=6)	Nera (240 mg) + Vin (N=6)	Arm A Nera (MTD) + Vin (N=64)	Arm B Nera (MTD) + Vin (N=16)	Total Nera (MTD) + Vin (N=80)	Total (N=92)
Enrolled (mITT)	6	6	64	16	80	92
Evaluable for safety/mITT[a,b]	6 (100)	6 (100)	64 (100)	15 (93.8)	79 (98.8)	91 (98.9)
Evaluable for efficacy	5 (83.3)	5 (83.3)	56 (87.5)	12 (75.0)	68 (85.0)	78 (84.8)
Nera + vin Rx, then continued on-study Nera + vin Rx [c]	0	0	8 (12.5)	2 (13.3)	10 (12.7)	10 (11.0)
Nera + vin Rx, then continued nera Rx with d/c vin Rx [c,d]	0	0	11 (17.2)	1 (6.7)	12 (15.2)	12 (13.2)
Nera + vin Rx, then study d/c[c]	6 (100)	6 (100)	56 (87.5)	13 (86.7)	69 (87.3)	81 (89.0)
Nera Rx duration prior to study d/c[c]						
<6 months	5 (83.3)	5 (83.3)	22 (34.4)	8 (53.3)	30 (38.0)	40 (44.0)
≥6 to <12 months	1 (16.7)	1 (16.7)	21 (32.8)	4 (26.7)	25 (31.6)	27 (29.7)
≥12 to <24 months	0	0	12 (18.8)	1 (6.7)	13 (16.5)	13 (14.3)
≥24 months	0	0	1 (1.6)	0	1 (1.3)	1 (1.1)

Arm A=no prior lapatinib exposure.
Arm B=prior lapatinib exposure.
d/c=discontinuation; mITT=modified intent-to-treat; ErbB-2=human epidermal growth factor receptor 2; Nera=neratinib; MTD=maximum tolerated dose; N=number of total subjects in dose cohort; No.=number; Rx=treatment; Vin=vinorelbine 25 mg/m^2.

a. Percentages based on the mITT population.
b. Safety population included all subjects who received ≥1 dose of neratinib or vinorelbine.
c. Percentages based on the safety population.
d. Subjects discontinuing vinorelbine after ≥2 doses due to toxicity and continuing on neratinib monotherapy.

Table 2. Discontinuations From Study (Safety Population)

No. (%) of Subjects	Treatment					
	Part 1 (Advanced Tumors)		Part 2 (Metastatic ErbB-2+ Breast Cancer)			
	Nera (160 mg) + Vin (N=6)	Nera (240 mg) + Vin (N=6)	Arm A Nera (MTD) + Vin (N=64)	Arm B Nera (MTD) + Vin (N=15)	Total Nera (MTD) + Vin (N=79)	Total (N=91)
Discontinued[a]	6 (100)	6 (100)	56 (87.5)	13 (86.7)	69 (87.3)	81 (89.0)
Disease progression	4 (66.7)	6 (100)	43 (67.2)	10 (66.7)	53 (67.1)	63 (69.2)
Adverse event	1 (16.7)	0	4 (6.3)	2 (13.3)	6 (7.6)	7 (7.7)
Subject request	1 (16.7)	0	2 (3.1)	0	2 (2.5)	3 (3.3)
Investigator request	0	0	2 (3.1)	0	2 (2.5)	2 (2.2)
Other	0	0	2 (3.1)	0	2 (2.5)	2 (2.2)
Protocol violation	0	0	1 (1.6)	1 (6.7)	2 (2.5)	2 (2.2)
Failed to return	0	0	1 (1.6)	0	1 (1.3)	1 (1.1)
Symptomatic deterioration	0	0	1 (1.6)	0	1 (1.3)	1 (1.1)

Arm A=no prior lapatinib exposure.
Arm B=prior lapatinib exposure.
ErbB-2=human epidermal growth factor receptor 2; Nera=neratinib; MTD=maximum tolerated dose; N=number of total subjects in dose cohort; No.=number; Vin=vinorelbine 25 mg/m^2.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.

The demographic and baseline characteristics of subjects are summarized in Table 3.

Table 3. Demographic and Baseline Characteristics (Safety Population)

No. (%) of Subjects	Treatment					
	Part 1 (Advanced Tumors)		Part 2 (Metastatic ErbB-2+ Breast Cancer)			
	Nera (160 mg) + Vin (N=6)	Nera (240 mg) + Vin (N=6)	Arm A Nera (MTD) + Vin (N=64)	Arm B Nera (MTD) + Vin (N=15)	Nera (MTD) + Vin (N=79)	Total (N=91)
Sex, n (%)						
Female	6 (100)	4 (66.7)	64 (100)	15 (100)	79 (100)	89 (97.8)
Male	0	2 (33.3)	0	0	0	2 (2.2)
Race, n (%)						
Asian	0	0	18 (28.1)	6 (40.0)	24 (30.4)	24 (26.4)
Black or African American	0	1 (16.7)	1 (1.6)	0	1 (1.3)	2 (2.2)
Other	2 (33.3)	0	2 (3.1)	0	2 (2.5)	4 (4.4)
White	4 (66.7)	5 (83.3)	43 (67.2)	9 (60.0)	52 (65.8)	61 (67.0)
Age (years)						
Mean	53.2	54.3	51.1	52.1	51.3	51.6
(SD)	(14.8)	(13.9)	(10.6)	(9.8)	(10.4)	(10.8)

Arm A=no prior lapatinib exposure.
Arm B=prior lapatinib exposure.
ErbB-2=human epidermal growth factor receptor 2; Nera=neratinib; MTD=maximum tolerated dose; n=number of subjects meeting prespecified criteria; N=number of total subjects in dose cohort; No.=number; SD=standard deviation; Vin=vinorelbine 25 mg/m^2.

Efficacy, Pharmacokinetics and Pharmacogenomic Results:

Primary Efficacy Results: For the evaluable population with no prior lapatinib exposure (MTD-Part 2, Arm A), an objective response was observed in 23 subjects (41.1%) and 33 subjects (58.9%), according to independent and Investigator assessments, respectively (Table 4). For the evaluable population with prior lapatinib exposure (MTD-Part 2, Arm B), an objective response was observed in 1 subject (8.3%) and 6 subjects (50.0%), according to independent and Investigator assessments, respectively (Table 5).

Table 4. Objective Response Rate - Part 2, Arm A (Evaluable Population)

ORR Assessments	Arm A Nera (MTD) + Vin (N=56)
Independent assessment[a]	
Number of subjects with CR or PR, n (%)	23 (41.1)
80% CI for objective response rate	(32.1, 50.5)
95% CI for objective response rate	(28.1, 55.0)
Investigator assessment[b]	
Number of subjects with CR or PR, n (%)	33 (58.9)
80% CI for objective response rate	(49.5, 67.9)
95% CI for objective response rate	(45.0, 71.9)

Arm A=no prior lapatinib exposure.
CI=confidence interval; CR=complete response; MTD=maximum tolerated dose; n=number of subjects meeting prespecified criteria; N=number of total subjects in dose cohort; Nera=neratinib; ORR=objective response rate; PR=partial response; Vin=vinorelbine 25 mg/m^2.
a. Disease assessment was based on radiographic review by independent radiologists.
b. Disease assessment was based on review of radiographic and clinical data by the Investigator.

Table 5. Objective Response Rate - Part 2 (Evaluable Population)

	MTD - Lapatinib (N=12)
Independent assessment[a]	
Number of subjects with CR or PR, n (%)	1 (8.3)
80% CI for objective response rate	(0.9, 28.7)
95% CI for objective response rate	(0.2, 38.5)
Investigator assessment[b]	
Number of subjects with CR or PR, n (%)	6 (50.0)
80% CI for objective response rate	(28.8, 71.2)
95% CI for objective response rate	(21.1, 78.9)

CI=confidence interval; CR=complete response; n=number of subjects meeting prespecified criteria; PR=partial response.
a. Disease assessment was based on radiographic review by independent radiologists.
b. Disease assessment was based on review of radiographic and clinical data by the Investigator.

Secondary Efficacy Results:

Clinical Benefit: For the mITT population with no prior lapatinib exposure (MTD - Part 2, Arm A), clinical benefit was observed in 41 subjects (64.1%) and 43 subjects (67.2%), according to independent and Investigator assessments, respectively (Table 6).

Table 6. Clinical Benefit Rate - Part 2, Arm A (mITT Population)

CBR Assessments	Arm A Nera (MTD) + Vin (N=64)
Independent assessment[a]	
Number of subjects with CR, PR or SD ≥24 weeks, n (%)	41 (64.1)
80% CI for clinical benefit rate	(55.3, 72.1)
95% CI for clinical benefit rate	(51.1, 75.7)
Investigator assessment[b]	
Number of subjects with CR, PR or SD ≥24 weeks, n (%)	43 (67.2)
80% CI for clinical benefit rate	(58.6, 75.0)
95% CI for clinical benefit rate	(54.3, 78.4)

Arm A=no prior lapatinib exposure.
CBR=clinical benefit rate; CI=confidence interval; CR=complete response; mITT=modified intent-totreat; MTD=maximum tolerated dose; n=number of subjects meeting prespecified criteria; N=number of total subjects in dose cohort; Nera=neratinib; PR=partial response; SD=stable disease; Vin=vinorelbine 25 mg/m^2.
a. Disease assessment was based on radiographic review by independent radiologists
b. Disease assessment was based on review of radiographic and clinical data by the Investigator.

Progression-Free Survival: PFS was summarized using the Kaplan-Meier method for the mITT population. For the mITT with no prior lapatinib exposure (MTD - Part 2, Arm A), median progression free survival intervals (median along with 95% CI) were 47.7 (30.9, 65.1) weeks and 43.9 (31.3, 54.1) weeks, according to independent and Investigator assessments respectively (Table 7).

Table 7. Progression-Free Survival - Part 2, Arm A (mITT Population)

PFS Assessments	Arm A Nera (MTD) + Vin (N=64)
Independent assessment[a]	
No. of subjects with PD or death, n (%)	36 (56.3)
No. of censored subjects, n (%)	28 (43.8)
Median PFS in weeks (80% CI)[b]	47.7 (42.0, 56.1)
Median PFS in weeks (95% CI)[b]	47.7 (30.9, 65.1)
Investigator Assessment[c]	
No. of subjects with PD or death, n (%)	44 (68.8)
No. of censored subjects, n (%)	20 (31.3)
Median PFS in weeks (80% CI)[b]	43.9 (35.1, 48.0)
Median PFS in weeks (95% CI)[b]	43.9 (31.3, 54.1)

Arm A=no prior lapatinib exposure.
PFS rate at 12 weeks was the proportion of subjects alive and progression-free at 12 weeks. Likewise for the other rate at the other weeks.
CI=confidence interval; mITT=modified intent-to-treat; MTD=maximum tolerated dose; n=number of subjects meeting prespecified criteria; N=number of total subjects in dose cohort; Nera=neratinib; PD=progressive disease; PFS=progression-free survival; Vin=vinorelbine 25 mg/m^2.
a. Disease assessment was based on radiographic review by independent radiologists.
b. The Kaplan-Meier method was used to estimate the PFS median time and associated 80% and 95% CI.
c. Disease assessment was based on review of radiographic and clinical data by the Investigator.

Duration of Response: For the mITT population with no prior lapatinib exposure (MTD-Part 2), the median duration of response intervals (median along with 95%

CI) were 52.7 (38.4, not estimable) weeks and 48.9 (36.9, 66.1) weeks, according to independent and Investigator assessments, respectively (Table 8).

Table 8. Duration of Response - Part 2, Arm A (mITT Population)

Duration of Response Assessments	Arm A Nera (MTD) + Vin (N =64)
Independent assessment[a]	
Number of subjects with CR or PR, n (%)	23 (35.9)
Median duration in weeks (80% CI)[b]	52.7 (48.6, 96.1)
Median duration in weeks (95% CI)[b]	52.7 (38.4, NE)
Range (min, max)	(11.6, 96.1)
Number of subjects with progressive disease, n (%)	12 (52.2)
Number of censored subjects, n (%)	11 (47.8)
Investigator assessment[c]	
Number of subjects with CR or PR, n (%)	34 (53.1)
Median duration in weeks (80% CI)[b]	48.9 (38.0, 60.3)
Median duration in weeks (95% CI)[b]	48.9 (36.9, 66.1)
Range (min, max)	(13.1, 102.1)
Number of subjects with progressive disease, n (%)	24 (70.6)
Number of censored subjects, n (%)	10 (29.4)

Arm A=no prior lapatinib exposure.
CI=confidence interval; CR=complete response; max=maximum; min=minimum; mITT=modified intent-to-treat; MTD=maximum tolerated dose; n=number of subjects meeting prespecified criteria; N=number of total subjects in dose cohort; NE=not estimable; Nera=neratinib; PR=partial response; Vin=vinorelbine 25 mg/m^2.
a. Disease assessment was based on radiographic review by independent radiologists.
b. The Kaplan-Meier method was used to estimate the median duration and associated CI.
c. Disease assessment was based on review of radiographic and clinical data by the Investigator.

Pharmacokinetic Results: The preliminary evaluation of neratinib PK parameters indicated neratinib exposures (ie, maximum observed plasma concentration and area under the plasma concentration-time curve from 0 to 24 hours) were similar to those observed for neratinib monotherapy, suggesting no interaction between neratinib and vinorelbine (Table 9).

Table 9. Summary of Pharmacokinetic Parameters

Parameter, Mean (%CV)	Neratinib		Vinorelbine	
	Nera (240 mg) + Vin on Day 8 (n=46)	Nera (240 mg) Monotherapy on Day 21 (n=3)	Nera (240 mg) + Vin on Day 8 (n=65)	Vin (25 mg/m^2) Monotherapy on Day 1 (n=72)
C_{max}, ng/mL	81.8 (57)	73.5 (37)	535 (141)	513 (158)
$AUC_{(0-24)}$, ng•h/mL	1151 (49)	939 (34)	437 (56)	395 (62)

$AUC_{(0-24)}$=area under the concentration-time curve from time 0 to time 24 hours; C_{max}=maximum observed plasma concentration; CV=coefficient of variation; Nera=neratinib; n=number of subjects meeting prespecified criteria; Vin=vinorelbine 25 mg/m^2.

Pharmacogenomic Results: Data not available.

Safety Results:

Serious Adverse Events: The most frequent treatment-emergent serious adverse events (SAEs) overall were diarrhea (4 subjects, 4.4%), vomiting (3 subjects, 3.3%), and metastases to the central nervous system (CNS) (3 subjects, 3.3%). The most frequent treatment-related SAEs were diarrhea (4 subjects, 4.4%), vomiting and dehydration (each occurring in 2 subjects, 2.2%). Overall, treatment-related SAEs by dose cohort (all cycles) in >1 subject are summarized in Table 10. Overall treatment-emergent SAEs by dose cohort and frequency of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 (all causalities, all cycles) in >2% of total subjects are summarized in Table 11. The most frequent Grade 3 treatment-emergent SAEs overall were diarrhea (3 subjects, 3.3%), fatigue (2 subjects, 2.2%), and metastases to the CNS (2 subjects, 2.2%). Overall, treatment-related SAEs by dose cohort and frequency of CTCAE Grade ≥3 (all cycles) in >2% of total subjects are also summarized in Table 11. The only Grade 3 treatment-related SAE was diarrhea (3 subjects, 3.3%).

Table 10. Treatment-Emergent Serious Adverse Events by Dose Cohort in >1 Subject (All Causalities, Treatment-Related, All Cycles)

No. of Subjects (%) MedDRA Preferred Term	Treatment					
	Part 1 (Advanced Tumors)		Part 2 (Metastatic ErbB-2+ Breast Cancer)			
	Nera (160 mg) + Vin (N=6)	Nera (240 mg) + Vin (N=6)	Arm A Nera (MTD) + Vin (N=64	Arm B Nera (MTD) + Vin (N=15)	Total Nera (MTD) + Vin (N=79)	Total (N=91)
Treatment-Emergent SAEs due to All Causalities						
Any adverse vent	3 (50.0)	3 (50.0)	21 (32.8)	4 (26.7)	25 (31.6)	31 (34.1)
Diarrhoea	0	0	4 (6.3)	0	4 (5.1)	4 (4.4)
Vomiting	0	0	3 (4.7)	0	3 (3.8)	3 (3.3)
Metastases to CNS	0	0	2 (3.1)	1 (6.7)	3 (3.8)	3 (3.3)
Fatigue	0	1 (16.7)	1 (1.6)	0	1 (1.3)	2 (2.2)
Dehydration	0	0	2 (3.1)	0	2 (2.5)	2 (2.2)
Grand mal convulsion	1 (16.7)	0	1 (1.6)	0	1 (1.3)	2 (2.2)
Treatment-Related SAEs						
Any adverse event	1 (16.7)	1 (16.7)	8 (12.5)	1 (6.7)	9 (11.4)	11 (12.1)
Diarrhoea	0	0	4 (6.3)	0	4 (5.1)	4 (4.4)
Vomiting	0	0	2 (3.1)	0	2 (2.5)	2 (2.2)
Dehydration	0	0	2 (3.1)	0	2 (2.5)	2 (2.2)

Classifications of adverse events are based on the MedDRA.
Arm A=no prior lapatinib exposure.
Arm B=prior lapatinib exposure.
CNS=central nervous system; ErbB-2=human epidermal growth factor receptor-2; MedDRA=Medical Dictionary for Regulatory Activities; MTD=maximum tolerated dose; N=number of total subjects in dose cohort; Nera=neratinib; No.=number; SAE=serious adverse event; Vin=vinorelbine 25 mg/m^2.

Table 11. Treatment-Emergent Serious Adverse Events by Dose Cohort and Frequency of CTCAE Grade ≥3 AEs (All Causalities and Treatment-Related, All Cycles, >2% of Total Subjects)

No. of Subjects (%) MedDRA Preferred Term	Treatment					
	Part 1 (Advanced Tumors)		Part 2 (Metastatic ErbB-2+ Breast Cancer)			
	Nera (160 mg) + Vin (N=6)	Nera (240 mg) + Vin (N=6)	Arm A Nera (MTD) + Vin (N=64	Arm B Nera (MTD) + Vin (N=15)	Total Nera (MTD) + Vin (N=79)	Total (N=91)
All Causalities, All Cycles						
Any adverse event	2 (33.3)	3 (50.0)	16 (25.0)	2 (13.3)	18 (22.8)	23 (25.3)
Diarrhoea	0	0	3 (4.7)	0	3 (3.8)	3 (3.3)
Fatigue	0	1 (16.7)	1 (1.6)	0	1 (1.3)	2 (2.2)
Metastases to CNS	0	0	2 (3.1)	0	2 (2.5)	2 (2.2)
Treatment-Related, All Cycles						
Any Adverse Event	1 (16.7)	1 (16.7)	8 (12.5)	2 (13.3)	10 (12.7)	12 (13.2)
Diarrhoea	0	0	3 (4.7)	0	3 (3.8)	3 (3.3)

Classifications of adverse events are based on the MedDRA.
Arm A=no prior lapatinib exposure.
Arm B=prior lapatinib exposure.
AE=adverse event; CNS=central nervous system; CTCAE=common terminology criteria for adverse events; ErbB-2=human epidermal growth factor receptor 2; MedDRA=Medical Dictionary for Regulatory Activities; MTD=maximum tolerated dose; N=number of total subjects in dose cohort; Nera=neratinib; No.=number; Vin=vinorelbine 25 mg/m^2.

Adverse Events: Overall, TEAEs by dose cohort (all causalities, all cycles) in >15% of total subjects are summarized in Table 12. The most frequent TEAEs were diarrhea (88 subjects, 96.7%), neutropenia (50 subjects, 54.9%), nausea (47 subjects, 51.6%), and vomiting (37 subjects, 40.7%). The most frequent treatment-related AEs were diarrhea (87 subjects, 95.6%), neutropenia (49 subjects, 53.8%), nausea (45 subjects, 49.5%), and vomiting (35 subjects, 38.5%). Although the majority of subjects had treatment-emergent diarrhea events (88/91, 96.7%), no subject experienced a Grade 4 diarrhea AE. The most frequent treatment-emergent Grade 3 AEs were neutropenia (43 subjects, 47.3%), diarrhea (26 subjects, 28.6%), and leukopenia (15 subjects, 16.5%). The most frequent treatment-related Grade 3 AEs were neutropenia (42 subjects, 46.2%), diarrhea (25 subjects, 27.5%), and leukopenia (15 subjects, 16.5%).

Table 12. Treatment-Emergent Adverse Events by Dose Cohort (All Causalities, All Cycles, >15% of Total Subjects)

No. of Subjects (%) MedDRA Preferred Term	Treatment					
	Part 1 (Advanced Tumors)		Part 2 (Metastatic ErbB-2+ Breast Cancer)			
	Nera (160 mg) + Vin (N=6)	Nera (240 mg) + Vin (N=6)	Arm A Nera (MTD) + Vin (N=64	Arm B Nera (MTD) + Vin (N=15)	Total Nera (MTD) + Vin (N=79)	Total (N=91)
Any adverse event	6 (100)	6 (100)	64 (100)	15 (100)	79 (100)	91 (100)
Diarrhoea	6 (100)	6 (100)	61 (95.3)	15 (100)	76 (96.2)	88 (96.7)
Neutropenia	3 (50.0)	2 (33.3)	36 (56.3)	9 (60.0)	45 (57.0)	50 (54.9)
Nausea	4 (66.7)	3 (50.0)	33 (51.6)	7 (46.7)	40 (50.6)	47 (51.6)
Vomiting	2 (33.3)	1 (16.7)	24 (37.5)	10 (66.7)	34 (43.0)	37 (40.7)
Fatigue	3 (50.0)	3 (50.0)	24 (37.5)	3 (20.0)	27 (34.2)	33 (36.3)
Decreased appetite	1 (16.7)	2 (33.3)	20 (31.3)	7 (46.7)	27 (34.2)	30 (33.0)
Abdominal pain	1 (16.7)	2 (33.3)	22 (34.4)	4 (26.7)	26 (32.9)	29 (31.9)
Headache	2 (33.3)	2 (33.3)	18 (28.1)	2 (13.3)	20 (25.3)	24 (26.4)
Leukopenia	0	0	21 (32.8)	2 (13.3)	23 (29.1)	23 (25.3)
Anaemia	2 (33.3)	2 (33.3)	15 (23.4)	3 (20.0)	18 (22.8)	22 (24.2)
Asthenia	0	2 (33.3)	16 (25.0)	4 (26.7)	20 (25.3)	22 (24.2)
Pyrexia	0	1 (16.7)	18 (28.1)	2 (13.3)	20 (25.3)	21 (23.1)
Constipation	2 (33.3)	5 (83.3)	10 (15.6)	3 (20.0)	13 (16.5)	20 (22.0)
Cough	0	1 (16.7)	14 (21.9)	3 (20.0)	17 (21.5)	18 (19.8)
Dizziness	1 (16.7)	0	11 (17.2)	3 (20.0)	14 (17.7)	15 (16.5)
Myalgia	0	2 (33.3)	10 (15.6)	3 (20.0)	13 (16.5)	15 (16.5)
Alopecia	1 (16.7)	0	12 (18.8)	1 (6.7)	13 (16.5)	14 (15.4)
Muscle spasms	1 (16.7)	1 (16.7)	12 (18.8)	0	12 (15.2)	14 (15.4)
Arthralgia	4 (66.7)	0	8 (12.5)	2 (13.3)	10 (12.7)	14 (15.4)
ALT increased	0	0	11 (17.2)	3 (20.0)	14 (17.7)	14 (15.4)
Mucosal inflammation	1 (16.7)	0	12 (18.8)	1 (6.7)	13 (16.5)	14 (15.4)

Classifications of adverse events are based on the MedDRA.
Arm A=no prior lapatinib exposure.
Arm B=prior lapatinib exposure.
ALT=alanine aminotransferase; ErbB-2=human epidermal growth factor receptor-2; MedDRA=Medical Dictionary for Regulatory Activities; MTD=maximum tolerated dose; N=number of total subjects in dose cohort; Nera=neratinib; No.=number; Vin=vinorelbine 25 mg/m^2.

Overall, treatment-related AEs by dose cohort (all cycles) in >15% of total subjects are summarized in Table 13. The most frequent treatment-related AEs were diarrhea (87 subjects, 95.6%), neutropenia (49 subjects, 53.8%), nausea (45 subjects, 49.5%), and vomiting (35 subjects, 38.5%). Other frequent treatment-related AEs included fatigue (29 subjects, 31.9%), decreased appetite (27 subjects, 29.7%), leukopenia (23 subjects, 25.3%), and abdominal pain (22 subjects, 24.2%).

Table 13. Treatment-Emergent Adverse Events by Dose Cohort (Treatment-Related, All Cycles, >15% of Total Subjects)

No. of Subjects (%) MedDRA Preferred Term	Treatment					
	Part 1 (Advanced Tumors)		Part 2 (Metastatic ErbB-2+ Breast Cancer)			
	Nera (160 mg) + Vin (N=6)	Nera (240 mg) + Vin (N=6)	Arm A Nera (MTD) + Vin (N=64	Arm B Nera (MTD) + Vin (N=15)	Total Nera (MTD) + Vin (N=79)	Total (N=91)
Any adverse event	6 (100)	6 (100)	64 (100)	15 (100)	79 (100)	91 (100)
Diarrhoea	6 (100)	5 (83.3)	61 (95.3)	15 (100)	76 (96.2)	87 (95.6)
Neutropenia	3 (50.0)	2 (33.3)	35 (54.7)	9 (60.0)	44 (55.7)	49 (53.8)
Nausea	4 (66.7)	3 (50.0)	31 (48.4)	7 (46.7)	38 (48.1)	45 (49.5)
Vomiting	2 (33.3)	1 (16.7)	23 (35.9)	9 (60.0)	32 (40.5)	35 (38.5)
Fatigue	3 (50.0)	3 (50.0)	20 (31.3)	3 (20.0)	23 (29.1)	29 (31.9)
Decreased appetite	1 (16.7)	2 (33.3)	19 (29.7)	5 (33.3)	24 (30.4)	27 (29.7)
Leukopenia	0	0	21 (32.8)	2 (13.3)	23 (29.1)	23 (25.3)
Abdominal pain	1 (16.7)	0	18 (28.1)	3 (20.0)	21 (26.6)	22 (24.2)
Asthenia	0	2 (33.3)	12 (18.8)	3 (20.0)	15 (19.0)	17 (18.7)
Headache	1 (16.7)	2 (33.3)	10 (15.6)	1 (6.7)	11 (13.9)	14 (15.4)
ALT increased	0	0	11 (17.2)	3 (20.0)	14 (17.7)	14 (15.4)
Pyrexia	0	1 (16.7)	11 (17.2)	2 (13.3)	13 (16.5)	14 (15.4)

Classifications of adverse events are based on the MedDRA, version 14.0.
Arm A=no prior lapatinib exposure.
Arm B=prior lapatinib exposure.
ALT=alanine aminotransferase; ErbB-2=human epidermal growth factor receptor-2; MedDRA=Medical Dictionary for Regulatory Activities; MTD=maximum tolerated dose; N=number of total subjects in dose cohort; Nera=neratinib; No.=number; Vin=vinorelbine 25 mg/m^2.

Deaths: Four (4) subjects (4.4%) died during the study, with 3 subjects (3.3%) dying within 28 days of the last dose. All 4 subjects died as a result of disease progression (Table 14).

Table 14. Summary of Deaths

Parameter, n (%)	Treatment					
	Part 1 (Advanced Tumors)		Part 2 (Metastatic ErbB-2+ Breast Cancer)			
	Nera (160 mg) + Vin (N=6)	Nera (240 mg) + Vin (N=6)	Arm A Nera (MTD) + Vin (N=64	Arm B Nera (MTD) + Vin (N=15)	Total Nera (MTD) + Vin (N=79)	Total (N=91)
Subject who died[a]						
Yes	0	2 (33.3)	1 (1.6)	1 (1.6)	2 (2.5)	4 (4.4)
No	6 (100)	4 (66.7)	63 (98.4)	14 (93.3)	77 (97.5)	87 (95.6)
Number of subjects who died within 28 days of last dose						
Yes	0	2 (33.3)	0	1 (1.6)	1 (1.3)	3 (3.3)
No[b]	0	0	1 (1.6)	0	1 (1.3)	1 (1.1)
Reason for death[c]						
Disease progression	0	2 (33.3)	0	1 (1.6)	1 (1.3)	3 (3.3)

Arm A=no prior lapatinib exposure.
Arm B=prior lapatinib exposure.
Classifications of adverse events were based on the MedDRA.
ErbB-2=human epidermal growth factor receptor-2; MTD=maximum tolerated dose; N=number of total subjects in dose cohort; Nera=neratinib; n=number of subjects meeting prespecified criteria; Vin=vinorelbine 25 mg/m^2.

a. After disease progression, subjects were no longer followed for survival.
b. Subject who died >28 days after the last dose also died due to disease progression.
c. Reasons for death are only displayed for subjects who died within 28 days after last dose.

Discontinuation due to Adverse Events: A total of 19 subjects (20.9%) discontinued study treatment due to an AE. The most frequent AEs leading to discontinuations in >2% of total subjects were diarrhea, fatigue, and peripheral sensory neuropathy (each occurring in 3 subjects, 3.3%) (Table 15).

Table 15. Discontinuations Due to Adverse Events in >2% of Total Subjects

No. of Subjects (%) MedDRA Preferred Term	Treatment					
	Part 1 (Advanced Tumors)		Part 2 (Metastatic ErbB-2+ Breast Cancer)			
	Nera (160 mg) + Vin (N=6)	Nera (240 mg) + Vin (N=6)	Arm A Nera (MTD) + Vin (N=64	Arm B Nera (MTD) + Vin (N=15)	Total Nera (MTD) + Vin (N=79)	Total (N=91)
Discontinuations due to AEs						
Any adverse event	1 (16.7)	0	15 (23.4)	3 (20.0)	18 (22.8)	19 (20.9)
Diarrhoea	0	0	3 (4.7)	0	3 (3.8)	3 (3.3)
Fatigue	0	0	3 (4.7)	0	3 (3.8)	3 (3.3)
Peripheral sensory neuropathy	0	0	3 (4.7)	0	3 (3.8)	3 (3.3)
Neuropathy peripheral	1 (16.7)	0	0	1 (6.7)	1 (1.3)	2 (2.2)
Metastases to CNS	0	0	1 (1.6)	1 (6.7)	2 (2.5)	2 (2.2)

Arm A=no prior lapatinib exposure.
Arm B=prior lapatinib exposure.
Classifications of adverse events were based on the MedDRA.
AE=adverse event; CNS=central nervous system; ErbB-2=human epidermal growth factor receptor-2; MedDRA=Medical Dictionary for Regulatory Activities; MTD=maximum tolerated dose; N=number of total subjects in dose cohort; Nera=neratinib; No.=number; Vin=vinorelbine 25 mg/m^2.

CONCLUSIONS:

- Treatment with neratinib in combination with vinorelbine demonstrated encouraging safety, tolerability, and efficacy results in subjects with ErbB-2 positive metastatic or locally advanced breast cancer. The efficacy results observed in lapatinib-naive subjects (ORRs of 41.1% [independent assessment] and 58.9% [Investigator assessment]; evaluable population) suggest the combination treatment of neratinib with vinorelbine may be beneficial as an early-line of treatment for advanced breast cancer.

- The combination treatment of neratinib with vinorelbine also demonstrated efficacy in a limited number of subjects who received prior lapatinib therapy (ORRs of 8.3% [independent assessment] and 50.0% [Investigator assessment]; evaluable population), indicating that it may also be an important option for subjects who are intolerant or resistant to lapatinib.

- Treatment with neratinib in combination with vinorelbine also demonstrated encouraging secondary efficacy results in lapatinib-naive subjects (CBRs of 64.1% and 67.2%) and subjects with prior lapatinib exposure (CBRs of 40.0% and 60.0%).

- Despite the high frequency of diarrhea AEs (455 events), only 4 subjects had SAEs due to diarrhea, and only 3 subjects discontinued study treatment due to diarrhea AEs.

- No subject in any dose cohort experienced a Grade 4 diarrhea event (life-threatening consequences) and no subject died due to diarrhea. Overall, only 21 subjects (23.1%) experienced Grade 3 diarrhea AEs that lasted >2 days.

- Other AEs included neutropenia, nausea, and vomiting, which were manageable and of relatively short duration.

- Although sample sizes were small, no significant cardiotoxicity was reported with neratinib used as single agent and no synergistic toxicity was observed for the combination treatment of neratinib with vinorelbine.