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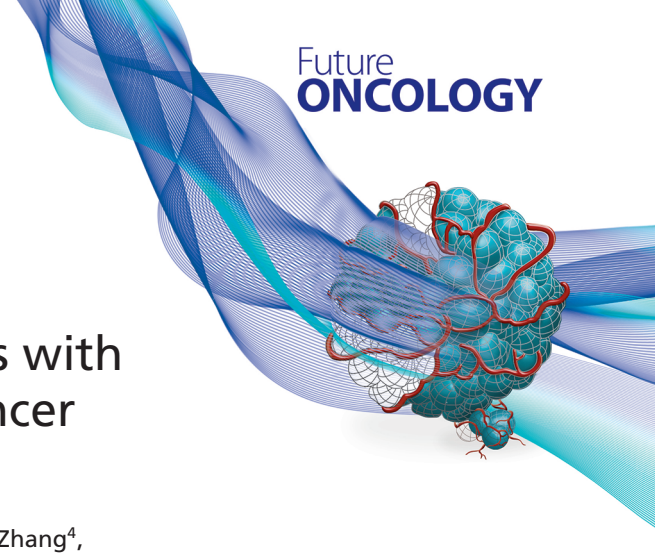

Neratinib-based therapy in patients with metastatic HER2-positive breast cancer from Asia

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Aim: To evaluate the safety and efficacy of neratinib-based therapy in Asian patients with HER2-positive metastatic breast cancer (MBC). **Patients & methods:** We performed a pooled analysis of seven early-phase studies of neratinib given either as monotherapy or in combination with chemotherapeutic agents or trastuzumab in patients with advanced solid tumors. **Results:** A total of 793 patients with HER2-positive MBC were included in the efficacy analysis (Asia: 271 patients; other regions: 522 patients). The overall response rate in patients from Asia was 66.4% (180/271) and the median progression-free survival was 55.6 weeks. The most common adverse event in patients from Asia was diarrhea (all-grade: 96.3%; grade 3: 27.4%). **Conclusion:** Neratinib-based therapy is safe and effective in patients with HER2-positive MBC from Asia.

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Keywords: Asia • efficacy • HER2 • metastatic breast cancer • neratinib • pooled analysis • safety • tyrosine kinase inhibitor

Breast cancer is one of the most common cancers among women in Asia [1]. With an estimated incidence of 26 cases per 100,000 individuals in Asia, though uniformly lower than in western populations, breast cancer is increasing at a rate of 1–3% per year [1] in parallel with westernization of many Asian countries [2]. Current breast cancer therapies are based largely on trials performed with a particular focus on western populations, yet there are potential differences between Asian and other populations that may impact the evaluation of treatment outcomes [3].

Neratinib is an irreversible pan-HER tyrosine kinase inhibitor of HER1, HER2 and HER4 [4]. It inhibits phosphorylation of all HER receptors (HER1, HER2, HER3 and HER4) [5], and also blocks the formation of HER2–HER3 receptor dimers *in vitro* [6]. Neratinib is approved in the USA to be given for 1 year in the extended adjuvant setting after completion of adjuvant trastuzumab in adult patients with early-stage HER2-overexpressed/amplified breast cancer [7]. It has also been granted marketing authorization by the European Commission for the extended adjuvant treatment of adult patients with early-stage hormone receptor-positive HER2-positive breast cancer who are less than 1 year from the completion of prior adjuvant trastuzumab-based therapy [8]. It is under review for regulatory approvals in Asia, and therefore the data from this article should be of relevance. The approvals are based on the findings from the Phase III ExteNET trial [9], which showed that neratinib significantly improved invasive disease-free survival compared with placebo after 2 years (stratified hazard ratio: 0.66; 95% CI: 0.49–0.90; p = 0.008) [7] and 5 years of follow-up (stratified hazard ratio: 0.73; 95% CI 0.57–0.92; p = 0.008) [10] in patients with early-stage HER2-positive breast cancer. In ExteNET, the most common all-grade adverse events with neratinib were diarrhea, nausea, fatigue, vomiting, abdominal pain, headache and

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rash; hematologic toxicities, such as neutropenia and leukopenia, were uncommon (all-grade: 1–2%; grade 3/4: ≤0.1% of patients) [9].

In the metastatic setting, the current preferred first-line regimen for the treatment of patients with HER2-positive breast cancer is dual anti-HER2 blockade with pertuzumab plus trastuzumab plus a taxane [11,12]. Trastuzumab emtansine, trastuzumab plus chemotherapy, or lapatinib (a reversible HER1/HER2 tyrosine kinase inhibitor) in combination with capecitabine or trastuzumab are other recommended regimens, although the optimal sequencing is unknown [11].

The efficacy of neratinib, both as a single agent and in combination with chemotherapeutic or targeted agents, in patients with metastatic HER2-positive breast cancer has been established in a series of early-phase studies, many of which involved Asian centers. We performed a *post hoc* pooled analysis of seven clinical trials to assess the safety and efficacy of neratinib in Asian patients with metastatic HER2-positive breast cancer. A companion analysis of Asian patients in the Phase III ExteNET trial in early-stage HER2-positive breast cancer has been reported separately [13].

Patients & methods

Study selection

Seven prospective, multicenter, open-label Phase I/II (four studies), Phase II (one study) or randomized controlled Phase II (two studies) studies from the sponsor's clinical trial database were included in the analysis [14–20]. All of the studies involved Asian centers and investigated neratinib (Puma Biotechnology, Inc., CA, USA) as a single agent or as part of a combination regimen.

Overall, 1199 patients were included in the seven studies, among which 407 patients were from Asian countries (China Mainland: 160 patients; Japan: 121 patients; Korea: 61 patients; Hong Kong: 32 patients; Singapore: 16 patients; Taiwan: ten patients; Malaysia: five patients; Thailand: two patients) and 792 patients from other regions (Europe, Australasia, North and South America and India) (Figure 1). Details about the design, participants and interventions of each study are presented in Table 1.

Study protocols were approved by the institutional review boards or independent ethics committees of participating centers. Each of the studies was performed in accordance with the Declaration of Helsinki, and applicable local regulatory requirements and laws. Patients gave written informed consent prior to study participation. All studies are registered on Clinicaltrials.gov (Table 1).

Treatment

Neratinib was administered orally once daily on a continuous schedule either as monotherapy or in combination with trastuzumab, paclitaxel, vinorelbine or capecitabine; dosage schedules are summarized in Table 1. Study treatment was continued until disease progression, unacceptable toxicity [14–17,20], symptomatic deterioration, death or withdrawal [18,19]. Dose modifications for treatment-related toxicities were permitted. Treatment with loperamide for diarrhea was recommended at its earliest occurrence in all studies; loperamide prophylaxis for the prevention of neratinib-associated diarrhea was either not mandatory or recommended at a low dose (2 mg/day).

Data extraction

Individual patient data were extracted for all studies. The information retrieved included: country of enrollment; assigned treatment; age; gender; baseline Eastern Cooperative Oncology Group (ECOG) performance status; tumor type, stage and grade; hormone receptor status; prior anticancer treatments in the metastatic setting; tumor response; progression-free survival; treatment exposure; and adverse events.

Outcome measures

Tumor responses were assessed by investigators according to modified Response Evaluation Criteria in Solid Tumors. Efficacy end points considered in the present analysis were: confirmed objective response rate (i.e., complete or partial response); clinical benefit rate (i.e., confirmed objective response, or stable disease lasting at least 24 weeks); and progression-free survival (i.e., time from first dose or randomization until first recurrence/progression or death from any cause). Response confirmation required assessment at least 4 weeks after the first response assessment. Treatment-emergent adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Table 1. Details of studies included in the pooled analysis.

Study name/protocol [Clinicaltrial.gov ID]	Design	Population	Prior trastuzumab for metastatic disease, %	Treatment	Patients enrolled, n	Ref
3144A1-201-WW Burstein *et al.* [NCT00300781]	Multicenter, open-label Phase II	Previously treated advanced HER2+ breast cancer	44.1	Neratinib 240 mg/day po	136	[17]
3144A1-202-WW Blackwell *et al.* [NCT00398567]	Multicenter, open-label, dose-escalation Phase I/II	Trastuzumab-pretreated advanced HER2+ breast cancer	97.8	Phase I: Neratinib 160 or 240 mg/day po + trastuzumab 4 then 2 mg/kg weekly iv. Phase II: Neratinib 240 mg/day po + trastuzumab 4 then 2 mg/kg weekly iv.	45	[20]
3144A1-203-WW Chow *et al.* [NCT00445458]	Multicenter, open-label, dose-escalation Phase I/II	Trastuzumab-pretreated advanced HER2+ breast cancer†	20.9	Phase I: Neratinib 160 or 240 mg/day po + paclitaxel 80 mg/m^2 on days 1, 8 and 15 q28 days iv. Phase II: Neratinib 240 mg/day po + paclitaxel 80 mg/m^2 on days 1, 8 and 15 q28 days iv.	110	[14]
3144A1-2204-WW Awada *et al.* [NCT00706030]	Multicenter, open-label, dose-escalation Phase I/II	Trastuzumab-pretreated advanced HER2+ breast cancer†	73.6	Phase I: Neratinib 160 or 240 mg/day po + vinorelbine 25 mg/m^2 on days 1 and 8 q21 days iv. Phase II: Neratinib 240 mg/day po + vinorelbine 25 mg/m^2 on days 1 and 8 q21 days iv.	91	[15]
3144A1-2206-WW Saura *et al.* [NCT00741260]	Multicenter, open-label, dose-escalation Phase I/II	Trastuzumab-pretreated advanced HER2+ breast cancer†	73.3	Phase I: Neratinib 160, 200 or 240 mg/day po. + capecitabine 1500 or 2000 mg/m^2/day po. on days 1–14 q21 days Phase II: Neratinib 240 mg/day po. + capecitabine 1500 mg/m^2/day po. on days 1–14 q21 days	105	[16]
3144A2-3003-WW Martin *et al.* [NCT00777101]	Multicenter, randomized, open-label, parallel Phase II	Trastuzumab-pretreated advanced HER2+ breast cancer	94.9	Neratinib 240 mg/day po. Comparator: Lapatinib 1250 mg/day po. + capecitabine 2000 mg/m^2/day po. on days 1–14 q21 days	117 116	[18]
NEfERT-T 3144A2-3005-WW Awada *et al.* [NCT00915018]	Multicenter, randomized, open-label, parallel	First-line metastatic HER2+ breast cancer	0	Neratinib 240 mg/day po. + paclitaxel 80 mg/m^2 on days 1, 8 and 15 q28 days iv. Comparator: trastuzumab 4 then 2 mg/kg weekly iv. + paclitaxel 80 mg/m^2 days 1, 8 and 15 q28 days iv.	242 237	[19]

†Phase II population; patients with advanced solid tumors were eligible for Phase I but are not described.
d: Day; ID: Identifier; iv.: Intravenous; po.: Oral; q: Every.

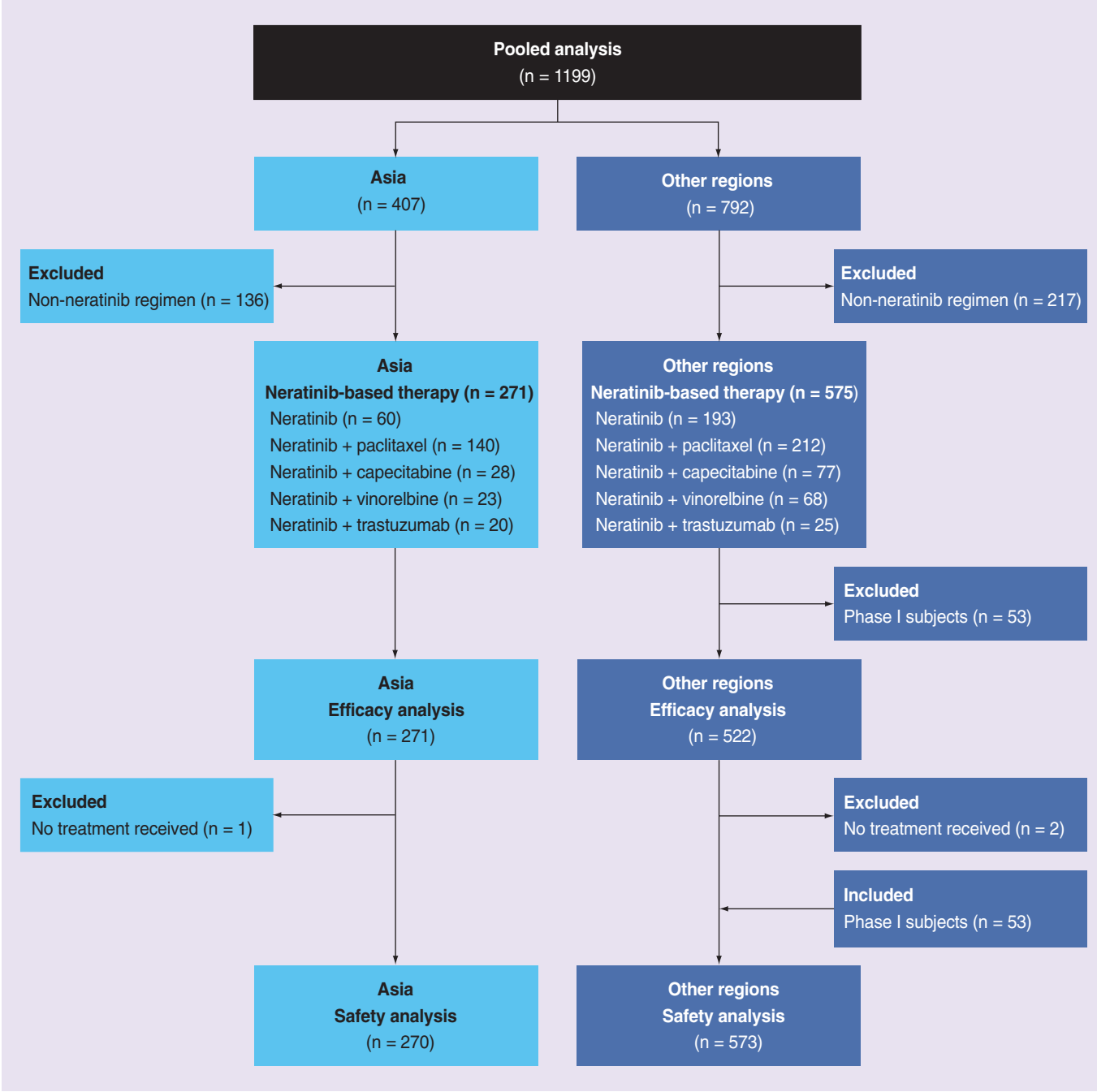

Figure 1. Analysis flowchart.

Data analysis

Patients were divided into two cohorts according to place of enrollment: Asia and other regions. The efficacy analysis included patients who were assigned to neratinib-based therapy, received neratinib at a dosage of 240 mg/day, and had HER2-positive metastatic breast cancer; patients randomized to study treatment that did not include neratinib and patients enrolled in the Phase I component of Phase I/II studies (i.e., those with solid tumors other than breast cancer and those who received neratinib doses <240 mg/day) were excluded. The safety analysis included patients assigned to neratinib-based therapy and who received at least one dose of study treatment. Efficacy and safety data were summarized descriptively. Progression-free survival was analyzed using the Kaplan–Meier method.

Table 2. Patient demographics and characteristics at baseline (n = 1199).

Variable	Asia (n = 407)	Other regions (n = 792)
Age, years:		
– Mean (standard deviation)	51.7 (10.6)	53.5 (11.1)
– Median (range)	52.0 (20.0–83.0)	53.0 (26.0–83.0)
Gender, n (%):		
– Female	403 (99.0)	777 (98.1)
– Male	4 (1.0)	15 (1.9)
ECOG performance status, n (%):		
– 0	248 (60.9)	403 (50.9)
– 1	139 (34.2)	344 (43.4)
– 2	9 (2.2)	24 (3.0)
– Missing	11 (2.7)	21 (2.7)
Tumor type, n (%):		
– Breast cancer	403 (99.0)	765 (96.6)
– HER2-positive	403 (99.0)	750 (94.7)
– Other solid tumor	4 (1.0)	27 (3.4)
Stage at screening, n (%):		
– 0	3 (0.7)	2 (0.3)
– I	14 (3.4)	19 (2.4)
– II	41 (10.1)	78 (9.9)
– III	45 (11.1)	92 (11.6)
– IV	301 (74.0)	592 (74.8)
– Missing	3 (0.7)	9 (1.1)
Hormone receptor status, n (%):		
– Positive	195 (47.9)	379 (47.9)
– Negative	204 (50.1)	377 (47.6)
– Unknown/missing	8 (2.0)	36 (4.5)
Previous trastuzumab therapy for metastatic disease, n (%)†	106 (39.1)	276 (48.0)
Median lines of prior therapy for metastatic disease, n (range)†	1 (0–7)	1 (0–10)
Lines of prior therapy for metastatic disease, n (%)†:		
– 0	105 (38.7)	216 (37.6)
– 1–2	117 (43.2)	244 (42.4)
– ≥3	41 (15.1)	92 (16.0)
– Unknown	8 (3.0)	23 (4.0)

†Only patients assigned to neratinib-based therapy are included.
ECOG: Eastern Cooperative Oncology Group.

Results

A total of 1199 patients were enrolled in the seven studies of the pooled analysis (Asia: 407 patients; other regions: 792 patients). After excluding patients who did not receive neratinib (353 patients) and those who participated in Phase I of Phase I/II studies (i.e., neratinib doses <240 mg/day and/or had solid tumors other than breast cancer; 53 patients), a total of 793 women with HER2-positive metastatic breast cancer were included in the efficacy analysis (Asia: 271 patients; other regions: 522 patients). For the safety analysis, a total of 843 patients were included who received at least one dose of neratinib-based therapy (Asia: 270 patients; other regions: 573 patients). A detailed flowchart of patients included in the analysis is shown in Figure 1.

Baseline demographics and characteristics are described in Table 2, and for each individual study in Supplementary Tables 1–7. Patients from Asia had a mean age of 51.7 years, 95.1% had a good performance status (ECOG score 0 or 1), and 39.1% had had prior exposure to trastuzumab in the metastatic setting.

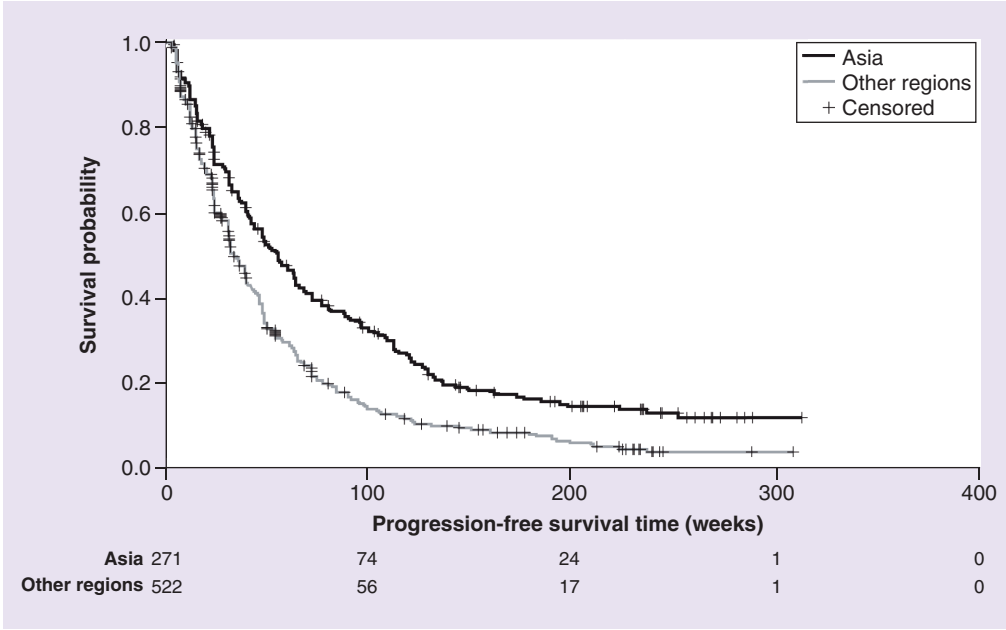

Figure 2. Progression-free survival. Pooled analysis.

Treatment exposure

The median duration of neratinib-based treatment in patients from Asia was 328 days (range: 1–2393 days; Supplementary Table 8). A total of 123 (45.6%) patients from Asia received neratinib-based treatment for more than 1 year, and ten (3.7%) patients received neratinib-based treatment for more than 5 years. The duration of neratinib-based treatment tended to be shorter in patients from other regions (median: 196 days; range: 1–2352 days), and fewer patients from other regions received neratinib-based treatment for more than 1 year (145 patients, 25.3%) or 5 years (five patients, 0.9%). The median relative actual dose intensity exceeded 99% in both cohorts.

Efficacy

The overall response rate among efficacy-evaluable patients from Asia was 66.4% (180 patients) and the clinical benefit rate was 72.0% (195 patients) (Table 3). The median duration of progression-free survival across all studies in patients from Asia was 55.6 (95% CI: 44.1–64.0) weeks (Figure 2). Among efficacy-evaluable patients from other regions, the overall response rate was 51.3% (268 patients), the clinical benefit rate was 60.2% (314 patients), and the median duration of progression-free survival was 36.1 (95% CI: 32.1–40.0) weeks. Kaplan–Meier curves for progression-free survival in each individual study are shown in Supplementary Figure 1.

Safety

A total of 843 patients were included in the safety population (Asia: 270 patients; other regions: 573 patients). The most frequently reported treatment-emergent adverse events are presented in Table 4, and an overall summary of treatment-emergent adverse events is presented in Supplementary Table 9. Among patients from Asia, 60 patients (22.2%) received neratinib monotherapy, and the remaining 210 patients (77.7%) received neratinib in combination with either a chemotherapeutic agent or trastuzumab.

Among patients from Asia, the overall incidence of all-grade adverse events was 100.0% (270 patients) and grade 3/4 adverse events was 65.6% (177 patients; Table 4). The incidence of diarrhea, the most common toxicity associated with neratinib, among patients from Asia was 96.3% (260 patients) for all-grade events and 27.4% (74 patients) for grade 3 diarrhea; no grade 4 diarrhea was reported in patients from Asia. Many of the other common toxicities reported (i.e., neutropenia, leukopenia, palmar–plantar erythrodysesthesia, alopecia, peripheral sensory neuropathy and stomatitis) (Table 4) were related to the chemotherapy component of study treatment rather than neratinib, as these events are either uncommon or not observed with neratinib monotherapy [7,9]. A similar profile of adverse events was observed among patients from other regions (Table 4).

Table 3. Efficacy analysis in patients with HER2-positive metastatic breast cancer who received neratinib-based therapy.

Study	Treatment	Objective response rate, n (%)		Clinical benefit rate, n (%)		Median progression-free survival (95% CI), weeks	
		Asia (n = 271)	Other regions (n = 522)	Asia (n = 271)	Other regions (n = 522)	Asia (n = 271)	Other regions (n = 522)
3144A1-201-WW[†]	Neratinib	19/28 (67.9)	45/108 (41.7)	23/28 (82.1)	50/108 (46.3)	71.9 (40.1–112.4)	24.0 (20.7–32.0)
3144A1-202-WW	Neratinib + trastuzumab	7/20 (35.0)	3/17 (17.6)	9/20 (45.0)	3/17 (17.6)	20.7 (15.7–101.1)	15.1 (6.7–23.6)
3144A1-203-WW	Neratinib + paclitaxel	48/63 (76.2)	25/47 (53.2)	49/63 (77.8)	33/47 (70.2)	55.6 (39.0–80.3)	52.4 (37.3–81.6)
3144A1-2204-WW	Neratinib + vinorelbine	11/23 (47.8)	30/56 (53.6)	12/23 (52.2)	40/56 (71.4)	30.9 (12.0–44.0)	47.7 (35.9–65.0)
3144A1-2206-WW[‡]	Neratinib + capecitabine	19/28 (67.9)	27/44 (61.4)	21/28 (75.0)	29/44 (65.9)	42.5 (29.9–66.0)	36.3 (18.9–70.9)
3144A2-3003-WW	Neratinib	9/32 (28.1)	24/85 (28.3)	12/32 (37.5)	38/85 (44.7)	18.1 (8.9–69.1)	23.9 (17.7–30.0)
3144A2-3005-WW	Neratinib + paclitaxel	67/77 (87.0)	114/165 (69.1)	69/77 (89.6)	121/165 (73.3)	88.1 (62.7–120.6)	48.1 (40.4–57.3)
All studies	Neratinib-based therapy	180 (66.4)	268 (51.3)	195 (72.0)	314 (60.2)	55.6 (44.1–64.0)	36.1 (32.1–40.0)

[†]Includes cohorts with prior and no prior trastuzumab therapy.
[‡]Includes cohorts with prior and no prior lapatinib therapy.

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Table 4. Treatment-emergent adverse events (all-grade events in >15% of patients) in patients who received neratinib-based therapy.

Adverse event	All-grade events, n (%)		Grade 3/4 events, n (%)	
	Asia (n = 270)	Other regions (n = 573)	Asia (n = 270)	Other regions (n = 573)
Any event	270 (100.0)	566 (98.8)	177 (65.6)	345 (60.2)
Diarrhea	260 (96.3)	517 (90.2)	74 (27.4)	154 (26.9)
Nausea	108 (40.0)	252 (44.0)	6 (2.2)	14 (2.4)
Neutropenia	106 (39.3)	104 (18.2)	52 (19.3)	49 (8.6)
Decreased appetite	99 (36.7)	150 (26.2)	11 (4.1)	10 (1.7)
Leukopenia	96 (35.6)	65 (11.3)	31 (11.5)	24 (4.2)
Vomiting	93 (34.4)	198 (34.6)	6 (2.2)	23 (4.0)
Rash	87 (32.2)	103 (18.0)	2 (0.7)	5 (0.9)
Alopecia	77 (28.5)	125 (21.8)	0	1 (0.2)
Anemia	64 (23.7)	109 (19.0)	9 (3.3)	16 (2.8)
Peripheral sensory neuropathy	64 (23.7)	65 (11.3)	3 (1.1)	7 (1.2)
ALT increased	55 (20.4)	49 (8.6)	12 (4.4)	21 (3.7)
Stomatitis	54 (20.0)	52 (9.1)	0	1 (0.2)
Fatigue	53 (19.6)	181 (31.6)	7 (2.6)	21 (3.7)
Pyrexia	49 (18.1)	84 (14.7)	0	0
Palmar–plantar erythrodysesthesia syndrome	47 (17.4)	47 (8.2)	12 (4.4)	11 (1.9)
Asthenia	46 (17.0)	127 (22.2)	5 (1.9)	14 (2.4)
AST increased	45 (16.7)	47 (8.2)	9 (3.3)	15 (2.6)
Headache	45 (16.7)	113 (19.7)	0	4 (0.7)
Weight decreased	45 (16.7)	55 (9.6)	3 (1.1)	2 (0.3)
Abdominal pain	33 (12.2)	118 (20.6)	4 (1.5)	5 (0.9)

A total of 252 (29.9%) patients received neratinib monotherapy (Asia: 60 patients; other regions: 192 patients), and the remaining 591 (70.1%) patients received neratinib in combination with another agent (i.e., paclitaxel, capecitabine, vinorelbine or trastuzumab) (Asia: 210 patients; other regions: 381 patients).

Discontinuation of neratinib because of adverse events among patients from Asia was reported in 23.3% of patients (63 patients), and neratinib dose reductions and dose holds because of adverse events were reported in 31.9% (86 patients) and 50.4% (136 patients), respectively (Supplementary Table 9).

Discussion

By combining individual patient data from seven international Phase I/II or Phase II studies which investigated neratinib alone or in various combination regimens, we were able to evaluate the effects of neratinib-based therapy in a cohort of Asian patients with advanced or metastatic solid tumors. According to this analysis, neratinib-based therapy produced an overall response rate of 66% with a median progression-free survival of over 1 year in Asian patients with HER2-positive metastatic breast cancer. Diarrhea, the dose-limiting toxicity of neratinib, was the most common adverse event among Asian patients. Other commonly reported adverse events in the present analysis (i.e., neutropenia, leukopenia, alopecia, anemia and peripheral sensory neuropathy) were likely caused by chemotherapeutic agents given with neratinib, rather than by neratinib itself. This is consistent with a companion analysis of the ExteNET trial in which the most common all-grade events with single-agent neratinib in Asian patients were gastrointestinal (i.e., diarrhea, nausea and vomiting); hematological events, alopecia and peripheral sensory neuropathy were either rare or were not reported at all [13].

While the primary aim of the analysis was to examine the effects of neratinib-based therapy in a pan-Asian population, pooling of patients from multiple studies also provided an opportunity to examine subgroups by region. An unanticipated finding from our analysis was that patients from Asia appeared to have better outcomes (i.e., improved tumor response rates, longer progression-free survival) than patients from other regions. As the studies included in the analysis were not controlled or matched for such a comparison, it is likely that confounding factors were involved. These included the longer duration of neratinib-based therapy among Asian patients; 45% of Asian patients received neratinib for at least 1 year compared with 25% of patients from other regions. In addition, fewer Asian patients had been pretreated with trastuzumab for metastatic disease than patients from other

regions (39 vs 48%, respectively). The Asian population was also younger with a better performance status (lower ECOG scores) than the population from other regions, all differences that likely favored better outcomes among Asian patients. Differences in the underlying genetics or biology of breast cancers [21] may also have been involved although, without the support of biomarker data, we are unable to determine if this was the case.

At the time the studies included in our analysis were performed, trastuzumab in combination with a taxane was the preferred first-line regimen for HER2-positive metastatic breast cancer. Almost half (45%) of the patients included in our analysis had received prior trastuzumab for metastatic disease, and our data provide support for the clinical activity of neratinib in trastuzumab-pretreated patients. Other HER2-directed agents – pertuzumab and trastuzumab emtansine – have since been introduced into clinical practice, and while our analysis does not provide any insight into the efficacy of neratinib following treatment with these newer agents, ongoing Phase II and III studies may help to provide some answers. NALA (ClinicalTrials.gov ID: NCT01808573), an international, randomized, open-label, Phase III trial that includes 57 sites in the Asia-Pacific region, is comparing neratinib plus capecitabine with lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer who have received at least two prior HER2-directed regimens in the metastatic setting. The study met its primary objective and showed that neratinib plus capecitabine was superior to lapatinib plus capecitabine in terms of progression-free survival (hazard ratio: 0.76; p = 0.0059) with a trend towards improved overall survival (hazard ratio: 0.88; p = 0.2086) [22]. The Phase Ib/II NSABP FB-10 study (Clinicaltrials.gov ID: NCT02236000) is evaluating neratinib in combination with trastuzumab emtansine in women with HER2-positive breast cancer previously treated with one prior HER2-directed regimen [23]. The investigators reported an interim overall response rate of 60% (12 of 20 evaluable patients) in this patient population [23]; the Phase II portion of this trial is ongoing.

Diarrhea was common in our study population (all-grade events >90%), although antidiarrheal prophylaxis with loperamide was not mandated in most of the studies or was recommended at a low dose only. An improved understanding of the pattern of diarrheal events with neratinib has led to the use of a prophylactic regimen of high-dose loperamide for the first one to two cycles of therapy [24]. Neratinib dose escalation, as well as additional agents given in conjunction with loperamide prophylaxis to target inflammation (i.e., budesonide) or bile acid malabsorption (i.e., colestipol), are also being investigated in the management of neratinib-associated diarrhea with promising results [24]. As the studies included in our analysis predate the introduction of loperamide prophylaxis, it is anticipated that lower rates of diarrhea may be expected in Asian patients with its use than are reported here.

We noted some inconsistencies between studies investigating the same regimens. For example, single-agent neratinib performed better in terms of overall response rate and progression-free survival in Asian than non-Asian patients in one study (3144A1-201-WW), whereas overall response rate was similar and progression-free survival shorter with single-agent neratinib in Asian patients compared with non-Asian patients in another study (3144A2-3003-WW). Imbalances in the number of lines of prior therapy for metastatic disease may have contributed to these observations as patients in study 3144A1-201-WW had received a median of one prior line of therapy, whereas Asian patients in study 3144A2-3003-WW had received two prior lines compared with one for non-Asian patients. It is possible that other factors, including small patient numbers in some studies, may also have been involved in inconsistent results.

The present analysis was not preplanned, but rather a hypothesis-generating study conducted to investigate the effects of neratinib in a pan-Asian population. We acknowledge that our analysis was exploratory in nature, and that we cannot definitively compare Asian and non-Asian groups without inherent confounding effects. A randomized, controlled trial of neratinib-based treatment by region, including a test for interaction, would be of interest. The studies included in our analysis were identified from the sponsor's clinical trials database rather than from a systematic search of the literature and, while this approach enabled us to use individual patient data, we recognize that some relevant studies may have been omitted.

Conclusion

Our pooled analysis suggests that neratinib-based therapy is safe and effective among Asian patients with HER2-positive metastatic breast cancer, and that findings from international studies of neratinib can be extended to Asian populations. Patients from Asia appeared to have better tumor response rates and progression-free survival with neratinib-based therapy than patients from other regions, but confounding factors cannot be excluded from this comparison and it should be viewed as hypothesis-generating only.

Practice points

- Much of the evidence guiding the treatment of breast cancer is based on Western patients, yet outcomes may vary between patients from different regions because of differences in pharmacogenetics, tumor biology and environmental factors.
- The aim of the current study is to evaluate the safety and efficacy of neratinib-based therapy in patients from Asia with HER2-positive metastatic breast cancer.
- A pooled analysis of individual patient data from seven prospective clinical trials of neratinib-based therapy in metastatic solid tumors was performed.
- A total of 793 patients with HER2-positive metastatic breast cancer were evaluable for efficacy (Asia: 271 patients; other regions: 522 patients).
- The median duration of neratinib-based treatment in patients from Asia was 328 days (range: 1–2393).
- In patients from Asia, the overall response rate with neratinib-based therapy was 66.4% and median progression-free survival was 55.6 weeks.
- The most common adverse event in patients from Asia was diarrhea (all-grade: 96.3%; grade 3: 27.4%).
- Neratinib-based therapy is safe and effective in patients with HER2-positive metastatic breast cancer from Asia.

Note

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Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2019-0222

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Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of this data is: NCT00300781; NCT00398567; NCT00445458; NCT00706030; NCT00741260; NCT00777101; NCT00915018.

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