Safety and efficacy of neratinib (HKI-272) plus vinorelbine in the treatment of patients with ErbB2-positive metastatic breast cancer pretreated with anti-HER2 therapy

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Background: Neratinib (HKI-272) is a potent irreversible pan-ErbB tyrosine kinase inhibitor with clinical activity in patients with ErbB2/HER2-positive breast cancer.

Patients and methods: Phase I of this open-label, phase I/II study investigated the maximum tolerated dose (MTD) of oral neratinib (160 or 240 mg/day) plus vinorelbine (25 mg/m²; days 1 and 8 of each 21-day cycle) in patients with solid tumors. Phase II assessed the safety, clinical activity, and pharmacokinetics of the combination in patients with HER2-positive metastatic breast cancer; the primary efficacy end point was objective response (OR).

Results: In phase I (n = 12), neratinib (240 mg) plus vinorelbine (25 mg/m²) was established as the MTD. In phase II, 79 patients with HER2-positive metastatic breast cancer were treated at the MTD. The most common treatment-related adverse events were diarrhea (96%), neutropenia (54%), and nausea (50%). Three patients discontinued treatment due to diarrhea. No clinically important skin side-effects were observed. The OR rate in assessable phase II patients was 41% (no prior lapatinib) and 8% (prior lapatinib). There was no evidence of pharmacokinetic interaction between neratinib and vinorelbine.

Conclusion: Neratinib plus vinorelbine showed promising antitumor activity and no unexpected toxic effects in HER2-positive metastatic breast cancer patients.

Trial registration: ClinicalTrials.gov #NCT00706030.

Key words: breast cancer, HER2, neratinib, tyrosine kinase inhibitor, vinorelbine

Introduction

Patients diagnosed with metastatic breast cancer face a poor prognosis, with less than one-third surviving 5 years or more [1]. The human epidermal growth factor receptor 2 (ErbB2/HER2) has been shown to be an important target for breast cancer treatment [2], as increased HER2 expression is found in up to 30% of breast cancers, and correlates with more aggressive breast tumors and poorer prognosis [3].

Although the introduction of HER2-targeted therapies, such as trastuzumab and lapatinib, has improved outcomes for the treatment of HER2-positive breast cancer [4–6], some patients are unresponsive or develop resistance to anti-HER2 agents [5, 7–13]. For these patients, combinations of HER2-targeted therapy with chemotherapy or other targeted agents may provide more robust antitumor activity via actions on complementary cellular pathways.

Neratinib (HKI-272) is a potent, orally administered, small molecule, irreversible pan-ErbB receptor tyrosine kinase inhibitor that binds covalently to the intracellular tyrosine kinase domain of ErbB receptors to inhibit autophosphorylation and subsequent downstream signaling cascades [14–16]. In phase I and II studies, neratinib monotherapy was well-tolerated and exhibited antitumor activity in patients with advanced solid tumors, including those with HER2-positive breast cancer [17, 18]. Although the HER2-specific monoclonal antibody trastuzumab has been
associated with cardiotoxicity in some patients [19], healthy subjects given neratinib have demonstrated neither a significant left ventricular ejection fraction (LVEF) decrease nor a prolonged QTc interval [17, 20].

Vinorelbine is a semi-synthetic vinca alkaloid that has demonstrated activity in many tumor types and is currently approved for the treatment of advanced breast cancer and non-small-cell lung cancer [21]. Vinorelbine has shown synergistic activity in combination with trastuzumab in both preclinical [22, 23] and clinical studies [24, 25], which provides the rationale for vinorelbine’s evaluation in combination with other anti-HER2 agents, such as neratinib.

The current phase I/II trial evaluated the combination of neratinib and vinorelbine in patients with solid tumors and HER2-positive metastatic breast cancer.

methods

patients

Eligible patients were either adults with a confirmed diagnosis of a solid tumor not curable with available therapies (phase I) or females with a confirmed diagnosis of stage IV HER2-positive breast cancer (defined as an amplification ratio of 2.0 or more by fluorescent or chromogenic in situ hybridization), for which vinorelbine plus neratinib was a reasonable treatment option (phase II). Patients eligible for phase II also must have received at least one prior antineoplastic treatment of metastatic disease or relapse during adjuvant treatment, including at least one prior trastuzumab-containing regimen for 6 weeks or longer. All patients were required to have at least one measurable lesion by modified RECIST (version 1.0) or Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 2; and screening laboratory values and LVEF within normal limits. Key exclusion criteria included active central nervous system (CNS) metastases; any cancer therapy within 2 weeks before study start. For phase II only, additional exclusion criteria included having more than two prior cytotoxic chemotherapy treatment regimens for metastatic disease; prior treatment with vinorelbine for metastatic disease or with any HER2-targeted agents except trastuzumab; and taking greater than pre-specified cumulative prior doses of anthracyclines. Full inclusion and exclusion criteria are summarized in supplementary Table S1, available at Annals of Oncology online.

study design

This was a phase I/II, multicenter, open-label study. Phase I was a dose-escalation study using the standard 3+3 design, in which successive cohorts of three to six patients with advanced solid tumors were enrolled in each dose group and evaluated for the determination of the maximum tolerated dose (MTD). Patients received daily oral doses of neratinib (160 or 240 mg) plus i.v. vinorelbine (25 mg/m² on days 1 and 8 of each 21-day cycle). Each patient participated in only one dose group. Adverse events (AEs) and dose-limiting toxic effects (DLTs) were assessed from day 1 to day 21 of study drug, before escalation to the next dose level. If one of the three patients experienced a DLT, the cohort was expanded to six assessable patients. The MTD was defined as the highest dose at which no more than one patient experienced a DLT; if two or more patients in a cohort experienced a DLT, dose escalation was stopped and the prior dose level was considered the MTD. A DLT was defined as any of the following events: grade 3/4 non-hematologic toxicity (except grade 3 asthenia unless lasting more than 3 days, grade 3 nausea or vomiting unless the patient is already receiving optimal medical therapy, grade 3/4 infection unless associated with grade 3/4 neutropenia); grade 3 diarrhea lasting more than 2 days during optimal medical therapy or associated with fever or dehydration; grade 4 neutropenia lasting 7 or more days or grade 4 febrile neutropenia; grade 4 thrombocytopenia lasting 3 or more days or complicated with bleeding; or delayed recovery (to grade 1/0 or baseline) from one of the above drug-related toxic effects delaying the initiation of the next dose by more than 3 weeks.

After the determination of the MTD, phase II evaluated the efficacy and safety of neratinib plus vinorelbine in patients with HER2-positive metastatic breast cancer. One interim analysis was to be carried out after ~20 assessable subjects with no prior lapatinib exposure were enrolled, and if five or fewer responders were observed, stopping enrollment was to be considered.

All patients provided written informed consent; the study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each participating study center.

study assessments

Safety was assessed by physical examinations, interim history, and laboratory assessments. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Tumor assessments were carried out at screening and then every two cycles (~6 weeks) throughout the course of the study. Response was assessed by the investigator and by independent assessment based on modified RECIST version 1.0 guidelines (see supplementary Table S2, available in Annals of Oncology online for modifications to the RECIST Criteria). All disease sites were documented by computed tomography or magnetic resonance imaging scans. Partial response (PR) and complete response (CR) were confirmed by repeat assessments at least 4 weeks after the criteria for response were first met. Stable disease (SD) could first be assessed 6 weeks after the first dose of study drug.

Blood samples for pharmacokinetic analysis were taken before dosing and at 0, 0.25, 1, 2, 4, 6, 8, and 21 to 24 h after treatment on cycle 1 day 1 (vinorelbine alone) and cycle 2 day 8 (both agents). Pharmacokinetic analyses were carried out using a non-compartmental method.

statistical analyses

In phase I, the sample size was determined by clinical rather than statistical considerations, and no formal statistical analysis was carried out. In phase II, the null hypothesis for objective response rate (ORR) in patients with no prior lapatinib was set at 30% and the alternative of interest was set at 55%, based on previously reported data from phase II studies of vinorelbine–trastuzumab [26–28]. The sample size was chosen for the study to have a significance level of 0.025 and a power of 95% for no prior lapatinib patients. To compensate for the expected dropout or non-evaluable rate of 15%, ~60 patients needed to be enrolled. Up to 20 patients with prior lapatinib were also to be enrolled (no formal testing was planned).

The modified intent-to-treat (mITT) population (phase II only) was defined as all enrolled patients who had at least one dose of neratinib. The safety analysis included all patients who received at least one dose of neratinib or vinorelbine. (The mITT and safety populations are identical (phase II) since all treated patients received at least one dose of neratinib. Data snapshot of 27 September 2011 was used for all results except for efficacy results, which were based on the 25 October 2011 snapshot.) To be considered assessable for efficacy (phase II only), patients must have met all eligibility criteria, have completed at least 2 weeks of neratinib treatment, at least two doses of vinorelbine, and at least two follow-up tumor assessments (or have had only one follow-up tumor assessment of progressive disease or have had symptomatic deterioration or death before
the first follow-up tumor assessment). Two patient groups were analyzed separately: those with no prior lapatinib exposure and those with prior lapatinib exposure, for which group exploratory analyses were conducted. The primary efficacy end point was OR (CR or PR) in phase II patients with no prior lapatinib exposure. Secondary efficacy end points included clinical benefit (CB; OR or SD ≥ 24 weeks), progression-free survival (PFS), and duration of response. Response rates were presented with associated 95% confidence intervals (CIs). For time-to-event end points (i.e., PFS, duration of response), median values (using the Kaplan–Meier method) and the corresponding 95% CIs (using the Brookmeyer and Crowley method) were calculated. PFS was calculated from the date of first dose of study drug administered until the date of first documentation of recurrence/progression or death due to any cause; patients were otherwise censored at the last evaluation. Duration of response was calculated from the first date of response until the date of disease progression.

results

patients

A total of 92 patients were enrolled in the study; baseline demographic and disease characteristics are shown in Table 1. In phase I, six patients with solid tumors received neratinib 160 mg plus vinorelbine 25 mg/m² and six patients received neratinib 240 mg plus vinorelbine 25 mg/
m². A total of 79 patients with HER2-positive advanced breast cancer (64 without prior lapatinib and 15 with prior lapatinib) were treated in phase II (supplementary Figure S1, available at Annals of Oncology online). Of these 64 patients without prior lapatinib exposure, 56 were assessable for efficacy per definition of the assessable population.

At the time of analysis, 10 patients were continuing treatment with neratinib plus vinorelbine. Most study discontinuations in phase II were due to disease progression (n = 53; supplementary Figure S1, available at Annals of Oncology online); 12 patients discontinued vinorelbine treatment mainly due to intolerance, but continued with neratinib monotherapy. All four patients who died during the study died due to disease progression: three patients died either during treatment or within 28 days of the last dose and one patient died after 28 days of the last dose. Patients were not followed in this study for survival. The duration of neratinib therapy before discontinuation from phase II was less than 6 months for 30 (38%) patients, between 6 and 12 months for 25 (32%) patients, between 12 and 24 months for 13 (17%) patients, and more than 24 months for 1 (1%) patient.

dose escalation (phase I)

One of the six patients in the initial dose cohort (neratinib 160 mg plus vinorelbine) experienced a DLT (peripheral neuropathy); no DLTs were observed at the escalated dose of neratinib 240 mg plus vinorelbine. Thus, the MTD was determined to be neratinib 240 mg plus vinorelbine 25 mg/m², corresponding to the full recommended dose previously determined for neratinib as monotherapy [17] and a vinorelbine dose commonly used in other combination regimens [25, 27, 29, 30]. This MTD was further evaluated in phase II.

safety and tolerability (phases I and II)

The most common treatment emergent AEs that were treatment related (phases I and II) were diarrhea (96%), neutropenia (54%), nausea (50%), vomiting (39%), and fatigue (32%) (supplementary Table S3, available at Annals of Oncology online). The most common grade 3/4 treatment emergent AEs that were treatment related were neutropenia (46%), diarrhea (28%), and leukopenia (17%). A total of 26 (29%) patients experienced treatment emergent grade 3 diarrhea; no patient experienced grade 4 diarrhea. The mean (standard deviation) time to first onset of diarrhea was 7.3 (13.7) days and cumulative duration of diarrhea was 80.4 (98.2) days. Overall, 75% of patients had their diarrhea resolve spontaneously or with treatment modification (dose reduction, 15%; dose delay, 23%). Three (3%) patients discontinued treatment due to diarrhea. Interestingly, no clinically important skin side-effects were observed when compared with those observed with other agents such as lapatinib. Clinically important sinus rhythm (electrocardiogram) abnormalities were observed in one patient at baseline, six patients during treatment, and two patients at the final visit. Per investigators’ judgment, no clinically important changes in % LVEF from screening were observed.

Dose reductions and delays due to AEs were required by 36 (40%) and 55 (60%) of all study patients, respectively (supplementary Table S4, available at Annals of Oncology online). The AEs most frequently leading to dose reductions and delays were diarrhea (15% and 23%, respectively) and neutropenia (10% and 33%, respectively). Of the 34 and 54 patients in phase II who required toxicity-related dose reductions and delays, respectively, 28 and 43 patients had no prior lapatinib, while 6 and 11 had prior lapatinib. A total of 19 patients discontinued study treatment due to an AE, most commonly for diarrhea, fatigue, peripheral sensory neuropathy (n = 3 each, all in the phase II no prior lapatinib cohort), and peripheral neuropathy and CNS metastases (n = 2 each).

antitumor activity (phase II)

In February 2010, an interim analysis was conducted on the first 32 assessable patients with no prior lapatinib exposure. An ORR of 56% (17 PRs and 1 CR) with 95% CI (37.7%–73.6%) was consistent with the alternative ORR of 55% defined in the study protocol to continue patient accrual.

As of 25 October 2011, best overall responses and their durations based on independent and investigator assessment of tumor data are summarized for the assessable mITT populations in Table 2. Supplementary Table S5 (available at Annals of Oncology online) provides the reasons for patients being excluded from the assessable population. ORR was 41% (n = 23/56; 95% CI 28.10%–55.02%) for assessable patients in phase II without prior lapatinib (independent assessment). The probability of observing an ORR of 41% or greater under the null hypothesis of an ORR of 30% is 0.051, which is not statistically significant at the 0.025 level per study design. The median duration of response for assessable patients for the cohort without prior lapatinib (independent assessment) was 52.7 (range 11.6–96.1) weeks. CBR in the same cohort was 70% (n = 39/56) by independent assessment. Among assessable patients with prior lapatinib, PR was achieved by 1 of 12 (8%) patients and SD of at least 24 weeks was achieved by 4 patients, for a CBR of 42% (all independent assessment).

The median PFS was 48.0 weeks (95% CI 30.9–65.1 weeks; independent assessment) for assessable patients in phase II with no prior lapatinib and 22.7 weeks (95% CI 12.0–41.0 weeks) for assessable patients who had received prior lapatinib (Figure 1).

pharmacokinetics

Preliminary evaluation of neratinib and vinorelbine pharmacokinetic parameters from combination neratinib and vinorelbine therapy indicated that neratinib and vinorelbine exposures [maximum plasma concentration (Cmax) and area under the curve (AUC)] were similar to those observed for neratinib [18] and vinorelbine monotherapy [31], respectively. These results suggested no pharmacokinetic interaction between neratinib and vinorelbine (supplementary Table S6, available at Annals of Oncology online).
This phase I/II study investigating the combination of neratinib plus vinorelbine established an MTD of neratinib 240 mg and vinorelbine 25 mg/m² in patients with solid tumors. Subsequent phase II investigation of this dose regimen in patients with HER2-positive advanced breast cancer demonstrated that this combination was associated with an acceptable safety and tolerability profile—no unexpected toxic effects were observed, and the observed profile was generally characteristic of each agent given as monotherapy, suggesting no synergistic toxicity. Diarrhea and neutropenia were the most common treatment-related toxic effects; other common treatment-related AEs included nausea, vomiting, fatigue, decreased appetite, and leukopenia. Similar rates and severity of AEs were observed in the phase II patients with and without prior lapatinib treatment. Nineteen patients (20.9%) discontinued the treatment due to treatment emergent AEs, and 16 patients (17.6%) discontinued due to treatment emergent AEs that were also treatment-related.

Table 2. Efficacy results

<table>
<thead>
<tr>
<th>Response</th>
<th>No prior lapatinib</th>
<th>Prior lapatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Independent</td>
<td>Investigator</td>
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<tr>
<td></td>
<td>assessment</td>
<td>assessment</td>
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<tr>
<td>Phase II assessable population</td>
<td>n = 56</td>
<td>n = 12</td>
</tr>
<tr>
<td>ORR*</td>
<td>23 (41)</td>
<td>33 (59)</td>
</tr>
<tr>
<td>95% CI</td>
<td>28–55</td>
<td>45–72</td>
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<tr>
<td>CR</td>
<td>0</td>
<td>3 (5)</td>
</tr>
<tr>
<td>PR</td>
<td>23 (41)</td>
<td>30 (54)</td>
</tr>
<tr>
<td>Duration of response (weeks)</td>
<td>Median (range)</td>
<td>52.7 (11.6–96.1)</td>
</tr>
<tr>
<td>95% CI</td>
<td>38.4–NE</td>
<td>36.9–66.1</td>
</tr>
<tr>
<td>SD [n (%)]</td>
<td>&lt;24 weeks</td>
<td>11 (20)</td>
</tr>
<tr>
<td>≥24 weeks</td>
<td>16 (29)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Duration of SD (weeks)</td>
<td>Median (range)</td>
<td>42.0 (6.1–78.1)</td>
</tr>
<tr>
<td>95% CI</td>
<td>23.7–54.3</td>
<td>17.1–31.3</td>
</tr>
<tr>
<td>CBRb</td>
<td>n (%)</td>
<td>39 (70)</td>
</tr>
<tr>
<td>95% CI</td>
<td>56–81</td>
<td>58–83</td>
</tr>
<tr>
<td>Progressive disease [n (%)]</td>
<td>6 (11)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Phase II mITT population</td>
<td>n = 64</td>
<td>n = 15</td>
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<tr>
<td>ORR*</td>
<td>23 (36)</td>
<td>34 (53)</td>
</tr>
<tr>
<td>95% CI</td>
<td>24–49</td>
<td>40–66</td>
</tr>
<tr>
<td>CR</td>
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<td>3 (5)</td>
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<tr>
<td>PR</td>
<td>23 (36)</td>
<td>31 (48)</td>
</tr>
<tr>
<td>Duration of response (weeks)</td>
<td>Median (range)</td>
<td>52.7 (11.6–96.1)</td>
</tr>
<tr>
<td>95% CI</td>
<td>38.4–NE</td>
<td>36.9–66.1</td>
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<tr>
<td>SD [n (%)]</td>
<td>&lt;24 weeks</td>
<td>11 (17)</td>
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<td>≥24 weeks</td>
<td>18 (28)</td>
<td>9 (14)</td>
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<tr>
<td>Duration of SD (weeks)</td>
<td>Median (range)</td>
<td>42.0 (6.1–114.6)</td>
</tr>
<tr>
<td>95% CI</td>
<td>24.1–NE</td>
<td>18.3–35.9</td>
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<tr>
<td>CBRb</td>
<td>n (%)</td>
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<tr>
<td>95% CI</td>
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<td>54–78</td>
</tr>
<tr>
<td>Progressive disease [n (%)]</td>
<td>8 (13)</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

*ORR includes CR and PR.

bCBR includes CR, PR, and SD ≥24 weeks.

ORR, overall response rate; CI, confidence interval; CR, complete response; PR, partial response; NE, not estimable; SD, stable disease; CBR, clinical benefit rate.

discussion

This phase I/II study investigating the combination of neratinib plus vinorelbine established an MTD of neratinib 240 mg and vinorelbine 25 mg/m² in patients with solid tumors. Subsequent phase II investigation of this dose regimen in patients with HER2-positive advanced breast cancer demonstrated that this combination was associated with an acceptable safety and tolerability profile—no unexpected toxic effects were observed, and the observed profile was generally characteristic of each agent given as monotherapy, suggesting no synergistic toxicity. Diarrhea and neutropenia were the most common treatment-related toxic effects; other common treatment-related AEs included nausea, vomiting, fatigue, decreased appetite, and leukopenia. Similar rates and severity of AEs were observed in the phase II patients with and without prior lapatinib treatment. Nineteen patients (20.9%) discontinued the treatment due to treatment emergent AEs, and 16 patients (17.6%) discontinued due to treatment emergent AEs that were also treatment-related.
In previous studies, neratinib has been associated with reports of gastrointestinal events (i.e. diarrhea, nausea, and vomiting), and fatigue [17, 18], with incidences similar to those observed in the current study. Diarrhea typically occurred within a few days of neratinib initiation in the current study (mean 7.3, median 3 days), consistent with previous studies (median time to onset of diarrhea of 2–8.5 days across studies), and has generally been managed with dose adjustments or antidiarrheal medications [17, 18]. Furthermore, diarrhea led to treatment discontinuation in only three (3%) patients in this study, consistent with previous neratinib monotherapy studies [17, 18]. More stringent diarrhea management guidelines have been implemented in later neratinib studies, but data regarding their efficacy are still limited. No clinically important skin toxic effects were observed.

The most frequent toxic effects associated with vinorelbine monotherapy are hematological, with non-hematological side-effects including grade 1/2 peripheral neuropathy, constipation, and phlebitis [32–36]. There was no tendency toward a higher incidence of these types of AEs with the addition of neratinib in the current study.

In the current study, the following results were observed based on independent assessment. For assessable patients with HER2-positive breast cancer and no prior lapatinib exposure, the ORR was 41% (31.6% in all treated patients with or

Figure 1. Progression-free survival (PFS) in patients receiving neratinib (240 mg) plus vinorelbine (25 mg/m²) with no prior lapatinib treatment (assessable population). The Kaplan–Meier median PFS estimates were based on both independent and investigator assessment of tumor data. Based on independent assessments, 33 (59%) patients with no prior lapatinib and 9 (75%) patients with prior lapatinib experienced progressive disease or death as of the date of this analysis; 23 and 3 patients, respectively, were censored in this analysis. Based on investigator assessments, 42 (75%) patients with no prior lapatinib and 10 (83%) patients with prior lapatinib experienced progressive disease or death; 14 and 2 patients, respectively, were censored in this analysis. PFS, progression-free survival; CI, confidence interval.
without prior lapatinib exposure), and the median duration of response was 52.7 weeks; this ORR is consistent with that observed in previous neratinib monotherapy studies (24%–32%) [17, 18]. Due to many patients with long-term stable disease, the CBR was 70% for assessable patients with no prior lapatinib exposure. The median PFS with neratinib and vinorelbine was 48.0 weeks in the no prior lapatinib cohort (assessable population), higher than the PFS observed with neratinib monotherapy (22.3 weeks in patients who received prior trastuzumab) [17]. Response rates in the current study also appear to be comparable with those investigating the combination of vinorelbine–trastuzumab, which have ranged from 30% to 70%—note, however, that in most of these studies, patients were not previously treated with trastuzumab [25–28, 37, 38].

Preliminary evaluation of pharmacokinetic parameters in the current study suggested no interaction between neratinib and vinorelbine. In contrast, concomitant administration of lapatinib with vinorelbine has been shown to reduce the plasma clearance of vinorelbine, possibly due to lapatinib inhibition of CYP450–3A4 [39].

In summary, oral neratinib 240 mg in combination with vinorelbine revealed no unexpected toxic effects, demonstrated no drug–drug interactions, and demonstrated encouraging antitumor activity in patients with advanced HER2-positive breast cancer, thus warranting further studies of neratinib in this patient population. Studies investigating other neratinib-based combinations are currently underway, such as trials of neratinib in combination with trastuzumab [40], capecitabine [41], paclitaxel [42], and temsirolimus [43].

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disclosure

The following authors of this paper declare that there is no conflict of interest involved in this paper: LD, LMS, BX, TL, and ES. AA and VD received honoraria for advisory board participation from Wyeth/Pfizer; DLH received investigators fees for conducting the study; RA is an employee of Inventiv Clinical Solutions who was a paid consultant to Pfizer in connection with the development of this manuscript and VA is an employee at Pfizer, which is the sponsor of the study.

references

Breast cancer management and outcome according to surgeon’s affiliation: a population-based comparison adjusted for patient’s selection bias

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Background: Studies have reported that breast cancer (BC) units could increase the quality of care but none has evaluated the efficacy of alternative options such as private BC networks, which is our study objective.

Patients and methods: We included all 1404 BC patients operated in the public unit or the private network and recorded at the Geneva Cancer Registry between 2000 and 2005. We compared quality indicators of care between the

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