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Dual HER2 inhibition in combination with anti-VEGF treatment is active in heavily pretreated HER2-positive breast cancer†

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Background: Preclinical data indicate that dual HER2 inhibition overcomes trastuzumab resistance and that use of an HER2 inhibitor with an anti-angiogenic agent may augment responses.
Patients and methods: We conducted a dose-escalation, phase I study of a combination of trastuzumab, lapatinib and bevacizumab. The subset of patients with metastatic breast cancer was analyzed for safety and response.
Results: Twenty-six patients with metastatic breast cancer (median = 7 prior systemic therapies) (all with prior trastuzumab; 23 with prior lapatinib; one with prior bevacizumab) received treatment on a range of dose levels. The most common treatment-related grade 2 or higher toxicities were diarrhea ($n = 11$, 42%) and skin rash ($n = 2$, 8%). The recommended phase 2 dose was determined to be the full Food and Drug Administration (FDA) approved doses for all the three agents (trastuzumab 8 mg/kg loading dose, 6 mg/kg maintenance dose, intravenously every 3 weeks; lapatinib 1250 mg daily, bevacizumab 15 mg/kg intravenously every 3 weeks). The overall rate of stable disease (SD) ≥6 months and partial or complete remission (PR/CR) was 50% (five patients with SD ≥6 months; seven PRs (including one unconfirmed); one CR). The rate of SD ≥6 months/PR/CR was not compromised in patients who had previously received study drugs, those with brain metastases, and patients treated at lower dose levels.

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Conclusions: The combination of trastuzumab, lapatinib and bevacizumab was well-tolerated at maximally approved doses of each drug, and its activity in heavily pretreated patients with metastatic breast cancer suggests that it warrants further investigation.

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Key words: breast cancer, her2, bevacizumab, trastuzumab, lapatinib

introduction

HER2 and EGFR play fundamental roles in cancer pathophysiology [1]. HER2 overexpression is present in 25%–30% of invasive breast cancers [2], and is associated with decreased survival [3]. Trastuzumab, a monoclonal antibody directed against the extracellular domain of HER2, is approved for the treatment of HER2-positive breast cancer and improves overall survival [4]. In addition to HER2 expression, EGFR amplification is present in ~6% of primary breast cancers [5]. Lapatinib, a dual kinase inhibitor, is approved for the treatment of metastatic HER2-positive breast cancer after progression on prior trastuzumab treatment [6].

HER2 overexpression is associated with vascular endothelial growth factor (VEGF) upregulation, which plays an important role in breast cancer development and metastases [7]. Bevacizumab, a recombinant monoclonal antibody to VEGF, has demonstrated improved response rate and progression-free survival in combination with paclitaxel, but has not improved overall survival, in patients with metastatic breast cancer [8]. Although targeting HER2, EGFR or VEGF alone does not provide adequate tumor control in many patients [9, 10], preclinical studies suggest potential for increased efficacy with combination therapy [11–13]. Furthermore, clinical trials of various doublet combinations of trastuzumab, lapatinib and bevacizumab suggest increased efficacy and that combined anti-HER2 and anti-VEGF treatment may overcome resistance to anti-HER2 monotherapy [14–18]. Here, we report the results of administering a dual HER2/EGFR inhibitor (lapatinib) and an HER2 antibody (trastuzumab) together with an anti-angiogenic agent (bevacizumab) in 26 patients with heavily pretreated breast cancer.

methods

study design and patients

The study was conducted at The University of Texas MD Anderson Cancer Center (MDACC) in accordance with Institutional Review Board guidelines. The breast cancer cohort reported herein included all patients with breast cancer who started therapy between 21 February 2008 and 28 October 2011 as part of a dose-escalation study conducted in patients with advanced cancer. The dose-escalation portion of the study determined the recommended phase II dose (RP2D) (Table 1). A cycle was 21 days. Patients with breast cancer reported herein were treated at variable dose levels, depending on the time of study entry (Table 1). Patients had metastatic or advanced breast cancer not amendable to established forms of therapy, an Eastern Cooperative Oncology Group (ECOG) performance status 0–2 [19], and adequate hematologic, hepatic and renal function. Further details on the exclusion criteria and molecular testing are available in supplementary methods, available at *Annals of Oncology* online.

safety

Clinically significant adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Clinical history, physical examination, hematology, blood chemistry and urinalysis were carried out at baseline and at regular intervals while receiving treatment.

evaluation of efficacy

Treatment efficacy was evaluated by diagnostic imaging per Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [20]. Radiologic assessments were conducted at baseline and about every 8 weeks thereafter. Patients with known brain metastases before enrollment underwent brain imaging at baseline and at regular intervals.

molecular testing

Molecular testing was carried out in the Clinical Laboratory Improvement Amendments approved MDACC laboratory, including estrogen and progesterone receptor by standard immunohistochemistry (IHC) [21], HER2 amplification by fluorescent *in situ* hybridization, HER2 expression by IHC (AB8 Neomarkers primary antibody (1:3000 dilution, Labvision, Fremont, California)) and EGFR and PIK3CA mutation analysis.

statistical analysis

Spearman's correlation, chi-square or Fisher's exact test, and an independent samples *t*-test were used to analyze correlations, dichotomous variables and mean differences, respectively.

results

demographics

Twenty-six patients with metastatic breast cancer were enrolled (Table 2). Most patients were heavily pretreated, with a median of seven prior systemic therapies in the adjuvant or metastatic setting (range 2–17). Histological features, molecular/receptor characteristics and prior therapies are described in Table 2.

adverse events

Twelve patients (46%) experienced no drug-related toxicity higher than grade 1. The most common treatment-related grade 2 or higher adverse events were diarrhea ($n = 11$, 42%) and rash ($n = 2$, 8%) (Table 1). Three patients experienced dose-limiting toxicity (DLT) due to diarrhea ($n = 3$, dose levels 7, 11 and 12). Seven patients required dose reduction for toxicity, including for diarrhea ($n = 4$), comorbid rash and elevated bilirubin ($n = 1$), comorbid diarrhea and skin fissures ($n = 1$), and comorbid diarrhea and mucositis ($n = 1$). Two patients (8%) withdrew due to toxicity, including diarrhea ($n = 1$) and fatigue ($n = 1$). No deaths resulted from adverse events.

Table 1. Treatment-related grade 2–4 adverse events

Dose level	1	2	3	4	5	6	7	8	9	10	11	12[a]	Total
	$n=0$	$n=1$	$n=0$	$n=1$	$n=1$	$n=1$	$n=3$	$n=2$	$n=2$	$n=2$	$n=3$	$n=10$	$n=26$
Bevacizumab dose, mg/kg IV q3w	2.5	2.5	5	5	5	7.5	7.5	7.5	10	10	10	15	
Trastuzumab dose, mg/kg IV q3w[b]	2,1	2,1	2,1	4,2	4,2	4,2	6,4	6,4	6,4	8,6	8,6	8,6	
Lapatinib dose, mg po daily	250	500	500	500	750	750	750	1000	1000	1000	1250	1250	
Fatigue													
Grade 3	0	0	0	0	0	0	0	1	0	0	0	0	1 (4%)
Skin rash													
Grade 2	0	0	0	0	0	0	0	0	0	1	1	0	2 (8%)
Hypertension													
Grade 2	0	0	0	0	0	0	1	0	0	0	0	0	1(4%)
Nausea													
Grade 2	0	0	0	0	0	0	1	0	0	0	0	0	1(4%)
Anorexia													
Grade 2	0	0	0	0	0	0	1	0	0	0	0	0	1(4%)
Diarrhea													
Grade 2	0	0	0	0	0	0	0	0	0	1	0	6	7 (26.9%)
Grade 3	0	0	0	0	0	0	1(DLT)	1	0	0	1(DLT)	1(DLT)	4 (15%)
Mucositis													
Grade 2	0	0	0	0	0	0	0	0	0	0	0	1	1 (4%)
Skin fissure													
Grade 2	0	0	0	0	0	0	0	0	0	0	0	1	1 (4%)
Elevated bilirubin													
Grade 2	0	0	0	0	0	0	0	0	0	1	0	0	1 (4%)

[a]Recommended phase II dose [22]. This includes full approved doses of each drug.

[b]Trastuzumab dose shown as loading dose, maintenance dose.

DLT, dose-limiting toxicity; IV, intravenous; po, orally; q3w, every 3 weeks.

responses

In total, SD ≥6 months, PR or CR was achieved in 13 patients (50%). The overall confirmed response rate was 27% (PR + CR) (Figure 1). One patient (4%) achieved a CR, but was noted to have brain metastases at 11 months (after non-specific complaints of memory loss); she did not have any evidence of systemic recurrence. It was unclear whether these brain metastases were new since no prior scans of the brain had been carried out. Her treatment was continued after stereotactic brain radiation, and she remains on treatment at 34+ months. This patient was the only individual on the study with micropapillary histology. No other patients received concomitant radiation or surgery while on study. Seven patients (27%) achieved a PR (one was an unconfirmed PR). The duration on study for six patients with confirmed PR was 4, 5, 6, 8+, 9 and 12, months.

prior HER2 inhibitor, EGFR inhibitor or VEGF inhibitor therapy and response

Prior trastuzumab and lapatinib, even if given concurrently, did not preclude SD ≥6 months/PR/CR. One of the two patients (50%) who received prior trastuzumab and no prior bevacizumab or lapatinib, achieved a PR. Of the 16 patients who received prior sequential trastuzumab and lapatinib, 9 (56%) achieved SD ≥6 months/PR/CR. Of the seven patients who had previously received concurrent trastuzumab and lapatinib, three (43%) achieved SD ≥6 months/PR/CR. The patient who had received prior concurrent trastuzumab and bevacizumab achieved SD for 4 months. Of the 13 patients with SD ≥6 months/PR/CR, 9 (69%) had received prior sequential trastuzumab and lapatinib, three (23%) had received prior concurrent trastuzumab and lapatinib and one (8%) had prior trastuzumab and no lapatinib nor any prior bevacizumab (Table 3 and Figure 1).

Among patients who previously received concurrent trastuzumab and lapatinib, the time from the prior exposure until starting the current clinical trial was 1, 1, 3, 4, 6 and 7 months, respectively. The prior concurrent trastuzumab and lapatinib treatment was discontinued for progressive disease in all patients, except for one who discontinued treatment because of diarrhea. The duration of prior trastuzumab and lapatinib was similar to the duration of treatment on the current clinical trial in two cases, and one patient (#227) was on the current trial for 4+ months longer than the prior treatment with concurrent trastuzumab and lapatinib. She continues receiving treatment on this trial without progression.

Among the five patients who had received prior HER2 kinase inhibitor ARRY-380, two had also received prior sequential trastuzumab and lapatinib, and three had received prior concurrent trastuzumab and lapatinib. One of these five patients, who was previously treated with ARRY-380 and had also received prior sequential trastuzumab and lapatinib, achieved SD of 8 months.

brain metastases and response

Of the 10 patients with brain metastases, 6 (60%) achieved SD ≥6 months/PR/CR (Table 3), with the longest duration being

Table 2. Patient demographics

Characteristics ($n = 26$)	
Age (years)	
Median	56
Range	28–72
Gender, *n* (%)	
Women	26 (100%)
Histologies, *n* (%)	
Invasive ductal	20 (77%)
Mixed ductal and lobular	2 (8%)
Poorly differentiated carcinoma	1 (4%)
Unspecified carcinoma	1 (4%)
Unspecified adenocarcinoma	1 (4%)
Micropapillary carcinoma	1 (4%)
No. of prior systemic therapies[a]	
Median	7
Range	2–17
Prior trastuzumab	26
Prior trastuzumab (but no prior bevacizumab or lapatinib)	2
Prior trastuzumab and lapatinib (sequential)	13
Prior trastuzumab and lapatinib (sequential) and ARRY-380	3
Prior trastuzumab and lapatinib (concurrent)	5
Prior trastuzumab and lapatinib (concurrent) and ARRY-380	2
Prior trastuzumab and bevacizumab	1
Months since the last exposure to trastuzuamb or lapatinib	
Median	2
Range	1–9
Estrogen and/or progesterone receptor expression, *n* (%)	
Positive	12 (46%)
Negative	14 (54%)
EGFR mutations, *n* (%)	
Positive	0 (0%)
Negative	12 (46%)
Unknown	14 (54%)
HER2 amplification	
Positive	26 (100%)
Negative	0 (0%)
ECOG performance status, *n* (%)	
0	5 (19%)
1	21 (81%)

[a]Includes both adjuvant and metastatic regimens.
ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor 1; HER2, human epidermal growth factor receptor 2.

12+ months. Therefore, the presence of brain metastases did not preclude SD ≥6 months/PR/CR. Only one patient attained measurable decrease in brain metastases; in the other five patients the brain lesions remained stable. Of the four patients with progressing brain metastases at the time of enrollment, one achieved an unconfirmed PR and received treatment for 6 months. None of the patients experienced adverse events related to brain metastases.

dosing and response

Of the 15 patients on dose levels 10–12 (Table 1, Figure 1), 7 (47%) achieved SD ≥6 months/PR/CR. For the patients treated at dose levels 1–9, 6 of 11 (55%) achieved SD ≥6 months/PR/CR ($P = 1.00$, Table 1 and Figure 1). The only patient who achieved CR was treated at dose level 6 and remains on treatment at 34+ months. Therefore, there was no obvious dose–response correlation, although the number of patients was small. The treatment duration was 7.55 (SD = 9.37) and 4.93 (SD = 3.63) months for patients who received lower (levels 1–9) and higher (levels 10–12) dose levels, respectively. There was a non-significant trend toward longer treatment duration for individuals given low doses versus high doses ($t(24) = .9884$, $P = 0.33$).

molecular aberrations and responses

Achievement of SD ≥6 months/PR/CR was observed in 4 of the 12 patients (33%) positive for estrogen or progesterone receptors, versus 9 of 14 patients (64%) negative for both estrogen and progesterone receptors ($P = 0.24$).

All 26 patients in this study (100%) had HER2 amplification. Of the 12 patients tested, all were EGFR wild type, and 7 (58%) achieved SD ≥6 months/PR/CR.

Of the two patients tested, only one had a PIK3CA mutation (H1047R), and she received treatment for only 2.3 months before progressing.

histology and response

The patient with the best response to treatment (CR by RECIST) was the only patient in the study with micropapillary histology. Of the six patients with non-ductal histology, four (67%) achieved SD ≥6 months/PR/CR. Nine of the 20 patients (45%) with tumors with ductal histology achieved SD ≥6 months/PR/CR.

toxicity and response

Diarrhea was the most frequently observed adverse event (Table 1), with 11 patients (42%) experiencing grade 2 or higher diarrhea. Of the 11 patients with grade 2 or higher diarrhea, 6 (55%) achieved SD ≥6 months/PR/CR. Of the 15 patients with grade 1 or no diarrhea, 7 (47%) achieved SD ≥6 months/PR/CR ($P = 1.00$).

discussion

We report the results of the cohort of patients with metastatic breast cancer, treated on a phase I dose-escalation trial of combination bevacizumab, trastuzumab and lapatinib. This combination of drugs was well tolerated, and the recommended phase 2 dose was determined to be the full FDA-approved doses for all the three drugs [22]. In contrast to previous studies in which trastuzumab was combined with lapatinib 1000 mg daily [14, 15], our study demonstrated that combination with lapatinib 1250 mg daily was well tolerated. The prevalence and severity of diarrhea, the most commonly observed adverse effect on this study, were similar to what has been reported previously in lapatinib monotherapy studies [23]. This regimen demonstrated antitumor activity with 13 patients (50%) who had a best overall response of SD ≥6 months ($n = 5$), PR ($n = 7$) (one PR was unconfirmed), or CR ($n = 1$). Antitumor activity was observed even in patients who were heavily pretreated, who

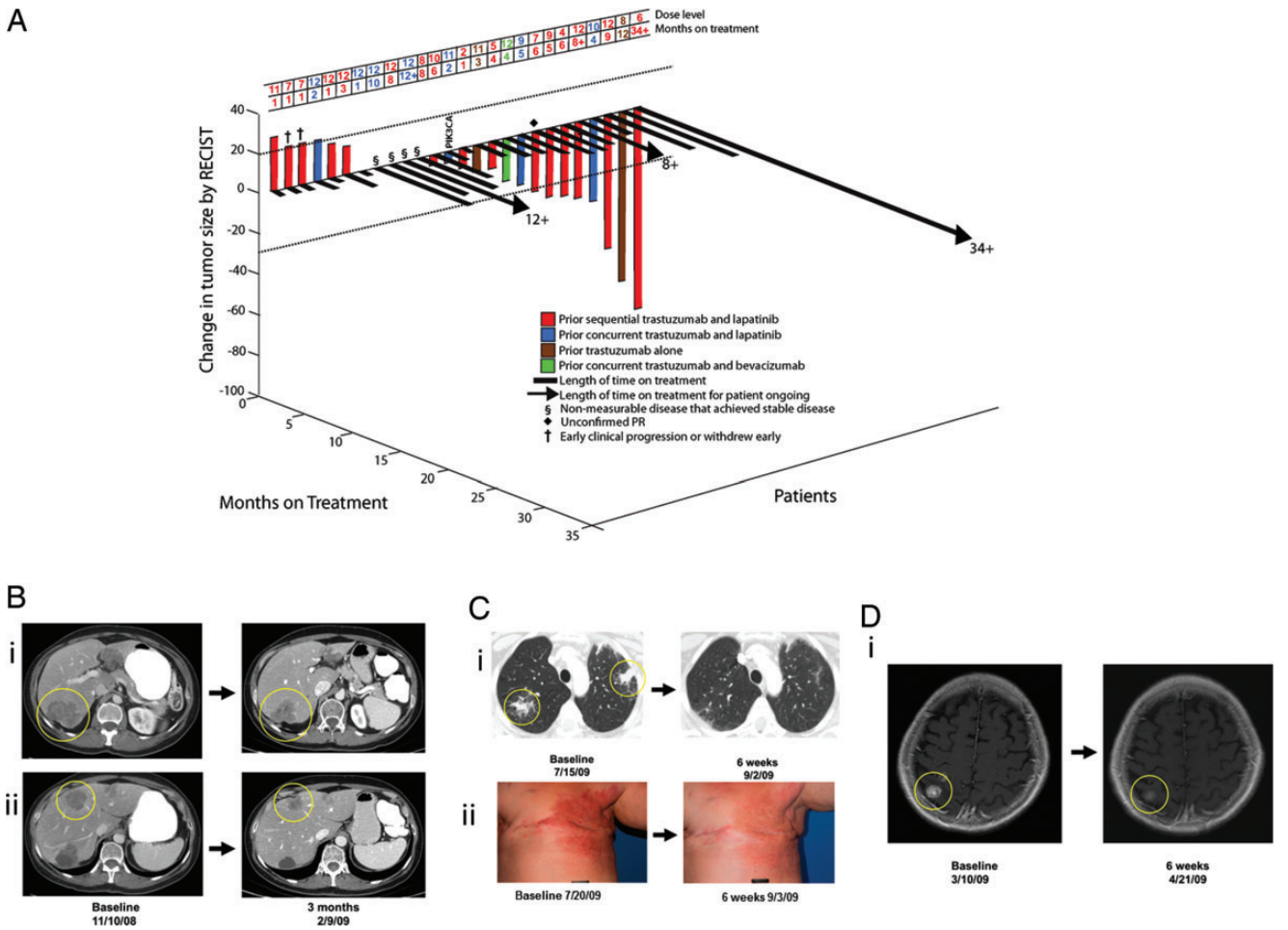

Figure 1. (A) 3DWaterfall plot showing best response as determined by Response Evaluation Criteria in Solid Tumors (RECIST) and the time on study in all 26 breast cancer patients treated. The patient who withdrew before first restaging due to grade 3 diarrhea and any patients with clinical progression or new lesions are arbitrarily depicted as 21% increase by RECIST and are considered treatment failures. Patients with non-measurable disease that achieved best response of stable disease (SD) are depicted in the figure as +0.5%. None of the patients had prior cetuximab or erlotinib. The patient with a PIK3CA mutation is noted as such. The dose level for each patient and the number of months the patient received treatment on study are shown in the table above the waterfall plot. Patients still on treatment have a '+' after the number of months and are indicated with an arrow (>) on the black bar for that patient. (B) Patient with partial response (36% decrease, seven prior systemic therapies) on treatment for 6 months. (i) and (ii) computed tomography (CT) scans showing decrease in size of liver metastases. (C) Patient with partial response (86% decrease, three prior systemic therapies), (i) CT scans showing decreased size of lung metastases, (ii) response in skin metastases. (D) Patient with brain metastases only and partial response (30% decrease, six prior systemic therapies), CT scans showing the decrease in size of brain metastases.

had received prior trastuzumab and/or lapatinib, those with brain metastases and patients treated at lower dose levels. Of interest, the best response was in the only individual on study with micropapillary histology. Invasive micropapillary cancer of the breast is a distinct and aggressive HER2+ variant of breast cancer with high relapse rates and short disease-free intervals [24]. This patient continues on study at 34+ months.

Remarkably, patients who had failed prior concurrent or sequential trastuzumab and lapatinib achieved SD ≥6 months/PR/CR. In fact, overcoming resistance to prior concurrent trastuzumab and lapatinib and achieving a longer treatment duration with the combination of trastuzumab, lapatinib and bevacizumab was demonstrated, which may suggest that the contribution of bevacizumab to this treatment combination is significant.

The presence of brain metastases did not compromise the rate of SD ≥6 months/PR/CR, suggesting that patients with HER2+ breast cancer and brain metastases can safely receive this regimen and that it has activity. None of the patients experienced intracranial hemorrhage as a result of the treatment. Although brain metastasis involvement has been an exclusion criterion in many breast cancer trials that include bevacizumab [25], recent studies suggest that brain metastases do not preclude safe treatment with bevacizumab [26], and our study further supports the safety of bevacizumab in the presence of brain metastases.

Low dose levels did not preclude response, which is in accordance with the previous literature [27]. No maximum tolerated dose was found in this study, and a non-significant trend of longer treatment duration was observed in patients

Table 3. Patient characteristics for those who achieved stable disease (SD) of at least 6 months, partial response or complete response

Case #	Histology	Best Response %	Treatment duration (months)	Estrogen Receptor positive	Progesterone receptor positive	EGFR mutation	HER2 Amplification	PIK3CA mutation	Prior trastuzumab	Prior bevacizumab	Prior lapatinib	Prior ARRY-380	Brain metastases	Dose Level	Diarrhea Grade
64	Papillary carcinoma	−100	34+[a]	No	No	ND	Yes	ND	Yes	No	Yes	No	No	6	0
103	Invasive ductal carcinoma	−86	12	No	No	ND	Yes	ND	Yes	No	No	No	No	8	0
210	Carcinoma	−67	9	Yes	Yes	No	Yes	ND	Yes	No	Yes	No	Yes	12	2
230	Invasive ductal carcinoma	−41	4	No	No	ND	Yes	ND	Yes[b]	No	Yes[b]	No	Yes	10	2
236	Invasive ductal carcinoma	−38	8+	No	No	ND	Yes	ND	Yes	No	Yes	No	No	12	2
121	Invasive ductal carcinoma	−35	5	Yes	Yes	No	Yes	ND	Yes	No	Yes	No	Yes	9	0
49	Invasive ductal carcinoma	−36	6	No	No	No	Yes	ND	Yes	No	Yes	No	No	4	0
68	Invasive ductal carcinoma	−30[c]	6	No	No	No	Yes	ND	Yes	No	Yes	No	Yes	7	0
127	Invasive ductal carcinoma	−5	6	No	No	No	Yes	ND	Yes	No	Yes	No	No	10	1
227	Ductal and lobular carcinoma	0[d]	12+	Yes	Yes	ND	Yes	ND	Yes[b]	No	Yes[b]	No	Yes	12	2
170	Invasive ductal carcinoma	0[d]	10	No	No	No	Yes	ND	Yes[b]	No	Yes[b]	No	No	12	1
109	Poorly differentiated carcinoma	0[d]	8	Yes	Yes	ND	Yes	ND	Yes	No	Yes	Yes	Yes	8	3
203	Invasive ductal carcinoma	0[d]	8	No	No	No	Yes	ND	Yes	No	Yes	No	No	12	2

[a]Patient 64 was discovered to have brain metastases at 11 months but did not have any evidence of systemic recurrence. Her brain metastases were treated with radiation, and her treatment was continued. She remains on treatment at 34+ months without systemic recurrence.

[b]Indicates patients who received prior study drugs concurrently.

[c]Indicates an unconfirmed PR.

[d]Patients 109, 170, 203 and 227 had non-measurable disease by RECIST guidelines.

EGFR, epidermal growth factor receptor 1; HER2, human epidermal growth factor receptor 2; ND, not done; PIK3CA, phosphoinositide-3-kinase, catalytic, alpha polypeptide; +, indicates ongoing therapy.

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receiving low dose levels. As such, while the R2PD includes full FDA recommended doses, lower doses may also be considered.

One limitation of our study was the inability to identify a relevant biomarker for response. In the AVEREL phase III trial of bevacizumab with trastuzumab in combination with docetaxel, analysis suggested that high VEGF-A levels were associated with better response in the bevacizumab arm, but not significantly so [28]. In contrast, other trials have failed to identify correlation between VEGF-A level and efficacy, and further studies are needed to validate VEGF-A isoforms and other prospective biomarkers [29].

In conclusion, the results presented here demonstrate that dual inhibition of HER2 with trastuzumab and lapatinib, combined with the VEGF antibody bevacizumab, is well tolerated, allowing full doses of all the three drugs in patients with HER2+ breast cancer. SD ≥6 months/PR/CR was achieved in 50% of this heavily pretreated patient population, suggesting that this regimen merits further investigation, perhaps in a randomized trial in comparison with combination of trastuzumab and lapatinib, with biomarker correlates to identify patient subgroups which may be more likely to benefit from bevacizumab.

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disclosure

All the remaining authors have declared no conflicts of interest.

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Diabetes in relation to breast cancer relapse and all-cause mortality in elderly breast cancer patients: a FOCUS study analysis

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Background: In developed countries, 40% of breast cancer patients are >65 years of age at diagnosis, of whom 16% additionally suffer from diabetes. The aim of this study was to assess the impact of diabetes on relapse-free period (RFP) and overall mortality in elderly breast cancer patients.
Patients and Methods: Patients were selected from the retrospective FOCUS cohort, which contains detailed information of elderly breast cancer patients. RFP was calculated using Fine and Gray competing risk regression models for patients with diabetes versus patients without diabetes. Overall survival was calculated by Cox regression models, in which patients were divided into four groups: no comorbidity, diabetes only, diabetes and other comorbidity or other comorbidity without diabetes.
Results: Overall, 3124 patients with non-metastasized breast cancer were included. RFP was better for patients with diabetes compared with patients without diabetes (multivariable HR 0.77, 95% CI 0.59–1.01), irrespective of other comorbidity and most evident in patients aged ≥75 years (HR 0.67, 95% CI 0.45–0.98). The overall survival was similar for patients with diabetes only compared with patients without comorbidity (HR 0.86, 95% CI 0.45-0.98), while patients with diabetes and additional comorbidity had the worst overall survival (HR 1.70, 95% CI 1.44–2.01).
Conclusion: When taking competing mortality into account, RFP was better in elderly breast cancer patients with diabetes compared with patients without diabetes. Moreover, patients with diabetes without other comorbidity had a similar overall survival as patients without any comorbidity. Possibly, unfavourable effects of (complications of) diabetes on overall survival are counterbalanced by beneficial effects of metformin on the occurrence of breast cancer recurrences.
Key words: breast cancer, diabetes, elderly, geriatric oncology, metformin, observational study

introduction

With the aging of Western Societies, elderly will account for an increasing percentage of breast cancer patients in developed countries [1]. High age is predictive of comorbidity and decreased functioning [2, 3] both associated with decreased overall survival in elderly breast cancer patients [4]. The incidence of diabetes is increasing worldwide. Importantly, diabetes mellitus type 2 has been shown to increase breast cancer risk in postmenopausal women [5]. High levels of insulin may have a direct effect on breast tissue, or indirect effects through increase in sex steroids due to inhibition of sex hormone-binding globulin, disruption of adipokines and increased insulin-like growth factor-I production[6]. Additionally, diabetes is associated with obesity and excess body weight is related to increased cancer risk in postmenopausal women [7].

At present, up to 16% of elderly breast cancer patients additionally suffer from diabetes [8]. In several cohort studies, it

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