Open-Label, Phase II, Multicenter, Randomized Study of the Efficacy and Safety of Two Dose Levels of Pertuzumab, a Human Epidermal Growth Factor Receptor 2 Dimerization Inhibitor, in Patients With Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer

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See accompanying editorials on pages 1089 and 1091 and articles on pages 1124, 1138, and 1215

ABSTRACT

Purpose

Pertuzumab is a humanized monoclonal antibody inhibiting human epidermal growth factor receptor 2 (HER2) dimerization. The aim of this phase II trial was to assess the antitumor activity and safety profile of pertuzumab monotherapy in patients with HER2-negative metastatic breast cancer. The utility of biomarkers detected in paraffin-embedded tissue as predictors of response was also explored.

Patients and Methods

This was an international, multicenter, open-label, randomized phase II study. Patients ($n = 79$) with centrally confirmed HER2-negative metastatic breast cancer were randomly assigned to receive pertuzumab once every 3 weeks with a loading dose of 840 mg followed thereafter by either 420 mg (arm A) or 1,050 mg (arm B). Patients were stratified by country and prior taxane therapy.

Results

Of 79 patients who were randomly assigned, 78 were included in the intent-to-treat population. In arm A ($n = 41$), two patients had partial responses, and 18 patients (44%) experienced stable disease (SD) lasting ≥ 12 weeks. In arm B ($n = 37$), SD was observed in 14 patients (38%). Overall, six of 78 patients responded or had SD ≥ 6 months. Pertuzumab was generally well tolerated, and most adverse events were mild to moderate. Decline in left ventricular ejection fraction of $\geq 10\%$ and/or to less than 50% was observed in eight patients, with one case of congestive heart failure in arm A. Pharmacokinetic data supported a fixed dose of pertuzumab once every 3 weeks.

Conclusion

The limited efficacy observed in this study, generally SD of relatively short duration, suggested little benefit of further investigation of single-agent pertuzumab in unselected patients with HER2-negative disease.

J Clin Oncol 28:1131-1137. © 2010 by American Society of Clinical Oncology

INTRODUCTION

The human epidermal growth factor family of receptors (HER1/EGFR, HER2, HER3, and HER4) mediates cell growth and is dysregulated in many types of cancer.¹⁻³ Ligand-driven heterodimerization of HER2 with other HER family members leads to downstream signal transduction, which plays an important part in neoplastic transformation and disease progression.³⁻⁶ Receptor heterodimerization may have a critical role in breast cancers that overexpress multiple members of the

HER family.⁷⁻¹¹ Furthermore, dysregulation of HER signaling, including ligand overexpression or abnormal activity, decreased receptor turnover, or receptor mutation can also increase HER signaling activity and is associated with aggressive disease and poor prognosis in many solid tumor types, including breast cancer.^{3,12}

Pertuzumab (rhuMab 2C4; F. Hoffmann-La Roche, Basel, Switzerland), a recombinant humanized monoclonal antibody directed against the highly conserved dimerization domain of HER2, inhibits HER2 homo- and heterodimerization.¹³⁻¹⁵

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Submitted May 18, 2009; accepted August 13, 2009; published online ahead of print at www.jco.org on February 1, 2010.

Supported by F. Hoffmann-La Roche (Roche).

Presented in part at the 41st Annual Meeting of the American Society of Clinical Oncology, May 13-17, 2005, Orlando, FL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2807-1131/\$20.00

DOI: 10.1200/JCO.2009.24.1661

Blockage of HER2 dimerization by pertuzumab inhibits HER family downstream signaling, such as activation of the AKT cell survival pathway and the mitogen-activated protein kinase pathway.¹⁵⁻¹⁷

Preclinical models have shown that pertuzumab inhibits tumor growth in the absence of HER2 overexpression, unlike trastuzumab, presumably by preventing ligand-stimulated HER2 heterodimer formation.¹⁸⁻²⁰ A phase I study demonstrated that pertuzumab is generally well tolerated and clinically active in patients with locally advanced recurrent or metastatic solid tumors²¹ and that the pharmacokinetic profile of pertuzumab supports a dosing regimen of a fixed dose (420 or 1,050 mg) once every 3 weeks.^{20,22-25} On the basis of these observations, this phase II study was designed to evaluate the efficacy and safety of two dose levels of pertuzumab in patients with HER2-negative metastatic breast cancer.

PATIENTS AND METHODS

Study Design

This open-label, phase II, multicenter, randomized study was conducted at 14 centers in eight countries. The primary objective was response rate for each treatment regimen per Response Evaluation Criteria in Solid Tumors (RECIST).²⁶ The secondary objectives were time to progression (TTP), time to treatment failure, time to response, duration of response, and rate of stable disease (SD). Characterizing the pharmacokinetics of pertuzumab and evaluating its safety and tolerability were secondary end points for both dose levels. An exploratory analysis evaluated the utility of biomarkers in predicting response to pertuzumab.

Patients

Women were enrolled who were age ≥ 18 years, had a prior histologically documented diagnosis of breast cancer with a measurable lesion according to RECIST, had a Karnofsky performance status $\geq 80\%$, had metastatic disease treated with up to two lines of chemotherapy, and had anthracycline-containing therapy either in an adjuvant setting or for metastatic disease. Central laboratory confirmation, using fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC), of the lack of HER2 amplification or high expression (FISH-negative and IHC HER2 0, 1+, or 2+) was required. Patients were required to have tumor blocks available for evaluation or to have a biopsy of lymph nodes or accessible tumor lesions. Adequate hematologic, renal, and hepatic function were required. Exclusion criteria included any major surgery, investigational drug or cytotoxic chemotherapy ≤ 28 days before starting pertuzumab, previous malignancy, pulmonary metastases with lymphangitis or dyspnea at rest, history or clinical evidence of CNS metastases, history of cardiac disease, poorly controlled hypertension or significant valvular disease, left ventricular ejection fraction (LVEF) less than 50%, prior cumulative dose of doxorubicin at more than 360 mg/m² or epirubicin at more than 720 mg/m², prior treatment with any agent targeting the HER family, or prior serious uncontrolled intercurrent illness. Women who were pregnant, lactating, or of childbearing age not using adequate contraception were also not eligible. The study was approved by the local ethics committees of all participating institutions. Written informed consent was obtained from all patients.

All patients had a screening assessment at baseline that included a physical examination, determination of performance status and vital signs, complete blood count, blood chemistry, pregnancy test for women of childbearing potential, electrocardiography (ECG), echocardiography (ECHO), chest x-ray, and tumor assessment.

Study Treatment

Patients were randomly assigned by a central randomization service in a 1:1 ratio to either arm A or arm B and stratified by country of origin and previous exposure to taxane therapy. Intravenous pertuzumab infusion was administered at two dose levels as previously described²⁷: a loading dose of 840 mg on day 1 to rapidly achieve steady-state levels, followed by 420 mg every 3 weeks (arm A) or no loading dose and 1,050 mg every 3 weeks (arm B).

Treatment was continued until disease progression, unacceptable toxicity, or death.

Tolerability Assessments

Adverse events (AEs) were assessed during all visits. The incidence, severity, and relationship to study drug of AEs were recorded using the National Cancer Institute Common Toxicity Criteria v2.0. ECHO with LVEF measurements was performed at baseline within 28 days before the first pertuzumab infusion, at cycles 2, 4, 8, 12, and 16, and at final visit. For patients with inadequate acoustic windows for ECHO, multiple-gated acquisition scans were used to assess LVEF. ECGs were required at baseline and on study exit. Copies of ECGs, ECHO recordings, or multiple-gated acquisition scans were sent to a central laboratory for independent review. Serum samples for cardiac troponin T and plasma samples for nitrogen terminal pro-brain natriuretic protein were collected at baseline and within 15 minutes of the end of pertuzumab infusions.

Response Assessments

Tumors were assessed using identical techniques every 6 weeks (2 cycles) until cycle 8 and every fourth cycle thereafter. Response to therapy was assessed according to RECIST. For tumor assessment, all films were duplicated and sent for centralized radiology evaluation.

Biomarker and Tumor Biopsy Analyses

The following tests were performed on tumor blocks (paraffin-embedded tissue) following random assignment: HER2 IHC and/or FISH estrogen receptor/progesterone receptor status; quantitative reverse transcriptase polymerase chain reaction for HER1 and HER ligand mRNA expression (amphiregulin, betacellulin, EGF, transforming growth factor- α [TGF- α], and neuregulin 1); IHC for HER1, HER3, and phosphorylated HER2; and IHC testing for components of downstream or alternative signal transduction pathway from HER family receptors (phosphorylated AKT, phosphatase and tensin homolog [PTEN], insulin-like growth factor 1 receptor [IGF-1R]), and HER ligand expression (EGF, TGF- α , amphiregulin). Serum samples for biomarker analyses were collected at screening. Assessments included serum levels of HER2 extracellular domain and HER ligands (EGF, TGF- α , amphiregulin, and neuregulin 1).

Pharmacokinetic Analyses

Serum pharmacokinetic samples were collected at cycles 1 and 2 immediately before infusion and 15 minutes following the end of infusion on days 1, 8, and 15. Additional samples were collected before drug administration on day 1 of subsequent cycles.

Pertuzumab concentrations were determined by a receptor-binding, enzyme-linked immunosorbent assay, using the antigen p185HER2 extracellular domain to capture pertuzumab from serum samples. Validation data show that p185HER2 extracellular domain at 100 ng/mL interferes with pertuzumab quantitation at 60 ng/mL. Bound pertuzumab was detected with mouse antihuman Fc-horseradish peroxidase (Jackson ImmunoResearch Laboratories, West Grove, PA), and tetramethyl benzidine (Kirkegaard & Perry Laboratories, Gaithersburg, MD) was used as the substrate for color development to quantify serum pertuzumab against a standard curve. The assay had a minimum quantifiable concentration of 0.25 μ g/mL for pertuzumab in human serum. Serum pharmacokinetics of pertuzumab were summarized by arm (mean, standard deviation, and range) for area under the plasma concentration-time curve, maximum plasma concentration, clearance, volume of distribution, elimination half-life, and mean residence time.

Statistical Analyses

A sample size of 56 evaluable patients per arm was used, with a Simon's two-stage design allowing for stopping the study due to lack of treatment activity ($\leq$ one response in 23 patients per arm) after the first stage. The type I error rate was 4.12% and the power to reject the null hypothesis (objective response rate $\leq 5\%$) was approximately 57% in both study arms when the true response rate in each arm was 15%. The null hypotheses were rejected after the second stage if there were more than six responses from 56 patients. To account for a possible unevaluable rate of less than 10%, four additional patients were added to each arm, bringing the total patient number per arm to 60.

Fig 1. CONSORT diagram.

The intent-to-treat population included all patients who received at least one dose of pertuzumab. All patients who received at least two cycles of therapy and had their disease re-evaluated were considered evaluable for efficacy analysis, including patients who exhibited objective disease progression before the end of cycle 1 as long as they had received at least one dose of pertuzumab. Kaplan-Meier estimates of TTP and survival time were calculated. All patients who received at least one dose of the study drug were included in safety analyses.

RESULTS

Patient Characteristics

Because enrollment was stopped following a protocol-defined interim analysis, 79 patients enrolled in the study, 78 of whom were evaluable for intent-to-treat and efficacy analyses (arm A, $n = 41$; arm B, $n = 37$; Fig 1). One patient was not evaluable because she did not receive study medication. Baseline characteristics of patients were well balanced between the two arms (Table 1). Patients in both arms received a median of two cycles of pertuzumab. The majority of patients (92.4%) discontinued study treatment because of disease progression.

Response to Treatment

Of the 78 patients evaluable for efficacy (using independent review as described in Patients and Methods), six patients (7.7%) had either a partial response (PR) or SD ≥ 24 weeks. Two patients (4.9%) who received the pertuzumab 420 mg dose experienced a PR lasting 18 weeks in one patient with target lesions in the liver (HER2 IHC 2+) and 31 weeks in the other, who had target lesions on the skin (posterior axillary pillar; HER2 IHC 1+), with time to response of 18 and 6.1 weeks, respectively (Table 2). SD lasting ≥ 24 weeks was reported in two patients in each arm. The median duration of clinical benefit (complete response, PR, or SD ≥ 24 weeks) was 36.5 weeks (range, 22.1 to 74.9 weeks) in arm A and 33.6 weeks (range, 31.0 to 36.3 weeks) in arm B. SD lasting ≥ 12 weeks was observed in 18 patients (43.9%) in arm A and 14 (37.8%) in arm B. Median time to treatment failure was 6.3 weeks (range, 2 to 80.1 weeks) in arm A and 6.0 weeks (range, 2.7 to 36.3 weeks) in arm B. Median TTP (Fig 2) was 44 days in arm A (95% CI, 38 to 82 days) and 43 days in arm B (95% CI, 39 to 85 days).

Safety

Both dose levels of pertuzumab were generally well tolerated. Most frequent toxicities in both arms were grade 1 to 2 diarrhea,

Table 1. Baseline Characteristics of Patients (N = 78) and Characteristics of Treatment

Characteristic	Arm A (n = 41)		Arm B (n = 37)	
	No.	%	No.	%
Age, years				
Median	54		55	
Range	33-76		36-78	
Karnofsky performance status, %				
100		44		46
90		37		35
80		20		19
Total number of lesions				
Median	5		5	
Range	1-16		1-14	
Number of tumor sites				
1	1	2	1	3
2-5	25	61	25	68
6-10	14	34	9	24
11-15	0	0	2	5
> 15	1	2	0	0
Metastatic sites				
Visceral	32	78	31	84
Liver	19	46	19	51
Bone	14	34	16	43
Lung	13	32	17	46
Soft tissue	11	27	2	5
Other	33	80	25	68
ER/PgR status, %/%				
Positive	71/51		76/57	
Negative	24/32		24/35	
Unknown	5/17		0/8	
HER2 status by IHC*				
0	3	7	1	3
1+	19	46	14	38
2+	19	46	22	60
3+	0	0	0	0
Prior treatment for metastatic disease				
Anthracycline	41	100	37	100
Radiotherapy	36	88	32	87
Hormone therapy	30	73	31	84
Taxane	26	63	24	6
Capecitabine	8	20	7	19
Pertuzumab cycles completed				
Median	2		2	
Range	1-24		1-12	

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry.

*Assessed in the central laboratory.

asthenia, nausea, and vomiting. Table 3 summarizes the most frequent drug-related AEs. Only two toxicities led to drug discontinuation; one congestive heart failure (CHF; arm A), and one grade 3 diarrhea (arm B). Drug-related serious AEs in arm A included the previously mentioned CHF, two episodes of sepsis in one patient, and two patients with asymptomatic decreases in LVEF; serious AEs in arm B included grade 3 diarrhea and an infusion-associated reaction (urticaria).

Eight patients (three in arm A and five in arm B) experienced drops in LVEF of $\geq 10\%$ such that LVEF fell to less than 50%. All cases were asymptomatic, except in two patients in arm A including the previously mentioned patient with CHF who had received prior doxo-

Table 2. Efficacy End Points (N = 78)

Variable	Arm A (n = 41)		Arm B (n = 37)	
	No.	%	No.	%
PR	2	4.9	0	
SD ≥ 12 weeks	18	43.9	14	37.8
SD ≥ 24 weeks	2	4.9	2	5.4
Progressive disease	21	51.2	22	59.5
Missing	0		1	2.7
Clinical benefit (CR + PR + SD ≥ 24 weeks)	4	9.8	2	5.4
Duration of clinical benefit, weeks				
Median	36.5		33.6	
Range	22.1-74.9		31.0-36.3	
Time to progression, weeks				
Median	6.1		6.1	
Range	2.0-37.0		2.7-36.3	

Abbreviations: PR, partial response; SD, stable disease; CR, complete response.

rubin therapy and withdrew from the study. The second patient, who had previously received epirubicin in the metastatic setting, experienced syncope, dyspnea, and blackouts (LVEF, 25% of absolute value) that resolved and treatment was continued. A follow-up LVEF assessment 3 weeks later showed a recovery to baseline (60%). The median time to lowest LVEF in these eight patients was 100 days (range, 41 to 175 days) and, of the patients with a drop in LVEF that required a repeat assessment after 3 weeks, all LVEFs recovered to allow treatment to continue (LVEF, 40% to 45% absolute value and < 10 percentage points from that at baseline or LVEF $> 45\%$ absolute value) in the absence of disease progression or unacceptable toxicity. Because baseline LVEF was $\leq 55\%$ at study entry in all patients who experienced cardiac dysfunction, this may be a subgroup of susceptible patients. No correlation was observed between NT-pBMP and cardiac events (data not shown). Furthermore, no cardiac events occurred in the two patients who had increased troponin T levels.

Tumor and Blood Biomarkers

Analysis by quantitative reverse transcriptase polymerase chain reaction was performed in 46 of the 78 tumor blocks that met test requirements. IHC analyses were performed on between 37 and 49 tumor samples for the following analytes: pHER2, EGFR, HER3, EGF, phosphorylated AKT, PTEN, IGF-1R, and TGF- α . There was

Fig 2. Progression-free survival.

Table 3. Drug-Related Adverse Events: Grade 1-2 ($\geq 10\%$) and All Grade 3-4

Adverse Event	Arm A (n = 41)								Arm B (n = 37)							
	Grade 1		Grade 2		Grade 3		Total		Grade 1		Grade 2		Grade 3		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Any event	26	63.4	19	46.3	6	14.6	31	75.6	28	75.7	19	51.4	5	13.5	32	86.5
Diarrhea	10	24.4	8	19.5	3	7.3	21	51.2	9	24.3	8	21.6	2	5.4	19	51.4
Nausea	8	19.5	2	4.9	0		10	24.4	6	16.2	4	10.8	0		10	27.0
Fatigue/asthenia	5	12.2	3	7.3	1	2.4	9	22.0	5	13.5	4	10.8	0		9	24.3
Rash*	8	19.5	0		0		8	19.5	5	13.5	3	8.1	0		8	21.6
Vomiting	3	7.3	2	4.9	1	2.4	6	14.6	3	8.1	3	8.1	0		6	16.2
Abdominal pain	2	4.9	3	7.3	0		5	12.2	4	10.8	1	2.7	0		5	13.5
Headache	2	4.9	3	7.3	0		5	12.2	1	2.7	0		0		1	2.7
Stomatitis	1	2.4	3	7.3	0		4	9.8	1	2.7	3	8.1	0		4	10.8
Anorexia	1	2.4	1	2.4	0		2	4.9	3	8.1	2	5.4	0		5	13.5
Anemia	1	2.4	0		0		1	2.4	2	5.4	2	5.4	0		4	10.8

*Includes rash, erythema, eczema, macular rash, maculopapular rash, pruritic rash, and urticaria.

no relevant correlation between clinical end points and immuno-reactive scores.

Blood serum markers were assessed for all patients. Multivariate analyses showed that combinations of serum markers may improve prediction of benefit from pertuzumab in this patient population, though in general little benefit was observed.

Pharmacokinetic Results

Plasma pharmacokinetics were assessed in 40 patients in arm A and 37 patients in arm B (Table 4). The mean terminal half-life obtained in the study appears to be short (15.6 days in arm A and 19.5 days in arm B) compared with those of other immunoglobulin G monoclonal antibodies (3 to 4 weeks).

DISCUSSION

This trial was designed to evaluate the efficacy and safety of two dose levels of pertuzumab administered every 3 weeks in patients with metastatic breast cancer without HER2 overexpression or amplification. The data presented here show that single-agent pertuzumab generally caused SD of relatively short duration in approximately 40%

of patients with HER2-negative breast cancer, with 7.7% of patients experiencing either PR or SD ≥ 6 months (clinical benefit).

Pertuzumab was generally well tolerated at both dose levels in this study, with a broadly similar toxicity profile to that which has previously been reported.^{21,27-30} The most common AEs were mild to moderate GI toxicities and rash, which would be expected from an agent inhibiting HER family dimerization and therefore HER1 signaling.³¹⁻³⁵ The low rate of cardiac dysfunction observed suggests that pertuzumab-associated cardiotoxicity occurred only in a subset of susceptible individuals shortly after first exposure. While the limited number of cardiac events means these data should be interpreted with caution, they are consistent with LVEF results from four pertuzumab monotherapy phase II studies.^{27,28,30,36} The rate of cardiac events reported in this study is similar to that described in the pivotal trastuzumab trials; a recent pooled analysis demonstrated that 11% of patients who received trastuzumab experienced an LVEF decrease to less than 50%.³⁷

Pertuzumab interferes with HER2 heterodimer formation and downstream signaling, while trastuzumab is unable to block HER dimer formation. Additionally pertuzumab, but not trastuzumab, inhibited the growth of cancer cells expressing both low/normal and high levels of HER2 in the preclinical setting.^{19,38} However, in this study, the measurable therapeutic benefit of pertuzumab in women with HER2-negative breast cancer was mostly in the form of SD of relatively short duration. Other preclinical studies have shown that a trastuzumab and pertuzumab combination may act in synergy to induce tumor regression in xenograft models of HER2-positive tumors, even after the tumor progressed on trastuzumab.³⁹ This strongly suggests that pertuzumab might have the greatest clinical benefit among patients with HER2-positive disease. Trastuzumab in combination with chemotherapy is associated with a survival benefit in patients with both early and metastatic HER2-positive breast cancer.⁴⁰⁻⁴² However, some patients with HER2-overexpressing breast cancer who progress on trastuzumab may benefit from the addition of pertuzumab to trastuzumab therapy. Indeed, clinical data from trials investigating trastuzumab and pertuzumab for treatment beyond first-line trastuzumab therapy have shown good response data and long progression-free survival.⁴³

Table 4. Pharmacokinetic Parameters of Pertuzumab Following First Infusion of Pertuzumab

Parameter	Arm A			Arm B		
	No.	Mean	CV (%)	No.	Mean	CV (%)
$t_{1/2}$, days	38	15.6	32	36	19.5	71
C_{max} , $\mu\text{g/mL}$	40	289	37	37	409	39
AUC_{last} , $\mu\text{g}\cdot\text{day/mL}$	40	2,520	35	37	3,470	30
AUC_{∞} , $\mu\text{g}\cdot\text{day/mL}$	38	3,880	38	36	6,350	61
Cl, mL/d	38	243	45	36	213	49
V_d , mL	38	5,120	39	36	4,710	36
MRT, days	38	19.5	32	36	25.4	74

Abbreviations: CV, coefficient of variation; $t_{1/2}$, terminal half-life; C_{max} , maximum concentration; AUC , area under the curve; Cl, clearance; V_d , volume of distribution; MRT, mean residence time.

The relatively short half-life for pertuzumab reported in this study can be explained by a number of factors; both the dosing schedule and the noncompartmental analysis (NCA) contribute to the underestimate of the terminal half-life. The sampling schedule of 3 weeks, at which point the next dose was administered, prevents a detailed assessment of the terminal elimination phase. In addition, the nature of the NCA and the inherent interindividual variability of the data across studies are also factors in this underestimate. Thus, these pharmacokinetic data do not contradict dosing once every 3 weeks. NCA is model-independent and relies on the number and timing of the plasma samples, typically yielding different values than a compartment modeling approach. The latter gives the best fit for the data for pertuzumab using a two-compartment model and is therefore the one used for the population pharmacokinetic analyses which are reported separately.

As a comparison, in the phase I dose-escalation study, the terminal half-life ranged from 15.3 to 27.6 days with a mean terminal half-life of 18.9 days (standard deviation, 8 days),²¹ and in a similar phase I study in Japan, the half-life range was 11 to 18 days,⁴⁴ both of which support dosing once every 3 weeks.

In this study, only two of the 41 patients who received the 420-mg dose experienced a PR, and the rate of SD $\geq$ 12 weeks was 44% for patients in arm A and 38% for patients in arm B. The rate of clinical benefit at 6 months in this trial, while limited, was similar to that reported with pertuzumab in advanced ovarian cancer.²⁷ It is notable that the durations of response observed in the two patients with PR were 18 and 31 weeks and, in contrast to observations made with cytotoxic therapy, they occurred after a median of 18 and 6 weeks, respectively. Prolonged progression-free survival without tumor response has also been observed in trials of pertuzumab in non-small-cell lung cancer and castration-resistant prostate cancer.^{28,30} The RECIST and WHO criteria for response were designed primarily for cytotoxic agents and, hence, these criteria may not translate to targeted therapies. For example, the EGFR tyrosine kinase inhibitor erlotinib as second-line therapy for non-small-cell lung cancer produced a PR in less than 10% of patients, although both progression-free and overall survival were significantly increased.⁴⁵ However, in our study, median TTP was reported as 44 and 43 days in arms A and B, respectively, suggesting that the majority of the patients with HER2-negative disease derived minimal benefit from HER2-targeted therapy.

In conclusion, the use of single-agent pertuzumab in HER2-negative breast cancer was justified by preclinical evidence but did not meet expectations of clinical benefit in the metastatic setting. Biologic effects were measured and were possibly associated with clinical benefit that supported investigation of pertuzumab in combination with trastuzumab in women with breast cancer characterized by HER2 overexpression or amplification.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Veronica Hersberger, F. Hoffmann La Roche (C) **Consultant or Advisory Role:** Luca Gianni, F. Hoffmann La Roche (C), Wyeth (C), Genentech (C), GlaxoSmithKline (C), Novartis (C); Javier Cortes, F. Hoffmann La Roche (C); Pirkko-Liisa Kellokumpu-Lehtinen, sanofi-aventis (C); David A. Cameron, F. Hoffmann La Roche (C); David Miles, F. Hoffmann La Roche (C); Andrew Wardley, F. Hoffmann La Roche (C); José Baselga, F. Hoffmann La Roche (C), Exelixis (C), Merck (C), Novartis (C) **Stock Ownership:** None **Honoraria:** Javier Cortes, F. Hoffmann La Roche; Pirkko-Liisa Kellokumpu-Lehtinen, F. Hoffmann La Roche, sanofi-aventis, Pfizer; David A. Cameron, F. Hoffmann La Roche; David Miles, F. Hoffmann La Roche; Andrew Wardley, F. Hoffmann La Roche **Research Funding:** Pirkko-Liisa Kellokumpu-Lehtinen, sanofi-aventis, F. Hoffmann La Roche, Pfizer; David A. Cameron, F. Hoffmann La Roche; Andrew Wardley, F. Hoffmann La Roche **Expert Testimony:** None **Other Remuneration:** Andrew Wardley, F. Hoffmann La Roche

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