A Phase I Study of the Safety and Pharmacokinetics of the Combination of Pertuzumab (rhuMab 2C4) and Capecitabine in Patients with Advanced Solid Tumors

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Abstract

Purpose: To study the safety, pharmacokinetics, and recommended dose of the combination of pertuzumab, a humanized monoclonal antibody HER2-dimerization inhibitor, and capecitabine in patients with advanced malignancies.

Experimental Design: Patients that had progressed to standard treatment were treated with pertuzumab at a fixed dose of 1,050 mg given i.v. on day 1 plus capecitabine at doses of 825-1,000-1,250 mg/m2, twice daily orally on days 1 to 14 of each 21-day treatment cycle, in three sequential cohorts. The pharmacokinetics of capecitabine and pertuzumab were studied. Patients received a single dose of capecitabine in a pretreatment phase (day -7) followed by serum sampling for capecitabine and its metabolites.

Results: Nineteen patients were accrued and 18 were assessable. The combination of capecitabine and pertuzumab was well tolerated at all dose levels and no dose-limiting toxicities were observed. The most frequent adverse event was asthenia, which was grade 3 in two patients. One asymptomatic pulmonary embolism occurred. No other grade 3 or 4 adverse events or cardiac or left ventricular ejection fraction events were reported. There was no apparent change in the pharmacokinetics of capecitabine and its metabolites when combined with pertuzumab. The pharmacokinetics of pertuzumab was apparently not modified when administered with capecitabine. Disease stabilization was observed in 11 patients.

Conclusions: Pertuzumab and capecitabine were well tolerated at all dose levels. Escalation beyond the highest dose level tested was not planned, as this included the recommended doses of monotherapy for both drugs. In conclusion, this combination is ready for phase II testing.

The HER or human epidermal growth factor receptor family of tyrosine kinase receptors is important for cell growth, survival, and differentiation (1, 2). HER2 has no direct ligand, acting instead as a coreceptor forming heterodimers with other receptors of the family (HER1, HER3, or HER4). This results in a cascade of signaling events that may lead to neoplastic transformation and/or progression (2–5). Pertuzumab (recombinant humanized monoclonal antibody 2C4; Genentech, Inc.) is a monoclonal antibody that binds to HER2 at the extracellular dimerization domain (6), thus inhibiting its potential to bind with the other HER family members (7–12). Unlike trastuzumab (Herceptin; Genentech) whose binding epitope lies within subdomain-4 of HER2, the epitope for pertuzumab lies within subdomain-2, resulting in its different mode of action (13, 14).

Pertuzumab inhibits ligand-dependent growth of breast cancer cell lines (9, 15) with activity that seems to be independent of the level of immunohistochemical expression of HER2 (7). Notably, however, there seems to be synergy between trastuzumab and pertuzumab in high HER2–expressing breast cancer cells (16). In in vivo preclinical studies, pertuzumab has been active in various tumor types including breast (7, 9, 15, 17, 18), prostate (7, 12), ovary (15), non–small cell lung carcinoma (17, 18), and colon (19). Agus et al. showed dose-dependent inhibition of xenograft tumor growth (7).

In a phase I clinical study, pertuzumab was well-tolerated at all dose levels with no maximum tolerated dose being reached. The most frequent toxicities (mostly grade 1-2) were asthenia, vomiting, nausea, abdominal pain, rash, diarrhea, pain, and anemia. Grade 3 to 4 toxicities were rare. No antibodies to pertuzumab were detected. At doses of 5 to 15 mg/kg, serum concentrations were maintained at >20 μg/mL, with elimination half-life ranging from 18.6 to 20.6 days, supporting the 21-day dosing regimen. Encouragingly, two patients achieved partial responses (20).
Capcitabine is an orally available prodrug which is rapidly absorbed by the intestine, undergoing enzymatic activation in the liver and the tumor to 5-fluorouracil (5-FU; refs. 21–23). Capcitabine has a broad spectrum of activity including colorectal and breast cancers as well as other tumors sensitive to 5-FU. Phase III studies have shown equivalent efficacy to 5-FU in both advanced (24) and adjuvant treatment (25) of colorectal cancer. Capcitabine can be also be added safely to either oxaliplatin (26) or irinotecan (27) in colorectal cancer. In advanced breast cancer, the addition of capcitabine to docetaxel improved survival compared with docetaxel alone (28). Capcitabine is also active for breast cancer patients who have failed both anthracycline and taxane chemotherapy (29). The toxicity profile of capcitabine includes diarrhea, nausea, and hand-foot syndrome (30).

Pertuzumab has at least additive antitumor efficacy in combination with cytotoxic drugs, such as cisplatin, paclitaxel, and gemcitabine without enhancing toxicity (poster B213 presented at EORTC-NCI-AACR 2003). Moreover, it has minimal overlapping toxicities with capcitabine. This phase I study was planned to determine the maximum tolerated dose of the combination as a primary end point, as well as tolerability, pharmacokinetics, and antitumor activity as secondary end points.

**Patients and Methods**

**Patient population.** Adult patients (aged ≥18 years) with histologically confirmed locally advanced or metastatic solid tumors and a life expectancy of ≥12 weeks were considered eligible if there was no standard therapy available for them. Other eligibility criteria included Eastern Cooperative Oncology Group performance scores of 0 to 1, the presence of radiologically assessable disease or validated tumor size (breast cancer), baseline left ventricular ejection fraction of ≥50%, adequate bone marrow, renal and hepatic function [evidenced by neutrophil count ≥1,500/μL, platelet count ≥75,000/μL, hemoglobin >9 g/dL, serum creatinine ≤upper limit of normal or a creatinine clearance ≥60 mL/min, serum bilirubin ≤1.5 × the upper limit of normal, alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase ≤2.5 × the upper limit of normal (for patients with liver or bone metastases: alkaline phosphatase, ≤4 × the upper limit of normal, for patients with liver metastases aspartate aminotransferase and alanine aminotransferase, ≤5 × the upper limit of normal)].

Patients were excluded if there was clinical evidence of central nervous system metastases (history of controlled brain metastases was allowed) or if they had received chemotherapy, radiotherapy (other than a short course of palliative radiotherapy for bone pain), or immunotherapy within 4 weeks of commencing the study drug (6 weeks for mitomycin, 2 weeks for hormones), ensuring that a full recovery had been made from that therapy. Patients who had experienced prior plantar-palmar erythema of grade ≥2; who had received prior anti-HER2 receptor therapy; who had received a prior doxorubicin dose of >360 mg/m² (or equivalent); who were receiving corticosteroids as anticancer therapy or who had received prior capcitabine (or infusional 5-FU in regimens of >48-h duration) were excluded. A history of other prior malignancy or other concurrent or previous medical conditions (including pregnancy) likely to increase the risk of complications or affect compliance with the protocol or interpretation of the results precluded enrollment of the patient.

The Institutional Review Boards and Ethics Committees of the participating centers approved the protocol and all patients were required to give written informed consent before entry.

**Treatment schedule.** Patients were allocated to one of three planned treatment cohorts; all patients received 1,050 mg of pertuzumab as a fixed dose (provided by F Hoffmann-La Roche, Ltd., Inc., AG, Geneva, Switzerland) by i.v. infusion on day 1 with capcitabine at doses of 825-1,000-1,250 mg/m² in sequential cohorts twice daily orally on days 1 to 4 of each 21-day treatment cycle. Pertuzumab administered in a fixed-dose regimen is justified by the lack of relationship between trastuzumab clearance and body weight previously published by Bruno et al. (31) and has recently been shown to be feasible in a pharmacokinetic study with pertuzumab (32). The first dose of pertuzumab was administered over 90 min; this was reduced to 30 min on subsequent dosings if well tolerated, followed by a 2-h observation period. At least three patients were planned for dose level 1 followed by at least six patients in each of dose levels 2 and 3 to determine the maximum tolerated dose. Escalation beyond these doses was not planned as this represented the recommended doses of monotherapy for both drugs. A 3-week observation period (one cycle) was required for patients at one cohort prior to opening of a new cohort; and dose escalation continued only if no more than one in six patients experienced a dose-limiting toxicity in the first cycle, and included any nonhematologic toxicity ≥grade 3 according to the Common Terminology Criteria for Adverse Events version 3.0 except for fever, chills, and flu-like symptoms; in spite of adequate toxicity management, grade 4 neutropenia lasting more than 7 days, febrile neutropenia, thrombocytopenia grade 4 or any thrombocytopenia requiring platelet transfusion, or any subjective intolerable toxicity felt by the investigator to be related to either one of the compounds. Dose delays for reasons not meeting the above defined criteria were not considered dose-limiting toxicities. Dose modifications for toxicity were predetermined in the protocol.

**Tolerability and safety.** Patients were reviewed weekly for the duration of therapy and at 4 weeks after completion of the last cycle. At each visit, patients were assessed for adverse events which were graded according to the CTCAE version 3.0. Laboratory evaluations included complete blood count, serum biochemistry, and assessment of renal function (either by 24-h urine measurement or calculated by Cockcroft and Gault formula). Left ventricular ejection fraction or two-dimensional echocardiography or isotope multiple-gated acquisition scan was done every two cycles. An electrocardiogram was done at baseline and upon completion of the study.

**Pharmacokinetic analysis.** All patients received a single dose of capcitabine (at the allocated cohort dose level) in a pretreatment phase (day -2) followed by serum sampling for capecitabine and its metabolites [5'-deoxy-5-fluorocytidine (5'-DFCR), 5'-deoxy-5-fluorouridine (5'-DFUR), 5-fluorouracil (5-FU), and α-fluoro-β-alanine (FBAL)], using a validated specific liquid chromatography tandem mass spectrometry method] at pre-dose, and at 0.5, 1, 2, 3, 4, 5, 6, and 10 h post-dose. This schedule was repeated on day 1 of the first cycle when patients received pertuzumab over 90 min followed by a dose of capecitabine. Additionally, patients underwent pharmacokinetic sampling for pertuzumab using a receptor-binding ELISA with immobilized antigen p185HER2 ECD to capture pertuzumab from serum samples; bound pertuzumab was detected with mouse anti-human Fc-horseradish peroxidase and tetramethyl benzidine as a substrate for color development to quantify pertuzumab against a known standard curve. This was done at pre-dose and at 15 min, 1.5, 4, and 8 h post-completion of infusion on day 1 and on days 2, 5, 8, and 15 post-dose. This schedule was repeated on cycle 2 with a final sample taken on day 22 of cycle 2.

**Tumor assessments.** Patients underwent evaluation of disease by appropriate imaging (computerized tomography or magnetic resonance scan) at baseline and every two cycles. Tumor marker assays were done only where appropriate. Patients with stable or responsive disease, according to Response Evaluation Criteria in Solid Tumors standards, were

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4 M. Hasmann, R. Juchem, W. Scheuer, T. Friess, unpublished data.
allowed to continue beyond six cycles if, in the opinion of the investigator, they were deemed to be benefiting from therapy and if there was no toxicity to preclude continued dosing. In this event, evaluation of disease and cardiac function continued every two cycles.

Data analysis. Patient characteristics and demographic data were recorded using medians (with ranges) and means (with SD) for continuous variables and proportions for categorical variables. Median (with range) was used to register cycles of treatment. All adverse events were recorded and analyzed by dose level, CTC grade of toxicity, treatment cycle, and subject number.

A noncompartmental analysis of pharmacokinetic data was done using WinNonlin version 5.0.1 (PharSight Corporation) for capecitabine, its metabolites (5′-DFCR, 5′-DFUR, 5-FU, and FBAL) and pertuzumab serum concentrations from the samples were obtained from patients during treatment. In order to determine the influence of pertuzumab on the pharmacokinetics of capecitabine, the mean pharmacokinetic variables area under the curve (AUC), peak plasma concentration after dosing (C_{max}), time to concentration half-life (t_{1/2}), and time to maximum plasma concentration (t_{max}) of capecitabine and its metabolites obtained in the pre–cycle treatment phase were compared with those obtained on day 1 of cycle 1, within each cohort of patients.

Results

Patients. Nineteen patients were accrued to this study, 18 of which were assessable for toxicity. One patient at dose level 2 withdrew prior to day 1 of cycle 1 due to early tumor progression. The patient characteristics and demographic data are presented in Table 1.

Patients received a median of six cycles of treatment (range, 2-12), with 10 patients (56%) completing the six cycles. Three patients (17%) were treated beyond cycle 6 because they experienced clinical benefit.

Safety and tolerability. The combination of capecitabine and pertuzumab was generally well-tolerated at all dose levels studied and no dose-limiting toxicities were observed.

The most frequent adverse events are shown in Table 2. The most frequent nonhematologic toxicities per patient were asthenia (72% grade 1/2; 11% grade 3), diarrhea (72%), nausea (67%), anorexia (61%), neutropenia (39%), hand-foot syndrome (44%), and vomiting (39%). Grade 1 to 2 hematologic toxicities were anemia (83%), neutropenia (39%), and thrombocytopenia (33%). All adverse events were of grade 1 or 2 except for one patient in cohort 1 and another patient in cohort 2 who experienced grade 3 asthenia. No grade 4 toxicities were observed. None of the patients experienced left ventricular ejection fraction symptomatic decrease of 10% or more, or a left ventricular ejection fraction symptomatic decrease during pertuzumab infusion, no grade 3 to 4 toxicities were observed. One patient experienced a reaction during the first infusion, consisting of grade 2 hypotension and dizziness. A 68-year-old patient with metastatic breast cancer developed hypotension 75 minutes after starting pertuzumab. She did not have dyspnea or other symptoms. Corticosteroids and

<table>
<thead>
<tr>
<th>Table 2. Most frequent adverse events (per patient and cycle)</th>
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<tbody>
<tr>
<td><strong>Adverse event</strong></td>
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<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>No. of total evaluable cycles</td>
</tr>
<tr>
<td>No. of total evaluable patients</td>
</tr>
<tr>
<td>Asthenia (grades 1/2)</td>
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<tr>
<td>Per patient 2</td>
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<tr>
<td>Asthenia (grades 3/4)</td>
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<tr>
<td>Per patient 1</td>
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<tr>
<td>Diarrhea (grades 1/2)</td>
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<tr>
<td>Per patient 3</td>
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<tr>
<td>Nausea (grades 1/2)</td>
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<tr>
<td>Per patient 4</td>
</tr>
<tr>
<td>Vomiting (grades 1/2)</td>
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<tr>
<td>Per patient 2</td>
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<tr>
<td>Hand-foot syndrome (grades 1/2)</td>
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<td>Per patient 3</td>
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<tr>
<td>Neutropenia (grades 1/2)</td>
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<td>Per patient 2</td>
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<tr>
<td>Mucositis (grades 1/2)</td>
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<tr>
<td>Per patient 0</td>
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<tr>
<td>Neutropenia (grades 1/2)</td>
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<td>Per patient 3</td>
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<tr>
<td>Thrombocytopenia (grades 1/2)</td>
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*Eastern Cooperative Oncology Group.
H2-antagonists were administered and pertuzumab infusion was interrupted until the blood pressure was normalized. Pertuzumab infusion was then restarted at a lower rate until the total planned amount of pertuzumab could be delivered. The subsequent pertuzumab infusions were administered with corticosteroids and H2-antagonist premedication with an infusion duration of 90 minutes. During the second pertuzumab administration, the patient developed dizziness without hypotension. Symptoms improved after administration of a benzodiazepine. The patient received eight cycles of pertuzumab with premedication (corticosteroids, H2-antagonists, and benzodiazepine) with no further infusion-related events.

### Table 3. Mean (SD) pharmacokinetic variables of capecitabine given alone (on pre-cycle day -7) and in combination with pertuzumab (day 1 of the same cycle)

<table>
<thead>
<tr>
<th>Capcitabine dose (mg)</th>
<th>Day -7 capcitabine alone</th>
<th>Day 1 capcitabine + pertuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t_{1/2}$ (h)</td>
<td>$t_{\text{max}}$ (h)</td>
</tr>
<tr>
<td>825 (n = 5)</td>
<td>0.89 (0.27)</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>5'-DFCR</td>
<td>0.75 (0.26)</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>5'-DFUR</td>
<td>0.67 (0.22)</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>S-FU</td>
<td>0.54 (0.19)</td>
<td>1.2 (0.7)</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>2.54 (0.3)</td>
<td>2.4 (0.5)</td>
</tr>
<tr>
<td>FBAL (n = 7)</td>
<td>0.82 (0.28)</td>
<td>0.8 (0.3)</td>
</tr>
<tr>
<td>1,000 (n = 6)</td>
<td>0.76 (0.23)</td>
<td>1.1 (0.5)</td>
</tr>
<tr>
<td>S-FU</td>
<td>0.64 (0.13)</td>
<td>1.1 (0.5)</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>0.4 (0.1)</td>
<td>0.8 (0.3)</td>
</tr>
<tr>
<td>FBAL</td>
<td>2.69 (0.39)</td>
<td>2.2 (0.4)</td>
</tr>
<tr>
<td>1,250 (n = 7)</td>
<td>0.82 (0.23)</td>
<td>1.0 (0.5)</td>
</tr>
<tr>
<td>5'-DFCR</td>
<td>0.66 (0.09)</td>
<td>1.0 (0.5)</td>
</tr>
<tr>
<td>5'-DFUR</td>
<td>0.7 (0.16)</td>
<td>1.0 (0.5)</td>
</tr>
<tr>
<td>S-FU</td>
<td>0.36 (0.11)</td>
<td>0.8 (0.35)</td>
</tr>
<tr>
<td>Capcitabine</td>
<td>3.08 (0.78)</td>
<td>2.2 (0.4)</td>
</tr>
</tbody>
</table>

### Table 4. Mean (±SD) pharmacokinetic variables of 1,050 mg of pertuzumab

<table>
<thead>
<tr>
<th>Dose</th>
<th>$t_{1/2}$ (d)</th>
<th>$t_{\text{max}}$ (d)</th>
<th>$C_{\text{max}}$ (ng/mL)</th>
<th>AUC0-last (ng d/mL)</th>
<th>AUC0-8 (ng d/mL)</th>
<th>CL (mL/d)</th>
<th>Vss (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,050 mg (n = 18)</td>
<td>14.6 (41)</td>
<td>0.137 (0.076)</td>
<td>355 (59,051)</td>
<td>2,742,561 (743,598)</td>
<td>4,096,501 (1,282,130)</td>
<td>283 (98)</td>
<td>5,202 (1,007)</td>
</tr>
</tbody>
</table>

NOTE: AUC0-∞, area under the curve versus time extrapolated to infinity; AUC0-last, area under the curve to last time point measured; CL, clearance; $C_{\text{max}}$, maximum concentration of plasma; $t_{1/2}$, time to half-life; $t_{\text{max}}$, time to maximum clearance; Vss, volume of distribution.
pharmacokinetics variables (Table 4) and mean concentration-time profiles, interpatient variability was moderate at ~35% for clearance.

**Efficacy data.** No responses were observed. Eleven patients had stable disease whereas seven patients progressed. Three patients were treated beyond six cycles. A 68-year-old patient with HER2 negative-metastatic breast cancer with pleural and liver lesions previously treated with anthracycline- and taxane-based regimens had stable disease that lasted at least 24 weeks (cycle 8 of treatment). At that point, the patient had an asymptomatic pulmonary embolism and decided to withdraw from treatment. A 59-year-old male patient with rectal carcinoma with liver and lung metastaes in progression after an irinotecan plus 5-FU regimen had stable disease lasting 12 cycles of pertuzumab plus capecitabine. The third patient was a 69-year-old with a metastatic breast cancer to the mediastinum and pleura, who had stable disease lasting >30 weeks (10 cycles of treatment). After cycle 10, the patient withdrew from treatment for personal reasons.

**Discussion**

Pertuzumab is a first-in-class drug that disrupts ligand-mediated HER2 heterodimerization. The novel mechanism of action of pertuzumab requires HER2 expression but does not depend on HER2 amplification or overexpression and is therefore applicable to a wide range of tumor types as most human epithelial cells express HER2 (33).

Due to the potential antitumor enhancement of pertuzumab in combination with cytotoxics, trials that explore the addition of pertuzumab to chemotherapy are of interest. Moreover, preclinical data suggest that coexpression of HER2 and HER3 is a major factor determining chemotherapy resistance (34). Therefore, inhibition of HER2/HER3 heterodimers by pertuzumab could potentially overcome resistance. This study is the first phase I trial of pertuzumab combined with capecitabine. Capecitabine was chosen because it is active in a wide range of tumors and has no serious overlapping toxicities with pertuzumab.

The combination of pertuzumab and capecitabine was shown to be well tolerated, with both drugs administered at full doses. The most frequent toxicity was asthenia, which was grade 3 only in two cases, and was unrelated to dose level. Nausea (67%) and vomiting (39%) were also frequent but not severe. Both capecitabine and pertuzumab could cause diarrhea and skin toxicity (20, 30); however, co-treatment did not enhance these toxicities. Diarrhea was reported in 72% of patients, most of them at dose level 3, and all grade 1 and 2. Skin toxicity was mostly grade 1 and 2 hand-foot syndrome (44%).

The pharmacokinetics of capecitabine and its metabolites compared well with historical capecitabine clinical data (35), and were not modified when administered with pertuzumab. In our study, capecitabine was used on the basis of body surface area, according to the product label and also because this is commonly used in clinical practice. However, further studies should consider that data for capecitabine are accumulating in which fixed dosing results in the same toxicity, efficacy, and large interpatient variability in exposure to the active metabolites as body surface area-based dosing (36).

The pharmacokinetics of pertuzumab are similar to those observed in previous phase I studies of pertuzumab alone (20), and with phase II data using the same 1,050 mg dose (37, 38). This can be explained because both drugs have different clearance mechanisms. At the time of the study design, we chose a fixed dose of 1,050 mg of pertuzumab based on population pharmacokinetics data that fixed dosing equates with weight-based and body surface area dosing (32). Of note, in subsequent trials, the dose of pertuzumab was reduced to 420 mg with a loading dose of 840 mg because no differences in pharmacokinetics, toxicities, and clinical activity were established between the lower dose of 420 mg and the higher dose of 1,050 mg (32, 38). A loading dose of 840 mg of pertuzumab in such studies was used to achieve concentrations above a preclinical target $C_{\text{min}}$ earlier and lead to steady state levels by cycle 2, whereas not using a loading dose could mean steady state levels taking 4 months or more to achieve.

Disease stabilization was reported in 11 patients (61%), and in 3 patients, this lasted more than 6 months. Of note, all patients were metastatic and heavily pretreated. Moreover, no biological selection criteria to response to pertuzumab were used. Along this line, efforts have been directed to finding the critical molecules predictive of response to pertuzumab that could help in identifying patients more likely to respond. Interestingly, in breast cancer and non–small cell lung cancer xenografts, the presence of HER2/HER3 heterodimers predicted response to pertuzumab (39). In ovarian cancer, patients with HER2 activation (determined by pHER2+) had a trend toward higher clinical benefit (38). An ongoing trial in patients with lung cancer is assaying for pHER2 in fresh tumor biopsies as a predictor of response to pertuzumab (40).

Other clinical trials with pertuzumab are ongoing. As a single agent, preliminary results of phase II studies in patients with breast, ovarian, prostate, and lung cancer have recently been reported. In breast cancer, despite having limited activity in patients with low HER2 expression (36), promising results have been shown in combination with trastuzumab (41, 42) and a phase II study in combination with trastuzumab in HER2-positive breast cancer patients is ongoing. Exciting results have also been reported in advanced ovarian cancer patients with no HER2 overexpression (38). Combination trials are ongoing with docetaxel and gemcitabine in ovarian cancer.

In conclusion, pertuzumab, in combination with capecitabine, is safe and well tolerated with no unexpected additive toxicity. Further studies of pertuzumab in combination with capecitabine or other chemotherapy or targeted drugs with high emphasis on patient selection strategy are warranted.

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