Pertuzumab: Optimizing HER2 Blockade

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Abstract

Pertuzumab has been approved by the U.S. Food and Drug Administration for use in combination with trastuzumab and docetaxel for the first-line treatment of patients with advanced HER2-positive (HER2+; breast cancer. Pertuzumab is a recombinant humanized monoclonal antibody that binds to the extracellular dimerization domain II of HER2 and inhibits heterodimerization of HER2 with other HER family members, including EGF receptor (EGFR), HER3, and HER4. The HER2–HER3 heterodimer is a robust activator of phosphoinositide 3-kinase (PI3K) pathway signaling and functions as the most transforming and mitogenic of the receptor complexes formed by the HER family of proteins; thus, blockade of HER2–HER3 likely represents the most relevant action of pertuzumab. In the seminal phase III study, patients with HER2+ metastatic breast cancer were randomized to receive trastuzumab and docetaxel, with or without pertuzumab: Addition of pertuzumab significantly prolonged progression-free survival with an increase of 6.1 months (12.4 vs. 18.5 months, respectively). In a subsequent analysis with 30 months of median follow-up, pertuzumab conferred a 34% reduction in the risk of mortality. Here, we review the mechanism of action of pertuzumab, the rationale for combining it with trastuzumab/pertuzumab, clinical data, and future directions for this work. Clin Cancer Res; 19(20); 5552–6. ©2013 AACR.

Introduction

Blockade of a critical oncogenic target is envisioned as a promising strategy for treating cancer. The blockade of HER2 with anti-HER2 agents represents one such strategy that has been successful in the treatment of HER2-overexpressing breast cancer. Trastuzumab was the first agent that was developed to target the HER2 pathway; trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain (ECD) of HER2, thereby inhibiting tumor cell growth and proliferation. The mechanism of action of trastuzumab includes inhibition of ligand-independent receptor dimerization and thereby of downstream signaling transduction pathways [e.g., phosphoinositide 3-kinase (PI3K) signaling]. In the advanced-stage setting, trastuzumab-based regimens have improved the survival of patients diagnosed with HER2-positive (HER2+) breast cancer, and have favorably changed the dire natural history of advanced HER2+ disease. In the early-stage setting, the addition of trastuzumab to adjuvant chemotherapy has led to a striking reduction in the risk of relapse and death, by 50% and 30%, respectively. Nevertheless, in the advanced setting, disease progression while on trastuzumab remains inevitable, and a significant minority of patients in the early-stage setting relapse after trastuzumab-based adjuvant therapy.

Over the past 15 years since the first approval of trastuzumab, there have been significant improvements in our understanding of the biology of HER2+ disease, and novel anti-HER2 drugs have been approved for the treatment of HER2+ breast cancer. Pertuzumab represents the first of a novel class of drugs that have the ability to block the function of HER2 as a coreceptor and thereby inhibit HER2 heterodimerization with other members of the HER family (e.g., HER1 and HER3). The resulting complimentary and enhanced efficacy of HER2 blockade that is provided by the combination of trastuzumab plus pertuzumab has been proven in a randomized phase III clinical trial in which patients with advanced HER2+ breast cancer were randomized to receive trastuzumab plus docetaxel, with or without pertuzumab.

Rationale for the dual blockade of HER2 and HER3

HER2 gene amplification and/or overexpression occur in approximately 20% of breast cancers and predict the clinical effectiveness of anti-HER2 therapies. HER2 is a member of the HER family of transmembrane receptor tyrosine kinases, which also include EGF receptor (EGFR; also known as HER1), HER3, and HER4. The HER receptors are composed of an ECD, a transmembrane segment, and an intracellular tyrosine kinase domain. Ligand binding to the ECD triggers conformational rearrangements that expose dimerization domain(s) for binding to another receptor. Following dimerization, the kinase domain of one dimer allosterically activates its neighbor and becomes trans-autophosphorylated (1, 2). The phosphorylation of kinase domains is followed by the activation of downstream signaling pathways that ultimately foster tumor cell proliferation and survival.
In HER2+ tumors, the abundance of HER2 at the cell surface facilitates heterodimerization of HER2 with other HER family members (e.g., to form HER2–EGFR, HER2–HER3) and the spontaneous formation of HER2 homodimers (HER2–HER2; ref. 3). Importantly, no specific ligand for HER2 has been identified, and HER2 is constitutively present at the cell surface in an active conformation, making HER2 the preferential dimerization partner for itself (3). In contrast, HER3 can bind several ligands, but has only weak intrinsic tyrosine kinase activity (4); in addition, upon ligand binding, HER3 is not able to form homodimers, but can form only heterodimers (5).

Trastuzumab binds to domain IV in the ECD of HER2, thereby inhibiting ligand-independent dimerization of the receptor and the subsequent activation of downstream signaling pathways. However, the antibody is not effective in blocking ligand-induced HER2 heterodimer formation. Such heterodimers (EGFR–HER2 and HER2–HER3) have been extensively studied as mediators of oncogenic signaling, with the HER2–HER3 heterodimer being the most potent of the HER signaling dimers. In preclinical studies (in vitro and in vivo models), HER2–HER3 signaling was required for the proliferation of HER2-amplified cancer cells, whereas HER2–EGFR was less important (6). As a consequence, blockade of ligand-induced HER2–HER3 het-

erodimers in combination with inhibition of ligand-inde-
pendent homodimerization of HER2, offers a promising synergistic therapeutic strategy for HER2+ breast cancer (7). In keeping with this, pertuzumab binds to the dimerization domain (ECD II) of HER2 blocking ligand-induced HER2 heterodimerization (Fig. 1). In preclinical models, admin-

istration of pertuzumab in combination with trastuzumab is associated with a more complete HER2 blockade, and the treatment combination is more effective in HER2+ tumor xenografts than administration of either antibody alone. Moreover, the enhanced efficacy of the combined use of trastuzumab and pertuzumab is also observed in cases where the tumor has progressed following trastuzumab monotherapy (8).

Clinical Studies

Phase 1 development

Pertuzumab has been evaluated as monotherapy in several phase I clinical studies, in combination with chemotherapy (docetaxel and capecitabine), or with trastuzumab emtansine (T-DM1). The maximum-tolerated dose of per-

tuzumab was not reached in any of the studies, and the recommended dose for future studies was based on phar-

macokinetic findings (see later). Overall, pertuzumab was well tolerated, with the most common adverse events being asthenia, vomiting, diarrhea, and a mild-to-moderate grade rash.

Pharmacokinetics

The pharmacokinetic profile of pertuzumab is similar to that of trastuzumab (which has a terminal half-life of ~3 weeks). Data from a phase I study (9), in which pertuzu-

mab monotherapy was administered at doses ranging from 0.5 to 15 mg/kg, indicate that the mean terminal half-life of the drug for the 2.0- to 15-mg/kg dose groups ranged from 15 to 23 days; this ~3-week terminal half-life of pertuzu-

mab supports the choice to administer it at 3-week intervals. Moreover, at doses of 2.0 to 15 mg/kg, no variations in systemic clearance or volume of distribution at steady-state were observed. Systemic clearance was 3.4 ± 1.2 mL/d/kg, and the volume of distribution at steady-state was 80 ± 28 mL/kg. In preclinical dose–response studies, a steady-state trough concentration of 5 to 25 μg/mL was associated with an 80% suppression of tumor growth. Furthermore, the phase I data show that administering doses of more than 5 mg/kg at 3-week intervals guarantees that serum concentrations of pertuzumab will be more than 20 μg/mL. On the basis of these findings, an initial loading dose of 840 mg (to decrease the time needed to attain a steady-state...
concentration), followed by a fixed dose of 420 mg (equivalent to 6 mg/kg for a 70-kg patient) administered every 3 weeks was used in the subsequent clinical studies.

Phase II studies

The antitumor activity observed in preclinical experiments with use of the pertuzumab–trastuzumab combination, along with the promising safety data from phase I studies, motivated a trial to evaluate the pertuzumab/trastuzumab combination in the phase II setting. In a single-arm phase II study, a total of 11 patients with HER2+ breast cancer were treated with pertuzumab/trastuzumab (10). The study had a target accrual of 37 patients but was stopped early when 6 of 11 (54%) patients experienced a decline in left ventricular ejection fraction (LVEF). Cardiotoxicity was more commonly observed among patients who had previously developed LVEF decline while on trastuzumab therapy, and in all 6 of the patients who had previously received anthracycline-containing regimens. In addition, all patients had received trastuzumab treatment before entering the study, with a cumulative median duration of 82 weeks. The overall response rate (ORR) for the combination treatment was 18% and the median time-to-progression (TTP) was 6 weeks.

A subsequent single-arm phase II study aimed at evaluating the same combination (trastuzumab and pertuzumab) enrolled a total of 66 HER2+ patients who had documented disease-progression on a previous trastuzumab-based regimen (11). Patients were excluded if they had experienced a symptomatic decrease in LVEF to less than 50% absolute value during prior trastuzumab therapy. Cardiac safety on the study was carefully monitored, and all echocardiograms were centrally reevaluated. Three patients experienced a LVEF drop of 10 or more points and to less than 50%, but no patient experienced symptoms related to cardiac toxicity. Two of 3 patients that experienced LVEF drop remained on trastuzumab/pertuzumab treatment, and experienced subsequent recovery of cardiac function. The ORR was 24%, and the clinical benefit rate (ORR plus stable disease ≥ 6 months) was 50%. The observed benefit was durable, with an overall median progression-free survival (PFS) of 5.5 months (range, 0.9–17 months). The promising results of the trastuzumab/pertuzumab combination led to the recruitment of an additional cohort of patients who were treated with pertuzumab monotherapy, to investigate whether trastuzumab was actually required (12). A total of 29 patients whose disease progressed during prior trastuzumab therapy were treated with single-agent pertuzumab until disease progression or unacceptable toxicity. A minimum of 4 weeks from the last dose of trastuzumab was required to reduce the confounding effect of the prior trastuzumab treatment on pertuzumab efficacy. The ORR and clinical benefit rate (CBR) for pertuzumab monotherapy were 3.4% and 10.3%, respectively. Seventeen of 29 patients progressing on pertuzumab monotherapy continued treatment with the addition of trastuzumab. The ORR and CBR for the combination in this population were 17.6% and 41.2%, respectively. These objective responses observed with the addition of trastuzumab to patients progressing on single-agent pertuzumab seem to confirm the synergistic interaction of the two antibodies that was shown in preclinical models.

In addition to the cardiac safety issues, the most frequent adverse events observed in the phase II setting with pertuzumab/trastuzumab, or with pertuzumab monotherapy, were diarrhea, nausea, fatigue, and rash, with most being of mild to moderate intensity (grade 1 or 2).

Neoadjuvant setting

The results from the phase II setting were important for guiding the design of studies in the neoadjuvant setting. Pertuzumab was combined with trastuzumab and/or chemotherapy in two neoadjuvant studies for the treatment of early-stage HER2+ breast cancer. NEOSphere (Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation) evaluated the efficacy of 12 weeks of neoadjuvant treatment with docetaxel plus pertuzumab or trastuzumab, or the combination of trastuzumab and pertuzumab in 417 women with early-stage HER2+ breast cancer (13). A fourth arm in this study assessed the activity of the trastuzumab/pertuzumab combination without accompanying chemotherapy. The primary endpoint of the study was pathologic complete response (pCR) in the breast. Patients treated with the dual anti-HER2 combination plus docetaxel experienced a higher pCR rate (45.8%) compared with those who received only docetaxel/trastuzumab (29%) or only docetaxel/pertuzumab (24%). Interestingly, 17% of patients treated with trastuzumab plus pertuzumab for 12 weeks (without chemotherapy) also achieved pCR, suggesting that a subset of HER2 patients is highly sensitive to these anti-HER2 agents. In a subgroup analysis, lower pCR rates were observed across the four study arms among patients whose cancers were hormone receptor–positive, compared with those patients with hormone receptor–negative disease. Overall, neutropenia and febrile neutropenia were the most common serious adverse events and they occurred at similar frequencies in the chemotherapy-containing arms of the study. The mean maximum decrease in LVEF was 4% to 5% and was similar across the four treatment arms. A total of 6 patients experienced a decrease in LVEF of more than 10% from baseline, and to less than 50%; 5 of these 6 patients recovered LVEF to more than 50% by cycle 4, and 1 patient with a previous history of cardiac disease had to discontinue treatment because of congestive heart failure.

In the TRYphaena (Trastuzumab plus Pertuzumab in Neoadjuvant HER2+ Breast Cancer) study, a total of 225 patients with HER2+ breast cancer were randomized to receive trastuzumab and pertuzumab in combination with one of three chemotherapy regimens: concurrently with an anthracycline–taxane–containing regimen [FEC (fluorouracil, epirubicin, cyclophosphamide)–docetaxel]; after FEC, but concurrently with docetaxel; or concurrently with the docetaxel/carboplatin combination (14). The primary endpoint of the study was safety and tolerability. LVEF
dropped by 6% in the concurrent anthracycline arm; by 4% in the sequential arm; and by 3% in the carboplatin/docetaxel arm. Symptomatic LVEF dysfunction (grade 3 or higher) was recorded in 2.7% of the patients. The pCR rates were 62%, 57%, and 66% in the concurrent anthracycline, sequential, and docetaxel/carboplatin treatment arms, respectively.

Phase III studies
The CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) study was a randomized double-blind, placebo-controlled phase III trial that was designed to evaluate the effectiveness of the trastuzumab/pertuzumab combination (15). A total of 808 patients with advanced HER2+ breast cancer were randomized to receive trastuzumab and docetaxel, with either pertuzumab or placebo. Eligible patients could not have received prior chemotherapy or targeted therapy in the metastatic setting, and only 10% of enrolled patients had received trastuzumab in the early-stage setting. In the study, the primary endpoint was independently assessed to be PFS, whereas secondary endpoints were overall survival (OS), ORR, and safety. The addition of pertuzumab to trastuzumab and docetaxel significantly prolonged PFS, from a median of 12.4 to 18.5 months [HR, 0.62; 95% confidence interval, 0.51–0.75; P < 0.001]. LVEF dysfunction was more common in the control arm (trastuzumab/docetaxel) than in the pertuzumab-containing arm (8.3% vs. 4.4%, respectively). The following adverse events were more common in the former arm: diarrhea (66.8% vs. 46.3%), mucosal inflammation (33.7% vs. 24.2%), febrile neutropenia (13.8% vs. 7.6%), and dry skin (10.6% vs. 4.3%). In a subsequent analysis with 30 months of median follow-up, the addition of pertuzumab to the trastuzumab/docetaxel combination conferred a 34% reduction in the risk of mortality (HR, 0.66; P = 0.0008; ref. 16). In a subgroup analysis by age, treatment benefit was similar in patients 65 years or older as compared with that in younger patients (17). Quality-of-life assessment showed no detrimental effect with the addition of pertuzumab (18). In the biomarker analysis of the CLEOPATRA study, PIK3CA gene mutations were identified in 32% of patients (176/557 patients), and patients with PIK3CA gene mutation had worse outcome when compared with those with wild-type PIK3CA gene status. However, PIK3CA mutation(s) were not associated with resistance to pertuzumab, and the magnitude of benefit of pertuzumab was independent of PIK3CA mutational status (19). The positive results from CLEOPATRA led to approval by the U.S. Food and Drug Administration for use of pertuzumab, in combination with trastuzumab and docetaxel, for the treatment of patients with HER2+ advanced breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.

Pertuzumab is under evaluation in additional phase III trials. Trastuzumab emtansine (T-DM1) was recently approved for the second-line treatment of advanced HER2+ breast cancer with superior OS and a better adverse event profile compared with the lapatinib/capcitabine combination (20). In the MARIANNE study, T-DM1 plus pertuzumab and T-DM1 plus placebo are being compared with trastuzumab plus a taxane for the first-line treatment of patients with advanced HER2+ breast cancer. Results from the MARIANNE study will show whether pertuzumab is able to improve the therapeutic efficacy of T-DM1 in the first-line setting. Pertuzumab is also under evaluation in a large randomized phase III, double-blind, placebo-controlled study to compare the efficacy and safety of chemotherapy plus trastuzumab with or without pertuzumab as adjuvant therapy in patients with operable HER2+ primary breast cancer.

Conclusions and Future Directions
The striking benefits gained with the use of trastuzumab are now being further improved with the addition of pertuzumab. Pertuzumab given in combination with trastuzumab has improved the outcome of patients with HER2+ metastatic breast cancer and represents the standard of care in the first-line advanced setting. However, some additional points warrant discussion. First, biomarker analyses conducted in the pertuzumab studies failed to identify predictors of treatment benefit. In the NEOSPHERE study, the finding that a subset of patients experienced pCR with trastuzumab/pertuzumab therapy alone (without chemotherapy) is promising, but the inability to identify such patients with particularly sensitive cancers poses a challenge to the design of subsequent studies. Second, long-term cardiac safety with trastuzumab/pertuzumab has not yet been established, and careful follow-up should not be overlooked in clinical practice. Third, it is as yet unclear whether the benefit gained with the addition of pertuzumab to trastuzumab continues beyond disease progression on this regimen. Continuation of trastuzumab has clearly shown benefit after a patient has developed progression on an initial trastuzumab regimen (21), and one could imagine that an "optimal" dual anti-HER2 blockade could also potentially offer similar benefit beyond progression in some patients. At this point, however, pertuzumab should be stopped at the time of disease progression and not continued with subsequent regimens. And finally, it is important to note that available anti-HER2 agents have had a minimal impact on central nervous system metastases, which remain an important cause of death for patients with HER2+ breast cancer. In summary, the field of developing treatments for HER2+ breast cancer is constantly evolving, and an "optimized" new standard of care is likely to emerge in the near future.

Disclosure of Potential Conflicts of Interest
E.P. Winer is a consultant/advisory board member for Genentech. I. Krop received a commercial research grant from Genentech. No potential conflicts of interest were disclosed by the other author.
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