Research Highlight

Pertuzumab in metastatic breast cancer: unanswered questions

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Submitted Mar 29, 2012. Accepted for publication Apr 25, 2012.
DOI: 10.3978/j.issn.2218-676X.2012.04.03
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Recently, Baselga and colleagues published in *New England Journal of Medicine* the analyses of the Clinical Evaluation of Pertuzumab and Trastuzumab Study (CLEOPATRA) (1). CLEOPATRA is a phase III trial in 808 patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer receiving first line therapy with docetaxel and trastuzumab with placebo or pertuzumab until disease progression or unacceptable toxicity.

After 19.3 months of median follow-up (during which 165 events occurred), the interim results showed that the addition of pertuzumab improved progression-free-survival (PFS) by 6 months in comparison with placebo arm (18.5 versus 12.4 months; hazard ratio [HR] for progression 0.62; 95% CI 0.51 to 0.75; P<0.001). Among patients with measurable disease, overall response rate was significantly higher with pertuzumab (80.2% versus 69.3%, 95% CI 4.2 to17.5; P=0.001) with manageable toxicity. Even though the improvement in overall survival (OS) was not statistically significant, there was a trend toward prolonged survival with pertuzumab (HR=0.64, 95% CI 0.47 to 0.88; P=0.005; but it did not meet the O'Brien-Fleming stopping boundary of the Lan-DeMets alpha spending function) (1).

The addition of pertuzumab was associated with increased incidence of diarrhea, rash, mucosal inflammation, febrile neutropenia and dry skin. Interestingly, febrile neutropenia was more common in patients from Asia (26% in the pertuzumab group and 12% in the control group) than from other regions (approximately 10% in both groups). On the other hand, the toxicity observed more often in the control arm was edema and constipation. The incidence of cardiac toxicities was comparable between treatment arms. Finally, there was no difference in treatment related death (1).

In the last decade, many new drugs have demonstrated activity in metastatic breast cancer, with the anti-HER2 therapies seemingly having the greatest impact on survival (2,3). Approximately 20-25% of early-stage breast cancers over-express HER2 and are associated with poor outcome (4). This subtype of breast cancer is currently treated with a combination of chemotherapy and HER2-targeted agents, and a significant increase in OS has been noted since the introduction of these targeted agents. Trastuzumab, a monoclonal antibody directed against domain IV of the HER2 receptor, and lapatinib, a small molecule tyrosine kinase inhibitor binding both HER1 and HER2, are currently available for clinical use in combination with chemotherapy or hormotherapy in metastatic breast cancer (3,5,6).

Primary and secondary resistance to anti-HER2 therapies is frequently encountered in the metastatic setting, underscoring the need to identify new targeted treatments for advanced disease. Many mechanisms of resistance have been proposed, including HER2 crosstalk with other HER members or insulin-like growth factor-1 receptor, and increased phosphatidylinositol 3-kinase (PI3K)/Akt pathway activation due to PTEN deficiency or *PIK3CA* activating mutations (7).

Several new therapeutic agents are currently in development, including pertuzumab, a human monoclonal antibody that binds to domain II of the HER2 receptor and inhibits the ligand-dependent dimerization and signaling of HER2 (8). Given the fact that pertuzumab and trastuzumab bind different epitopes on the HER2 receptor, the two antibodies are thought to be complementary in action. A phase II trial in which the combination of trastuzumab and pertuzumab was given (without chemotherapy) to patients who had progressed on trastuzumab, showed an objective response rate of 24% and acceptable toxicity (9). In the neoadjuvant

NeoSphere study, the addition of pertuzumab to docetaxel and trastuzumab significantly increased pathological complete response rate compared to trastuzumab plus docetaxel alone (45.8% versus 29.0% respectively, P=0.0141) (10).

BIG 4-11 (APHINITY) is an ongoing large, randomized phase III, double-blind, placebo-controlled study comparing the efficacy and safety of chemotherapy plus trastuzumab and placebo with that of chemotherapy plus trastuzumab and pertuzumab as adjuvant therapy in patients with operable, HER2-positive, primary breast cancer (11). It is expected to enroll 3806 patients from about 44 countries worldwide.

While pertuzumab has shown impressive activity and acceptable toxicity in studies conducted so far, it is crucial to consider some additional points. Firstly, in the interim analysis of the CLEOPATRA trial, although there was a trend toward improvement in OS, the actual OS did not reach statistical significance. The final OS analysis is eagerly awaited, and could be available in 2013. Secondly, the economic impact on the healthcare system of administering two targeted therapies concomitantly should be carefully evaluated. Thirdly, results of other new anti-HER2 agents, such as trastuzumab-DM1 (antibody-drug conjugate), neratinib, and afatinib (both HER2 tyrosine kinase inhibitors) etc are expected in the near future, and it will be a challenge to know how best to optimally use the many available anti-HER2 therapeutic options (12-14). Fourthly, long-term safety needs to be robustly established. Finally, it is extremely important to identify new biomarkers in order to prospectively select those patients that are expected to derive benefit from targeted agents.

The development of many new anti-HER2 molecules in the last two decades have lead to a paradigm shift in the treatment of this subgroup of patients and has vastly improved their clinical outcome. Pertuzumab may turn out to be another effective option for these patients. However the molecular biology, drug resistance, cost effectiveness, and drug side effects are not yet fully understood. HER2-positive breast cancer has been intensively studied in the recent but it continues to be an intriguing subtype.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2012.04.03). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Lohmann AE, Saini KS, Metzger-Filho O. Pertuzumab in metastatic breast cancer: unanswered questions. Transl Cancer Res 2012;1(2):122-124. DOI: 10.3978/j.issn.2218-676X.2012.04.03

