Research Highlight

Pertuzumab: a step forward in treating HER2-positive breast cancer

Dimitrios Mavroudis

Department of Medical Oncology, University Hospital of Heraklion, University of Crete, Greece

Corresponding to: Dimitrios Mavroudis, MD. Department of Medical Oncology, University Hospital of Heraklion, University of Crete, Greece. Email: mavrudis@med.uoc.gr.

Submitted Mar 04, 2012. Accepted for publication Mar 27, 2012.
DOI: 10.3978/j.issn.2218-676X.2012.03.05
Scan to your mobile device or view this article at: http://tcr.thepbpc.org/article/view/377/739

HER2-positive breast cancer represents an aggressive subtype of the disease occurring in approximately 20% of patients. While trastuzumab has revolutionized the treatment of HER2-positive breast cancer, a proportion of patients have *de novo* trastuzumab-resistant disease and even those who initially respond will eventually develop trastuzumab-resistance. The recent publication in the *New England Journal of Medicine* of the promising results of the CLEOPATRA trial for the combination of pertuzumab plus trastuzumab plus docetaxel in HER2-positive metastatic breast cancer (MBC) represented a significant advancement in the treatment of this illness (1).

Pertuzumab (formerly called Omnitarg or 2C4) is a humanized monoclonal antibody that targets a different extracellular domain of the HER2 receptor than does trastuzumab and inhibits heterodimerization of HER2 with HER1 and especially with HER3 which is a more critical partner for HER2 pathway activation (2). In a seminal publication it was shown that the combination of trastuzumab and pertuzumab induced increased apoptosis in the HER2-overexpressing BT474 breast cancer cell line via reduced levels of total and phosphorylated HER-2 protein and blocked receptor signalling through Akt (3). Moreover, in a mouse HER2-positive xenograft model, the combination was synergistic with anti-estrogen therapy and gefitinib, an EGFR tyrosine kinase inhibitor, in delaying tumor progression (4). Based on these results the combination of pertuzumab and trastuzumab was initially tested in a phase II study in women with HER2-positive MBC that had progressed during prior trastuzumab therapy; an encouraging objective response rate of 24% and a clinical benefit rate of 50% were observed thus verifying that the combination of the two monoclonal antibodies was active in trastuzumab-resistant disease (5). This effect was primarily due to the synergistic action of both antibodies since pertuzumab alone had minimal activity in this setting (6).

The therapeutic value of pertuzumab plus trastuzumab in combination with docetaxel chemotherapy was evaluated in a randomized, double-blind, placebo-controlled phase III study and compared with the "standard" regimen of docetaxel plus trastuzumab as first-line treatment in patients with HER2-positive MBC (1). The study was powered to detect a 33% improvement in independently-assessed median progression-free survival (PFS) in the pertuzumab group as the primary endpoint. Four hundred patients were randomized on each arm according to geographic region and prior therapy in the adjuvant or neoadjuvant setting. Surprisingly, only half of patients had prior exposure to chemotherapy and 10% had received trastuzumab as adjuvant or neoadjuvant treatment. At least six cycles of docetaxel were administered while the monoclonals were continued until disease progression. After a median follow up period of 19 months in both groups, there was a 6.1 month improvement in independently-assessed PFS in the pertuzumab group with 38% reduction in the odds of disease progression or death ($P<0.001$). This effect was observed across all predefined subgroups including the small subgroup of patients who had previously received trastuzumab with chemotherapy as adjuvant or neoadjuvant treatment. In the interim analysis of overall survival there was a strong trend toward a survival benefit as well. The objective response rate, which was a secondary endpoint, was also 10% higher for the pertuzumab group. All these improvements of the efficacy endpoints came at a low price

of increased toxicity. Although several side effects such as rash, mucositis, diarrhea, febrile neutropenia were more common, only the latter two of grade 3 or above were increased with pertuzumab. Additional cardiac toxicity was not observed with pertuzumab despite a very close monitoring.

To put the results of this trial into perspective we should consider that response to trastuzumab-based therapy of HER2-positive breast cancer is indeed variable and may depend on the high or low levels of HER2 homodimers (7). For those patients with HER2 pathway activation primarily due to ligand binding, the formation of HER2-HER3 heterodimers is critical (2) and can be effectively inhibited by the co-administration of pertuzumab (1). This has now been proven in MBC and also validated in the neoadjuvant setting with the recently published NeoSphere trial where the co-administration of pertuzumab plus trastuzumab with docetaxel chemotherapy achieved a significantly improved pathologic complete response rate compared to either monoclonal alone (8). Taken together, it appears that the more comprehensive blockade of HER2 with the two antibodies has the potential to improve survival of HER2-positive breast cancer and represents once more a paradigm shift in the treatment of this disease.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2012.03.05). The author has no conflicts of interest to declare.

Ethical Statement: The author is 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.

References

1. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
2. Lee-Hoeflich ST, Crocker L, Yao E, et al. A central role for HER3 in HER2-amplified breast cancer: implications for targeted therapy. Cancer Res 2008;68:5878-87.
3. Nahta R, Hung MC, Esteva FJ. The HER-2-targeting antibodies trastuzumab and pertuzumab synergistically inhibit the survival of breast cancer cells. Cancer Res 2004;64:2343-6.
4. Arpino G, Gutierrez C, Weiss H, et al. Treatment of human epidermal growth factor receptor 2-overexpressing breast cancer xenografts with multiagent HER-targeted therapy. J Natl Cancer Inst 2007;99:694-705.
5. Baselga J, Gelmon KA, Verma S, et al. Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy. J Clin Oncol 2010;28:1138-44.
6. Cortés J, Fumoleau P, Bianchi GV, et al. Pertuzumab Monotherapy After Trastuzumab-Based Treatment and Subsequent Reintroduction of Trastuzumab: Activity and Tolerability in Patients With Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. J Clin Oncol 2012;30:1594-600.
7. Ghosh R, Narasanna A, Wang SE, et al. Trastuzumab has preferential activity against breast cancers driven by HER2 homodimers. Cancer Res 2011;71:1871-82.
8. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:25-32.

Cite this article as: Mavroudis D. Pertuzumab: a step forward in treating HER2-positive breast cancer. Transl Cancer Res 2012;1(2):117-118. DOI: 10.3978/j.issn.2218-676X.2012.03.05