Editorial

Safety and Efficacy of Human Epidermal Growth Factor Receptor 2-Targeted Therapies in Advanced Breast Cancer: A Head-to-Head Comparison of Margetuximab versus Trastuzumab

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It is estimated that 2.26 million new cases of breast cancer occurred globally in 2020, ranking first among all cancer types.[1] Breast cancer is a major public health burden in the world, especially in China.[2] With the goal to reduce the burden on public health, development of efficient chemotherapeutic strategies has become an important milestone in the treatment of breast cancer patients.[3] Human epidermal growth factor receptor 2-positive (HER2$^+$) breast cancer accounts for approximately 25% of all breast cancer cases and denotes an aggressive phenotype.[4,5] Adding trastuzumab (a monoclonal antibody-targeting HER2) to chemotherapy can greatly improve the progression-free survival (PFS) and overall survival (OS) of patients with HER2$^+$ cancers.[6,7] However, most of the patients treated with trastuzumab have a disease progression within 1 year.[8]

CD16A, an activating Fcγ receptor expressed on innate immune cells, can trigger antibody-dependent cellular cytotoxicity.[9] A previous study showed that CD16A polymorphisms at amino acid 158 change affinity for immunoglobulin (Ig) G antibody, with CD16A-158F binding IgG at a lower affinity than CD16A-158V.[10] Clinical benefit of trastuzumab appears worse for patients with the low-affinity CD16A-158F (FF and FV genotypes) compared with the high-affinity CD16A-158V (VV genotype).[11] Unfortunately, more than 85% of patients carry CD16A-158F allele. To address the issue of affinity between CD16A and IgG, margetuximab, a novel immune-enhancing antibody-targeting HER2, was designed. Unlike the wild-type Fc domain in trastuzumab, the Fc domain in margetuximab is engineered to increase affinity for activating all CD16A-158 V/F variants but decrease affinity for inhibitory CD32B (inhibitory Fcγ receptor).[12] Therefore, compared to trastuzumab, margetuximab can trigger the innate and adaptive immune response against HER2 more effectively. Currently, a Phase I clinical trial of margetuximab monotherapy reported that 17% (4/24) of patients with HER2-positive advanced breast cancer had a confirmed partial response after receiving margetuximab treatment.[13] However, whether margetuximab plus chemotherapy can have a better effect than trastuzumab plus chemotherapy in the treatment of HER2$^+$ advanced breast cancer remains largely unknown.

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In a head-to-head trial recently published in the *JAMA Oncology*, titled "Efficacy of Margetuximab vs. Trastuzumab in Patients with Pretreated ERBB2-Positive Advanced Breast Cancer: A Phase 3 Randomized Clinical Trial," Rugo *et al.*[14] compared the safety and efficacy of margetuximab versus trastuzumab, each with chemotherapy, in pretreated HER2$^+$ advanced breast cancer patients. They enrolled 536 patients from 17 countries between August 26, 2015, and October 10, 2018. All enrolled patients had disease progression on 1–3 lines of therapy for metastatic disease and ≥2 prior anti-HER2 therapies. Among them, 266 (49.6%) patients were randomized to receive margetuximab (15 mg/kg in 3-week cycles) and 270 (50.4%) were received trastuzumab (6 mg/kg in 3-week cycles). Groups were balanced. The median PFS of margetuximab group was 5.8 months (95% confidence interval [CI] = 5.5–7.0 months) and that of trastuzumab group was 4.9 months (95% CI = 4.2–5.6 months). The data indicated that margetuximab plus chemotherapy improved primary PFS over trastuzumab plus chemotherapy with 24% relative risk reduction (hazard ratio [HR] =0.76; 95% CI = 0.59–0.98; P = 0.03). As of September 10, 2019, a total of 270 deaths have occurred. The authors analyzed the OS of these cases and found that the median OS of margetuximab recipients was 21.6 months and that of trastuzumab recipients was 19.8 months (HR = 0.89; 95% CI = 0.69–1.13; P = 0.33). In addition, investigator-assessed PFS showed 29% relative risk reduction in favor of margetuximab (median PFS: 5.7 vs. 4.4 months; HR = 0.71; 95% CI = 0.58–0.86; P < 0.001). The objective response rate of margetuximab recipients was higher than that of trastuzumab recipients (22% vs. 16% and P = 0.06 at October 10, 2018; 25% vs. 14% and P < 0.001 at September 10, 2019). The safety of the two treatment groups was comparable, except that margetuximab had a higher incidence of infusion-related reactions (IRRs) than trastuzumab (13.3% vs. 3.4%).

This is the first randomized Phase III trial to compare margetuximab plus chemotherapy to trastuzumab plus chemotherapy in patients with pretreated HER2$^+$ advanced breast cancer. This study was positive for its PFS primary end point. Although it is impossible to draw conclusions about OS currently, the immature data based on 40% and 70% of target OS events have shown that margetuximab plus chemotherapy could improve OS as compared with control trastuzumab counterpart. Furthermore, the safety of margetuximab plus chemotherapy was acceptable. The IRR rate for margetuximab recipients is a bit higher, but it is consistent with that in a published study on the first exposure of trastuzumab (16%).[15] On the other hand, this clinical trial tested the hypothesis that increasing the affinity between Fc domain and Fcγ receptor can improve the clinical efficacy of anti-HER2 antibodies and thereby drive clinical benefit in HER2$^+$ advanced breast cancer. The results from this clinical trial indicated that those CD16A-158F carriers with a diminished clinical response to trastuzumab may benefit from immune-enhancing antibodies with engineered Fc domain, such as margetuximab. Conversely, margetuximab provided no clinical benefit in CD16A-158V carriers compared with trastuzumab. However, there is no biological explanation for his observation.

This study has several limitations. First, breast cancer patients with active brain metastases were not included in this study. Second, the primary end point did not allocate α to the analysis of CD16A. Despite the limitations mentioned above, this study provides useful information by head-to-head comparison of margetuximab versus trastuzumab. It suggested that margetuximab plus chemotherapy had a statistically significant improvement in PFS compared with trastuzumab plus chemotherapy in patients with HER2$^+$ advanced breast cancer that progressed after treatment with trastuzumab and pertuzumab. These findings lay the foundation for the application of margetuximab in breast cancer.

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Conflicts of interest

There are no conflicts of interest.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
2. Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: Good or bad news from the 2018 Global Cancer Statistics? Cancer Commun (Lond) 2019;39:22.
3. Cao M, Li H, Sun D, Chen W. Cancer burden of major cancers in China: A need for sustainable actions. Cancer Commun (Lond) 2020;40:205-10.
4. Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, *et al.* Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989;244:707-12.
5. Yi Z, Ma F, Rong G, Guan Y, Li C, Xu B. Clinical spectrum and prognostic value of TP53 mutations in circulating tumor DNA from breast cancer patients in China. Cancer Commun (Lond) 2020;40:260-9.
6. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, Andre F, *et al.* 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. Ann Oncol 2018;29:1634-57.
7. Liu T, Qin Y, Li J, Xu R, Xu J, Yang S, *et al.* Pertuzumab in combination with trastuzumab and chemotherapy for Chinese patients with HER2-positive metastatic gastric or gastroesophageal junction cancer: A subpopulation analysis of the JACOB trial. Cancer Commun (Lond) 2019;39:38.
8. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr.,

Davidson NE, *et al*. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84.

9. Nimmerjahn F, Ravetch JV. Fcgamma receptors as regulators of immune responses. Nat Rev Immunol 2008;8:34-47.
10. Bruhns P, Iannascoli B, England P, Mancardi DA, Fernandez N, Jorieux S, *et al*. Specificity and affinity of human Fcgamma receptors and their polymorphic variants for human IgG subclasses. Blood 2009;113:3716-25.
11. Musolino A, Naldi N, Bortesi B, Pezzuolo D, Capelletti M, Missale G, *et al*. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. J Clin Oncol 2008;26:1789-96.
12. Nordstrom JL, Gorlatov S, Zhang W, Yang Y, Huang L, Burke S, *et al*. Anti-tumor activity and toxicokinetics analysis of MGAH22, an anti-HER2 monoclonal antibody with enhanced Fcgamma receptor binding properties. Breast Cancer Res 2011;13:R123.
13. Bang YJ, Giaccone G, Im SA, Oh DY, Bauer TM, Nordstrom JL, *et al*. First-in-human Phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors. Ann Oncol 2017;28:855-61.
14. Rugo HS, Im SA, Cardoso F, Cortes J, Curigliano G, Musolino A, *et al*. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: A Phase 3 randomized clinical trial. JAMA Oncol 2021;7:573-84.
15. Thompson LM, Eckmann K, Boster BL, Hess KR, Michaud LB, Esteva FJ, *et al*. Incidence, risk factors, and management of infusion-related reactions in breast cancer patients receiving trastuzumab. Oncologist 2014;19:228-34.