

Letter in response to “Our HER2 is same as yours”

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Molecular-targeted drugs have increasing promise in the treatment of cancer, and some predictive biomarkers for targeted therapies have been reported (1). Trastuzumab (Herceptin), a monoclonal antibody that specifically targets human epidermal growth factor receptor 2 (HER2) (2), was first approved as a targeted drug for advanced gastric cancer. The ToGA study (3), as a pivotal trial, was an open-label, international, multicenter, phase III randomized controlled trial that examined the clinical efficacy and safety of first-line trastuzumab with chemotherapy for HER2-positive advanced gastric or gastroesophageal junction cancers. This study showed that a median survival time of 13.8 months for the trastuzumab with chemotherapy arm compared with 11.1 months for the chemotherapy alone arm ($P=0.0046$). Trastuzumab with chemotherapy improved median survival, time-to-progression and progression-free survival compared with chemotherapy alone. As a result, trastuzumab therapy with chemotherapy has become the standard treatment for HER2-positive advanced gastric cancer patients.

HER2 evaluation is important when selecting patients who could benefit from trastuzumab, so it is necessary to standardize the protocol of HER2 assessment using immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH). Previous studies have shown that HER2-positivity varied widely, at a rate of ~10–20% in Japanese gastric cancer patients (4-6). This variability resulted from a failure to employ standardized methods to test HER2-positivity. The purpose of the JFMC44-1101 study was to evaluate HER2 protein expression and gene amplification in Japanese metastatic or recurrent gastric cancer patients with a standardized method, which was used to prospectively interpret both the IHC data and the FISH data of the ToGA study (7). Our evidence indicates

that the rate of HER2 positivity was 21.2%, whereas the rate of HER2 IHC 3+/FISH-positive expression was 15.6% in this previous cohort. While Song and Park (8) showed that HER2 positivity is similar in Asian patients, we would like to emphasize that this rate of HER2 positivity was comparable with that reported in the ToGA study and that there are few differences in ethnicity. We believe that the strategy for cancer treatment should include the establishment of clinical evidence through large-scale clinical trials and the standardization of analysis protocols for molecular classification.

Gastric cancer is a heterogeneous cancer, exhibiting the Lauren classification intestinal and diffuse types (9). Our data suggested that intestinal type was an independent factor related to HER2 positivity. In future studies, we will investigate the detailed pathological data and clinical outcomes of our cohort. *HER2* is a driver gene, and many driver genes have the potential to be targeted for personalized cancer treatment. Matsusaka *et al.* reported that amplification of *FGFR2*, *EGFR*, *HER2*, *MET* and *KRAS*, which are associated with the receptor tyrosine kinase (RTK)/RAS pathway, was observed in 4.4%, 5.9%, 9%, 3.7% and 10.3% of gastric cancer patients, respectively (10). Moreover, microsatellite instability-high (MSI-H) disease predicts better outcome for pembrolizumab, an anti-programmed death-1 (PD-1) monoclonal antibody in colorectal cancer patients (11). Therefore, molecular classification by microsatellite instability (MSI) status in gastric cancer may be invaluable for predicting responders to the PD-1/programmed death-ligand 1 (PD-1L) antibodies. In summary, precision medicine by molecular classification could lead a new era of cancer treatment that is not dictated by clinical differences between Asian and Western

patients. The molecular classification of gastric cancer should be conducted in parallel with a number of clinical trials currently being conducted for targeted therapies. Furthermore, gastric cancer patients could be treated with new molecular-targeting agents or drug repositioning if cancer mutations can be detected by targeted deep sequencing of plasma DNA.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. La Thangue NB, Kerr DJ. Predictive biomarkers: a paradigm shift towards personalized cancer medicine. *Nat Rev Clin Oncol* 2011;8:587-96.
2. Cuello M, Ettenberg SA, Clark AS, et al. Down-regulation of the erbB-2 receptor by trastuzumab (herceptin) enhances tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis in breast and ovarian cancer cell lines that overexpress erbB-2. *Cancer Res* 2001;61:4892-900.
3. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;376:687-97.
4. Yonemura Y, Ninomiya I, Yamaguchi A, et al. Evaluation of immunoreactivity for erbB-2 protein as a marker of poor short term prognosis in gastric cancer. *Cancer Res* 1991;51:1034-8.
5. Uchino S, Tsuda H, Maruyama K, et al. Overexpression of c-erbB-2 protein in gastric cancer. Its correlation with long-term survival of patients. *Cancer* 1993;72:3179-84.
6. Ooi A, Kobayashi M, Mai M, et al. Amplification of c-erbB-2 in gastric cancer: detection in formalin-fixed, paraffin-embedded tissue by fluorescence in situ hybridization. *Lab Invest* 1998;78:345-51.
7. Matsusaka S, Nashimoto A, Nishikawa K, et al. Clinicopathological factors associated with HER2 status in gastric cancer: results from a prospective multicenter observational cohort study in a Japanese population (JFMC44-1101). *Gastric Cancer* 2015. [Epub ahead of print].
8. Song HN, Park SH. Our HER2 is same as yours. *Transl Gastrointest Cancer* 2015;4:410-2.
9. Chun N, Ford JM. Genetic testing by cancer site: stomach. *Cancer J* 2012;18:355-63.
10. Matsusaka S, Kobunai T, Yamamoto N, et al. Prognostic impact of KRAS mutant type and MET amplification in metastatic and recurrent gastric cancer patients treated with first-line S-1 plus cisplatin chemotherapy. *Genes & Cancer* 2016. (In Press).
11. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015;372:2509-20.

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