Prognostic and clinical significance of HER-2 low expression in early-stage gastric cancer

Tao Yang1†, Rui Xu1†, Junhao You1, Fang Li1, Bing Yan1* and Jia-nan Cheng2*

Abstract

Introduction: Gastric cancer is the fifth most common tumor worldwide. Human epidermal growth factor receptor 2 (HER2) overexpression is associated with poor prognosis and clinical characteristics in gastric cancer. Nevertheless, the biology of HER2-low expression has not been reported in gastric cancer.

Materials and methods: A total of 157 patients with early-stage gastric cancer were retrospectively analyzed. The associations between HER2-low expression and clinical characteristics were analyzed by Chi-square test. And the prognostic value of HER2-low expression and clinical characteristics in disease-free survival (DFS) and overall survival (OS) were analyzed by univariate and multivariate Cox regression analysis.

Results: Of 157 patients with early-stage gastric cancer, 31.8% had HER2-low tumors and 50.3% had HER2-negative tumors. HER2-low expression was associated with age, histological differentiation, tumor location and Ki-67 index. However, HER2-low expression was not associated with DFS or OS in early-stage gastric cancer.

Conclusion: HER2-low expression might result in distinct biology, but it was not an independent prognostic factor of DFS or OS in early-stage gastric cancer.

Keywords: Gastric cancer, HER-2, Prognosis, Clinical characteristics

Introduction

Gastric cancer is one of the most common malignant tumors of the digestive system. The incidence and mortality rate rank the fifth and fourth among all malignancies, respectively [1]. Human epidermal growth factor receptor 2 (HER2) overexpression has been reported in 10–30% of gastric cancer patients [2, 3]. Currently, chemotherapy plus anti-HER2 antibody have been the standard treatment in advanced gastric cancer patients with HER2 overexpression. The result of ToGA study revealed that trastuzumab plus chemotherapy significantly improved overall survival than chemotherapy alone in patients with HER2-positive gastric cancer [4]. Moreover, trastuzumab treatment did not result in significantly increased drug-related cardiac adverse effects [4].

Activation of HER-2 signal pathway might be involved in tumor cell proliferation, differentiation, and vascular and lymphatic angiogenesis [5]. Previous studies reported that HER2 overexpression correlated with tumor location, histologic subtype and tumor grade in gastric cancer [3, 6]. However, the prognostic role of HER-2 in gastric cancer still remains controversial due to conflicting results in several studies [6–8].

Recently, trastuzumab deruxtecan (T-DXd; DS-8201), as a novel anti-HER2 antibody drug conjugates (ADCs) have demonstrated a superior efficacy in breast cancer patients with HER-2 low expression [9]. The encouraging results expand the targetability of HER-2 to a much wider population. In addition, T-DXd treatment could result in significant improvements in objective response rate.
(ORR) and overall survival (OS) in patients with HER2-positive gastric cancer [10]. Although about 10% patients receiving T-DXd treatment had drug-related interstitial lung disease or pneumonitis, most events were grade 1–2 and tolerant [10]. Moreover, T-DXd has also shown some clinical activity in patients with HER2-low gastric cancer in the DESTINY-Gastric01 trial.

Nevertheless, the biology of HER2-low expression has not reported in gastric cancer. In this study, we retrospectively analyzed the correlation of HER-2 low expression and clinical characteristics, and its prognostic significance in early-stage gastric cancer.

Patients and methods

 Patients enrollment and data collection

Between January 2012 and December 2020, a total of 157 patients with early-stage gastric cancer (stage I–III) were investigated in Hainan Hospital of PLA General Hospital. All of patients had received curative surgery and adjuvant chemotherapy of oxaliplatin and 5-fluorouracil, except for those who were clarified as T1N0M0. Clinical characteristics were collected, including age, gender, differentiation degree, TNM stage, HER-2 expression and Ki-67 index. This study was supervised by the ethics committee of Hainan Hospital of PLA General Hospital, and written informed consent was not needed since this was a retrospective study.

Detection of HER-2 expression

In this study, HER-2 expression was determined by immunohistochemistry (IHC) in 142 of 157 surgical specimens. Additionally, HER-2 expression was examined in at least 3 slides by two independent pathologists to minimize the error of intratumorally heterogeneity. HER-2 immunostaining was scored as 0, 1+, 2+, and 3+ by the universal scoring system as previously reported [11]. Moreover, tumor tissues with scores of 2+ were further detected by fluorescence in situ hybridization (FISH). Scores of 0 were considered negative for HER-2 expression, score of 1+ and 2+ (FISH-) were considered low expression, and scores of 3+ and 2+ (FISH +) were considered positive.

Follow-up of disease-free survival and overall survival

Patients were evaluated during follow-up by computed tomography (CT) of lung, abdomen and pelvic cavity. Disease-free survival (DFS) was defined as the time from the beginning of operation until the appearance of recurrence. Overall survival was defined as the time from the beginning of operation until death. The last follow-up time was on August 31th, 2022, and the medium follow-up time was 62.6 months (range: 11.7–130.4 months).

Statistical analysis

The associations between HER-2 expression and clinical characteristics were analyzed by Fisher exact test and univariate and multivariate Cox regression analysis were used to determine the associations between clinicopathological and survival. All the statistical analyses were conducted by using SPSS 20.0 software.

Results

Clinicopathological characteristics in overall population

A total of 157 patients with early gastric cancer were enrolled, and their baseline characteristics were shown in Table 1. There were 91 (58.0%) older patients (Age ≥ 60), and the average age was 61 (28–88) years. And most of patients were male (73.9%), with lymph node metastasis (73.9%), poor differentiation (63.1) and stage III (55.4%) in this study. In the overall population, 13 patients (8.3%) had HER2-positive tumors, 50 patients (31.8%) had HER2-low tumors, and 79 patients (50.3%) had HER2-negative tumors, while HER-2 expression of 15 patients (9.6%) was unknown.

Clinicopathological characteristics in HER2-low vs HER2-0 tumors

The associations of HER2-low expression and clinicopathological characteristics were summarized in Table 2. HER2-low tumors were significant more common in older patients compared to HER2-negative tumors (70% vs 49.3%, \( P = 0.021 \)). Moreover, there were more well-differentiated tumors in patients with HER-2 low expression than those without HER-2 expression (44% vs 25.3%, \( P = 0.027 \)). In addition, HER2-low tumors had higher Ki-67 index compared to HER2-0 tumors (70% vs 49.3%, \( P = 0.021 \)). Conversely, less HER-2 low tumors were located in antrum than HER-2 negative tumors (34% vs 49.4%, \( P = 0.032 \)). However, no significant difference was observed between the 2 groups in terms of sex, tumor invasion, lymph node metastasis and TNM stage.

Disease outcome of HER2-low tumors vs HER2-0 tumors

Then the disease-free survival (DFS) and overall survival (OS) analysis were performed in these 129 patients. In univariate analysis of DFS, histological differentiation (HR: 1.93[1.08–3.45], \( P = 0.044 \)), tumor invasion depth (HR: 0.15[0.08–0.28], \( P = 0.001 \)), lymph node metastasis (HR: 0.08[0.04–0.14], \( P < 0.001 \)) and TNM stage (HR: 0.21[0.12–0.37], \( P < 0.001 \)) were all associated with poor survival. Further multivariate Cox analysis revealed that lymph node metastasis (HR: 0.08[0.04–0.14], \( P < 0.001 \)) and TNM stage (HR: 0.21[0.12–0.37], \( P < 0.001 \)) were
independently associated with poor survival. However, HER-2 low expression was not associated with DFS in early-stage gastric cancer (HR: 0.90[0.47–1.70], P=0.741) (Table 3).

Similarly, the univariate analysis of OS revealed that poor differentiation (HR: 1.31[1.16–3.60], P=0.009), deep tumor invasion (HR: 0.13[0.06–0.25], P<0.001), lymph node metastasis (HR: 0.07[0.04–0.14], P<0.001) and stage III (HR: 0.24[0.13–0.44], P<0.001) were also associated with poor survival in early-stage gastric cancer. Final multivariate analysis identified lymph node metastasis as bearing prognostic importance (HR: 13.76[1.88–100.5], P=0.01). However, HER-2 low expression was not associated with OS in early-stage gastric cancer (HR: 1.11[0.60–2.06], P=0.73) (Table 4).

Discussion
HER-2 is a transmembrane protein with tyrosine kinase activity to mediate cell growth and differentiation and encoded by ERBB-2 (Erb-B2 receptor tyrosine kinase 2) gene. HER-2 overexpression or ERBB-2 amplification is universal in many cancers, including breast cancer [12], colorectal cancer [13], lung cancer [14], ovarian cancer [15], gastric or gastroesophageal junction cancer [16], and so on. Moreover, HER-2 overexpression has been reported to be associated with poor prognosis in patients with breast cancer [17], prostate cancer [18], and ovarian cancer [19]. Although several studies reported the prognostic significance of HER-2 overexpression in gastric cancer [6], other studies reported converse conclusions [8, 20].

As approval of anti-HER2 ADCs drugs in treatment of breast cancer patients, the traditional negative expression of HER-2 has been classified as two

---

**Table 1** Clinical characteristics of patients with early-stage gastric cancer

| Characteristics         | n (%)     |
|-------------------------|-----------|
| Total                   | 157 (100) |
| Age                     |           |
| ≥ 60y                   | 91 (58.0) |
| < 60y                   | 66 (42.0) |
| Sex                     |           |
| Male                    | 116 (73.9)|
| Female                  | 41 (26.1)|
| Tumor location          |           |
| Cardia                  | 33 (21.0) |
| Corpus                  | 58 (37.0) |
| Antrum                  | 66 (42.0) |
| Differentiation         |           |
| Poor                    | 99 (63.1) |
| Well                    | 58 (36.9) |
| Tumor invasion          |           |
| T1                      | 18 (11.5) |
| T2                      | 20 (12.7) |
| T3                      | 73 (46.5) |
| T4                      | 46 (29.3) |
| Lymph node              |           |
| N0                      | 41 (26.1) |
| N+                      | 116 (73.9)|
| TNM stage               |           |
| I                       | 27 (17.2) |
| II                      | 43 (27.4) |
| III                     | 87 (55.4) |
| HER-2 expression        |           |
| Negative                | 79 (50.3) |
| Low                     | 50 (31.8) |
| Positive                | 13 (8.3)  |
| Unknown                 | 15 (9.6)  |

**Table 2** Clinical characteristics of patients with HER2-low vs HER2-0 expression

|             | HER2-0 | HER2-low | P value |
|-------------|--------|----------|---------|
| Age         |        |          |         |
| ≥ 60y       | 39     | 35       | 0.021   |
| < 60y       | 40     | 15       |         |
| Sex         |        |          | 0.154   |
| Male        | 56     | 41       |         |
| Female      | 23     | 9        |         |
| Tumor location |      |          | 0.032   |
| Cardia      | 13     | 11       |         |
| Corpus      | 20     | 29       |         |
| Antrum      | 17     | 39       |         |
| Differentiation |     |          | 0.027   |
| Poor        | 59     | 28       |         |
| Well        | 20     | 22       |         |
| Tumor invasion |      |          | 0.304   |
| T1          | 11     | 3        |         |
| T2          | 12     | 8        |         |
| T3          | 36     | 20       |         |
| T4          | 20     | 19       |         |
| Lymph node  |        |          | 0.668   |
| N0          | 20     | 11       |         |
| N+          | 59     | 39       |         |
| TNM stage   |        |          | 0.15    |
| I           | 18     | 5        |         |
| II          | 17     | 15       |         |
| III         | 44     | 30       |         |
| Ki-67 index |        |          | 0.021   |
| Low         | 40     | 15       |         |
| High        | 39     | 35       |         |

---
subgroups, HER2-0 for tumors scored IHC 0 and HER2-low for tumors scored IHC 1+ or 2+ with a nonamplified FISH assay. Recently, a large cohort study analyzed the biology significance of HER2-low expression in early-stage of breast cancer [21]. Although the prognostic value was not observed, tumors with HER2-low expression exhibited many different clinical characteristics compared to those with HER2-0 expression, including sex, ER expression, histology type, tumor grade and germline mutation. However, the biology significance of HER2-low expression in gastric cancer remains unclear.

To our knowledge, this study firstly reported the clinical and prognostic significance of HER-2 low expression in gastric cancer. We found that HER-2 low expression was associated with age, histological differentiation, Ki-67 index and tumor location, but not with sex, tumor invasion, lymph node metastasis or TNM stage. The association of HER2-low expression with tumor differentiation is consistent with that of HER2-overexpression in previous studies [7, 22]. Previous studies report that HER2-overexpression tumors are more common in gastroesophageal junction (GEJ) than HER2-negative tumors [3]. In our study, the vulnerable sites of HER2-low tumors are cardia and corpus, while HER2-0 tumors are antrum. And the higher Ki-67 index might be contributed to the function of HER-2 in promoting tumor cell proliferation [23].

Nevertheless, HER-2 low expression was not an independent factor of DFS and OS in early-stage gastric cancer, which is consistent with the findings in breast cancer [21]. The results might be explained in many respects. Firstly, the HER2-0 tumors include those faintly expressing HER-2 in 10% or less of tumor cells according to the latest guidelines [24], which might also activate downstream signal to promote tumor progression. Secondly, distinguishing HER2-0 (IHC0) and HER2-low (especially IHC1) might be difficult and not inaccurate [25], which might result in the incorrect subgroup. Thirdly, the intratumoral heterogeneity is commonly seen in gastric cancer [26]. Although testing in at least 3–4 slides was recommended to minimize the error caused by intratumorally heterogeneous [27], more exhaustive and accurate determination of HER-2 expression remains an open problem.

Unlike in breast cancer, gastric cancer patients with HER-2 overexpression might not benefit from majority of anti-HER2 agents other than trastuzumab [4].

### Table 3 Univariate and multivariate disease-free survival analysis

|                | Univariate | Multivariate |
|----------------|------------|--------------|
|                | HR  | 95%CI   | P    | HR  | 95%CI   | P    |
| Age(≥ 60 vs < 60) | 0.85 | 0.47–1.51 | 0.484 |     |     |     |
| Sex (M vs F)    | 1.35 | 0.72–2.52 | 0.377 |     |     |     |
| Differentiation (Poor vs Well) | 1.93 | 1.08–3.45 | 0.044 |     |     |     |
| Tumor invasion (T1-2 vs T3-4) | 0.15 | 0.08–0.28 | 0.001 | 4.20 | 0.98–18.00 | 0.053 |
| Lymph node (N0 vs N+) | 0.08 | 0.04–0.14 | <0.001 | 3.56 | 1.87–4.25 | 0.038 |
| TNM stage (I-II vs III) | 0.21 | 0.12–0.37 | <0.001 | 4.88 | 2.03–11.71 | 0.000 |
| Ki-67 index (Low vs High) | 0.76 | 0.40–1.45 | 0.402 |     |     |     |
| Her-2 (0 vs Low) | 0.90 | 0.47–1.70 | 0.741 |     |     |     |

### Table 4 Univariate and multivariate overall survival analysis

|                | Univariate | Multivariate |
|----------------|------------|--------------|
|                | HR  | 95%CI   | P    | HR  | 95%CI   | P    |
| Age(≥ 60 vs < 60) | 0.68 | 0.36–1.29 | 0.226 |     |     |     |
| Sex (M vs F)    | 1.13 | 0.59–2.22 | 0.719 |     |     |     |
| Differentiation (Poor vs Well) | 1.31 | 1.16–3.60 | 0.009 |     |     |     |
| Tumor invasion (T1-2 vs T3-4) | 0.13 | 0.06–0.25 | <0.001 |     |     |     |
| Lymph node (N0 vs N+) | 0.07 | 0.04–0.14 | <0.001 | 13.76 | 1.88–100.5 | 0.010 |
| TNM stage (I-II vs III) | 0.24 | 0.13–0.44 | <0.001 |     |     |     |
| Ki-67 index (Low vs High) | 0.82 | 0.42–1.60 | 0.55 |     |     |     |
| Her-2 (0 vs Low) | 1.11 | 0.60–2.06 | 0.73 |     |     |     |
Pertuzumab combined with trastuzumab and chemotherapy did not prolong PFS or OS in first-line treatment for metastatic gastric cancer [28]. Similarly, lapatinib combined with chemotherapy did not improve survival outcomes in first-line or second-line treatment in gastric cancer [29, 30]. Moreover, continued treatment of trastuzumab cloud not prolong survival in gastric cancer patients with disease progression [31]. The heterogeneous of HER2 expression might be the critical factor that limit the efficacy of HER2-targeted treatments in gastric cancer patients [32, 33].

As the first ADC targeting HER-2, trastuzumab emtansine (T-DM1) resulted in effective clinical responses in breast cancer patients with HER-2 overexpression [34], but not in gastric cancer patients [35]. However, as a novel ADC drug, T-DXd treatment results in significant improvements in ORR and OS in patients with HER2-positive gastric cancer [10]. Moreover, T-DXd has also shown some clinical activity in patients with HER2-low gastric cancer. Therefore, there is clinical importance to distinguish HER-2 low tumors from HER-2 negative tumors in gastric cancer patients. Nevertheless, more patients and studies are still needed to verify our conclusion.

Conclusion
HER2-low expression might result in distinct biology, but it was not an independent prognostic factor of DFS or OS in early-stage gastric cancer.

Abbreviations
HER-2: Human epidermal growth factor receptor 2; ADCs: Antibody drug conjugates; ORR: Objective response rate; OS: Overall survival; DFS: Disease-free survival; IHC: Immunohistochemistry; FISH: Fluorescence in situ hybridization; ERBB-2: Erb-B2 receptor tyrosine kinase 2.

Acknowledgements
Not applicable.

Authors' contributions
Study concept and design – J.C and B.Y. Study materials – J.Y and FL. Data collection – TY and RX. Statistical analysis – TY and JY. Manuscript preparation – TY and J.C. Manuscript review – J.C and B.Y. All authors contributed to the article and approved the submitted version.

Funding
The study was supported by National Nature Science Foundation of China (No.82003006, No.82102878) and Nature Science Foundation of Hainan Province (No.821QN384).

Availability of data and materials
The datasets supporting the conclusions of this article are included within the article.

Declarations
Ethics approval and consent to participate
This study was supervised by the ethics committee of Hainan Hospital of PLA General Hospital, and written informed consent was not needed since this was a retrospective study by decision of the ethics committee of Hainan Hospital of PLA General Hospital. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflict of interest.

Received: 25 September 2022 Accepted: 31 October 2022

Published online: 12 November 2022

References
1. Sung H, 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(3):209–49.
2. Gravalos C, Jimeno A. HER2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol. 2008;19(9):1523–9.
3. Rajagopal J, et al. HER 2 Expression in Gastric and Gastro‑esophageal Junction (GEJ) Adenocarcinomas. J Clin Diagn Res. 2015;9(3):EC06-10.
4. Bang YJ, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for HER2-negative advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):867–77.
5. Akiyama T, et al. The product of the human c-erbB-2 gene: a 185-kilodalton glycoprotein with tyrosine kinase activity. Science. 1986;232(4758):1644–6.
6. Park DI, et al. HER-2/neu amplification is an independent prognostic factor in gastric cancer. Dig Dis Sci. 2006;51(8):1371–9.
7. Barros-Silva JD, et al. Association of ERBB2 gene status with histopathological parameters and disease-specific survival in gastric carcinoma patients. Br J Cancer. 2009;100(3):487–93.
8. Zhou F, et al. Prognosis significance of HER-2/neu overexpression amplification in Chinese patients with curatively resected gastric cancer after the ToGA clinical trial. World J Surg Oncol. 2012;10:274.
9. Modi S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer. N Engl J Med. 2022;387(1):9–20.
10. Shitara K, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med. 2020;382(25):2419–30.
11. Hoffman M, et al. Assessment of a HER2 scoring system for gastric cancer results from a validation study. Histopathology. 2008;52(7):797–805.
12. Kaptain S, Tan LK, Chen B. Her-2/neu and breast cancer. Diagn Mol Pathol. 2001;10(3):139–52.
13. Ooi A, et al. Protein overexpression and gene amplification of HER-2 and EGFR in colorectal cancers: an immunohistochemical and fluorescent in situ hybridization study. Mod Pathol. 2004;17(8):895–904.
14. Hirsch FR, et al. Evaluation of HER-2/neu gene amplification and protein expression in non-small cell lung carcinomas. Br J Cancer. 2002;86(9):1449–56.
15. Hellstrom I, et al. Overexpression of HER-2 in ovarian carcinomas. Cancer Res. 2001;61(6):2420–3.
16. Moelans CB, et al. Her-2/neu testing and therapy in gastroesophageal adenocarcinoma. Patholog Res Int. 2010;2011:674182.
17. Press MF, et al. HER-2/neu gene amplification characterized by fluorescence in situ hybridization: poor prognosis in node-negative breast carcinomas. J Clin Oncol. 1997;15(8):2894–904.
18. Sadasivan R, et al. Overexpression of Her-2/neu may be an indicator of poor prognosis in prostate cancer. J Urol. 1993;150(1):126–31.
19. Camilleri-Broet S, et al. HER-2 expression is an independent marker of poor prognosis of advanced primary ovarian carcinoma: a multicenter study of the GINECO group. Ann Oncol. 2004;15(11):1042–1048.
20. Hsu JT, et al. Impact of HER-2 overexpression/amplification on the prognosis of gastric cancer patients undergoing resection: a single-center study of 1,036 patients. Oncologist. 2011;16(12):1706–13.
21. Tarantino P, et al. Prognostic and Biologic Significance of ERBB2-Low Expression in Early-Stage Breast Cancer. JAMA Oncol. 2022;8(8):1177–83.
22. Tanner M, et al. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase I/lalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Oncol. 2005;16(2):273–8.
23. Volpi A, et al. HER-2 expression and cell proliferation: prognostic markers in patients with node-negative breast cancer. J Clin Oncol. 2003;21(14):2708–12.
24. Wolff AC, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol. 2018;36(20):2105–22.
25. Fernandez AI, et al. Examination of Low ERBB2 Protein Expression in Breast Cancer Tissue. JAMA Oncol. 2022;8(4):1–4.
26. Janjigian YY, et al. Genetic Predictors of Response to Systemic Therapy in Esophageogastric Cancer. Cancer Discov. 2018;8(1):49–58.
27. Satala CB, et al. HER-2 Heterogeneity in Gastric Cancer: A Comparative Study. Using Two Commercial Antibodies J Oncol. 2020;2020:8860174.
28. Tabernero J, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018;19(10):1372–84.
29. Satoh T, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN—a randomized, phase III study. J Clin Oncol. 2014;32(19):2039–49.
30. Hecht JR, et al. Lapatinib in Combination With Capecitabine Plus Oxaliplatin in Human Epidermal Growth Factor Receptor 2-Positive Advanced or Metastatic Gastric, Esophageal, or Gastroesophageal Adeno-carcinoma. TRIO-013/LOGiC–A Randomized Phase III Trial. J Clin Oncol. 2016;34(5):443–51.
31. Takayama A, et al. Randomized, Phase II Study of Trastuzumab Beyond Progression in Patients With HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer: WIOG7112G (T-ACT Study). J Clin Oncol. 2020;38(17):1919–27.
32. Van Cutsem E, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer. 2015;18(3):476–84.
33. Grillo F, et al. HER2 heterogeneity in gastric/gastroesophageal cancers: From benchside to practice. World J Gastroenterol. 2016;22(26):5879–87.
34. Verma S, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783–91.
35. Thuss-Patience PC, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol. 2017;18(5):640–53.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.