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Review of survival, safety, and clinical outcomes in HER2+ metastatic gastric cancer following the administration of trastuzumabPost-Trastuzumab Gastric Cancer

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ABSTRACT

Background: Therapies targeting human epidermal growth factor receptor 2 (HER2) have become a focus for improving treatment outcomes in patients with gastric cancer. This literature review sought to assesses clinical outcomes, including safety, survival, and treatment outcomes, of patients who received trastuzumab for the treatment of HER2+ metastatic gastric cancer.

Methods: Searches were conducted in PubMed and Embase to identify observational research studies investigating the clinical outcomes of trastuzumab and combination therapies for the treatment of HER2+ metastatic gastric cancer, published January 1, 2014–August 22, 2019. Article screening was a two-phase process, and the results of each screening level were documented in accordance with PRISMA.

Results: Twenty articles met the selection criteria for data extraction. Studies focused on treatment patterns or survival, safety, and clinical outcomes, as well as the natural history of disease. In the combined HER2+ patient populations included in this review, tumors were located in the stomach (33.7%), gastroesophageal junction (GEJ, 14.2%), unspecific GEJ or stomach (50.3%), or esophagus (1.9%). Studies observed increases in both overall survival and progression-free survival with the use of trastuzumab-based chemotherapy compared with chemotherapy treatment alone. Additionally, trastuzumab-based chemotherapy appeared to improve survival and clinical outcomes regardless of the presence of multi-organ metastases or tumor location.

Conclusions: Trastuzumab-treated patients have longer survival times than those not treated with trastuzumab and tolerate treatment well, with few serious adverse events. New treatments for second- and subsequent-line therapies would increase regimen options.

Mini-abstract: The treatment patterns and clinical outcomes observed in this literature review suggest patients treated with trastuzumab have longer survival times compared with chemotherapy treatment alone and tolerate treatment

Introduction

Gastric cancer, including cancers of the stomach or gastro-esophageal junction (GEJ), is one of the most frequently diagnosed cancer and is a leading cause of cancer-related deaths. Excluding non-melanoma skin cancer, stomach cancer was the fifth-most diagnosed cancer, accounting for 5.7% of new cancer cases, and it was the second most frequent cause of cancer-related deaths, with an estimated 783,000 deaths in 2018 (8.2%) [1]. The prognosis for patients with gastric cancer, especially those with inoperable, recurrent, or metastatic disease, is poor, with a median overall survival time of approximately 7–11 months [2–5]. One of the most common genetic variations seen in patients with gastric cancer is elevated levels of human epidermal growth factor receptor 2 (HER2), with approximately 20% of gastric cancers being HER2 positive (HER2+) [6, 7].

Guidelines developed by the National Comprehensive Cancer Network (NCCN),the European Society for Medical Oncology (ESMO), and the Japanese Gastric Cancer Association recommend inclusion of

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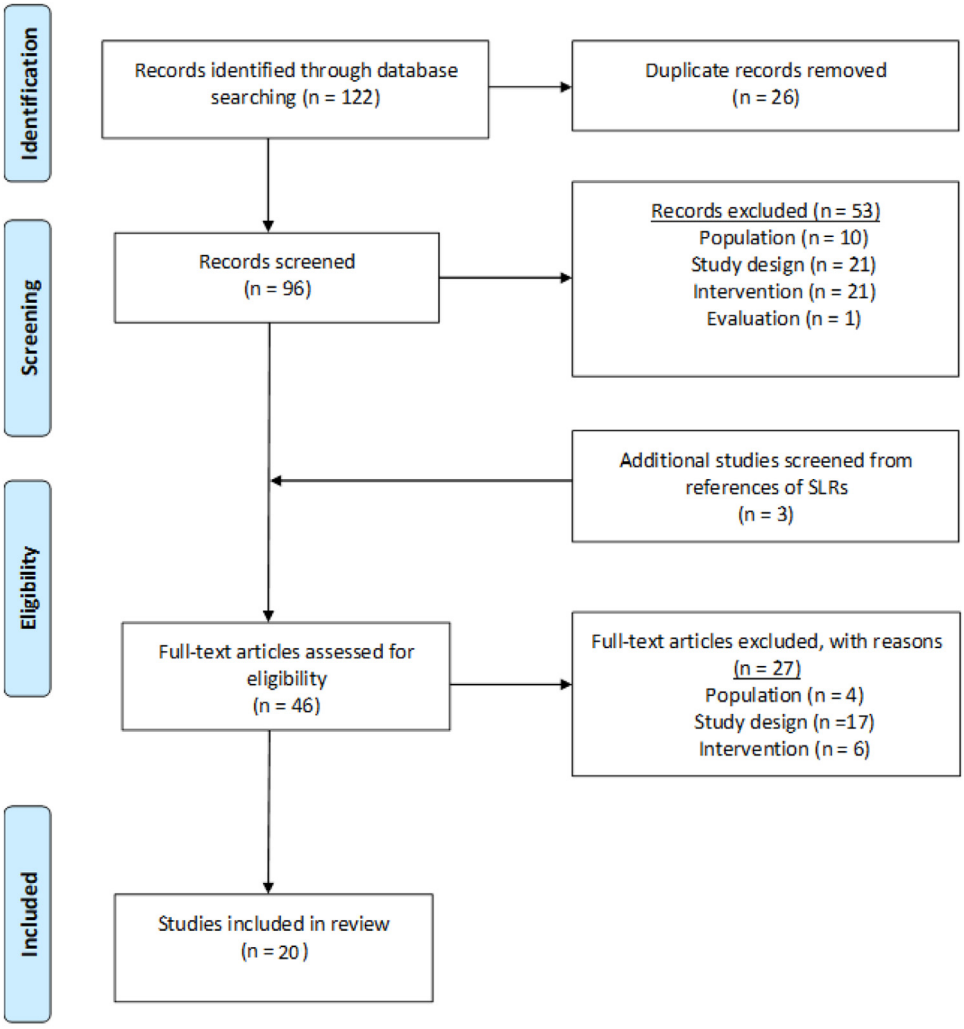

Fig. 1. PRISMA diagram of articles included in literature review SLR = systematic literature review.

trastuzumab as first-line therapy for inoperable or metastatic HER2+ gastric cancer [7–9]. In 2010, trastuzumab obtained regulatory approval in both Europe and the United States (US) as a treatment for HER2+ gastric cancer [10, 11], and trastuzumab in combination with chemotherapy is the current standard of care for patients with HER2+ advanced, recurrent, or metastatic disease [7, 8, 12]. However, therapeutic options are limited for disease progression beyond first-line treatment, and there are no approved HER2-targeted therapies for second-line and later courses. Other molecularly targeted agents are available for gastric cancer, particularly for second and later lines of treatment. Ramucirumab, administered with chemotherapy or as a single agent, is the recommended second-line treatment for advanced gastric cancer or GEJ adenocarcinoma [7–9]. This IgG1 (immunoglobulin G1) monoclonal antibody binds to vascular endothelial growth factor receptor 2 (VEGFR2), limiting tumor blood supply [13]. For third-line treatment, the immunotherapies pembrolizumab and nivolumab are approved for patients with esophagogastric cancer for whom chemotherapy has been ineffective [12]; and pembrolizumab is approved for the treatment of patients with locally advanced or metastatic gastric or GEJ adenocarcinoma with PD-L1-expressing tumors. Pembrolizumab and nivolumabare IgG4 (immunoglobulin G4) monoclonal antibody inhibitors that can disrupt the PD-1/PD-L1 axis, targeting PD-L1 (programmed death-ligand 1), which results in a T-cell–mediated immune response to tumor cells [14, 15]. Nivolumab is approved for use in Japan, but not the US [16]. The tyrosine kinase inhibitor apatinib, which binds to and inhibits VEGFR2, limiting endothelial cell proliferation, migration, and tumor microvascular density [17, 18], may also be used for late-stage gastric cancer that has progressed and is typically used in third-line treatment. Apatinib is currently approved for use in China, but not the US [16]. In early 2019, trifluridine/tipiracil was approved by the US Food and Drug Administration for the third- or fourth-line treatment of cancers of the stomach or GEJ adenocarcinoma. With this combination oral cytotoxic chemotherapy, trifluridine becomes incorporated into the DNA, causing DNA dysfunction; tipiracil is a thymidine phosphorylase inhibitor that blocks the breakdown of trifluridine, increasing trifluridine's bioavailability [19].

While these treatments offer varied continuing therapeutic regimens, limited HER2-targeted agents are available and therapies targeting HER2 have become a focus for both improving first-line therapy outcomes and for use in subsequent lines of treatment. Trastuzumab deruxtecan (T-DXd) is composed of a humanized monoclonal antibody that specifically targets HER2 with the same amino acid sequence as trastuzumab, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor payload [20, 21]. The FDA recently approved T-DXd in December 2019 as third-line treatment for HER2+ metastatic breast cancer. Phase 1 and 2 studies have suggested T-DXd to have a manageable safety profile and the ability to reduce tumor burden in patients heavily pretreated with trastuzumab [20, 22, 23].While the preliminary results are encouraging, a thorough review of the

epidemiologic data and clinical outcomes of patients after receiving trastuzumab is needed to further determine the potential role of T-DXd for the treatment of HER2+ metastatic gastric cancer.

The primary objective of this review was to assess clinical outcomes, including safety, survival, and treatment outcomes, of patients with HER2+ gastric cancer after receiving trastuzumab. Additionally, the review explored real-world disease and treatment patterns of patients with HER2+ gastric cancer.

Methods

Search design

Searches were conducted in MEDLINE In-Process using the PubMed platform and Embase using the Dialog Platform. Each database was searched using a predefined search strategy (Online Resource 1 and Online Resource 2) to identify observational research studies investigating trastuzumab and other therapies for the treatment of HER2+ metastatic gastric cancer. The search strategy included a combination of free text and MeSH (Medical Search Headings) search terms and a restriction to studies published in English during the period January 1, 2014–August 22, 2019. No geographic limits were applied. The bibliographies of systematic literature reviews and meta-analyses relevant to the study objectives were reviewed to identify potential additional publications. Titles and abstracts identified from the electronic databases were exported to Excel (Microsoft Corporation; Redmond, Washington) for screening.

Screening and extraction

Articles were screened in a two-phase process. In Level 1 screening, one researcher reviewed the titles and abstracts of the identified articles according to the inclusion and exclusion criteria (Fig. 1) and selected articles for further review. In Level 2 screening, the full text of articles selected at Level 1 were obtained and reviewed by a researcher using the same set of inclusion and exclusion criteria. If there was any uncertainty about the inclusion of articles, the Level 2 reviewer discussed the publication with a second researcher who had not been involved with Level 1 screening to confirm if the article met the study inclusion and exclusion criteria. The results of each screening level were documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [24] to detail the volume of articles included and excluded at each screening level, as well as the reasons for exclusion.

Data were extracted using full-text publications. Reviewers extracted the data from each article according to prespecified data fields and recorded the data in a data extraction template.

Results

Fig. 1 displays the PRISMA diagram with the number of studies included and excluded at each stage of screening. Preliminary searches were conducted on July 30, 2019, and updated queries were completed on August 22, 2019. The final searches yielded a total of 122 titles (Embase = 67; PubMed = 55), of which 26 records (21.3%) were duplicates, resulting in a total of 96 abstracts being eligible for manual screening. After Level 1 screening removed an additional 53 abstracts, 43 publications (44.8%) remained for Level 2 screening of the full-text articles. A review of the references of six systematic review or meta-analysis articles yielded an additional 3 studies to be included for Level 2 screening of full-text articles. A total of 27 articles (58.7%) were excluded during Level 2 screening, with most (n = 17, 63.0%) being removed due to failing to meet the study design criterion. An additional manuscript was identified post-screening and added to the list. A total of 20 articles met the predefined inclusion and exclusion criteria and were selected for data extraction (Table 1).

Study and patient population characteristics

Details of the 20 articles included in this review are provided in Table 2. The study populations include patients previously treated with trastuzumab and those who are new users in order to present a complete picture of burden of disease for gastric cancer. Trastuzumab-based therapies were reviewed as various lines of treatment. Patient eligibility periods for all studies were from 2006 to 2017. The majority of studies (70%) were conducted in Asia (China, n = 6; Japan, n = 6; Korea, n = 2), with the remainder in Europe (n = 5) and the US (n = 1). Patient characteristics varied across studies (Table 3). Most of the studies did not specifically provide information on race or ethnicity. The majority of studies in this review included patient populations that were predominantly male, which reflects recent worldwide demographic gastric cancer estimates [1]. A total of 16 studies provided information on patient age, either for the overall study population or for the individual study evaluation groups. The median age ranged from 57 to 64 years for the 8 studies providing information on the overall study population [12, 25–31, 44]. The median age ranged from 56 to 71 years for the remaining 7 studies that reported information only at the level of the individual study evaluation groups [32–38]. Information on the enrollment of patients ≥ 65 years old was available in 8 studies (42.1%), and only one study [39] specifically restricted its study population to elderly patients (median age = 71 years).

Most studies focused on treatment effectiveness (e.g., overall response rate, tumor shrinkage, disease control rate) or safety (n = 13), while the other studies explored survival (progression-free survival and/or overall survival) as the main outcome assessed (n = 5), specific treatment outcomes (n = 1), and natural history of the disease (n = 1). Most studies (n = 18) assessed survival as an outcome, even if not as the primary study objective. Three studies specifically reported on use of trastuzumab as second-line therapy following disease progression with trastuzumab-based first-line treatment [32, 40, 44]. Data were collected on HER2+ gastric cancer by tumor location, histology, and HER2 expression. Five studies evaluated specific clinical prognostic factors in patients treated with trastuzumab [2, 25, 31, 35, 41]. Hwang et al. [25] investigated the relevance of the neutrophil-to-lymphocyte ratio as a prognostic factor for chemotherapy response in patients whose treatment regimen included trastuzumab. Jiang et al. [41] studied patients with gastric cancer and liver metastasis and looked both at the correlation between HER2 expression and liver metastasis and the impact of HER2 status and trastuzumab use on the prognosis for these patients. Pietrantonio et al. [35] assessed the clinical utility of genomic alterations in predicting primary resistance to trastuzumab.

All studies included patients with HER2+ gastric cancer; however, four studies also assessed the prognostic role of HER2 status and included a comparator group of patients with HER2-negative (HER2–) disease determined using immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH) [11, 29, 36, 41]. In addition, most studies (n = 17, 85%) included both advanced gastric cancer and metastatic disease in their patient populations.

Disease patterns

Characterization of disease patterns can be found in Table 3. Tumor location information was obtained for 1565 patients with HER2+ status across all 20 studies. Stomach tumors represented the majority of tumors in these studies (527 patients, 33.7%), with GEJ tumors occurring in 222 patients (14.2%), esophageal tumors occurring in 29 patients (1.9%), and stomach or GEJ tumor without more specific definition being classified in 787 patients (50.3%). In contrast to these overall proportions, tumors of the GEJ were reported in a majority of the patients studied by Soularue et al. [30] (71%), Ilhan-Mutlu et al. [26] (67%) and Palle et al. [44]. (55%). Four of the studies included in this review did not specify location of the gastric tumors [25,28, 32, 38], and three studies only provided a general description of tumor

Table 1
Inclusion and exclusion criteria for level 1 (Titles and Abstracts) and level 2 (Full-Text) screening.

Criterion	Included	Excluded
Study design	Population evaluation of mGC treatment, and/or mGC trajectory Observational research studies (e.g., prospective cohort study, retrospective database study, cohort study, case-control study) Literature reviews and meta-analyses[a] Natural history studies Incidence and prevalence studies	Consensus reports Preclinical studies Nonsystematic reviews Case reports Case studies/series Editorials Commentaries Letters Guideline or position statements Economic analyses Animal or other nonhuman (e.g., bench) studies Single-arm studies Studies including < 25 people Randomized controlled trials (phase 1, 2, 3 or 4)
Population	Patients diagnosed with metastatic, recurrent, advanced, incurable, or unresectable mGC (stages III-IV) HER2+	Under 18 years old Patients not screened, assessed, or diagnosed with mGC Nonmetastatic GC HER2–; HER2 low
Treatment	Any treatment or comparator, including currently approved and investigational treatments for mGC: chemotherapy, surgery, and/or radiation	
Evaluation	Prognostic, predictive factors Treatment outcomes (safety and/or effectiveness) Disease trajectory	Pharmacokinetic or pharmacodynamic studies of treatments

GC = gastric cancer; HER2 = human epidermal growth factor receptor 2; mGC = metastatic GC.
[a] Literature reviews and meta-analyses were not included in their own right but were used to identify primary studies not previously identified.

location [11,27,33]. Osumi et al. [29] reported tumor location by upper (42%), middle (35%), or lower sites (23%), according to the Japanese Classification of Gastric Carcinoma. Pietrantonio et al. [35] reported tumor location by section of the stomach (cardia, fundus/body, antrum) for trastuzumab-resistant and trastuzumab-sensitive evaluation groups. Most studies provided the number of metastatic sites, which can be used as an indication of disease severity and progression.

Data were also collated on HER2 expression/status as ascertained by review of staining patterns of biopsy or tumor specimens using IHC and FISH protocols [37]. Expression of HER2 in the study populations in this review was generally IHC3+ (range, 63.2%−97%) or IHC2+/FISH+ (range, 3%−36.8%) for studies providing data on overall patient populations [11, 26, 28, 30, 33, 44]. Osumi et al. [29] reported IHC levels only (89% IHC3+ and 11% IHC2+). Two studies included in this review [2, 31] specifically investigated trastuzumab treatment effectiveness based on the homogeneity or heterogeneity of HER2 expression (Table 4). Each of their evaluation arms were also predominantly IHC3+.

Treatment patterns

Trastuzumab treatment patterns and drug utilization were available for 17 studies (Online Resource 3). Nine studies included trastuzumab-based chemotherapy as only first-line treatment, in accordance with NCCN and ESMO treatment guidelines [7, 8]. Three studies assessed trastuzumab-based chemotherapy in second-line treatment, two did not specify treatment line, two had varied treatment lines, and one investigated the differences among trastuzumab-based chemotherapies as first-, second-, and third-line treatments (Table 5). No literature included in this review described molecularly targeted agents other than trastuzumab. Five of these studies also evaluated a comparator group not receiving trastuzumab [32, 36, 40, 41, 44]. Jiang et al. [41] and Qiu et al. [36] compared trastuzumab-receiving patients with patients who did not receive trastuzumab. The treatment lines were varied, and previous use of trastuzumab was not specified. Li et al. [40], Narita et al. [32] and Palle et al. [44]. evaluated the use of trastuzumab as part of continuation therapy in second-line treatments, with all patients having had received trastuzumab as part of first-line therapy regimens. Janjigian et al. [12], Jimenez-Fonseca et al. [11], and Okita et al. [34] did not provide data on previous treatments or number of treatment cycles and were not included in this section.

Chemotherapy regimens varied across the studies, and most were not specified in the protocols. Ten studies reported the median number of treatment cycles, ranging from 4 cycles of trastuzumab plus chemotherapy [36, 40] to 23.7 such cycles in the homogeneous HER2 group [2]. Oh et al. [33] examined the safety and efficacy of administering 30-minute maintenance infusions of trastuzumab and specified a median of six trastuzumab-containing chemotherapy cycles and three trastuzumab single-agent maintenance cycles for the overall population.

Most of the studies did not provide data on radiotherapy administered before trastuzumab-based chemotherapy began. Studies that provided data indicated that the rate of previous radiotherapy was quite low, with rates ranging from 6%−12% of the overall population [26, 30] and 0% in each of the first-line treatment groups [37]. Most of the 14 studies that provided information on prior gastrectomy or other surgical treatments reported that fewer than one-third of the patients had previous surgical interventions. Outliers included studies by Wakatsuki et al. [2], which contained only patients who had undergone previous gastrectomy, and by Jiang et al. [41], which reported that 82.1% of the trastuzumab-treated group and 100% of the non–trastuzumab-treated group had undergone radical surgery.

In the 13 studies that provided details on tumor location [2, 12, 26, 29–31, 34–37, 40, 41, 44], no differences were noted in treatment regimen, line of treatment, or previous treatments by location of the gastric tumor. The two studies that investigated trastuzumab treatment effectiveness based on the homogeneity or heterogeneity of HER2 expression [2, 31] used different treatment protocols, which made direct comparison difficult. Xu et al. [31] and Palle et al. [44]. assessed first-line trastuzumab use, with approximately 44% and 38% of patients respectively continuing use beyond first line, and there were no protocol-specified chemotherapy regimens. Wakatsuki et al. [2] assessed only first-line treatments, although chemotherapy regimens were restricted to capecitabine plus cisplatin or capecitabine alone.

Table 2
Details of studies included in the review.

Study	Study type	Population	Study size	Observation period (Years)	Country
Hwang et al. (2018) [25]	Outcomes	Patients with HER2+ metastatic AGC (stage IV) treated with combination chemotherapy including trastuzumab; prior trastuzumab use not specified	73	2011–2017	South Korea
Ilhan-Mutlu et al. (2018) [26]	Treatment effectiveness/safety	Patients with HER2+ upper GI tumor using trastuzumab-based chemotherapy. Prior trastuzumab use not specified; 39% identified with trastuzumab as maintenance treatment	33	2010–2016	Austria
Janjigian et al. (2018) [12]	Survival	Patients with stage IV esophagogastric adenocarcinoma on first-line platinum therapy and first-line chemotherapy with trastuzumab	52[a]	2014–2017	United States
Jiang et al. (2017) [41]	Survival	Patients with advanced or metastatic gastric adenocarcinoma with liver metastasis studied for prognostic role of HER2 status and trastuzumab therapy; first-line chemotherapy with trastuzumab	94[b]	2012–2015	China
Jimenez-Fonseca et al. (2017) [11]	Survival	Patients with unresectable or metastatic adenocarcinoma of the distal esophagus, GEJ, or stomach; received at least 1 cycle of polychemotherapy in first-line treatment	165[c]	2008–2016	Spain
Kadowaki et al. (2017) [27]	Treatment effectiveness/safety	Patients with HER2+ AGC treated with trastuzumab in combination with fluoropyrimidines plus cisplatin therapy as first-line treatment	57	2016–2014	Japan
Li et al. (2016) [40]	Treatment effectiveness/safety	Patients with HER2+ AGC and with disease progression during trastuzumab + first-line chemotherapy and who had second-line chemotherapy with or without trastuzumab	59	2012–2015	China
Li et al. (2018) [28]	Treatment effectiveness/safety	Patients with previously untreated HER2+ advanced or metastatic gastric adenocarcinoma receiving trastuzumab plus chemotherapy as the first-line palliative chemotherapy; excluded trastuzumab-based adjuvant or neoadjuvant therapy	107	2012–2016	China
Namikawa et al. (2016) [38]	Treatment effectiveness/safety	Patients with unresectable advanced or recurrent gastric cancer treated with chemotherapy with or without trastuzumab	213	2007–2013	Japan
Narita et al. (2017) [32]	Treatment effectiveness/safety	Patients with HER2+ AGC who received trastuzumab combined with fluoropyrimidine plus platinum as first-line treatment and who received cytotoxic agents with or without trastuzumab as second-line treatment	46	2006–2014	Japan
Oh et al. (2019) [33]	Treatment effectiveness/safety	Patients with HER2+ gastric or GEJ adenocarcinoma treated with first-line trastuzumab plus chemotherapy (5-fluorourcil or capecitabine plus platinum); patients with trastuzumab given as second-line or subsequent therapy were excluded	128[d]	2011–2017	Korea
Okita et al. (2018) [34]	Treatment effectiveness/safety	Patients with HER2+ AGC receiving first-line therapy of trastuzumab-XP or trastuzumab-SP	58	2011–2016	Japan
Osumi et al. (2018) [29]	Treatment effectiveness/safety	Patients with AGC treated with first-line chemotherapy with trastuzumab	286[e]	2010–2016	Japan
Pietrantonio et al. (2018) [35]	Natural history/ trajectory of disease	Patients with HER2-positive metastatic gastric or gastroesophageal junction cancers with trastuzumab-based first-line treatments	37	2011–2016	Italy
Qiu et al. (2014) [36]	Survival	Patients with AGC treated with chemotherapy only or chemotherapy and trastuzumab, varied lines of treatment	349[f]	2010–2012	China
Soularue et al. (2015) [30]	Treatment effectiveness/safety	Patients receiving trastuzumab in combination with mFOLFOX6 or trastuzumab in combination with XELOX as first-line treatment for HER+ AGC and advanced GEJ cancer	34	2009–2012	France
Wakatsuki et al. (2018) [2]	Treatment effectiveness/safety	Patients with HER2+ AGC or mGC treated with trastuzumab-based chemotherapy as first-line treatment and who had previous gastrectomy	28	2011–2015	Japan
Xu et al. (2017) [31]	Treatment effectiveness/safety	Patients with AGC receiving trastuzumab; varied lines of treatment. All patients received trastuzumab in first-line therapy, with 21 patients continuing use beyond first line	48	2010–2016	China
Zhu et al. (2015) [37]	Treatment effectiveness/safety	Elderly HER2+ AGC patients receiving trastuzumab + cisplatin (HP) or trastuzumab + capecitabine (HX) as first-line chemotherapy	92	NR	China
Palle et al. (2017) [44]	Treatment effectiveness	HER2 + advanced Gastric/GEJ adenocarcinoma who received a second line of chemotherapy with or without trastuzumab after progression on platinum-based chemotherapy plus trastuzumab	104	2010–2015	France

AE = adverse event; AGC = advanced gastric cancer; GEJ = gastroesophageal junction; GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2; HER2+ = HER2 positive; HER2– = HER2 negative; mFOLFOX6 = modified leucovorin/5-fluorouracil/oxaliplatin; mGC = metastatic gastric cancer; NR = not reported; RECIST = Revised Evaluation Criteria in Solid Tumor; trastuzumab-SP = trastuzumab with S-1 plus cisplatin; trastuzumab-XP = trastuzumab with capecitabine plus cisplatin; XELOX = capecitabine plus oxaliplatin.

[a] Patients treated with first-line chemotherapy with trastuzumab.
[b] Gastric cancer patients with liver metastasis; includes 59 HER2– patients.
[c] Of 1170 patients meeting eligibility criteria and who received trastuzumab in first-line therapy; includes 2 HER2– patients.
[d] Efficacy population, 128 overall; safety population, 123 (5 who received induction therapy only were excluded).
[e] Includes 186 HER2– patients.
[f] Includes 251 HER2– patients.

Table 3
Patient characteristics and disease patterns.

Study	Treatment group	Median (Mean) Age, Years	Female (%)	Tumor location (%)	Number of metastatic sites (%)	HER2 expression/status (%)
Hwang et al. (2018) [25]	Trastuzumab-combined chemotherapy	63.0	16.4%	Gastric tumors, NS	1 site (57.5%) 2 sites (23.3%) ≥ 3 sites (19.2%)	All patients were IHC3+ or IHC2+ and FISH/SISH+ (% NR) Retrospective analysis, tumors not prospectively collected
Ilhan-Mutlu et al. (2018) [26]	Trastuzumab + chemotherapy (first line) Trastuzumab + chemotherapy (second line) Trastuzumab + chemotherapy (third line)	Overall population: 57	Overall population: 24%	Overall population: ■ GEJ (67%) ■ Stomach (33%)	Overall population: ■ 1 site (45%) ■ 2 metastatic sites (36%) ■ 3–4 metastatic sites (12%)	Overall population: ■ IHC3+: 97% ■ IHC2+/FISH+: 3% Retrospective analysis, tumors not prospectively collected
Janjigian et al. (2018) [12]	5FU + cisplatin + trastuzumab	40 (40)	0%	GEJ (100%)	≥ 2 sites (100%)	NR
	Capecitabine + oxaliplatin + trastuzumab	74 (67)	0%	Esophageal adenocarcinoma (66%); stomach (33%)	■ 1 site (33.3%) ■ ≥ 2 sites (66.7%)	
	FOLFOX + trastuzumab	66 (64)	21%	GEJ (7%); esophageal (57%); stomach (36%)	■ 1 site (39.3%) ■ ≥ 2 sites (60.7%)	
	mDCF + trastuzumab	56 (52)	33%	GEJ (17%); esophageal (58%); stomach (25%)	■ 1 site (41.7%) ■ ≥ 2 sites (58.3%)	
	PEMBRO + trastuzumab + 5FU	63 (63)	100%	GEJ (50%); stomach (50%)	■ 1 site (50%) ■ ≥ 2 sites (50%)	
	Other trastuzumab	56 (53)	17%	GEJ (17%); esophageal (67%); stomach (17%)	■ 1 site (16.7%) ■ ≥ 2 sites (83.3%)	
Jiang et al. (2017) [41]	Gastric cancer patients with liver metastasis and	Overall: 61 (60)				NR
	■ HER2+, with trastuzumab	■ NR	■ 17.9%	■ GEJ (10.7%); other stomach location (89.3%)	■ 57.1% with multi-organ metastasis	
	■ HER2+, without trastuzumab	■ NR	■ 42.9%	■ GEJ (42.9%); other stomach location (57.1%)	■ 14.3% with multi-organ metastasis	
Jimenez-Fonseca et al. (2017) [11]	HER2+, with trastuzumab	NR	NR	Distal esophagus; GEJ; stomach (% NR)	NR	■ IHC3+: 63.2% ■ IHC2+/FISH+: 36.8% Prospective review of tumor tissue to determine eligibility for trastuzumab
Kadowaki et al. (2017) [27]	First-line standard trastuzumab-based chemotherapy	63.0	21.1%	Stomach or GEJ (% NR)	■ 1 site (28.1%) ■ 2 sites (43.9%) ■ ≥ 3 sites (28.1%)	■ IHC3+: 70.2% ■ IHC2+/ISH+: 29.8% ■ ISH-negative: 5.3% ■ ISH-positive: 35.1% ■ ISH unknown: 29.8% Prospective review of tumor tissue as part of routine clinical care
Li et al. (2016) [40]	Second-line regimen with trastuzumab	NR	31%	GEJ (34%); other stomach (66%)	≥3 sites (28%)	Second-line regimen with trastuzumab ■ IHC3+: 59% ■ IHC2+/FISH+: 41% Review of tumor tissue to determine HER2 status prior to initiation of first-line treatment
	Second-line regimen without trastuzumab	NR	11%	GEJ (33%); other stomach (67%)	≥ 3 sites (19%)	Second-line regimen without trastuzumab ■ IHC3+: 60% ■ IHC2+/FISH+: 40% Review of tumor tissue to determine HER2 status prior to initiation of first-line treatment

(*continued on next page*)

Table 3 (*continued*)

Study	Treatment group	Median (Mean) Age, Years	Female (%)	Tumor location (%)	Number of metastatic sites (%)	HER2 expression/status (%)
Li et al. (2018) [28]	■ Trastuzumab with platinum plus fluoropyrimidine ■ Trastuzumab with taxane plus fluoropyrimidine ■ Trastuzumab with other	Overall population: 64	Overall population: 23.36%	NR	NR	Overall population[a]: ■ IHC3+: 65.42% ■ IHC2+/FISH+: 34.58% Prospective review of tumor tissue to determine HER2 status prior to initiating treatment
Namikawa et al. (2016) [38]	Trastuzumab plus chemotherapy	66	13.3%	NR	≥ 2 sites (6.7%)	Trastuzumab plus chemotherapy ■ IHC3+: 93.3% ■ IHC2+/FISH+: 6.7% Tumors not prospectively collected; review of tumor tissue was to determine eligibility for trastuzumab
	Chemotherapy alone	70	37.4%	NR	NR	Chemotherapy alone ■ NR
Narita et al. (2017) [32]	Second-line treatment with trastuzumab	62	19.2%	NR	≥ 2 sites (73.1%)	Second-line treatment with trastuzumab ■ IHC3+: 80.8% ■ IHC2+/FISH+: 19.2% Review of tumor tissue for HER2 status conducted before the start of first-line therapy
	Second-line treatment without trastuzumab	64	30.0%	NR	≥ 2 sites (80.0%)	Second-line treatment without trastuzumab ■ IHC3+: 60.0% ■ IHC2+/FISH+: 40.0% Review of tumor tissue for HER2 status conducted before the start of first-line therapy
Oh et al. (2019) [33]	Efficacy (overall) population[b]	63	19.5%	GEJ or gastric (% NR)	≥ 3 sites (14.0%)	Overall population: ■ IHC3+: 91.4% ■ IHC2+/FISH+: 8.6% Tumors not prospectively collected; HER2 scoring and treatment with trastuzumab were inclusion criteria for the retrospective analysis
	Safety population[a]	NR	NR			
Okita et al. (2018) [34]	Trastuzumab + XP	68.5	10.7%	■ GEJ (17.9%) ■ Gastric (82.1%)	NR	Trastuzumab-XP ■ IHC3+: 82.1% ■ IHC2+/FISH+: 14.3% ■ Unknown: 3.6% Review of tumor tissue for HER2 status conducted before the start of first-line therapy
	Trastuzumab + SP	63.5	13.3%	■ GEJ (23.3%) ■ Gastric (76.7%)	NR	Trastuzumab-SP ■ IHC3+: 83.3% ■ IHC2+/FISH+: 16.7% ■ Unknown: 0% Review of tumor tissue for HER2 status conducted before the start of first-line therapy
Osumi et al. (2018) [29]	HER2+ with FPT HER2+ with XPT HER2+ with SOXT	Overall HER2+ group: 64	Overall HER2+ group: 33%	Overall HER2+ group: ■ Upper (42%) ■ Middle (35%) ■ Lower (23%)	Overall HER2+ group: ■ > 2 sites (12%)	All treatment groups: ■ IHC3+: 89% ■ IHC2+: 11% Review of tumor tissue for HER2 status conducted before the start of first-line therapy
Pietrantonio et al. (2018) [35]	Trastuzumab resistant	69	30%	■ Cardia (55%) ■ Fundus/body (30%) ■ Antrum (15%)	> 1 site (65%)	Trastuzumab resistant ■ IHC3+: 50% ■ IHC2+: 50% Review of tumor tissue for HER2 status conducted before the start of therapy; tumor tissue was retrospectively reviewed for genomic alterations

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Table 3 (*continued*)

Study	Treatment group	Median (Mean) Age, Years	Female (%)	Tumor location (%)	Number of metastatic sites (%)	HER2 expression/status (%)
	Trastuzumab sensitive	56	35%	■ Cardia (35%) ■ Fundus/body (41%) ■ Antrum (24%)	> 1 site (35%)	Trastuzumab sensitive ■ IHC3+: 76% ■ IHC2+: 24% Review of tumor tissue for HER2 status conducted before the start of therapy; tumor tissue was retrospectively reviewed for genomic alterations
Qiu et al. (2014) [36]	HER2+ treated with chemotherapy and trastuzumab	57	25.5%	■ Stomach (72.5%) ■ GEJ (27.5%)	> 2 sites (57.8%)	HER2+ treated with chemotherapy and trastuzumab ■ FISH+/IHC3+: 62.7% ■ FISH-/IHC3+: 4.0% ■ FISH+/IHC2+: 33.3% Prospective collection and review of tumor tissue prior to start of study to determine HER2 status and eligibility for receiving trastuzumab
	HER2+ treated with chemotherapy only	59	29.8%	■ Stomach (70.2%) ■ GEJ (29.8%)	> 2 sites (59.5%)	HER2+ treated with chemotherapy only ■ FISH+/IHC3+: 70.2% ■ FISH-/IHC3+: 2.1% ■ FISH+/IHC2+: 27.7% Prospective collection and review of tumor tissue prior to start of study to determine HER2 status and eligibility for receiving trastuzumab
Soularue et al. (2015) [30]	mFOLFOX6-trastuzumab XELOX-trastuzumab	Overall population: 63	Overall population: 21%	Overall population: ■ GEJ (71%) ■ Stomach (29%)	Overall population: ■ > 2 sites (14.7%)	Overall population: ■ IHC3+: 88% ■ IHC2+/FISH+: 12% Review of tumor tissue for HER2 status conducted before the start of treatment
Wakatsuki et al. (2018) [2]	Homogeneously HER2[c]	NR	35.7%	■ GEJ (28.6%) ■ Distal stomach (71.4%)	50.0% visceral metastasis (lung or liver, no. of sites NR)	Homogeneously HER2 ■ IHC3+: 100.0% ■ IHC2+/FISH+: 0.0% Archived primary tumor tissue from previous gastrectomy reviewed for HER2 status and intratumoral HER2 heterogeneity
	Heterogeneously HER2[c]	NR	14.3%	■ GEJ (28.6%) ■ Distal stomach (71.4%)	57.1% visceral metastasis (lung or liver, no. of sites NR)	Heterogeneously HER2 ■ IHC3+: 85.7% ■ IHC2+/FISH+: 14.3% Archived primary tumor tissue from previous gastrectomy reviewed for HER2 status and intratumoral HER2 heterogeneity
Xu et al. (2017) [31]	Trastuzumab and HER2 homogeneous[d]	Overall population: 64.0 (63.0)	32.1%	■ GEJ (39.3%) ■ Other stomach (60.7%)	≥ 3 sites (35.7%)	Trastuzumab and HER2 homogeneous ■ IHC3+: 92.9% ■ IHC2+/FISH+: 7.1% HER2 status determined prior to treatment; biopsy or radical resection tumor specimens of HER2+ patients retrospectively reviewed for intratumoral HER2 heterogeneity
	Trastuzumab and HER2 heterogeneous[d]		15.0%	■ GEJ (30.0%) ■ Other stomach (70.0%)	≥ 3 sites (25.0%)	Trastuzumab and HER2 heterogeneous ■ IHC3+: 85.0% ■ IHC2+/FISH+: 15.0% HER2 status determined prior to treatment; biopsy or radical resection tumor specimens of HER2+ patients retrospectively reviewed for intratumoral HER2 heterogeneity
Zhu et al. (2015) [37]	Trastuzumab + cisplatin	71	25%	■ Stomach (79%) ■ GEJ (21%)	≥ 2 sites (54%)	NR

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Table 3 (*continued*)

Study	Treatment group	Median (Mean) Age, Years	Female (%)	Tumor location (%)	Number of metastatic sites (%)	HER2 expression/status (%)
	Trastuzumab + capecitabine	71	25%	■ Stomach (75%) ■ GEJ (25%)	≥ 2 sites (41%)	
Palle et al. (2017) [44]	Second line therapy with trasuzumab	57.9	17.9%	■ Stomach (17.9%) ■ GEJ (82.1%)	■ sites (43.6%) ■ ≥ 2 sites (56.4%)	■ IHC 3 + 87.2% ■ IHC 2 + /FISH-positive 7.7% ■ Unknown 5.1%
	Second line therapy without trasuzumab	61.3	23,1%	■ Stomach (61.5%) ■ GEJ (38.5%)	■ sites (23.1%) ■ ≥ 2 sites (76.9%)	■ IHC 3 + 75.4% ■ IHC 2 + /FISH-positive 21.5% ■ Unknown 3.1%

5FU = fluorouracil; FISH = fluorescence in situ hybridization; FOLFOX = leucovorin/5-fluorouracil/oxaliplatin; FPT = 5-fluorouracil, cisplatin, and trastuzumab; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; mDCF = modified docetaxel, cisplatin, and fluorouracil; mFOLFOX = modified FOLFOX; NR = not reported; NS = not specified; PEMBRO = pembrolizumab; SISH = silver ISH; SOXT = S-1, oxaliplatin, and trastuzumab; SP = S-1 and cisplatin; XELOX = capecitabine plus oxaliplatin; XP = capecitabine and cisplatin; XPT = capecitabine, cisplatin, and trastuzumab.

[a] Study included only patients with high levels of HER2 expression.

[b] Both groups treated with trastuzumab + chemotherapy.

[c] Homogeneously HER2 defined at those tumors with all cells overexpressing HER2 protein; all other tumors were heterogeneously HER2.

[d] HER2 homogeneous defined as uniform IHC3 + staining in all biopsy tumor cells and > 90% of tumor cells in blocks of resected specimens; all others were considered HER2 heterogeneous.

Table 4
HER2 expression in studies assessing HER2 heterogeneity.

Study	IHC3 + (%)	IHC2 + /FISH + (%)
HER2 homogenous		
Xu et al. (2017) [31]	92.9	7.1
Wakatsuki et al. (2018) [2]	100.0	0.0
HER2 heterogeneous		
Xu et al. (2017) [31]	85.0	15.0
Wakatsuki et al. (2018) [2]	85.7	14.3

FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry.

Survival, safety, and other clinical outcomes

Table 6 summarizes survival, safety, and clinical outcomes by study for 18 of the 20 studies included in the review. Hwang et al. [25] and Pietrantonio et al. [35] were excluded from this section for including only highly specific outcomes, such as the prognostic capability of neutrophil-to-lymphocyte ratios or candidate genomic alterations.

Survival

Eighteen studies provided some measure of survival data (e.g., overall survival, progression-free survival) as a measure of trastuzumab efficacy by examining survival following the administration of trastuzumab and after other therapies. Twelve studies included trastuzumab in all treatment arms (Table 6), which made comparative assessment of trastuzumab efficacy challenging. Six studies examined overall survival, progression-free survival, or both of trastuzumab-based chemotherapy treatment compared with treatment with chemotherapy alone [32, 36, 38, 40, 41, 44]. Each trastuzumab-containing group had longer survival times with differences in overall survival with and without trastuzumab ranging from 1.3–11.3 months and differences in progression-free survival with and without trastuzumab ranging from 1.1–2.1 months.

Other clinical outcomes

The response rate, which indicates the proportion of patients with a complete or partial response according to Revised Evaluation Criteria in Solid Tumor (RECIST) criteria, was reported in ten studies. In studies where treatment regimens with and without trastuzumab were evaluated, response rates were higher in those groups receiving trastuzumab in all but one study [32], although none of the differences were reported as statistically significant. Li et al. [40] observed a response rate of 9.3% in patients who continued with trastuzumab as part of second-line treatments compared with 3.7% in patients who did not continue trastuzumab with second-line treatment ($P = 0.617$). Narita et al. [32] found a response rate of 13.6% in patients receiving continued trastuzumab during second-line therapy compared with 15.8% for patients not continuing trastuzumab ($P = 1.00$). Qiu et al. [36] noted a response rate of 60.8% for trastuzumab compared with 40.4% for treatment without trastuzumab (*P*-value not reported). Palle et al. [44]. reported a complete and partial response rate of 5.1% and 10.3% respectively for trastuzumab group compared with 1.5% and 3.1% for the group who did not continue trastuzumab in the second line (Table 6).

The disease control rate was consistently higher in groups that received trastuzumab. Li et al. [40] observed a disease control rate of 59.3% for trastuzumab compared with 33.3% for therapy without trastuzumab. Narita et al. [32] reported a disease control rate of 54.5% compared with 36.8% for therapy without trastuzumab. Lastly, Namikawa et al. [38] noted a disease control rate of 86.7% for the trastuzumab-receiving group only. Palle et al. [44] noted a disease control rate of 50.0% compare to 27.3% in the group without trastuzumab.

Safety and adverse events

The most common hematological events reported in the reviewed

Table 5
Treatment Regimens for HER2+ Patients.

Treatment regimen	Patients, n (%)			
Trastuzumab + chemotherapy (first line)[a]	855 (54.6)			
Trastuzumab + chemotherapy (second line)	151 (9.6)			
Trastuzumab + chemotherapy (third line)	3 (0.2)			
Unspecified or varied trastuzumab treatment lines	239 (15.3)			
Chemotherapy only	317 (20.3)			
Total	**1565**			
Previous treatments	**Yes, n (%)**	**No, n (%)**	**Unknown, n (%)**	**Total**
Surgery	305 (19.5)	732 (46.8)	528 (33.7)	**1565**
Radiotherapy	6 (0.4)	210 (13.4)	1349 (86.2)	**1565**

HER2 = human epidermal growth factor receptor 2.
[a] Count excluded the 59, 46 and 104 patients, respectively, in Li et al. (2016) [40], Narita et al. (2017) [32] and Palle et al. (2017) [44] who had received first-line treatments including trastuzumab (included in count of second-line treatment).

literature were leucopenia and neutropenia. Among studies assessing treatments of trastuzumab-based chemotherapy compared with chemotherapy alone, three provided comparative data on the incidence of leucopenia and neutropenia. Two studies reported specifically on the incidence of grade 3–4 hematological events, which were higher in the trastuzumab-receiving groups. Narita et al. [32] observed grade 3–4 leucopenia in 27% of patients treated with trastuzumab compared with 25% of patients treated without trastuzumab. Qiu et al. [36] noted similar rates with grade 3–4 leucopenia in 23.5% of patients treated with trastuzumab compared with 21.3% of patients treated without trastuzumab. Narita et al. [32] observed grade 3–4 neutropenia in 42% of patients treated with trastuzumab compared with 40% of patients treated without trastuzumab. Qiu et al. [36] reported a comparable difference in rates, with grade 3–4 neutropenia observed in 19.6% of patients treated with trastuzumab compared with 19.1% of patients treated without trastuzumab.

Li et al. [40] reported a lower incidence of leucopenia and neutropenia in second-line treatment groups with or without trastuzumab, although that study's assessment was not limited to grade 3–4 events. Leucopenia was observed in 9.3% of patients who received trastuzumab compared with 3.7% of patients treated without trastuzumab. The difference in rates for neutropenia was closer than that for leucopenia with neutropenia observed in 12.5% of patients treated with trastuzumab compared with 11.1% of patients treated without trastuzumab. Across all types of grade 3–4 adverse events, Li et al. [40] reported a total of 15 events in 32 patients whose treatment included trastuzumab in the second line and 9 events in 27 patients whose treatment did not include second-line trastuzumab. None of the 11 studies where details on safety and adverse events were provided reported a grade 5 event (death).

HER2 heterogeneity and clinical outcomes

The two studies that assessed HER2 heterogeneity reported conflicting clinical outcomes [2, 31], although there were differences in the definitions used by the studies for homogenous and heterogenous groups. Xu et al. [31] observed identical overall survival in the heterogeneous and homogeneous groups treated with trastuzumab (median, 16.0 months) and similar progression-free survival (median, 6.3 versus 5.8 months; respectively, $P = 0.804$). Additionally, the response rate for the heterogeneous group (55.0%) was higher than that of the homogeneous group (46.4%), although this difference was not statistically significant ($P = 0.558$). Conversely, Wakatsuki et al. [2] reported that the median overall survival for the homogeneous group treated with trastuzumab-based chemotherapy was not reached, whereas that for the heterogenous group was 14.0 months ($P = 0.003$). The progression-free survival was significantly longer for the homogeneous group than the heterogenous group (median, 20.0 versus 6.0 months; $P = 0.001$). However, the response rate was not significantly higher in the homogeneous group (77.8%) than the heterogenous group (36.4%) ($P = 0.092$).

Geographic regions and clinical outcomes

Most of the studies included in this review ($n = 14$, 70%) were conducted in Asia, and five of these had large sample sizes of over 100 participants with HER2+ status. In contrast, the single study conducted in the US included 52 patients with HER2+ status, and three of the five European studies had fewer than 40 patients with HER2+ status in each study. The limited number of studies and small sample sizes of studies conducted outside of Asia prevent a meaningful ascertainment of outcomes or treatment patterns by region.

Discussion

The literature review of the 20 studies presented here provides a comprehensive description of real-world trastuzumab treatment patterns, as well as survival, safety, and other clinical outcomes data for trastuzumab use in varied lines of therapy for patients with HER2+ gastric cancer. Trastuzumab continues to be predominantly used in combination with various chemotherapy regimens as first-line therapy for the treatment of HER2+ advanced and metastatic gastric cancer. Although increasingly used in later lines of treatment for progressive disease, particularly in patients with a high degree of HER2 overexpression (generally IHC3+), scant literature was available assessing trastuzumab-based therapies following disease progression on first-line trastuzumab-based therapy. The three studies that reported specifically and exclusively on trastuzumab use in the second line following disease progression in the first line [32, 40, 44] suggest an expanded use of the drug in continuing lines of therapy. The frequent inclusion of trastuzumab in chemotherapy regimens is likely related to the efficacy of this intervention in treating patients with HER2+ gastric cancer, with observed increases in median survival time, including in patients with multi-organ metastases. For the six articles [32, 36, 38, 40, 41, 44] that compared survival of trastuzumab-based chemotherapy regimens to treatment with chemotherapy alone, the range of difference in progression-free survival with and without trastuzumab was 1.1–2.1 month, and the range of difference in overall survival for trastuzumab-treated versus non–trastuzumab-treated patients was 1.3–11.3 months. The three studies comparing treatment response rates of trastuzumab-based treatments versus treatments without trastuzumab noted conflicting results, with three studies reporting higher response rates with trastuzumab [36, 40, 44] and the forth study observing a greater response rate for patients not treated with trastuzumab [32]. Notably, the disease control rate for the trastuzumab-receiving groups in Li et al. [40], Narita et al. [32] and Palle et al. [44]. were higher than that for the groups not receiving trastuzumab (59.3% vs. 33.3% in Li; 54.5% vs. 36.8% in Narita; 50.0% vs 27.3% in Palle), possibly suggesting a clinical benefit to continuing trastuzumab into later lines of therapy. However, the findings of these studies should be interpreted with caution, as all of them had small sample sizes [32, 40, 44] ($n = 46$, 59 and 104respectively), which could limit generalizability. In addition, the study by Narita et al. [32] did not specify

Table 6
Survival and clinical outcomes detailed by study.

Study	Treatment group	Overall survival (Median months)	Progression-free survival (Median months)	Treatment response (Measure Used, Result)	Most common adverse events
Ilhan-Mutlu et al. (2018) [26]	Trastuzumab + chemotherapy (first line) Trastuzumab + chemotherapy (second line) Trastuzumab + chemotherapy (third line)	Overall population: 21	Overall population: 11	Overall population, tumor response: Complete response for 12% of overall population	Overall population: Nausea: 24% Neutropenia: 18%
Janjigian et al. (2018) [12]	1) 5FU + cisplatin + trastuzumab 2) Capecitabine + oxaliplatin + trastuzumab 3) FOLFOX + trastuzumab 4) mDCF + trastuzumab 5) PEMBRO + trastuzumab + 5FU 6) Other trastuzumab	1) 17.9 (mean) 2) 34.1 (mean) 3) 28.1 (mean) 4) 31.1 (mean) 5) 4.8 (mean) 6) 22.7 (mean)	1) 8.4 (mean) 2) 12.9 (mean) 3) 15.3 (mean) 4) 18 (mean) 5) 6.6 (mean) 6) 6.4 (mean)	NR	NR
Jiang et al. (2017) [41]	Patients with gastric cancer, liver metastasis, and: 1) HER2 +, with trastuzumab 2) HER2 +, without trastuzumab	1) 12.00 2) 10.47	1) 7.83 2) 6.30	NR	NR
Jimenez-Fonseca et al. (2017) [11]	HER2 +, with trastuzumab	14.6	NR	NR	NR
Kadowaki et al. (2017) [27]	First-line standard, trastuzumab-based chemotherapy	23.1	8.1	Depth of response: median, 56.8%Overall response rate: 77.2%RECIST tumor response: ■ Complete response: 1.8% ■ Partial response: 75.4% Stable disease: 15.8%Progressive disease: 7.0%Time to maximal tumor shrinkage, median: 3.8 months	NR
Li et al. (2016) [40]	1) Second-line regimen with trastuzumab 2) Second-line regimen without trastuzumab	1) 10.5 2) 6.5	1) 3.1 2) 2.0	Response rate: 1) 9.3% 2) 3.7% Disease control rate: 1) 59.3% 2) 33.3%	Incidence of hematological AEs (leucopenia): 1) 9.3% 2) 3.7% Incidence of hematological AEs (neutropenia): 1) 12.5% 2) 11.1% Grade 3 + AE: 1) Total of 15 events in 32 patients 2) Total of 9 events in 27 patients
Li et al. (2018) [28]	1) Trastuzumab with platinum plus fluoropyrimidine 2) Trastuzumab with taxane plus fluoropyrimidine 3) Trastuzumab with other	Overall population: 16.0	Overall population: 7.7	NR	Incidence of hematological AEs (leucopenia): 1) 60% 2) 50% 3) 58% Incidence of hematological AEs (neutropenia): 1) 60% 2) 55% 3) 83% Incidence of nonhematological AEs (anorexia): 1) 40% 2) 50% 3) 25%
Namikawa et al. (2016) [38]	1) Trastuzumab plus chemotherapy 2) Chemotherapy alone	1) 22.9 2) 11.6	NR	Response rate: 1) 46.7% 2) NR Disease control rate: 1) 86.7% 2) NR	1) Grade 3–4 AEs: ■ Neutropenia: 26.7% ■ Anemia: 13.3% ■ Fatigue: 13.3% ■ Total of 11 events in 15 patients 2) Grade 3–4 AEs: NR

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Table 6 (*continued*)

Study	Treatment group	Overall survival (Median months)	Progression-free survival (Median months)	Treatment response (Measure Used, Result)	Most common adverse events
Narita et al. (2017) [32]	1) Second-line treatment with trastuzumab 2) Second-line treatment without trastuzumab	1) 10.8 2) 9.5	1) 4.0 2) 2.3	Response rate: 1) 13.6% (n = 22 assessable patients) 2) 15.8% (n = 19 assessable patients) Disease control rate: 1) 54.5% 2) 36.8%	Incidence of hematological AEs (leucopenia, grade 3–4): 1) 27% 2) 25% Incidence of hematological AEs (neutropenia, grade 3–4): 1) 42% 2) 40% Incidence of grade 3–4 AE: 1) 62% 2) 50%
Oh et al. (2019) [33]	1) Efficacy (overall) population[a] 2) Safety population[a]	1) 14.8	1) 11.6	1) Response rate: 62.5%	AEs assessed in safety population (2 only): ■ Infusion-related reactions (nausea and vomiting): 26.0% ■ Cardiac-related events: 0% ■ Grade 3–4 AE: total of 12 events in 123 patients
Okita et al. (2018) [34]	1) Trastuzumab + XP 2) Trastuzumab + SP	1) 20.0 2) 16.7	1) 7.9 2) 6.9	Response rate: 1) 39.3% 2) 50.0% Disease control rate: 1) 89.3% 2) 86.7%	Any AE (all grades): 1) 92.9% 2) 93.3% Grade 3+ AE: 1) 60.7% 2) 56.7%
Osumi et al. (2018) [29]	HER2+ with FPT HER2+ with XPT HER2+with SOXT	Overall HER2+ population: 20.8	Overall HER2+ population: 7.9	Overall HER2+ population: Early tumor shrinkage[b] rate: 70%	NR
Qiu et al. (2014) [36]	1) HER2+ treated with chemotherapy and trastuzumab 2) HER2+ treated with chemotherapy only	1) 14.8 2) 11.3	1) 7.4 2) 6.0	Response rate: 1) 60.8% 2) 40.4% Time to best response[c]: 1) 6 weeks (median) 2) 12 weeks (median)	Incidence of hematological AEs (leucopenia, grade 3–4): 1) 23.5% 2) 21.3% Incidence of hematological AEs (neutropenia, grade 3–4): 1) 19.6% 2) 19.1% Grade 3–4 AE: 1) Total of 77 events in 51 patients 2) Total of 61 events in 47 patients
Soularue et al. (2015) [30]	1) mFOLFOX6-trastuzumab 2) XELOX-trastuzumab	Overall population: 17.3	Overall population: 9.0	Overall response rate: 47% (n = 30 evaluable patients)	Overall populationAEs, all grades: ■ Thrombocytopenia: 50% ■ Anemia 59% ■ Neuropathy 97% Grade 3–4: total of 12 events in 34 patients; events in 32% of patients
Wakatsuki et al. (2018) [2]	1) Homogeneously HER2 2) Heterogeneously HER2	1) Not reached 2) 14.0	1) 20.0 2) 6.0	Response rate: 1) 77.8% 2) 36.4%	NR
Xu et al. (2017) [31]	1) Trastuzumab and HER2 homogeneous 2) Trastuzumab and HER2 heterogeneous	1) 16.0 2) 16.0	1) 5.8 2) 6.3	Response rate: 1) 46.4% 2) 55.0%	NR

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Table 6 (*continued*)

Study	Treatment group	Overall survival (Median months)	Progression-free survival (Median months)	Treatment response (Measure Used, Result)	Most common adverse events
Zhu et al. (2015) [37]	1) Trastuzumab + cisplatin 2) Trastuzumab + capecitabine	1) 15.5 2) 17.0	1) 6.6 2) 7.2	Response rate: 1) 58.3% 2) 59.1%	1) Grade 3–4 AEs: ■ Neutropenia: 35.4% ■ Anorexia: 25.0% ■ Anemia: 16.7% ■ Total of 60 events in 48 patients 2) Grade 3–4 AEs: ■ Neutropenia: 29.5% ■ Anorexia: 22.7% ■ Anemia: 13.6% ■ Total of 46 events in 44 patients
Palle et al. (2017) [44]	1) Trastuzumab + Chemotherapy 2) Chemotherapy	1) 12.6 2) 6.1	1) 4.4 2) 2.3	Response rate (Complete+ Partial) 1) 15.4% 2) 4.6%	NR

5FU = fluorouracil; AE = adverse event; FOLFOX = leucovorin/5-fluorouracil/oxaliplatin; FPT = 5-fluorouracil, cisplatin, and trastuzumab; HER2 = human epidermal growth factor receptor 2; mDCF = modified docetaxel, cisplatin, and fluorouracil; mFOLFOX6 = modified FOLFOX; NR = not reported; PEMBRO = pembrolizumab; RECIST = revised evaluation criteria in solid tumor; SOXT = *S*-1, oxaliplatin, and trastuzumab; XELOX = capecitabine plus oxaliplatin; XPT = capecitabine, cisplatin, and trastuzumab.

[a] Both groups treated with trastuzumab + chemotherapy.

[b] Changes from baseline of total longest diameters in target lesions at 8 (± 4) weeks [29].

[c] Calculated from date of first-line chemotherapy to the date of best response [36].

tumor location, whereas a majority of the population in both Li et al. [40] and Qiu et al. [36]had tumors of the stomach and Palle et al. [44]. had tumor of the GEJ. Finally, study populations in Li et al. [40], Narita et al. [32] and Palle et al. [44]. included patients whose disease had progressed following first-line trastuzumab-based chemotherapy; the study by Qiu et al. [36]included various lines of chemotherapy, but use of trastuzumab was limited to first line. Overall, the reports from the literature suggested increases in both overall survival and progression-free survival associated with the use of trastuzumab-based chemotherapy compared with chemotherapy treatment alone.

Trastuzumab-based chemotherapy appeared to improve survival and clinical outcomes regardless of tumor location in the stomach, GEJ, or esophagus. The presence of multi-organ metastases also did not meaningfully impact survival or clinical outcomes in patients treated with trastuzumab. However, a gap in the knowledge exists as to the effect of HER2 heterogeneity on clinical outcomes. Wakatsuki et al. [2] reported a longer progression-free survival for the homogeneous group compared with the heterogenous group, while Xu et al. [31] found a slightly longer progression-free survival in the heterogeneous group compared with the homogeneous group. However, the samples were small, with a combined population of 76 patients from both studies, so additional research on the effect of HER2 heterogeneity is needed.

The safety profile of trastuzumab appeared manageable; no fatal events were reported in any of the studies assessing adverse events related to use of trastuzumab. This supports the findings of previously conducted phase 1 studies that reported reasonable safety profiles associated with trastuzumab [20, 22]. The most common grade 3–4 hematological events were neutropenia and leucopenia, although only two studies provided comparative data on the incidence of these events in trastuzumab-treated and non–trastuzumab-treated groups [32, 36]. While additional research is needed, recent literature has associated the timing of chemotherapy-induced neutropenia with improved outcomes for different types of tumors, including those in patients with gastric cancer [42]. Chemotherapy-induced leucopenia has been linked to improved survival in patients with small-cell lung cancer [43]; however, more evidence is needed to show a relationship in patients with gastric cancer. The safety profile information combined with observed treatment and outcome patterns suggest patients treated with trastuzumab have longer survival times than those not treated with trastuzumab and tolerate treatment well and have few adverse events.

In a recent randomized control trial Makiyama et al. (2020) [45] evaluated the continuous use of trastuzumab beyond progression in HER2+ Gastric/GEJ adenocarcinoma patients who received trastuzumab in the first line. Ninty one patients were randomly assigned to either paclitaxel (n = 46) or paclitaxel plus trastuzumab (PT) (n = 45) arm. Paclitaxel and PT arms had a median PFS of 3.2 and 3.7 months respectively and both arms had a median OS of 10 months. Authors did not find any benefit of using trastuzumab beyond progression after first line contrary to other studies (Li [40], Narita [32] and Palle[44]) where patients who used trastuzumab had a longer survival time.There are several limitations associated with this review. The literature search was restricted to the past 5 years, which excluded articles published prior to 2014. However, the impact of this search limitation should be minor since trastuzumab was initially approved for the treatment of gastric cancer in 2010 and the review focuses on outcomes following the administration of trastuzumab. Additionally, the search was limited to articles written in English, which may have resulted in the exclusion of some articles since most of the studies published in the literature were conducted in Asian countries and some articles may have been published in non-English journals. Most of the review articles (84.2%) included both advanced gastric cancer and metastatic disease in their patient populations, which made it difficult to assess the treatment patterns, efficacy, and clinical outcomes in those with purely metastatic disease. Additionally, direct comparisons between different regimens would be challenging since clinical outcomes of alternate treatment regimens were not described in the identified literature. Furthermore, no studies provided relevant data on burden of disease or directly assessed the overall incidence or prevalence of HER2+ gastric cancer after the previous administration of trastuzumab. Although articles of trastuzumab use in varied lines of treatment were included, only three articles specifically limited the patient populations to those for whom disease had progressed following trastuzumab-based first-line therapy and who were receiving trastuzumab in a later line of therapy. Other articles included trastuzumab in varied lines of treatment without specifying prior trastuzumab use. Lastly, tumor and biopsy specimens for the reviewed articles were typically collected prior to the initiation of first-line therapy. Consequently, assessments of HER2 status were either made at the outset of the study or archived tissue was examined retrospectively. Therefore, potential changes in HER2 status or HER2 heterogeneity as trastuzumab treatment progressed were not captured.

Conclusions

Patients with gastric cancer are being treated with trastuzumab in various lines of treatment regimens, regardless of HER2 status, gastric tumor location, or level of multi-organ metastatic involvement. In this review, trastuzumab-treated patients have longer survival times and tolerate treatment well with few serious (> grade 2) adverse events. Although trastuzumab in combination with chemotherapy is the current standard of care for patients with HER2+ advanced, recurrent, or metastatic disease, HER2-targeted treatments for second and subsequent-line therapies are limited.

Compliance with ethical standards

Human and animal rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

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CRediT authorship contribution statement

Michelle D. Hackshaw: Conceptualization, Methodology, Supervision, Writing - review & editing. **Christine L. Bui:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Amy Ladner:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Nora Tu:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Zahidul Islam:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Mary E. Ritchey:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Maribel Salas:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interests

MS, MDH, NT, and ZI are Daiichi Sankyo, Inc. employees. CB, AL, and MER are employees of RTI Health Solutions, an independent nonprofit research organization that does work for government agencies and pharmaceutical companies.

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Supplementary materials

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References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018 Nov) 394–424.

[2] T. Wakatsuki, N. Yamamoto, T. Sano, K. Chin, H. Kawachi, D. Takahari, et al., Clinical impact of intratumoral HER2 heterogeneity on trastuzumab efficacy in patients with HER2-positive gastric cancer, J. Gastroenterol. 53 (11) (2018 Nov) 1186–1195.

[3] A.A. Jacome, A.K. Coutinho, E.M. Lima, A.C. Andrade, J.S Dos Santos, Personalized medicine in gastric cancer: where are we and where are we going? World J. Gastroenterol. 22 (3) (2016 Jan 21) 1160–1171.

[4] J.A. Ajani, W. Rodriguez, G. Bodoky, V. Moiseyenko, M. Lichinitser, V. Gorbunova, et al., Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial, J. Clin. Oncol. 28 (9) (2010 Mar 20) 1547–1553.

[5] E. Van Cutsem, V.M. Moiseyenko, S. Tjulandin, A. Majlis, M. Constenla, C. Boni, et al., Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group, J. Clin. Oncol. 24 (31) (2006 Nov 1) 4991–4997.

[6] J.T. Jorgensen, M. Hersom, HER2 as a prognostic marker in gastric cancer - a systematic analysis of data from the literature, J. Cancer 3 (2012) 137–144.

[7] J.A. Ajani, T.A. D'Amico, K. Almhanna, D.J. Bentrem, J. Chao, P. Das, et al., Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology, J. Natl. Compr. Canc. Netw. 14 (10) (2016 Oct) 1286–1312.

[8] E.C. Smyth, M. Verheij, W. Allum, D. Cunningham, A. Cervantes, D. Arnold, et al., Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 27 (suppl 5) (2016 Sep) v38–v49.

[9] A Japanese Gastric Cancer, Japanese gastric cancer treatment guidelines 2014 (ver. 4), Gastric Cancer 20 (1) (2017 Jan) 1–19.

[10] M. Urabe, T. Ushiku, Y. Seto, M Fukayama, Pathologic response of HER2-positive gastric cancer to trastuzumab-based chemotherapy, Am. J. Surg. Pathol. 40 (10) (2016 Oct) 1326–1333.

[11] P. Jimenez-Fonseca, A. Carmona-Bayonas, M.L. Sanchez Lorenzo, J.G. Plazas, A. Custodio, R. Hernandez, et al., Prognostic significance of performing universal HER2 testing in cases of advanced gastric cancer, Gastric Cancer 20 (3) (2017 May) 465–474.

[12] Y.Y. Janjigian, F. Sanchez-Vega, P. Jonsson, W.K. Chatila, J.F. Hechtman, G.Y. Ku, et al., Genetic predictors of response to systemic therapy in esophagogastric cancer, Cancer Discov. 8 (1) (2018 Jan) 49–58.

[13] CenterWatch. Cyramza (ramucirumab). 2014. Available at: https://www.centerwatch.com/directories/1067-fda-approved-drugs/listing/3366-cyramza-ramucirumab. Accessed: 11-26-2019.

[14] C.S. Fuchs, T. Doi, R.W. Jang, K. Muro, T. Satoh, M. Machado, et al., Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial, JAMA Oncol. 4 (5) (2018 May 10) e180013.

[15] Y.K. Kang, N. Boku, T. Satoh, M.H. Ryu, Y. Chao, K. Kato, et al., Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet 390 (10111) (2017 Dec 2) 2461–2471.

[16] D. Zhao, S.J. Klempner, J Chao, Progress and challenges in HER2-positive gastroesophageal adenocarcinoma, J. Hematol. Oncol. 12 (1) (2019 May 17) 50.

[17] NCI. Drug dictionary. National Cancer Institute 2019. Available at: https://www.cancer.gov/publications/dictionaries/cancer-drug. Accessed: 20 October 2019.

[18] J. Li, S. Qin, J. Xu, J. Xiong, C. Wu, Y. Bai, et al., Randomized, double-blind, placebo-controlled phase III trial of apatinib in patients with chemotherapy-refractory advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction, J. Clin. Oncol. 34 (13) (2016 May 1) 1448–1454.

[19] K. Shitara, T. Doi, M. Dvorkin, W. Mansoor, H.T. Arkenau, A. Prokharau, et al., Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Oncol. 19 (11) (2018 Nov) 1437–1448.

[20] T. Doi, K. Shitara, Y. Naito, A. Shimomura, Y. Fujiwara, K. Yonemori, et al., Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study, Lancet Oncol. 18 (11) (2017 Nov) 1512–1522.

[21] Daiichi Sankyo Inc. Daiichi Sankyo announces [Fam-] trastuzumab deruxtecan demonstrated clinically meaningful response in patients with refractory HER2 positive metastatic breast cancer, a population with high unmet need. May 8, 2019. Available at: https://www.daiichisankyo.com/media_investors/media_relations/press_releases/detail/007006.html. Accessed: October 30, 2019.

[22] K. Shitara, H. Iwata, S. Takahashi, K. Tamura, H. Park, S. Modi, et al., Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study, Lancet Oncol. 20 (6) (2019 Jun) 827–836.

[23] S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.B. Kim, K. Tamura, et al., Trastuzumab Deruxtecan in previously treated HER2-positive breast cancer, N. Engl. J. Med. (2019 Dec 11).

[24] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, P Group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, PLoS Med. 6 (7) (2009 Jul 21) e1000097.

[25] G.Y. Hwang, D.W. Baek, H.J. Cho, S.J. Lee, Y.S. Chae, B.W. Kang, et al., Elevated neutrophil-to-lymphocyte ratio predicts survival in patients with advanced gastric cancer treated with trastuzumab combination chemotherapy, Anticancer Res. 38 (5) (2018 May) 3151–3156.

[26] A. Ilhan-Mutlu, H. Taghizadeh, A. Beer, W. Dolak, A. Ba-Ssalamah, S.F. Schoppmann, et al., Correlation of trastuzumab-based treatment with clinical characteristics and prognosis in HER2-positive gastric and gastroesophageal junction cancer: a retrospective single center analysis, Cancer Biol. Ther. 19 (3) (2018 Mar 4) 169–174.

[27] S. Kadowaki, T. Masuishi, T. Eto, Y. Narita, H. Taniguchi, T. Ura, et al., Depth of response predicts the clinical outcome of advanced HER2-positive gastric cancer to trastuzumab-based first-line chemotherapy, Cancer Chemother. Pharmacol. 80 (4) (2017 Oct) 807–813.

[28] Q. Li, H. Li, H. Jiang, Y. Feng, Y. Cui, Y. Wang, et al., Predictive factors of trastuzumab-based chemotherapy in HER2 positive advanced gastric cancer: a single-center prospective observational study, Clin. Transl. Oncol. 20 (6) (2018) 695–702.

[29] H. Osumi, D. Takahari, E. Shinozaki, K. Chin, M. Ogura, T. Wakatsuki, et al., Associations between early tumor shrinkage and depth of response and clinical outcomes in patients treated with 1st-line chemotherapy for advanced gastric cancer, Gastric Cancer 21 (2) (2018 Mar) 267–275.

[30] E. Soularue, R. Cohen, C. Tournigand, A. Zaanan, C. Louvet, J.B. Bachet, et al., Efficacy and safety of trastuzumab in combination with oxaliplatin and fluorouracil-based chemotherapy for patients with HER2-positive metastatic gastric and gastro-oesophageal junction adenocarcinoma patients: a retrospective study, Bull. Cancer 102 (4) (2015 Apr) 324–331.

[31] C. Xu, Y. Liu, D. Jiang, Q. Li, X. Ge, Y. Zhang, et al., Poor efficacy response to trastuzumab therapy in advanced gastric cancer with homogeneous HER2 positive and non-intestinal type, Oncotarget 8 (20) (2017) 33185–33196.

[32] Y. Narita, S. Kadowaki, T. Masuishi, H. Taniguchi, D. Takahari, T. Ura, et al., Correlation between human epidermal growth factor receptor 2 expression level and efficacy of trastuzumab beyond progression in metastatic gastric cancer, Oncol. Lett. 14 (2) (2017 Aug) 2545–2551.

[33] S.Y. Oh, S. Lee, S.J. Huh, J. Lee, S.T. Kim, S.H. Park, et al., Safety and efficacy of trastuzumab administered as a 30-min infusion in patients with HER2-positive advanced gastric cancer, Cancer Chemother Pharmacol 83 (3) (2019 Mar) 501–508.

[34] A. Okita, H. Imai, M. Takahashi, H. Takahashi, S. Umegaki, Y. Kawamura, et al., Efficacy and safety of trastuzumab in combination with S-1 and cisplatin therapy for Japanese patients with HER2-positive advanced gastric cancer: retrospective analysis, Tohoku J. Exp. Med. 245 (2) (2018 Jun) 123–129.

[35] F. Pietrantonio, G. Fuca, F. Morano, A. Gloghini, S. Corso, G. Aprile, et al., Biomarkers of primary resistance to trastuzumab in HER2-positive metastatic gastric cancer patients: the AMNESIA case-control study, Clin. Cancer Res. 24 (5) (2018 Mar 1) 1082–1089.

[36] M.Z. Qiu, Q. Li, Z.Q. Wang, T.S. Liu, Q. Liu, X.L. Wei, et al., HER2-positive patients receiving trastuzumab treatment have a comparable prognosis with HER2-negative advanced gastric cancer patients: a prospective cohort observation, Int. J. Cancer 134 (10) (2014 May 15) 2468–2477.

[37] B. Zhu, J.R. Wu, X.P Zhou, A retrospective comparison of trastuzumab plus cisplatin and trastuzumab plus capecitabine in elderly HER2-positive advanced gastric cancer patients, Medicine (Baltimore) 94 (34) (2015 Aug) e1428.

[38] T. Namikawa, E. Munekage, M. Munekage, H. Maeda, T. Yatabe, H. Kitagawa, et al., Evaluation of a trastuzumab-containing treatment regimen for patients with unresectable advanced or recurrent gastric cancer, Mol. Clin. Oncol. 5 (1) (2016) 74–78.

[39] X. Zhu, A.A. Joy, Targeting HER2 in advanced breast cancer, Methods Mol. Biol. 1652 (2017) 63–77.

[40] Q. Li, H. Jiang, H. Li, R. Xu, L. Shen, Y. Yu, et al., Efficacy of trastuzumab beyond progression in HER2 positive advanced gastric cancer: a multicenter prospective observational cohort study, Oncotarget 7 (31) (2016 Aug 2) 50656–50665.

[41] H. Jiang, Q. Li, S. Yu, Y. Yu, Y. Wang, W. Li, et al., Impact of HER2 expression on outcome in gastric cancer patients with liver metastasis, Clin. Transl. Oncol. 19 (2) (2017 Feb) 197–203.

[42] Y. Wang, Y. Chen, H. Yin, X. Gu, Y. Shi, G Dai, Timing of chemotherapy-induced neutropenia is a prognostic factor in patients with advanced gastric cancer undergoing first-line chemotherapy with oxaliplatin and capecitabine: a retrospective study, Cancer Med. 7 (4) (2018 Apr) 997–1005.

[43] W. Liu, C.C. Zhang, K Li, Prognostic value of chemotherapy-induced leukopenia in small-cell lung cancer, Cancer Biol. Med. 10 (2) (2013 Jun) 92–98.

[44] J. Palle, D. Tougeron, A. Pozet, E. Soularue, P. Artru, F. Leroy, et al., Trastuzumab beyond progression in patients with HER2-positive advanced gastric adenocarcinoma: a multicenter AGEO study, Oncotarget 8 (60) (2017) 101383–101393.

[45] A. Makiyama, Y. Sukawa, T. Kashiwada, J. Kawada, A. Hosokawa, Y. Horie, et al., Randomized phase II study of Trastuzumab beyond progression in patients with HER2-positive advanced gastric or Gastroesophageal junction cancer, J. Clin. Oncol. 38 (17) (2020 Jun) 1919–1927.