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REVIEW

Safety and efficacy of HER2 blockade by trastuzumab-based chemotherapy-containing combination strategies in HER2+ gastroesophageal adenocarcinoma

D. V. T. Catenacci[1*], H. C. Chung[2], L. Shen[3], M. Moehler[4], H. H. Yoon[5], M. K. Rosales[6] & Y.-K. Kang[7]

[1]Department of Medicine, The University of Chicago Medical Center, Chicago, USA; [2]Department of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [3]Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [4]Johannes-Gutenberg University, Mainz, Germany; [5]Division of Medical Oncology, Mayo Clinic Comprehensive Cancer Center, Rochester; [6]MacroGenics Inc., Rockville, USA; [7]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Available online xxx

Since completion of the Trastuzumab for Gastric Cancer study, trastuzumab with doublet chemotherapy (a fluoropyrimidine and a platinum) has been the gold-standard first-line therapy for patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2-positive (HER2+) gastroesophageal adenocarcinoma (GEA). The safety and efficacy of 23 studies of first-line trastuzumab plus doublet chemotherapy, without checkpoint inhibitors ($n = 19$) or with checkpoint inhibitors ($n = 4$), conducted in patients with locally advanced unresectable or metastatic HER2+ GEA, including phase II/III, prospective, and retrospective observational studies, were summarized. In studies without checkpoint inhibitors, the median duration of trastuzumab treatment ranged from 19.5 to 39.0 weeks and from 15.3 to 30.0 weeks for chemotherapy. In studies with checkpoint inhibitors, the median duration of pembrolizumab/trastuzumab/chemotherapy was 30 weeks, and 18 weeks for chemotherapy. In studies without checkpoint inhibitors, treatment-emergent adverse events (TEAEs) of grade ≥3 ranged from 32% to 84%. Serious adverse events (SAEs) ranged from 15% to 39%. Adverse events resulting in discontinuation ranged from 0% to 30%. Treatment-related deaths occurred in 0%-9% of patients. In studies with checkpoint inhibitors, TEAEs of grade ≥3 were 57%. SAEs ranged from 31% to 38%. Adverse events resulting in discontinuation ranged from 5% to 24%. Treatment-related deaths occurred in 0%-3% of patients. In studies without checkpoint inhibitors, objective response rate (ORR) ranged from 39% to 82%, median progression-free survival (PFS) from 5.7 to 11.6 months, and median overall survival (OS) from 11.2 to 27.6 months. In studies with checkpoint inhibitors, ORR ranged from 39% to 86%, median PFS from 8.0 to 13.0 months, and median OS from 19.3 to 27.3 months. This review provides a historical benchmark on safety and efficacy of available first-line chemotherapy-based standard of care for patients with locally advanced unresectable or metastatic HER2+ GEA.

Key words: first-line chemotherapy, gastroesophageal adenocarcinoma, human epidermal growth factor receptor 2, pembrolizumab, safety, trastuzumab

INTRODUCTION

For more than a decade, trastuzumab has been given in combination with chemotherapy as first-line therapy to patients with locally advanced and metastatic human epidermal growth factor receptor 2 (HER2+) gastroesophageal adenocarcinoma (GEA), defined as esophageal, gastroesophageal junction (GEJ), and gastric adenocarcinoma.[1-5] The Trastuzumab for Gastric Cancer (ToGA) study established the standard-of-care (SOC) first-line therapy of trastuzumab plus doublet chemotherapy (a fluoropyrimidine and a platinum).[6] On the basis of these findings, trastuzumab combined with a chemotherapy regimen consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin is the standard option for patients with HER2+ advanced gastric or GEJ cancer. While technically ToGA and other studies did not include esophageal adenocarcinoma, practically these patients are treated with chemotherapy plus trastuzumab in the first-line setting.[1,2] The doublet chemotherapy backbone used in the ToGA

*Correspondence to: Daniel V. T. Catenacci, MD, Associate Professor, Department of Medicine, Section of Hematology & Oncology, Director, Interdisciplinary Gastrointestinal Oncology Program; Assistant Director, Translational Research, Comprehensive Cancer Center, The University of Chicago Medical Center & Biological Sciences, 900 East 57th Street, KCBD Building, Office 7128, Chicago, IL 60637, USA. Tel: +1-773-702-7596; Fax: +1-773-702-9268
E-mail: dcatenac@bsd.uchicago.edu (D. V. T. Catenacci).

study (either capecitabine plus cisplatin or 5-fluorouracil [5-FU] plus cisplatin) was associated with a well-documented toxicity profile, including neutropenia, anemia, diarrhea, nausea, anorexia, and vomiting.[6]

Currently, there are several doublet chemotherapy backbones (fluoropyrimidine/platin) that can be used in combination with trastuzumab.[1-3] The fluoropyrimidine component may include 5-FU, capecitabine,[1,3] or the 5-FU prodrug S-1 (approved in Japan and Europe).[7,8] S-1, also called TS-1, is a combination of the following three compounds: tegafur, gimeracil, and oteracil potassium. The platinum component may be either cisplatin or oxaliplatin. Oxaliplatin is generally preferred over cisplatin because of lower toxicity.[9]

Programmed cell death (PD) protein 1 (PD-1) and PD-ligand 1 (PD-L1) are key regulatory elements in the immune response and have an important role in tumor surveillance and evasion.[10] PD-L1 positivity by combined positive score $\geq$1 is found in $\sim$60% of patients with gastric cancer and anti-PD-1/PD-L1 antibodies have shown encouraging clinical activity in advanced gastric or GEJ cancer.[11,12] Moreover, trastuzumab has been reported to increase PD-L1 expression on syngeneic mouse tumor cells;[13] therefore, the addition of the checkpoint inhibitor pembrolizumab to SOC trastuzumab/chemotherapy has been tested in clinical trials,[14-17] and recently led to the United States Food and Drug Administration approval of pembrolizumab in combination with trastuzumab, and fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2+ gastric or GEJ adenocarcinoma,[18] based on data from the phase III KEYNOTE-811 study (NCT03615326).[14]

Therefore, in this narrative review, we summarize safety and efficacy of 23 studies, 20 primary studies, and 3 subgroup analyses of first-line trastuzumab plus doublet chemotherapy, with or without checkpoint inhibitors, conducted in patients with locally advanced unresectable or metastatic HER2+ GEA, including phase II/III, prospective, and retrospective observational real-world evidence studies, published in PubMed over the last 11 years.

This analysis is meant to provide a historical benchmark on safety and efficacy of available first-line chemotherapy-based SOC for patients with locally advanced unresectable or metastatic HER2+ GEA.

FEATURES OF THE STUDIES ANALYZED

For the purposes of this narrative review, titles and abstracts were searched in PubMed from 2008 to 2021 for "trastuzumab" AND "chemotherapy" AND "gastric"; 285 hits were found. Articles were selected if they were conducted in patients with HER2+ metastatic GEA, including gastric adenocarcinoma, esophageal cancer, GEA/GEJ cancer, in the first-line setting. Prospective phase II, phase III, or observational studies, as well as retrospective studies involving trastuzumab with fluoropyrimidine plus platinum doublet therapy, were included. Meta-analyses and systematic reviews were excluded. Cut-off numbers for patients in studies were $\geq$35 patients. For studies on checkpoint inhibitors in combination with trastuzumab and chemotherapy, there was no cut-off. Key congresses were searched when considering treatment of patients with metastatic HER2+ GEA and first-line checkpoint inhibitors plus trastuzumab and chemotherapy.

The key details of each of the studies included in this analysis are provided in Table 1. The median age of patients across the studies examined ranged between 57 and 70 years. Most of the studies included both gastric cancer and GEJ cancer, with gastric cancer being the most common type (65%-96%). There was only one study where most of the patients (71%) had GEJ cancer.[19] There were two studies where all patients enrolled had gastric cancer.[20,21] Patients with esophageal cancer were included in two studies.[15,22] Finally, the breakdown between gastric cancer and GEJ cancer was not provided in six studies.[16,17,23-27] Most studies included only patients with HER2+ overexpression (defined as IHC3$^+$ or IHC2$^+$/FISH$^+$), with IHC3$^+$ being the most common biomarker subgroup (63%-91%). In three studies, the breakdown between IHC3$^+$ and IHC2$^+$/FISH$^+$ was not provided;[22,24,28] three studies included patients with IHC0-1 and/or IHC2$^+$/FISH$^-$ (16%-26%).[6,15,29]

The studies that were analyzed include data from the ToGA study[6] and three additional phase III studies (HELOISE,[28] JACOB,[32] and KEYNOTE-811[14]) conducted after the ToGA study, reporting safety and efficacy data of first-line trastuzumab plus chemotherapy in patients with metastatic gastric/GEJ cancer. Besides, the data that were reviewed included a subgroup analysis of ToGA, which focused on the population of Japan,[29] and two subgroup analyses of the JACOB study (one investigating the population of China[31] and the other Japan[30]). The patients treated in the phase III studies received trastuzumab plus cisplatin or oxaliplatin plus capecitabine or 5-FU.[6,14,28,32]

Seven phase II studies,[23,26,27,33-36] five retrospective studies,[19,20,22,25,37] and a prospective observational study[21] were also included. Four phase II studies used S-1, with two in combination with cisplatin[23,35] and two with oxaliplatin.[27,34] The other three phase II studies[26,33,36] used capecitabine in combination with oxaliplatin. The remaining retrospective and prospective observational studies examined various regimens containing trastuzumab and fluoropyrimidine/platinum chemotherapy.[19-22,25,37] Three of the studies[19,22,33] reporting data of first-line trastuzumab plus chemotherapy were conducted exclusively outside Asia.

Checkpoint inhibitor therapy was administered in combination with trastuzumab and chemotherapy in four studies.[14-17,24] Three of these studies investigated pembrolizumab (including the phase III KEYNOTE-811[14] and the phase I/II PANTHERA[16,17]), and one tested avelumab.[24]

Overall, median follow-up across all studies ranged from 10 to 34 months (Table 2). Median follow-up for the Asian studies[20,21,23,25-27,29-31,34-37] ranged from 14 to 34 months, while global studies[6,14,28,32] ranged from 10 to 25 months, and European studies[19,22,33] ranged from 14 to 15 months.

Table 1. Baseline characteristics

Study	Study design (study number)	Tx type	Region	Race	*N*	Male/female	Median age (range or IQR)	Tumor location	Stage of the disease	HER2+ expression status
Shitara *Int J Clin Oncol* 2020 (JACOB subgroup analysis)[30]	Phase III[a] (NCT01774786)	Placebo + Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cis 80 mg/m^2 IV Q3W + Cape 1000 mg/m^2 PO BID for 28 doses (D1-15) Q3W	Japan: 100%	Asian: 100%	40	70%/ 30%	70 (range, 53-82)	Stomach: 90% GEJ: 10%	Met: 100% 1-2 mets: 87.5% >2 mets: 12.5%	IHC3$^+$: 62.5% IHC2$^+$/ISH$^+$: 37.5%
Liu *Cancer Commun* 2019 (JACOB subgroup analysis)[31]	Phase III[a] (NCT01774786)	Placebo + Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cis 80 mg/m^2 IV Q3W + Cape 1000 mg/m^2 PO BID for 28 doses (D1-15), Q3W OR 5-FU 800 mg/m^2 IV every 24 h (D1-5) Q3W	China: 100%	Asian: 100%	81 Cape: 86.4% 5-FU: 16.0%	87.7%/ 12.3%	59 (range, 23-73)	Stomach: 85.2% GEJ: 14.8%	Met: 100% 1-2 mets: 89% >2 mets: 11%	IHC3$^+$: 79% IHC2$^+$/ISH$^+$: 21%
Tabernero *Lancet Oncol* 2018 (JACOB)[32]	Phase III[a] (NCT01774786)	Placebo + Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cis 80 mg/m^2 IV Q3W + Cape 1000 mg/m^2 PO BID for 28 doses (D1-15), Q3W OR 5-FU 800 mg/m^2 IV every 24 h (D1-5) Q3W	Asia: 37% Japan: 10% North America, Western Europe, Australia: 34% South America, Eastern Europe: 19%	Asian: 47.9% White: 47.7% Other: 3.8%	392	82%/ 18%	61 (IQR, 54-68)	Stomach: 75% GEJ: 25%	Met: 100% 1-2 mets: 77% >2 mets: 23%	IHC3$^+$: 67% IHC2$^+$/ISH$^+$: 33%
Shah *J Clin Oncol* 2017 (HELOISE)[28]	Phase III[a] (NCT01450696)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cis 80 mg/m^2 IV Q3W + Cape 800 mg/m^2 PO BID for 28 doses over 14 days Q3W	China: 25.8% ROW: 74.1%	Asian: 29.8% White: 60.5% Other: 9.7%	124	76.6%/ 23.4%	60 (range, 26-83)	Stomach: 76.6% GEJ: 23.4%	Met: 100% 1-2 mets: 59.7% >2 mets: 40.3%	IHC3$^+$ or IHC2$^+$/FISH$^+$ (breakdown NR)
Sawaki *Gastric Cancer* 2012 (ToGA subgroup analysis)[29]	Phase III[b] (NCT01041404)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cis 80 mg/m^2 IV D1 Q3W + Cape 1000 mg/m^2 PO BID for 28 doses (D1-14) Q3W	Japan: 100%	Asian: 100%	51	78.4%/ 21.6%	63 (range, 29-76)	Stomach: 96.1% GEJ: 3.9%	Met: 100% 1-2 mets: 54.9% >2 mets: 45.1%	IHC3$^+$/FISH$^+$: 31.4% IHC2$^+$/FISH$^+$: 35.3% IHC3$^+$/FISH$^-$: 2% IHC3$^+$/FISH^{unk}: 5.9% IHC1$^+$/FISH$^+$: 19.6% IHC0/FISH$^+$: 5.9%
Bang *Lancet* 2010 (ToGA)[6]	Phase III[b] (NCT01041404)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cis 80 mg/m^2 IV D1 Q3W + Cape 1000 mg/m^2 PO BID for 28 doses (D1-14) Q3W OR 5-FU 800 mg/m^2 IV every 24 h (D1-5) Q3W	Asia: 54.6% Europe: 32.5% Central or South America: 8.9% Other: 3.9% (N = 584)	Asian: 51% White: 39% Black: <1% Other: 9%	294 Cape: 87% 5-FU: 13%	77%/ 23%	Mean 59.4 (SD, 10.8)	Stomach: 80% GEJ: 20%	Met: 97% Locally advanced: 3% 1-2 mets: 52% >2 mets: 48%	IHC3$^+$/FISH$^+$: 45% IHC2$^+$/FISH$^+$: 27% IHC3$^+$/FISH$^-$: 3% IHC3$^+$/FISH^{unk}: 3% IHC1$^+$/FISH$^+$: 13% IHC0/FISH$^+$: 8% IHC^{unk}/FISH$^+$: 2%

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https://doi.org/10.1016/j.esmoop.2021.100360

Table 1. Continued

Study	Study design (study number)	Tx type	Region	Race	*N*	Male/female	Median age (range or IQR)	Tumor location	Stage of the disease	HER2+ expression status
Yuki *Cancer Chemother Pharmacol* 2020 (KSCC/HGCSG/CCOG/Perseus 1501B)[27]	Phase II (UMIN000017552)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Oxal 130 mg/m^2 IV D1 Q3W + S-1 80 mg/m^2 PO BID (D1-14) Q3W	Japan: 100%	Asian: 100%	39	79%/ 21%	66.0 (range, 44-79)	Upper: 36% Middle: 28% Low: 36%	Liver mets: 56% No liver mets: 44%	IHC3$^+$: 87% IHC2$^+$/FISH$^+$: 13%
Rivera *Cancer Chemother Pharmacol* 2019 (HERXO)[33]	Phase II (NCT01503983)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Oxal 130 mg/m^2 IV D1 Q3W + Cape 1000 mg/m^2 PO BID (D1-14) Q3W	Spain: 100%	White: 100%	45	82%/ 18%	65 (range, 44-80)	Stomach: 69% GEJ: 31%	Met: 82% Relapsed: 16% Unresectable locally advanced: 2%	IHC3$^+$: 73% IHC2$^+$: 27%
Takahari *Gastric Cancer* 2019 (HIGHSOX)[34]	Phase II (UMIN000017602)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Oxal 130 mg/m^2 IV D1 Q3W + S-1 40-60 mg/m^2 PO BID (D1-14) Q3W (40 mg for BSA <1.25 m^2; 50 mg for BSA 1.25-1.5 m^2; 60 mg for BSA >1.5 m^2)	Japan: 100%	Asian: 100%	75	78.7%/ 21.3%	64 (range, 21-75)	Stomach: 85.3% GEJ: 14.7%	Advanced: 100% Mets, median (range): 1 (1-5)	IHC3$^+$: 73.3% IHC2$^+$/ISH$^+$: 26.7%
Miura *Gastric Cancer* 2018 (WJOG7212G/T-SPACE)[35]	Phase II (UMIN000008389)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cis 60 mg/m^2 IV D8 Q5W + S-1 40-60 mg/m^2 PO BID (D1-21) Q5W (40 mg for BSA <1.25 m^2; 50 mg for BSA 1.25−1.5 m^2; 60 mg for BSA >1.5 m^2)	Japan: 100%	Asian: 100%	44	77.3%/ 22.7%	64.5 (range, 31-77)	Stomach: 84.1% GEJ: 15.9%	Met: 100% 0-1 mets: 54.5% ≥2 mets: 45.5%	IHC3$^+$: 72.7% IHC2$^+$/FISH$^+$: 27.3%
Ryu *Eur J Cancer* 2015[26]	Phase II (NCT01396707)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Oxal 130 mg/m^2 IV D1 Q3W + Cape 1000 mg/m^2 PO BID (D1-14) Q3W	South Korea: 100%	Asian: 100%	55	66%/ 34%	57 (range, 29-74)	Stomach or GEJ (breakdown NR)	Met: 82% Recurrent: 14% Inoperable locally advanced: 4% Met sites: Liver: 49% Peritoneum: 27% Lung: 20% Bone: 13% Lymph node: 76%	IHC3$^+$: 89% IHC2$^+$/FISH$^+$: 11%
Kurokawa *Br J Cancer* 2014 (HERBIS-1)[23]	Phase II (UMIN000005739)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cis 60 mg/m^2 IV D1 Q3W + S-1 40-60 mg/m^2 PO BID (D1-14) Q3W (40 mg for BSA <1.25 m^2; 50 mg for BSA 1.25-1.5 m^2; 60 mg for BSA ≥1.5 m^2)	Japan: 100%	Asian: 100%	54	78%/ 22%	66 (range, 34-75)	Stomach or GEJ (breakdown NR)	Unresectable: 94% Recurrent: 6% Met sites: Lymph nodes: 81% Liver: 59% Lung: 9% Peritoneum: 9% Bone: 4% Other: 2%	IHC3$^+$: 83% IHC2$^+$/FISH$^+$: 17%
Gong *BMC Cancer* 2016 (CGOG1001)[36]	Phase II (NCT01364493)	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Oxal 130 mg/m^2 IV D1 Q3W + Cape 1000 mg/m^2 PO BID (D1-14) Q3W	China: 100%	Asian: 100%	51	71%/ 29%	57 (range, 27-78)	Stomach: 65% GEJ: 35%	Met: 86% Locally advanced: 14%	IHC3$^+$: 75% IHC2$^+$/dual SISH$^+$: 25%
Oh *Cancer Chemother Pharmacol* 2019[25]	Retrospective	Trast IV on D1 (loading dose, 8 mg/kg, 90-min infusion; maintenance dose, 6 mg/kg, 30-min infusion) Q3W + Cis 60-100 mg/m^2 IV D1 Q3W + Cape 1000 mg/m^2 PO BID (D1-14) Q3W OR 5-FU 1000 mg/m^2 IV every 24 h (D1-5) Q3W	Korea: 100%	Asian: 100%	128 Cape: 96% (3 pts received oxal vs cis) 5-FU: 3.1%	80.5%/ 19.5%	63 (range, 20-87)	Stomach or GEJ (breakdown NR)	Met: 100% 1 met: 60.2% 2 mets: 25.8% ≥3 mets: 14.0%	IHC3$^+$: 91.4% IHC2$^+$/ISH$^+$: 8.6%

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Table 1. Continued

Study	Study design (study number)	Tx type	Region	Race	*N*	Male/female	Median age (range or IQR)	Tumor location	Stage of the disease	HER2+ expression status
Okita *Tohoku J Exp Med* 2018[17]	Retrospective	**T-XP** (cape + cis) ($n = 28$) Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cape 1000 mg/m^2 PO BID (D1-14) Q3W + Cis 80 mg/m^2 IV D1 Q3W **T-SP** (S-1 + cis) ($n = 30$) Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + S-1 40 mg/m^2 PO BID (D1-14) Q3W + Cis 60 mg/m^2 IV D1 Q3W	Japan: 100%	Asian: 100%	28 (T-XP) 30 (T-SP)	89.3%/10.7% 86.7%/ 13.3%	68.5 (range, 44-81) 63.5 (range, 38-74)	Stomach: 82.1% GEJ: 17.9% Stomach: 76.7% GEJ: 23.3%	Inoperable advanced or recurrent: 100% Inoperable advanced or recurrent: 100%	IHC3$^+$: 82.1% IHC2$^+$/ISH$^+$: 14.3% Unk: 3.6% IHC3$^+$: 83.3% IHC2$^+$/ISH$^+$: 16.7%
Soularue *Bull Cancer* 2015[19]	Retrospective	Trast IV on D1 (loading dose, 6 mg/kg; maintenance dose, 4 mg/kg) Q3W + mFOLFOX6 Oxal 85 mg/m^2 IV D1 Q2W + Leucovorin 400 mg/m^2 IV D1 Q2W + 5-FU bolus 400 mg/m^2 IV D1 Q2W + 5-FU 2400 mg/m^2 continuous IV D1 Q2W OR Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + XELOX Oxal 130 mg/m^2 IV D1 Q3W + Cape 1000 mg/m^2 PO BID (D1-14) Q3W	France: 100%	NR	34	79%/ 21%	63 (range, 30-82)	GEJ: 71% Stomach: 29%	Met: 100% Mets, median (range): 2 (1-4) 1 met: 64.7% 2 mets: 20.6% >2 mets: 14.7%	IHC3$^+$: 88% IHC2$^+$/FISH$^+$: 12%
Kim *BMC Cancer* 2021[20]	Retrospective	Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + Cis 80 mg/m^2 IV D1 Q3W + Cape 1000 mg/m^2 PO BID (D1-14) Q3W OR 5-FU 800 mg/m^2 IV every 24 h (D1-5) Q3W	Korea: 100%	Asian: 100%	47	81%/ 19%	59 (range, 36-83)	Stomach: 100%	Met: 77% Recurrent: 23% Liver mets: 51% No liver mets: 49%	IHC3$^+$: 85% IHC2$^+$/SISH$^+$: 15%
Dijksterhuis *Int J Cancer* 2020[22]	Retrospective	Trast + oxal + cape ($n = 73$) OR Trast + cis + cape ($n = 65$) OR Trast + other doublet CTX ($n = 29$) OR Trast + other CTX ($n = 47$) OR Trast monotherapy ($n = 1$)	Netherlands: 100%	White: 100%	215	79.5%/ 21.5%	63 (IQR, 55-69)	Esophagus: 54% GEJ or cardiac: 19.1% Stomach: 27.0%	Met: 100% 1-2 mets: 44% >2 mets: 56%	IHC3$^+$ or IHC2$^+$/FISH$^+$ (breakdown NR)
Li *Clin Transl Oncol* 2018[21]	Prospective observational	Trast + platinum (cis, oxal) + fluoropyrimidine (5-FU, cape, S-1) ($n = 75$) Trast + taxane (doce, pacli) + fluoropyrimidine (5-FU, cape, S-1) ($n = 20$) Trast + monotherapy CTX ($n = 10$) Trast + iri + cis ($n = 2$) Trast IV (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W	China: 100%	Asian: 100%	107 (75 pts [70%] had fluoropyrimidine + platinum)	77%/ 23%	64 (range, 26-87)	Stomach: 100%	Advanced/met: 100% <2 mets: 35.7% >2 mets: 64.3%	IHC3$^+$: 65% IHC2$^+$/FISH$^+$: 35%
Janjigian *Lancet Oncol* 2020[15]	Phase II (NCT02954536)	Pembro 200 mg IV D1 Q3W + Trast IV on D1 (loading dose, 8 mg/kg in C1; maintenance dose, 6 mg/kg in C2+) Q3W + Oxal 130 mg/m^2 OR cis 80 mg/m^2 IV on D1C2+ Q3W + Cape 850 mg/m^2 PO BID (D1-14) C2+ OR 5-FU 800 mg/m^2 IV (D1-5) Q2W	USA: 100%	White: 86% Asian: 5% Black/ Hispanic/ other: 8%	37 Oxal: 97% Cis: 3% Cape: 65% 5-FU: 35%	78%/22%	60 (IQR, 21-84)	Esophagus: 38% GEJ: 32% Stomach: 30%	Met: 100%	IHC3$^+$ or IHC2$^+$/FISH$^+$: 84% IHC2$^+$/FISH$^-$ or IHC1$^+$ or IHC0: 16% PD-L1$^-$ (CPS <1): 35% PD-L1$^+$ (CPS ≥1): 38% PD-L1^{unkn}: 27%

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https://doi.org/10.1016/j.esmoop.2021.100360

Table 1. Continued

Study	Study design (study number)	Tx type	Region	Race	*N*	Male/female	Median age (range or IQR)	Tumor location	Stage of the disease	HER2+ expression status
Lee AACR 2021, Abstr. CT174 (HCRN GI17-319)[24]	Phase II (NCT03783936)	Ave 800 mg IV D1 + Trast IV on D1 (loading dose, 8 mg/kg in C1; maintenance dose, 6 mg/kg in C2+) Q3W + mFOLFOX Oxal 85 mg/m^2 IV D1 Q2W + Leucovorin 400 mg/m^2 IV D1 Q2W + 5-FU bolus 400 mg/m^2 IV D1 Q2W + 5-FU 2400 mg/m^2 continuous IV D1 Q2W	USA: 100%	NR	NR	NR	NR	Stomach or GEJ (breakdown NR)	Met: 100%	IHC3$^+$ or IHC2$^+$/FISH$^+$ (breakdown NR)
Rha ASCO 2020, Abstr. 3031 Rha ASCO GI 2021, Abstr. 218 (PANTHERA)[17]	Phase Ib/II (NCT02901301)	Pembro 200 mg IV D1 Q3W + Trast biosimilar IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W (trastuzumab-pkrb) + Cape 1000 mg/m^2 PO BID (D1-14) Q3W + Cis 80 mg/m^2 IV D1 Q3W	Korea: 100%	Asian: 100%	43	77%/23%	63 (range, 34-82)	Stomach or GEJ (breakdown NR)	Advanced: 100%	IHC3$^+$: 70% IHC2$^+$/SISH: 30%
Janjigian ASCO 2021, Abstr. 4013 (KEYNOTE-811)[14]	Phase III (NCT03615326)	Placebo + Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + FP 5-FU 800 mg/m^2 IV (D1-5) Q3W + Cis 80 mg/m^2 IV on D1 Q3W OR CAPOX Cape 1000 mg/m^2 PO BID (D1-14) Q3W + Oxal 130 mg/m^2 IV D1 Q3W OR SOX S-1 40-60 mg/m^2 PO BID (D1-14) Q3W (40 mg for BSA <1.25 m^2; 50 mg for BSA 1.25-1.5 m^2; 60 mg for BSA ≥1.5 m^2) + Oxal 130 mg/m^2 IV D1 Q3W	North America, Europe, Israel, Australia: 34% Asia: 30% ROW: 37%	NR	131 CAPOX: 88% FP: 12%	79% 21%	61 (range, 32-83)	Stomach: 68% GEJ: 32%	Met: 100%	IHC3$^+$: 79% IHC2$^+$/ISH$^+$: 21%
		Pembro 200 mg IV D1 Q3W + Trast IV on D1 (loading dose, 8 mg/kg; maintenance dose, 6 mg/kg) Q3W + FP 5-FU 800 mg/m^2 IV (D1-5) Q3W + Cis 80 mg/m^2 IV on D1 Q3W OR CAPOX Cape 1000 mg/m^2 PO BID (D1-14) Q3W + Oxal 130 mg/m^2 IV D1 Q3W OR SOX S-1 40-60 mg/m^2 PO BID (D1-14) Q3W (40 mg for BSA <1.25 m^2; 50 mg for BSA 1.25-1.5 m^2; 60 mg for BSA ≥ 1.5 m^2) + Oxal 130 mg/m^2 IV D1 Q3W	North America, Europe, Israel, Australia: 31% Asia: 30% ROW: 39%	NR	133 CAPOX: 86% FP: 14% SOX: 0%	84%/16%	62 (range, 19-84)	Stomach: 72% GEJ: 28%	Met: 100%	IHC3$^+$: 82% IHC2$^+$/ISH$^+$: 18%

5-FU, 5-fluorouracil; ave, avelumab; BID, twice daily; BSA, body surface area; C, cycle; cape, capecitabine; CAPOX, capecitabine plus oxaliplatin; cis, cisplatin; CPS, combined positive score; CTX, chemotherapy; D, day; doce, docetaxel; FP, 5-fluorouracil plus platinum; GEJ, gastroesophageal junction; HER2+, human epidermal growth factor receptor 2 positive; IHC, immunohistochemistry; IQR, interquartile range; iri, irinotecan; ISH, *in situ* hybridization; IV, intravenous; met, metastatic; mets, metastases; NR, not reported; oxal, oxaliplatin; pacli, paclitaxel; PD-L1, programmed death-ligand 1; PO, oral; pembro, pembrolizumab; pts, patients; Q2W, every 2 weeks; Q3W, every 3 weeks; Q5W, every 5 weeks; ROW, rest of the world; SD, standard deviation; SISH, silver-enhanced *in situ* hybridization; SOX, S-1 plus oxaliplatin; T-SP, trastuzumab plus S-1 plus cisplatin; ToGA, Trastuzumab for Gastric Cancer; trast, trastuzumab; tx, treatment; T-XP, trastuzumab plus capecitabine plus cisplatin; unk, unknown.

[a] Only details on the control arm are reported in this table.

[b] Only details on the experimental arm are reported in this table.

Table 2. Overall safety

Study	Exposure and follow-up	*N*	Tx-emergent AEs[a]		Tx-related AEs[a]		SAEs		AEs resulting in tx modification or interruption	AEs resulting in tx discontinuation	AEs resulting in death
			All grades	Grade ≥3	All grades	Grade ≥3	Any	Tx related			
Shitara *Int J Clin Oncol* 2020 (JACOB subgroup analysis)[30]	Median number of cycles (range) per pt: 8 (1-51) for trast 6 (1-51) for cape 6 (1-51) for cis Median follow-up: 34.0 mo	40	NR	75.0%	NR	NR	32.5%	NR	NR	10.0%	2.5% (1 multiple organ dysfunction syndrome)
Liu *Cancer Commun* 2019 (JACOB subgroup analysis)[31]	Average number of cycles ± SD per pt: 11.81 ± 8.35 (placebo + trast) NR for CTX Median follow-up: 18.0 mo	80	97.5%	65.0%	NR	NR	15.0%	NR	NR	6.3%	7.5% (1 anemia, 1 septic shock, 1 respiratory failure, and 3 deaths)
Tabernero *Lancet Oncol* 2018 (JACOB)[32]	Mean number of cycles ± SD per pt: 11.2 ± 10.0 for trast 5.1 ± 2.7 for cis 7.4 ± 7.6 for cape 5.2 ± 3.5 for 5-FU Median follow-up: 25.0 mo	388	99%	73%	NR	NR	39% (5% diarrhea)	10%	54% for cape 28% for 5-FU 19% for cis	12% (disc of placebo and trast)	8% (2% tx related: 1 multiple organ failure, 1 pulmonary embolism, 1 hemodynamic instability, 1 unexplained death, and 3 septic shock)
Shah *J Clin Oncol* 2017 (HELOISE)[28]	Median number of cycles (range) per pt: 6.5 (1-36) for trast 6 (1-7) for cape 6 (1-7) for cis	124	91.1%	59.7%	88.7% (38.7% related to trast)	NR	24.2% (all grade ≥3)	18.5%	NR	7.3% (any tx disc) 2.4% (trast disc)	5.6%
Sawaki *Gastric Cancer* 2012 (ToGA subgroup analysis)[29]	Median number of cycles (range) per pt: 8 (1-24) for trast NR for cape NR for cis Median follow-up: 18.6 mo	51	100%	84%	2%	NR	NR	NR	NR	2%	3.9% (1 cardiac failure & unstable angina likely related to trast, and 1 gastrointestinal perforation)
Bang *Lancet* 2010 (ToGA)[6]	Median number of cycles (range) per pt: 8 (1-49) for trast 6 (1-14) for cis 6 (1-20) for cape 6 (1-6) for 5-FU Median follow-up: 18.6 mo	294	99%	68%	NR	NR	32%	NR	84%	NR	3% (tx related)
Yuki *Cancer Chemother Pharmacol* 2020 (KSCC/ HGCSG/CCOG/ Perseus 1501B)[27]	Median number of cycles (range) per pt: 8 (1-33) Median follow-up: 22.4 mo	39	NR	NR	NR	NR	NR	NR	NR	16%	0% (tx related)

Continued

https://doi.org/10.1016/j.esmoop.2021.100360

Table 2. Continued

Study	Exposure and follow-up	*N*	Tx-emergent AEs[a]		Tx-related AEs[a]		SAEs		AEs resulting in tx modification or interruption	AEs resulting in tx discontinuation	AEs resulting in death
			All grades	Grade ≥3	All grades	Grade ≥3	Any	Tx related			
Rivera *Cancer Chemother Pharmacol* 2019 (HERXO)[33]	Median follow-up: 13.7 mo	45	93%	44%	NR	NR	NR	NR	Tx modif: 38% for oxal 36% for cape 18% for trast	NR	NR
Takahari *Gastric Cancer* 2019 (HIGHSOX)[34]	Median number of cycles (range) per pt: 8 (1-36+) Median follow-up: 15.6 mo	75	NR	NR	98.6%	45.3%	NR	NR	Tx modif: 54.6% for S-1 50.6% for oxal 10.6% for trast Tx interr: 50.6% for S-1 46.6% for oxal 40.0% for trast	18.6% (disc of S-1) 29.3% (disc of oxal) 0% (disc of trast)	0% (tx related)
Miura *Gastric Cancer* 2018 (WJOG721 2G/T-SPACE)[35]	Median number of cycles (range) per pt: 5.0 (1.0-17.0) for S-1 5.0 (0-8.0) for cis 8.5 (1.0-29.0) for trast Median follow-up: 19.3 mo	44	NR	NR	NR	NR	NR	NR	NR	15.9%	2% (tx related)
Ryu *Eur J Cancer* 2015[26]	Median number of cycles (range) per pt: 10 (1-30) for cape 8 (1-30) for oxal 10 (1-30) for trast Median follow-up: 13.8 mo	55	NR	NR	NR	NR	NR	NR	NR	2%	2% (tx-related diarrhea and sepsis)
Kurokawa *Br J Cancer* 2014 (HERBIS-1)[23]	Median number of cycles (range) per pt: 6 (1-27) Median follow-up: 13.5 mo	53	NR	NR	NR	NR	NR	NR	NR	30%	2% (tx-related myelosuppression)
Gong *BMC Cancer* 2016 (CGOG1001)[36]	Median number of cycles (range) per pt: 8 (1-32) Median follow-up: 28.6 mo	51	NR	NR	NR	NR	16%	NR	Tx modif: 24% for oxal 33% for cape Tx interr: 4% for trast	4%	2% (septic shock)
Oh *Cancer Chemother Pharmacol* 2019[25]	Median number of cycles (range) per pt: 6 (1-17) for trast + CTX 3 (0-61) for trast single-agent maintenance	123	NR	NR	NR	NR	NR	NR	NR	0%	NR
Okita *Tohoku J Exp Med* 2018[37]	Mean delivered dose intensity (cis): 14.8 mg/m^2/week Relative dose intensity (cis): 55.6%	28	92.9%	60.7%	NR	NR	NR	NR	NR	NR	NR
Okita *Tohoku J Exp Med* 2018[37]	Mean delivered dose intensity (cis): 10.5 mg/m^2/week Relative dose intensity (cis): 52.6%	30	93.3%	56.7%	NR	NR	NR	NR	NR	NR	NR

Continued

Table 2. Continued

Study	Exposure and follow-up	*N*	Tx-emergent AEs[a]		Tx-related AEs[a]		SAEs		AEs resulting in tx modification or interruption	AEs resulting in tx discontinuation	AEs resulting in death
			All grades	Grade ≥3	All grades	Grade ≥3	Any	Tx related			
Soularue *Bull Cancer* 2015[19]	Median number of cycles (range) per pt: 13 (3-38) for trast 8 (2-12) for oxal Median follow-up: 14.7 mo	34	NR	32%	NR	NR	NR	NR	NR	NR	0% (tx related)
Kim *BMC Cancer* 2021[20]	Median number of cycles (range) per pt: 8 (1-56) for trast 6 (1-15) for cis 7 (1-56) for cape 6 (1-8) for 5-FU Median follow-up: 18.8 mo	47	NR	NR	NR	NR	NR	NR	NR	17% (disc of cis)	8.5% (tx-related pneumonia and sepsis, heart failure, cerebral infarction)
Dijksterhuis *Int J Cancer* 2020[22]	NR	71	45.1%	40.8%	NR	NR	NR	NR	NR	NR	4%
Li *Clin Transl Oncol* 2018[21]	Median number of cycles (range) per pt: 9 (1-44) Median follow-up: 14.0 mo	107	NR	NR	NR	NR	NR	NR	NR	1% (disc of trast for ↓ LVEF)	0% (tx related)
Janjigian *Lancet Oncol* 2020[15]	Median number of cycles (IQR) per pt: 6 (5-8) for oxal 10 (7-17) for pembro/trast/ fluoropyrimidine combined Median follow-up: 13 mo	37	NR	NR	97%	57%	5%	5%	97% (tx modif)	5% (tx related)	0% (tx related)
Lee AACR 2021, Abstr. CT174 (HCRN GI17-319)[24]	NR	18	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rha ASCO 2020, Abstr. 3031 Rha ASCO GI 2021, Abstr. 218 (PANTHERA)[17]	Median follow-up: 18.2 mo	43	NR	NR	98%	81%	NR	NR	NR	NR	NR
Janjigian ASCO 2021, Abstr. 4013 (KEYNOTE-811)[14]	Median follow-up for safety: 9.9 mo Median follow-up for efficacy: 12.0 mo	216 (placebo) 217 (pembro)	98% 97%	57% 57%	NR NR	NR NR	38% 31%	NR NR	NR NR	26% 24%	5% 3%

5-FU, 5-fluorouracil; AE, adverse event; cape, capecitabine; cis, cisplatin; CTX, chemotherapy; disc, discontinuation; IQR, interquartile range; LVEF, left ventricular ejection fraction; modif, modification of dosage; NR, not reported; oxal, oxaliplatin; pembro, pembrolizumab; pt, patient; SAE, serious adverse event; SD, standard deviation; ToGA, Trastuzumab for Gastric Cancer; trast, trastuzumab; tx, treatment.

[a]While treatment emergent AEs refers to adverse events that occur only once treatment has started, regardless of causality, treatment-related AEs refer to adverse events that are considered by the investigator as related to treatment.

https://doi.org/10.1016/j.esmoop.2021.100360

CONSIDERATIONS ON SAFETY

Overall safety profile of trastuzumab plus fluoropyrimidine plus platin

The overall safety profile was assessed among the 20 studies[6,14,19-23,25-37] of various regimens containing trastuzumab, fluoropyrimidine, and platinum (Table 2, Figure 1). The median number of cycles administered per patient ranged from 6.5 to 13.0 for trastuzumab (corresponding to 19.5-39.0 weeks of treatment), and 5 to 10 for chemotherapy (corresponding to 15.3-30.0 weeks of treatment). The median follow-up time ranged from 10 to 34 months. Treatment-emergent adverse events (TEAEs) of all grades ranged from 45% to 100%. TEAEs are adverse events (AEs) that emerge during treatment, regardless of causality. Grade ≥3 TEAEs ranged from 32% to 84%. Serious adverse events (SAEs) of all grades ranged from 15% to 39%. SAEs are life-threatening AEs that may require hospitalization, may result in significant disability, or in birth defects of the offspring. AEs resulting in treatment discontinuation ranged from 0% to 30%. Treatment-related deaths occurred in 0%-9% of patients.

The TEAEs of all grades occurring in ≥70% of patients in at least two studies were peripheral neuropathy (19%-97%), anemia (32%-97%), thrombocytopenia (28%-95%), nausea (29%-86%), anorexia (40%-84%), fatigue (20%-75%), leukopenia (43%-74%), and neutropenia (25%-66%; Table 3). Grade ≥3 TEAEs occurring in ≥15% of patients in at least two studies were neutropenia (7%-36%), anorexia (4%-25%), anemia (3%-25%), thrombocytopenia (4%-22%), and leukopenia (4%-17%; Table 3).

Analysis of a select type of TEAEs across the 20 studies[6,14,19-23,25-37] of regimens containing trastuzumab and chemotherapy reveals the following ranges (Table 4): fatigue (all grades: 10%-75%; grade ≥3: 0%-14%); nausea (all grades: 19%-86%; grade ≥3: 2%-20%); diarrhea (all grades: 13%-53%; grade ≥3: 0%-27%); neutropenia (all grades: 22%-79%; grade ≥3: 7%-36%); anemia (all grades: 3%-97%; grade ≥3: 0%-25%); peripheral neuropathy (all grades: 11%-97%; grade ≥3: 0%-18%); pneumonitis (all grades: 1%; grade ≥3: 0%); stomatitis (all grades: 5%-57%; grade ≥3: 0%-5%); and palmar-plantar erythrodysesthesia (PPE)/hand-foot syndrome (HFS; all grades: 10%-63%; grade ≥3: 1%-14%).

Overall safety profile of checkpoint inhibitors plus trastuzumab plus fluoropyrimidine plus platin

The overall safety profile was determined among the four studies[14-17,24] of various regimens containing checkpoint inhibitors (pembrolizumab or avelumab), trastuzumab, fluoropyrimidine, and platinum (Table 2, Figure 1). The median number of cycles administered per patient was 10 (30 weeks) for pembrolizumab/trastuzumab/chemotherapy combined and 6 (18 weeks) for chemotherapy.[15] The median follow-up time ranged from 9.9 to 18.2 months for safety and from 12.0 to 18.2 months for efficacy. TEAE of all grades ranged from 97% to 98%. Grade ≥3 TEAEs were 57%. SAEs of all grades ranged from 31% to 38%. AEs resulting in treatment discontinuation ranged from 5% to 24%. Treatment-related deaths occurred in 0%-3% of patients.

The TEAEs of all grades occurring in ≥30% of patients in the pembrolizumab arm of one phase III study[14] were diarrhea (53%), nausea (49%), anemia (41%), decreased appetite (31%), and vomiting (31%; Table 3). Grade ≥3 TEAEs occurring in ≥5% of patients in the pembrolizumab arm of one phase III study[14] were anemia (9%), thrombocytopenia (8%), neutropenia (7%), diarrhea (7%), nausea (5%), and vomiting (5%; Table 3). The treatment-related AEs of all grades occurring in ≥30% of patients in at least two studies were nausea (33%-84%), anemia (33%-81%), and diarrhea (30%-73%; Table 3).[15,17] Grade ≥3 treatment-related AEs occurring in ≥10% of patients in at least two studies were neutropenia (28%-42%), anemia (11%-16%), and thrombocytopenia (7%-11%; Table 3).[15,17,24]

Analysis of a select type of TEAEs across the four studies[14-17,24] of regimens containing checkpoint inhibitors, trastuzumab, and chemotherapy reveals the following ranges (Table 4): fatigue (all grades: 24%-86%; grade ≥3: 0%-4%); nausea (all grades: 49%-84%; grade ≥3: 0%-5%); diarrhea (all grades: 53%-73%; grade ≥3: 2%-7%); neutropenia (all grades: 19%-47%; grade ≥3: 0%-42%); anemia (all grades: 33%-81%; grade ≥3: 9%-16%); peripheral neuropathy (all grades: 19%-97%; grade ≥3: 0%-3%); pneumonitis (all grades: 5%; grade ≥3: 1%); stomatitis (all grades: 23%-38%; grade ≥3: 2%-5%); and PPE/HFS (all grades: 22%-23%; grade ≥3: 0%).

Considerations by type of platin backbone

Of the 11 studies[6,20,23,25,28-32,35,37] with cisplatin plus capecitabine or S-1 or 5-FU as the chemotherapy regimen used in combination with trastuzumab, the range of grade ≥3 AEs was 57%-84% (Tables 1 and 2). Four[20,23,25,35] of these studies did not report grade ≥3 AEs. Of the seven studies[14,19,26,27,33,34,36] with oxaliplatin plus capecitabine or S-1 or 5-FU as the chemotherapy regimen used in combination with trastuzumab, the range of grade ≥3 AEs was 32%-57% (Tables 1 and 2). Four[26,27,34,36] of these studies did not report grade ≥3 AEs.

Considerations by type of fluoropyrimidine backbone

Of the eight studies[14,26,28,29,30,33,36,37] in which capecitabine was used as the fluoropyrimidine backbone in combination with trastuzumab, the range of grade ≥3 AEs was 44%-84% (Tables 1 and 2). Two[26,36] of these studies did not report grade ≥3 AEs. Of the five studies[23,27,34,35,37] in which S-1 was used as the fluoropyrimidine backbone in combination with trastuzumab, grade ≥3 AEs occurred in 57%[37] (Tables 1 and 2). Four[23,27,34,35] of these studies did not report grade ≥3 AEs. Because there were no studies in which 5-FU was the only choice as fluoropyrimidine backbone, a safety comparison between 5-FU and the other fluoropyrimidine backbones was not possible.

Considerations by geographical region

Studies conducted in Asia. Geographical location was considered among the 13 studies[20,21,23,25-27,29-31,34-37] conducted exclusively in Asia testing various regimens containing trastuzumab, fluoropyrimidine, and platinum (Table 2). TEAEs of all grades ranged from 93% to 100%. Grade ≥3 TEAEs ranged from 57% to 84%. SAEs of all grades ranged from 15% to 33%. AEs resulting in treatment discontinuation ranged from 0% to 30%. Treatment-related deaths occurred in 0% to 9% of patients. Analysis of a select type of TEAEs, among 12 Asian studies[21,23,25-27,29-31,34-37] testing various regimens containing trastuzumab, fluoropyrimidine, and platinum, revealed the following ranges (Table 4): fatigue (all grades: 10%-75%; grade ≥3: 0%-14%); nausea (all grades: 19%-86%; grade ≥3: 2%-14%); diarrhea (all grades: 13%-52%; grade ≥3: 1%-11%); neutropenia (all grades: 53%-79%; grade ≥3: 10%-36%); anemia (all grades: 3%-97%; grade ≥3: 0%-25%); peripheral neuropathy (all grades: 11%-84%; grade ≥3: 0%-16%); pneumonitis (all grades: 3%; grade ≥3: 3%); stomatitis (all grades: 5%-57%; grade ≥3: 0%-5%); and PPE/HFS (all grades: 11%-63%; grade ≥3: 0%-14%).

Studies conducted globally. Four studies[6,14,28,32] conducted in various locations worldwide and testing various regimens containing trastuzumab, fluoropyrimidine, and platinum were reviewed (Table 2). TEAEs of all grades ranged from 91% to 99%. Grade ≥3 TEAEs ranged from 57% to 73%. SAEs of all grades ranged from 24% to 39%. AEs resulting in treatment discontinuation ranged from 7% to 26%. Treatment-related deaths occurred in 2%-3% of patients. Analysis of a select type of AEs, among four studies[6,14,28,32] conducted in various locations worldwide, testing various regimens containing trastuzumab, fluoropyrimidine, and platinum, revealed the following ranges (Table 4): fatigue (all grades: 15%-35%; grade ≥3: 3%-4%); nausea (all grades: 42%-67%; grade ≥3: 5%-7%); diarrhea (all grades: 17%-44%; grade ≥3: 6%-9%); neutropenia (all grades: 25%-53%; grade ≥3: 7%-28%); anemia (all grades: 28%-44%; grades ≥3: 9%-17%); peripheral neuropathy (all grades: 19%; grade ≥3: 1%); pneumonitis (all grades: 1%-4%; grade ≥3: 0%-2%); stomatitis (all grades: 13%-24%; grade ≥3: 1%-2%); and PPE/HFS (all grades: 10%-26%; grade ≥3: 1%-3%).

Studies conducted in Europe. Three studies[19,22,33] conducted exclusively in Europe testing various regimens containing trastuzumab, fluoropyrimidine, and platinum were reviewed (Table 2). TEAEs of all grades ranged from 45% to 93%. TEAEs of grade ≥3 ranged from 32% to 44%. SAEs of all grades were not reported. AEs resulting in treatment discontinuation were not reported. Treatment-related deaths did not occur. Analysis of a select type of AEs, among two studies[19,33] conducted exclusively in Europe, testing various regimens containing trastuzumab, fluoropyrimidine, and platinum, revealed the following ranges (Table 4): fatigue (all grades: 73%; grade ≥3: 16%); nausea (all grades: 47%; grade ≥3: 3%-20%); diarrhea (all grades: 32%-53%; grade ≥3: 0%-27%); neutropenia (all grades: 22%-29%; grade ≥3: 2%-9%); anemia (all grades: 38%-59%; grades ≥3: 2%-3%); peripheral neuropathy (all grades: 78%-97%; grade ≥3: 2%-18%); pneumonitis was not reported; stomatitis (all grades: 13%-32%; grade ≥3: 0%-2%); and PPE/HFS (all grades: 13%-32%; grade ≥3: 2%-3%).

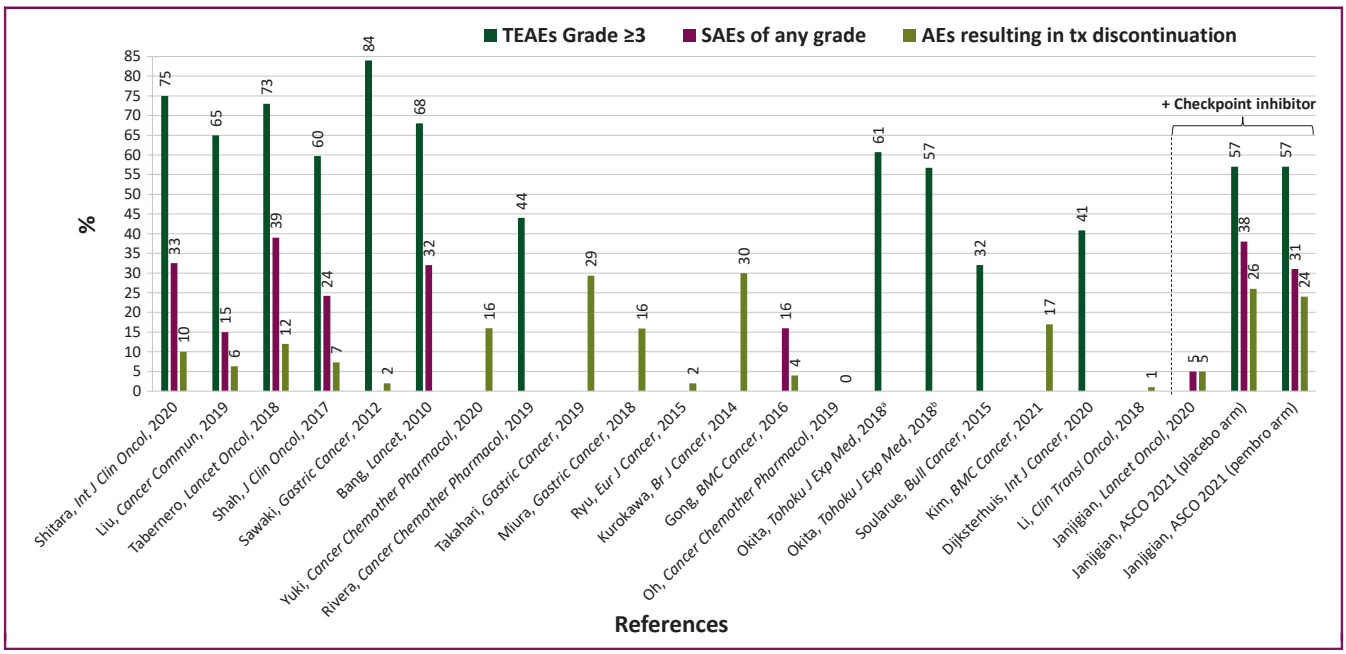

Figure 1. Safety comparison across the trials analyzed. See also [6,15,17,19-37]
AEs, adverse events; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; Tx, treatment.
[a]Trastuzumab + capecitabine + cisplatin.
[b]Trastuzumab + S-1 + cisplatin.

Table 3. Detailed safety and efficacy

Study	Safety							Efficacy			
	N	Tx-emergent AEs		Tx-related AEs							
		All grades	Grade ≥3	All grades		Grade ≥3		*N*	Median OS	Median PFS	ORR
				Trast related	CTX related	Trast related	CTX related				
Shitara *Int J Clin Oncol* 2020 (JACOB subgroup analysis)[30]	40	Occurring in ≥50% of pts • ↓ appetite: 82.5% • PPE: 62.5% • Nausea: 60% • Neutropenia: 52.5% • Stomatitis: 50%	Occurring in ≥10% of pts • Neutropenia: 30% • ↓ appetite: 27.5% • Hyponatremia: 20% • Nausea: 10%	NR	NR	NR	NR	40	15.6 mo (primary endpoint)	6.3 mo	40.5%
Liu *Cancer Commun* 2019 (JACOB subgroup analysis)[31]	80	Occurring in ≥45% of pts • Neutropenia: 65% • Nausea: 61.3% • Leukopenia: 58.8% • Anemia: 53.8% • Vomiting: 45%	Occurring in ≥7% of pts • Neutropenia: 30% • Anemia: 22.5% • Leukopenia: 15% • Thrombocytopenia: 8.8% • Vomiting: 7.5% • PPE syndrome: 7.5%	NR	NR	NR	NR	81	16.1 mo (primary endpoint)	8.6 mo	55.7%
Tabernero *Lancet Oncol* 2018 (JACOB)[32]	388	Occurring in ≥35% of pts • Nausea: 57% • Neutropenia: 52% • ↓ appetite: 42% • Anemia: 39% • Diarrhea: 35%	Occurring in ≥6% of pts • Neutropenia: 28% • Anemia: 17% • ↓ appetite: 7% • Diarrhea: 6% • Vomiting: 6% • Hypokalemia: 6%	NR	NR	NR	NR	392	14.2 mo (primary endpoint)	7.0 mo	48.3%
Shah *J Clin Oncol* 2017 (HELOISE)[28]	124	Occurring in ≥20% of pts • Neutropenia: 46.8% • Nausea: 41.9% • Anemia: 32.3% • Vomiting: 27.4% • ↓ appetite: 21.8%	NR	NR	NR	NR	NR	124	12.5 mo (primary endpoint)	5.7 mo	58.9%
Sawaki *Gastric Cancer* 2012 (ToGA subgroup analysis)[29]	51	Occurring in ≥50% of pts • Nausea: 86% • Anorexia: 84% • Vomiting: 65% • Renal impairment: 63% • Fatigue: 61% • Neutropenia: 59% • Stomatitis: 57% • ↓ weight: 53%	Occurring in ≥10% of pts • Neutropenia: 35% • Anemia: 25% • Anorexia: 24% • Nausea: 14% • Febrile neutropenia: 10%	2%	NR	NR	NR	51	15.9 mo (primary endpoint)	6.2 mo	64.4%
Bang *Lancet* 2010 (ToGA)[6]	294	Occurring in ≥30% of pts • Nausea: 67% • Neutropenia: 53%	Occurring in ≥6% of pts • Neutropenia: 27% • Anemia: 12%	NR	NR	NR	NR	294	13.8 mo (primary endpoint)	6.7 mo	47%

Continued

Table 3. Continued

Study	Safety							Efficacy			
	N	Tx-emergent AEs		Tx-related AEs							
		All grades	Grade ≥3	All grades		Grade ≥3		*N*	Median OS	Median PFS	ORR
				Trast related	CTX related	Trast related	CTX related				
		• Vomiting: 50% • Anorexia: 46% • Diarrhea: 37% • Fatigue: 35%	• Diarrhea: 9% • Nausea: 7% • Anorexia: 6% • Vomiting: 6%								
Yuki *Cancer Chemother Pharmacol* 2020 (KSCC/HGCSG/CCOG/Perseus 1501B)[27]	39	Occurring in ≥75% of pts • Hypoalbuminemia: 100% • Anemia: 97% • Thrombocytopenia: 95% • ↑ AST: 92% • Anorexia: 82% • Peripheral neuropathy: 82%	Occurring in ≥6% of pts • Thrombocytopenia: 18% • Anorexia: 18% • Anemia: 13% • Neutropenia: 10% • Hyponatremia: 10% • Diarrhea: 8% • Nausea: 8%	NR	NR	NR	NR	39	27.6 mo	7.0 mo	82.1% (primary endpoint)
Rivera *Cancer Chemother Pharmacol* 2019 (HERXO)[33]	45	NR	NR	Occurring in ≥30% of pts • Neurotoxicity: 78% • Fatigue: 73% • Diarrhea: 53% • Nausea: 47% • Vomiting: 38% • Anemia: 38%		Occurring in ≥10% of pts • Diarrhea: 27% • Nausea: 20% • Fatigue: 16% • Vomiting: 13%		45	13.8 mo	7.1 mo	46.7% (primary endpoint)
Takahari *Gastric Cancer* 2019 (HIGHSOX)[34]	75	NR	NR	Occurring in ≥60% of pts • Anemia: 96% • ↑ AST: 92% • Peripheral neuropathy: 84% • Thrombocytopenia: 79% • Neutropenia: 79% • Anorexia: 77% • Nausea: 65% • ↑ ALT: 60%		Occurring in ≥5% of pts • Peripheral neuropathy: 16% • Neutropenia: 11% • Anemia: 7% • Diarrhea: 7% • Anorexia: 5%		75	18.1 mo	8.8 mo	70.7% (primary endpoint)
Miura *Gastric Cancer* 2018 (WJOG7212G/T-SPACE)[35]	44	Occurring in ≥50% of pts • Anemia: 86% • Anorexia: 82% • Fatigue: 75% • Neutropenia: 66% • Nausea: 61% • Hypoalbuminemia: 59% • Diarrhea: 50%	Occurring in ≥10% of pts • Neutropenia: 30% • Anorexia: 25% • Anemia: 18% • Fatigue: 14% • Thrombocytopenia: 11% • Nausea: 11% • Diarrhea: 11% • Hypoalbuminemia: 11%	NR	NR	NR	NR	44	16.5 mo	5.9 mo	61.4% (primary endpoint)
Ryu *Eur J Cancer* 2015[26]	55	Occurring in ≥50% of pts • Anemia: 96%	Occurring in ≥4% of pts • Neutropenia: 18%	NR	NR	NR	NR	55	21.0 mo	9.8 mo	67% (primary endpoint)

Continued

https://doi.org/10.1016/j.esmoop.2021.100360

Table 3. Continued

Study	Safety							Efficacy			
	N	Tx-emergent AEs		Tx-related AEs							
		All grades	Grade ≥3	All grades		Grade ≥3		*N*	Median OS	Median PFS	ORR
				Trast related	CTX related	Trast related	CTX related				
		• Peripheral neuropathy: 71% • Thrombocytopenia: 67% • Neutropenia: 56% • Anorexia: 56% • Nausea: 55% • Fatigue: 55%	• Anemia: 11% • Peripheral neuropathy: 11% • Fatigue: 5% • Anorexia: 4% • Thrombocytopenia: 4%								
Kurokawa *Br J Cancer* 2014 (HERBIS-1)[23]	53	Occurring in ≥50% of pts • Anorexia: 79% • Leukopenia: 74% • Anemia: 66% • Fatigue: 64% • Nausea: 62% • Neutropenia: 60%	Occurring in ≥8% of pts • Neutropenia: 36% • Anorexia: 23% • Anemia: 15% • Hypoalbuminemia: 9% • Leukopenia: 8% • Diarrhea: 8%	NR	NR	NR	NR	53	16.0 mo	7.8 mo	67.9% (primary endpoint)
Gong *BMC Cancer* 2016 (CGOG1001)[36]	51	Occurring in ≥30% of pts • Leukopenia: 67% • Neutropenia: 65% • Thrombocytopenia: 57% • Nausea/vomiting: 55% • Anemia: 49% • Hepatic dysfunction: 45% • HFS: 37%	Occurring in ≥4% of pts • Thrombocytopenia: 22% • Neutropenia: 14% • Anemia: 6% • Leukopenia: 4% • Nausea/vomiting: 4% • Diarrhea: 4% • HFS: 4% • Neurotoxicity: 4%	• ↓ LVEF: 12%	NR	NR	• Thrombocytopenia: 22% • Neutropenia: 14%	51	19.5 mo	9.2 mo	66.7% (primary endpoint)
Oh *Cancer Chemother Pharmacol* 2019[25]	123 (excludes 5 pts who received induction tx only)	NR	NR	Occurring in ≥10% of pts • Nausea: 19% • Anorexia: 16% • Fatigue: 11% • Mucositis: 11% • Sensory neuropathy: 11% • HFS: 11%		Occurring in ≥1 pts • Nausea: 3% • Leukopenia: 2% • Anorexia: 2% • Mucositis: 1% • Sensory neuropathy: 1%		128	14.8 mo	11.6 mo	62.5%
Okita *Tohoku J Exp Med* 2018[37]	28	Occurring in ≥40% of pts • Anemia: 75% • Anorexia: 71.4% • Neutropenia: 57.1% • Thrombocytopenia: 50% • Leukopenia: 42.9% • Fatigue: 42.9%	Occurring in ≥10% of pts • Neutropenia: 28.6% • Anemia: 21.4% • Anorexia: 14.3% • Fatigue: 14.3% • HFS: 14.3%	NR		NR		28	20.0 mo	7.9 mo	39.3%
Okita *Tohoku J Exp Med* 2018[37]	30	Occurring in ≥40% of pts • Anemia: 86.7% • Neutropenia: 56.7%	Occurring in ≥10% of pts • Neutropenia: 26.7% • Anemia: 23.3%	NR		NR		30	16.7 mo	6.9 mo	50.0%

Continued

Table 3. Continued

Study	Safety							Efficacy			
	N	Tx-emergent AEs		Tx-related AEs				*N*	Median OS	Median PFS	ORR
		All grades	Grade ≥3	All grades		Grade ≥3					
				Trast related	CTX related	Trast related	CTX related				
		• Thrombocytopenia: 53.3% • Anorexia: 46.7% • Fatigue: 43.3%	• Anorexia: 10% • Fatigue: 10% • Nausea: 10% • Vomiting: 10%								
Soularue *Bull Cancer* 2015[19]	34	Occurring in ≥30% of pts • Neuropathy: 97% • Anemia: 59% • Thrombocytopenia: 50% • Nausea: 47% • Vomiting: 32% • Diarrhea: 32% • Stomatitis: 32% • HFS: 32%	Occurring in ≥3% of pts • Neuropathy: 18% • Neutropenia: 9% • Anemia: 3% • Nausea: 3% • HFS: 3%	NR		NR		34	17.3 mo (primary endpoint)	9.0 mo	41%
Kim *BMC Cancer* 2021[20]	47	NR	NR	NR		NR		47	12.8 mo	6.9 mo	53%
Dijksterhuis *Int J Cancer* 2020[22]	215	NR	NR	NR		NR		215	11.2 mo	NR	NR
Li *Clin Transl Oncol* 2018[21]	75	Occurring in ≥25% of pts • Leukopenia: 60% • Neutropenia: 60% • Anorexia: 40% • Nausea: 29% • Fatigue: 27% • Peripheral neuropathy: 27%	Occurring in ≥4% of pts • Leukopenia: 17% • Neutropenia: 15% • Thrombocytopenia: 8% • Nausea: 5% • Vomiting: 5% • Anemia: 4%	NR		NR		107	16.0 mo	7.7 mo	58.9%
Janjigian *Lancet Oncol* 2020[15]	37	NR	NR	Occurring in ≥50% of pts • Paraesthesia or peripheral neuropathy: 97% • Hyperglycemia: 89% • Fatigue: 86% • Nausea: 84% • Anemia: 81% • Electrolyte disturbance: 76% • Diarrhea: 73% • Vomiting: 68% • ↑ ALT or AST: 62% • Lymphocytopenia: 59% • Thrombocytopenia: 57%		Occurring in ≥5% of pts • Lymphocytopenia: 24% • Electrolyte disturbance: 16% • Anemia: 11% • Interstitial nephritis: 8% • Nausea: 5% • Dry skin/pruritus/maculopapular rash: 5% • Oral mucositis: 5%		37	27.3 mo	13.0 mo	86.4%

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https://doi.org/10.1016/j.esmoop.2021.100360

Table 3. Continued

Study	Safety							Efficacy			
	N	Tx-emergent AEs		Tx-related AEs							
		All grades	Grade ≥3	All grades		Grade ≥3		*N*	Median OS	Median PFS	ORR
				Trast related	CTX related	Trast related	CTX related				
Lee AACR 2021, Abstr. CT174 (HCRN GI17-319)[24]	18	NR	NR	NR	NR	• Neutropenia: 28% • Thrombocytopenia: 11% • Anemia: 11% • Hypokalemia: 11%		18	NR	8.0 mo	61% at 24 weeks (primary endpoint) 39% confirmed RR
Rha ASCO 2020, Abstr. 3031 Rha ASCO GI 2021, Abstr. 218 (PANTHERA)[17]	43	NR	NR	Occurring in ≥20% of pts • Neutropenia: 46.5% • Anorexia: 39.5% • Anemia: 32.6% • Nausea: 32.6% • ↑ creatinine: 30.2% • Diarrhea: 30.2% • HFS: 23.3% • Oral mucositis: 23.3%		Occurring in ≥5% of pts • Neutropenia: 42% • Anemia: 16% • Febrile neutropenia: 9% • Thrombocytopenia: 7% • Colitis: 7% • Anorexia: 5% • Hyperkalemia: 5% • ↑ creatinine: 5%		43	19.3 mo	8.6 mo	76.7% (primary endpoint)
Janjigian ASCO 2021, Abstr. 4013 (KEYNOTE-811)[14]	216 (placebo)	Occurring in ≥20% of pts • Diarrhea: 44% • Nausea: 44% • Anemia: 44% • ↓ appetite: 32% • Thrombocytopenia: 28% • Vomiting: 27% • Neutropenia: 25% • Fatigue: 20% • Peripheral sensory neuropathy: 19% • ↑ AST: 13%	• Anemia: 9% • Diarrhea: 8% • Thrombocytopenia: 7% • Neutropenia: 7% • Nausea: 6% • ↓ appetite: 4% • Fatigue: 3% • Vomiting: 2% • Peripheral sensory neuropathy: 1% • ↑ AST: <1%	NR	NR	NR	NR	131	NR (primary endpoint)	NR (primary endpoint)	51.9%
	217 (pembro)	Occurring in ≥20% of pts • Diarrhea: 53% • Nausea: 49% • Anemia: 41% • ↓ appetite: 31% • Vomiting: 31% • Thrombocytopenia: 24% • Fatigue: 24% • Neutropenia: 24% • Peripheral sensory neuropathy: 23% • ↑ AST: 21%	• Anemia: 9% • Thrombocytopenia: 8% • Neutropenia: 7% • Diarrhea: 7% • Nausea: 5% • Vomiting: 5% • Fatigue: 4% • Peripheral sensory neuropathy: 3% • ↓ appetite: 2% • ↑ AST: <1%	NR	NR	NR	NR	133	NR (primary endpoint)	NR (primary endpoint)	74.4%

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTX, chemotherapy; HFS, hand-foot syndrome; LVEF, left ventricular ejection fraction; mo, months; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PPE, palmar-plantar erythrodysesthesia; pts, patients; RR, response rate; ToGA, Trastuzumab for Gastric Cancer; trast, trastuzumab; tx, treatment.

Considerations by tumor location among studies of trastuzumab plus fluoropyrimidine plus platin

Among 12 studies[6,14,28-37] in which gastric cancer was the most common, grade ≥3 AEs ranged from 44% to 84% (Tables 1 and 2). Grade ≥3 AEs occurred at 32% in the study[19] where GEJ was the predominant type and 41% in the study[22] where esophageal cancer was the predominant type (Tables 1 and 2).

By comparing the global ToGA and the JACOB studies with their respective subgroup analyses in Asian patients, we observed that the prevalence of GEJ cancer, known to have high HER2 positivity,[38] was lower among Asian patients (ranging from 3.9% to 14.8%),[29,30,31] compared with the overall study populations (ranging from 20% to 25%; Table 1).[6,32] Moreover, the prevalence of HER2 IHC 3+ was lower among Japanese patients (ranging from 31.4% to 62.5%),[29,30] compared with the overall study population (ranging from 45% to 67%; Table 1).[6,32]

CONSIDERATIONS ON EFFICACY

Trastuzumab plus fluoropyrimidine plus platinum

Objective response rate (ORR)[6,14,19-21,23,25-37] ranged from 39% to 82%, median progression-free survival (PFS)[6,19-21,23,25-37] from 5.7 to 11.6 months, and median overall survival (OS)[6,19-21,23,25-37] from 11.2 to 27.6 months (Table 3, Figures 2 and 3). ORR ranged from 39% to 82% in the Asian studies;[20,21,23,25-27,29-31,34-37] in the global studies, 47% to 59%;[6,14,28,32] and in the European studies, 41% to 47%.[19,33] The median PFS ranged from 5.9 to 11.6 months in the Asian studies;[20,21,23,25-27,29-31,34-37] in the global studies, 5.7 to 7.0 months;[6,28,32] and in the European studies, 7.1 to 9.0 months.[19,33] The median OS ranged from 12.8 to 27.6 months in the Asian studies;[20,21,23,25-27,29-31,34-37] in the global studies, 12.5 to 14.2 months;[6,28,32] and in the European studies, 11.2 to 17.3 months.[19,22,33]

Checkpoint inhibitors plus trastuzumab plus fluoropyrimidine plus platin

ORR[14-17,24] ranged from 39% to 86%, median PFS[15-17,24] from 8.0 to 13.0 months, and median OS[15-17] from 19.3 to 27.3 months (Table 3).

DISCUSSION

The trastuzumab plus fluoropyrimidine plus platin regimen has considerable toxicity in patients with HER2+ GEA; therefore, less toxic regimens while maintaining clinical benefit are critical in these patients. TEAEs of all grades ranged from 45% to 100% and grade ≥3 TEAEs ranged from 32% to 84%. Efforts to improve safety and efficacy are essential. To this end, safety and efficacy study endpoints of checkpoint inhibitors combined with trastuzumab plus fluoropyrimidine and platin have begun to read out.[14-17,24]

Regimens using oxaliplatin rather than cisplatin have potentially reduced toxicity.[9] Although a direct comparison cannot be made in this review, regimens with a cisplatin backbone had higher rates of grade ≥3 AEs (57%-84%) compared with regimens with an oxaliplatin backbone (32%-57%).

Oral capecitabine and S-1, the oral form of 5-FU, have some logistical advantages over intravenously administered 5-FU. Given the few studies using S-1 as a fluoropyrimidine backbone reporting grade ≥3 AEs, and the fact that there were no studies in which 5-FU was used exclusively, it is not possible to appropriately compare safety across the three fluoropyrimidine backbones that are available. In general, patients with GEJ cancer have more dysphagia from partial obstruction, which causes more nausea and vomiting than antral or other body locations, and many of these patients prefer intravenous over oral agents.

When considering the trastuzumab plus fluoropyrimidine plus platinum regimen by geographic region, we did not observe striking differences in terms of safety between the Asian population and the rest of the world across the studies analyzed. Grade ≥3 TEAEs ranged from 57% to 84% in studies conducted in Asia[20,21,23,25-27,29-31,34-37] and from 57% to 73% in the studies conducted globally;[6,14,28,32] similarly, SAEs of all grades ranged from 15% to 33% in studies conducted in Asia[20,21,23,25-27,29-31,34-37] and from 24% to 39% in the studies conducted globally.[6,14,28,32] If we consider the specific example of the JACOB study and its Asian subgroup analyses, we confirmed a similar safety profile, as Grade ≥3 TEAEs were 73% in the total population[32] and ranged from 65% to 75% in the subgroup analyses with Asian patients.[31,30] Similarly, SAEs of all grades were 39% in the JACOB overall population[32] and ranged from 15% to 33% in the JACOB subgroup analyses with Asian patients.[31,30]

The trastuzumab plus fluoropyrimidine plus platinum regimen has demonstrated clinical efficacy in patients with GEA, with ORR reaching up to 82%, median PFS up to 11.6 months, and median OS up to 27.6 months. In the Asian studies,[20,21,23,25-27,29-31,34-37] the median OS and median PFS were up to 27.6 and 11.6 months, respectively; in the European studies,[19,22,33] they were up to 17.3 and 9.0 months, respectively; and in the global studies,[6,28,32] they were up to 14.2 and 7.0 months, respectively. In the ToGA study, the median OS that the Japanese population achieved with trastuzumab plus chemotherapy was longer (15.9 months), compared with the total population (13.8 months).[6,29] However, there were some confounding factors including that all Japanese patients in ToGA received capecitabine, while 16% of the non-Japanese population in ToGA received 5-FU, and that no ECOG 2 Japanese patients enrolled, while 12% of the non-Japanese population in ToGA were ECOG 2.[29] In the JACOB study, the median OS that the Japanese population achieved with trastuzumab plus chemotherapy was slightly longer (15.6 months), compared with the total population (14.2 months).[30,32] The median OS in the Chinese population of JACOB was longer (16.1 months) than the total population (14.2 months).[31,32] In general, the follow-up period was longer in the Asian studies (up to 34 months[30] when including the subgroup analyses of JACOB/ToGA; up to 29 months[36] when these subgroup analyses are

Table 4. Focus on specific AEs

Study	*N*	Fatigue/general weakness		Nausea		Diarrhea		Neutropenia		Anemia		Peripheral neuropathy/ neurotoxicity		Pneumonitis		Stomatitis/mucositis/ mucosal inflammation		PPE/HFS	
		All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3
Shitara *Int J Clin Oncol* 2020 (JACOB subgroup analysis)[30]	40	35%	2.5%	60%	10%	37.5%	5%	52.5%	30%	NR	NR	17.5%	0%	NR	NR	50%	2.5%	62.5%	0%
Liu *Cancer Commun* 2019 (JACOB subgroup analysis)[31]	80	20%	1.3%	61.3%	2.5%	16.3% (10% tx related)	1.3%	65%	30%	53.8%	22.5%	NR	NR	NR	NR	8.8%	1.3%	20%	7.5%
Tabernero *Lancet Oncol* 2018 (JACOB)[32]	388	31%	4%	57%	5%	35%	6%	52%	28%	39%	17%	7%	0%	4%	2%	18%	2%	25%	3%
Shah *J Clin Oncol* 2017 (HELOISE)[28]	124	15.3%	NR	41.9%	NR	16.9%	NR	46.8%	NR	32.3%	NR	NR	NR	NR	NR	NR	NR	9.7%	NR
Sawaki *Gastric Cancer* 2012 (ToGA subgroup analysis)[29]	51	61%	8%	86%	14%	45%	8%	59%	35%	29%	25%	31%	2%	NR	NR	57%	0%	41%	0%
Bang *Lancet*[6] 2010 (ToGA)	294	35%	4%	67%	7%	37%	9%	53%	27%	28%	12%	NR	NR	NR	NR	24% (stomatitis) 13% (mucosal inflammation)	1% (stomatitis) 2% (mucosal inflammation)	26%	1%
Yuki *Cancer Chemother Pharmacol* 2020 (KSCC/HGCSG/CCOG/ Perseus 1501B)[27]	39	62%	5%	59%	8%	51%	8%	74%	10%	97%	13%	82%	5%	3%	3%	49%	0%	41%	0%
Rivera *Cancer Chemother Pharmacol* 2019 (HERXO)[33]	45	73% (tx related)	16% (tx related)	47% (tx related)	20% (tx related)	53% (tx related)	27% (tx related)	22% (tx related)	2% (tx related)	38% (tx related)	2% (tx related)	78% (tx related)	2% (tx related)	NR	NR	13% (tx related)	2% (tx related)	13% (tx related)	2% (tx related)
Takahari *Gastric Cancer* 2019 (HIGHSOX)[34]	75	57% (tx related)	3% (tx related)	65% (tx related)	4% (tx related)	52% (tx related)	7% (tx related)	79% (tx related)	11% (tx related)	96% (tx related)	7% (tx related)	84% (tx related)	16% (tx related)	NR	NR	25% (tx related)	1% (tx related)	NR	NR
Miura *Gastric Cancer* 2018 (WJOG7 212G/T-SPACE)[35]	44	75%	14%	61%	11%	50%	11%	66%	30%	86%	18%	NR	NR	NR	NR	46%	5%	18%	0%
Ryu *Eur J Cancer* 2015[26]	55	55%	5%	55%	2%	38%	2%	56%	18%	96%	11%	71%	11%	NR	NR	22%	2%	33%	2%
Kurokawa *Br J Cancer* 2014 (HERBIS-1)[23]	53	64%	4%	62%	2%	40%	8%	60%	36%	66%	15%	11%	0%	NR	NR	32%	2%	NR	NR
Gong *BMC Cancer* 2016 (CGOG1001)[36]	51	10%	2%	55%[a]	4%[a]	22%	4%	65%	14%	49%	6%	14%	4%	NR	NR	NR	NR	37%	4%
Oh *Cancer Chemother Pharmacol* 2019[25]	123	11%	0%	19%	3%	NR	NR	NR	NR	3%	0%	11%	1%	NR	NR	11%	1%	11%	0%
Okita *Tohoku J Exp Med* 2018[37]	28	42.9%	14.3%	32.1%	3.6%	17.9%	3.6%	57.1%	28.6%	75%	21.4%	14.3%	3.6%	NR	NR	21.4%	0%	32.1%	14.3%

Continued

Table 4. Continued

Study	*N*	Fatigue/general weakness		Nausea		Diarrhea		Neutropenia		Anemia		Peripheral neuropathy/ neurotoxicity		Pneumonitis		Stomatitis/mucositis/ mucosal inflammation		PPE/HFS	
		All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3	All gr	Gr ≥3
Okita *Tohoku J Exp Med* 2018[37]	30	43.3%	10%	36.7%	10%	26.7%	6.7%	56.7%	26.7%	86.7%	23.3%	13.3%	0%	NR	NR	16.7%	0%	23.3%	0%
Soularue *Bull Cancer* 2015[19]	34	NR	NR	47%	3%	32%	0%	29%	9%	59%	3%	97%	18%	NR	NR	32%	0%	32%	3%
Kim *BMC Cancer* 2021[20]	47	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dijksterhuis *Int J Cancer* 2020[22]	71	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Li *Clin Transl Oncol* 2018[21]	75	27%	1%	29%	5%	13%	1%	60%	15%	24%	4%	27%	3%	NR	NR	5%	1%	NR	NR
Janjigian *Lancet Oncol* 2020[15]	37	86%	0%	84%	5%	73%	3%	19%	0%	81%	11%	97%	0%	NR	NR	38%	5%	22%	0%
Lee AACR 2021, Abstr. CT174 (HCRN GI17-319)[24]	18	NR	NR	NR	NR	NR	NR	NR	28%	NR	11%	NR	NR	NR	NR	NR	NR	NR	NR
Rha ASCO 2020, Abstr. 3031[17] Rha ASCO GI 2021, Abstr. 218 (PANTHERA)[16]	43	18.6%	2.3%	32.6%	0%	30.2%	2.3%	46.5%	41.8%	32.6%	16.3%	18.6%	0%	NR	NR	23.3%	2.3%	23.3%	0%
Janjigian ASCO 2021, Abstr. 4013 (KEYNOTE-811)[14]	216 (placebo)	20%	3%	44%	6%	44%	8%	25%	7%	44%	9%	19%	1%	1%	0%	NR	NR	NR	NR
	217 (pembro)	24%	4%	49%	5%	53%	7%	24%	7%	41%	9%	23%	3%	5%	1%	NR	NR	NR	NR

AE, adverse event; gr, grade; HFS, hand-foot syndrome; NR, not reported; pembro, pembrolizumab; PPE, palmar-plantar erythrodysesthesia; ToGA, Trastuzumab for Gastric Cancer; tx, treatment.
[a]Preferred term is nausea/vomiting.

https://doi.org/10.1016/j.esmoop.2021.100360

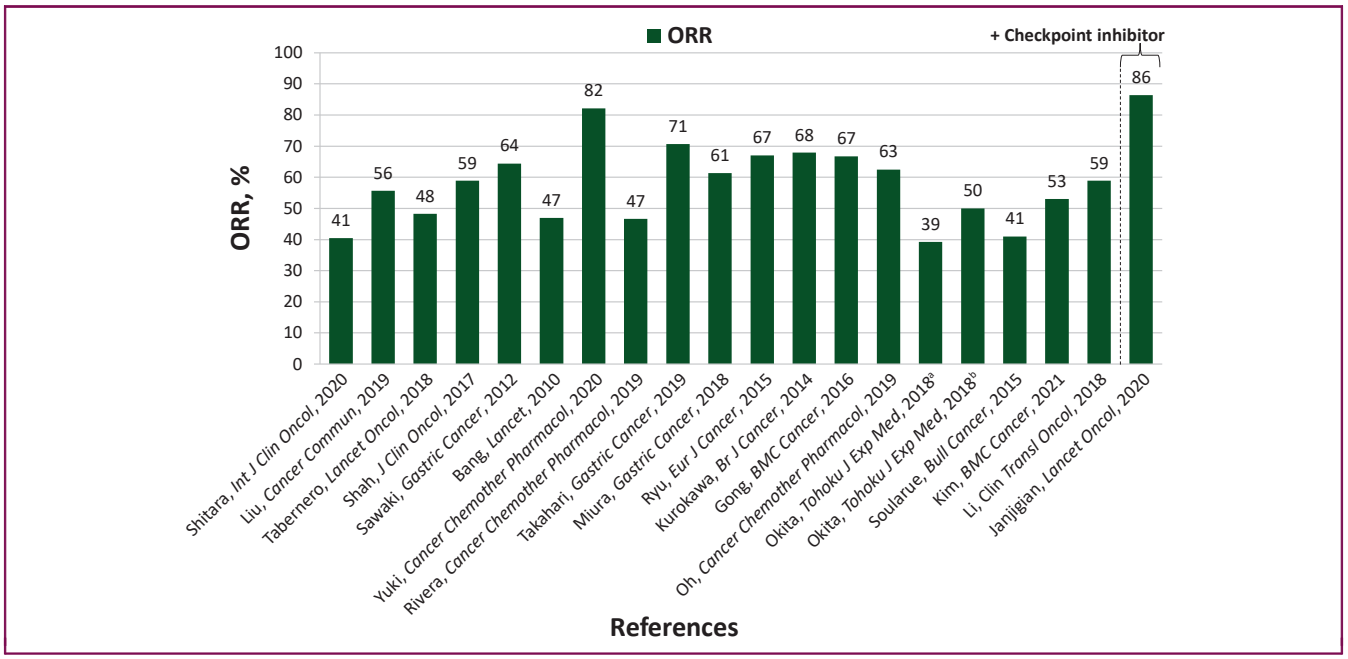

Figure 2. ORR comparison across the trials analyzed. See also [6,15,19-21,23,25-37]
ORR, objective response rate.
[a]Trastuzumab + capecitabine + cisplatin.
[b]Trastuzumab + S-1 + cisplatin.

excluded), compared with the global (up to 25 months)[32] and European studies (up to 15 months)[19] because of longer median PFS and median OS. Among the few studies of checkpoint inhibitors plus trastuzumab plus chemotherapy, the follow-up time for efficacy analyses was similar, ranging from 12.0 to 18.2 months, and because there were only 3 studies providing follow-up times, one US-based, one Asian, and one global, it is not possible to assess potential correlations between clinical efficacy and follow-up period. The addition of checkpoint inhibitors further increased the ORR up to 86% and extended the median PFS up to 13 months, while maintaining the median OS at ∼27 months. It is possible that to detect a longer OS advantage with the addition of checkpoint inhibitors, a longer follow-up time

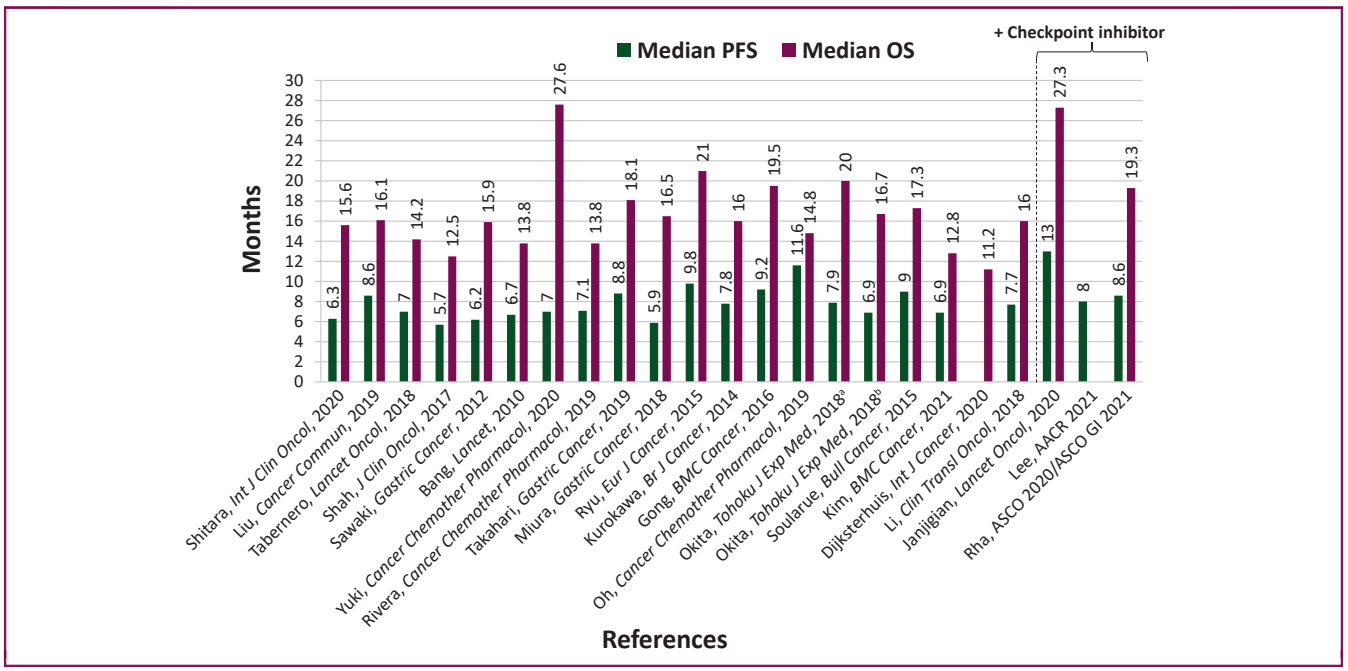

Figure 3. Median PFS and OS comparison across the trials analyzed. See also [6,15,17,19-23,25-37]
OS, overall survival; PFS, progression-free survival.
[a]Trastuzumab + capecitabine + cisplatin.
[b]Trastuzumab + S-1 + cisplatin.

may be necessary. One limitation to consider is that several of the studies analyzed in this review, especially those related to immunotherapy, have quite short follow-up times; therefore, the survival outcomes may change in the future as new analyses at longer follow-up become available.

Over a decade has passed since the ToGA study investigators published their seminal findings about HER2+ metastatic gastric cancer, and trastuzumab plus fluoropyrimidine and platinum has been the mainstay of therapy in those patients. Novel chemotherapy-free regimens may have potential benefit, especially in patients who cannot tolerate chemotherapy. Recently, the chemotherapy-free combination of anti-HER2+ monoclonal antibodies margetuximab and pembrolizumab was studied in a phase I/II study (NCT02689284) in the second-line treatment of patients with metastatic HER2+, PD-L1-unselected gastric and GEJ cancer refractory to trastuzumab. The study provided an initial proof of concept of clinically meaningful activity with a manageable safety profile with the combination of an anti-HER2+ agent along with an anti-PD-1 checkpoint blockade.[39] It would be desirable to develop novel anti-HER2+-based combination strategies without chemotherapy as first-line treatment for appropriate patients with locally advanced unresectable or metastatic HER2+ GEA. Of note, 25 patients in a first-line study received an initial induction cycle of 200 mg flat dose pembrolizumab and an 8 mg/kg loading dose of trastuzumab, followed by pembrolizumab, trastuzumab, and chemotherapy beginning with cycle 2.[15] Among these 25 patients who received one induction cycle of pembrolizumab and trastuzumab, 2 achieved partial responses (ORR of 8%) before initiation of chemotherapy.[15] The phase II/III MAHOGANY study (NCT04082364) is ongoing to investigate the safety and efficacy of margetuximab plus checkpoint inhibitors with or without chemotherapy in the first-line setting for patients with HER2+ GEA.[40] An initial report of MAHOGANY Cohort A Part 1 observed a grade $\geq$3 treatment-related AE rate of 18.6%, and an ORR of 52.5% in 40 patients with HER2 IHC3+ and PD-L1 CPS$\geq$1 tumors, providing support for further evaluation of this first-line chemotherapy-free concept in appropriately selected patients.[41]

ACKNOWLEDGEMENTS

Medical writing and/or editorial assistance was provided by Emily Cullinan, PhD, CMPP, and Francesca Balordi, PhD, of The Lockwood Group (Stamford, CT, USA), in accordance with Good Publication Practice (GPP3) guidelines, funded by MacroGenics, Inc.

FUNDING

Funding for this review was provided by MacroGenics, Inc.

DISCLOSURE

DVTC reports personal fees from Archer, Astellas Pharma, Bristol-Myers Squibb, Daiichi Sankyo, Five Prime, Foundation Medicine, Guardant Health, Genentech/Roche, Gritstone Oncology, Lilly, Merck, Natera, Pieris Pharmaceuticals, QED Therapeutics, Seattle Genetics, Taiho Pharmaceutical, Tempus Labs, and Zymeworks; HCC has received consultation fees from Taiho Pharmaceutical, Celltrion, Merck Sharpe & Dohme, Eli Lilly, Bristol Myers Squibb, Merck-Serono, Gloria Pharmaceuticals, BeiGene, Amgen, and Zymeworks; grants to institution for clinical trial from Eli Lilly, GlaxoSmithKline, Merck Sharpe & Dohme, Merck-Serono, Bristol Myers Squibb/Ono Pharmaceutical, Taiho Pharmaceutical, Amgen, BeiGene, and Incyte; and honoraria from Merck-Serono and Eli Lilly; LS reports grants from Beijing Xiantong Biomedical Technology, Beihai Kangcheng (Beijing) Medical Technology, Boehringer Ingelheim, Jacobio Pharmaceuticals, Qilu Pharmaceutical, and Zaiding Pharmaceutical (Shanghai); and consulting fees from Harbour BioMed and Merck; MM reports grants and nonfinancial support from Arbeitsgemeinschaft Internistische Onkologie, German Ministry of Education and Research, the European Organisation for Research and Treatment of Cancer, and German Cancer Aid; personal fees from Amgen, Bristol-Myers Squibb, Falk Foundation, Lilly, MCI Group, Merck Serono, Merck Sharp & Dohme Corp., Pfizer and Roche; grants to the university from Amgen, Bristol-Myers Squibb, Merck Serono, Merck Sharp & Dohme Corp., and Pfizer; and nonfinancial support from Amgen and Bristol-Myers Squibb; HHY reports honoraria for advisory board and steering committee from MacroGenics, honoraria for advisory boards from Bristol-Myers Squibb and Zymeworks, and honoraria for steering committees from BeiGene and Merck; Y-KK reports consulting fees from ALX Oncology, Amgen, Astellas Pharma, Bristol-Myers Squibb, Daehwa Pharmaceutical, MacroGenics, Merck, Novartis, Ono Pharmaceutical, Surface Oncology, Taiho Pharmaceutical, and Zymeworks; MKR is a full-time employee of MacroGenics.

DATA SHARING

Not applicable.

ETHICAL APPROVAL

Not applicable.

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