Systematic Review and Meta-Analysis

Medicine

OPEN

Trastuzumab combined chemotherapy for the treatment of HER2-positive advanced gastric cancer

A systematic review and meta-analysis of randomized controlled trial

Chuan Xue, MM[a], Yong-Hong Xu, MM[a,*]

Abstract

Background: This systematic review and meta-analysis aimed to assess the efficacy of trastuzumab combined with chemotherapy for the treatment in HER2-positive advanced gastric cancer (HER2-PAGC).

Methods: This systematic review and meta-analysis was designed using randomized controlled trials that compared trastuzumab in combination with chemotherapy and chemotherapy alone. A comprehensive search was conducted in the following databases from their inception onwards: PubMed, EMBASE, Cochrane Library, WANGFANG, and CNKI. We also searched other literature sources to avoid missing relevant studies. Two reviewers independently performed all record selection, data collection, and methodological assessments. Any confusion was resolved by discussion or referral to a third reviewer. If there were ample data from eligible studies, we performed a fixed-effects meta-analysis. Whenever this was not possible, we conducted a narrative synthesis.

Results: Meta-analysis results showed that trastuzumab in combination with chemotherapy achieved better outcomes on response rate (trastuzumab plus CFC vs CFC: odds ratio [OR] = 1.56, 95% confidence interval [CI] [1.17–2.09], I^2 = 0%, P < .003; trastuzumab plus OT vs OT: OR = 2.97, 95% CI [1.74–5.09], I^2 = 0%, P < .0001; and trastuzumab plus CC vs CC: OR = 2.62, 95% CI [1.84–3.73], I^2 = 0%, P < .0001), and disease control rate (trastuzumab plus CFC vs CFC: OR = 1.61, 95% CI [1.17–2.21], I^2 = 0%, P = .004; trastuzumab plus OT vs OT: OR = 4.29, 95% CI [2.33–7.90], I^2 = 0%, P < .0001; and trastuzumab plus CC vs CC: OR = 2.99, 95% CI [1.99–4.48], I^2 = 0%, P < .0001). However, there were no significant differences in the adverse events.

Conclusions: The results of this study revealed that the efficacy of trastuzumab combined with chemotherapy was superior to that of chemotherapy alone for the treatment of HER2-PAGC. The 2 modalities showed similar safety profiles.

Abbreviations: AGC = advanced GC, CAF = cyclophosphamide+azithromycin+5-fluorouracil, CC = capecitabine+cisplatin, CFC = capecitabine or 5-fluorouracil+cisplatin, CI = confidence interval, DCF = docetaxel+cisplatin+5-fluorouracil, GC = gastric cancer, HER2 = human epidermal growth factor receptor type 2, HER2-PAGC = HER2-positive advanced gastric cancer, IC = irinotecan+cisplatin, RCT = randomized controlled trial, OF = oxaliplatin+5-fluorouracil, OL = oxaliplatin+leucovorin, OT = oxaliplatin+tegafur.

Keywords: efficacy, HER2-positive advanced gastric cancer, meta-analysis, randomized controlled trial, safety, systematic review, trastuzumab

1. Introduction

Gastric cancer (GC) is one of the most common gastrointestinal cancers and the leading cause of cancer-related deaths worldwide.[1–4] More than 1 million new GC cases were reported in 2018, and approximately 780,000 GC patients died.[5] Patients with GC are often diagnosed at an advanced stage, which presents challenges for management.[6,7] Although surgery is recommended as a potentially curative treatment, many patients still experience regional and distant recurrence after operation.[8–11] Chemotherapy is often considered the standard treatment for advanced GC (AGC).[12] However, the prognosis is poor owing to the restriction of accurate targets. A previous study reported that AGC survival varies from approximately 4 to 16.6 months with chemotherapy.[13–15]

This study was supported by Zhejiang Traditional Chinese Medicine Science and Technology Plan Project (2013ZQ029).

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

The supporter did not involve in this study.

[a] Department of Gastroenterology, Sunshine Union Hospital, Weifang, China.

**Correspondence: Yong-Hong Xu, MM, Department of Gastroenterology, Sunshine Union Hospital, No. 9000 Yingqian Street, High-tech District, Weifang, Shandong Province 261061, China (e-mail: susmuez20@21cn.com).*

How to cite this article: Xue C, Xu Y-H. Trastuzumab combined chemotherapy for the treatment of HER2-positive advanced gastric cancer: A systematic review and meta-analysis of randomized controlled trial. Medicine 2022;101:34(e29992).

Received: 4 June 2022 / Received in final form: 21 June 2022 / Accepted: 23 June 2022

http://dx.doi.org/10.1097/MD.0000000000029992

Trastuzumab is a monoclonal antibody utilized to manage GC.[16–18] It binds to human epidermal growth factor receptor type 2 (HER2).[18–20] It is effective against tumors that overexpress HER2.[18,21] Although previous studies have reported that trastuzumab can be used specifically to treat patients with HER2-positive advanced GC (HER2-PAGC), its monotherapy efficacy remains unsatisfactory.[22–31] Fortunately, several clinical trials have investigated the efficacy and safety of trastuzumab combined with chemotherapy for the treatment of patients with HER2-PAGC with promising outcomes.[32–49]

Previous similar studies investigated the efficacy of trastuzumab combined with chemotherapy in the treatment of patients with HER2-PAGC.[50–52] However, the overall methodological quality of included trials in these studies was poor.[50–52] In addition, there were more eligible trials published after those studies.[36,38,39,43,44] This systematic review and meta-analysis summarized the evidence of latest clinical trials and updated the evidence-based medical evidence for this topic. Therefore, this study aimed to update the present evidence on the efficacy and safety of trastuzumab combined chemotherapy in the treatment of patients with HER2-PAGC.

2. Methods

2.1. Ethical statement

No ethical approval was provided for this study because the individual data were not collected. The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.

Table 1

Search strategy for PubMed.

Number	Search terms
1	Gastric cancer
2	Stomach neoplasm
3	Gastric neoplasm
4	Cancer of stomach
5	Cancer, stomach
6	Cancer, gastric
7	Neoplasm, gastric
8	Human epidermal growth factor receptor 2
9	HER2
10	HER2-positive
11	Advanced
12	Or 1–11
13	Trastuzumab
14	Herceptin
15	Monoclonal antibody
16	Trastuzumab-anns
17	Trastuzumab dkst
18	Trastuzumab-dttb
19	Trastuzumab-pkrb
20	Trastuzumab-qyy
21	Chemotherapy
22	Or 13–21
23	Controlled trials
24	Clinical trials
25	Random
26	Randomly
27	Control
28	Allocation
29	Blind
30	Trial
31	Study
32	Or 23–31
33	12 AND 22 AND 32

2.2. Eligibility criteria

2.2.1. Inclusion criteria. This study included randomized controlled trials (RCTs) that compared the efficacy and safety of trastuzumab combined with chemotherapy with chemotherapy alone for the treatment of HER2-PAGC. For experimental intervention, any type of trastuzumab combined with chemotherapy was included. For controls, the same chemotherapy regimen as that in the intervention group was considered. We included patients with histopathologically confirmed HER2-PAGC, regardless sex, country, duration, severity, stage of HER2-PAGC, and educational background. Outcomes included efficacy (response rate, disease control rate, overall survival, progression-free survival, survival rate at month 6, 12, 18, 24, mean survival months of death) and safety (neutropenia, leukopenia, nausea and vomiting, diarrhea, liver function impairment, neurotoxicity, cardiac toxicity, rash, myelosuppression, and hand-foot syndrome).

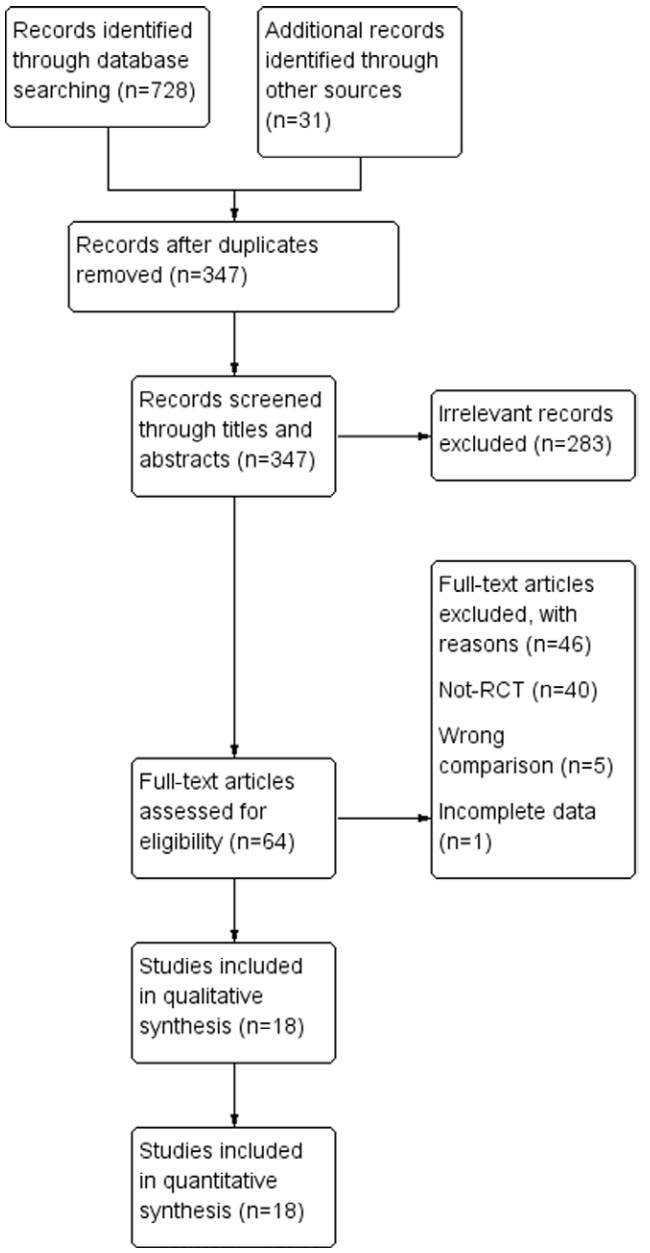

Figure 1. Flow diagram of study selection. RCT = randomized controlled trial.

2.2.2. Exclusion criteria. We excluded studies of repetitive reports, animal experiments, reviews, case studies, conference abstracts, nonclinical trial, uncontrolled trial, and non-RCTs.

2.3. Data source and search strategy

We comprehensively searched PubMed, EMBASE, Cochrane Library, WANGFANG, and CNKI to check any potential studies. All electronic databases were retrieved from inception onwards. We also searched other literature, including websites of clinical trial registry, conference abstracts, and reference lists of associated reviews. The search terms included "gastric cancer", "stomach neoplasm", "gastric neoplasm", "cancer of stomach", "cancer, stomach", "cancer, gastric", "neoplasm, gastric", "human epidermal growth factor receptor 2", "HER2", "HER2-positive", "advanced", "trastuzumab", "herceptin", "monoclonal antibody", "trastuzumab-anns", "trastuzumab dkst", "trastuzumab-dttb", "trastuzumab-pkrb", "trastuzumab-qyy", "chemotherapy", "controlled trials", "clinical trials", "random", "randomly", "control", "allocation", "placebo", "blind", "trial", and "study". The detailed search strategy for PubMed is presented in Table 1.

2.4. Study selection

All citations were managed using Endnote X8 (Clarivate Analytics) and duplicates were removed. Two reviewers independently screened the records by title and abstract, and irrelevant studies were eliminated. The full text of the remaining articles was then carefully read against all eligibility criteria. If any divergence occurred between the 2 reviewers, we invited a third experienced reviewer to resolve it through a discussion.

2.5. Data collection and management

Two reviewers independently extracted data utilizing a standardized data collection form with the following items: trial information (first author, year of publication, title, country, language, trial setting, sample size, etc); trial methods (methods of randomization, blind, allocation, concealment, etc); patient information (sex, age, type and stage of AGC, duration of AGC onset, diagnostic criteria, inclusion and exclusion criteria, etc); intervention and control (types of interventions and controls, dosage, frequency, duration, et al); and outcomes, follow-up information, and adverse events. If any disagreement occurred between the 2 reviewers, a third experienced reviewer was consulted to settle the division.

Table 2

General characteristics of included studies.

Study	Location	Sample size (T/C)	Age (yr, T/C)	Gender (M/F)	Intervention	Control	Outcomes	Follow-up (mo)
Bang et al[32]	Asia, USA, Europe	292/290	T:59.4 ± 10.8 C:58.5 ± 11.2	T:226/66 C:218/72	Trastuzumab + CFC	CFC	①②③④⑤⑦⑧⑨⑩⑯	34
Cao et al[33]	China	24/24	T:61.2 ± 9.4 C:60.4 ± 8.1	T:16/8 C:15/9	Trastuzumab + OT	OT	①②⑪⑫⑬	2
Chen et al[34]	China	24/24	T:60* C:64*	T:17/7 C:13/9	Trastuzumab + OT	OT	①②⑨⑩⑪⑫⑬	NR
Huang and Gao[35]	China	40/40	T:60.7 ± 5.2 C:61.4 ± 4.2	T:26/14 C:22/18	Trastuzumab + CC	CC	①②⑨⑪⑮⑯	4.2
Lan et al[36]	China	39/39	T:59.5 ± 8.2 C:60.3 ± 8.3	T:21/18 C:23/16	Trastuzumab + IC	IC	①②⑨⑪⑮⑯	1.5
Li et al[37]	China	15/14	53.4*	NR	Trastuzumab + OT	OT	①②	NR
Li and Shi[38]	China	100/100	T:58.4 ± 2.1 C:58.4 ± 2.1	T:54/46 C:57/43	Trastuzumab + CC	CC	①②⑨⑪⑮⑯	4.2
Lv et al[39]	China	38/38	T:61.5 ± 6.3 C:63.4 ± 6.7	T:26/12 C:24/14	Trastuzumab + CC	CC	①②⑨⑪⑮⑯	4.2
Sawaki et al[40]	Japan	51/50	T:63* C:60*	T:40/11 C:40/10	Trastuzumab + CFC	CFC	①②③④⑤⑦⑧⑨⑩⑫⑭	34
Shen et al[41]	China	36/48	T:58.7 ± 10.5 C:58.2 ± 10.5	T:28/8 C:39/9	Trastuzumab + CFC	CFC	①②③④⑦⑧⑨⑩⑫⑭⑯	34
Song et al[42]	China	30/30	T:63.5 ± 11.3 C:66.3 ± 11.8	T:18/12 C:20/10	Trastuzumab + OT	OT	①②	NR
Wang et al[43]	China	35/35	T:55.5 ± 4.7 C:55.5 ± 4.6	T:21/14 C:20/15	Trastuzumab + OL	OL	①②⑧⑨⑪⑫⑬⑭	2
Wu and Xie[44]	China	63/63	T:62.2 ± 5.5 C:61.4 ± 5.5	T:37/26 C:39/24	Trastuzumab + CC	CC	①②③④⑨⑪⑮⑯	2
Yang et al[45]	China	25/25	56.5 ± 2.3	NR	Trastuzumab + OT	OT	①②⑨⑩⑪⑫⑬	NR
Yang[46]	China	39/39	T:63.6 ± 5.3 C:64.3 ± 5.4	T:16/23 C:18/21	Trastuzumab + CC	CC	①②⑨⑪⑮	4.2
Yu et al[47]	China	48/48	T:48.5 ± 2.2 C:47.3 ± 2.1	T:27/21 C:29/19	Trastuzumab + CAF	CAF	①②⑧⑨⑪⑫	NR
Zhu et al[48]	China	44/40	T:59.5 ± 7.2 C:57.7 ± 7.5	T:25/19 C:18/22	Trastuzumab + OF	OF	①⑥⑪⑫⑬⑭⑮	24
Zhu et al[49]	China	37/35	56.8 ± 4.5	42/30	Trastuzumab + DCF	DCF	①②⑤⑥⑦⑫⑬⑭	24

①response rate; ②disease control rate; ③overall survival; ④progression-free survival; ⑤survival rate at month 6, 12, 18, 24; ⑥mean survival months of death; ⑦neutropenia; ⑧leukopenia; ⑨nausea and vomiting; ⑩diarrhea; ⑪liver function impairment; ⑫neurotoxicity; ⑬cardiac toxicity; ⑭rash; ⑮myelosuppression; ⑯hand-foot syndrome.

C = control group, CAF = cyclophosphamide + azithromycin + 5-fluorouracil, CC = capecitabine + cisplatin, CFC = capecitabine or 5-fluorouracil + cisplatin, DCF = docetaxel + cisplatin + 5-fluorouracil, F = female, IC = irinotecan + cisplatin, M = male, NR = not report, OF = oxaliplatin + 5-fluorouracil, OL = oxaliplatin + leucovorin, OT = oxaliplatin + tegafur, T = treatment group.

*Age reported as median age.

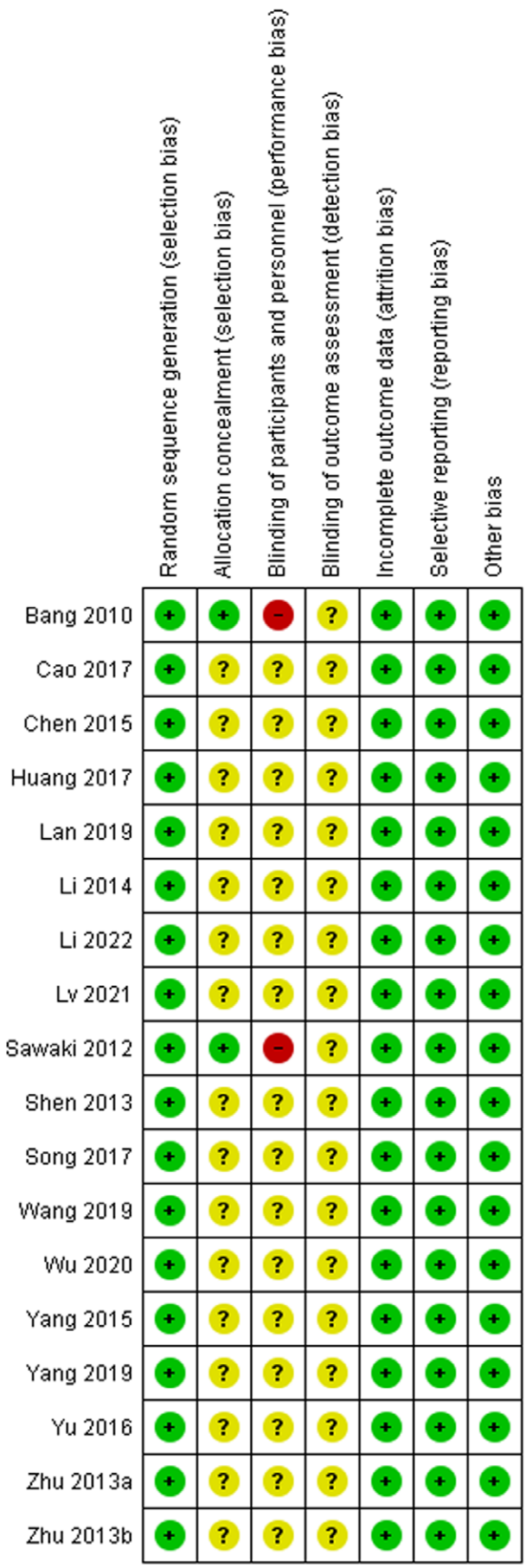

Figure 2. Risk of bias summary.

2.6. Study methodological quality assessment

Two reviewers independently appraised the methodological quality of each eligible trial using the Cochrane Risk of Bias Tool. This tool had 7 aspects, and each one was rated as "high risk of bias", "unclear risk of bias", or "low risk of bias". Any differences were resolved by a third experienced reviewer through a discussion or consultation.

2.7. Statistical analysis

This study utilized the RevMan 5.4 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) for data analysis. The treatment effect of dichotomous data was calculated as the risk ratio and 95% confidence interval (CI), while that of continuous data was estimated as the MD and 95% CI. I^2 statistics were utilized to identify heterogeneity across eligible trials. I^2 ≤50% indicated reasonable heterogeneity and a random-effects model was applied, whereas I^2 >50% exerted remarkable heterogeneity and a random-effects model was used. If insufficient data were available, we performed a meta-analysis. We reported the results of a narrative and descriptive summary if insufficient data were pooled.

3. Results

3.1. Study selection

A total of 759 records were identified from electronic databases and other sources using the previously defined search criteria. After duplications were excluded, the titles and abstracts of the potential records were screened, and the remaining full-text articles were carefully read. Finally, 18 RCTs, including 1964 patients, were eligible for inclusion (Fig. 1).

3.2. General characteristics

The intervention and control arms included capecitabine or 5-fluorouracil plus cisplatin (CFC), oxaliplatin plus tegafur (OT), capecitabine plus cisplatin (CC), irinotecan and cisplatin (IC), oxaliplatin and leucovorin (OL), cyclophosphamide, azithromycin and 5-fluorouracil (CAF), oxaliplatin and 5-fluorouracil (OF), and docetaxel, cisplatin, and 5-fluorouracil (DCF) in combination with or without trastuzumab. The main characteristics of the included RCTs are summarized in Table 2.

3.3. Study quality assessment

The methodological quality of the 18 included trials was assessed using the Cochrane risk of bias tool (Fig. 2). All 18 studies reported sufficient information on random sequence generation, incomplete outcomes, selective reporting, and other bias.[32–49] However, only 2 studies reported details of allocation concealment and insufficient details of the blinding of participants and investigators.[32,40] In addition, none of the 18 studies clearly reported blinding to outcome assessors clearly[32–49] (Fig. 2).

3.4. Comparison between trastuzumab in combination with CFC and CFC

Three studies with 769 patients compared the efficacy and safety of trastuzumab in combination with CFC and CFC. Meta-analysis results showed that there were significant differences on response rate (odds ratio [OR] = 1.56, 95% confidence interval [CI] [1.17, 2.09], I^2 = 0%, P < .003; Table 3, Fig. 3),[32,40,41] and disease control rate (OR = 1.61, 95% CI [1.17, 2.21], I^2 = 0%, P = .004; Table 3, Fig. 3).[32,40,41] Meta-analysis results of overall survival rate showed at

Table 3

Qualitative synthesis of comparison between trastuzumab plus CFC and CFC.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
1.1 Efficacy				
1.1.1 Response rate	3	769	Odds ratio (M-H, fixed, 95% CI)	1.56 (1.17–2.09)
1.1.2 Disease control rate	3	769	Odds ratio (M-H, fixed, 95% CI)	1.61 (1.17–2.21)
1.2 Survival rate at different follow-up visits	2		Odds ratio (M-H, fixed, 95% CI)	Subtotals only
1.2.1 6 months	2	685	Odds ratio (M-H, fixed, 95% CI)	1.37 (0.98–1.92)
1.2.2 12 months	2	685	Odds ratio (M-H, fixed, 95% CI)	1.36 (0.99–1.87)
1.2.3 18 months	2	685	Odds ratio (M-H, fixed, 95% CI)	1.56 (1.04–2.32)
1.2.4 24 months	2	685	Odds ratio (M-H, fixed, 95% CI)	1.39 (0.82–2.36)
1.3 Occurrence rate of adverse events				
1.3.1 Neutropenia	3	769	Odds ratio (M-H, fixed, 95% CI)	0.89 (0.67–1.19)
1.3.2 Leukopenia	3	769	Odds ratio (M-H, fixed, 95% CI	1.91 (0.93–3.92)
1.3.3 Nausea	3	769	Odds ratio (M-H, fixed, 95% CI	1.17 (0.85–1.61)
1.3.4 Vomiting	3	769	Odds ratio (M-H, fixed, 95% CI	1.24 (0.92–1.66)
1.3.5 Diarrhea	3	769	Odds ratio (M-H, fixed, 95% CI	1.43 (1.04–1.96)
1.3.6 Neurotoxicity	2	185	Odds ratio (M-H, fixed, 95% CI	1.05 (0.47–2.37)
1.3.7 Rash	2	185	Odds ratio (M-H, fixed, 95% CI	1.77 (0.62–5.06)
1.3.8 Hand-foot syndrome	2	668	Odds ratio (M-H, fixed, 95% CI	1.19 (0.82–1.74)

CFC = capecitabine or 5-fluorouracil + cisplatin; CI = confidence interval.

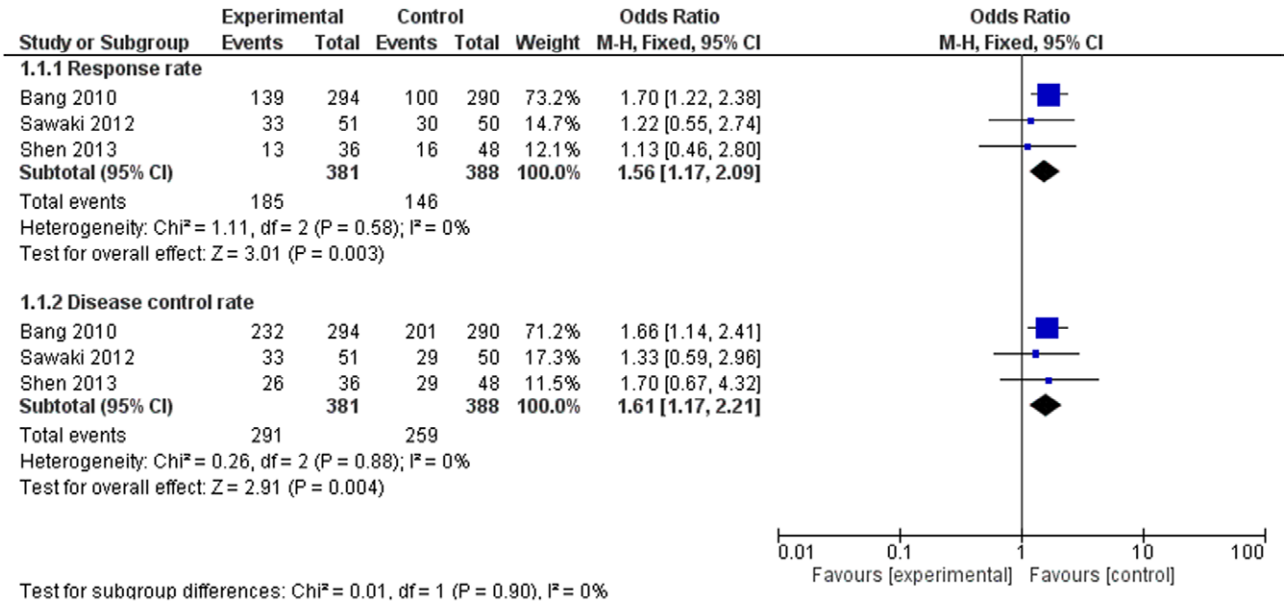

Figure 3. Trastuzumab plus CFC vs CFC: meta-analysis of response rate and disease control rate. CFC = capecitabine or 5-fluorouracil+cisplatin, CI = confidence interval.

6 months (OR = 1.37, 95% CI [0.98–1.92], I^2 = 0%, P = .07), 12 months (OR = 1.36, 95% CI [0.99–1.87], I^2 = 0%, P = .05), 18 months (OR = 1.56, 95% CI [1.04–2.32], I^2 = 62%, P = .03), and 24 months (OR = 1.39, 95% CI [0.82–2.36], I^2 = 0%, P = .22; Table 3, Fig. 4).[32,40] As for safety, meta-analysis results showed that no significant differences were identified on occurrence rate of adverse events: neutropenia (OR = 0.89, 95% CI [0.67–1.19], I^2 = 7%, P = .44),[32,40,41] leukopenia (OR = 1.91, 95% CI [0.93–3.92], I^2 = 0%, P = .08),[32,40,41] nausea (OR = 1.17, 95% CI [0.85–1.61], I^2 = 0%, P = .35),[32,40,41] vomiting (OR = 1.24, 95% CI [0.92– 1.66], I^2 = 0%, P = .16),[32,40,41] diarrhea (OR = 1.43, 95% CI [1.04–1.96], I^2 = 0%, P = .03),[32,40,41] neurotoxicity (OR = 1.05, 95% CI [0.47–2.37], I^2 = 0%, P = .90),[40,41] rash (OR = 1.77, 95% CI [0.62–5.06], I^2 = 0%, P = .28),[40,41] and hand-foot syndrome (OR = 1.19, 95% CI [0.82–1.74], I^2 = 0%, P = .36)[32,41] (Table 3, Fig. 5).

3.5. Comparison between trastuzumab in combination with OT and OT

Five studies with 235 patients compared the efficacy and safety of trastuzumab in combination with OT and OT. Meta-analysis results showed that there were significant differences in response rate (OR = 2.97, 95% CI [1.74–5.09], I^2 = 0%, P < .0001; Table 4, Fig. 6)[33,34,37,42,45] and disease control rate (OR = 4.29, 95% CI [2.33–7.90], I^2 = 0%, P < .0001; Table 4, Fig. 6).[32,40,41] However, meta-analysis results of safety showed that no significant differences were identified on nausea and vomiting (OR = 0.66, 95% CI [0.30–1.47], I^2 = 0%, P = .31),[32,45] diarrhea (OR = 1.23, 95% CI [0.50–3.03], I^2 = 0%, P = .65),[34,45] liver function impairment (OR = 0.91, 95% CI [0.38–2.15], I^2 = 0%, P = .83),[33,34,45] neurotoxicity (OR = 0.85, 95% CI [0.44–1.63], I^2 = 0%, P = .62),[33,34,45] and

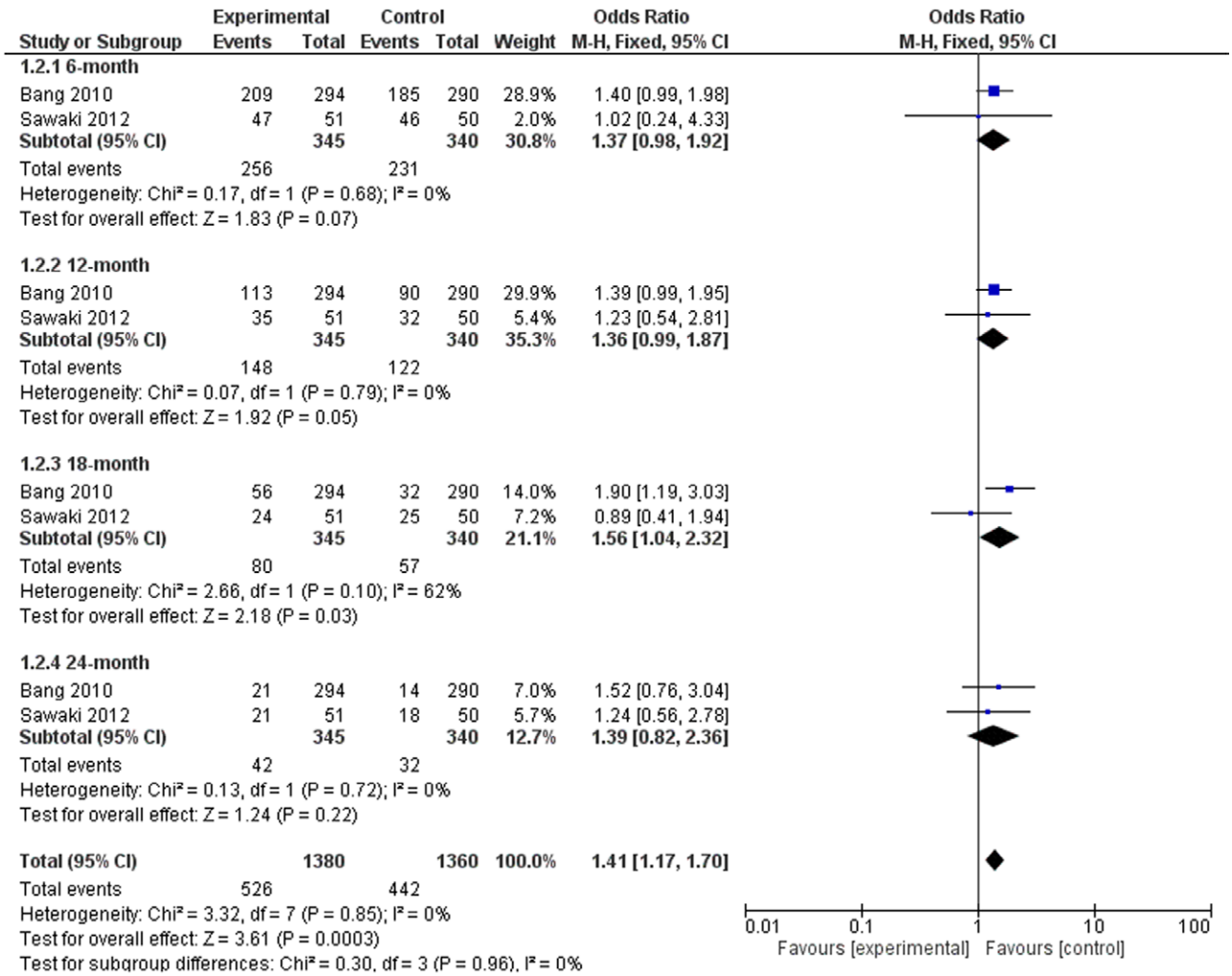

Figure 4. Trastuzumab plus CFC vs CFC: overall survival rate at different follow-up visits. CFC = capecitabine or 5-fluorouracil+cisplatin, CI = confidence interval.

cardiac toxicity (OR = 1.00, 95% CI [0.22–4.55], I^2 = 0%, P = 1.00)[33,34,45] (Table 4, Fig. 7).

3.6. Comparison between trastuzumab in combination with CC and CC

Five studies with 560 patients compared the efficacy and safety of trastuzumab in combination with CC and CC. Meta-analysis results showed that there were significant differences in response rate (OR = 2.62, 95% CI [1.84–3.73], I^2 = 0%, P < .0001, Table 5, Fig. 8),[35,38,39,44,46] and disease control rate (OR = 2.99, 95% CI [1.99–4.48], I^2 = 0%, P < .0001; Table 5, Fig. 8).[35,38,39,44,46] However, meta-analysis results of safety showed that there were no significant differences on nausea and vomiting (OR = 1.03, 95% CI [0.64–1.67], I^2 = 0%, P = .90),[35,38,39,44,46] liver function impairment (OR = 1.08, 95% CI [0.70–1.66], I^2 = 0%, P = .74),[35,38,39,44,46] myelosuppression (OR = 1.08, 95% CI [0.77–1.52], I^2 = 0%, P = .66),[35,38,39,44,46] and hand-foot syndrome (OR = 1.09, 95% CI [0.73–1.62], I^2 = 0%, P = .69)[35,38,39,44] (Table 5, Fig. 9). One study explored the efficacy on overall survival (mean difference [MD] = 2.62, 95% CI [1.94–3.30], P < .001; Table 5), and progression-free survival (MD = 3.8, 95% CI [3.22–4.38], I^2 = 99%, P < .001; Table 5).[44]

3.7. Comparison between trastuzumab in combination with IC and IC

One study with 78 patients compared the efficacy and safety of trastuzumab in combination with IC and IC on efficacy (response rate, disease control rate) and safety (nausea and vomiting, liver function impairment, myelosuppression, and hand-foot syndrome; Table 6).[36]

3.8. Comparison between trastuzumab in combination with OL and OL

One study with 70 patients compared the efficacy and safety of trastuzumab in combination with OL and OL on efficacy (response rate and disease control rate) and safety (leukopenia, nausea and vomiting, liver function impairment, neurotoxicity, cardiac toxicity, and rash; Table 7).[36]

3.9. Comparison between trastuzumab in combination with CAF and CAF

One study with 96 patients investigated the efficacy and safety of trastuzumab in combination with CAF and CAF on efficacy

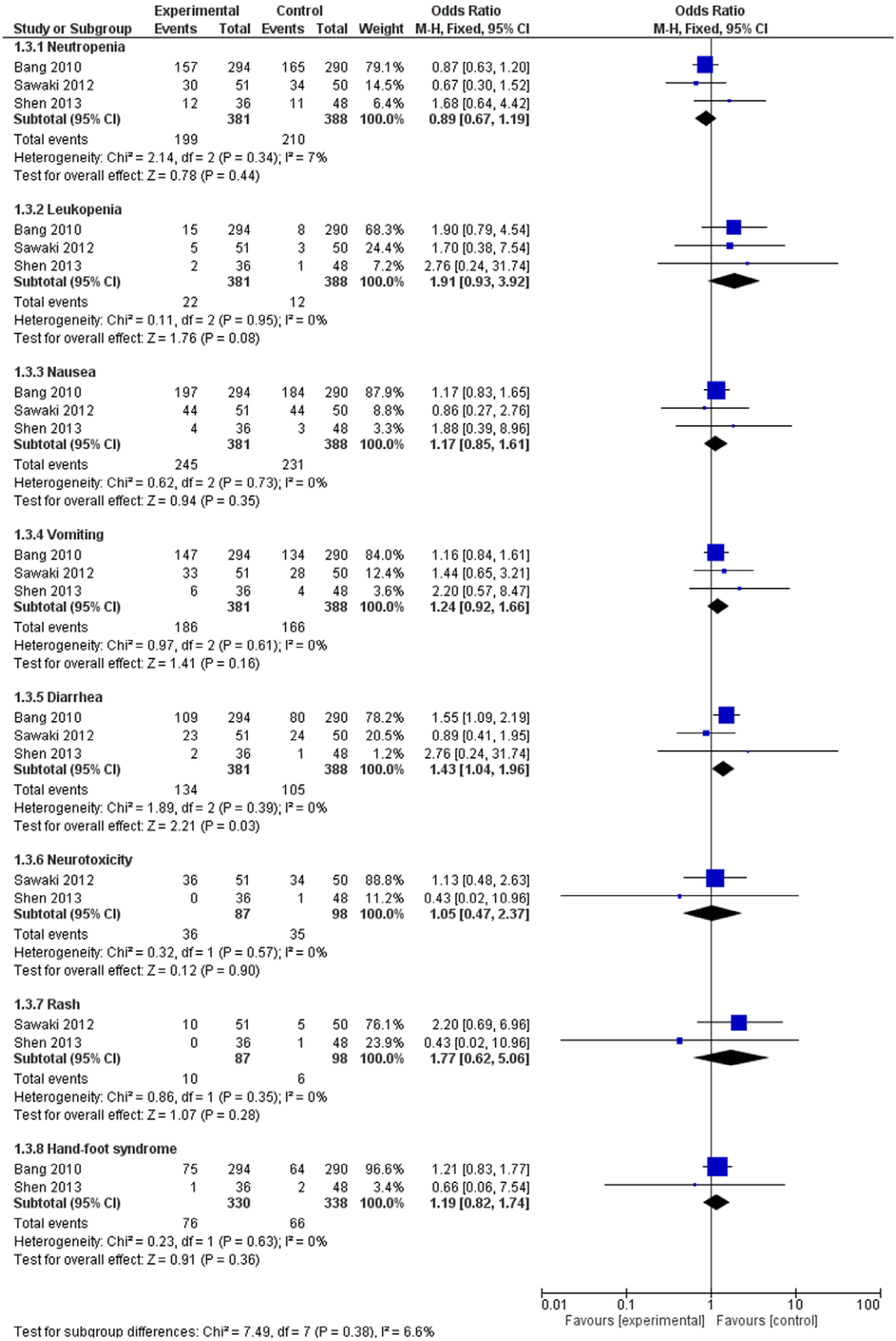

Figure 5. Trastuzumab plus CFC vs CFC: occurrence rate of adverse events. CFC = capecitabine or 5-fluorouracil+cisplatin, CI = confidence interval.

Table 4

Qualitative synthesis of comparison between trastuzumab plus OT and OT.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
2.1 Efficacy				
2.1.1 Response rate	5	235	Odds ratio (M-H, fixed, 95% CI)	2.97 (1.74–5.09)
2.1.2 Disease control rate	5	235	Odds ratio (M-H, fixed, 95% CI)	4.29 (2.33–7.90)
2.2 Occurrence rate of adverse events				
2.2.1 Nausea and vomiting	2	98	Odds ratio (M-H, fixed, 95% CI)	0.66 (0.30–1.47)
2.2.2 Diarrhea	2	98	Odds ratio (M-H, fixed, 95% CI	1.23 (0.50–3.03)
2.2.3 Liver function impairment	3	146	Odds ratio (M-H, fixed, 95% CI	0.91 (0.38–2.15)
2.2.4 Neurotoxicity	3	146	Odds ratio (M-H, fixed, 95% CI	0.85 (0.44–1.63)
2.2.5 Cardiac toxicity	3	146	Odds ratio (M-H, fixed, 95% CI	1.00 (0.22–4.55)

CI = confidence interval, OT = oxaliplatin + tegafur.

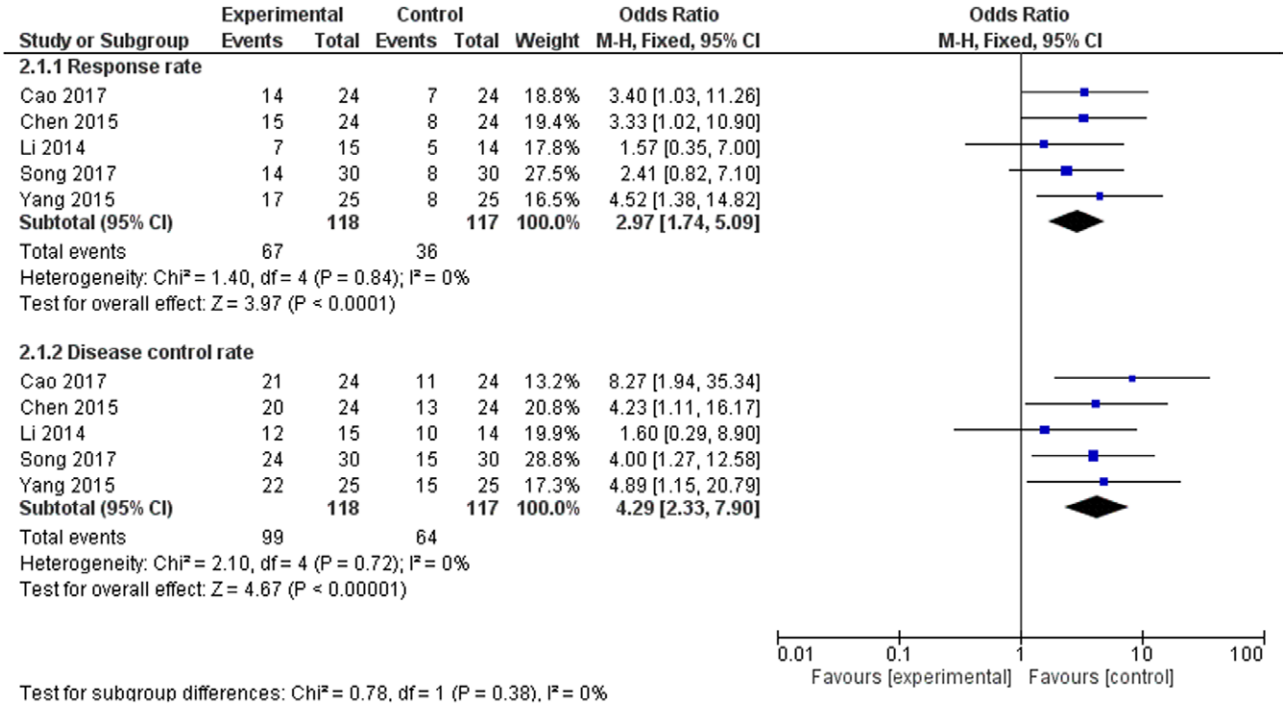

Figure 6. Trastuzumab plus OT vs OT: meta-analysis of response rate and disease control rate. CI = confidence interval, OT = oxaliplatin+tegafur.

(response rate and disease control rate) and safety (leukopenia, nausea and vomiting, liver function impairment, and neurotoxicity; Table 8).[47]

3.10. Comparison between trastuzumab in combination with OF and OF

One study with 84 patients explored the efficacy and safety of trastuzumab in combination with OF and OF on efficacy (response rate and disease control rate) and safety (liver function impairment, neurotoxicity, cardiac toxicity, rash, and myelosuppression; Table 9).[48]

3.11. Comparison between trastuzumab in combination with DCF and DCF

One study with 72 patients assessed the efficacy and safety of trastuzumab in combination with DCF and DCF on efficacy (response rate, disease control rate, overall survival rate at 6, 12, 18, and 24 months, and mean survival of death) and safety (neutropenia, neurotoxicity, cardiac toxicity, and rash; Table 10).[49]

4. Discussion

Previous studies have explored the efficacy of trastuzumab combined with chemotherapy for the management of HER2-PAGC.[50–52] Of these 3 systematic reviews and meta-analyses, the latest one was published in 2019, and its literature search date was up to November 2017.[51] In addition, the overall methodological quality of the included trials was very poor.[50–52] In this study, we included and updated more recent clinical studies[36,38,39,43,44] than previous systematic reviews and meta-analyses.[50–52] Additionally, the overall quality of the trials in this study was higher than that of previous studies.[50–52]

This systematic review and meta-analysis included 18 RCTs with 1964 patients, and focused on investigating the efficacy of trastuzumab in combination with chemotherapy for the treatment of patients with HER2-PAGC. It summarizes the most recent evidence on eligible trials and appraises their methodological quality. Whenever available, outcome data were synthesized to provide helpful evidence-based medical evidence and bridge this gap in research in this field.

Meta-analysis results showed that trastuzumab in combination with CFC, OT, and CC achieved better outcomes in response and disease control rates than CFC, OT, and CC alone.

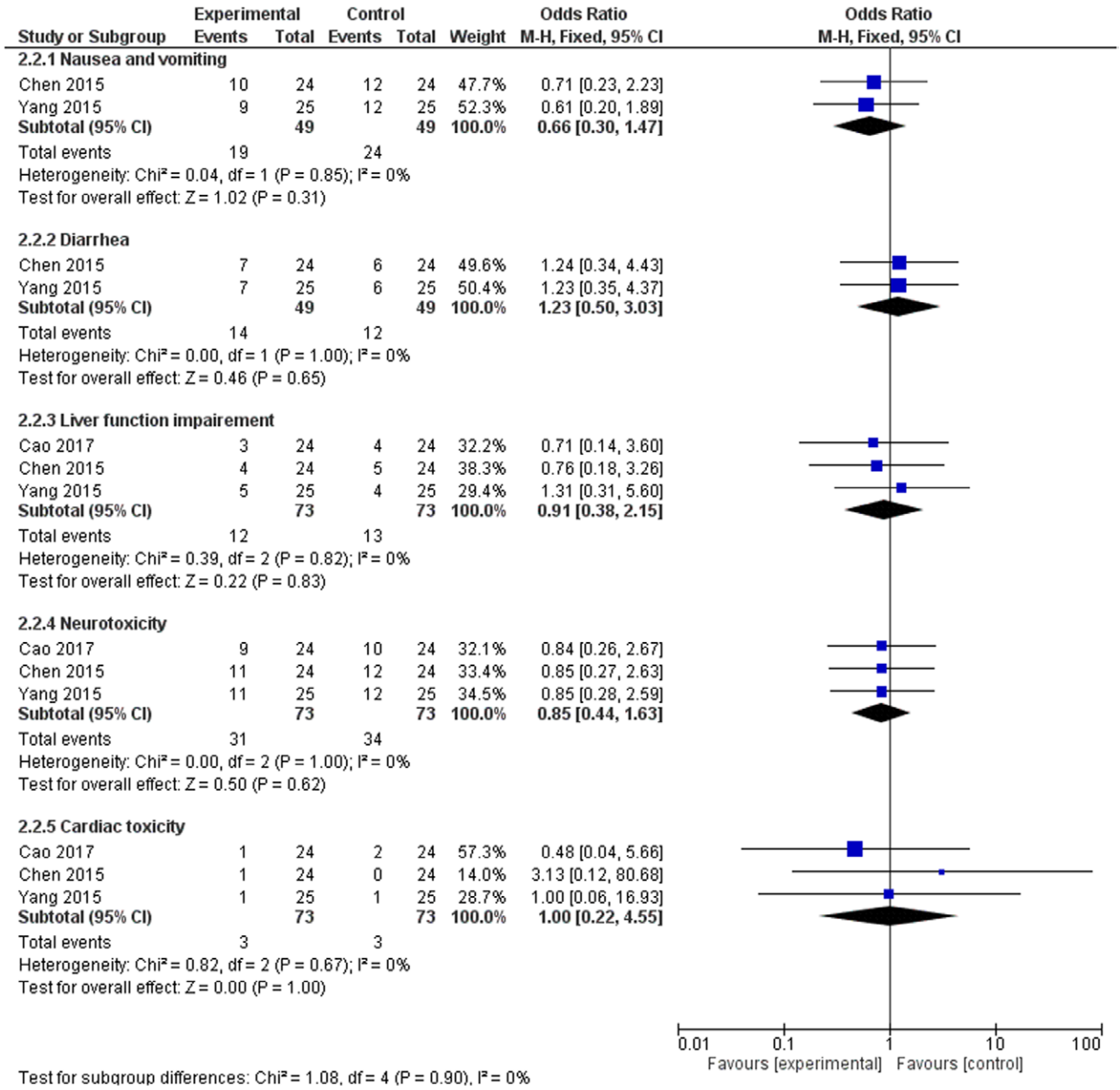

Figure 7. Trastuzumab plus OT vs OT: occurrence rate of adverse events. CI = confidence interval, OT = oxaliplatin+tegafur.

Table 5

Qualitative synthesis of comparison between trastuzumab plus CC and CC.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
3.1 Efficacy				
3.1.1 Response rate	5	560	Odds ratio (M-H, fixed, 95% CI)	2.62 (1.84–3.73)
3.1.2 Disease control rate	5	560	Odds ratio (M-H, fixed, 95% CI)	2.99 (1.99–4.48)
3.2 Efficacy				
3.2.1 Overall survival	1	126	Mean difference (IV, fixed, 95% CI)	2.62 (1.94–3.30)
3.2.2 Progression-free survival	1	126	Mean difference (IV, fixed, 95% CI)	3.80 (3.22–4.38)
3.3 Occurrence rate of adverse events				
3.3.1 Nausea and vomiting	5	560	Odds ratio (M-H, fixed, 95% CI)	1.03 (0.64–1.67)
3.3.2 Liver function impairment	5	560	Odds ratio (M-H, fixed, 95% CI	1.08 (0.70–1.66)
3.3.3 Myelosuppression	5	560	Odds ratio (M-H, fixed, 95% CI	1.08 (0.77–1.52)
3.3.4 Hand-foot syndrome	4	482	Odds ratio (M-H, fixed, 95% CI	1.09 (0.73–1.62)

CC = capecitabine + cisplatin, CI = confidence interval.

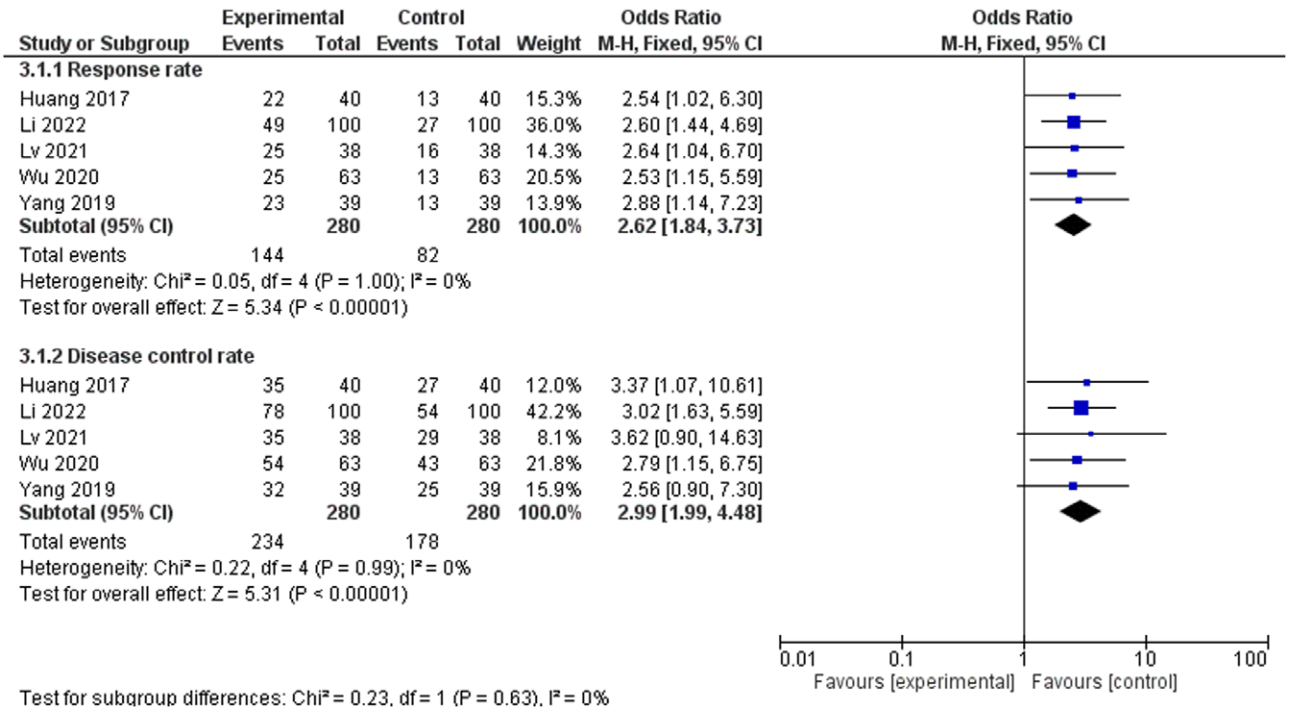

Figure 8. Trastuzumab plus CC vs CC: meta-analysis of response rate and disease control rate. CC = capecitabine+cisplatin, CI = confidence interval.

However, there were no significant differences in the occurrence rates of neutropenia, leukopenia, nausea and vomiting, diarrhea, liver function impairment, neurotoxicity, cardiac toxicity, rash, myelosuppression, or hand-foot syndrome. These findings indicate that trastuzumab combined with chemotherapy may have a more promising efficacy than chemotherapy alone, with a similar safety profile.

This systematic review and meta-analysis had several limitations: there was an insufficient number of eligible trials with the same combined chemotherapy; the sample size of some included studies was quite small, and their effectiveness was limited; and there was an unclear risk of bias in allocation and blinding to patients, investigators, and outcome assessors, which affected the overall quality of the included RCTs. Future studies should address these limitations.

5. Conclusion

The results of this study showed that the efficacy of trastuzumab combined with chemotherapy is superior to that of chemotherapy alone. Both modalities showed similar safety profiles.

References

[1] Yang L, Ying X, Liu S, et al. Gastric cancer: epidemiology, risk factors and prevention strategies. Chin J Cancer Res. 2020;32:695–704.
[2] Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893–917.
[3] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2001;61:69–90.
[4] Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 2017;3:524–48.
[5] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
[6] Patel TH, Cecchini M. Targeted therapies in advanced gastric cancer. Curr Treat Options Oncol. 2020;21:70.
[7] Leiting JL, Grotz TE. Advancements and challenges in treating advanced gastric cancer in the West. World J Gastrointest Oncol. 2019;11:652–64.
[8] Tan Z. Recent advances in the surgical treatment of advanced gastric cancer: a review. Med Sci Monit. 2019;25:3537–41.
[9] Fugazzola P, Ansaloni L, Sartelli M, et al. Advanced gastric cancer: the value of surgery. Acta Biomed. 2018;89(8-S):110–6.
[10] Wei B, Wei H. Surgical treatment strategy for advanced gastric cancer. Chin J Gastrointest Surg. 2018;21:1099–102.
[11] Marano L, Polom K, Patriti A, et al. Surgical management of advanced gastric cancer: an evolving issue. Eur J Surg Oncol. 2016;42:18–27.
[12] Wagner AD, Syn NL, Moehler M, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2017;8:CD004064.
[13] van Cutsem E, Sagaert X, Topal B, et al. Gastric cancer. Lancet. 2016;388:2654–64.
[14] Fujitani K, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol. 2016;17:309–18.
[15] Yamada Y, Higuchi K, Nishikawa K, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naive patients with advanced gastric cancer. Ann Oncol. 2015;26:141–8.
[16] Kotani D, Shitara K. Trastuzumab deruxtecan for the treatment of patients with HER2-positive gastric cancer. Ther Adv Med Oncol. 2021;13:1758835920986518.
[17] Bouché O, Penault-Llorca F. HER2 and gastric cancer: a novel therapeutic target for trastuzumab. Bull Cancer. 2010;97:1429–40.
[18] Croxtall JD, McKeage K. Trastuzumab: in HER2-positive metastatic gastric cancer. Drugs. 2010;70:2259–67.
[19] Fujimoto-Ouchi K. Current status and prospects of antibody drugs-trastuzumab. Nihon Yakurigaku Zasshi. 2010;136:210–4.
[20] Meza-Junco J, Au HJ, Sawyer MB. Trastuzumab for gastric cancer. Expert Opin Biol Ther. 2009;9:1543–51.
[21] Akbari V, Chou CP, Abedi D. New insights into affinity proteins for HER2-targeted therapy: beyond trastuzumab. Biochim Biophys Acta Rev Cancer. 2020;1874:188448.
[22] Cortés J, Diéras V, Lorenzen S, et al. Efficacy and safety of trastuzumab emtansine plus capecitabine vs trastuzumab emtansine alone in patients with previously treated ERBB2 (HER2)-positive metastatic breast cancer: a phase 1 and randomized phase 2 trial. JAMA Oncol. 2020;6:1203–9.

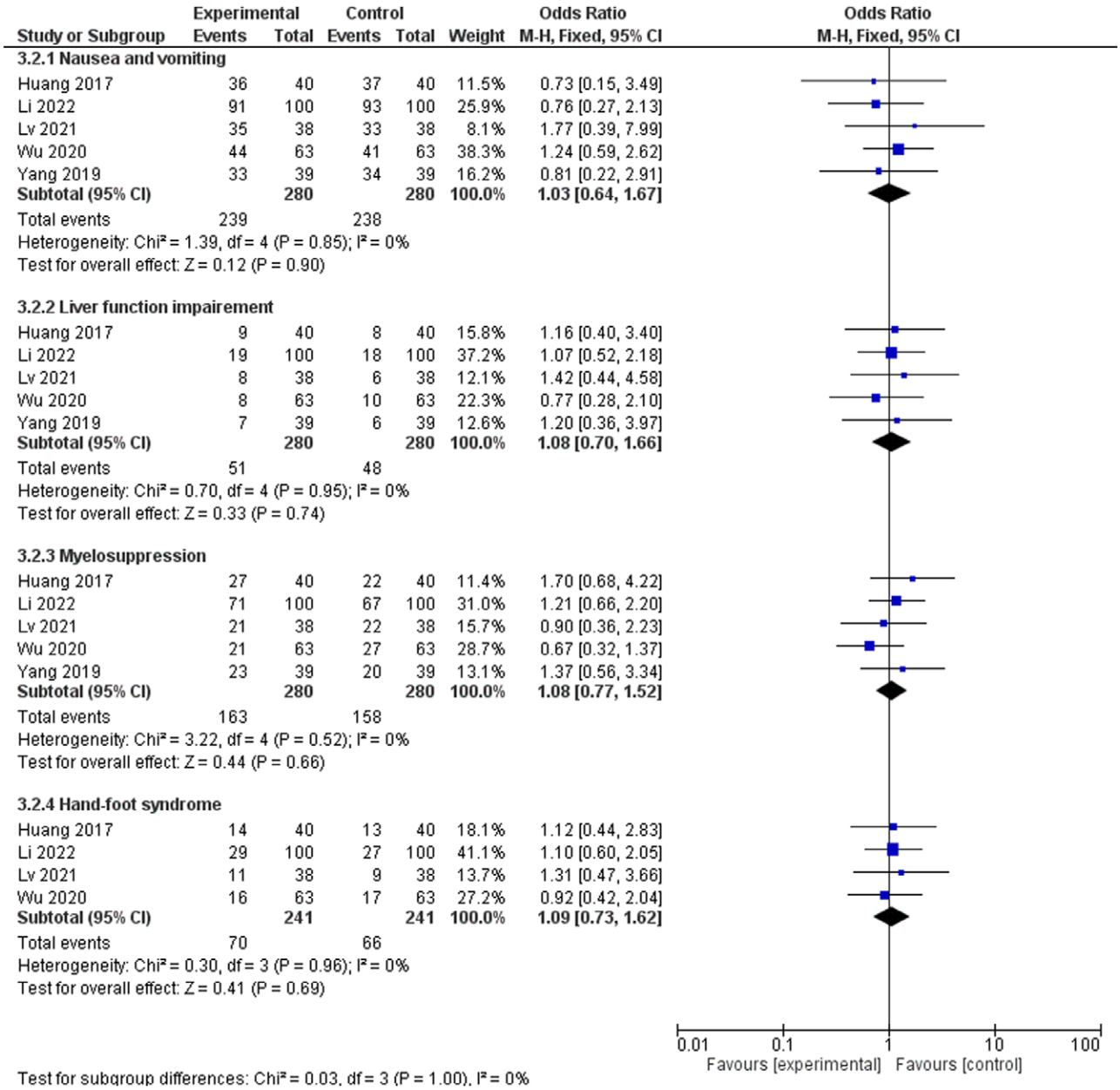

Figure 9. Trastuzumab plus CC vs CC: occurrence rate of adverse events. CC = capecitabine+cisplatin, CI = confidence interval.

Table 6

Qualitative synthesis of comparison between trastuzumab plus IC and IC.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
4.1 Efficacy				
4.1.1 Response rate	1	78	Odds ratio (M-H, fixed, 95% CI)	2.59 (1.03–6.49)
4.1.2 Disease control rate	1	78	Odds ratio (M-H, fixed, 95% CI)	3.60 (0.89–14.51)
4.2 Occurrence rate of adverse events				
4.2.1 Nausea and vomiting	1	78	Odds ratio (M-H, fixed, 95% CI)	0.73 (0.15–3.50)
4.2.2 Liver function impairment	1	78	Odds ratio (M-H, fixed, 95% CI	1.16 (0.40–3.41)
4.2.3 Myelosuppression	1	78	Odds ratio (M-H, fixed, 95% CI	1.48 (0.54–4.06)
4.2.4 Hand-foot syndrome	1	78	Odds ratio (M-H, fixed, 95% CI	1.18 (0.38–3.65)

CI = confidence interval, IC = irinotecan + cisplatin.

Table 7

Qualitative synthesis of comparison between trastuzumab plus OL and OL.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
5.1 Efficacy				
5.1.1 Response rate	1	70	Odds ratio (M-H, fixed, 95% CI)	2.00 (0.77–5.18)
5.1.2 Disease control rate	1	70	Odds ratio (M-H, fixed, 95% CI)	1.83 (0.61–5.47)
5.2 Occurrence rate of adverse events				
5.2.1 Leukopenia	1	70	Odds ratio (M-H, fixed, 95% CI	1.50 (0.43–5.28)
5.2.2 Nausea and vomiting	1	70	Odds ratio (M-H, fixed, 95% CI	1.26 (0.49–3.22)
5.2.3 Liver function impairment	1	70	Odds ratio (M-H, fixed, 95% CI	0.49 (0.04–5.61)
5.2.4 Neurotoxicity	1	70	Odds ratio (M-H, fixed, 95% CI	0.52 (0.14–1.95)
5.2.5 Cardiac toxicity	1	70	Odds ratio (M-H, fixed, 95% CI	5.67 (0.63–51.27)
5.2.6 Rash	1	70	Odds ratio (M-H, fixed, 95% CI	4.89 (0.96–24.97)

CI = confidence interval, OL = oxaliplatin + leucovorin.

Table 8

Qualitative synthesis of comparison between trastuzumab plus CAF and CAF.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
6.1 Efficacy				
6.1.1 Response rate	1	96	Odds ratio (M-H, fixed, 95% CI)	2.14 (0.95–4.83)
6.1.2 Disease control rate	1	96	Odds ratio (M-H, fixed, 95% CI)	1.84 (0.61–5.55)
6.2 Occurrence rate of adverse events				
6.2.1 Leukopenia	1	96	Odds ratio (M-H, fixed, 95% CI	1.36 (0.29–6.45)
6.2.2 Nausea and vomiting	1	96	Odds ratio (M-H, fixed, 95% CI	0.60 (0.22–1.63)
6.2.3 Liver function impairment	1	96	Odds ratio (M-H, fixed, 95% CI	1.28 (0.32–5.09)
6.2.4 Neurotoxicity	1	96	Odds ratio (M-H, fixed, 95% CI	0.65 (0.22–1.88)

CAF = cyclophosphamide + azithromycin + 5-fluorouracil, CI = confidence intervals.

Table 9

Qualitative synthesis of comparison between trastuzumab plus OF and OF.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
7.1 Efficacy				
7.1.1 Response rate	1	84	Odds ratio (M-H, fixed, 95% CI)	2.37 (0.98–5.69)
7.1.2 Mean survival months of death	1	84	Mean difference (IV, fixed, 95% CI)	2.30 (1.04–3.56)
7.2 Occurrence rate of adverse events				
3.3.1 Liver function impairment	1	84	Odds ratio (M-H, fixed, 95% CI)	1.41 (0.58–3.41)
3.3.2 Neurotoxicity	1	84	Odds ratio (M-H, fixed, 95% CI	0.78 (0.29–2.09)
3.3.3 Cardiac toxicity	1	84	Odds ratio (M-H, fixed, 95% CI	7.38 (0.87–62.90)
3.3.4 Rash	1	84	Odds ratio (M-H, fixed, 95% CI	4.11 (1.06–16.02)
3.3.3 Myelosuppression	1	84	Odds ratio (M-H, fixed, 95% CI	1.43 (0.59–3.46)

CI = confidence interval, OF = oxaliplatin + 5-fluorouracil.

Table 10

Qualitative synthesis of comparison between trastuzumab plus DCF and DCF.

Outcome or subgroup	Studies	Participants	Statistical method	Effect estimate
9.1 Efficacy				
9.1.1 Response rate	1	72	Odds ratio (M-H, fixed, 95% CI)	2.46 (0.95–6.37)
9.1.2 Disease control rate	1	72	Odds ratio (M-H, fixed, 95% CI)	2.83 (0.67–11.98)
9.2 Survival rate at different follow-up visits				
9.2.1 6 months	1	72	Odds ratio (M-H, fixed, 95% CI)	3.26 (0.13–82.75)
9.2.2 12 months	1	72	Odds ratio (M-H, fixed, 95% CI)	1.75 (0.67–4.57)
9.2.3 18 months	1	72	Odds ratio (M-H, fixed, 95% CI)	2.64 (0.99–7.01)
9.2.4 24 months	1	72	Odds ratio (M-H, fixed, 95% CI)	3.05 (1.06–8.74)
9.3 Mean survival months of death	1	72	Mean difference (IV, fixed, 95% CI)	2.20 (1.06–3.34)
9.4 Occurrence rate of adverse events				
9.4.1 Neutropenia	1	72	Odds ratio (M-H, fixed, 95% CI)	1.42 (0.56–3.62)
9.4.2 Neurotoxicity	1	72	Odds ratio (M-H, fixed, 95% CI	1.13 (0.34–3.76)
9.4.3 Cardiac toxicity	1	72	Odds ratio (M-H, fixed, 95% CI	9.54 (0.49–183.98)
9.4.4 Rash	1	72	Odds ratio (M-H, fixed, 95% CI	1.16 (0.32–4.21)

CI = confidence interval, DCF = docetaxel + cisplatin + 5-fluorouracil.

[23] Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382:2419–30.
[24] Yuki S, Shinozaki K, Kashiwada T, et al. Multicenter phase II study of SOX plus trastuzumab for patients with HER2(+) metastatic or recurrent gastric cancer: KSCC/HGCSG/CCOG/PerSeUS 1501B. Cancer Chemother Pharmacol. 2020;85:217–23.
[25] Shitara K, Honma Y, Omuro Y, et al. Efficacy of trastuzumab emtansine in Japanese patients with previously treated HER2-positive locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma: a subgroup analysis of the GATSBY study. Asia Pac J Clin Oncol. 2020;16:5–13.
[26] Takahari D, Chin K, Ishizuka N, et al. Multicenter phase II study of trastuzumab with S-1 plus oxaliplatin for chemotherapy-naive, HER2-positive advanced gastric cancer. Gastric Cancer. 2019;22:1238–46.
[27] Shitara K, Iwata H, Takahashi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. Lancet Oncol. 2019;20:827–36.
[28] Kimura Y, Fujii M, Masuishi T, et al. Multicenter phase II study of trastuzumab plus S-1 alone in elderly patients with HER2-positive advanced gastric cancer (JACCRO GC-06). Gastric Cancer. 2018;21:421–7.
[29] Kataoka H, Mori Y, Shimura T, et al. A phase II prospective study of the trastuzumab combined with 5-weekly S-1 and CDDP therapy for HER2-positive advanced gastric cancer. Cancer Chemother Pharmacol. 2016;77:957–62.
[30] Gong J, Liu T, Fan Q, et al. Optimal regimen of trastuzumab in combination with oxaliplatin/ capecitabine in first-line treatment of HER2-positive advanced gastric cancer (CGOG1001): a multicenter, phase II trial. BMC Cancer. 2016;16:68.
[31] Chua C, Tan IB, Yamada Y, et al. Phase II study of trastuzumab in combination with S-1 and cisplatin in the first-line treatment of human epidermal growth factor receptor HER2-positive advanced gastric cancer. Cancer Chemother Pharmacol. 2015;76:397–408.
[32] Bang YJ, Cutsem EV, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97.
[33] Cao RH, Su WY, Hu Q, et al. The clinical efficacy of trastuzumab and SOX regimen in the treatment of HER-2 positive advanced gastric cancer. Prog Modern Biomed. 2017;17:680–3.
[34] Chen HZ, Pang LR, Chen J. A clinical study of trastuzumab combined with SOX regimen in the treatment of advanced gastric cancer. Modern Pract Med. 2015;27:335–7.
[35] Huang F, Gao F. The short-term and long-term efficacy of HER2-positive trastuzumab in the treatment of advanced gastric cancer and its effect on tumor markers. J Pract Cancer. 2017;32:26:2014–6.
[36] Lan H, Xie YR, Zhou YF, et al. The effect of trastuzumab adjuvant chemotherapy on the expression of P53 and EGFR in HER-2 positive advanced gastric cancer. Modern Chin Doc. 2019;57:36–8.
[37] Li P, Fan LX, Zhang YM. Analysis of the efficacy of trastuzumab combined with oxaliplatin and Teggio in the treatment of Her-2 positive advanced gastric cancer. J Chin Med. 2014;B12:491.
[38] Li H, Shi CS. Safety of trastuzumab adjuvant therapy for HER2-positive advanced gastric cancer and its effect on serum tumor markers. J Changchun Univ Chin Med. 2022;38:88–92.
[39] Lv L, Guo LY, Wei WH. The clinical efficacy of trastuzumab chemotherapy combined with XP chemotherapy in the treatment of human Egfr 2 positive advanced gastric cancer. Chin Foreign Med Res. 2021;19:151–3.
[40] Sawaki A, Ohashi Y, Omuro Y, et al. Efficacy of trastuzumab in Japanese patients with HER2-positive advanced gastric or gastroesophageal junction cancer: a subgroup analysis of the trastuzumab for gastric cancer (ToGA) study. Gastric Cancer. 2012;118:313–22.
[41] Shen L, Xu JM, Feng FY, et al. A multicenter, randomized, controlled, phase III trial of trastuzumab chemotherapy in the first-line treatment of EGFR, inoperable locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction in a Chinese subgroup is reported. Chin J Oncol. 2013;35:295–300.
[42] Song ZG, Zhang X, Wang JD, et al. The effect of tegafur+oxaliplatin trastuzumab on HER-2-positive patients with advanced gastric cancer. Chin J Integr Trad Western Med Dig. 2017;10:730–3.
[43] Wang YY, Guo LB, Tan SY. The efficacy and safety of trastuzumab and Folfox regimen in the treatment of HER-2 positive advanced gastric cancer. Modern Med. 2019;47:170–4.
[44] Wu JY, Xie YR. The efficacy of trastuzumab combined with capecitabine and cisplatin in the treatment of HER2-positive advanced gastric cancer. Clin Educ Gen Pract Med. 2020;18:10–3.
[45] Yang YW, Zheng JC, Chen F, et al. To evaluate the efficacy of trastuzumab and SOX regimen in the treatment of advanced gastric cancer. China Continuing Medical Education. 2015;30:148–9.
[46] Yang GY. The clinical efficacy of trastuzumab chemotherapy combined with XP chemotherapy in the treatment of HER2-positive advanced gastric cancer. Henan Med Res. 2019;28:1648–50.
[47] Yu XL, Li F, Liu J. Clinical evaluation of CAF chemotherapy regimen, trastuzumab and emotional intervention in the treatment of gastric cancer. China Pharm. 2016;20:39–41.
[48] Zhu LB, Ma R, Li LL, et al. The clinical efficacy of trastuzumab combined with oxaliplatin and 5-fluorouracil in the treatment of advanced gastric cancer with high expression of HER-2 NEU. Chin J Difficult and Complicated Cases. 2013;12:930–2.
[49] Zhu LB, Ma R, Liu X, et al. The clinical effect and 2-year prognosis of advanced cardiac cancer patients with Her-2 overexpression treated with trastuzumab and conventional chemotherapy. Adv Modern Biomed. 2013;13:67–70.
[50] Zeng XH, Li KX. Clinical efficiency of trastuzumab combined with chemotherapy on HER2 positive advanced gastric cancer: a meta analysis. J Clin Exp Med. 2017;16:1722–5.
[51] Zhang HH, Tian XD, Liu MY. Meta-analysis of the efficacy and safety of trastuzumab combined with chemotherapy in the treatment of HER2-positive gastric cancer. Strait Pharma J. 2019;31:87–91.
[52] Li CL. Effects of trastuzumab plus chemoheraphy for the HER-2-positive advanced gastric cancer patients: a meta-analysis. Guangxi Med University. 2014:1–40.