Submitted: 26 February, 2023 Accepted: 23 April, 2023 Published: 15 January, 2025 DOI:10.22514/ejgo.2025.002

SYSTEMATIC REVIEW

European Journal of Gynaecological Oncology

Efficacy and safety of *anti-HER2* therapy in solid tumors except breast cancer: a systematic-review and meta-analysis

Xuan Chen[1,*], Yuqing Li[2], Yufu Lu[1], Mingfei Lin[1]

[1]Department of Thoracic Surgery, The People's Hospital of Wenchang, 571300 Wenchang, Hainan, China
[2]Department of Orthopaedic Surgery, Graduate School of Medicine, Tohoku University, 980-8577 Sendai, Japan

***Correspondence**
owenlee@alumni.nudt.edu.cn
(Xuan Chen)

Abstract

Background: A meta-analysis was conducted to systematically evaluate the efficacy and safety of anti-Human epidermal growth factor receptor 2 (anti-HER2) therapy in solid tumors except breast cancer. **Methods**: The Cochrane Library, PubMed, EMbase, Clinical Trials and Web of Science databases were searched for studies published up to August 2022, which reported clinical randomized controlled trials (RCTs) of groups with anti-HER2 therapy (the experimental groups) and without anti-HER2 therapy (the control groups) for solid tumors except breast cancer. A structured meta analysis was conducted on fifteen studies using R 4.2.1, based on the extraction of the data and the risk of bias assessment under the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. **Results**: Ten studies reported progression-free survival (PFS) with significantly lower risk of tumor progression in experimental groups than in control groups (hazard ratio (HR) = 0.82, 95% confidence interval (CI) (0.75, 0.90), $p < 0.01$). Seven studies reported overall survival (OS) with significantly longer overall survival in experimental groups than in control groups (HR = 0.89, 95% CI (0.79, 0.99), $p = 0.03$). The incidences of serious adverse events (SAEs) and any adverse events (AEs) in experimental groups were significantly higher than those in control groups (risk ratio (RR) = 1.35, 95% CI (1.04, 1.75), $p = 0.03$), (RR = 1.03, 95% CI (1.01, 1.06), $p < 0.01$). There was no significant difference between the incidences of anemia and fatigue in grade $\geq$3 AEs between the two groups ($p > 0.05$). The incidences of diarrhea, neutropenia, nausea, and vomiting were significantly higher in experimental groups than those in control groups ($p < 0.05$). **Conclusions**: The results reveal that anti-HER2 therapy is effective in the treatment of solid tumors except breast cancer, however some side effects should be carefully managed in clinical practice. **The PROSPERO Registration**: CRD42024625436.

Keywords

Anti-HER2 therapy; Solid tumors; Breast cancer; Efficacy; Safety; Systematic-review; Meta-analysis

1. Introduction

Human epidermal growth factor receptor 2 (*HER2*) is a proto-oncogene, located on the 17th chromosome q21, encoding the transmembrane tyrosine kinase receptor. *HER2* is capable of activating key signaling pathways of cells, including phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) (PI3K-AKT) and mitogen-activated protein kinase (MAPK) signaling pathways, involved in the regulation of cell proliferation, apoptosis, differentiation, and migration. Therefore, the activation of tyrosine kinase receptor caused by *HER2* overexpression or amplification contributes to the occurrence and development of various malignant tumors [1–4]. In addition to replicating number variation, it has been established through the expanding clinical use of second-generation sequencing technology that *HER2* mutations occur in a variety of malignancies, including bladder, breast, lung, colorectal, pancreatic and gallbladder cancers [5–11]. In the clinical use, targeting the rescue treatment of neoadjuvant or advanced breast cancer, *anti-HER2* therapy has achieved significant levels of efficacy in the treatment of breast cancer [12]. However, for the treatment of gastric cancer, trastuzumab is only recommended by guidelines in first-line medication in patients with advanced *HER2* positive gastric cancer. Thus, for the application of *anti-HER2* therapy in other tumors except breast cancer, there is still a controversy among the findings in literature [13–15]. In recent years, *anti-HER2* drugs were increasingly used in the treatment of solid tumors except breast cancer [16]. Currently, *anti-HER2* drugs mainly include monoclonal antibodies, small molecule tyrosine kinase inhibitors, antibody-

conjugated drugs, and other therapeutic drugs being explored for *HER2* targets [17]. Specific therapies involving monoclonal antibodies can directly inhibit the proliferation, differentiation, and migration of cancer cells. Such treatments include drugs such as trastuzumab and pertuzumab, *etc.* [18]. Small molecule tyrosine kinase inhibitors such as Lapatinib are a tyrosine kinase inhibitor that blocks the signaling cascade produced by *HER2* to achieve the purpose of *anti-HER2* [19]. The antibody-conjugated drugs (antibody-drug conjugates, ADC) are regarded as a combination of conventional chemotherapy and monoclonal antibody advantages such as trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (DS-8201/T-DXd), and gosatzumab, *etc.* [20]. The present meta-analysis aimed at assessing the efficacy and safety of the group with *anti-HER2* (experimental group) and the group without *anti-HER2* (control group) in solid tumors except breast cancer, to provide a scientific basis for clinical applications.

2. Materials and methods

2.1 Inclusion criteria

2.1.1 Study design

Randomized controlled trials (RCT) of treatment with *anti-HER2* for solid tumors except breast cancer, whether blind or not.

2.1.2 Study subjects

① The pathological diagnosis was solid tumors except breast cancer; ② Patients were ≥18 years old; ③ According to Eastern Cooperative Oncology Group (ECOG), the physical performance status should be 0 or 1 (0 represents fully active and capable of all activities freely; 1 represents limited physical activity but suffers from ambulatory and mild or sedentary work) [21]; ④ Left ventricular ejection fraction (LVEF) was ≥50%.

2.1.3 Interventions

The experimental groups were the treatments with *anti-HER2* therapy, while the control groups were the treatments without *anti-HER2* therapy. The treatments of both groups are not limited by the dosage and course of treatment.

2.1.4 Outcome indicators

Efficacy outcomes: progression-free survival (PFS), and overall survival (OS). Safety outcomes: incidences of serious adverse reactions (SAEs), any AEs, and Grade ≥3 AEs. The adverse reactions include Diarrhea, Neutropenia, Nausea, Anemia, Vomiting, Fatigue. Grade refers to the severity of the AEs. The National Cancer Institute Common Toxicity Criteria (NCICTC) (Version 2) or the Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) displays Grades 1~5 with unique clinical descriptions of severity for each AE based on the general guideline.

2.2 Exclusion criteria

① The clinical trial was not completed; ② The purpose of the trials were inconsistent with our study's; ③ The studies reported non-randomized control trials, such as observational studies, retrospective studies, *etc.*; ④ Abstracts only without full text, duplicate publications or incomplete data; ⑤ The review, reviews, expert views, experience summaries, individual cases, animal experiments and other non-clinical trial studies.

2.3 Search strategy

Studies were identified by searching PubMed (January 1966 to August 2022), EMbase (January 1974 to August 2022), ClinicalTrials.gov, Cochrane Library, and web of science, using medical subject headings (MeSH) and the keywords: "Cancer", "Neoplasm(s)", "Tumor(s)", "Neoplasm(s)", "Cancer(s)", "*HER2*-targeted", "*anti-HER2*", "Trastuzumab", "Pertuzumab", "T-DM1", "Lapatinib", "pyrotinib", "Neratinib", "Tucatinib", "T-DXd" and so on. In terms of the characteristics of the different databases, corresponding search strategies were used.

2.4 Data extraction and quality evaluation

Literature screening and data extraction were independently conducted by two authors. The articles that lacked original data or did not meet the inclusion criteria were excluded. If more than one publication reported results from the same trial or included the same or overlapping patient cohorts, only the outcomes from the largest and most recent publications were included [22]. The following information was recorded from eligible studies:

① basic information of the studies including title, first author's name, year of publication, publishing journal, *etc.*;

② the basic characteristics of the studies, including the number of cases and age;

③ interventions;

④ primary outcome indicators;

⑤ the risk assessment of bias.

The risk of bias in the studies included in the analysis was evaluated using the RCT bias assessment tool, that is using the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [23, 24]: ① random sequence generation (selection bias); ② allocation concealment (selection bias); ③ blinding of participants and personnel (performance bias); ④ blinding of outcome assessment (detection bias); ⑤ incomplete outcome data (attrition bias); ⑥ selective reporting (reporting bias); ⑦ other biases. The risk of bias was rated as high, low or unclear [25]. The Egger's test and Begg's test was used to evaluate the occurrence of publication bias.

2.5 Statistical methods

The preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines were followed to perform this meta-analysis using the R software (version 4.2.1, GNU project, Cambridge, MA, USA) [26, 27]. The hazard ratio (HR) and 95% confidence interval (CI) were pooled for PFS and OS, the number of events extracted directly from clinical trials was used to calculate the risk ratio (RR) and 95% CI for adverse events (AEs). Heterogeneity in the results of the included studies was evaluated both visually through forest plots and *p*-values using the I-squared (I^2). If statistically significant heterogeneity was observed ($I^2 \geq 50\%$), the pooled effect was

calculated using a random-effect model; otherwise, a fixed-effect model was employed ($I^2 < 50\%$) [28]. Sensitivity analysis was performed by recalculating the pooled outcome estimates after excluding each study one at a time (leave-one-out procedure) [29].

The HR is usually calculated from a Cox proportional hazards model, which is one of the standard methods for analyzing survival end points in oncology RCTs. The HR provides an estimate of the ratio of the hazard rates between the experimental group and the control group over the entire study duration. If the HR (E (Experimental) versus C (Control)) is <1, then the experimental treatment is better than the control and *vice versa* if HR (E versus C) >1. If the log HR is taken, it not only determines whether the benefits of the treatments are different (or not) but also indicates how one treatment compares to the other [30]. Furthermore, both PFS and OS can only be compared with studies of the same type, while HR values can be compared across studies and even diseases by adjusting the influence of confounding factors through multivariate Cox proportional hazard regression model.

3. Results

3.1 Studies inclusion

A total of 3717 studies were initially identified. These studies were processed by screening the titles and/or abstracts, removing duplicates, and removing articles with similar data and study designs. Finally, fifteen eligible studies were included. The PRISMA flow diagram detailing the process of inclusion and exclusion of publications is shown in Fig. 1. The PRISMA 2020 Checklist is in the **Supplementary material**.

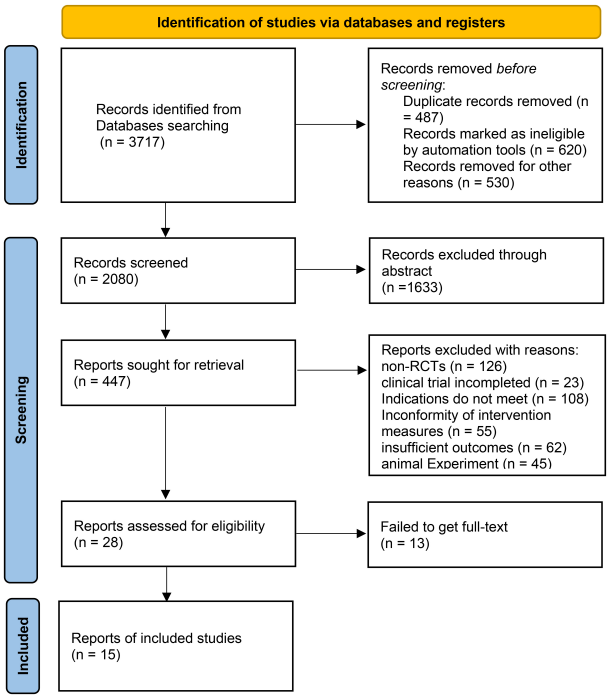

FIGURE 1. Flow diagram of the trial search and selection process. RCT: Randomized controlled trials.

3.2 Basic characteristics of the included studies

Of the fifteen RCTs included, there were 3302 patients, including 1681 patients in the experimental groups and 1621 patients in the control groups. The basic characteristics of the included studies are presented in Table 1 (Ref. [31–45]).

3.3 Quality evaluation

The fifteen included studies were all RCTs and six among them were double-blind trials. The baseline of Patient Demographics and Disease Characteristics are reported in all the studies. Based on the risk of bias assessment of the studies, the overall quality assessment was moderate. The risk of bias summary and bias graph of the included studies are shown in Figs. 2,3.

3.4 Progression-free survival

Ten studies reported that progression-free survival (PFS) exhibited low heterogeneity between studies ($p = 0.11$, $I^2 = 38\%$). There were 1079 cases in the experimental groups and 1063 cases in the control groups. The pooled results using a fixed-effects model demonstrated that the risk of tumor progression in the experimental groups was significantly lower than that in the control groups (HR = 0.82, 95% CI (0.75, 0.90), $p < 0.01$), as shown in Fig. 4. The sensitivity analysis yielded $I^2 = 25\%$ after sequential exclusion of the data from Amanda N 2018, Thomas Powles 2017, indicating the heterogeneity source, as shown in Fig. 5. Additionally, there was found no evidence of publication bias in any of the analysis, using both Begg's test ($p = 0.4843$) and Egger's test ($p = 0.5234$).

3.5 Overall survival

There were seven studies that revealed no heterogeneity in overall survival (OS) ($p = 0.29$, $I^2 = 18\%$), considering 1163 cases in the experimental groups and 1158 cases in the control groups. The pooled results using a fixed-effects model demonstrated that the overall survival of patients in the experimental groups was significantly longer than that in the control groups (HR = 0.89, 95% CI (0.79, 0.99), $p = 0.03$). This suggest that the treatment with *anti-HER2* therapy could reduce the risk of tumor progression, as shown in Fig. 6. There was found no evidence of publication bias in any of the analysis using Begg's test ($p = 0.1361$) and Egger's test ($p = 0.1053$).

3.6 Serious adverse events

Three studies reported the incidence of serious adverse events (SAEs) with no heterogeneity between studies ($p = 0.96$, $I^2 = 0\%$), considering an analysis of 428 and 421 patients in the experimental groups and control groups, respectively. The pooled results using a fixed-effects model demonstrated that the incidence of SAEs in the experimental groups was significantly higher than that in the control groups (RR = 1.35, 95% CI (1.04, 1.75), $p = 0.03$), as shown in Fig. 7.

TABLE 1. Basic characteristics of included studies.

First Author Year	Cancer	Line	Treatment status	Treatment arms	Populations	Eiffcacy endpoint	HER2 status	Age (median (range)/mean (SD)), years
S.B. Kaye 2013 [31]	Ovarian	≥Second line	Relapsed	A: P + Chemotherapy B: Chemotherapy	A: 74 B: 75	PFS	Undefined	A: 58.1 (26–76) B: 55.3 (19–83)
J.Randolph Hecht 2016 [32]	Gastric, Esophageal, or Gastroesophageal Adenocarcinoma	First line	Advanced/Metastat	A: CapeOx + Lapatinib B: CapeOx + Placebo	A: 249 B: 238	PFS OS	FISH+ and/or IHC 3+	A: 61.0 (19–86) B: 59.0 (27–84)
Tianshu Liu 2019 [33]	Gastric or gastroesophageal junction cancer	First line	Metastatic	A: H + P + Chemotherapy B: H + Chemotherapy + Placebo	A: 82 B: 81	PFS OS ORR	IHC 3+ or IHC 2+ and FISH+	A: 59.0 (25–78) B: 59.0 (23–73)
Amanda N 2018 [34]	Uterine Serous Carcinomas	≥Second line	Advanced/recurren	A: C + Paclitaxel + H B: C + Paclitaxel	A: 32 B: 29	PFS	IHC 3+ or IHC 2+ and FISH+	A: 67.0 (64–69) B: 73.0 (68–78)
Akitaka Makiyama 2020 [35]	Gastric or Gastroesophageal Junction Cancer	First line	Advanced	A: Paclitaxel + H B: Paclitaxel	A: 45 B: 46	PFS OS	IHC 3+ or IHC 2+ and FISH+	A: 65.0 (50–89) B: 67.0 (33–81)
JM del Campo 2011 [36]	Squamous cell carcinoma of the head and neck	First line	Locally advanced	A: Lapatinib + Chemoradiotherapy B: Placebo + Chemoradiotherapy	A: 71 B: 36	ORR	Undefined	A: 58.0 (33–80) B: 55.0 (37–78)
Kevin Harrington 2015 [37]	Squamous Cell Carcinoma of the Head and Neck	First line	Adjuvant	A: Lapatinib + Chemoradiotherapy B: Placebo + Chemoradiotherapy	A: 346 B: 342	DFS OS	Undefined	A: 54.0 (27–74) B: 55.0 (24–74)
Thomas Powles 2017 [38]	Bladder Cancer	≥Second line	Metastatic	A: Lapatinib B: Placebo	A: 116 B: 116	PFS OS	IHC 3+ or IHC 2+	A: 70.7 (63.9–77.2) B: 71.1 (63.8–76.3)

TABLE 1. Continued.

First Author Year	Cancer	Line	Treatment status	Treatment arms	Populations	Eiffcacy endpoint	HER2 status	Age (median (range)/mean (SD)), years
U Gatzemeier 2004 [39]	NSCLC	≥Second line	Advanced	A: Gemcitabine + Cisplatin + H B: Gemcitabine + Cisplatin	A: 51 B: 50	PFS OS	IHC 3+ or FISH+	A: 57.0 (35.0–76.0) B: 60.0 (35.0–76.0)
Sharmila Makhija 2010 [40]	Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	≥Second line	Advanced	A: Gemcitabine + Pertuzumab B: Gemcitabine + Placebo	A: 65 B: 65	PFS ORR	Undefined	NR
Christian Kurzeder 2016 [41]	Ovarian Cancer, Fallopian Tube Cancer, or Primary Peritoneal Cancer	≥Second line	Refractory	A: P + Chemotherapy B: Chemotherapy + Placebo	A: 78 B: 78	PFS	Undefined	A: 65.0 (32.0–79.0) B: 64.0 (26.0–80.0)
Yung-Jue Bang 2010 [42]	Gastric or gastro-oesophageal junction cancer	First line	Advanced	A: H + Chemotherapy B: Chemotherapy	A: 294 B: 290	OS	FISH+ and/or IHC 3+	NR
Howard P Safran 2022 [43]	Esophageal adenocarcinoma	First line	Neoadjuvant	A: H + Chemoradiotherapy B: Chemoradiotherapy	A: 102 B: 101	DFS	FISH+ and/or IHC 3+	NR
Stéphane Oudard 2015 [44]	Urothelial carcinoma	First line	Advanced/metastat	A: H + Chemotherapy B: Chemotherapy	A: 32 B: 29	PFS OS ORR	IHC 3+ or IHC 2+ and FISH+	NR
Taito Esaki 2018 [45]	Gastric cancer	≥Second line	Advanced	A: H + Paclitaxel B: Paclitaxel	A: 44 B: 45	PFS OS	FISH+ and/or IHC 3+	NR

A: Experiment group; B: Control group; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; D: Docetaxel; P: Pertuzumab; H: Trastuzumab; T-DM1: Trastuzumab emtansine; cap: Capecitabine; NR: not reported; ORR: objective response rate; PFS: progression-free survival; OS: overall survival; DFS: Disease-free survival; CapeOx: capecitabine and oxaliplatin; C: carboplatin; NSCLC: non-small-cell lung cancer; IHC: Immunohistochemistry; ISH: In situ hybridization; SD: standard deviation.

3.7 Any adverse events

Four studies reported the incidence of any AEs with no heterogeneity between studies ($p = 0.25$, $I^2 = 27\%$). There were 777 and 757 patients in the experimental groups and control groups, respectively. The pooled results using a random-effects model demonstrated that the incidence of any AEs in the experimental groups was significantly higher than that in the control groups (RR = 1.03, 95% CI (1.01, 1.06), $p < 0.01$), as shown in Fig. 8.

3.8 Grade ≥3 adverse events

For the incidence of grade ≥3 adverse events (AEs), including diarrhea, neutropenia, nausea, anemia, vomiting, and fatigue in both groups, no significant study heterogeneity was observed. The pooled estimates using a fixed-effects model showed that there was no significant difference in the incidence of anemia and fatigue between the two groups (RR = 1.34, 95% CI (0.95, 1.89), $p = 0.10$), (RR = 1.21, 95% CI (0.71, 2.06), $p = 0.49$), indicating that the incidence of anemia and fatigue was comparable between two groups. The incidence rates of diarrhea, neutropenia, nausea, and vomiting in the experimental groups were both significantly higher than those in the control groups ($p < 0.05$), as shown in Fig. 9.

3.9 Comparison between studies on PFS and OS

As introduced in 2.5, log (HR) below the horizontal axis (zero line) indicates benefit of groups with *anti-HER2* therapy (experimental), while log (HR) above the zero line indicates benefit of groups without *anti-HER2* therapy (control), and greater absolute value indicates greater benefit. Accordingly, log (HR) was used to investigate the comparison of studies in PFS and OS on the *HER2* positive (*HER2*+) *vs.* *HER2* not-reported (*HER2* undefined) trials and on the therapy naive patients (first line) *vs.* patients previously received multiple therapies (≥second line).

PFS were reported in 10 studies, of which 7 studies were *HER2*+ and 3 studies were undefined in *HER2* expression. OS was reported in 7 studies, of which 6 studies were *HER2*+ and 1 study were undefined in *HER2* expression. For PFS, the log (HR) values of the two *HER2* states were distributed at both sides of the zero line, indicating that the PFS benefit of the *HER2*+ population was not significantly superior to the PFS benefit of the population with undefined *HER2* expression, as shown in Fig. 10A. However, OS cannot be analyzed due to the limited studies included, as shown in Fig. 10B.

PFS were reported in 10 studies, of which 4 studies' *anti-HER2* regiments were first line therapies, and 6 studies' *anti-HER2* regiments were ≥second line therapies. The log (HR) values in the first line trials were all distributed below the zero line, suggesting that the *anti-HER2* regiments in the former trials had better PFS benefits. The log (HR) values in ≥second line treatment trials were distributed at both sides of the zero line, indicating that the PFS benefit trend of the first line treatment trials was better than that of the ≥second line treatment trials, as shown in Fig. 11A. The OS in two groups had no obvious advantage benefit trend, as shown in Fig. 11B.

4. Discussion

It has been proved that abnormal *HER2* gene activation may lead to tumor formation. Meanwhile, the *HER2* protein could promote angiogenesis, increase vascular permeability, and provide rich nutrients for tumors, thus significantly enhancing the invasive ability of tumors [46]. The *HER2* gene was found to be associated with the occurrence and development of malignant tumors, and the poor prognosis of patients. The *HER2* gene is highly expressed in breast cancer, colorectal cancer, cervical cancer, ovarian cancer, endometrial cancer, prostate cancer, and many other tumors, leading to the phosphorylation of intracellular tyrosine kinase residues, which ultimately promotes cell proliferation, differentiation, migration, and survival. Yu-ying Lei reported that *HER2* over-expression was associated with poor prognosis in patients with gastric carcinoma (GC), and the *HER2* positive rate in GC patients may be related to gender, tumor site, tumor-node-metastasis (TNM) staging system, distant metastasis, lymph node metastasis, Lauren grade, and differentiation grade. *HER2* rates may be higher in Asians than in Europeans [47]. Junjie Zhao studied the prognostic role of *HER2* in bladder cancer, and assigned it to the presence of *HER2* expression with poor prognosis. Therefore, *HER2* was known as a useful biomarker for clinical prediction [48]. The Jung-Soo Pyo study revealed the clinicopathological significance and diagnostic accuracy of *HER2* immunohistochemistry in colorectal cancer, and indicated that *HER2* IHC over-expression was significantly associated with lymph node metastasis and distant metastasis, and the colorectal cancer (CRC) cases with a *HER2* IHC score of 0/1+ matched well with the ISH data [49]. Studies have proved that *HER2*/neu over-expression is associated with reduced overall survival rate and shortened time to recurrence in advanced ovarian cancer, and is one of the prognostic factors for poor treatment outcomes of ovarian cancer.

In recent years, many *anti-HER2* therapies were used in the clinical treatment of tumors. According to the targeted sequencing, Jhaver studied ado-trastuzumab emtansine (T-DM1) in patients with *HER2*-amplified tumors except breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas and patients received T-DM1 at 3.6 mg/kg i.v. every 3 weeks until toxicity or disease progression [50]. The test results indicated that T-DM1 tolerance was high, however, the objective response rate of the tumor did not show a curative effect. Bob *et al*. [51] noted that trastuzumab (6.4 mg/kg) was used in patients with metastatic her-2-mutant NSCLC patients that did not respond to standard therapy, and concluded that trastuzumab demonstrated durable anticancer activity in previously treated her-2-mutant NSCLC patients. Yelena combined pembrolizumab with trastuzumab in the first-line treatment of positive esophagogastric (EG, or gastric, esophageal, or gastro-esophageal junction) cancer, and concluded that pembrolizumab can be safely combined with trastuzumab and chemotherapy and exhibit strong activity against *HER2*-positive metastatic oesophageal and gastric cancer [52]. Salvatore applied trastuzumab (DS-8201) in patients with *HER2*-expressing metastatic colorectal cancer and concluded that trastuzumab showed promising and

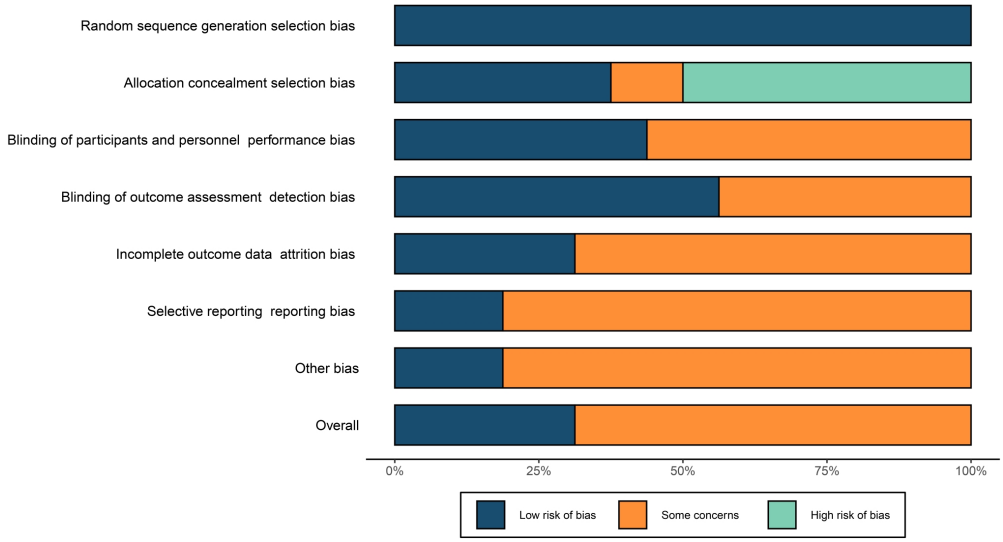

FIGURE 2. The risk of bias summary.

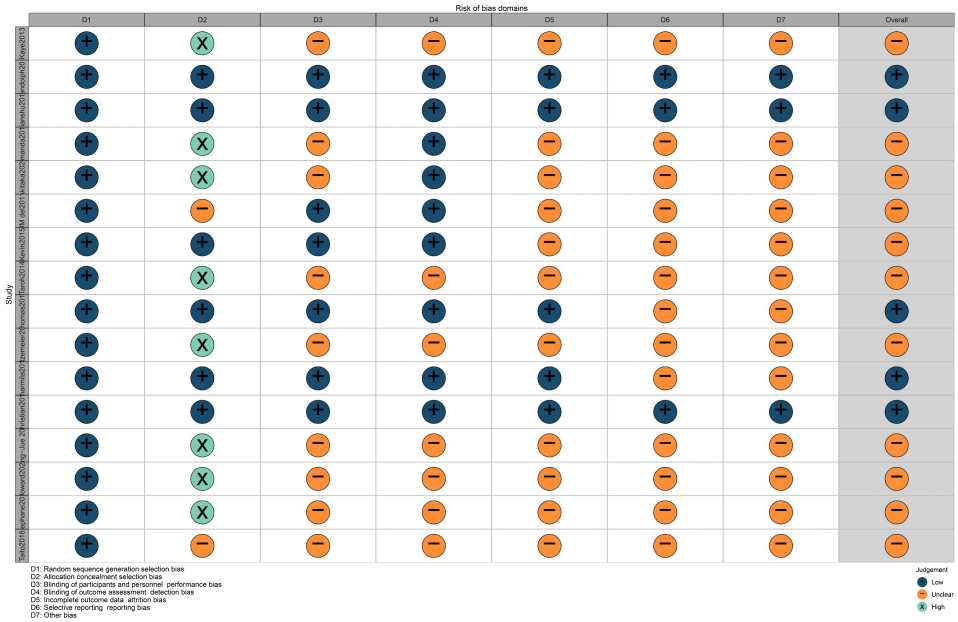

FIGURE 3. The risk of bias graph.

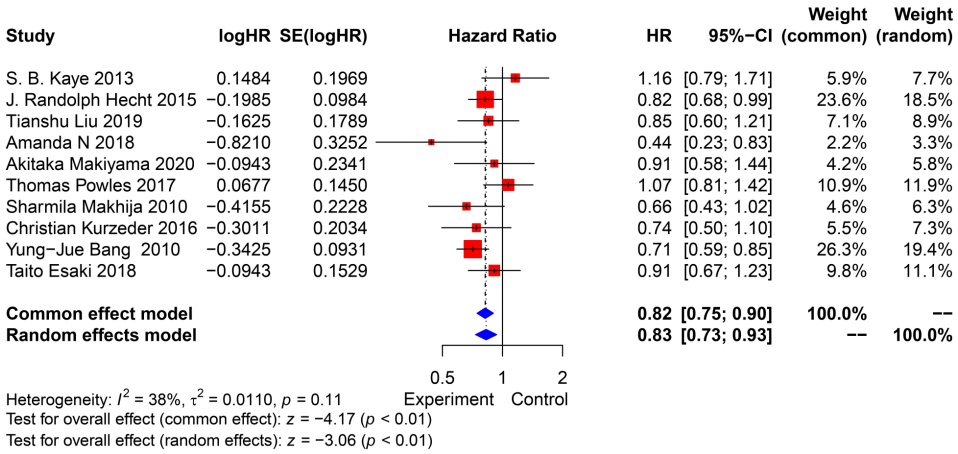

FIGURE 4. Forest plot of PFS (progression-free survival). CI: confidence interval; SE: Standard Error of Mean; HR: hazard ratio.

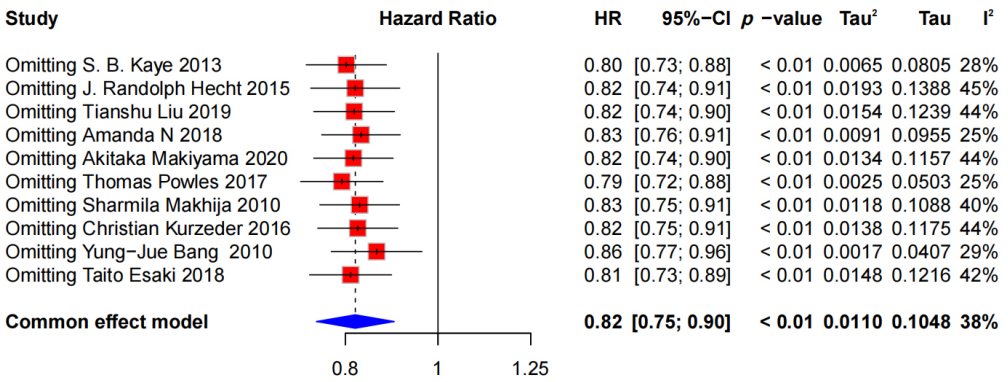

FIGURE 5. Sensitivity analysis of PFS (progression-free survival). CI: confidence interval; HR: hazard ratio.

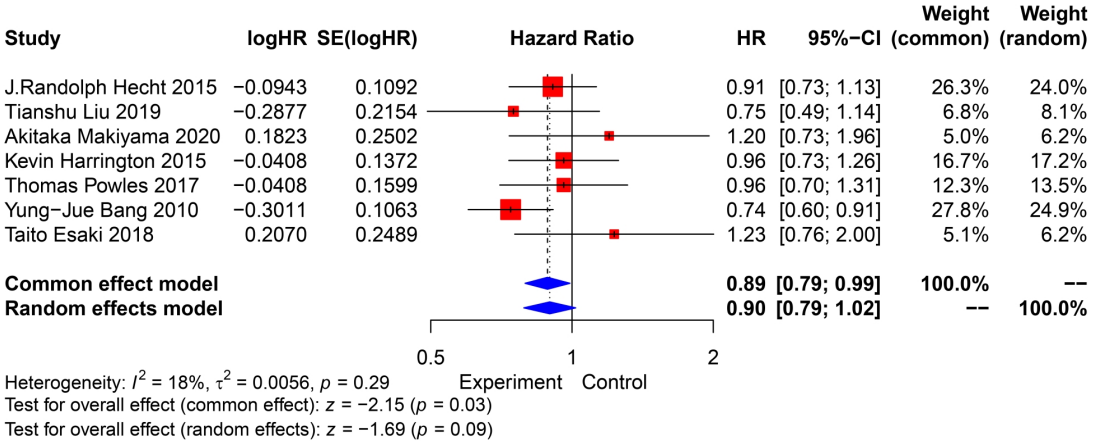

FIGURE 6. Forest plot of OS (overall survival). CI: confidence interval; SE: Standard Error of Mean; HR: hazard ratio.

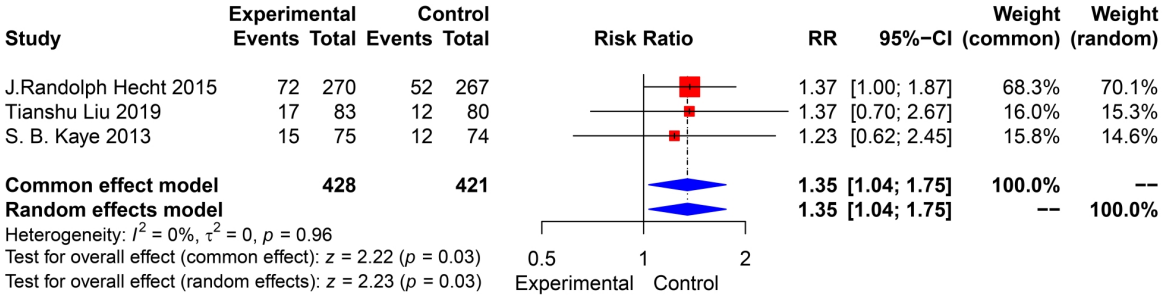

FIGURE 7. Forest plot of SAEs (serious adverse events). CI: confidence interval; RR: Risk Ratio.

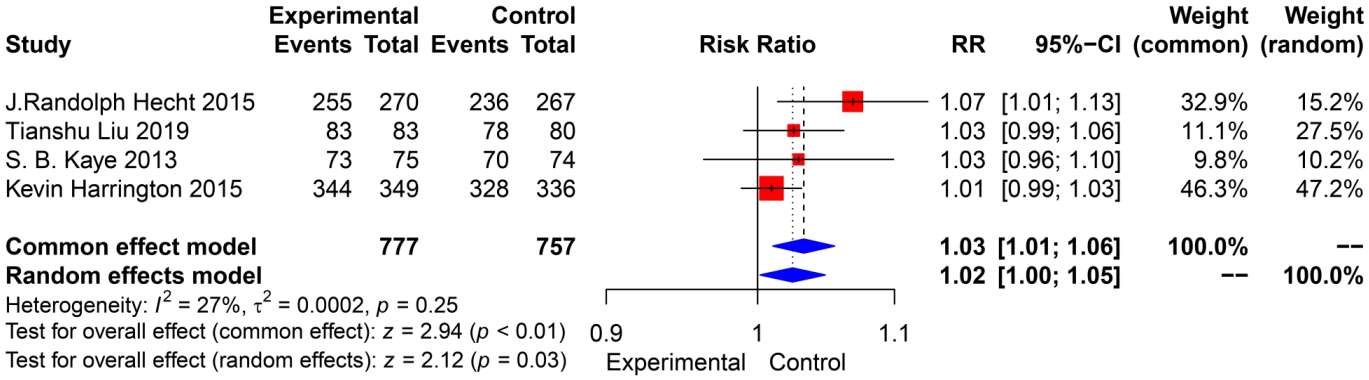

FIGURE 8. Forest plot of any AEs. CI: confidence interval; RR: Risk Ratio.

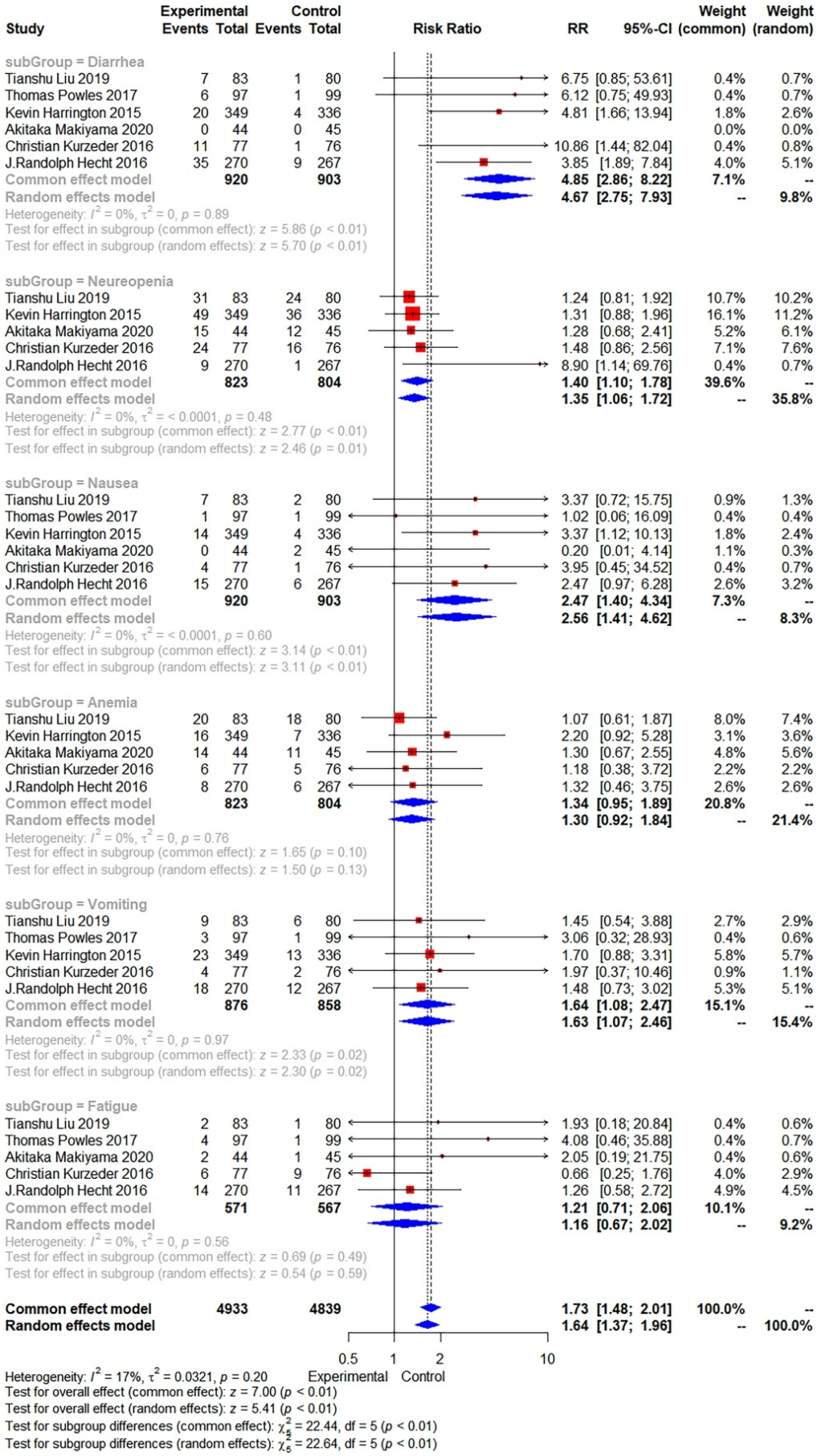

FIGURE 9. Forest plot of grade ≥3 AEs (adverse events). CI: confidence interval; RR: Risk Ratio.

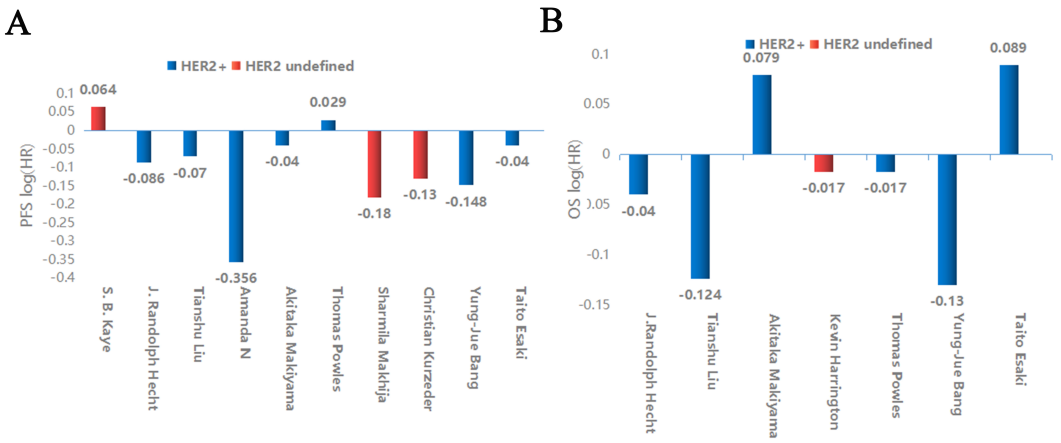

FIGURE 10. Comparison of HER2+ and HER2 undefined between studies on PFS and OS. (A) PFS. (B) OS. PFS: progression-free surviva; OS: overall survival; HR: hazard ratio; HER: Human epidermal growth factor receptor.

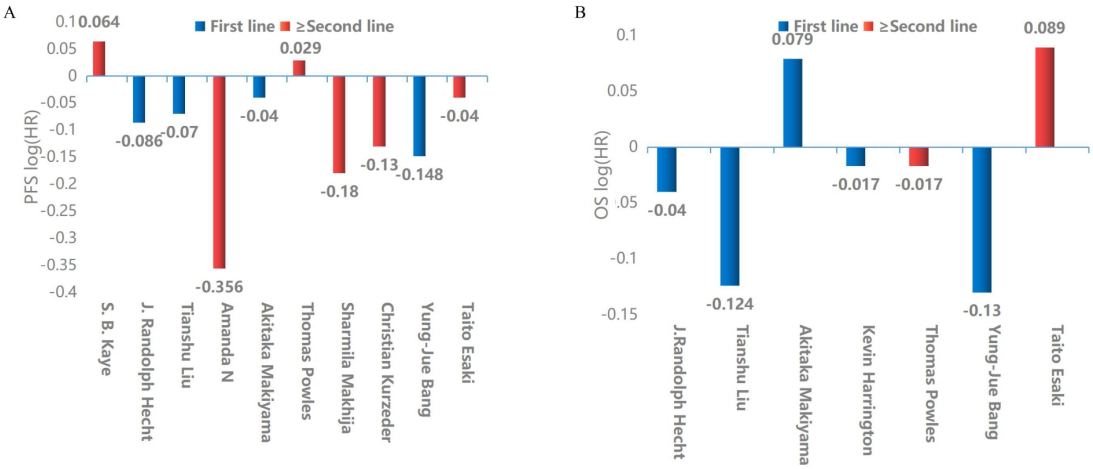

FIGURE 11. Comparison of first line and ≥second line between studies on PFS and OS. (A) PFS. (B) OS. PFS: progression-free surviva; HR: hazard ratio; OS: overall survival.

durable activity against *HER2*-positive metastatic colorectal cancer, and its safety was consistent with that reported in previous trastuzumab trials [53]. Additionally, interstitial lung disease and pneumonia are important risks that require careful monitoring and timely intervention.

Fifteen clinical trials with a total of 3302 patients were included in this study, all of which were randomized clinical trials. According to the effectiveness evaluation results of meta-analysis, in terms of PFS, the treatment with *anti-HER2* therapy reduced the risk of tumor progression compared with the treatment without *anti-HER2* therapy. In terms of OS, the treatment with *anti-HER2* therapy reduced the risk of death in advanced tumors compared with the treatment without *anti-HER2* therapy. In this study, log (HR) values of PFS and OS were used for comparative analysis of benefits in different groups, and the results showed that the treatment regimen containing *anti-HER2* had certain advantages and benefits in the application of first line treatment, but due to the small sample size, the conclusions were not accurate to some extent. According to the safety evaluation results of meta-analysis, the incidences of SAEs and any AEs in the treatments with *anti-HER2* were higher than those of treatments without *anti-HER2* (RR = 1.35, 95% CI (1.04, 1.75), $p = 0.03$), (RR = 1.03, 95% CI (1.01, 1.06), $p < 0.01$). In terms of the incidence of grade ≥3 adverse events, there was no significant difference in the incidence of anemia and fatigue between the two groups ($p > 0.05$). The incidence rates of diarrhea, neutropenia, nausea, and vomiting in the experimental groups were both significantly higher than those in the control groups ($p < 0.05$).

This study further analyzed the cause of increase of adverse reactions associated with *anti-HER2* therapy. First, of the 15 *anti-HER2* therapy studies included in this study, 14 of them were *anti-HER2* therapy combined with other chemotherapies, while the common adverse reactions of *anti-HER2* drugs include diarrhea, drug-induced liver injury, nausea, vomiting, dermo-toxicity, cardiotoxicity, and oral mucositis, *etc.* [54]. Common adverse reactions of chemotherapy include myelosuppression, liver and kidney function injury, nausea, vomiting, hair loss, *etc.* [55]. In this study, the incidences of nausea and vomiting in grade ≥3 AEs were compared. The presence of nausea in *anti-HER2* therapy group was significantly higher than that in the group without *anti-HER2* therapy, indicating that the combination of the two drugs may increase the severity of adverse reactions. It was found that the incidences of diarrhea in grade ≥3 AEs with *anti-HER2* therapy were significantly higher than those of without

anti-HER2 therapy, indicating that *anti-HER2* drugs also had common adverse reactions to diarrhea.

This study had several limitations. First, not all studies met the inclusion and exclusion criteria and the efficacy determination criteria of publications. Second, limited by the original data, a subgroup analysis of ECOG scores and regional differences was not conducted.

5. Conclusions

In conclusion, the treatments with *anti-HER2* therapy could significantly prolong PFS and OS in tumor patients compared with the treatments without *anti-HER2* therapy. Nonetheless, this is with significant risk of increased incidence of adverse events. During clinical application, attention should be paid to the relevant adverse events under real-time monitoring. To the best of our knowledge, this study evaluated the solid tumors treated with *anti-HER2* therapy based on existing clinical data to provide a novelty reference for the clinical treatment of breast cancer. However, considering that the number of included studies was not substantial, more reasonably designed clinical trials with larger sample size and multi-center clinical trials are needed to draw more reliable evidence to guide clinical medication in the future.

ABBREVIATIONS

HER2+, human epidermal growth factor receptor-2-positive; RCT, Randomized controlled trial; PFS, progression-free survival; OS, overall survival; AEs, adverse events; SAEs, serious adverse events; HR, Hazard ratio; RR, Risk ratio; CI, confidence interval; PI3K, phosphatidylinositol 3 kinase; AKT, protein kinase B; MAPK, mitogen-activated protein kinase, T-DM1, trastuzumab emtansine; ADC, antibody-drug conjugates; ECOG, Eastern Cooperative Oncology Group; LVEF, Left ventricular ejection fraction; NCICTC, National Cancer Institute Common Toxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; MeSH, medical subject headings; PRISMA, preferred Reporting Items for Systematic reviews and Meta-analysis; I^2, I-squared; GC, gastric carcinoma; TNM, tumor-node-metastasis; CRC, colorectal cancer; GEJ, gastroesophageal junction.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

XC and YQL—designed the research study, analyzed the data. XC—performed the research. MFL and YFL—provided help and advice on the ELISA experiments. XC and YFL—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in the included studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. This article does not contain any studies with human participants performed by any of the authors.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1879409240660951040/attachment/Supplementary%20material.docx.

REFERENCES

[1] Cocco E, Lopez S, Santin AD, Scaltriti M. Prevalence and role of HER2 mutations in cancer. Pharmacology & Therapeutics. 2019; 199: 188–196.

[2] Cen S, Liu Z, Pan H, Han W. Clinicopathologic features and treatment advances in cancers with HER2 alterations. Biochimica Et Biophysica Acta. Reviews on cancer. 2021; 1876: 188605.

[3] Dhritlahre RK, Saneja A. Recent advances in HER2-targeted delivery for cancer therapy. Drug Discovery Today. 2021; 26: 1319–1329.

[4] Vranić S, Bešlija S, Gatalica Z. Targeting HER2 expression in cancer: new drugs and new indications. Bosnian Journal of Basic Medical Sciences. 2021; 21: 1–4.

[5] Li BT, Ross DS, Aisner DL, Chaft JE, Hsu M, Kako SL, *et al*. HER2 amplification and HER2 mutation are distinct molecular targets in lung cancers. Journal of Thoracic Oncology. 2016; 11: 414–419.

[6] Halle MK, Tangen IL, Berg HF, Hoivik EA, Mauland KK, Kusonmano K, *et al*. HER2 expression patterns in paired primary and metastatic endometrial cancer lesions. British Journal of Cancer. 2018; 118: 378–387.

[7] Teplinsky E, Muggia F. Targeting HER2 in ovarian and uterine cancers: challenges and future directions. Gynecologic Oncology. 2014; 135: 364–370.

[8] Ellina M, Bouris P, Aletras AJ, Theocharis AD, Kletsas D, Karamanos NK. EGFR and HER2 exert distinct roles on colon cancer cell functional properties and expression of matrix macromolecules. Biochimica et Biophysica Acta. 2014; 1840: 2651–2661.

[9] Sanguedolce F, Russo D, Mancini V, Selvaggio O, Calo B, Carrieri G, *et al*. Prognostic and therapeutic role of HER2 expression in micropapillary carcinoma of the bladder. Molecular and Clinical Oncology. 2019; 10: 205–213.

[10] Marinović S, Cigrovski Berković M, Zjačić-Rotkvić V, Kapitanović S. Analysis of polymorphisms in EGF, EGFR and HER2 genes in pancreatic

neuroendocrine tumors (PNETs). Cancer Genetics. 2022; 266–267: 44–50.

[11] Sung YN, Kim SJ, Jun SY, Yoo C, Kim KP, Lee JH, *et al*. Expression of HER2 and mismatch repair proteins in surgically resected gallbladder adenocarcinoma. Frontiers in Oncology. 2021; 11: 658564.

[12] Musolino A, Boggiani D, Pellegrino B, Zanoni D, Sikokis A, Missale G, *et al*. Role of innate and adaptive immunity in the efficacy of anti-Her2 monoclonal antibodies for HER2-positive breast cancer. Critical Reviews in Oncology/Hematology. 2020; 149: 102927.

[13] Park JY, Dunbar KB, Vemulapalli R, Wang DH, Zhang PJ. Human epidermal growth factor receptor 2 testing in gastric and gastroesophageal junction adenocarcinomas: role of the gastroenterologist. Gastrointestinal Endoscopy. 2015; 81: 977–982.

[14] Wang D, Liu Z, Lu Y, Bao H, Wu X, Zeng Z, *et al*. Liquid biopsies to track trastuzumab resistance in metastatic HER2-positive gastric cancer. Gut. 2019; 68: 1152–1161.

[15] Gürbüz M, Akkuş E, Sakin A, Urvay S, Demiray AG, Şahin S, *et al*. Combination of trastuzumab and taxane-containing intensified chemotherapy in first-line treatment of HER2-positive advanced gastric cancer. Tumori Journal. 2021; 107: 416–423.

[16] Gaye E, Penel N, Lebellec L. Novel treatment approaches for HER2 positive solid tumors (excluding breast cancer). Current Opinion in Oncology. 2022; 34: 570–574.

[17] Tarantino P, Trapani D, Curigliano G. Mastering the use of novel anti-HER2 treatment options. JCO Oncology Practice. 2021; 17: 605–606.

[18] Xu Y, Wang Y, Gong J, Zhang X, Peng Z, Sheng X, *et al*. Phase I study of the recombinant humanized anti-HER2 monoclonal antibody—MMAE conjugate RC48-ADC in patients with HER2-positive advanced solid tumors. Gastric Cancer. 2021; 24: 913–925.

[19] Nielsen DL, Kümler I, Palshof JAE, Andersson M. Efficacy of HER2-targeted therapy in metastatic breast cancer. Monoclonal antibodies and tyrosine kinase inhibitors. The Breast. 2013; 22: 1–12.

[20] Zhang X, Huang AC, Chen F, Chen H, Li L, Kong N, *et al*. Novel development strategies and challenges for anti-HER2 antibody-drug conjugates. Antibody Therapeutics. 2022; 5: 18–29.

[21] Liu C, Yang ZG, Lu Y, Ai DD, Chang F. Pertuzumab combined with trastuzumab for treatment of HER2-positive breast cancer: a meta-analysis. Chinese Journal of New Drugs. 2019; 28: 3035–3041.

[22] Chen S, Liang Y, Feng Z, Wang M. Efficacy and safety of HER2 inhibitors in combination with or without pertuzumab for HER2-positive breast cancer: a systematic review and meta-analysis. BMC Cancer. 2019; 19: 973.

[23] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011; 343: d5928.

[24] Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. 2011. Available at: https://training.cochrane.org/handbook (Accessed: 04 August 2022).

[25] Jawa Z, Perez RM, Garlie L, Singh M, Qamar R, Khandheria BK, *et al*. Risk factors of trastuzumab-induced cardiotoxicity in breast cancer. Medicine. 2016; 95: e5195.

[26] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLOS Medicine. 2009; 6: e1000097.

[27] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLOS Medicine. 2009; 6: e1000100.

[28] Genuino AJ, Chaikledkaew U, The DO, Reungwetwattana T, Thakkinstian A. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis. Expert Review of Clinical Pharmacology. 2019; 12: 815–824.

[29] Zhu C, Ling W, Zhang J, Gao H, Shen K, Ma X. Safety and efficacy evaluation of pertuzumab in patients with solid tumors. Medicine. 2017; 96: e6870.

[30] Barraclough H, Simms L, Govindan R. Biostatistics primer: what a clinician ought to know: hazard ratios. Journal of Thoracic Oncology. 2011; 6: 978–982.

[31] Kaye SB, Poole CJ, Dańska-Bidzińska A, Gianni L, Del Conte G, Gorbunova V, *et al*. A randomized phase II study evaluating the combination of carboplatin-based chemotherapy with pertuzumab versus carboplatin-based therapy alone in patients with relapsed, platinum-sensitive ovarian cancer. Annals of Oncology. 2013; 24: 145–152.

[32] Hecht JR, Bang YJ, Qin SK, Chung HC, Xu JM, ParkKrzysztof Jeziorski JO, *et al*. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC—a randomized phase III trial. Journal of Clinical Oncology. 2016; 34: 443–451.

[33] Liu T, Qin Y, Li J, Xu R, Xu J, Yang S, *et al*. Pertuzumab in combination with trastuzumab and chemotherapy for Chinese patients with HER2-positive metastatic gastric or gastroesophageal junction cancer: a subpopulation analysis of the JACOB trial. Cancer Communications. 2019; 39: 38.

[34] Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, *et al*. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. Journal of Clinical Oncology. 2018; 36: 2044–2051.

[35] Makiyama A, Sukawa Y, Kashiwada T, Kawada J, Hosokawa A, Horie Y, *et al*. Randomized, phase II study of trastuzumab beyond progression in patients with HER2-positive advanced gastric or gastroesophageal junction cancer: WJOG7112G (T-ACT study). Journal of Clinical Oncology. 2020; 38: 1919–1927.

[36] Del Campo JM, Hitt R, Sebastian P, Carracedo C, Lokanatha D, Bourhis J, *et al*. Effects of lapatinib monotherapy: results of a randomised phase II study in therapy-naive patients with locally advanced squamous cell carcinoma of the head and neck. British Journal of Cancer. 2011; 105: 618–627.

[37] Harrington K, Temam S, Mehanna H, D'Cruz A, Jain M, D'Onofrio I, *et al*. Postoperative adjuvant lapatinib and concurrent chemoradiotherapy followed by maintenance lapatinib monotherapy in high-risk patients with resected squamous cell carcinoma of the head and neck: a phase III, randomized, double-blind, placebo-controlled study. Journal of Clinical Oncology. 2015; 33: 4202–4209.

[38] Powles T, Huddart RA, Elliott T, Sarker SJ, Ackerman C, Jones R, *et al*. Phase III, double-blind, randomized trial that compared maintenance lapatinib versus placebo after first-line chemotherapy in patients with human epidermal growth factor receptor 1/2-positive metastatic bladder cancer. Journal of Clinical Oncology. 2017; 35: 48–55.

[39] Gatzemeier U, Groth G, Butts C, Van Zandwijk N, Shepherd F, Ardizzoni A, *et al*. Randomized phase II trial of gemcitabine-cisplatin with or without trastuzumab in HER2-positive non-small-cell lung cancer. Annals of Oncology. 2004; 15: 19–27.

[40] Makhija S, Amler LC, Glenn D, Ueland FR, Gold MA, Dizon DS, *et al*. Clinical activity of gemcitabine plus pertuzumab in platinum-resistant ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Journal of Clinical Oncology. 2010; 28: 1215–1223.

[41] Kurzeder C, Bover I, Marmé F, Rau J, Pautier P, Colombo N, *et al*. Double-blind, placebo-controlled, randomized phase III trial evaluating pertuzumab combined with chemotherapy for low tumor human epidermal growth factor receptor 3 Mrna—expressing platinum-resistant ovarian cancer (PENELOPE). Journal of Clinical Oncology. 2016; 34: 2516–2525.

[42] Bang Y, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki 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. The Lancet. 2010; 376: 687–697.

[43] Safran HP, Winter K, Ilson DH, Wigle D, DiPetrillo T, Haddock MG, *et al*. Trastuzumab with trimodality treatment for oesophageal adenocarcinoma with HER2 overexpression (NRG Oncology/RTOG 1010): a multicentre, randomised, phase 3 trial. The Lancet Oncology. 2022; 23: 259–269.

[44] Oudard S, Culine S, Vano Y, Goldwasser F, Théodore C, Nguyen T, *et al*. Multicentre randomised phase II trial of gemcitabine+platinum, with or without trastuzumab, in advanced or metastatic urothelial carcinoma overexpressing Her2. European Journal of Cancer. 2015; 51: 45–54.

[45] Esaki T, Tsukuda H, Machida N, Ishida H, Kadowaki S, Minashi K, *et al*. A randomized phase II study to assess trastuzumab beyond progression

in HER2-positive advanced gastric cancer: WJOG7112G. Annals of Oncology. 2018; 29: vii55.

[46] Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (HER2) in cancers: overexpression and therapeutic implications. Molecular Biology International. 2014; 2014: 1–9.

[47] Lei Y, Huang J, Zhao Q, Jiang N, Xu H, Wang Z, *et al*. The clinicopathological parameters and prognostic significance of HER2 expression in gastric cancer patients: a meta-analysis of literature. World Journal of Surgical Oncology. 2017; 15: 68.

[48] Zhao J, Xu W, Zhang Z, Song R, Zeng S, Sun Y, *et al*. Prognostic role of HER2 expression in bladder cancer: a systematic review and meta-analysis. International Urology and Nephrology. 2015; 47: 87–94.

[49] Pyo J, Kang G, Park K. Clinicopathological significance and diagnostic accuracy of HER2 immunohistochemistry in colorectal cancer: a meta-analysis. The International Journal of Biological Markers. 2016; 31: e389–e394.

[50] Jhaveri KL, Wang XV, Makker V, Luoh SW, Mitchell EP, Zwiebel JA, *et al*. Ado-trastuzumab emtansine (T-DM1) in patients with HER2-amplified tumors excluding breast and gastric/gastroesophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH trial (EAY131) subprotocol Q. Annals of Oncology. 2019; 30: 1821–1830.

[51] Itkin B, Garcia A, Straminsky S, Adelchanow ED, Pereyra M, Haab GA, *et al*. Prevalence of HER2 overexpression and amplification in cervical cancer: a systematic review and meta-analysis. PLOS ONE. 2021; 16: e0257976.

[52] Janjigian YY, Maron SB, Chatila WK, Millang B, Chavan SS, Alterman C, *et al*. First-line pembrolizumab and trastuzumab in her2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial. The Lancet Oncology. 2020; 21: 821–831.

[53] Siena S, Di Bartolomeo M, Raghav K, Masuishi T, Loupakis F, Kawakami H, *et al*. Trastuzumab deruxtecan (DS-8201) in patients with her2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. The Lancet Oncology. 2021; 22: 779–789.

[54] Sodergren SC, Copson E, White A, Efficace F, Sprangers M, Fitzsimmons D, *et al*. Systematic review of the side effects associated with anti-HER2-targeted therapies used in the treatment of breast cancer, on behalf of the EORTC quality of life group. Targeted Oncology. 2016; 11: 277–292.

[55] Zraik IM, Heß-Busch Y. Management of chemotherapy side effects and their long-term sequelae. Urologe A. 2021; 60: 862–871. (In German)

How to cite this article: Xuan Chen, Yuqing Li, Yufu Lu, Mingfei Lin. Efficacy and safety of *anti-HER2* therapy in solid tumors except breast cancer: a systematic-review and meta-analysis. European Journal of Gynaecological Oncology. 2025; 46(1): 10-22. doi: 10.22514/ejgo.2025.002.