



Meta-Analysis of Paclitaxel-Based Chemotherapy Combined With Traditional Chinese Medicines for Gastric Cancer Treatment

Yicong Li^{1†}, Xinbing Sui^{2,3†}, Zeqi Su⁴, Chunyue Yu¹, Xiaoguang Shi⁵, OPEN ACCESS Nadia L. Johnson¹, Fuhao Chu², Yuan Li¹, Kexin Li¹ and Xia Ding^{2*}

Edited by:

Jiangjiang Qin, Zhejiang Chinese Medical University, China

Reviewed by:

Xu Tian, Chongqing University, China Xiao Ma, Chengdu University of Traditional Chinese Medicine, China

*Correspondence:

Xia Ding dingx@bucm.edu.cn [†]These authors have contributed equally to this work

Specialty section:

This article was submitted to Pharmacology of Anti-Cancer Drugs, a section of the journal Frontiers in Pharmacology

> Received: 26 November 2019 Accepted: 31 January 2020 Published: 27 February 2020

Citation:

Li Y, Sui X, Su Z, Yu C, Shi X, Johnson NL, Chu F, Li Y, Li K and Ding X (2020) Meta-Analysis of Paclitaxel-Based Chemotherapy Combined With Traditional Chinese Medicines for Gastric Cancer Treatment. Front. Pharmacol. 11:132. doi: 10.3389/fphar.2020.00132 Nadia L. Johnson¹, Fuhao Chu², Yuan Li¹, Kexin Li¹ and Xia Ding^{2*} ¹ Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, ² School of Traditional Chinese Medicine,

Beijing University of Chinese Medicine, Beijing, China, ³ Department of Cancer Pharmacology, Holistic Integrative Pharmacy Institutes, College of Medicine, Hangzhou Normal University, Hangzhou, China, ⁴ Beijing Research Institute of Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China, ⁵ Department of Surgery, Dongzhimen Hospital of Beijing University of Chinese Medicine, Beijing, China

This study aimed to compare the efficacy and safety of traditional Chinese medicines (TCMs) combined with paclitaxel-based chemotherapy and paclitaxel-based chemotherapy alone for gastric cancer treatment. Literature searches (up to September 25, 2019) were performed using the Cochrane Library, EMBASE, PubMed, Chinese Science and Technology Journals (CQVIP), Wanfang, and China Academic Journals (CNKI) databases. Data from 14 randomized controlled trials (RCTs), with 1,109 participants, were included. The results indicated that, compared with paclitaxel-based chemotherapy alone, the combination of TCMs and paclitaxel-based chemotherapy significantly improved the tumor response rate (TRR: RR: 1.39: 95% CI: 1.24–1.57: p < 0.001. $l^2 = 12\%$), increased the quality of life based on the Karnofsky Performance Scale score (RR: 1.53; 95% CI: 1.19–1.96; p < 0.001, $l^2 =$ 0%), and reduced the side effects, such as neutropenia (RR: 0.68; 95% CI: 0.55–0.84; p <0.001, $l^2 = 44\%$), leukopenia (RR: 0.69; 95% CI: 0.54–0.90; p < 0.01, $l^2 = 40\%$), thrombocytopenia (RR: 0.66; 95% CI: 0.46–0.96; p < 0.05, $l^2 = 32\%$), and nausea and vomiting (RR: 0.50; 95% CI: 0.32–0.80; p < 0.01, $l^2 = 85\%$). Hepatic dysfunction (RR: 0.63; 95% CI: 0.33–1.20; p = 0.16, $l^2 = 0$ %), neurotoxicity (RR: 0.64; 95% CI: 0.26–1.55; p = 0.32, $l^2 = 0\%$), and anemia (RR: 0.65; 95% CI: 0.40–1.04; p = 0.07, $l^2 = 0\%$) were similar between the two groups. Evidence from the meta-analysis suggested that compared with paclitaxelbased chemotherapy alone, the combination of TCMs and paclitaxel-based chemotherapy may increase the TRR, improve quality of life, and reduce multiple chemotherapy-related side effects in gastric cancer patients. Additional rigorously designed large RCTs are required to confirm the efficacy and safety of this treatment.

Keywords: gastric cancer, paclitaxel, traditional Chinese medicine, chemotherapy, meta-analysis

INTRODUCTION

Gastric cancer (GC) is the fifth-most commonly diagnosed cancer and the third leading cause of cancer-related death in the world. In 2018, there were more than 1,000,000 new GC cases and GC resulted in an estimated 783,000 deaths (Bray et al., 2018). Despite the progress in diagnosis and treatment, the initial detection of most GC cases occurs at advanced stages, which leads to poor prognosis, with a median overall survival of 11 months (Wagner et al., 2017). Currently, chemotherapy is widely used as the main treatment for GC. However, the side effects and the development of resistance to chemotherapy in clinical practice reveal its limitations and have prompted more attention to be paid to the study of complementary treatments (Biagioni et al., 2019).

Paclitaxel is a widely used second-line chemotherapy drug for advanced GC (Bang et al., 2017). However, it has a low response rate (16–22%) (Bang et al., 2002) and significant side effects (such as neutropenia and gastrointestinal adverse reactions) (Shitara et al., 2010), so a paclitaxel-based combination regimen may be more beneficial.

Traditional Chinese medicines (TCMs), which can be used as complementary treatments for cancer patients, have been widely used in China for years (Wong et al., 2001; Chen et al., 2016). TCM combinations have been reported to alleviate chemotherapy drug resistance and enhance the efficacy of chemotherapy. However, it remains uncertain whether paclitaxel-based chemotherapy combined with TCMs is more effective than paclitaxel-based chemotherapy alone for GC.

In this study, we aimed to use a meta-analysis to summarize and analyze high-quality RCTs in order to evaluate the efficacy and safety of combination therapy using paclitaxel and TCMs compared to paclitaxel alone for GC. We further aimed to identify the most frequently used TCM herbal compounds in order to provide a reference for the selection of a reasonable TCM regimen for the treatment of GC.

MATERIALS AND METHODS

Study Selection

Databases, comprising PubMed, EMBASE, Cochrane Library, Wanfang, Chinese Science and Technology Journals (CQVIP), and China Academic Journals (CNKI), were independently searched from their inceptions to September 25, 2019 by two reviewers (Yicong Li and Chunyue Yu). The search terms (in English and Chinese) involved the following: "paclitaxel OR Taxol" AND "Chinese herb OR traditional medicine" AND "stomach neoplasm OR gastric neoplasm OR stomach cancer OR gastric cancer". There was no restriction on the language. The Jadad scale was used to assess study quality (Jadad et al., 1996).

Inclusion and Exclusion Criteria

Studies were included if they met the following PICOS criteria: (1) participants: GC patients (diagnosed based on pathology results); (2) intervention: paclitaxel-based chemotherapy

regimen combined with TCM; (3) comparator: paclitaxel-based chemotherapy regimen alone; (4) outcomes: tumor response rate (TRR), Karnofsky Performance Scale (KPS) score, and/or side effects (at least one of these outcomes); (5) study design: randomized controlled trial (RCT).

The exclusion criteria were as follows: (1) outcomes not reported clearly or appropriate data could not be extracted; (2) Jadad score <2; (3) duplicate studies by the same authors.

Data Extraction

All the included studies were screened independently by two reviewers (Yicong Li and Chunyue Yu) to extract the following data: first author (year), study period, sample sizes, tumor, node, metastasis (TNM) stage, TCM intervention, paclitaxel regimen, drug administration route, treatment duration, and outcomes. Any differences were resolved by discussion between the two reviewers, and differences that could not be resolved were settled by a third reviewer (Xinbing Sui).

Risk of Bias Assessment

We used the Cochrane risk of bias tool (Higgins et al., 2011) to assess the risk of bias of the RCTs. The domains of this tool include selection bias, performance bias, detection bias, attrition bias, and reporting bias. Low, high, and unclear risk of bias indicate that the study met the criteria, did not meet the criteria, and did not provide enough information to make a judgment, respectively.

Primary Outcomes

Tumor response rate (TRR), containing the criteria of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), was the primary outcome. CR plus PR was also included as TRR. Subgroup analyses were then used to assess whether there was a difference in TRR between the paclitaxel+TCM and control groups in various subgroups of studies, according to administration route (studies were categorized into an oral administration subgroup in which TCMs were taken orally as a decoction or capsules [seven studies] or an injection subgroup [six studies]), TNM stage (studies were categorized into a stage IV-only subgroup [two studies] or other stages subgroup [eleven studies]), treatment duration (studies were categorized into ≤ 4 weeks [four studies], 4–8 weeks [six studies], and >8 weeks [three studies] subgroups), and the three most commonly used TCM combinations (studies were categorized into overlapping subgroups depending on whether they used a combination of Dangshen and Gancao [eight studies], Dangshen, Gancao, Baizhu and Fuling [seven studies], or Dangshen, Gancao, Baizhu, Fuling, Chenpi, Shanyao, Yiyiren, and Sharen [three studies]).

Secondary Outcomes

KPS score was used to assess quality of life (QOL). Improvement of QOL was defined as a KPS score increase of ≥ 10 points after treatment. Side effects, which included blood abnormalities (neutropenia, leukopenia, anemia, and thrombocytopenia), nausea and vomiting, hepatic dysfunction, and neurotoxicity, were also evaluated as secondary outcomes.

Data Analysis

Cochrane Review Manager (RevMan) software version 5.3 was utilized for statistical analysis. Risk ratio (RR) with a 95% confidence interval (CI) for the dichotomous outcomes was used to estimate the pooled effects. Heterogeneity was estimated by Cochran's Q test and assessed using I^2 . A fixed-effects model was used to estimate the pooled effect when heterogeneity was absent ($I^2 < 50\%$). Otherwise, a random-effects model was used to assess publication bias regarding TRR data.

RESULTS

Literature Search

As shown in **Figure 1**, 237 articles were retrieved in the literature search. After removal of duplicate articles, 165 articles remained. After reviewing the titles and abstracts, 100 irrelevant articles

were excluded. After adding two articles based on a review of the references of the remaining 65 articles, there were 67 articles. The full-text articles were then evaluated based on the inclusion and exclusion criteria, and 53 articles were excluded due to: Jadad score <2 (n = 22), not being an RCT (n = 19), not providing a clear evaluation of tumor responses (n = 7), duplicate reports (n = 3), and comparator not based on paclitaxel (n = 2). Further details are shown in **Supplementary Table 1**. Fourteen articles were finally included in our meta-analysis.

Study Characteristics

The main characteristics of the 14 included studies are shown in **Table 1**. The publication years ranged from 2009 to 2018 and there were 1,109 included patients, with 502 in the paclitaxel +TCM group and 506 in the control group.

Risk of Bias and Methodological Quality

We selected the risk of bias tool provided by the Cochrane Collaboration (Higgins et al., 2011) to assess the risk of bias of the included studies. All of the included studies exhibited bias



First Author (Year)	Study Period	Sample size (T/C n)	TNM Stage	Drug Delivery	TCM Duration	TCM Intervention	Paclitaxel Regimen	TRR (T/C n)
Chen (2009)	2005–2007	34/33	IIIb: 23/24; IV: 11/9	Injection	6w	Huachansu injection	TPF: PTX+PDD+5-FU	15/12
Ge et al. (2014)	NR	20/20	Advanced stage	Orally	8w	Jianpixiaozheng decoction	TS: PTX+S-1	10/9
Huang et al. (2018)	2015–2016	50/50	Advanced stage	Injection	18w	Kanglaite injection + Jianpiyiqi decoction	TP: PTX+PDD	35/20
Lai et al. (2018)	2015-2018	30/30	IV	Orally	6w	Shenlingbaizhu decoction	TCF: PTX+CF+5-FU	NR
Li N. J., et al (2016)	2013–2014	25/25	Advanced stage	Orally	4w	Rg3+Shenyi capsule	TCF: PTX+CF+5-FU	17/11
Li et al. (2010)	2007-2009	42/40	Advanced stage	Orally	22d	Liujunzi decoction	TCF: PTX+CF+5-FU	25/23
Li et al. (2016a)	2012–2015	33/32	IV	Injection	8w	Fufangkushen injection + Yiqiyangwei decoction	PTX	27/18
Li et al. (2016b)	2014–2015	50/50	Advanced stage	Orally	8w	Shenlingbaizhu decoction	TS: PTX+S-1	27/22
Liao (2018)	2015-2016	31/31	Advanced stage	Injection	4w	Kang'ai injection	PTX+CF	27/19
Liu and Zhang (2009)	2006–2008	30/30	IIIb: 17/14; IV: 13/ 16	Injection	20d	Aidi injection	TPF: PTX+PDD+5-FU	16/16
Meng (2019)	2015-2016	50/50	III: 34/36; IV: 16/14	Injection	12w	Fufangkushen injection	PTX	35/15
Tan et al. (2013)	2007–2011	40/46	IV	Orally	6w	Fufangbanmao capsule	PTX+5-FU+LV	19/12
Xue and Mao (2017)	2013–2015	45/45	Advanced stage	Orally	8w	Rg3	TCF: PTX+CF+5-FU	35/28
You and Huang (2009)	2007–2008	22/24	III:6/5; IV:16/19	Orally	24w	Fuzhenghewei liquid medicament	TP: PTX+PDD/TCF: PTX +CF+5-FU	8/8

 TABLE 1 | Characteristics of the included studies.

T, treatment group; C, control group; TNM, cancer staging system; NR, not reported; TCM, traditional Chinese medicine, TRR, tumor response rate; w, week; d, day; PTX, paclitaxel; PDD, cisplatin; 5-FU, 5-fluorouracil; CF, calcium folinate; LV, leucovorin.

according to at least one of the bias categories. "Random" or "randomized" or "randomization" was mentioned in all 14 studies, along with descriptions of the specific randomization methods. One study reported allocation concealment and blinding of participants and healthcare providers, but there was unclear blinding of outcome assessment (Ge et al., 2014). One study lacked essential data TRR (Lai et al., 2018), while the other 13 studies reported detailed outcome data. None of the 14 studies provided clear descriptions of detection bias, reporting bias, or other bias. **Figure 2** shows detailed overviews of the scores in each bias category for each study.

Meta-Analysis of TRR

We extracted the TRR data from 13 of the 14 included studies. The fixed-effects meta-analysis showed that the TRR was significantly improved in the paclitaxel+TCM group compared to the control group (RR: 1.39; 95% CI: 1.24–1.57; p < 0.001, $I^2 = 12\%$) (**Figure 3**).

Regarding the administration route subgroup analysis, the TRR was significantly enhanced in the paclitaxel+TCM group compared with the control group in the oral administration subgroup (seven studies; RR: 1.55; 95% CI: 1.31–1.84; p < 0.001, $I^2 = 0\%$) and the injection subgroup (six studies; RR: 1.24; 95% CI: 1.05–1.47; p < 0.05, $I^2 = 0\%$) (**Figure 3**).

Regarding the TNM subgroup analysis, the TRR was significantly improved in the paclitaxel+TCM group compared with the control group in the stage IV-only subgroup (two studies; RR: 1.59; 95% CI: 1.16–2.18; p < 0.01, $I^2 = 0\%$) and the other stages subgroup (eleven studies; RR: 1.36; 95% CI: 1.20–1.55; p < 0.001, $I^2 = 20\%$) (**Figure 4**).

Regarding the treatment duration subgroup analysis, there were no significant effects on TRR in the ≤ 4 weeks subgroup (four studies; RR: 1.21; 95% CI: 0.99–1.48; p = 0.06, $I^2 = 6\%$), but there was significant improvement in the 4–8 weeks subgroup

(six studies; RR: 1.33; 95% CI: 1.12–1.58; p < 0.01, $I^2 = 0\%$) and the >8 weeks subgroup (three studies; RR: 1.84; 95% CI: 1.39–2.42; p < 0.001, $I^2 = 28\%$) (**Figure 5**).

Meta-Analysis of KPS

The fixed-effects meta-analysis showed a significant difference between the two groups in the rate of KPS improvement (≥ 10 points) (four studies; RR: 1.53; 95% CI: 1.19–1.96; p < 0.001, $I^2 = 0\%$) (**Figure 6**). The KPS was significantly higher in the paclitaxel +TCM group than the control group. The results indicated that, compared with paclitaxel-based chemotherapy alone, combined therapy with TCMs can significantly improve the QOL of patients with GC.

Meta-Analysis of Blood Abnormalities

The fixed-effects meta-analyses showed significant decreases in the paclitaxel+TCM group in the rate of neutropenia (five studies; RR: 0.68; 95% CI: 0.55–0.84; p < 0.001, $I^2 = 44\%$), the rate of leukopenia (four studies; RR: 0.69; 95% CI: 0.54–0.90; p < 0.01, $I^2 = 40\%$), and the rate of thrombocytopenia (six studies; RR: 0.66; 95% CI: 0.46–0.96; p < 0.05, $I^2 = 32\%$) (**Figure 7**). The rate of anemia did not differ significantly (five studies; RR: 0.65; 95% CI: 0.40–1.04; p = 0.07, $I^2 = 0\%$) (**Figure 7**). The results showed that paclitaxel-based chemotherapy combined with TCMs significantly reduced the rate of neutropenia, leukopenia, and thrombocytopenia, but had no significant effect on the rate of anemia during the treatment of GC.

Meta-Analysis of Nausea and Vomiting, Hepatic Dysfunction, and Neurotoxicity

The random-effects meta-analysis showed a significantly lower rate of nausea and vomiting in the paclitaxel+TCM group compared to the control group (eight studies; RR: 0.50; 95%



FIGURE 2 [Risk of bias summary and diagram. (A) Risk of bias summary: review of authors' judgments about each risk of bias item for all included studies. (B) Risk of bias diagram: review of authors' judgments about each risk of bias item presented as percentages across all included studies. Red, green, and yellow indicate high, low, and unclear risk of bias, respectively.

CI: 0.32–0.80; p < 0.01, $I^2 = 85\%$). However, there were no significant differences in hepatic dysfunction (three studies; RR: 0.63; 95% CI: 0.33–1.20; p = 0.16, $I^2 = 0\%$) or neurotoxicity (three studies; RR: 0.64; 95% CI: 0.26–1.55; p = 0.32, $I^2 = 0\%$) (**Figure 8**). Regarding the analysis of nausea and vomiting, a random-effects model was used to calculate the pooled RR (and 95% CI) due to significant heterogeneity (p < 0.001, $I^2 = 72\%$). These results indicated that paclitaxel combined with TCMs can significantly reduce nausea and vomiting compared to paclitaxel-based chemotherapy alone, without causing additional hepatic dysfunction or neurotoxicity.

TCM Formulae and Frequently Used Herbal Compounds

Among the studies in the oral administration subgroup that used multi-ingredient TCM regimens, there were eight studies with a total of 29 TCM ingredients. Nine of these ingredients were used in four or more formulations. Ordered according to their frequency of use, the TCMs were as follows: Dangshen (n = 8), Gancao (n = 8), Baizhu (n = 7), Fuling (n = 7), Chenpi (n = 5), Banxia (n = 4), Shanyao (n = 4), Yiyiren (n = 4), and Sharen (n = 4) (**Table 2** and **Figure 9**). Using fixed-effects models, we performed a subgroup analysis of the three most commonly used combinations. Regarding the subgroup involving the

combination of Dangshen and Gancao, TRR was significantly improved in the paclitaxel+TCM group compared to the control group (eight studies; RR: 1.44; 95% CI: 1.22–1.70; p < 0.001, $I^2 =$ 40%). Moreover, regarding the subgroup involving the combination of Dangshen, Gancao, Baizhu and Fuling, there was a significant improvement (seven studies; RR: 1.31; 95% CI: 1.09–1.56; p < 0.01, $I^2 = 0$ %). Furthermore, regarding the subgroup involving the combination of Dangshen, Gancao, Baizhu, Fuling, Chenpi, Shanyao, Yiyiren, and Sharen, there was also a significant improvement (three studies; RR: 1.30; 95% CI: 1.20–1.41; p < 0.001, $I^2 = 0$ %).

Publication Bias

A funnel plot of the 13 studies that reported TRR data was used to assess publication bias (**Figure 10**). The funnel plot was asymmetrical, indicating the existence of publication bias.

DISCUSSION

Paclitaxel, which is a representative second-line chemotherapy drug for GC, is generally recognized as being able to inhibit cancer (Zhang et al., 2019). However, because of its stronger side effects compared with the first-line chemotherapy drugs, it

[
	Study or Subgroup	E: Ev

1.1 Tumor Response Rate (<i>Total Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen HM 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.9, 2.57] ITC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] IZ 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] IZ 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] ato LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] tetrogeneity: Ch ² = 1.36, df = 12 (P = 0.32); l ² = 12% est for overall effect: Z = 5.45 (P < 0.00001) 1.1 Tumor Response Rate (<i>Oral Administration Group</i>) HE 2016 27 50 22 50 5.2% 1.23 [0.92, 2.59] IZ 2016 27 50 22 50 5.2% 1.23 [0.92, 2.59] tetrogeneity: Ch² = 1.5.63, df = 12 (P = 0.32); l² = 12% est for overall effect: Z = 5.45 (P < 0.00001) 1.1 Tumor Response Rate (<i>Injection Administration Group</i>) HE 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] IZ 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] ato LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] Herg QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ubit 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] ato LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] Herg QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ubit 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] ato LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] Herg QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ubit 2016 27 50 (22 50 5.5% 1.55 [1.31, 1.84] dotal events 160 US 2019 25 22 22 24 24.5% 1.55 [1.31, 1.84] dotal events 160 HI 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] HI 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] Ubit 2014 205 21 258 24.5% 1.55 [1.31, 1.84] dotal events 160 HI 2014 10 20 9 20 2.1% 1.11 [0.57, 2.19] HI 2015 25 42 22 34 05 5.5% 1.24 [1.05, 1.47] HI 2014 2015 25 42 22 34 05 5.5% 1.24 [1.05, 1.47] HI 2014 2015 25 42 23 40 5.5% 1.24 [1.05, 1.47] HI 2014 2015 25 42 25 42 45 6.6% 1.25 [0.95, 1.65] HI 2014 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] HI 2014 2017 35 45 24 45 6.6% 1.25 [0.95, 1.65] HI 2014 2017 35 45 24 45 6.6	Study or Subgroup	Events T	Total Ev	vents	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
hen HW 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] e HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] ung HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] IT C 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] I C 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] I 2 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] I 2 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] I L H 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] I L H 2019 35 50 15 50 3.5% 2.03 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] otal events 296 213 eterogeneity: Ch ² = 13.63, df = 12 ($P = 0.32$); $l^2 = 12\%$ est for overall effect: Z = 5.65 ($P < 0.00001$) 1.2 Tumor Response Rate (<i>Oral Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] eterogeneity: Ch² = 5.79, df = 6 ($P = 0.05$); $l^2 = 0\%$ est for overall effect: Z = 5.05 ($P < 0.00001$) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] eterogeneity: Ch² = 5.79, df = 6 ($P = 0.05$); $l^2 = 0\%$ est for overall effect: Z = 5.05 ($P < 0.00001$) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] eterogeneity: Ch² = 5.79, df = 6 ($P = 0.05$); $l^2 = 0\%$ est for overall effect: Z = 5.05 ($P < 0.00001$) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] eterogeneity: Ch² = 5.79, df = 6 ($P = 0.05$); $l^2 = 0\%$ est for overall effect: Z = 5.05 ($P < 0.00001$) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2019 16 30 16 30 3.8% 1.00 [0.62, 1.61] 1.3 Unor 3.55 4.52 4.24 5.5% 1.24 [1.05, 1.47] 1.3 Cunor 3.5 4.52 2.42 4.5% 1.55 [1.31, 1.84] 1.3 Lang Administration Group) hen HM 2019 16 30 16 30 3.8% 1.00 [0.62, 1.61] 1.3 Unor 3.5 4.52 2.42 4.5% 1.55 [1.31, 1.65] 1.3 Lang Administration Group) hen HM 2019 16 30 16 30 3.8% 1.00 [0.62, 1.61] 1.3 Unor 3.5 4.52 2.42 4.55% 1.24 [1.05, 1.47] 1.3 Cunor 3.5 4.52 2.42 4.56% 1.55 [1.31, 1.24] 1	1.1.1 Tumor Respon	ise Rate (<i>Tot</i>	tal Grou	(p)				
e HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] [F 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] T C 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] T C 2016 27 50 22 50 5.2% 1.35 [0.92, 2.59] [Z P 2016 27 50 22 50 5.2% 1.32 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.45 [1.03, 2.05] L P 2016 30 16 30 3.8% 1.00 [0.62, 1.61] leng Q 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ubtotal (95% CI) 472 476 50.0% 1.39 [1.24, 1.57] otal events 296 213 letreogeneity: Ch ² = 13.63, df = 12 (P = 0.32); l ² = 12% est for overall effect: Z = 5.45 (P < 0.00001) L12 Tumor Response Rate (Oral Administration Group) H 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2016 27 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 251 258 24.5% 1.55 [0.92, 2.59] I 2 2016 27 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 leterogeneity: Ch ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.00001) .1.3 Tumor Response Rate (Injection Administration Group) hen HM 2009 16 30 16 30 3.8% 1.04 [0.72, 1.49] ubtotal (95% CI) 251 42 23 40 5.5% 1.24 [1.05, 2.19] e HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] IT C 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] u LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] TT C 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] u LH 2014 10 20 9 20 2.1% 1.75 [1.19, 2.57] TT C 2010 25 42 23 40 5.5% 1.24 [1.05, 1.47] otal events 136 108 tetroogeneity: Chi ² = 4.93, df = 5 (P = 0.42). I ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Chen HM 2009	15	34	12	33	2.9%	1.21 [0.67, 2.19]	
uang HT 2018 35 50 20 50 4.7% 1.75 $[1.19, 2.57]$ IF 2016 17 25 11 25 2.6% 1.55 $[0.92, 2.59]$ IT C 2010 25 42 23 40 5.5% 1.04 $[0.72, 1.49]$ IZ 2016 27 33 18 32 4.3% 1.45 $[1.03, 2.05]$ IZ 2016 27 31 19 31 4.5% 1.42 $[1.04, 1.94]$ Iu LH 2009 16 30 16 30 3.5% 2.33 $[1.47, 3.70]$ an Y 2013 19 40 12 46 2.6% 1.82 $[1.01, 3.27]$ ub Z 2017 35 45 28 45 6.6% 1.25 $[0.92, 2.59]$ I Z 2016 27 33 18 32 4.3% 1.45 $[1.03, 2.05]$ au JZ 2017 35 45 28 45 6.6% 1.55 $[0.92, 2.59]$ Ub Z 2017 35 45 28 45 50.0% 1.39 $[1.24, 1.57]$ Otal events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 (P = 0.32); l ² = 12% est for overall effect: Z = 5.45 (P < 0.00001) 1.2 Tumor Response Rate (Oral Administration Group) Heterogeneity: Chi ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.00001) 1.3 Tumor Response Rate (Oral Administration Group) Het Q12 019 35 50 15 50 3.5% 2.33 $[1.47, 3.70]$ an Y 2013 19 40 12 46 2.6% 1.42 $[1.04, 1.94]$ Het Q10 10 7 25 11 25 2.6% 1.55 $[0.92, 2.59]$ I Z 2016 27 31 18 32 4.3% 1.42 $[1.04, 1.94]$ Het Q10 2019 35 50 15 50 3.5% 2.33 $[1.47, 3.70]$ and Y 2013 19 40 12 46 2.6% 1.428 $[1.01, 3.27]$ ou JL 2009 8 22 8 24 1.8% 1.09 $[0.49, 2.41]$ ubtotal (95% CI) 251 258 24.5% 1.55 $[1.31, 1.84]$ otal events 160 105 Het rogeneity: Chi ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.00001) 1.3 Tumor Response Rate (Injection Administration Group) hen HM 2009 15 34 12 33 2.9% 1.21 $[0.67, 2.19]$ He HL 2014 10 20 9 20 2.1% 1.11 $[0.58, 2.14]$ ubtotal (95% CI) 221 218 25.5% 1.24 $[1.05, 1.47]$ otal events 136 108 Heterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01) 1.4 Unt 2009 16 30 16 30 3.8% 1.00 $[0.62, 1.61]$ ubtotal (95% CI) 221 228 24 40 5.5% 1.24 $[1.05, 1.47]$ otal events 136 108 Heterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Ge HL 2014	10	20	9	20	2.1%	1.11 [0.58, 2.14]	
i E $\frac{1}{2}$ O16 17 25 11 25 2.6% 1.55 $[0.92, 2.59]$ TT C 2010 25 42 23 40 5.5% 1.04 $[0.72, 1.49]$ TT C 2016 27 33 18 32 4.3% 1.45 $[1.03, 2.05]$ i Z P 2016 27 50 22 50 5.2% 1.23 $[0.82, 1.84]$ iao LF 2018 27 31 19 31 4.5% 1.42 $[1.04, 1.94]$ iu LH 2009 16 30 16 30 3.8% 1.00 $[0.62, 1.61]$ leng QJ 2019 35 50 15 50 3.5% 2.33 $[1.47, 3.70]$ an Y 2013 19 40 12 46 2.6% 1.82 $[1.01, 3.27]$ ue JZ 2017 35 45 28 45 6.6% 1.25 $[0.95, 1.65]$ ou JL 2009 8 22 8 24 1.8% 1.09 $[0.49, 2.41]$ ubtotal (95% Ct) 472 476 50.0% 1.39 $[1.24, 1.57]$ otal events 296 213 tetreogeneity: Ch ² = 13.63, df = 12 (P = 0.32); l ² = 12% est for overall effect: Z = 5.45 (P < 0.00001) 1.2 Tumor Response Rate (Oral Administration Group) i EJ 2016 27 50 22 50 5.2% 1.23 $[0.82, 1.84]$ iao LF 2018 27 51 12 25 2.6% 1.55 $[0.92, 2.59]$ i Z 2016 27 50 22 50 5.2% 1.23 $[1.47, 3.70]$ an Y 2013 19 40 12 46 2.6% 1.82 $[1.01, 3.27]$ ou JL 2009 8 22 8 24 1.8% 1.09 $[0.49, 2.41]$ ubtotal (95% Ct) 251 258 24.5% 1.55 $[1.31, 1.84]$ otal events 160 105 teterogeneity: Ch ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.00001) 1.3 Tumor Response Rate (Injection Administration Group) hen HM 2009 15 34 12 33 2.9% 1.21 $[0.67, 2.19]$ i e HL 2014 10 20 9 20 2.1% 1.11 $[0.58, 2.14]$ uang HT 2018 35 50 20 50 4.7% 1.75 $[1.31, 1.84]$ otal events 160 105 teterogeneity: Ch ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.00001) 1.3 Tumor Response Rate (Injection Administration Group) hen HM 2009 15 34 12 33 2.9% 1.21 $[0.67, 2.19]$ i e HL 2014 10 20 9 20 2.1% 1.17 $[0.58, 2.14]$ uang HT 2018 35 50 20 50 4.7% 1.75 $[1.31, 1.84]$ otal events 136 108 tetroogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01) est for overall effect: Z = 2.54 (P = 0.01)	Huang HT 2018	35	50	20	50	4.7%	1.75 [1.19, 2.57]	
TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] IZ 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] IZ 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] tu H 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] terg QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ubtotal (95% C1) 27 476 50.0% 1.39 [1.24, 1.57] otal events 296 213 teterogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); $I^{2} = 12\%$ est for overall effect: Z = 5.45 ($P < 0.0001$) 1.2 Tumor Response Rate (<i>Oral Administration Group</i>) El 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] i Z 2016 27 33 18 32 4.3% 1.42 [1.04, 1.94] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] end Y 2013 19 40 12 46 2.6% 1.55 [0.92, 2.59] i Z 2016 27 50 (22 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] end Y 2013 19 40 12 46 2.6% 1.55 [1.31, 1.84] otal events 160 105 teterogeneity: Chi ² = 5.79, df = 6 ($P = 0.45$); $I^{2} = 0\%$ est for overall effect: Z = 5.05 ($P < 0.00001$) 1.1 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] her HW 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] u LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] u LH 2009 16 30 16 30 8.8% 1.00 [0.62, 1.61] u LH 2009 16 30 16 30 8.8% 1.00 [0.62, 1.61] u LH 2009 16 30 16 30 8.8% 1.00 [0.62, 1.61] u LH 2009 16 30 16 30 8.8% 1.00 [0.62, 1.61] u LH 2017 35 45 28 45 6.6% 1.25 [0.55], 1.65] ubtotal (95% C1) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 teterogeneity: Chi ² = 4.93, df = 5 ($P = 0.42$); $I^{2} = 0\%$ est for overall effect: Z = 2.54 ($P = 0.01$)	Li El 2016	17	25	11	25	2.6%	1.55 [0.92, 2.59]	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Li TC 2010	25	42	23	40	5.5%	1.04 [0.72, 1.49]	
$\frac{12P}{2016} = \frac{27}{50} = 50 + 52\% + \frac{123}{50} = \frac{123}{50} $	Li Z 2016	27	33	18	32	4.3%	1.45 [1.03, 2.05]	
ao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] u LH 2009 16 30 16 30 3.6% 1.00 [0.62, 1.61] leng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 472 476 50.0% 1.39 [1.24, 1.57] otal events 296 213 teterogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); $I^2 = 12%$ est for overall effect: 2 = 5.45 ($P < 0.00001$) .1.2 Tumor Response Rate (Oral Administration Group) i Z 2016 27 50 5.2% 1.23 [0.82, 1.84] ao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] au LT 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng QJ 2013 <t< td=""><td>Li ZP 2016</td><td>27</td><td>50</td><td>22</td><td>50</td><td>5.2%</td><td>1.23 [0.82, 1.84]</td><td></td></t<>	Li ZP 2016	27	50	22	50	5.2%	1.23 [0.82, 1.84]	
In LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] leng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 472 476 50.0% 1.39 [1.24, 1.57] otal events 296 213 leterogeneity: Chi ² = 1.53, df = 12 ($P = 0.32$); l ² = 12% est for overall effect: Z = 5.45 ($P < 0.00001$) 1.2 Tumor Response Rate (<i>Oral Administration Group</i>) i g 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] i Z 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] i Z 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.6% 1.09 [0.49, 2.41] ubtotal (95% CI) 251 7 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 leterogeneity: Chi² = 5.79, df = 6 ($P = 0.45$); l² = 0% est for overall effect: Z = 5.05 ($P < 0.00001$) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] u LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.55], 1.65] ubtotal (95% CI) 221 221 221 221 221 221 221 221 221 22	Liao LF 2018	27	31	19	31	4.5%	1.42 [1.04, 1.94]	
leng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] u J2 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 472 476 50.0% 1.39 [1.24, 1.57] otal events 296 213 teterogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); $I^2 = 12\%$ est for overall effect: $Z = 5.45$ ($P < 0.0001$) 1.2 Tumor Response Rate (<i>Oral Administration Group</i>) EJ 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] 12 2016 27 50 22 50 5.2% 1.25 [0.92, 2.59] 12 2016 27 50 12 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 251 258 24.5% 1.55 [3.31, 1.84] otal events 160 105 teterogeneity: Chi ² = 5.79, df = 6 ($P = 0.45$); $I^2 = 0\%$ est for overall effect: $Z = 5.05$ ($P < 0.0001$) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen HM 2009 15 34 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] hu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] u LH 2009 16 30 4.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 ($P = 0.42$); $I^2 = 0\%$ est for overall effect: $Z = 2.54$ ($P = 0.042$); $I^2 = 0\%$ est for overall effect: $Z = 2.54$ ($P = 0.042$); $I^2 = 0\%$ est for overall effect: $Z = 2.54$ ($P = 0.042$); $I^2 = 0\%$ est for overall effect: $Z = 2.54$ ($P = 0.042$); $I^2 = 0\%$	Liu LH 2009	16	30	16	30	3.8%	1.00 [0.62, 1.61]	
an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] uo JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 472 476 50.0% 1.39 [1.24, 1.57] otal events 296 213 teterageneity: Chi ² = 13.63, df = 12 ($P = 0.32$); $I^2 = 12\%$ est for overall effect: Z = 5.45 ($P < 0.00001$) 1.2 Tumor Response Rate (<i>Oral Administration Group</i>) EJ 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] i Z 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] i Z 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] i Z 2016 27 50 22 50 5.2% 1.23 [0.43, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 tetrerageneity: Chi ² = 5.79, df = 6 ($P = 0.45$); $I^2 = 0\%$ est for overall effect: Z = 5.05 ($P < 0.00001$) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] he HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] ubtotal (95% CI) 251 42 23 40 5.5% 1.04 [0.72, 1.49] iu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.51, 1.65] ubtotal (95% CI) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 tetrogeneity: Chi ² = 4.93, df = 5 ($P = 0.42$); $I^2 = 0\%$ est for overall effect: Z = 2.54 ($P = 0.01$)	Meng OI 2019	35	50	15	50	3.5%	2.33 [1.47, 3.70]	
$\begin{array}{c} ue 2 \ 2017 & 35 & 45 & 28 & 45 & 6.6\% & 1.25 \ [0.95, 1.65] \\ ou 1. 2009 & 8 & 22 & 8 & 24 & 1.8\% & 1.09 \ [0.49, 2.41] \\ ubtotal (95\% CI) & 472 & 476 & 50.0\% & 1.39 \ [1.24, 1.57] \\ otal events & 296 & 213 \\ eterogeneity: Chi^2 = 13.63, df = 12 \ (P = 0.32); l^2 = 12\% \\ est for overall effect Z = 5.45 \ (P < 0.00001) \\ \hline 1.2 \ Tumor Response Rate (Oral Administration Group) \\ i \ El \ 2016 & 17 & 25 & 11 & 25 & 2.6\% & 1.55 \ [0.92, 2.59] \\ i \ El \ 2016 & 27 & 33 & 18 & 32 & 4.3\% & 1.45 \ [1.03, 2.05] \\ i \ Z \ 2016 & 27 & 50 & 22 & 50 & 5.2\% & 1.23 \ [0.82, 1.84] \\ iao \ LF \ 2018 & 27 & 31 & 19 & 31 & 4.5\% & 1.42 \ [1.04, 1.94] \\ eng \ Ql \ 2019 & 35 & 50 & 15 & 50 & 3.5\% & 2.33 \ [1.47, 3.70] \\ an \ Y \ 2013 & 19 & 40 & 12 & 46 & 2.6\% & 1.55 \ [1.33, 1.84] \\ otal events & 160 & 105 \\ eterogeneity: \ Chi^2 = 5.79, \ df = 6 \ (P = 0.45); \ l^2 = 0\% \\ est \ for overall effect Z = 5.05 \ (P < 0.00001) \\ \hline 1.3 \ Tumor Response Rate (Injection Administration Group) \\ hen \ HM \ 2009 & 15 & 34 & 12 & 33 & 2.9\% & 1.21 \ [0.67, 2.19] \\ hen \ HM \ 2009 & 15 & 34 & 12 & 33 & 2.9\% & 1.21 \ [0.67, 2.19] \\ hen \ HM \ 2009 & 15 & 34 & 12 & 33 & 2.9\% & 1.21 \ [0.67, 2.19] \\ hen \ HM \ 2009 & 16 & 30 & 16 & 30 & 3.8\% & 1.00 \ [0.62, 1.61] \\ uu \ U \ 22017 & 35 & 45 & 28 & 45 & 6.6\% & 1.25 \ [0.55] \ 1.24 \ [1.05, 1.47] \\ otal events & 136 & 108 \\ eterogeneity: \ Chi^2 = 4.93, \ df = 5 \ (P = 0.42); \ l^2 = 0\% \\ est \ for overall effect Z = 2.54 \ (P = 0.01) \\ \hline \end \ eterogeneity: \ Chi^2 = 4.93, \ df = 5 \ (P = 0.42); \ l^2 = 0\% \\ est \ for overall effect Z = 2.54 \ (P = 0.01) \\ \hline \end \ 2018 \ 201$	Tan Y 2013	19	40	12	46	2.6%	1.82 [1.01, 3.27]	
bu jL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 472 476 50.0% 1.39 [1.24, 1.57] otal events 296 213 leterogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); l ² = 12% est for overall effect: Z = 5.45 ($P < 0.00001$) .1.2 Tumor Response Rate (Oral Administration Group) i Z 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] i Z 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] i Z 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] i ao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng Q 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.55 [1.31, 1.84] otal events 160 105 leterogeneity: Chi ² = 5.79, df = 6 ($P = 0.45$); l ² = 0% est for overall effect: Z = 5.05 ($P < 0.00001$) .1.3 Tumor Response Rate (Injection Administration Group) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] le HL 2014 10 20 9 20 2.11% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] lu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue J2 2017 35 45 28 45 6.6% 1.25 [0.55], 1.65] ubtotal (95% CI) 221 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 ($P = 0.42$); l ² = 0% est for overall effect: Z = 5.54 ($P = 0.042$); l ² = 0% est for overall effect: Z = 2.54 ($P = 0.042$); l ² = 0%	Xue IZ 2017	35	45	28	45	6.6%	1.25 [0.95, 1.65]	
biotal (05% Cl) 472 476 50.0% 1.39 [1.24, 1.57] otal events 296 213 letrerogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); l ² = 12% est for overall effect: Z = 5.45 ($P < 0.00001$) .1.2 Tumor Response Rate (<i>Oral Administration Group</i>) i g 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] i Z 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] i ZP 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng Q] 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% Cl) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 leterogeneity: Chi ² = 5.79, df = 6 ($P = 0.45$); l ² = 0% est for overall effect: Z = 5.05 ($P < 0.00001$) .1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen U2014 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] iu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue J2 2017 03 5 45 28 45 6.6% 1.25 [0.51, 1.65] ubtotal (95% Cl) 221 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 ($P = 0.42$); l ² = 0% est for overall effect: Z = 2.54 ($P = 0.01$)	You IL 2009	8	22	- 8	24	1.8%	1.09 [0.49, 2.41]	
otal events 296 213 teterogeneity: Chi ² = 13.63, df = 12 (P = 0.32); l^2 = 12% est for overall effect: Z = 5.45 (P < 0.00001) 1.2 Tumor Response Rate (<i>Oral Administration Group</i>) i EJ 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] i Z 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] i Z 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] iber QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 teterogeneity: Chi ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.042); l ³ = 0% est for overall effect: Z = 2.54 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Subtotal (95% CI)	•	472	÷	476	50.0%	1.39 [1.24, 1.57]	♦
teterogeneity: $Chi^2 = 13.63$, $df = 12 (P = 0.32)$; $l^2 = 12\%$ est for overall effect: $Z = 5.45 (P < 0.00001)$ 1.12 Tumor Response Rate (<i>Oral Administration Group</i>) i Ej 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] i Z 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] i Z 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.05 [0.49, 2.41] ubtotal (95% Cl) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 leterogeneity: $Chi^2 = 5.79$, $df = 6 (P = 0.45)$; $l^2 = 0\%$ est for overall effect: $Z = 5.05 (P < 0.00001)$ 1.13 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] le HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] u LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] ubtotal (95% Cl) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: $Chi^2 = 4.93$, $df = 5 (P = 0.42)$; $l^2 = 0\%$ est for overall effect: $Z = 2.54 (P = 0.01)$	Total events	296		213				
est for overall effect: $Z = 5.45$ ($P < 0.00001$) 1.2 Tumor Response Rate (<i>Oral Administration Group</i>) i $Z 2016$ 17 25 11 25 2.6% 1.55 [0.92, 2.59] i $Z 2016$ 27 33 18 32 4.3% 1.45 [1.03, 2.05] i $Z 2016$ 27 50 22 50 5.2% 1.23 [0.82, 1.84] i $Z 2016$ 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng Q1 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% Cl) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 leterogeneity: Chi ² = 5.79, df = 6 ($P = 0.45$); $l2 = 0$ % est for overall effect: $Z = 5.5$ ($P < 0.00001$) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] het HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] iu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.55], 1.65] ubtotal (95% Cl) 221 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 ($P = 0.42$); $l2 = 0$ % est for overall effect: $Z = 2.54$ ($P = 0.01$)	Heterogeneity: Chi ² =	= 13.63. df =	12 (P =	0.32):	$ ^2 = 1$	2%		
1.12 Tumor Response Rate (<i>Oral Administration Group</i>) i 2 2016 17 25 11 25 $2.6%$ 1.55 $[0.92, 2.59]$ $i 2 2016$ 27 33 18 32 $4.3%$ 1.45 $[1.03, 2.05]$ 1.22 $10.62, 1.84]$ $1ao$ LF 2018 27 31 19 31 $4.5%$ 1.42 $[1.04, 1.94]$ $1ao$ LF 2018 27 31 19 31 $4.5%$ 1.42 $[1.04, 1.94]$ $1ao$ LF 2018 27 31 19 31 $4.5%$ 1.42 $[1.47, 3.70]$ $1ao$ Y 2013 19 40 12 46 $2.6%$ 1.52 $[1.47, 3.70]$ $1ao$ Y 2013 19 40 12 46 $2.6%$ 1.62 $[1.47, 3.70]$ $1ao$ Y 2013 251 258 $24.5%$ 1.55 $[1.31, 1.84]$ 1.09 $[0.49, 2.41]$ $1.00 total (95% CI)$ 251 258 $24.5%$ 1.55 $[1.31, 1.84]$ 1.55 $[1.31, 1.84]$ 1.31 100 105 113 100 105 113 100 105 113 100 105 113 100 105 113 100 105 113 100 105 113 100 105 113 100 105 113 100 105 113 100 105 113 100 105 113 100 105 113 110 1058 $2.14]$ 100 20 9 20 $2.1%$ 111 $[0.58, 2.14]$ 100 20 9 20 $2.1%$ 1.11 $[0.58, 2.14]$ 100 25 42 23 40 $5.5%$ 1.04 $[0.72, 1.49]$ 100 100 105 112 100 105 121 218 $25.5%$ 1.24 $[1.05, 1.47]$ 100 10	Test for overall effect	t: Z = 5.45 (P	< 0.000	001)				
1.2 Tumor Response Rate (<i>Oral Administration Group</i>) i EJ 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] i Z 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] i Z P 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 letreogeneity: Chi ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.00001) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] ie HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uuang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] ui LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ui LH 2009 16 30 1.6 30 3.8% 1.24 [1.05, 1.61] ui LH 2009 16 30 1.6 30 3.8% 1.24 [1.05, 1.61] ui LH 2009 16 30 1.6 30 3.8% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi² = 4.93, df = 5 (P = 0.42); l² = 0% est for overall effect: Z = 2.54 (P = 0.01)				,				
i EJ 2016 17 25 11 25 2.6% 1.55 [0.92, 2.59] i Z 2016 27 33 18 32 4.3% 1.45 [1.03, 2.05] i Z 2016 27 50 22 50 5.2% 1.23 [0.82, 1.84] iao LF 2018 27 31 19 31 4.5% 1.42 [1.04, 1.94] leng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 teterogeneity: Chi ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect Z = 5.50 (P < 0.00001) 1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen HM 2019 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen HM 2019 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen U 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] iu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.55] ubtotal (95% CI) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	1.1.2 Tumor Respon	ise Rate (<i>Ora</i>	al Admiı	nistrat	ion Gr	oup)		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Li El 2016	17	25	11	25	2.6%	1.55 [0.92, 2.59]	<u> </u>
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Li Z 2016	27	33	18	32	4.3%	1.45 [1.03, 2.05]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Li ZP 2016	27	50	22	50	5.2%	1.23 [0.82, 1.84]	+
teng QJ 2019 35 50 15 50 3.5% 2.33 [1.47, 3.70] an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] output QJ 2009 8 22 8 24 1.8% 1.59 [0.49, 2.41] ubtotal (95% CI) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 teterogeneity: Chi ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.00001) 1.13 Tumor Response Rate (Injection Administration Group) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] te HL 2014 10 20 9 20 2.13% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] iTC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] uu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] uu [J 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] uu [J 2009 16 30 16 30 3.8% 1.22 [0.95, 1.65] ubtotal (95% CI) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 tetrogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Liao LF 2018	27	31	19	31	4.5%	1.42 [1.04, 1.94]	
an Y 2013 19 40 12 46 2.6% 1.82 [1.01, 3.27] ou JL 2009 8 22 8 24 1.8% 1.09 [0.49, 2.41] ubtotal (95% CI) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 leterogeneity: $Chi^2 = 5.79$, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 2.54 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.41); l ² = 0% est for overall effect: Z = 2.54 (P = 0.41); l ² = 0% est for overall effect: Z = 2.54 (P = 0.41); l ² = 0% est for overall effect: Z = 2.54 (P = 0.41); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Meng OI 2019	35	50	15	50	3.5%	2.33 [1.47, 3.70]	
ou jL 2009 8 22 8 24 1.8% 1.09 $[0.49, 2.41]$ ubtotal (95% Cl) 251 258 24.5% 1.55 [1.31, 1.84] otal events 160 105 teterogeneity: Chi ² = 5.79, df = 6 ($P = 0.45$); l ² = 0% est for overall effect: Z = 5.05 ($P < 0.00001$) .1.3 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.%% 1.21 [0.67, 2.19] i HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] iu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue J2 2017 35 45 28 45 6.6% 1.25 [0.55], 1.65] ubtotal (95% Cl) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 ($P = 0.42$); l ² = 0% est for overall effect: Z = 2.54 ($P = 0.01$)	Tan Y 2013	19	40	12	46	2.6%	1.82 [1.01, 3.27]	
ubtotal (95% Cl) 251 258 24.5% 1.55 $[1.31, 1.84]$ otal events 160 105 tetrogeneity: Chi ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.00001)	You IL 2009	8	22	8	24	1.8%	1.09 [0.49, 2.41]	_
total events 160 105 teterogeneity: $Chi^2 = 5.79$, $df = 6$ (P = 0.45); $l^2 = 0\%$ est for overall effect: Z = 5.05 (P < 0.00001)	Subtotal (95% CI)		251		258	24.5%	1.55 [1.31, 1.84]	◆
leterogeneity: Chi ² = 5.79, df = 6 (P = 0.45); l ² = 0% est for overall effect: Z = 5.05 (P < 0.00001) 1.13 Tumor Response Rate (<i>Injection Administration Group</i>) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] H L 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] ITC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] u L H 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] ubtotal (95% CI) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Total events	160		105				
est for overall effect: Z = 5.05 (P < 0.00001) .1.3 Tumor Response Rate (Injection Administration Group) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] ie HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] iT C 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] iu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] ubtotal (95% CI) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Heterogeneity: Chi ² =	= 5.79, df = 6	5 (P = 0.	45); I ²	= 0%			
1.13 Tumor Response Rate (Injection Administration Group) hen HM 2009 15 34 12 33 2.% 1.21 [0.67, 2.19] hen HM 2019 15 34 12 33 2.% 1.21 [0.67, 2.19] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] ua HZ 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] u LH 2009 16 30 28 45 6.6% 1.25 [0.95; 1.65] ubtotal (95% CI) 221 218 25.5% 1.24 [1.05; 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Test for overall effect	t: Z = 5.05 (P	< 0.000	001)				
1.3 Tumor Response Rate (Injection Administration Group) hen HM 2009 15 34 12 33 2.9% 1.21 [0.67, 2.19] hen HM 2009 15 34 12 32 2.9% 1.21 [0.67, 2.19] hen HM 2018 35 50 20 2.1% 1.11 [0.58, 2.14] huang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] iTC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49]								
hen HM 2009 15 34 12 33 2.9% $1.21 [0.67, 2.19]$ e HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] i TC 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] iu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue JZ 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] ubtotal (95% CI) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	1.1.3 Tumor Respon	ise Rate (<i>Inje</i>	ection A	dminis	stratio	n Group)	
ie HL 2014 10 20 9 20 2.1% 1.11 [0.58, 2.14] uang HT 2018 35 50 20 50 4.7% 1.75 [1.19, 2.57] ir C 2010 25 42 23 40 5.5% 1.04 [0.72, 1.49] iu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue J2 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] ubtotal (95% Cl) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: $Z = 2.54 (P = 0.01)$	Chen HM 2009	15	34	12	33	2.9%	1.21 [0.67, 2.19]	_
uang HT 2018 35 50 20 50 4.7% 1.75 [$1.19, 2.57$] iTC 2010 25 42 23 40 5.5% 1.04 [$0.72, 1.49$] ui LH 2009 16 30 1.63 1.00 [$0.62, 1.61$] ue JZ 2017 35 45 28 45 6.6% 1.25 [$0.95, 1.65$] ubtotal (95% CI) 221 218 25.5% 1.24 [$1.05, 1.47$] 4.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Ge HL 2014	10	20	9	20	2.1%	1.11 [0.58, 2.14]	_
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Huang HT 2018	35	50	20	50	4.7%	1.75 [1.19, 2.57]	
iu LH 2009 16 30 16 30 3.8% 1.00 [0.62, 1.61] ue J2 2017 35 45 28 45 6.6% 1.25 [0.95, 1.65] ubtotal (95% CI) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Li TC 2010	25	42	23	40	5.5%	1.04 [0.72, 1.49]	+-
ue JZ 2017 35 45 28 45 6.6% 1.25 $[0.95, 1.65]$ ubtotal (95% CI) 221 218 25.5% 1.24 $[1.05, 1.47]$ otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Liu LH 2009	16	30	16	30	3.8%	1.00 [0.62, 1.61]	_ + _
ubtotal (95% Cl) 221 218 25.5% 1.24 [1.05, 1.47] otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Xue JZ 2017	35	45	28	45	6.6%	1.25 [0.95, 1.65]	
otal events 136 108 leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Subtotal (95% CI)		221		218	25.5%	1.24 [1.05, 1.47]	◆
leterogeneity: Chi ² = 4.93, df = 5 (P = 0.42); l ² = 0% est for overall effect: Z = 2.54 (P = 0.01)	Total events	136		108				
est for overall effect: Z = 2.54 (P = 0.01)	Heterogeneity: Chi ² =	= 4.93. df = 5	5 (P = 0.	42): I ²	= 0%			
	Test for overall effect	t: Z = 2.54 (P	= 0.01))				
otal (95% CI) 944 952 100.0% 1.39 [1.28 1.52] ▲	Total (95% CI)		944		952	100.0%	1 39 [1 28 1 52]	
	Total events	592	5.11	426	552	100.0/0	1.55 [1.20, 1.52]	•
522 420	Heterogeneity: Chi2 -	- 27 26 df -	25 (P -	-0.34)-	12 _ 0	*	+	
$\dot{0.02}$ $\dot{0.11}$ $\dot{1}$	Tast for overall offer	-27.20, ul =	2 - 0.000	001)	0	/0	ó.	02 0.1 İ 1'0

FIGURE 3 | Forest plot of meta-analysis of tumor response rate (TRR) (all studies and subgroups of studies: oral administration subgroup, injection subgroup).



Study or Subgroup Events Total Events Total Events Total Events Total Events M-H, Fixed, 95% C1 1.3.1 Tumor Response Rate (Duration 5 4w) 11 25 5.2% 1.55 [0.92, 2.59] 1.1 1.04 [0.72, 1.49] Lia CF 2010 25 42 23 40 11.1% 1.04 [1.04, 1.94] 1.04 [0.72, 1.49] Lia CF 2018 27 31 19 31 8.9% 1.42 [1.04, 1.94] 1.04 [0.72, 1.49] Lia CF 2018 27 31 19 31.7% 1.20 [0.62, 1.61] 1.04 [0.72, 1.49] Use Vents 85 69 1.00 [0.62, 1.61] 1.00 [0.62, 1.61] 1.04 [0.72, 1.49] Test for overall effect: Z = 1.90 (P = 0.06) 12.8 8.6% 1.45 [1.03, 2.05] 1.11 [0.58, 2.14] 1.10 [0.67, 2.19] Che HU 2016 27 50 12.2 1.22 kol [1.01, 3.207] 1.33 [1.12, 1.58] 1.33 [1.12, 1.58] Value 2017 35 45 2.8 45 1.32 [1.04, 3.27] 1.33 [1.12, 1.58] 1.33 [1.12, 1.58]		Experim	ental	Contr	ol		Risk Ratio	Risk Ratio	
1.3.1 Tumor Response Rate (Duration 5 4w) Li El 2016 17 25 11 25 5.2% 1.55 [0.92, 2.59] Li TC 2010 25 42 23 40 11.1% 1.04 [0.72, 1.49] Liao LF 2018 27 31 19 31 8.9% 1.42 [1.04, 1.94] Liu LH 2009 16 30 16 30 (P = 0.36); 1 ² = 6% Total events 85 69 Heterogeneity: Ch ² = 3.20, df = 3 (P = 0.36); 1 ² = 6% Test for overall effect: Z = 1.90 (P = 0.06) 1.3.2 Tumor Response Rate (Duration 4-8w) Chen HM 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Chen HM 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Chen HM 2019 15 34 12 23 0.42% 1.11 [0.58, 2.14] Li Z 2016 27 33 18 32 8.6% 1.45 [1.03, 2.05] Li ZP 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.82 [1.01, 3.27] Xue JZ 2017 35 45 28 45 13.2% 1.25 [0.95, 1.65] Subtotal (95% CI) 222 22 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: Ch ² = 2.69, df = 5 (P = 0.84); 1 ² = 0% Test for overall effect: Z = 3.20 (P = 0.001) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JL 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.09% 1.39 [1.24, 1.57] Total events 78 43 Heterogeneity: Ch ² = 2.6, df = 2 (P = 0.32); 1 ² = 12% Test for overall effect: Z = 4.31 (P < 0.0001) Total (95% CI) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: Ch ² = 2.5, df = 2 (P = 0.32); 1 ² = 12% Test for overall effect: Z = 5.45 (P < 0.00001) Total (95% CI) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: Ch ² = 2.5, df = 2 (P = 0.32); 1 ² = 12% Test for overall effect: Z = 5.45 (P < 0.00001) Total (95% CI) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: Ch ² = 2.5, df = 2 (P = 0.32); 1 ² = 12% Test for overall effect: Z = 5.45 (P < 0.00001) Test for subgroup differences: Ch ² = 5.87, df = 2 (P = 0.05); 1 ² = 65.9%	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl	
Li Ej 2016 17 25 11 25 5.2% 1.55 $[0.92, 2.59]$ Li TC 2010 25 42 23 40 11.1% 1.04 $[0.72, 1.49]$ Lia LF 2018 27 31 19 31 8.9% 1.42 $[1.04, 1.94]$ Liu LH 2009 16 30 16 30 7.5% 1.00 $[0.62, 1.61]$ Subtotal (95% CI) 128 126 32.7% 1.21 $[0.99, 1.48]$ Total events 85 69 Heterogeneity: Ch ² = 3.20, df = 3 ($P = 0.36$); h ² = 0.66 1.3.2 Tumor Response Rate (Duration 4-8w) Chen HM 2009 15 34 12 33 5.7% 1.21 $[0.67, 2.19]$ Ge HL 2014 10 20 9 20 4.2% 1.11 $[0.58, 2.14]$ Li Z 2016 27 33 18 32 8.6% 1.45 $[1.32, 2.05]$ Li Z P2016 27 50 22 50 10.3% 1.23 $[0.82, 1.84]$ Tan Y 2013 19 40 12 46 5.2% 1.25 $[0.95, 1.65]$ Subtotal (95% CI) 222 226 47.3% 1.33 $[1.12, 1.58]$ Total events 133 101 Heterogeneity: Ch ² = 2.0, df = 5 ($P = 0.84$); h ² = 0% Test for overall effect: Z = 3.20 ($P = 0.001$) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 15 50 7.0% 2.33 $[1.47, 3.70]$ You JL 2009 8 22 8 24 3.6% 1.09 $[0.49, 2.41]$ Subtotal (95% CI) 122 124 20.0% 1.84 $[1.39, 2.42]$ Total events 78 43 Heterogeneity: Ch ² = 2.5, df = 2 ($P = 0.32$); h ² = 12% Total events 296 213 Heterogeneity: Ch ² = 2.5, df = 2 ($P = 0.32$); h ² = 12% Test for overall effect: Z = 5.45, ($P < 0.32$); h ² = 12% Test for overall effect: Z = 5.45, ($P < 0.32$); h ² = 12% Test for overall effect: Z = 5.45, ($P < 0.32$); h ² = 12% Test for overall effect: Z = 5.45, ($P < 0.0001$) Total (95% CI) 472 476 100.0% 1.39 $[1.24, 1.57]$ Total events 296 213 Heterogeneity: Ch ² = 2.5, df = 2 ($P = 0.32$); h ² = 12% Test for overall effect: Z = 5.45, ($P < 0.32$); h ² = 12% Test for overall effect: Z = 5.45, ($P < 0.32$); h ² = 12% Test for overall effect: Z = 5.47, df = 2 ($P = 0.05$), h ² = 65.9%	1.3.1 Tumor Respon	se Rate (D	uration	≤ 4w)					
Li TC 2010 25 42 23 40 11.1% 1.04 [0.72, 1.49] Lia 0L 7 2018 27 31 19 31 8.9% 1.42 [1.04, 1.94] Liu LH 2009 16 30 16 30 7.5% 1.00 [0.62, 1.61] Subtotal (95% CI) 128 126 32.7% 1.21 [0.99, 1.48] Total events 85 69 Heterogeneity: Ch ² = 3.20, df = 3 (P = 0.36); l ² = 6% Test for overall effect: Z = 1.90 (P = 0.06) 1.3.2 Tumor Response Rate (Duration 4-8w) Chen HM 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Ge HL 2014 10 20 9 20 4.2% 1.11 [0.58, 2.14] Li Z 2016 27 33 18 32 8.6% 1.45 [1.03, 2.05] Li Z P 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.82 [1.01, 3.27] Xue JZ 2017 35 45 28 45 13.2% 1.32 [0.52, 1.65] Subtotal (95% CI) 2222 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: Ch ² = 2.09, df = 5 (P = 0.84); l ² = 0% Test for overall effect: Z = 3.20 (P = 0.001) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JL 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.39 [1.24, 1.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JL 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.39 [1.24, 1.57] Total events 78 43 Heterogeneity: Ch ² = 2.5, df = 2 (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45, (P < 0.00001) Test for subgroup differences: Ch ² = 5.47, df = 2 (P = 0.05), l ² = 65.9%	Li EJ 2016	17	25	11	25	5.2%	1.55 [0.92, 2.59]		
Liao LF 2018 27 31 19 31 8.9% 1.42 [1.04, 1.94] Liu LH 2009 16 30 16 30 7.5% 1.00 [0.62, 1.61] Subtotal (95% CI) 128 126 32.7% 1.21 [0.99, 1.48] Total events 85 69 Heterogeneity: Ch ² 3.2.0 df = 3 (P = 0.36); l ² = 6% Test for overall effect: Z = 1.90 (P = 0.06) 1.3.2 Tumor Response Rate (Duration 4-8w) Chen HM 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Ge HL 2014 10 20 9 20 4.2% 1.11 [0.58, 2.14] Li Z 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Li Z 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Li Z P 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.32 [0.95, 1.65] Subtotal (95% CI) 222 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: Chi ² = 2.09, df = 5 (P = 0.84); l ² = 0% Test for overall effect: Z = 3.20 (P = 0.001) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 15 50 7.0% 2.33 [1.47, 3.70] Huang HT 2018 35 50 12 28 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.25); l ² = 28% Test for overall effect: Z = 4.31 (P < 0.0001) Total events 296 213 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.32); l ² = 12% Total events 296 213 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.05), l ² = 65.9%	Li TC 2010	25	42	23	40	11.1%	1.04 [0.72, 1.49]	+	
Liu LH 2009 16 30 16 30 7.5% 1.00 [0.62, 1.61] Subtotal (95% CI) 128 126 32.7% 1.21 [0.99, 1.48] Total events 85 69 Heterogeneity: Chi ² = 3.20, df = 3 (P = 0.36); l ² = 6% Test for overall effect: Z = 1.90 (P = 0.06) 1.3.2 Tumor Response Rate (Duration 4-8w) Chen HM 2009 15 3 4 12 33 5.7% 1.21 [0.67, 2.19] Ge HL 2014 10 20 9 20 4.2% 1.11 [0.58, 2.14] Li Z 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.82 [1.01, 3.27] Xue JZ 2017 35 45 28 45 13.2% 1.25 [0.95, 1.65] Subtotal (95% CI) 222 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: Chi ² = 2.30 (P = 0.001) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JL 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.25); l ² = 28% Test for overall effect: Z = 4.31 (P < 0.0001) Total events 296 213 Heterogeneity: Chi ² = 2.76, df = 12 (P = 0.32); l ² = 12% Total events 296 213 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.32); l ² = 12% Total events 296 213 Heterogeneity: Chi ² = 5.45, df = 2 (P = 0.05), l ² = 65.9%	Liao LF 2018	27	31	19	31	8.9%	1.42 [1.04, 1.94]		
Subtotal (95% CI) 128 126 32.7% 1.21 [0.99, 1.48] Total events 85 69 Heterogeneity: Chi ² = 3.20, df = 3 (P = 0.36); l ² = 6% Test for overall effect: Z = 1.90 (P = 0.06) 1.3.2 Tumor Response Rate (Duration 4-8w) Chen HM 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Chen HM 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Chen HM 2009 15 34 12 33 5.7% 1.21 [0.68, 2.14] Li Z 2016 27 33 18 32 8.6% 1.45 [1.03, 2.05] Li Z 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.82 [1.01, 3.27] Xue JZ 2017 35 45 28 45 13.2% 1.25 [0.95, 1.65] Subtotal (95% CI) 222 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: Chi ² = 2.09, df = 5 (P = 0.84); l ² = 0% Test for overall effect: Z = 3.20 (P = 0.001) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JJ 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.25); l ² = 28% Test for overall effect: Z = 4.31 (P < 0.0001) Total (95% CI) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: Chi ² = 3.63, df = 1 (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45 (P < 0.00001) Total (95% CI) 472 476 100.0% 1.39 [1.24, 1.57] Test for overall effect: Z = 5.45 (P < 0.00001) Favours [experimental] Favours [control]	Liu LH 2009	16	30	16	30	7.5%	1.00 [0.62, 1.61]		
Total events 85 69 Heterogeneity: Ch ² = 2.0, df = 3 ($P = 0.36$); l ² = 6% Test for overall effect: Z = 1.90 ($P = 0.06$) 1.3.2 Tumor Response Rate (Duration 4-8w) Chen HM 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Ge HL 2014 10 20 9 20 4.2% 1.11 [0.58, 2.14] LI Z 2016 27 33 18 32 8.6% 1.45 [1.03, 2.05] LI ZP 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.82 [1.01, 3.27] Xue JZ 2017 35 45 28 45 13.2% [0.55, 1.65] Subtoal (95% CI) 222 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: Chi ² = 2.09, df = 5 ($P = 0.84$); l ² = 0% Test for overall effect: Z = 3.20 ($P = 0.001$) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Mung QI 2019 35 50 15 57 7.0% 2.33 [1.47, 3.70] You JL 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtoal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 ($P = 0.25$); l ² = 28% Test for overall effect: Z = 4.31 ($P < 0.0001$) Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); l ² = 12% Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); l ² = 65.9% b 100 Favours [experimental] Favours [control]	Subtotal (95% CI)		128		126	32.7%	1.21 [0.99, 1.48]	•	
Heterogeneity: $Ch^2 = 3.20$, $df = 3$ (P = 0.36); $l^2 = 6\%$ Test for overall effect: Z = 1.90 (P = 0.06) 1.3.2 Tumor Response Rate (Duration 4-8w) Chen HW 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Ge HL 2014 10 20 9 20 4.2% 1.11 [0.58, 2.14] Li Z 2016 27 30 12 25 0 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.82 [1.01, 3.27] Xue JZ 2017 35 45 28 45 13.2% 1.25 [0.65, 1.65] Subtotal (95% CI) 222 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: $Ch^2 = 2.09$, $df = 5$ (P = 0.84); $l^2 = 0\%$ Test for overall effect: Z = 3.20 (P = 0.001) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JL 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: $Ch^2 = 2.76$, $df = 2$ (P = 0.25); $l^2 = 28\%$ Test for overall effect: Z = 4.31 (P < 0.0001) Total events 296 213 Heterogeneity: $Ch^2 = 13.63$, $df = 12$ (P = 0.32); $l^2 = 12\%$ Total events 296 213 Heterogeneity: $Ch^2 = 13.63$, $df = 12$ (P = 0.32); $l^2 = 65.9\%$ Total events 206 213 Heterogeneity: $Ch^2 = 13.63$, $df = 12$ (P = 0.32); $l^2 = 65.9\%$	Total events	85		69					
Test for overall effect: $Z = 1.90$ ($P = 0.06$) 1.3.2 Tumor Response Rate (Duration 4-8w) Chen HM 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Ge HL 2014 10 20 9 20 4.2% 1.11 [0.58, 2.14] Li Z 2016 27 33 18 32 8.6% 1.45 [1.03, 2.05] Li ZP 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.82 [1.01, 3.27] Xue JZ 2017 35 45 28 45 13.2% 1.25 [0.95, 1.65] Subtotal (95% CI) 222 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: Chi ² = 2.09, df = 5 ($P = 0.84$); l ² = 0% Test for overall effect: Z = 3.20 ($P = 0.01$) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JJ 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 ($P = 0.25$); l ² = 28% Test for overall effect: Z = 4.31 ($P < 0.0001$) Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); l ² = 12% Total events 296 213 Heterogeneity: Chi ² = 5.87, df = 2 ($P = 0.05$), l ² = 65.9% Total events 296 213 Heterogeneity: Chi ² = 5.87, df = 2 ($P = 0.05$), l ² = 65.9%	Heterogeneity: Chi ² =	3.20, df =	= 3 (P =	0.36); l ²	= 6%				
1.3.2 Tumor Response Rate (Duration 4-8w) Chen HM 2009 15 34 12 33 5.7% 1.21 [0.67, 2.19] Ge HL 2014 10 20 9 20 4.2% 1.11 [0.58, 2.14] LI Z 2016 27 33 18 32 8.6% 1.45 [1.03, 2.05] LI ZP 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.82 [1.01, 3.27] Xue JZ 2017 35 45 28 45 13.2% [0.55, 1.65] Subtal (95% CI) 222 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: Chi ² = 2.09, df = 5 (P = 0.84); l ² = 0% Test for overall effect: Z = 3.20 (P = 0.001) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Mung QI 2019 35 50 15 57 7.0% 2.33 [1.47, 3.70] You JL 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.25); l ² = 28% Test for overall effect: Z = 4.31 (P < 0.0001) Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 (P = 0.32); l ² = 12% Total events 296 213 Heterogeneity: Chi ² = 5.87, df = 2 (P = 0.05), l ² = 65.9% Heterogeneity: Chi ² = 5.87, df = 2 (P = 0.05), l ² = 65.9%	Test for overall effect	: Z = 1.90	(P = 0.0)	(6)					
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	1 2 2 Tumor Pornon	co Poto (D	uration	4					
Chen Imi 2009 13 34 12 33 5.7% 1.21 [0.67, 2.19] Ge HL 2014 10 20 9 20 4.2% 1.11 [0.58, 2.14] Li Z 2016 27 33 18 32 8.6% 1.45 [1.03, 2.05] Li ZP 2016 27 50 22 50 10.3% 1.23 [0.82, 1.84] Tan Y 2013 19 40 12 46 5.2% 1.82 [1.01, 3.27] Xue JZ 2017 35 45 28 45 13.2% 1.25 [0.95, 1.65] Subtotal (95% CI) 222 226 47.3% 1.33 [1.12, 1.58] Total events 133 101 Heterogeneity: Chi ² = 2.09, df = 5 ($P = 0.84$); l ² = 0% Test for overall effect: Z = 3.20 ($P = 0.01$) 1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JJ 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 ($P = 0.25$); l ² = 28% Test for overall effect: Z = 4.31 ($P < 0.0001$) Total (95% CI) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); l ² = 12% Test for overall effect: Z = 5.45 ($P < 0.00001$) Total effect: Z = 5.45 ($P < 0.00001$) Test for subgroup differences: Chi ² = 5.87, df = 2 ($P = 0.05$), l ² = 65.9%	Char UM 2000	se rate (D	uracion	4-8W)	22	F 70/	1 21 [0 67 2 10]		
$\begin{array}{c} \text{Ce} \ n.2 \ 2044 & 10 & 20 & 9 & 20 & 4.2\% & 1.11 \ [0.58, 2.14] \\ \text{Li Z 2016} & 27 & 33 & 18 & 32 & 8.6\% & 1.45 \ [1.03, 2.05] \\ \text{Li Z P 2016} & 27 & 50 & 22 & 50 & 10.3\% & 1.23 \ [0.82, 1.84] \\ \text{Tan Y 2013} & 19 & 40 & 12 & 46 & 5.2\% & 1.82 \ [1.01, 3.2.7] \\ \text{Xue J Z 2017} & 35 & 45 & 28 & 45 & 13.2\% & 1.25 \ [0.55, 1.65] \\ \text{Subtal (95% CI)} & 2222 & 226 & 47.3\% & 1.33 \ [1.12, 1.58] \\ \text{Total events} & 133 & 101 \\ \text{Heterogeneity: Chi^2 = 2.09, df = 5 \ (P = 0.84); i^2 = 0\% \\ \text{Test for overall effect: Z = 3.20 \ (P = 0.001) \\ \hline \textbf{1.3.3 Tumor Response Rate (Duration > 8w) \\ \text{Huang HT 2018} & 35 & 50 & 20 & 50 & 9.4\% & 1.75 \ [1.19, 2.57] \\ \text{Meng QJ 2019} & 35 & 50 & 15 & 57 & 7.0\% & 2.33 \ [1.47, 3.70] \\ \text{You JL 2009} & 8 & 22 & 8 & 24 & 3.6\% & 1.09 \ [0.49, 2.41] \\ \text{Subtal (95% CI)} & 122 & 124 & 20.0\% & 1.84 \ [1.39, 2.42] \\ \text{Total events} & 78 & 43 \\ \text{Heterogeneity: Chi^2 = 2.76, df = 2 \ (P = 0.25); \ i^2 = 28\% \\ \text{Test for overall effect: Z = 4.31 \ (P < 0.0001) \\ \hline \text{Total events} & 296 & 213 \\ \text{Heterogeneity: Chi^2 = 13.63, df = 12 \ (P = 0.32); \ i^2 = 12\% \\ \text{Total events} & 296 & 213 \\ \text{Heterogeneity: Chi^2 = 5.87, df = 2 \ (P = 0.05), \ i^2 = 65.9\% \\ \hline \begin{array}{c} 0.01 & 0.1 & 1 & 0 \\ \text{Favours [experimental] Favours [control]} \\ \hline \end{array}$	Cnen HM 2009	15	54	12	33	5.7%	1.21 [0.67, 2.19]		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Ge HL 2014	10	20	10	20	4.2%	1.11 [0.58, 2.14]		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	LI Z 2016	27	55	18	32	8.6%	1.45 [1.03, 2.05]		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	LI ZP 2016	27	50	12	50	10.3% E 2%	1.23 [0.82, 1.84]	-	
All $(2501)^{-1}$ (1) $(2501)^{-1}$ (2) (2501)	Tall F 2015	25	40	20	40	12 20/	1.02 [1.01, 5.27]		
$\begin{array}{c} \textbf{Lie or NSW (15) C(1)} & \textbf{Lie or NSW (115) (114) (150)} \\ \textbf{Heterogeneity: Chi^2 = 2.09, df = 5 (P = 0.84); l^2 = 0\% \\ \textbf{Test for overall effect: Z = 3.20 (P = 0.001)} \\ \textbf{I.3.3 Tumor Response Rate (Duration > 8w) \\ \textbf{Huang HT 2018 } 35 50 20 50 9.4\% 1.75 [1.19, 2.57] \\ \textbf{Meng QJ 2019 } 35 50 15 50 7.0\% 2.33 [1.47, 3.70] \\ \textbf{You JJ 2009 } 8 22 8 24 3.6\% 1.09 [0.49, 2.41] \\ \textbf{Subtotal (95% CI) } 122 124 20.0\% 1.84 [1.39, 2.42] \\ \textbf{Total events } 78 43 \\ \textbf{Heterogeneity: Chi^2 = 2.76, df = 2 (P = 0.25); l^2 = 28\% \\ \textbf{Test for overall effect: Z = 4.31 (P < 0.0001) \\ \textbf{Total (95% CI) } 472 476 100.0\% 1.39 [1.24, 1.57] \\ \textbf{Total events } 296 213 \\ \textbf{Heterogeneity: Chi^2 = 13.63, df = 12 (P = 0.32); l^2 = 12\% \\ \textbf{Test for overall effect: Z = 5.45 (P < 0.00001) \\ \textbf{Test for subgroup differences: Chi^2 = 5.87, df = 2 (P = 0.05), l^2 = 65.9\% \\ \end{array}$	Subtotal (95% CI)	20	222	20	226	47.3%	1.33 [1.12, 1.58]		
$\begin{array}{c} \text{Hereogeneity: Chi^2 = 2.09, df = 5 (P = 0.84); l^2 = 0\%\\ \text{Test for overall effect: Z = 3.20 (P = 0.001) \\ \hline \textbf{1.3.3 Tumor Response Rate (Duration > 8w)\\ \text{Huang HT 2018} & 35 & 50 & 20 & 50 & 9.4\% & 1.75 [1.19, 2.57]\\ \text{Meng QJ 2019} & 35 & 50 & 15 & 50 & 7.0\% & 2.33 [1.47, 3.70]\\ \text{You JL 2009} & 8 & 22 & 8 & 24 & 3.6\% & 1.09 [0.49, 2.41]\\ \text{Subtatal (95% CI)} & 122 & 124 & 20.0\% & 1.84 [1.39, 2.42]\\ \text{Total events} & 78 & 43\\ \text{Heterogeneity: Chi^2 = 2.76, df = 2 (P = 0.25); l^2 = 28\%\\ \text{Test for overall effect: Z = 4.31 (P < 0.0001)}\\ \hline \textbf{Total events} & 296 & 213\\ \text{Heterogeneity: Chi^2 = 13.63, df = 12 (P = 0.32); l^2 = 12\%\\ \text{Test for overall effect: Z = 5.45 (P < 0.00001)}\\ \hline \text{Test for subgroup differences: Chi^2 = 5.87, df = 2 (P = 0.05), l^2 = 65.9\%}\\ \hline \end{array}$	Total events	133		101			1.00 [1.11, 1.00]	•	
$\begin{array}{c} Inclusion of the constraint of the cons$	Heterogeneity: Chi ² =	= 10 00 c	5 (P =	0.84).12	= 0%				
1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JL 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% Cl) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.25); l ² = 28% Test for overall effect: Z = 4.31 (P < 0.0001) Total (95% Cl) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45 (P < 0.00001) Test for subgroup differences: Chi ² = 5.87, df = 2 (P = 0.05), l ² = 65.9%	Test for overall effect	Z = 3.20	(P = 0.0)	01)	•				
1.3.3 Tumor Response Rate (Duration > 8w) Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JJ 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.25); l ² = 28% 78 Test for overall effect: Z = 4.31 (P < 0.0001)				/					
Huang HT 2018 35 50 20 50 9.4% 1.75 [1.19, 2.57] Meng QJ 2019 35 50 15 50 7.0% 2.33 [1.47, 3.70] You JL 2009 8 22 8 24 3.6% 1.09 [0.49, 2.41] Subtotal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 ($P = 0.25$); l ² = 28% Test for overall effect: Z = 4.31 ($P < 0.0001$) Total (95% CI) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 ($P = 0.32$); l ² = 12% Test for overall effect: Z = 5.45 ($P < 0.00001$) Test for subgroup differences: Chi ² = 5.87, df = 2 ($P = 0.05$), l ² = 65.9%	1.3.3 Tumor Respon	se Rate (D	uration	> 8w)					
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Huang HT 2018	35	50	20	50	9.4%	1.75 [1.19, 2.57]		
You JL 2009 8 22 8 24 3.6% 1.09 $[0.49, 2.41]$ Subtotal (95% CI) 122 124 20.0% 1.84 $[1.39, 2.42]$ Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.25); l ² = 28% Test for overall effect: Z = 4.31 (P < 0.0001) Total (95% CI) 472 476 100.0% 1.39 $[1.24, 1.57]$ Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45 (P < 0.00001) Test for subgroup differences: Chi ² = 5.87, df = 2 (P = 0.05), l ² = 65.9% 0.01 0.1 1 10 Favours [experimental] Favours [control]	Meng QJ 2019	35	50	15	50	7.0%	2.33 [1.47, 3.70]		
Subtotal (95% CI) 122 124 20.0% 1.84 [1.39, 2.42] Total events 78 43 Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.25); l ² = 28% Test for overall effect: Z = 4.31 (P < 0.0001)	You JL 2009	8	22	8	24	3.6%	1.09 [0.49, 2.41]		
Total events 78 43 Heterogeneity: $Chi^2 = 2.76$, $df = 2$ (P = 0.25); $l^2 = 28\%$ Test for overall effect: Z = 4.31 (P < 0.001) 1.39 [1.24, 1.57] Total (95% Cl) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: $Chi^2 = 13.63$, $df = 12$ (P = 0.32); $l^2 = 12\%$ 0.01 0.1 1 10 100 Test for overall effect: Z = 5.45 (P < 0.00001) Favours [experimental] Favours [control] Favours [experimental] Favours [control]	Subtotal (95% CI)		122		124	20.0%	1.84 [1.39, 2.42]	•	
Heterogeneity: Chi ² = 2.76, df = 2 (P = 0.25); $l^2 = 28\%$ Test for overall effect: Z = 4.31 (P < 0.0001) Total (95% Cl) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 (P = 0.32); $l^2 = 12\%$ Test for overall effect: Z = 5.45 (P < 0.00001) Test for subgroup differences: Chi ² = 5.87, df = 2 (P = 0.05), $l^2 = 65.9\%$ Favours [experimental] Favours [control]	Total events	78		43					
Test for overall effect: Z = 4.31 (P < 0.0001)	Heterogeneity: Chi ² =	= 2.76, df =	= 2 (P =	0.25); I ²	= 28%				
Total (95% Cl) 472 476 100.0% 1.39 [1.24, 1.57] Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 (P = 0.32); l ² = 12% 0.01 0.1 1 10 100 Test for overall effect: Z = 5.45 (P < 0.00001)	Test for overall effect	: Z = 4.31	(P < 0.0	001)					
Total events 296 213 Heterogeneity: Chi ² = 13.63, df = 12 (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45 (P < 0.00001) Test for subgroup differences: Chi ² = 5.87, df = 2 (P = 0.05), l ² = 65.9% Favours [experimental] Favours [control]	Total (95% CI)		472		476	100.0%	1.39 [1.24, 1.57]	•	
Note Vertex 2 = 13.63, df = 12 (P = 0.32); l ² = 12% Heterogeneity: Chi ² = 13.63, df = 12 (P = 0.32); l ² = 12% Test for overall effect: Z = 5.45 (P < 0.00001)	Total events	296	=	213			1.00 [1.1 ., 1.0.]	•	
Test for overall effect: $Z = 5.45$ (P < 0.00001) Test for subgroup differences: Chi ² = 5.87, df = 2 (P = 0.05), l ² = 65.9% 0.01 0.1 1 10 100 Favours [experimental] Favours [control]	Heterogeneity: Chi ² =	13 63 df	= 12 (P	= 0.32	$1^2 = 1$	2%		· · · · · ·	
Test for subgroup differences: Chi ² = 5.87, df = 2 (P = 0.05), l ² = 65.9%	Test for overall effect	Z = 5.45	(P < 0.0)	0001)	, 1			0.01 0.1 1 10	100
	Test for subgroup dif	ferences: ($hi^2 = 5$.87. df =	2 (P =	0.05), l ²	= 65.9%	Favours [experimental] Favours [control]	
	. se ioi sabgioup un					2.00,1			



represents a double-edged sword in GC treatment. This has become an urgent problem to be solved, potentially with TCM combination therapy. Our study showed that, overall, paclitaxel +TCM significantly improved the TRR in GC patients, and it particularly improved the TRR in the subgroups of studies that used oral administration of TCM, included only stage IV patients, and had a long treatment duration. As the primary outcome, TRR can directly reflect the efficacy of chemotherapy regimens on tumors. A meta-analysis by Xie et al. (2013) also showed that TCM (Huachansu) combined with chemotherapy increased the TRR in patients with GC, which is consistent with our findings. In addition, it is necessary to assess QOL to evaluate the effects of chemotherapy combined with TCMs. Among the included studies, four reported the number of patients in each group with a KPS increase ≥10 points. We evaluated the dichotomous variable (KPS improvement) in the meta-analysis, which showed a positive result in the paclitaxel+TCM group compared to the control group.

In addition to enhancing the effect of chemotherapy, combining chemotherapy with TCMs can reduce the side effects and decrease mild drug resistance. Accordingly, our study comprehensively compared the side effects of the two regimens. The blood abnormality results showed that the paclitaxel+TCM group reduced the rates of neutropenia, leukopenia, and thrombocytopenia. Paclitaxel+TCM also alleviated nausea and vomiting after chemotherapy, which shows the positive effect of TCMs on the gastrointestinal system. Furthermore, given that there are a few reports on the adverse effects of TCMs, we evaluated negative effects related to hepatic dysfunction and neurotoxicity. It is gratifying to note that the paclitaxel+TCM group had fewer cases of hepatic dysfunction and neurotoxicity than the groups involving paclitaxel-based chemotherapy alone.

LI et al.	Li	et	al.	
-----------	----	----	-----	--

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.5.1 Neutropenia							
Huang HT 2018	1	50	9	50	3.6%	0.11 [0.01, 0.84]	
Lai YQ 2018	20	30	28	30	11.2%	0.71 [0.54, 0.94]	
Meng QJ 2019	23	50	23	50	9.2%	1.00 [0.65, 1.53]	+
Tan Y 2013	15	40	31	46	11.5%	0.56 [0.36, 0.87]	
You JL 2009 Subtotal (95% CI)	9	22 192	14	24 200	5.3% 40.7%	0.70 [0.38, 1.28] 0.68 [0.55, 0.84]	•
Total events	68		105				
Heterogeneity: Chi ² = Test for overall effec	= 7.15, df t: Z = 3.61	= 4 (P = (P = 0.)	0.13); l ² 0003)	= 44%			
1.5.2 Leukopenia							
Huang HT 2018	1	50	8	50	3.2%	0.13 [0.02, 0.96]	
Liu LH 2009	19	30	25	30	10.0%	0.76 [0.55, 1.04]	-
Tan Y 2013	13	40	23	46	8.5%	0.65 [0.38, 1.11]	
You JL 2009	12	22	13	24	5.0%	1.01 [0.59, 1.71]	
Subtotal (95% CI)		142		150	26.6%	0.69 [0.54, 0.90]	◆
Total events	45		69				
Heterogeneity: Chi ² = Test for overall effec	= 4.97, df t: Z = 2.75	= 3 (P = (P = 0.)	0.17); l ² 006)	= 40%			
1.5.3 Anemia							
Lai YO 2018	2	30	5	30	2.0%	0.40 [0.08, 1.90]	
Li Z 2016	4	33	11	32	4.4%	0.35 [0.13, 0.99]	
Liao LF 2018	1	31	3	31	1.2%	0.33 [0.04, 3.03]	
Meng QJ 2019	12	50	12	50	4.8%	1.00 [0.50, 2.01]	
Tan Y 2013	4	40	5	46	1.9%	0.92 [0.27, 3.19]	
Subtotal (95% CI)		184		189	14.3%	0.65 [0.40, 1.04]	•
Total events	23		36				
Heterogeneity: Chi ² = Test for overall effec	= 3.83, df t: Z = 1.79	= 4 (P = 0.0)	0.43); l ² 07)	= 0%			
1.5.4 Thrombocytop	penia						
Huang HT 2018	2	50	10	50	4.0%	0.20 [0.05, 0.87]	
Lai YQ 2018	6	30	8	30	3.2%	0.75 [0.30, 1.90]	
Liao LF 2018	1	31	4	31	1.6%	0.25 [0.03, 2.11]	
Liu LH 2009	18	30	19	30	7.6%	0.95 [0.64, 1.41]	+
Tan Y 2013	0	40	2	46	0.9%	0.23 [0.01, 4.64]	
You JL 2009	3	22	3	24	1.1%	1.09 [0.25, 4.85]	
Subtotal (95% CI)		203		211	18.4%	0.66 [0.46, 0.96]	•
Total events	30		46				
Heterogeneity: Chi ² =	= 7.39, df	= 5 (P =	0.19); l ²	= 32%			
Test for overall effec	t: $Z = 2.20$	(P = 0.)	03)				
Total (95% CI)		721		750	100.0%	0.68 [0.58, 0.78]	♦
Total events	166		256				
Heterogeneity: Chi ² =	= 23.51, d	f = 19 (l	P = 0.22)	$ ^{2} = 1$	9%		0.005 0.1 1 10 20
Test for overall effec	t: Z = 5.29	(P < 0.	00001)				Favours [experimental] Favours [control]
Test for subgroup di	fferences:	$Chi^2 = 0$).08, df =	3 (P =	0.99), l ²	= 0%	

	Experim	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight M	-H, Random, 95% Cl	M-H, Random, 95% Cl
1.6.1 Nausea and V	omiting						
Chen HM 2009	11	34	22	33	10.8%	0.49 [0.28, 0.83]	
Ge HL 2014	3	20	8	20	5.6%	0.38 [0.12, 1.21]	
Li TC 2010	14	42	31	40	11.7%	0.43 [0.27, 0.68]	
Li Z 2016	2	33	12	32	4.3%	0.16 [0.04, 0.67]	
Li ZP 2016	7	50	19	50	8.6%	0.37 [0.17, 0.80]	
Liao LF 2018	2	31	6	31	3.9%	0.33 [0.07, 1.53]	
Liu LH 2009	20	30	26	30	13.3%	0.77 [0.58, 1.03]	-
Tan Y 2013	34	40	39	46	14.1%	1.00 [0.84, 1.20]	. †
Subtotal (95% CI)		280		282	72.3%	0.50 [0.32, 0.80]	•
Total events	93		163				
Heterogeneity: Tau ²	= 0.30; Ch	$i^2 = 45.$	72, df = 1	7 (P <)	0.00001); I ²	= 85%	
Test for overall effec	t: Z = 2.89	(P = 0.0)04)				
1.6.2 Hepatic Dysfu	nction						
Li ZP 2016	4	50	9	50	6.0%	0.44 [0.15, 1.35]	
Liu LH 2009	4	30	6	30	5.7%	0.67 [0.21, 2.13]	
Meng QJ 2019	5	50	6	50	5.9%	0.83 [0.27, 2.55]	
Subtotal (95% CI)		130		130	17.5%	0.63 [0.33, 1.20]	◆
Total events	13		21				
Heterogeneity: Tau ²	= 0.00; Ch	$i^2 = 0.6i$	3, df = 2	(P = 0)	.73); I ² = 0%		
Test for overall effec	t: $Z = 1.41$	(P = 0.1)	L6)				
1.6.3 Neurotoxicity							
Ge HL 2014	4	20	7	20	6.3%	0.57 [0.20, 1.65]	
Liao LF 2018	0	31	1	31	1.1%	0.33 [0.01, 7.88]	
Tan Y 2013	2	40	2	46	2.8%	1.15 [0.17, 7.79]	
Subtotal (95% CI)		91		97	10.2%	0.64 [0.26, 1.55]	
Total events	6		10				
Heterogeneity: Tau ²	= 0.00; Ch	$^{2} = 0.5$	7, df = 2	(P = 0)	.75); I ² = 0%		
Test for overall effec	t: $Z = 0.99$	(P = 0.3	32)				
Total (95% CI)		501		509	100.0%	0.55 [0.39, 0.78]	◆
Total events	112		194				
Heterogeneity: Tau ²	= 0.22; Ch	$i^2 = 45.0$	67, df = 3	13 (P <	: 0.0001); I ²	= 72%	
Test for overall effec	t: Z = 3.34	(P = 0.0)	(8000				0.001 0.1 I I0 100
Test for subgroup di	fferences: ($Chi^2 = 0$.38, df =	2 (P =	0.83), I ² =	0%	ravours (experimental) ravours (control)

TABLE 2 | Name of High Frequency TCMs.

Chinese Name	Pharmaceutical name	Family	No. of Studies
Dangshen	Codonopsis Radix	Campanulaceae	8
Gancao	Glycyrrhizae Radix et Rhizoma	Leguminosae	8
Baizhu	Atractylodis Macrocephalae Rhizoma	Asteraceae	7
Fuling	Poria	Polyporaceae	7
Chenpi	Citri Reticulatae Pericarpium	Rutaceae	5
Shanyao	Dioscoreae Rhizoma	Dioscoreaceae	4
Yiyiren	Coicis Semen	Gramineae	4
Sharen	Amomi Fructus	Zingiberaceae	4
Banxia	Pineelliae Rhizoma	Araceae	4

To discern the commonalities between the TCM formulae that were combined with paclitaxel in the various studies, we analyzed the frequency and compatibility of the oral Chinese herbal compounds in the included studies. As the most effective qi tonic among the administered TCMs, the combination of Dangshen and Gancao was used in all eight studies in the oral administration subgroup that used multi-ingredient TCM regimens. In addition, seven of these studies (87.5%) used a combination of Dangshen, Gancao, Baizhu and Fuling, which is the most representative basic qi tonic TCM formula and is known as Sijunzi Decoction. According to these findings, we can infer that when treating GC using paclitaxel-based chemotherapy combined with TCMs, most of the studies invigorated the qi and strengthened the spleen as the standard treatment approach. This is also supported by the existing evidence on TCM treatment for advanced GC and TCMs combined with chemotherapy (Chen et al., 2018). In addition, we found a frequently recurring combination of eight ingredients (Dangshen, Gancao, Baizhu, Fuling, Chenpi, Shanyao, Yiyiren, and Sharen). This combination could be used to guide the prescribing of TCMs in paclitaxel+TCM regimens for the clinical treatment of GC and can be used as a candidate treatment for further RCTs.

An advantage of our study was the use of strict inclusion and exclusion criteria, excluding studies with Jadad scale <2 to improve the quality of the meta-analysis. Furthermore, we not only systematically searched the databases (from their inceptions) for studies in English, but we also searched the databases in Chinese; therefore, the included literature was not





limited to English. Additionally, we comprehensively evaluated and compared the side effects of paclitaxel+TCM with paclitaxelbased chemotherapy alone. The results indicate that paclitaxel +TCM is more effective and safer. Finally, we discovered a frequently used combination of herbal compounds, which should be assessed in future RCTs.

Our research has several limitations. There was a lack of large, multicenter, standardized RCTs, and our included studies were mostly small, which may have led to some bias in the outcomes. We look forward to more high-quality RCTs being published in international journals. Moreover, the included studies lacked assessment of the efficacy of paclitaxel+TCM regimens in paclitaxel-resistant patients. In the future, we plan to focus on drug resistance in order to facilitate a more comprehensive evaluation of the role of TCMs in combination therapies.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/ **Supplementary Material**.

REFERENCES

- Bang, Y. J., Kang, W. K., Kang, Y. K., Kim, H. C., Jacques, C., Zuber, E., et al. (2002). Docetaxel 75 mg/m(2) is active and well tolerated in patients with metastatic or recurrent gastric cancer: a phase II trial. *Jpn J. Clin. Oncol.* 32, 248–254. doi: 10.1093/jjco/hyf057
- Bang, Y. J., Xu, R. H., Chin, K., Lee, K. W., Park, S. H., Rha, S. Y., et al. (2017). Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy (GOLD): a doubleblind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 18, 1637– 1651. doi: 10.1016/S1470-2045(17)30682-4

AUTHOR CONTRIBUTIONS

XD, XSu, and YiL contributed to conception and design. YiL, CY, FC, YuL, and KL contributed to article collection, data analysis and manuscript drafting. XSu, ZS, XSh, and NJ contributed to the revised version. The final submitted version has been confirmed by all authors.

FUNDING

Our research was funded by the National Natural Science Foundation of China (Grant No. 81630080, 91129714 and 81874380) and the National Key R&D Program of China (Grant No. 2018YFC1704100 and 2018YFC1704106).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020. 00132/full#supplementary-material

Biagioni, A., Skalamera, I., Peri, S., Schiavone, N., Cianchi, F., Giommoni, E., et al. (2019). Update on gastric cancer treatments and gene therapies. *Cancer Metastasis Rev.* 38 (3), 537–548. doi: 10.1007/s10555-019-09803-7

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., and Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 68, 394–424. doi: 10.3322/caac.21492

Chen, X., Deng, L., Jiang, X., and Wu, T. (2016). Chinese herbal medicine for oesophageal cancer. *Cochrane Database Syst. Rev.* 1, CD004520. doi: 10.1002/ 14651858.CD004520.pub7.Cd 004520

- Chen, Y., Zhang, G., Chen, X., Jiang, X., Bie, F., Yuan, N., et al. (2018). Jianpi Bushen, a traditional chinese medicine therapy, combined with chemotherapy for gastric cancer treatment: a meta-analysis of randomized controlled trials. *Evid. Based Complement Alternat. Med.* 2018, 4924279. doi: 10.1155/2018/4924279
- Chen, H. M. (2009). Effect of Huachansu combined with TPF in the treatment of advanced gastric cancer. J. Emergency Tradi. Chin. Med. 18, 0035–0036. doi: 10.3969/j.issn.1004-745X.2009.01.020
- Ge, H. L., Li, H., Ding, Y. X., and Hu, S. Y. (2014). Clinical observation of Jianpixiaozheng Decoction combined with chemotherapy in the treatment of advanced gastric cancer. J. Sichuan Tradi. Chin. Med. 32, 0093–0095.
- Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., et al. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343, d5928. doi: 10.1136/bmj.d5928
- Huang, H. T., Zhao, J., Wei, X. C., Su, F., and Wang, S. T. (2018). Clinical observation of Jianpi Yiqi method combined with TP chemotherapy in treating advanced gastric cancer. *J. Liaoning Univ. TCM* 20, 0200–0203. doi: 10.13194/ j.issn.1673-842x.2018.10.053
- Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., et al. (1996). Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin. Trials* 17, 1–12. doi: 10.1016/0197-2456(95) 00134-4
- Lai, Y. Q., Huang, Z. R., and Wang, Y. (2018). Effect of Shenlingbaizhu Decoction on the immunosuppressive state of gastric cancer treated with dose intensive chemotherapy. *Fujian J. TCM* 49, 0018–0022. doi: 10.13260/ j.cnki.jfjtcm.011725
- Li, T. C., Chen, N. J., Wu, D. H., Lai, Y. Q., Chen, Y. Y., and Yu, J. P. (2010). Liujunzi Decoction combined with chemotherapy in the treatment of advanced gastric cancer. J. Shandong Univ. TCM 34, 0154–0155. doi: 10.16294/ j.cnki.1007-659x.2010.02.039
- Li, N. J., Gong, Z. J., Qing, D. J., and Liu, H. (2016). Clinical effect of Rg3 combined with paclitaxel in the treatment of liver metastasis after gastric cancer operation. *Strait Phar. J.* 28, 0122–0123. doi: 10.3969/j.issn.1006-3765.2016.01.059
- Li, Z., Li, K., Wang, W., and Li, Q. H. (2016a). Observation of Paclitaxel liposome Fufang Kushen injection and Yiqi Yangwei decoction combined with in the treatment of advanced gastric cancer with malignant ascites. J. Liaoning Univ. TCM 18, 0138–0140. doi: 10.13194/j.issn.1673-842x.2016.11.042
- Li, Z. P., Xu, L., Xue, T., Liu, S. L., and Li, H. (2016b). Clinical observation on 50 cases of advanced gastric cancer treated with Shenlingbaizhu decoction combined with TS chemotherapy. J. Tradi. Chin. Med. 57, 1393–1396. doi: 10.13288/j.11-2166/r.2016.16.012
- Liao, L. F. (2018). Investigation on short-term efficacy and safety of Docetaxel and Cisplatin combined with Kang'ai injection in the treatment of advanced gastric cancer. *Chin. J. Ration. Drug Use* 15, 0033–0035. doi: 10.3969/j.issn.2096-3327.2018.07.011

- Liu, L. H., and Zhang, C. X. (2009). Clinical efficacy of Aidi injection combined with TPF in the treatment of advanced gastric carcinoma. *China Mod. Doct.* 47, 16–17. doi: 10.3969/j.issn.1673-9701.2009.29.007
- Meng, Q. J. (2019). Paclitaxel liposome combined with Fufangkushen injection and Yiqiyangwei Decoction in the treatment of advanced gastric cancer with malignant ascites. *Clin. J. Mod. Drug Appl.* 13, 0139–0141. doi: 10.14164/ j.cnki.cn11-5581/r.2019.09.081
- Shitara, K., Matsuo, K., Takahari, D., Yokota, T., Shibata, T., Ura, T., et al. (2010). Neutropenia as a prognostic factor in advanced gastric cancer patients undergoing second-line chemotherapy with weekly paclitaxel. *Ann. Oncol.* 21, 2403–2409. doi: 10.1093/annonc/mdq248
- Tan, Y., Zhao, F. Y., and Wu, Q. (2013). Efficacy of Fufangbanmao capsules combined chemotherapy in the treatment of advanced gastric cancer in gerontal patients. *Chongqing Med.* 04, 0393–0395. doi: 10.3969/j.issn.1671-8348.2013.04.012
- Wagner, A. D., Syn, N. L., Moehler, M., Grothe, W., Yong, W. P., Tai, B. C., et al. (2017). Chemotherapy for advanced gastric cancer. *Cochrane Database Syst. Rev.* 8. doi: 10.1002/14651858.CD004064.pub4
- Wong, R., Sagar, C. M., and Sagar, S. M. (2001). Integration of Chinese medicine into supportive cancer care: a modern role for an ancient tradition. *Cancer Treat Rev.* 27, 235–246. doi: 10.1053/ctrv.2001.0227
- Xie, X., Huang, X., Li, J., Lv, X., Huang, J., Tang, S., et al. (2013). Efficacy and safety of Huachansu combined with chemotherapy in advanced gastric cancer: a meta-analysis. *Med. Hypotheses* 81, 243–250. doi: 10.1016/j.mehy.2013.04.038
- Xue, J. Z., and Mao, Q. Y. (2017). Clinical effect of Rg3 combined with paclitaxel in the treatment of liver metastasis after gastric cancer operation. *Mod. Diagn. Treat* 28, 4577–4578.
- You, J. L., and Huang, X. N. (2009). The effect of Fuzhenghewei liquid medicament on the quality of life in the treatment of advanced gastric cancer. *Shaanxi J. Tradi. Chin. Med.* 9, 1112–1114. doi: 10.3969/j.issn.1000-7369.2009.09.004
- Zhang, D., Wu, J. R., Duan, X. J., Wang, K. H., Zhao, Y., Ni, M. W., et al. (2019). A Bayesian network meta-analysis for identifying the optimal taxane-based chemotherapy regimens for treating gastric cancer. *Front. Pharmacol.* 10, 717. doi: 10.3389/fphar.2019.00717

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Li, Sui, Su, Yu, Shi, Johnson, Chu, Li, Li and Ding. This is an openaccess article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.