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# First-line systemic therapy for advanced gastric cancer: a systematic review and network meta-analysis

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***Abstract***

**Background:** Systemic therapy is the standard treatment against advanced gastric cancer. Fluoropyrimidine plus platinum doublet has been recommended as the preferred first-line strategy. However, there is still a lack of a comprehensive and hierarchical evidence that compares all eligible literature simultaneously.

**Methods:** Record retrieval was conducted in PubMed, Web of Science, Cochrane Central Register of Controlled Trials, Embase, ASCO, and ESMO meeting library from inception to October 2018. Randomized controlled trials featuring comparisons between different first-line systemic treatments against advanced gastric cancer were eligible. Overall survival was utilized as the primary endpoint. Pairwise and network calculations were based on a random-effects model and the hierarchical ranking was numerically indicated by P-score. All procedures were conducted according to Cochrane Handbook 5.1 and PRISMA for Network Meta-analysis (Registration identifier: CRD42018084951).

**Results:** A total of 119 studies were eligible for our pooled analysis. Concerning general analysis, 'fluoropyrimidine plus platinum-based triplet' topped the overall survival hierarchy (HR 0.91 [0.83–0.99], P-score = 0.903, $p = 0.04$) while it ranked in second place for progression-free survival and objective response rate. However, it displayed worse tolerability against 'fluoropyrimidine plus platinum doublet'. More specifically, 'Capecitabine plus cisplatin-based triplet plus targeted medication' topped the ranking among all fluoropyrimidine plus platinum-based regimens in additional analysis. Nevertheless, it did not reach statistical advantage against fluoropyrimidine plus oxaliplatin doublet in terms of survival benefits, while still displaying significantly worse safety profile.

**Conclusions:** Taken together, fluoropyrimidine plus oxaliplatin doublet (especially capecitabine or S-1) should still be considered as the preferred first-line regimen owing to its comparable survival benefits and lower toxicity.

***Keywords:*** advanced gastric cancer, first-line systemic therapy, fluoropyrimidine plus oxaliplatin, network meta-analysis, systematic review

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## Introduction

Gastric cancer is the third leading cause of cancer-related mortality worldwide, and more than half of the cases occur in East Asia.[1,2] It is estimated that over 950,000 cases were newly diagnosed in 2012, while 720,000 fatalities were reported, highlighting its relatively poor prognosis.[1]

For early localized gastric cancer cases, surgery has been recognized as the optimal therapeutic option owing to its curability.[3,4] Nonetheless, for

those bearing incurable factors, such as locally advanced inoperable, recurrent, or metastatic gastric cancer, systemic therapy is often used as the preferred palliative treatment among cancer patients, which offers survival benefits compared with supportive treatments alone.[5]

Currently, owing to its survival benefits and satisfactory safety profile, fluoropyrimidine and platinum-based doublet is widely recommended as the preferred first-line systemic regimen against advanced gastric cancer. Specifically, fluorouracil (5-FU) or capecitabine plus cisplatin, capecitabine plus cisplatin or oxaliplatin, S-1 or capecitabine plus cisplatin, and S-1 or capecitabine plus oxaliplatin are the first choices recommended by National Comprehensive Cancer Network (NCCN),[5] European Society for Medical Oncology (ESMO),[6] Japanese,[7] and Chinese[8] guidelines, respectively. In terms of fluoropyrimidine and platinum-based triplet, no consensus has been reached despite several phase III studies reporting positive survival results when comparing fluoropyrimidine and platinum-based triplet with the doublet regimen.[9–11] Higher toxicity is the major concern about the clinical application of the three-drug regimen, therefore current guidelines only recommend the three-drug regimen for patients with better performance status (PS).[5,6] Furthermore, the addition of targeted medications displayed comparable survival benefits against fluoropyrimidine and platinum-based triplet alone,[12–15] adding more options on potential alternatives of fluoropyrimidine and platinum-based doublet in terms of preferred first-line systemic regimens.

However, comprehensive evidence of this topic is still scarce. Although three previously published high-quality systematic reviews had reported relevant results, each of them had specific imperfections. Wagner *et al.* updated their systematic review based on studies up to June 2016 ($n = 64$).[16] However, this systematic review was only quantitatively synthesized by pairwise meta-analyses rather than hierarchical network meta-analysis. Meanwhile, it only included first-line chemotherapy while excluding studies with targeted medications. Song *et al.* published a systematic review and pairwise meta-analysis based on studies up to December 2015 ($n = 11$), which was also an non-comprehensive review since it only included studies with molecular-targeted first-line therapy.[17] Moreover, Ter Veer *et al.* conducted a systematic review with network meta-analysis based on studies until June 2015 ($n = 65$).[18] Nonetheless, this systematic review contained both advanced esophageal and gastric cancer patients, while it discussed first-line chemotherapy only. Therefore, those systematic reviews were lopsided, outdated, or inadequate in their use of hierarchical rankings, which urged us to provide an updated and by far the most comprehensive systematic review and network meta-analysis.

## Methods

### *Registration and guidelines*

The protocol of our systematic review and network meta-analysis had been published in PROSPERO (CRD42018084951). The design, conduct, and writing of this systematic review and network meta-analysis was strictly in accordance with the requirements from the PRISMA Checklist for Network Meta-analysis and Cochrane Handbook 5.1. Each step was conducted by two investigators of our research group. Any discrepancy was resolved by a third investigator.

### *Search strategy*

Electronic databases including PubMed, Web of Science, Cochrane Central Register of Controlled Trials, and Embase were examined comprehensively. In addition, we also thoroughly searched major databases for meeting abstracts, including American Society of Clinical Oncology (ASCO) and ESMO Meeting Library. The searching process started on 1 March until 4 October 2018, covering possible indexes published from inception to October 2018. Both the abstract and the main text of the retrieved entries were rigorously assessed in order to guarantee the accuracy of selection. Furthermore, in the case of omission, the reference lists of three previously published high-quality systematic reviews were also reviewed.[16–18] The full electronic search strategy is presented in the supplementary material.

### *Selection criteria*

Studies that simultaneously met the following inclusion criteria were eligible (PICOS framework).

1. Participant: patients with previously untreated advanced gastric cancer, including locally inoperable, recurrent, and metastatic cases. Studies that contained both gastric and esophageal cancer cases were

eligible. However, if other types of malignancies existed such as pancreatic cancer, it was not qualified unless subgroup data were offered.
2. Intervention: different first-line systemic treatments against advanced gastric cancer, including chemotherapy and targeted medications. Regarding chemotherapeutic types, since intraperitoneal chemotherapy was still controversial among different countries, we only included oral and intravenous chemotherapeutic regimens. Moreover, the comparisons between different regimens of chemotherapy were qualified while the comparisons between different dosages or methods of administration by the same chemotherapeutic regimen were not eligible. Comparisons between auxiliary therapeutics (such as anti-inflammatory medications, nutritional supportive methods, unspecified herbal medicine, and immunomodulators) were also not qualified.
3. Comparator: 'FP2' (fluoropyrimidine plus platinum-based doublet), 'FC2' (5-FU plus cisplatin doublet), and 'XC2' (capecitabine plus cisplatin doublet) were common comparator nodes of network meta-analysis under different scenarios.
4. Outcome: time-to-event overall or progression-free survival (PFS) data [hazard ratio (HR) or Kaplan–Meier curves] were mandatory, while results of objective response rate (ORR) and adverse events were dispensable.
5. Study design: phase II and phase III randomized controlled trials reported from inception to October 2018 without language limitations. We only included the one with the longest follow-up period among different reports of the same registered trial.

Studies were excluded from systematic review owing to the following reasons.

1. Could not incorporate into network calculation among unselected population.
2. Sequential first-line therapy (Supplementary Table 1).

### *Risk of bias assessment*

The quality of each eligible study was evaluated by The Cochrane Risk of Bias Tool. The entire scale was constituted by seven domains, namely random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.[19] According to the criteria in Cochrane Handbook 5.1, each domain could be judged as any of the three levels, low risk, unclear risk, or high risk of bias. If the majority of items were judged as low risk of bias, then the entire methodological design of network meta-analysis was regarded as low risk of bias, and vice versa. Here, studies were defined to be low quality if four or more items were scored as high risk of bias.

### *Data extraction*

Predesigned forms were utilized to collect and organize the original data. General information, survival, and safety data were extracted from the main text, tables, survival curves, or supplementary materials, which had been cross-checked by two different investigators in our team before quantitative synthesis.

### *Nodes, baseline parameters, and endpoints*

Our major principle for node classifications was to combine similar and less-significant regimens together so that sample size and the advantages of direct randomization could be enhanced, and meanwhile also individualize the clinically significant components based on their known mechanisms to lower the heterogeneity and maintain clinical availability. For general analysis among the unselected population, all nodes were in the form of alphanumeric combination. Each type of alphanumeric combination was selected based on the clinical significance and availability. Since leucovorin was routinely considered as a chemomodulator, it was not calculated into a separate node. The node abbreviations in the general analysis were as follows: F, fluoropyrimidine; P, platinum; R, targeted medication; T, taxane; I, irinotecan; A, anthracycline; M, methotrexate; E, etoposide; Y, mitomycin-C; S, best supportive care; U, nitrosourea; 1, monotherapy; 2, doublet; 3, triplet. For example, 'FP3R' suggested that this regimen was a fluoropyrimidine plus platinum-based triplet plus one targeted medication, while 'F1' indicated that it was a fluoropyrimidine monotherapy. Meanwhile, different drugs within each regimen were orderly listed according to their clinical significance for systemic therapy (fluoropyrimidine, platinum, leucovorin, taxane,

other drugs), which helped to eliminate the possible false classification of the same regimen into two different nodes. For additional analysis among unselected population, similar rationale had been applied. Moreover, since fluoropyrimidine and platinum were crucial components for gastric cancer systemic treatments with different subtypes inside each category that might function differently, we individualized diverse types of fluoropyrimidine and platinum when combining them into separate nodes. All abbreviations of nodes in additional analysis were as follows: S, S-1; C, cisplatin; X, capecitabine; R, targeted medication; O, oxaliplatin; F, 5-FU; H, heptaplatin; 1, monotherapy; 2, doublet; 3, triplet. For instance, 'XC3' was the node for capecitabine plus cisplatin-based triplet.

Unselected patients were those without specific pathological positivity, in contrast to those featuring specific positivity such as HER-2 positive gastric cancer. Since most studies were completed *via* multinational cooperation, the leading country of each study was defined by the nationality of its first corresponding author, who usually led the project. Age referred to the median age of overall population. Here, region referred to the source region of patients that had been analyzed in the studies. Western regions included Europe, North America, and Australia, while eastern regions usually referred to East Asian countries including Japan, South Korea, and China. If the study contained patients from both western and eastern regions, or patients from other areas of the world (such as South America), it was regarded as a versatile region. Visceral involvement suggested the metastatic involvement of liver and lung. In term of measurability, those nonmeasurable but assessable patients were also included as measurable cases. Owing to the potential disparity of efficacy in terms of different tumor locations and histological types, ratios between gastric cancer and gastroesophageal junction cancer, as well as intestinal type and diffused type were collected, respectively. Usually, patients with gastric cancer should significantly outnumber those with gastroesophageal junction cancer.

The primary endpoint was overall survival (OS), while secondary endpoints included PFS, ORR, hematological adverse events, and nonhematological adverse events. OS and PFS were defined as the time from randomization to death from any cause and the time from randomization to disease progression or death from any cause, respectively. ORR was the percentage of patients with complete and partial response. The hematological adverse events included leukopenia, neutropenia, anemia, thrombocytopenia, and other relevant events such as febrile neutropenia and infection with neutropenia. The remaining adverse events were categorized as nonhematological adverse events. We only counted grade 3 or higher (National Cancer Institute Common Terminology Criteria for Adverse Events) adverse events owing to their clinical significances. For early studies that failed to use this numerical grading system, we collected severe-toxicity adverse events in the nonhematological category and leukocyte count $<2000/\mu l$, platelets $<50{,}000/\mu l$, or hemoglobin $<9.5\,g/dl$ were collected in the hematological category.

### Statistical analysis

HRs and 95% confidence intervals (95% CIs) were used as the effect size for OS and PFS. Risk ratios (RR) and 95% CIs were applied as the effect size for ORR, hematological and nonhematological adverse events. If survival data or its CI was not directly provided, we estimated the values from the Kaplan–Meier curves by methods described elsewhere.[20] In terms of adverse events, the total amount of grade 3 or higher adverse events were used for calculation, instead of the number of patients suffering grade 3 or higher adverse events.

As was known to all, the prominent strength of network meta-analysis was to provide a hierarchical ranking for multiple arms even without direct comparisons.[21] This key feature reflected on and highlighted the two fundamental assumptions of network meta-analysis, known as transitivity and consistency.[22]

When the head-to-head results of A *versus* C and B *versus* C were respectively provided, then the hypothesis of transitivity also validated a statistical comparison between A and B. However, it required comparable general features within each node as the prerequisite condition to eliminate selection bias and justify statistical connections among indirect arms.[23] Since all included studies were randomized controlled trials without significant methodological heterogeneity, the baseline parameters were the crucial factors to determine the clinical heterogeneity and therefore transitivity. We carefully compared the main baseline features of different arms within each node and

eliminated those with significant differences by sensitivity analysis. Apart from clinical and methodological heterogeneity, we also evaluated statistical heterogeneity of the network meta-analysis, which was known as the overall degree of disparity within the same pairwise comparison.[24] The $I^2$ statistic was the chief indicator of statistical heterogeneity, with values of <25%, 25–50%, and >50% indicating low, moderate, and high heterogeneity, respectively. In addition, the $Q$ statistic of heterogeneity and its $p$ value also facilitated the assessment of statistical heterogeneity. If the $p$ value of the $Q$ statistic was less than 0.05, it suggested that there was significant heterogeneity.

On the other hand, the consistency, another crucial assumption for network meta-analysis, referred to the statistically consistent results between direct and indirect effect sizes regarding the same comparison. Significant differences between direct and indirect calculations might indicate inconsistency within the network meta-analysis while also suggest the unsuitability for transitivity.[25] Here, we employed several methods to assess the network consistency, including the comparison between direct and indirect results as well as the $Q$ statistic. We performed a pairwise meta-analysis *via* both fixed-effects and random-effects calculations to generate direct results before network meta-analysis. Concerning the same therapeutic comparison, the results were regarded as consistent if the 95% CI of both pairwise and network meta-analysis significantly overlapped. Meanwhile, the $Q$ statistic of inconsistency was another statistical indicator to numerically estimate the consistency within the comparisons, whose $p$ value (<0.05) could suggest a significant inconsistency between pairwise and network meta-analysis. Both consistency and homogeneity were crucial bases to offer reliable outcomes by network meta-analysis. If inconsistency or significant heterogeneity occurred, we deleted the original data from the most inconsistent or heterogeneous pairwise comparisons to examine whether the results remained unchanged, otherwise it was not appropriate for pooled analysis.[24,26]

For the network calculation of general analysis, 'fluoropyrimidine plus platinum' (FP2) was chosen as the common comparator since it was the regimen preferred by different guidelines. A network plot and comparison-adjusted funnel plot were used to display the network structure and examine the publication bias across the included trials, respectively, where the more symmetrical it was, the lower the probability of publication bias the merged results would have.[27,28] We conducted the random-effects network meta-analysis based on a frequentist model, with either HR or RR as the effect size. A network forest plot or league table were used to demonstrate the entire regimens with their relative CIs. In addition, we also utilized P-score to rank all regimens based on their network estimates. The closer the P-score moved to 1, the better the regimen. Sensitivity analysis was performed to detect the stability of pooled outcomes, which included using fixed-effects model and deleting studies with significant clinical heterogeneity. For the network calculation of additional analysis, '5-FU plus cisplatin' (FC2) was chosen as the common comparator since they were recommended by NCCN guidelines, while the remaining statistical methods were similar to those of the general analysis.

Both pairwise and network meta-analysis were conducted in R software 3.4.3, assisted by STATA 14.0 in terms of graphical functions.

### *Role of the funding source*

The sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

### *Literature retrieval*

After screening through 15,262 preliminary records, a total of 119 randomized controlled trials were eligible for inclusion in our systematic review (Figure 1). Among 119 eligible trials, 94 studies were included in the general analysis of unselected population, 39 studies were selected into the additional analysis of unselected population (including 22 studies overlapping with general analysis), while 8 trials were systematically reviewed in terms of specific pathological positivity. Both systematic review and network meta-analysis were conducted among unselected population, irrespective of general or additional analysis. However, owing to the limited number of eligible studies, we only performed systematic review for studies concerning specific pathological positivity.

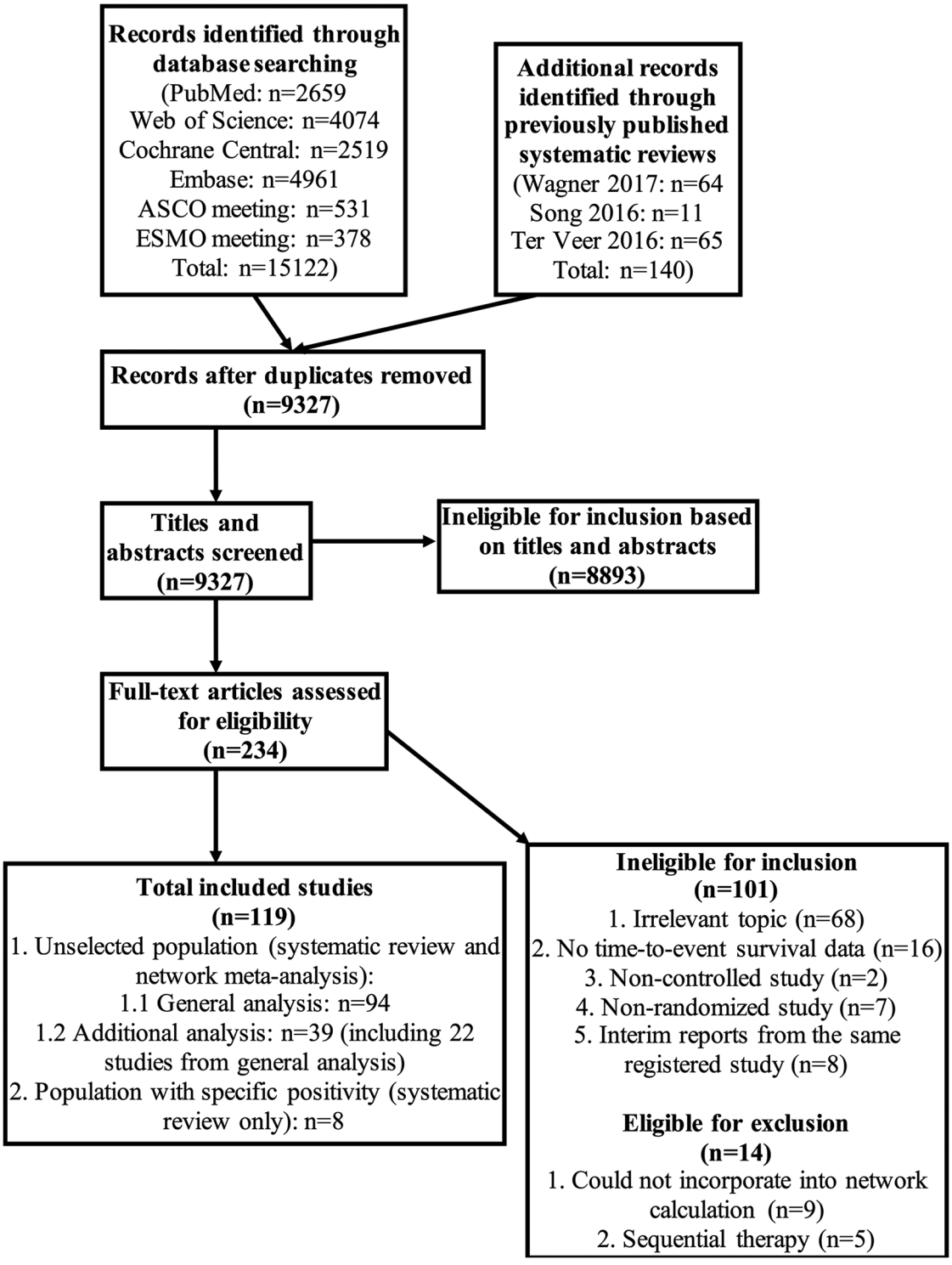


**Figure 1.** Selection flow chart for network meta-analysis.

### *General analysis: baseline features and transitivity*

Overall, 94 randomized controlled trials were included in the general analysis, containing a total of 17,976 participants. Japan ($n=19$), USA ($n=15$), and China ($n=12$) were the top three leading countries. A total of 52 studies recruited patients from western region, while 37 and 5 studies featured patients from the eastern region and versatile region, respectively, displaying a

relatively balanced geographical distribution between eastern and western regions. 'Fluoropyrimidine plus platinum doublet' was the most frequent node in the network ($n = 45$), followed by 'fluoropyrimidine plus platinum-based triplet' ($n = 31$), and 'fluoropyrimidine monotherapy' ($n = 28$). The majority of the studies featured populations with a median-age around 60 and male-dominant sex ratio. Predominantly, patients were metastatic measurable cases and had a PS of either 0 or 1. Meanwhile, the ratio of visceral or peritoneal involvement, primary locations (dominant proportion of gastric cancer cases) and histological types were largely comparable across different studies. Therefore, the demographic characteristics of included trials were generally comparable. Several studies might introduce potential heterogeneity owing to incompatible baseline features with other studies, such as recruiting elderly patients (>70 years old),[12,29–32] containing esophageal,[13–15,29,31,33–36] fake registration identifier,[37] nonmeasurable cases only,[38] and peritoneal metastasis only[39] (Table 1). The influence on pooled results by these studies was further detected in sensitivity analysis.

First, all included studies were randomized controlled trials that minimized the methodological heterogeneity induced by different study designs. Second, patients in most studies shared similar and comparable baseline characteristics that guaranteed the treatment effects not to be artificially biased owing to unbalanced confounding information. For example, in most studies, patients were PS < 2, metastatic, measurable, and gastric cancer cases, without specific inclination of histological types. Other potential difference in baseline features were either unable to alter the results (such as small amount of esophagogastric junction cases) or addressed by sensitivity analysis (Table 1). All these had justified the transitivity and performance of our network meta-analysis.

### *General analysis: risk of bias*

Overall, the included studies had low risk of bias since nearly half of the assessment parameters were scored as low risk of bias (45%), while unclear risk (39%) or high risk of bias (16%) took up relatively small proportions (Figure 2). None of the eligible studies were at high risk of bias concerning methodological design (Supplementary Table 2). Specifically, 31% and 48% of the studies were evaluated as low risk of bias concerning random sequence generation and allocation concealment, respectively, while no high risk of bias was reported in these two key domains. Largely due to the open-label design, 90% of the included trials were scored as high risk of bias in terms of blinding or participants and personnel. Meanwhile, since there was a lack of details on whether the response evaluation was independent enough, more than half of the studies (63%) were evaluated as unclear risk of bias regarding blinding of outcome assessment. In addition, because most of the studies were analyzed based on the intent-to-treat population as well as having reported enough endpoints, 79% and 72% of the eligible trials had low risk of bias in terms of incomplete outcome data and selective reporting, respectively. Moreover, since the majority of studies were completely performed without early termination and also described adequate baseline details, nearly half of the studies (48%) were appraised as low risk of bias with respect to other source of bias (Figure 2).

### *General analysis: primary endpoint (OS)*

*Network geometry.* There were a total of 91 randomized controlled trials merged into the quantitative analysis, with 17,529 participants and 24 nodes of therapeutic regimen (Figure 3 and Table 1).

*Consistency and statistical heterogeneity.* In addition to the value of $Q$ statistic ($Q$ inconsistency: $p = 0.08$), the effect size and CI between direct and indirect results were highly overlapped (Supplementary Table 3), both of which suggested that results inside the entire network were consistent. In terms of statistical heterogeneity, both $I^2$ statistic ($I^2 = 15.00\%$) and $Q$ statistic ($Q$ heterogeneity: $p = 0.29$) implied that there was no significant heterogeneity across the network.

*Publication bias.* There was no publication bias among the included studies owing to the symmetrical distribution of effect sizes inside the funnel plot (Supplementary Figure 1).

*Network calculation.* Based on P-score ranking of the network meta-analysis, 'fluoropyrimidine plus platinum-based triplet' (network HR 95% CI: 0.91 (0.83–0.99), P-score = 0.903) was the best ranking regimen, displaying statistical superiority against common comparator 'fluoropyrimidine plus platinum doublet' ($p = 0.04$). The network

**Table 1.** Baseline characteristics of eligible studies for general analysis (unselected population).

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yamada 2018 | Japan | UMIN000 007652 | III | April 2012—March 2016 | S-1 plus cisplatin plus docetaxel | FP3 | 370 | Adult | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | S-1 plus cisplatin | FP2 | 371 | | | | | | |
| Muro 2018 | Japan | NCT02539225 | II | October 2015—October 2017 | S-1 plus oxaliplatin plus ramucirumab | FP2R | 96 | Adult | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | S-1 plus oxaliplatin | FP2 | 93 | | | | | | |
| Lu 2018 | China | NCT01015339 | III | December 2009—February 2014 | Capecitabine plus paclitaxel | FT2 | 160 | 56.6 | 115/45 | Eastern | 151/9 | 71/89 | 8/152 |
| | | | | | Capecitabine plus cisplatin | FP2 | 160 | 56.2 | 118/42 | | 142/18 | 76/84 | 4/156 |
| Fuchs 2018 | USA | NCT02314117 | III | January 2015—May 2017 | 5-FU/capecitabine plus cisplatin plus ramucirumab | FP2R | 326 | 58.9 | 214/112 | Versatile | Metastatic | NA | NA |
| | | | | | 5-FU/capecitabine plus cisplatin | FP2 | 319 | 60.1 | 215/104 | | | | |
| Matsuyama 2018 | Japan | UMIN000 006179 | II | August 2011—September 2015 | S-1 plus docetaxel | FT2 | 30 | 18–75 | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | S-1 plus cisplatin | FP2 | 31 | 11/31-2 | | | | | |
| Iqbal 2017 | USA | NCT01498289 | II | February 2012—March 2018 | 5-FU plus oxaliplatin plus leucovorin | FP2 | 99 | Adult | NA | Western | Metastatic and locally unresectable | NA | NA |
| | | | | | Docetaxel plus irinotecan | TI2 | 104 | | | | | | |
| Li 2017 | China | ChiCTR-TRC-08000167 | II | April 2008—September 2012 | 5-FU plus leucovorin plus irinotecan | FI2 | 71 | 53 | 50/21 | Eastern | 65/6 | 33/38 | NA |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FP2 | 74 | 52 | 54/20 | | 67/7 | 21/53 | |
| Hwang 2017 | South Korea | NCT01470742 | III | August 2010—October 2014 | Capecitabine plus oxaliplatin | FP2 | 24 | **75*** | 18/6 | Eastern | 15/9 | NA | NA |
| | | | | | Capecitabine | F1 | 26 | **77*** | 16/10 | | 15/11 | | |
| Hall 2017 | UK | ISC-TRN33934807 | II | June 2009—January 2011 | Capecitabine plus oxaliplatin plus epirubicin | FP3 | 17 | **74*** | 13/4 | Western | 17/0 | NA | NA |
| | | | | | Capecitabine plus oxaliplatin | FP2 | 19 | **77*** | 13/6 | | 17/2 | | |
| | | | | | Capecitabine | F1 | 19 | **75*** | 15/4 | | 18/1 | | |
| Li 2016 | China | NA | NA | NA | 5-FU plus leucovorin plus irinotecan | FI2 | 50 | Adult | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | Capecitabine plus oxaliplatin plus epirubicin | FP3 | 55 | | | | | | |
| Yoon 2016 | USA | NCT01246960 | II | April 2011—August 2012 | 5-FU plus oxaliplatin plus leucovorin plus ramucirumab | FP2R | 84 | 64.5 | 63/21 | Western | 80/4 | NA | NA |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FP2 | 84 | 60 | 61/23 | | 79/5 | | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NA | NA | 0–1 | Gastric | 259/428 | 0.99 (95% CI, 0.85–1.16) | 0.99 (95% CI, 0.86–1.15) | 219/370 | 245/370-2 | 26/370-1 | J Clin Oncol | J Clin Oncol 36, 2018 (suppl; abstr 4009) | Abstract |
| | | | | | | | 208/371 | 140/371-2 | 27/371-1 | | | |
| NA | NA | 0–1 | Gastric and junction | NA | NA | 1.07 (95% CI, 0.86–1.33) | 32/55 | NA | NA | J Clin Oncol | J Clin Oncol 36, 2018 (suppl; abstr 4036) | Abstract |
| | | | | | | | 27/54 | | | | | |
| 51/109 | Measurable | 0–2 | 92/68 | 40/40 | 0.88 (95% CI, 0.69–1.13) | 0.91 (95% CI, 0.71–1.16) | 69/160 | 100/158 | 24/158 | Gastric Cancer | 29488121 | |
| 50/110 | | | 97/63 | 31/35 | | | 46/160 | 91/147 | 65/147 | | | |
| NA | Measurable | 0–2 | Gastric and junction | NA | 0.96 (95% CI, 0.80–1.16) | 0.75 (95% CI, 0.61–0.94) | 134/326 | 125/326-2 | 32/326-1 | J Clin Oncol | 10.1200/JCO.2018.36.4_suppl.5 | Abstract |
| | | | | | | | 116/319 | 131/319-2 | 5/319-1 | | | |
| NA | **Non-measurable*** | 0–2 | Gastric | NA | 0.62 (95% CI, 0.34–1.13) | 0.70 (95% CI, 0.40–1.21) | NA | 15/30-2 | 4/30-3 | J Clin Oncol | 10.1200/JCO.2018.36.4_suppl.119 | Abstract |
| | | | | | | | | 10/31-3 | | | | |
| NA | Measurable | 0–2 | **Gastric and esophageal*** | NA | 0.82 (95% CI, 0.61–1.10) | 0.70 (95% CI, 0.52–0.93) | 33/80 | NA | NA | J Clin Oncol | 10.1200/JCO.2017.35.15_suppl.4009 | Abstract |
| | | | | | | | 23/86 | | | | | |
| 49/22 | Measurable | 12/25/35 | Gastric | Balanced | 1.23 (95% CI, 0.87–1.75) | 1.23 (95% CI, 0.89–1.69) | 6/54 | 22/71 | 12/71 | Oncotarget | 29228659 | |
| 49/25 | | 10/29/35 | | | | | 7/74 | 27/74 | 14/74 | | | |
| 11/13 | Measurable | 20/4 | Gastric | NA | 0.58 (95% CI, 0.30–1.12) | 0.32 (95% CI, 0.17–0.61) | 10/24 | 4/24 | 10/24 | J Geriatr Oncol | 28119041 | |
| 15/11 | | 20/6 | | | | | 8/26 | 5/26 | 7/26 | | | |
| NA | NA | 0/11/6 | **10/2/5*-E** | Balanced | 1 *versus* 2: 1.24 (95% CI, 0.39–3.94) | 1 *versus* 2: 0.83 (95% CI, 0.36–1.93) | 5/17 | NA | 14/17 | Br J Cancer | 28095397 | |
| | | 4/10/5 | **5/1/11*-E** | | 1 *versus* 3: 0.84 (95% CI, 0.41–1.73) | 1 *versus* 3: 0.64 (95% CI, 0.24–1.71) | 9/19 | | 7/19 | | | |
| | | 2/10/7 | **7/4/8*-E** | | 2 *versus* 3: 0.38 (95% CI, 0.14–1.03) | 2 *versus* 3: 0.78 (95% CI, 0.34–1.79) | 2/19 | | 8/19 | | | |
| NA | NA | NA | Gastric | NA | 1.23 (95% CI, 0.81–1.88) | 0.87 (95% CI, 0.59–1.27) | 24/50 | NA | NA | World Chinese Journal of Digestology | 28850174 | Abstract |
| | | | | | | | 22/55 | | | | | |
| NA | 67/17 | 40/43/0 | **19/26/39*-E** | Balanced | 1.08 (95% CI, 0.73–1.58) | 0.98 (95% CI, 0.69–1.37) | 38/84 | 27/82 | 65/82 | Ann Oncol | 27765757 | |
| | 70/14 | 43/41/0 | **20/23/41*-E** | | | | 39/84 | 31/80 | 35/80 | | | |

*(Continued)*

**Table 1.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Shah 2016 | South Korea | NCT01590719 | II | July 2012—May 2013 | 5-FU plus oxaliplatin plus leucovorin plus onartuzumab | FP2R | 62 | 58.5 | 40/22 | Versatile | Metastatic | NA | NA |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FP2 | 61 | 57 | 36/25 | | | | |
| Tebbutt 2016 | Australia | ACTRN12609000109202 | II | April 2010—November 2011 | 5-FU/capecitabine plus cisplatin plus docetaxel plus panitumumab | FP3R | 37 | 64 | 33/4 | Western | Metastatic and locally unresectable | 26/11 | 13/24 |
| | | | | | 5-FU/capecitabine plus cisplatin plus docetaxel | FP3 | 39 | 59 | 30/9 | | | 23/16 | 5/34 |
| Hironaka 2016 | Japan | JapicCTI-111635 | II | October 2011—December 2012 | S-1 plus oxaliplatin plus leucovorin | FP2 | 47 | 65 | 33/14 | Eastern | 40/7 | NA | 12/35 |
| | | | | | S-1 plus leucovorin | F1 | 47 | 65 | 37/10 | | 40/7 | | 11/36 |
| | | | | | S-1 plus cisplatin | FP2 | 48 | 65 | 38/10 | | 41/7 | | 14/34 |
| Wang 2016 | China | NCT00811447 | III | November 2008—June 2012 | 5-FU plus cisplatin plus docetaxel | FP3 | 119 | 56.6 | 81/38 | Eastern | 89/30 | NA | NA |
| | | | | | 5-FU plus cisplatin | FP2 | 115 | 55.5 | 88/27 | | 89/26 | | |
| Du 2015 | China | NCT02370849 | II | October 2009—February 2012 | S-1 plus cisplatin plus nimotuzumab | FP2R | 31 | 58 | 17/14 | Eastern | 22/9 | 6/25 | 4/27 |
| | | | | | S-1 plus cisplatin | FP2 | 31 | 53 | 26/5 | | 18/13 | 3/28 | 5/26 |
| Wu 2015 | China | **ChiCTR-TRC-13003993*** | NA | July 2009—June 2011 | S-1 plus cisplatin | FP2 | 36 | 64.1 | 25/11 | Eastern | 31/5 | NA | NA |
| | | | | | Cisplatin | P1 | 36 | 62.7 | 23/23 | | 30/6 | | |
| Van Cutsem 2015 | Belgium | NCT00382720 | II | September 2006—September 2007 | 5-FU plus oxaliplatin plus leucovorin plus docetaxel | FP3 | 89 | 58 | 61/28 | Western | Metastatic and locally unresectable | 63/26 | 17/72 |
| | | | | | Capecitabine plus oxaliplatin plus docetaxel | FP3 | 86 | 59 | 64/22 | | | 50/36 | 17/69 |
| | | | | | Oxaliplatin plus docetaxel | PT2 | 79 | 59 | 51/28 | | | 55/24 | 7/72 |
| Shen 2015 | China | NCT00887822 | III | March 2009—July 2010 | Capecitabine plus cisplatin plus bevacizumab | FP2R | 100 | 54.2 | 68/32 | Eastern | 95/5 | 39/61 | NA |
| | | | | | Capecitabine plus cisplatin | FP2 | 102 | 55.5 | 74/28 | | 94/8 | 40/62 | |
| Guimbaud 2014 | France | NCT00374036 | III | June 2005—May 2008 | 5-FU plus leucovorin plus irinotecan | FI2 | 207 | 61.4 | 155/52 | Western | 176/31 | NA | NA |
| | | | | | Capecitabine plus cisplatin plus epirubicin | FP3 | 209 | 61.4 | 154/55 | | 173/36 | | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23/39 | NA | 24/35/0 | 46/16 | 20/31 | 1.06 (95% CI, 0.64–1.75) | 1.08 (95% CI, 0.71–1.63) | 26/43 | 41/60-2 | 10/60-2 | Oncologist | 27401892 | |
| 20/41 | | 24/36/0 | 48/13 | 23/26 | | | 24/42 | 29/60-2 | 1/60-2 | | | |
| NA | Measurable | 34/3 | **13/10/15*-E** | Balanced | 1.02 (95% CI, 0.51–2.05) | 1.08 (95% CI, 0.59–2.01) | 22/37 | NA | 26/37 | Br J Cancer | 26867157 | |
| | | 37/2 | **15/11/13*-E** | | | | 17/39 | | 18/39 | | | |
| NA | Measurable | 37/10/0 | Gastric | 24/23 | 1 *versus* 2: 0.76 (95% CI, 0.47–1.24) | 1 *versus* 2: 0.52 (95% CI, 0.30–0.88) | 31/47 | 25/47 | 28/47-3 | Lancet Oncol | 26640036 | |
| | | 37/10/0 | | 24/23 | 1 *versus* 3: 0.59 (95% CI, 0.37–0.93) | 1 *versus* 3: 0.60 (95% CI, 0.35–1.02) | 20/47 | 11/47 | 10/47-3 | | | |
| | | 38/10/0 | | 18/30 | 2 *versus* 3: 0.77 (95% CI, 0.49–1.22) | 2 *versus* 3: 1.08 (95% CI, 0.67–1.74) | 22/48 | 43/48 | 22/48-3 | | | |
| 46/73 | Measurable | 115/4 | 99/20 | Balanced | 0.71 (95% CI, 0.52–0.97) | 0.58 (95% CI, 0.42–0.80) | 58/119 | 72/119-1 | 31/119 | Gastric Cancer | 25604851 | |
| 39/76 | | 108/7 | 86/29 | | | | 39/115 | 11/115-1 | 21/115 | | | |
| 8/23 | Measurable | 5/26/0 | 25/6 | Balanced | 1.78 (95% CI, 0.97–3.25) | 2.14 (95% CI, 1.19–3.83) | 17/31 | 8/31 | 6/31 | Medicine | 26061330 | |
| 9/22 | | 7/24/0 | 25/6 | | | | 18/31 | 4/31 | 1/31 | | | |
| 16/20 | Measurable | 15/21/0 | Gastric | 21/13 | 0.81 (95% CI, 0.46–1.43) | 0.76 (95% CI, 0.40–1.46) | 19/36 | 25/36 | 30/36 | Anticancer Drugs | 25933246 | |
| 18/18 | | 16/20/0 | | 22/11 | | | 15/36 | 19/36 | 24/36 | | | |
| 35/54 | 77/12 | 87/2 | 75/14 | NA | 1 *versus* 2: 0.73 (95% CI, 0.48–1.09) | 1 *versus* 2: 0.80 (95% CI, 0.55–1.18) | 41/88 | 49/88-1 | 67/88 | Ann Oncol | 25416687 | |
| 40/46 | 80/6 | 84/2 | 75/11 | | 1 *versus* 3: 0.51 (95% CI, 0.35–0.76) | 1 *versus* 3: 0.43 (95% CI, 0.30–0.63) | 21/81 | 50/82-1 | 73/82 | | | |
| 23/56 | 69/10 | 77/2 | 70/9 | | 2 *versus* 3: 0.75 (95% CI, 0.51–1.10) | 2 *versus* 3: 0.69 (95% CI, 0.49–0.96) | 18/78 | 52/78-1 | 76/78 | | | |
| 24/76 | 81/19 | 95/5 | 85/15 | Balanced | 1.11 (95% CI, 0.79–1.56) | 0.89 (95% CI, 0.66–1.21) | 33/81 | 54/100 | 66/100 | Gastric Cancer | 24557418 | |
| 20/82 | 86/16 | 97/5 | 82/20 | | | | 29/86 | 68/101 | 45/101 | | | |
| 48/159 | Measurable | 71/102/27 | 138/63 | Balanced | 1.01 (95% CI, 0.82–1.24) | 0.99 (95% CI, 0.81–1.21) | 75/198 | 78/203 | 108/203 | J Clin Oncol | 25287828 | |
| 54/155 | | 61/108/36 | 133/73 | | | | 74/189 | 129/200 | 107/200 | | | |

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**Table 1.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Iveson 2014 | UK | NCT00719550 | II | October 2009—June 2010 | Capecitabine plus cisplatin plus epirubicin plus rilotumumab | FP3R | 82 | 61 | 57/25 | Western | 73/9 | NA | NA |
| | | | | | Capecitabine plus cisplatin plus epirubicin | FP3 | 39 | 60 | 31/8 | | 34/5 | | |
| Zhang 2014 | China | NA | NA | August 2010—September 2012 | S-1 plus oxaliplatin plus cetuximab | FP2R | 30 | 49 | 37/19 | Eastern | Metastatic and locally unresectable | 26/30 | 8/48 |
| | | | | | S-1 plus oxaliplatin | FP2 | 26 | | | | | | |
| Lu 2014 | China | NA | II | January 2009—December 2011 | S-1 plus oxaliplatin | FP2 | 47 | 63 | 34/13 | Eastern | Metastatic and locally unresectable | 18/29 | 19/28 |
| | | | | | S-1 | F1 | 47 | 65 | 33/14 | | | 16/31 | 20/27 |
| Sugimoto 2014 | Japan | UMIN 000000638 | II | December 2004—November 2007 | S-1 plus paclitaxel | FT2 | 51 | 62 | 38/13 | Eastern | 40/11 | NA | NA |
| | | | | | S-1 plus irinotecan | FI2 | 51 | 64 | 38/13 | | 40/11 | | |
| Koizumi 2014 | Japan | NCT00287768 | III | September 2005—September 2008 | S-1 plus docetaxel | FT2 | 314 | 65 | 227/87 | Eastern | 260/54 | 127/187 | 119/195 |
| | | | | | S-1 | F1 | 321 | 65 | 229/92 | | 267/54 | 135/186 | 131/190 |
| Koizumi 2013 | Japan | Japi-cCTI-101327 | II | December 2008—February 2012 | S-1 plus cisplatin plus orantinib | FP2R | 45 | 62 | 30/15 | Eastern | 39/6 | 19/26 | 15/30 |
| | | | | | S-1 plus cisplatin | FP2 | 46 | 63.5 | 35/11 | | 39/7 | 24/22 | 15/31 |
| Shirao 2013 | Japan | NCT00149201 | III | October 2002—April 2007 | 5-FU plus leucovorin plus methotrexate | FM2 | 118 | 59 | 70/48 | Eastern | Metastatic | NA | **118/0*** |
| | | | | | 5-FU | F1 | 119 | 61 | 66/53 | | | | **119/0*** |
| Richards 2013 | USA | NCT00517829 | II | December 2007—April 2010 | Oxaliplatin plus docetaxel | PT2 | 75 | 61.7 | 59/16 | Western | 62/13 | 65/10 | NA |
| | | | | | Oxaliplatin plus docetaxel plus cetuximab | PT2R | 75 | 64 | 60/15 | | 55/20 | 63/12 | |
| Waddell 2013 | UK | NCT00824785 | III | June 2008—October 2011 | Capecitabine plus oxaliplatin plus epirubicin plus panitumumab | FP3R | 278 | 63 | 232/46 | Western | 244/34 | NA | NA |
| | | | | | Capecitabine plus oxaliplatin plus epirubicin | FP3 | 275 | 62 | 226/49 | | 250/25 | | |
| Lordick 2013 | Germany | EudraCT2007-004219-75 | III | June 2008—December 2010 | Capecitabine plus cisplatin plus cetuximab | FP2R | 455 | 60 | 339/116 | Versatile | 439/16 | NA | 113/342 |
| | | | | | Capecitabine plus cisplatin | FP2 | 449 | 59 | 334/115 | | 436/12 | | 116/333 |
| Wang 2013 | China | NA | II | January 2008—September 2010 | S-1 plus paclitaxel | FT2 | 41 | 63 | 32/9 | Eastern | Metastatic and locally unresectable | 16/25 | 15/26 |
| | | | | | S-1 | F1 | 41 | 61 | 30/11 | | | 14/27 | 17/24 |
| Eatock 2013 | UK | NCT00583674 | II | December 2007—July 2009 | Capecitabine plus cisplatin plus trebananib | FP2R | 115 | 59 | 85/30 | Western | Metastatic | NA | NA |
| | | | | | Capecitabine plus cisplatin | FP2 | 56 | 62 | 45/11 | | | | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13/69 | 76/6 | 34/47/1 | 66/12 | NA | 0.70 (95% CI, 0.45–1.09) | 0.60 (95% CI, 0.45–0.79) | 30/76 | 56/81 | 68/81 | Lancet Oncol | 24965569 | |
| 9/30 | 38/1 | 16/22/1 | 31/4 | | | | 8/38 | 16/39 | 32/39 | | | |
| 12/44 | Measurable | 3/47/6 | Gastric | 25/31 | 0.74 (95% CI, 0.42–1.30) | 0.67 (95% CI, 0.38–1.18) | 17/30 | 10/30 | 3/30 | World J Surg Oncol | 24758484 | |
| | | | | | | | 11/26 | 11/26 | 5/26 | | | |
| NA | Measurable | 34/8/5 | Gastric | 12/32 | 0.60 (95% CI, 0.39–0.94) | 0.57 (95% CI, 0.36–0.91) | 24/47 | 39/47 | 27/47 | J Chem-other | 24621155 | |
| | | 33/10/4 | | 10/33 | | | 13/47 | 15/47 | 15/47 | | | |
| 14/37 | Measurable | 39/12/0 | Gastric | 33/16 | 0.99 (95% CI, 0.64–1.52) | 1.18 (95% CI, 0.79–1.79) | 16/51 | 3/51 | 14/51 | Anticancer Res | 24511022 | |
| 14/37 | | 41/8/2 | | 28/22 | | | 17/51 | 22/48 | 15/48 | | | |
| 168/146 | 242/72 | 137/177/0 | Gastric and junction | NA | 0.84 (95% CI, 0.71–0.99) | 0.77 (95% CI, 0.65–0.90) | 92/237 | 208/310 | 130/310 | J Cancer Res Clin Oncol | 24366758 | |
| 163/158 | 249/72 | 147/174/0 | | | | | 65/243 | 49/313 | 129/313 | | | |
| NA | Measurable | 28/17/0 | Gastric | 22/23 | 0.74 (95% CI, 0.46-1.19) | 1.23 (95% CI, 0.74–2.05) | 28/45 | 36/45-2 | 27/45 | Br J Cancer | 24045669 | |
| | | 30/16/0 | | 25/20 | | | 26/46 | 28/46-2 | 14/46 | | | |
| 96/22 | NA | 46/68/4 | Gastric | 26/92 | 0.94 (95% CI, 0.72–1.22) | NA | NA | 81/116 | 110/116 | Jpn J Clin Oncol | 24014884 | |
| 91/28 | | 46/69/4 | | 25/94 | | | | 13/117 | 77/117 | | | |
| NA | Measurable | 26/42/7 | 37/38 | Balanced | 0.94 (95% CI, 0.65–1.36) | 1.00 (95% CI, 0.67–1.49) | 18/68 | 53/68 | 25/68 | Eur J Cancer | 23747051 | |
| | | 33/33/9 | 34/41 | | | | 27/71 | 58/72 | 46/72 | | | |
| NA | Measurable | 118/144/16 | **78/94/106*-E** | Balanced | 1.37 (95% CI, 1.07–1.76) | 1.22 (95% CI, 0.98–1.52) | 116/254 | 69/276 | 264/276 | Lancet Oncol | 23594787 | |
| | | 117/143/15 | **89/75/111*-E** | | | | 100/238 | 137/266 | 190/266 | | | |
| 92/363 | Measurable | 237/218/0 | 376/71 | 162/76 | 1.00 (95% CI, 0.87–1.17) | 1.09 (95% CI, 0.92–1.29) | 136/455 | 178/446 | 430/446 | Lancet Oncol | 23594786 | |
| 90/359 | | 228/220/0 | 371/73 | 149/94 | | | 131/449 | 234/436 | 278/436 | | | |
| 15/26 | Measurable | 31/6/4 | Gastric | 11/28 | 0.55 (95% CI, 0.34–0.90) | 0.60 (95% CI, 0.37–0.97) | 19/41 | 32/41 | 36/41 | Clin Transl Oncol | 23381898 | |
| 17/24 | | 29/9/3 | | 10/30 | | | 10/41 | 13/41 | 14/41 | | | |
| 7/108 | 100/15 | 54/60/1 | **76/21/18*-E** | NA | Median OS time | 0.98 (95% CI, 0.67–1.43) | 35/100 | 33/114 | 44/114-3 | Ann Oncol | 23108953 | |
| 5/51 | 49/7 | 29/25/2 | **33/11/12*-E** | | | | 17/49 | 24/53 | 22/49-3 | | | |

*(Continued)*

**Table 1.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Al-Batran 2013 | Germany | NCT00737373 | II | August 2007—October 2008 | 5-FU plus oxaliplatin plus leucovorin plus docetaxel | FP3 | 72 | **69*** | 51/21 | Western | 50/22 | 33/39 | 14/58 |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FP2 | 71 | **70*** | 45/26 | | 49/22 | 32/39 | 14/57 |
| Andrić 2012 | Serbia | NA | NA | 2006–2009 | 5-FU plus doxorubicin plus mitomycin-C | FA3 | 25 | 61 | 18/7 | Western | 21/4 | NA | NA |
| | | | | | 5-FU plus cisplatin plus leucovorin | FP2 | 25 | 57 | 20/5 | | 20/5 | | |
| Roy 2012 | UK | NA | II | August 1999—August 2000 | Docetaxel plus irinotecan | TI2 | 42 | 62 | 35/7 | Western | 40/2 | NA | NA |
| | | | | | 5-FU plus docetaxel | FT2 | 43 | 60 | 35/8 | | 40/3 | | |
| Mochiki 2012 | Japan | NA | II | January 2006—November 2010 | S-1 plus paclitaxel | FT2 | 42 | 63.3 | 31/11 | Eastern | Metastatic and locally unresectable | 14/28 | 11/31 |
| | | | | | S-1 plus cisplatin | FP2 | 41 | 63 | 30/11 | | | 12/29 | 8/33 |
| Ohtsu 2011 | Japan | NCT00548548 | III | September 2007—December 2008 | Capecitabine plus cisplatin plus bevacizumab | FP2R | 387 | 58 | 257/130 | Versatile | 367/20 | 130/257 | NA |
| | | | | | Capecitabine plus cisplatin | FP2 | 387 | 59 | 258/129 | | 378/9 | 126/261 | |
| Jeung 2011 | South Korea | NA | II | July 2005—April 2007 | S-1 plus docetaxel | FT2 | 39 | 56 | 31/8 | Eastern | 29/10 | 10/29 | 14/25 |
| | | | | | Cisplatin plus docetaxel | PT2 | 41 | 60 | 28/13 | | 34/7 | 10/31 | 12/29 |
| Komatsu 2011 | Japan | NA | II | August 2003—March 2005 | S-1 plus irinotecan | FI2 | 48 | **70*** | 34/14 | Eastern | 33/15 | NA | NA |
| | | | | | S-1 | F1 | 47 | **63*** | 37/10 | | 33/14 | | |
| Li 2011 | China | NA | II | January 2003—December 2007 | 5–FU plus cisplatin plus paclitaxel | FP3 | 50 | 59 | 32/18 | Eastern | 28/22 | NA | NA |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FP2 | 44 | 58 | 31/13 | | 27/17 | | |
| Narahara 2011 | Japan | Japi-cCTI-050083 | III | June 2004—November 2005 | S-1 plus irinotecan | FI2 | 155 | 63 | 110/45 | Eastern | 129/26 | 110/205 | 105/210 |
| | | | | | S-1 | F1 | 160 | 63 | 127/33 | | 133/27 | | |
| Tebbutt 2010 | Australia | NA | II | June 2004—May 2006 | 5-FU plus cisplatin plus docetaxel | FP3 | 50 | 60.5 | 42/8 | Western | 48/2 | 32/18 | 10/40 |
| | | | | | Capecitabine plus docetaxel | FT2 | 56 | 59.1 | 42/14 | | 51/5 | 43/13 | 6/50 |
| Yun 2010 | South Korea | NCT00743964 | II | April 2008—October 2009 | Capecitabine plus cisplatin plus epirubicin | FP3 | 44 | 55 | 28/16 | Eastern | Metastatic and locally unresectable | 12/32 | 26/18 |
| | | | | | Capecitabine plus cisplatin | FP2 | 45 | 58 | 34/11 | | | 19/26 | 23/22 |
| Moehler 2010 | Germany | NA | II | October 2003—December 2006 | Capecitabine plus irinotecan | FI2 | 57 | 61 | 42/15 | Western | Metastatic | 44/13 | 18/39 |
| | | | | | Capecitabine plus cisplatin | FP2 | 55 | 64 | 36/19 | | | 38/17 | 20/35 |
| Ikeda 2009 | Japan | NA | II | June 2005—August 2008 | S-1 plus docetaxel | FT2 | 24 | 58 | 19/5 | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | 5-FU plus cisplatin | FP2 | 25 | 65 | 23/2 | | | | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 18/54 | Measurable | 67/5 | 45/27 | NA | 0.83 (95% CI, 0.54–1.28) | 0.80 (95% CI, 0.54–1.20) | 35/72 | 59/72-2 | 58/72 | Eur J Cancer | 23063354 | |
| 18/53 | | 65/6 | 47/24 | | | | 20/71 | 16/70-2 | 46/70 | | | |
| 9/16 | NA | 3/22/0 | Gastric | 7/18 | 1.17 (95% CI, 0.55–2.47) | NA | 5/25 | 3/25 | 22/25 | Srp Arh Celok Lek | 22826983 | Serbian |
| 10/15 | | 6/19/0 | | 6/19 | 6/25 | | 0/25 | 7/25 | | | | |
| 16/26 | Measurable | 7/29/6 | 27/15 | Balanced | 0.79 (95% CI, 0.52–1.22) | Median PFS time | 13/42 | 35/42-1 | 35/42-3 | Br J Cancer | 22767144 | |
| 15/28 | | 9/22/12 | 19/24 | | | | 11/43 | 30/43-1 | 18/43-3 | | | |
| 9/33 | Measurable | 38/4/0 | Gastric | 16/26 | 0.94 (95% CI, 0.55–1.63) | 0.84 (95% CI, 0.50–1.40) | 22/42 | 8/42 | 6/42 | Br J Cancer | 22617130 | |
| 8/33 | | 39/2/0 | | 16/25 | | | 20/41 | 8/41 | 7/41 | | | |
| 110/277 | 311/76 | 365/22 | 333/54 | NA | 0.87 (95% CI, 0.73–1.04) | 0.80 (95% CI, 0.68–0.93) | 143/311 | 194/386 | 165/386 | J Clin Oncol | 21844504 | |
| 107/280 | 297/90 | 367/20 | 338/49 | | | | 111/297 | 209/381 | 183/381 | | | |
| 12/27 | Measurable | 35/4 | Gastric | Balanced | 0.56 (95% CI, 0.35–0.88) | 0.63 (95% CI, 0.38–1.05) | 18/39 | Description | 24/39 | Cancer | 21523716 | |
| 9/32 | | 35/6 | | | | | 10/41 | | 16/41 | | | |
| 2/46 | Measurable | 38/10/0 | Gastric | Balanced | 0.95 (95% CI, 0.64–1.41) | 0.78 (95% CI, 0.54–1.13) | 12/48 | 21/48 | 30/48 | Anticancer Drugs | 21512394 | |
| 4/43 | | 35/12/0 | | | | | 7/47 | 12/47 | 16/47 | | | |
| NA | Measurable | 24/26 | Gastric | Balanced | 1.02 (95% CI, 0.63–1.66) | NA | 24/50 | 4/50-1 | 5/50-1 | World J Gastroenterol | 21448363 | |
| | | 21/23 | | | | | 20/44 | 4/44-1 | 0/44-1 | | | |
| 93/62 | Measurable | 102/48/5 | Gastric | 61/93 | 0.89 (95% CI, 0.70–1.15) | 0.86 (95% CI, 0.68–1.08) | 39/94 | 89/155 | 98/155 | Gastric Cancer | 21340666 | |
| 93/67 | | 109/46/5 | | 71/88 | | | 25/93 | 53/160 | 87/160 | | | |
| NA | Measurable | 21/28/1 | **26/13/11*-E** | Balanced | 0.84 (95% CI, 0.50–1.39) | 0.73 (95% CI, 0.48–1.13) | 22/47 | 8/49 | 38/49-4 | Br J Cancer | 20068567 | |
| | | 31/23/2 | **23/13/20*-E** | | | | 14/53 | 2/55 | 23/55-4 | | | |
| 17/27 | Measurable | 40/1 | Gastric | NA | NA | 0.96 (95% CI, 0.58–1.57) | 16/43 | 31/44 | 40/44 | Eur J Cancer | 20060288 | |
| 20/25 | | 41/4 | | | | | 17/45 | 22/45 | 32/45 | | | |
| 20/37 | NA | 0–2 | 49/7 | NA | 0.77 (95% CI, 0.51–1.17) | 1.14 (95% CI, 0.59–2.21) | 20/53 | 33/57 | 50/57 | Ann Oncol | 19605504 | |
| 14/41 | | | 38/17 | | | | 21/50 | 48/55 | 54/55 | | | |
| NA | NA | 21/3 | Gastric | NA | 0.53 (95% CI, 0.28–0.99) | 0.53 (95% CI, 0.28–0.97) | 21/24 | 22/24-2 | 3/24-3 | J Clin Oncol | 10.1200/jco.2009.27.15s.4595 | Abstract |
| | | 23/2 | | | | | 13/25 | 8/25-2 | 18/25-3 | | | |

*(Continued)*

**Table 1.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Boku 2009 | Japan | NCT00142350 | III | November 2000—January 2006 | Cisplatin plus irinotecan | PI2 | 236 | 63 | 180/56 | Eastern | 190/46 | NA | 76/160 |
| | | | | | S-1 | F1 | 234 | 64 | 175/59 | | 188/46 | | 69/165 |
| | | | | | 5-FU | F1 | 234 | 63.5 | 176/58 | | 189/45 | | 87/147 |
| Ridwelski 2008 | Germany | NA | III | NA | Cisplatin plus docetaxel | PT2 | 137 | 62 | NA | Western | 243/27 | NA | NA |
| | | | | | 5-FU plus cisplatin plus leucovorin | FP2 | 133 | | | | | | |
| Tesselaar 2008 | Netherlands | NA | II | NA | 5-FU plus leucovorin plus paclitaxel | FT2 | 47 | NA | NA | Western | Metastatic | NA | NA |
| | | | | | 5-FU plus cisplatin plus leucovorin | FP2 | 49 | | | | | | |
| Jin 2008 | China | NCT00202969 | III | July 2005—October 2006 | S-1 | F1 | 77 | 57 | 56/21 | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | S-1 plus cisplatin | FP2 | 74 | 56.5 | 55/19 | | | | |
| | | | | | 5-FU plus cisplatin | FP2 | 73 | 58 | 61/12 | | | | |
| Dank 2008 | Hungary | NA | III | June 2000—March 2002 | 5-FU plus cisplatin | FP2 | 163 | 59 | 108/55 | Western | 155/8 | 91/72 | 41/122 |
| | | | | | 5-FU plus leucovorin plus irinotecan | FI2 | 170 | 58 | 125/45 | | 163/7 | 101/69 | 40/130 |
| Koizumi 2008 | Japan | NCT00150670 | III | March 2002—November 2004 | S-1 plus cisplatin | FP2 | 148 | 62 | 108/40 | Eastern | 118/30 | 60/88 | 51/97 |
| | | | | | S-1 | F1 | 150 | 62 | 116/34 | | 119/31 | 60/90 | 36/114 |
| Park 2008 | South Korea | NCT00320294 | II | October 2004—November 2006 | 5-FU plus cisplatin plus leucovorin plus irinotecan | FP3 | 45 | 51 | 30/15 | Eastern | Metastatic and locally unresectable | 16/29 | 26/19 |
| | | | | | 5-FU plus leucovorin plus irinotecan | FI2 | 46 | 55 | 30/16 | | | 21/25 | 30/16 |
| Popov 2008 | Serbia | NA | II | August 1998—September 2001 | Cisplatin plus doxorubicin plus etoposide | PA3 | 30 | 57 | 21/9 | Western | 27/3 | 18/12 | 10/20 |
| | | | | | 5-FU | F1 | 30 | 55 | 23/7 | | 22/8 | 17/13 | 11/19 |
| Roth 2007 | Switzerland | NA | II | September 1999—July 2003 | 5-FU plus cisplatin plus docetaxel | FP3 | 41 | 61 | 30/11 | Western | 39/2 | 17/24 | 9/32 |
| | | | | | 5-FU plus cisplatin plus epirubicin | FP3 | 40 | 59 | 30/10 | | 33/7 | 16/24 | 5/35 |
| | | | | | Cisplatin plus docetaxel | PT2 | 38 | 58 | 29/9 | | 31/7 | 15/23 | 3/34 |
| Lutz 2007 | Germany | NA | II | January 1996—August 1999 | 5-FU plus cisplatin plus leucovorin | FP2 | 51 | 62 | 40/11 | Western | 45/6 | NA | NA |
| | | | | | 5-FU plus leucovorin | F1 | 53 | 53 | 42/11 | | 47/6 | | |
| | | | | | 5-FU | F1 | 37 | 37 | 30/7 | | 29/8 | | |
| Van Cutsem 2006 | Belgium | NA | III | November 1999—January 2003 | 5-FU plus cisplatin | FP2 | 224 | 55 | 158/66 | Western | 217/6 | NA | NA |
| | | | | | 5-FU plus cisplatin plus docetaxel | FP3 | 221 | 55 | 159/62 | | 213/6 | | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NA | NA | 151/81/4 | Gastric | 102/134 | 1 *versus* (2+3): 0.82 (95% CI, 0.68–0.99) | 1 *versus* (2+3): 0.73 (95% CI, 0.64–0.83) | 68/181 | 152/234-1 | 172/234 | Lancet Oncol | 19818685 | |
| | | 151/80/3 | | 110/124 | | | 49/174 | 30/234-1 | 94/234 | | | |
| | | 152/79/3 | | 111/121 | | | 15/175 | 36/232-1 | 57/232 | | | |
| NA | NA | 0–2 | Gastric | NA | 1.06 (95% CI, 0.82–1.37) | 1.10 (95% CI, 0.85–1.42) | 32/117 | 56/137-1 | 27/137-1 | J Clin Oncol | 10.1200/jco.2008.26.15_suppl.4512 | Abstract |
| | | | | | | | 33/117 | 16/133-1 | 38/133-1 | | | |
| NA | Measurable | NA | Gastric and junction | NA | 0.79 (95% CI, 0.52–1.20) | Median PFS time | 21/47 | Description | 13/47 | J Clin Oncol | 10.1200/jco.2008.26.15_suppl.4567 | Abstract |
| | | | | | | | 23/49 | | 17/49 | | | |
| NA | NA | 65/12 | Gastric | NA | (2+3) *versus* 1: 0.55 (95% CI, 0.36–0.83) | Median PFS time | 19/77 | 6/77 | 4/77 | J Clin Oncol | 10.1200/jco.2008.26.15_suppl.4533 | Abstract |
| | | 66/8 | | | | | 28/74 | 26/74 | 17/74 | | | |
| | | 63/10 | | | | | 14/73 | 23/73 | 22/73 | | | |
| 66/97 | Measurable | 27/134/2 | 132/31 | 42/46 | 1.08 (95% CI, 0.86–1.35) | 1.23 (95% CI, 0.97–1.57) | 42/163 | 155/166-3 | 128/166 | Ann Oncol | 18558665 | |
| 70/100 | | 45/124/1 | 136/34 | 49/60 | | | 54/170 | 88/167-3 | 119/167 | | | |
| 53/95 | NA | 106/38/4 | Gastric | 45/103 | 0.77 (95% CI, 0.61–0.98) | 0.57 (95% CI, 0.44–0.73) | 47/87 | 127/148 | 88/148 | Lancet Oncol | 18282805 | |
| 58/92 | | 106/39/5 | | 60/89 | | | 33/106 | 27/150 | 24/150 | | | |
| 29/16 | Measurable | 38/7 | Gastric | NA | 0.84 (95% CI, 0.38–1.89) | 0.72 (95% CI, 0.44–1.19) | 19/45 | 27/45 | 29/45 | Ann Oncol | 18083691 | |
| 43/3 | | 35/11 | | | | | 19/46 | 17/45 | 36/45 | | | |
| 24/6 | Measurable | 3/22/5 | 21/9 | Balanced | 0.86 (95% CI, 0.32–2.29) | Median PFS time | 10/30 | Cycles | Cycles | Med Oncol | 17972024 | |
| 22/8 | | 6/19/5 | 19/11 | | | | 3/30 | | | | | |
| 13/28 | Measurable | 25/16 | Gastric | NA | (1+2) *versus* 3: 0.96 (95% CI, 0.59–1.54) | (1+2) *versus* 3: 0.79 (95% CI, 0.49–1.27) | 15/41 | 33/41-1 | 37/41 | J Clin Oncol | 17664469 | |
| 7/33 | | 24/16 | | | | | 10/40 | 24/40-1 | 23/40 | | | |
| 9/29 | | 23/15 | | | | | 7/38 | 29/38-1 | 32/38 | | | |
| 23/28 | 50/1 | 49/2 | Gastric | 22/13 | 1 *versus* 2: 0.66 (95% CI, 0.42–1.06) | Median PFS time | 21/46 | 20/51 | 32/51 | J Clin Oncol | 17577037 | |
| 26/27 | 53/0 | 49/4 | | 27/10 | 1 *versus* 3: 0.57 (95% CI, 0.35–0.94) | | 12/48 | 4/53 | 12/48 | | | |
| 22/15 | 36/1 | 34/3 | | 20/6 | 2 *versus* 3: 0.83 (95% CI, 0.50–1.37) | | 2/33 | 5/37 | 12/33 | | | |
| 71/153 | Measurable | 29/192/3 | 168/56 | 45/77 | 1.29 (95% CI, 1.02–1.63) | 1.47 (95% CI, 1.19–1.82) | 57/224 | 126/224-1 | 206/224-3 | J Clin Oncol | 17075117 | |
| 68/153 | | 28/190/3 | 179/42 | 40/92 | | | 81/221 | 181/221-1 | 197/221-3 | | | |

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**Table 1.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ajani 2005 | USA | NA | II | June 1998—September 1999 | 5-FU plus cisplatin plus docetaxel | FP3 | 79 | 57 | 61/18 | Western | 75/4 | NA | NA |
| | | | | | Cisplatin plus docetaxel | PT2 | 76 | 57 | 53/23 | | 72/4 | | |
| Moehler 2005 | Germany | NA | II | November 2000—April 2003 | 5-FU plus leucovorin plus etoposide | FE2 | 58 | 63 | 49/9 | Western | Metastatic and locally unresectable | 42/16 | 11/47 |
| | | | | | 5-FU plus leucovorin plus irinotecan | FI2 | 56 | 61 | 40/16 | | | 46/10 | 10/46 |
| Thuss-Patience 2005 | Germany | NA | II | NA | 5-FU plus docetaxel | FT2 | 45 | 62 | 29/16 | Western | 44/1 | 26/19 | 15/30 |
| | | | | | 5-FU plus cisplatin plus epirubicin | FP3 | 45 | 63 | 36/9 | | 44/1 | 20/25 | 20/25 |
| Pozzo 2004 | Italy | NA | II | January 1999—April 2000 | 5-FU plus leucovorin plus irinotecan | FI2 | 74 | 57 | 57/17 | Western | 68/6 | 33/41 | 13/61 |
| | | | | | Cisplatin plus irinotecan | PI2 | 72 | 59 | 46/26 | | 69/3 | 39/33 | 16/56 |
| Bouché 2004 | France | NA | II | January 1999—October 2001 | 5-FU plus leucovorin plus irinotecan | FI2 | 45 | 65 | 38/7 | Western | Metastatic | 41/4 | 9/36 |
| | | | | | 5-FU plus cisplatin plus leucovorin | FP2 | 44 | 64 | 35/9 | | | 42/2 | 6/44 |
| | | | | | 5-FU plus leucovorin | F1 | 45 | 64 | 37/8 | | | 43/2 | 10/45 |
| Koizumi 2004 | Japan | NA | II | July 1991—December 1996 | Doxifluridine plus cisplatin plus mitomycin-C | FP3 | 32 | 58 | 17/15 | Eastern | Metastatic and locally unresectable | 10/22 | 8/24 |
| | | | | | Doxifluridine plus cisplatin | FP2 | 29 | 58 | 19/10 | | | 11/18 | 6/23 |
| Cocconi 2003 | Italy | NA | NA | May 1993—November 1999 | 5-FU plus cisplatin plus leucovorin plus epirubicin | FP3 | 98 | 62 | 67/31 | Western | 82/16 | NA | NA |
| | | | | | 5-FU plus doxorubicin plus methotrexate | FA3 | 97 | 62 | 66/31 | | 83/14 | | |
| Ohtsu 2003 | Japan | NA | III | September 1992—March 1997 | UFT plus mitomycin-C | FY2 | 70 | 60.5 | 55/15 | Eastern | 61/9 | 31/39 | 20/50 |
| | | | | | 5-FU plus cisplatin | FP2 | 105 | 63 | 77/28 | | 90/15 | 55/50 | 28/77 |
| | | | | | 5-FU | F1 | 105 | 63 | 75/29 | | 90/15 | 49/56 | 23/82 |
| Tebbutt 2002 | UK | NA | III | July 1994—February 2001 | 5-FU | F1 | 123 | **72*** | 94/29 | Western | 71/29 | NA | NA |
| | | | | | 5-FU plus mitomycin-C | FY2 | 127 | **72*** | 95/32 | | 73/30 | | |
| Kim 2001 | South Korea | NA | III | March 1997—April 2000 | 5-FU plus cisplatin plus epirubicin | FP3 | 61 | 55 | 45/15 | Eastern | 57/3 | 32/29 | NA |
| | | | | | 5-FU plus cisplatin | FP2 | 60 | 56.5 | 42/18 | | 57/3 | 28/32 | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 28/51 | Measurable | 7/72/0 | 50/29 | 16/30 | 1.19 (95% CI, 0.83–1.69) | 0.80 (95% CI, 0.52–1.22) | 34/79 | 66/79-1 | 73/79-4 | J Clin Oncol | 16110025 | |
| 30/46 | | 10/65/1 | 56/20 | 20/17 | | | 20/76 | 65/76-1 | 39//76-4 | | | |
| 31/27 | Measurable | 8/43/7 | 42/16 | NA | 1.25 (95% CI, 0.83–1.86) | 1.10 (95% CI, 0.75–1.62) | 14/58 | 45/58 | 31/58 | Br J Cancer | 15942629 | |
| 29/27 | | 4/49/3 | 37/19 | | | | 24/56 | 15/56 | 29/56 | | | |
| NA | Measurable | 14/28/2 | 31/14 | 14/12 | 1.02 (95% CI, 0.68–1.54) | 0.96 (95% CI, 0.63–1.48) | 17/45 | 24/45 | 23/45 | J Clin Oncol | 15659494 | |
| | | 16/28/1 | 33/12 | 12/19 | | | 16/45 | 32/45 | 21/45 | | | |
| 28/46 | 57/17 | 11/63/0 | 61/12 | 22/34 | 0.56 (95% CI, 0.39–0.81) | 0.41 (95% CI, 0.26–0.64) | 25/74 | 33/74 | 36/74 | Ann Oncol | 15550582 | |
| 30/42 | 57/15 | 7/65/0 | 49/23 | 27/29 | | | 18/72 | 68/72 | 33/72 | | | |
| 23/22 | Measurable | 35/10 | 31/14 | Balanced | 1 *versus* 2: 0.93 (95% CI, 0.54–1.58) | 1 *versus* 2: 0.84 (95% CI, 0.52–1.35) | 18/45 | 25/45-2 | 24/45 | J Clin Oncol | 15514373 | |
| 22/22 | | 33/11 | 31/13 | | 1 *versus* 3: 0.64 (95% CI, 0.38–1.08) | 1 *versus* 3: 0.47 (95% CI, 0.29–0.78) | 18/45 | 25/45-2 | 24/45 | | | |
| 23/22 | | 33/12 | 32/13 | | 2 *versus* 3: 0.65 (95% CI, 0.39-1.10) | 2 *versus* 3: 0.59 (95% CI, 0.36–0.97) | 12/44 | 40/44-2 | 16/44 | | | |
| 3/29 | Measurable | 5/20/6 | Gastric | Balanced | 0.78 (95% CI, 0.43–1.41) | NA | 8/32 | 14/32 | 7/32 | Anticancer Res | 15330199 | |
| 2/27 | | 3/13/9 | | | | | 5/29 | 6/29 | 8/29 | | | |
| 49/49 | Measurable | 0–2 | Gastric | NA | 0.90 (95% CI, 0.77–1.05) | Median PFS time | 38/98 | 62/94 | 50/94 | Ann Oncol | 12881389 | |
| 50/47 | | | | | | | 21/97 | 60/93 | 30/93 | | | |
| 21/49 | Measurable | 63/7 | Gastric | 29/39 | 1 *versus* 2: 1.53 (95% CI, 1.11–2.11) | 1 *versus* 2: 2.16 (95% CI, 1.47–3.17) | 6/70 | 45/67-2 | 25/67 | J Clin Oncol | 12506170 | |
| 29/76 | | 95/10 | | 49/52 | 1 *versus* 3: 1.29 (95% CI, 0.93–1.79) | 1 *versus* 3: 1.19 (95% CI, 0.84–1.69) | 36/105 | 81/102-2 | 40/102 | | | |
| 27/78 | | 95/10 | | 47/56 | 2 *versus* 3: 0.84 (95% CI, 0.63–1.11) | 2 *versus* 3: 0.63 (95% CI, 0.46–0.86) | 12/105 | 15/104-2 | 26/104 | | | |
| NA | NA | 11/72/37 | **55/33/29*-E** | Balanced | 0.96 (95% CI, 0.75–1.22) | 1.09 (95% CI, 0.86–1.38) | 19/118 | 17/123 | 59/123 | Ann Oncol | 12377644 | |
| | | 9/70/44 | **69/30/27*-E** | | | | 23/121 | 27/127 | 56/127 | | | |
| NA | Measurable | 55/6 | Gastric | NA | 0.83 (95% CI, 0.42–1.61) | Median PFS time | 22/61 | 23/61-2 | 32/61-3 | Eur J Cancer | 10.1016/S0959-8049(01)81651-8 | Abstract |
| | | 53/7 | | | | | 20/60 | 10/60-2 | 10/60-3 | | | |

*(Continued)*

**Table 1.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Vanhoefer 2000 | Germany | NA | III | July 1991—April 1995 | 5-FU plus leucovorin plus etoposide | FE2 | 132 | 59 | 90/38 | Western | 110/22 | NA | NA |
| | | | | | 5-FU plus cisplatin | FP2 | 134 | 57 | 91/41 | | 113/21 | | |
| | | | | | 5-FU plus doxorubicin plus methotrexate | FA3 | 133 | 58 | 96/34 | | 111/22 | | |
| Roth 1999 | Croatia | NA | NA | NA | 5-FU plus cisplatin plus epirubicin | FP3 | 54 | 55 | NA | Western | 74/36 | NA | NA |
| | | | | | 5-FU plus epirubicin | FA2 | 56 | | | | | | |
| Waters 1999 | UK | NA | NA | July 1992—June 1995 | 5-FU plus doxorubicin plus methotrexate | FA3 | 130 | 60 | 110/20 | Western | 79/51 | NA | NA |
| | | | | | 5-FU plus cisplatin plus epirubicin | FP3 | 126 | 59 | 99/27 | | 79/47 | | |
| Içli 1998 | Turkey | NA | III | 1994–1997 | 5-FU plus cisplatin plus epirubicin | FP3 | 67 | 52.7 | 40/27 | Western | 53/14 | NA | NA |
| | | | | | Cisplatin plus epirubicin plus etoposide | PA3 | 64 | 52.7 | 44/20 | | 53/11 | | |
| Yamamura 1998 | Japan | NA | NA | NA | 5-FU plus pirarubicin plus methotrexate | FA3 | 37 | NA | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | 5-FU | F1 | 34 | | | | | | |
| Barone 1998 | Italy | NA | II | January 1993—December 1995 | Cisplatin plus epirubicin plus etoposide | PA3 | 36 | 57.3 | 26/10 | Western | Metastatic and locally unresectable | 19/17 | 17/19 |
| | | | | | 5-FU plus leucovorin | F1 | 36 | 59 | 24/12 | | 17/19 | 18/18 | 20/16 |
| Scheithauer 1996 | Austria | NA | NA | NA | 5-FU plus leucovorin plus doxorubicin | FA2 | 52 | NA | NA | Western | 65/38 | NA | NA |
| | | | | | Supportive care | S | 51 | | | | | | |
| Colucci 1995 | Italy | NA | NA | NA | 5-FU plus leucovorin plus etoposide | FE2 | 31 | 56 | 20/11 | Western | Metastatic and locally unresectable | 14/17 | 1/30 |
| | | | | | 5-FU plus leucovorin | F1 | 31 | 58 | 20/11 | | | 17/14 | 1/30 |
| Pyrhönen 1995 | Finland | NA | III | July 1986—June 1992 | 5-FU plus leucovorin plus epirubicin | FA2 | 21 | 58 | 15/6 | Western | 15/6 | 8/13 | 4/17 |
| | | | | | Supportive care | S | 20 | 58 | 10/10 | | 14/6 | 8/12 | 2/18 |
| Coombes 1994 | UK | NA | NA | August 1985—September 1988 | Epirubicin | A1 | 36 | 59.9 | 27/9 | Western | 34/2 | 18/18 | 8/28 |
| | | | | | 5-FU | F1 | 33 | 55.6 | 24/9 | | 31/2 | 15/18 | 5/28 |
| Cocconi 1994 | Italy | NA | III | August 1988—November 1991 | 5-FU plus cisplatin plus leucovorin plus epirubicin | FP3 | 85 | 62 | 60/25 | Western | 78/7 | NA | NA |
| | | | | | 5-FU plus doxorubicin plus mitomycin-C | FA3 | 52 | 65 | 42/10 | | 43/9 | | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 78/54 | 122/10 | 54/66/12 | Gastric | 57/45 | 1 *versus* 3: 0.95 (95% CI, 0.74–1.24) | 1 *versus* 3: 1.02 (95% CI, 0.79–1.32) | 7/79 | 68/129 | 62/129 | J Clin Oncol | 10894863 | |
| 73/61 | 125/9 | 43/71/20 | | 65/43 | 2 *versus* 3: 0.98 (95% CI, 0.86–1.12) | 2 *versus* 3: 0.94 (95% CI, 0.83–1.07) | 16/81 | 73/127 | 84/127 | | | |
| 67/66 | 122/11 | 36/81/16 | | 59/47 | | | 10/85 | 89/122 | 57/122 | | | |
| NA | Measurable | 57/53 | Gastric | NA | 0.74 (95% CI, 0.55–0.99) | NA | 16/56 | Description | Description | Tumori | 10587023 | |
| | | | | | | | 23/54 | | | | | |
| 48/82 | NA | 97/32 | **73/33/24[*]-E** | Balanced | 1.52 (95% CI, 1.19–1.95) | 1.79 (95% CI, 1.40–2.29) | 24/116 | 126/130-2 | 111/130 | Br J Cancer | 10390007 | |
| 51/75 | | 96/30 | **72/27/27[*]-E** | | | | 56/121 | 60/126-2 | 122/126 | | | |
| NA | Measurable | 8/38/21 | Gastric | NA | 1.23 (95% CI, 0.76–1.98) | 1.07 (95% CI, 0.58–1.96) | 9/59 | 4/67 | 15/67 | Cancer | 9874451 | |
| | | 6/36/22 | | | | | 12/59 | 6/64 | 10/64 | | | |
| NA | NA | NA | Gastric | NA | 0.88 (95% CI, 0.55–1.41) | NA | NA | Description | Description | Gan To Kagaku Ryoho | 9725047 | Japanese |
| 22/14 | Measurable | 28/8 | Gastric | NA | 0.89 (95% CI, 0.55–1.42) | Median PFS time | 6/33 | Cycles | Cycles | Cancer | 9554521 | |
| 28/8 | | | | | | | 7/32 | | | | | |
| NA | NA | 73/30 | Gastric | NA | 0.49 (95% CI, 0.33–0.74) | 0.31 (95% CI, 0.21–0.45) | NA | NA | NA | Ann Hematol | 28850174 | Abstract |
| 18/13 | Measurable | 0–2 | Gastric | NA | 0.70 (95% CI, 0.42–1.16) | NA | 13/31 | 4/31 | 15/31 | Am J Clin Oncol | 8526196 | |
| 20/11 | | | | | | | 9/31 | 2/31 | 4/31 | | | |
| 15/6 | Measurable | 4/15/2 | Gastric | NA | 0.35 (95% CI, 0.15–0.81) | 0.29 (95% CI, 0.13–0.65) | 6/21 | 12/21 | 13/21 | Br J Cancer | 7533517 | |
| 16/4 | | 3/15/2 | | | | | 0/20 | 0/20 | 0/20 | | | |
| NA | Measurable | 0–2 | Gastric | NA | 1.09 (95% CI, 0.56–2.12) | NA | 3/36 | 3/36 | 25/36 | Ann Oncol | 8172789 | |
| | | | | | | | 2/33 | 4/33 | 9/33 | | | |
| 31/21 | 46/6 | 0–3 | Gastric | NA | 0.69 (95% CI, 0.51–0.93) | Median PFS time | 37/85 | 13/85 | 28/85 | J Clin Oncol | 7989945 | |
| 54/31 | 76/9 | | | | | | 8/52 | 1/52 | 8/52 | | | |

*(Continued)*

**Table 1.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Loehrer 1994 | USA | NA | NA | January 1985—January 1987 | 5-FU | F1 | 69 | 59 | NA | Western | 44/25 | 34/35 | 16/53 |
| | | | | | Epirubicin | A1 | 26 | 57 | | | 15/11 | 11/15 | 5/21 |
| | | | | | 5-FU plus epirubicin | FA2 | 70 | 62 | | | 45/25 | 35/35 | 16/54 |
| Cullinan 1994 | USA | NA | NA | February 1984—March 1992 | 5-FU plus doxorubicin plus Me-CCNU plus triazinate | FA4 | 79 | 60 | 53/26 | Western | Metastatic and locally unresectable | NA | NA |
| | | | | | 5-FU plus cisplatin plus doxorubicin | FP3 | 51 | 61 | 40/11 | | | | |
| | | | | | 5-FU plus doxorubicin plus Me-CCNU | FA3 | 53 | 63 | 43/10 | | | | |
| | | | | | 5-FU | F1 | 69 | 63 | 52/17 | | | | |
| Murad 1993 | Brazil | NA | II | 1988–1991 | 5-FU plus doxorubicin plus methotrexate | FA3 | 30 | 58 | 20/10 | Versatile | 21/9 | NA | NA |
| | | | | | Supportive care | S | 10 | 57 | 7/3 | | 6/4 | | |
| Kim 1993 | South Korea | NA | III | August 1986—June 1990 | 5-FU plus doxorubicin plus mitomycin-C | FA3 | 98 | 54 | 68/30 | Eastern | Metastatic and locally unresectable | 34/64 | NA |
| | | | | | 5-FU plus cisplatin | FP2 | 103 | 51 | 71/32 | | | 38/65 | |
| | | | | | 5-FU | F1 | 94 | 54 | 66/28 | | | 33/61 | |
| KRGGC 1992 | South Korea | NA | NA | NA | 5-FU plus cisplatin plus epirubicin | FP3 | 25 | NA | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | 5-FU plus cisplatin | FP2 | 22 | | | | | | |
| Kelsen 1992 | USA | NA | NA | June 1988—October 1990 | 5-FU plus leucovorin plus doxorubicin plus methotrexate | FA3 | 30 | 56 | 22/8 | Western | 19/11 | 16/14 | 2/28 |
| | | | | | Cisplatin plus doxorubicin plus etoposide | PA3 | 30 | 57 | 24/6 | | 21/9 | 16/14 | 3/27 |
| Kikuchi 1990 | Japan | NA | NA | NA | 5-FU plus cisplatin plus doxorubicin | FP3 | 32 | NA | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | 5-FU plus doxorubicin | FA2 | 33 | | | | | | |
| GITSG 1988 | USA | NA | III | November 1981—July 1985 | 5-FU plus cisplatin plus doxorubicin | FP3 | 85 | 18–75 | 63/22 | Western | Metastatic | 41/44 | NA |
| | | | | | 5-FU plus doxorubicin plus triazinate | FA3 | 81 | | 60/21 | | | 32/49 | |
| | | | | | 5-FU plus doxorubicin plus Me-CCNU | FA3 | 81 | | 51/30 | | | 40/41 | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NA | 47/22 | 12/34/22 | Gastric | NA | 1 *versus* 2: 0.75 (95% CI, 0.43–1.31) | 1 *versus* 2: 0.42 (95% CI, 0.21–0.83) | 5/40 | 21/69 | 48/69 | Invest New Drugs | 7960608 | |
| | 17/9 | 7/11/5 | | | 1 *versus* 3: 0.98 (95% CI, 0.67–1.44) | 1 *versus* 3: 1.02 (95% CI, 0.69–1.53) | 1/16 | 6/26 | 18/26 | | | |
| | 50/20 | 16/31/14 | | | 2 *versus* 3: 1.25 (95% CI, 0.73–2.14) | 2 *versus* 3: 4.55 (95% CI, 2.40–8.65) | 4/33 | 48/70 | 68/70 | | | |
| 31/48 | 16/63 | 55/24 | Gastric | Balanced | 1 *versus* 4: 0.95 (95% CI, 0.65–1.38) | 1 *versus* 4: 0.65 (95% CI, 0.46–0.94) | NA | 47/79 | 47/79 | J Clin Oncol | 8113849 | |
| 21/30 | 6/45 | 35/16 | | | 2 *versus* 4: 1.17 (95% CI, 0.77–1.76) | 2 *versus* 4: 0.84 (95% CI, 0.57–1.26) | | 29/51 | 30/51 | | | |
| 18/35 | 6/47 | 36/17 | | | 3 *versus* 4: 0.97 (95% CI, 0.62–1.52) | 3 *versus* 4: 0.90 (95% CI, 0.60–1.34) | | 34/53 | 16/53 | | | |
| 24/45 | 14/55 | 50/19 | | | | | | 28/69 | 12/69 | | | |
| 13/17 | Measurable | 5/16/9 | Gastric | NA | 0.33 (95% CI, 0.17–0.64) | NA | 15/30 | 2/30 | 7/30 | Cancer | 8508427 | |
| 3/7 | | 3/4/3 | | | | | 0/10 | 0/10 | 0/10 | | | |
| 22/76 | 57/41 | 75/23 | Gastric | 22/48 | 1 *versus* 2: 1.36 (95% CI, 0.99–1.86) | Median PFS time | 14/57 | Cycles | 93/98-2 | Cancer | 8508349 | |
| 15/88 | 55/48 | 83/20 | | 30/52 | 1 *versus* 3: 1.21 (95% CI, 0.88–1.67) | | 28/55 | | 101/103-2 | | | |
| 10/84 | 54/50 | 76/18 | | 26/45 | 2 *versus* 3: 0.84 (95% CI, 0.61–1.17) | | 14/54 | | 44/94-2 | | | |
| NA | NA | NA | Gastric | NA | 0.57 (95% CI, 0.27–1.20) | NA | 5/21 | Description | Description | Anticancer Res | 1295444 | |
| | | | | | | | 6/22 | | | | | |
| NA | Measurable | 0–2 | Gastric and junction | NA | 0.79 (95% CI, 0.42–1.46) | NA | 10/30 | Description | Description | J Clin Oncol | 1548519 | |
| | | | | | | | 6/30 | | | | | |
| NA | NA | NA | Gastric | NA | 0.58 (95% CI, 0.36–0.95) | NA | 6/18 | Description | Description | Gan To Kagaku Ryoho | 2181941 | Japanese |
| | | | | | | | 0/19 | | | | | |
| NA | 31/54 | 58/27 | Gastric | NA | 1 *versus* 2: 0.98 (95% CI, 0.67–1.45) | NA | 6/30 | 64/85 | 33/85 | J Natl Cancer Inst | 2900901 | |
| | 30/51 | 53/28 | | | 1 *versus* 3: 0.71 (95% CI, 0.49–1.02) | | 6/31 | 23/81 | 25/81 | | | |
| | 33/48 | 51/30 | | | 2 *versus* 3: 0.71 (95% CI, 0.49–1.03) | | 5/33 | 61/81 | 12/81 | | | |

*(Continued)*

**Table 1.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lacave 1987 | Spain | NA | III | April 1979—June 1983 | 5-FU plus doxorubicin plus Me-CCNU | FA3 | 85 | 58 | 55/30 | Western | 65/20 | 32/53 | 43/42 |
| | | | | | 5-FU plus doxorubicin | FA2 | 88 | 59 | 65/23 | | 74/14 | 50/38 | 48/40 |
| Levi 1986 | Australia | NA | NA | NA | 5-FU plus doxorubicin plus BCNU | FA3 | 94 | 61 | 68/26 | Western | Metastatic and locally unresectable | 28/66 | 22/72 |
| | | | | | Doxorubicin | A1 | 93 | 59 | 68/25 | | | 26/67 | 17/76 |
| De Lisi 1986 | Italy | NA | III | NA | 5-FU plus doxorubicin plus mitomycin-C plus BCNU | FA4 | 42 | 64 | NA | Western | Metastatic and locally unresectable | NA | NA |
| | | | | | 5-FU | F1 | 42 | | | | | | |
| Cullinan 1985 | USA | NA | NA | NA | 5-FU | F1 | 51 | 18–75 | 36/15 | Western | 32/19 | NA | NA |
| | | | | | 5-FU plus doxorubicin | FA2 | 49 | | 37/12 | | 31/18 | | |
| | | | | | 5-FU plus doxorubicin plus mitomycin-C | FA3 | 51 | | 39/12 | | 31/20 | | |
| Douglass 1984 | USA | NA | NA | NA | 5-FU plus doxorubicin plus Me-CCNU | FA3 | 39 | 62 | 31/8 | Western | Metastatic and locally unresectable | NA | NA |
| | | | | | 5–FU plus doxorubicin plus mitomycin–C | FA3 | 46 | 61 | 35/11 | | | | |
| | | | | | 5-FU plus Me-CCNU | FU2 | 44 | 58 | 35/9 | | | | |
| | | | | | Doxorubicin plus mitomycin-C | AY2 | 46 | 59.5 | 33/13 | | | | |
| O'Connel 1984 | USA | NA | NA | December 1978—March 1981 | 5-FU plus doxorubicin plus Me-CCNU | FA3 | 76 | 62 | 53/23 | Western | 60/16 | 29/41 | NA |
| | | | | | 5-FU plus doxorubicin plus mitomycin-C | FA3 | 78 | 62 | 52/26 | | 62/16 | 23/46 | |
| | | | | | 5-FU plus doxorubicin | FA2 | 78 | 60 | 57/21 | | 60/18 | 21/54 | |
| Friedman 1983 | USA | NA | III | December 1977–December 1980 | Tegafur plus doxorubicin plus BCNU | FA3 | 36 | 18–75 | 24/12 | Western | 27/9 | NA | NA |
| | | | | | 5-FU plus doxorubicin | FA2 | 38 | | 22/16 | | 28/10 | | |
| | | | | | Tegafur plus doxorubicin plus mitomycin-C | FA3 | 34 | | 22/12 | Eastern | 28/6 | | |
| | | | | | 5-FU plus doxorubicin | FA2 | 34 | | 21/13 | | 27/7 | | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 60/25 | 28/57 | 0–3 | Gastric | NA | 0.82 (95% CI, 0.59–1.14) | NA | 5/28 | Description | Description | J Clin Oncol | 3305795 | |
| 63/25 | 29/59 | | | | | | 3/29 | | | | | |
| 42/52 | 75/19 | 68/18 | Gastric | Balanced | 0.58 (95% CI, 0.43–0.77) | 0.62 (95% CI, 0.30–1.28) | 30/75 | 13/94 | 10/94 | J Clin Oncol | 3528404 | |
| 41/52 | 70/24 | 63/23 | | | | | 9/70 | 5/93 | 14/93 | | | |
| NA | NA | NA | Gastric | NA | 1.16 (95% CI, 0.26–5.15) | NA | 9/41 | Description | Description | Cancer Treat Rep | 3516397 | |
| | | | | | | | 6/41 | | | | | |
| NA | 11/40 | 37/14 | Gastric | NA | 1 *versus* 2: 0.96 (95% CI, 0.60–1.52) | 1 *versus* 2: 0.99 (95% CI, 0.62–1.59) | 2/11 | Description | Description | JAMA | 2579257 | |
| | 10/39 | 33/16 | | | 1 *versus* 3: 0.91 (95% CI, 0.56–1.48) | 1 *versus* 3: 1.17 (95% CI, 0.70–1.96) | 3/11 | | | | | |
| | 13/38 | 32/19 | | | 2 *versus* 3: 0.99 (95% CI, 0.64–1.53) | 2 *versus* 3: 1.30 (95% CI, 0.82–2.06) | 5/13 | | | | | |
| NA | Measurable | 9/21/6 | Gastric | Balanced | 1 *versus* 2: 1.61 (95% CI, 0.88–2.92) | NA | 11/39 | 14/39 | 3/39 | J Clin Oncol | 6439836 | |
| | | 11/19/13 | | | 1 *versus* 3: 0.72 (95% CI, 0.39–1.35) | | 18/46 | 14/46 | 1/46 | | | |
| | | 9/23/10 | | | 1 *versus* 4: 0.94 (95% CI, 0.54–1.64) | | 6/44 | 13/44 | 4/44 | | | |
| | | 8/20/14 | | | 13/46 | | 13/46 | 6/46 | | | | |
| NA | 16/44 | 18/38/20 | Gastric | Balanced | 1 *versus* 2: 0.89 (95% CI, 0.58–1.37) | NA | 4/16 | 60/76 | 11/76 | Cancer | 6418371 | |
| | 18/44 | 17/38/23 | | | 1 *versus* 3: 0.82 (95% CI, 0.54–1.26) | | 3/18 | 40/78 | 7/78 | | | |
| | 19/41 | 16/40/22 | | | 2 *versus* 3: 0.92 (95% CI, 0.62–1.39) | | 1/19 | 32/78 | 7/78 | | | |
| 15/21 | 22/14 | 0–3 | Gastric | NA | 1.03 (95% CI, 0.64–1.66) | NA | 3/22 | 9/36 | 4/36 | Cancer | 6414682 | |
| 19/19 | 19/19 | | | | | | 1/19 | 14/38 | 2/38 | | | |
| 8/29 | 12/22 | | | | 0.79 (95% CI, 0.39–1.59) | NA | 1/12 | 10/34 | 0/34 | | | |
| 5/26 | 22/12 | | | | | | 3/22 | 5/34 | 1/34 | | | |

*(Continued)*

**Table 1.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| O'Connel 1982 | USA | NA | NA | NA | 5-FU plus doxorubicin plus mitomycin-C | FA3 | 43 | 62 | 29/14 | Western | Metastatic and locally unresectable | NA | NA |
| | | | | | 5-FU plus doxorubicin plus Me-CCNU | FA3 | 34 | 59 | 25/9 | | | | |
| | | | | | 5-FU plus Me-CCNU plus razoxane | FU3 | 46 | 62 | 32/14 | | | | |
| | | | | | 5-FU plus Me-CCNU | FU2 | 58 | 64 | 34/24 | | | | |
| Buroker 1979 | USA | NA | II | March 1975–March 1977 | 5-FU plus mitomycin-C | FY2 | 80 | 18–75 | NA | Western | Metastatic and locally unresectable | 28/52 | NA |
| | | | | | 5-FU plus Me-CCNU | FU2 | 88 | | | | | 40/48 | |

**Notes:** Items that may produce significant heterogeneity are emphasized with bold-type letters and asterisks. Underlined data in PS (0/1/2) indicates that the numbers should be interpreted as PS (0 and 1) *versus* PS (2). The additional letter 'E' in certain items of 'Location (G/J)' suggested that there were additional esophageal cancer cases in addition to gastric and gastroesophageal junction cancer cases. The word 'Balanced' in 'Histological type (I/D)' indicated that although there was no description about the ratio of intestinal and diffused types, there were other classifications of histological grades and both arms were well balanced. In multi-arm studies, for example, '1 *versus* 2' in survival data referred to the hazard ratio of first regimen *versus* the second regimen. In terms of adverse events, since the number of events sometimes surpassed the total number of patients, therefore in those situations we only calculated the most significant types of adverse event in each category. The numbers of selected types of adverse events were identified inside the cells and underlined. Moreover, the words 'Description' or 'Cycles' inside adverse events suggested that there was no quantitative data or the quantitative data was calculated by chemotherapeutic cycles rather than patient-level comparison, respectively. Regarding 'PMID', those studies without a specific PubMed ID were either replaced by a DOI number or the PubMed ID of previous systematic reviews carrying relevant information. Unless clarified, the hazard ratios were the results of upper arm *versus* lower arm in each trial.
E/T, events/total patients; G/J, gastric/junction; hAE, hematological adverse events; HR, hazard ratio; I/D, intestinal/diffused; M/F, male/female; NA, not available; non-hAE, nonhematological adverse events; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; P/T, responsive patients/total patients;
**Nodes:** 1, monotherapy; 2, doublet; 3, triplet; A, anthracycline; E, etoposide; F, fluoropyrimidine; I, irinotecan; M, methotrexate; P, platinum; R, targeted medication; S, best supportive care; T, taxane; Y, mitomycin-C; U, nitrosourea. Details of the rationale for organizing the nodes are described in main text.

forest plot and league table are shown in Figures 4 and 5, respectively. These results were also consistent with pairwise meta-analysis, where 'fluoropyrimidine plus platinum-based triplet' was better than 'fluoropyrimidine plus platinum doublet' (random HR 95% CI: 0.86 (0.75–0.98), $p = 0.03$; Supplementary Table 3).

*Sensitivity analysis.* After changing to a fixed-effects model (network HR 95% CI: 0.91 (0.84–0.98), P-score = 0.916) or removing clinically heterogeneous studies (network HR 95% CI: 0.90 (0.82–0.99), P-score = 0.903), 'fluoropyrimidine plus platinum-based triplet' remained as the top node with statistical advantage against 'fluoropyrimidine plus platinum doublet' (figures not shown).

### *General analysis: secondary endpoint*

*PFS.* A total of 63 studies were included in the network calculation. 'Fluoropyrimidine plus platinum-based triplet plus targeted medication' became the best regimen in the entire hierarchy (network HR 95% CI: 0.75 (0.54–1.04), P-score = 0.919), closely followed by 'fluoropyrimidine plus platinum-based triplet' (network HR 95% CI: 0.83 (0.71–0.96), P-score = 0.881). However, only 'fluoropyrimidine plus platinum-based triplet' had shown statistical superiority against 'fluoropyrimidine plus platinum doublet' ($p = 0.01$) (Supplementary Figure 2).

*ORR.* A total of 89 studies were eligible and merged into the hierarchical comparisons. 'Fluoropyrimidine plus platinum-based triplet plus

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NA | 12/31 | 18/25 | Gastric | NA | 1 *versus* 2: 1.13 (95% CI, 0.57–2.25) | Median PFS time | 3/12 | 7/43 | Description | Cancer | 7037163 | |
| 10/24 | 21/13 | 1 *versus* 3: 0.69 (95% CI, 0.38–1.26) | | | 3/10 | | 7/34 | | | | | |
| 19/27 | 17/29 | 1 *versus* 4: 0.87 (95% CI, 0.46–1.64) | | | 4/19 | | 15/46 | | | | | |
| 18/40 | 29/29 | | | | 1/18 | | 17/58 | | | | | |
| NA | 43/37 | NA | Gastric | NA | 0.86 (95% CI, 0.60–1.21) | NA | 6/43 | Cycles | Cycles | Cancer | 387204 | |
| | 55/33 | | | | | | 5/54 | | | | | |

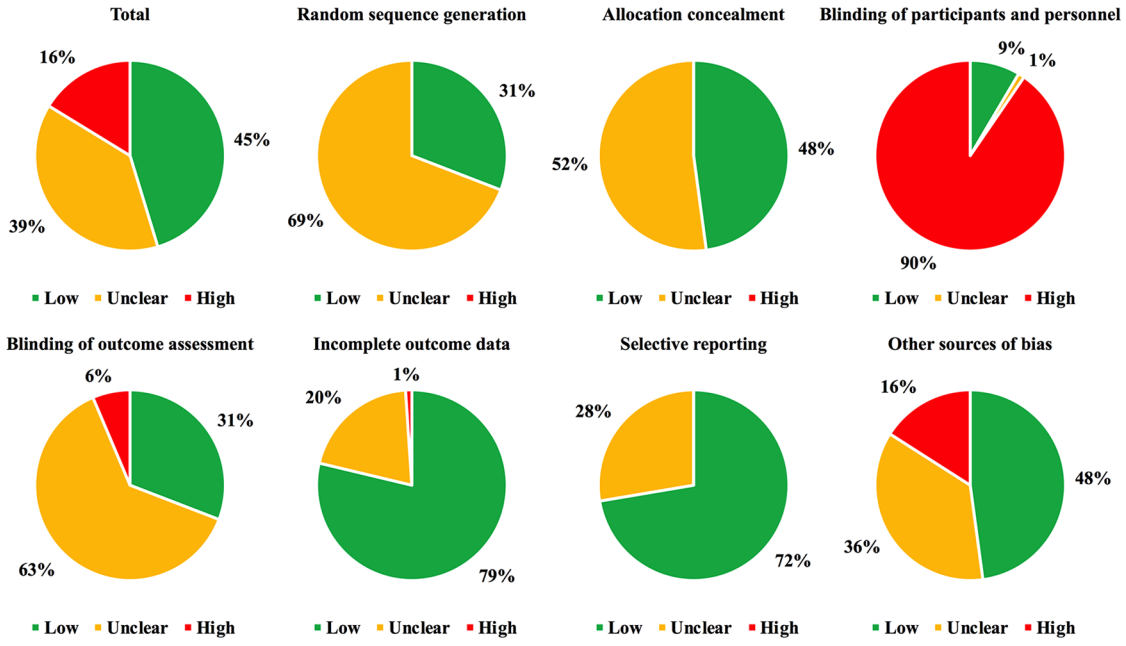


**Figure 2.** Risk of bias assessment in general analysis.

targeted medication' (network RR 95% CI: 1.48 (1.11–1.98), P-score = 0.964) and 'fluoropyrimidine plus platinum-based triplet' (network RR 95% CI: 1.20 (1.06–1.36), P-score = 0.857) again ranked as the top two nodes in the entire hierarchy, both of which demonstrated statistical advantage against common comparator 'fluoropyrimidine plus platinum doublet' (FP3R: $p = 0.008$; FP3: $p = 0.004$) (Supplementary Figure 3).

*Hematological adverse events.* A total of 74 studies were included in the network meta-analysis. 'Best supportive care' was certainly the most tolerable node in the rankings (network RR 95% CI: 0.16 (0.02–1.28), P-score = 0.952). Meanwhile, based

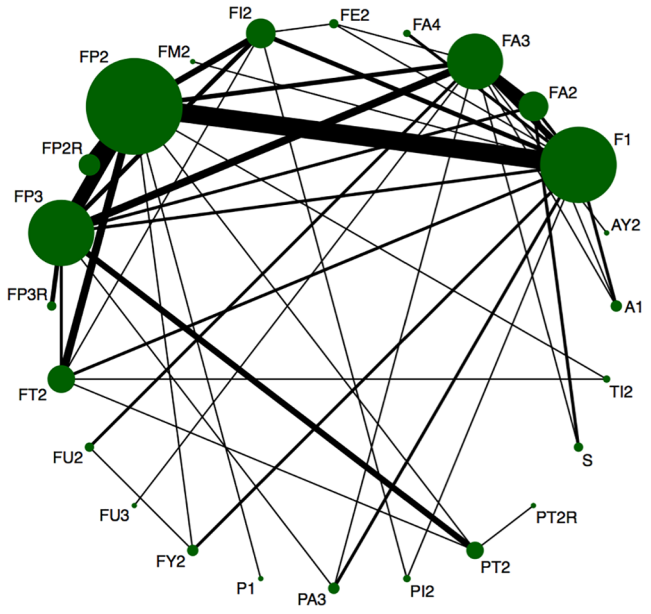


**Figure 3.** Network structure plot of overall survival in general analysis.
**Note:** The size of nodes implicates the number of studies of each regimen while the width of the lines is proportional to the amount of mutual direct comparisons.
**Nodes:** 1, monotherapy; 2, doublet; 3, triplet; A, anthracycline; E, etoposide; F, fluoropyrimidine; I, irinotecan; M, methotrexate; P, platinum; R, targeted medication; S, best supportive care; T, taxane; U, nitrosourea; Y, mitomycin-C.

on the hierarchical data, both 'fluoropyrimidine plus platinum-based triplet plus targeted medication' (network RR 95% CI: 1.31 (0.75–2.29), P-score = 0.414) and 'fluoropyrimidine plus platinum-based triplet' (network RR 95% CI: 1.55 (1.25–1.90), P-score = 0.272) had worse rankings than 'fluoropyrimidine plus platinum doublet' while the difference between 'fluoropyrimidine plus platinum-based triplet' and 'fluoropyrimidine plus platinum doublet' was statistically meaningful ($p = 0.0001$) (Supplementary Figure 4).

*Nonhematological adverse events.* A total of 78 studies were included in the network meta-analysis. Undoubtedly, 'Best supportive care' was the most tolerable node concerning nonhematological adverse events (network RR 95% CI: 0.07 (0.01–0.50), P-score = 0.993). Both 'fluoropyrimidine plus platinum-based triplet' (network RR 95% CI: 1.15 (0.99–1.34), P-score = 0.315) and 'fluoropyrimidine plus platinum-based triplet plus targeted medication' (network RR 95% CI: 1.44 (1.02–2.03), P-score = 0.176) displayed lower rankings than 'fluoropyrimidine plus platinum doublet' while the difference between 'fluoropyrimidine plus platinum-based triplet plus targeted medication' and 'fluoropyrimidine plus platinum doublet' was statistical meaningful ($p = 0.04$) (Supplementary Figure 5).

### *Additional analysis*

Although the results from general analysis seemed to be very consistent, however, since there were several subtypes of medications included in fluoropyrimidines and platinum, we decided to perform an additional analysis by only including studies with pairwise comparisons between fluoropyrimidine plus platinum-based regimens. This not only helped to lower the heterogeneity across the network but also enhanced the clinical specificity and availability. Overall 39 randomized controlled trials were eligible for additional analysis, containing a total of 10,959 patients. '5-FU plus cisplatin' (FC2) was chosen as the common comparator. Since fluoropyrimidine plus oxaliplatin doublet (especially capecitabine plus oxaliplatin) was commonly used in clinical applications, we also observed relative results between fluoropyrimidine plus oxaliplatin doublet and other alternative regimens by network league tables. Similar to that of general analysis, the majority of studies featured metastatic and measurable gastric cancer cases, exhibiting a low level of clinical heterogeneity and therefore a well transitivity (Table 2). Overall, none of the included studies were at high risk of bias regarding methodological design (Supplementary Table 4).

*Primary endpoint: OS.* A total of 38 studies were included in the network calculation. The pooled results were in low heterogeneity and high consistency ($I^2 = 0.16\%$, $Q$ heterogeneity: $p = 0.405$, $Q$ inconsistency: $p = 0.508$). 'Capecitabine plus cisplatin-based triplet plus targeted medication', '5-FU plus oxaliplatin-based triplet', and 'Capecitabine plus oxaliplatin-based triplet' closely ranked as the top three regimens in the entire hierarchy, all of which displayed superiority against '5-FU plus cisplatin' and 'Capecitabine plus cisplatin'. However, none of them displayed superiority against '5-FU plus oxaliplatin', 'S-1 plus oxaliplatin', or 'Capecitabine plus oxaliplatin' (Supplementary Figures 6 and 7).

*Secondary endpoint: PFS.* A total of 36 randomized controlled trials were merged into the pooled analysis. Again, 'Capecitabine plus cisplatin-based triplet plus targeted medication', '5-FU plus oxaliplatin-based triplet', and 'Capecitabine plus oxaliplatin-based triplet' were the best three

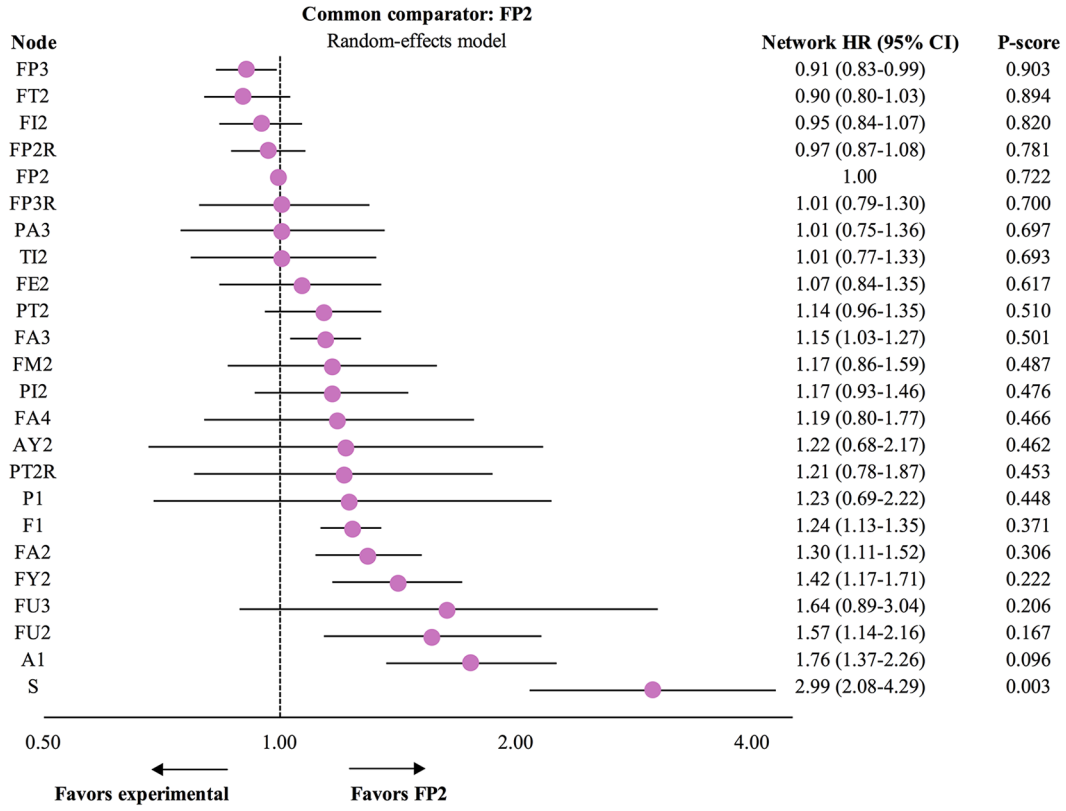


**Figure 4.** Network forest plot of overall survival in general analysis.

**Figure 5.** Network league table of overall survival in general analysis.
**Note:** Treatments are hierarchically ranked according to their P-score. The higher the position in the table a regimen is located, the better survival benefits it could offer. Values situated at the intersection of a specific column and row are the network effect sizes (HR and 95% CI) of row-defining regimen *versus* column-defining regimen.

nodes in the rankings, statistically superior to '5-FU plus cisplatin' and 'Capecitabine plus cisplatin'. In addition, except for 'Capecitabine plus cisplatin-based triplet plus targeted medication', none of the top three regimens demonstrated enough advantage against '5-FU plus oxaliplatin', 'S-1 plus oxaliplatin', or 'Capecitabine plus oxaliplatin' (Supplementary Figures 8 and 9).

*Secondary endpoint: ORR.* A total of 37 studies were eligible for the network calculation. 'Capecitabine plus cisplatin-based triplet plus targeted medication', '5-FU plus oxaliplatin-based triplet', and 'Capecitabine plus cisplatin plus targeted medication' reigned the hierarchy with statistical advantage against '5-FU plus cisplatin'. However, none of them displayed superiority against '5-FU plus oxaliplatin', 'S-1 plus oxaliplatin', or 'Capecitabine plus oxaliplatin' (Supplementary Figures 10 and 11).

*Secondary endpoint: hematological adverse events.* A total of 34 trials were included into the pooled analysis. 'Capecitabine plus cisplatin-based triplet plus targeted medication' appeared to have statistical inferiority against '5-FU plus cisplatin',

**Table 2.** Baseline characteristics of eligible studies for additional analysis (unselected population).

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kawakami 2018 | Japan | UMIN000006755 | II | NA | S-1 plus cisplatin | SC2 | 41 | 68 | 33/8 | Eastern | 33/8 | 22/19 | 8/33 |
| | | | | | Capecitabine plus cisplatin | XC2 | 43 | 64 | 36/7 | | 38/5 | 20/23 | 13/30 |
| Nishikawa 2018 | Japan | NCT00140624 | II | July 2011–June 2013 | Capecitabine plus cisplatin | XC2 | 55 | 65 | 45/10 | Eastern | 43/12 | 11/44 | 23/32 |
| | | | | | S-1 plus cisplatin | SC2 | 55 | 65 | 30/25 | | 42/13 | 12/43 | 23/32 |
| Yamada 2018 | Japan | UMIN000007652 | III | April 2012–March 2016 | S-1 plus cisplatin plus docetaxel | SC3 | 370 | Adult | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | S-1 plus cisplatin | SC2 | 371 | | | | | | |
| Fuchs 2018 | USA | NCT02314117 | III | January 2015–May 2017 | 5-FU/capecitabine plus cisplatin plus ramucirumab | XC2R | 326 | 58.9 | 214/112 | Versatile | Metastatic | NA | NA |
| | | | | | 5-FU/capecitabine plus cisplatin | XC2 | 319 | 60.1 | 215/104 | | | | |
| Ajani 2017 | USA | NCT01285557 | III | April 2011–August 2014 | S-1 plus cisplatin | SC2 | 239 | 56 | 124/115 | Western | Metastatic | NA | NA |
| | | | | | 5-FU plus cisplatin | FC2 | 122 | 56 | 60/62 | | | | |
| Hall 2017 | UK | ISCTRN33934807 | II | June 2009–January 2011 | Capecitabine plus oxaliplatin plus epirubicin | XO3 | 17 | **74*** | 13/4 | Western | 17/0 | NA | NA |
| | | | | | Capecitabine plus oxaliplatin | XO2 | 19 | **77*** | 13/6 | | 17/2 | | |
| | | | | | Capecitabine | 19 | **75*** | 15/4 | | | 18/1 | | |
| Yoon 2016 | USA | NCT01246960 | II | April 2011–August 2012 | 5-FU plus oxaliplatin plus leucovorin plus ramucirumab | FO2R | 84 | 64.5 | 63/21 | Western | 80/4 | NA | NA |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FO2 | 84 | 60 | 61/23 | | 79/5 | | |
| Shah 2016 | South Korea | NCT01590719 | II | July 2012–May 2013 | 5-FU plus oxaliplatin plus leucovorin plus onartuzumab | FO2R | 62 | 58.5 | 40/22 | Versatile | Metastatic | NA | NA |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FO2 | 61 | 57 | 36/25 | | | | |
| Tebbutt 2016 | Australia | ACTRN1 2609000109202 | II | April 2010–January 20111 | 5-FU/capecitabine plus cisplatin plus docetaxel plus panitumumab | XC3R | 37 | 64 | 33/4 | Western | Metastatic and locally unresectable | 26/11 | 13/24 |
| | | | | | 5-FU/capecitabine plus cisplatin plus docetaxel | XC3 | 39 | 59 | 30/9 | | | 23/16 | 5/34 |
| Hironaka 2016 | Japan | JapicCTI-111635 | II | October 2011–December 2012 | S-1 plus oxaliplatin plus leucovorin | SO2 | 47 | 65 | 33/14 | Eastern | 40/7 | NA | 12/35 |
| | | | | | S-1 plus leucovorin | | 47 | 65 | 37/10 | | 40/7 | | 11/36 |
| | | | | | S-1 plus cisplatin | SC2 | 48 | 65 | 38/10 | | 41/7 | | 14/34 |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6/35 | NA | 22/19 | Gastric | NA | 0.78 (95% CI, 0.49–1.24) | 0.76 (95% CI, 0.46–1.26) | 21/41 | 27/39 | 26/39 | Oncologist | 30115736 | New study |
| 2/41 | | 24/19 | | | | | 23/43 | 38/43 | 37/43 | | | |
| 17/38 | 36/19 | 45/8/2 | Gastric | 19/29 | 0.94 (95% CI, 0.62–1.42) | 1.13 (95% CI, 0.75–1.69) | 25/36 | 23/55 | 40/55 | Eur J Cancer | 30096702 | New study |
| 17/38 | 33/22 | 47/7/1 | | 26/24 | | | 14/33 | 16/55 | 39/55 | | | |
| NA | NA | 0–1 | Gastric | 259/428 | 0.99 (95% CI, 0.85–1.16) | 0.99 (95% CI, 0.86–1.15) | 219/370 | 245/370-2 | 26/370-1 | J Clin Oncol | J Clin Oncol 36, 2018 (suppl; abstr 4009) | From general analysis, abstract |
| | | | | | | | 208/371 | 140/371-2 | 27/371-1 | | | |
| NA | Measurable | 0–2 | Gastric and junction | NA | 0.96 (95% CI, 0.80–1.16) | 0.75 (95% CI, 0.61–0.94) | 134/326 | 125/326-2 | 32/326-1 | J Clin Oncol | 10.1200/JCO.2018.36.4_suppl.5 | From general analysis, abstract |
| | | | | | | | 116/319 | 131/319-2 | 5/319-1 | | | |
| 55/184 | 193/46 | 74/165/0 | 223/16 | **Balanced*-D** | 0.99 (95% CI, 0.76–1.28) | 0.86 (95% CI, 0.65–1.14) | 67/193 | 138/230 | 166/230 | Ann Oncol | 28911091 | New study |
| 34/88 | 91/31 | 38/83/0 | 117/5 | | | | 18/91 | 50/118 | 84/118 | | | |
| NA | NA | 0/11/6 | **10/2/5*-E** | Balanced | 1 *versus* 2: 1.24 (95% CI, 0.39–3.94) | 1 *versus* 2: 0.83 (95% CI, 0.36–1.93) | 5/17 | NA | 14/17 | Br J Cancer | 28095397 | From general analysis |
| | | 4/10/5 | **5/1/11*-E** | | 1 *versus* 3: 0.84 (95% CI, 0.41–1.73) | 1 *versus* 3: 0.64 (95% CI, 0.24–1.71) | 9/19 | | 7/19 | | | |
| | | 2/10/7 | **7/4/8*-E** | | 2 *versus* 3: 0.38 (95% CI, 0.14–1.03) | 2 *versus* 3: 0.78 (95% CI, 0.34–1.79) | 2/19 | | 8/19 | | | |
| NA | 67/17 | 40/43/0 | **19/26/39*-E** | Balanced | 1.08 (95% CI, 0.73–1.58) | 0.98 (95% CI, 0.69–1.37) | 38/84 | 27/82 | 65/82 | Ann Oncol | 27765757 | From general analysis |
| | 70/14 | 43/41/0 | **20/23/41*-E** | | | | 39/84 | 31/80 | 35/80 | | | |
| 23/39 | NA | 24/35/0 | 46/16 | 20/31 | 1.06 (95% CI, 0.64–1.75) | 1.08 (95% CI, 0.71–1.63) | 26/43 | 41/60-2 | 10/60-2 | Oncologist | 27401892 | From general analysis |
| 20/41 | | 24/36/0 | 48/13 | 23/26 | | | 24/42 | 29/60-2 | 1/60-2 | | | |
| NA | Measurable | 34/3 | **13/10/15*-E** | Balanced | 1.02 (95% CI, 0.51–2.05) | 1.08 (95% CI, 0.59–2.01) | 22/37 | NA | 26/37 | Br J Cancer | 26867157 | From general analysis |
| | | 37/2 | **15/11/13*-E** | | | | 17/39 | | 18/39 | | | |
| NA | Measurable | 37/10/0 | Gastric | 24/23 | 1 *versus* 2: 0.76 (95% CI, 0.47–1.24) | 1 *versus* 2: 0.52 (95% CI, 0.30–0.88) | 31/47 | 25/47 | 28/47-3 | Lancet Oncol | 26640036 | From general analysis |
| | | 37/10/0 | | 24/23 | 1 *versus* 3: 0.59 (95% CI, 0.37–0.93) | 1 *versus* 3: 0.60 (95% CI, 0.35–1.02) | 20/47 | 11/47 | 10/47-3 | | | |
| | | 38/10/0 | | 18/30 | 2 *versus* 3: 0.77 (95% CI, 0.49–1.22) | 2 *versus* 3: 1.08 (95% CI, 0.67–1.74) | 22/48 | 43/48 | 22/48-3 | | | |

**Table 2.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Wang 2016 | China | NCT00811447 | III | November 2008–June 2012 | 5-FU plus cisplatin plus docetaxel | FC3 | 119 | 56.6 | 81/38 | Eastern | 89/30 | NA | NA |
| | | | | | 5-FU plus cisplatin | FC2 | 115 | 55.5 | 88/27 | | 89/26 | | |
| Ryu 2016 | South Korea | NCT01671449 | III | October 2012–October 2014 | S-1 plus oxaliplatin | SO2 | 338 | 56 | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | S-1 plus cisplatin | SC2 | | | | | | | |
| Li 2015 | China | NCT01198392 | III | October 2008–June 2011 | S-1 plus cisplatin | SC2 | 120 | 53.2 | 84/36 | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | 5-FU plus cisplatin | FC2 | 116 | 55.3 | 85/31 | | | | |
| Ochendusz-ko 2015 | Poland | NCT02445209 | III | September 2010–February 2014 | Capecitabine plus oxaliplatin plus epirubicin | XO3 | 29 | 57.9 | 16/13 | Western | 28/1 | 6/23 | 16/13 |
| | | | | | 5-FU plus cisplatin plus leucovorin plus docetaxel | FC3 | 27 | 60.3 | 13/14 | | 24/3 | 15/12 | 12/15 |
| Du 2015 | China | NCT02370849 | II | October 2009–February 2012 | S-1 plus cisplatin plus nimotuzumab | SC2R | 31 | 58 | 17/14 | Eastern | 22/9 | 6/25 | 4/27 |
| | | | | | S-1 plus cisplatin | SC2 | 31 | 53 | 26/5 | | 18/13 | 3/28 | 5/26 |
| Van Cutsem 2015 | Belgium | NCT00382720 | II | September 2006–September 2007 | 5-FU plus oxaliplatin plus leucovorin plus docetaxel | FO3 | 89 | 58 | 61/28 | Western | Metastatic and locally unresectable | 63/26 | 17/72 |
| | | | | | Capecitabine plus oxaliplatin plus docetaxel | XO3 | 86 | 59 | 64/22 | | | 50/36 | 17/69 |
| | | | | | Oxaliplatin plus docetaxel | | 79 | 59 | 51/28 | | | 55/24 | 7/72 |
| Yamada 2015 | Japan | JapicCTI-101021 | III | January 2010–October 2011 | S-1 plus oxaliplatin | SO2 | 318 | 65 | 240/78 | Eastern | 261/57 | 160/158 | 61/257 |
| | | | | | S-1 plus cisplatin | SC2 | 324 | 65 | 237/87 | | 272/52 | 164/160 | 64/260 |
| Shen 2015 | China | NCT00887822 | III | March 2009–July 2010 | Capecitabine plus cisplatin | XC2R | 102 | 55.5 | 74/28 | Eastern | 94/8 | 40/62 | NA |
| | | | | | Capecitabine plus cisplatin plus bevacizumab | XC2 | 100 | 54.2 | 68/32 | | 95/5 | 39/61 | |
| Chen 2015 | China | NA | NA | August 2009–June 2011 | S-1 plus oxaliplatin plus docetaxel | SO3 | 30 | 18–75 | 18/12 | Eastern | Metastatic | NA | NA |
| | | | | | 5-FU plus cisplatin plus docetaxel | FC3 | 30 | 14/16 | | | | | |
| Iveson 2014 | UK | NCT00719550 | II | October 2009–June 2010 | Capecitabine plus cisplatin plus epirubicin plus rilotumumab | XC3R | 82 | 61 | 57/25 | Western | 73/9 | NA | NA |
| | | | | | Capecitabine plus cisplatin plus epirubicin | XC3 | 39 | 60 | 31/8 | | 34/5 | | |
| Zhang 2014 | China | NA | NA | August 2010–September 2012 | S-1 plus oxaliplatin plus cetuximab | SO2R | 30 | 49 | 37/19 | Eastern | Metastatic and locally unresectable | 26/30 | 8/48 |
| | | | | | S-1 plus oxaliplatin | SO2 | 26 | | | | | | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 46/73 | Measurable | 115/4 | 99/20 | Balanced | 0.71 (95% CI, 0.52–0.97) | 0.58 (95% CI, 0.42–0.80) | 58/119 | 72/119-1 | 31/119 | Gastric Cancer | 25604851 | From general analysis |
| 39/76 | | 108/7 | 86/29 | | | | 39/115 | 11/115-1 | 21/115 | | | |
| NA | 172/166 | 331/7 | Gastric and junction | NA | 0.86 (95% CI, 0.66–1.11) | 0.85 (95% CI, 0.67–1.07) | Des-cription | Description | Description | J Clin Oncol | 10.1200/JCO.2016.34.15_suppl.4015 | New study, abstract |
| 65/55 | Measurable | 28/85/7 | 98/22 | Balanced | 1.05 (95% CI, 0.73–1.50) | 1.03 (95% CI, 0.76–1.39) | 27/120 | 112/120 | 22/120 | Oncotarget | 26439700 | New study |
| 64/52 | | 29/83/4 | 106/10 | | | | 25/116 | 41/116 | 20/116 | | | |
| 16/13 | Measurable | 26/3 | Gastric and junction | 5/10 | 1.25 (95% CI, 0.72–2.18) | 1.06 (95% CI, 0.63–1.80) | NA | 25/29 | 7/29 | Med Oncol | 26354521 | New study |
| 14/13 | | 25/2 | | 6/10 | | | | 19/26 | 4/26 | | | |
| 8/23 | Measurable | 5/26/0 | 25/6 | Balanced | 1.78 (95% CI, 0.97–3.25) | 2.14 (95% CI, 1.19–3.83) | 17/31 | 8/31 | 6/31 | Medicine | 26061330 | From general analysis |
| 9/22 | | 7/24/0 | 25/6 | | | | 18/31 | 4/31 | 1/31 | | | |
| 35/54 | 77/12 | 87/2 | 75/14 | NA | 1 *versus* 2: 0.73 (95% CI, 0.48–1.09) | 1 *versus* 2: 0.80 (95% CI, 0.55–1.18) | 41/88 | 49/88-1 | 67/88 | Ann Oncol | 25416687 | From general analysis |
| 40/46 | 80/6 | 84/2 | 75/11 | | 1 *versus* 3: 0.51 (95% CI, 0.35–0.76) | 1 *versus* 3: 0.43 (95% CI, 0.30–0.63) | 21/81 | 50/82-1 | 73/82 | | | |
| 23/56 | 69/10 | 77/2 | 70/9 | | 2 *versus* 3: 0.75 (95% CI, 0.51–1.10) | 2 *versus* 3: 0.69 (95% CI, 0.49–0.96) | 18/78 | 52/78-1 | 76/78 | | | |
| 74/244 | Measurable | 224/91/3 | Gastric | 144/174 | 0.96 (95% CI, 0.80–1.14) | 1.00 (95% CI, 0.84–1.20) | 117/318 | 151/338-3 | 174/338 | Ann Oncol | 25316259 | New study |
| 72/252 | | 228/92/4 | | 145/179 | | | 169/324 | 314/335-3 | 200/335 | | | |
| 20/82 | 86/16 | 97/5 | 82/20 | Balanced | 1.11 (95% CI, 0.79–1.56) | 0.89 (95% CI, 0.66–1.21) | 29/86 | 68/101 | 45/101 | Gastric Cancer | 24557418 | From general analysis |
| 24/76 | 81/19 | 95/5 | 85/15 | | | | 33/81 | 54/100 | 66/100 | | | |
| NA | Measurable | 6/20/4 | Gastric | Balanced | 0.97 (95% CI, 0.78–1.22) | 0.97 (95% CI, 0.87–1.08) | 16/30 | 8/30 | 7/30 | Chinese Journal of Cancer-Prevention and Treat-ment | 28850174 | New study, Chinese |
| | | 9/17/4 | | | | | 14/30 | 6/30 | 6/30 | | | |
| 13/69 | 76/6 | 34/47/1 | 66/12 | NA | 0.70 (95% CI, 0.45–1.09) | 0.60 (95% CI, 0.45–0.79) | 30/76 | 56/81 | 68/81 | Lancet Oncol | 24965569 | From general analysis |
| 9/30 | 38/1 | 16/22/1 | 31/4 | | | | 8/38 | 16/39 | 32/39 | | | |
| 12/44 | Measurable | 3/47/6 | Gastric | 25/31 | 0.74 (95% CI, 0.42–1.30) | 0.67 (95% CI, 0.38–1.18) | 17/30 | 10/30 | 3/30 | World J Surg Oncol | 24758484 | From general analysis |
| | | | | | | | 11/26 | 11/26 | 5/26 | | | |

*(Continued)*

**Table 2.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Li 2014 | China | NA | NA | NA | S-1 plus oxaliplatin | SO2 | 16 | 42.1 | 9/7 | Eastern | Metastatic and locally unre-sectable | NA | NA |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FO2 | 16 | 45.7 | 11/5 | | | | |
| Koizumi 2013 | Japan | JapicCTI-101327 | II | December 2008–February 2012 | S-1 plus cisplatin plus orantinib | SC2R | 45 | 62 | 30/15 | Eastern | 39/6 | 19/26 | 15/30 |
| | | | | | S-1 plus cisplatin | SC2 | 46 | 63.5 | 35/11 | | 39/7 | 24/22 | 15/31 |
| Waddell 2013 | UK | NCT00824785 | III | June 2008–October 2011 | Capecitabine plus oxaliplatin plus epirubicin plus panitumumab | XO3R | 278 | 63 | 232/46 | Western | 244/34 | NA | NA |
| | | | | | Capecitabine plus oxaliplatin plus epirubicin | XO3 | 275 | 62 | 226/49 | | 250/25 | | |
| Lordick 2013 | Germany | EudraCT 2007-004219-75 | III | June 2008–December 2010 | Capecitabine plus cisplatin plus cetuximab | XC2R | 455 | 60 | 339/116 | Versatile | 439/16 | NA | 113/342 |
| | | | | | Capecitabine plus cisplatin | XC2 | 449 | 59 | 334/115 | | 436/12 | | 116/333 |
| Al-Batran 2013 | Germany | NCT00737373 | II | August 2007–October 2008 | 5-FU plus oxaliplatin plus leucovorin plus docetaxel | FO3 | 72 | **69*** | 51/21 | Western | 50/22 | 33/39 | 14/58 |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FO2 | 71 | **70*** | 45/26 | | 49/22 | 32/39 | 14/57 |
| Kim 2012 | South Korea | NCT00985556 | II | March 2008–September 2009 | S-1 plus oxaliplatin | SO2 | 65 | 60 | 44/21 | Eastern | 47/18 | NA | NA |
| | | | | | Capecitabine plus oxaliplatin | XO2 | 64 | 61 | 45/19 | | 46/18 | | |
| Ocvirk 2012 | Slovenia | ISRCTN34052674 | II | January 2003–March 2007 | 5-FU plus cisplatin plus epirubicin | FC3 | 45 | 54.7 | 34/11 | Western | 37/8 | 7/38 | 13/32 |
| | | | | | Capecitabine plus cisplatin plus epirubicin | XC3 | 40 | 55.6 | 32/8 | | 35/5 | 5/35 | 12/28 |
| Ohtsu 2011 | Japan | NCT00548548 | III | September 2007–December 2008 | Capecitabine plus cisplatin plus bevacizumab | XC2R | 387 | 58 | 257/130 | Versatile | 367/20 | 130/257 | NA |
| | | | | | Capecitabine plus cisplatin | XC2 | 387 | 59 | 258/129 | | 378/9 | 126/261 | |
| Li 2011 | China | NA | II | January 2003–December 2007 | 5-FU plus cisplatin plus paclitaxel | FC3 | 50 | 59 | 32/18 | Eastern | 28/22 | NA | NA |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | FO2 | 44 | 58 | 31/13 | | 27/17 | | |
| Ajani 2010 | USA | NCT00400179 | III | May 2005–March 2007 | S-1 plus cisplatin | SC2 | 521 | 59 | 382/139 | Western | 497/24 | NA | NA |
| | | | | | 5-FU plus cisplatin | FC2 | 508 | 60 | 347/161 | | 488/20 | | |
| Lee 2009 | South Korea | NA | III | July 2000–January 2004 | 5-FU plus heptaplatin | FH2 | 88 | 53.5 | 66/22 | Eastern | 84/3 | NA | NA |
| | | | | | 5-FU plus cisplatin | FC2 | 86 | 53.5 | 62/24 | | 79/4 | | |

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NA | Measurable | 0–2 | Gastric | Balanced | Median OS time | 0.78 (95% CI, 0.18–3.39) | 9/16 | 2/16-1 | NA | Cancer Research and Clinic | 28850174 | New study, Chinese |
| | | | | | | | 7/16 | 5/16-1 | | | | |
| NA | Measurable | 28/17/0 | Gastric | 22/23 | 0.74 (95% CI, 0.46–1.19) | 1.23 (95% CI, 0.74–2.05) | 28/45 | 36/45-2 | 27/45 | Br J Cancer | 24045669 | From general analysis |
| | | 30/16/0 | | 25/20 | | | 26/46 | 28/46-2 | 14/46 | | | |
| NA | Measurable | 118/144/16 | **78/94/106*-E** | Balanced | 1.37 (95% CI, 1.07–1.76) | 1.22 (95% CI, 0.98–1.52) | 116/254 | 69/276 | 264/276 | Lancet Oncol | 23594787 | From general analysis |
| | | 117/143/15 | **89/75/111*-E** | | | | 100/238 | 137/266 | 190/266 | | | |
| 92/363 | Measurable | 237/218/0 | 376/71 | 162/76 | 1.00 (95% CI, 0.87–1.17) | 1.09 (95% CI, 0.92–1.29) | 136/455 | 178/446 | 430/446 | Lancet Oncol | 23594786 | From general analysis |
| 90/359 | | 228/220/0 | 371/73 | 149/94 | | | 131/449 | 234/436 | 278/436 | | | |
| 18/54 | Measurable | 67/5 | 45/27 | NA | 0.83 (95% CI, 0.54–1.28) | 0.80 (95% CI, 0.54–1.20) | 35/72 | 59/72-2 | 58/72 | Eur J Cancer | 23063354 | From general analysis |
| 18/53 | | 65/6 | 47/24 | | | | 20/71 | 16/70-2 | 46/70 | | | |
| NA | 53/12 | 11/54/0 | Gastric | Balanced | 1.08 (95% CI, 0.74–1.58) | 1.06 (95% CI, 0.72–1.57) | 21/53 | 29/65 | 17/65 | Eur J Cancer | 22243774 | New study |
| | 45/19 | 8/54/2 | | | | | 20/45 | 16/64 | 23/64 | | | |
| NA | NA | 21/21/3 | Gastric | NA | 1.16 (95% CI, 0.75–1.80) | 1.48 (95% CI, 0.94–2.35) | 14/45 | 14/45 | 16/45 | Am J Clin Oncol | 21399488 | New study |
| | | 21/18/2 | | | | | 12/40 | 12/40 | 15/40 | | | |
| 110/277 | 311/76 | 365/22 | 333/54 | NA | 0.87 (95% CI, 0.73–1.04) | 0.80 (95% CI, 0.68–0.93) | 143/311 | 194/386 | 165/386 | J Clin Oncol | 21844504 | From general analysis |
| 107/280 | 297/90 | 367/20 | 338/49 | | | | 111/297 | 209/381 | 183/381 | | | |
| NA | Measurable | 24/26 | Gastric | Balanced | 1.02 (95% CI, 0.63–1.66) | NA | 24/50 | 4/50-1 | 5/50-1 | World J Gastroenterol | 21448363 | From general analysis |
| | | 21/23 | | | | | 20/44 | 4/44-1 | 0/44-1 | | | |
| NA | 499/22 | 226/295/0 | 438/83 | Balanced | 0.92 (95% CI, 0.80–1.05) | 0.99 (95% CI, 0.86–1.14) | 117/402 | 254/521 | 295/521 | J Clin Oncol | 20159816 | New study |
| | 485/23 | 200/308/0 | 417/91 | | | | 123/385 | 446/508 | 422/508 | | | |
| 68/20 | Measurable | 36/46/5 | Gastric | NA | 0.83 (95% CI, 0.61–1.11) | 1.22 (95% CI, 0.84–1.77) | 27/78 | 34/88 | 38/88 | Cancer Res Treat | 19688066 | New study |
| 68/18 | | 30/51/4 | | | | | 28/78 | 2/86 | 64/86 | | | |

*(Continued)*

**Table 2.** (Continued)

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Node | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) | Peritoneal involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kang 2009 | South Korea | NA | III | April 2003–January 2005 | Capecitabine plus cisplatin | XC2 | 160 | 56 | 103/57 | Versatile | Metastatic and locally unresectable | 94/66 | 30/130 |
| | | | | | 5-FU plus cisplatin | FC2 | 156 | 56 | 108/48 | | | 84/72 | 29/127 |
| Popov 2008 | Serbia | NA | NA | NA | 5-FU plus oxaliplatin plus leucovorin | FO2 | 36 | 57 | 24/12 | Western | 29/7 | 21/15 | 13/23 |
| | | | | | 5-FU plus cisplatin plus leucovorin | FC2 | 36 | 55 | 26/10 | | 28/8 | 20/16 | 14/22 |
| Al-Batran 2008 | Germany | NA | III | June 2003–January 2006 | 5-FU plus oxaliplatin plus leucovorin | FO2 | 112 | 64 | 64/48 | Western | 109/3 | 70/42 | 37/75 |
| | | | | | 5-FU plus cisplatin plus leucovorin | FC2 | 108 | 64 | 81/27 | | | | |
| Cunningham 2008 | UK | ISRCTN51678883 | III | June 2000–May 2005 | 5-FU plus cisplatin plus epirubicin | FC3 | 249 | 65 | 202/47 | Western | 198/51 | NA | NA |
| | | | | | Capecitabine plus cisplatin plus epirubicin | XC3 | 241 | 64 | 194/47 | | 185/56 | | |
| | | | | | 5-FU plus oxaliplatin plus epirubicin | FO3 | 235 | 61 | 191/44 | | 181/54 | | |
| | | | | | Capecitabine plus oxaliplatin plus epirubicin | XO3 | 239 | 62 | 198/41 | | 181/58 | | |
| Van Cutsem 2006 | Belgium | NA | III | November 1999–January 2003 | 5-FU plus cisplatin | FC2 | 224 | 55 | 158/66 | Western | 217/6 | NA | NA |
| | | | | | 5-FU plus cisplatin plus docetaxel | FC3 | 221 | 55 | | | 159/62 | | |
| Kim 2001 | South Korea | NA | III | March 1997–April 2000 | 5-FU plus cisplatin plus epirubicin | FC3 | 61 | 55 | 45/15 | Eastern | 57/3 | 32/29 | NA |
| | | | | | 5-FU plus cisplatin | FC2 | 60 | 56.5 | 42/18 | | 57/3 | 28/32 | |
| KRGGC 1992 | South Korea | NA | NA | NA | 5-FU plus cisplatin plus epirubicin | FC3 | 25 | NA | NA | Eastern | Metastatic and locally unresectable | NA | NA |
| | | | | | 5-FU plus cisplatin | FC2 | 22 | | | | | | |

**Notes:** Items that may produce significant heterogeneity are emphasized with bold-type letters and asterisks. Underlined data in PS (0/1/2) indicates that the numbers should be interpreted as PS (0 and 1) *versus* PS (2). The additional letter 'E' in certain items of 'Location (G/J)' suggested that there were additional esophageal cancer cases in addition to gastric and gastroesophageal junction cancer cases. The additional letter 'D' in 'Histological type (I/D)' suggested that the study featured diffuse gastric cancer specifically. The word 'Balanced' in 'Histological type (I/D)' indicates that although there was no description about the ratio of intestinal and diffused types, there were other classifications of histological grades and both arms were well balanced. In multi-arm studies, for example, '1 *versus* 2' in survival data referred to the hazard ratio of first regimen *versus* the second regimen. In terms of adverse events, since the number of events sometimes surpassed the total number of patients, therefore in those situations we only calculated the most significant types of adverse event in each category. The numbers of selected types of adverse events were identified inside the cells and underlined. Moreover, the words 'Description' or 'Cycles' inside adverse events suggested that there was no quantitative data or the quantitative data was calculated by chemotherapeutic cycles rather than patient-level comparison, respectively. Regarding 'PMID', those studies without a specific PubMed ID were either replaced by a DOI number or the PubMed ID of previous systematic reviews carrying relevant information. Unless clarified, the hazard ratios were the results of upper arm *versus* lower arm in each trial.
E/T, events/total patients; G/J, gastric/junction; hAE, hematological adverse events; HR, hazard ratio; I/D, intestinal/diffused; M/F, male/female; NA, not available; non-hAE, nonhematological adverse events; ORR, objective response rate; OS, overall survival; PFS: progression-free survival; P/T, responsive patients/total patients; Y/N, yes/no.
**Nodes:** 1, monotherapy; 2, doublet; 3, triplet; S, S-1; C, cisplatin; F, 5-FU; H, heptaplatin; O, oxaliplatin; R, targeted medication; X, capecitabine. Details of the rationale for organizing the nodes are described in the main text.

| Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 40/120 | Measurable | 0–2 | Gastric | NA | 0.85 (95% CI, 0.65–1.11) | 0.80 (95% CI, 0.63–1.03) | 64/139 | 29/156 | 38/156 | Ann Oncol | 19153121 | New study |
| 34/122 | | | | | | | 44/137 | 35/155 | 37/155 | | | |
| 27/9 | Measurable | 3/22/11 | 21/15 | Balanced | 0.70 (95% CI, 0.54–0.90) | 0.66 (95% CI, 0.34–1.27) | 15/36 | Cycles | Cycles | J BUON | 19145671 | New study |
| 25/11 | | 6/20/10 | 19/17 | | | | 9/36 | | | | | |
| 51/71 | NA | 103/9 | 92/20 | NA | 0.89 (95% CI, 0.66–1.21) | 0.76 (95% CI, 0.57–0.99) | 39/112 | 28/112 | 48/112 | J Clin Oncol | 18349393 | New study |
| 98/10 | 69/39 | 30/78 | 45/63 | | 97/11 | 84/24 | | | | | | |
| 19/230 | Measurable | 220/29 | **90/72/87*-E** | Balanced | 2 *versus* 1: 0.92 (95% CI, 0.76–1.11) | 2 *versus* 1: 0.98 (95% CI, 0.82–1.17) | 107/263 | 161/234 | 186/234 | N Engl J Med | 18172173 | New study |
| 18/223 | | 211/30 | **102/68/71*-E** | | 3 *versus* 1: 0.96 (95% CI, 0.79–1.15) | 3 *versus* 1: 0.97 (95% CI, 0.81–1.17) | 116/250 | 171/234 | 209/234 | | | |
| 18/217 | | 215/20 | **87/55/93*-E** | | 4 *versus* 1: 0.80 (95% CI, 0.66–0.97) | 4 *versus* 1: 0.85 (95% CI, 0.70–1.02) | 104/245 | 111/225 | 181/225 | | | |
| 21/217 | | 215/24 | **104/53/82*-E** | | | | 117/244 | 112/227 | 197/227 | | | |
| 71/153 | Measurable | 29/192/3 | 168/56 | 45/77 | 1.29 (95% CI, 1.02–1.63) | 1.47 (95% CI, 1.19–1.82) | 57/224 | 126/224-1 | 206/224-3 | J Clin Oncol | 17075117 | From general analysis |
| 213/6 | | 68/153 | 28/190/3 | 179/42 | | | 40/92 | 81/221 | 181/221-1 | 197/221-3 | | |
| NA | Measurable | 55/6 | Gastric | NA | 0.83 (95% CI, 0.42–1.61) | Median PFS time | 22/61 | 23/61-2 | 32/61-3 | Eur J Cancer | 10.1016/S0959-8049(01)81651-8 | From general analysis, abstract |
| | | 53/7 | | | | | 20/60 | 10/60-2 | 10/60-3 | | | |
| NA | NA | NA | Gastric | NA | 0.57 (95% CI, 0.27–1.20) | NA | 5/21 | Description | Description | Anticancer Res | 1295444 | From general analysis |
| | | | | | | | 6/22 | | | | | |

'5-FU plus oxaliplatin', 'S-1 plus oxaliplatin', and 'Capecitabine plus oxaliplatin' (Supplementary Figures 12 and 13).

*Secondary endpoint: nonhematological adverse events.* A total of 35 studies were eligible for network meta-analysis. 'Capecitabine plus cisplatin-based triplet plus targeted medication' was statistically inferior to 'S-1 plus oxaliplatin' while comparable to '5-FU plus cisplatin', '5-FU plus oxaliplatin,' and 'Capecitabine plus oxaliplatin' (Supplementary Figures 14 and 15).

### *Patients with specific positivity*

There were a total of eight randomized controlled trials were analyzed in this section of the systematic review, including four HER-2 positive studies, two MET-1 positive studies, one CLDN18.2 positive study, and one EGFR positive study (Table 3). None of the included studies were at high risk of bias with regard to methodological design (Supplementary Table 5).

*HER-2 positive.* Three studies were large-scale phase III randomized controlled trials and only one trial reported phase II results, with sample sizes ranging from 28 to 780 patients. According to Bang *et al*,[40] adding trastuzumab to capecitabine plus cisplatin could significantly enhance its survival benefits among HER-2 positive patients compared with capecitabine plus cisplatin alone (OS HR: 0.74 [95% CI, 0.60–0.91]; PFS HR: 0.71 [95% CI, 0.59–0.85]). Recently, Tabernero *et al*.[41] also confirmed that dual HER-2 targeting strategy with both pertuzumab and trastuzumab failed to generate OS benefit compared with trastuzumab-based regimen, despite the difference of OS coming close to crossing the boundary value (OS HR: 0.84 (95% CI, 0.71–1.00); PFS HR: 0.73 (95% CI, 0.62–0.86)). Moreover, either pertuzumab or trastuzumab was well tolerable compared with its control arm. On the other hand, however, adding lapatinib failed to produce survival benefits in contrast to capecitabine plus oxaliplatin alone[42] (OS HR: 0.91 [95% CI, 0.73–1.12]; PFS HR: 0.84 [95% CI, 0.69–1.03]), irrespective of gastric ($p = 0.30$), gastroesophageal junction ($p = 0.77$), or esophageal cancer subgroups ($p = 0.77$). Similarly, the addition of lapatinib to capecitabine-based triplet also failed to have enough survival benefit (OS HR: 0.90 [95% CI, 0.35–2.27]; PFS HR: 0.86 [95% CI, 0.37–1.99]), despite that the results were less credible owing to lower statistical power on small sample size ($n = 28$)[43] (Table 3).

*MET-1 positive.* Two large-scale phase III randomized controlled trials reported the first-line options for MET-1-positive gastric cancer patients. Based on 609 patients, Catenacci *et al*.[44] surprisingly described that adding rilotumumab not only failed to increase but also significantly decreased the survival time among MET-1-positive patients compared with capecitabine plus cisplatin plus epirubicin alone (OS HR: 1.34 [95% CI, 1.10–1.63]; PFS HR: 1.26 [95% CI, 1.04–1.51]). Furthermore, Shah *et al*.[45] reported that addition of onartuzumab also failed to display survival benefit among MET-1-positive patients compared to 5-FU plus oxaliplatin plus leucovorin alone (OS HR: 0.82 [95% CI, 0.59–1.15]; PFS HR: 0.90 [95% CI, 0.71–1.16]) (Table 3).

*Others.* Based on a CLDN18.2-positive 161-patient phase II trial, adding IMAB362 could significantly enhance the survival time while maintaining comparable tolerability against capecitabine plus oxaliplatin plus epirubicin alone[46] (OS HR: 0.51 [95% CI, 0.36–0.73]; PFS HR: 0.47 [95% CI, 0.31–0.70]). For EGFR-positive patients, the addition of matuzumab failed to generate survival benefits compared with capecitabine plus cisplatin plus epirubicin alone[47] (OS HR: 1.02 [95% CI, 0.61–1.70]; PFS HR: 1.13 [95% CI, 0.63–2.01]) (Table 3).

## Discussion

Currently, systemic therapy is still the preferred measure against advanced inoperable gastric cancer, in which fluoropyrimidine plus cisplatin doublet is the most recommended regimen in virtue of both clinical efficacy and tolerability.[5] However, previously published systematic reviews failed to make a panoramic summary about the systemic therapy against gastric cancer, let alone a credible hierarchical ranking that fit the diversity of regimens.[16–18] Therefore, we have conducted by far the most comprehensive systematic review and network meta-analysis based on 119 high-quality randomized controlled trials, covering both chemotherapy and targeted medications.

In general, analysis among unselected population, 'fluoropyrimidine plus platinum-based triplet' was the top-ranking node regarding OS, which was consistent with the result of pairwise

meta-analysis and was confirmed to be stable by sensitivity analysis. In terms of PFS and ORR, 'fluoropyrimidine plus platinum-based triplet plus targeted medication' and 'fluoropyrimidine plus platinum-based triplet' ranked as the top two nodes, demonstrating statistical superiority against 'fluoropyrimidine plus platinum doublet'. However, in 2014, one ASCO expert meeting stated that a risk reduction of HR 0.80 might be clinically relevant. In addition, the ESMO clinical benefit scale even recommends that HR 0.65 is clinically relevant. Therefore, in consideration of survival efficacy and safety profile, it is still inappropriate to conclude that 'fluoropyrimidine plus platinum doublet' could be replaced by 'fluoropyrimidine plus platinum-based triplet' in terms of first-line regimens. Moreover, since the general analysis did not further clarify different subtypes inside fluoropyrimidine and platinum, we still had concerns about the statistical credibility about the pooled results and, thus, we performed a specific additional analysis.

The additional analysis that individualized different types of fluoropyrimidine and platinum gave detailed comparisons across diverse fluoropyrimidine and platinum-based regimens. Concerning survival benefits, 'capecitabine plus cisplatin-based triplet plus targeted medication' was the best regimen in the entire hierarchy, statistically superior against both '5-FU plus cisplatin' and 'capecitabine plus cisplatin' while comparable with '5-FU plus oxaliplatin', 'S-1 plus oxaliplatin', and 'Capecitabine plus oxaliplatin'. On the other hand, it also featured unfavorable tolerability as expected, especially compared with 'S-1 plus oxaliplatin'. However, although more specific categorizations helped to lower heterogeneity, it also raised concerns about low statistical power owing to the small sample-size in each node. In addition, the third component and targeted medication besides fluoropyrimidine and platinum were not always consistent within the same node, which could introduce heterogeneity into the final results as well. Therefore, we feel that it is more appropriate to maintain the recommendation of fluoropyrimidine plus oxaliplatin doublet (especially capecitabine or S-1) as the preferred first-line regimen, which has been widely applied in clinical settings.

Among patients with specific pathological positivity, HER-2 is the most widely investigated target against advanced gastric cancer. Based on a large-scale phase III randomized controlled trial by Bang *et al.*,[40] the addition of trastuzumab to fluoropyrimidine plus cisplatin doublet has been confirmed as the preferred regimen against HER-2 overexpressing metastatic gastric cancer. Despite the negative result of OS ($p = 0.056$), a dual HER-2-targeting strategy with both pertuzumab and trastuzumab displayed a significant benefit in terms of PFS, as well as the comparable tolerability compared with trastuzumab-based first-line regimen.[41] Since the difference in OS was quite close to statistical boundary, it hinted that other combination of dual HER-2-targeting strategy might possibly reach statistical significance in future designs. In addition, lapatinib plus capecitabine plus oxaliplatin failed to surpass capecitabine plus oxaliplatin doublet,[42] therefore fluoropyrimidine plus cisplatin plus trastuzumab is still the best regimen for HER-2 overexpressing advanced gastric cancer at present. According to two large-scale phase III studies, adding rilotumumab or onartuzumab failed to generate survival benefits among MET-1-positive patients compared with fluoropyrimidine plus platinum-based chemotherapy alone.[44,45] This suggests that fluoropyrimidine plus cisplatin may still serve as the preferred first-line regimen against MET-1-positive advanced gastric cancer. Moreover, in a phase II trial by Schuler *et al.*[46], the addition of IMAB362 significantly elongated survival lifespan among patients with CLDN18.2 positivity compared with capecitabine plus oxaliplatin plus epirubicin alone. Since CLDN18.2 is believed to widely exist in nearly half of gastric cancer cells, IMAB362 is a very promising medication and, thus, a phase III trial is currently ongoing.

Although our systematic review was rigorously designed and conducted, there were still some limitations within. First, this network meta-analysis was not based on individual-patient data. However, since the network was verified to be highly consistent, stable, and homogenous, conclusions of our pooled analysis were therefore also credible and applicable. Second, even though in additional analysis, several different regimens were still forced to merge into one node in order to perform the network calculations, since the third component and targeted medication in addition to fluoropyrimidine and platinum were not further specified. All these could bring potential biases into the network meta-analysis despite of the low overall statistical heterogeneity as mentioned previously. Third, the overall number of studies especially for top-ranking nodes such as 'capecitabine plus cisplatin-based triplet plus

**Table 3.** Baseline characteristics of eligible studies for patients with specific positivity.

| Study | Leading country | Registration | Phase | Enrollment | Regimen | Sample size | Age | Gender (M/F) | Region | Metastatic (Y/N) | Visceral involvement (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tabernero 2018 | USA | NCT01774786 | III | June 2013–January 2016 | 5-FU/Capecitabine plus cisplatin plus trastruzumab plus pertuzumab | 388 | 62 | 294/94 | Versatile | Metastatic | NA |
| | | | | | 5-FU/Capecitabine plus cisplatin plus trastruzumab | 392 | 61 | 323/69 | | | |
| Moehler 2018 | Germany | NCT01123473 | II | February 2011–August 2013 | 5-FU/Capecitabine plus cisplatin plus epirubicin plus lapatinib | 14 | 66 | 12/2 | Western | Metastatic | NA |
| | | | | | 5-FU/Capecitabine plus cisplatin plus epirubicin | 14 | 58 | 10/4 | | | |
| Hecht 2016 | USA | NCT00680901 | III | June 2008–January 2012 | Capecitabine plus oxaliplatin plus lapatinib | 249 | 61 | 189/60 | Versatile | 236/13 | NA |
| | | | | | Capecitabine plus oxaliplatin | 238 | 59 | 176/62 | | 227/11 | |
| Bang 2010 | South Korea | NCT01041404 | III | September 2005–December 2008 | 5-FU/Capecitabine plus cisplatin plus trastruzumab | 294 | 59.4 | 226/68 | Versatile | 284/10 | NA |
| | | | | | 5-FU/Capecitabine plus cisplatin | 290 | 58.5 | 218/72 | | 280/10 | |
| Catenacci 2017 | UK | NCT01697072 | III | November 2012–November 2014 | Capecitabine plus cisplatin plus epirubicin plus rilotumumab | 304 | 61 | 205/99 | Western | 284/20 | 118/186 |
| | | | | | Capecitabine plus cisplatin plus epirubicin | 305 | 59 | 220/85 | | 283/22 | 136/169 |
| Shah 2017 | UK | NCT01662869 | III | November 2012–March 2014 | 5-FU plus oxaliplatin plus leucovorin plus onartuzumab | 279 | 60 | 188/91 | Versatile | Metastatic | NA |
| | | | | | 5-FU plus oxaliplatin plus leucovorin | 283 | 58 | 183/100 | | | |
| Schuler 2016 | Germany | NCT01630083 | II | NA | Capecitabine plus oxaliplatin plus epirubicin plus IMAB362 | 161 | 58 | NA | Western | Metastatic and locally unresectable | NA |
| | | | | | Capecitabine plus oxaliplatin plus epirubicin | 161 | | | | | |
| Rao 2010 | UK | NCT00215644 | II | August 2005–November 2006 | Capecitabine plus cisplatin plus epirubicin plus matuzumab | 35 | 59 | 24/11 | Western | Metastatic | NA |
| | | | | | Capecitabine plus cisplatin plus epirubicin | 36 | 64 | 27/9 | | | |

**Notes:** Items that may produce significant heterogeneity are emphasized with bold-type letters and asterisks. Underlined data in PS (0/1/2) indicates that the numbers should be interpreted as PS (0 and 1) *versus* PS (2). The additional letter 'E' in certain items of 'Location (G/J)' suggested that there were additional esophageal cancer cases besides of gastric and gastroesophageal junction cancer cases. The word 'Balanced' in 'Histological type (I/D)' indicated that although there was no description about the ratio of intestinal and diffused types, there were other classifications of histological grades and both arms were well balanced. Moreover, the words 'Description' or 'Cycles' inside adverse events suggested that there was no quantitative data or the quantitative data was calculated by chemotherapeutic cycles rather than patient-level comparison, respectively. Regarding 'PMID', those studies without a specific PubMed ID were either replaced by a DOI number or the PubMed ID of previous systematic reviews carrying relevant information. Unless clarified, the hazard ratios were the results of upper arm *versus* lower arm in each trial.
E/T, events/total patients; G/J, gastric/junction; hAE, hematological adverse events; HR, hazard ratio; I/D, intestinal/diffused; M/F, male/female; NA, not available; non-hAE, non-hematological adverse events; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; P/T, responsive patients/total patients; Y/N, yes/no.

targeted medication' were still inadequate, which might lower the statistical power of the entire quantitative analysis.

Taken together, fluoropyrimidine plus oxaliplatin doublet (especially capecitabine or S-1) should still be considered as the preferred first-line regimen owing to its comparable survival benefits and lower toxicity.

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| Peritoneal involvement (Y/N) | Prior resection (Y/N) | Measurable (Y/N) | PS (0/1/2) | Location (G/J) | Histological type (I/D) | OS-HR | PFS-HR | ORR (P/T) | hAE (E/T) | non-hAE (E/T) | Journal | PMID | Note |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NA | NA | 351/37 | 162/226/0 | 278/110 | 353/18 | 0.84 (95% CI, 0.71–1.00) | 0.73 (95% CI, 0.62–0.86) | 199/351 | 218/385 | 335/385 | Lancet Oncol | 30217672 | HER2-positive |
| | | 352/40 | 162/229/0 | 294/98 | 350/21 | | | 170/352 | 220/388 | 241/388 | | | |
| NA | NA | NA | 10/4/0 | 10/4 | Balanced | 0.90 (95% CI, 0.35–2.27) | 0.86 (95% CI, 0.37-1.99) | 6/14 | 7/14 | 11/14 | Cancer Chemother Pharmacol | 30105460 | HER2 and/or EGFR-positive |
| | | | 9/5/0 | 10/4 | | | | 3/14 | 4/14 | 14/14 | | | |
| NA | 18/231 | NA | 79/149/21 | **214/23/12*-E** | 225/9 | 0.91 (95% CI, 0.73–1.12) | 0.84 (95% CI, 0.69–1.03) | 131/249 | 17/270 | 113/270 | J Clin Oncol | 26628478 | HER2-positive |
| | 20/218 | | 63/153/22 | **210/20/8*-E** | 211/10 | | | 93/238 | 7/267 | 75/267 | | | |
| NA | 71/223 | 269/25 | 264/30 | 236/58 | 225/26 | 0.74 (95% CI, 0.60–0.91) | 0.71 (95% CI, 0.59–0.85) | 139/294 | 144/294 | 173/294 | Lancet | 20728210 | HER2-positive |
| | 62/228 | 257/33 | 263/27 | 242/48 | 213/2 | | | 100/290 | 134/290 | 140/290 | | | |
| NA | 48/256 | 262/42 | 117/187/0 | **227/53/24*-E** | Balanced | 1.34 (95% CI, 1.10–1.63) | 1.26 (95% CI, 1.04–1.51) | 78/262 | 130/298 | 182/298 | Lancet Oncol | 28958504 | MET-1 positive |
| | 48/257 | 267/38 | 115/189/1 | **195/71/39*-E** | | | | 119/267 | 148/299 | 169/299 | | | |
| NA | 98/181 | Measurable | 112/162/0 | 214/65 | 136/83 | 0.82 (95% CI, 0.59–1.15) | 0.90 (95% CI, 0.71–1.16) | 84/207 | 124/279 | 101/279 | JAMA Oncol | 27918764 | MET-1 positive |
| | 101/182 | | 118/158/0 | 218/65 | 133/98 | | | 100/217 | 100/280 | 80/280 | | | |
| NA | NA | NA | NA | 257/65 | 106/141 | 0.51 (95% CI, 0.36–0.73) | 0.47 (95% CI, 0.31–0.70) | 69/161 | Description | Description | Ann Oncol | 10.1093/annonc/mdw371.06 | CLDN18.2 positive, abstract |
| | | | | | | | | 45/161 | | | | | |
| 10/25 | NA | NA | 13/22/0 | **14/21*-E** | Balanced | 1.02 (95% CI, 0.61–1.70) | 1.13 (95% CI, 0.63–2.01) | 11/35 | 16/35 | 31/35 | Ann Oncol | 20497967 | EGFR positive |
| 9/27 | | | 12/24/0 | **16/20*-E** | | | | 21/36 | 17/36 | 24/36 | | | |

## Author contributions

Study design: Ji Cheng, Guobin Wang and Kaixiong Tao; Manuscript writing and revision: Ji Cheng and Kaixiong Tao; Literature retrieval: Ji Cheng and Ming Cai; Discretion of eligibility: Ji Cheng and Ming Cai; Quality assessment: Ji Cheng and Xiaoming Shuai; Data extraction: Ji Cheng and Jinbo Gao; Statistical analysis: Ji Cheng and Kaixiong Tao.

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## Conflict of interest statement

The authors declare that there is no conflict of interest.

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## Supplemental material

Supplemental material for this article is available online.

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