Comparative efficacy and tolerability of target agents and immune checkpoint inhibitors in combination with chemotherapy as First-line treatment for advanced gastric cancer: A Bayesian network meta-analysis

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Article

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Abstract

Background

The use of target agents and immune checkpoint inhibitors have changed the treatment landscape for AGC in the first-line setting. However, the crosswise comparison between each regimen is rare. Therefore, we estimated the efficacy and safety of targeted therapy or immunotherapy with chemotherapy in AGC patients as the first-line treatment;

Method

Included studies were divided into “unselected” or “selected” group according to whether the patients were selected by a certain pathological expression. We conducted a Bayesian network meta-analysis for all regimens in both groups;

Results

In unselected group, no regimen showed significant improvements in overall survival (OS) and progression free survival (PFS), while pembrolizumab and nivolumab combined with chemotherapy were ranked first and second respectively without an obvious safety difference. In selected group, zolbetuximab plus chemo-therapy significantly prolonged OS (HR 0.53, 95%CI 0.31–0.89) and PFS (HR 0.45, 95%CI 0.23–0.89). The top three regimens were zolbetuximab-chemotherapy, tratuzumab plus pertuzumab-chemotherapy and nivolumab-chemotherapy respectively, with no significant safety risk.

Conclusion

For average patients, immune checkpoint inhibitor PD-1 plus chemotherapy will be the promising regimen. For patients with overexpression of HER-2 or CLDN18.2, dual HER-2 targeting strategy or zolbetuximab combined with chemotherapy comes with greater survival benefits.

1. Introduction

Gastric cancer was the fifth most commonly diagnosed cancer and the fourth leading cause of cancer death in 2020, with an especially high incidence in Eastern Asia [1]. It was estimated that over one million new cases occurred in 2020 with 769,000 re-ported deaths, which illustrates its relatively poor prognosis [2]. The reason for the high mortality in gastric cancer patients is attributed to the fact that approximately 50% of the patients are presented for late-stage diagnoses.

For early-stage gastric cancer patients, curative surgical resection is recommended as the optimal therapeutic option [3]. However, in the case of advanced gastric cancer (AGC) that is unresectable, metastatic, recurring, or locally advanced, systemic therapies including chemotherapy, targeted therapy, immunotherapy, and their combined regimens are often used as preferred palliative treatments, which not only offer survival benefits but also increase the chances for the next curative surgery.

Recently, great progress has been made in first-line regimens for untreated AGC. Firstly, double or triple platinum-fluoropyrimidine combinations have become the standard first-line chemotherapy in the National Comprehensive Cancer Network (NCCN) clinical practice guidelines [4]. Secondly, trastuzumab, a target agent against human epidermal growth factor receptor II (HER-2), was recommended as an additional targeted therapy combined with first-line chemotherapy for HER-2 positive patients. Furthermore, based on successful results from two randomized trials reported in European Society for Medical Oncology (ESMO) 2020 [5, 6], nivolumab, an anti-programmed cell death protein 1 (PD-1) antibody, combined with chemotherapy has become the new standard first-line treatment for AGC among patients whose programmed death-ligand 1 (PD-L1) combined positive score (CPS) is 5 or higher.

Since 2010, large number of randomized controlled trials (RCTs) have explored the efficacy and safety of different targeted therapies or immunotherapies and compared them with standard chemotherapy as first-line treatment among AGC patients. Although these research progresses are likely to change the landscape of first-line treatments, comparisons between different regimens are still lacking, especially evaluation between targeted therapy and immunotherapy. Network meta-analyses can evaluate and rank the effects of various treatments via direct or indirect evidence, which provides an ideal approach to the field of cancer research. Although Cheng *et al*. summarized first-line systemic therapies for AGC in 2019 by network meta-analysis, all target medications were combined into one node rather than evaluating the efficacy and establishing ranks between them [7]. In 2017, Xie *et al.* published a comparison of target agents used in combination with chemotherapy in untreated AGC patients [8], but this study erroneously mixed several second-line therapy RCTs. Furthermore, neither study included any immunotherapy trials owing to their early publication when the evaluation of targeted therapy and immunotherapy was still lacking.

In this study, we conducted a Bayesian network meta-analysis to evaluate and rank the efficacy and tolerability of target agents or immune checkpoint inhibitors combined with standard chemotherapy as first-line treatment in untreated AGC patients, which will help in clinical decision-making for future patients receiving first-line AGC therapy.

2. Materials And Methods

2.1. Search strategy

PubMed, Cochrane Central Register of Controlled Trials databases and Embase database were searched for studies published before August 25, 2021.We used relevant combinations, keywords and MeSH (Medical Subject Heading) terms pertaining to disease (e.g., gastric cancer, stomach neoplasm, esophagogastric cancer), therapy (e.g., chemotherapy, immunotherapy, targeted-therapy), disease stage (e.g., advanced, unresected, metastatic). Furthermore, several previously published high-quality systematic reviews were also reviewed in case of omission. Full electronic search strategy is shown in the supplementary material (Supplement Table S1).

2.2. Selection Criteria

Under the PICOS framework, studies were considered eligible when they met all of the following inclusion criteria. The protocol of our systematic review and network meta-analysis had been published in PROSPERO (CRD42021271480)

1. Participant: patients bore untreated AGC, including locally inoperable or unresectable, advanced, recurrent, and metastatic cases. Studies containing lower esophageal cancer cases were eligible. Studies whose patients received the last adjuvant chemotherapy more than 6 months past were also eligible, but studies without a clear indication of the time of the last adjuvant chemotherapy were not included.
2. Intervention: different target agents or immune checkpoint inhibitors in combination with standard first-line chemotherapy against AGC. We only included studies in which chemotherapy was the first-line regimen in accordance with NCCN 2020 guidelines for AGC. Otherwise, studies were not qualified.
3. Comparator: chemotherapy with or without placebo compared with chemotherapy plus different target agents or immune checkpoint inhibitors.
4. Outcome: overall survival (OS) and progression free survival (PFS) are primary outcomes, while objective response rate (ORR) and adverse events (AE) are secondary outcomes.
5. Study design: phase II and phase III randomized controlled trials reported before August 2021 without language limitation. When one registered trial had several different reports, we only included the one with the longest follow-up rather than the subgroup report.

Studies were excluded if they met at least one of the following exclusion criteria.

1. Comparison between each arm cannot be incorporated into network calculation.
2. Chemotherapy regimens are not qualified with first-line chemotherapy standard.
3. Patients in studies had received their last adjuvant chemotherapy within 6 months, or the precise time of the last adjuvant chemotherapy is not reported.

2.3. Data extraction and risk of bias assessment

The following information in studies has been extracted by two authors independently. 1. General characteristics of the studies: name of the first-author, publication year, and the national clinical trial (NCT) registration number. 2. Patient baseline characteristics: age, region, follow-up time, number of peritoneal metastases, tumor location, and whether they had any specific pathological positivity. 3. Treatment in different arms: the regimens of chemotherapy, target agents or immune checkpoint inhibitors, and the sample size in each treatment. 4. Primary and secondary outcomes: including OS, PFS, ORR and AE ≥ 3, presented with hazard ratios (HRs) and 95% confidence intervals (95% CIs). Engauge Digitizer 4.0 was used to estimate HR values from Kaplan-Meier curves when HRs and 95%CIs were not directly provided [9]. ORR was defined as the proportion of patients who reached a partial or complete response. AE ≥ 3 means only Grade 3 or higher adverse events were counted, following the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). The risk of bias in each included study was assessed by Cochrane Collaboration tool [10], which assigns grades of “high risk”, “unclear risk”, or “low risk”.

2.4. Statistical analysis

A random-effects network meta-analysis was conducted by Bayesian framework. Firstly, we evaluated the global heterogeneity between treatment effects across all studies by using the I2 statistic, with values of < 25%, 25–50%, and > 50% indicating low, moderate, and high heterogeneity, respectively [11]. Secondly, analyses of residual deviance were performed to evaluate global consistency by comparing the Deviance In-formation Criterion (DIC) difference value between “consistency” model and “inconsistency” model. In addition, node splitting was used to assess local inconsistencies when there were closed loops in the network [12]. The Surface Under the Cumulative Ranking (SUCRA) probability was the tool to estimate the ranking of each treatment [13]. Funnel plots were conducted to check publication bias of the outcomes. The Bayesian network meta-analysis was performed by the “gemtc” package in the R software through the software JAGS, while version 3.1.2. STATA 14.0 and Review Manager software were used to assist graphical functions.

3. Results

3.1. Literature search and study characteristics

A total of 5992 records were identified using the search strategy, and finally 96 records were selected for the full text review. Among these, 40 studies were omitted due to their single-arm design or unrandomized trials. One study was excluded because it could not be incorporated into network calculation [14]. Another study was excluded as the chemotherapy regimens did not meet the criteria for the standard first-line chemotherapy in NCCN 2021 guidelines [15]. Two other studies were not included because patients had previously received systemic chemotherapy within 6 months or the time of administration was not clearly indicated [16, 17]. One study did not process in meta-analysis because of without primary and secondary outcomes reported [18]. The flow diagram of literature search is summarized in Fig. 1 and the details of reasons for exclusion are shown in Supplement Table S2. Finally, 31 RCTs were included for the network meta-analysis.

To avoid potential heterogeneity, we divided the included studies into two large subgroups. Among the 31 eligible studies, 13 studies were allocated into the “selected group” analysis because these trials included patients with specific pathological positivity or PD-L1 expression (CPS ≥ 1). Meanwhile, 20 studies

were included in “unselected group” analysis for the pathologically unselected general population. Two studies are overlapping because the subgroup data for both the selected and unselected groups were completely reported.

In unselected group, 20 RCTs described 13 treatment nodes. Treatment drugs included Andecaliximab (ADX), Bevacizumab (Bev), Cetuximab, Chemotherapy, Ipatasertib, Nivolumab, Nimotuzumab, Onartuzumab, Pembrolizumab, Panitumumab, Rilotumumab, Ramucirumab and Ziv-aflibercept (Ziv). For the sake of simplicity, we will use target agents or immune checkpoint inhibitors’ name instead of regimens’ full title in following. Placebo control was used in 11 trials. While 3 studies used three-drug cytotoxic regimens and others used two-drug cytotoxic regimens, all chemotherapy regimens contained fluoropyrimidine and platinum (Oxaliplatin or cisplatin). Ten trials included both Gastric cancer (GC) and Gastroesophageal junction cancer (GEJ), while 8 trials included GC, GEJ and partial esophageal cancer (EC). Three trials included AGC cases only with metastasis, while others also included locally inoperable and recurrent cases. Overall, the demographic characteristics of included trials were generally comparable. Several studies that may have introduced potential heterogeneity owing to their specific base-line features, such as three-drug cytotoxic regimens and those containing only EC and EGJ cases, were further detected in sensitivity analysis. Network plots of primary outcomes, OS and PFS, are shown in Figs. 2A and 2B. Characteristics of included studies are presented in Table 1.

Table 1
Baseline characteristics of eligible studies in unselected group.

Study	Regimen	Age	Region	Peritoneal involvement	Location	Advanced situation	PFS-HR	OS-HR
Shan 2021 ChiCTR2000038900 [18]	1. S-1 plus docetaxel/ cisplatin (n = 21) 2. S-1 plus docetaxel/ cisplatin plus Apatinib (n = 24)	N/A	Western/Eastern countries	N/A	GC	Locally advanced	N/A	N/A
Shah 2021 NCT02545504 (GAMMA-1) [28]	1. Fluorouracil plus oxaliplatin plus leucovorin plus PBO (n = 214) 2. Fluorouracil plus oxaliplatin plus leucovorin plus Andecaliximab (ADX ; n = 218)	1. 63 2. 61	Europe US	N/A	GC,GEJ	Locally advanced, Metastatic	0.84 (95%CI 0.67–1.04)	0.93(95%CI 0.74–1.18)
Boku 2020 NCT02746796 (ATTRACTION-4) [6]	1. S-1/Capecitabin plus PBO (n = 362) 2. S-1/Capecitabin plus nivolumab (n = 362)	N/A	N/A	N/A	GC, GEJ	Advanced, recurrent	0.68 (98.51%CI 0.51–0.90)	0.90(95%CI 0.75–1.08)
Kato 2020 NCT03189719 (KETNOTE-590) [25]	1. 5-FU plus cisplatin plus PBO (n = 376) 2. 5-FU plus cisplatin plus pembrolizumab (n = 373)	N/A	N/A	N/A	GEJ, EC	Locally advanced, metastatic	0.65 (95%CI 0.55–0.76)	0.73(95%CI0.62-0.86)
Mochler 2020 NCT02872116 (CheckMate649) [29]	1. S-1 plus oxaliplatin plus PBO (n = 792) 2. S-1 plus oxaliplatin plus nivolumab (n = 789)	N/A	N/A	N/A	GC, GJE	Unresectable advanced, metastatic	0.77(95%CI 0.68–0.87)	0.80 (99.3%CI 0.68–0.94)
Yoshikawa 2019 NCT02539225 (RAINSTORM) [30]	1. S-1 plus oxaliplatin plus PBO (n = 93) 2. S-1 plus oxaliplatin plus ramucirumab (n = 96)	1. 63 2. 61	Asia	1. 56 2. 63	GC, GEJ	Metastatic	1.07 (95%CI 0.86–1.33)	1.11(95%CI0.89-1.40)

Notes. GC, Gastric Cancer; GEJ, Gastroesophageal junction cancer; EC; Esophageal Cancer

Study	Regimen	Age	Region	Peritoneal involvement	Location	Advanced situation	PFS-HR	OS-HR
Malka 2019 PRODIGE 17-ACCORD 20-MEGA [31]	1. Fluorouracil plus oxaliplatin plus leucovorin (n = 56) 2. Fluorouracil plus oxaliplatin plus leucovorin plus panitumumab (n = 49) 3. Fluorouracil plus oxaliplatin plus leucovorin plus rilotumumab (n = 57)	1. 64 2. 64 3. 65	Europe	N/A	GC, GEJ, EC	Locally advanced, Metastatic	0.99 (95%CI 0.77–1.27) 1.01 (95%CI 0.80–1.28)	0.99(95%CI 0.93–1.07) 0.99(95%CI 0.91–1.08)
Fuchs 2019 NCT02314117 (RAINFALL) [32]	1. Fluoropyrimidine plus cisplatin plus PBO (n = 319) 2. Fluoropyrimidine plus cisplatin plus ramucirumab (n = 326)	1. 62 2. 60	Versatile	1. 111 2. 130	GC, GEJ	Metastatic	0.753 (95%CI 0.607–0.935)	0.962(95%CI0.801-1.156)
Cleary 2019 NCT01747551 (ZAMEGA) [33]	1. Fluorouracil plus oxaliplatin plus leucovorin plus PBO (n = 21) 2. Fluorouracil plus oxaliplatin plus leucovorin plus ziv-aflibercept (n = 43)	1. 62 2. 62	Versatile	1. 7 2. 11	GC, GEJ, EC	Metastatic	1.11 (95%CI 0.64–1.91)	1.24(95%CI0.71-2.15)
Bang 2019 NCT01896531 [34]	1 Fluorouracil plus oxaliplatin plus leucovorin plus PBO (n = 82) 2 Fluorouracil plus oxaliplatin plus leucovorin plus ipatasertib (n = 71)	1. 63 2. 58	Versatile	1. 25 2. 30	GC, GEJ	Locally advanced, metastatic, recurrent	1.12 (95%CI 0.81–1.55)	1.85 (95%CI 1.23–2.79)
Yoon 2016 NCT01246960 [35]	1. Fluorouracil plus oxaliplatin plus leucovorin plus PBO (n = 84) 2. Fluorouracil plus oxaliplatin plus leucovorin plus ramucirumab (n = 84)	1. 60 2. 64.5	USA	N/A	GC, GEJ, EC	Locally advanced, metastatic	0.98 (95%CI 0.69–1.37)	1.08(95%CI0.73-1.58)

Notes. GC, Gastric Cancer; GEJ, Gastroesophageal junction cancer; EC; Esophageal Cancer

Study	Regimen	Age	Region	Peritoneal involvement	Location	Advanced situation	PFS-HR	OS-HR
Tebbutt 2016 ATTAX3 [36]	1. Fluoropyrimidine plus cisplatin plus docetaxel (n = 39) 2. Fluoropyrimidine plus cisplatin plus docetaxel plus panitumumab (n = 34)	1. 59 2. 64	Australia	1. 5 2. 13	GC, GEJ, EC	Metastatic,locally recurrent	1.08 (95%CI 0.59–2.01)	1.02(95%CI 0.51–2.05)
Shah 2016 NCT01590719 (YO28252) [37]	1. Fluorouracil plus oxaliplatin plus leucovorin plus PBO (n = 61) 2. Fluorouracil plus oxaliplatin plus leucovorin plus Onartuzumab (n = 62)	1. 57 2. 58.5	Asia	N/A	GC, GEJ	Inoperable, metastatic	1.08 (95%CI 0.71–1.63)	1.06(95%CI 0.64–1.75)
Shen 2016 NCT00887822 (AVATAR) [38]	1. Capecitabine plus cisplatin plus PBO (n = 102) 2. Capecitabine plus cisplatin plus Bevacizumab (n = 100)	1. 55.5 2. 54.2	Chinese	N/A	GC, GEJ	Locally advanced, metastatic, recurrent	0.89 (95%CI 0.66–1.21)	1.11(95%CI 0.79–1.56)
Du 2015 NCT02370849 [39]	1. S-1 plus cisplatin (n = 31) 2. S-1 plus cisplatin plus Nimotuzumab (n = 31)	1. 53 2. 58	Chinese	1. 5 2. 4	GC, GEJ	Locally advanced, metastatic	2.136 (95%CI 1.193–3.826)	1.776(95%CI 0.972–3.246)
Zhang 2014 N/A [40]	1. S-1 plus oxaliplatin (n = 30) 2. S-1 plus oxaliplatin plus cetuximab (n = 27)	1. 49 2. 49	Chinese	8	GC	Unresectable or recurrence after surgery	0.67 (95%CI 0.38–1.18)	0.74(95%CI 0.42–1.30)
Iveson 2014 NCT00719550 [41]	1. Epirubicin plus cisplatin plus capecitabine plus PBO (n = 39) 2. Epirubicin plus cisplatin plus capecitabine plus Rilotumumab (n = 82)	1. 60 2. 60.7	Asia	N/A	GC, GEJ, EC	Unresectable locally advanced, metastatic	0.60 (95%CI 0.45–0.79)	0.70(95%CI 0.45–1.09)
Waddell 2013 NCT00824785 (REAL3) [42]	1. Epirubicin plus oxaliplatin plus capecitabine (n = 238) 2. Epirubicin plus oxaliplatin plus capecitabine plus panitumumab (n = 254)	1. 62 2. 63	UK	N/A	GC, GEJ, EC	Locally advanced, metastatic	1.22 (95%CI 0.98–1.52)	1.37(95%CI 1.07–1.76)

Notes. GC, Gastric Cancer; GEJ, Gastroesophageal junction cancer; EC; Esophageal Cancer

Study	Regimen	Age	Region	Peritoneal involvement	Location	Advanced situation	PFS-HR	OS-HR
Lordick 2013 EXPAND [43]	1. Capecitabine plus cisplatin (n = 449) 2. Capecitabine plus cisplatin plus Cetuximab (n = 455)	1. 59 2. 60	Versatile	1. 116 2.113	GC, GEJ, EC	Locally advanced, metastatic	1.09 (95%CI 0.92–1.29)	1.00(95%CI 0.87–1.17)
Eatock 2013 NCT00583674 [44]	1. Capecitabine plus cisplatin plus PBO (n = 56) 2. Capecitabine plus cisplatin plus Trebananib (n = 115)	1. 62 2. 58.9	UK	N/A	GC, GEJ, EC	Metastatic	0.98 (95%CI 0.67–1.43)	NA
Ohtsu 2011 NCT00548548 (AVAGAST) [45]	1. Capecitabine plus cisplatin plus PBO (n = 387) 2. Capecitabine plus cisplatin plus Bevacizumab (n = 387)	1. 59 2. 58	Versatile	N/A	GC, GEJ	Locally advanced, metastatic	0.80 (95%CI 0.68–0.93)	0.87 (95%CI 0.73–1.03)

Notes. GC, Gastric Cancer; GEJ, Gastroesophageal junction cancer; EC; Esophageal Cancer

In selected group, there were 11 treatment nodes among 13 RCTs. Treatment drugs included Chemotherapy, Lapatinib, Matuzumab, Nivolumab, Onartuzumab, Pembrolizumab, Rilotumumab, Tratuzumab, Tratuzumab plus Pertuzumab, Tratuzumab plus Pembrolizumab and Zolbetuximab. Six trials used placebo control while others used an open-label design. Five trials chose a three-drug cytotoxic regimen, Epirubicin plus fluoropyrimidine plus platinum, while others used a two-drug regimen containing fluoropyrimidine plus platinum. Three trials included partial lower EC cases, while 1 trial included EC and GEJ without any GC patients. Three trials included AGC cases only with metastasis, while others also included locally inoperable and recurrent cases. To confirm the comparable baseline, studies with potential heterogeneity were checked for their influence by sensitivity analysis. Network plots of primary outcomes, OS and PFS, are presented in Figs. 2C and 2D. Baseline characteristics of included studies are summarized in Table 2.

Table 2
Baseline characteristics of eligible studies in selected group

Study	Regimen	Age	Region	Peritoneal involvement	Location	Advanced situation	PFS-HR	OS-HR
Janjigan 2021 NCT03615326 (KEYNOTE-811) [21]	1. Pembrolizumab plus trastuzumab plus Cisplatin/Oxaliplatin plus fluorouraciln(n = 133) 2. trastuzumab plus Cisplatin/Oxaliplatin plus fluorouraciln(n = 131)	N/A	N/A	NA/A	GC, GJE	Unresectable, metastatic	N/A	N/A
Sahin 2021 NCT01630083 (FAST) [23]	1. Epirubicin plus oxaliplatin plus capecitabine (n = 84) 2. Epirubicin plus oxaliplatin plus capecitabine plus zolbetuximab (n = 77)	1. 57 2. 59	N/A	1. 23 2. 20	GC, GEJ, EC	Locally advanced, inoperable, recurrent, metastatic	0.44(95%CI 0.29–0.67)	0.55(95% 0.39–0.
Shitara 2020 NCT02494583 (KEYNOTE-062) [24]	1. Cisplatin plus fluorouraciln plus PBO (n = 250) 2. Cisplatin plus fluorouraciln plus pembrolizumab (n = 257)	1. 62.5 2. 62	Versatile	N/A	GC, GEJ	Locally advanced/unresectable, metastatic	0.84(95%CI 0.70–1.02)	0.85(95% 0.70–1.
Kato 2020 NCT03189719 (KEYNOTE-590) [25]	1. 5-FU plus cisplatin plus PBO (n = N/A) 2. 5-FU plus cisplatin plus Pembrolizumab (n = N/A)	N/A	N/A	N/A	GEJ, EC	Locally advanced, metastatic	0.51(95% CI, 0.41–0.65)	0.62(95% 0.49–0.
Mochler 2020 NCT02872116 (CheckMate649) [29]	1. S-1 plus oxaliplatin plus PBO (n = 465) 2. S-1 plus oxaliplatin plus nivolumab (n = 468)	N/A	N/A	N/A	GC, GJE	Unresectable advanced, metastatic	0.68(95% CI, 0.56–0.81)	0.71(95% 0.59–0.
Tabernero 2018 NCT01774786 (JACOB) [46]	1. Cisplatin plus fluorouraciln plus tratuzumab (n = 392) 2. Cisplatin plus fluorouraciln plus tratuzumab plus pertuzumab (n = 388)	1. 61 2. 62	Versatile	N/A	GC, GEJ	Metastatic	0.73(95%CI 0.62–0.86)	0.84(95% 0.71-1.0
Mochler 2018 NCT01123473 [47]	1. Epirubicin plus cisplatin plus 5-fluorouracil/capecitabine plus PBO (n = 14) 2. Epirubicin plus cisplatin plus 5-fluorouracil/capecitabine plus Laptinib (n = 14)	1. 58 2. 66	Europe	N/A	GC, GEJ	Unresectable, metastatic	0.86(95%CI0.37-1.99)	0.90(95% 2.27)
Shah 2017 NCT01662869 [48]	1. Fluorouracil plus oxaliplatin plus leucovorin plus PBO (283) 2. Fluorouracil plus oxaliplatin plus leucovorin plus Onartuzumab (n = 279)	1.<65: 189; >65: 94 2.<65: 183; >65: 96	Versatile	No	GC, GEJ	Metastatic	0.90(95%CI 0.71–1.16)	0.82(95% 1.15)
Catenacci 2017 NCT01697072 (RILOMET-1) [49]	1 Epirubicin plus cisplatin plus capecitabine plus PBO (n = 305) 2 Epirubicin plus cisplatin plus capecitabine plus Rilotumumab (n = 304)	1. 59 2. 61	Versatile	N/A	GC, GEJ	Locally advanced, metastatic, recurrent	1.26 (95%CI 1.04–1.51)	1.34(95% 1.10–1.

Notes. GC, Gastric Cancer; GEJ, Gastroesophageal junction cancer; EC; Esophageal Cancer

Study	Regimen	Age	Region	Peritoneal involvement	Location	Advanced situation	PFS-HR	OS-HR
Schuler 2016 NCT01246960 [22]	1. Epirubicin plus oxaliplatin plus capecitabine (n = 161) 2. Epirubicin plus oxaliplatin plus capecitabine plus IMAB362 (n = 161)	Median: 58	Europe	N/A	GC, GEJ	Locally advanced, metastatic, recurrent	0.47(95%CI 0.31–0.70)	0.51(95 0.73)
Hecht 2016 NCT00680901 (TRIO013/LOGiC) [50]	1. Capecitabine Plus Oxaliplatin (n = 267) 2. Capecitabine Plus Oxaliplatin plus lapatinib (n = 270)	1. 59 2. 61	Versatile	N/A	GC, GEJ, EC	Unresectable	0.82(95%CI 0.68-1.0)	0.91(95 0.73–1.
Rao 2010 NCT0021564436 [51]	1. Epirubicin plus cisplatin plus capecitabine (n = 36) 2. Epirubicin plus cisplatin plus capecitabine plus Matuzumab (n = 35)	1. 64 2. 69	Europe	1. 25 2. 29	GC, GEJ, EC	Metastatic	1.13 (95%CI 0.63–2.01)	1.02(95 0.61–1.
Bang 2010 NCT01041404 (ToGA) [20]	1. Capecitabine/5-FU plus cisplatin (n = 290) 2. Capecitabine/5-FU plus cisplatin plus Trastuzumab (n = 294)	1. 58.5 2. 59.4	Versatile	N/A	GC, GEJ	Locally advanced, metastatic, recurrent	0.71(95%CI 0.59–0.85)	0.74(95 0.60–0.

Notes. GC, Gastric Cancer; GEJ, Gastroesophageal junction cancer; EC; Esophageal Cancer

3.2. Risk of bias assessment

Generally, the risk of bias was low in the 31 included studies. The primary source of high-risk bias was in the domain of blinding of participants and personnel due to the open-label design, which resulted in 39.39% of the studies scoring as high-risk of bias. Meanwhile, 9.09% of the trials had a high risk of bias mostly due to an early termination of patient recruitment. The summary of bias is shown in Figs. 3A and 3B, and the detailed assessment of each study is shown in supplement Tables S3 and S4.

3.3. Heterogeneity, consistency and publication bias

Statistical heterogeneity was low across the studies for primary and secondary outcomes in both unselected group and selected group (all $I^2 < 25\%$, ranging from 0.005–15%) by fitting a random-effects model. The differences in values of DIC in both "consistency" and "inconsistency" models were used to evaluate the global consistency. In all outcomes the differences in DIC values were low, ranging from 0.007 to 0.15, which indicates a good level of global consistency. Local consistency analysis was only conducted in the unselected group because selected group had no closed loops for comparison. The p-values of indirect and direct comparisons between Rilotumumab and Panitumumab were 0.14, 0.09, 0.65 and 0.91 for OS, PFS, ORR and AE ≥ 3, respectively, which indicates no significant local inconsistency. There was no publication bias among the included studies both in the unselected group and selected group, which can be seen from the symmetrical distribution of effect sizes in the funnel plots (Supplementary Figures S3 and S4).

3.4. Primary outcome: Overall Survival (OS)

In the network meta-analysis of OS, 19 trials containing 13 separated nodes in the unselected group reported the primary outcomes of OS. Unfortunately, no regimen had a statistically significant difference in prolonging the OS in comparison to chemotherapy. Two immunotherapy drugs, pembrolizumab and nivolumab, showed a trend for survival advantage (HR 0.73, 95%CI 0.47–1.13; HR 0.86, 95%CI 0.67–1.09, respectively), while others were comparable to standard chemotherapy except two poor effect regimens, nimotuzumab and ipatasertib. (Fig. 4A). Results of different treatments in both direct and indirect comparisons are shown in a league table (Supplement Table S5). In addition, we ranked the comparative effects of all regimens based on their SUCRA values: pembrolizumab (90.4%) was the most likely to improve OS, followed by nivolumab (81.37%) and cetuximab (67.78%), while ipatasertib was ranked last (8.53%) (Fig. 5A).

In selected group, 12 trials reported the endpoint of OS, including 10 independent nodes. Zolbetuximab was the only regimen with a significant difference from standard chemotherapy (HR 0.53, 95%CI 0.31–0.89). Tratuzumab, tratuzumab plus pertuzumab, pembrolizumab and nivolumab, showed an improved trend for OS compared to standard chemotherapy (Fig. 4C). Onartuzumab, matuzumab, and lapatinib plus chemotherapy, were comparable to standard chemotherapy, while rliotumumab had a more negative effect on OS (Fig. 4C). Ultimately, taking into account the comparative effects of all regimens regarding OS, zolbetuximab, tratuzumab plus pertuzumab and nivolumab occupied top three by the SUCRA score (90.42%, 81.96% and 70.58% respectively), while rilotumumab came bottom (7.37%) (Fig. 5B).

3.5. Primary outcome: progression-free survival (PFS)

With respect to PFS in unselected group for network meta-analysis, there are 20 trails containing 13 separated nodes. No regimen showed an obviously improvement than standard chemotherapy, although nivolumab was very close to statistical significance (HR 0.73, 95%CI 0.52–1.03). Pembrolizumab, ADX

and bevacizumab, also showed an improved trend compared to standard chemotherapy (HR 0.65, 95%CI 0.37–1.14; HR 0.83, 95%CI 0.65–1.26; HR 0.86, 95%CI 0.64–1.13, respectively). All other regimens were comparable to standard chemotherapy except nimotuzumab, which had inferiority effect than standard chemotherapy alone (Fig. 4B). League table summarizing the direct and indirect comparisons between the regimens is shown in Supplement Table S6. Furthermore, from SUCRA score of PFS, Pembrolizumab (88.85%) was ranked first in improving PFS, followed by nivolumab (86.36%) and ADX (72.65%), while nimotuzumab was ranked last (4.07%) (Fig. 5A).

In selected group, the network plot analysis was the same as OS results. Zolbetuximab showed a significant improvement in PFS (HR 0.45, 95%CI 0.23–0.89). Tratuzumab, tratuzumab plus pertuzumab, lapatinib, pembrolizumab and nivolumab, had improvement trend in PFS than standard chemotherapy. Except rilotumumab, other regimens were comparable to standard chemotherapy (Fig. 4D). Furthermore, in the rank of SUCRA score, zolbetuximab, tratuzumab plus pertuzumab and nivolumab occupied the top three ranks (89.24%, 83.03% and 67.06% respectively), while rilotumumab, with its score at 10.32%, was ranked last (Fig. 5B).

3.6. Secondary outcomes: Objective response rate (ORR) and Adverse events (AEs) ≥ 3

A total of 19 and 11 studies in unselected group and selected group were eligible and merged for the analysis of ORR. From the result of interval comparisons, only pembrolizumab in unselected group revealed a significant advantage compared to standard chemotherapy (HR 1.96, 95%CI 1-3.87), although pembrolizumab plus tratuzumab was very close to statistical significance (HR 4.73, 95%CI 0.99–22.41) (supplement Figure S5B). Pembrolizumab, nivolumab and rilotumumab were ranked at the top three by SUCRA scores in unselected group (84.91%, 64.87% and 64.82%, respectively) (Fig. 5A), meanwhile pembrolizumab plus tratuzumab (93.83%) was the best, followed by tratuzumab plus pertuzumab (76.23%) and lapatinib (64.64%) in selected group. In the analysis of AE ≥ 3 outcomes, 18 and 10 studies in unselected group and selected group respectively were included. The safest regimens were revealed to be bevacizumab, ADX, and chemotherapy in unselected group by SUCRA score (83.29%, 78.83% and 74.47% respectively) (Fig. 5A) while nimotuzumab was ranked at the bottom (10.06%). In selected group, the highest three were rilotumumab, chemotherapy and tratuzumab (71.99%, 67.82% and 66.14% respectively), while the lowest-ranked regimen was nivolumab (18.81%) (Fig. 5B).

4. Discussion

In this study, we performed a Bayesian network meta-analysis to analyze the efficacy and tolerability in untreated AGC patients who received target agents or immune checkpoint inhibitors along with chemotherapy as first-line treatments. We divided the included studies into unselected and selected groups, which was based on whether the study population had specific pathological positivity or a certain PD-L1 CPS. As a result, in unselected group, pembrolizumab and nivolumab improved patients' OS, PFS and ORR, but also had a higher AE rate than standard chemotherapy. In selected group, zolbetuximab, tratuzumab plus pertuzumab and nivolumab occupied the top three ranks for OS and PFS, while they had a moderate AE rate among all regimens.

In general, among the unselected group, none of the target agent treatments showed a significant superiority compared to standard chemotherapy. Although there were 6 and 8 regimens that ranked higher than chemotherapy in OS and PFS respectively, the HRs of OS and PFS were still comparable to chemotherapy. In 2014, American Society of Clinical Oncology (ASCO) expert meeting stated that a risk reduction of HR 0.80 might be clinically relevant with metastatic disease [19]. Therefore, in consideration of survival efficacy and safety profile, it is appropriate to conclude that among the existing target agents, there are no regimens superior to first-line standard chemotherapy in the population of patients who are not selected by specific pathological positivity. However, immunotherapy combined with chemotherapy showed potential benefits, especially nivolumab, which HR and 95%CI of PFS were very close to statistical significance in our meta-analysis, indicating that immune checkpoint therapy on PD-1 receptor may have a positive effect on PFS, which may bring about a promising direction for general patients.

Since Bang *et al.*[20] reported the largescale phase III RCT ToGA, HER-2 gradually evolved as the most widely investigated target against AGC. The addition of trastuzumab to standard chemotherapy has been confirmed as the first-line therapy among AGC patients with HER-2 overexpression. In our meta-analysis, the regimens of trastuzumab plus pertuzumab combined with chemotherapy occupied the top three ranks for OS and PFS, which indicates that the dual HER-2 targeting strategy displays an obvious benefit in terms of survival. The tolerability is also comparable to both chemotherapy and trastuzumab plus chemotherapy. Meanwhile, KEYNOTE-811 [21] had reported the combination of pembrolizumab, trastuzumab and chemotherapy, which provided a substantial, statistically significant improvement in ORR compared with placebo, trastuzumab, and chemotherapy for HER2-positive advanced gastric cancer patients. In our meta-analysis, it was the first at the rank of ORR in selected group. Although initial data did not report OS and PFS, we will continuously concern the following results. Moreover, in the pooled result of Schuler *et al.* [22] and Sahin *et al.* [23], the addition of zolbetuximab (IMAB362) significantly elongated OS and PFS among patients with CLDN18.2 positivity compared with triplet chemotherapy alone, which indicates that zolbetuximab may be a promising medication for AGC patients. Unfortunately, adding rilotumumab or onartuzumab failed to generate survival benefits among MET-1 positive patients from this network meta-analysis. This suggests that standard first-line chemotherapy may still serve as the preferred first-line regimen in MET-1 positive AGC patients.

In the selected population with PD-L1 expression, immune checkpoint inhibitors of PD-1 also revealed their survival benefits. The addition of nivolumab to standard first-line chemotherapy obviously prolonged OS and PFS among patients who had CPS of 5 or higher. This regimen was also recommended as first-line therapy in HER-2-negative patients in NCCN 2021 guideline [4]. Our network meta-analysis is consistent with this conclusion in that among patients without HER-2 and CLDN18.2 positivity, nivolumab was the preferred option, which is shown by the SUCRA ranks. Although nivolumab has higher risk of AE ≥ 3 than chemotherapy, there was no statistical significance and fatal AEs are reported to be very rare. Another PD-1 checkpoint inhibitor, pembrolizumab, with chemotherapy, also showed some superiority in OS and PFS over standard chemotherapy. In RCT KEYNOTE-062 [24], whose patients had GC and GEJ, with CPS of 1 or greater, the difference in OS was quite close to the statistical boundary. Meanwhile, KEYNOTE-590 [25], which included GEJ and EC patients with CPS of 10 or higher, showed a significant improvement in survival benefits. After pooling these two RCTs together, pembrolizumab plus chemotherapy was ranked second when patients had no HER-2 and CLDN18.2 overexpression.

Targeted agents or immune checkpoint inhibitors as monotherapy was common in second or third line advanced gastric cancer treatment. Monotherapy of ramucirumab was recommended as second-line therapy and pembrolizumab as third-line therapy in NCCN 2021 guideline [4]. Since chemotherapy is standard treatment in first-line therapy of advanced gastric cancer, clinical trials of targeted agents or immune checkpoint inhibitors as monotherapy were rare. However, there are still some phase II/III clinical trials which can give us new insight [26, 27]. Pembrolizumab monotherapy was one arm in KEYNOTE-062 [24] trial, investigated as first-line treatment. Trial reported that pembrolizumab was noninferior but not superior to chemotherapy for OS in patients with CPS of 1 or greater, while prolonged OS in patients CPS ≥ 10. Meanwhile, pembrolizumab monotherapy showed less AEs grade 3–5 than chemotherapy (17% vs 69%), indicated comparable efficiency but higher safety. Will monotherapy of immune checkpoint inhibitors become first-line treatment for advanced gastric cancer? Except for waiting more high-quality RCTs, economic cost will be a very important concern.

Our study has some limitations. Firstly, this study was limited to estimations that were based on data availability. For example, for studies that did not report HRs directly, we estimated the HRs and 95% CIs from Kaplan-Meier curves. In addition, we did not include the AE data of some studies owing to the lack of accurate number of patients with AE ≥ 3, which may lead to inconsistencies in terms of AE. Secondly, we pooled triple-chemotherapy and double-chemotherapy regimens into one node, which could bring potential biases into the network meta-analysis despite the low overall statistical heterogeneity as mentioned previously. Further studies could analyze the results in patients with different chemotherapy regimens by subgroup analysis.

5. Conclusions

In conclusion, among average patients who were not selected by pathological positivity or PD-L1 expression, immune checkpoint inhibitor of PD-1 plus chemotherapy will be the promising regimen. Patients who have the overexpression of HER-2 or CLDN18.2, dual HER-2 targeting strategy or zolbetuximab combined with chemotherapy has higher survival benefits. Furthermore, for patients who have PD-L1 expression with no HER-2 or CLDN18.2 positivity, additional immune checkpoint inhibitor of PD-1 will be a good considered option.

Declarations

Contributions: Conceptualization, QT.D and CG.X; methodology, HY.W; software, S.L. DH.S and NX.L; formal analysis, S.L. and HY.W; writing—original draft preparation, S.L. and L.X; writing—review and editing, YJ.K. and QT.D. All authors have read and agreed to the published version of the manuscript.

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Figures

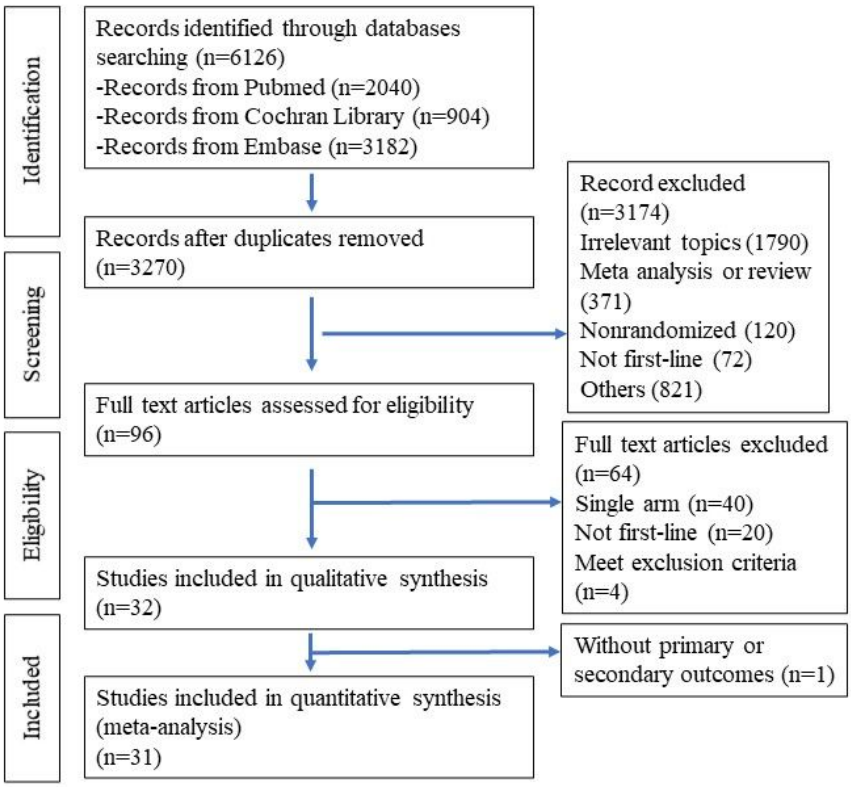

Figure 1

Flowchart of the study selection process.

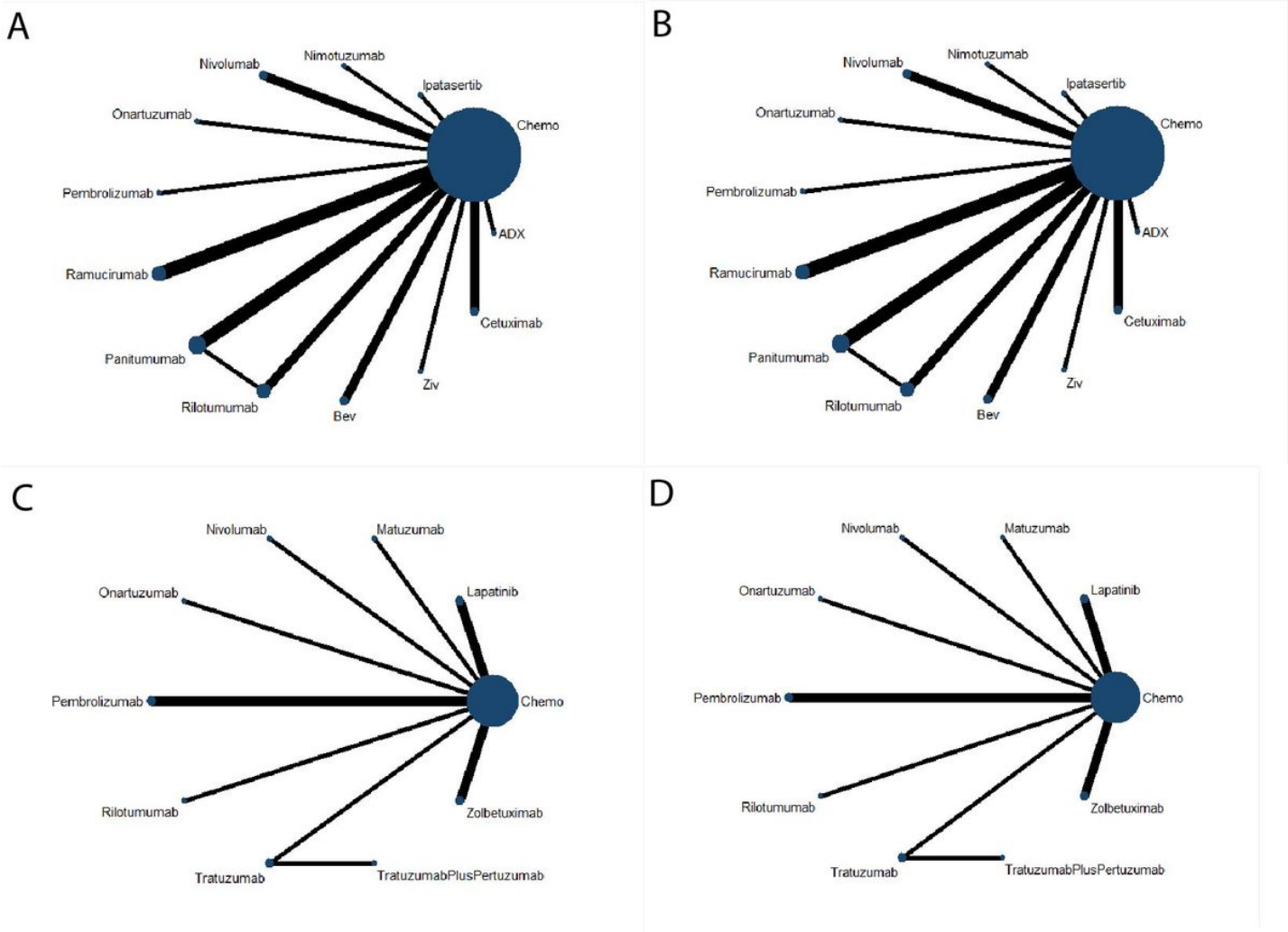

Figure 2

The network comparison plots of primary outcomes. A, The network plots of OS in unselected group; B, The network plots of PFS in unselected group; C, The network plots of OS in selected group; D, The network plots of PFS in unselected group. Chemo: Chemotherapy; ADX: Andecaliximab; Ziv: Ziv-aflibercept; Bev: Bevacizumab. All regimens omitted with chemotherapy.

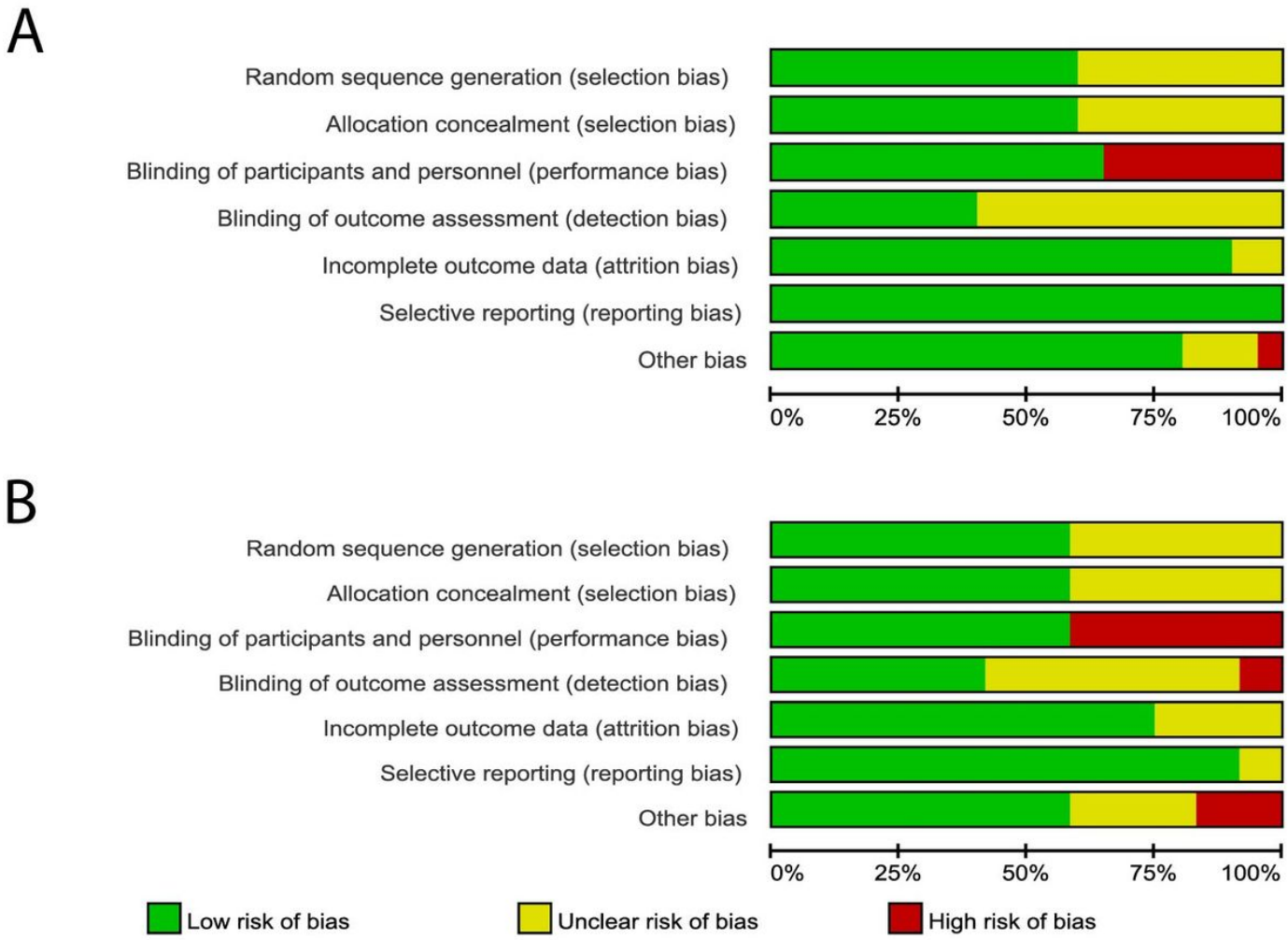

Figure 3

Risk of bias assessment. A, Risk of bias assessment in unselected group; B, Risk of bias assessment in selected group.

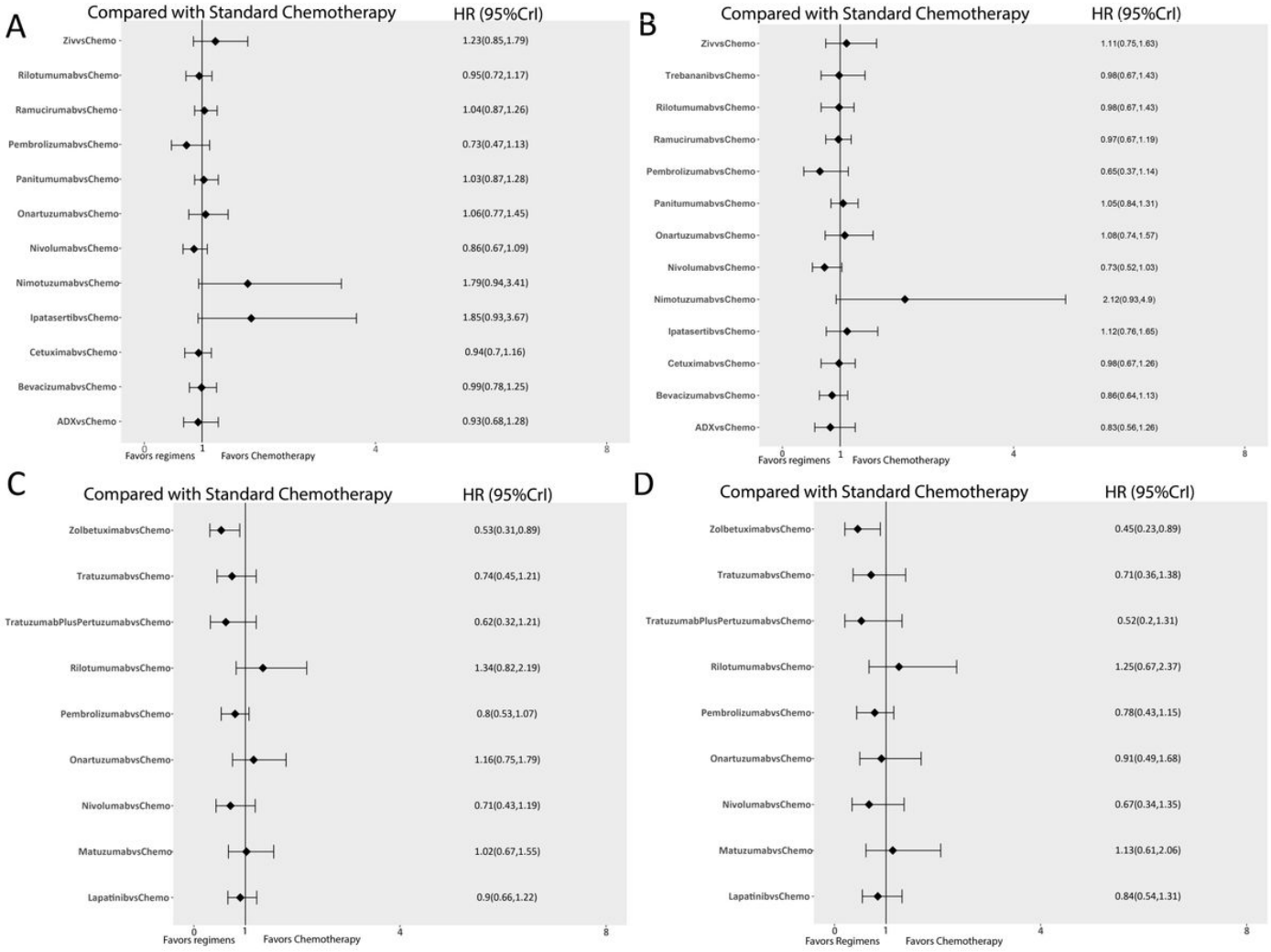

Figure 4

Forest plots of primary outcomes compared with Standard Chemotherapy. A, Forest plots of OS compared with chemotherapy in unselected group; B, Forest plots of PFS compared with chemotherapy in unselected group; C, Forest plots of OS compared with chemotherapy in selected group; D, Forest plots of PFS compared with chemotherapy in selected group.

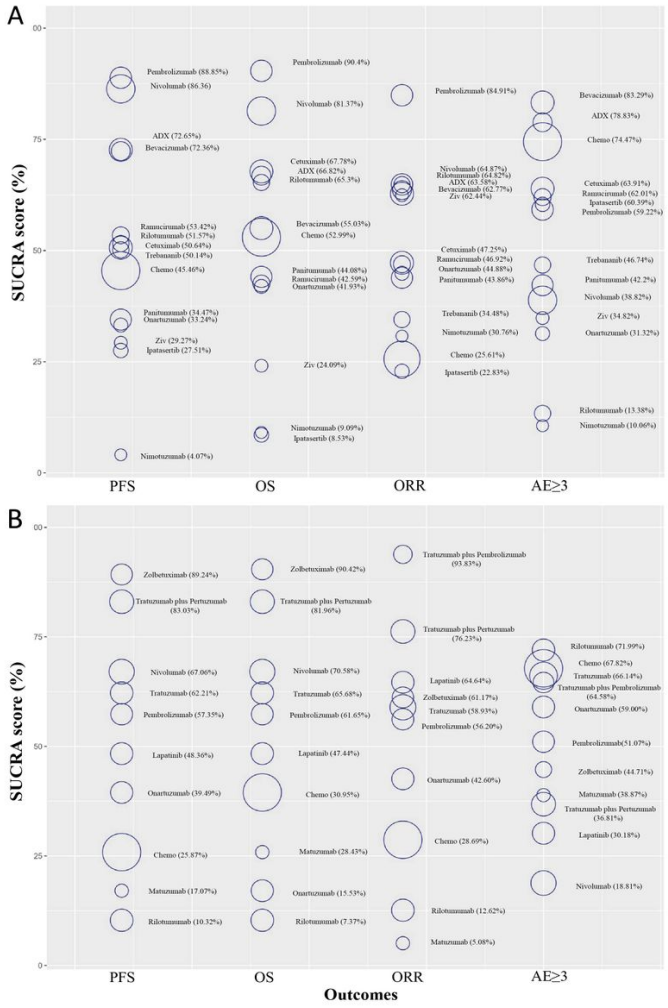

Figure 5

SUCRA score of each regimen in all outcomes. A, SUCRA score in unselected group; B, SUCRA score in selected group. The size of each circle is weighted by the square root of the patient number. All regimens are combined with chemotherapy, ADX: Andecaliximab; Ziv: Ziv-aflibercept; Chemo: Chemotherapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMA2020checklist.docx
- SupplementaryMaterials.docx